Applied Physiology in Intensive Care Medicine

M.R. Pinsky
L. Brochard
J. Mancebo
G. Hedenstierna
Editors

Second Edition

Springer

M. R. Pinsky · L. Brochard · J. Mancebo · G. Hedenstierna (Eds.)

Applied Physiology in Intensive Care Medicine

M. R. Pinsky · L. Brochard · J. Mancebo
G. Hedenstierna (Eds.)

Applied Physiology in Intensive Care Medicine

Second Edition

With 155 Figures and 27 Tables

Springer

MICHAEL R. PINSKY, MD
University of Pittsburgh Medical Center
Dept. of Critical Care Medicine
Scaife Hall 616
3550 Terrace Street
Pittsburgh, PA 15261
USA

JORDI MANCEBO, MD
Hospital de Sant Pau
Dept. Intensive Care Medicine
Avda. S. Antonio M. Claret, 167
08025 Barcelona
Spain

LAURENT BROCHARD, MD
Hôpital Henri Mondor
Dept. Intensive Care Medicine
51 av. Maréchal Lattre de Tassigny
94010 Créteil CX
France

GÖRAN HEDENSTIERNA, MD
Uppsala University Hospital
Dept. Clinical Physiology
751 85 Uppsala
Sweden

The articles in this book appeared in the journal "Intensive Care Medicine" between 2002 and February 2009.

ISBN 978-3-642-01768-1 e-ISBN 978-3-642-01769-8
DOI 10.1007/978-3-642-01769-8
Springer Dordrecht Heidelberg London New York

Library of Congress Control Number: 2009926064

Cover design: eStudio Calamar, Spain

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Introduction

The practice of intensive care medicine is at the very forefront of titration of treatment and monitoring response. The substrate of this care is the critically ill patient who, by definition, is at the limits of his or her physiologic reserve. Such patients need immediate, aggressive but balanced life-altering interventions to minimize the detrimental aspects of acute illness and hasten recovery. Treatment decisions and response to therapy are usually assessed by measures of physiologic function, such as assessed by cardio-respiratory monitoring. However, how one uses such information is often unclear and rarely supported by prospective clinical trials. In reality, the bedside clinician is forced to rely primarily on physiologic principles in determining the best treatments and response to therapy. However, the physiologic foundation present in practicing physicians is uneven and occasionally supported more by habit or prior training than science.

A series of short papers published in Intensive Care Medicine since 2002 under the heading Physiologic Notes attempts to capture the essence of the physiologic perspectives that underpin both our understanding of disease and response to therapy. This present volume combines the complete list of these Physiologic Notes up until February 2009 with the associated review articles over the same interval that also addressed these central issues. This volume was created to address this fundamental unevenness in our understanding of applied physiology and underscore what is known and how measures and monitoring interact with organ system function and response to therapy. This collection of physiologic perspectives and reviews, written by some of the most respected experts in the field, represent an up-to-date and invaluable compendium of practical bedside knowledge essential to the effective delivery of acute care medicine. Although this text can be read from cover to cover, the reader is encouraged to use this text as a reference source reading individual Physiologic Notes and Review articles as they pertain to specific clinical issues. In that way the relevant information will have immediate practical meaning and hopefully become incorporated into routine practice.

We hope that the reader finds these papers and reviews useful in their practice and enjoy reading them as much as we enjoyed editing the original articles that it comprises.

Michael R. Pinsky, MD
Laurent Brochard, MD
Jordi Mancebo, MD
Göran Hedenstierna, MD

Contents

Contributors

Jérôme Aboab
Réanimation Médicale
Hôpital Henri Mondor
Créteil, France

Lars Algotsson
Department of Anaesthesiology–
Heart-Lung Division
University Hospital of Lund,
22185 Lund, Sweden

Peter J. D. Andrews
Department of Anaesthetics, Intensive
Care and Pain Medicine
University of Edinburgh, Western General Hospital
Crewe Road, EH4 2XU Edinburgh, Scotland, UK

Michel Aubier
INSERM U 700 and IFR 02, Facult Xavier Bichat
16 rue Henri Huchard, 75018 Paris, France

Elie Azoulay
Department of Clinical Immunology,
and Hôpital Saint-Louis, Medical ICU, AP–HP,
University Paris-7 Diderot, UFR de Médecine,
1 avenue Claude Vellefaux, 75010 Paris, France

Andreas Bacher
Department of Anesthesiology
and General Intensive Care
Medical University of Vienna, AKH
Währinger Gürtel 18–20, 1090 Vienna, Austria

Jan Bakker
Department of Intensive Care, Erasmus MC
University Medical Center Rotterdam
P.O. Box 2040, 3000 CA
Rotterdam, The Netherlands

Rinaldo Bellomo
Department of Intensive Care
and Division of Surgery
Austin & Repatriation Medical Centre
3084 Heidelberg, Melbourne, Victoria, Australia

Karim Bendjelid
Surgical Intensive Care Division,
Geneva University Hospitals
1211 Geneva 14, Switzerland

Anuj Bhatia
Department of Anaesthesia,
Addenbrooke's Hospital,
Hills Road, CB2 2QQ Cambridge, UK

Luis Blanch
Critical Care Center
Hospital de Sabadell
Parc Taulis/n, 08208 Sabadell, Spain

Frank Bloos
Klinik für Anästhesiologie und Intensivtherapie
Klinikum der Friedrich-Schiller-Universität
Erlanger Allee 101, 07747 Jena, Germany

Jorge Boczkowski
INSERM U 700 and IFR 02, Facult Xavier Bichat
16 rue Henri Huchard, 75018 Paris, France

Alain F. Broccard
Medical Intensive Care Unit,
Regions Hospital Pulmonary and Critical Care Division,
Regions Hospital, St Paul,
MN 55101-2595, USA

Laurent Brochard
Réanimation Médicale
Hôpital Henri Mondor,
Université Paris 12, INSERM
U651, 94010 Créteil, France

Sophie Buyse
Department of Clinical Immunology,
and Hôpital Saint-Louis, Medical ICU,
AP–HP, University Paris-7 Diderot, UFR de Médecine,
1 avenue Claude Vellefaux, 75010 Paris, France

Belen Cabello
Hospital Santa Creu i Sant Pau,
Servicio de Medicina Intensiva
Av/ Sant Antoni Maria Claret 167,
CP 08025 Barcelona, Spain

Enrico Calzia
Sektion Anästhesiologische Pathophysiologie
und Verfahrensentwicklung Universitätsklinik
für Anästhesiologie, Universität Ulm
Parkstrasse 11, 89070 Ulm, Germany

Giuseppe Citerio
Neurorianimazione, Dipartimento
di Anestesia e Rianimazione
Nuovo Ospedale San Gerardo
Via Donizetti 106, 20052 Monza, Italy

Caroline Créput
Department of Clinical Immunology,
and Hôpital Saint-Louis, Medical ICU, AP–HP,
University Paris-7 Diderot, UFR de Médecine,
1 avenue Claude Vellefaux, 75010 Paris, France

Jacques Creteur
Department of Intensive Care,
Erasme University Hospital, Free
University of Brussels
Route de Lennik 808, 1070 Brussels, Belgium

Daniel De Backer
Department of Intensive Care,
Erasme University Hospital
Free University of Brussels
Route de Lennik 808, 1070 Brussels, Belgium

Lisa L. Dever
UMDNJ-New Jersey Medical School,
VA New Jersey Health Care System
385 Tremont, East Orange, NJ 07018, USA

Ioanna Dimopoulou
Second Department of Critical Care Medicine,
Attikon Hospital, Medical School National
and Kapodistrian University of Athens
2 Pesmazoglou Street, 14561
Kifissia, Athens, Greece

Andrew Durward
Evelina Children's Hospital, Guy's and
Saint Thomas' NHS Trust,
Paediatric Intensive Care Unit,
SE1 7EH London, UK

Lennart Edmark
Department of Anesthesia and Intensive Care
Central Hospital
72335 Vasteras, Sweden

Jean-François Enrico
Former Chief of Intensive Care Unit
Hôpital des Cadolles,
Neuchâtel, Switzerland

Timothy W. Evans
Imperial College School of Medicine
Department of Intensive Care Medicine
Royal Brompton Hospital, London, UK

Konrad J. Falke
Klinik für Anaesthesiology und
operative Intensivmedizin Berlin
Campus Virchow Klinikum,Charite,
Berlin, Germany

François Feihl
Division of Clinical Pathophysiology,
University Hospital (CHUV)
and Lausanne University (UNIL),
1011 Lausanne, Switzerland

Evans R. Fernández Pérez
Mayo Clinic College of Medicine
Rochester, MN 55905, USA

Lionel Galicier
Department of Clinical Immunology,
and Hôpital Saint-Louis, Medical ICU, AP–HP,
University Paris-7 Diderot, UFR de Médecine,
1 avenue Claude Vellefaux, 75010 Paris, France

Jean-Roger Le Gall
Department of Intensive Care Medicine
Saint-Louis University Hospital, Paris, France

Luciano Gattinoni
Istituto di Anestesia e Rianimazione
Fondazione IRCCS Ospedale Maggiore Policlinico
Mangiagalli, Regina Elena di
Milano, Università degli Studi
Via Francesco Sforza 35, 20122 Milan, Italy

Ian S. Grant
Department of Anaesthesia,
University of Edinburgh,
Western General Hospital, Edinburgh,
Scotland, UK

Claude Guerin
Hôpital de la Croix Rousse and Université de Lyon,
Service de Réanimation Médicale,
103 Grande Rue de la Croix Rousse,
69004 Lyon, France

Arun Kumar Gupta
Department of Anaesthesia,
Addenbrooke's Hospital, Hills Road,
CB2 2QQ Cambridge, UK
and
Neuroscience Critical Care Unit,
Addenbrooke's Hospital, Hills Road,
CB2 2QQ Cambridge, UK

Göran Hedenstierna
Clinical Physiology, Department of
Medical Sciences, University Hospital
75185 Uppsala, Sweden

Rolf D. Hubmayr
Mayo Clinic College of Medicine
Rochester, MN 55905, USA

François Jardin
Hôpital Ambroise Paré,
Service de Réanimation Médicale,
9 avenue Charles de Gaulle,
92104 Boulogne, France

Waldemar G. Johanson †
UMDNJ-New Jersey Medical School
185 South Orange, Newark, NJ 07018, USA

Björn Jonson
Department of Clinical Physiology
University Hospital of Lund
22185 Lund, Sweden

Amal Jubran
Division of Pulmonary and Critical Care Medicine
Edward Hines Jr. Veterans Affairs Hospital
Route 111 N, Hines, IL, 60141, USA

Peter Karpati
Department of Anaesthesiology
and Critical Care Medicine
Hopital Lariboisie`re, 2 Rue Ambroise Pare
75475 Paris Cedex 10, France

Brian P. Kavanagh
Department of Critical Care Medicine,
Hospital for Sick Children
555 University Avenue, Toronto,
ONT, M5G 1X8, Canada

John A. Kellum
Division of Critical Care Medicine, Scaife Hall
University of Pittsburgh Medial Centre,
Terrace Street, Pittsburgh, PA 15260, USA

Ioanna Korovesi
Department of Critical Care & Pulmonary
Medicine and "M. Simou" Laboratory
Medical School, University of
Athens, Evangelismos Hospital
45–47 Ipsilandou St., 10675 Athens, Greece

John G. Laffey
Department of Anaesthesia,
University College Hospital
Galway and Clinical Sciences Institute,
National University of Ireland, Galway, Ireland

Sophie Lanone
INSERM U 700 and IFR 02, Facult Xavier Bichat
16 rue Henri Huchard, 75018 Paris, France

Alexandre Lima
Department of Intensive Care, Erasmus MC
University Medical Center Rotterdam
P.O. Box 2040, 3000 CA
Rotterdam, The Netherlands

Bruno Louis
Inserm Unit 651
Department of Medecine Paris 12
Créteil, France

Umberto Lucangelo
Department of Perioperative Medicine,
Intensive Care and Emergency, Cattinara
Hospital, Trieste University School of Medicine
34139 Trieste, Italy

Jordi Mancebo
Hospital Santa Creu i Sant Pau,
Servicio de Medicina Intensiva
Av/ Sant Antoni Maria Claret 167,
CP 08025 Barcelona, Spain

Alexandre Toledo Maciel
Department of Intensive Care,
Erasme University Hospital, Free
University of Brussels
Route de Lennik 808, 1070 Brussels, Belgium

Carol S. A. Macmillan
University of Dundee, Department of Anaesthesia
Ninewells Hospital, Dundee DD1 9SY, UK

Manu L. N. G. Malbrain
Medical Intensive Care Unit,
ACZA Campus Stuivenberg
Lange Beeldekensstraat 267, B-
2060 Antwerpen, Belgium

Paul E. Marik
Department of Critical Care Medicine
University of Pittsburgh Medical Center
640A Scaife Hall, 3550 Terrace
Street, Pittsburgh, PA, 15261, USA

George M. Matuschak
Division of Pulmonary, Critical Care
and Occupational Medicine
Departments of Internal Medicine and
Pharmacological and Physiological Science
School of Medicine
Saint Louis University, 3635 Vista Ave.,
Saint Louis, MO 63110-0250, USA

Irene Mavrommati
Department of Critical Care & Pulmonary
Medicine and "M. Simou" Laboratory
Medical School, University of
Athens, Evangelismos Hospital
45–47 Ipsilandou St., 10675 Athens, Greece

Paul McLoughlin
Department of Physiology,
University College Dublin
Dublin, Ireland

Alexandre Mebazaa
Department of Anaesthesiology
and Critical Care Medicine
Hopital Lariboisière, 2 Rue Ambroise Pare
75475 Paris Cedex 10, France

L. Joanne Meyer
Department of Medicine,
St. Joseph's Hospital
Toronto, Canada

Xavier Monnet
Hôpital de Bicêtre, AP-HP,
Service de réanimation médicale,
78 rue du Général Leclerc,
94270 Le Kremlin-Bicêtre, France
and
Université Paris-Sud, Equipe d'accueil EA 4046,
Faculté de Médecine Paris-Sud,
94270 Le Kremlin-Bicêtre, France

Robert Naeije
Department of Physiology,
Faculty of Medicine of the Free University
of Brussels, Erasme Campus
808 Route de Lennik, CP 604,
1070 Brussels, Belgium

Luis J. Noronha
Division of Pulmonary, Critical Care
and Occupational Medicine
Departments of Internal Medicine and
Pharmacological and Physiological Science
School of Medicine
Saint Louis University, 3635 Vista Ave.,
Saint Louis, MO 63110-0250, USA

Donall O'Croinin
Department of Physiology,
University College Dublin
Dublin, Ireland

Stylianos E. Orfanos
2nd Department of Critical Care,
University of Athens Medical
School, Attikon Hospital
1, Rimini St., 12462 Haidari (Athens), Greece

Sairam Parthasarathy
Division of Pulmonary and Critical
Care, Medicine Edward Hines Jr.
Veterans Administrative Hospital, Loyola
University of Chicago Stritch School of Medicine
Route 111 N, Hines, IL 60141, USA

Michael Piagnerelli
Department of Intensive Care,
Erasme University Hospital
Free University of Brussels
808 route de Lennik, 1070 Brussels, Belgium

Claude Perret
Former Chief of Intensive Care Department
University Hospital of Lausanne, Switzerland
Ruelle des Halles 4, CH-1095 Lutry, Switzerland

Antonio Pesenti
Dipartimento di Medicina
Perioperatoria e Terapia Intensiva
A.O. Ospedale S.Gerardo
Monza, Università degli Studi
Milan-Bicocca, Italy

Michael R. Pinsky
Department of Critical Care Medicine
University of Pittsburgh Medical Center,
604 Scaife, 3550 Terrace Street,
Pittsburgh, PA 15261, USA

Murugan Raghavan
Conemaugh Memorial Medical Center
Johnstown, Pennsylvania, USA

Peter Radermacher
Sektion Anästhesiologische Pathophysiologie
und Verfahrensentwicklung Universitätsklinik
für Anästhesiologie, Universität Ulm
Parkstrasse 11, 89070 Ulm, Germany

Konrad Reinhart
Klinik für Anästhesiologie und Intensivtherapie
Klinikum der Friedrich-Schiller-Universität
Erlanger Allee 101, 07747 Jena, Germany

Estelle Renaud
Department of Anaesthesiology
and Critical Care Medicine
Hopital Lariboisie`re, 2 Rue Ambroise Pare
75475 Paris Cedex 10, France

Jean-Christophe Richard
Hôpital de la Croix Rousse and Université de Lyon,
Service de Réanimation Médicale,
103 Grande Rue de la Croix Rousse,
69004 Lyon, France

Charis Roussos
Department of Critical Care & Pulmonary
Medicine and "M. Simou" Laboratory
Medical School, University of
Athens, Evangelismos Hospital
45–47 Ipsilandou St., 10675 Athens, Greece

Josep Roca
Servei de Pneumologia, Hospital Clínic
Institut d'Investigaciones Biomédiques
Ausgust Pi i Sunyer, Universitat de Barcelona
Villarroel 170, 08036 Barcelona, Spain

Robert Rodríguez-Roisin
Servei de Pneumologia, Hospital Clínic
Institut d'Investigaciones Biomédiques
Ausgust Pi i Sunyer, Universitat de Barcelona
Villarroel 170, 08036 Barcelona, Spain

Jacques-André Romand
Surgical Intensive Care Division,
Geneva University Hospitals
1211 Geneva 14, Switzerland

Claudio Ronco
Divisione di Nefrologia, Ospedale San Bortolo
Via Ridolfi, 36100 Vicenza, Italy

Frédérique Schortgen
Réanimation Médicale et Infectieuse
Hôpital Bichat-Claude Bernard
75018 Paris, France

Suveer Singh
Chelsea and Westminster Hospital
Department of Intensive Care Medicine
369 Fulham Road, SW10 9NH London, UK

Arthur S. Slutsky
Queen Wing, St. Michael's Hospital
30 Bond St., Toronto, ONT, M5B 1W8, Canada

Pierre Squara
CERIC Clinique Ambroise Pare
27 Boulevard Victor Hugo, 92200
Neuilly-sur-Seine, France

Camille Taillé
INSERM U 700 and IFR 02, Facult Xavier Bichat
16 rue Henri Huchard, 75018 Paris, France

Jukka Takala
Department of Intensive Care Medicine,
University Hospital Bern (Inselspital),
University of Bern, 3010 Bern, Switzerland

Jean-Louis Teboul
Hôpital de Bicêtre, AP-HP,
Service de réanimation médicale,
78 rue du Général Leclerc,
94270 Le Kremlin-Bicêtre, France
and
Université Paris-Sud, Equipe d'accueil EA 4046,
Faculté de Médecine Paris-Sud,
94270 Le Kremlin-Bicêtre, France

Shane M. Tibby
Paediatric Intensive Care Unit,
Evelina Children's Hospital,
Guy's and Saint Thomas' NHS Trust,
SE1 7EH London, UK

Martin J. Tobin
Division of Pulmonary and Critical Care Medicine
Edward Hines Jr. VA Hospital, 111N
5th Avenue and Roosevelt Road
Hines, Illinois 60141, USA

Lorraine N. Tremblay
Department of Surgery
Sunnybrook and Women's Health Sciences Center
Toronto, Ont., Canada

Stylianos Tsagarakis
Department of Endocrinology, Athens Polyclinic
Athens, Greece

Michel Vanhaeverbeek
Experimental Medicine Laboratory,
André Vésale Hospital
Montigny-le-Tilleul, Belgium

Theodoros Vassilakopoulos
Department of Critical Care and Pulmonary Services,
University of Athens Medical School,
Evangelismos Hospital,
45–47 Ipsilandou Street, 10675 Athens, Greece
and
Critical Care Department,
Evangelismos Hospital,
45–47 Ipsilandou Strasse, 10675 Athens, Greece

Antoine Vieillard-Baron
University Hospital Ambroise Paré,
Assistance Publique Hôpitaux de Paris
Medical Intensive Care Unit
9 avenue Charles de Gaulle, 92104
Boulogne Cedex, France

Jean-Louis Vincent
Department of Intensive Care,
Erasme University Hospital
Free University of Brussels
Route de Lennik 808, 1070 Brussels, Belgium

Peter D. Wagner
Department of Medicine, Division of Physiology,
University of California, San Diego, 9500 Gilman Drive,
Dept. 0623A, La Jolla CA 92093-0623A, USA

Karim Zouaoui-Boudjeltia
Experimental Medicine Laboratory,
André Vésale Hospital
Montigny-le-Tilleul, Belgium

Laurent Brochard

Intrinsic (or auto-) PEEP during controlled mechanical ventilation

Introduction

Extrinsic positive end-expiratory pressure (PEEP) applied to the patient at the airway opening is used artificially to increase end-expiratory lung volume. Extrinsic PEEP is increased or decreased in small increments in ventilator-dependent patients because of its marked effects on cardiorespiratory status. Unintentional or unmeasured end-expiratory hyperinflation, called intrinsic or auto-PEEP, can also occur and have similarly marked profound cardiorespiratory effects in ventilator-dependent patients during controlled mechanical ventilation. Ventilatory settings can interact with the passive process of expiration and generate intrinsic or auto-PEEP [1, 2].

What is intrinsic (or auto-) PEEP?

During passive expiration of the lungs the elastic forces of the respiratory system are the driving forces and can be described by the relationship between lung volume and the elastic recoil pressure of the respiratory system. The lower the elastic forces, or the higher the resistive forces, the longer will be the time needed to fully expire the inspired tidal volume. In a single-compartment model of the lung in which the lung behaves as if it has a single resistance and compliance, the volume at any given time during expiration (V) is described by the monoexponential equation, $V=V_o-Ve^{-kt}$, where k is the time constant of the equation and is the product of resistance times compliance (the reverse of elastance), and V_o is the end-inspiratory volume. In practical terms a time constant is the time required for the lungs to expire 63% of their initial volume. Thus the time needed passively to expire the inspired tidal volume is determined by the two main characteristics of the respiratory system: elastance and resistance. If expiration is interrupted before its natural end, i.e., by occurrence of the next inspiration, end-expiratory lung volume is higher than the so-called relaxation volume of the respiratory system, usually referred to as functional residual capacity. As a result the alveolar pressure at the end of expiration is higher than zero (zero being the atmospheric pressure), as predicted by the relationship between lung volume and the elastic recoil pressure of the respiratory system. This process is called dynamic hyperinflation, and the positive end-expiratory alveolar pressure associated with a higher than resting lung volume, is called intrinsic or auto-PEEP. Importantly for the clinician, this pressure is not directly measured at the airway opening and is thus not shown on the pressure dial of the ventilator. What the ventilator measures is the pressure in the ventilator circuit. Because the direction of the flow is still expiratory, the pressure measured by the ventilator at the end of expiration reflects only the relationship between flow and the resistance of the expiratory line, above the set PEEP. It does not give the clinician any information about the real alveolar pressure.

How one can suspect the presence of intrinsic (or auto-) PEEP

The presence of a positive alveolar pressure higher than the atmospheric pressure or higher than the external PEEP set on the ventilator (which is a new "reference pressure" for the lungs) can be identified by inspection of the expiratory flow-time curve. When the expiratory time is sufficient for lung emptying, expiratory flow de-

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_1, © Springer-Verlag Berlin Heidelberg 2009

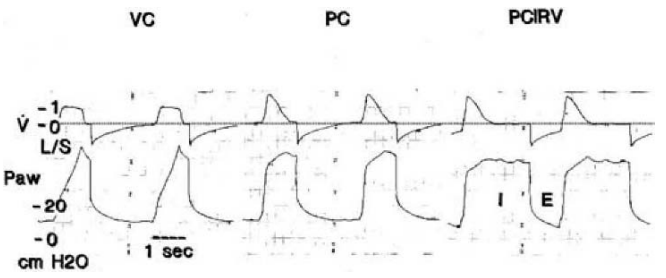


Fig. 1 Tracings of flow ($\dot{V}$) and airway pressure (*Paw*) at the airway opening during volume controlled (*VC*), pressure-controlled (*PC*), and pressure-controlled inverse ratio ventilation (*PCIRV*). In the first two situations the expiratory flow declines gradually to zero; in the third case inspiration is lengthened by the inverse ratio setting and expiration shortened; the expiratory flow is abruptly interrupted, indicating the presence of dynamic hyperinflation and intrinsic or auto-PEEP. (From Lessard et al. [3])

clines from a maximum to zero or to the set PEEP. An interruption in this process results in an abrupt change in the slope of this curve, immediately continued by the next inspiratory flow. In other words, the next "inspiration" starts during "expiration." Since the ventilator, which cannot generate flow into the patient's lungs until the pressure at the airway opening exceeds the end-expiratory alveolar pressure, one way in which to measure intrinsic or auto-PEEP is to determine the airway pressure at the exact time of inspiratory flow. One can measure the intrinsic PEEP level by simultaneously recording airway pressure and flow data using a high-speed tracing. Figure 1 illustrates how shortening the expiratory phase generates such dynamic hyperinflation [3].

Is the level of intrinsic (or auto-) PEEP predictable?

If one assumes the respiratory system to be homogeneous and behave as a single compartment, a monoexponential equation can be used. By simple mathematics it takes three time constants (one being the product of resistance and compliance) to expire 96% of the inspired tidal volume. Therefore any longer expiratory time minimizes or fully avoids incomplete emptying. For instance, a resistance of 10 $cmH_2O.l^{-1}.s^{-1}$ and a compliance of 100 $ml.cmH_2O^{-1}$ (0.1 $l.cm\ H_2O^{-1}$) results in a time constant of 1 s. Thus 3 s represents the minimal expiratory time needed to avoid intrinsic or auto-PEEP. Unfortunately, the diseased lungs are not only frequently inhomogeneous, making this calculation overly simplistic, but the presence of small airway collapse during expiration, also referred to as expiratory flow limitation, makes this even more complicated. Because of an abnormal structure of the small airways, when the pressure surrounding these conducts becomes higher than the pressure inside the airway, these small conducts collapse. The relationship between the "driving pressure" (pressure in the alveoli minus pressure at the airway opening) on which is based the equation, disappears. In the setting of expiratory flow-limitation, the expiratory time required to minimize intrinsic PEEP is much longer than predicted by the time constant alone. By minimizing inspired minute ventilation the clinician can minimize intrinsic (auto-) PEEP.

Can intrinsic (or auto-) PEEP be reliably measured?

Since the reason for the presence of intrinsic PEEP is flow-dependent pressure gradients from the alveolus to the airway opening, occluding of the expiratory port of the ventilator at the exact end of expiration causes airway pressure to equilibrate rapidly with alveolar pressure and reliably measure the end-expiratory alveolar pressure. This occlusion takes place at the exact time where the next inspiration should start and is now available on most modern ventilators ("expiratory hold or pause"). If the patient is fully relaxed, this pressure measurement reflects the mean alveolar pressure at the end of expiration. Most of the time a plateau is reached after less than 1 s, but in the case of inhomogeneous lungs this pressure may require a few seconds to also reflect some very slow compartments. This airway occlusion pressure may not be homogeneously present in the whole lung but represents an average pressure of all regional levels of end-expiration alveolar pressure. Usually the difference between the expiratory pause airway pressure and the set external PEEP is called intrinsic or auto-PEEP, while the measured pressure is referred to as total PEEP.

Can the set external PEEP influence the total PEEP in the case of dynamic hyperinflation?

A frequent confusion is the belief that external PEEP could be useful in reducing the level of dynamic hyperinflation because it helps to reduce the value of auto- or intrinsic PEEP. Obviously this is not the case. The effect of external PEEP is to minimize the difference between the alveolar and the ventilator proximal airway pressure. This difference being called intrinsic or auto-PEEP, external PEEP application results in a decreased intrinsic or auto-PEEP. The level of dynamic hyperinflation, however, depends on the level of total PEEP and is either not influenced by external PEEP when external PEEP is less than intrinsic PEEP or is even worsened if external PEEP is set higher than the minimal level of regional intrinsic PEEP.

References

1. Pepe PE, Marini JJ (1982) Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. Am Rev Respir Dis 216:166–169
2. Rossi A, Polese G, Brandi G, Conti G (1995) Intrinsic positive end-expiratory pressure (PEEPi). Intensive Care Med 21:522–536
3. Lessard M, Guérot E, Lorino H, Lemaire F, Brochard L (1994) Effects of pressure-controlled with different I:E ratios versus volume-controlled ventilation on respiratory mechanics, gas exchange, and hemodynamics in patients with adult respiratory distress syndrome. Anesthesiology 80:983–991

Laurent Brochard

Intrinsic (or auto-) positive end-expiratory pressure during spontaneous or assisted ventilation

Introduction

The mechanisms generating intrinsic or auto-positive end-expiratory pressure (PEEP) during controlled mechanical ventilation in a relaxed patient also occur during spontaneous breathing or when the patient triggers the ventilator during an assisted mode [1, 2]. These include an increased time constant for passive exhalation of the respiratory system, a short expiratory time resulting from a relatively high respiratory rate and/or the presence of expiratory flow limitation. Whereas dynamic hyperinflation and intrinsic or auto-PEEP may have haemodynamic consequences, this is not frequently a major concern in spontaneously breathing patients or during assisted ventilation because the spontaneous inspiratory efforts result in a less positive or more negative mean intrathoracic pressure than during controlled mechanical ventilation. The main consequence of dynamic hyperinflation during spontaneous and assisted ventilation is the patient's increased effort to breathe and work of breathing [1, 2].

To what extent does intrinsic (or auto-) positive end-expiratory pressure influence work of breathing?

For air to enter the lungs, the pressure inside the chest has to be lower than the pressure at the mouth (spontaneous breathing) or at the airway opening (assisted ventilation). In the case of intrinsic (or auto-) PEEP, by definition, the end-expiratory alveolar pressure is higher than the pressure at the airway opening. When the patient initiates the breath, there is an inevitable need to reduce airway pressure to zero (spontaneous breathing) or to the value of end-expiratory pressure set on the ventilator (assisted ventilation) before any gas can flow into the lungs. For this reason, intrinsic or (auto-) PEEP has been described as an inspiratory threshold load. In patients with chronic obstructive pulmonary disease (COPD) this load has sometimes been measured to be the major cause of increased work of breathing [3].

During assisted ventilation, is the trigger sensitivity important to reduce intrinsic (or auto-) positive end-expiratory pressure?

Because the problem of intrinsic or (auto-) PEEP has to do with the onset of inspiration, one may reason that increasing the inspiratory trigger sensitivity to initiate a breath with a lower pressure or flow deflection should reduce the work of breathing induced by hyperinflation. These systems are based on the detection of a small pressure drop relative to baseline (pressure-triggering system) or on the presence of a small inspiratory flow (flow-triggering systems). Unfortunately, increasing the trigger sensitivity induces only a small reduction in the total work of breathing. The reason for this lack of effect relates to the need for the inspiratory trigger to sense changes in airway pressure or in inspiratory flow. Thus, intrinsic PEEP needs to be counterbalanced first by the

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_2, © Springer-Verlag Berlin Heidelberg 2009

effort of the inspiratory muscles, in order for this effort to generate a small pressure drop (in the presence of a closed circuit) or to initiate the inspiratory flow (in an open circuit) [4]. The consequence of intrinsic or (auto-) PEEP is that the inspiratory effort starts during expiration. This is easily identified by inspection of the expiratory flow-time curve [1]. As a consequence, it cannot be detected by any of the commercially available trigger systems.

Can the set external positive end-expiratory pressure reduce dynamic hyperinflation and work of breathing?

Responses to these two questions are the same as during controlled mechanical ventilation in a relaxed patient [1]. Their consequences are, however, very different. External PEEP reduces the difference between the alveolar and the ventilator proximal airway pressure, i.e., intrinsic (or auto-) PEEP. The inspiratory threshold load resulting from intrinsic (or auto-) PEEP is thus reduced by addition of external PEEP. Thus, the total work of breathing is reduced, especially in patients with high levels of intrinsic (or auto-) PEEP, such as those subjects with COPD [5, 6].

Although external PEEP reduces work of breathing, it does not minimise hyperinflation. The level of dynamic hyperinflation is not modified by external PEEP, unless this PEEP is set higher than the minimal level of regional intrinsic PEEP, and then hyperinflation increases. Increasing hyperinflation can aggravate the working conditions of the respiratory muscles by placing them at a mechanical disadvantage and can result in significant haemodynamic compromise by decreasing venous return and increasing right ventricular outflow resistance. Hyperinflation in excess of intrinsic (or auto-) PEEP occurs usually when the set PEEP is positioned at values above 80% of the mean "static" intrinsic PEEP [7]. For this reason, titration of external PEEP based on measuring intrinsic (or auto-) PEEP would be desirable. Unfortunately, a reliable measurement of intrinsic (or auto-) PEEP in the spontaneously breathing subject is much more difficult to obtain than in passive positive-pressure ventilation conditions.

Can standard ventilatory settings influence intrinsic (or auto-) positive end-expiratory pressure?

During assisted ventilation, the patient is supposed to determine the respiratory rate freely, and one may suppose that he/she will govern his/her respiratory rate to control expiratory time and minimise hyperinflation. Unfortunately, most patients will not be able to counteract fully the effects of a ventilator inspiratory time longer than their own inspiratory time [8]. Although some compensatory mechanism may exist, it will frequently be insufficient. Every setting influencing the ventilator inspiratory time may thus influence the level of dynamic hyperinflation.

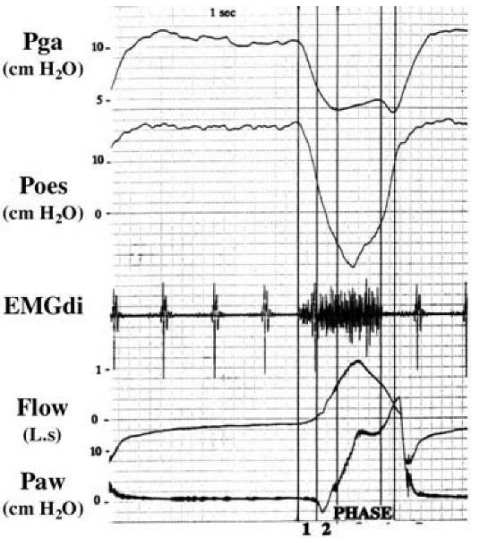


Fig. 1 Tracings of gastric (*Pga*), oesophageal (*Poes*) and airway (*Paw*) pressures, flow and diaphragmatic electromyographic activity (*EMGdi*) during an assisted breath (pressure-support ventilation). The *vertical lines* help to delineate the different phases of the inspiratory effort. During phase 1, the flow is still expiratory: the start of EMGdi and the abrupt decrease in both Pes and Pga all indicate that the patient performs an active inspiratory effort against intrinsic positive end-expiratory pressure (PEEP) at the same time that his/her expiratory muscles relax. Phase 2 is the triggering of the ventilator and occurs once intrinsic (or auto-) PEEP has been counterbalanced

Is intrinsic (or auto-) positive end-expiratory pressure always synonymous with dynamic hyperinflation?

In patients with spontaneous respiratory activity, recruitment of the expiratory muscles frequently participates in generating intrinsic (or auto-) PEEP independently of dynamic hyperinflation. In the case of airflow obstruction, the main consequence of an activation of the expiratory muscles is to augment intrathoracic pressure, whereas their effects on expiratory flow may be very modest, especially in the case of airflow limitation, thus promoting small airways to collapse. The activation of the expiratory muscles results from an increase in respiratory drive. Many patients with COPD already have a recruitment of their expiratory muscles at rest. This expiratory muscle recruitment results in a measurable increase in alveolar pressure. However, such expiratory muscle recruitment, although creating an intrinsic (or au-

to-) PEEP, does not contribute to the inspiratory threshold load and the increased work of breathing. Indeed, at the same time that the inspiratory muscles start to decrease intrathoracic pressure, the expiratory muscles relax and their release almost immediately abolishes this part of intrinsic (or auto-) PEEP due to the expiratory muscles [9]. This is illustrated in Fig. 1.

Can intrinsic (or auto-) positive end-expiratory pressure be reliably measured?

The commonly applied end-expiratory airway occlusion method that measures intrinsic (or auto-) PEEP in patients on controlled ventilation cannot be readily applied to the patient making spontaneous inspiratory efforts. For example, it is not possible to determine which amount of measured positive airway occlusion pressure, if not all, is due to expiratory muscle activity [9]. Setting the external PEEP based on this measurement could induce considerable mistakes by overestimating intrinsic (or auto-) PEEP. The only readily available and reliable method of measuring intrinsic (or auto-) PEEP in the spontaneously breathing subject is to measure the drop in oesophageal pressure occurring before flow becomes inspiratory, and subsequently subtract the part due to expiratory muscle activity determined from an abdominal pressure signal [9]. The reasoning is as follows: any rise in abdominal pressure occurring during expiration is transmitted to the intrathoracic space and increases alveolar pressure.

Intrinsic PEEP is measured from the abrupt drop observed on the oesophageal pressure signal until flow becomes inspiratory (phase 1 on Fig. 1). Part of this drop in oesophageal pressure is caused by the relaxation of the expiratory muscles. This part needs to be subtracted from the oesophageal pressure drop, in order to evaluate a "corrected" intrinsic PEEP due to hyperinflation. Two main possibilities exist: to subtract the rise in gastric pressure that occurred during the preceding expiration [9] or to subtract the concomitant decrease in gastric pressure at the onset of the effort [10]. Because the correction of intrinsic (or auto-) PEEP for expiratory muscle activity has not been used in early studies, one can hypothesise that the magnitude of intrinsic (or auto-) PEEP has often been overestimated. This combined oesophageal and gastric pressure measuring technique requires the insertion of a nasogastric tube equipped with both oesophageal and gastric balloon catheters. This technique is often used for research purposes but cannot be easily used at the bedside for routine clinical monitoring.

References

1. Brochard L (2002) Intrinsic (or auto-) PEEP during controlled mechanical ventilation. Intensive Care Med 28:1376–1378
2. Rossi A, Polese G, Brandi G, Conti G (1995) Intrinsic positive end-expiratory pressure (PEEPi). Intensive Care Med 21:522–536
3. Coussa ML, Guérin C, Eissa NT, Corbeil C, Chassé M, Braidy J, Matar N, Milic-Emili J (1993) Partitioning of work of breathing in mechanically ventilated COPD patients. J Appl Physiol 75:1711–1719
4. Ranieri VM, Mascia L, Petruzelli V, Bruno F, Brienza A, Giuliani R (1995) Inspiratory effort and measurement of dynamic intrinsic PEEP in COPD patients: effects of ventilator triggering systems. Intensive Care Med 21:896–903
5. Smith TC, Marini JJ (1988) Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. J Appl Physiol 65:1488–1499
6. Petrof BJ, Legaré M, Goldberg P, Milic-Emili J, Gottfried SB (1990) Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease (COPD). Am Rev Respir Dis 141:281–289
7. Ranieri MV, Giuliani R, Cinnella G, Pesce C, Brienza N, Ippolito E, Pomo V, Fiore T, Gottried S, Brienza A (1993) Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. Am Rev Respir Dis 147:5–13
8. Younes M, Kun J, Webster K, Roberts D (2002) Response of ventilator-dependent patients to delayed opening of exhalation valve. Am J Respir Crit Care Med 166:21–30
9. Lessard MR, Lofaso F, Brochard L (1995) Expiratory muscle activity increases intrinsic positive end-expiratory pressure independently of dynamic hyperinflation in mechanically ventilated patients. Am J Respir Crit Care Med 151:562–569
10. Appendini L, Patessio A, Zanaboni S, Carone M, Gukov B, Donner CF, Rossi A (1994) Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 149:1069–1076

Belen Cabello
Jordi Mancebo

Work of breathing

Introduction

The main goal of mechanical ventilation is to help restore gas exchange and reduce the work of breathing (WOB) by assisting respiratory muscle activity. Knowing the determinants of WOB is essential for the effective use of mechanical ventilation and also to assess patient readiness for weaning. The active contraction of the respiratory muscles causes the thoracic compartment to expand, inducing pleural pressure to decrease. This negative pressure generated by the respiratory pump normally produces lung expansion and a decrease in alveolar pressure, causing air to flow into the lung. This driving pressure can be generated in three ways: entirely by the ventilator, as positive airway pressure during passive inflation and controlled mechanical ventilation; entirely by the patient's respiratory muscles during spontaneous unassisted breathing; or as a combination of the two, as in assisted mechanical ventilation. For positive-pressure ventilation to reduce WOB, there needs to be synchronous and smooth interaction between the ventilator and the respiratory muscles [1, 2, 3]. This note will concentrate on how to calculate the part of WOB generated by the patient's respiratory muscles, especially during assisted ventilation.

Esophageal pressure and the Campbell diagram

Measuring WOB is a useful approach to calculate the total expenditure of energy developed by the respiratory muscles [4]. In general, the work performed during each respiratory cycle is mathematically expressed as WOB = $\int$ Pressure $\times$ Volume, i.e. the area on a pressure–volume diagram. Esophageal pressure, which is easily measured, is usually taken as a surrogate for intrathoracic (pleural) pressure. The dynamic relation between pleural pressure and lung volume during breathing is referred to as the Campbell diagram [5] (Fig. 1). Esophageal pressure swings during inspiration are needed to overcome two forces: the elastic forces of the lung parenchyma and chest wall, and the resistive forces generated by the movement of gas through the airways. One can calculate these two components (elastic and resistive) by comparing the difference between esophageal pressure during the patient's effort during the breath and the pressure value in passive conditions, represented by the static volume–pressure curve of the relaxed chest wall. This passive volume–pressure curve is a crucial component of the Campbell diagram. It is calculated from the values of esophageal pressure obtained over lung volume when the airways are closed and the muscles are completely relaxed. Unfortunately, as this is difficult to do (because it requires passive inflation and often muscle paralysis), a theoretical value for the slope of this curve is frequently used. However, if a patient is passively ventilated and an esophageal balloon is placed, a true value for the volume–pressure relationship of the chest wall during passive tidal breathing can be obtained [6]. This passive pressure–volume relationship can be used as a reference value for subsequent calculations when the patient develops spontaneous inspiratory efforts.

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_3, © Springer-Verlag Berlin Heidelberg 2009

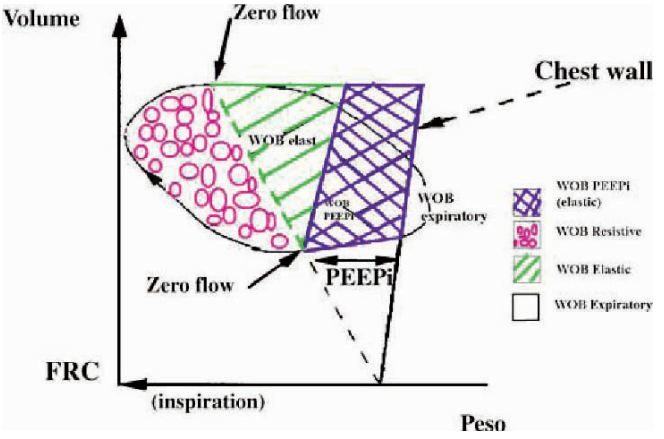


Fig. 1 Campbell's diagram. Work of breathing measured by the esophageal pressure: resistive WOB (W_{resist}), elastic WOB (W_{elast}), WOB related to active expiration (*WOB expiratory*) and WOB related to intrinsic PEEP (W_{PEEPi}). *Chest wall*: this *thick line* (the chest wall compliance) represents the pleural (esophageal) pressure obtained when muscles are totally relaxed and lung volume increases above functional residual capacity, measured in static conditions

The WOB is normally expressed in joules. One joule is the energy needed to move 1 l of gas through a 10-cmH_2O pressure gradient. The work per liter of ventilation (J/l) is the work per cycle divided by the tidal volume (expressed in liters). In a healthy subject the normal value is around 0.35 J/l [7]. Lastly, WOB can be expressed in work per unit of time, multiplying joules per cycle by the respiratory rate (expressed in breaths per minute) to obtain the power of breathing (joules/minute). In a healthy subject the normal value is around 2.4 J/min [7]. As illustrated by the Campbell diagram, two other phenomena affect the WOB: intrinsic PEEP (positive end-expiratory pressure, or PEEPi) and active expiration.

PEEPi and active expiration

The distending pressure of the lungs is called the transpulmonary pressure and it can be estimated as the difference between airway and esophageal (pleural) pressure. At the end of a normal expiration, alveolar and airway pressures are zero relative to atmosphere, and esophageal pressure is negative, reflecting the resting transpulmonary pressure (around 5 cmH_2O in normal conditions). However, in the presence of PEEPi, the alveolar pressure remains positive throughout expiration, because of either dynamic airway collapse or inadequate time to exhale [8]. This implies that some degree of dynamic hyperinflation does exist (lung volume at end-expiration is higher than passive functional residual capacity). Importantly, for lung volume to further increase in a patient with PEEPi, the inspiratory muscles contract to an amount equal to PEEPi before any volume is displaced.

PEEPi can be quite high in patients with chronic obstructive pulmonary disease (COPD) and may represent a high proportion of the total WOB [9]. For example, a patient who displaces 0.5 l of tidal volume through a 7-cmH_2O pressure gradient will perform an amount of work of 0.35 J/cycle. If nothing else changes except that this patient develops 5 cmH_2O of PEEPi, 0.25 J will be required to counterbalance this, meaning that the total WOB will be 0.60 J (0.35 + 0.25), which represents around 40% of the total work required for the inspiration. The PEEPi value is measured as the drop in esophageal pressure occurring during expiration when the inspiratory muscles start contraction, until the flow reaches the point of zero (see Fig. 1).

In the case of ineffective respiratory efforts, that is, muscle contraction without volume displacement, WOB cannot be measured from the Campbell diagram, since this calculation is based on volume displacement. In this situation, measurement of the pressure–time product (PTP) may more accurately reflect the energy expenditure of these muscles. The PTP is the product of the pressure developed by the respiratory muscles multiplied by the time of muscle contraction, expressed in cmH_2O per second. The relevant pressure is again the difference between the measured esophageal pressure and the static relaxation curve of the chest wall.

Expiration normally occurs passively. However, the coexistence of PEEPi and active expiration is common, especially in COPD patients [10]. Positive expiratory swings in gastric pressure are observed during active expiration as a consequence of abdominal muscle recruitment. When the patient starts contracting the inspiratory muscles, the expiratory muscles also start to relax. The drop in esophageal pressure used to estimate PEEPi is therefore also due to the relaxation of the expiratory muscles. To avoid overestimating the value of PEEPi, the abdominal pressure swing resulting from the active expiration must thus be subtracted from the initial drop in esophageal pressure [10].

Technical aspects of WOB calculation

Two other calculations can be obtained from pressure and volume measurements: airway pressure WOB and transpulmonary pressure WOB. The airway pressure WOB displays the energy dissipated by the ventilator to inflate the respiratory system. The transpulmonary pressure WOB shows the energy needed to inflate the lung parenchyma and reflects the mechanical characteristics of the pulmonary tissue. The limitation of these two measurements is that the amount of WOB performed by the patient's respiratory muscles is ignored.

The main tools used to measure the WOB are a double-lumen polyethylene gastro-esophageal catheter–balloon system and a pneumotachygraph. The catheter has an esophageal and a gastric balloon, usually filled with

0.5 and 1 ml of air to measure the esophageal and gastric pressures, respectively. Correct positioning of the esophageal balloon is assessed by an occlusion test: when the airways are closed at the end of expiration and an active inspiration occurs, a drop in esophageal pressure occurs. In this scenario, there are no changes in lung volume and the decrease in esophageal pressure equals the decrease in airway pressure (because in the absence of volume displacement, the transpulmonary pressure has to be nil) [11]. The catheter–balloon system should be placed to obtain a ratio between airway pressure and esophageal pressure changes as close as possible to 1. Also, the correct positioning of the gastric balloon needs to be checked [12].

Limitations

The calculation of WOB has several limitations. The first is that it requires insertion of a double-balloon gastro-esophageal catheter system. The second is the validity of the esophageal pressure value. Since pleural pressure is influenced by gravity, it can be modified by the weight of the thoracic content and by the posture. In the supine position, end-expiratory esophageal pressure is usually positive because of the weight of the heart and mediastinum on the esophagus. However, the amplitude of the changes in esophageal pressure is not usually affected. The third limitation is that the theoretical value for chest wall compliance is often used rather than a true measured value. Furthermore, chest wall deformation can occur if levels of ventilation are high [13]. Lastly, it is difficult to determine what the optimal WOB level should be for each patient on clinical grounds.

Conclusion

From the standpoint of clinical research, the measurement of WOB is extremely useful in the field of mechanical ventilation, having contributed to important progress in the management of patients for optimizing and understanding the effects of ventilator settings such as trigger, external PEEP, peak inspiratory flow, etc. WOB has also been used to evaluate the physiological effects of a number of agents such as helium and bronchodilators [9, 14, 15, 16, 17, 18, 19]. Studies on WOB have given us greater insight into the pathophysiology of weaning failure [3] and have also contributed to the progress made in the field of non-invasive mechanical ventilation [20, 21]. Bedside measurements of WOB in clinical practice, however, should be reserved for individuals in whom assessment of this parameter can provide further insight into the patient ability to breath and the patient–ventilator interactions.

Acknowledgements. The authors wish to thank Carolyn Newey for her help in editing the manuscript. Belen Cabello is the recipient of a research grant from the Instituto de Salud Carlos III (expedient CM04/00096, Ministerio de Sanidad) and the Institut de Recerca Hospital de la Santa Creu i Sant Pau.

References

1. Nava S, Bruschi C, Rubini F, Palo A, Iotti G, Braschi A (1995) Respiratory response and inspiratory effort during pressure support ventilation in COPD patients. Intensive Care Med 21:871–879
2. Leung P, Jubran A, Tobin M (1997) Comparison of assisted ventilator modes on triggering, patient effort and dyspnea. Am J Respir Crit Care Med 155:1940–1948
3. Jubran A, Tobin MJ (1997) Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med 155:906–915
4. Roussos C (1985) Structure and function of the thorax: energetics. In: Roussos C, Macklem PT (eds) The thorax. Dekker, New York, pp 437–492
5. Mead J, Loring SJ (1985) Volume displacements of the chest wall and their mechanical significance. In: Roussos C, Macklem PT (eds) The thorax: part A. Dekker, New York, pp 369–392
6. Jubran A, Van de Graaff WB, Tobin MJ (1995) Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152:129–136
7. Mancebo J, Isabey D, Lorino H, Lofaso F, Lemaire F, Brochard L (1995) Comparative effects of pressure support ventilation and intermittent positive pressure breathing (IPPB) in non intubated healthy subjects. Eur Respir J 8:1901–1909
8. Brochard L (2002) Intrinsic (or auto-) PEEP during controlled mechanical ventilation. Intensive Care Med 28:1376–1378
9. Brochard L, Harf A, Lorino H, Lemaire F (1989) Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. Am Rev Respir Dis 139:513–521
10. Lessard MR, Lofaso F, Brochard L (1995) Expiratory muscle activity increases intrinsic positive end-expiratory pressure independently of dynamic hyperinflation in mechanically ventilated patients. Am J Respir Crit Care Med 151:562–569
11. Baydur A, Behrakis PK, Zin WA, Jaeger MJ, Milic-Emili J (1982) A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 126:788–791
12. Diehl JL, Lofaso F, Deleuze P, Similowski T, Lemaire F, Brochard L (1994) Clinically relevant diaphragmatic dysfunction after cardiac operations. J Thoracic Cardiovasc Surg 107:487–498
13. Fleury B, Murciano D, Talamo C, Aubier M, Pariente R, Milic Emili J (1985) Work of breathing in patients with chronic obstructive pulmonary disease in acute respiratory failure. Am Rev Respir Dis 131:822–827

14. Jaber S, Fodil R, Carlucci A, Boussarsar M, Pigeot J, Lemaire F, Harf A, Lofaso F, Isabey D, Brochard L (2000) Noninvasive ventilation with helium–oxygen in acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161:1191–1200
15. Tassaux D, Gainnier M, Battisti A, Jolliet P (2005) Helium–oxygen decreases inspiratory effort and work of breathing during pressure support in intubated patients with chronic obstructive pulmonary disease. Intensive Care Med 31:1501–1507
16. Mancebo J, Amaro P, Lorino H, Lemaire F, Harf A, Brochard L (1991) Effects of albuterol inhalation on the work of breathing during weaning from mechanical ventilation. Am Rev Respir Dis 144:95–100
17. Mancebo J, Albaladejo P, Touchard D, Bak E, Subirana M, Lemaire F, Harf A, Brochard L (2000) Airway occlusion pressure to titrate positive end-expiratory pressure in patients with dynamic hyperinflation. Anesthesiology 93:81–90
18. Cinnella G, Conti G, Lofaso F, Lorino H, Harf A, Lemaire F, Brochard L (1996) Effects of assisted ventilation on the work of breathing: volume-controlled versus pressure-controlled ventilation. Am J Respir Crit Care Med 153:1025–1033
19. Aslanian P, El Atrous S, Isabey D, Valente E, Corsi D, Harf A, Lemaire F, Brochard L (1998) Effects of flow triggering on breathing effort during partial ventilatory support. Am J Respir Crit Care Med 157:135–143
20. Lellouche F, Maggiore SM, Deye N, Taille S, Pigeot J, Harf A, Brochard L (2002) Effect of the humidification device on the work of breathing during noninvasive ventilation. Intensive Care Med 28:1582–1589
21. L'Her E, Deye N, Lellouche F, Taille S, Demoule A, Fraticelli A, Mancebo J, Brochard L (2005) Physiologic effects of noninvasive ventilation during acute lung injury. Am J Respir Crit Care Med 172:1112–1118

Evans R. Fernández-Pérez
Rolf D. Hubmayr

Interpretation of airway pressure waveforms

Abstract Most mechanical ventilators display tracings of airway pressure (Paw) volume (V) and flow ($\dot{V}$). In volume preset modes, Paw informs about the mechanical properties of the respiratory system and about the activity of respiratory muscles acting on the system. When monitoring ventilator waveforms, it is important to appropriately scale the tracing so that nuances in time profiles may be appreciated. In this short monograph, we offer three examples of how clinicians may use this information for patient assessment and care.

The Paw waveform

The interactions between a ventilator and a relaxed intubated patient can be modeled as a piston connected to a tube (flow-resistive element) and balloon (elastic element). Accordingly, at any instant in time (t), the pressure at the tube inlet reflects the sum of a resistive pressure (*Pres*) and an elastic pressure (*Pel*) [1]. *Pres* is determined by the product of tube resistance with $\dot{V}$, while *Pel* is determined by the product of balloon elastance (a measure of balloon stiffness) with volume [1]. In this model, the resistive element reflects the properties of the intubated airways, while the elastic element reflects those of lungs and chest wall. When applied to volume preset ventilation with constant inspiratory $\dot{V}$ and a short post-inflation pause, the resulting *Paw* tracing has three distinct components: (1) an initial step change proportional to *Pres*; (2) a ramp that reflects the increase in *Pel* as the lungs fill to their end-inflation volume; and (3) a sudden decay from a pressure maximum (*Ppeak*) to a plateau (*Pplat*) that reflects the elastic recoil (*Pel*) of the relaxed respiratory system at the volume at end-inflation. Since in this example flow is held constant throughout inflation, *Pres* must remain constant unless flow resistance changes volume and time. Consequently, the initial step change in *Paw* and its decay from *Ppeak* to *Pplat* are of similar magnitude. Fig. 1a demonstrates these features. Since, in pneumatic systems, there are invariable delays in the pressure and flow transients, in practice the step changes in pressure are never as sudden as they are depicted in Fig. 1a [2]. Nevertheless, the amplitude of transients can be easily estimated by extrapolating the tracing relative to the slope of the pressure ramp. Finally, while the principles that govern the interactions between pressure, volume and flow apply to all modes of mechanical ventilation, the specific pressure waveforms depicted in Fig. 1 refer only to constant flow inflation (square wave) and look very different when other flow profiles (e.g., decelerating, sine wave) are used. Our use of square wave profiles in Fig. 1 should not be interpreted as an endorsement of a specific mode, but rather as the most convenient means to present this information.

The tracing in Fig. 1b differs in several important respects: the *Paw* ramp is steeper and it is nonlinear with respect to time. Since $\dot{V}$ is constant the nonlinearity between *Paw* and t means that the relationship between *Paw* and V

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_4, © Springer-Verlag Berlin Heidelberg 2009

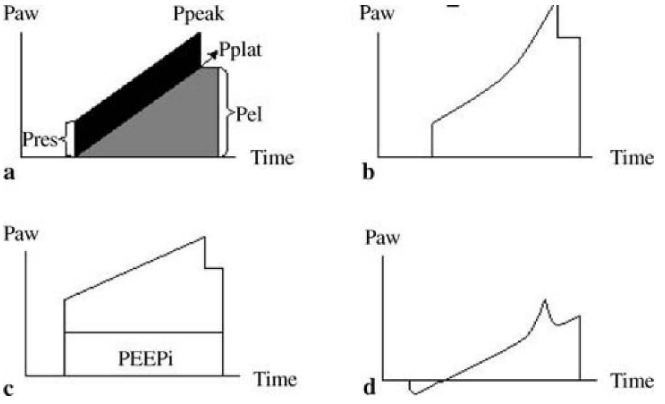


Fig. 1 Schematic illustration of the Paw profile with time during constant-flow, volume-cycle ventilation. **a** Passive respiratory system with normal elastance and resistance. Work to overcome the resistive forces is represented by the *black shaded area*, and the *gray shaded area* represents the work to overcome the elastic forces. **b** Up-sloping of the *Paw tracing* representing increased respiratory system elastance. **c** *Paw tracing* in the presence of inadvertent PEEP. **d** scalloping of the *Paw tracing* generated by a large patient effort (*Paw* airway pressure, *Pel* elastic pressure, *Ppeak* pressure maximum, *Pplat* pressure plateau, *PEEPi* inadvertent PEEP, *Pres* resistive pressure)

must be nonlinear as well. Assuming identical ventilator settings as in Fig. 1a the increased steepness of the ramp and its convexity to the time axis indicates a stiffening of the respiratory system with volume and time and suggests that the lungs may be overinflated to volumes near or exceeding their capacity. At the bedside, such an observation should raise concern for injurious ventilator settings [2].

The tracing in Fig. 1c is characterized by a larger-than-expected initial step change in *Paw* that exceeds the peak-to-plateau pressure difference. In an otherwise relaxed patient, such an observation should raise suspicion for dynamic hyperinflation and inadvertent PEEP (*PEEPi*). If *Pel* at end-expiration is greater than *Paw* at that time (i.e., *PEEPi* is present), then gas will flow in the expiratory direction. The step change in *Paw* during the subsequent inflation will therefore not only reflect *Pres* but also *PEEPi* that must be overcome to reverse flow at the tube entrance [1]. Tracings like the one in Fig. 1c should therefore alert the clinician to the presence of dynamic hyperinflation and provide an estimate of the extrinsic PEEP necessary to minimize the associated work of breathing. *PEEPi* is invariably associated with a sudden transient in expiratory flow prior to ventilator-assisted lung inflation [3]. However, this flow transient need not be associated with dynamic hyperinflation, because it is also seen in patients with increased respiratory effort and active expiration.

The tracing in Fig. 1d represents a significant departure from relaxation patters. There is no initial step change in *Paw*; the ramp is nonlinear, and the end-inspiratory pressure plateau is lower than expected. This tracing suggests that the inspiratory muscles are active throughout machine inflation and that their work represents a considerable fraction of the work performed on the respiratory system. This pattern should alert clinicians to the presence of a potentially fatiguing load.

References

1. de Chazal I, Hubmayr RD (2003) Novel aspects of pulmonary mechanics in intensive care. Br J Anaesth 91: 81–91
2. Grasso S, Terragni P, Mascia L, Fanelli V, Quintel M, Herrmann P, Hedenstierna G, Slutsky AS, Ranieri VM (2004) Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. Crit Care Med 32:1018–1027
3. Brochard L (2002) Intrinsic (or auto-) PEEP during controlled mechanical ventilation. Intensive Care Med. 28:1376–1378

Claude Guerin
Jean-Christophe Richard

Measurement of respiratory system resistance during mechanical ventilation

Abstract *Background:* The measurement of respiratory system resistance during mechanical ventilation is important to ascertain the causes of increase in airway pressure during volume-controlled ventilation, which may include airways resistance and decreased respiratory system compliance. *Discussion:* Separation of total resistance from compliance of the respiratory system can be assessed by the end-inspiratory hold maneuver that separates peak pressure from plateau pressure. *Conclusions:* Although this method assumes a homogeneous respiratory system, it has proven useful clinically to separate flow-dependence issues such as bronchospasm or endotracheal tube obstruction from stiff lungs (acute lung injury) or decrease chest wall (abdominal distension) compliance.

Keywords Airway pressure · Mechanical ventilation · Respiratory system compliance · Respiratory system resistance

Introduction

Change in the resistance of the respiratory system to gas flow (Rrs) commonly occurs in critically ill patients and is manifest in mechanically ventilated patients on volume-controlled ventilation as an increase in airway pressure (Paw). Increases in Paw commonly occur with many processes and can profoundly alter gas exchange and cardiovascular function. Inspiratory gas flowing from the ventilator must overcome two primary components of Rrs before it can distend the alveoli. These include airway resistive forces needed to cause airflow associated with the endotracheal tube (ETT) and airways and elastic forces needed to distend the tissues associated with baseline positive end-expiratory pressure (PEEPt) and tidal volume (V) as they interact with the combined lung and chest wall tissue elastance. In patients receiving noninvasive mechanical ventilation the upper airways are an important, but difficult to assess [1] contributing factor to Rrs. At any given time *t* during mechanical inflation Paw can be described by the equation of motion that reflects the sum of resistive (Pres) and elastic (Pel) forces at that moment:

$$\begin{aligned} \mathrm{Paw}(t) &= \mathrm{PEEPt} + \mathrm{Pres}(t) + \mathrm{Pel}(t) \\ &= \mathrm{PEEPt} + \mathrm{V}'(t) \times \mathrm{R} + \mathrm{V}(t) \times \mathrm{E} \end{aligned} \quad (1)$$

where V' is inflation flow, R and E resistance and elastance of the respiratory system. Although Eq. 1 depicts the behavior of the respiratory system as a single-compartment model (Fig. 1a), this approach tends to describe respiratory function under most conditions. However, the model described in Eq. 1 also assumes both R and E are constant as V and V' change, which is incorrect. For example, airway resistance (Raw) decreases with increasing V [2]. More refined models have therefore been described (Fig. 1b) [3, 4]. In particular, such complex models are needed to take into account the V' dependence of Rrs [5]. An immediate practical implication of this is that any value of Rrs must be referred to the levels of V' set on the ventilator.

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_5,

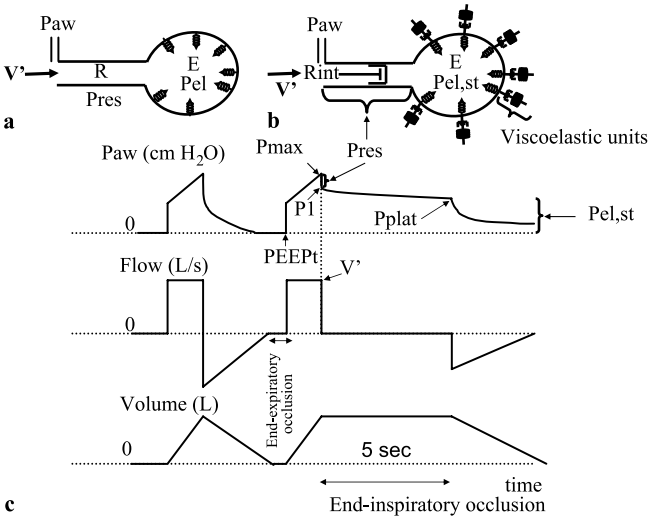


Fig. 1 **a** Single-compartment model of respiratory system with a standard resistance (dashpot *R*) and elastance (spring *E*). **b** Multiple-compartment model of respiratory system comprising the standard resistance (dashpot *Rint*) and the standard elastance (spring *E*), both arranged serially, and the viscoelastic units which are arranged in parallel around *E*. The viscoelastic units comprise a dashpot and a spring that are arranged serially. **c** Interrupter technique during mechanical ventilation with constant flow inflation. From *top* to *bottom*, schematic drawing of airway pressure (*Paw*), flow and change in lung volume against time. At the end of a baseline breath the airways are occluded for 5 s (*second horizontal double arrow*). After occlusion the sudden pressure drop from maximal pressure (*Pmax*) to pressure at first zero flow (*P1*) is the pure resistive pressure drop (*Pres*). The slow decay from P1 to the plateau pressure (*Pplat*) is the pressure dissipation into the viscoelastic units. The elastic pressure (*Pel*) is above the static elastic end-expiratory pressure (*PEEPt*) obtained from end-expiratory occlusion (*first horizontal double arrow*)

Techniques of measurement of Rrs

Although more complex methods exist, a simple bedside approach to measuring Rrs and its components appears to also be accurate. The first method is based on the rapid interruption of V' at the airways while measuring Paw downstream the location of occlusion as described 80 years ago [6] and validated in mechanically ventilated patients 40 years ago [7]. The occlusion is performed at end-inflation during constant V' and V conditions. One observes the resultant Paw behavior. This end-inspiratory hold maneuver results in the Paw rapidly decreasing from a peak Paw, called Pmax, at end-inspiration to P1 (Fig. 1c) and then by a slow decay from P1 to plateau pressure (Pplat), as end-inspiratory lung volume is held constant. Pplat represents the static elastic end-inspiratory recoil pressure of the respiratory system (Pel, st). By dividing (Pmax-P1) by the V' immediately preceding the occlusion, the interrupter resistance (Rint, rs) can be computed. By dividing (P1-Pplat) by the same V' the additional viscoelastic resistance (ΔRrs) can be obtained. Rrs is the sum of Rint, rs and ΔRrs. Rint, rs mainly reflects airway resistance [8] and ΔRrs dynamic pressure dissipation due to tissue viscoelastic properties in normal lung [4] and time-constant inequality in diseased lungs [9, 10]. The technique is easy to do by instructing the ventilator to perform an inspiratory hold maneuver of 3 s [11]. This diagnostic technique is often an automated function on many ventilators. The accuracy of the results requires patients to not be actively participating in inspiratory efforts and thus works best in those patients in synchrony with the ventilator, including those deeply sedated and/or paralyzed.

The second method of assessing Rrs is based on the forced oscillation technique introduced 50 years ago [12]. This method determines the respiratory input impedance (Z), which is the response of the respiratory system to an external oscillatory stimulus at various respiratory frequencies usually between 0.5 and 20 Hz. Z is computed as the ratio of the Fourier transform of Paw to the Fourier transform of V'. The resultant Z has two components, a "real" part that is related to Rrs and an imaginary part, or reactance, which is related to elastance. This method can be used in patients receiving invasive [13] or noninvasive mechanical ventilation [14] but requires additional equipment. Accordingly, it is not routinely used in most ICUs to assess Rrs even though it is accurate.

Airway and endotracheal tube resistance

In normal subjects under mechanical ventilation Rint, rs amounts to 2.2 $cmH_2O\,l^{-1}\,s^{-1}$ at V' of 0.6 $l\,s^{-1}$, whereas greater values have been measured in various diseased conditions [9, 10, 15, 16]. Rint, rs is V' dependent, linearly increasing with V' for a constant V, in both normals [4] and in patients with lung disease [9, 10]. In the mechanically ventilated patient Paw is usually measured at the proximal tip of the ETT. Thus the measured Rint, rs reflects both Raw and ETT resistance. The pressure drop across the ETT depends highly on V' and ETT size such that the higher the V' and smaller the ETT size, the higher is ETT flow resistance. This relationship can be described by the model proposed by Rohrer [17] as:

$$\text{Pres} = \text{K1 V'} + \text{K2 V'}^2 \quad (2)$$

where K1 and K2 are constants. Although the physiological meaning of K_1 and K_2 is not clear, the presence of K_2 underlines the nonlinear V' dependence of Pres. This nonlinear Pres-V' relationship has been described with other models based on the physical characteristics of the conducts and of the gas (Reynolds number, Blasius equation). Although beyond the scope of this note, it is important to bear in mind that V' can change from laminar to fully turbulent, explaining this nonlinearity in the Pres-V' relationship. This has important consequences

for V' delivery during inhaled therapy or justifies to change the nature of the gas such as helium in case of highly turbulent conditions. Equation 2 is used in many ventilators as an "automatic tube compensation mode" (ATC) during pressure support breathing to compensate for the resulting additional work of breathing due to the ETT [18]. ATC may also use equation as $Pres = V'^{b}$ where b, which depends on the size of the ETT tube, is usually slightly lower than 2.

Tissue resistance

The tissue resistance ΔRrs is equal to or slightly greater than Rint, rs. Tissue resistance has two components, lung parenchyma and chest wall, which includes the diaphragm. In patients with chronic obstructive lung disease (COPD) the contribution of chest wall to Rrs is modest [10], whereas in patients with the acute respiratory distress syndrome (ARDS) the lung and chest wall contribution to ΔRrs is highly variable and depends to a great degree on whether lung injury is the primary cause of ARDS (primary) or secondary. In secondary ARDS abdominal distension often increases intra-abdominal pressure limiting chest wall expansion making the chest wall component the dominate factor in increasing ΔRrs [19]. ΔRrs also exhibits V' dependence in both normals [4] and patients [9, 10]. However, unlike Rint, rs, ΔRrs decreases progressively with increasing V' [2]. Thus Rrs depends on the respective contributions of Rint, rs and ΔRrs. From the clinical perspective Rrs is maximal at low V' and decreases with increasing V' to a minimal value that occurs at V' of about $1\,l\,s^{-1}$ in both COPD [10] and ARDS [9, 20] patients.

Clinical Implications

Assessing Rrs during mechanical ventilation is important in order to: (a) attribute to increased Rrs an increase in Paw during volume-controlled mode or a decline in tidal volume during pressure-controlled mode, (b) identify the mechanism of increased Rrs as an increase in resistance of ETT or Raw or tissue resistance, (c) assess the effects of bronchodilating agents, and (d) detect ETT obstruction. Rrs can easily be measured with the interrupter technique in patients receiving invasive mechanical ventilation in ICU from the values of Pmax, Pplat, and V' provided by the ventilator. Clinicians must have in mind the V' dependence of the values of Rrs when interpreting the results.

References

1. Jounieaux V, Aubert G, Dury M, Delguste P, Rodenstein D (1995) Effects of nasal positive-pressure hyperventilation on the glottis in normal awake subjects. J Appl Physiol 79:176–185
2. Bates JH, Baconnier P, Milic-Emili J (1988) A theoretical analysis of interrupter technique for measuring respiratory mechanics. J Appl Physiol 64:2204–2214
3. Mount LE (1955) The ventilation-flow resistance and compliance of rats lungs. J Physiol (Lond) 127:157–167
4. D'Angelo E, Calderini E, Torri G, Robatto FM, Bono D, Milic-Emili J (1989) Respiratory mechanics in anesthetized paralyzed humans: effects of flow, volume, and time. J Appl Physiol 67:2556–2564
5. Bates JH, Rossi A, Milic-Emili J (1985) Analysis of the behavior of the respiratory system with constant inspiratory flow. J Appl Physiol 58:1840–1848
6. Neegaard KV, Wirtz K (1927) Die Messung der Strömungswiderstände in den Atemwegen des Menschen, insbesondere bei Asthma und Emphysem. Z Klin Med 105:51–82
7. Don HF, Robson JG (1965) The mechanics of the respiratory system during anesthesia. Anesthesiology 26:168–178
8. Bates JH, Brown KA, Kochi T (1989) Respiratory mechanics in the normal dog determined by expiratory flow interruption. J Appl Physiol 67:2276–2285
9. Eissa NT, Ranieri VM, Corbeil C, Chasse M, Robatto FM, Braidy J, Milic-Emili J (1991) Analysis of behavior of the respiratory system in ARDS patients: effects of flow, volume, and time. J Appl Physiol 70:2719–2729
10. Guerin C, Coussa ML, Eissa NT, Corbeil C, Chasse M, Braidy J, Matar N, Milic-Emili J (1993) Lung and chest wall mechanics in mechanically ventilated COPD patients. J Appl Physiol 74:1570–1580
11. Barberis L, Manno E, Guerin C (2003) Effect of end-inspiratory pause duration on plateau pressure in mechanically ventilated patients. Intensive Care Med 29:130–134
12. DuBois AB, Brody AW, Lewis DH, Burgess BF (1956) Oscillation mechanics of lungs and chest in man. J Appl Physiol 8:587–594
13. Farre R, Ferrer M, Rotger M, Torres A, Navajas D (1998) Respiratory mechanics in ventilated COPD patients: forced oscillations versus occlusion techniques. Eur Respir J 12:170–176
14. Farre R, Gavela E, Rotger M, Ferrer M, Roca J, Navajas D (2000) Noninvasive assessment of respiratory resistance in severe chronic respiratory patients with nasal CPAP. Eur Respir J 15:314–319
15. Conti G, Rocco M, Antonelli M, Bufi M, Tarquini S, Lappa A, Gasparetto A (1997) Respiratory system mechanics in the early phase of acute respiratory failure due to severe kyphoscoliosis. Intensive Care Med 23:539–544

16. Pelosi P, Croci M, Ravagnan I, Vicardi P, Gattinoni L (1996) Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. Chest 109:144–151
17. Rohrer F (1915) Der Strömungswiderstand in den menschlichen Atemwegen und der Einfluss der unregelmässigen Verzweigung des Bronchialsystems auf den Atmungsverlauf in verschiedenen Lungenbezirken. Pfluegers Arch Gesamte Physiol Menschen Tiere 162:225–299
18. Elsasser S, Guttmann J, Stocker R, Mols G, Priebe HJ, Haberthur C (2003) Accuracy of automatic tube compensation in new-generation mechanical ventilators. Crit Care Med 31:2619–2626
19. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A (1998) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? Am J Respir Crit Care Med 158:3–11
20. Tantucci C, Corbeil C, Chasse M, Robatto FM, Nava S, Braidy J, Matar N, Milic-Emili J (1992) Flow and volume dependence of respiratory system flow resistance in patients with adult respiratory distress syndrome. Am Rev Respir Dis 145:355–260

Theodoros Vassilakopoulos

Understanding wasted/ineffective efforts in mechanically ventilated COPD patients using the Campbell diagram

Introduction

Wasted or ineffective efforts are inspiratory efforts that fail to trigger the ventilator [1]. Nearly 25% of mechanically ventilated patients exhibit ineffective efforts which are even more frequent in COPD patients [2]. The pathophysiology of wasted efforts can be illustratively presented using the Campbell diagram.

Campbell diagram

The Campbell diagram is constructed by plotting the dynamic relation between pleural pressure (measured with an esophageal balloon) and lung volume during breathing in relation to the passive pressure-volume curves of the lung Pel(L) and the chest wall Pel(cw) [3]. The Pel(cw) is constructed by connecting the values taken by the esophageal pressure during passive inflation (i. e., with no respiratory muscle activity) at different lung volumes; thus, any change in esophageal pressure is referred to this line in the Campbell diagram in order to calculate the true muscular pressure developed by the patient.

In normal subjects inspiration starts from the relaxation volume of the respiratory system (Vr), where the Pel(L) and Pel(cw) intersect (i. e., where the tendency of the lung to recoil inward is equal to the tendency of the chest wall to expand; Fig. 1a). Inspiratory muscle action results in pressure development (Pinsp) on the left of the Pel(cw). Inspiratory flow, and thus increases in volume (V_L), take place on the left of the Pel(L) and coincide with the beginning of inspiratory muscle action. At any volume, the horizontal distance between the Pel(cw) and Pel(L) represents the portion of inspiratory muscle action devoted to expanding the lung at this volume with open airways and the portion on the left of the Pel(L) represents the pressure dissipated to generate airflow. Inspiration ends on the Pel(L) (point of zero flow) and the inspiratory muscles relax [so that pressure returns on the Pel(cw)]. Expiration is usually passive, and the respiratory system returns to its relaxation volume on the Pel(cw); however, in patients with respiratory distress, such as mechanically ventilated COPD patients, expiration is frequently active. In the case of active expiration, pressure develops on the right of the Pel(cw) due to activity of expiratory muscles (Pexp). This returns volume back to the relaxation volume of the respiratory system.

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_6, © Springer-Verlag Berlin Heidelberg 2009

Why are COPD patients prone to develop wasted/ineffective efforts?

In COPD patients with dynamic hyperinflation, inspiration starts from an increased end-expiratory lung volume (Fig. 1b). Inspiratory muscle action has to overcome the intrinsic positive end expiratory pressure [PEEPi, horizontal distance between the Pel(L) and Pel(cw)] before it results in inspiratory flow and thus increases in volume (V_L). In mechanically ventilated patients, inspiratory muscle action has to additionally overcome the trigger sensitivity (Ptr) of the ventilator [horizontal distance between the $Pel_{(L)}$ and Ptr] before it results in inspiratory flow and thus increases in volume (V_L); thus, in mechanically ventilated COPD patients, inspiratory muscle action has to overcome PEEPi plus the trigger sensitivity (Ptr).

When the magnitude of inspiratory muscle action is less than the sum of PEEPi plus Ptr this inspiratory effort (Fig. 1b, orange line) cannot trigger the ventilator, and consequently does not result in inspiratory flow and thus increases in volume (V_L). This inspiratory effort is called ineffective or wasted.

Is the Campbell diagram useful for estimating the work of breathing during wasted efforts?

The Campbell diagram is useless to estimate inspiratory work of breathing when inspiratory triggering does not happen (i. e., during wasted efforts): work is physically defined as the area subtended in a pressure/volume loop. Since there is no inspiratory volume, the work is zero (albeit muscles, indeed, consume energy). The energy expenditure during non-triggered wasted inspiratory efforts can be estimated by the pressure/time product: the product of the pressure developed by the inspiratory muscles [difference between the measured esophageal pressure and the Pel(cw)] multiplied by the time of muscle contraction (i. e., neural Ti).

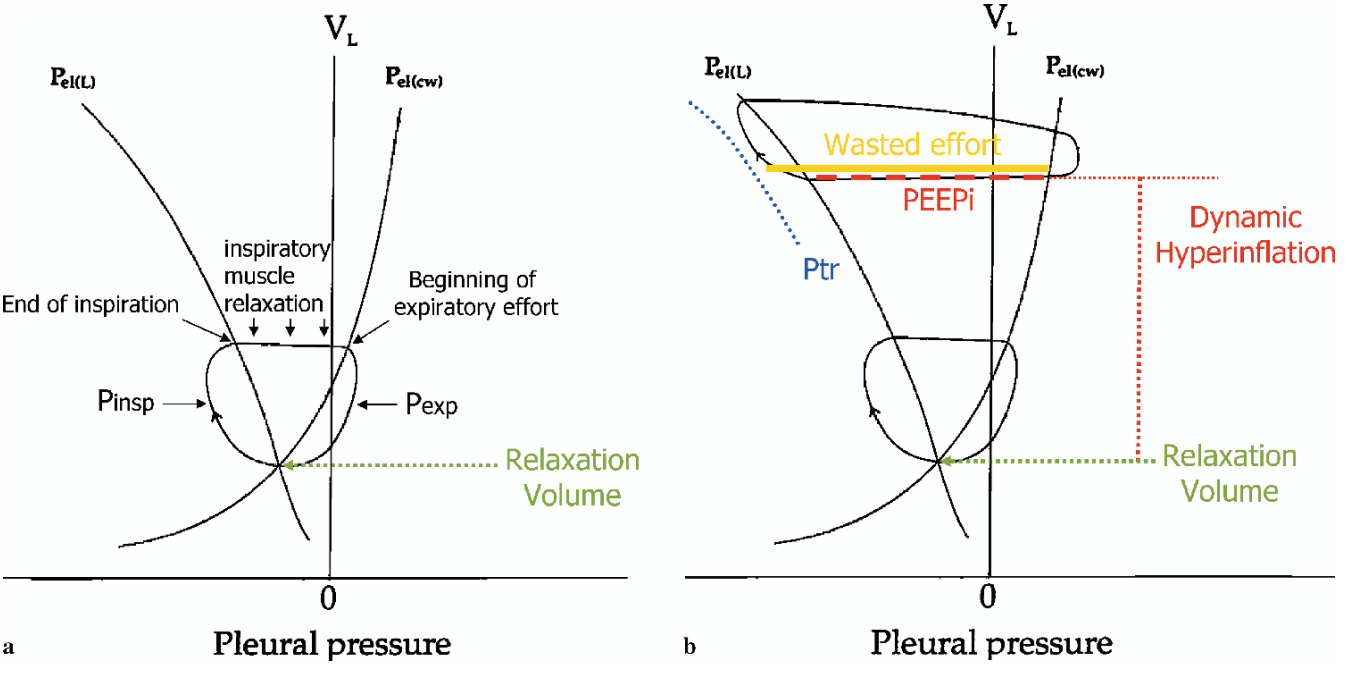


Fig. 1 **a** In normal subjects inspiration starts from the relaxation volume of the respiratory system, where the passive pressure-volume curves of the lung [*Pel(L)*] and chest wall [*Pel(cw)*] intersect. Inspiratory muscle action results in pressure development (*Pinsp*) on the left of the pressure-volume curve of the chest wall [*Pel(cw)*]. Inspiratory flow, and thus increases in volume (V_L) take place on the left of the pressure-volume curve of lung and coincide with the beginning of inspiratory muscle action. Inspiration ends on the pressure-volume curve of the lung and the inspiratory muscles relax (so that pressure returns on the pressure-volume curve of the chest wall). In the case shown, expiration is active so that pressure develops on the right of the pressure-volume curve of the chest wall due to activity of expiratory muscles (*Pexp*). This returns volume back to the relaxation volume of the respiratory system. **b** In COPD patients with dynamic hyperinflation, inspiration starts from an increased end-expiratory lung volume. Inspiratory muscle action has to overcome the intrinsic positive end expiratory pressure [*PEEPi*, *red dashed line*, horizontal distance between the *Pel(L)* and *Pel(cw)*] before it results in inspiratory flow and thus increases in volume. In mechanically ventilated patients, inspiratory muscle action has to overcome PEEPi plus the trigger sensitivity (*Ptr*) before it results in inspiratory flow and thus increases in volume (V_L). When the magnitude of inspiratory muscle action is less than the sum of PEEPi + Ptr this inspiratory effort (*orange line*) cannot trigger the ventilator and consequently does not result in inspiratory flow and thus increases in volume (V_L). This inspiratory effort is called ineffective or wasted

How are ventilator settings affecting the incidence of wasted/ineffective efforts?

Excessive ventilator support predisposes to ineffective efforts irrespective of the mode used [2, 4–7]. This is because, in the case of COPD, excessive pressure or volume delivered by the ventilator combined with the long time constant of the respiratory system (which retards lung emptying) and/or a short imposed expiratory time (in case of volume or pressure control) results in further increased end-expiratory lung volume before the next inspiratory effort begins (Fig. 2a, green curve). At the same time, excessive ventilator assistance reduces inspiratory muscle effort, via either a phenomenon called neuromechanical inhibition (the main mechanism most likely being the Hering–Breuer reflex) [8], and/or by producing alkalemia via excessive CO_2 reduction in patients with chronic bicarbonate elevation, thus reducing the drive to breathe [2]. The ensuing inspiratory effort is inadequate to overcome PEEPi plus Ptr and thus, this inspiratory effort fails to trigger the ventilator (Fig. 2a, red line). This is of course exaggerated in the presence of respiratory muscle weakness [7]. The following expiratory effort (Fig. 2a, blue curve) decreases the end expiratory lung volume. When the end expiratory lung volume decreases to a level where the ensuing inspiratory effort exceeds PEEPi plus Ptr, the ventilator is triggered again to deliver a machine breath (Fig. 2a, mauve curve). The breath-to-breath variability in breathing pattern contributes to the variability in the end-expiratory lung volume and thus to the frequency of ineffective efforts [7].

Alternatively, during assist control mechanical ventilation, prolonged imposed inspiratory time (machine Ti) greater than the patient's neural Ti results in a situation where the ventilator is inflating the patient long after the inspiratory muscles have stopped their contraction, i. e., during the neural expiration [6, 9]. During pressure support ventilation, the expiratory trigger threshold (percentage of peak inspiratory flow at which the ventilator cycles to expiration) might be quite low, leading to pressure support being delivered well beyond the patient's neural Ti [10]. In either case, the next inspiratory effort (controlled by the patient's respiratory controller) begins during the early

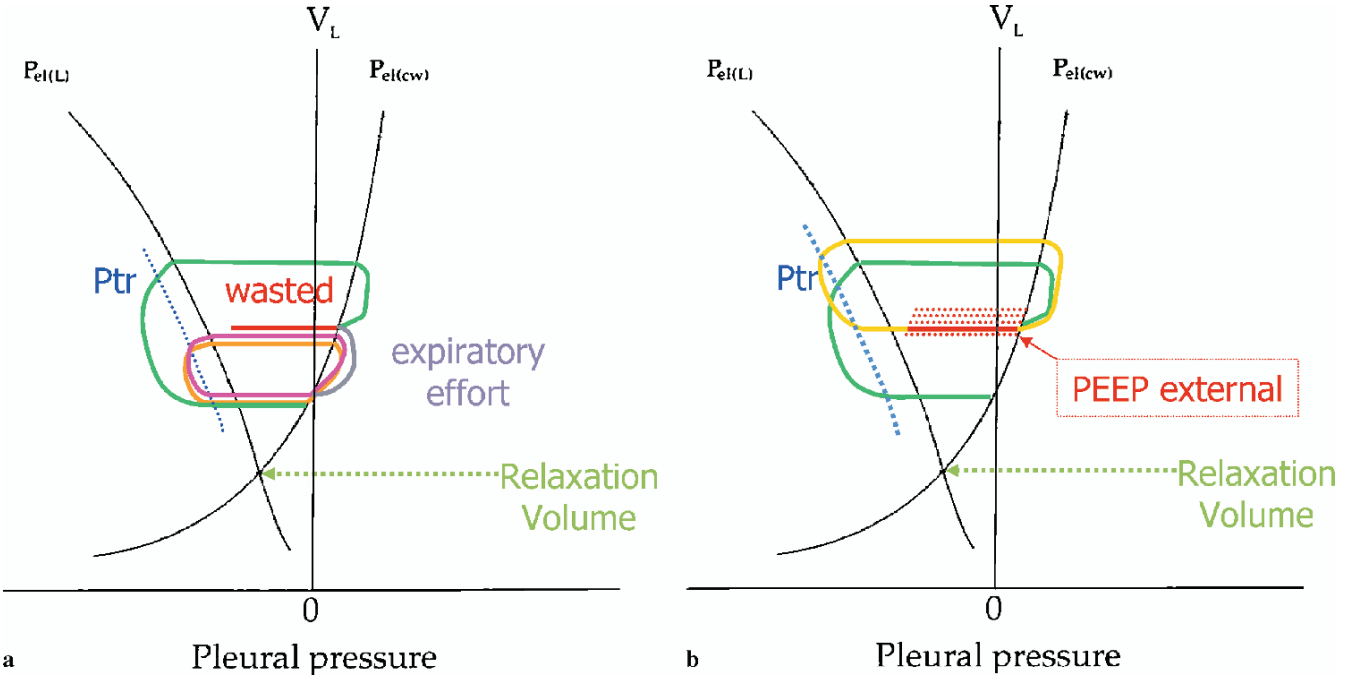


Fig. 2 **a** In the case of COPD presented, the first inspiratory effort (*orange curve*) triggers the ventilator. In the next breath that triggered the ventilator, excessive ventilator assistance (either pressure or volume) resulted in large tidal volume (*green curve*), which combined with the long time constant of the respiratory system (which retards lung emptying) and/or a short imposed expiratory time (in case of volume or pressure control) led to further increased end-expiratory lung volume before the next inspiratory effort begins (*green curve*). The ensuing inspiratory effort is inadequate to overcome PEEPi + Ptr due to the increased end expiratory lung volume; thus, this inspiratory effort fails to trigger the ventilator (wasted or ineffective effort, *red line*). The following expiratory effort (*blue curve*) decreases the end-expiratory lung volume. When the end-expiratory lung volume decreases to a level where the ensuing inspiratory effort exceeds PEEPi + Ptr, the ventilator is triggered again to deliver a machine breath (*mauve curve*). **b** In the presence of increased end-expiratory lung volume (*green curve*), addition of an amount of external PEEP lower than the intrinsic PEEP (*red dotted lines*) offers part of the pressure required to overcome PEEPi + Ptr. The inspiratory effort starts closer to the passive pressure-volume curve of the lung [*Pel(L)*]. The horizontal distance between this point and the passive pressure-volume curve of the chest wall [*Pel(cw)*] is the applied PEEP (*PEEP external*). The inspiratory effort is now adequate to trigger the ventilator (*orange curve*)

phase of ventilator expiration, i. e., at an increased lung volume [5]. This effort might not be sufficient to overcome PEEPi plus Ptr, and thus this inspiratory effort also fails to trigger the ventilator.

How can wasted efforts be detected at the bedside?

Wasted efforts can be clinically detected when the breaths delivered by the ventilator (measured rate on the ventilator display) are less than the number of inspiratory efforts of the patient (on clinical examination) at the same time interval (see ESM, slides 1 and 2). On modern ventilator screens, ineffective efforts can be detected as abrupt airway pressure drop simultaneous to an abrupt decrease in expiratory flow (from the flow trajectory established earlier during expiration) and not followed by a machine breath (see ESM, slide 2). Monitors that can automatically detect wasted efforts are under clinical testing and will be become available in the future [11, 12].

What ventilator adjustments should be done in the presence of wasted/ineffective efforts?

The self-evident solution to reduce the frequency of wasted efforts is to decrease the level of excessive ventilator assistance, thus reducing hyperinflation and the pathophysiology presented above [4, 6, 7]; however, this might not be always clinically feasible, since it might lead to respiratory distress and to derangement of blood gases [6].

Another solution is the use of PEEP [1, 6]. The addition of an amount of external PEEP lower than the intrinsic PEEP (Fig. 2b, red dotted lines) offers part of the pressure required to overcome PEEPi plus Ptr (Fig. 2b). The inspiratory effort starts closer to the Pel(L) [the horizontal distance between this point and the [Pel(cw) being the applied PEEP (PEEP external)]. The inspiratory effort is now adequate to trigger the ventilator (orange curve).

During assist control reducing machine Ti (or equivalently increasing the inspiratory flow) may prevent ventilator delivery beyond the patients' neural Ti and will reduce wasted efforts. Similarly, during pressure support increasing the expiratory trigger threshold will stop the breath earlier and will reduce wasted efforts [13].

Conclusion

Wasted efforts are a major cause of patient ventilator dyssynchrony that increase the energy expenditure of the respiratory muscles and may injure them. Understanding their pathophysiology is essential to properly adjust the ventilator settings to attenuate or eliminate them. Wasted efforts should be searched before any change in ventilator settings is implemented during assisted modes of mechanical ventilation, since any ensuing increase in ventilator rate might be caused by the attenuation of wasted efforts (the ventilator rate now approaching the patient's respiratory controller rate) and not by the development of respiratory distress with the new settings.

References

1. Fernandez R, Benito S, Blanch L, Net A (1988) Intrinsic PEEP: a cause of inspiratory muscle ineffectivity. Intensive Care Med 15:51–52
2. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L (2006) Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 32:1515–1522
3. Cabello B, Mancebo J (2006) Work of breathing. Intensive Care Med 32:1311–1314
4. Leung P, Jubran A, Tobin MJ (1997) Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. Am J Respir Crit Care Med 155:1940–1948
5. Tobin MJ, Jubran A, Laghi F (2001) Patient-ventilator interaction. Am J Respir Crit Care Med 163:1059–1063
6. Nava S, Bruschi C, Rubini F, Palo A, Iotti G, Braschi A (1995) Respiratory response and inspiratory effort during pressure support ventilation in COPD patients. Intensive Care Med 21:871–879
7. Chao DC, Scheinhorn DJ, Stearn-Hassenpflug M (1997) Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. Chest 112:1592–1599
8. Dempsey JA, Skatrud JB (2001) Apnea following mechanical ventilation may be caused by nonchemical neuromechanical influences. Am J Respir Crit Care Med 163:1297–1298
9. Parthasarathy S, Jubran A, Tobin MJ (1998) Cycling of inspiratory and expiratory muscle groups with the ventilator in airflow limitation. Am J Respir Crit Care Med 158:1471–1478
10. Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, Sinderby C (2001) Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am J Respir Crit Care Med 164:419–424
11. Younes M, Brochard L, Grasso S, Kun J, Mancebo J, Ranieri M, Richard JC, Younes H (2007) A method for monitoring and improving patient: ventilator interaction. Intensive Care Med 33:1337–1346
12. Mulqueeny Q, Ceriana P, Carlucci A, Fanfulla F, Delmastro M, Nava S (2007) Automatic detection of ineffective triggering and double triggering during mechanical ventilation. Intensive Care Med 33:2014–2018
13. Tassaux D, Gainnier M, Battisti A, Jolliet P (2005) Impact of expiratory trigger setting on delayed cycling and inspiratory muscle workload. Am J Respir Crit Care Med 172:1283–1289

U. Lucangelo
L. Blanch

Dead space

Introduction

Dead space is that part of the tidal volume that does not participate in gas exchange. Although the concept of pulmonary dead space was introduced more than a hundred years ago, current knowledge and technical advances have only recently lead to the adoption of dead space measurement as a potentially useful bedside clinical tool.

Concept of dead space

The homogeneity between ventilation and perfusion determines normal gas exchange. The concept of dead space accounts for those lung areas that are ventilated but not perfused. The volume of dead space (Vd) reflects the sum of two separate components of lung volume: 1) the nose, pharynx, and conduction airways do not contribute to gas exchange and are often referred to as anatomical Vd or herein as airway Vd (Vd_{aw}); 2) well-ventilated alveoli but receiving minimal blood flow comprise the alveolar Vd (Vd_{alv}). Mechanical ventilation, if present, adds additional Vd as part of the ventilator equipment (endotracheal tubes, humidification devices, and connectors). This instrumental dead space is considered to be part of the Vd_{aw}. Physiologic dead space (Vd_{phys}) is comprised of Vd_{aw} (instrumental and anatomic dead space) and Vd_{alv} and it is usually reported in mechanical ventilation as the portion of tidal volume (Vt) or minute ventilation that does not participate in gas exchange [1, 2].

A device that measures partial pressures (PCO_2) or fractions (FCO_2) of CO_2 during the breathing cycle is called a capnograph. The equation to transform FCO_2 into PCO_2 is $PCO_2 = FCO_2$ multiplied by the difference between barometric pressure minus water-vapour pressure. Time-based capnography expresses the CO_2 signal as a function of time and from this plot mean expiratory (Douglas bag method) or end-expiratory (end-tidal) CO_2 values can be obtained. The integration of the volume signal using an accurate flow sensor (pneumotachograph) and CO_2 signal (with a very fast CO_2 sensor) is known as volumetric capnography. Combined with the measurement of arterial PCO_2 ($PaCO_2$) it provides a precise quantification of the ratio of Vd_{phys} to Vt. The three phases of a volumetric capnogram are shown in Fig. 1 and Fig. 2. The combination of airflow and mainstream capnography monitoring allows calculation of breath by breath CO_2 production and pulmonary dead space. Therefore, the use of volumetric capnography is clinically more profitable than time-based capnography.

Measurement of dead space using CO_2 as a tracer gas

Bohr originally defined Vd/Vt [2] as: $Vd/Vt = (F_ACO_2 - F_ECO_2)/F_ACO_2$, where F_ACO_2 and F_ECO_2 are fractions of CO_2 in alveolar gas and in mixed expired gas, respectively. End-tidal CO_2 is used to approximate F_ACO_2,

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_7, © Springer-Verlag Berlin Heidelberg 2009

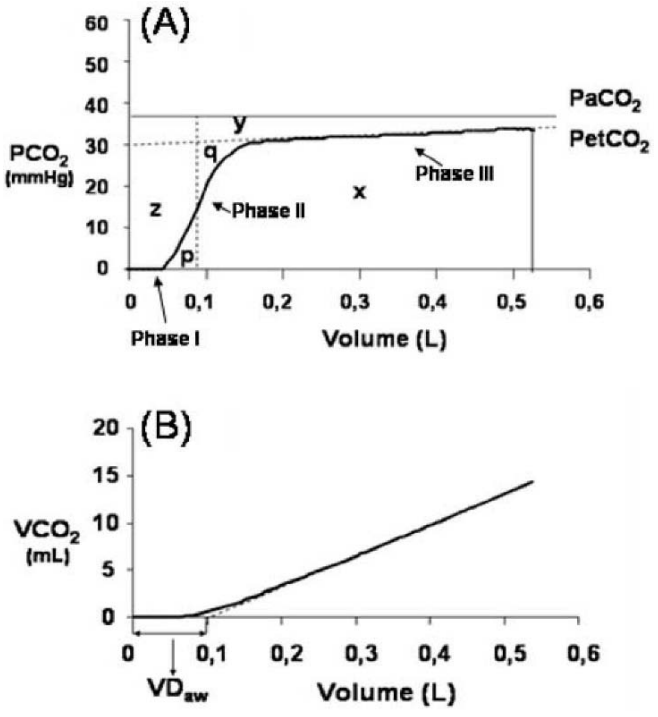


Fig. 1 **A** Single-breath expiratory volumetric capnogram recorded in a healthy patient receiving controlled mechanical ventilation. Dead-space components are shown graphically and equations are depicted and explained in the text. Phase I is the CO_2 free volume which corresponds to Vd_{aw}. Phase II represents the transition between airway and progressive emptying of alveoli. Phase III represents alveolar gas. $PaCO_2$ is arterial PCO_2; $PetCO_2$ is end-tidal PCO_2. Drawings adapted from [2]; **B** Single-breath expiratory carbon dioxide volume (VCO_2) plotted as a function of exhaled tidal volume. The alternative method to measure airway dead space (Vd_{aw}) described by Langley et al. [3] is graphically shown in a healthy patient receiving controlled mechanical ventilation

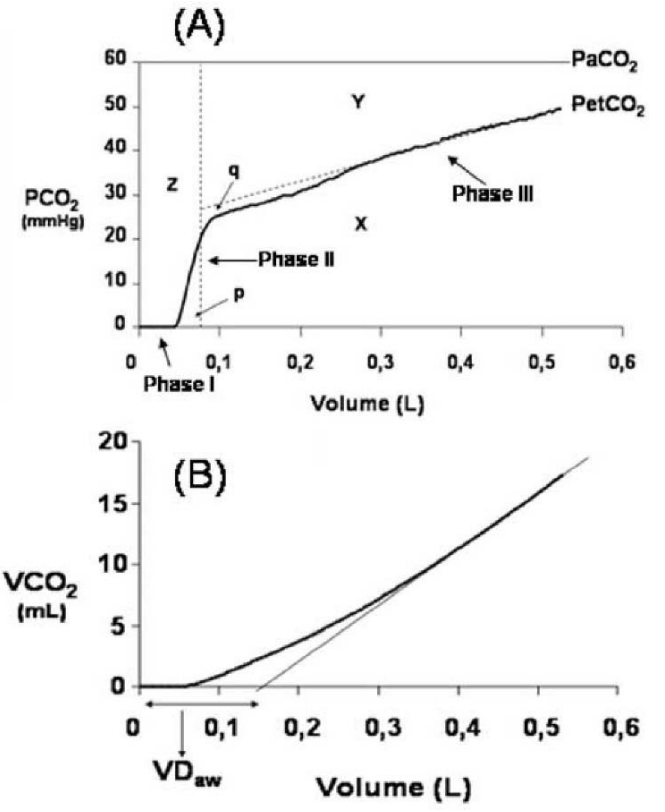


Fig. 2 **A** Single-breath expiratory volumetric capnogram recorded in a chronic obstructive pulmonary disease patient receiving controlled mechanical ventilation. The three phases of the volumetric capnogram are depicted. The transition from phase II to III is less evident due to heterogeneity of ventilation and perfusion ratios. Dead-space components are shown graphically and equations are depicted and explained in the text. $PaCO_2$ is arterial PCO_2; $PetCO_2$ is end-tidal PCO_2. Drawings adapted from [2]; **B** Single-breath expiratory carbon dioxide volume (VCO_2) plotted as a function of exhaled tidal volume. The alternative method to measure airway dead space (Vd_{aw}) described by Langley et al. [3] is graphically shown in a chronic obstructive pulmonary disease patient receiving controlled mechanical ventilation

assuming end-tidal and alveolar CO_2 fractions are identical. Physiologic dead space calculated from the Enghoff modification of the Bohr equation uses $PaCO_2$ with the assumption that $PaCO_2$ is similar to alveolar PCO_2 [2], such that: $Vd_{phys}/Vt = (PaCO_2–P_ECO_2)/PaCO_2$, where P_ECO_2 is the partial pressure of CO_2 in mixed expired gas and is equal to the mean expired CO_2 fraction multiplied by the difference between the atmospheric pressure and the water-vapour pressure. Since Vd_{phys}/Vt measures the fraction of each tidal breath that is wasted on both Vd_{alv} and Vd_{aw}, the Vd_{aw} must be subtracted from Vd_{phys}/Vt to obtain the Vd_{alv}/Vt. Vd_{phys}/Vt is the most commonly and commercially (volumetric capnographs) formula used to estimate pulmonary dead space at the bedside.

Additional methods mostly used in research to calculate all the Vd components are shown in Fig. 1A and Fig. 2A. Fowler [1] introduced a procedure for measuring Vd_{aw} based on the geometric method of equivalent areas (p = q), obtained by crossing the back extrapolation of phase III of the expired CO_2 concentration over time with a vertical line traced so as to have equal p and q areas. Airway dead space is then measured from the beginning of expiration to the point where the vertical line crosses the volume axis [1]. By tracing a line parallel to the volume axis and equal to the $PaCO_2$, it is possible to determine the readings from areas y and z, which respectively represent the values of alveolar and airway dead space. Referring these values to the Vt, it is possible to single out several Vd components [2]:

$$Vd_{phys}/Vt = (Y + Z)/(X + Y + Z)$$

$$Vd_{alv}/Vt = Y/(X + Y + Z)$$

$$Vd_{aw}/Vt = Z/(X + Y + Z)$$

An alternative method to measure airway dead space introduced by Langley et al. [3] is based on determination of the VCO_2 value, which corresponds to the area inscribed within the CO_2 versus volume curve (indicated in Fig. 1A and Fig. 2A as X area). Figure 1B and Fig. 2B are examples of Vd_{aw} calculation using the Langley et al. [3] method. Briefly, VCO_2 is plotted versus expired breath volume. Thereafter, Vd_{aw} can be calculated from the value obtained on the volume axis by back extrapolation from the first linear part of the VCO_2 versus volume curve.

Although these indexes are clinically useful, they are always bound to visual criteria for the definition of phase III of the expired capnogram. Often, the geometric analysis establishing the separation between the phase II and phase III is hardly seen and the rate of CO_2 raising of the phase III is nonlinear in patients with lung inhomogeneities (Fig. 2A).

Utility of dead space in different clinical scenarios

The CO_2 tension difference between pulmonary capillary blood and alveolar gas is usually small in normal subjects and end-tidal PCO_2 is close to alveolar and arterial PCO_2. Physiologic dead space is the primary determinant of the difference between arterial and end-tidal PCO_2 (ΔPCO_2) in patients with a normal cardio-respiratory system. Patients with cardiopulmonary diseases have altered ventilation to perfusion (V_A/Q_T) ratios producing abnormalities of Vd, as well as in intrapulmonary shunt, and the latter may also affect the ΔPCO_2. A ΔPCO_2 beyond 5 mmHg is attributed to abnormalities in Vd_{phys}/Vt and/or by an increase in venous admixture (the fraction of the cardiac output that passes through the lungs without taking oxygen) or both. The increase in Vd_{phys}/Vt seen in normal patients when anaesthetised may be attributed to muscle paralysis, which causes a reduction of functional residual capacity and alters the normal distribution of ventilation and perfusion across the lung [2, 4, 5, 6].

Ventilation to regions having little or no blood flow (low alveolar PCO_2) affects pulmonary dead space. In patients with airflow obstruction, inhomogeneities in ventilation are responsible for the increase in Vd. Shunt increase VD_{phys}/Vt as the mixed venous PCO_2 from shunted blood elevates the $PaCO_2$, increasing VD_{phys}/Vt by the fraction that $PaCO_2$ exceeds the nonshunted pulmonary capillary PCO_2 [7]. Vd_{alv} is increased by shock states, systemic and pulmonary hypotension, obstruction of pulmonary vessels (massive pulmonary embolus and microthrombosis), even in the absence of a subsequent decrease in ventilation and low cardiac output. Vd_{aw} is increased by lung overdistension and additional ventilatory apparatus dead space. Endotracheal tubes, heat and moisture exchangers, and other common connectors may increase ventilator dead space and induce hypercapnia during low Vt or low minute ventilation. Vd_{aw} calculations include the ventilator dead space. Because the anatomic dead space remains relatively constant as Vt is reduced, very low Vt is associated with a high Vd/Vt ratio [1, 2, 7, 8, 9].

Positive end-expiratory pressure (PEEP) is used to increase lung volume and to improve oxygenation in patients with acute lung injury. Vd_{alv} is large in acute lung injury and does not vary systematically with PEEP. However, when the effect of PEEP is to recruit collapsed lung units resulting in an improvement of oxygenation, Vd_{alv} may decrease, and alveolar recruitment is associated with decreased arterial minus end-tidal CO_2 difference [4, 5, 6]. Conversely, PEEP-induced overdistension may increase Vdalv and widen this difference [7].

In patients with sudden pulmonary vascular occlusion due to pulmonary embolism, the resultant high V_A/Q_T mismatch produces an increase in Vd_{alv}. The association of a normal D-dimer assay result plus a normal Vd_{alv} is a highly sensitive screening test to rule out the diagnosis of pulmonary embolism [9].

Dead space and outcome prediction

Characteristic features of acute lung injury are alveolar and capillary endothelial cell injuries that result in alterations of pulmonary microcirculation. Consequently, adequate pulmonary ventilation and blood flow across the lungs are compromised and Vd_{phys}/Vt increases. A high dead-space fraction represents an impaired ability to excrete CO_2 due to any kind of V_A/Q_T mismatch [7]. Nuckton et al. [10] demonstrated that a high Vd_{phys}/Vt was independently associated with an increased risk of death in patients diagnosed with acute respiratory distress syndrome.

Conclusions

The advanced technology combination of airway flow monitoring and mainstream capnography allows breath-by-breath bedside calculation of pulmonary Vd and CO_2 elimination. For these reasons, the use of volumetric capnography is clinically more useful than time capnography. Measurement of dead-space fraction early in the course of acute respiratory failure may provide clinicians with important physiologic and prognostic information. Further studies are warranted to assess whether the continuous measurement of different derived capnographic indices is useful for risk identification and stratification, and to track the effect of a therapeutic intervention during the course of disease in critically ill patients.

References

1. Fowler WS (1948) Lung function studies II: the respiratory dead-space. Am J Physiol 154:405–410
2. Fletcher R, Jonson B, Cumming G, Brew J (1981) The concept of dead space with special reference to the single breath test for carbon dioxide. Br J Anesth 53:77–88
3. Langley F, Even P, Duroux P, Nicolas RL, Cumming G (1975) Ventilatory consequences of unilateral pulmonary artery occlusion. In: Distribution des exchanges gaseaux pulmonaires. INSERM, 1976. WF D613. Paris, France, pp 209–212
4. Blanch L, Fernandez R, Benito S, Mancebo J, Net A (1987) Effect of PEEP on the arterial minus end-tidal carbon dioxide gradient. Chest 92:451–454
5. Blanch L, Lucangelo U, Lopez-Aguilar J, Fernandez R, Romero P (1999) Volumetric capnography in patients with acute lung injury: effects of positive end-expiratory pressure. Eur Respir J 13:1048–1054
6. Beydon L, Uttman L, Rawal R, Jonson B (2002) Effects of positive end-expiratory pressure on dead space and its partitions in acute lung injury. Intensive Care Med 28:1239–1245
7. Coffey RL, Albert RK, Robertson HT (1983) Mechanisms of physiological dead space response to PEEP after acute oleic acid lung injury. J Appl Physiol 55:1550–1557
8. Feihl F (2003) Respiratory dead space and survival in the acute respiratory distress syndrome. In: Gullo A (ed) Anesthesia pain intensive care and emergency medicine, vol. 1. Springer, Berlin Heidelberg New York, pp 275–287
9. Kline JA, Israel EG, Michelson EA, O'Neil BJ, Plewa MC, Portelli DC (2001) Diagnostic accuracy of a bedside D-dimer assay and alveolar dead space measurement for rapid exclusion of pulmonary embolism. JAMA 285:761–768
10. Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, Matthay A (2002) Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Eng J Med 346:1281–1286

Peter D. Wagner

The multiple inert gas elimination technique (MIGET)

Abstract This brief review centers on the multiple inert gas elimination technique (MIGET). This technique, developed in the 1970s, measures the pulmonary exchange of a set of six different inert gases dissolved together in saline (or dextrose) and infused intravenously. It then uses those measurements to compute the distribution of ventilation/perfusion ratios that best explains the exchange of the six gases simultaneously. MIGET is based on the very same mass-conservation principles underlying the classic work of Rahn and Fenn and of Riley and coworkers in the 1950s, which defines the relationship between the ventilation/perfusion ratio and the alveolar and capillary partial pressures of any gas. After a brief history of MIGET, its principles are laid out, its information content is explained, and its limitations are described. It is noted that in addition to quantifying ventilation/perfusion inequality and pulmonary shunting, MIGET can identify and quantify diffusion limitation of O_2 exchange, when present, as well as explain the contributions of extrapulmonary influences such as inspired O_2 concentration, ventilation, cardiac output, Hb concentration/P_{50}, body temperature and acid/base state on arterial oxygenation. An overview of the technical details of implementing MIGET is given, and the review ends with potential future applications.

Keywords Ventilation/perfusion inequality · Shunt · Alveolar–capillary diffusion limitation · Hypoxemia · Hypercapnia · Inert gases

Introduction

Most patients cared for in the ICU have inefficient pulmonary gas exchange, causing hypoxemia and requiring increased inspired O_2 levels to sustain O_2 availability to tissues. Most medical students know that hypoxemia may be caused by one or more of four different physiological processes [1]: (1) Hypoventilation, (2) diffusion limitation, (3) ventilation/perfusion inequality, and (4) shunt (right to left). Most residents know that hypoxemia can be assessed by any of five common parameters: (1) arterial PO_2 (and PCO_2) itself, (2) arterial PO_2/FIO_2 ratio, (3) alveolar–arterial PO_2 difference, (4) venous admixture (also termed physiological shunt), and (5) physiological dead space. Most intensivists know that these several parameters, while readily available and clinically useful, offer quite limited information and are open to misinterpretation when the underlying assumptions and requirements are not met. For the most part, the four causes of hypoxemia are difficult to distinguish in any given patient using these tools. Intensivists also know that in addition to the above four causes of hypoxemia, so-called extrapulmonary factors can greatly modulate arterial PO_2. These factors are, in addition to FIO_2, total ventilation, cardiac output, metabolic rate, Hb concentration, Hb P_{50}, body temperature, and acid/base status.

The multiple inert gas elimination technique (MIGET) [2–5] was introduced in the early 1970s as a way to overcome many of the limitations imposed by the classical methods mentioned above. This short review will

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_8, © Springer-Verlag Berlin Heidelberg 2009

discuss the MIGET in terms of its history, its theoretical basis, its implementation, and its future, in that order.

A brief history of the MIGET

In the late 1940s, 1950s and early 1960s, prior to the availability of digital computation, three groups of investigators developed the modern foundations of pulmonary gas exchange. Rahn and Fenn published their remarkable graphical analysis of the relationship between PO_2, PCO_2, and the ventilation perfusion ratio, $\dot{V}A/\dot{Q}$ [6]; Riley and coworkers developed the concepts of quantifying gas exchange disturbances by calculating venous admixture and physiological dead space [7, 8], and Briscoe and King added to this new scientific domain by exploring the relationship between ventilation/perfusion inequality and diffusion limitation of O_2 transport in the lung [9, 10].

The foundation of all of their efforts was one simple principle: steady-state gas exchange in the lung obeyed mass-conservation principles. Simple mass-conservation equations for O_2 (and CO_2) were written down for both disappearance of O_2 from alveolar gas and its subsequent appearance in the pulmonary capillary blood. This led to the famous ventilation/perfusion equation, approximated for O_2 as follows:

$$\dot{V}A/\dot{Q} = 8.63 \times [Cc'O_2 - CvO_2]/[PIO_2 - PAO_2] \quad (1)$$

and for CO_2:

$$\dot{V}A/\dot{Q} = 8.63 \times [CvCO_2 - Cc'CO_2]/[PACO_2]. \quad (2)$$

Here, Cc′ and Cv represent end-capillary and mixed venous concentrations (ml/dl) while PI and PA represent inspired and alveolar partial pressures (mmHg). Note that 7.5 mmHg = 1 kP. The constant 8.63 reconciles the units and conventional conditions of expression (O_2 and CO_2 concentrations in ml/dl, STPD; $\dot{V}A$ in l/min, BTPS, $\dot{Q}$ in l/min. Its value is actually given by $0.01 \times 760 \times [(273 + T)/273]$, where 760 is standard barometric pressure in mmHg (101.3 kP) and T is body temperature in °C, assumed here to be 37.

What do these equations tell us? That local alveolar PO_2 (and PCO_2) is uniquely set by the local $\dot{V}A/\dot{Q}$ ratio – for a given set of "boundary conditions" (the inspired and venous blood composition and the particulars of the O_2 and CO_2 dissociation curves).

These rather simple equations are tantalizingly hard to actually solve – that is, to come up with the actual PO_2 for any $\dot{V}A/\dot{Q}$ ratio – because the dissociation curve is so complex. The principles apply to all gases, however, and if gas exchange is examined for a gas whose transport in blood is only by physically dissolving, the above equations become much simpler.

Suppose such a gas (we shall call it an inert gas) is being eliminated from the body (just as is CO_2). Equation 2 applies and looks like this:

$$\dot{V}A/\dot{Q} = 8.63 \times \text{solubility} \times [Pv_{IG} - Pc'_{IG}]/[PA_{IG}] \quad (3)$$

[because concentration = solubility × partial pressure (Henry's Law)]. Using this nomenclature, solubility is the ratio of concentration to partial pressure, and is usually expressed in ml (of the gas dissolved in blood) per dl (of blood) per mmHg partial pressure (of the gas in blood). Now, if we assume that diffusion equilibration for an inert gas is complete, $Pc'_{IG} = PA_{IG}$. Dropping the subscript IG and recognizing that λ, the blood–gas partition coefficient of the inert gas, =8.63 × solubility, we have:

$$\dot{V}A/\dot{Q} = \lambda \times [Pv - PA]/[PA]. \quad (4)$$

Note that λ, in words, is the ratio of concentrations of the gas in blood and (alveolar) gas, at equilibrium. Equation 4 can be rearranged as follows:

$$PA/Pv = \lambda/[\lambda + \dot{V}A/\dot{Q}] = Pc'/Pv. \quad (5)$$

This equation says that for an inert gas being eliminated from the blood by the lung, the fraction that is *not* eliminated (i.e., the fraction that is retained in the end-capillary blood, Pc′/Pv) is a simple function of the partition coefficient (λ) and the $\dot{V}A/\dot{Q}$ ratio.

The point of this exercise is to show that Eq. 5, which turns out to be the complete foundation of the MIGET, is nothing more than the ventilation/perfusion equation of mass conservation applied to an inert gas. Seymour Kety [11] and then Leon Farhi and his colleagues [12, 13] used this equation extensively to understand inert gas exchange in the lung, and Farhi et al. went on to propose a method for characterizing the lung as a two-compartment distribution of ventilation and blood flow using measured PA/Pv ratios for three gases forced to exchange across the lungs [13].

Before moving to MIGET itself, another advance must be mentioned: Lenfant and coworkers developed an approach to use the pattern of arterial PO_2 response to increasing FIO_2 to calculate a continuous distribution of ventilation and blood flow [14, 15]. While an approach based on PO_2 has some attraction, there were too many concerns to support its widespread use. However, it laid the groundwork for the concept of (essentially) continuous $\dot{V}A/\dot{Q}$ distributions as the "holy grail" of gas exchange research.

Theoretical basis of the MIGET

Returning to inert gases, Eq. 5 is the basis of MIGET. It reflects precisely the same physiological principles of mass conservation as for O_2 and CO_2.

How does it work?

Suppose we introduce a foreign inert gas into the body by venous infusion of a solution of that gas, and we measure retention as measured from an arterial blood sample as the ratio Pa/Pv (arterial to mixed venous inert gas partial pressure ratio, termed R). Further suppose the lung is perfectly homogeneous. We have:

$$R = \lambda/[\lambda + \dot{V}A/\dot{Q}]. \quad (6)$$

where $\dot{V}A/\dot{Q}$ is the ratio of alveolar ventilation to cardiac output.

Figure 1 (upper panel) shows R (calculated from Eq. 6) plotted against the $\dot{V}A/\dot{Q}$ ratio for gases of different λ. It shows that for any gas, R falls as $\dot{V}A/\dot{Q}$ ratio rises. Look at a gas with $\lambda = 0.01$ as an example: When $\dot{V}A/\dot{Q}$ is less than about 0.001, the gas is essentially fully retained in the blood. At even lower $\dot{V}A/\dot{Q}$ ratios, retention therefore does not change and this gas cannot discriminate between $\dot{V}A/\dot{Q}$ ratios of, say, 0.001 and any lower value. Similarly, elimination is essentially complete at $\dot{V}A/\dot{Q}$ ratios of 0.1 or higher, and this gas will not discriminate among $\dot{V}A/\dot{Q}$ ratios higher than 0.1. However, in the range 0.001 to 0.1, retention of this gas is very sensitive to $\dot{V}A/\dot{Q}$ ratio, and is thus a good gas to use to identify alveoli with $\dot{V}A/\dot{Q}$ ratios in that range. Similar arguments apply to all other gases.

Figure 1 (lower panel) plots exactly the same data, but this time retention is plotted against λ, not $\dot{V}A/\dot{Q}$. The message here is that a gas of a particular λ is best suited to identifying alveoli whose $\dot{V}A/\dot{Q}$ ratios approximate the value of λ. For $\dot{V}A/\dot{Q}$ ratios 10 times (or more) lower than λ, retention is essentially complete, and is essentially zero when $\dot{V}A/\dot{Q}$ is 10 times (or more) higher than λ. Thus, if several inert gases (whose λ vary over several decades) are exchanged simultaneously and their retentions measured, we have the potential to determine what kinds of $\dot{V}A/\dot{Q}$ regions are present in any given lung.

Figure 2 captures this concept more clearly with three examples: the upper panel represents a perfectly homogeneous lung (with $\dot{V}A/\dot{Q}$ ratio = 1), the middle panel a lung with 50% of its blood flow perfusing a region whose $\dot{V}A/\dot{Q}$ ratio is low, at 0.01 (the remaining 50% perfusing normal regions), and the lower panel a lung with 50% of its blood flow perfusing completely unventilated regions (i.e., shunt, $\dot{V}A/\dot{Q} = 0$). In each, the arterial retention values that would result for six different inert gases (named in the upper panel) are shown by the solid circles. The end-capillary/mixed venous ratios associated with each of the contributing regions are shown by the dashed lines in each case. It is clear that the shape and position of these "retention–solubility" curves vary widely according to the particular pattern of $\dot{V}A/\dot{Q}$ regions present. What this means is that from the measured pattern of retentions of such a set of six gases, it is possible to deduce the underlying pattern of

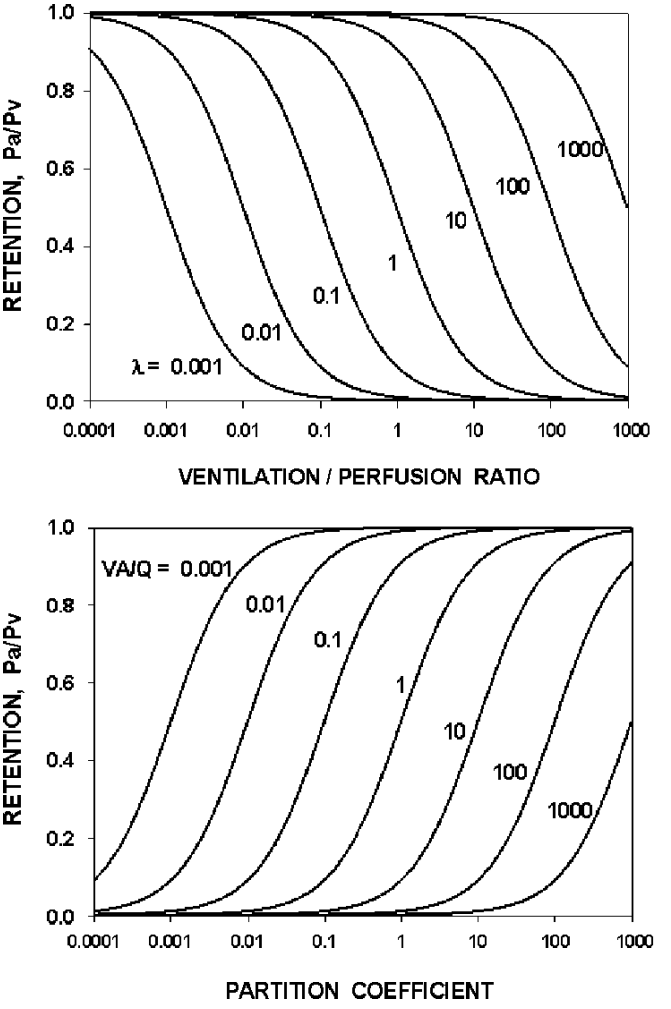


Fig. 1 *Upper panel:* Inert gas retention (as defined in, and computed from, Eq. 5) as a function of the ventilation/perfusion ratio ($\dot{V}A/\dot{Q}$). Each line reflects a gas of indicated partition coefficient, λ. While retention falls as $\dot{V}A/\dot{Q}$ increases, and is higher for more soluble gases at any given $\dot{V}A/\dot{Q}$ ratio, the key point is that a given gas is sensitive to $\dot{V}A/\dot{Q}$ in only a fairly narrow range (from $\dot{V}A/\dot{Q} = 10\times$ lower to $10\times$ higher than λ for that gas). *Lower panel:* Identical data as for upper panel, but now plotting retention against λ (defining the retention/solubility relationship) for lung regions of indicated $\dot{V}A/\dot{Q}$. The major point is that a gas of given λ is most sensitive to $\dot{V}A/\dot{Q}$ ratios from $10\times$ lower to $10\times$ higher than its λ

distribution of $\dot{V}A/\dot{Q}$ ratios. The mathematics underlying this relationship is somewhat complex and cannot be laid out in such a brief review as this, but has been presented on several occasions [5, 16–18]. It entails searching for the distribution of blood flow and ventilation that best fits, according to least-squares principles, the measured set of retentions of the six gases. It is conceptually similar to a simple two-variable linear regression between a set of two variables, X and Y, where the slope and intercept of a straight line are found that best fit the paired (X,Y) data by minimizing the sum of squares between the

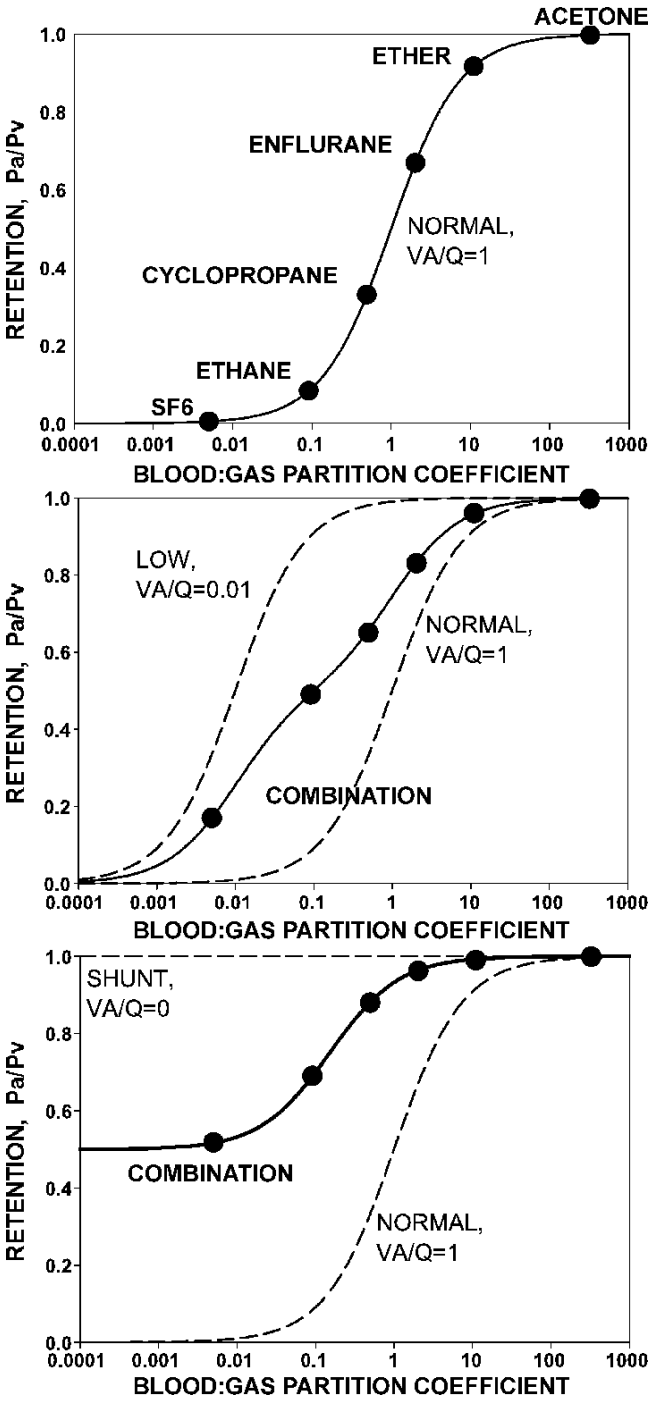


Fig. 2 Three examples of retention/solubility relationships. *Top panel:* Retention values expected in a normal lung, indicating the six inert gases commonly used in MIGET. Importantly, the six gases are chosen to sample the full extent of the curve. *Middle panel:* Retention/solubility curve in a lung with equally perfused regions of both normal and greatly reduced $\dot{V}A/\dot{Q}$ ratios. The shape and position are grossly different from the normal lung. *Bottom panel:* Retention/solubility curve in a lung with equally perfused regions of both normal and zero $\dot{V}A/\dot{Q}$ ratios. Note that when $\dot{V}A/\dot{Q} = 0$, this means an unventilated lung region, i.e., a shunt. The shape and position is grossly different from that in both the normal lung and the lung with low $\dot{V}A/\dot{Q}$ regions

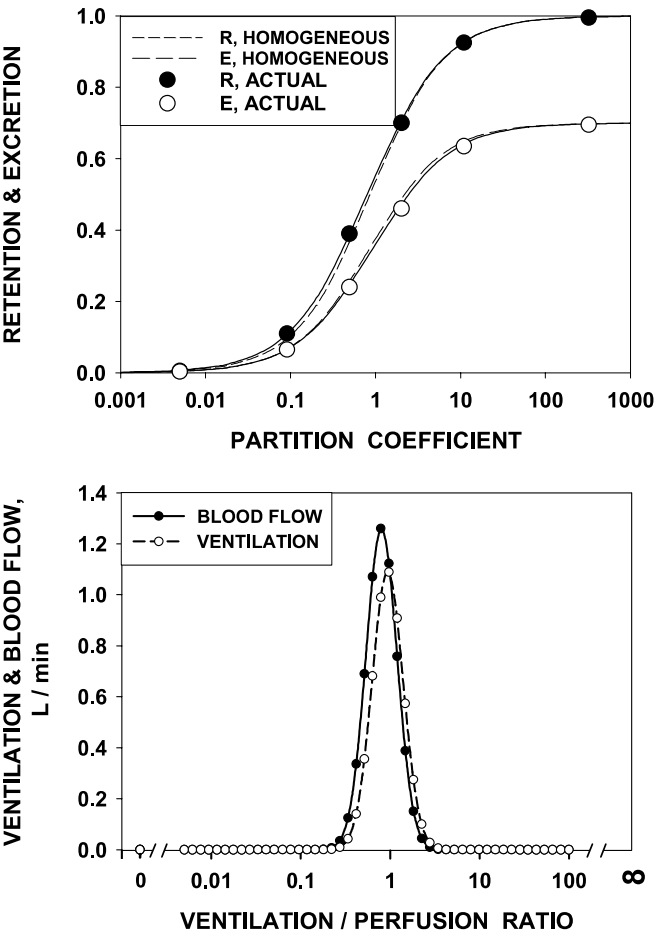


Fig. 3 Retention (and excretion)/solubility curves for a normal lung (*upper panel*) and corresponding distributions of ventilation and blood flow (*lower panel*). The range of $\dot{V}A/\dot{Q}$ in health is only about one decade ($\sim$0.3 to $\sim$3) as shown

actual Y values and those predicted from the regression equation.

Figure 2 is limited to arterial retention of the six gases, as would be measured from samples of arterial blood. It is also possible to measure the mixed expired concentrations of the same six gases at the same time, and we have called the ratio of mixed expired to mixed venous concentration excretion, E. Just as retention, R, reflects the pattern of allocation of blood flow to regions of different $\dot{V}A/\dot{Q}$ ratio, excretion reflects the pattern of distribution of ventilation to the same regions. In any given lung, the values of E and R for the lung as a whole must obey mass conservation, such that:

$$\dot{V}_{IG} = \dot{V}E \times E = \lambda \times \dot{Q}T \times [1 - R] \quad (7)$$

Here, $\dot{V}_{IG}$ is the volume of each inert gas eliminated per minute, $\dot{V}E$ is total minute ventilation and QT is total pulmonary blood flow (cardiac output). In addition, in any gas-exchange unit [i.e., a collection of alveoli in which PO_2 (and PCO_2) is uniform], local alveolar ventilation and

local blood flow define the $\dot{V}A/\dot{Q}$ ratio, or as written here:

$$\dot{V}A = \dot{Q} \times \dot{V}A/\dot{Q} \quad (8)$$

Equations 7 and 8 show that knowledge of retention implies knowledge of excretion and that knowing the distribution of blood flow, we know the distribution of ventilation. From a theoretical point of view, it means we could measure the $\dot{V}A/\dot{Q}$ distribution either from the excretions or the retentions – they are two reflections of the same function. However, in using MIGET, we measure both excretion and retention because together they provide two views of the distribution and improve its information content, much as a PA and lateral chest X-ray together are better than either alone, even though both are seeing the same lung.

Figures 3, 4 and 5 bring all of this together and show retentions, excretions, and the distributions of ventilation and blood flow for three representative lungs: a normal lung; a lung with 10% shunt; and a lung with 33% of the cardiac output perfusing very poorly ventilated alveoli, respectively. In each case, anatomic dead space (at 30% of tidal volume) is present. Such dead space serves to dilute expired inert gas concentrations, reducing excretion values for all gases by the same proportion (here, by 30%).

These figures take some getting used to, but the main point here is that different $\dot{V}A/\dot{Q}$ patterns underlie different retention/excretion patterns, such that by measuring the latter we can deduce the characteristics of the former.

What is MIGET's information content?

What MIGET obviously provides is the quantitative shape and position of the distributions of ventilation and blood

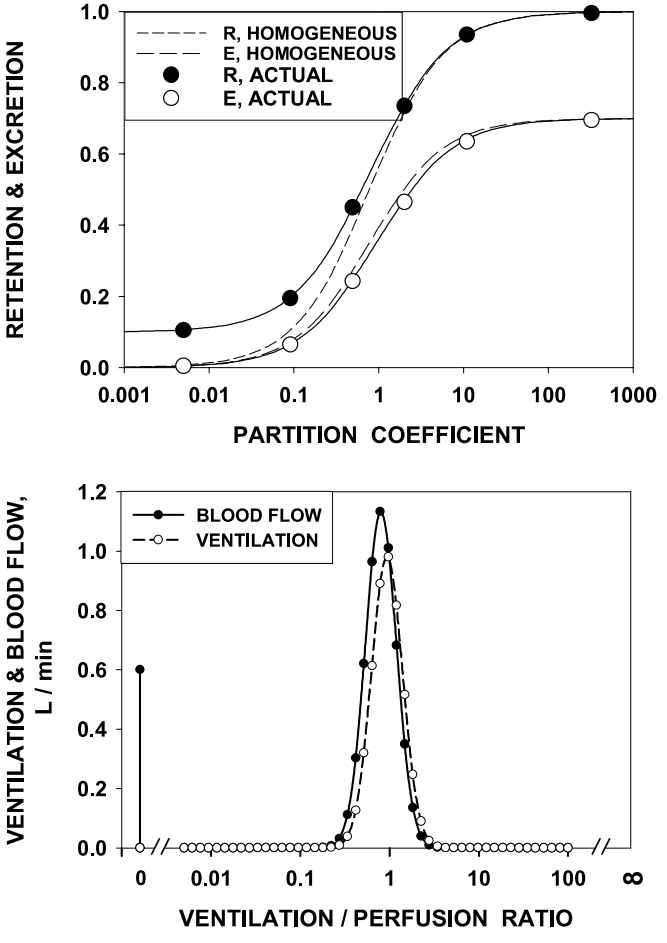


Fig. 4 Retention (and excretion)/solubility curves for a lung that contains a 10% shunt (in which $\dot{V}A/\dot{Q} = 0$) but is otherwise normal (*upper panel*) and corresponding distributions of ventilation and blood flow (*lower panel*). Shunt is shown by the *closed circle* at $\dot{V}A/\dot{Q} = 0$. Such distributions commonly reflect atelectasis, pneumonia, pulmonary edema, or pneumothorax

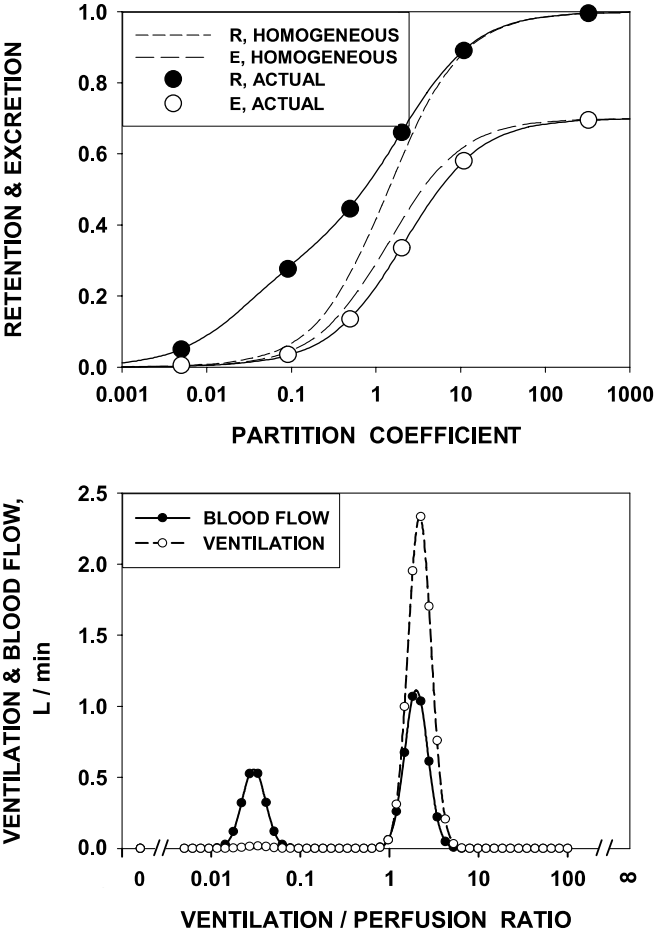


Fig. 5 *Upper panel:* Retention (and excretion)/solubility curves for a lung in which 33% of the blood flow perfuses units with a very low $\dot{V}A/\dot{Q}$ and the rest flows through units of normal $\dot{V}A/\dot{Q}$. *Lower panel:* Corresponding distributions of ventilation and blood flow. This pattern is common in chronic airway obstruction from asthma or COPD

flow with respect to $\dot{V}A/\dot{Q}$ ratio, as shown in Figs. 3–5. This pictorial representation can be reduced to a number of parameters that summarize the modality, position, dispersion, and (a)symmetry of the two curves. These parameters complement the visual image and are useful in allowing statistical comparison of distributions under different conditions. Importantly, as Figs. 4 and 5 show, a special strength of MIGET is that it distinguishes regions of low $\dot{V}A/\dot{Q}$ ratio from unventilated regions (shunt). Symmetrically, it also separates areas of high $\dot{V}A/\dot{Q}$ ratio from unperfused regions (which thus have infinitely high $\dot{V}A/\dot{Q}$ ratio).

MIGET allows additional insights into gas exchange, however. First, the presence of diffusion limitation for O_2 can be identified. Second, the role of so-called extrapulmonary factors on arterial PO_2 and PCO_2 can be quantified.

Diffusion limitation of O_2 exchange

All gases cross the pulmonary blood–gas barrier by diffusion. If the end-capillary partial pressure of any exchanging gas is not equal to its alveolar value in any homogeneous lung region, diffusion limitation is said to be present. For O_2, this may cause hypoxemia additional to that caused by any $\dot{V}A/\dot{Q}$ inequality that is present. The key point here is that inert gases reach equilibration (between capillary blood and alveolar gas) about 10 times faster than does O_2. Even when O_2 is diffusion-limited, inert gases are not. As a result, MIGET's inert gases faithfully indicate only $\dot{V}A/\dot{Q}$ inequality even when O_2 is diffusion-limited. Under such circumstances, the actual arterial PO_2 will be lower than that which MIGET would predict from $\dot{V}A/\dot{Q}$ inequality alone. Such a difference, due to diffusion limitation of O_2, is exploited within the MIGET software by computing the O_2 diffusing capacity that would have to exist to explain the additional hypoxemia [19].

Role of extrapulmonary factors in O_2 exchange

Arterial hypoxemia is classically considered due to one or more of four phenomena: $\dot{V}A/\dot{Q}$ inequality, shunt, diffusion limitation, and hypoventilation [1]. What is less well appreciated is that so-called extrapulmonary factors play a modulating role, affecting the level of hypoxemia produced by the above four factors. For example, if cardiac output suddenly falls in a patient with $\dot{V}A/\dot{Q}$ inequality, so too will arterial PO_2 because of the concomitant reduction in pulmonary arterial PO_2. MIGET software allows the user to separate out the quantitative effects of such changes in extrapulmonary variables. The extrapulmonary variables that can play a role are: FIO_2, metabolic rate ($\dot{V}O_2$), total alveolar ventilation, cardiac output, Hb concentration and P_{50}, acid/base status, and body temperature [20]. Each forms a specific input to the MIGET software such that desired changes in each can be read in and the consequences for arterial PO_2 assessed.

What are MIGET's limitations?

MIGET can only approximate the true distribution of $\dot{V}A/\dot{Q}$ ratios in the lung. We estimate that the human lung consists of about 100,000 individual gas exchange units (in essence, the acini) [21]. Thus, it is theoretically possible that 100,000 different $\dot{V}A/\dot{Q}$ ratios could exist, and using just six gases it would be impossible to identify them individually – it would take 100,000 gases! This is more of a theoretical than a practical concern, however, because just as with any distributed biological variable, by the time you have 100,000 units the ensuing distribution is highly likely to be smooth and therefore basically definable by a small number of measurements. The other major limitation is that caused by random experimental error. We use a smoothing algorithm [5] to control error effects. In other words, we enforce a measure of smoothing just sufficient to stabilize results when measurements are repeated (i.e., when sequential distributions would vary only due to random error). What this does is limit the resolution of MIGET—it is not possible to accurately recover a distribution that is very narrow. In numbers, any distribution whose actual dispersion is < 0.3 cannot be identified as such and will likely be depicted as having a dispersion at that limit. (This unit of dispersion is called "LOG SD" and is a dimensionless number that is the second moment (on a log scale) of the distribution about its mean). Normal subjects usually show log SD values of 0.4–0.6; moderate disease is reflected by log SD in the range of 1.0; and severe disease such as acute lung injury and ARDS would show values of 1.5–2.5. Again, this limitation is more theoretical than practical as normal subjects rarely show log SD values at the lower limit of 0.3. Finally, it needs to be mentioned that while the distributions recovered by MIGET describe the total functional abnormality of the lung, there is no regional anatomical information available, just as is the case with the classical indices of gas exchange – venous admixture, physiological dead space and the alveolar–arterial PO_2 difference.

Implementation of the MIGET

Implementing MIGET is relatively straightforward:

1. The six gases (Fig. 2) are dissolved in a sterile bag of saline or dextrose by bubbling gas (SF6, ethane, cyclopropane) or injecting liquid (enflurane, ether, acetone) into that bag in a sterile manner.
2. This sterile solution is infused into any peripheral vein at a rate in ml/min equal to about 1/4 of the minute

ventilation expressed in l/min. Thus, at rest the rate is about 2–3 ml/min. This rate of infusion produces concentrations of each gas in the ppm range or lower. At rest, the infusion should run about 20 min before samples are collected to allow development of steady-state inert gas exchange. During exercise, a steady state is reached far more quickly, and by the time O_2 uptake itself is stable, so too is inert gas exchange.

3. When desired, samples are then collected: about 7–8 ml each of systemic and pulmonary arterial blood (heparinized) and 20 ml of mixed expired gas, all in gas-tight, glass syringes. Samples for conventional blood gases (PO_2, PCO_2, pH, O_2 saturation, [Hb]) are taken simultaneously. We almost always take duplicate samples for both conventional and inert gases to both estimate and reduce error variance. Note that should pulmonary arterial blood not be available, it is just as good to calculate the mixed venous inert gas levels. However, this requires an estimate or measurement of cardiac output so that the Fick principle can be used with measured arterial and expired inert gas values.
4. The inert gas concentrations are measured by gas chromatography. Details can be found elsewhere [3, 22]. In brief, SF6 is measured by ECD (electron capture detector) while the other five gases are measured by FID (flame ionization detector). Stainless-steel (1/8th in., 6–12 ft long) columns packed with Poropak-T 80/100 mesh are used to separate the gases, which are eluted in a total of 4–5 min isothermally at about 150°C at a carrier flow rate (FID: helium; ECD: N_2) of around 30 ml/min. A constant-volume (1–2 ml) gas sample valve is used to introduce samples into the column. Mixed expired gas from the subject is directly injected into the chromatograph, but inert gases in blood samples must first be extracted by equilibrating the blood sample with N_2 gas in a closed syringe [3], and then introducing that gas to the chromatograph. Through principles of mass conservation, the original blood concentrations (prior to N_2 equilibration) can then be calculated if the partition coefficients of the gases and the volumes of blood and gas in the syringe are measured. It is recommended that the partition coefficients of all six gases be measured in each subject. This is done by (a) equilibrating a sample of the inert gases between blood and N_2 in a closed syringe, (b) measuring their levels in that N_2, (c) repeating the equilibration process with a fresh sample of N_2, and (d) measuring the new, equilibrated, inert gas levels in the N_2. The ratio of the inert gas concentrations from the two successive equilibrations reflects, and is thus used to calculate, the partition coefficient [3]. While these measurements by chromatography are not difficult, they are undeniably painstaking and must be done with great care and accuracy.
5. The inert gas concentrations and partition coefficients together with ancillary data (arterial/mixed venous blood gases, ventilation, cardiac output, inspired gas, acid/base status, and temperature conditions) are then read into the MIGET software. This software consists of two programs that are run in sequence. The first program simply takes all of the input data, computes the retention and excretion values for the sample, and creates an input data file for the second program, which reads those data and performs the least-squares analysis to come up with the $\dot{V}A/\dot{Q}$ distributions and their associated summary parameters mentioned above. It also computes the arterial PO_2 and PCO_2 expected to result from the $\dot{V}A/\dot{Q}$ inequality estimated from the inert gases, and, if requested, will compute the O_2 diffusing capacity when measured arterial PO_2 is less than that estimated from $\dot{V}A/\dot{Q}$ inequality. The two programs could easily be merged into one, but great value is seen in looking at the data produced by the first program for obvious problems before submitting them to the second program.

Conclusions: what does the future hold for MIGET?

MIGET was initially developed in the early 1970s. It remains in use in a small number of centers around the world, but the flurry of research in its first 20 years has subsided as many of the key questions it was able to shed light on have been answered. It has never evolved from a research tool to a clinical test for two reasons: First, because of its operational complexity. However, some attempts are currently under way to simplify the method and make it usable by the non-expert. Second, it provides more information than we can currently use clinically in patient management and therefore is difficult to justify.

That said, there is one key domain in which MIGET has not yet been rigorously evaluated as a clinical monitoring tool: the intensive care unit. In this setting, patients have often rapidly evolving lung disease, and extrapulmonary factors such as ventilation, FIO_2, cardiac output, hemoglobin concentration, acid/base status, and body temperature can all change quickly. We all have experiences with, or know of, patients with pre-existing heart and lung disease undergoing unrelated surgery and having a difficult recovery. Post-operative atelectasis and/or lung infection causing a shunt and low $\dot{V}A/\dot{Q}$ regions; use of PEEP causing high $\dot{V}A/\dot{Q}$ regions; post-operative bleeding reducing hemoglobin concentration; worsening cardiac function reducing cardiac output; fever; and the need to elevate and frequently change FIO_2 are all common problems in this situation, and MIGET has the capability of separating and quantifying the effects on arterial PO_2 of every one of these phenomena. Separating what is evolving lung disease from the effects of changes in extrapulmonary variables could have great clinical value, yet this is difficult to do using simpler, conventional tools. It would be useful to design and implement a clinical

trial of MIGET as an evaluative tool guiding therapy in the ICU to answer the question of whether the large amount of information MIGET provides would lead to more rational therapy and thereby improve morbidity or mortality. While this would require substantial effort, it would help to answer the question of whether such detailed physiological information was of clinical value in critically ill patients who have multiple abnormalities with complex interactions that together determine arterial oxygenation.

References

1. West JB (2008) Pulmonary pathophysiology – the essentials. Lippincott Williams & Wilkins, Baltimore
2. Wagner PD, Saltzman HA, West JB (1974) Measurement of continuous distributions of ventilation–perfusion ratios: theory. J Appl Physiol 36:588–599
3. Wagner PD, Naumann PF, Laravuso RB (1974) Simultaneous measurement of eight foreign gases in blood by gas chromatography. J Appl Physiol 36:600–605
4. Wagner PD, Laravuso RB, Uhl RR, West JB (1974) Continuous distributions of ventilation–perfusion ratios in normal subjects breathing air and 100% O_2. J Clin Invest 54:54–68
5. Evans JW, Wagner PD (1977) Limits on VA/Q distributions from analysis of experimental inert gas elimination. J Appl Physiol 42:889–898
6. Rahn H, Fenn WO (1955) A graphical analysis of the respiratory gas exchange. American Physiological Society, Washington, DC
7. Riley RL, Cournand A (1949) "Ideal" alveolar air and the analysis of ventilation/perfusion relationships in the lung. J Appl Physiol 1:825–847
8. Riley RL, Cournand A (1951) Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: theory. J Appl Physiol 4:77–101
9. Briscoe WA (1959) A method for dealing with data concerning uneven ventilation of the lung and its effects on blood gas transfer. J Appl Physiol 14:291–298
10. King TKC, Briscoe WA (1967) Bohr integral isopleths in the study of blood gas exchange in the lung. J Appl Physiol 22:659–674
11. Kety SS (1951) The theory and applications of the exchange of inert gas at the lungs and tissues. Pharmacol Rev 3:1–41
12. Farhi LE (1967) Elimination of inert gas by the lungs. Respir Physiol 3:1–11
13. Yokoyama T, Farhi LE (1967) The study of ventilation/perfusion ratio distribution in the anesthetized dog by multiple inert gas washout. Respir Physiol 3:166–176
14. Lenfant C (1963) Measurement of ventilation/perfusion distribution with alveolar-arterial differences. J Appl Physiol 18:1090–1094
15. Lenfant C, Okubo T (1968) Distribution function of pulmonary blood flow and ventilation/perfusion ratio in man. J Appl Physiol 24:668–677
16. Wagner PD (1977) A general approach to evaluation of ventilation/perfusion ratios in normal and abnormal lungs. Physiologist 20:18–25
17. Wagner PD (1981) Estimation of distributions of ventilation/perfusion ratios. Ann Biomed Eng 9:543–556
18. Wagner PD (1982) Calculation of the distribution of ventilation/perfusion ratios from inert gas elimination data. Fed Proc 41:136–139
19. Hammond MD, Hempleman SC (1987) Oxygen diffusing capacity estimates derived from measured VA/Q distributions in man. Respir Physiol 69:129–147
20. West JB (1969) Ventilation/perfusion inequality and overall gas exchange in computer models of the lung. Respir Physiol 7:88–110
21. Young I, Mazzone RW, Wagner PD (1980) Identification of functional lung unit in the dog by graded vascular embolization. J Appl Physiol Respirat Environ Exercise Physiol 49:132–141
22. Wagner PD, López FA (1984) Gas chromatography techniques in respiratory physiology. In: Otis AB (ed) Techniques in the life sciences. Elsevier Ireland, Co Clare, Ireland, pp 403/1–403/24

Enrico Calzia
Peter Radermacher

Alveolar ventilation and pulmonary blood flow: the $\dot{V}_A/\dot{Q}$ concept

Given a stable cardiac output (CO) and inspiratory oxygen concentration (F_{IO_2}), any gas exchange abnormality leading to hypoxia or hypercapnia may be explained solely on the basis of an altered distribution of the ventilation and perfusion ($\dot{V}_A/\dot{Q}$) regardless of the underlying disease [1].

1. The alveolus is the functional unit of the lung

The alveolus and the surrounding capillaries represent the functional lung gas exchange unit. Diffusive gas transport across the alveolar–capillary membrane is very rapid [2]. Even under pathologic conditions gas exchange at the alveolar level is *not* limited by diffusion across the gas–blood barrier, but mainly by the interplay between gas transport to (and from) the alveolar space (ventilation, $\dot{V}_A$) and blood flow across the alveolar capillaries (perfusion, $\dot{Q}$). End-capillary gas partial pressures exactly reflect alveolar gas composition. Therefore, since arterial blood is the sum of the blood from each alveolar region and the blood that bypasses the alveolar compartments (i.e., shunt), the gas composition in each alveolus will determine the arterial blood gas values in direct dependence on both ventilation and perfusion. In lung regions where ventilation exceeds perfusion, the alveolar gas partial pressures will approach the inspired ones. In contrast, if perfusion exceeds ventilation, the alveolar gas composition will more closely resemble the composition of mixed venous blood. Consequently, at a $\dot{V}_A/\dot{Q}$ ratio near unity, O_2 and CO_2 gas exchange is optimally balanced. Since alveoli with such an optimal $\dot{V}_A/\dot{Q}$ ratio are the main contributors to the achievement of "normal" arterial blood gas values they are called "ideal" alveoli. At $\dot{V}_A/\dot{Q}$ ratios exceeding the ideal value the gas composition of each alveolus will approach that of inspired gas, at lower $\dot{V}_A/\dot{Q}$ ratios that of mixed venous blood. In reality, the $\dot{V}_A/\dot{Q}$ ratio is slightly less than unity, because the respiratory quotient, which is the ratio of O_2 absorbed to CO_2 excreted, is usually less than unity.

2. Graphic analysis of pulmonary gas exchange: the P_{O_2}-P_{CO_2} diagram

The effects of a ventilation–perfusion mismatch on gas exchange are graphically described by the P_{O_2}–P_{CO_2} diagram first introduced by Rahn and Farhi (Fig. 1) [3]. Since the P_{O_2} and P_{CO_2} in each alveolus is determined by the $\dot{V}_A/\dot{Q}$ ratio, a line through all P_{O_2}–P_{CO_2} value pairs can be drawn connecting two endpoints of mixed venous blood and inspired gas composition. Each point on this line represents $\dot{V}_A/\dot{Q}$ values from 0 (representing perfused but not ventilated alveoli, thus corresponding to shunt areas) to ∞ (representing ventilated but not perfused alveoli, thus corresponding to dead space). Theoretically, the most efficient gas exchange should be expected in a perfectly homogeneous lung, with an overall $\dot{V}_A/\dot{Q}$ value near unity. However, even in healthy subjects a limitation in gas exchange is imposed by the inhomo-

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_9, © Springer-Verlag Berlin Heidelberg 2009

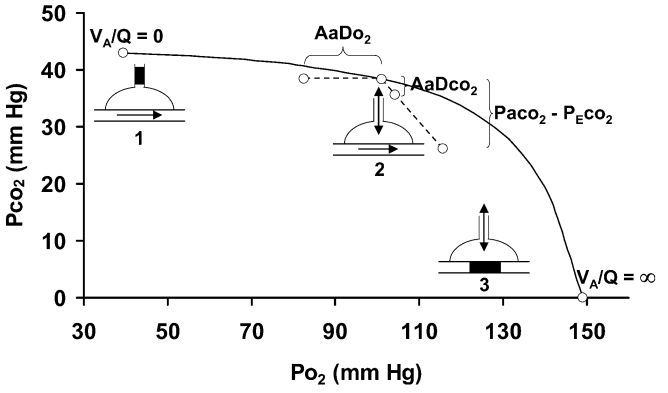


Fig. 1 The P_{O_2}-P_{CO_2} diagram of Rahn and Farhi graphically explains the theoretical concepts of ventilation/perfusion distribution and pulmonary gas exchange. (From [13], with permission)

geneous distribution of the $\dot{V}_A/\dot{Q}$ values, mainly as a result of gravitational forces. In normal physiologic states, however, this inhomogeneity is fairly moderate, but it substantially increases with disease.

3. $\dot{V}_A/\dot{Q}$ mismatch is quantified by the three-compartment model of ideal alveoli, shunt, and dead space

Assuming a perfectly homogeneous $\dot{V}_A/\dot{Q}$ distribution and no shunt, alveolar (=end capillary) and arterial gas partial pressures should be equal. Consequently, any alveolar-to-arterial P_{O_2} or P_{CO_2} differences reflect inhomogeneous $\dot{V}_A/\dot{Q}$ distribution and are used to quantify the $\dot{V}_A/\dot{Q}$ mismatch. Conceptually, as suggested by Riley and Cournand [4], alveolar gas exchange can be simplified to occurring within three types of alveoli: those with matched $\dot{V}_A/\dot{Q}$ (ideal), those with no $\dot{Q}$ (dead space), and those with no $\dot{V}_A$ (shunt). This "three-compartment" simplification is attractive because it allows one to quantify gas exchange abnormalities by the proportion of gas exchange units in each compartment.

Although "ideal" alveolar zones contribute to minimizing alveolar-to-arterial differences, blood from shunt perfusion zones joins blood coming from alveolar regions with gas values identical to mixed venous ones, thus increasing both alveolar-to-arterial O_2 differences and arterial CO_2 levels. An unappreciated result of increased shunt fraction is the increase in arterial P_{CO_2} as mixed venous CO_2 passes the alveoli and mixes with the arterial blood. Based on these considerations, the amount of right-to-left shunt can be derived from the calculated gas content in capillary, arterial, and mixed venous blood using the equation

$$Q_s/Q_t = (CcO_2 - CaO_2)/(CcO_2 - CvO_2) \quad (1)$$

where Q_s/Q_t=shunt fraction or venous admixture, CaO_2=arterial blood O_2 content, CcO_2=end-capillary O_2 content, and CvO_2=mixed venous blood O_2 content.

Since capillary O_2 content cannot be measured directly, it is assumed to equal ideal alveolar O_2 content ($C_{AI}O_2$), which is estimated by the ideal alveolar O_2 partial pressure ($P_{AI}O_2$) obtained by the simplified alveolar gas equation

$$P_{AI}O_2 = P_iO_2 - (PaCO_2/RQ) \quad (2)$$

where $P_{AI}O_2$="ideal" alveolar O_2 partial pressure, P_IO_2=inspired O_2 partial pressure, $PaCO_2$=arterial blood CO_2 partial pressure, and RQ=respiratory quotient.

The accuracy of these formulas is limited by mainly three factors. First, the calculation of CcO_2 from $P_{AI}O_2$ assumes equilibration of alveolar and end-capillary gas and ignores the impact that changes in pH and P_{CO_2} may have on gas exchange. Second, although $PaCO_2$ is presumed to equal $P_{AI}CO_2$, this assumption is incorrect when shunt causes P_{CO_2} to increase more than $P_{AI}CO_2$. And finally, the respiratory exchange ratio (RQ) is assumed to be 0.8, but may actually vary between 1.0 and 0.7 based on metabolic activity and diet. Despite these limitations, however, these formulae are remarkably accurate, allowing the estimation of right-to-left shunt in the clinical setting.

In contrast to shunts, gas exchange abnormalities due to increased dead space ventilation result in partial exclusion of inspired gas from gas exchange. Thus, expired gas partial pressures are maintained closer to the inspired ones. Commonly, the dead space fraction is calculated by the Bohr equation

$$V_D/V_T = (PaCO_2 - P_ECO_2)/PaCO_2 \quad (3)$$

where V_D/V_T=dead space fraction, $PaCO_2$=arterial blood CO_2 partial pressure, and P_ECO_2=mid-expired CO_2 partial pressure.

Although this three-compartment model is useful in calculating shunt and dead space, clearly, gas exchange units can have local ventilation to perfusion ratios anywhere from 0 to ∞, and not just 0, 1, and ∞. However, the three-compartment model forces parts of the lung to be in one of these three compartments. Under normal resting conditions, this assumption is not so far off of reality, because most alveolar regions are characterized by $\dot{V}_A/\dot{Q}$-values between 1 and 0.8, or very near 0 and ∞ respectively. Experimentally, one may measure the exact $\dot{V}_A/\dot{Q}$ distribution of the entire lung using the multiple inert gas technique. However, the utility of this approach to bedside assessment of gas exchange abnormalities is low because of its impracticality.

4. Hypoxia and hypercapnia are caused by severe $\dot{V}_A/\dot{Q}$ mismatching

Both oxygenation and CO_2 homeostasis may be considerably impaired by $\dot{V}_A/\dot{Q}$ mismatch, although usually only hypoxia is referred to as the result of increased venous admixture, while hypercapnia is generally considered the result of increased dead space ventilation or hypoventilation. However, if minute ventilation is fixed, as is the case during controlled ventilation, then increasing shunt fraction will cause hypercarbia. In the awake, spontaneously breathing subject, CO_2 elimination may be sufficiently maintained through chemoreceptor feedback even in the presence of low $\dot{V}_A/\dot{Q}$ alveoli, so that arterial CO_2 remains normal. In contrast, due to the narrow limits imposed by hemoglobin O_2 saturation, blood O_2 content cannot be increased by hyperventilation, and is therefore more susceptible to be decreased by increasing venous admixture. Obviously, however, substantial hypercapnia will also result from hugely increased venous admixture exceeding the limits of compensation, especially if venous admixture is almost completely caused by true shunt (e.g., atelectatic regions).

5. Clinical implications

Beneficial effects of different recommended recruitment and ventilation strategies for patients receiving mechanical ventilation are generally explained by their impact of ventilation to perfusion matching [5], even though the precise interplay between lung mechanics, hemodynamics, and $\dot{V}_A/\dot{Q}$ distribution is complex. Preventing alveolar collapse by the use of continuous positive airway pressure (CPAP) and positive end-expiratory pressure (PEEP) minimizes shunt, as do recruitment maneuvers, whereas vasodilator therapy, including aerosolized bronchodilator therapy, by increasing blood flow to potentially underventilated lung units increases shunt and arterial desaturation. This is the cause of hypoxemia following bronchodilator therapy in severe asthmatics. Pressure-limited ventilation and smaller tidal volume ventilation with attention paid to avoiding dynamic hyperinflation minimize dead space [6]. Prone positioning of the patient and interspacing spontaneous ventilatory efforts by causing diaphragmatic contraction improve $\dot{V}_A/\dot{Q}$ matching.

When one takes into account the effects of systemic blood flow on gas exchange, the interactions become more complex again. The interactions between intra- and extrapulmonary factors, such as changes in cardiac output, systemic oxygen uptake, and mixed venous O_2 saturation, can directly alter arterial oxygenation and CO_2 content independent of changes in $\dot{V}_A/\dot{Q}$. For example, although intravenous vasodilators usually increase intrapulmonary shunt in patients with adult respiratory distress syndrome or cardiogenic pulmonary edema, the associated increase in cardiac output, especially in the heart failure group, may offset the increased shunt by increasing mixed venous O_2 saturation [7]. Thus, the resultant change in arterial oxygenation cannot be predicted ahead of time [8]. Furthermore, some intravenous vasodilators may affect CO_2 elimination through several mechanisms. They may impair CO_2 elimination by increasing shunt fraction or increasing blood flow and CO_2 delivery to the lungs; also, if cardiac output does not increase in response of the intravenous administration of vasodilators, the intrathoracic blood volume may decrease, thus increasing the amount of hypoperfused areas especially in apical lung zones [9]. Giving vasodilators by inhalation should minimize shunt because only ventilated lung units will receive the vasodilating agent. Thus, inhalational vasodilating therapy should improve $\dot{V}_A/\dot{Q}$ matching. This has been shown to occur in patients with gas exchange abnormalities when treated with nitric oxide (NO) inhalation or aerosolized prostacyclin [10, 11]. The underlying pathology seems to be crucially important in regard to the effects on arterial oxygenation. While patients with adult respiratory distress syndrome or right heart failure improve their gas exchange, inhaled vasodilators may worsen arterial oxygenation by inhibiting hypoxic vasoconstriction in patients with chronic obstructive pulmonary disease, since $\dot{V}_A/\dot{Q}$ mismatch in hypoventilated areas rather than true shunt is the predominant cause of arterial hypoxemia in such cases [12].

References

1. Radermacher P, Cinotti L, Falke KJ (1988) Grundlagen der methodischen Erfassung von Ventilations/Perfusions-Verteilungsstörungen. Anaesthesist 37:36–42
2. Piiper J, Scheid P (1981) Model for capillary-alveolar equilibration with special reference to O_2 uptake in hypoxia. Respir Physiol 46:193–208
3. Fahri LE (1966) Ventilation-perfusion relationship and its role in alveolar gas exchange. In: Caro CG (ed) Advances in respiratory physiology. Arnold, London, pp 148–197
4. Riley RL, Cournand A (1951) Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs. 4:77–101
5. Pappert D, Rossaint R, Slama K, Grüning T, Falke KJ (1994) Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. Chest 106:1511–1516
6. Ralph DD, Robertson HT, Weaver NJ, Hlastala MP, Carrico CJ, Hudson LD (1985) Distribution of ventilation and perfusion during positive end-expiratory pressure in the adult respiratory distress syndrome. Am Rev Respir Dis 131:54–60

7. Rossaint R, Hahn SM, Pappert D, Falke KJ, Radermacher P (1995) Influence of mixed venous PO_2 and inspired O_2 fraction on intrapulmonary shunt in patients with severe ARDS. J Appl Physiol 78:1531–1536
8. Radermacher P, Santak B, Wüst HJ, Tarnow J, Falke KJ (1990) Prostacyclin for the treatment of pulmonary distress syndrome: effects on pulmonary capillary pressure and ventilation-perfusion distributions. Anesthesiology 72:238–244
9. Radermacher P, Huet Y, Pluskwa F, Hérigault R, Mal H, Teisseire B, Lemaire F (1988) Comparison of ketanserin and sodium nitroprusside in patients with severe ARDS. Anesthesiology 68:152–157
10. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM (1993) Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 328:399–405
11. Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W (1993) Aerosolised prostacyclin in adult respiratory distress syndrome. Lancet 342:961–962
12. Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB (1977) Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 59:203–216
13. Calzia E, Radermacher P (2002) Klinische Bedeutung von Ventilations/Perfusions-Beziehungen. In: Eckart J, Forst H, Burchardi H (eds) Intensivmedizin, vol 3. Ecomed, Landsberg, pp 17/1–17/8

Robert Rodríguez-Roisin
Josep Roca

Mechanisms of hypoxemia

This research was supported by the Red Respira-ISCIII-RTIC-03/11 and the Comissionat per a Universitats i Recerca de la Generalitat de Catalunya (2001 SGR00386). R.R.-R. holds a career scientist award from the Generalitat de Catalunya.

Introduction

A fundamental aspect of cardiopulmonary homeostasis is the adequate delivery of oxygen to meet the metabolic demands of the body. Cardiac output, O_2-carrying capacity (i.e., hemoglobin concentration and quality), and arterial PO_2 (PaO_2) determine O_2 transport. Relevant to this discussion, arterial hypoxemia commonly occurs in patients with acute respiratory failure (ARF). If arterial hypoxemia is severe enough, it is not compatible with life. The two primary causes of ARF are acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and chronic obstructive lung disease (COPD). Although the treatment for arterial hypoxemia always includes increases in the fractional inspired O_2 concentration (FIO_2), the degree to which patients' PaO_2 improves and the need for adjuvant therapies differ markedly between these two groups of disease processes. The mechanisms by which arterial hypoxemia occurs in ALI/ARDS and COPD have been characterized using the multiple inert gas elimination technique (MIGET) approach [1]. MIGET provides precise estimates of the distributions of alveolar ventilation and pulmonary perfusion (V_A/Q) and their relationships, there is no need to change the FIO_2 during measurements, hence avoiding variations in the pulmonary vascular tone, and it facilitates the unraveling of the active interplay between intrapulmonary, namely V_A/Q imbalance, intrapulmonary shunt and limitation of alveolar to end-capillary O_2 diffusion, and extrapulmonary (i.e., FIO_2, total ventilation, cardiac output and oxygen consumption) factors governing hypoxemia [2].

The cardinal gas exchange features under which the lung operates that uniquely determine the PO_2 and PCO_2 in each gas exchange unit of the lung are the V_A/Q ratio, the composition of the inspired gas, and the mixed venous blood gas composition [3]. Each of these three factors may play key role influencing oxygenation. For example, the major mechanism of arterial hypoxemia in ALI/ARDS is intrapulmonary shunt (zero V_A/Q ratios) induced by the presence of collapsed or flooded alveolar units, whereas in COPD the primary mechanism of hypoxemia is V_A/Q mismatching.

Effect of breathing oxygen on oxygenation

In ALI/ARDS, as FIO_2 increases, PaO_2 increases as long as the amount of shunt is limited. The greater the degree of shunt, the less PaO_2 increases. In contrast, in COPD, in which the prime mechanism of hypoxemia is V_A/Q mismatching, the response to high FIO_2 levels is broadly similar irrespective of disease severity. With moderate V_A/Q imbalance PaO_2 increases almost linearly as FIO_2 is increased. In severely acute COPD the degree of very low V_A/Q ratios resembles shunt; the increase in PaO_2 in response to increasing FIO_2 is only slightly limited, becoming less responsive to increases FIO_2.

Importantly, FIO_2 can also alter V_A/Q balance through two additional mechanisms: hypoxic pulmonary vasoconstriction (HPV) and reabsorption atelectasis (RA).

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_10, © Springer-Verlag Berlin Heidelberg 2009

One of the main means by which the normal lung adjusts to low regional V_A is to induce vasoconstriction of the associated pulmonary vasculature to redirect perfusion away from nonventilated or under ventilated alveolar units. Thus HPV minimizes V_A/Q inequality, limiting the decrease in PaO_2 that would have occurred if such redistribution of blood flow had not occurred. One of the best V_A/Q indicators of the presence of HPV, as measured by MIGET, is the behavior of the area with normal and low V_A/Q ratios, reflected in the dispersion of pulmonary blood flow. In sequential measures one sees a significant increase in the latter V_A/Q descriptor while breathing 100% O_2. By contrast, shunt and the dispersion of alveolar ventilation that incorporates areas with normal and high V_A/Q ratios remain unchanged during HPV release.

Breathing 100% O_2 (FIO_2=1.0) can induce intrapulmonary shunt because lung units with low inspired V_A/Q ratios, termed "critical" V_A/Q ratios, can result in absent expired ventilation because all the inflated gas is absorbed. This results in alveolar denitrogenation, allowing complete gas resorption with atelectasis (RA) to develop spontaneously [4]. These critical V_A/Q units are dependent on the FIO_2, increasing both their potential area of collapse and rate of collapse considerably as FIO_2 approaches 1.0. Alternatively, these critical units may remain open despite increasing FIO_2 levels if functional residual capacity and tidal volume are increased, owing to alveolar interdependence. This is the rationale for using positive end-expiratory pressure (PEEP) and larger tidal volumes in patients with ALI/ARDS to prevent RA.

Both RA and HPV and can be observed, respectively, in the responses of patients with ALI/ARDS and COPD needing mechanical support who are given an FIO_2 of 1.0 [5] (Fig. 1). Intrapulmonary shunt increases moderately then remains stable for at least 30 min in ALI/ARDS patients given an FIO_2 of 1.0. In contrast, in COPD patients the dispersion of pulmonary blood flow, one of the most common V_A/Q indicators in COPD, further increases to an FIO_2 of 1.0 while the modest levels of intrapulmonary shunt remain unchanged, a response that strongly suggests HPV release. Both responses to pure O_2 breathing are accompanied with increases in PaO_2, which are much more prominent in patients with COPD.

The increase in intrapulmonary shunt in ALI/ARDS is likely due to RA. If cardiac output increases as part of the sympathetic response to arterial hypoxemia, one may also see a parallel increase in mixed venous PO_2 owing to increased O_2 delivery. This can offset the increased shunt fraction minimizing the decrease in PaO_2. The deleterious effects of RA on pulmonary gas exchange may be enhanced by the mechanical trigger imposed on peripheral airways by ventilator support. Indeed, the repeated opening and closing of distal airways and/or the overexpansion of closed alveolar units with abnormally high shear stresses may result in more inflammatory lung changes, aggravating the initial mechanical stress injury.

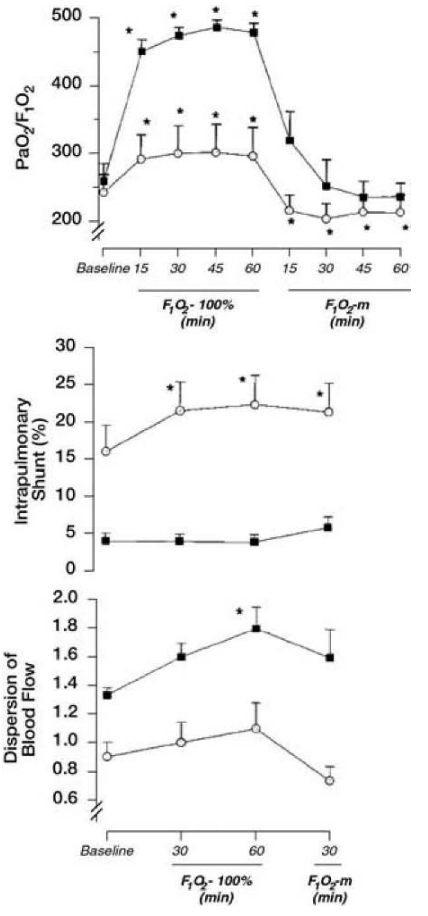


Fig. 1 Index of oxygenation (PaO_2/FIO_2), intrapulmonary shunt (expressed as percentage of cardiac output), and dispersion of pulmonary blood flow (log SDQ, dimensionless) while breathing 100% O_2. In ALI/ARDS (*open circles*) both PaO_2/FIO_2 and log SDQ remain essentially unchanged while shunt increases significantly, indicating RA; note that after reinstatement of maintenance FIO_2 shunt still remains increased. In COPD exacerbation (*closed squares*) PaO_2/FIO_2 and log SDQ substantially increase while the very modest shunt unvaried, indicating HPV release (by permission from [5])

On the other hand, the changes observed in COPD during hyperoxia suggest that inhibition of HPV is the primary process. Interestingly, gas exchange abnormalities in both entities take place in the absence of measurable changes in pulmonary hemodynamics, suggesting that regional blood flow redistribution can have relevant effects on gas exchange despite minimal changes in pulmonary arterial pressure and blood flow.

If V_A were to decrease or dead space to increase, arterial PCO_2 ($PaCO_2$) would increase. Hyperoxia-induced increases in $PaCO_2$ in response to FIO_2 1.0 breathing are more notable in ALI/ARDS than in COPD and can be attributed almost completely to the parallel increases in dead space, with a marginal role of the Haldane effect (i.e., decreasing PaO_2 increases $PaCO_2$ off-loading from

hemoglobin). Conceivably, the increased dead space indicates redistribution of pulmonary blood flow from high V_A/Q areas either to regions with no ventilated (shunt) alveolar units in ALI/ARDS or to those poorly ventilated with low V_A/Q areas in COPD. This process, however, has not been definitely characterized. An alternative and/or complementary mechanism in ALI/ARDS for the observed increase in $PaCO_2$ could be overexpansion of remaining normal lung zones provoked by RA, but in COPD by bronchodilation secondary to the hypercapnia.

Protective ventilator support

Protective ventilator support with low tidal volume and high PEEP levels has become the preferred approach to decrease the impact of ventilator-associated lung injury [6]. This protective support causes a substantial improvement in gas exchange by increasing PaO_2 and decreasing intrapulmonary shunt. However, this strategy of increased PEEP and small tidal volumes is often accompanied by hypercapnia. Hypercapnia induces both vasodilatation and increased cardiac output, both of which increase intrapulmonary shunt and potentially impair arterial oxygenation. The principal factor to explain the observed reduction in shunt in protective lung ventilation is the recruitment of previously collapsed alveoli, as shown by the close correlation between the decreased intrapulmonary shunt and the amount of PEEP-induced lung volume recruitment. Furthermore, the parallel increase in cardiac output caused by the hypercapnia-induced vasodilatation does not induce any proportional injurious increases in intrapulmonary shunt. Conceivably, the alveolar recruitment induced by recruitment efficiently redistributes pulmonary blood flow to regions with alveolar units with normal V_A/Q balance. A parallel finding in protective lung ventilation is the significant increase in physiological dead space, possibly related to the combined effects of a decreased alveolar ventilation and increased functional residual capacity. Thus the application of a protective ventilator support combining low tidal volumes and high PEEP levels represent a beneficial ventilator strategy in ALI/ARDS both in terms of minimizing lung stress and augmenting gas exchange.

Summary

The primary mechanisms leading to arterial hypoxemia in ARF secondary to COPD exacerbations and ALI/ARDS are V_A/Q imbalance and intrapulmonary shunt while the conditions that uniquely determine the PO_2 and PCO_2 in gas exchange units of the lung are the V_A/Q ratio and the composition of inspired gas and mixed venous blood. This is why the extrapulmonary factors governing hypoxemia, i.e., FIO_2, total ventilation, cardiac output, and O_2 consumption, always need to be considered. The increase in intrapulmonary shunt characteristically shown in ALI/ARDS patients breathing high FIO_2 levels is secondary to the development of RA, whereas in COPD patients it is usually due to withdrawal of HPV, reflected by further V_A/Q worsening only without parallel increases in intrapulmonary shunt.

References

1. Glenny R, Wagner PD, Roca J, Rodriguez-Roisin R (2000) Gas exchange in health: rest, exercise, and aging. In: Roca J, Rodriguez-Roisin R, Wagner PD (eds) Pulmonary and peripheral gas exchange in health and disease. Dekker, New York, pp 121–148
2. Rodriguez-Roisin R, Wagner PD (1990) Clinical relevance of ventilation-perfusion inequality determined by inert gas elimination. Eur Respir J 3:469–482
3. West JB (1977) State of the art: Ventilation-perfusion relationships. Am Rev Respir Dis 116:919–943
4. Dantzker DR, Wagner PD, West JB (1975) Instability of lung units with low V_A/Q ratios during O_2 breathing. J Appl Physiol 38:886–895
5. Santos C, Ferrer M, Roca J, Torres A, Hernandez C, Rodriguez-Roisin R (2000) Pulmonary gas exchange response to oxygen breathing in acute lung injury. Am J Respir Crit Care Med 161:26–31
6. Mancini M, Zavala E, Mancebo J, Fernandez C, Barbera JA, Rossi A, Roca J, Rodriguez-Roisin R (2001) Mechanisms of pulmonary gas exchange improvement during a protective ventilatory strategy in acute respiratory distress syndrome. Am J Respir Crit Care Med 164: 1448–1453

Amal Jubran

Pulse oximetry

Introduction

Continuous monitoring of arterial blood saturation using pulse oximetry has become the standard of care in the ICU. With the proliferation of pulse oximeters, episodic hypoxemia is detected much more commonly than previously suspected. By alerting the clinician to the presence of hypoxemia, pulse oximeters can lead to a more rapid treatment of serious hypoxemia and possibly avoid serious complication. Moreover, pulse oximetry can reduce arterial blood gas analysis and potentially decrease health care costs [1].

Principles of pulse oximetry

Pulse oximeters determine oxygen (O_2) saturation by measuring light absorption of arterial blood at two specific wavelengths, 660 nm (red) and 940 nm (infrared) [2]. The ratio of absorbencies at the wavelengths is then calibrated empirically against direct measurements of arterial blood oxygen saturation (SaO_2), and the resulting calibration curve is used to generate the pulse oximeter's estimate of arterial saturation (SpO_2). In addition to the digital read-out of O_2 saturation, most pulse oximeters display a plethysmographic waveform, which can help clinicians distinguish an artifactual signal from the true signal (Fig. 1).

The accuracy of commercially available oximeters in critically ill patients has been validated in several studies [3]. Compared with the measurement standard (multi-wavelength CO oximeter), pulse oximeters have a mean difference (bias) of less than 1% and a standard deviation (precision) of less than 2% when SaO_2 is 90% or above [4]. While pulse oximetry is accurate in reflecting one-point measurements of SaO_2, it does not reliably predict changes in SaO_2 [4]. Moreover, the accuracy of pulse oximeters deteriorates when SaO_2 falls to 80% or less. In critically ill patients, poor agreement between the oximeter and a CO oximeter has been observed, with bias the

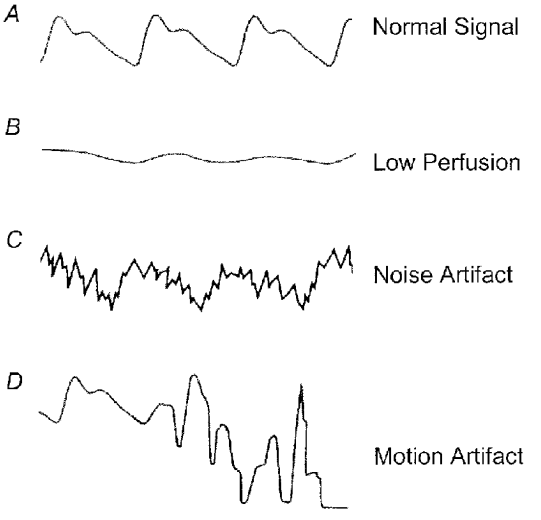


Fig. 1 Common pulsatile signals on a pulse oximeter. *Top panel* Normal signal showing the sharp waveform with a clear dicrotic notch. *Second panel* Pulsatile signal during low perfusion showing a typical sine wave. *Third panel* Pulsatile signal with superimposed noise artifact giving a jagged appearance. *Lowest panel* Pulsatile signal during motion artifact showing an erratic waveform. (From [1])

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_11, © Springer-Verlag Berlin Heidelberg 2009

ranging from −12% to 18%, and oximetry tends systematically to underestimate SaO_2 when it is 80% or less.

Limitations of pulse oximetry

Oximeters have a number of limitations which may lead to inaccurate readings [1]; these are presented below.

Physiological limitations

Oxyhemoglobin dissociation curve

Pulse oximeters measure SaO_2, which is physiologically related to arterial oxygen tension (PaO_2) according to the oxyhemoglobin dissociation curve. Because the dissociation curve has a sigmoid shape, oximetry is relatively insensitive in detecting the development of hypoxemia in patients with high baseline levels of PaO_2.

Limitation in the signal processing

Ambient light

Although pulse oximeters correct for ambient light, falsely low SpO_2 readings have been reported with fluorescent and xenon arc surgical lamps. Wrapping the probe with an opaque shield can minimize this effect.

Low perfusion

Pulse oximetry depends on satisfactory arterial perfusion of the skin, and thus low cardiac output, vasoconstriction, or hypothermia can make it difficult for a sensor to distinguish the true signal from background noise. In cardiac surgery patients experiencing hypothermia and poor perfusion, only 2 of 20 oximeters (Criticare CSI 503, Datex Satlite) provide measurements within ±4% of the CO oximeter value.

Motion artifact

The occurrence of motion artifacts continues to be a significant source of error and false alarms. In 235 surgical patients managed in the ICU, 67% of pulse oximeter alarms were false [5]. An innovative technological approach, termed Masimo signal extraction technology, was introduced to extract the true signal from artifact due to noise and low perfusion. When tested in 50 postoperative patients, the pulse oximeter's alarm frequency was decreased twofold with the new system vs. a conventional oximeter. When tested under conditions of low perfusion and motion, the ability to track changes in SpO_2 and reduce nuisance alarms was improved with this technology [3].

Interference from substances

Dyshemoglobins

Pulse oximeters employ only two wavelengths of light and thus can distinguish only two substances, oxyhemoglobin and reduced hemoglobin. Accordingly, elevated carboxyhemoglobin and methemoglobin levels can cause inaccurate oximetry readings [1].

Intravenous dyes

Intravenous dyes such as methylene blue, indocyanine green, and indigo carmine can cause falsely low SpO_2 readings, an effect that persists for up to 20 min.

Skin pigmentation and other pigments

Inaccurate oximetry readings have been observed in pigmented patients. In critically ill patients, a bias of more than 4% has been observed to occur more frequently in black (27%) than in white patients (11%). Nail polish, if blue, green, or black, causes inaccurate SpO_2 readings; however, mounting the oximeter probe sideways alleviates the problem with nail polish. Acrylic nails do not interfere with readings.

Limited knowledge of technique

Many users have only a limited understanding of pulse oximetry. One survey revealed that 30% of physicians and 93% of nurses thought that the oximeter measured PaO_2. A more recent audit demonstrated that less than 50% of nurses and physicians were able to identify that motion artifact, arrhythmias, and nail polish can affect the accuracy of pulse oximeter [6].

Clinical applications

Detection of hypoxemia

With the introduction of pulse oximetry hypoxemia (defined as an SpO_2 value less than 90%) is detected more often in critically ill patients. Moreover, myocardial ischemia (defined as angina or ST segment depression) in postoperative patients is less common in patients monitored with pulse oximetry than those without oximetry [7].

Assessing pulmonary gas exchange

Pulse oximeters measure SaO_2, which is physiologically related to PaO_2. In critically ill patients receiving mechanical ventilation, changes in SpO_2 may not accurately reflect changes in PaO_2 and may in fact be in an opposite direction to the change in PO_2. Decisions in therapy made on the basis of SpO_2 alone can also differ from those based on PO_2. Accordingly, caution is required when making decisions in critically ill patients based solely on pulse oximetry. While pulse oximetry is a suitable way of measuring arterial oxygenation, it does not assess ventilation. Indeed, measurements of SpO_2 have been shown to be inaccurate in assessing abnormal pulmonary gas exchange, defined as an elevated alveolar-arterial O_2 difference [1].

Titration of fractional inspired oxygen concentration

Pulse oximetry can assist with titration of fractional inspired oxygen concentration (FIO_2) in ventilator-dependent patients, although the appropriate SpO_2 target depends on a patient's pigmentation. In white patients, an SpO_2 target value of 92% predicts a satisfactory level of oxygenation, whereas black patients required an SpO_2 target of 95%. In patients with severe acute respiratory distress syndrome, an SpO_2 target of 88–90% is acceptable in order to minimize oxygen toxicity.

Blood pressure measurements

In pulse oximeters that display a pulsatile waveform, systolic blood pressure can be measured by noting the reappearance of the pulsatile waveform during cuff deflation or the waveform disappearance during slow cuff inflation (Fig. 1). In healthy volunteers, good agreement (i.e., bias <1.0 mmHg) was obtained when the average of oximetry based-systolic pressure estimates at the disappearance and reappearance of the waveform were compared with Korotokoff sound pressures and noninvasive equipment blood pressures.

Cardiopulmonary arrest

The usefulness of pulse oximetry as part of the first-line resuscitation equipment at the site of a cardiopulmonary arrest was assessed in 20 patients [8]. A signal in which the pulse rate on the oximeter was correlated with the electrocardiogram or chest compression rate was observed in the three patients who suffered only a respiratory arrest and in only 4 of 17 patients who suffered a cardiac arrest. The physicians judged the pulse oximeter was to be of definite benefit in the management of 7 of 20 patients, 5 of whom survived.

Screening test for cardiopulmonary disease

The potential usefulness of pulse oximetry as a screening tool for cardiopulmonary disease that could supplement or supplant respiratory rate as a "pulmonary vital sign" was investigated in patients managed in the emergency department [9]. An inverse but weak relationship (correlation coefficient −0.16) was observed between SpO_2 and respiratory rate. Overall only one-third of patients with an SpO_2 value below 90% would exhibit an increase in respiratory rate. While pulse oximetry could be used as a screening tool for cardiopulmonary disease, there are no data to suggest that decisions based on SpO_2 improve outcome over decisions based on respiratory rate.

Screening for respiratory failure in asthma

Pulse oximetry has been evaluated as a means of screening for respiratory failure in patients with severe asthma [10]. Respiratory failure occurred in only 4% of the patients with an SaO_2 value higher than 92%. The investigators concluded that an SpO_2 higher than 92% in this setting suggests that respiratory failure is unlikely and therefore arterial blood gas measurements are unnecessary. Interestingly, this threshold value of 92% is the same target value that predicted reliably a satisfactory level of oxygenation during titration of FIO_2 in ventilator-dependent patients.

Pulmonary embolus

In patients with documented pulmonary embolism the room air SpO_2 level may be an important predictor of death; mortality was found in one study to be 2% in patients with pulse oximetry of 95% or higher vs. 20% with pulse oximetry less than 95% [11]. When the threshold value was prospectively evaluated in 119 patients, 10 of whom developed hospital complications, SpO_2 less than 95% had a sensitivity of 90%, specificity of 64%, and overall diagnostic accuracy of 67%. Although the number of patients with complications were low, these data suggest that pulse oximetry may be useful in predicting outcome in patients with pulmonary embolus.

In summary, pulse oximetry is probably one of the most important advances in respiratory monitoring. The major challenge facing pulse oximetry is whether this technology can be incorporated effectively into diagnostic and management algorithms that improve the efficiency of clinical management in the ICU.

References

1. Jubran A (1998) Pulse oximetry. In: Tobin MJ (ed) Principles and practice of intensive care monitoring. McGraw-Hill, New York, pp 261–287
2. Wukitisch MW, Peterson MT, Tobler DR, Pologe JA (1988) Pulse oximetry: analysis of theory, technology, and practice. J Clin Monit 4:290–301
3. Emergency Care Research Institute (2003) Next-generation pulse oximetry. Health Devices 32:49–103
4. Van de Louw A, Cracco C, Cerf C, Harf A, Duvaldestin P, Lemaire F, Brochard L (2001) Accuracy of pulse oximetry in the intensive care unit. Intensive Care Med 27:1606–1613
5. Lutter NO, Urankar S, Kroeber S (2002) False alarm rates of three third-generation pulse oximeters in PACU, ICU and IABP patients. Anesth Analg 94:S69–S75
6. Howell M (2002) Pulse oximetry: an audit of nursing and medical staff understanding. Br J Nurs 11:91–197
7. Moller JT, Pedersen T, Rasmussen LS, Jensen PF, Pedersen BD, Ravlo O, Rasmussen NH, Espersen K, Johannessen NW, Cooper JB (1993) Randomized evaluation of pulse oximetry in 20,802 patients. I. Design, demography, pulse oximetry failure rate and overall complication rate. Anesthesiology 78:436–444
8. Spitall MJ (1993) Evaluation of pulse oximetry during cardiopulmonary resuscitation. Anaesthesia 48:701–703
9. Mower WR, Sachs C, Nicklin EL, Safa P, Baraff LJ (1996) A comparison of pulse oximetry and respiratory rate in patient screening. Respir Med 90:593–599
10. Carruthers DM, Harrison BDW (1995) Arterial blood gas analysis or oxygen saturation in the assessment of acute asthma. Thorax 50:186–188
11. Kline JA, Hernandez-Nino J, Newgard CD, Cowles DN, Jackson RE, Courtney DM (2003) Use of pulse oximetry to predict in-hospital complications in normotensive patients with pulmonary embolism. Am J Med 115:203–208

Andreas Bacher

Effects of body temperature on blood gases

Abstract *Background:* Changes in body temperature have important impact on measurements of blood gases. In blood gas analyzers the samples are always kept constant at a temperature of exactly 37°C during the measurements, and therefore results are not correct if body temperature differs from 37°C. *Objective:* Lack of knowledge of the effects of body temperature on results of blood gas monitoring may lead to wrong and potentially harmful interpretations and decisions in the clinical setting. The following article elucidates alterations in monitoring of blood gases and oxyhemoglobin saturation (SO_2) that occur during changes in body temperature.

Keywords Blood gas monitoring · Oxyhemoglobin saturation · Hypothermia · Hyperthermia

Blood gas monitoring

Blood gases (oxygen and carbon dioxide) are usually reported as partial pressures (gas tensions) since according to Henry's law the partial pressure of a gas is proportional to its concentration at a given temperature and pressure. However, as temperature decreases, the solubility of oxygen and carbon dioxide in blood or any other fluid increases, which means that the relationship of partial pressure to the total content of oxygen or carbon dioxide in the fluid changes.

Carbon dioxide

If blood containing a given amount of carbon dioxide at a certain tension (PCO_2) at 37°C is cooled, with the possibility to equilibrate with air, the total content of CO_2 in this blood sample remains constant, whereas PCO_2 decreases due to the increased proportion of dissolved CO_2 at lower temperature. Since the PCO_2 of air or any inspired gas mixture is almost zero, no additional molecules of CO_2 diffuse into the blood. If a blood sample is rewarmed to 37°C in a blood gas analyzer under vacuum-sealed conditions, the previously increased dissolved proportion of CO_2 again contributes to PCO_2. The measured PCO_2 of this blood sample is the same as at 37°C.

Hypothermia reduces the metabolic rate and the rate of CO_2 production. To hold the arterial CO_2 content constant during cooling it is necessary to reduce CO_2 elimination (i.e., by reducing minute ventilation in anesthetized patients) equivalently to the decrease in CO_2 production. If this is performed, arterial carbon dioxide tension ($PaCO_2$) measured in a blood gas analyzer at 37°C remains at the same level as during normothermia. Blood gas analyzers are usually equipped with algorithms that enable the true $PaCO_2$ to be calculated at the actual body temperature (Fig. 1) [1]. True $PaCO_2$ corrected for current body temperature is of course lower during hypothermia than the $PaCO_2$ value measured at 37°C. The difference between these two values corresponds to the increase in CO_2 solubility during cooling. The concept of CO_2 management in which the PCO_2 obtained by measurement at 37°C is kept constant at 40 mmHg regardless of current body temperature is called alpha-stat. If the PCO_2 value corrected for current body temperature is held constant during cooling at the same level as during normothermia (37°C), the total amount of CO_2 increases during hypothermia because of the constant $PaCO_2$ and the increased proportion of CO_2 that is soluble in blood. In this case

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_12, © Springer-Verlag Berlin Heidelberg 2009

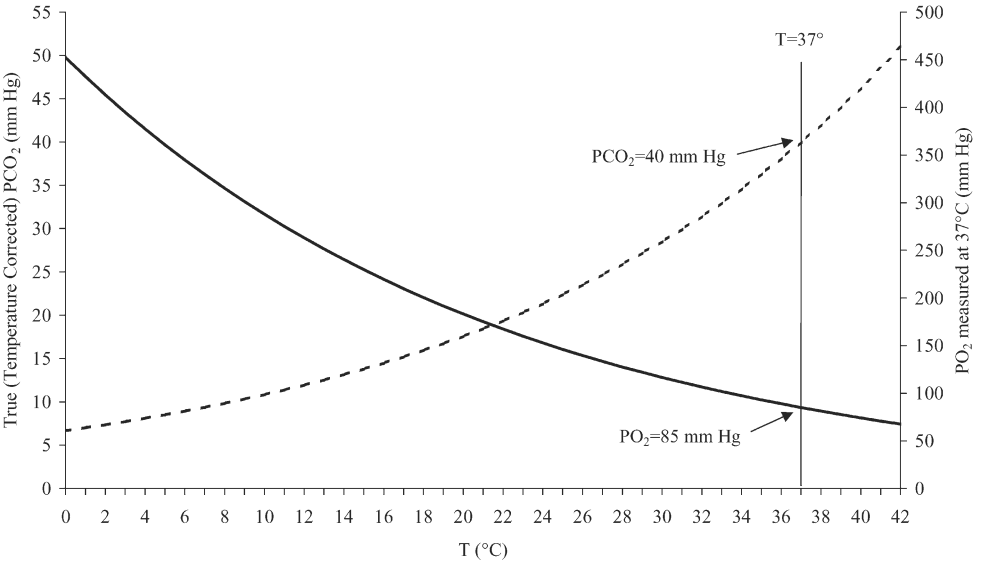


Fig. 1 *Dashed line* True (temperature corrected) PCO_2 during changes in body temperature. PCO_2 measured at 37°C remains constant at 40 mmHg. *Solid line* PO_2 measured at 37°C during changes in body temperature. True (temperature corrected) PO_2 remains constant at 85 mmHg

CO_2 elimination is not only reduced by the amount of decreased CO_2 production but additionally by the increased amount of CO_2 dissolved in blood during hypothermia. The latter concept of CO_2 management is called pH-stat.

pH

pH varies with CO_2 during variations in body temperature. If alpha-stat CO_2 management is applied, pH that is not corrected for current body temperature remains constant. True pH increases since true $PaCO_2$ has decreased during hypothermia. If pH-stat CO_2 management is applied, both true $PaCO_2$ and true pH remain constant during cooling, and pH that is not corrected for current body temperature decreases. The amount of true pH change resulting from a change in body temperature may be calculated as follows: $pH_T=pH_{37}-[0.0146+0.0065 (pH_{37}-7.4)](T-37)$, where pH_T is true pH at current body temperature, pH_{37} is pH at 37°C, and T is current body temperature (°C).

Oxygen

The effects of temperature changes on oxygen tension (PO_2) differ markedly from those on PCO_2. The principal effect that hypothermia leads to increased solubility of O_2 in blood is the same as for CO_2. Therefore during hypothermia one could expect a lower PO_2 for a given amount of oxygen. However, in contrast to CO_2, the oxygen content of room air or any inspired gas mixture and of alveolar gas is never zero. The PO_2 of room air at standard atmospheric pressure (patm) of 760 mmHg is approximately 159 mmHg. If an increased amount of O_2 molecules dissolve in blood during cooling, PO_2 does not decrease as does PCO_2 because O_2 from the environment and from alveolar gas diffuse into blood, and the PO_2 values equilibrate between these two compartments. The O_2 content in blood thus thereby increases. This schematic model is in fact representative of that which occurs in the alveoli and capillaries of the lungs. If we take a blood sample at hypothermia and put it into a blood gas analyzer, this sample is rewarmed to 37°C under vacuum-sealed conditions. The previously increased proportion of dissolved O_2 then contributes to PO_2, which thereby increases. Thus PO_2 values that are not corrected for current body temperature are higher than during normothermia (Fig. 1) [1]. Temperature-corrected PO_2 is equal to the values obtained during normothermia.

The clinical relevance of these effects is clear: Whenever we measure arterial oxygen tension (PaO_2) and do not correct these values for current (hypothermic) body temperature, true PaO_2 does not increase during cooling, but the observed increase in measured PaO_2 is due only to the fact that body temperature and the temperature at which the sample is analyzed differ. Considering that the gradient between PaO_2 and cellular (mitochondrial) PO_2 is the driving force that maintains normal O_2 extraction by the tissue, it would be a mistake to adapt inspired oxygen fraction (FIO_2) to the uncorrected, apparently high values of PaO_2 obtained during hypothermia. To maintain true PaO_2 in the normal range the measured PaO_2 should always be corrected for current body temperature in hypothermic patients.

Apart from the effects of increased O_2 solubility there is another effect that slightly affects PaO_2 during hypothermia. Since PaO_2 is related to the alveolar oxygen tension (PAO_2), true PaO_2 might indeed increase a very

Table 1 An example of changes in blood gases during alpha-stat and pH-stat regimens as body temperature (*BT*) decreases from 37°C to 30°C

	BT 37°C		BT 30°C
Alpha-stat			
PCO_2 (mmHg)	40	After rewarming to 37°C in blood gas analyzer	40
		True value (corrected):	29
PO_2 (mmHg)	85	After rewarming to 37°C in blood gas analyzer	117
		True value (corrected)	85
pH	7.40	After rewarming to 37°C in blood gas analyzer	7.40
		True value (corrected)	7.50
pH-stat			
PCO_2 (mmHg)	40	After rewarming to 37°C in blood gas analyzer	40
		True value (corrected)	56
PO_2 (mmHg)	85	After rewarming to 37°C in blood gas analyzer	117
		True value (corrected):	85
pH	7.40	After rewarming to 37°C in blood gas analyzer	7.30
		True value (corrected)	7.40

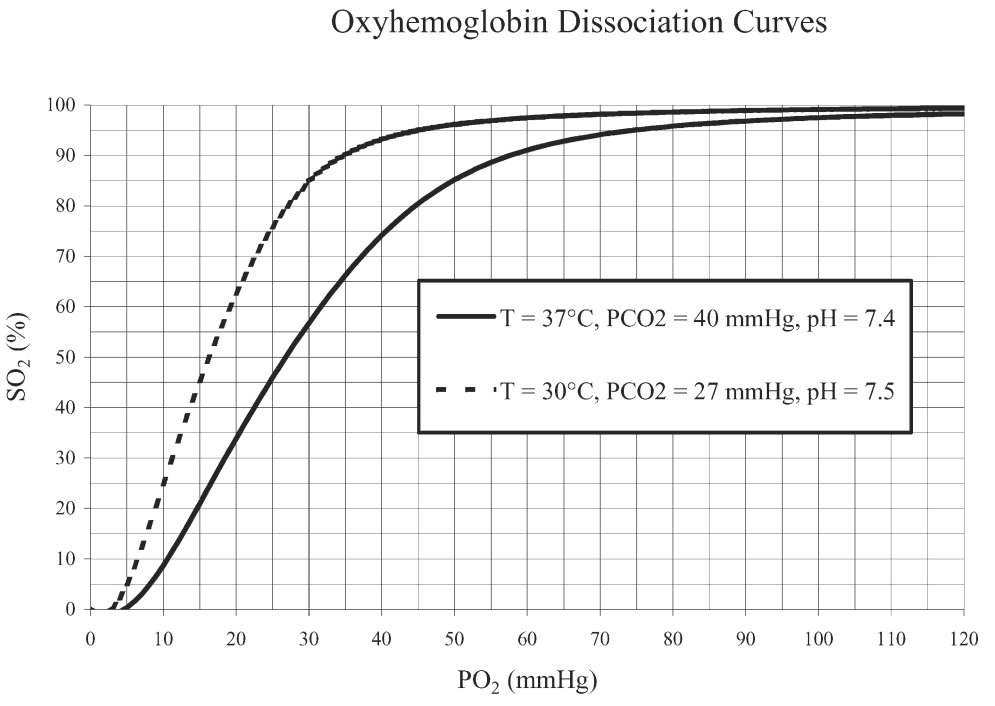


Fig. 2 Leftward shift of the oxyhemoglobin dissociation curve caused by hypothermia. Temperature (*T*) is 30°C for the *dotted curve*. The true carbon dioxide tension (PCO_2) of 27 mmHg and pH of 7.5 at 30°C correspond to a PCO_2 of 40 mmHg and pH of 7.4 at 37°C. Oxyhemoglobin saturation $(SO_2)=100(a_1PO_2+a_2PO_2^2+a_3PO_2^3+PO_2^4)/(a_4+a_5PO_2+a_6PO_2^2+a_7PO_2^3+PO_2^4)$. The seven coefficients (a_1–a_7) were determined by a least-squares fitting of the equation to paired values of PO_2 and SO_2 (a_1=−8532.2289, a_2=2121.4010, a_3=−67.073989, a_4=935960.87, a_5=−31346.258, a_6=2396.1674, a_7=−67.104406). Oxygen tension is measured at current conditions of pH, PCO_2, and T. Then it must be converted into a PO_2 that would be obtained at a pH of 7.40, a PCO_2 of 40 mmHg, and T of 37°C. The equation to convert the actual PO_2 to this virtual PO_2 is: $[PO_2 \text{ virtual}]=[PO_2 \text{ actual}]\times 10^{0.0024\ (37-T)+0.40\ (pH-7.40)+0.06[\log 10\ (40)-\log 10\ (PCO2)]}$. Then the equation for the standard oxyhemoglobin dissociation curve is again applied to predict actual SO_2

small amount during moderate hypothermia if pulmonary gas exchange conditions and the gradient between PaO_2 and PAO_2 ($aADO_2$) remain constant. PAO_2 depends on FIO_2, patm, water vapor pressure (pH_2O), $PaCO_2$, and the respiratory quotient (RQ=CO_2 production rate/O_2 consumption rate). $PAO_2=FIO_2(patm-pH_2O)-PaCO_2\times RQ^{-1}$. Water vapor pressure decreases exponentially with a decrease in temperature. At 37°C pH_2O is approx. 47 mmHg, at 30°C approx. 31 mmHg, and at 15°C approx. 12 mmHg. At FIO_2 of 0.21, patm of 760 mmHg, $PaCO_2$ of 40 mmHg, and RQ of 0.8, PAO_2 is 99.7 mmHg at 37°C, 103.1 mmHg at 30°C, and 107.1 mmHg at 15°C. Table 1 illustrates changes in blood gases during alpha-stat and pH-stat regimens as body temperature decreases from 37°C to 30°C.

Effects of hypothermia on SO_2

Arterial (SaO_2), mixed venous (SvO_2), and jugular bulb ($SjvO_2$) oxyhemoglobin saturation are strongly affected by changes in body temperature. The curve of the relationship between SO_2 and PO_2, i.e., the oxyhemoglobin dissociation curve, is S-shaped. Hypothermia, a decrease in the intracellular concentration of 2,3-diphosphoglycerate in erythrocytes, a decrease in PCO_2, and an increase in pH cause a leftward shift of the oxyhemoglobin dissociation curve, which means that at a given PO_2 the SO_2 value is higher than under normal conditions. The corresponding SO_2 to a given PO_2 may be calculated with sufficient accuracy (Fig. 2) [2]. Due to the S-shape of the oxyhemoglobin dissociation curve changes in SO_2 caused by a leftward shift are more pronounced when PO_2 is in the medium range. Therefore hypothermia leads to an increase in SvO_2 and $SjvO_2$ rather than SaO_2 because normal SaO_2 is already close to 100%. Hypothermia inhibits oxygen release from hemoglobin in the capillaries (i.e., oxygen extraction) without providing any benefits with regard to increasing SaO_2. In other words, a much lower tissue PO_2 would be required to obtain the same degree of oxyhemoglobin desaturation in the capillary. The total amount of O_2 flow from the capillary to the cells and mitochondria would then decrease because the driving force of O_2 diffusion, i.e., the gradient between mitochondrial PO_2 and capillary or tissue PO_2 is reduced.

Oxygen consumption (VO_2) decreases during hypothermia. The relationship between cerebral VO_2 and temperature has been well investigated [3, 4]. This is determined by the factor Q10: Q10=cerebral VO_2 at Tx/cerebral VO_2 at Ty, whereTx–Ty=10°C. Q10 is not constant over the entire temperature range that is clinically possible [3, 4]. In dogs Q10 is approx. 2.2 when T=37–27°C, approx. 4.5 when T=27–14°C, and approx. 2.2 when T=13–7°C [3, 4]. Cerebral VO_2 at a given temperature may be calculated as follows: VO_2 at Ty= VO_2 at $Tx \times Q10^{(Ty-Tx)/10}$

Because hypothermia leads to a leftward shift of the oxyhemoglobin dissociation curve and to a decrease in VO_2, SvO_2 should significantly increase during cooling, particularly if O_2 delivery remains unchanged. This has in fact been found in hypothermic (32°C) patients under endogenous circulation, i.e., without the use of extracorporeal circulation [5].

In conclusion, variations in body temperature significantly affect the results of important and frequently used monitoring techniques in intensive care, anesthesia, and emergency medicine. The knowledge of physical and technical changes during hypothermia or hyperthermia is necessary to avoid pitfalls in monitoring of blood gases, SO_2, and $etCO_2$. Ignoring these effects may lead to harmful and incorrect conclusions derived from our measurements in the clinical setting as well as for scientific purposes.

References

1. Hansen D, Syben R, Vargas O, Spies C, Welte M (1999) The alveolar-arterial difference in oxygen tension increases with temperature-corrected determination during moderate hypothermia. Anesth Analg 88:538–542
2. Kelman GR (1966) Digital computer subroutine for the conversion of oxygen tension into saturation. J Appl Physiol 21:1375–1376
3. Michenfelder JD, Milde JH (1992) The effect of profound levels of hypothermia (below 14 degrees C) on canine cerebral metabolism. J Cereb Blood Flow Metab 12:877–880
4. Michenfelder JD, Milde JH (1991) The relationship among canine brain temperature, metabolism, and function during hypothermia. Anesthesiology 75:130–136
5. Bacher A, Illievich UM, Fitzgerald R, Ihra G, Spiss CK (1997) Changes in oxygenation variables during progressive hypothermia in anesthetized patients. J Neurosurg Anesthesiol 9:205–10

Frank Bloos
Konrad Reinhart

Venous oximetry

Introduction

The primary physiological task of the cardiovascular system is to deliver enough oxygen (O_2) to meet the metabolic demands of the body. Shock and tissue hypoxia occur when the cardiorespiratory system is unable to cover metabolic demand adequately. Sustained tissue hypoxia is one of the most important cofactors in the pathophysiology of organ dysfunction [1]. Therefore determining the adequacy of tissue oxygenation in critically ill patients is central to ascertain the health of the patient. Unfortunately, normal values in blood pressure, central venous pressure, heart rate, and blood gases do not rule out tissue hypoxia or imbalances between whole-body oxygen supply and demand [2]. This discrepancy has led to increased interest in more direct indicators of adequacy of tissue oxygenation such as mixed and central venous oxygen saturations. Pulmonary artery catheterization allows obtaining true mixed venous oxygen saturation (SvO_2) while measuring central venous oxygen saturation ($ScvO_2$) via central venous catheter reflects principally the degree of oxygen extraction from the brain and the upper part of the body. This brief review discusses the role and limitations of SvO_2 and $ScvO_2$ as indicators of the adequacy of tissue oxygenation.

Physiology of mixed venous and central venous oxygen saturation

O_2 delivery (DO_2) describes whole-body oxygen supply according to the following formula:

$$DO_2 = CO \times CaO_2 \tag{1}$$

where CO is cardiac output and CaO_2 is arterial oxygen content, which itself is the sum of oxygen bound to hemoglobin [product of hemoglobin concentration (Hb) and arterial O_2 saturation (SaO_2)] and physically dissolved oxygen [arterial PO_2 (PaO_2)]:

$$CaO_2 = (Hb \times 1.36 \times SaO_2) + (PaO_2 \times 0.0031) \tag{2}$$

Oxygen demand can be summarized in the whole-body oxygen consumption (VO_2), which is expressed mathematically by the Fick principle as the product of CO and arteriovenous O_2 content difference (CaO_2–CvO_2):

$$VO_2 = CO \times (CaO_2 - CvO_2) \tag{3}$$

where mixed venous O_2 content (CvO_2) is:

$$CvO_2 = (Hb \times 1.36 \times SvO_2) + (PvO_2 \times 0.0031) \tag{4}$$

Equation 3 may be transposed to:

$$CvO_2 = CaO_2 - \frac{VO_2}{CO} \tag{5}$$

As physically dissolved oxygen can be neglected, Eq. 5 may be written as:

$$Hb \times 1.36 \times SvO_2 \approx (Hb \times 1.36 \times SaO_2) - \frac{VO_2}{CO}$$
$$\Leftrightarrow SvO_2 \sim \frac{VO_2}{CO} \tag{6}$$

Equation 6 also demonstrates that SvO_2 is directly proportional to the ratio of VO_2 to CO. Thus SvO_2 reflects the relationship between whole-body O_2 consumption and cardiac output. Indeed, it has been shown that the SvO_2 is well correlated with the ratio of O_2 supply to demand [3].

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_13, © Springer-Verlag Berlin Heidelberg 2009

Pathophysiology of central or mixed venous O_2 saturation during shock

Usually VO_2 is independent of DO_2 since tissues can maintain O_2 needs by increasing O_2 extraction when DO_2 decreases. However, this mechanism has its limits. Below a so-called critical DO_2 compensatory increase in O_2 extraction is exhausted, and VO_2 becomes dependent on DO_2. In this case tissue hypoxia occurs, and a rise in serum lactate levels may be observed [4].

A decrease in SvO_2 and $ScvO_2$ represents an increased metabolic stress, because the O_2 demands of the body are not completely met by DO_2. The causes of a decreasing SvO_2 are multiple and reflect the forces operative in Eqs. 5 and 6. That is, either DO_2 does not increase in such a way to cover an increased VO_2, or DO_2 drops because of decrease in either arterial O_2 content, cardiac output, or both. Importantly, the normal cardiovascular response of increasing VO_2 is to increase O_2 extraction and cardiac output. Thus SvO_2 normally decreases during exercise despite increasing DO_2. Therefore a drop in SvO_2 or $ScvO_2$ does not necessarily mean that tissue hypoxia occurs. The magnitude of the decrease indicates the extent to which the physiological reserves are stressed (Table 1). Whereas in otherwise healthy individuals anaerobic metabolism may occur when SvO_2 drops below its normal value of 75% to 30–40% for a substantial period of time, patients with chronic heart failure may live with an SvO_2 in this low range without apparent tissue hypoxia, presumably because they have adapted to higher oxygen extraction. These patients can increase their VO_2 to a limited degree, however, because O_2 extraction is close to its limits as is cardiac output.

The cardiocirculatory system may be challenged by two different conditions. Firstly, a drop in DO_2 can be induced by anemia, hypoxia, hypovolemia, or heart failure. Secondly, fever, pain, stress etc. may also decrease SvO_2 or $ScvO_2$ by increasing whole-body VO_2 (Table 2)

Since central venous catheterization is commonly performed for a variety of reasons in critically ill patients, it would be useful if $ScvO_2$ could function as a surrogate for SvO_2. The central venous catheter sampling site usually resides in the superior vena cava. Thus central venous blood sampling reflects the venous blood of the upper body but neglects venous blood from the lower body (i.e., intra-abdominal organs). As presented in Fig. 1, venous O_2 saturations differ among several organ systems since they extract different amounts of O_2. $ScvO_2$ is usually less than SvO_2 by about 2–3% because the lower body extracts less O_2 than the upper body making inferior vena caval O_2 saturation higher. The primary cause of the lower O_2 extraction is that many of the vascular circuits that drain into the inferior vena cava use blood flow for nonoxidative phosphorylation needs (e.g., renal blood flow, portal flow, hepatic blood flow). However, SvO_2 and $ScvO_2$ change in parallel when the whole-body ratio of O_2 supply to demand is altered [5].

Table 1 Limits of mixed venous oxygen saturation

SvO_2 >75%	Normal extraction O_2 supply >O_2 demand
75% >SvO_2 >50%	Compensatory extraction Increasing O_2 demand or decreasing O_2 supply
50% >SvO_2 >30%	Exhaustion of extraction Beginning of lactic acidosis O_2 supply <O_2 demand
30% >SvO_2 >25%	Severe lactic acidosis
SvO_2 <25%	Cellular death

Table 2 Clinical conditions and their effects on O_2 delivery and O_2 consumption and on venous oximetry

Decrease in $ScvO_2$/SvO_2
O_2 consumption ↑
Stress
Pain
Hyperthermia
Shivering
O_2 delivery ↓
CaO_2 ↓ (anemia, hypoxia)
Cardiac output ↓
Increase in $ScvO_2$/SvO_2
O_2 delivery ↑
CaO_2 ↑
Cardiac output ↑
O_2 consumption ↓
Analgesia
Sedation
Mechanical ventilation
Hypothermia

The difference between the absolute value of $ScvO_2$ and SvO_2 changes under conditions of shock [6]. In septic shock $ScvO_2$ often exceeds SvO_2 by about 8% [7]. During cardiogenic or hypovolemic shock mesenteric and renal blood flow decreases followed by an increase in O_2 extraction in these organs. In septic shock regional O_2 consumption of the gastrointestinal tract and hence regional O_2 extraction increases despite elevated regional blood flows [8]. On the other hand, cerebral blood flow is maintained over some period in shock. This would cause a delayed drop of $ScvO_2$ in comparison to SvO_2, and the correlation between these two parameters would worsen. Some authors therefore argued that $ScvO_2$ cannot be used as surrogate for SvO_2 under conditions of circulatory shock [9].

However, changes in SvO_2 are closely mirrored by changes in $ScvO_2$ under experimental [10] and clinical conditions [7] despite a variable difference between these two variables. This may explain why Rivers et al. [11] were able to use $ScvO_2$ higher than 70% in addition to conventional hemodynamic parameters as therapeutic endpoint for hemodynamic resuscitation to improve outcome in patients with severe sepsis and septic shock. From a physiological point of view, SvO_2 monitoring for "early goal directed therapy" should provide similar re-

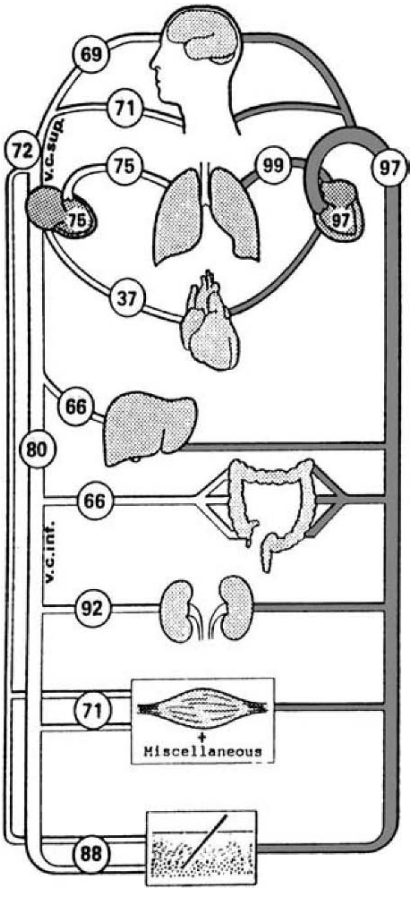


Fig. 1 Arterial and venous oxygen saturations in various vascular regions [2]

sults. Given the fact that $ScvO_2$ exceeds SvO_2 on average by 8% in patients with septic shock, an SvO_2 of about 62–65% should suffice as endpoint for hemodynamic resuscitation in these conditions, although this has not been tested prospectively. However, the placement of pulmonary artery catheters and the potentially higher risk of this should not result in a delay in the start of the resuscitation of critically ill patients.

Venous oximetry can reflect the adequacy of tissue oxygenation only if the tissue is still capable of extracting O_2. In the case of arteriovenous shunting on the microcirculatory level or cell death, SvO_2 and $ScvO_2$ may not decrease or even show elevated values despite severe tissue hypoxia. As demonstrated in patients after prolonged cardiac arrest, venous hyperoxia with an $ScvO_2$ higher than 80% is indicative of impaired oxygen use [12].

Conclusion

Low values of SvO_2 or $ScvO_2$ indicate a mismatch between O_2 delivery and tissue O_2 need. While measurement of SvO_2 requires the insertion of a pulmonary artery catheter, measurement of $ScvO_2$ requires only central venous catheterization. $ScvO_2$ directed early goal-directed therapy improves survival in patients with septic shock who are treated in an emergency department. However, $ScvO_2$ values may differ from SvO_2 values, and this difference varies in direction and magnitude with cardiovascular insufficiency. $ScvO_2$ should not be used alone in the assessment of the cardiocirculatory system but combined with other cardiocirculatory parameters and indicators of organ perfusion such as serum lactate concentration and urine output.

References

1. Marshall JC (2001) Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med 29:S99–S106
2. Reinhart K (1989) Monitoring O_2 transport and tissue oxygenation in critically ill patients. In: Reinhart K, Eyrich K (ed) Clinical aspects of O_2 transport and tissue oxygenation. Springer, Berlin Heidelberg New York, pp 195–211
3. Reinhart K, Schäfer M, Rudolph T, Specht M (1989) Mixed venous oxygen saturation. Appl Cardiopulm Pathophysiol 2:315–325
4. Vincent JL, De Backer D (2004) Oxygen transport-the oxygen delivery controversy. Intensive Care Med 30:1990–1996
5. Scheinman MM, Brown MA, Rapaport E (1969) Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. Circulation 40:165–172
6. Lee J, Wright F, Barber R, Stanley L (1972) Central venous oxygen saturation in shock: a study in man. Anesthesiology 36:472–478
7. Reinhart K, Kuhn HJ, Hartog C, Bredle DL (2004) Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. Intensive Care Med 30:1572–1578
8. Meier-Hellmann A, Specht M, Hannemann L, Hassel H, Bredle DL, Reinhart K (1996) Splanchnic blood flow is greater in septic shock treated with norepinephrine than in severe sepsis. Intensive Care Med 22:1354–1359
9. Edwards JD, Mayall RM (1998) Importance of the sampling site for measurement of mixed venous oxygen saturation in shock. Crit Care Med 26:1356–1360
10. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM (1989) Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. Chest 95:1216–1221
11. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
12. Rivers EP, Rady MY, Martin GB, Fenn NM, Smithline HA, Alexander ME, Nowak RM (1992) Venous hyperoxia after cardiac arrest. Characterization of a defect in systemic oxygen utilization. Chest 102:1787–1793

Jérôme Aboab
Bruno Louis
Bjorn Jonson
Laurent Brochard

Relation between PaO_2/F_IO_2 ratio and F_IO_2: a mathematical description

Introduction

The acute respiratory distress syndrome (ARDS) is characterized by severe hypoxemia, a cornerstone element in its definition. Numerous indices have been used to describe this hypoxemia, such as the arterial to alveolar O_2 difference, the intrapulmonary shunt fraction, the oxygen index and the PaO_2/F_IO_2 ratio. Of these different indices the PaO_2/F_IO_2 ratio has been adopted for routine use because of its simplicity. This ratio is included in most ARDS definitions, such as the Lung Injury Score [1] and in the American–European Consensus Conference Definition [2]. Ferguson et al. recently proposed a new definition including static respiratory system compliance and PaO_2/F_IO_2 measurement with PEEP set above 10 cmH_2O, but F_IO_2 was still not fixed [3]. Important for this discussion, the PaO_2/F_IO_2 ratio is influenced not only by ventilator settings and PEEP but also by F_IO_2. First, changes in F_IO_2 influence the intrapulmonary shunt fraction, which equals the true shunt plus ventilation–perfusion mismatching. At F_IO_2 1.0, the effects of ventilation–perfusion mismatch are eliminated and true intrapulmonary shunt is measured. Thus, the estimated shunt fraction may decrease as F_IO_2 increases if V/Q mismatch is a major component in inducing hypoxemia (e.g., chronic obstructive lung disease and asthma). Second, at an F_IO_2 of 1.0 absorption atelectasis may occur, increasing true shunt [4]. Thus, at high F_IO_2 levels (> 0.6) true shunt may progressively increase but be reversible by recruitment maneuvers. Third, because of the complex mathematical relationship between the oxy-hemoglobin dissociation curve, the arterio-venous O_2 difference, the $PaCO_2$ level and the hemoglobin level, the relation between PaO_2/F_IO_2 ratio and F_IO_2 is neither constant nor linear, even when shunt remains constant.

Gowda et al. [5] tried to determine the usefulness of indices of hypoxemia in ARDS patients. Using the 50-compartment model of ventilation–perfusion inhomogeneity plus true shunt and dead space, they varied the F_IO_2 between 0.21 and 1.0. Five indices of O_2 exchange efficiency were calculated (PaO_2/F_IO_2, venous admixture, $P(A\text{-}a)O_2$, PaO_2/alveolar PO_2, and the respiratory index). They described a curvilinear shape of the curve for PaO_2/F_IO_2 ratio as a function of F_IO_2, but PaO_2/F_IO_2 ratio exhibited the most stability at F_IO_2 values ≥ 0.5 and PaO_2 values ≤ 100 mmHg, and the authors concluded that PaO_2/F_IO_2 ratio was probably a useful estimation of the degree of gas exchange abnormality under usual clinical conditions. Whiteley et al. also described identical relation with other mathematical models [6, 7].

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_14,

This nonlinear relation between PaO_2/F_IO_2 and F_IO_2, however, underlines the limitations describing the intensity of hypoxemia using PaO_2/F_IO_2, and is thus of major importance for the clinician. The objective of this note is to describe the relation between PaO_2/F_IO_2 and F_IO_2 with a simple model, using the classic Berggren shunt equation and related calculation, and briefly illustrate the clinical consequences.

Berggren shunt equation (Equation 1)

The Berggren equation [8] is used to calculate the magnitude of intrapulmonary shunt (S), "comparing" the theoretical O_2 content of an "ideal" capillary with the actual arterial O_2 content and taking into account what comes into the lung capillary, i.e., the mixed venous content. $Cc'O_2$ is the capillary O_2 content in the ideal capillary, CaO_2 is the arterial O_2 content, and $C\bar{v}O_2$ is the mixed venous O_2 content,

$$S = \frac{\dot{Q}s}{\dot{Q}t} = \frac{(Cc'O_2 - CaO_2)}{(Cc'O_2 - C\bar{v}O_2)}$$

This equation can be written incorporating the arteriovenous difference (AVD) as:

$$Cc'O_2 - CaO_2 = \left(\frac{S}{1-S}\right) \times \text{AVD}.$$

Blood O_2 contents are calculated from PO_2 and hemoglobin concentrations as:

Equation of oxygen content (Equation 2)

$$CO_2 = (\text{Hb} \times SO_2 \times 1.34) + (PO_2 \times 0.0031)$$

The formula takes into account the two forms of oxygen carried in the blood, both that dissolved in the plasma and that bound to hemoglobin. Dissolved O_2 follows Henry's law – the amount of O_2 dissolved is proportional to its partial pressure. For each mmHg of PO_2 there is 0.003 ml O_2/dl dissolved in each 100 ml of blood. O_2 binding to hemoglobin is a function of the hemoglobin-carrying capacity that can vary with hemoglobinopathies and with fetal hemoglobin. In normal adults, however, each gram of hemoglobin can carry 1.34 ml of O_2. Deriving blood O_2 content allows calculation of both $Cc'O_2$ and CaO_2 and allows Eq. 1 to be rewritten as follows:

$$\begin{aligned}&\left[(\text{Hb} \times Sc'O_2 \times 1.34) + (Pc'O_2 \times 0.0031)\right]\\ &-\left[(\text{Hb} \times SaO_2 \times 1.34) + (PaO_2 \times 0.0031)\right]\\ &= \left(\frac{S}{1-S}\right) \times \text{AVD}\end{aligned}$$

In the ideal capillary (c'), the saturation is 1.0 and the $Pc'O_2$ is derived from the alveolar gas equation:

$$Pc'O_2 = PAO_2 = (P_B - 47) \times F_IO_2 - \frac{PaCO_2}{R}.$$

This equation describes the alveolar partial pressure of O_2 (PAO_2) as a function, on the one hand, of barometric pressure (P_B), from which is subtracted the water vapor pressure at full saturation of 47 mmHg, and F_IO_2, to get the inspired O_2 fraction reaching the alveoli, and on the other hand of $PaCO_2$ and the respiratory quotient (R) indicating the alveolar partial pressure of PCO_2. Saturation, $Sc'O_2$ and SaO_2 are bound with O_2 partial pressure (PO_2) $Pc'O_2$ and PaO_2, by the oxy-hemoglobin dissociation curve, respectively. The oxy-hemoglobin dissociation curve describes the relationship of the percentage of hemoglobin saturation to the blood PO_2. This relationship is sigmoid in shape and relates to the nonlinear relation between hemoglobin saturation and its conformational changes with PO_2. A simple, accurate equation for human blood O_2 dissociation computations was proposed by Severinghaus et al. [9]:

Blood O_2 dissociation curve equation (Equation 4)

$$SO_2 = \left(\left(\left(PO_2^3 + 150PO_2\right)^{-1} \times 23\,400\right) + 1\right)^{-1}$$

This equation can be introduced in Eq. 1:

$$\begin{aligned}&\left[\left(\text{Hb} \times \left(\left(\left(\left((P_B - 47) \times F_IO_2 - \frac{PaCO_2}{R}\right)^3\right.\right.\right.\right.\right.\\ &\left.\left.\left.\left.\left. + 150\left((P_B - 47) \times F_IO_2 - \frac{PaCO_2}{R}\right)\right)^{-1} \times 23\,400\right) + 1\right)^{-1} \times 1.34\right) + \left(\left((P_B - 47)\right.\right.\right.\\ &\left.\left.\left. \times F_IO_2 - \frac{PaCO_2}{R}\right) \times 0.0031\right)\right]\\ &-\left[\left(\text{Hb} \times \left(\left(\left(PaO_2^3 + 150PaO_2\right)^{-1} \times 23\,400\right)\right.\right.\right.\\ &\left.\left.\left. + 1\right)^{-1} \times 1.34\right) + (PaO_2 \times 0.0031)\right)\right]\\ &= \left(\frac{S}{1-S}\right) \times \text{AVD}\end{aligned}$$

Equation 1 modified gives a relation between F_IO_2 and PaO_2 with six fixed parameters: Hb, $PaCO_2$, the respiratory quotient R, the barometric pressure (P_B), S and AVD. The resolution of this equation was performed here with Mathcad® software, (Mathsoft Engineering & Education, Cambridge, MA, USA).

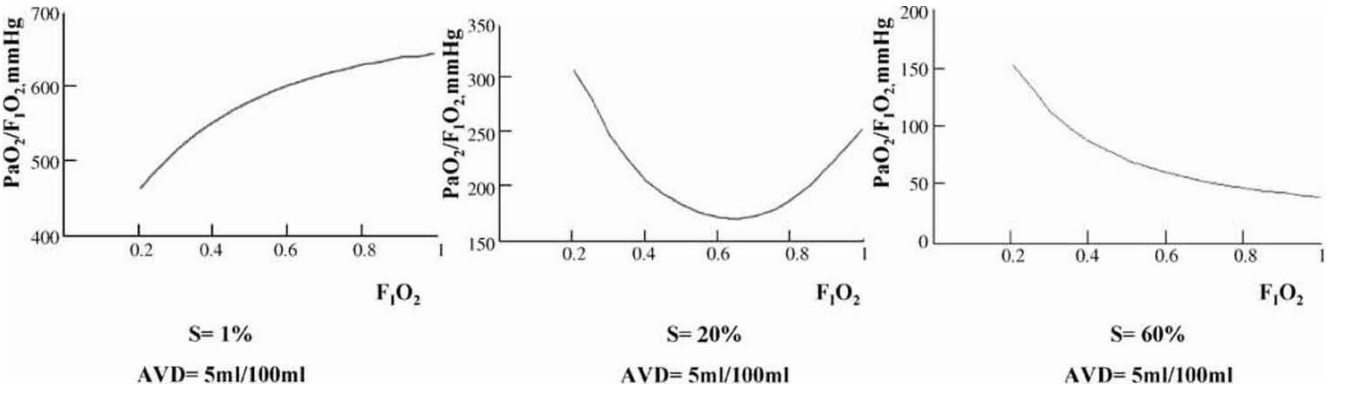


Fig. 1 Relation between PaO_2/FIO_2 and FIO_2 for a constant arterio-venous difference (*AVD*) and different shunt levels (*S*)

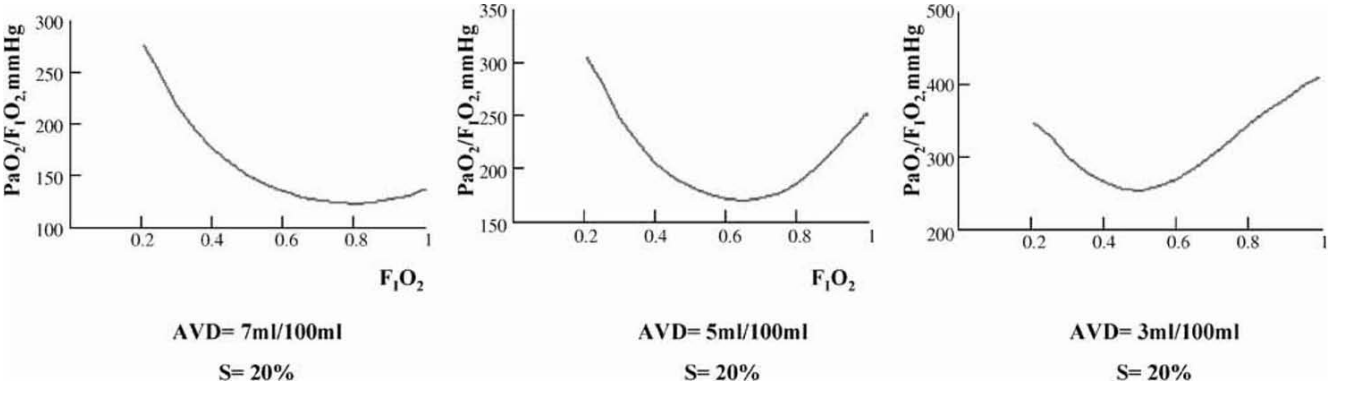


Fig. 2 Relation between PaO_2/FIO_2 and FIO_2 for a constant shunt (*S*) level and different values of arterio-venous differences (*AVD*)

Resolution of the equation

The equation results in a nonlinear relation between F_IO_2 and PaO_2/F_IO_2 ratio. As previously mentioned, numerous factors, notably nonpulmonary factors, influence this curve: intrapulmonary shunt, AVD, $PaCO_2$, respiratory quotient and hemoglobin. The relationship between PaO_2/F_IO_2 and F_IO_2 is illustrated in two situations. Figure 1 shows this relationship for different shunt fractions and a fixed AVD. For instance, in patients with 20% shunt (a frequent value observed in ARDS), the PaO_2/F_IO_2 ratio varies considerably with changes in F_IO_2. At both extremes of F_IO_2, the PaO_2/F_IO_2 is substantially greater than at intermediate F_IO_2. In contrast, at extremely high shunt ($\cong$ 60%) PaO_2/F_IO_2 ratio is greater at low F_IO_2 and decreases at intermediate F_IO_2, but does not exhibit any further increase as inspired F_IO_2 continue to increase, for instance above 0.7. Figure 2 shows the same relation but with various AVDs at a fixed shunt fraction. The larger is AVD, the lower is the PaO_2/F_IO_2 ratio for a given F_IO_2. AVD can vary substantially with cardiac output or with oxygen consumption.

These computations therefore illustrate substantial variation in the PaO_2/F_IO_2 index as F_IO_2 is modified under conditions of constant metabolism and ventilation–perfusion abnormality.

Consequences

This discussion and mathematical development is based on a mono-compartmental lung model and does not take into account dynamic phenomena, particularly when high F_IO_2 results in denitrogenation atelectasis. Despite this limitation, large nonlinear variation and important morphologic differences of PaO_2/F_IO_2 ratio curves vary markedly with intrapulmonary shunt fraction and AVD variation. Thus, not taking into account the variable relation between F_IO_2 and the PaO_2/F_IO_2 ratio could introduce serious errors in the diagnosis or monitoring of patients with hypoxemia on mechanical ventilation.

Recently, the accuracy of the American–European consensus ARDS definition was found to be only moderate when compared with the autopsy findings of diffuse alveolar damage in a series of 382 patients [10]. The problem discussed here with F_IO_2 may to some extent participate in these discrepancies. A study by Ferguson et al. [11] illustrated the clinical relevance of this dis-

cussion. They sampled arterial blood gases immediately after initiation of mechanical ventilation and 30 min after resetting the ventilator in 41 patients who had early ARDS based on the most standard definition [2]. The changes in ventilator settings chiefly consisted of increasing F_IO_2 to 1.0. In 17 patients (41%), the hypoxemia criterion for ARDS persisted after this change ($PaO_2/F_IO_2 < 200$ mmHg), while in the other 24 patients (58.5%) the PaO_2/F_IO_2 had become greater than 200 mmHg after changing the F_IO_2, essentially "curing" them of their ARDS in a few minutes. Of note, outcome varied greatly between the "persistent" and "transient" ARDS groups. There was a large difference in mortality, and duration of ventilation, favoring the "transient" ARDS group. Thus, varying F_IO_2 will alter the PaO_2/F_IO_2 ratio in patients with true and relative intrapulmonary shunt of $\geq 20\%$. In clinical practice, when dealing with patients with such shunt levels, one should know that the increasing PO_2/F_IO_2 with F_IO_2 occurs only after F_IO_2 increase to > 0.6 (depending on the AVD value). Thus, the use of the PO_2/F_IO_2 ratio as a dynamic variable should be used with caution if F_IO_2, as well as other ventilatory settings, varies greatly.

References

1. Murray J, Matthay MA, Luce J, Flick M (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720–723
2. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R (1994) The American–European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
3. Ferguson ND, Davis AM, Slutsky AS, Stewart TE (2005) Development of a clinical definition for acute respiratory distress syndrome using the Delphi technique. J Crit Care 20:147–154
4. Santos C, Ferrer M, Roca J, Torres A, Hernandez C, Rodriguez-Roisin R (2000) Pulmonary gas exchange response to oxygen breathing in acute lung injury. Am J Respir Crit Care Med 161:26–31
5. Gowda MS, Klocke RA (1997) Variability of indices of hypoxemia in adult respiratory distress syndrome. Crit Care Med 25:41–45
6. Whiteley JP, Gavaghan DJ, Hahn CE (2002) Variation of venous admixture, SF6 shunt, PaO_2, and the PaO_2/FIO_2 ratio with FIO_2. Br J Anaesth 88:771–778
7. Whiteley JP, Gavaghan DJ, Hahn CE (2002) Mathematical modelling of oxygen transport to tissue. J Math Biol 44:503–522
8. Berggren S (1942) The oxygen deficit of arterial blood caused by nonventilating parts of the lung. Acta Physiol Scand 11:1–92
9. Severinghaus J (1979) Simple, accurate equations for human blood O_2 dissociation computations. J Appl Physiol 46:599–602
10. Esteban A, Fernandez-Segoviano P, Frutos-Vivar F, Aramburu JA, Najera L, Ferguson ND, Alia I, Gordo F, Rios F (2004) Comparison of clinical criteria for the acute respiratory distress syndrome with autopsy findings. Ann Intern Med 141:440–445
11. Ferguson ND, Kacmarek RM, Chiche JD, Singh JM, Hallett DC, Mehta S, Stewart TE (2004) Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial. Intensive Care Med 30:1111–1116

Jukka Takala

Hypoxemia due to increased venous admixture: influence of cardiac output on oxygenation

Introduction

In the hypoxemic patient under mechanical ventilation, changes in cardiac output may influence the level of arterial oxygenation, with several and sometimes opposite effects. The purpose of this Physiological Note is to give the reader the physiological background to understand these effects, which are often highly relevant for the bedside management of patients with acute lung injury.

In the healthy lung, the venous blood returning to the right heart and flowing through the pulmonary artery to the pulmonary capillaries will be fully saturated by oxygen during the passage through the alveolar part of the capillary. The prerequisite for complete saturation of hemoglobin with oxygen is sufficiently high oxygen partial pressure in the alveoli. Complete saturation is approached if the alveolar partial pressure of oxygen exceeds 13.3 kPa (100 mmHg). This prerequisite is achieved during normoventilation of ambient air with normal lungs at the sea level. Hypoventilation (increased alveolar CO_2) and decrease in barometric pressure (increased altitude) both reduce the alveolar PO_2 – an effect which can be readily counteracted by increasing the inspired fraction of oxygen. The degree of hypoxemia in these circumstances can be predicted from the PO_2 of ideal alveolar gas and the oxyhemoglobin dissociation curve.

What does venous admixture measure?

Venous admixture is used to describe situations in which the oxygenation of the arterial blood is less than that expected for the pulmonary end-capillary blood (100%, if the alveolar partial pressure of oxygen exceeds 13.3 kPa). Venous admixture is the *calculated* amount of mixed venous blood needed to bypass the alveoli and mix with the arterial blood to produce the observed degree of arterial hypoxemia. In other words, venous admixture represents the *calculated* fraction of cardiac output completely bypassing oxygenation in the lung if the rest of the cardiac output is fully oxygenated (assumed to be the case in the absence of inspired gas hypoxia) [1]. A pulmonary artery catheter is necessary to obtain true mixed venous blood.

The venous admixture (Qs/Qt) can be calculated as

$$\mathrm{Qs/Qt} = (\mathrm{CcO_2} - \mathrm{CaO_2})/(\mathrm{CcO_2} - \mathrm{CvO_2}), \qquad (1)$$

where CcO_2 is the pulmonary venous capillary oxygen content in the ideal (i.e., normally ventilated and perfused) alveoli, and CaO_2 and CvO_2 are the arterial and mixed venous oxygen content, respectively. For the ideal alveoli, $CcO_2 = \mathrm{Hgb}$ (hemoglobin; g/l) $\times\ 1.34 + 0.2325 \times$ alveolar PO_2 (kPa), assuming 100% saturation of the pulmonary and capillary blood.

Apart from hypoventilation, increased venous admixture or physiologic intrapulmonary shunt is the most

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_15, © Springer-Verlag Berlin Heidelberg 2009

common cause of hypoxemia in critically ill patients. In this paper, "venous admixture" and "physiologic shunt" are used interchangeably. The term "physiologic shunt" should not be confused with the presence of slight venous admixture in the normal lungs (around or below 5%); the venous admixture in the normal lungs results from venous blood flow through the thebesian veins (cardiac venous effluent directly into the left heart) and the deep true bronchial veins (into the pulmonary veins), and from the presence of a small amount of ventilation/perfusion mismatch.

What causes increased venous admixture?

Venous admixture can be caused by true shunt (blood flow through alveoli that are not ventilated at all, i.e., alveoli with a ventilation/perfusion = 0), and by ventilation/perfusion mismatch (alveoli with a low ventilation/perfusion). For further information on the concept of ventilation/perfusion matching see the Physiological Note by Calzia and Radermacher [2]. In the non-ventilated alveoli, oxygen will be transported to the capillary blood until the alveolar PO_2 approaches the mixed venous PO_2. In the alveoli with low ventilation/perfusion, the amount of oxygen reaching the alveoli per unit of time is smaller than the amount needed to fully saturate the venous blood arriving at the alveolar capillary per unit of time. Hence, the alveolar PO_2 will decrease until the amount of oxygen reaching the alveoli through ventilation equals the amount transferred to the blood flowing through the alveoli (blood flow × arteriovenous oxygen content difference); the consequence of the low ventilation/perfusion is that only partly oxygenated blood will be mixed in the pulmonary venous blood. The calculation of venous admixture assumes that the mixed venous blood is either fully oxygenated or not oxygenated at all – hence, it cannot differentiate between true shunt and low ventilation/perfusion [3, 4]. It should be noted that hypoxemia due to diffusion problems also causes an increase in the calculated venous admixture, although no shunt or ventilation/perfusion mismatch would be present.

Venous admixture and interaction between mixed venous and arterial oxygenation

In the healthy lungs, arterial oxygenation is defined almost completely by the alveolar oxygen partial pressure. When venous admixture increases, mixed venous oxygenation will have a progressively larger impact on arterial oxygenation. This interaction can be interpreted using the Fick equation (Eq. 2) for oxygen consumption (VO_2) together with the equation for venous admixture (Eq. 1). The VO_2 can be calculated as the product of cardiac output (CO) and arterial-mixed venous oxygen content difference:

$$VO_2 = CO \times (CaO_2 - C\bar{v}O_2), \tag{2}$$

This can be rewritten as

$$C\bar{v}O_2 = CaO_2 - VO_2/CO, \tag{3}$$

or as

$$CaO_2 = C\bar{v}O_2 + VO_2/CO. \tag{3'}$$

The equation for venous admixture (Eq. 1) can be rearranged and written as

$$\begin{aligned} CaO_2 = {} & CcO_2 \times (1 - Qs/Qt) \\ & + C\bar{v}O_2 \times Qs/Qt. \end{aligned} \tag{4}$$

Equations 3 and 4 can be combined to

$$\begin{aligned} CaO_2 = {} & CcO_2 - (VO_2/CO) \\ & \times (Qs/Qt)/(1 - Qs/Qt) \end{aligned} \tag{5}$$

and Eqs. 3′ and 4 to

$$\begin{aligned} C\bar{v}O_2 = {} & CcO_2 - (VO_2/CO) \\ & \times [1 + (Qs/Qt)/(1 - Qs/Qt)]. \end{aligned} \tag{6}$$

If the dissolved oxygen is ignored, Eqs. 5 and 6 can be written as

$$\begin{aligned} SaO_2 = {} & 1 - (VO_2/CO \times Hgb \times 1.34) \\ & \times (Qs/Qt)/(1 - Qs/Qt), \end{aligned} \tag{5'}$$

$$\begin{aligned} SvO_2 = {} & 1 - (VO_2/CO \times Hgb \times 1.34) \\ & \times [1 + (Qs/Qt)/(1 - Qs/Qt)]. \end{aligned} \tag{6'}$$

Equations 5′ and 6′ demonstrate that in the presence of increased venous admixture, arterial oxygenation (SaO_2) is directly related to cardiac output and hemoglobin, and inversely related to oxygen consumption. The effect of these variables on arterial oxygenation will be markedly magnified in the presence of large Qs/Qt [5]. These equations can be applied to demonstrate the interactions between venous admixture, arterial and mixed venous oxygenation, cardiac output, hemoglobin and oxygen consumption (Figs. 1, 2).

Cardiac output and increased venous admixture

In the interactions between venous admixture, arterial oxygenation, and mixed venous oxygenation in the clinical setting, cardiac output has the largest variability. As shown in Fig. 1, an infinite number of arterial and mixed venous saturation lines form two concave surfaces, as a function of cardiac output and venous admixture. These surfaces slope progressively downwards when cardiac output decreases and the venous admixture increases. An increase in oxygen consumption and a decrease in

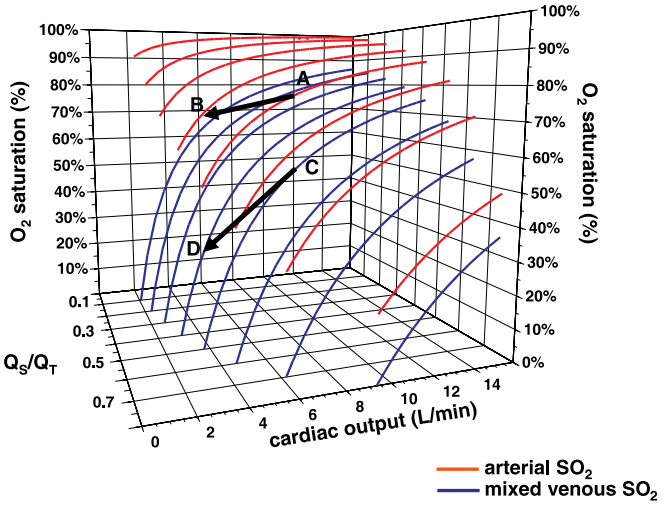


Fig. 1 The relationship between venous admixture (*Qs/Qt*), arterial and mixed venous saturation and cardiac output. For the calculations, dissolved oxygen has been ignored; a hemoglobin of 100 g/l and an oxygen consumption of 250 ml/min have been assumed. Points *A* and *B* represent the effect of cardiac output decreasing from 8 l/min to 4 l/min. The venous admixture is likely to decrease – in this case from 0.50 to 0.40. Since the decrease in cardiac output is accompanied by increased oxygen extraction, the mixed venous saturation decreases substantially (points *C* and *D*), and the net effect is worsened arterial hypoxemia

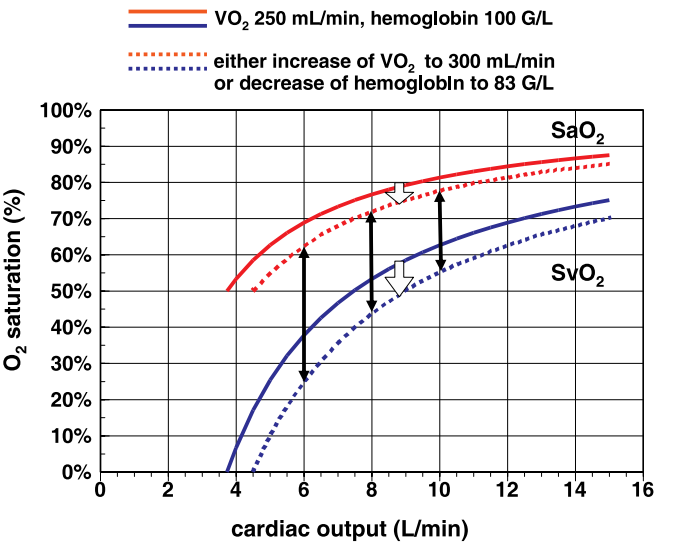


Fig. 2 Effect of oxygen consumption and hemoglobin on arterial (*red*) and mixed venous (*blue*) oxygenation. The *solid curves* are taken from Fig. 1 and represent a physiologic shunt of 50%. A similar proportional increase in oxygen consumption and decrease in hemoglobin have identical effects: in both cases the whole family of arterial (*red dotted line*) and mixed venous (*blue dotted line*) saturation curves shown in Fig. 1 shifts downwards (*open arrows*) and the arterial–venous saturation difference widens (*solid arrows*)

hemoglobin both move the surfaces down and increase the distance between them. This is shown for one pair of saturation lines at 50% physiologic shunt in Fig. 2. In order to maintain a given level of metabolic activity (250 ml/min of VO_2, hemoglobin 100 g/l in Fig. 1), the cardiac output has to increase if the venous admixture increases. Thus a cardiac output of approximately 4 l/min under the conditions shown in Fig. 2 (250 ml/min of VO_2, hemoglobin 100 g/l) would result in mixed venous saturation approaching zero – a situation incompatible with survival. Assuming that a mixed venous saturation of 40–50% could be tolerated in the acutely ill patient over a reasonable period of time, a minimum cardiac output of 6–7.5 l/min would be necessary. A higher metabolic activity or a lower hemoglobin (Fig. 2) would necessitate even higher levels of cardiac output. This example demonstrates the fundamental role of cardiac output in states with acute major increases in physiologic shunt, such as in severe acute respiratory distress syndrome (ARDS).

Acute changes in cardiac output are likely to cause parallel changes in physiologic shunt, which tend to counteract the changes imposed on arterial oxygenation [6, 7]: when cardiac output decreases, the physiologic shunt decreases as well. Decreased cardiac output reduces mixed venous oxygenation, and thereby also arterial oxygenation. Although the physiologic shunt is likely to decrease in parallel with cardiac output, the favorable effect of reduced shunt on arterial oxygenation is at least in part set off by the lower mixed venous oxygenation. Even if the venous admixture were to decrease enough to completely abolish the effect of a concomitant reduction of mixed venous oxygenation on arterial oxygenation, this would result in decrease in oxygen delivery to the tissues in proportion with the decrease in cardiac output. Conversely, if an acute increase in cardiac output increases the physiologic shunt enough to abolish the impact of an increased mixed venous oxygenation on arterial oxygenation, the oxygen delivery to the tissues will increase in proportion with the increase in cardiac output.

If an increase in cardiac output from 6.5 l/min to 9.5 l/min increases venous admixture from 40% to 50% while the hemoglobin and oxygen consumption remain unchanged, the arterial saturation remains unchanged (at around 81% in the example in Fig. 3), but the mixed venous saturation increases from 52% to 61% and the systemic oxygen delivery by 46%. In the clinical setting, the magnitude of individual responses in physiologic shunt to acute changes in cardiac output varies widely, although the directional changes are usually parallel. In contrast to deliberately induced increases in cardiac output, acute spontaneous increases in cardiac output are often accompanied by increased metabolic demand. As discussed before, an increase in oxygen consumption will shift the relationship between arterial and mixed venous saturation towards desaturation of both, and widen the arterio-venous oxygen content difference (Figs. 1, 2),

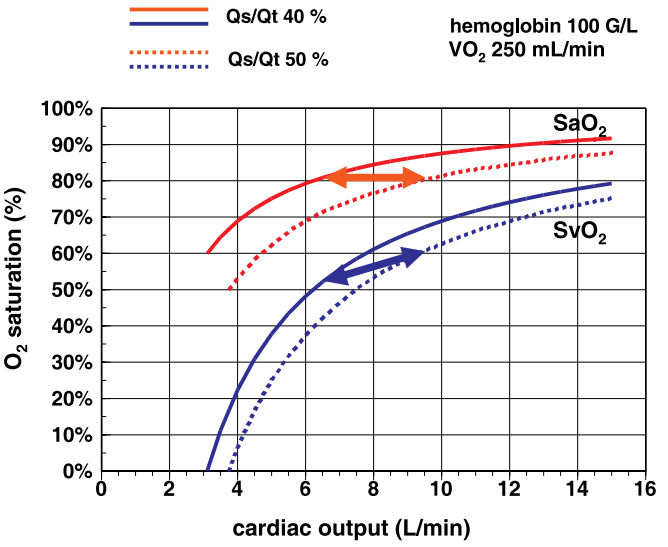


Fig. 3 Effect of an increase in cardiac output from 6.5 to 9.5 l/min and a simultaneous increase in physiologic shunt from 40% to 50% on arterial (*red arrow*) and mixed venous (*blue arrow*) oxygenation. The effect of increased physiologic shunt on arterial oxygenation is completely eliminated due to increased mixed venous saturation, and the whole body oxygen delivery is increased substantially (by 46%)

thereby reducing the positive effect of an increased cardiac output.

The mechanism by which cardiac output and the physiologic shunt change in parallel is not certain; the most likely explanation is that changes in mixed venous oxygenation alter the hypoxic pulmonary vasoconstriction [8]. This would also explain the intra- and interindividual variability in the changes in physiologic shunt in response to changes in cardiac output observed in the clinical setting: changes in local and circulating endo- and exogenous vasoactive substances in sepsis, acute lung injury/ARDS and shock may modify the hypoxic pulmonary vasoconstriction.

Implications for treatment of acute hypoxemia

Diverse pathologies increase the venous admixture, e.g., atelectasis, pulmonary edema of any etiology, and infections and inflammatory processes that reduce the ventilation/perfusion locally or regionally in the lung. The treatment strategy should aim at prompt correction of the cause. While this may be possible in atelectasis, in most other conditions prolonged support of oxygenation is likely to be necessary. Since atelectatic components are common in many situations in which hypoxemia is due to increased venous admixture, maneuvers to re-expand the atelectatic lung regions and to keep them open (recruitment, positive airway pressure, prone positioning) should be considered. When hypoxemia and increased physiologic shunt persist despite these maneuvers, it is advisable to consider the interaction of arterial and mixed venous oxygenation in the management of the hypoxemia. Typical therapeutic measures (increased positive end-expiratory and mean airway pressure) are likely to reduce cardiac output and mixed venous oxygenation. Hence, the cost of attempts to improve or maintain arterial oxygenation may be reduced oxygen delivery to the tissues. On the other hand, increased cardiac output, even if accompanied by increased venous admixture, may result in well-maintained arterial oxygenation and increased oxygen delivery. In addition, reducing oxygen consumption and increasing hemoglobin should be considered (Fig. 2). All these measures to increase mixed venous oxygenation may be worthwhile, especially in patients with low mixed venous saturation and large physiologic shunt.

References

1. Lumb AB (2000) Distribution of pulmonary ventilation and perfusion. In: Lumb AB (ed) Nunn's applied respiratory physiology, 5th edn. Butterworth-Heinemann, Oxford, UK, pp 163–199
2. Calzia E, Radermacher P (2003) Alveolar ventilation and pulmonary blood flow: the V(A)/Q concept. Intensive Care Med 29:1229–1232
3. Ratner ER, Wagner PD (1982) Resolution of the multiple inert gas method for estimating V_A/Q maldistribution. Respir Physiol 49:293–313
4. Siggaard-Anderson O, Gothgen IH (1995) Oxygen parameters of arterial and mixed venous blood—new and old. Acta Anaesthesiol Scand 39:41–46
5. Giovannini I, Boldrini G, Sganga G, Castiglioni G, Castagneto M (1983) Quantification of the determinants of arterial hypoxemia in critically ill patients. Crit Care Med 11:644–645
6. Dantzker DR, Lynch JP, Weg JG (1980) Depression of cardiac output is a mechanism of shunt reduction in the therapy of acute respiratory failure. Chest 77:636–642
7. Freden F, Cigarini I, Mannting F, Hagberg A, Lemaire F, Hedenstierna G (1993) Dependence of shunt on cardiac output in unilobar oleic acid edema: distribution of ventilation and perfusion. Intensive Care Med 19:185–90
8. Marshall BE, Hanson CW, Frasch F, Marshall C (1994) Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution. Basic science series: 2. Pathophysiology. Intensive Care Med 20:379–389

Robert Naeije

Pulmonary vascular resistance

A meaningless variable?

Introduction

Almost 20 years ago, Adriaan Versprille published an editorial in this journal to explain why, in his opinion, the calculation of pulmonary vascular resistance (PVR) is meaningless [1]. The uncertainties of PVR were underscored a year later by McGregor and Sniderman in the *American Journal of Cardiology* [2]. Obviously, both papers failed to convince. A Medline search from 1985 to the end of 2002 reveals no less than 7,158 papers with PVR calculations. What is it that could be wrong in all this literature?

What is a resistance calculation?

A resistance calculation derives from a physical law first developed by the French physiologist Poiseuille in the early nineteenth century. Poiseuille invented the U-tube mercury manometer. He used the device to show that blood pressure does not decrease from large to small arteries to the then existing limit of cannula size of about 2 mm, and rightly concluded that the site of systemic vascular resistance could only be at smaller-sized vessels [3]. Since he could not penetrate to these minute vessels, he used small size glass tubes to investigate the determinants of resistance. Numerous painstaking measurements of pressures at variable continuous streamlined flows of Newtonian and non-Newtonian fluids of different viscosities, through variable dimension capillary glass tubes, led to what is presently known as Poiseuille's law. It states that the resistance R to flow, defined as a pressure drop (ΔP) to flow (Q) ratio, is equal to the product of the length (l) of the tube by a viscosity constant (η) divided by the product of fourth power of the internal radius (r) by π:

$$R = \Delta P/Q = 8 \cdot 1 \cdot \eta/\pi \cdot r^4$$

A remarkable feature of Poiseuille's resistance equation is its exquisite sensibility to changes in internal radius r, because it is at the fourth power.

Transposition to the pulmonary circulation

The transposition of Poiseuille's law to the pulmonary circulation rests on the invalid assumptions that blood is a Newtonian fluid (that is with a velocity-independent viscosity), that the pulmonary resistive vessels are unbranched small rigid tubes of circular surface sections and that pulmonary blood flow is streamlined and non-pulsatile. But the approximations have less impact on calculated PVR values than the internal arteriolar radius, to which the Poiseuille's resistance variable is so sensitive. Accordingly, it is reasonable to calculate PVR as the ratio of the pressure drop through the pulmonary circulation [mean pulmonary artery pressure (Ppa) minus left atrial pressure (Pla)] to pulmonary blood flow (Q) using the electrical principles described as Ohm's law:

$$PVR = (Ppa - Pla)/Q$$

The resulting PVR value is a valid indicator of structural changes at the small resistive pulmonary arteriole level,

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_16, © Springer-Verlag Berlin Heidelberg 2009

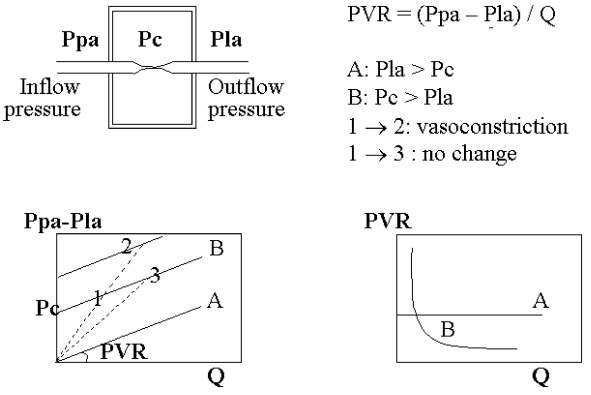


Fig. 1 Starling resistor model to explain the concept of closing pressure within a circulatory system. Flow (Q) is determined by the gradient between an inflow pressure, or mean pulmonary artery pressure (Ppa), and an outflow pressure which is either closing pressure (Pc) or left atrial pressure (Pla). When Pla is greater than Pc, the (Ppa–Pla)/Q relationship crosses the origin (A curve) and PVR is constant. When Pc is greater than Pla, the (Ppa–Pla)/Q relationship has a positive pressure intercept (B curve) and PVR decreases curvilinearly with increasing Q. Also shown are possible misleading PVR calculations: PVR, the slope of (Ppa–Pla)/Q may remain unchanged in the presence of a vasoconstriction (from 1 to 2) or decrease (from 1 to 3) with no change in the functional state of the pulmonary circulation (unchanged pressure/flow line)

which is the major site of most types of acute and chronic pulmonary hypertension states.

Pulmonary vascular pressure-flow relationships

However, PVR is flow-sensitive and this can be a source of confusion. The Ohm's law resistance equation of pressure drop divided by flow implies that the (inflow minus outflow) pressure difference as a function of flow is linear and crosses the origin. If correct, resistance would be independent of either flow or pressure (Fig. 1). A PVR calculation assumes that if one were to increase Ppa and examine the resultant Ppa/Q relationship, it would display an extrapolated pressure axis intercept at a value equal to Pla. This assumption appears valid in well-oxygenated healthy lungs. Accordingly, normal healthy lungs appear to be fully recruited and maximally distended. Also, in intact animal models, progressive decreases in pulmonary vascular pressures with their associated decreasing flow do not induce a systemic baroreflex, thus changes in pulmonary sympathetic vasomotor tone is constant over a wide range of pulmonary arterial pressures and flow. However, hypoxia and many cardiac and respiratory diseases increase both the slope (PVR) and the extrapolated intercepts of multipoint (Ppa–Pla)/Q plots. Importantly, these pulmonary vascular pressure-flow relations still tend to remain linear over a physiological range of flows [2].

How is it possible that the extrapolated pressure intercepts of (Ppa–Pla)/Q plots are positive, meaning that the apparent back-flow pressure for pulmonary blood flow exceeds Pla? A possible answer is that pulmonary vessels are collapsible. Consider a circulatory system made of two rigid tubes connected by a collapsible tube surrounded by a pressure chamber (Fig. 1). This model is called the "Starling resistor", because Starling used such a device in his heart-lung preparation to control arterial blood pressure. If the outflow pressure (Pla) is higher than the chamber pressure (Pc), then several aspects of the circulation exist. First, flow starts when the inflow pressure (Ppa) is higher than Pla and it increases linearly with the increase in the Ppa–Pla difference. Second, the (Ppa–Pla)/Q line crosses the origin. And third, PVR, the slope of the (Ppa–Pla)/Q relationship, is constant. If the Pc is higher than Pla, however, then flow starts when Ppa is higher than Pc, independent of the lower Pla value, and flow increases linearly with the increase in (Ppa–Pc). The Pc is also referred to as the closing pressure, because when intraluminal pressure decreases below Pc, the vessels collapse and flow ceases. Importantly, both the (Ppa–Pla)/Q line has a positive extrapolated intercept that is equal to Pla and PVR decreases with increasing flow. If either alveolar pressure or pulmonary vascular tone are increased enough to cause vascular collapse at values above Pla, then these conditions will also exist in vivo.

Permutt et al. conceived a vascular waterfall model made of parallel collapsible vessels with a distribution of closing pressures [4]. At low flow, these vessels would be progressively derecruited, accounting for a low flow Ppa/Q curve that is concave to the flow axis and intercepts the pressure axis at the lowest closing pressure to be overcome to generate a flow. At higher flows, completed recruitment and negligible distension account for a linear Ppa/Q curve with an extrapolated pressure intercept representing a weighted mean of all the parallel circuit Pc values. In this model, the mean Pc is the effective outflow pressure of the pulmonary circulation. A Pla lower than the mean Pc is then only an apparent downstream pressure, irrelevant to flow as is the height of a waterfall. Resistance calculations remain applicable to evaluate the functional state of the pulmonary circulation even in these conditions, provided that the apparent downstream pressure (Pla) is replaced by the effective one (Pc).

But pulmonary vessels are also distensible. Accordingly, pulmonary circulation models have been developed that explain Ppa/Q relationships by a distribution of both resistances and compliances [5]. Positive extrapolated pressure intercepts of (Ppa–Pla)/Q plots can be predicted by concomitant increases in resistance and compliance of small resistive vessels [6]. Intuitively, one would rather imagine constricted vessels to be stiffer. However, it has been shown experimentally that con-

stricted arterioles become more distensible, probably because decreased surface section area places them on the steeper portion of the dimension-pressure curve.

In reality, provided a large enough number of Ppa/Q coordinates are generated and submitted to an adequate fitting procedure, Ppa/Q curves can always be shown to be curvilinear with concavity to the flow axis [7]. On the other hand, derecruitment can be directly observed at low pressures and flows. Both recruitment and distension probably explain most of the Ppa/Q curves. According to this integrated view, at low inflow pressures many pulmonary vessels are closed as their intrinsic tone and surrounding alveolar pressure exceed intraluminal pressure and those that are open are relatively narrow. As inflow pressure increases, previously closed vessels progressively open (recruitment) and previously narrow vessels progressively dilate (distension). Both mechanisms explain a progressive decrease in the slope of pulmonary vascular pressure/flow relationships (resistance) with increasing flow or pressure and account for apparent functional dissociation between Ppa and Q as reported, for example, in the acute respiratory distress syndrome [8].

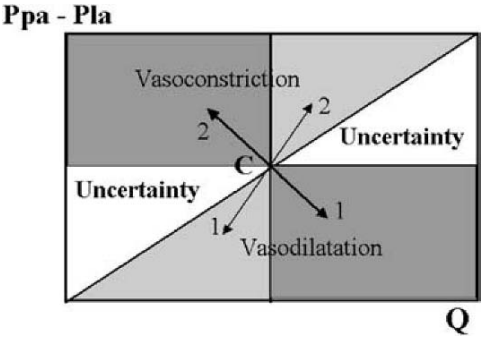


Fig. 2 Pressure/flow diagram for the interpretation of pulmonary hemodynamic measurements. The central point *C* corresponds to initial mean pulmonary artery pressure (*Ppa*), left atrial pressure (*Pla*) and flow (*Q*) measurements. A decrease in (Ppa–Pla) at increased Q can only be explained by pulmonary vasodilatation. An increase in (Ppa–Pla) at decreased Q can only be explained by pulmonary vasoconstriction. Rectangles of certainty are extended to adjacent triangles because negative slopes or pressure intercepts of (Ppa–Pla)/Q lines are impossible. *Arrows* indicate changes in measured (Ppa–Pla) and Q, (1) vasodilatation, (2) vasoconstriction

A pressure/flow diagram to avoid errors based on isolated pulmonary vascular resistance calculations

As illustrated in Fig. 1, PVR calculations can give misleading information under conditions of changing cardiac output. Vasomotor tone in subjects with pulmonary hypertension may appear to be either increasing or decreasing while, in fact, the functional state of the pulmonary circulation remains unchanged. In his original physiological note on this topic 17 years ago Versprille apologized to the clinicians for not being able to offer an alternative solution while pointing at the limitations of PVR measures [1]. However, PVR measures are similar to other composite variables in having inherent limitations. Systemic vascular resistance carries similar limitations and for related reasons. Importantly, when assessing pulmonary vasomotor tone, measurements of primary variables always minimize the inherent inaccuracies of calculating derived measurements. For example, in pulmonary hemodynamic studies, directly measured pressures and pulmonary blood flow can be plotted on a pressure/flow diagram (Fig. 2).

On such a diagram, connecting the central starting point C to the origin defines PVR. However, a closing pressure Pc higher than the apparent outflow pressure Pla is possible, which causes the pressure/flow line drawn from point C to cross the pressure axis at increasing pressures up to a maximum corresponding to a horizontal line. It is indeed physically impossible that (Ppa–Pc) would decrease at increasing flow. On the other hand, a (Ppa–Pla)/Q line cannot cross the pressure axis at a negative pressure in the absence of a change in vasomotor tone. The (Ppa–Pla)/Q line and the line of maximum possible Pc at an actually measured initial point C determine a series of areas on the pressure/flow diagram. At increasing flow, any decrease in (Ppa–Pla) can only be vasodilation. At decreasing flow, any increase in (Ppa–Pla) can only be vasoconstriction. In addition, a decrease in (Ppa–Pla) at decreasing flow that is more than predicted by the initial PVR equation can only be vasodilatation. An increase in (Ppa–Pla) more than predicted by the initial PVR equation can only be vasoconstriction. As shown in Fig. 2, zones of uncertainties remain because the actual value of closing pressure is not known. An additional uncertainty is related to the assumption that the pressure/flow coordinates are best described by a linear approximation, but this is generally reasonable in the absence of extreme changes in flow.

Improved definition of pulmonary vascular resistance by a multipoint pulmonary vascular pressure/flow plot

Still, the resistive properties of the pulmonary circulation are best defined by the measurement of pulmonary vascular pressures at several levels of flow. The problem is to increase or to decrease flow with interventions that do not affect vascular tone. Exercise changes cardiac output but may lead to spuriously increased slopes with Ppa/Q plots [9]. This is probably due to exercise-induced pulmonary vasoconstriction, because of a decrease in mixed venous PO_2, sympathetic nervous system activation and

exercise-associated increase in left atrial pressure. A better option may be to increase flow by an infusion of low dose dobutamine. There is experimental evidence that dobutamine has no effect on pulmonary vascular tone doses below 10 μg/kg per min [10].

Conclusions

The calculation of PVR is sensitive to pulmonary arteriolar tone and dimensions, but can be misleading when used to assess the functional state of the pulmonary circulation at increased or decreased cardiac output. In case of doubt, pulmonary hemodynamic determinations are better interpreted with the help of a pressure/flow diagram. The ideal is to define PVR using a multipoint pulmonary vascular pressure/flow plot.

References

1. Versprille A (1984) Pulmonary vascular resistance. A meaningless variable. Intensive Care Med 10:51–53
2. McGregor M, Sniderman A (1985) On pulmonary vascular resistance: the need for more precise definition. Am J Cardiol 55:217–221
3. Landis EM (1982) The capillary circulation. In: Fishman AP, RichardsDW (eds) Circulation of the Blood. Men and Ideas. American Physiological Society, Bethesda, Maryland, pp 355–406
4. Permutt S, Bromberger-Barnea B, Bane HN (1962) Alveolar pressure, pulmonary venous pressure and the vascular waterfall. Med Thorac 19:239–260
5. Zhuang FY, Fung YC, Yen RT (1983) Analysis of blood flow in cat's lung with detailed anatomical and elasticity data. J Appl Physiol 55:1341–1348
6. Mélot C, Delcroix M, Lejeune P, Leeman M, Naeije R (1995) Starling resistor versus viscoelastic models for embolic pulmonary hypertension. Am J Physiol 267 (Heart Circ Physiol 36:H817–827)
7. Nelin LD, Krenz GS, Rickaby DA, Linehan JH, Dawson CA (1992) A distensible vessel model applied to hypoxic pulmonary vasoconstriction in the neonatal pig. J Appl Physiol 73:987–994
8. Zapol WM, Snider MT (1977). Pulmonary hypertension in severe acute respiratory failure. N Engl J Med 296:476–480
9. Kafi A S, Mélot C, Vachiéry JL, Brimioulle S, Naeije R (1998) Partitioning of pulmonary vascular resistance in primary pulmonary hypertension. J Am Coll Cardiol 31:1372–1376
10. Pagnamenta A, Fesler P, Vandivinit A, Brimioulle S, Naeije R (2003) Pulmonary vascular effects of dobutamine in experimental pulmonary hypertension. Crit Care Med (in press)

Michael R. Pinsky

Pulmonary artery occlusion pressure

Introduction

The bedside estimation of left ventricular (LV) performance of critically ill patients is an important aspect of the diagnosis and management of these patients. Ever since the introduction of the balloon flotation pulmonary catheterization, health care providers have used measurements of pulmonary artery occlusion pressure (Ppao) to estimate both pulmonary venous pressure and LV preload. However, the significance of any specific value for Ppao in the diagnosis and treatment of cardiovascular insufficiency in patients with diseases other than cardiogenic shock has never been validated. The reasons for this continued uncertainty reflect both intrinsic inaccuracies in the measurement of Ppao and misconceptions about their physiological significance. In this first Physiological Note we shall discuss problems in the accurate measurement of Ppao at the bedside, while in the second Physiological Note we shall discuss the physiological significance of Ppao measurements.

Measurement of pulmonary artery occlusion pressure

Balloon occlusion

Intravascular pressure, as determined using a water-filled catheter connected to an electronic pressure transducer, measures the pressure at the first point of flow and with a frequency response determined primarily by the stiffness and length of the tubing. Balloon occlusion of the pulmonary artery stops all flow distal to that point until the pulmonary veins converge about 1.5 cm from the left atrium. Thus, if a continuous column of blood is present from the catheter tip to the left heart, then Ppao measures pulmonary venous pressure at this first junction, or J-1 point, of the pulmonary veins [1].

Hydrostatic influences

If one places the pressure transducer at a point lower than the catheter tip, then the pressure recorded will be greater than the pressure at the catheter tip by an amount equal to that height difference. Since pressure is usually measured in millimeters of mercury and the density of mercury relative to water is 13.6, for every 1.36 cm the transducer lies lower than the catheter tip the measured pressure will increase by 1 mmHg. Placing the transducer at the mid-axillary line references both the catheter tip and the transducer to a common cardiovascular point, such that even if the catheter tip is higher or lower than this reference point, the hemodynamic measure still uses the heart's level as zero [2].

Pressure profile during occlusion maneuver

The stiffer a vascular catheter is, the more faithfully it will transmit rapid changes in pressure at the catheter tip

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_17, © Springer-Verlag Berlin Heidelberg 2009

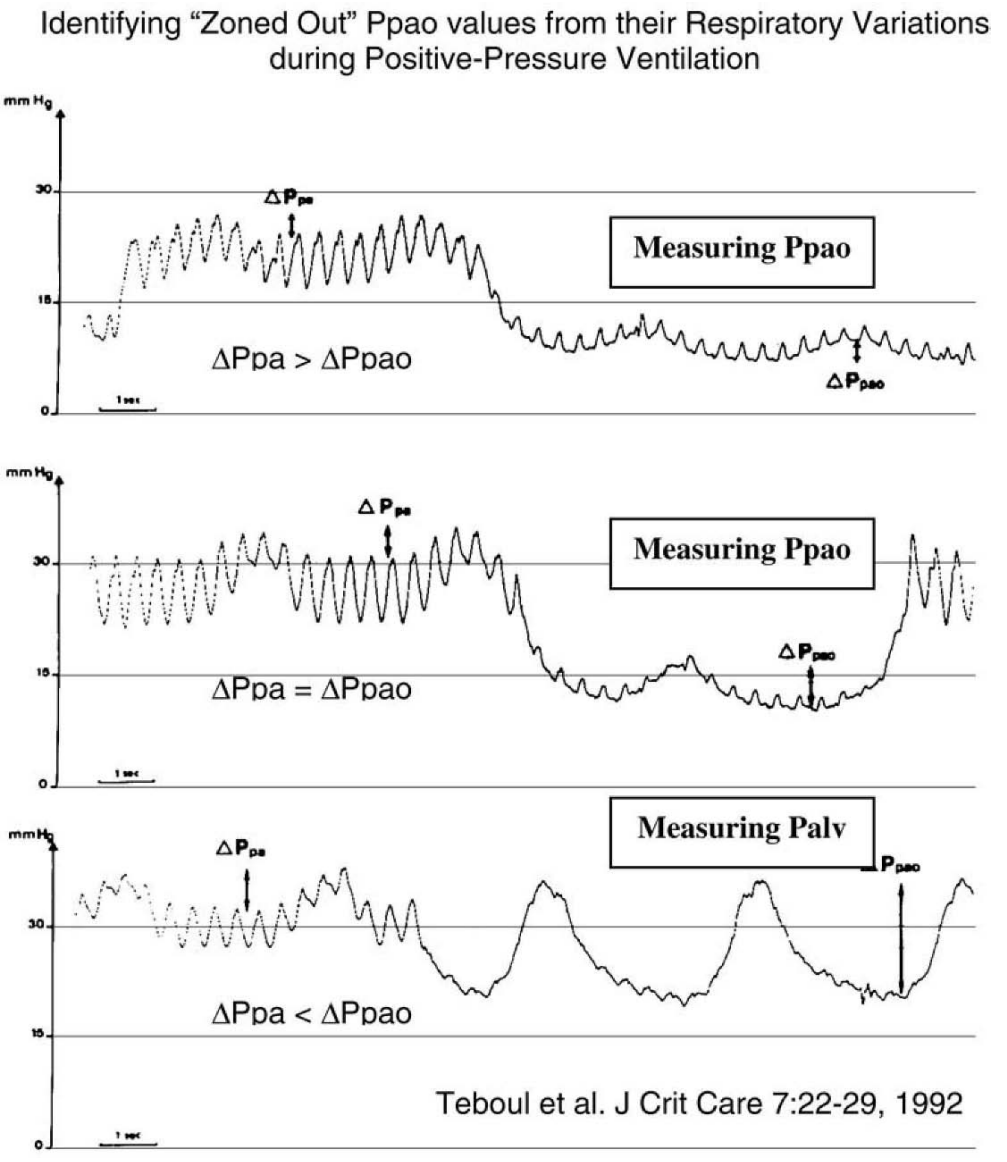


Fig. 1 Strip chart recording of pulmonary artery pressure (Ppa) to balloon occlusion (Ppao) as hemodynamic conditions change. Note the change in pressure waveform with occlusion and the logarithmic nature of the pressure decay. Also note that when alveolar pressure compresses the pulmonary capillaries, the change in Ppao during ventilation exceeds the change in Ppa

to the electronic pressure transducer. When a pulmonary arterial catheter's distal balloon is inflated, three things happen simultaneously (Fig. 1). First, the catheter rapidly migrates more distally into the pulmonary vasculature, carried by the force of pulmonary blood flow against the inflated balloon until it impacts upon a medium-sized pulmonary artery whose internal diameter is the same or less than that of the balloon. This rapid swing induces a ringing of the pressure system as the tip impacts onto the smaller vessel. Second, as downstream pulmonary blood flow ceases, distal pulmonary arterial pressure falls in a double exponential fashion to a minimal value, reflecting the pressure in the pulmonary vasculature downstream from the point of occlusion. Third, the column of water at the end of the catheter is now extended to include the pulmonary vascular circuit up to the point of blood flow. Since the vasculature is compliant relative to the catheter, vascular pressure signals dampen. Thus, the two primary aspects of Ppao measurements are that they are less than pulmonary arterial diastolic pressure and their waveforms are dampened relative to the non-occluded state.

Pulmonary capillary pressure

It is very important to understand that Ppao is not the pulmonary capillary pressure. The pressure at the capillary site, however, can be estimated from the pulmonary artery pressure tracing during an occlusion. At the in-

stant of balloon occlusion, the pressure distal to the catheter tip decreases as pressure and blood discharge into the downstream pulmonary vessels. Flow across the pulmonary vasculature can be considered to reflect two dynamic components: flow from a proximal pulmonary arterial capacitance system across an arterial resistance into a pulmonary capillary capacitance system, then across a pulmonary venous resistor into the pulmonary venous capacitor. Pressure in the latter is measured as Ppao. Thus, the downstream pulmonary arterial pressure decreases as the pulmonary arterial capacitor discharges its blood into the pulmonary capillary system. When the pressure in the pulmonary artery and capillary are equal, the pressure continues to discharge across the venous resistor. Plotting the log of pulmonary arterial pressure over time during its pressure decay can separate these two distinct pressure decay patterns. A clear inflection point is often seen, reflecting pulmonary capillary pressure. Usually it occurs two-thirds of the way between pulmonary diastolic pressure and Ppao, because two-thirds of the pulmonary vascular resistance is in the arteries.

By separating the pressure drop into arterial and venous components, one can calculate total pulmonary vascular resistance as the ratio of the difference between mean pulmonary artery pressure and Ppao to cardiac output, and pulmonary arterial and venous resistances as the proportional amounts of this pressure drop on either side of the capillaries [3]. Using such an analysis, it has been shown that, in acute respiratory distress syndrome (ARDS), once pulmonary vascular obliteration occurs, pulmonary capillary pressure often exceeds Ppao by a considerable amount because pulmonary venous resistance increases. Thus, some “low pressure” pulmonary edema characterized by low Ppao values in a hyperdynamic state may actually reflect hydrostatic pulmonary edema.

Since the pulmonary vasculature has a measurable resistance, pressure inside the pulmonary arteries decreases along its length. The original pulmonary artery catheter method to measure left-sided pressures was to “wedge” a very small catheter into a small pulmonary arteriole, the so-called “wedge” pressure measurement. Wedge pressure is not Ppao. Since collateral flow and vessel diameter are different, wedge pressure tends to be slightly lower than Ppao values. Realistically, this is of little importance, except in remembering not to call Ppao “wedge pressure.”

Airway pressure and pulmonary artery occlusion pressure

Since a continuous column of fluid is required for a stop-flow pulmonary arterial catheter to sense pulmonary venous pressure at the J-1 point, if alveolar pressure (Palv) increases too much above left atrial pressure, the pulmonary vasculature in the zone of the occluded vessels may collapse such that the occlusion pressure senses actually reflect more airway pressure (Paw) than Ppao. Such conditions classically occur in West zones 1 and 2. However, under conditions in which Paw exceeds left atrial pressure, Ppao may still reflect left atrial pressure and its change. The reasons are two-fold. First, if the vascular region occluded is in a dependent region, then pulmonary capillary pressure will be greater than Ppao because of the effect of gravity on dependent vessels. Since balloon occlusion tends to occur in vessels with flow and more flow goes to dependent regions, this is a common event. However, even in non-dependent regions, a continuous column of fluid may persist in clear Zone 2 conditions (i.e. Paw >Ppao) when Paw is not much greater than Ppao. Presumably the corner vessel alveolar capillaries remain patent while the mid-wall capillaries flatten.

Once Paw increases enough relative to left atrial pressure, the distal tip of the balloon-occluded catheter senses Palv rather than Ppao. However, such conditions are easy to identify at the bedside because the respiratory increases in Ppao during this condition exceed the respiratory swings in pulmonary arterial diastolic pressure. This is because the pulmonary vasculature senses pleural pressure (Ppl) as its surrounding pressure, whereas the alveoli sense Paw as their pressure. With inspiration, transpulmonary pressure, the difference between Ppl and Paw, increases. Prior to balloon occlusion, pulmonary arterial pressures reflect a patent vasculature, thus pulmonary diastolic pressure will vary with pleural pressure. Thus, if Ppao senses Paw rather than Ppl, then it will increase more during inspiration [4] (Fig. 1).

Pleural pressure and pulmonary artery occlusion pressure

Ventilation causes significant swings in Ppl. Pulmonary vascular pressures, when measured relative to atmospheric pressure, will reflect these respiratory changes. To minimize the impact that ventilation has on the pulmonary vascular values measured, these variables are conventionally measured at end-expiration. This point is picked because it reflects a common point easily returned to even as ventilation changes, rather than the average hemodynamic position. During quiet spontaneous breathing, end-expiration occurs at the highest vascular pressure values whereas, during positive-pressure breathing, end-expiration occurs at the lowest vascular pressure values. With assisted ventilation, where both spontaneous and positive-pressure breathing coincide, it is often difficult to define end-expiration. In addition, a high respiratory drive during spontaneous or assisted breathing usually results in expiratory muscles recruitment, making end-expiration unreliable for estimating intravascular pressures [5]. These limitations are the primary

reasons for inaccuracies in estimating Ppao at the bedside.

Positive-end expiratory pressure (PEEP) and hyperinflation

Even if one measures an actual Ppao value reflecting a continuous column of fluid from the catheter tip to the J-1 point and correctly identified end-expiration, one may still overestimate Ppao if Ppl is elevated. Hyperinflation, either due to extrinsic or intrinsic PEEP, will increase end-expiratory Ppl relative to the increase in PEEP and lung and chest wall compliance. Because Palv is partly transmitted to Ppl, end-expiratory Ppao overestimates LV filling pressure if PEEP is present. Unfortunately, it is not possible to predict with much accuracy the degree to which increases in PEEP will increase Ppl. One can remove a patient from PEEP to measure Ppao, but this will cause blood volume shifts with increases in Ppao that will not reflect the on-PEEP cardiovascular state. What the clinician needs is a measure of LV filling pressure while on PEEP. Regrettably, because of differences in lung and chest wall compliance among patients and changes in each over time, one cannot assume a fixed relation between increases in Paw and Ppl. Thus, in subjects with compliant lungs but stiff chest walls most of the increase in PEEP will be reflected in an increase in Ppl, whereas in those with markedly reduced lung compliance Ppl may increase very little, if at all, with the application of PEEP [6].

Two techniques allow for the accurate estimation of Ppao even if lung hyperinflation is present. In patients on PEEP without airflow obstruction, measuring Ppao at end-expiration while the airway is transiently disconnected (<3 s) results in a sudden loss of hyperinflation and a fall in Ppao to a nadir value. This nadir Ppao value accurately reflects on-PEEP LV filling pressure in patients on 15 cmH_2O or less [6]. It may be accurate above this value, but that question has not been studied. However, in subjects with intrinsic PEEP, transiently removing them from a ventilator may not result in lung deflation to off-PEEP levels. Ppao values can still be measured, but using a more indirect technique. One may calculate a transmural value of end-expiratory Ppao as a ratio of airway to pleural pressure changes during a breath. Since Ppao will vary with Ppl and Paw can be measured directly, the proportional transmission of pressure from the airway to the pleural surface, referred to as the index of transmission (IT), equals the ratio of the differences between changes in Ppao and Paw during a breath. Thus, one may calculate the transmural Ppao = end-expiratory Ppao –(IT × total PEEP), where IT is an index of transmission of Palv to Ppao calculated as IT = (end-inspiratory Ppao –end-expiratory Ppao)/(plateau pressure –total PEEP). Paw needs to be transformed from centimeters of water into millimeters of mercury. Recall that total PEEP equals intrinsic plus extrinsic PEEP. This formula, though complicated, can be easily derived at the bedside from readily available values, and carries the added advantage of not requiring airway disconnection to derive it [7].

Summary

Technical limitations in the accurate measurement of Ppao and its change in response to therapy are daunting, but surmountable. By using a firm understanding of the technical determinants of Ppao during ventilation one may measure it accurately at the bedside under almost any situation. In the next Physiological Note we shall address the physiological significance of Ppao values.

References

1. Swan HJC, Ganz W, Forrester JS, Marcus H, Diamond G, Chonette D (1970) Catheterization of the heart in man with the use of a flow-directed balloon tipped catheter. N Engl J Med 283:447–451
2. Rajacich N, Burchard KW, Hasan FM, Singh AK (1989) Central venous pressure and pulmonary capillary wedge pressure as estimate of left atrial pressure: effects of positive end-expiratory pressure and catheter tip malposition. Crit Care Med 17:7–11
3. Maarek J, Hakim T, Chang H (1990) Analysis of pulmonary arterial pressure profile after occlusion of pulsatile blood flow. J Appl Physiol 68:761–769
4. Teboul JL, Besbes M, Andrivet P, Besbes M, Rekik N, Lemaire F, Brun-Buisson C (1992) A bedside index assessing the reliability of pulmonary artery occlusion pressure measurements during mechanical ventilation with positive end-expiratory pressure. J Crit Care 7:22–29
5. Hoyt JD, Leatherman JW (1997) Interpretation of pulmonary artery occlusion pressure in mechanically ventilated patients with large respiratory excursions in intrathoracic pressure. Intensive Care Med 23:1125–1131
6. Pinsky MR, Vincent JL, DeSmet JM (1991) Estimating left ventricular filling pressure during positive end-expiratory pressure in humans. Am Rev Respir Dis 143:25–31
7. Teboul JL, Pinsky MR, Mercat A, Anguel N, Bernardin G, Achard JM, Boulain T, Richard C (2000) Estimating cardiac filling pressure in mechanically ventilated patients with hyperinflation. Crit Care Med 28:3631–3636

Michael R. Pinsky

Clinical significance of pulmonary artery occlusion pressure

Abstract *Background*: Ppao values are routinely used to assess pulmonary vascular status and LV performance. Regrettably, under many common clinically relevant conditions, even when Ppao values are measured accurately, Ppao values at baseline and in response to therapy often reflect an inaccurate measure of cardiovascular status.
Results and conclusions: Thus, caution should be used when applying measures of Ppao in determining therapy if changes in RV volume, hyperinflation, or LV diastolic compliance are simultaneously occurring.

Keywords Bedside measurements · Pulmonary hemodynamics · Left ventricular performance · Critically ill patients · Pulmonary artery occlusion pressure · Pulmonary vascular status

Introduction

Balloon floatation pulmonary arterial catheterization has permitted the bedside estimation of pulmonary hemodynamics and left ventricular (LV) performance of critically ill patients. Present-day pulmonary artery catheters can routinely estimate cardiac output and right ventricular (RV) ejection fraction, by the thermodilution technique, mixed venous oxygen saturation, by reflective oximetry, and three intrapulmonary vascular pressures: right atrial, pulmonary arterial and pulmonary artery occlusion pressure. Of all of these, pulmonary artery occlusion pressure (Ppao) is perhaps subject to the most error in its measurement and interpretation. The previous "Physiological Note" discussed problems in the accurate measure of Ppao at the bedside. In this one we discuss the physiological significance of Ppao measures.

Pulmonary artery occlusion pressure is used most often in the bedside assessment of: (a) pulmonary edema, (b) pulmonary vasomotor tone, (c) intravascular volume status and LV preload, and (d) LV performance. We address each separately.

Pulmonary edema

Acute pulmonary edema can be life threatening because of the systemic hypoxemia that it creates. Pulmonary edema can be caused by either elevations in pulmonary capillary pressure (hydrostatic or secondary pulmonary edema), increased capillary and/or alveolar epithelial permeability (primary pulmonary edema), or a combination of the two. If pulmonary capillary pressure increases above 18–20 mmHg, increased fluid flux across the capillary membrane occurs, promoting alveolar flooding. However, if capillary or alveolar cell injury is present, alveolar flooding can occur at much lower pulmonary capillary pressures. Measures of Ppao are commonly used to determine the cause of pulmonary edema. Thus Ppao values lower than 18–20 mmHg suggest a nonhydrostatic cause,

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_18, © Springer-Verlag Berlin Heidelberg 2009

whereas values higher than 18–20 mmHg suggest a hydrostatic cause of pulmonary edema [1]. However, these are not hard values.

Ppao may be lower than 18–20 mmHg in a patient with secondary pulmonary edema if either the Ppao increase had been transient and is now gone, or if pulmonary capillary pressure significantly exceeds Ppao. Transient severe LV dysfunction can transiently increase Ppao during upper airway obstruction with vigorous inspiratory efforts (inspiratory stridor, obstructive sleep apnea), unstable angina (reversible ischemia), and arrhythmias. Increased pulmonary capillary pressure can occur due to massive sympathetic discharge (e.g., intracerebral hemorrhage and heroin overdose), which rapidly reverses, but the pulmonary edema lingers. Furthermore, persistently elevated pulmonary capillary pressures may coexist with normal Ppao values if pulmonary venous resistance is increased and cardiac output not decreased (e.g., high altitude pulmonary edema, pulmonary venoocclusive disease, and end-stage acute respiratory distress syndrome).

Ppao may be higher than 18–20 mmHg in a patient without hydrostatic pulmonary edema. Since Ppao is measured relative to atmospheric pressure, elevations in pleural pressure artificially elevate Ppao values. Any increase in pleural pressure increases measured Ppao. Hyperinflation, either intrinsic or extrinsic, increases pleural pressure. Furthermore, when active expiratory muscle effort persists, pleural pressure increases.

Pulmonary vasomotor tone

Increased pulmonary arterial pressure (Ppa) impedes RV ejection, causing RV dilation and a decreased cardiac output. If pulmonary hypertension occurs rapidly, as with massive pulmonary embolism or marked hyperinflation, acute cor pulmonale and cardiovascular collapse also occurs. Pulmonary hypertension can be due to either an increase in pulmonary vasomotor tone or passive increases in Ppao due to LV failure. The pulmonary circulation normally has a low resistance, with pulmonary arterial diastolic pressure only slightly higher than Ppao and mean pulmonary arterial pressure thus a few mmHg higher than Ppao Global pulmonary vascular resistance, by Ohm's law, equals the ratio of the driving pressure (mean Ppa–Ppao) and flow (cardiac output). Normal pulmonary vascular resistance is between 1.8 and 3.1 mmHg l^{-1} min^{-1}. Usually these values are multiplied by 80 to give normal pulmonary vascular resistance range of 150–250 dynes s^{-1} /cm^{-5} of. Thus by measuring Ppa, Ppao, and cardiac output in patients with pulmonary hypertension, one may determine whether the increase in Ppa is due to increased pulmonary vascular resistance (PVR) or a passive pressure build-up. If pulmonary hypertension is associated with an increased PVR then the causes are primarily within the lung, whereas if PVR is normal then LV dysfunction is the more likely cause [2].

Regrettably, PVR is not a good measure of pulmonary vasomotor tone. Pulmonary vascular pressure does not decrease linearly from input to output and may vary from region to region due to lung distention, structural damage and acute processes, such as hyperinflation, pneumonia, emphysema, pulmonary fibrosis, and acute lung injury. Thus PVR as a lumped parameter may not identify local injury or define why PVR is elevated. As alveolar pressure increases above Ppao (West zone 2 conditions) alveolar pressure becomes the backpressure to pulmonary blood flow. Thus measures aimed at decreasing pulmonary vasomotor tone (e.g., inhaled nitric oxide) have little effect on Ppa [3]. Furthermore, with nonhomogeneous lung disease blood flow is preferentially shifted to those circuits with the lowest resistance, thus making the lung vascular pathology appear less than it actually is. By examining the change in Ppa in response to interventions that alter cardiac output, one may obtain a better understanding of the determinants of pulmonary hypertension. If the extrapolated zero-flow pulmonary artery pressure created from such a maneuver is much higher than Ppao, Ppao is probably not the downstream pressure to flow thus measures aimed at reducing zone 2 conditions (reverse hyperinflation) should be more effective at decreasing Ppa.

Intravascular volume status and LV preload

Hemodynamically unstable patients often benefit for fluid resuscitation, as manifested by increases in organ perfusion and function, resolution of lactic acidosis, and increased survival. A fundamental tenant of such therapy is that fluid resuscitation increases LV end-diastolic volume (EDV), and that such increases in EDV translates into increased cardiac output. For a given level of contractile function, increasing LV EDV increases both LV stroke volume (and thus cardiac output) and LV stroke work. It is difficult to make repeated measures of LV EDV at the bedside to titrate fluid resuscitation and vasoactive therapy. Ppao values are often taken to reflect LV filling pressure, and by inference LV EDV. Operationally, subjects with cardiovascular insufficiency and a low Ppao are presumed to be hypovolemic and initially treated with fluid resuscitation, whereas patients with similar presentations but and elevated Ppao are not. Although there is no accepted high and low Ppao values for which LV under filling is presumed to occur, Ppao values lower than 10 mmHg are usually used as presumed evidence of a low LV EDV, whereas values higher than 18 mmHg suggest a distended LV [4].

Regrettably, of all the uses of Ppao in the management of the critically ill, this one use is the least accurate. The reasons for this are multiple and relate to the

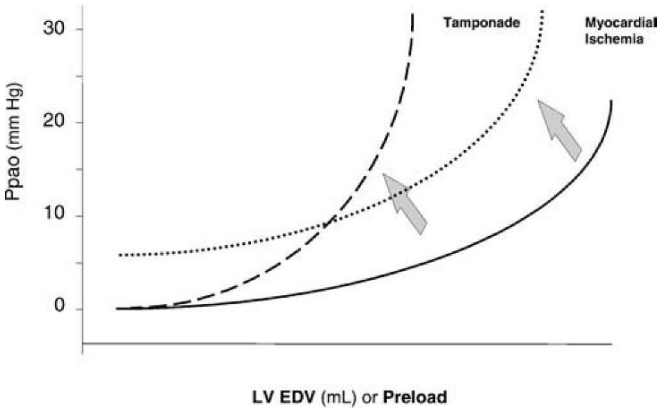


Fig. 1 Schematic representation of the relationship between left ventricular end-diastolic volume (LV EDV) and pulmonary artery occlusion pressure (Ppao) under a variety of circumstances. *Solid line* Idealized LV diastolic compliance; *other two curves* increased external pressure and volume constraint (tamponade) and diastolic stiffening (myocardial ischemia), respectively

determinants of LV diastolic compliance and contractile function (Fig. 1) [5]. First, the relationship between Ppao and LV EDV is curvilinear and may be very different between subjects. Thus neither absolute values of Ppao or changes in Ppao define a specific LV EDV or its change. Second, Ppao is not the distending pressure for LV filling. Assuming that Ppao approximates left atrial pressure, it would poorly reflect LV end-diastolic pressure because it poorly follows the late diastolic pressure rise induced by atrial contraction and does not measure pericardial pressure, which is the outside pressure for LV distention. Thus changes in pericardial pressure alter LV EDV independently of Ppao. Hyperinflation, tamponade, and active inspiratory and expiratory muscle activity can rapidly alter pericardial pressure. Finally, even if one knew that pericardial pressure and Ppao do accurately reflect LV end-diastolic pressure, LV diastolic compliance can vary rapidly, changing the relationship between LV filling pressure and LV EDV. Myocardial ischemia, arrhythmias, and acute RV dilation can all occur over a few heartbeats. Thus it is not surprising that Ppao is a very poor predictor of preload responsiveness. The use of Ppao as a measure of LV EDV and preload responsiveness has not been validated by clinical trials. Accordingly, using Ppao to predict response to fluid resuscitation is not recommended, except at the extremes of Ppao values, and during those conditions one rarely needs to measure Ppao to make the correct diagnosis.

LV performance

As stated above, LV EDV is a fundamental determinant of stroke volume and LV stroke work. The bedside assessment of LV performance is important in determining the causes of cardiovascular insufficiency and the potential of the patient to response to fluid challenge, increasing arterial pressure and afterload reduction. Although many factors converge on the resultant LV stroke volume, including valvular function, synchrony of contraction, and diastolic filling time the four primary determinants of LV performance are preload (LV EDV), afterload (LV wall stress, which is itself the product of LV EDV and diastolic arterial pressure), heart rate, and contractility. To the extent that Ppao mirrors LV EDV, Ppao can be used to construct Starling curves that plot Ppao vs. LV stroke work (LV stroke volume × developed pressure). Patients with heart failure can be divided into four groups depending on their Ppao (>or <than 18 mmHg) and cardiac index values (>or <2.2 l min^{-1} m^{-2}) [4]. Those patients with low cardiac indices and high Ppao are presumed to have primary heart failure, and low Ppao hypovolemia. Those with high cardiac indices and high Ppao are presumed to be volume overloaded, and low Ppao increased sympathetic tone.

Again, as above, if LV diastolic compliance is reduced or pericardial pressure increased, Ppao underestimates LV EDV. This interaction is the primary reason why both acute pulmonary embolism-induced cor pulmonale and PEEP-induced hyperinflation were erroneously thought to cause myocardial depression. In both clinical scenarios baseline Ppao values markedly increase without a proportional increase in stroke volume. Accordingly, the same limitations on the use of Ppao in assessing LV preload must be considered when using it to assess LV performance. Thus in subjects without lung or pericardial disease, tamponade, or pulmonary embolism the relationship between Ppao and LV stroke work can be used to assess LV performance.

Summary

Ppao values are routinely used to assess pulmonary vascular status and LV performance. Regrettably, under many common clinically relevant conditions, even when Ppao values are measured accurately, Ppao values at baseline and in response to therapy often reflect an inaccurate measure of cardiovascular status. Thus caution should be used when applying measures of Ppao in determining therapy if changes in RV volume, hyperinflation, or LV diastolic compliance are simultaneously occurring.

References

1. Fishman AP (1985) Pulmonary circulation. In: Handbook of physiology. The Respiratory system. Circulation and nonrespiratory functions, vol 1. American Physiological Society, Bethesda, pp 93–166
2. Abraham AS, Cole RB, Green ID, Hedworth-Whitty RB, Clarke SW, Bishop JM (1969) Factors contributing to the reversible pulmonary hypertension of patients with acute respiratory failure studied by serial observations during recovery. Circ Res 24:51–60
3. West JB, Dollery CT, Naimark A (1964) Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. J Appl Physiol 19:713–724
4. Forrester JS, Diamond G, Chatterjee K, Swan HJC (1976) Medical therapy of acute myocardial infarction by application of hemodynamic subsets. N Engl J Med 295:1356–1362
5. Raper R, Sibbald WJ (1986) Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. Chest 89:427–434

Jukka Takala

Pulmonary capillary pressure

Introduction

Pulmonary capillary pressure is a primary determinant of fluid flux across the pulmonary capillary wall [1]. Increasing pulmonary capillary pressure increases fluid flux out of the capillaries into the interstitium and in the extreme induces pulmonary edema. Pulmonary capillary pressure is itself determined by the mean pulmonary artery pressure, pulmonary vascular resistance, and total blood flow. The distribution of the pulmonary vascular resistance from precapillary arterial to postcapillary venous compartments varies. Accordingly, at any given blood flow rate the hydrostatic pressure in the pulmonary capillaries depends on the magnitude of the resistance to blood flow across the pulmonary circulation and its distribution between precapillary and postcapillary vessels. Since pulmonary capillary pressure cannot be directly measured, the presence and relevance of increased pulmonary capillary hydrostatic pressures to values in excess of pulmonary artery occlusion pressure are often overlooked.

What are the components of the pressure drop across the pulmonary vasculature?

The resistance to flow across the pulmonary circulation results in the pressure drop from the large pulmonary artery to the left atrium. This resistance can be separated into arterial and venous components, with relatively little resistance seen in the compliant capacitance pulmonary capillary vessels. This physical situation can be modeled as an electrical circuit consisting of two or several resistances in series with one or several capacitors connected between the resistances (Fig. 1). The simplest model assumes one arterial and one venous resistance with one capacitance located in the capillaries [2, 3]. A three-compartment model consisting of compliant arterial, capillary and venous capacitance compartments between four resistances (resistance of large and small arterial and venous vessels, respectively) is probably more representative but does not improve the accuracy of measuring pulmonary capillary pressure [1].

Because of this series resistance interposed by a compliant pulmonary capillary network, pulmonary capillary pressure can be measured from the pressure decay profile of an acute pulmonary artery balloon occlusion maneuver. When the pulmonary artery is occluded, there is a rapid decrease in blood flow as the occluded downstream pulmonary artery discharges its blood volume sequentially into the pulmonary capillaries across the arterial resistance and then into the pulmonary veins across the venous resistance. This two-part pressure discharge is reflected in the pulmonary artery pressure decay curve. The initial rapid pressure drop approaches the pressure in the capillaries (the main capacitance component) as the blood trapped in the downstream pulmonary capillaries equilibrates with pulmonary capillary pressure. This is followed by a slower pressure decrease approaching the pulmonary artery occlusion pressure as pulmonary capillary pressure equilibrates with pulmonary venous pressure (Fig. 1a). The initial pressure drop re-

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_19, © Springer-Verlag Berlin Heidelberg 2009

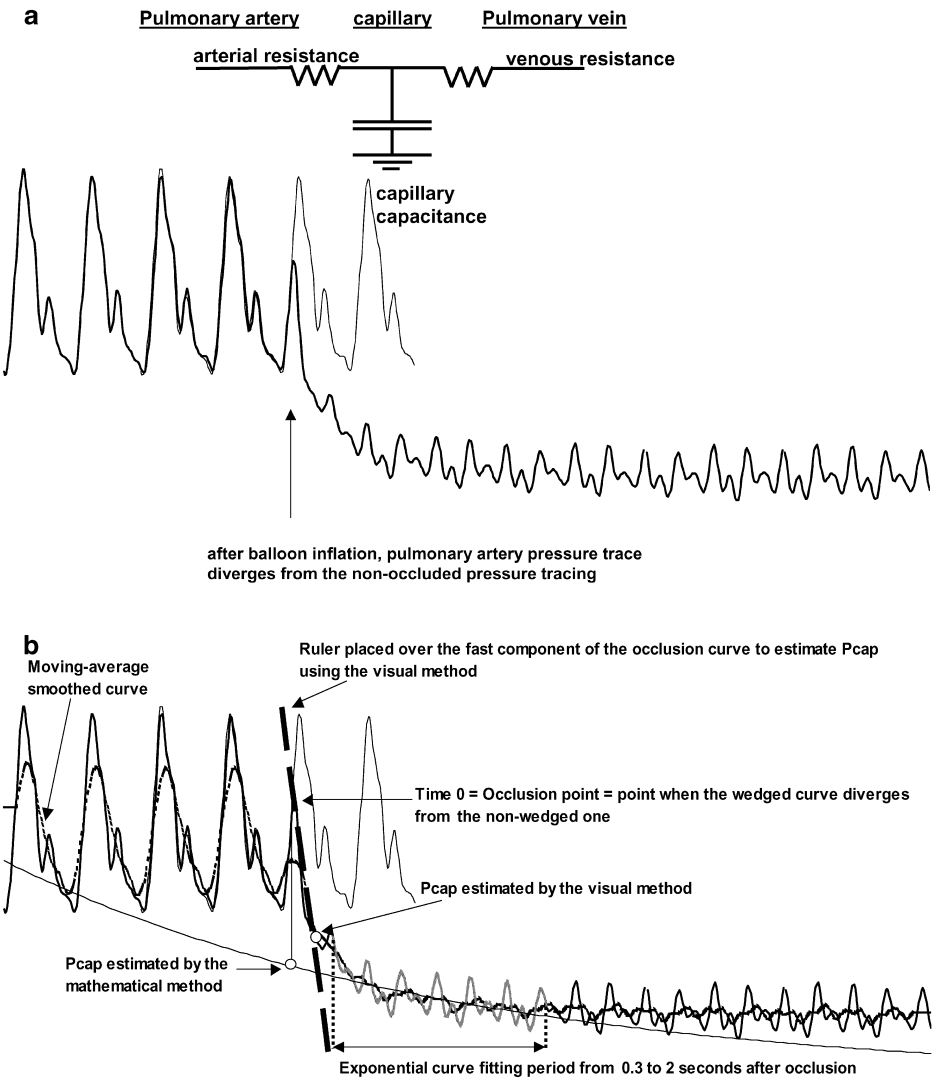


Fig. 1 A schematic representation of the electric circuit analogue of the pulmonary circulation is superimposed on the two pressure recordings. **a** Pulmonary artery pressure decay after the balloon of the Swan-Ganz catheter has been occluded. For better visualization the occlusion trace is superimposed on a nonoccluded trace, both recorded during an expiratory hold during mechanical ventilation. **b** Capillary pressure has been estimated from the trace shown in **a**. An additional trace using 20 data point moving average smoothing of the original trace (collected at 100 Hz) is superimposed on the curves. This further facilitates the visual estimation of the capillary pressure by defining more exactly the point of divergence of the occluded and nonoccluded curves. In addition, an exponential curve has been fitted on the curve 0.3–2 s after occlusion. This fitted curve has then been extrapolated to the time of occlusion to provide the capillary pressure

flects the proximal arterial resistance, and the slower pressure drop reflects the distal, venous resistance. The model shown in Fig. 1 consisting of serial resistance and capacitances does not represent the simultaneous discharge of the different capacitance components of the pulmonary circulation. Nevertheless, it provides a close approximation of the decay of pressure after a pulmonary arterial occlusion for most clinical conditions.

What is the physiological relevance of the pulmonary capillary pressure?

Pulmonary capillary pressure is a major determinant of fluid flux across the capillary wall and lung edema formation. Under normal conditions some fluid and protein is filtered through the capillary into the pulmonary interstitium and subsequently drained into the systemic circulation by the lung lymphatics. When the capacity of the lymphatics is exceeded, first interstitial and then alveolar edema ensues. The rate of fluid filtration from the capillary to the interstitium can be estimated by the Starling equation:

$$\text{Fluid efflux} = K_{fc} \times \left[\left(P_{capillary} - P_{interstitium}\right)\right] - K_d \left[\left(\pi_{capillary} - \pi_{interstitium}\right)\right]$$

where P=hydrostatic pressure, π=oncotic pressure, K_{fc}=capillary filtration coefficient (product of capillary wall hydraulic conductivity and capillary surface area), and K_d=reflection coefficient (values from 0 to 1; 0=capillary freely permeable to proteins, 1=capillary impermeable to proteins). When fluid efflux increases for any reason, lymph flow increases as well, washing out interstitial protein and decreasing $\pi_{interstitium}$, thus increasing the oncotic gradient for fluid flux back into the blood

and counteracting edema formation. When the permeability to protein increases, the influence of the term K_d ($\pi_{capillary}-\pi_{interstitium}$) in the Starling equation is reduced due to the decreased K_d as well as the decreased ($\pi_{capillary}-\pi_{interstitium}$) (loss of protein to the tissue). However, no matter what the oncotic pressure gradient, based on the Starling equation, increasing pulmonary capillary pressure always increases fluid efflux. If the capillary permeability to protein is normal, a higher capillary pressure is needed for a given rate of fluid efflux. Conversely, in the presence of increased capillary permeability, lower capillary pressure is needed for a given rate of fluid efflux.

Since the capillary pressure is the major determinant of fluid efflux from the capillaries both in normal and abnormal permeability states, division between "hydrostatic" or "cardiogenic" lung edema and "permeability" or "low-pressure" edema when pulmonary capillary pressure is unknown is artificial and arbitrary. Indeed, capillary hydrostatic pressure and capillary permeability interact in all types of lung edema. An increase in the pulmonary venous resistance increases the pulmonary capillary pressure. Under these conditions the pulmonary artery occlusion pressure or left atrial pressure underestimates the pulmonary capillary pressure [4, 5]. Furthermore, the pressure difference between pulmonary capillary pressure and left atrial pressure varies with blood flow. The higher the blood flow then for the same pulmonary venous resistance the greater the pulmonary capillary pressure and the greater the pressure drop.

How to interpret an increased transpulmonary pressure gradient?

A positive pressure gradient must exist between the pulmonary arterial diastolic pressure and the left atrium for blood to flow. Under normal circumstances this gradient is less than 6–8 mmHg, increasing slightly with increasing flow and decreasing to near zero at rest when pulmonary blood flow almost ceases during each diastole. A widening gradient between the pulmonary arterial diastolic pressure and the left atrial pressure is a signal of increased pulmonary vascular resistance, increased pulmonary blood flow, or both, and is an indicator that pulmonary capillary pressure may exceed pulmonary artery occlusion pressure. While the pulmonary artery occlusion pressure may overestimate the left atrial pressure in the presence of Starling resistor forces causing pulmonary venous collapse [6], an increased gradient between the pulmonary arterial diastolic pressure and the pulmonary artery occlusion pressure is still a valid indicator of increased capillary pressure. An isolated increase in the arterial resistance does not increase the capillary pressure by itself.

Normally two-thirds of the transpulmonary pressure drop occurs over the arterial resistance, with approximately one-third of the pressure drop occurring over the venous resistance. However, a selective increase in pulmonary venous resistance can occur and directly increases pulmonary capillary pressure in proportion to blood flow. Many normal physiological responses and disease states are associated with increased pulmonary venous resistance. Increased pulmonary vasomotor tone occurs with hypoxic pulmonary vasoconstriction. If associated with increased blood flow, as with exercise at high altitude, one can rapidly understand how high altitude pulmonary edema may occur. Disease states associated with transient massive sympathetic discharge, such as acute cerebral hemorrhage and heroin overdose, produce transient massive increases in pulmonary capillary pressure. Finally, during the reparative phase of acute lung injury, pulmonary fibrosis may occur. Fibrosis is indiscriminate of the vasculature and obstructs all vessels, thus making increased pulmonary vascular resistance a hallmark of end-stage acute lung injury. Persistent pulmonary edema in a patient with late-stage acute respiratory distress syndrome may reflect occult hydrostatic pulmonary edema.

How can the pulmonary capillary pressure be estimated at the bedside?

Bedside assessment of pulmonary capillary pressure is based on visual inspection of the pulmonary artery pressure decay during balloon occlusion using a balloon floatation pulmonary artery catheter [1, 2, 3] (Fig. 1). Ideally the occlusion should be performed during an expiratory hold to avoid the effect of dynamic changes in intrathoracic pressure and lung volume on the pressure curve. After occlusion, one sees a rapid decrease in pressure, followed by a slower pressure decrement approaching the pulmonary artery occlusion pressure (Fig. 1a). When a straight line is drawn tangent to the rapid component, pulmonary capillary pressure can be estimated as the point at which the pressure transient begins to deviate from the rapid portion of the pressure tracing (Fig. 1b). The assessment can be facilitated by the use of a strip chart recorder or a computer sampling of the signal, and by superimposing the occlusion tracing on a nonoccluded one (Fig. 1a). More sophisticated approaches include the use of moving average smoothing of the pressure signal and mathematical curve fitting of the signal (Fig. 1b). The visual inspection method has been thoroughly validated in experimental conditions and gives values very similar to those of the more complex approaches. In the clinical routine a rough estimate of capillary pressure can even be obtained directly from the monitor screen by freezing the pressure trace when measuring the pulmonary artery occlusion pressure.

To assess the risk of pulmonary edema in the presence of pulmonary hypertension and increased transpulmona-

ry pressure gradient it is necessary to estimate the capillary pressure. Importantly, once pulmonary capillary pressure is known, the arterial and venous components of the pulmonary vascular resistance can be calculated as the ratio of their respective pressure gradients (pulmonary artery diastolic to pulmonary capillary and pulmonary capillary to left atrial) to total blood flow. If pulmonary venous resistance is elevated, effective strategies to minimize pulmonary capillary pressure may include reducing total blood flow (hypothermia, sedation, paralysis) and the use of pulmonary vasodilator substances (inhaled nitric oxide, calcium channel blockers, and infusions of potent vasodilators such as prostaglandin E, prostacyclin, nitroglycerin, hydralazine) with appropriate intermittent monitoring of pulmonary capillary pressure to document its reduction.

References

1. Cope DK, Grimbert F, Downey JM, Taylor AE (1992) Pulmonary capillary pressure: a review. Crit Care Med 20:1043–1056
2. Holloway H, Perry M, Downey J, Parker J, Taylor A (1983) Estimation of effective pulmonary capillary pressure in intact lungs. J Appl Physiol 54:846–851
3. Cope DK, Allison RC, Parmentier JL, Miller JN, Taylor AE (1986) Measurement of effective pulmonary capillary pressure using the pressure profile after pulmonary artery occlusion. Crit Care Med 14:16–22
4. Pellett AA, Lord KC, Champagne MS, deBoisblanc BP, Johnson RW, Levitzky MG (2002) Pulmonary capillary pressure during acute lung injury in dogs. Crit Care Med 30:403–409
5. Benzing A, Bräutigam P, Geiger K, Loop T, Beyer U, Moser E (1995) Inhaled nitric oxide reduces pulmonary transvascular albumin flux in patients with acute lung injury. Anesthesiology 83:1153–1161
6. Fang K, Krahmer RL, Rypins EB, Law WR (1996) Starling resistor effects on pulmonary artery occlusion pressure in endotoxin shock provide inaccuracies in left ventricular compliance assessments. Crit Care Med 24:1618–1625

François Jardin

Ventricular interdependence: how does it impact on hemodynamic evaluation in clinical practice?

The left (LV) and right ventricles (RV) are enclosed in a stiff envelope, the pericardium. They have similar end-diastolic volumes, and there is no free space for acute ventricular dilatation within a normal pericardial space. Thus, when RV end-diastolic volume increases owing to increased RV loading, it can only occur at the expense of the space devoted to the left ventricle, which is prevented from dilating to as large an end-diastolic volume as it would otherwise given its distending pressure. From a practical point of view this reduced LV end-diastolic volume is accompanied by decreases in LV diastolic compliance, such that for the same LV distending pressure LV end-diastolic volume is less. This point was described in a previous Physiological Note [1]. LV impaired relaxation by RV enlargement is evidenced by Doppler examination of mitral flow velocity (Fig. 1).

Such competition for end-diastolic volume between the right and left ventricles is enhanced when mediastinal pressure (i.e., pleural, pericardial, or both) or lung volume are increased. Moreover, relative ventricular compliance, that is, the relation between LV end-diastolic pressure and LV end-diastolic volume, is markedly affected by pericardial pressure. If pericardial pressure were to increase but not accounted for in the calculation of LV distending pressure, LV diastolic compliance would appear to be decreased. Often esophageal pressure is used to estimate intrathoracic pressure and, by extension, pericardial pressure. Importantly, many processes can alter pericardial pressure independent of esophageal pressure, such as hyperinflation, pericardial effusions and acute RV dilation

Another aspect of ventricular interdependence relates to the fact that both ventricles are arranged in series. Since LV filling requires RV output, adequate left ventricular filling can be only supplied by adequate RV output. In turn, adequate RV output requires adequate venous return, and nonobstructed pulmonary circulation.

The "age of oil lamps": ventricular interdependence renders inaccurate the classical hemodynamic evaluation by a pulmonary artery catheter. For a long time, fluid management in critically ill patients requiring mechanical ventilation was guided by measurement of both RV and LV filling pressures. Moreover, evidence of de-

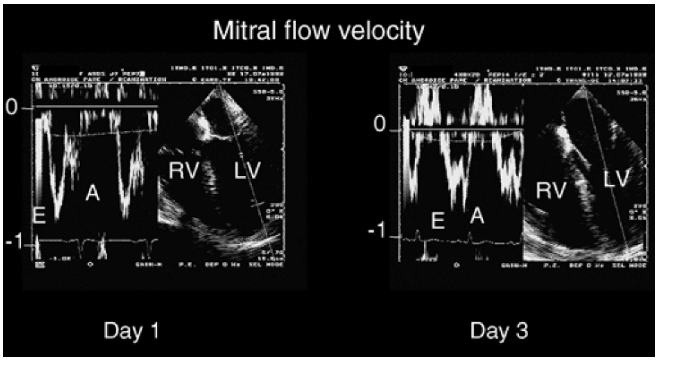


Fig. 1 Illustration of left ventricular (*LV*) relaxation impairment by right ventricular (*RV*) dilatation, in a mechanically ventilated patient with acute respiratory distress syndrome. During the first day of mechanical ventilation (*left*) a normal right ventricular size, observed in the two-dimensional view, was associated with a normal pattern of Doppler mitral flow velocity, with a preeminent peak velocity of the E wave (early filling) and a less marked peak velocity of the A wave (atrial systole). After 48 h of respiratory support (*right*) right ventricular dilatation, observed on the two-dimensional view, was associated with a modified pattern of Doppler mitral flow velocity, with equalization of peak velocities

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_20, © Springer-Verlag Berlin Heidelberg 2009

pressed systolic ventricular function was based upon observational changes in filling pressure related to changes in cardiac output during a fluid challenge. Pulmonary arterial catheterization is commonly used to assess these parameters. Direct measures of right atrial (or central venous, CV) pressure (P) and pulmonary artery occlusion pressure (Ppao) can be made from a pulmonary arterial catheter. And using a distal tip thermistor, pulmonary blood flow as a surrogate of cardiac output can be measured. Clinically CVP is used to reflect RV filling pressure and Ppao LV filling pressure. This allows the construction of RV and LV "Frank-Starling curves" when filling pressures are plotted against stroke volume or cardiac output. It is theoretically possible to discriminate between an insufficient preload (requiring volume expansion) and a contractile defect (requiring inotropic support) in the hemodynamically unstable patient using this analysis.

A major drawback of the above method results from the lack of measurement of ventricular volume. Since RV and LV diastolic compliance can and do vary rapidly in unstable patients, filling pressures or their changes in response to therapy may poorly reflect preload. Regrettably, at the present time it is not possible to measure diastolic compliance at the bedside. As a result a high filling pressure may coexist with a reduced preload if ventricular compliance is low, and a low filling pressure may coexist with a normal preload if ventricular compliance is high [2]. This drawback characterizes particularly patients with acute respiratory distress syndrome, in whom a progressive increase in PEEP produces a progressive increase in measured LV end-diastolic pressure, associated with a progressive decrease in LV end-diastolic size [3].

The "age of electricity": ventricular interdependence does not affect the accuracy of hemodynamic evaluation by bedside echocardiography. Whereas knowledge of ventricular diastolic compliance is fundamental in interpreting ventricular intracavitary pressure, it is less important with the use of echocardiography, which permits direct visualization of venous distention, biventricular maximal chamber size, and a rough approximation of systolic function.

In clinical practice, the adequacy of venous return under respiratory support can be evaluated by inspection of respiratory changes in the superior vena caval diameter (Fig. 2). In particular, a high collapsibility index (i.e., major expiratory diameter minus minor inspiratory diameter divided by major expiratory diameter) of the superior vena cava identified potential differences between measured CVP and actual RV filling pressure, because the external pressure for the vessel, which is pleural pressure, causes vascular collapse. Such a condition in a hemodynamically unstable person denotes a need for volume expansion [4].

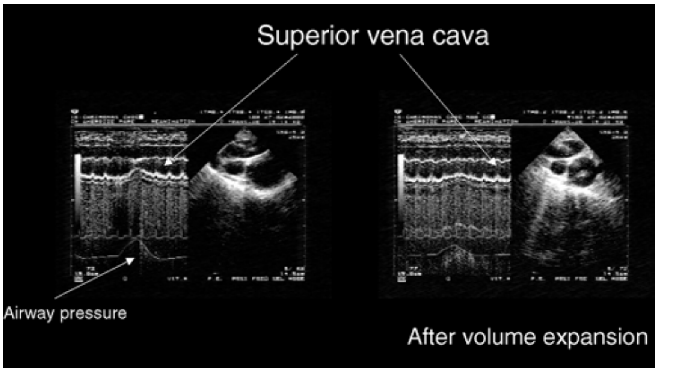


Fig. 2 Illustration of the gauge for central blood volume constituted by vena caval collapsibility. Before volume expansion (*left*) the patient exhibited a marked reduction in superior vena caval diameter during tidal ventilation. After volume expansion (*right*) inspiratory reduction in vena caval diameter was minimized

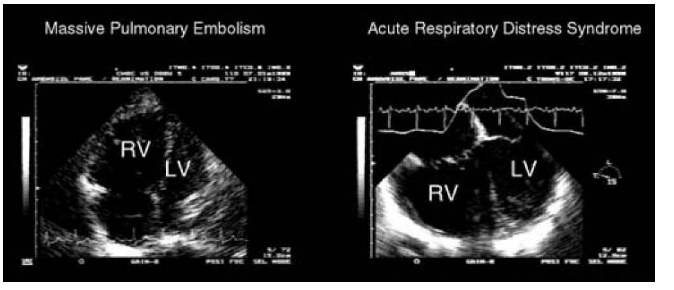


Fig. 3 Two illustrations of ventricular interdependence, where acute right ventricular dilatation is associated with a reduced size of the left ventricular cavity. This interdependence was observed by a long-axis view, in a patient with massive pulmonary embolism (*left*, transthoracic examination) and in a patient with acute respiratory distress syndrome (*right*, transesophageal examination)

RV and LV end-diastolic dimensions can be obtained by bedside echocardiography. These measurements are particularly relevant in the clinical setting of acute cor pulmonale, where hemodynamic impairment resulting from ventricular interdependence has been documented (Fig. 3) [5]. Echocardiographic measurements of LV size has documented an inability of the left ventricular of septic patients to dilate [6].

References

1. Pinsky MR (2003) Significance of pulmonary artery occlusion pressure. Intensive Care Med 29:19–22
2. Jardin F, Bourdarias JP (1995) Right heart catheterization at bedside: a critical view. Intensive Care Med 21:291–295
3. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP (1981) Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 1981:304:387–392
4. Vieillard-Baron A, Augarde R, Prin S, Page B, Beauchet A, Jardin F (2001) Influence of superior vena caval zone condition on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 95:1083–1088
5. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F (2002) Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. Am J Respir Crit Care Med 166:1310–1319
6. Vieillard-Baron A, Schmitt JM, Beauchet A, Augarde R, Prin S, Page B, Jardin F (2001) Early preload adaptation in septic shock? A transesophageal echocardiographic study. Anesthesiology 94:400–406

François Jardin

Cyclic changes in arterial pressure during mechanical ventilation

For a given level of arterial distensibility, the amplitude of the arterial pulse is directly related to the left ventricular (LV) stroke volume. Thus, rapid changes in arterial pulse pressure, the difference between systolic and diastolic pressures, essentially reflect changes in LV stroke volume.

During mechanical ventilation, cyclic inspiratory increases in pleural pressure are transmitted to the intrathoracic aorta, resulting in a cyclic inspiratory increase in arterial pressure [1]. However, this transmission of pleural pressure produces a similar increase in both systolic and diastolic pressures, and does not increase the arterial pulse pressure.

Cyclic changes in arterial pulse pressure during positive-pressure ventilation, in patients ventilated on controlled mode and without spontaneous breathing, can be described as a succession of inspiratory increases, followed by expiratory decreases [2]. The inspiratory increase in systolic arterial pressure observed in this setting has also been termed delta Up (ΔUp) (Fig. 1, upper panel), whereas the expiratory decrease in systolic arterial pressure has been termed delta Down (ΔDown) (Fig. 1, lower panel) [3].

Cyclic changes in arterial pulse pressure during respiratory support are produced by cyclic changes in pulmonary venous return altering LV preload. The main role of inspiratory increase in transpulmonary pressure in determining these changes has been demonstrated by chest strapping in a clinical study performed in acute respiratory distress syndrome (ARDS) patients [4]. Mechanical lung inflation produces a sudden increase in distal airway pressure, whereas, at the same time, pleural pressure increases to a lesser extent. As a result, transpulmonary pressure, i.e., alveolar pressure minus pleural pressure, is suddenly increased. These cyclic changes in transpulmonary pressure have an instantaneous impact on the pulmonary circulation, particularly on the capillary bed, which is intra-alveolar. The blood present in this capillary bed, approximately 100 ml, constitutes, with the blood present in pulmonary veins, the filling reserve of the left ventricle [2, 5, 6]. As a result, the pulmonary capillary bed is emptied, and LV filling is increased, resulting in an inspiratory increase in LV ejection [6].

At the same time, the sudden increase in transpulmonary pressure increases right ventricular (RV) outflow impedance [4], and produces a drop in RV ejection [6, 7]. This drop causes a delay in re-filling of the pulmonary capillary bed, and, as a consequence, a late inspiratory and early expiratory decrease in LV filling produces an expiratory decrease in LV ejection [6].

The amplitude of cyclic changes in arterial pulse pressure, pulse pressure variation (PPV), can be measured as a percentage of expiratory decrease, as proposed by Michard et al. [8]. In the original formula given by these authors, PPV = maximal inspiratory value − minimal expiratory value/1/2 (maximal inspiratory value + minimal expiratory value) [8]. With the recently accepted respiratory strategy limiting airway pressure (low stretch strategy), PPV, which is present in all mechanically ventilated patients, is usually small, between 1% and 5%. This amplitude may be increased by either hypervolemia or hypovolemia.

When hypervolemia is present, the amount of blood filling the pulmonary capillary bed is increased, and,

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_21, © Springer-Verlag Berlin Heidelberg 2009

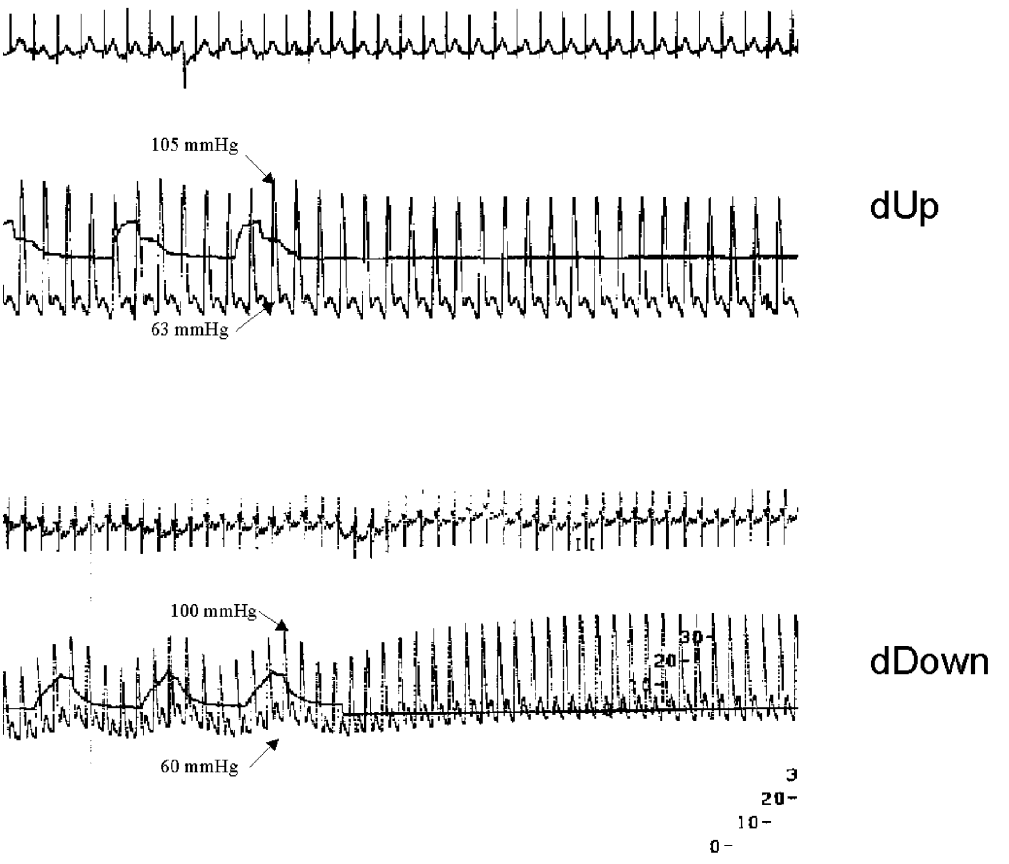


Fig. 1 Two illustrative examples of simultaneous recording of invasive arterial pulse and tracheal pressure in mechanically ventilated patients. In the *upper panel*, a short disconnection from the respirator shows that previous cyclic changes were exclusively produced by a ΔUp (*dUp*). Conversely, in the *lower panel*, the same disconnection indicates that previous cyclic changes were exclusively produced by a ΔDown (*dDown*). Note that systolic arterial pressure is in a normal range in the upper example, whereas it is low in the lower example

with each lung inflation, a greater amount of blood is boosted toward the left ventricle. This squeeze of blood enlarges PPV by increasing ΔUp (Fig. 2, upper left panel). A rapid fluid removal may reduce PPV (Fig. 2, lower left panel). Importantly, this pattern of increased PPV is usually observed in patients with a normal or elevated arterial pressure, but may also occur in patients with low arterial pressure, especially if heart failure is present [3].

When hypovolemia is present, the right ventricle may be on the initial ascending part of its Starling curve, and sensitive to preload changes. Thus, inspiratory increases in pleural pressure will induce an additional decrease in RV preload, resulting from the transient decrease in venous return, accentuating the inspiratory drop in RV ejection [9]. This preload impairment enlarges PPV by enlarging ΔDown (Fig. 2, upper right panel). A rapid volume expansion may reduce PPV (Fig. 2, lower right panel). Importantly, this pattern of increased PPV is usually observed in patients with low arterial pressure. In these patients, volume expansion usually significantly increases cardiac output and arterial pressure. Measurement of PPV has thus been proposed and documented to be a sensitive index of fluid responsiveness in the hemodynamically unstable patient, provided that sinus rhythm is regular and there is no spontaneous breathing effort [8]. In a recent clinical study conducted in septic patients by Michard et al. [8], a PPV >13% detected subsequent fluid responsiveness with 94% sensitivity and 96% specificity. Additionally, hypovolemia may not be absolute, but only relative to the level of pleural pressure change [10]. Conversely, and probably more importantly, when a patient with septic shock does not exhibit marked change in arterial pulse pressure under respiratory support, fluid expansion is likely unprofitable, and perhaps deleterious.

More recently, we have observed that septic patients with acute RV dysfunction may be associated with a large PPV coexisting with a low arterial pressure. Importantly, such conditions, usually referred to as cor pulmonale, may not respond to volume expansion (Fig. 3). This finding illustrates the main role of the right ventricle in cyclic changes in arterial pulse pressure during mechanical ventilation. When RV systolic function is markedly impaired and/or pulmonary vascular resistance markedly increased, volume expansion at the venous level cannot attain pulmonary circulation and cannot correct a LV preload defect [11].

Thus, cyclic changes in arterial pulse pressure and its systolic component during mechanical ventilation are induced by complex interactions between systemic venous return, RV ejection, intrathoracic blood volume

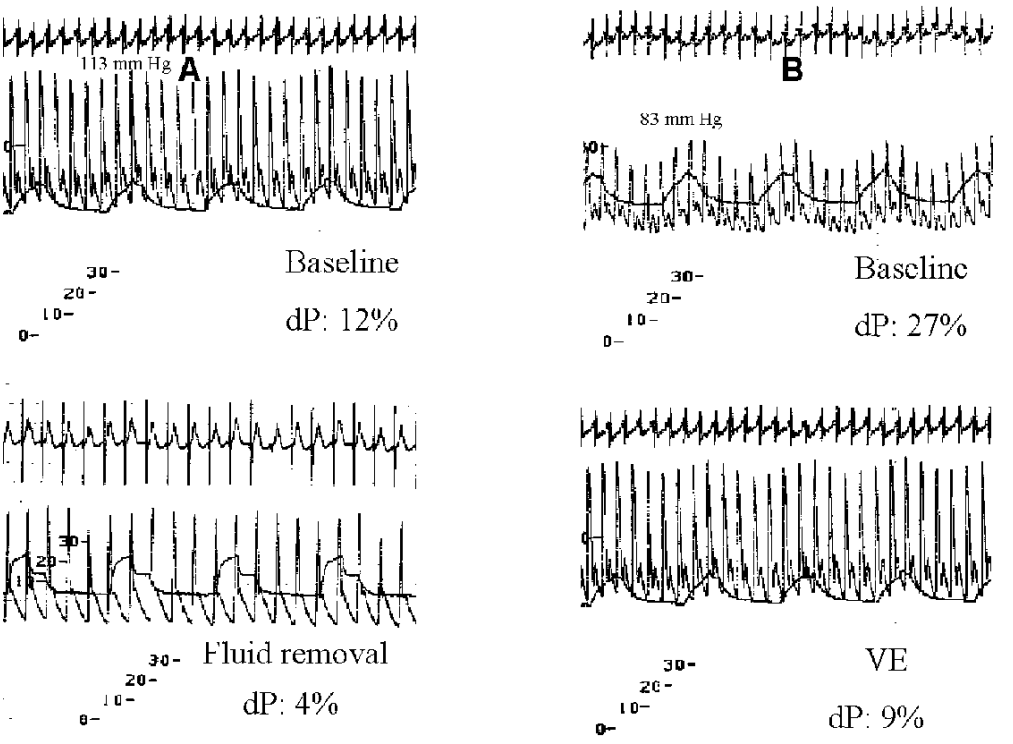


Fig. 2 In the *left panel*, the overfilled patient A exhibits an expiratory drop in arterial pulse of 12% at baseline (*upper panel*), coexisting with a normal systolic arterial pressure. Rapid fluid removal by veno-venous hemodiafiltration reduces this expiratory drop to 4%. In the *right panel*, the hypovolemic patient B exhibits a major expiratory drop in arterial pulse of 27% at baseline, coexisting with an abnormally low systolic arterial pressure. Rapid volume expansion reduces this expiratory drop to 9%

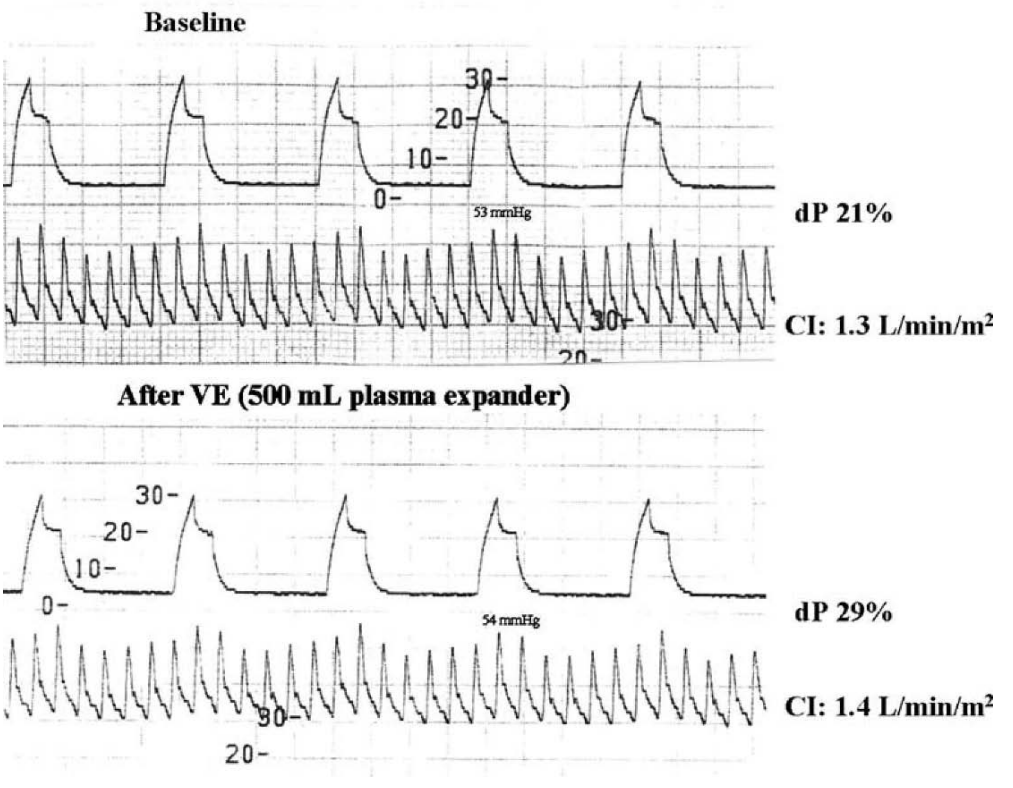


Fig. 3 Two successive recordings of arterial pulse in a mechanically ventilated patient with ARDS due to bacterial pneumonia. Transesophageal echocardiography demonstrates severe acute cor pulmonale. In the *upper panel*, this patient exhibits hypodynamic circulatory failure, with depressed systolic arterial pressure and Doppler cardiac output. Because this critical hemodynamic state was associated with a large 21% PPV, it was decided to apply a rapid volume expansion. After volume expansion (*lower panel*), the hemodynamic status was unchanged. This illustrates the key role of right ventricular function in determining the cyclic changes in arterial pulse under respiratory support. Norepinephrine infusion promptly and completely corrected circulatory failure in this patient

shifts and LV performance. Although the existence of a ΔUp usually identifies those patients with impaired LV contractility and volume expansion, and an enlarged PPV volume responsive hypovolemia, if RV function is impaired, these simple rules may not apply. Importantly, RV dysfunction often occurs in the setting of acute respiratory failure and may complicate the non-specific application of pulse pressure as a monitoring tool.

References

1. Denault A, Gasior T, Gorcsan J, Mandarino W, Deneault L, Pinsky M (1999) Determinants of aortic pressure variation during positive-pressure ventilation in man. Chest 116:178–186
2. Jardin F, Farcot JC, Gueret P, Prost JF, Ozier Y, Bourdarias JP (1983) Cyclic changes in arterial pulse during respiratory support. Circulation 68:266–274
3. Preisman S, Pfeiffer U, Liberman N, Perel A (1997) New monitors of intravascular volume: a comparison of arterial pressure waveform analysis and the intrathoracic blood volume. Intensive Care Med 23:651–657
4. Vieillard-Baron A, Loubières Y, Schmitt JM, Page B, Dubourg O, Jardin F(1999) Cyclic changes in right ventricular outflow impedance during mechanical ventilation. J Appl Physiol 87:1644–1650
5. Versprille A (1990) The pulmonary circulation during mechanical ventilation. Acta Anaesthesiol Scand 34 (Suppl) 94:51–62
6. Vieillard-Baron A, Chergui K, Augarde R, Prin S, Page B, Beauchet A, Jardin F (2003) Cyclic changes in arterial pulse during respiratory support revisited by Doppler echocardiography. Am J Respir Crit Care Med 168:671–676
7. Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias JP (1990) Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. Anesthesiology 72:966–970
8. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky M, Teboul JL (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138
9. Vieillard-Baron A, Augarde R, Prin S, Page B, MD, Beauchet A, Jardin F (2001) Influence of superior vena caval zone conditions on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 95:1083–1088
10. Michard F, Chemla D, Richard C, Wysocki M, Pinsky M (1999) Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effect of PEEP. Am J Respir Crit Care Med 159:935–939
11. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F (2003) Hemodynamic instability in sepsis: bedside assessment by Doppler echocardiography. Am J Respir Crit Care Med 168:1270–1276

Daniel De Backer

Lactic acidosis

Introduction

Hyperlactatemia is considered a hallmark of ongoing tissue hypoxia, but this is not always the case, and erroneous conclusions may sometimes be drawn that lead to unjustified therapeutic interventions. In this note we discuss the possible implications of hyperlactatemia

Lactate metabolism

Lactate is a byproduct of glycolysis. In the energy-producing metabolism of glucose two distinct processes occur. The first series of enzymatic reactions (Enden-Mierhoff pathway), occurring in the cytoplasm of cells, anaerobically transforms 1 molecule of glucose into 2 molecules of pyruvate, generating 2 molecules of ATP. This is the primary energy process for all cells functioning in a low oxygen environment, such as in poorly perfused tissues. Pyruvate may either be converted to lactate, producing one additional molecule of ATP, or move into the second series of reactions. The second series of enzymatic reactions (Krebs cycle) takes place in the mitochondria and requires oxygen: pyruvate is oxidized into CO_2 and H_2O producing 18 ATP molecules. In the absence of oxygen, pyruvate cannot enter the Krebs cycle and is preferentially transformed into lactate to maintain ATP production. This causes the lactate to pyruvate ratio to increase (normal ratio 10/1). Once molecular oxygen is again available, assuming that mitochondrial function is preserved, the excess lactate is rapidly metabolized back through pyruvate into CO_2 and H_2O via the Krebs cycle. Some cells, such as red blood cells, do not have mitochondria and thus are primary lactate producers. Since lactate is rapidly metabolized by liver and skeletal muscle, these functional anaerobic cells result in minimal blood lactate levels.

Lactate in the blood is metabolized mainly by the liver (50%) and kidneys (20%). Liver function and liver blood flow influence hepatic lactate clearance, but extreme conditions of pH can also decrease lactate clearance. Renal lactate clearance occurs in the cortex, and this area is very sensitive to a reduction in blood flow. Striated muscle, the heart, and the brain also metabolize lactate and in some conditions this clearance can be significant. In basal metabolic conditions arterial lactate levels are between 0.5 and 1 mEq/l, and this value represents the balance between lactate production and consumption. Traditionally, elevated blood lactate levels in hemodynamically unstable subjects are often taken to reflect circulatory shock, arterial hypoxemia or both. However, other factors may coexist, complicating the interpretation of hyperlactatemia.

Lactate vs. pH measurements in assessing anaerobic metabolism?

Monitoring the blood pH, base deficit, or anion gap may fail to detect hyperlactatemia. Hyperventilation corrects arterial pH. Measurements of base excess and anion gap reflect lactate levels in pure lactic acidosis, buts may be influenced by other factors in complex situations. Concomitant renal failure, preexisting acid base disorders, and decreased albumin levels alter the specificity and sensitivity of base excess. Hence measurements of

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_22, © Springer-Verlag Berlin Heidelberg 2009

blood lactate levels are mandatory to detect hyperlactatemia.

Lactate measurements

Measurement has long involved sampling blood on iced fluoride tubes to inhibit in vitro red blood cells lactate production. Lactate is then measured on plasma using enzymatic colorimetry with lactate dehydrogenase. More recent analyzers use enzymatic amperometry with lactate oxidase generating H_2O2, which is detected by the electrode. The time response with these two methods is approximately 1 h. Alternatively, blood lactate levels can be measured by a blood gas analyzer using the same enzymatic amperometry technique. The time response is only 2 min. To be valid, blood gas analyzer measurements must be made with a short delay between sampling and analysis (less than 5 min, with the syringe stored on ice). Blood lactate concentrations overestimate plasma concentrations by 1 or 2 decimals. Measurement of plasma lactate with enzymatic amperometry is the reference method, which should be used when accurate measurements are required (especially for estimating arteriovenous lactate differences). Pyruvate measurements may be useful to identify anaerobic lactate production, but these are cumbersome, time consuming, and subject to many errors.

Anaerobic lactate production

In experimental conditions blood lactate concentrations rise when O_2 consumption becomes dependent on O_2 delivery (VO_2/DO_2 dependency), reflecting anaerobic metabolism. In critically ill patients in low flow states hyperlactatemia is mostly of hypoxic origin, although some impairment in liver metabolism may coexist. Tissue wash out may also be present following acute resuscitation.

In septic conditions hyperlactatemia can also be observed, but its hypoxic origin is less clear. In patients with acute circulatory failure treated with high doses of vasoactive agents there is a strong suspicion that hyperlactatemia is related to tissue hypoxia [1]. However, tissue hypoxia and anaerobic metabolism cannot be sustained for long periods of time without inducing cell death, as the energy produced by anaerobic metabolism is quite low compared to aerobic metabolism. Mild hyperlactatemia (2–4 mEq/l) in hemodynamically stable septic patients is probably not related to tissue hypoxia.

Aerobic lactate production

Experimental studies in rodents have reported that pyruvate dehydrogenase, an enzyme essential for the incorporation of pyruvate into the Krebs cycle, is inhibited after endotoxin administration or cecal ligation. However, the impact of pyruvate dehydrogenase inhibition in septic patients remains to be determined as the administration of dichloroacetate, bypassing pyruvate dehydrogenase, results in small and clinically insignificant changes in blood lactate levels and arterial pH [2].

More importantly, sepsis-induced inflammatory mediators accelerate aerobic glycolysis, increasing pyruvate availability. In hemodynamically stable septic patients Gore et al. [3] reported that lactate and pyruvate were both markedly increased and related to an accelerated glucose turnover, as glucose production was fourfold higher in septic patients than in healthy volunteers.

Regional lactate production

Animal studies have reported that the lungs are major lactate producers in sepsis [4]. In patients with acute lung injury, several groups have reported that lung lactate production is markedly increased and proportional to the severity of lung injury. The amount of lactate produced by the lungs in acute lung injury is tremendous and can higher than basal endogenous lactate production by the entire body. De Backer et al. [5] demonstrated that lung lactate production occurs in subjects with acute lung injury states but not in patients with normal lungs, cardiogenic pulmonary edema, or pneumonia. Thus lung lactate production requires a diffuse inflammatory process.

Other organs can also produce lactate. Experimental studies suggest that the gut can produce lactate in sepsis, which is likely from anaerobic metabolism as portal lactate to pyruvate ratio is increased. The investigation of splanchnic lactate turnover in humans is much more complicated as access to the portal vein is not possible outside the operating room. Since the liver is usually able to clear this small amount of gut-produced lactate, splanchnic ischemia may go unsuspected. Accordingly, De Backer et al. [6] reported that splanchnic lactate release is uncommon in patients with severe sepsis and was not related to arterial lactate concentrations, abdominal infection or signs of gut or liver dysoxia.

Finally, white blood cells may also take an active part in the increased tissue lactate production. Under basal conditions, only 10% of ATP production is of mitochondrial origin; hence anaerobic glycolysis provides most of the additional energy requirements when white blood cells are activated, producing large amounts of lactate. Although generated by anaerobic metabolism, this increase in lactate production is not due to O_2 deprivation. After exposure to endotoxin in vitro, whole blood lactate production almost doubles, and this is due exclusively to an increase in white blood cell lactate production [7], as red blood cell lactate production is not modified. Hence

large amounts of lactate can be produced in inflammatory processes even in the absence of tissue hypoxia. Presumably this is the cause of the positive lactate flux from the lung in acute lung injury.

Decreased lactate clearance

Blood lactate concentrations are the result of the balance between lactate production and clearance. In normal conditions at rest the liver accounts for more than one-half of lactate clearance, with kidneys and muscles accounting for the remaining part. The respective contribution of these organs can be influenced by several factors including exercise, liver dysfunction and glucose and O_2 availability.

Liver dysfunction is frequent in critically ill patients and can affect blood lactate concentrations. Using an external lactate load in hemodynamically stable septic patients, Levraut et al. [8] reported that lactate clearance was altered in patients with mildly elevated blood lactate levels (2–4 mEq/l) but not in patients with normal blood lactate concentrations. However, blood lactate concentrations are within normal values in patients with very severely impaired liver function such as in ambulatory cirrhotic patients. Hence, an increased blood lactate concentration suggests that lactate is actively, or has been recently, produced in increased amounts; the impairment in liver function being responsible for a delayed clearance.

Interpretation of blood lactate concentrations

Increased blood lactate can only be caused by increased anaerobic or aerobic lactate production, eventually combined with decreased lactate clearance (Fig. 1). Hence tissue hypoxia should always be excluded first, as persistent tissue hypoxia can lead to multiple organ failure and death. Tissue hypoxia can be global, especially in low flow states and hypoxemia, but it can also be localized, especially within the gut microcirculation. Sometimes impaired mitochondrial performance can induce hyperlactemia. In particular, antiretroviral therapies can induce uncoupling of cytochrome energy transfer, leading to severe and often lethal lactic acidosis. Aerobic lactate production, either global or focal (especially in the lungs), is the result of activation of the inflammation cascade. Hence hyperlactatemia may be a warning indicator of a very severe inflammatory state. One should examine any patient with unexplained lactic acidosis in order to ensure that no focus of infection remains uncovered. When an altered lactate clearance is involved, it can be due to an altered liver metabolism, usually insensitive to hemodynamic manipulations, but also to a decreased perfusion of the liver, which can be improved by hemodynamic interventions.

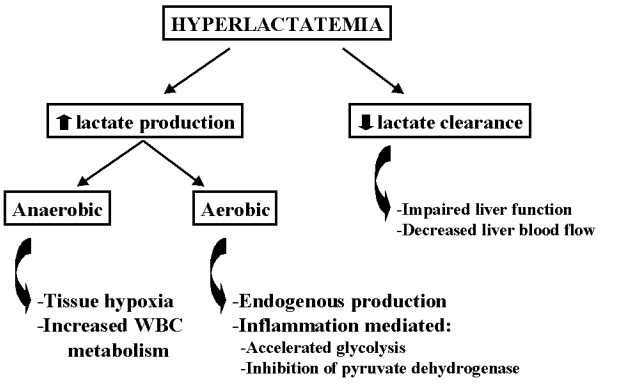


Fig. 1 Interpretation of hyperlactatemia. Blood lactate concentrations reflect the balance between lactate production, either anaerobic (mainly in tissue hypoxia) or aerobic, and lactate clearance (i.e., the sum of the endogenous oxidative-phosphorylation lactate production and the additional lactate production under the influence of overwhelming inflammation, and lactate clearance, mainly by the liver). *WBC* White blood cells

Prognostic value

Whatever its source, lactic acidosis is associated with impaired survival. Admission blood lactate levels are strongly associated with outcome [9]. Interestingly, the prognostic value is better for lactate than for pyruvate or the lactate to pyruvate ratio, suggesting that the prognostic value is not related to tissue hypoxia alone. The course of blood lactate concentrations give the best prognostic value. A decrease in blood lactate levels during the first 24 h is associated with a better outcome while persistent hyperlactatemia and increasing lactate levels are associated with a worse outcome.

Early recognition of hyperlactatemia is essential, as early interventions targeted on hemodynamic endpoints can decrease mortality in patients with severe sepsis and elevated blood lactate levels [10]. However, it has not been confirmed that interventions targeted specifically to normalize blood lactate concentrations can improve outcome.

Conclusions

Measurements of blood lactate concentrations are useful to detect occult tissue hypoxia and to monitor the effects of therapy. However, hyperlactatemia can be due to other causes than tissue hypoxia, in particular inflammatory processes, and therefore hemodynamic interventions in subjects with elevated blood lactate levels may not always be warranted.

References

1. Levy B, Sadoune LO, Gelot AM, Bollaert PE, Nabet P, Larcan A (2000) Evolution of lactate/pyruvate and arterial ketone body ratios in the early course of catecholamine-treated septic shock. Crit Care Med 28:114–119
2. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan CA, Harman EM, Henderson GN, Jenkinson S (1992) A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. N Engl J Med 327:1564–1569
3. Gore DC, Jahoor F, Hibbert JM, DeMaria EJ (1996) Lactic acidosis during sepsis is related to increased pyruvate production, not deficits in tissue oxygen availability. Ann Surg 224:97–102
4. Bellomo R, Kellum JA, Pinsky MR (1996) Transvisceral lactate fluxes during early endotoxemia. Chest 110:198–204
5. De Backer D, Creteur J, Zhang H, Norrenberg M, Vincent JL (1997) Lactate production by the lungs in acute lung injury. Am J Respir Crit Care Med 156:1099–1104
6. De Backer D, Creteur J, Silva E, Vincent JL (2001) The hepatosplanchnic area is not a common source of lactate in patients with severe sepsis. Crit Care Med 29:256–261
7. Haji-Michael PG, Ladriere L, Sener A, Vincent JL, Malaisse WJ (1999) Leukocyte glycolysis and lactate output in animal sepsis and ex vivo human blood. Metabolism 48:779–785
8. Levraut J, Ciebiera JP, Chave S, Rabary O, Jambou P, Carles M, Grimaud D (1998) Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 157:1021–1026
9. Weil MH, Afifi AA (1970) Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 41:989–1001
10. Rivers E, Nguyen B, Havstadt S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377

Rinaldo Bellomo
John A. Kellum
Claudio Ronco

Defining acute renal failure: physiological principles

Introduction

Definitions are never "right" or "wrong". They are simply more or less "useful" for a given purpose. The same is true of the clinical syndrome of acute renal failure (ARF), which is common in the ICU [1, 2]. In many ways, its nature and epidemiology resemble those of other loosely defined ICU syndromes, such as sepsis or ARDS. In this physiological note, however, we wish to focus on how our understanding of renal physiology can be used to guide the definition of ARF.

What are the physiological functions of the kidney?

Many renal functions are shared with other organs (acid-base control with lung; blood pressure control via the renin-angiotensin-aldosterone axis with liver, lung and adrenal glands). Other functions are not routinely measured (small peptide excretion, tubular metabolism, hormonal production) in the ICU and are not considered clinically important. There are only two physiological functions that are routinely and easily measured in the ICU, which are "unique" to the kidney and which are considered clinically important: the production of urine and the excretion of water soluble waste products of metabolism. Thus, clinicians have focused on these two aspects of renal function to help them define the presence of ARF.

Renal solute excretion: glomerular filtration

Renal solute excretion is the result of glomerular filtration and the glomerular filtration rate (GFR) is a convenient and time-honoured way of quantifying renal function. However, GFR varies as a function of normal physiology as well as disease. For example, subjects on a vegetarian diet may have a GFR of 45–50 ml/min, while subject on a large animal protein intake may have a GFR of 140–150 ml/min, both with the same normal renal mass [3].

Baseline GFR can be incremented by efferent arteriolar vasoconstriction or afferent arteriolar vasodilatation or both. Angiotensin converting enzyme (ACE) inhibitors induce the opposite effect and reduce filtration fraction and GFR [4]. It is not clear what the maximum GFR value can be, but it can be approached with an acute animal protein or amino acid load. The concept of a baseline and maximal GFR in humans has been defined as the "renal functional reserve". Figure 1 displays a series of examples describing the GFR/functional renal mass domain graph. For the purposes of this illustration, GFR can be considered a continuous function, which is maximal in subjects with 100% renal mass, absent in anephric patients and 50% in subjects with a unilateral nephrectomy.

Patients 1 and 2 have the same renal mass but different baseline GFRs owing to different basal protein in-

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_23, © Springer-Verlag Berlin Heidelberg 2009

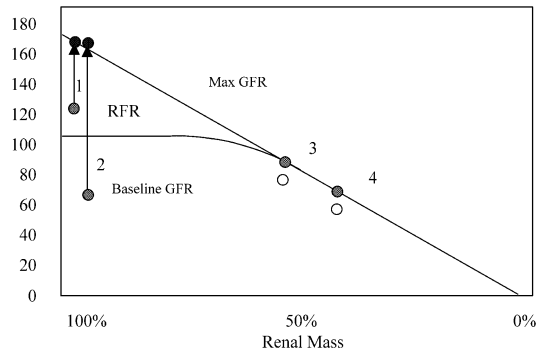


Fig. 1

takes levels. Subject 1 has a GFR of 120 ml/min that can be stimulated to 170 ml/min [3, 4, 5, 6]. Patient 2 is a vegetarian and has a baseline GFR of 65 ml/min that also can be stimulated to 170 ml/min. In other words, the renal functional reserve in these two patients is different because they are using their GFR capacity at a different level. Patient 3 has undergone a unilateral nephrectomy. His baseline GFR corresponds to his maximal GFR under unrestricted dietary conditions. If a moderate protein restriction is applied to his diet, his baseline GFR may decrease and some degree of renal functional reserve become evident. The same concept is true for patient 4; however, to restore some functional reserve, severe protein restriction is needed. Thus, *baseline GFR does not necessarily correspond to the extent of functioning renal mass* and even very careful measurements of GFR will not allow us to define renal function without placing it in the context of maximal capacity. In this regard GFR is not unlike a resting ECG for the kidney. When it is grossly abnormal, renal function is impaired, but when it is normal, a stress test is required. Another approach, is to compare measurements taken over time. Serial measurements of GFR may be impractical but surrogates are readily available. Because urea, or blood urea nitrogen (BUN), is such a non-specific indicator of renal function [7] it is a very poor surrogate for GFR and will not be discussed further.

Serum creatinine, its physiology and defining acute renal failure

Creatinine is much more specific at assessing renal function than BUN, but it only loosely corresponds to GFR. For example, a serum creatinine (S_{cr}) of 1.5 mg/dl (133 mol/l) at steady-state, corresponds to a GFR of about 36 ml/min in an 80-year-old white female, but of about 77 ml/min in a 20-year-old black male. Similarly, a serum creatinine of 3.0 mg/dl (265 mol/l) in a patient suspected of having renal impairment would reflect a GFR of 16 ml/min in the elderly female but 35 ml/min in the young male. In both cases, a doubling of serum creatinine corresponds to an approximate decrease in GFR of 50% (exactly a 55% decrease in the above example) because there is a linear relationship between GFR and 1/Scr. Thus, while every classification of ARF in the literature relies on some threshold value for serum creatinine concentration, *no single creatinine value corresponds to a given GFR across all patients*. Therefore, it is *the change* in creatinine that is clinically and physiologically useful in determining the presence of ARF.

Unfortunately, like all estimates of GFR (including creatinine clearance), the S_{cr} is not an accurate reflection of GFR in the non-steady state condition of ARF. During the evolution of dysfunction, S_{cr} will *underestimate* the degree of dysfunction. Nonetheless, the degree to which S_{cr} changes from baseline (and perhaps the rate of change as well) will reflect the change in GFR. S_{cr} is easily measured and it is reasonably specific for renal function. Thus, S_{cr} is a reasonable approximation of GFR in most patients with normal renal function [8]. Creatinine is formed from non-enzymatic dehydration of creatine in the liver and 98% of the creatine pool is in muscle. Critically ill patients may have abnormalities in liver function and markedly decreased muscle mass. Additional factors influencing creatinine production include conditions of increased production such as trauma, fever and immobilisation; and conditions of decreased production including liver disease, decreased muscle mass and ageing. In addition, tubular re-absorption ("back-leak") may occur in conditions associated with low urine flow rate. Finally, the volume of distribution (V_D) for creatinine (total body water) influences S_{cr} and may be dramatically increased in critically ill patients and, in the short term, its concentration in plasma can be dramatically altered by rapid plasma volume expansion. There is currently no information on extra-renal creatinine clearance in ARF and a non-steady state condition often exists [9].

Creatinine clearance

Once GFR has reached a steady state it can be quantified by measuring a 24-h creatinine clearance. Unfortunately, the accuracy of a creatinine clearance (even when collection is complete) is limited because as GFR falls, creatinine secretion is increased, and thus the rise in S_{cr} is less [10, 11]. Accordingly, creatinine excretion is much greater than the filtered load, causing overestimation of the GFR [11]. Therefore creatinine clearance represents the upper limit of true GFR. A more accurate determination of GFR would require measurement of the clearance of inulin or radio-labelled compounds [12]. Unfortunately, these tests are not routinely available. However, for clinical purposes, *determining the exact GFR is rarely necessary*. Instead, it is important to determine whether

renal function is stable or getting worse or better. This can usually be determined by monitoring S_{cr} alone [8].

Other markers of renal failure

Urine output

Urine output is the commonly measured parameter of renal function in the ICU and is more sensitive to changes in renal haemodynamics than biochemical markers of solute clearance. However, it is far less specific—except when severely reduced or absent. Severe ARF can exist despite normal urine output (i.e. non-oliguric ARF) but changes in urine output often occur long before biochemical changes are apparent. Since non-oliguric ARF has a lower mortality rate than oliguric ARF, urine output is used to differentiate ARF conditions. Classically, oliguria is defined (approximately) as urine output less than 5 ml/kg per day or 0.5 ml/kg per h. It would be highly desirable to have markers which allow physicians to diagnose when oliguria is a true early marker of developing renal failure, because this would allow the identification of patients in whom early intervention may be justified.

Other markers

Kidney injury molecule-1 (KIM-1) expression is markedly up-regulated in the proximal tubule in the post-ischemic rat kidney [13]. A soluble form of human KIM-1 can be detected in the urine of patients with ARF and may serve as a useful biomarker for renal proximal tubule injury, possibly facilitating the early diagnosis of the disease and serving to discriminate between different forms of renal dysfunction [13].

Another marker of potential importance is cystatin C (cysC). Cys C is a cysteine proteinase inhibitor of low molecular weight that is produced constantly by nucleated cells (apparently independently of pathological states) and is excreted by the glomerulus, thus closely reflecting GFR. Thus, cysC may be a better marker of GFR than creatinine [14]. Unfortunately, little information exists on the usefulness of cysC in ARF. A recent pilot study suggested that it might be superior to both S_{cr} and the "modification of diet in renal disease" (MDRD) equation in the detection of ARF [15].

Defining acute renal failure when baseline renal function is unknown

One option is to calculate a theoretical baseline serum creatinine value for a given patient assuming a normal GFR of approximately 95±20ml/min in women and 120±25 ml/min in men [10]. A normal GFR of approximately 75–100 ml/min per 1.73 m^2 can be assumed by normalising the GFR to body surface area [16] and, thus, a change from baseline can be estimated for a given patient. The simplified MDRD formula provides a robust estimate of GFR relative to serum creatinine based on age, race and sex [17]. This estimate could then be used to calculate the relative change in GFR in a given patient. The application of the MDRD equation to estimate baseline creatinine requires a simple table with age, race and gender. Table 1 solves the MDRD equation for the lower end of the normal range (i.e. 75 ml/min per 1.73 m^2). Note, the MDRD formula is used only to estimate the baseline when it is not known. For example, a 50-year-old black female would be expected to have a baseline creatinine of 1.0 mg/dl (88 μmol/l). This approach may misclassify some patients, but is probably adequate for population studies.

Defining acute renal failure in the setting of known renal dysfunction

If the patient has pre-existing renal disease, the baseline GFR and S_{cr} will be different from those predicted by the MDRD equation. Also, the relative decrease in renal function required to reach a given level of S_{cr} will be less than that of a patient without pre-existing disease. For example, a patient with a S_{cr} of 1 mg/dl (88 mol/l) will have a steady-state S_{cr} of 3 mg/dl (264 mol/l) when

Table 1 Estimated baseline creatinine

Age (years)	Black males (mg/dl | μmol/l)	White males (mg/dl | μmol/l)	Black females (mg/dl | μmol/l)	White females (mg/dl | μmol/l)
20–24	1.5 | 133	1.3 | 115	1.2 | 106	1.0 | 88
25–29	1.5 |133	1.2 | 106	1.1 | 97	1.0 | 88
30–39	1.4 | 124	1.2 | 106	1.1 | 97	0.9 | 80
40–54	1.3 | 115	1.1 | 97	1.0 | 88	0.9 | 80
55–65	1.3 | 115	1.1 | 97	1.0 | 88	0.8 | 71
>65	1.2 | 106	1.0 | 88	0.9 | 80	0.8 | 71

Estimated glomerular filtration rate (GFR) =75 (ml/min per 1.73 m^2) =186x (Scr)–1.154x (age) 0.203x(0.742 if female) x(1.210 if African-American) = exp(5.228 1.154xIn(Scr)–0.203x In(age) (0.299 if female) +(0.192 if African-American))

75% of GFR is lost. By contrast, when only 50% of GFR is lost in a perfectly matched patient for age, race and sex with a baseline S_{cr} of 2.5 mg/dl (221 mol/l), the S_{cr} will be 5 mg/dl (442 mol/l). These S_{cr} change criteria fail to convey accurately the degree of loss of renal function and the severity of injury. Thus, separate criteria should be used for the diagnosis of ARF superimposed on chronic renal disease. One possible approach would be to use a relative change in S_{cr} (e.g. threefold) as the primary criterion for ARF, with an absolute cut-off (e.g. 4 mg/dl or about 350 mol/l) as a secondary criterion, when baseline S_{cr} is abnormal. For example, an acute rise in S_{cr} (of at least 0.5 mg/dl or 44 mol/l) to more than 4 mg/dl (350 mol/l) will serve to identify most patients with ARF when their baseline S_{cr} is abnormal.

Testing a definition of acute renal failure?

The ultimate value of a definition for ARF is determined by its utility. A classification scheme for ARF should be sensitive and specific and also predictive of relevant clinical outcomes such as mortality, use of dialysis and length of hospital stay. These are testable hypotheses despite the lack of renal specificity for such end points [18].

It is also understood that therapy can influence the primary criteria for the diagnosis of ARF. For example, volume status will influence urine output and even, to some degree, S_{cr}, by altering V_D. Large-dose diuretics may be used to force a urine output when it would otherwise fall into a category consistent with a diagnosis of ARF. Ultimately, these cases will generally fall into defined criteria but they may cause confusion in the early acute situation. In the end, for operative purposes, it must be assumed that patients are adequately hydrated, not treated with diuretics except in the case of volume overload and treated with renal replacement therapy when clinically indicated. Although this may not always be true for individuals, it should be broadly true for populations.

Conclusions

There are no perfect ways to measure renal function. Even very precise measures of GFR will fail to distinguish mild to moderate functional loss from normal function. Renal function reserve is important but cumbersome to measure. Surrogate measures such as serum creatinine, while routinely available at the bedside, show limited correlation to GFR, especially in the setting of critical illness. Injury markers are being developed which might aid us in the future but are not ready for use just yet. Nonetheless, the lessons of physiology can be used to guide the development of definitions for ARF. All the above physiological considerations have played an important role in guiding the members of the Acute Dialysis Quality Initiative (ADQI) [19] in the formulation of a consensus set of criteria to define ARF. These criteria are open for discussion and comments can be submitted to the ADQI website (http://www.ADQI.net). We believe this process to be fundamental to improving our care of ARF patients and hope to move to formal testing of a final set of criteria soon.

References

1. De Mendonca A, Vincent J-L, Suter PM et al. (2000) Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 26:915–921
2. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J (1998) Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 104:343–348
3. Bosch JP, Lauer A, Glabman S (1984) Short-term protein loading in assessment of patients with renal disease. Am J Med 77:873–879
4. Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M, Glabman S (1983) Renal functional reserve in humans. Effect of protein intake on glomerular filtration rate. Am J Med 75:943–950
5. Bosch JP, Lew S, Glabman S, Lauer A (1986) Renal hemodynamic changes in humans. Response to protein loading in normal and diseased kidneys. Am J Med 81:809–815
6. Ronco C, Brendolan A, Bragantini L, Chiaramonte S, Fabris A, Feriani M, Dell Aquila R, Milan M, Mentasti P, La Greca G (1988) Renal functional reserve in pregnancy. Nephrol Dial Transplant 3:157–161
7. Levey AS (1990) Measurement of renal function in chronic renal disease. Kidney Int 38:167–173
8. Perrone RD, Madias NE, Levey AS (1992) Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 38:1933–1953
9. Clark WR, Ronco C (1998) Renal replacement therapy in acute renal failure: solute removal mechanisms and dose quantification. Kidney Int (Suppl) 53:S133–S137
10. Doolan PD, Alpen EL, Theil GB (1962) A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med 32:65–72
11. Kim KE, Onesti G, Ramirez O (1969) Creatinine clearance in renal disease. A reappraisal. BMJ 4:11–19
12. Branstrom E, Grzegorczyk A, Jacobsson L (1998) GFR measurement with iohexol and 51Cr-EDTA. A comparison of the two favoured GFR markers in Europe. Nephrol Dial Transplant 13:1176–1181
13. Han WK, Bailly V, Abichandani R et al. (2002) Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int 62:237–244

14. Jovanovic D, Krstivojevic P, Obradovic I, Durdevic V, Dukanovic L (2003) Serum cystatin C and beta2-microglobulin as markers of glomerular filtration rate. Ren Fail 25:123–133
15. Herget-Rosenthal S, Marggraf G, Goering F, Phillip T, Kribben A (2003) Can serum cystatin C detect acute renal failure? (abstract). ISN-ERA/EDTA World Congress of Nephrology, Berlin:O11
16. Fliser D, Franek E, Joest M et al (1997) Renal function in the elderly: impact of hypertension and cardiac function. Kidney Int 51:1196–1204
17. National Kidney Foundation. K/DOQI (2002) Clinical practice guidelines for chronic kidney disease; evaluation, classification and stratification. Am J Kidney Dis (Suppl) 39:S76–S92
18. Bellomo R, Kellum J, Ronco C (2001) Acute renal failure: time for consensus. Intensive Care Med 27:1685–1688
19. Kellum JA, Mehta RL, Ronco C (2001) Acute dialysis quality initiative (ADQI). Contrib Nephrol 132:258–265

Frédérique Schortgen

Hypotension during intermittent hemodialysis: new insights into an old problem

Introduction

The main indication for renal replacement therapy in critically ill patients is ischemic acute tubular necrosis associated with multiple organ failure requiring mechanical ventilation and catecholamine administration. The kind of renal replacement therapy offering the best hemodynamic tolerance remains debated. Intermittent hemodialysis (IHD) is often viewed by many ICU physicians as inducing hemodynamic instability. The application of recent concepts regarding hemodialysis modalities is able to solve part of this old problem [1]. A major problem with IHD is the direct application of chronic hemodialysis concepts in the management of acute renal failure. This approach is responsible for much of the observed hemodynamic instability and can be minimized by thoughtful planning prior to IHD in the critically ill patient.

What are the mechanisms of hypotension during hemodialysis?

In critically ill patients intradialytic hypotension results from the underlying process and is exacerbated by the technique itself. Systemic blood pressure is determined by the interaction of blood flow and peripheral vasomotor tone, both of which may be altered by critical illness and hemodialysis. Vasomotor tone is the complex result of interactions between autonomic tone, metabolic demand, blood flow distribution, and the responsiveness of the vascular smooth muscle to vasoactive stimuli, such as ionized calcium, mediators of sepsis, and their vasoactive by-products (e.g., prostaglandin $F_{2\alpha}$, prostacyclin). Blood flow, on the other hand, is the result of another complex interaction between the determinants of both venous return and ventricular pump function. Importantly, venous return is determined by the pressure gradient from the periphery to the heart, such that either loss of circulating blood volume (hypovolemia) or loss of vasomotor tone (functional hypovolemia) decreases venous return. The main pathogenesis of intradialytic hypotension is a decrease in absolute or relative blood volume. Adaptation to this hypovolemic state includes fluid shift from the extra- to the intravascular space and increases in vascular resistance and myocardial contractility (Fig. 1). Although changes in cardiac contractility may also occur, these appear to less important. Hemodialysis settings have a direct impact on these adaptive mechanisms, and hemodynamic stability requires hemodialysis procedures to be optimized to facilitate plasma refilling and cardiovascular reactivity.

How to preserve blood volume?

Role of ultrafiltration

The volume of ultrafiltration ordered must be based on the patient's intravascular volume status (volemia) and not on the patient's dry weight. In contrast to chronic hemodialysis, where patients are always hypervolemic before starting IHD session, hypervolemia is rarely present in critically ill patients, except in the case of congestive

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_24, © Springer-Verlag Berlin Heidelberg 2009

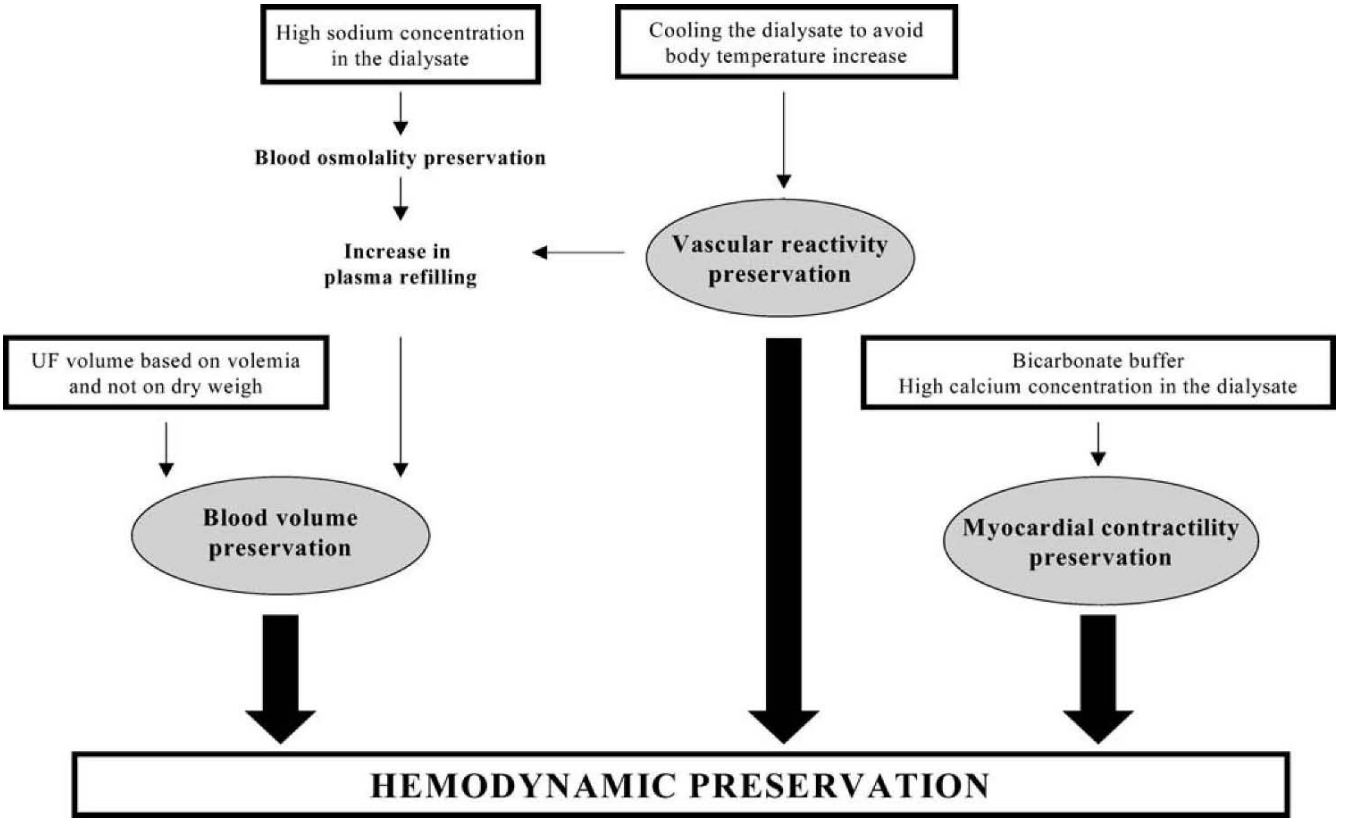


Fig. 1 Main mechanisms of hemodynamic stability during intermittent hemodialysis

heart failure. Patients needing renal replacement therapy in the ICU are typically treated in the context of septic shock complicated by oliguric acute tubular necrosis despite aggressive fluid loading and administration of vasoactive drugs. They often present interstitial edemas with a positive weight gain, whereas their plasma volume may not be yet fully restored, and vasopressor perfusions are still needed. During the acute phase of sepsis or hypovolemic shock the indication for ultrafiltration must be addressed cautiously. Fluid removal may be beneficial only in the case of acute respiratory distress syndrome with severe hypoxemia, where the removal of extravascular lung water is expected to improve oxygenation [1].

At the beginning of the hemodialysis session intravascular blood volume decreases due to ultrafiltration but usually remains stable thereafter despite continuous fluid removal because of the plasma refilling process (Fig. 2). Intravascular space filling comes at first from interstitial and then from intracellular fluids. The use of high ultrafiltration rates, approx. 1 l/h, promotes a high incidence of intradialytic hypotensions in critically ill patients [2]. Because plasma refilling is time dependent, a high rate of blood volume decrease must be avoided in the nonhypervolemic patient. To provide clinically effect dialysis and, if indicated, fluid removal without inducing hypotension, patients with acute renal failure require a longer hemodialysis run than that required for chronic IHD. Thus to receive an adequate dialysis dose, patients suffering from acute renal failure need prolonged (>4 to 6 h) or iterative (daily or every other day) IHD sessions, which allows the ultrafiltration rate per hour to be reduced [1, 2].

Role of osmolality

During hemodialysis solute removal is achieved by diffusion according to concentrations gradient across the membrane. Solute movements are independent of solvent shift and may occur in either direction between blood and dialysate depending on the respective solute concentrations in the dialysate and the blood. This dissociation between solute and solvent shifts may be responsible for changes in blood osmolality during the session. Removal of sodium, which represents the main osmotic agent during hemodialysis, decreases osmolality. Decrease in blood osmolality during IHD has been shown to be a risk factor for hemodynamic worsening [3]. Indeed, fall in plasma osmolality promotes water displacement into the cells and impedes plasma refilling (Fig. 2).

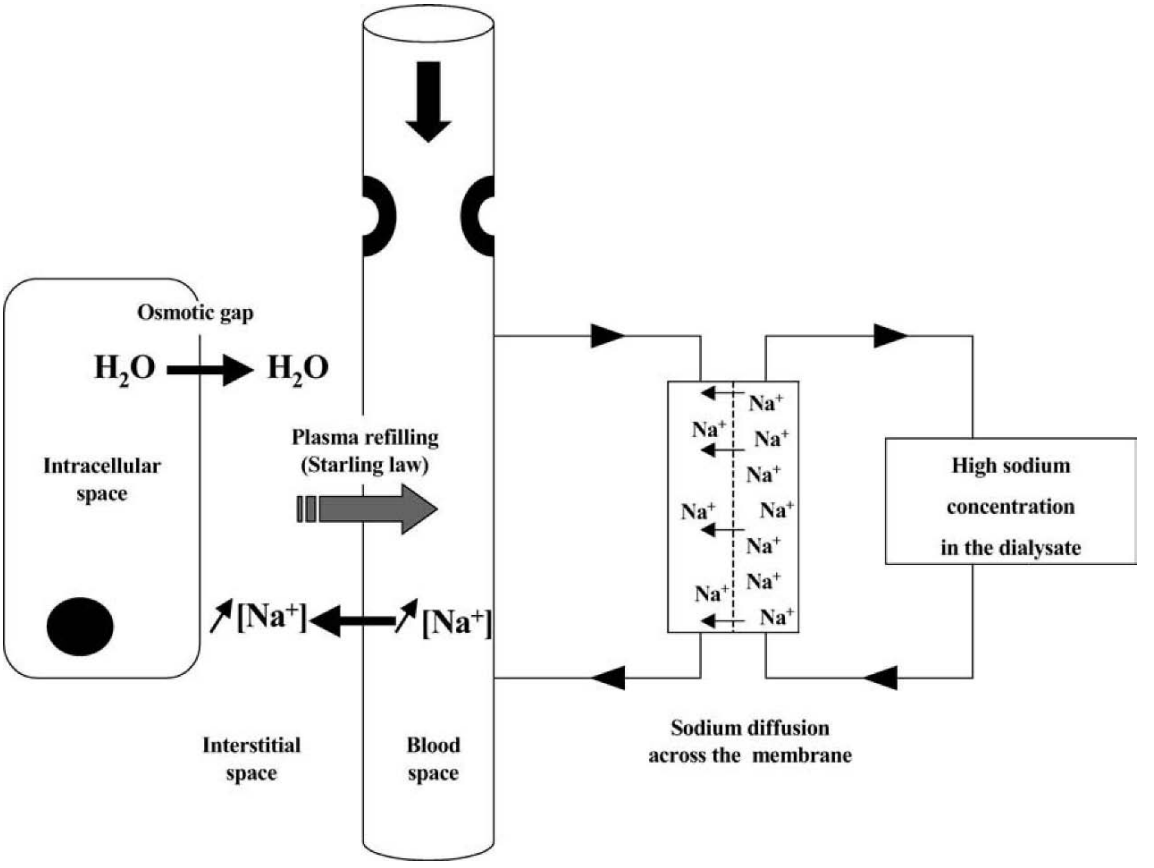


Fig. 2 Principle of plasma refilling during intermittent hemodialysis

Increasing sodium concentration in the dialysate above the plasma concentration permits sodium shift from the dialysate to the patient's blood. Increase in plasma and interstitial osmolality facilitates adequate fluid movements for plasma refilling (i.e., from intracellular to vascular space through the interstitium; Fig. 2). In comparison to the usual sodium concentration used in chronic hemodialysis patients (i.e., 138–140 mmol/l), the use of high concentration of sodium in the dialysate, 145–150 mmol/l, limits blood volume reduction despite a higher volume of ultrafiltration and reduces the incidence of hypotensions needing therapeutic intervention [1, 4]. In the absence of ultrafiltration the use of a high concentration of sodium in the dialysate is useful to increase blood volume, similarly to the use of hypertonic saline perfusion.

How to preserve vascular reactivity?

Improving adaptation of peripheral vascular resistances to volume depletion may reduce the risk of intradialytic hypotension. According to the Starling law, precapillary vasoconstriction can decrease intravascular hydrostatic pressure and facilitate plasma refilling. The main initiating factor for vasodilatation during IHD session is the increase in body temperature.

Role of thermal balance

An increase in core temperature is observed during a standard hemodialysis session (dialysate temperature 37°–37°5 C), which is associated with vasodilatation and impairment of vascular response to the decrease in blood volume. In chronic hemodialysis patients cardiovascular tolerance to IHD is improved when the dialysate temperature is adjusted to the range of 35°–35°5 C [5]. More important than the absolute dialysate temperature, a better hemodynamic tolerance is achieved if the dialysate temperature setting prevents any increase in core temperature and heat accumulation in the body [6]. To maintain the body temperature unchanged in chronic hemodialysis patient the dialysate temperature must be set 1°–2°C below the baseline body temperature recorded before connection. The level of the dialysate temperature setting avoiding increase in body temperature, however, has not been specifically studied in patients with acute renal failure.

Place of isolated ultrafiltration

That a better adaptation of peripheral vascular resistances exists during ultrafiltration alone (i.e., fluid removal without concomitant diffusive movements) was observed more than 20 years ago. The precise mechanism was unknown until recent studies showing that during isolated ultrafiltration the body temperature can easily decrease because the circulation of the dialysate is stopped in the membrane. Body temperature changes then depend on room temperature, which is lower than dialysate temperature. Ultrafiltration alone results in the same hemodynamic stability than hemodialysis with a dialysate temperature set to obtain the same decrease in body temperature [7]. Convective techniques (hemofiltration and hemodiafiltration) may have a better thermal effect explaining their better hemodynamic tolerance. Large amounts of replacement fluid may induce a larger decrease in body temperature than during IHD. In chronic dialysis patients van der Sande and colleagues [8] manipulated the dialysate temperature during IHD and the amount of replacement fluid infused at room temperature during hemodiafiltration to obtain the same thermal effect on patient body temperature. They found that hemodiafiltration had no advantage in preventing hemodynamic instability in comparison to IHD, when the body temperature decreased to the same degree with the two techniques.

How to preserve cardiac contractility?

Role of buffer solutions

Acetate hemodialysis promotes a large decrease in cardiac output in comparison to bicarbonate [9]. A direct negative impact of acetate on myocardial contractility has been suggested. Acetate has been also incriminated in promoting vasodilatation; this adverse effect remains uncertain because of discrepancies between studies.

Role of calcium

Variations in ionized calcium related to hemodialysis may have an impact on myocardial contractility. A low calcium concentration in the dialysate has been shown to be associated with calcium removal, decrease in serum ionized calcium concentration, and hemodynamic instability, particularly in patients suffering from cardiac failure [10]. In contrast to chronic hemodialysis in which the concentration of calcium is often low in the dialysate (e.g., high doses of oral calcium-based phosphate binder, hypercalcemia related to hyperparathyroidism), in critically ill patients the calcium concentration must be rather high (at least 1.75 mmol/l).

Conclusion

In critically ill patients the IHD settings may differ from those in chronic hemodialysis patients, in whom the main objective is the largest weight loss within the minimal session time. When IHD is the technique of renal replacement therapy used in critically ill patients, adequate settings must be used to avoid excessive blood volume loss, vasodilatation, and myocardial depression. Improving hemodynamic tolerance of IHD must be our primary goal to facilitate adequate dialysis dose delivery and organ failure recovery, avoiding shortened session time because of hypotension.

References

1. Schortgen F, Soubrier N, Delclaux C, Thuong M, Girou E, Brun-Buisson C, Lemaire F, Brochard L (2000) Hemodynamic tolerance of intermittent hemodialysis in critically ill patients: usefulness of practice guidelines. Am J Respir Crit Care Med 162:197–202
2. Schiffl H, Lang SM, Fischer R (2002) Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 346:305–310
3. Henrich WL, Woodard TD, Blachley JD, Gomez-Sanchez C, Pettinger W, Cronin RE (1980) Role of osmolality in blood pressure stability after dialysis and ultrafiltration. Kidney Int 18:480–488
4. Paganini EP, Sandy D, Moreno L, Kozlowski L, Sakai K (1996) The effect of sodium and ultrafiltration modelling on plasma volume changes and haemodynamic stability in intensive care patients receiving haemodialysis for acute renal failure: a prospective, stratified, randomized, cross-over study. Nephrol Dial Transplant 11 Suppl 8:32–37
5. Yu AW, Ing TS, Zabaneh RI, Daugirdas JT (1995) Effect of dialysate temperature on central hemodynamics and urea kinetics. Kidney Int 48:237–243
6. Maggiore Q, Pizzarelli F, Santoro A, Panzetta G, Bonforte G, Hannedouche T, Alvarez de Lara MA, Tsouras I, Loureiro A, Ponce A, Sulkova S, Van Roost G, Brink H, Kwan JT (2002) The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. Am J Kidney Dis 40:280–290
7. van der Sand FM, Gladziwa U, Kooman JP, Bocker G, Leunissen KM (2000) Energy transfer is the single most important factor for the difference in vascular response between isolated ultrafiltration and hemodialysis. J Am Soc Nephrol 11:1512–1517

8. van der Sand FM, Kooman JP, Konings JP, Leunissen KM (2001) Thermal effects and blood pressure response during postdilution hemodiafiltration and hemodialysis: the effect of amount of replacement fluid and dialysate temperature. J Am Soc Nephrol 12:1916–1920
9. Huyghebaert MF, Dhainaut JF, Monsallier JF, Schlemmer B (1985) Bicarbonate hemodialysis of patients with acute renal failure and severe sepsis. Crit Care Med 13:840–843
10. van der Sand FM, Cheriex EC, van Kuijk WH, Leunissen KM (1998) Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. Am J Kidney Dis 32:125–131

Peter J. D. Andrews
Giuseppe Citerio

Intracranial pressure

Part one: Historical overview and basic concepts

Introduction

One hundred and seventy years ago, Magendie (1783–1855) discovered a small foramen in the floor of the fourth ventricle, now bearing his name, and pointed out the connection between the cerebrospinal fluid (CSF) in the ventricular system and in the subarachnoid spaces of the brain and cord. By this momentous discovery, he led the way to understanding the circulation of CSF and to problems associated with increased CSF pressure.

Lumbar cerebral spinal fluid pressure measurement

Physiological exploration of human CSF started in the late 18th century. In 1891, Quinke published his studies on the diagnostic and therapeutic applications of lumbar puncture. He standardised the technique and made it a rule always to measure the pressure of the CSF by connecting the lumbar puncture needle with a fine glass pipette in which the fluid was allowed to rise.

Subsequently, repeated measurement of lumbar cerebral spinal fluid pressure, as an assessment of intracranial pressure (ICP), was widely used (Ayer 1929, Merrit and Fremont-Smith 1937, Browder and Meyer 1938, Cairns 1939, Landon 1917, Sharpe 1920 and Jackson 1922) and this was the earliest clinical method of ICP measurement.

Jackson pointed out the neglect by surgeons of the field of acute traumatic brain injuries. He demonstrated that the pulse, respiration and blood pressure are affected only once the medulla is compressed and stated that to wait for these changes as an indication for operation on the cerebrum in acute cerebral injury is to court disaster.

Furthermore, reports emerged that some patients, even if showing clinical signs of brain compression, had normal lumbar CSF pressures or died after the procedure. Lumbar puncture fell into disuse for the diagnosis of intracranial hypertension due to the possibility of inducing brain-stem compression through tentorial or tonsillar herniation, and because, if the system does not communicate, the spinal fluid pressure is not an accurate reflection of ICP as demonstrated by Langfitt's work [1].

Lundberg: a clinical pioneer

Researchers moved from the lumbar approach to direct cannulation of the ventricular system. Early clinical research in this field was reported by Nils Lundberg and involved conscious volunteers with a multiplicity of intracranial pathologies [2]. They were monitored by a fluid-filled transducer system attached to a ventricular catheter placed in the lateral ventricle. Recordings lasted, in some cases, several hours or days. Lundberg, enlighten by his clinical talent, reported a number of phenomena that are relevant today. However, a recording system connected to an analogue output from the ICP transducer is required for detection and this is frequently overlooked in modern ICU monitoring systems. A digital trend does not usually have sufficient resolution to detect ICP waves with a frequency of less than 2/min. The clinical importance of ventricular fluid pressure (VFP) waveform was

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_25, © Springer-Verlag Berlin Heidelberg 2009

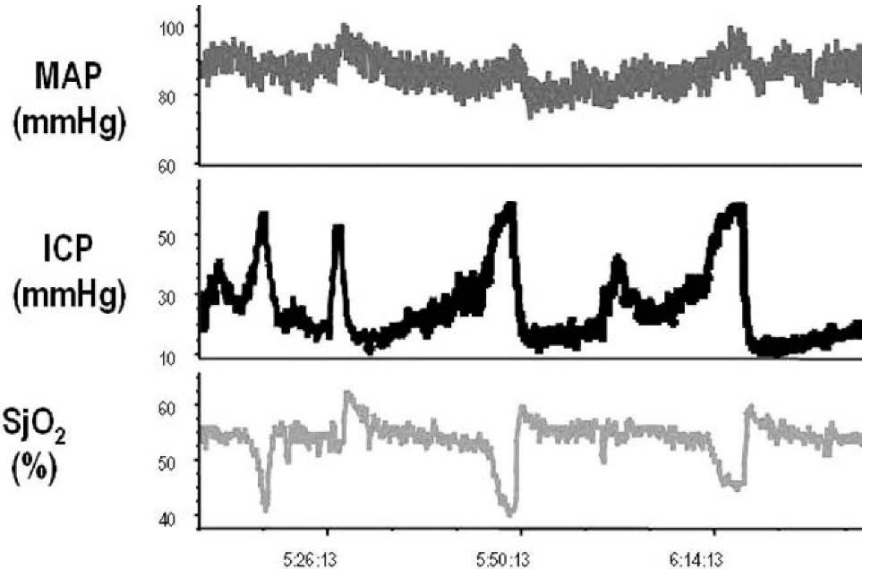


Fig. 1 Example of plateau waves recorded at bedside. The plateau waves are a haemodynamic phenomenon associated with cerebrovascular vasodilation. They are observed in patients with preserved cerebral autoregulation but reduced pressure-volume compensatory reserve. As documented by the tracing, during plateau waves, cerebral perfusion pressure falls below the ischaemic threshold, shown by jugular saturation oximetry. *MAP* mean arterial pressure, *ICP* intracranial pressure, SjO_2 continuous jugular saturation

elucidated in 48 patients and it was concluded that the spontaneous changes in VFP curve were of two main types, plateau waves and rhythmic oscillations[3]. Lundberg stated that the former could cause both transient and persistent damage to the brain and therefore diagnosis, utilising a ventricular catheter, and prevention of such pressure variations were of clinical importance. The rhythmic fluctuations in VFP at the frequency of 1/min can be normal but their incidence increases with pathology and then may represent cerebral dysfunction. This may also be true for the rhythmic waves with a frequency of 6/min. The waves described by Lundberg were:

- *A waves* or *"Plateau waves"* have amplitudes of 50–100 mmHg, lasting 5–20 min. These waves are always associated with intracranial pathology (Fig. 1). During such waves, it is common to observe evidence of early herniation, including bradycardia and hypertension. The aetiology is uncertain, but it is postulated that as cerebral perfusion pressure (i.e. the difference between mean arterial pressure and intracranial pressure, CPP) becomes inadequate to meet metabolic demand, cerebral vasodilatation ensues and cerebral blood volume increases. This leads to a vicious circle, with further CPP decrease, predisposing the patient to other plateau waves and, if low CPP is not corrected, to ruinous effects.
- *B waves* are oscillating and up to 50 mmHg in amplitude with a frequency 0.5–2/min and are thought to be due to vasomotor centre instability when CPP is unstable or at the lower limits of pressure autoregulation.
- *C waves* are oscillating and up to 20 mmHg in amplitude and have a frequency of 4–8/min. These waves have been documented in healthy individuals and are thought to occur because of interaction between cardiac and respiratory cycles.

Both A and B waves require intervention to reduce ICP and preserve CPP. Without the continuous recording of ICP, judgement of correct timing and evaluation of the efficacy of the therapy will be difficult.

Monro and Kellie doctrine

The fundamental principles of raised intracranial pressure were developed in Scotland and are condensed in the doctrine credited to Professors Monro (1783) [4] and Kellie (1824) [5], which states, once the fontanelles and sutures are closed, that:

- The brain is enclosed in a non-expandable case of bone;
- The brain parenchyma is nearly incompressible;
- The volume of the blood in the cranial cavity is therefore nearly constant and
- A continuous outflow of venous blood from the cranial cavity is required to make room for continuous incoming arterial blood.

The importance of these observations is that the skull cannot easily accommodate any additional volume. The craniospinal axis is essentially a partially closed box with container properties including both viscous and elastic elements. The elastic or, its inverse, the compliant properties of the container will determine what added volume can be absorbed before intracranial pressure begins to rise. In its original form the Monro-Kellie doctrine did not take into account the CSF as a component of the cranial

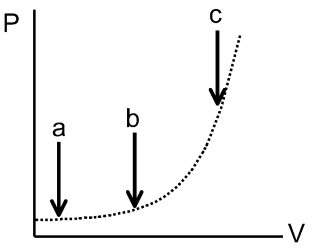


Fig. 2 Pressure-volume curve of the craniospinal compartment. This figure illustrates the principle that in the physiological range, i.e. near the origin of the x-axis on the graph (*point a*), intracranial pressure remains normal in spite of small additions of volume until a point of decompensation (*point b*), after which each subsequent increment in total volume results in an ever larger increment in intracranial pressure (*point c*)

compartment. The concept of reciprocal volume changes between blood and CSF was introduced in 1846 by Burrows and, later, extended in the early twentieth century by Weed to allow for reciprocal changes in all the craniospinal constituents.

An understanding of raised ICP encompasses an analysis of both intracranial volume and craniospinal compliance. Therefore, ICP is a reflection of the relationship between alterations in craniospinal volume and the ability of the craniospinal axis to accommodate added volume (Fig. 2).

If a new intracranial volume displaces venous blood and CSF, for example haematoma, tumour, oedema or hydrocephalus, initially there is little change in ICP. However, the ability to accept the cerebral blood flow component of the cardiac cycle is decreased and, provided the volume of each cerebral component of the cardiac cycle remains constant, close observation will recognise an increase in the ICP wave amplitude [6]. This is because intracranial compliance is reduced. Further exhaustion of the volumetric compensatory reserve leads to an increase in mean ICP and a further increase in ICP wave amplitude. At very high ICP the amplitude of the ICP wave decreases as cerebral blood flow (CBF) is reduced by a reduction in compliance and perfusion pressure. Avezaat and Van Eijdhoven were some of the original researchers to study the changing shape of the ICP wave as the patient moves along the volume-pressure curve. They developed a model showing that the ICP pulse amplitude (ΔP) was linearly proportional to the ICP and the elastic coefficient (E1). They used this method roughly to estimate the intracranial compliance of the patient.

Intracranial compliance

Intracranial compliance is the change in volume (ΔV) per unit change in pressure (ΔP). Compliance is the inverse of elastance (ΔP/ΔV), sometimes known as the volume-pressure response (VPR).

$$\text{Compliance}(C = \Delta V/\Delta P) = 1/\text{Elastance} = 1/VPR$$

Marmarou, interested in CSF dynamics, was the first to provide a full mathematical description of the craniospinal volume-pressure relationship. He developed a mathematical model of the CSF system which produced a general solution for the CSF pressure. The model parameters were subsequently verified experimentally in an animal model of hydrocephalus. As a corollary of this study, Marmarou demonstrated that the non-linear craniospinal volume-pressure relationship could be described as a straight line segment relating the logarithm of pressure to volume, which implies a mono-exponential relationship between volume and pressure. Marmarou termed the slope of this relationship the pressure-volume index (PVI), which is the notional volume required to raise ICP tenfold. PVI is expressed by the formula:

$$PVI = \Delta V/(\log_{10} P_o/P_m)$$

Where ΔV expresses the volume, in millilitres, added or withdrawn from the ventricular system, P_o is the initial pressure and P_m the final pressure.

Unlike elastance or its inverse, compliance, the PVI characterises the craniospinal volume-pressure relationship over the whole physiological range of ICP. The PVI is calculated from the pressure change resulting from a rapid injection or withdrawal of fluid from the CSF space and was utilised both clinically and experimentally as a measure of summed craniospinal compliance. In the clinical setting, PVI measures are obtained by first removing 2 ml and recording the reduction in pressure [7]. By this technique, the PVI can be estimated and, after deciding upon a peak pressure that should not be exceeded, a maximum volume injection can be calculated. Ordinarily, the PVI measures are obtained by repeated withdrawal and injections of 2 ml and the average PVI is calculated from multiple injections. Injection of fluid into the CSF space is not performed when ICP is high. In those cases, PVI is obtained only from withdrawal of known quantities of fluid.

However, the use of the PVI method is not without disadvantages:

- Variability exists between measurements due to the difficulty in manually injecting consistent volumes of fluid at a constant rate. As a result an average of repeated measures is usually required.
- There is an increased risk of infection with this technique. Aetiologies include: manipulation of the CSF access system to test the PVI, CSF sampling and recalibration of the pressure transducer, all of which potentially expose the patient to a higher risk of infection.
- Moreover, the procedure is time consuming and requires highly trained personal.

As a consequence of these limitations, the PVI tests are not routinely used in the clinical situation.

Conclusion

Intracranial pressure is a reflection of the relationship between alterations in craniospinal volume and the ability of the craniospinal axis to accommodate added volume. It can not be estimated without directly measuring it. In 1972, Mario Brock realised the interest in ICP monitoring and organised the first International Symposium on Intracranial Pressure in Hanover. This was the start of a very successful series of meetings and continues in Hong Kong this year, as ICP XII.

References

1. Langfitt TW, Weinstein JD, Kassell NF, Simeone FA (1964) Transmission of increased intracranial pressure I: within the craniospinal axis. J Neurosurg 21:989–997
2. Lundberg N (1960) Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiat Neurol Scand 36 (suppl):149
3. Lundberg N, Troupp H, Lorin H (1965) Continuous recording of the ventricular fluid pressure in patients with severe acute traumatic brain injury. J Neurosurg 22:581–590
4. Monro A (1823) Observations on the structure and function of the nervous system. Creech & Johnson, Edinburgh, p 5
5. Kellie G (1824) An account of the appearances observed in the dissection of two of the three individuals presumed to have perished in the storm of the 3rd, and whose bodies were discovered in the vicinity of Leith on the morning of the 4th November 1821 with some reflections on the pathology of the brain. Trans Med Chir Sci, Edinburgh 1:84–169
6. Ryder HW, Espey FF, Kristoff FV, Evans PP (1951) Observations on the interrelationships of intracranial pressure and cerebral blood flow. J Neurosurg 8:46–58
7. Maset AL, Marmarou A, Ward JD, Choi S, Lutz HA, Brooks D, Moulton RJ, DeSalles A, Muizelaar JP, Turner H (1987) Pressure-volume index in head injury. J Neurosurg. 67:832–840

Giuseppe Citerio
Peter J. D. Andrews

Intracranial pressure

Part two: Clinical applications and technology

Introduction

Intracranial pressure (ICP) is a reflection of the relationship between alterations in craniospinal volume and the ability of the craniospinal axis to accommodate added volume. It cannot be estimated without directly measuring it.

Systemic physiological variables and intracranial pressure

The physiological variables that regulate cerebral blood flow (CBF) are the factors that influence acute changes in ICP. Arterial carbon dioxide gas tension ($PaCO_2$) has a near linear relationship with CBF within the physiological range, producing a 2–6% increase of CBF for each millimetre of mercury of $PaCO_2$ rise. An inverse relationship links low arterial oxygen content and CBF.

A direct relationship exists between CBF and cerebral metabolic rate for oxygen and glucose. CBF is kept constant throughout the normal physiological range of arterial pressure in health. These responses are often impaired after acute injury and, importantly, the lower limit for pressure autoregulation may be increased markedly. When intracranial compliance is reduced, even a small increase in CBF and, therefore, cerebral blood volume will increase ICP.

In health the intracranial volume is regulated by the crystalloid osmotic pressure gradient across the impermeable blood brain barrier (BBB, crystalloid osmotic pressure about 5000 mmHg). In areas where the BBB is damaged, the considerably lower colloid osmotic (i.e. oncotic) pressure (~20 mmHg) is solely responsible. With complete BBB disruption there is a pressure force equilibrium between brain tissue and capillary hydrostatic pressures. Therefore, after acute injury it is important to maintain crystalloid osmotic pressure (principally serum $[Na^{++}]$), oncotic pressure (albumin) and, if ICP is pressure passive, control brain microvascular pressure.

Temperature and cerebral metabolic rate of oxygen ($CMRO_2$) are positively related. Control of brain temperature offers the potential benefit of reducing CBF by reducing $CMRO_2$.

Systemic physiology has an important influence on ICP and a systemic cause for raised ICP should always be sought before an ICP intervention is undertaken.

Intracranial pressure waveform

Brain tissue pressure and ICP increase with each cardiac cycle and, thus, the ICP waveform is a modified arterial pressure wave. The ICP pressure waveform has three distinct components that are related to physiological parameters (Fig. 1). The first peak (*P1*) is the "percussive" wave and is due to arterial pressure being transmitted from the choroid plexus to the ventricle. It is sharply peaked and fairly consistent in amplitude. The second wave (*P2*), often called the "tidal" wave, is thought to be due to brain tissue compliance. It is variable, indicates cerebral compliance and generally increases in amplitude

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_26, © Springer-Verlag Berlin Heidelberg 2009

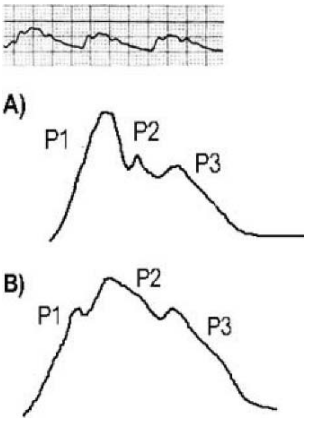


Fig. 1 The intracranial pressure waveforms. The upper tracing is an example of an ICP waveform from a patient monitoring system in which can be identified the three distinct components, as indicated in the text. **A** depicts the situation of a compliant system, **B** A high pressure wave recorded from a non-compliant system in which P2 exceeds the level of the P1 waveform, due to a marked decrease in cerebral compliance

as compliance decreases; if it elevates or exceeds the level of the P1 waveform there will be a marked decrease in cerebral compliance. P3 is due to the closure of the aortic valve and therefore represents the dicrotic notch.

Brain distortion

There are several different, but related, factors that have to be taken into consideration when a mass lesion within the cranial cavity starts to expand. One is distortion of the brain. Because of the viscoelastic properties of the brain, the tissues adjacent to the lesion will tend to flow away from it with axial movement of the brain as well as conventional displacement. Although this suggests that the local properties of the brain are important, the major factor responsible for spatial compensation is a reduction in the volume of intracranial cerebrospinal fluid (CSF). The sequence of events is, therefore, local deformity with displacement of CSF, shift and distortion of the brain and eventually the appearance of internal herniae in the intact cranium (Fig. 2). These are the displacement of brain tissue from one intracranial compartment to another or the spinal canal. These herniae, in turn, lead to the development of pressure gradients because of obliteration of subarachnoid space and cisterns and secondary vascular complications such as haemorrhage and ischaemic brain damage.

Prognosis

Almost from the time of the first attempt to monitor ICP in acute intracranial pathology, researchers have tried to

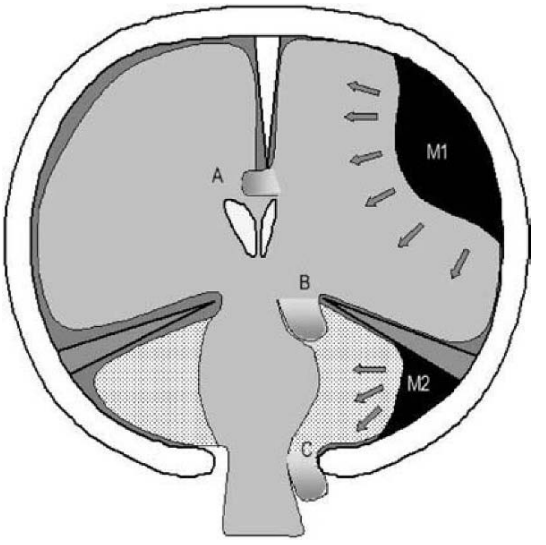


Fig. 2 Schematic representation of herniation syndromes. According to the Monro & Kellie doctrine, increased volume and pressure in one compartment of the brain may cause shift of brain tissue to a compartment in which the pressure is lower. *M1* is an expanding supratentorial lesion; *M2* is an expanding mass in the posterior fossa. *A* Increased pressure on one side of the brain may cause tissue to push against and slip under the falx cerebri toward the other side of the brain, *B* Uncal (lateral transtentorial) herniation. Increased ICP from a lateral lesion pushes tissue downward, initially compressing third cranial nerve and, subsequently, ascending reticular activating system, leading to coma, *C* Infratentorial herniation. Downward displacement of cerebellar tissue through the foramen magnum producing medullar compression and coma

determine whether the prognosis of a patient can be obtained from ICP. Data from large prospective trials carried out from single centres and from well-controlled multi-centre studies have provided the most convincing evidence for a direct relationship between ICP and outcome. J. Douglas Miller and others [1] made detailed documentation of ICP during intensive care after traumatic brain injury (TBI). A strong relationship exists with survival and a recent analysis of the same data-set by regression tree methodology shows a strong relationship between ICP and functional recovery.

Narayan, in a prospective study in 133 severely head-injured patients, demonstrated that the outcome prediction rate was increased when the standard clinical data such as age, Glasgow Coma Score on admission (GCS) and pupillary response with extra-ocular and motor activity were combined with ICP monitoring data [2]. Marmarou, reporting on 428 patients' data from the National Institute of Health's Traumatic Coma Data Bank, showed that, following the usual clinical descriptors of age, admission motor score and abnormal pupils, the proportion of hourly ICP recordings greater than 20 mmHg was the next most significant predictor of outcome [3]. Jones studied prospectively 124 adult head-injured patients during in-

tensive care using a computerised data collection system capable of minute-by-minute monitoring of up to 14 clinically indicated physiological variables [4]. She found that ICP above 30 mmHg, arterial pressure below 90 mmHg and cerebral perfusion pressure (CPP) below 50 mmHg significantly affected patient morbidity.

In children, after TBI, Jones examined the early predictive value of any physiological derangement in ICU monitored parameters. This multi-centred study was novel in that abnormalities in ICP, blood pressure, heart rate and temperature were recorded when age-specific normal physiological thresholds were breached. ICP, managed according to a CPP protocol, was strongly predictive if abnormal in the initial ICU 48 h.

Although, in the past, there have been differing opinions about the contribution of continuous monitoring of ICP to reduction in mortality and morbidity following head injury, there is now sufficient evidence to remove doubt about the value of ICP monitoring towards improving outcome and allowing more informed decisions to be made about patient management.

Monitoring technology

The modern era of ICP monitoring started in the decade between 1950 and 1960. In 1951, Guillaume and Janny reported, even if their work went largely unnoticed, continuous clinical measurement of ICP with the use of an inductance manometer. In the United States, Ryder and Evans extended their physiological studies to patients.

A milestone in the history of ICP recording was the work carried out by Nils Lundberg (1965) on the use of bedside strain gauge manometers to record ICP continuously by ventriculostomy in more than 400 patients. Lundberg, anticipating modern practice, wrote in 1965 that "*The greatest value of recording the ventricular fluid pressure is the information it gives in cases of severe injury of the brain without hematoma. In these cases, intervention to decrease intracranial pressure by such means as hypertonic solutions, hyperventilation, hypothermia, drainage of fluid and removal of localized contusions, may be more rationally applied.*" The systematic application of those monitoring systems to the management of acute TBI did not take place for almost another decade.

By the mid 1970s, monitoring by means of a strain gauge pressure transducer had begun to pervade neurosurgical practice influenced by Becker and Miller's good results in 160 traumatic brain-injured patients, using continuous ICP monitoring with a Statham strain gauge, treated according to defined clinical algorithms over a 4-year period.

In 1981, Flitter wrote that the technique used by Lundberg—the ventricular catheter and strain gauge transducer —for continuous monitoring "*continues to serve as a standard against which other devices can be compared*". This sentence still stands.

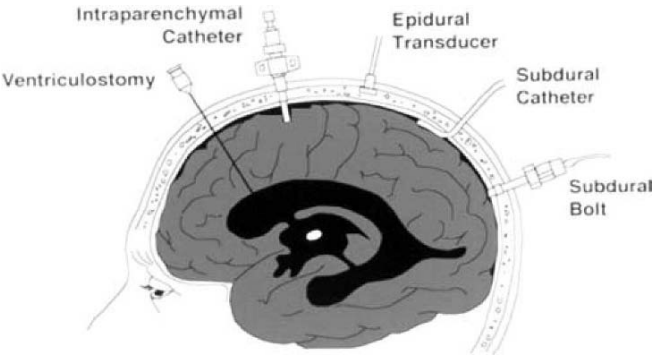


Fig. 3 Sites of measurement of intracranial pressure

A ventricular catheter connected to an external strain gauge is the most accurate and low-cost method for ICP monitoring. This method has proved to be reliable and permit periodic re-zeroing and it also allows the benefit of therapeutic CSF drainage. Nevertheless, the potential risks of difficult positioning, in the presence of ventricular compression, and obstruction have lead to alternative intracranial sites for ICP monitoring (Fig. 3). In 2004, the most common location for ICP monitoring is the cerebral parenchyma. ICP measurements obtained with intraparenchymal transducers correlate well with the values obtained with intraventricular catheters. Contemporary intraparenchymal transducers may be classified as solid state, based on silicon chips with pressure-sensitive resistors forming a Wheatstone bridge, or of fiberoptic design. Although both systems are very accurate at the time of placement, they have been reported to zero-drift over time, which can result in an error after 4 or 5 days. Most clinicians, however, use these devices for a short period of time and these potential inaccuracies may not be clinically relevant. The cost of these devices is higher than the conventional ventricular system. Subdural and epidural monitors (fluid-coupled, pneumatic, solid state and fiberoptic) and externally placed anterior fontanelle monitors are less accurate. As the wise Douglas Miller wrote: "*It is difficult to know when the subdural catheter is underreading. For this reason, the method is being used less and less*".

The overall safety of ICP monitoring devices is excellent, with clinically significant complications (e.g. infection and haematoma) occurring infrequently.

How do intracranial pressure data help patient management?

The care of patients with acute brain injury and ICP monitoring is a cause for ongoing debate. There are few prospective randomised controlled trials of ICP inter-

ventions and no trial of ICP monitoring against no-ICP monitoring. When the Traumatic Coma Data Bank (TCDB) members approached the NIH to fund such a trial more than 14 years ago the view was that there was already sufficient evidence to support the use of ICP monitoring after TBI. These data included observational trials that showed a progressive reduction in mortality after TBI when ICP monitoring was instituted and subsequently when ICP was managed to a lower threshold [5].

Nevertheless, no monitor will improve outcome on its own. ICP data allow the clinician to manage the patient with an acute brain injury based upon objective data and improved outcomes will only occur if the data obtained are integrated into an appropriate therapeutic strategy. To date there are no adequately powered trials with patient outcome as the primary measure that have assessed an intervention for raised ICP. The Cochrane injuries group reviewed the available data to assess the effectiveness of interventions routinely used in the intensive care management of severe head injury, specifically: hyperventilation, mannitol, CSF drainage, barbiturates and corticosteroids, using the methodology of systematic review of all unconfounded randomised trials [6, 7]. They concluded that existing trials have been too small to support or refute the existence of a real benefit from using these strategies and that further large-scale randomised trials of these interventions are required.

Conclusion

Current management strategies for acute brain injury patients encompass the principle of physiological stability. Although there is debate about which precise thresholds should be striven for, without monitoring intracranial pressure (ICP) considerable information is missing and objective management of the patient is not possible. Interventions to reduce ICP are double-edged swords and direct measurement will reduce their indiscriminate usage. ICP monitors are inexpensive and have an acceptably low complication rate. They offer a high yield in information gained and should be the cornerstone of all critical care management of acute brain injury.

References

1. Miller JD, Becker DP, Ward JD, Sullivan HG, Adams WE, Rosner MJ (1977) Significance of intracranial hypertension in severe head injury. Neurosurg 47:503–516
2. Narayan RK, Kishore PR, Becker DP, Ward JD, Enas GG, Greenberg RP, Domingues Da Silva A, Lipper MH, Choi SC, Mayhall CG, Lutz HA 3rd, Young HF (1982) Intracranial pressure: to monitor or not to monitor? A review of our experience with acute head injury. J Neurosurg 56:650–659
3. Marmarou A, Anderson RL, Ward JD et al. (1991) Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg 75:S59–S66
4. Jones PA, Andrews PJ, Easton VJ, Minns RA (2003) Traumatic brain injury in childhood: intensive care time series data and outcome. Br J Neurosurg 17:29–39
5. Marshall LF (2000) Head injury: recent past, present and future. Neurosurgery; 47:546–561
6. Roberts I, Schierhout G, Wakai A (2004) Mannitol for acute traumatic brain injury (Cochrane Review). In: The Cochrane Library, Issue 1. Wiley, Chichester UK, http://www.cochrane.org/cochrane/revabstr/AB001049.htm. Cited 20 Apr 2004
7. Roberts I, Schierhout G (2004) Hyperventilation therapy for acute traumatic brain injury (Cochrane Review). In: The Cochrane Library, Issue 1. Wiley, Chichester UK, http://www.cochrane.org/cochrane/revabstr/AB000566.htm. Cited 20 Apr 2004

Anuj Bhatia
Arun Kumar Gupta

Neuromonitoring in the intensive care unit. Part I. Intracranial pressure and cerebral blood flow monitoring

Abstract *Background:* Monitoring the injured brain is an integral part of the management of severely brain injured patients in intensive care. Brain-specific monitoring techniques enable focused assessment of secondary insults to the brain and may help the intensivist in making appropriate interventions guided by the various monitoring techniques, thereby reducing secondary brain damage following acute brain injury. *Discussion:* This review explores methods of monitoring the injured brain in an intensive care unit, including measurement of intracranial pressure and analysis of its waveform, and techniques of cerebral blood flow assessment, including transcranial Doppler ultrasonography, laser Doppler and thermal diffusion flowmetry. *Conclusions:* Various modalities are available to monitor the intracranial pressure and assess cerebral blood flow in the injured brain in intensive care unit. Knowledge of advantages and limitations of the different techniques can improve outcome of patients with acute brain injury.

Keywords Traumatic brain injury · Intracranial pressure · Ultrasonography, Doppler, transcranial · Flowmetry, laser Doppler · Thermal diffusion flowmetry

Abbreviations *ABP:* arterial blood pressure · *AMP:* amplitude of fundamental component of ICP waveform · *CBF:* cerebral blood flow · *CBV:* cerebral blood volume · CO_2*:* carbon dioxide · *CPP:* cerebral perfusion pressure · *CSF:* cerebrospinal fluid · *CT:* computerised tomography · *DID:* delayed ischaemic neurological deficit · *EDP:* effective downstream pressure · *FV:* flow velocity · *HDI:* haemodynamic impairment · *ICP:* intracranial pressure · *ICU:* intensive care unit · *LDF:* laser Doppler flowmetry · *MAP:* mean arterial pressure · *MCA:* middle cerebral artery · *MRI:* magnetic resonance imaging · *nCPP:* non-invasively determined cerebral perfusion pressure · *nICP:* non-invasive ICP measurement · *PET:* positron emission tomography · *PI:* pulsatility index · *PRx:* pressure reactivity index · *RI:* resistance index · *RAP:* correlation of amplitude and pressure of ICP waveform · *SAH:* subarachnoid haemorrhage · *TBI:* traumatic brain injury · *TCD:* transcranial Doppler · *TD:* thermal diffusion · *THRT:* transient hyperaemic response test · *US:* ultrasound · *ZFP:* zero flow pressure

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_27, © Springer-Verlag Berlin Heidelberg 2009

Introduction

Whilst there is little that neurointensive care can offer to prevent the brain damage sustained from the primary insult, the use of appropriate protocol-driven management can, however, minimise the effects of secondary insults on outcome [1]. Monitoring the injured brain is an integral part of the management of severely brain injured patients in intensive care and can be classified into general (systemic) and brain-specific methods. Although general systemic monitoring (e.g. invasive arterial blood pressure, end-tidal carbon dioxide, oxygen saturation of blood) is of vital importance in detecting gross global changes in physiology, brain-specific monitoring techniques enable more focused assessment of secondary insults to the brain and may help the intensivist in making appropriate interventions guided by the various monitoring techniques.

An important adjunct to these techniques is the use of a variety of imaging modalities, which, as a result of significant advances over the last two decades, allow us to assess the brain with respect to structural abnormalities, blood flow and metabolism. The advantage of these techniques [computerised tomography (CT), magnetic resonance imaging (MRI), xenon-CT, positron emission tomography, single photon emission computerised emission tomography, magnetic resonance spectroscopy] is that they allow us to assess the interindividual heterogeneity by providing detailed information of different regions of the brain. However this information is not continuous and at present cannot be obtained at the bedside.

This review focuses on brain-specific monitoring and will include aspects of intracranial pressure measurement and its interpretation, and methods to monitor cerebral blood flow.

Intracranial pressure monitoring

Intracranial pressure (ICP) is the pressure within the cranial vault relative to the ambient atmospheric pressure and is now regarded as a core monitoring parameter in the intensive care management of patients with acute brain injury. The ICP increases when compensatory mechanisms which control ICP, such as changes in cerebrospinal fluid (CSF) dynamics, cerebral blood flow (CBF) and cerebral blood volume (CBV), are exhausted.

Whilst routine ICP monitoring is widely accepted as a mandatory monitoring technique for management of patients with severe head injury and is a guideline suggested by the European Brain Injury Consortium [2], there is some debate over its efficacy in improving outcome from severe traumatic brain injury. A survey of Canadian neurosurgeons revealed that only 20.4% of the respondents had a high level of confidence in ICP monitoring [3], and a survey of neurointensive care units in the UK showing that only 75% of centres monitor ICP may reflect some of the drawbacks of ICP monitoring [4]. A recently published trial in survivors beyond 24 h following severe brain injury that compared ICP-targeted intensive care with management based on clinical observations and CT findings reported no improvement in outcome with ICP monitoring [5]. However, a review of neurocritical care and outcome from traumatic brain injury (TBI) suggested that ICP-/cerebral perfusion pressure (CPP)-guided therapy may benefit patients with severe head injury, including those presenting with raised ICP in the absence of a mass lesion and also patients requiring complex interventions [1].

Measurement of ICP

ICP can be measured at different sites in the brain–intraventricular and intraparenchymal measurements are more common, while extradural and subdural sensors are used occasionally. Intraventricular catheters are still thought of as the "gold standard" [6] as they allow direct measurement by insertion of a catheter into one of the lateral ventricles, which is connected to an external pressure transducer [7]. The advantages of these systems are that the clinician can check for zero drift and sensitivity of the measurement system in vivo. Access to the ventricular system also allows CSF drainage if the ICP rises. However, this interferes with ICP monitoring, and only one currently available catheter allows concomitant CSF drainage and ICP monitoring (Rehau, Switzerland). The drawbacks of such catheters include difficulty or failure of insertion in patients with advanced brain swelling, as the ventricles can be narrowed or effaced. An increase in risk of infection after a period of time is another potential problem, with reported rates of up to 10% [8] with modern ventricular micro-transducers even though these have excellent metrological properties [9]. There are now commercially available ventricular catheters with antibiotic-coated tips [Codman Bactiseal® external ventricular drain catheter] that may reduce infection rates but more studies are required before their use in clinical practice can be supported.

The intraparenchymal systems may be inserted through a support bolt or tunnelled subcutaneously from a burr hole. These have a micro-miniature strain gauge pressure sensor side-mounted at the tip (Codman) or a fibre-optic catheter (Camino, Innerspace). Change of pressure results in a change of resistance in the former and an alteration in reflection of the light beam in the latter. Intraparenchymal probes are a good alternative to ventricular catheters and have a low infection rate [10], but in one study a significant increase in colonisation at 5 days after insertion was reported [11]. The main problem with these catheters is a small drift of the zero line. Neither of these systems allows pressure calibration to be performed in vivo. After these systems are zeroed relative to atmospheric pressure during a pre-insertion calibration, their output

is dependent on the zero drift of the sensor. Technical complications such as kinking of the cable and dislocation of the sensor have also been reported [12]. It should be remembered that these sensors reflect a local pressure value that may be misleading, as the ICP is not uniform within the skull, e.g. supratentorial measurements may not reflect infratentorial pressure. However, this is also a problem with intraventricular catheters.

Subdural catheters are easily inserted following craniotomy but measurements are unreliable because when ICP is elevated, they are likely to underestimate the true ICP. These are also liable to blockage. Extradural probes have the advantage of avoiding penetration of the dura but are even more unreliable as the relationship between ICP and pressure in the extradural space is unclear. The Gaeltec ICP/B solid-state miniature ICP transducers are designed for use in the epidural space and are reusable, and the zero reference can be checked in vivo. However, measurement artefacts and decay in measurement quality with repeated use have limited the acceptance of this technology [13]. Despite these drawbacks, the subdural and epidural catheters are associated with a lower risk of infection, epilepsy and haemorrhage than ventricular catheters [14, 15].

The Spiegelberg ICP monitoring system is a fluid-filled catheter-transducer system that measures ICP using a catheter that has an air-pouch balloon situated at the tip. This device zeroes automatically in vivo and has shown lower zero drift than standard catheter-tip ICP devices [16]. This system can be used in epidural, subdural, intraparenchymal and intraventricular sites. Despite its obvious advantages, this system is still not used widely and requires further evaluation.

ICP monitoring has several important applications, some of which are discussed below:

Determination of CPP

Management of acute brain injury is largely CPP directed. ICP is an important determinant of CPP [CPP = mean arterial pressure (MAP)–ICP], which in turn affects CBF and CBV. The optimal level of CPP is still under some debate, with earlier studies recommending CPP > 70 mmHg [16] although many other centres maintain CPP between 60 and 70 mmHg and one centre permits CPP as low as 50 mmHg [17].

ICP correlation with outcome

Experience from various centres with expertise in ICP monitoring and research into TBI confirms that mean ICP correlates with outcome with a threshold in the region of 25 mmHg. However no prospective study has been undertaken (and is unlikely) to prove this and Brain Trauma Foundation guidelines recommend ICP treatment should be initiated at an upper threshold of 20–25 mmHg [18].

Waveform analysis

Analysis of ICP waveforms can be used to obtain information about brain compliance. A computer program to correlate mean ICP and AMP has been developed [19]. The ICP waveform consists of three components, which overlap in the time domain but can be separated in the frequency domain. The pulse waveform has several harmonic components; the fundamental component has a frequency equal to the heart rate. The amplitude of this component (AMP) is very useful for the evaluation of various indices. The linear correlation coefficient RAP (R = symbol of correlation, A = amplitude, P = pressure) describes the relationship between pulse amplitude of ICP and mean ICP value over short periods of time (1–3 min). When RAP is positive, changes in AMP are in the same direction as changes in mean ICP. When RAP is negative, the change in AMP is reciprocal to those in mean ICP value. Lack of synchronisation between fast changes in amplitude and mean ICP is depicted by a RAP of 0. A potential application of this model is to predict outcome after severe head injury. This is possible because of the nature of relationship between mean ICP and AMP—as the ICP increases, the linear correlation with AMP becomes distorted by an upper breakpoint which is associated with a decrease in RAP coefficient from +1 to negative values. A similar relationship between AMP and ICP is seen in patients with severe brain injury. A plot of RAP against ICP shows similar results—RAP is positively correlated to ICP in patients with good outcomes, whereas the correlation decreases above ICP values of 20 mmHg and becomes negative above 50 mmHg in patients who die (Fig. 1) [20]. In the latter group of patients, the decrease in RAP from +1 to 0 or negative precedes the final decrease in ICP pulse amplitude and is a sign of impending brainstem herniation.

Cerebrovascular pressure reactivity and derived indices

Cerebrovascular pressure reactivity, which is the change in basal tone of smooth muscle in cerebral arterial walls in response to changes in transmural pressure, can be estimated from the ICP waveform by deriving the pressure reactivity index (PRx). PRx has been used to determine time responses to intracranial hypertension or changes in mean arterial blood pressure in brain-injured patients [21]. PRx is calculated as a linear correlation coefficient between averaged arterial blood pressure and ICP from a time window of 3–4 min. Good cerebrovascular reactivity is associated with negative PRx and a poor reactivity with a positive PRx value (Fig. 2). The PRx may be analysed as

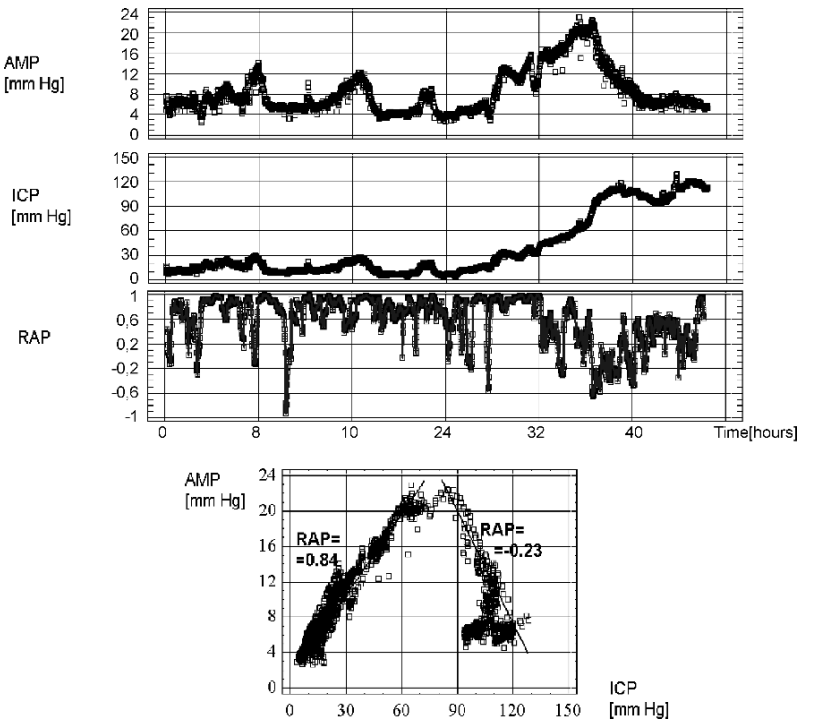


Fig. 1 Pulse amplitude of intracranial pressure (*ICP*) (*AMP*, fundamental harmonic component) increases with mean ICP until critical threshold is reached, above which it starts to decrease. The correlation coefficient between AMP and ICP (*RAP*) marks this threshold by decreasing from positive to negative values [20]

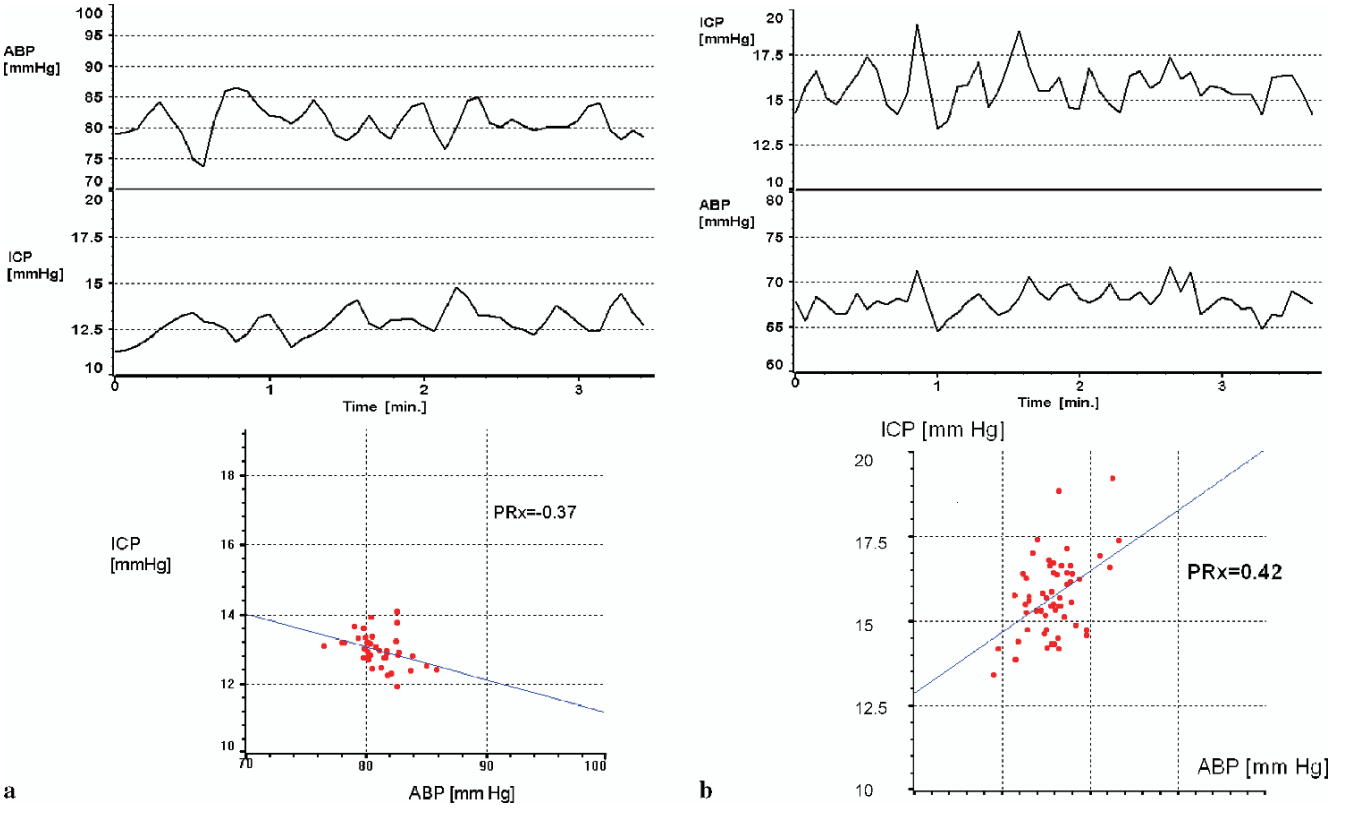


Fig. 2 PRx index, calculated as linear correlation coefficient between averaged ABP and ICP. Good cerebrovascular reactivity is associated with negative PRx (**a**) and poor reactivity with positive PRx (**b**) [21]

a time-dependent variable, responding to dynamic events such as ICP plateau waves or incidents of arterial hypo- and hypertension. The validity of PRx for monitoring and quantifying cerebral vasomotor reactivity has been studied in patients with brain injury. A close link was found between cerebral blood flow and intracranial pressure in head-injured patients. This suggested that increases in arterial blood pressure and cerebral perfusion pressure may be useful for reducing intracranial pressure in selected brain-injured patients, i.e. those with intact cerebral vasomotor reactivity [22].

There are drawbacks of monitoring ICP. It requires an invasive procedure and personnel to monitor as well as to react to changes. ICP monitoring is frequently performed by non-neurointensivists. A survey of intensive care units (ICU) in non-neurosurgical centres in the UK revealed that though more than half of all such ICUs were admitting patients with severe TBI, only 9% used ICP monitoring as a routine [23]. This has significant implications, especially as there is a lack of class I evidence about the efficacy of ICP monitoring in reducing morbidity and mortality.

It is possible that uptake of ICP monitoring may increase if a non-invasive technique can be used. There is currently keen interest in development of non-invasive methods of ICP monitoring which include the use of transcranial Doppler ultrasonography [24]. An example of this is a procedure for continuously simulated ICP derived from simultaneously recorded curves of ABP and flow velocity (FV) in the middle cerebral artery (MCA) that has been validated in patients with TBI [25]. This approach involves a dynamic systems analysis technique and enables modelling of physiological systems in which the inner structure is too complex to be described mathematically. The validity of this model was confirmed during infusion studies in patients with hydrocephalus [26]. Use of such non-invasive ICP (nICP) measurement techniques may make ICP monitoring accessible to a wider range of ICUs.

Assessment of blood flow

Transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography (TCD) is an extremely useful method for non-invasively monitoring cerebral haemodynamics, by measuring red cell FV in real time using the Doppler shift principle. Ultrasound (US) waves are generated using a 2-MHz pulsed Doppler instrument. In order to penetrate the skull, the same transducer is used both for transmitting and receiving wave energy at regular intervals. The moving blood acts as a reflector, first receiving the transmitted wave from the transducer and then reflecting it back. FV is calculated using the formula for Doppler shift. Changes in FV correlate with changes in CBF only if the angle of insonation and the diameter of the insonated vessel remain constant [27]. Data are generally derived from the MCA as it is easy to insonate, carries a large proportion of supratentorial blood and its location allows easy fixation of the probe (to keep the angle of insonation constant) for prolonged monitoring. The transtemporal window through the thin bone above the zygomatic arch is commonly used to insonate the proximal segment (M1) of the MCA. In each patient, the same insonation window should be used throughout the entire study period.

As the volume of blood flowing through a vessel depends on the velocity of the moving cells and the diameter of the vessel concerned, then for a given blood flow, the velocity will increase with decreases in vessel diameter. Figure 3 shows a diagrammatic representation of a typical TCD waveform from the MCA. Mean FV (FV_{mean}) is the weighted mean velocity that takes into account the different velocities of the formed elements in the blood vessel insonated and is normally around $55 \pm 12\ cm\ s^{-1}$. This represents the most physiological correlate with the actual CBF. The time-mean FV refers to the mean value of FV_{max} and is determined from the area under the spectral curve.

The shape of the envelope (maximal shift) of the Doppler spectrum from peak systolic flow to end-diastolic flow with each cardiac cycle is known as the waveform pulsatility. The FV waveform is determined by the ABP waveform, the viscoelastic properties of the cerebral vascular bed and blood rheology. In the absence of vessel stenosis or vasospasm, changes in ABP or blood rheology, the pulsatility reflects distal cerebrovascular resistance. This resistance is usually quantified by the pulsatility index (PI or Gosling index): $PI = (FV_{systolic} - FV_{diastolic}) / FV_{mean}$. Normal PI ranges from 0.6 to 1.1 with no significant side-to-side or cerebral interarterial differences and shows better correlation with

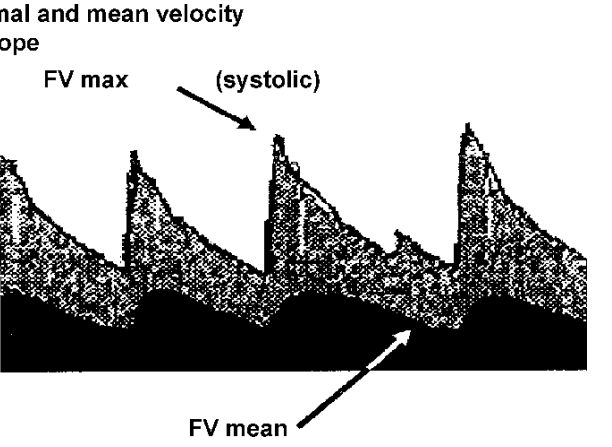


Fig. 3 Method of determining systolic (V_s), diastolic (V_d) and time-averaged mean flow velocity (V_{mean}) from the spectral outline. *FV* is flow velocity and *PI* is pulsatility index [$PI = (V_s - V_d) / V_{mean}$]. (Reproduced with permission from Greenwich Medical Media. In: Gupta AK, Summors A, Notes in Neuroanaesthesia and Critical Care, 2001)

CPP than ICP. Another index that can be used to quantify vessel resistance is the resistance index (RI or Pourcelot index): $RI = (FV_{systolic} - FV_{diastolic}) / FV_{systolic}$.

Applications of TCD

There are many advantages of using TCD. It is non-invasive, relatively inexpensive and provides real-time information with high temporal resolution. Some of the clinical applications of TCD include the following:

Assessment of cerebral autoregulation and vasoreactivity

TCD is used in assessment of cerebral autoregulation and vasoreactivity to carbon dioxide (CO_2) as loss of these mechanisms in patients with brain injury may indicate a poor prognosis. Autoregulation can be tested by response of the TCD trace to vasopressor infusion (static autoregulation) or thigh tourniquet deflation (dynamic autoregulation). Autoregulation may also be tested at the bedside using the transient hyperaemic response test (THRT) [28], which assesses the hyperaemic response in the TCD waveform following 5–9 s of digital carotid artery compression. Lam et al. found that following an aneurysmal subarachnoid haemorrhage, patients with an initial impairment of the response to THRT were more likely to develop delayed ischaemic neurological deficits (DIDs) than patients with a normal response [29]. In a study using induced oscillations in the ABP (by controlling ventilation) and calculating the phase shifts between FV (measured using TCD) and ABP, cerebral autoregulation was found to be impaired preceding the onset of clinical vasospasm [30].

Detection of vasospasm following subarachnoid haemorrhage

TCD is often used in the clinical setting to determine presence of vasospasm. The primary effect of a decrease in vessel lumen diameter is an increase in flow resistance, and this results in an increase in FV. An MCA FV_{mean} above 120 cm s^{-1} is regarded as being significant [31] and may indicate either hyperaemia or vasospasm. Although it is generally regarded that vasospasm is likely if the ratio of MCA FV to extracranial ICA FV (Lindegaard ratio) is greater than 3 [32] and hyperaemia is present if MCA FV > 120 cm s^{-1} with a Lindegaard ratio less than 3, the distinction is not well defined, especially when commonly used TCD indices for diagnosis of vasospasm are compared with cerebral perfusion findings using PET. PET scans of patients following subarachnoid haemorrhage (SAH) who developed DIDs showed a wide range of cerebral perfusion disturbances, with TCD indices failing to indicate these changes [33]. Thus detection of vasospasm on TCD may not be associated with delayed cerebral ischaemia and vice versa. Care must therefore be taken when interpreting TCD data, and these should be matched with clinical findings, and other investigations such as xenon-CT flow measurements may help to improve prediction of vasospasm and hence avoid repeated angiography [34]. However, when compared with angiography for the MCA, TCD has been shown to give high levels of specificity and positive predictive value for vasospasm. Ratsep et al. found that vasospasm detected by TCD is associated with haemodynamic impairment (HDI, defined as blood flow velocity values consistent with vasospasm in conjunction with impaired THRT); thus, detection of HDI could identify patients at risk for ischaemic complications [35].

Role of TCD in management of traumatic brain injury

Following traumatic brain injury, TCD monitoring can be used to observe changes in FV, waveform pulsatility and for testing cerebral vascular reserve. The autoregulatory "threshold" or "breakpoint" (the CPP at which autoregulation fails), which provides a target CPP value for treatment, can also be determined by continuously recording the FV from the MCA. At very low levels of CPP, as in brain death, the microcirculation collapses. The net blood flow diminishes, and the TCD pattern either shows low flow or reversed flow during diastole.

Non-invasive determination of CPP

There is currently much interest in the use of TCD for non-invasive determination of CPP (nCPP). This involves estimation of CPP from parameters derived from MCA FV and the ABP [24]. Schmidt et al. found that absolute difference between real CPP (i.e. MAP–ICP) and nCPP (i.e. determined using TCD) was less than 13 mmHg in the majority of measurements for a range of CPPs between 60 and 100 mmHg. Such a difference may have significant implications in patients with raised ICP (and possibly lower CPP). The absolute value of side-to-side (i.e. interhemispheric) difference in nCPP was significantly greater when CT evidence of brain swelling was present and was also correlated with mean ICP [36]. This technique needs to be evaluated in further randomised trials focusing on its accuracy, cost-effectiveness and validity before it can be recommended for routine use.

Measurement of zero flow pressure

A recent development is the use of TCD to measure zero flow pressure (ZFP), i.e. the pressure at which CBF ceases,

which gives an estimate of the effective downstream pressure (EDP) of the cerebral circulation (Fig. 4). EDP, rather than ICP, is believed to determine the effective CPP in the absence of intracranial hypertension. FV in the MCA is measured by TCD. EDP is derived from the ZFP as extrapolated by regression analysis of instantaneous ABP/MCA FV relationships. Buhre et al. reported that extrapolation of ZFP enables detection of elevated ICP in patients with severe head injury [37]. Thees et al. studied the correlation between critical closing pressure determined using TCD and ICP measured invasively. They found that using ICP to determine CPP might overestimate the effective CPP, i.e. the difference between MAP and CCP [38]. Further evaluation is needed before this non-invasive technique of measuring CPP can be accepted as a standard.

Confirmation of brain death

TCD has been suggested as a highly specific and sensitive test for confirmation of brain death. It can be a useful method to confirm brain death in patients in whom traditional brain death criteria cannot be used because of possible residual effects of sedative drugs [39]. The transtemporal approach is commonly used but the transorbital approach has also been successfully employed [40].

The limitations of using TCD are that it requires a certain degree of technical expertise, is operator dependent, and the skull thickness, which varies with age, gender and race, may cause problems with transmission of ultrasound. In fact, 10% of normal subjects cannot be assessed due to lack of an adequate temporal window. The incidence of failure can be reduced by increasing the power and perhaps by use of 1 MHz probes [41]. In addition, TCD monitoring focuses on the major cerebral arteries but flow characteristics in the cerebral microcirculation may be quite different to those in the major arteries. Despite these limitations, TCD holds promise of further applications for real-time indirect assessment of CBF, non-invasive ICP and CPP.

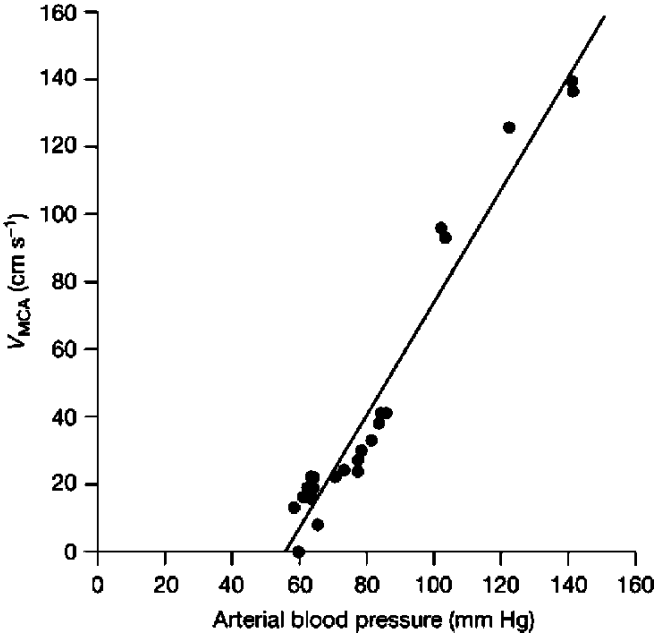


Fig. 4 Direct assessment of cerebral zero flow pressure. In a patient with severe intracranial hypertension, no flow was observed in the middle cerebral artery during diastole. The epidurally measured ICP was 48 mmHg. (Reproduced with permission from [37])

Laser Doppler flowmetry

Laser Doppler flowmetry (LDF) allows continuous real-time measurements of local microcirculatory blood flow (red cell flux) with good dynamic resolution. Doppler shift of reflected monochromatic laser light induced by movement of red blood cells within the microcirculation is measured. The magnitude and frequency distribution of the wavelength changes are directly related to the number and velocity of red blood cells but unrelated to the direction of their movement. A 0.5–1 mm diameter fibre-optic laser probe is placed in contact with or within brain tissue and conducts scattered light back to a photodetector within the flowmeter sensor. The signal is processed to give a continuous voltage fluctuation versus time which is linearly proportional to the real blood flow [42]. The probe can be positioned in proximity to an area of intracranial injury to monitor pathologic variations of microvascular blood flow.

LDF is considered an excellent technique for instantaneous, continuous and real-time measurements of regional CBF and for assessment of relative regional CBF changes. LDF has a quick response to fluctuations in tissue perfusion and is relatively inexpensive. The relationship between LDF and CPP has been found to change with time, and this can indicate an improvement or deterioration in autoregulation [43]. The main drawbacks of this technique are that it is not a quantitative measure of CBF and measures CBF in a small brain volume (1–2 mm^3). It is invasive and prone to artefacts produced by patient movement or probe displacement, which limits its clinical applicability. However, it is a useful measure of local microcirculatory changes in combination with other monitoring techniques and has been used to assess autoregulation, CO_2 reactivity and responses to therapeutic interventions [44] and to detect ischaemic insults [45, 46].

Thermal diffusion flowmetry

Thermal conductivity of cerebral cortical tissues varies proportionally with CBF, and measurement of thermal diffusion (TD) at the cortical surface can be used for CBF determination [47]. A monitor that measures TD

flowmetry consists of two small metal plates, which are thermistors, one of which is heated. Insertion of a TD probe on the surface of the brain at a cortical region of interest allows CBF to be calculated from the temperature difference between the plates. An intraparenchymal TD probe has also been evaluated and the results are encouraging [48]. Although the changes in CBF are relative, the probes may be calibrated against absolute methods such as xenon-133 or xenon-CT measurement of CBF to give absolute values that assess blood flow changes in a small volume of brain ($\pm$ 20–30 mm^3). Placement of the sensor over large surface vessels should be avoided. Similar sensors have been used to guide therapy for patients with severe brain injury and intracerebral haematomas [49, 50].

Animal studies by Vajkoczy et al. revealed that TD microprobes provide continuous real-time assessment of intraparenchymal regional blood flow that was comparable with measurement by xenon-enhanced CT [51]. TD flowmetry was characterised by more favourable diagnostic reliability and was reported to be more sensitive than TCD ultrasonography in assessing patients with reversible vasospasm following intra-arterial injection of papaverine in patients with SAH [52].

TD flowmetry has the potential for bedside monitoring of cerebral perfusion at the tissue level, but it is invasive and more clinical trials are needed to validate its use. The intraparenchymal probes have excellent temporal resolution and it is possible that in the future a large part of a single vascular territory may be monitored with single or multiple probes.

This review has explored methods of assessing and measuring intracranial pressure and cerebral blood flow in the injured brain in the intensive care unit. Appropriate use and knowledge of benefits and limitations of these techniques can improve the outcome of patients with acute brain injury.

References

1. Patel HC, Menon DK, Tebbs S, Hawker R, Hutchinson PJ, Kirkpatrick PJ (2002) Specialist neurocritical care and outcome from head injury. Intensive Care Med 28:547–553
2. Maas AI, Dearden M, Servadei F, Stocchetti N, Unterberg A (2000) Current recommendations for neurotrauma. Curr Opin Crit Care 6:281–292
3. Sahjpaul R, Girotti M (2000) Intracranial pressure monitoring in severe traumatic brain injury—results of a Canadian survey. Can J Neurol Sci 27:143–147
4. Wilkins IA, Menon DK, Matta BF (2001) Management of comatose head-injured patients: are we getting any better? Anaesthesia 56:350–352
5. Cremer OL, van Dijk GW, van Wensen E, Brekelmans GJ, Moons KG, Leenen LP, Kalkman CJ (2005) Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. Crit Care Med 33:2207–2213
6. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care (2000) Recommendations for intracranial pressure monitoring technology. J Neurotrauma 17:497–506
7. Miller JD (1989) Measuring ICP in patients: its value now and in the future. In: Hoff JT, Betz AL (eds) Intracranial pressure VII. Springer, Berlin Heidelberg New York, pp 5–15
8. Bekar A, Goren S, Korfali E, Aksoy K, Boyaci S (1998) Complications of brain tissue pressure monitoring with a fibreoptic device. Neurosurg Rev 21:254–259
9. Czosnyka M, Czosnyka Z, Pickard JD (1996) Laboratory testing of three intracranial pressure microtransducers: technical report. Neurosurgery 38:219–224
10. Mack WJ, King RG, Ducruet AF, Kreiter K, Mocco J, Maghoub A, Mayer S, Connolly ES Jr (2003) Intracranial pressure following aneurysmal subarachnoid hemorrhage: monitoring practices and outcome data. Neurosurg Focus 14:1–5
11. Ghajar J (1995) Intracranial pressure monitoring techniques. New Horiz 3:395–399
12. Stendel R, Heidenreich J, Schilling A, Akhavan-Sigari R, Kurth R, Picht T, Pietila T, Suess O, Kern C, Meisel J, Brock M (2003) Clinical evaluation of a new intracranial pressure monitoring device. Acta Neurochir (Wien) 145:185–193
13. Morgalla MH, Cuno M, Mettenleiter H, Will BE, Krasznai L, Skalej M, Bitzer M, Grote EH (1997) ICP monitoring with a re-usable transducer: Experimental and clinical evaluation of the Gaeltec ICT/b pressure probe. Acta Neurochir (Wien) 139:569–573
14. Gaab MR, Heissler HE, Ehrhardt K (1989) Physical characteristics of various methods for measuring ICP. In: Hoff JT, Betz AL (eds) Intracranial pressure VII. Springer, Berlin Heidelberg New York, pp 16–21
15. Raabe A, Totzauer R, Meyer O, Stockel R, Hohrein D, Schoeche J (1998) Reliability of extradural pressure measurement in clinical practice: behaviour of three modern sensors during simultaneous ipsilateral intraventricular or intraparenchymal pressure measurement. Neurosurgery 43:306–311
16. Czosnyka M, Czosnyka Z, Pickard JD (1997) Laboratory testing of the Spiegelberg brain pressure monitor: a technical report. J Neurol Neurosurg Psychiatry 63:732–735
17. Grände PO, Asgiersson B, Nordström CH (1997) Physiological principles for volume regulation of a tissue enclosed in a rigid shell with application to the injured brain. J Trauma 42(Suppl):S23–S31
18. Eker C, Asgeirsson B, Grande PO, Schalen W, Nordstrom CH (1998) Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. Crit Care Med 26:1881–1886
19. Czosnyka M, Guazzo E, Whitehouse H, Smielewski P, Czosnyka Z, Kirkpatrick P, Piechnik S, Pickard JD (1996) Significance of intracranial pressure waveform analysis after head injury. Acta Neurochir (Wien) 138:531–541
20. Balestreri M, Czosnyka M, Steiner LA, Schmidt E, Smielewski P, Matta B, Pickard JD (2004) Intracranial hypertension: what additional information can be derived from ICP waveform after head injury? Acta Neurochir (Wien) 146:131–141

21. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD (1997) Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 41:11–19
22. Lang E W, Lagopoulos J, Griffith J, Yip K, Yam A, Mudaliar Y, Mehdorn HM, Dorsch NW (2003) Cerebral vasomotor reactivity testing in head injury: the link between pressure and flow. J Neurolog Neurosurg Psychiatry 74:1053–1059
23. McKeating EG, Andrews PJ, Tocher JI, Menon DK (1998) The intensive care of severe head injury: a survey of non-neurosurgical centres in the United Kingdom. Br J Neurosurg 12:7–14
24. Czosnyka M, Matta BF, Smielewski P, Kirkpatrick PJ, Pickard JD (1998) Cerebral perfusion pressure in head injured patients: a non invasive assessment using transcranial Doppler ultrasonography. J Neurosurg 88:802–808
25. Schmidt B, Czosnyka M, Schwarze JJ, Sander D, Gerstner W, Lumenta CB, Pickard JD, Klingelhofer J (1999) Cerebral vasodilatation causing acute intracranial hypertension: a method for non-invasive assessment. J Cereb Blood Flow Metab 19:990–996
26. Schmidt B, Czosnyka M, Schwarze JJ, Sander D, Gerstner W, Lumenta CB, Klingelhofer J (2000) Evaluation of a method for non-invasive intracranial pressure assessment during infusion studies in patients with hydrocephalus. J Neurosurg 92:793–800
27. Dahl A, Russell D, Nyberg-Hansen R, Rootwelt K (1992) A comparison of regional cerebral blood flow and middle cerebral artery blood flow velocities: simultaneous measurements in healthy subjects. J Cereb Blood Flow Metab 12:1049–1054
28. Smielewski P, Czosnyka M, Iyer V, Piechneik S, Whitehouse H, Pickard JD (1995) Computerised transient hyperaemic response test—a method for assessing autoregulation. Ultrasound Med Biol 21:599–611
29. Lam JM, Smielweski P, Czosnyka M, Pickard JD, Kirkpatrick PJ (2000) Predicting delayed ischaemic deficits after aneurysmal subarachnoid haemorrhage using a transient hyperaemic response test of cerebral autoregulation. Neurosurgery 47:819–825
30. Lang EW, Diehl RR, Mehdorn HM (2001) Cerebral autoregulation testing after aneurysmal subarachnoid haemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. Crit Care Med 29:158–163
31. Jarus-Dziedzic K, Bogucki J, Zub W (2001) The influence of ruptured cerebral aneurysm localization on the blood flow velocity evaluated by transcranial Doppler ultrasonography. Neurol Res 23:23–28
32. Lindegaard KF, Nornes H, Bakke SJ, Sorteberg W, Nakstad P (1988) Cerebral vasospasm after subarachnoid haemorrhage investigated by means of transcranial Doppler ultrasound. Acta Neurochir (Wein) 42:81–84
33. Minhas PS, Menon DK, Smielewski P, Czosnyka M, Kirkpatrick PJ, Clark JC, Pickard JD (2003) Positron emission tomographic cerebral perfusion disturbances and transcranial Doppler findings among patients with neurological deterioration after subarachnoid haemorrhage. Neurosurgery 52:1017–1024
34. Horn P, Vajkoczy P, Bauhuf C, Munch E, Poeckler-Schoeniger C, Schmiedek P (2001) Quantitative regional cerebral blood flow techniques improve non-invasive detection of cerebrovascular vasospasm after aneurysmal subarachnoid haemorrhage. Cerebrovasc Dis 12:197–202
35. Ratsep T, Asser T (2001) Cerebral haemodynamic impairment after aneurysmal subarachnoid hemorrhage as evaluated using transcranial Doppler ultrasonography: relationship to delayed cerebral ischemia and clinical outcome. J Neurosurg 95:393–401
36. Schmidt EA, Czosnyka M, Gooskens I, Piechnik SK, Matta BF, Whitfield PC, Pickard JD (2001) Preliminary experience of the estimation of the estimation of cerebral perfusion pressure using transcranial Doppler ultrasonography. J Neurolog Neurosurg Psychiatry 70:198–204
37. Buhre W, Heinzel FR, Grund S, Sonntag H, Weyland A (2003) Extrapolation to zero-flow pressure in cerebral arteries to estimate intracranial pressure. Br J Anaesth 90:291–295
38. Thees C, Scholz M, Schaller C, Gass A, Pavlidis C, Weyland A (2002) Relationship between intracranial pressure and critical closing pressure in patients with neurotrauma. Anesthesiology 96:595–599
39. Hadani M, Bruk B, Ram Z, Knoller N, Spiegelmann R, Segal E (1999) Application of transcranial Doppler ultrasonography for the diagnosis of brain death. Intensive Care Med 25:822–828
40. Lampl Y, Gilad R, Eschel Y, Boaz M, Rapoport A, Sadeh M (2002) Diagnosing brain death using the transcranial Doppler with a transorbital approach. Arch Neurol 59:58–60
41. Klotzsch C, Popescu O, Berlit P (1998) A new 1 MHz probe for transcranial Doppler sonography in patients with inadequate temporal bone windows. Ultrasound Med Biol 24:101–103
42. Bolognese P, Miller JI, Heger IM, Milhorat TH (1993) Laser Doppler flowmetry in neurosurgery. J Neurosurg Anesthesiol 5:151–158
43. Lam JM, Hsiang JN, Poon WS (1997) Monitoring of autoregulation using laser Doppler flowmetry in patients with head injury. J Neurosurg 86:438–445
44. Kirkpatrick PJ, Smielweski P, Piechnik S, Pickard JD, Czosnyka M (1996) Early effects of mannitol in patients with head injuries assessed using bedside multimodality monitoring. Neurosurgery 39:714–720
45. Kirkpatrick PJ, Smielweski P, Czosnyka M, Pickard JD (1994) Continuous monitoring of cortical perfusion by laser Doppler flowmetry in ventilated patients with head injury. J Neurolog Neurosurg Psychiatry 57:1382–1388
46. Le Bihan D, Turner R (1992) The capillary network: a link between IVIM and classical perfusion. Magn Reson Med 27:171–178
47. Carter LP (1991) Surface monitoring of cerebral cortical blood flow. Cerebrovasc Brain Metab Rev 3:246–261
48. Vajkoczy P, Roth H, Horn P, Lucke T, Thome C, Hubner U, Martin GT, Zappletal C, Klar E, Schilling L, Schmiedek P (2000) Continuous monitoring of regional cerebral blood flow: experimental and clinical validation of a normal thermal diffusion microprobe. J Neurosurg 93:265–274
49. Carter LP, Weinand ME, Oommen KJ (1993) Cerebral blod flow (CBF) monitoring in intensive care by thermal diffusion. Acta Neurochir Suppl (Wien) 59:43–46
50. Choksey MS, Chambers IR, Jenkins A, Mendelow AD, Sengupta RP (1993) Cortical thermal clearance monitoring in surgery for giant middle cerebral artery aneurysm. Br J Neurosurg 7:673–676
51. Vajkoczy P, Horn P, Thome C, Munch E, Schmiedek P (2003) Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. J Neurosurg 98:1227–1234
52. Vajkoczy P, Horn P, Bauhuf C, Munch E, Hubner U, Thome C (2001) Effect of intra-arterial papaverine on regional cerebral blood flow in hemodynamically relevant cerebral vasospasm. Stroke 32:498–505

Anuj Bhatia
Arun Kumar Gupta

Neuromonitoring in the intensive care unit. Part II. Cerebral oxygenation monitoring and microdialysis

Abstract *Background:* Monitoring the injured brain is an integral part of the management of severely brain injured patients in intensive care. There is increasing interest in methods to monitor global and regional cerebral oxygenation. There have been significant advances in analysing tissue oxygenation and local metabolites in the injured brain over the past decade. *Discussion:* Cerebral oxygenation can be assessed on a global or regional basis by jugular venous oximetry and near infra-red spectroscopy respectively. Techniques of brain tissue oxygenation monitoring and microdialysis are also covered in this review. *Conclusions:* Various modalities are available to monitor oxygenation and the local milieu in the injured brain in the intensive care unit. Use of these modalities helps to optimise brain oxygen delivery and metabolism in patients with acute brain injury.

Keywords Traumatic brain injury · Oximetry, jugular venous · Spectroscopy, near-infrared · Microdialysis

Abbreviations *a-vDO$_2$:* arteriovenous oxygen content difference · *CBF:* cerebral blood flow · *CMRO$_2$:* cerebral metabolic rate of oxygen · *CPP:* cerebral perfusion pressure · *CT:* computerised tomography · *CytOx:* cytochrome aa$_3$ · *EEG:* electroencephalogram · *GABA:* γ-amino-butyric acid · *Hb:* haemoglobin (deoxygenated) · *HbO$_2$:* haemoglobin (oxygenated) · *ICP:* intracranial pressure · *NIRS:* near-infrared spectroscopy · *PbO$_2$:* brain tissue oxygen partial pressure · *PbCO$_2$:* brain tissue carbon dioxide partial pressure · *PET:* positron emission tomography · *SAH:* subarachnoid haemorrhage · *SjvO$_2$:* jugular venous oxygen saturation · *TBI:* traumatic brain injury · *TCD:* transcranial Doppler · *TOI:* tissue oxygenation index

Assessment of cerebral oxygenation

Methods for assessing whole body oxygenation (e. g. pulse oximetry, arterial blood gas analysis) are not reliable indicators of cerebral oxygenation in patients with traumatic brain injury (TBI) or brain pathology. Techniques to measure cerebral oxygenation should be employed in such patients to ensure optimal oxygen delivery to the injured brain. Measurement of cerebral oxygenation can be divided into global methods such as jugular venous oximetry and regional methods including near-infrared spectroscopy (NIRS) and tissue probes.

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_28, © Springer-Verlag Berlin Heidelberg 2009

Jugular venous oximetry

Jugular venous oxygen saturation ($SjvO_2$) provides an indirect assessment of cerebral oxygen utilisation and is used to guide therapy in the neurocritical care unit. Blood from the venous sinuses of the brain drains via the internal jugular veins into the right atrium. Measurement of $SjvO_2$ can determine adequacy of the balance between global cerebral blood flow (CBF) and cerebral metabolic demands. A fibre-optic catheter is inserted retrograde into the internal jugular vein and advanced cephalad beyond the inlet of the common facial vein into the jugular bulb at the base of the skull. Correct placement is confirmed when the catheter tip is level with the mastoid air cells on the lateral neck radiograph (level with the bodies of C1/C2).

Aspiration of blood from the jugular bulb is representative of mixed cerebral blood. Although there is no evidence to suggest that either side is better [1] and supratentorial venous drainage is less lateralised than previously thought, the right jugular vein is more frequently cannulated [2]. Continuous monitoring of $SjvO_2$ can be performed with catheters that employ two wavelengths of light (e. g. Edslab Sat II, Baxter-Edwards Critical Care Division). Such catheters need to be calibrated against a sample of the patient's own blood, whereas catheters using three wavelengths (Opticath Oximetrix, Abbott Critical Care System) have in-built calibration, thus allowing continuous monitoring.

Under physiological conditions, cerebral metabolic rate of oxygen ($CMRO_2$) and CBF are coupled and the ratio of these two parameters remains constant. The difference between the oxyhaemoglobin saturation of cerebral arterial and mixed venous (i. e. internal jugular) blood represents the oxygen extraction. Thus a low $SjvO_2$ (i. e. a high oxygen extraction ratio) may indicate low CBF in relation to $CMRO_2$. Whilst the normal $SjvO_2$ is 60–70%, changes in trends of measured $SjvO_2$ can reveal useful information about adequacy of cerebral blood flow, as $SjvO_2$ is proportional to $CBF/CMRO_2$. A variety of physiological and pathological conditions can alter the relationship between brain oxygen demand (as indicated by $CMRO_2$) and supply (i. e. CBF), thereby affecting $SjvO_2$ (Table 1).

In addition to measuring venous oxygen saturation, this technique allows estimation of arteriovenous oxygen content difference ($a\text{-}vDO_2$) and lactate by intermittent sampling. Increase in $a\text{-}vDO_2$ to greater than 9 ml/dl provides a useful marker of inadequate CBF. There is good evidence to suggest that increases in $a\text{-}vDO_2$ indicate increased oxygen extraction by the brain and/or inadequate blood flow [3, 4].

$SjvO_2$ has many potentially useful applications in management of patients in neurocritical care:

Monitoring adequacy of CBF

$SjvO_2$ monitoring allows detection of episodes of desaturation associated with raised intracranial pressure (ICP) and hyperventilation therapy. Robertson et al. reported episodes of jugular venous desaturation ($SjvO2 < 50\%$) in patients with severe brain injury; intracranial hypertension and systemic causes (hypoxia, hypotension, and pyrexia) were the main reasons for this desaturation. A poor neurological outcome was more likely with an increase in frequency of desaturation episodes with mortality rates of 21% in the group with no evidence of desaturation, compared with 37% in patients with one episode and 69% in patients with multiple episodes. Jugular venous desaturation was identified in a majority of patients undergoing emergency evacuation of a traumatic intracranial haematoma, and there was also an increase in $SjvO_2$ values following evacuation [5].

Hyperventilation therapy for reduction of ICP in patients with acute intracranial hypertension can be associated with significant reduction in CBF. Assuming a constant brain metabolism, this will lead to reduction in global brain oxygenation. $SjvO_2$ monitoring is therefore useful in optimising the use of hyperventilation. However, there is increasing evidence that hyperventilation therapy may still cause regions of reduced cerebral perfusion and potential ischaemia even when $SjvO_2$ is within normal limits [6].

Table 1 Factors affecting jugular venous oxygen saturation ($SjvO_2$)

Decrease in $SjvO_2$		Increase in $SjvO_2$	
Lowered O_2 delivery	Raised O_2 consumption	Raised O_2 delivery	Lowered O_2 consumption
Raised ICP, lowered CPP	Increased metabolism	Lowered ICP, raised CPP	Coma
Excessive hypocapnia	Hyperthermia	Hypercapnia	Hypothermia
Vasospasm	Pain	Drug induced vasodilation	Sedative drugs
Hypotension	Light plane of anaesthesia	Arterial hypertension	Cerebral infarction
Hypoxia	Seizures	Arteriovenous malformation	Brain death
Cardio-respiratory insufficiency		Raised PaO_2	
Anaemia			
Haemorrhage			
Hb abnormalities			
Sepsis			

Close monitoring with $SjvO_2$ and other methods of assessing tissue oxygenation may make detection of these hypoperfused regions easier.

Combination of $SjvO_2$ with other modalities

Another application of $SjvO_2$ is its use in conjunction with TCD to distinguish between hyperaemia and vasospasm following subarachnoid haemorrhage (SAH). If the TCD detects a high flow velocity, hyperaemia is confirmed by a high $SjvO_2$, whereas a low or normal $SjvO_2$ is more likely to indicate vasospasm. $SjvO_2$ has also been used as a complementary test for diagnosis of brain death. In a study on 118 patients meeting criteria of brain death with iso-electric electroencephalography (EEG), a ratio of < 1 between central venous blood (SvO_2) and $SjvO_2$ was associated with 96% sensitivity and 99% specificity for brain death [7].

Guiding therapy

The use of $SjvO_2$ monitoring to guide hyperventilation therapy is commonplace. One potential use of $SjvO_2$ monitoring is with therapy for vasospasm following SAH. Fandino et al. used $SjvO_2$ to monitor localised injection of the arterial vasodilator papaverine in a small series of patients and noted an immediate improvement [8]. However, the vasospastic area would need to be relatively large to affect global oxygenation markers.

Barbiturate-induced cerebral metabolic suppression in patients with severe brain injury can be guided by $SjvO_2$ monitoring. Cruz et al. used $SjvO_2$ to evaluate global cerebral oxygenation before and after intravenous administration of pentobarbital for the management of refractory intracranial hypertension in comatose patients with traumatic brain swelling. Outcomes were significantly better in patients whose $SjvO_2$ remained above 45% than in those in whom it dropped to below this value, despite the fact that there were no significant differences between the two groups with regard to ICP and cerebral perfusion pressure (CPP) [9].

Continuous $SjvO_2$ monitoring, however, has some limitations. Sheinberg et al. demonstrated that up to half of measured desaturations below 50% might be false positives [10]. Furthermore, continuous monitoring has limited ability to detect discrete regions of ischaemia or hyperaemia unless they are significantly large enough to influence the 'global' picture. A study that compared changes in $SjvO_2$ with brain tissue oxygen partial pressure (PbO_2) in response to hyperventilation in patients with severe brain injury found a good correlation between the two modalities when PbO_2 was measured outside of areas of focal pathology. However, changes in $SjvO_2$ could not be correlated to changes in PbO_2 when the latter was measured from within areas of local pathology, suggesting that differences in regional cerebral oxygenation may not be detected by measurement of $SjvO_2$ [11].

Inaccuracies in $SjvO_2$ can occur for a number of reasons. For example, there may be no blood draining from an infarcted area of the brain, therefore not affecting the $SjvO_2$ value. Blood samples may be contaminated with extracranial blood when the catheter is placed too proximally or blood is aspirated too rapidly, although this can be avoided if blood is sampled at a site within 2 cm of the jugular bulb and at a rate of < 2 ml/min. There may be substantial discrepancy between the readings in samples obtained from the two internal jugular veins. The continuous fibre optic catheters may give inaccurate readings if impacted against the vessel wall, if a thrombosis develops on the catheter tip or if the sensor is curled within the vessel. A few potential complications are associated with this technique (carotid artery puncture, thrombosis, raised ICP), but these are rare.

In conclusion, $SjvO_2$ monitoring is a safe and valuable aid in evaluating status of cerebral oxygenation and metabolism in patients with brain injury and also helps in our understanding of cerebral physiology. However, there are no randomised prospective trials that convincingly demonstrate a poor outcome in patients with low $SjvO_2$ values. Limitations of $SjvO_2$ monitoring should be kept in mind and values should be interpreted in conjunction with those from other cerebral monitoring devices.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive technique used for observing real-time changes in regional cerebral oxygenation at the bedside. The physical principle of NIRS is based upon the ability of light waves of near-infrared wavelength (i. e. 700–1,000 nm) to penetrate scalp, skull and brain to a depth of a few centimetres. These light waves are differentially absorbed by oxygenated haemoglobin (HbO_2), deoxygenated haemoglobin (Hb) and cytochrome aa_3 (CytOx). Quantification of this optical attenuation is achieved by using reflectance spectroscopy based upon the modified Beer–Lambert law. Measurements are obtained by optodes placed 4–6 cm apart on the forehead, thereby estimating oxygen content of all vascular compartments (arterial, capillary and venous) within a "banana"-shaped region of the brain. The measurements reflect relative concentrations of HbO_2, Hb and CytOx.

NIRS has been used to monitor patients with TBI, intracranial haemorrhage and in patients undergoing carotid endarterectomy. In one study in patients on the intensive care unit following head injury, NIRS detected 97% of desaturations while jugular venous oximetry detected only 53%, and NIRS was more specific and more sensitive [12]. NIRS has also been used to detect cerebral hypoxia during carotid endarterectomy, with more than

50% of patients developing cerebral desaturation on internal carotid artery cross-clamping [13]. NIRS can be easily combined with other bedside methods such as transcranial Doppler (TCD), and simultaneous use of both these modalities provides useful information about haemodynamic and metabolic cerebral adaptive status in patients with carotid artery occlusive disease [14].

Recent developments in NIRS technology have resulted in availability of single, easy-to-use numerators for measuring cerebral tissue oxygenation – the NIRO 300 (Hamamatsu Phototonics, Japan) measures tissue oxygenation index (TOI-the ratio of oxygenated to total tissue haemoglobin) and the INVOS 5100 (Somanetics, USA) provides regional cerebral oxygen saturation. Al-Rawi et al. found that in patients undergoing carotid endarterectomy, NIRS reflects changes in cerebral tissue oxygenation with high sensitivity and specificity when TOI is calculated [15]. Dunham et al. found a correlation between NIRS and cerebral perfusion in a pilot study on patients with severe head injury. Cerebral tissue saturation of $\geq 75\%$ was associated with CPP ≥ 70 mmHg, whereas saturation of $< 55\%$ was associated with CPP < 70 mmHg most of the time. The authors also found that desaturation occurred in some patients despite CPP being ≥ 70 mmHg [16]. TOI, as determined by NIRS, was compared with tissue microprobes and $SjvO_2$ for measuring cerebral oxygenation during normobaric hyperoxia in patients with severe brain injury. Tissue microprobes exhibited a time lag in reaching steady state following induction of hyperoxia, whereas TOI and $SjvO_2$ responded promptly to each change of inspired oxygen concentration [17]. A potential use of NIRS is in detection of intracranial haematomas. Gopinath et al. suggested use of NIRS to detect delayed traumatic intracranial haematomas in patients who have a subdural haematoma or massive amount of blood in the subarachnoid space, thus leading to better-timed follow-up CT scans and operations [18].

There are some limitations of NIRS in its present form. Increase in path length of near-infrared light in pathologic conditions, such as brain swelling following head injury can affect the accuracy and reliability of NIRS. Furthermore, although the algorithms that are employed in the system have improved, there is still lack of evidence that NIRS can reliably distinguish between intra- and extracranial changes in blood flow and oxygenation. Development of NIRS technology continues to improve the accuracy of the equipment, and validation by prospective trials could qualify it as a reliable continuous non-invasive monitor of brain oxygenation in coming years [19].

Brain tissue oxygenation monitoring

Measurement of PbO_2 is increasingly being used as a monitoring modality in the neurosciences critical care unit and as a marker of cerebral oxygenation in research protocols. The technique involves insertion of a microsensor into brain parenchyma either through a bolt inserted into the skull or directly through a craniotomy site and tunnelled under the skin. Two commercially available microsensors allow direct, continuous measurement of brain tissue gases. One of these sensors measures brain tissue oxygen tension using a polarographic Clarke-type electrode, whilst the other measures PbO_2, $PbCO_2$ and pH using fibre-optic technology. Both of these sensors are approximately 0.5 mm in diameter and have the ability to measure brain temperature using a thermocouple.

Whilst early animal studies demonstrated that these sensors respond to physiological responses in a predictable manner [20, 21], the majority of clinical experience with these sensors has been in patients following severe TBI and patients undergoing cerebrovascular surgery. Data from these patients have enabled a broad identification of baseline values. PbO_2 is normally lower than arterial PaO_2 due to the extravascular placement of probes and high metabolic activity of the brain (range 15–50 mmHg) [20]. $PbCO_2$ is normally higher than $PaCO_2$ but these are directly related, reflecting the high diffusibility of CO_2 (range 40–70 mmHg). pH is normally lower in brain tissue, also reflecting high brain metabolism (range 7.05–7.25). Attempts have also been made to identify thresholds of ischaemia, with different authors using different approaches. Although this threshold is as yet not clearly defined with relation to outcome, there are some reports indicating that PbO_2 values less than 8–10 mmHg represent a high risk of ischaemia [22, 23]. Data are beginning to emerge on the utility of other parameters, with evidence of increased risk of vasospasm if tissue pH is less than 7.0 and $PbCO_2$ greater than 60 mmHg in patients with cerebrovascular disease [24] and an increased risk of mortality in head injury if brain tissue pH level falls below 7 [25].

Validation of brain tissue oxygenation sensors requires comparison both with existing techniques, such as jugular bulb oximetry, and with a 'gold standard'. Changes in PbO_2 have correlated well with changes in $SjvO_2$, particularly when the sensor was inserted into non-contusional areas of brain [26], indicating that tissue sensors do reflect changes in cerebral oxygenation. A study comparing changes in PbO_2 with values of end-capillary oxygen tension derived from positron emission tomography (PET) found that changes in these values correlated well in response to a challenge of hyperventilation, confirming that brain tissue sensors can be used as a reliable clinical tool [27]. This study began to explore the hypothesis that variable diffusion gradients existed between the end capillary and the extracellular compartment of the injured brain, which was confirmed in a follow-up study in which the investigators performed end-capillary and extracellular measurements of oxygen tension in normoxic and hypoxic areas of tissue in response to hyperventilation (Fig. 1) and examination of some of the tissue specimens revealed perivascular oedema and endothelial swelling [28].

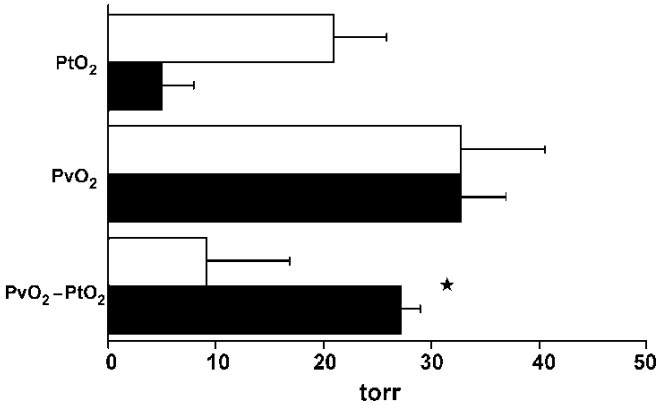


Fig. 1 Comparison of tissue and end-capillary pO_2 (PtO_2), cerebral venous pO_2 (PvO_2) and diffusion gradient for oxygen (PvO_2–PtO_2) in normoxic (*open bars*; $PtO_2 > 10$ torr) and hypoxic (*filled bars*; $PtO_2 \leq 10$ torr) ROIs. Note that the PvO_2 is similar for the two groups, and the low tissue pO_2 values are substantially due to differences in oxygen gradient between the microvasculature and the extracellular space ($^*p < 0.001$) [27]

As data continue to accrue from a number of centres using tissue oxygen sensors, this tool is now approaching the threshold where it will change from being an interesting research adjunct to a useful clinical monitor.

Microdialysis

The technique of cerebral microdialysis allows continuous on-line monitoring of changes in brain tissue chemistry, achieved by inserting a catheter (diameter 0.62 mm) lined with polyamide dialysis membrane into brain parenchyma, which is perfused with a physiological solution (e. g. Ringer's lactate) at ultra-low flow rates (0.1–2.0 μl/min) using a precision pump. Molecules below the cut-off size of the semipermeable membrane (approximately 20,000 Da) diffuse from the extracellular space into the perfusion fluid, which is then collected into vials that are changed every 10–60 min, allowing up to 70% equilibration across the dialysis membrane [29].

Microdialysis catheter insertion does cause some disruption of local tissues and may cause small haemorrhages into the catheter tract, mild astrogliosis and macrophage infiltration [30]. The catheter can be located in areas of uninjured brain or in tissue regarded as being "at risk" such as in areas of vasospasm [31] or in the penumbral area around a mass lesion [32]. In a recent consensus statement published by a group of experts in clinical microdialysis, it was suggested that catheters should be placed in the tissue at risk in SAH patients (most likely the parent vessel territory), in the right frontal region in patients with diffuse injury after TBI, and in patients with focal mass lesions one catheter should be placed in the penumbra (pericontusional tissue) and a second placed in uninjured or 'normal' tissue [33].

The substances that could potentially be measured are innumerable, but the key substances can be categorised as follows [34]:

1. *Energy-related metabolites*, e. g. glucose, lactate, pyruvate, adenosine, xanthine. The lactate/pyruvate ratio is a better marker of ischaemia than lactate alone [35].
2. *Neurotransmitters*, e. g. glutamate, aspartate, γ-aminobutyric acid (GABA).
3. *Markers of tissue damage and inflammation*, e. g. glycerol, potassium, cytokines.
4. *Exogenous substances*, e. g. administered drugs.

Cerebral microdialysis has been applied to patients in many different clinical situations, including TBI, SAH, epilepsy, ischaemic stroke, tumours and during neurosurgery [36]. In patients with severe brain injury derangements in metabolism have been associated with reductions in brain glucose and elevation of the lactate/pyruvate ratio during periods of intracranial hypertension and cerebral ischaemia. A high lactate/pyruvate ratio has been found to correlate with the severity of clinical symptoms and fatal outcome after severe head injury. Wide variations in the concentration of the excitatory amino acids glutamate and aspartate have also been detected, with extremely high levels in secondary ischaemia and contusions. A rise in glycerol levels has been found in microdialysis samples after severe head injury, possibly indicating that tissue ischemia has progressed to cell damage. During aneurysm surgery, changes in concentration of glucose, lactate, pyruvate and glutamate have been demonstrated during cerebro-spinal fluid drainage, brain retraction and temporary clipping. Epileptic foci in the temporal lobe are associated with elevated glutamate and reduced GABA levels prior to seizures, and both amino acids are found to increase during seizures.

Cerebral microdialysis has great potential for exploring the pathophysiology of acute brain injury, pharmacokinetics of drugs within the central nervous system and the response to therapeutic interventions.

References

1. Stocchetti N, Paparella A, Bridelli F, Bacchi M, Piazza P, Zuccoli P (1994) Cerebral venous oxygenation studied with bilateral samples in the internal jugular veins. Neurosurgery 34:38–44
2. Metz C, Holzschuh M, Bein T, Woertgen C, Rothoerl R, Kallenbach B, Taeger K, Brawanski A (1998) Monitoring of cerebral oxygen metabolism in the jugular bulb: reliability of unilateral measurements in severe head injury. J Cereb Blood Flow Metab 18:332–343
3. Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA (1984) Cerebral blood flow and metabolism in comatose patients with acute head injury: relationship to intracranial hypertension. J Neurosurg 61:245–253
4. Robertson CS, Narayan RK, Gokaslan Z, Pahwa R, Grossman RG, Caram P Jr, Allen E (1989) Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. J Neurosurg 70:222–230
5. Robertson CS, Gopinath SP, Goodman JC, Contant CF, Valadka AB, Narayan RK (1995) $SjvO_2$ monitoring in head-injured patients. J Neurotrauma 12:891–896
6. Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, Downey SP, Williams G, Chatfield D, Matthews JC, Gupta AK, Carpenter TA, Clark JC, Pickard JD, Menon DK (2002) Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med 30:1950–1959
7. Diaz-Reganon G, Minambres E, Holanda M, Gonzalez-Herrera S, Lopez-Espadas F, Garrido-Diaz C (2002) Usefulness of venous oxygen saturation in the jugular bulb for the diagnosis of brain death: report of 118 patients. Intensive Care Med 28:1724–1728
8. Fandino J, Kaku Y, Schuknecht B, Valavanis A, Yonekawa Y (1998) Improvement of cerebral oxygenation patterns and metabolic validation of super-selective intraarterial infusion of papaverine for the treatment of cerebral vasospasm. J Neurosurg 89:93–100
9. Cruz J (1996) Adverse effects of pentobarbital on cerebral venous oxygenation of comatose patients with acute traumatic brain swelling: relationship to outcome. J Neurosurg 85:758–761
10. Sheinberg M, Kanter MJ, Robertson CS, Constant CF, Narayan RK, Grossman RG (1992) Continuous monitoring of jugular venous oxygen saturation in head injured patients. J Neurosurg 76:212–217
11. Gupta AK, Hutchinson PJ, Al-Rawi P, Gupta S, Swart M, Kirkpatrick PJ, Menon DK, Datta AK (1999) Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg 88:549–553
12. Kirkpatrick PJ, Smielewski P, Czosnyka M, Menon DK, Pickard JD (1995) Near infrared spectroscopy use in patients with head injury. J Neurosurg 83:963–970
13. Kirkpatrick PJ, Smielewski P, Whitfield P, Czosnyka M, Menon D, Pickard JD (1995) An observational study of near infrared spectroscopy during carotid endarterectomy. J Neurosurg 82:756–763
14. Vernieri F, Tibuzzi F, Pasqualetti P, Rosato N, Passarelli F, Rossini PM, Silvestrini M (2004) Transcranial Doppler and near-infrared spectroscopy can evaluate the hemodynamic effect of carotid artery occlusion. Stroke 35:64–70
15. Al-Rawi PG, Smielewski P, Kirkpatrick PJ (2001) Evaluation of a Near-Infrared Spectrometer (NIRS 300) for the detection of intracranial oxygenation changes in the adult head. Stroke 32:2492–2500
16. Dunham CM, Sosnowski C, Porter JM, Siegal J, Kohli C (2002) Correlation of noninvasive cerebral oximetry with cerebral perfusion in the severe head injured patient: a pilot study. J Trauma 52:40–46
17. McLeod AD, Igielman F, Elwell C, Cope M, Smith M (2003) Measuring cerebral oxygenation during normobaric hyperoxia: a comparison of tissue microprobes, near-infrared spectroscopy, and jugular venous oximetry in head injury. Anesth Analg 97:851–856
18. Gopinath SP, Robertson CS, Constant CF, Narayan RK, Grossman RG, Chance B (1995) Early detection of delayed intracranial haematomas using near-infrared spectroscopy. J Neurosurg 83:438–444
19. Villringer A, Steinbrink J, Obrig H (2004) Cerebral near-infrared spectroscopy: how far away from a routine diagnostic tool? Stroke 35:70–72
20. Maas AIR, Fleckenstein W, Dejong DA, Van Santbrink H (1993) Monitoring cerebral oxygenation: experimental studies and preliminary clinical results of continuous monitoring of cerebral spinal fluid and brain tissue oxygen tension. Acta Neurochir Suppl (Wien) 59:50–57
21. Zauner A, Bullock R, Di X, Young HF (1995) Brain oxygen, CO_2, pH, and temperature monitoring: evaluation in the feline brain. J Neurosurg 37:1168–1177
22. Keining KL, Unterberg AW, Bardt TF, Schneider GH, Lanksch WR (1996) Monitoring cerebral oxygenation in patients with head injuries: brain tissue PO_2 versus jugular vein saturation. J Neurosurg 85:751–757
23. Kett-White R, Hutchinson PJ, Al-Rawi PG, Gupta AK, Pickard JD, Kirkpatrick PJ (2002) Adverse cerebral events detected after subarachnoid hemorrhage using brain oxygen and microdialysis probes. Neurosurgery 50:1213–1221
24. Charbel FT, Du X, Hoffman WE, Ausman JI (2002) Brain tissue PO_2, PCO_2, and pH during cerebral vasospasm. J Neurosurg 97:1302–1305
25. Gupta AK, Zygun D, Johnston AJ, Steiner LA, Al-Rawi PG, Chatfield D, Shepherd E, Kirkpatrick PJ, Hutchinson PJ, Menon DK (2004) Extracellular brain pH and outcome following severe traumatic brain injury. J Neurotrauma 21:678–684
26. Gupta AK, Hutchinson PJ, Al-Rawi P, Gupta S, Swart M, Kirkpatrick PJ, Menon DK, Datta AK (1999) Measurement of brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg 88:549–553
27. Gupta AK, Hutchinson PJ, Fryer T, Al-Rawi PG, Parry DA, Minhas PS, Kett-White R, Kirkpatrick PJ, Mathews JC, Downey S, Aigbirhio F, Clark J, Pickard JD, Menon DK (2002) Measurement of brain tissue oxygenation performed using positron emission tomography scanning to validate a novel monitoring method. J Neurosurg 96:263–268
28. Menon DK, Coles JP, Gupta AK, Fryer TD, Smielewski P, Chatfield DA, Aigbirhio F, Skepper JN, Minhas PS, Hutchinson PJ, Carpenter TA, Clark JC, Pickard JD (2004) Diffusion limited oxygen delivery following head injury. Crit Care Med 32:1384–1390
29. Hutchinson PJ, O'Connell MT, Al-Rawi PG, Maskell LB, Kett-White R, Gupta AK, Richards HK, Hutchinson DB, Kirkpatrick PJ, Pickard JD (2000) Clinical cerebral microdialysis: a methodological study. J Neurosurg 93:37–43
30. Whittle IR, Glasby M, Lammie A, Bell H, Ungerstedt U (1998) Neuropathological findings after intracerebral implantation of microdialysis catheters. Neuroreport 9:2821–2825

31. Sarrafzadeh AS, Sakowitz OW Keining KL, Benndorf G, Lanksch WR, Unterbrg AW (2002) Bedside microdialysis: a tool to monitor cerebral metabolism in subarachnoid hemorrhage patients? Crit Care Med 30:1062–1070
32. Stahl N, Schalen W, Ungerstedt U, Nordstrom CH (2003) Bedside biochemical monitoring of the penumbra zone surrounding an evacuated acute subdural haematoma. Acta Neurol Scand 108:211–215
33. Bellander B-M, Cantais E, Enblad P, Hutchinson P, Nordstrom C-H, Robertson CS, Sahuquillo J, Smith M, Stocchetti N, Ungerstedt U, Unterberg A, Vidiendal Olsen NV (2004) Consensus meeting on microdialysis in neurointensive care. Intensive Care Med 30: 2166–2169
34. Johnston AJ, Gupta AK (2002) Advanced monitoring in the neurology intensive care unit: microdialysis. Curr Opin Crit Care 8:121–127
35. Persson L, Valtysson J, Enblad P, Warme PE, Cesarini K, Lewen A, Hillered L (1996) Neurochemical monitoring using intracerebral microdialysis in patients with subarachnoid hemorrhage. J Neurosurg 84:606–616
36. Peerdeman SM, Girbes AR and Vandertop WP (2000) Cerebral microdialysis as a new tool for neurometabolic monitoring. Intensive Care Med 26:662–669

Karim Bendjelid
Jacques-A. Romand

Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care

Abstract *Objective:* In mechanically ventilated patients the indices which assess preload are used with increasing frequency to predict the hemodynamic response to volume expansion. We discuss the clinical utility and accuracy of some indices which were tested as bedside indicators of preload reserve and fluid responsiveness in hypotensive patients under positive pressure ventilation. *Results and conclusions:* Although preload assessment can be obtained with fair accuracy, the clinical utility of volume responsiveness-guided fluid therapy still needs to be demonstrated. Indeed, it is still not clear whether any form of monitoring-guided fluid therapy improves survival.

Keywords Positive pressure ventilation · Hypotension · Volume expansion · Cardiac index

Prediction is very difficult, especially about the future.
Niels Bohr

Introduction

Hypotension is one of the most frequent clinical signs observed in critically ill patients. To restore normal blood pressure, the cardiovascular filling (preload-defined as end-diastolic volume of both ventricular chambers), cardiac function (inotropism), and vascular resistance (afterload) must be assessed. Hemodynamic instability secondary to effective or relative intravascular volume depletion are very common, and intravascular fluid resuscitation or volume expansion (VE) allows restoration of ventricular filling, cardiac output and ultimately arterial blood pressure [1, 2]. However, in the Frank-Starling curve (stroke volume as a function of preload) the slope presents on its early phase a steep portion which is followed by a plateau (Fig. 1). As a consequence, when the plateau is reached, vigorous fluid resuscitation carries out the risk of generating volume overload and pulmonary edema and/or right-ventricular dysfunction. Thus in hypotensive patients methods able to unmask decreased preload and to predict whether cardiac output will increase or not with VE have been sought after for many years. Presently, as few methods are able to assess ventricular volumes continuously and directly, static pressure measurements and echocardiographically measured ventricular end-diastolic areas are used as tools to monitor cardiovascular filling. Replacing static measurements, dynamic monitoring consisting in assessment of fluid responsiveness using changes in systolic arterial pressure, and pulse pressure induced by positive pressure ventilation have been proposed. The present review analyses the current roles and limitations of the most frequently used methods in clinical practice to predict fluid responsiveness in patients undergoing mechanical ventilation (MV) (Table 1).

One method routinely used to evaluate intravascular volume in hypotensive patients uses hemodynamic response to a fluid challenge [3]. This method consists in infusing a defined amount of fluid over a brief period of time. The response to the intravascular volume loading can be monitored clinically by heart rate, blood pressure, pulse pressure (systolic minus diastolic blood pressure), and urine output or by invasive monitoring with the measurements of the right atrial pressure (RAP), pulmonary artery occlusion pressure (Ppao), and cardiac output. Such a fluid management protocol assumes that the in-

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_29, © Springer-Verlag Berlin Heidelberg 2009

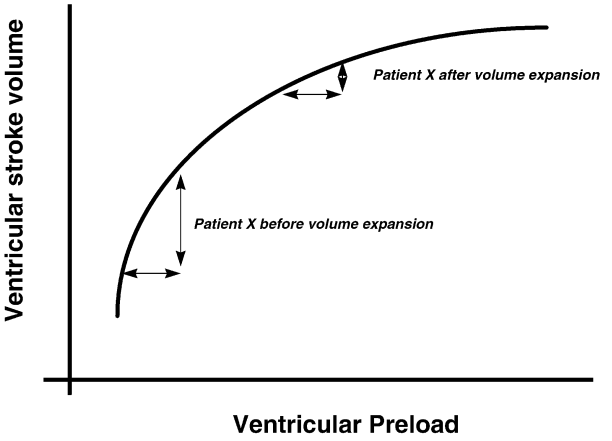


Fig. 1 Representation of Frank-Starling curve with relationship between ventricular preload and ventricular stroke volume in patient X. After volume expansion the same magnitude of change in preload recruit less stroke volume, because the plateau of the curve is reached which characterize a condition of preload independency

travascular volume of the critically ill patients can be defined by the relationship between preload and cardiac output, and that changing preload with volume infusion affects cardiac output. Thus an increase in cardiac output following VE (patient responder) unmasks an hypovolemic state or preload dependency. On the other hand, lack of change or a decrease in cardiac output following VE (nonresponding patient) is attributed to a normovolemic, to an overloaded, or to cardiac failure state. Therefore, as the fluid responsiveness defines the response of cardiac output to volume challenge, indices which can predict the latter are necessary.

Static measurements for preload assessment

Measures of intracardiac pressures

According to the Frank-Starling law, left-ventricular preload is defined as the myocardial fiber length at the end

Table 1 Studies of indices used as bedside indicators of preload reserve and fluid responsiveness in hypotensive patients under positive-pressure ventilation (*BMI* body mass index, *CO* cardiac output, *CI* cardiac index, *SV* stroke volume, *SVI* stroke volume index, *IAC* invasive arterial catheter, *MV* proportion of patients mechanically ventilated, ↑ increase, ↓ decrease, *PAC* pulmonary artery catheter, *R* responders, *NR* nonresponders, *FC* fluid challenge, *HES* hydroxyethyl starch, *RL* Ringer's lactate, *Alb* albumin, *Δdown* delta down, *ΔPP* respiratory variation in pulse pressure, *LVEDV* left-ventricular end diastolic volume, *SPV* systolic pressure variation, *SVV* stroke volume variation, *TEE* transesophageal echocardiography, *Ppao* pulmonary artery occlusion pressure, *RAP* right atrial pressure, *RVEDV* right-ventricular-end diastolic volume, *FC* fluid challenge)

Variable measured	Technique	*n*	MV (%)	Volume (ml) and type of plasma substitute	Duration of FC (min)	Definition of R	Definition of NR	*p*: difference in baseline values R vs. NR	Reference
Rap	PAC	28	46	250 Alb 5%	20–30	↑ SVI	↓ SVI or unchanged	NS	37
Rap	PAC	41	76	300 Alb 4.5%	30	↑ CI	CI ↓ or unchanged	NS	18
Rap	PAC	25	94.4	NaCl 9‰ + Alb 5% to ↑ Ppao	Until ↑Ppao	↑ SV ≥10%	↑ SV <10%	0.04	31
Rap	PAC	40	100	500 HES 6%	30	↑ CI >15%	↑ CI <15%	NS	36
Ppao	PAC	28	46	250 Alb 5%	20–30	↑ SVI	↓ SVI or unchanged	NS	37
Ppao	PAC	41	76	300 Alb 4.5%	30	↑ CI	CI ↓ or unchanged	NS	18
Ppao	PAC	29	69	300–500 RL	? bolus	↑ C0>10%	C0 ↓ or unchanged	<0.01	40
Ppao	PAC	32	84	300–500 RL	?	↑ CI >20%	↑ CI <20%	NS	41
Ppao	PAC	16	100	500 HES 6%	30	↑ CI >15%	↑ CI <15%	0.1	42
Ppao	PAC	41	100	500 pPentastarch	15	↑ SV ≥20%	↑ SV <20%	0.003	25
Ppao	PAC	25	94.4	NaCl 9‰, Alb 5% to↑ Ppao	Until ↑Ppao	↑ SV ≥10%	↑ SV <10%	0.001	31
Ppao	PAC	40	100	500 HES 6%	30	↑ CI >15%	↑ CI <15%	NS	36
Ppao	PAC	19	100	500–750 HES 6%	10	↑ C0>10%	↑ SV <10%	0.0085	39
RVEDV	PAC	29	69	300–500 RL	? bolus	↑ C0>10%	C0 ↓ or unchanged	<0.001	40
RVEDV	PAC	32	84	300–500 RL	?	↑ CI >20%	↑ CI <20%	<0.002	41
RVEDV	PAC	25	94.4	NaCl 9‰, Alb 5% to↑ Ppao	Until ↑Ppao	↑ SV ≥10%	↑ SV <10%	0.22	31
LVEDV	TEE	16	100	500 HES 6%	30	↑ CI >15%	↑ CI <15%	0.005	42
LVEDV	TEE	41	100	500 Pentastarch	15	↑ SV ≥20%	↑ SV <20%	0.012	25
LVEDV	TEE	19	100	8 ml/kg HES 6%	30	↑ CI >15%	↑ CI <15%	NS	79
LVEDV	TEE	19	100	500–750 HES 6%	10	↑ C0>10%	↑ SV <10%	NS	39
SPV	IAC	16	100	500 HES 6%	30	↑ CI >15%	↑ CI <15%	0.0001	42
SPV	IAC	40	100	500 HES 6%	30	↑ CI >15%	↑ CI <15%	<0.001	36
SPV	IAC	19	100	500–750 HES 6%	10	↑ C0>10%	↑ SV <10%	0.017	39
Δdown	IAC	16	100	500 HES 6%	30	↑ CI >15%	↑ CI <15%	0.0001	42
Δdown	IAC	19	100	500–750 HES 6%	10	↑ C0>10%	↑ SV <10%	0.025	39
ΔPP	IAC	40	100	500 HES 6%	30	↑ CI >15%	↑ CI <15%	<0.001	36

of the diastole. In clinical practice, the left-ventricular end-diastolic volume is used as a surrogate to define left-ventricular preload [4]. However, this volumetric parameter is not easily assessed in critically ill patients. In normal conditions, a fairly good correlation exists between ventricular end-diastolic volumes and mean atrial pressures, and ventricular preloads are approximated by RAP and/or Ppao in patients breathing spontaneously [5, 6]. Critically ill patients often require positive pressure ventilation, which modifies the pressure regimen in the thorax in comparison to spontaneous breathing. Indeed, during MV RAP and Ppao rise secondary to an increase in intrathoracic pressure which rises pericardial pressure. This pressure increase induces a decrease in venous return [7, 8] with first a decrease in right and few heart beats later in left-ventricular end-diastolic volumes, respectively [9, 10]. Under extreme conditions such as acute severe pulmonary emboli and/or marked hyperinflation, RAP may also rise secondary to an increase afterload of the right ventricle. Moreover, under positive pressure ventilation not only ventricular but also thoracopulmonary compliances and abdominal pressure variations are observed over time. Thus a variable relationship between cardiac pressures and cardiac volumes is often observed [11, 12, 13, 14]. It has also been demonstrated that changes in intracardiac pressure (RAP, Ppao) no longer directly reflect changes in intravascular volume [15]. Pinsky et al. [16, 17] have demonstrated that changes in RAP do not follow changes in right-ventricular end-diastolic volume in postoperative cardiac surgery patients under positive pressure ventilation. Reuse et al. [18] observed no correlation between RAP and right-ventricular end-diastolic volume calculated from a thermodilution technique in hypovolemic patients before and after fluid resuscitation. The discordance between RAP and right-ventricular end-diastolic volume measurements may result from a systematic underestimation of the effect of positive-pressure ventilation on the right heart [16, 17]. Nevertheless, the RAP value measured either with a central venous catheter or a pulmonary artery catheter is still used to estimate preload and to guide intravascular volume therapy in patient under positive pressure ventilation [19, 20].

On the left side, the MV-induced intrathoracic pressure changes, compared to spontaneously breathing, only minimally alters the relationship between left atrial pressure and left-ventricular end-diastolic volume measurement in postoperative cardiac surgery patients [21]. However, several other studies show no relationship between Ppao and left-ventricular end-diastolic volume measured by either radionuclide angiography [12, 22], transthoracic echocardiography (TTE) [23], or transesophageal echocardiography (TEE) [24, 25, 26]. The latter findings may be related to the indirect pulmonary artery catheter method for assessing left atrial pressure [27, 28], although several studies have demonstrated that Ppao using PAC is a reliable indirect measurement of left atrial pressure [29, 30] in positive-pressure MV patients.

Right atrial pressure used to predict fluid responsiveness

Wagner et al. [31] reported that RAP was significantly lower before volume challenge in responders than in nonresponders ($p=0.04$) when patients were under positive pressure ventilation. Jellinek et al. [32] found that a RAP lower than 10 mmHg predicts a decrease in cardiac index higher than 20% when a transient 30 cm H_2O increase in intrathoracic pressure is administrated. Presuming that the principle cause of decrease in cardiac output in the latter study was due to a reduction in venous return [9, 33, 34, 35], RAP predicts reverse VE hemodynamic effect. Nevertheless, some clinical investigations studying fluid responsiveness in MV patients have reported that RAP poorly predicts increased cardiac output after volume expansion [18, 36, 37]. Indeed, in these studies RAP did not differentiate patients whose cardiac output did or did not increase after VE (responders and nonresponders, respectively).

Ppao used to predict fluid responsiveness

Some studies have demonstrated that Ppao is a good predictor of fluid responsiveness [13, 31, 38]. Recently Bennett-Guerrero et al. [39] also found that Ppao was a better predictor of response to VE than systolic pressure variation (SPV) and left-ventricular end-diastolic area measured by TEE. However, several other studies noted that Ppao is unable to predict fluid responsiveness and to differentiate between VE-responders and VE-nonresponders [18, 25, 36, 37, 40, 41, 42]. The discrepancy between the results of these studies may partly reflect differences in patients' baseline characteristics (e.g., demographic differences, medical history, chest and lung compliances) at study entry. Furthermore, differences in location of the pulmonary artery catheter extremity relative to the left atrium may be present [43]. Indeed, according to its position, pulmonary artery catheter may display alveolar pressure instead of left atrial pressure (West zone I or II) [44]. The value of Ppao is also influenced by juxtacardiac pressure [45, 46] particularly if positive end-expiratory pressure (PEEP) is used [28]. To overcome the latter difficulty in MV patients when PEEP is used, nadir Ppao (Ppao measured after airway disconnection) may be used [46]. However, as nadir Ppao requires temporary disconnection from the ventilator, it might be deleterious to severely hypoxemic patients. No study has yet evaluated the predictive value of nadir Ppao for estimating fluid responsiveness in MV patients.

In brief, although static intracardiac pressure measurements such as RAP and Ppao have been studied and used for many years for hemodynamic monitoring, their low predictive value in estimating fluid responsiveness in MV patients must be underlined. Thus using only intravascular static pressures to guide fluid therapy can lead to inappropriate therapeutic decisions [47].

Measures of ventricular end-diastolic volumes

Radionuclide angiography [48], cineangiocardiography [49], and thermodilution [50] have been used to estimate ventricular volumes for one-half a century. In intensive care units, various methods have been used to measure ventricular end-diastolic volume at the bedside, such as radionuclide angiography [51, 52], TTE [23, 53, 54], TEE [55], and a modified flow-directed pulmonary artery catheter which allows the measurement of cardiac output and right-ventricular ejection fraction (and the calculation of right-ventricular end-systolic and end-diastolic volume) [31, 41].

Right-ventricular end-diastolic volume measured by pulmonary artery catheter used to predict fluid responsiveness

During MV right-ventricular end-diastolic volume measured with a pulmonary artery catheter is decreased by PEEP [56] but is still well correlated with cardiac index [57, 58] and is a more reliable predictor of fluid responsiveness than Ppao [40, 41]. On the other hand, other studies have found no relationship between change in right-ventricular end-diastolic volume measured by pulmonary artery catheter and change in stroke volume in two series of cardiac surgery patients [16, 18]. Similarly, Wagner et al. [31] found that right-ventricular end-diastolic volume measured by pulmonary artery catheter was not a reliable predictor of fluid responsiveness in patients under MV, and that Ppao and RAP were superior to right-ventricular end-diastolic volume. The discrepancy between the results of these studies may partly reflect the measurement errors of cardiac output due to the cyclic change induced by positive pressure ventilation [59, 60, 61, 62], the inaccuracy of cardiac output measurement obtained by pulmonary artery catheter when the flux is low [63], and the influence of tricuspid regurgitation on the measurement of cardiac output [64]. Moreover, as right-ventricular end-diastolic volume is calculated (stroke volume divided by right ejection fraction), cardiac output becomes a shared variable in the calculation of both stroke volume and right-ventricular end-diastolic volume, and a mathematical coupling may have contributed to the close correlation observed between these two variables. Nevertheless, right-ventricular end-diastolic volume compared to Ppao may be useful in a small group of patients with high intra-abdominal pressure or when clinicians are reluctant to obtain off-PEEP nadir Ppao measurements [65].

Right-ventricular end-diastolic volume measured by echocardiography used to predict fluid responsiveness

TTE has been shown to be a reliable method to assess right-ventricular dimensions in patients ventilated with continuous positive airway pressure or positive-pressure ventilation [66, 67]. Using this approach, right-ventricular end-diastolic area is obtained on the apical four chambers view [68]. When no right-ventricular window is available, TEE is preferred to monitor right-ventricular end-volume in MV patients [53, 55, 69, 70, 71]. The latter method has become more popular in recent years due to technical improvements [72]. Nevertheless, no study has evaluated right-ventricular size measurements by TTE or TEE as a predictor of fluid responsiveness in MV patients.

Left-ventricular end-diastolic volume measured by echocardiography used to predict fluid responsiveness

TTE has been used in the past to measure left-ventricular end-diastolic volume and/or area [23, 67, 73, 74] in MV patients. However, no study has evaluated the left-ventricular end-diastolic volume and/or area measured by TTE as predictors of fluid responsiveness in MV patients. Due to its greater resolving power, TEE easily and accurately assesses left-ventricular end-diastolic volume and/or area in clinical practice [53, 75] except in patients undergoing coronary artery bypass grafting [76]. However, different studies have reported conflicting results about the usefulness of left-ventricular end-diastolic volume and/or area measured by TEE to predict fluid responsiveness in MV patients. Cheung et al. [26] have shown that left-ventricular end-diastolic area measured by TEE is an accurate method to predict the hemodynamic effects of acute blood loss. Other studies have reported either a modest [25, 42, 77] or a poor [78, 79] predictive value of left-ventricular end-diastolic volume and area to predict the cardiac output response to fluid loading. Recent studies have also produced conflicting results. Bennett-Guerrero et al. [39] measuring left-ventricular end-diastolic area with TEE before VE found no significant difference between responders and nonresponders. Paradoxically, Reuter et al. [80] found that left-ventricular end-diastolic area index assessed by TEE before VE predicts fluid responsiveness more accurately than RAP, Ppao, and stroke volume variation (SVV). In the future three-dimensional echocardiography could supplant other methods for measuring left-ventricular end-diastolic volume and their predictive value of fluid responsiveness. In a word, although measurements of

ventricular volumes should theoretically reflect preload dependence more accurately than other indices, conflicting results have been reported so far. These negative findings may be related to the method used to estimate end-diastolic ventricular volumes which do not reflect the geometric complexity of the right ventricle and to the influences of the positive intrathoracic pressure on left-ventricular preload, afterload and myocardial contractility [81].

Dynamic measurements for preload assessment

Measure of respiratory changes in systolic pressure, pulse pressure, and stroke volume

Positive pressure breath decreases temporary right-ventricular end-diastolic volume secondary to a reduction in venous return [7, 82]. A decrease in right-ventricular stroke volume ensues which become minimal at end positive pressure breath. This inspiratory reduction in right-ventricular stroke volume induces a decrease in left-ventricular end-diastolic volume after a phase lag of few heart beats (due to the pulmonary vascular transit time [83]), which becomes evident during the expiratory phase. This expiratory reduction in left-ventricular end-diastolic volume induces a decrease in left-ventricular stroke volume, determining the minimal value of systolic blood pressure observed during expiration. Conversely, the inspiratory increase in left-ventricular end-diastolic volume determining the maximal value of systolic blood pressure is observed secondary to the rise in left-ventricular preload reflecting the few heart beats earlier increased in right-ventricular preload during expiration. Furthermore, increasing lung volume during positive pressure ventilation may also contribute to the increased pulmonary venous blood flow (related to the compression of pulmonary blood vessels [84]) and/or to a decrease in left-ventricular afterload [85, 86, 87], which together induce an increase in left-ventricular preload. Finally, a decrease in right-ventricular end-diastolic volume during a positive pressure breath may increase left-ventricular compliance and then left-ventricular preload [88]. Thus due to heart-lung interaction during positive pressure ventilation the left-ventricular stroke volume varies cyclically (maximal during inspiration and minimal during expiration).

These variations have been used clinically to assess preload status and predict fluid responsiveness in deeply sedated patients under positive pressure ventilation. In 1983 Coyle et al. [89] in a preliminary study demonstrated that the SPV following one mechanical breath is increased in hypovolemic sedated patients and decreased after fluid resuscitation. This study defined SPV as the difference between maximal and minimal values of systolic blood pressure during one positive pressure mechanical breath. Using the systolic pressure at end expiration as a reference point or baseline the SPV was further divided into two components: an increase (Δup) and a decrease (Δdown) in systolic pressure vs. baseline (Fig. 2). These authors concluded that in hypovolemic patients Δdown was the main component of SPV. These preliminary conclusions were confirmed in 1987 by Perel et al. [90] who demonstrated that SPV following a positive pressure breath is a sensitive indicator of hypovolemia in ventilated dogs. Thereafter Coriat et al. [91] demonstrated that SPV and Δdown predict the response of cardiac index to VE in a group of sedated MV patients after vascular surgery. Exploring another pathophysiological concept, Jardin et al. [92] found that pulse pressure (PP; defined as the difference between the systolic and the diastolic pressure) is related to left-ventricular stroke volume in MV patients. Using these findings, Michard et al. [35, 36,] have shown that respiratory changes in PP [ΔPP=maximal PP at inspiration (PPmax) minus minimal PP at expiration (PPmin); (Fig. 2) and calculated as: ΔPP (%)=100 (PPmax-PPmin)/(Ppmax+PPmin)/2] predict the effect of VE on cardiac index in patients with acute lung injury [35] or septic shock [36]. The same team proposed another approach to assess SVV in MV patients and to predict cardiac responsiveness to VE [79]. Using Doppler measurement of beat-to-beat aortic blood flow, they found that respiratory change in aortic blood flow maximal velocity predicts fluid responsiveness in septic MV patients. Measuring SVV during positive pressure ventilation by continuous arterial pulse contour analysis, Reuter et al. [80] have recently demonstrated that SVV accurately predicts fluid responsiveness following volume infusion in ventilated patients after cardiac surgery.

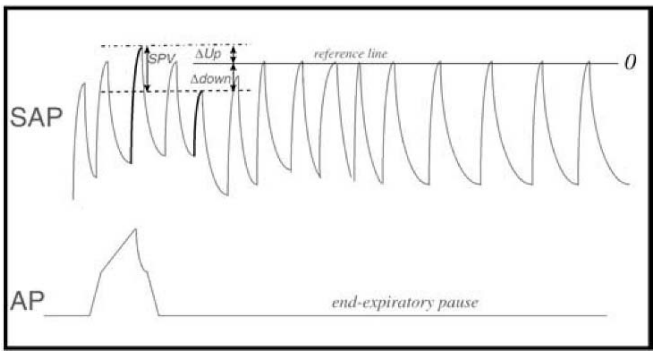


Fig. 2 Systolic pressure variation (*SPV*) after one mechanical breath followed by an end-expiratory pause. Reference line permits the measurement of Δup and Δdown. *Bold* Maximal and minimal pulse pressure. *AP* Airway pressure; *SAP* systolic arterial pressure

Systolic pressure variation used to predict fluid responsiveness

The evaluation of fluid responsiveness by SPV is based on cardiopulmonary interaction during MV [93, 94]. In 1995 Rooke et al. [95] found that SPV is a useful monitor of volume status in healthy MV patients during anesthesia. Coriat et al. [91] confirmed the usefulness of SPV for estimating response to VE in MV patients after vascular surgery. Ornstein et al. [96] have also shown that SPV and Δdown are correlated with decreased cardiac output after controlled hemorrhage in postoperative cardiac surgical patients. Furthermore, Tavernier et al. [42] found Δdown before VE to be an accurate index of the fluid responsiveness in septic patients, and that a Δdown value of 5 mmHg is the cutoff point for distinguishing responders from nonresponders to VE. Finally, in septic patients Michard et al. [36] found that SPV is correlated with volume expansion-induced change in cardiac output. However, Denault et al. [81] have demonstrated that SPV is not correlated with changes in left-ventricular end-diastolic volume measured by TEE in cardiac surgery patients. Indeed, in this study, SPV was observed despite no variation in left-ventricular stroke volume, suggesting that SPV involves processes independent of changes in the left-ventricular preload (airway pressure, pleural pressure, and its resultant afterload) [81].

Pulse pressure variation used to predict fluid responsiveness

Extending the concept elaborated by Jardin et al. [92], Michard et al. [36] found that ΔPP predicted the effect of VE on cardiac output in 40 septic shock hypotensive patients. These authors demonstrated that both ΔPP and SPV, when greater than 15%, are superior to RAP and Ppao, for predicting fluid responsiveness. Moreover, ΔPP was more accurate and with less bias than SPV. These authors proposed ΔPP as a surrogate for stroke volume variation concept [93], which has not been validated yet. In another study these authors [35] included VE in six MV patients with acute lung injury and found that ΔPP is a useful guide to predict fluid responsiveness.

Stroke volume variation to predict fluid responsiveness

Using Doppler TEE, Feissel et al. [79] studied changes in left-ventricular stroke volume induced by the cyclic positive pressure breathing. By measuring the respiratory variation in maximal aortic blood flow velocity these authors predicted fluid responsiveness in septic MV patients. Left-ventricular stroke volume was obtained by multiplying flow velocity time integral over aortic valve by valve opening area during expiration. However, this finding may be biased, as expiratory flow velocity time integral is a shared variable in the calculation of both cardiac output and expiratory maximal aortic blood flow velocity and a mathematical coupling may contribute to the observed correlation between changes in cardiac output and variation in maximal aortic blood flow velocity. Finally, Reuter et al. [80] used continuous arterial pulse contour analysis and found that SVV during positive pressure breath accurately predicts fluid responsiveness following VE in ventilated cardiac surgery patients [80]. Using the receiver operating characteristics curve, these authors demonstrated that the area under the curve is statistically greater for SVV (0.82; confidence interval: 0.64–1) and SPV (0.81; confidence interval: 0.62–1) than for RAP (0.45; confidence interval: 0.17–0.74) ($p<0.001$) [97]. Concisely, dynamic indices have been explored to evaluate fluid responsiveness in critically ill patients. All of them have been validated in deeply sedated patients under positive-pressure MV. Thus such indices are useless in spontaneously breathing intubated patients, a MV mode often used in ICU. Moreover, regular cardiac rhythm is an obligatory condition to allow their use.

Conclusion

Positive pressure ventilation cyclically increases intrathoracic pressure and lung volume, both of which decrease venous return and alter stroke volume. Thus VE which rapidly restore cardiac output and arterial blood pressure is an often used therapy in hypotensive MV patients and indices which would predict fluid responsiveness are necessary. RAP, Ppao, and right-ventricular end-diastolic volume, which are static measurements, have been studied but produced conflicting data in estimating preload and fluid responsiveness. On the other hand, SPV and ΔPP, which are dynamic measurements, have been shown to identify hypotension related to decrease in preload, to distinguish between responders and nonresponders to fluid challenge (Table 1), and to permit titration of VE in various patient populations.

Although there is substantial literature on indices of hypovolemia, only few studies have evaluated the cardiac output changes induced by VE in MV patients. Moreover, therapeutic recommendations regarding unmasked preload dependency states without hypotension need further studies. Finally, another unanswered question is related to patients outcome: does therapy guided by fluid responsiveness indices improve patients survival?

Acknowledgements The authors thank Dr. M.R. Pinsky, University of Pittsburgh Medical Center, for his helpful advice in the preparation of this manuscript. The authors are also grateful for the translation support provided by Angela Frei.

References

1. Guyton AC, Richardson TQ, Langston JB (1964) Regulation of cardiac output and venous return. Clin Anesth 3:1–34
2. Guyton AC (1967) Regulation of cardiac output. N Engl J Med 277:805–812
3. Horst HM, Obeid FN (1986) Hemodynamic response to fluid challenge: a means of assessing volume status in the critically ill. Henry Ford Hosp Med J 34:90–94
4. Suga H, Sagawa K (1974) Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. Circ Res 35:117–126
5. Crexells C, Chatterjee K, Forrester JS, Dikshit K, Swan HJ (1973) Optimal level of filling pressure in the left side of the heart in acute myocardial infarction. N Engl J Med 289:1263–1266
6. Buchbinder N, Ganz W (1976) Hemodynamic monitoring: invasive techniques. Anesthesiology 45:146–155
7. Cournand A, Motley H, Werko L, Richards D (1948) Physiological studies of the effect of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 152:162–174
8. Fessler HE, Brower RG, Wise RA, Permutt S (1992) Effects of positive end-expiratory pressure on the canine venous return curve. Am Rev Respir Dis 146:4–10
9. Potkin RT, Hudson LD, Weaver LJ, Trobaugh G (1987) Effect of positive end-expiratory pressure on right and left ventricular function in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 135:307–311
10. Fewell JE, Abendschein DR, Carlson CJ, Murray JF, Rapaport E (1980) Continuous positive-pressure ventilation decreases right and left ventricular end-diastolic volumes in the dog. Circ Res 46:125–132
11. McKenney PA, Apstein CS, Mendes LA, Connelly GP, Aldea GS, Shemin RJ, Davidoff R (1994) Increased left ventricular diastolic chamber stiffness immediately after coronary artery bypass surgery. J Am Coll Cardiol 24:1189–1194
12. Calvin JE, Driedger AA, Sibbald WJ (1981) Does the pulmonary capillary wedge pressure predict left ventricular preload in critically ill patients? Crit Care Med 9:437–443
13. Packman MI, Rackow EC (1983) Optimum left heart filling pressure during fluid resuscitation of patients with hypovolemic and septic shock. Crit Care Med 11:165–169
14. Jardin F, Gueret P, Dubourg O, Farcot JC, Margairaz A, Bourdarias JP (1985) Right ventricular volumes by thermodilution in the adult respiratory distress syndrome. A comparative study using two-dimensional echocardiography as a reference method. Chest 88:34–39
15. Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ (1992) Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. Intensive Care Med 18:142–147
16. Pinsky MR, Desmet JM, Vincent JL (1992) Effect of positive end-expiratory pressure on right ventricular function in humans. Am Rev Respir Dis 146:681–687
17. Pinsky MR (1994) Cardiovascular effects of ventilatory support and withdrawal. Anesth Analg 79:567–576
18. Reuse C, Vincent JL, Pinsky MR (1990) Measurements of right ventricular volumes during fluid challenge. Chest 98:1450–1454
19. Saarela E, Kari A, Nikki P, Rauhala V, Iisalo E, Kaukinen L (1991) Current practice regarding invasive monitoring in intensive care units in Finland. A nationwide study of the uses of arterial, pulmonary artery and central venous catheters and their effect on outcome. The Finnish Intensive Care Study Group. Intensive Care Med 17:264–271
20. Boldt J, Lenz M, Kumle B, Papsdorf M (1998) Volume replacement strategies on intensive care units: results from a postal survey. Intensive Care Med 24:147–151
21. Guyton RA, Chiavarelli M, Padgett CA, Cheung EH, Staton GW, Hatcher CR (1987) The influence of positive end-expiratory pressure on intrapericardial pressure and cardiac function after coronary artery bypass surgery. J Cardiothorac Anesth 1:98–107
22. Lemaire F, Teboul JL, Cinotti L, Giotto G, Abrouk F, Steg G, Macquin-Mavier I, Zapol WM (1988) Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 69:171–179
23. Jardin F, Valtier B, Beauchet A, Dubourg O, Bourdarias JP (1994) Invasive monitoring combined with two-dimensional echocardiographic study in septic shock. Intensive Care Med 20:550–554
24. Hinder F, Poelaert JI, Schmidt C, Hoeft A, Mollhoff T, Loick HM, Van Aken H (1998) Assessment of cardiovascular volume status by transoesophageal echocardiography and dye dilution during cardiac surgery. Eur J Anaesthesiol 15:633–640
25. Tousignant CP, Walsh F, Mazer CD (2000) The use of transoesophageal echocardiography for preload assessment in critically ill patients. Anesth Analg 90:351–355
26. Cheung AT, Savino JS, Weiss SJ, Aukburg SJ, Berlin JA (1994) Echocardiographic and hemodynamic indexes of left ventricular preload in patients with normal and abnormal ventricular function. Anesthesiology 81:376–387
27. Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D (1970) Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. N Engl J Med 283:447–451
28. Berryhill RE, Benumof JL (1979) PEEP-induced discrepancy between pulmonary arterial wedge pressure and left atrial pressure: the effects of controlled vs. spontaneous ventilation and compliant vs. noncompliant lungs in the dog. Anesthesiology 51:303–308
29. Humphrey CB, Gibbons JA, Folkerth TL, Shapiro AR, Fosburg RG (1976) An analysis of direct and indirect measurements of left atrial filling pressure. J Thorac Cardiovasc Surg 71:643–647
30. Lozman J, Powers SR Jr, Older T, Dutton RE, Roy RJ, English M, Marco D, Eckert C (1974) Correlation of pulmonary wedge and left atrial pressures. A study in the patient receiving positive end expiratory pressure ventilation. Arch Surg 109:270–277
31. Wagner JG, Leatherman JW (1998) Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. Chest 113:1048–1054
32. Jellinek H, Krafft P, Fitzgerald RD, Schwarz S, Pinsky MR (2000) Right atrial pressure predicts hemodynamic response to apneic positive airway pressure. Crit Care Med 28:672–688
33. Van Trigt P, Spray TL, Pasque MK, Peyton RB, Pellom GL, Christian CM, Fagraeus L, Wechsler AS (1982) The effect of PEEP on left ventricular diastolic dimensions and systolic performance following myocardial revascularization. Ann Thorac Surg 33:585–5892
34. Johnston WE, Vinten-Johansen J, Santamore WP, Case LD, Little WC (1989) Mechanism of reduced cardiac output during positive end-expiratory pressure in the dog. Am Rev Respir Dis 140:1257–1264

35. Michard F, Chemla D, Richard C, Wysocki M, Pinsky MR, Lecarpentier Y, Teboul JL (1999) Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. Am J Respir Crit Care Med 159:935–939
36. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky, MR, Teboul JL (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138
37. Calvin JE, Driedger AA, Sibbald WJ (1981) The hemodynamic effect of rapid fluid infusion in critically ill patients. Surgery 90:61–76
38. Krausz MM, Perel A, Eimerl D, Cotev S (1977) Cardiopulmonary effects of volume loading in patients in septic shock. Ann Surg 185:429–434
39. Bennett-Guerrero E, Kahn RA, Moskowitz DM, Falcucci O, Bodian CA (2002) Comparison of arterial systolic pressure variation with other clinical parameters to predict the response to fluid challenges during cardiac surgery. Mt Sinai J Med 69:96–100
40. Diebel LN, Wilson RF, Tagett MG, Kline RA (1992) End-diastolic volume. A better indicator of preload in the critically ill. Arch Surg 127:817–821
41. Diebel L, Wilson RF, Heins J, Larky H, Warsow K, Wilson S (1994) End-diastolic volume versus pulmonary artery wedge pressure in evaluating cardiac preload in trauma patients. J Trauma 37:950–955
42. Tavernier B, Makhotine O, Lebuffe G, Dupont J, Scherpereel P (1998) Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. Anesthesiology 89:1313–1321
43. Rajacich N, Burchard KW, Hasan FM, Singh AK (1989) Central venous pressure and pulmonary capillary wedge pressure as estimates of left atrial pressure: effects of positive end-expiratory pressure and catheter tip malposition. Crit Care Med 17:7–11
44. Shasby DM, Dauber IM, Pfister S (1981) Swan-Ganz catheter location and left atrial pressure determine the accuracy of the wedge pressure when positive end-expiratory pressure is used. Chest 80:666–670
45. Raper R, Sibbald WJ (1986) Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. Chest 89:427–434
46. Pinsky M, Vincent JL, De Smet JM (1991) Estimating left ventricular filling pressure during positive end-expiratory pressure in humans. Am Rev Respir Dis 143:25–31
47. Swenson JD, Bull D, Stringham J (2001) Subjective assessment of left ventricular preload using transesophageal echocardiography: corresponding pulmonary artery occlusion pressures. J Cardiothorac Vasc Anesth 15:580–583
48. Mullins CB, Mason DT, Ashburn WL, Ross J (1969) Determination of ventricular volume by radioisotope-angiography. Am J Cardiol 24:72–78
49. Kasser IS, Kennedy JW (1969) Measurement of left ventricular volumes in man by single-plane cineangiocardiography. Invest Radiol 4:83–90
50. Balcon R, Oram S (1968) Measurement of right ventricular end-systolic and end-diastolic volumes by the thermodilution technique. Br Heart J 30:690–695
51. Viquerat CE, Righetti A, Suter PM (1983) Biventricular volumes and function in patients with adult respiratory distress syndrome ventilated with PEEP. Chest 83:509–514
52. Dhainaut JF, Devaux JY, Monsallier JF, Brunet F, Villemant D, Huyghebaert MF (1986) Mechanisms of decreased left ventricular preload during continuous positive pressure ventilation in ARDS. Chest 90:74–80
53. Terai C, Uenishi M, Sugimoto H, Shimazu T, Yoshioka T, Sugimoto T (1985) Transesophageal echocardiographic dimensional analysis of four cardiac chambers during positive end-expiratory pressure. Anesthesiology 63:640–646
54. Jardin F, Brun-Ney D, Hardy A, Aegerter P, Beauchet A, Bourdarias JP (1991) Combined thermodilution and two-dimensional echocardiographic evaluation of right ventricular function during respiratory support with PEEP. Chest 99:162–168
55. Vieillard A, Schmitt JM, Beauchet A, Augarde R, Prin S, Page B, Jardin F (2001) Early preload adaptation in septic shock? A transesophageal echocardiographic study. Anesthesiology 94:400–406
56. Jellinek H, Krafft P, Hiesmayr M, Steltzer H (1997) Measurement of right ventricular performance during apnea in patients with acute lung injury. J Trauma 42:1062–1067
57. Diebel LN, Myers T, Dulchavsky S (1997) Effects of increasing airway pressure and PEEP on the assessment of cardiac preload. J Trauma 42:585–590
58. Cheatham ML, Nelson LD, Chang MC, Safcsak K (1998) Right ventricular end-diastolic volume index as a predictor of preload status in patients on positive end-expiratory pressure. Crit Care Med 26:1801–186
59. Jansen JR, Schreuder JJ, Bogaard JM, van Rooyen W, Versprille A (1981) Thermodilution technique for measurement of cardiac output during artificial ventilation. J Appl Physiol 51:584–591
60. Stevens JH, Raffin TA, Mihm FG, Rosenthal MH, Stetz CW (1985) Thermodilution cardiac output measurement. Effects of the respiratory cycle on its reproducibility. JAMA 253:2240–2242
61. Okamoto K, Komatsu T, Kumar V, Sanchala V, Kubal K, Bhalodia R, Shibutani K (1986) Effects of intermittent positive-pressure ventilation on cardiac output measurements by thermodilution. Crit Care Med 14:977–980
62. Jansen JR, Schreuder JJ, Settels JJ, Kloek JJ, Versprille A (1990) An adequate strategy for the thermodilution technique in patients during mechanical ventilation. Intensive Care Med 16:422–425
63. Siniorakis EE, Nikolaou NI, Sarantopoulos CD, Sotirelos KT, Iliopoulos NE, Bonoris PE (1994) Volume loading in predominant right ventricular infarction: bedside haemodynamics using rapid response thermistors. Eur Heart J 15:1340–1347
64. Spinale FG, Mukherjee R, Tanaka R, Zile MR (1992) The effects of valvular regurgitation on thermodilution ejection fraction measurements. Chest 101:723–731
65. Yu M, Takiguchi S, Takanishi D, Myers S, McNamara JJ (1995) Evaluation of the clinical usefulness of thermodilution volumetric catheters. Crit Care Med 23:681–686
66. Jardin F, Farcot JC, Gueret P, Prost JF, Ozier Y, Bourdarias JP (1984) Echocardiographic evaluation of ventricles during continuous positive airway pressure breathing. J Appl Physiol 56:619–627
67. Huemer G, Kolev N, Kurz A, Zimpfer M (1994) Influence of positive end-expiratory pressure on right and left ventricular performance assessed by Doppler two-dimensional echocardiography. Chest 106:67–73
68. Jardin F, Dubourg O, Bourdarias JP (1997) Echocardiographic pattern of acute cor pulmonale. Chest 111:209–217
69. Mathru M, Kleinman B, Dries DJ, Rao T, Calandra D (1990) Effect of opening the pericardium on right ventricular hemodynamics during cardiac surgery. Chest 98:120–123

70. Schuster S, Erbel R, Weilemann LS, Lu WY, Henkel B, Wellek S, Schinzel H, Meyer J (1990) Hemodynamics during PEEP ventilation in patients with severe left ventricular failure studied by transesophageal echocardiography. Chest 97:1181–1189
71. Le Tulzo Y, Seguin P, Gacouin A, Camus C, Suprin E, Jouannic I, Thomas R (1997) Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: a preliminary descriptive study. Intensive Care Med 23:664–670
72. Vignon P, Mentec H, Terre S, Gastinne H, Gueret P, Lemaire F (1994) Diagnostic accuracy and therapeutic impact of transthoracic and transesophageal echocardiography in mechanically ventilated patients in the ICU. Chest 106:1829–1834
73. Jardin F, Brun-Ney D, Auvert B, Beauchet A, Bourdarias JP (1990) Sepsis-related cardiogenic shock. Crit Care Med 18:1055–1060
74. Jardin F, Fourme T, Page B, Loubieres Y, Vieillard-Baron A, Beauchet A, Bourdarias JP (1999) Persistent preload defect in severe sepsis despite fluid loading: a longitudinal echocardiographic study in patients with septic shock. Chest 116:1354–1359
75. Clements FM, Harpole DH, Quill T, Jones RH, McCann RL (1990) Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography. Br J Anaesth 64:331–336
76. Urbanowicz JH, Shaaban MJ, Cohen NH, Cahalan MK, Botvinick EH, Chatterjee K, Schiller NB, Dae MW, Matthay MA (1990) Comparison of transesophageal echocardiographic and scintigraphic estimates of left ventricular end-diastolic volume index and ejection fraction in patients following coronary artery bypass grafting. Anesthesiology 72:607–612
77. van Daele ME, Trouwborst A, van Woerkens LC, Tenbrinck R, Fraser AG, Roelandt JR (1994) Transesophageal echocardiographic monitoring of preoperative acute hypervolemic hemodilution. Anesthesiology 81:602–609
78. Greim CA, Roewer N, Apfel C, Laux G, Schulte am Esch J (1997) Relation of echocardiographic preload indices to stroke volume in critically ill patients with normal and low cardiac index. Intensive Care Med 23:411–416
79. Feissel M, Michard F, Mangin I, Ruyer O, Faller JP, Teboul JL (2001) Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest 119:867–873
80. Reuter DA, Felbinger TW, Schmidt C, Kilger E, Goedje O, Lamm P, Goetz AE (2002) Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. Intensive Care Med 28:392
81. Denault AY, Gasior TA, Gorcsan J, 3rd, Mandarino WA, Deneault LG, Pinsky MR (1999) Determinants of aortic pressure variation during positive-pressure ventilation in man. Chest 116:176–186
82. Morgan BC, Martin WE, Hornbein TF, Crawford EW, Guntheroth WG (1966) Hemodynamic effects of intermittent positive pressure respiration. Anesthesiology 27:584–590
83. Scharf SM, Brown R, Saunders N, Green LH (1980) Hemodynamic effects of positive-pressure inflation. J Appl Physiol 49:124–131
84. Brower R, Wise RA, Hassapoyannes C, Bromberger-Barnea B, Permutt S (1985) Effect of lung inflation on lung blood volume and pulmonary venous flow. J Appl Physiol 58:954–963
85. Abel JG, Salerno TA, Panos A, Greyson ND, Rice TW, Teoh K, Lichtenstein SV (1987) Cardiovascular effects of positive pressure ventilation in humans. Ann Thorac Surg 43:198–206
86. Fessler HE, Brower RG, Wise RA, Permutt S (1988) Mechanism of reduced LV afterload by systolic and diastolic positive pleural pressure. J Appl Physiol 65:1244–1250
87. Pinsky MR, Matuschak GM, Klain M (1985) Determinants of cardiac augmentation by elevations in intrathoracic pressure. J Appl Physiol 58:1189–1198
88. Taylor RR, Covell JW, Sonnenblick EH, Ross J (1967) Dependence of ventricular distensibility on filling of the opposite ventricle. Am J Physiol 213:711–718
89. Coyle JP, Teplick RS, Michael CL, Davison JK (1983) Respiratory variations in systemic arterial pressure as an indicator of volume status. Anesthesiology 59:A53
90. Perel A, Pizov R, Cotev S (1987) Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesiology 67:498–502
91. Coriat P, Vrillon M, Perel A, Baron JF, Le Bret F, Saada M, Viars P (1994) A comparison of systolic blood pressure variations and echocardiographic estimates of end-diastolic left ventricular size in patients after aortic surgery. Anesth Analg 78:46–53
92. Jardin F, Farcot JC, Gueret P, Prost JF, Ozier Y, Bourdarias JP (1983) Cyclic changes in arterial pulse during respiratory support. Circulation 68:266–274
93. Michard F, Teboul JL (2000) Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Crit Care 4:282–289
94. Gunn SR, Pinsky MR (2001) Implications of arterial pressure variation in patients in the intensive care unit. Curr Opin Crit Care 7:212–217
95. Rooke GA, Schwid HA, Shapira Y (1995) The effect of graded hemorrhage and intravascular volume replacement on systolic pressure variation in humans during mechanical and spontaneous ventilation. Anesth Analg 80:925–932
96. Ornstein E, Eidelman LA, Drenger B, Elami A, Pizov R (1998) Systolic pressure variation predicts the response to acute blood loss. J Clin Anesth 10:137–140
97. Reuter DA, Felbinger TW, Kilger E, Schmidt C, Lamm P, Goetz AE (2002) Optimising fluid therapy in mechanically ventilated patients after cardiac surgery by on-line monitoring of left ventricular stroke volume variations. Comparison with aortic systolic pressure variations. Br J Anaesth 88:124–126

Manu L. N. G. Malbrain

Different techniques to measure intra-abdominal pressure (IAP): time for a critical re-appraisal

Abstract The diagnosis of intra-abdominal hypertension (IAH) or abdominal compartment syndrome (ACS) is heavily dependant on the reproducibility of the intra-abdominal pressure (IAP) measurement technique. Recent studies have shown that a clinical estimation of IAP by abdominal girth or by examiner's feel of the tenseness of the abdomen is far from accurate, with a sensitivity of around 40%. Consequently, the IAP needs to be measured with a more accurate, reproducible and reliable tool. The role of the intra-vesical pressure (IVP) as the gold standard for IAP has become a matter of debate. This review will focus on the previously described indirect IAP measurement techniques and will suggest new revised methods of IVP measurement less prone to error. Cost-effective manometry screening techniques will be discussed, as well as some options for the future with microchip transducers.

Keywords Intra-abdominal pressure · Intra-abdominal hypertension · Abdominal compartment syndrome · Intra-vesical pressure

Introduction

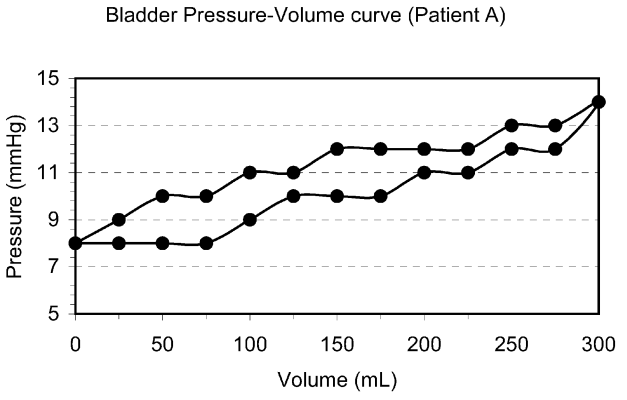
There is an exponential increase in studies on intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) in the literature. There is still controversy about the ideal method for measuring intra-abdominal pressure (IAP) [1, 2]. The intra-vesical route evolved as the gold standard. It, however, has considerable variability in the measurement technique, not only between individuals but also institutions. Common pitfalls are air bubbles in the system and wrong transducer positions. Variations in IAP from −6 to +30 mmHg have been reported previously [3]. A recent multicentre snapshot study showed that the coefficient of variation was around 25%, even up to 66% in some centres, raising questions on the reproducibility of the measurement itself. This makes it, difficult to compare literature data [4].

The volumes reported in the literature for bladder priming before the IAP measurement are not uniform (ranging from 50 to 250 ml). Injecting over 50 ml in a noncompliant bladder will raise intrinsic vesical pressure (IVP) and thus overestimate IAP [5, 6] (Fig. 1). By constructing bladder pressure volume curves we found that IVP was not raised when the volume instilled was limited to 50–100 ml [7] (Fig. 2). This is in accordance with others who found that baseline IAP alters the amount of volume in the bladder needed to increase IAP: the lower the baseline IAP, the higher the extra bladder volume needed for the same IAP increase [6].

The purpose of this report is: (1) to review the most commonly used indirect techniques for IAP measurement; (2) to provide the reader with a full description and important (dis)advantages of each technique; (3) to describe some new or revised techniques; and (4) to highlight the cost-effectiveness of each method.

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_30, © Springer-Verlag Berlin Heidelberg 2009

Panel A



Panel B

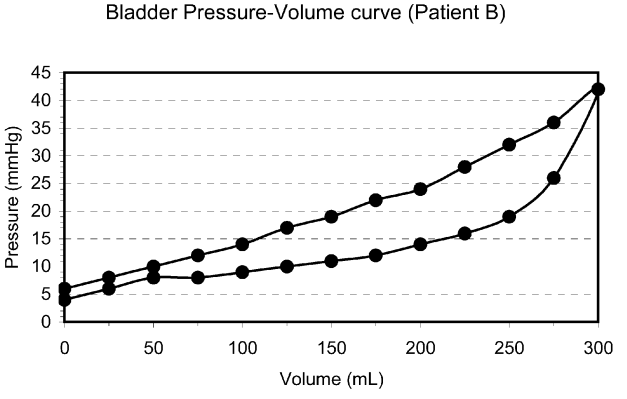


Fig. 1 A Bladder PV curve in a patient with a compliant bladder. Note that pressures are higher during insufflation than during deflation. Note that regardless of the amount of saline instilled in the bladder the pressures are comparable: 10 mmHg at 50 ml, 11 mmHg at 100 ml and 12 mmHg at 200 ml. **B** Bladder PV curve in a septic patient with a poor bladder compliance. Note that pressures are higher during insufflation than deflation. Note the significant difference in IAP value with regard to the amount of saline instilled in the bladder: 10 mmHg at 50 ml, 14 mmHg at 100 ml and 24 mmHg at 200 ml

IAP assessment

In analogy with the paradigm "if you don't take a temperature you can't find a fever" (in Samuel Shem, *The house of god*, Dell Publishing, ISBN: 0-440-13368-8), one can state that "if you don't measure IAP you cannot make a diagnosis of IAH or ACS". Abdominal perimeter cannot be used as an alternative method for IAP. In a recent study of 132 paired measurements in 12 ICU patients, we found a poor correlation between IAP and abdominal perimeter (R^2=0.12, P=0.04) [8]. Clinically significant IAH may be present in the absence of abdominal distension [9]. Chronic abdominal distension

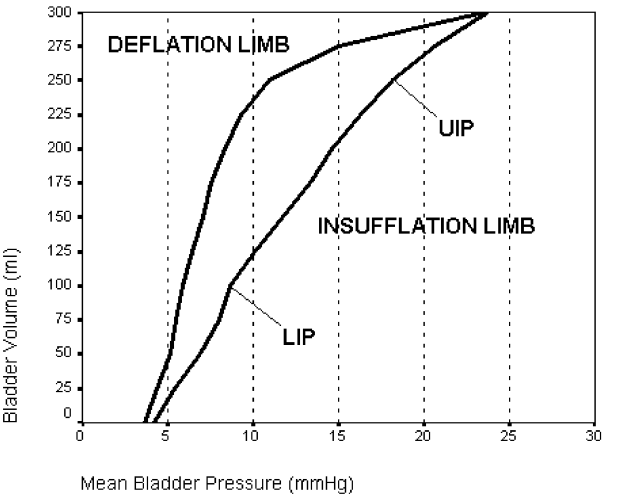


Fig. 2 Plot of the "insufflation" and "deflation" PV curve as a curve fit of the means of 13 measurements in six mechanically ventilated patients. The bladder PV curves were obtained by instilling sterile saline into the bladder with 25-ml increments. A lower inflection point can be seen at a bladder volume of 50–100 ml and an upper inflection point (UIP) at a bladder volume of 250 ml. The difference in bladder pressure was 2.7±3.3 mmHg between 0 and 50 ml volume, 1.7±1.2 mmHg between 50 and 100 ml, 7.7±5.7 mmHg between 50 and 200 ml and 16.8±13.4 mmHg between 50 and 300 ml. See text for explanation

with sufficient time for adaptation, as seen with pregnancy, obesity, cirrhosis, or ovarian tumours, is an example of increased abdominal perimeter that is not necessarily accompanied by an increase in IAP. Other studies have shown that clinical IAP estimation by putting one or two hands on the abdomen is also far from accurate, with a sensitivity of only around 40%. So, one needs to measure it [10–12]. The question then arises: how? Since the abdomen and its contents can be considered as relatively non-compressive and primarily fluid in character, subject to Pascal's law, the IAP can be measured in nearly every part of the abdomen. Different direct and indirect measurement methods have been reported.

Table 1 lists the different techniques and their major advantages and disadvantages, with an overall score calculated by dividing twice the number of advantages by the total number of (dis)advantages reported. Table 2 lists the cost estimate in Euros for the different techniques, with the cost of the initial set-up as well as the cost per measurement. Cost estimations were based on the number of measurements per day as well as the duration of the measurement period.

Table 1 Overview of the advantages (-) and disadvantages (+) of the different techniques for indirect IAP measurement. The overall score was calculated as the fraction of twice the number of advantages and the total number of (dis)advantages

General information	**Bladder techniques**				**Manometry**		
Author	Kron	Iberti	Cheatham	Malbrain	Harrahil	Lee	Malbrain
Reference	[13]	[16, 17]	[18]	Current	[26]	[27]	[28]
Publication year	1984	1987, 1989	1998	2003	1998	2002	2002
Properties	Fluid	Fluid	Fluid	Fluid	Fluid	Fluid	Fluid
General — Volume	50 ml	250 ml	50 ml	50 ml	?	?	50 ml
Manipulation	+++	++	+	+	-	-	-
Difficult	+	-	+	-	-	-	-
Time consuming initial set-up	+++	++	+	+	-	-	-
Time consuming next measurement	+++	++	-	-	-	-	-
Cost of device initial set-up	+	+	+	+	-	-	-
Cost per measurement	++	++	+	+	-	-	-
Interference urine output	+	+	+	+	-	-	-
Glass syringe	-	-	-	-	-	-	-
Technique							
No repeated measurements	+	+	-	-	-	-	-
No continuous trend	+	+	+	+	+	+	+
Not automated	+	+	+	+	+	+	+
Recalibration	+	+	+	+	-	-	-
Volume not standardised	+	+	+	+	+	+	-
Not accurate or reproducible	+	+	+	+	+	+	+
Not well validated	-	-	-	-	+	+	+
Air-bubbles	+	+	+	+	+	+	+
Multiple menisci	-	-	-	-	+	+	+
Bio-filter blocking	-	-	-	-	-	-	+
MMC interference	-	-	-	-	-	-	-
Hydrostatic fluid column							
Zero-reference problem	+	+	+	+	-	-	-
Over-under damping	+	+	+	+	+	+	+
Body position dependent	++	++	++	++	++	++	++
Risks							
Needle stick injury	+	+	+	-	-	-	-
Urinary infection	+	+	+	+	-	-	-
Sepsis	-	-	-	-	-	-	-
Contra-indications							
Bladder trauma	+	+	+	+	+	+	+
Neurogenic bladder	+	+	+	+	+	+	+
Hematuria	+	+	+	+	+	+	+
Gastric trauma	-	-	-	-	-	-	-
Other abdominal trauma	-	-	-	-	-	-	-
Overall conclusion							
Disadvantages	30	26	21	19	13	13	13
Advantages	8	9	10	12	18	18	18
Overall score	34.8%	0.9%	48.8%	55.8%	73.5%	73.5%	73.5%
Clinical indications	None	None	Screening	Intermittent monitoring	None	?	Quick screening

Bladder

The original open system single measurement technique [13]

Description

Traditionally the bladder has been used as the method of choice for measuring IAP. The technique was originally described by Kron and co-workers [13] and disrupts for each IAP measurement what is normally a closed sterile system. Thus, IAP measurement involves disconnecting the patient's Foley catheter and instilling 50–100 ml of saline using a sterile field. After reconnection, the urinary drainage bag is clamped distal to the culture aspiration port. For each individual IAP measurement a 16-gauche needle is then used to Y-connect a manometer or pressure

Table 1 (continued)

General Information	**IVC**	**Uterus**	**Rectum**	**Stomach**			
Author	Lacey	Dowdle	Shafik	Collee	Sugrue	Malbrain	Malbrain
Reference	[29]	[31]	[30]	[20]	[21, 22]	Current	Current
Publication	1987	1997	1997	1993	1994, 2000	2003	2003
Properties	Fluid	Microchip	Fluid-filled balloon	Fluid	Air-filled balloon	Air-filled balloon	Air-filled balloon
General-Volume			?	50 ml	2 ml	1–2 ml	0.1 ml
Manipulation	++	+++	+++	++	+	+	-
Difficult	+	++	++	+	+	+	-
Time taken for initial set-up	++	++	++	++	++	+	+
Time taken for next measurement	-	++	++	++	+	-	-
Cost of device initial set-up	++	++++	++	+	+++	++	++
Cost per measurement	-	-	-	++	-	-	-
Interference urine output	-	-	-	-	-	-	-
Glass syringe	-	-	-	-	+	+	-
Technique							
No Repeated measurements	-	+	+	+	-	-	-
No continuous trend	-	+	+	+	-	-	-
Not automated	+	+	+	+	+	+	-
Recalibration	+	+	+	+	+	+	-
Volume not standardised	-	+	+	+	+	+	-
Not accurate or reproducible	+	+	+	+	-	-	-
Not well validated	+++	+++	++	+	+	+	+
Air-bubbles	+	+	+	+	-	-	-
Multiple menisci	-	-	-	-	-	-	-
Bio-filter blocking	-	-	-	-	-	-	-
MMC interference	-	-	-	+	+	+	-
Hydrostatic fluid column							
Zero-reference problem	+	+	+	+	-	-	-
Over-under damping	+	+	+	+	-	-	-
Body position dependent	+	++	++	++	-	-	-
Risks							
Needle stick injury	+	-	-	-	-	-	-
Urinary infection	-	-	-	-	-	-	-
Sepsis	+++	-	-	-	-	-	-
Contra-indications							
Bladder trauma	-	-	-	-	-	-	-
Neurogenic bladder	-	-	-	-	-	-	-
Hematuria	-	-	-	-	-	-	-
Gastric trauma	-	-	-	+	+	+	+
Other abdominal trauma	-	+	+	-	-	-	-
Overall conclusion							
Disadvantages	21	28	25	24	15	12	5
Advantages	16	13	13	11	18	19	26
Overall score	60.4%	48%	50.1%	47.8%	70.6%	76%	91.2%
Clinical implications	?	None	?	Screening	Research	Research	APP trend, Research

transducer. The symphysis pubis is used as reference line. (See ESM addendum 1.)

Advantages and disadvantage (Table 1)

This technique implicates a lot of time-consuming manipulations that disrupt a closed sterile system at every measurement. It has all the problems that come along with the hydrostatic convective fluid column. Even though zero-reference at the symphysis pubis poses no problem, the problems come when the same pressure transducer is used for IAP and CVP, with zero-reference at the midaxillary line. Putting the patient upright with concomitant rise in the transducer may lead to underestimation of IAP, while putting the patient in the Trendelenburg position can lead to overestimation. The fact that recalibration needs to be done before every measurement augments the risk for errors. We have all seen the "magic" drop or rise in CVP at changes of nurse shifts, the same

Table 2 Cost estimation (in Euros) of the different IAP measurement techniques: cost of initial set-up and next measurement, as well as cost projection based on number of IAP measurements per day and duration of measurement period. The cost evaluation was based on the following estimates: transducer: €24.75; 50 ml of saline: €0.3; syringe: €0.36; needle: €0.023; Foley catheter: € 0.53; nasogastric tube: €0.53; oesophageal catheter (Ackrad): €55; tonometer (Datex): €175; IAP catheter (Spiegelberg): €100; Foleymanometer (Holtech): €17.5; rectal/uterinel probe: €34.8; microchip transducer (Rehau): €1,250; conical connector: €2.2; male-male connector: €0.4; stopcock: €0.31; sterile drapings: €1.36; nursing costs: €25 per hour

Technique	Author	Reference	Set-up cost	Cost per measurement	2 times per day				6 times per day				12 times per day			
					1week	2weeks	3weeks	4weeks	1week	2weeks	3weeks	4weeks	1week	2weeks	3weeks	4weeks
Bladder	Kron.	[13]	30.6	3.7	5.9	4.8	4.4	4.3	4.4	4.1	3.9	3.9	4.1	3.9	3.8	3.8
	Iberti	[17]	30.2	2.7	4.8	3.8	3.4	3.2	3.4	3.0	2.9	2.9	3.0	2.9	2.8	2.8
	Cheatham	[18]	31.3	1.3	3.7	2.6	2.3	2.1	2.1	1.7	1.6	1.6	1.7	1.5	1.5	1.4
	Malbrain	Current	34.7	1.0	3.6	2.3	1.9	1.7	1.8	1.4	1.3	1.2	1.4	1.2	1.1	1.1
Stomach	Collee	[20]	29.9	2.3	4.5	3.4	3.1	2.9	3.1	2.7	2.6	2.5	2.7	2.5	2.5	2.4
	Malbrain	Current	101.7	0.1	7.4	3.7	2.5	1.9	2.5	1.3	0.9	0.7	1.3	0.7	0.5	0.4
	Sugrue	[21]	202.7	0.3	14.7	7.5	5.1	3.9	5.1	2.7	1.9	1.5	2.7	1.5	1.1	0.9
	Malbrain	Current	83.7	0.3	6.2	3.2	2.2	1.8	2.2	1.3	0.9	0.8	1.3	0.8	0.6	0.5
Rectal	Shafik	[30]	70.1	0.2	5.2	2.7	1.8	1.4	1.8	1.0	0.7	0.6	1.0	0.6	0.4	0.4
Manometry	Lee	[27]	1.2	0.3	0.4	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.3	0.3	0.3
	Malbrain	[28]	18.2	0.3	1.6	1.0	0.8	0.7	0.8	0.6	0.5	0.4	0.6	0.4	0.4	0.4
Vena cava	Lacey	[29]	66.3	0.2	4.9	2.5	1.8	1.4	1.8	1.0	0.7	0.6	1.0	0.6	0.4	0.4
Microchip	Dowdle	[31]	1278.1	0.1	91.4	45.7	30.5	22.9	30.5	15.3	10.2	7.7	15.3	7.7	5.2	3.9

can happen with IAP. Furthermore, a fluid-filled system can produce artefacts that further distort the IAP pressure waveform. Failure to recognise these recording system artefacts can lead to interpretation errors [14]. It can oscillate spontaneously, and these oscillations can distort the IAP pressure curve. The performance of a resonant system is defined by the resonant frequency (this is the inherent oscillatory frequency) and the damping factor (this is a measure of the tendency of the system to attenuate the pressure signal). Therefore, any fluid-filled system is prone to changes in body-position and over- or underdamping due to the presence of air-bubbles, a tubing that is too compliant or too long, etc. A rapid flush test should, therefore, always be performed before an IAP reading in order to obtain an idea of the dynamic response properties and to minimise these distortions and artefacts [16]. Confirmation of correct measurement can be done by inspection of respiratory variations and by gently applying oscillations to the abdomen that should be immediately transmitted and seen on the monitor with a quick return to baseline (Fig. 3). In case of a damped signal the flush test should be repeated.

Other disadvantages are: it is an intermittent technique that interferes with urine output without the possibility of obtaining a continuous trend, it places the patient at increased risk of urinary tract infection or sepsis, and subjects healthcare providers to the risk of needle stick injuries and exposure to blood and body fluids [13]. In conclusion, the Kron technique has at the present time no clinical implications.

The closed system single measurement technique [16, 17]

Description

Iberti and co-workers reported the use of a closed system drain and transurethral bladder pressure monitoring method [16, 17]. Using a sterile technique they infused an average of 250 ml of normal saline through the urinary catheter to purge catheter tubing and bladder. The bladder catheter is clamped and a 20-gauche needle is inserted through the culture aspiration port for each IAP measurement. The transducer is zeroed at the symphysis and mean IAP is read after a 2-min equilibration period. (See ESM addendum 2)

Advantages and disadvantages (Table 1)

It has the same disadvantages related to the hydrostatic fluid column as the Kron technique, and since it is not needle-free it also subjects health care workers to needle-stick injuries [10, 11].

The advantage compared with the Kron technique is that it is simpler, less time-consuming, and there are fewer manipulations. In conclusion, the Iberti technique

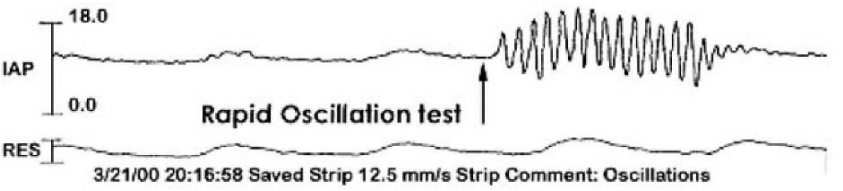


Fig. 3 Confirmation of correct IAP measurement can be done by inspection of respiratory variations and by gently applying oscillations to the abdomen that should be immediately transmitted and seen on the monitor with a quick return to the baseline

has at the present time limited clinical implications (e.g. screening for IAH).

The closed system repeated measurement technique [18]

Description

Cheatham and Safcsak reported a revision of Kron's original technique [18]. A standard intravenous infusion set is connected to 1,000 ml of normal saline, two stopcocks, a 60-ml Luer-lock syringe and a disposable pressure transducer. An 18-gauche plastic intravenous infusion catheter is inserted into the culture aspiration port of the Foley catheter and the needle is removed. The infusion catheter is attached to the pressure tubing and the system flushed with saline. (See ESM addendum 3.)

Advantages and disadvantages (Table 1)

It has the same inconveniencies related to any fluid-filled system as described with the Kron and Iberti techniques. It can pose problems after a couple of days because the culture aspiration port membrane can become leaky or the catheter kinky, leading to false IAP measurement. The fact that the infusion catheter needs to be replaced after a couple of days could increase the infection risk and needle-stick injuries.

This technique has minimal side effects and complications, e.g. without an increased risk for urinary tract infection [19]. It is safer and less invasive, takes less than 1 min, is more efficient with repeated measurements possible and thus is more cost-effective [18]. This technique is ideal for screening and monitoring for a short period of time (a couple of days) because of leakage.

The revised closed system repeated measurement technique

Description

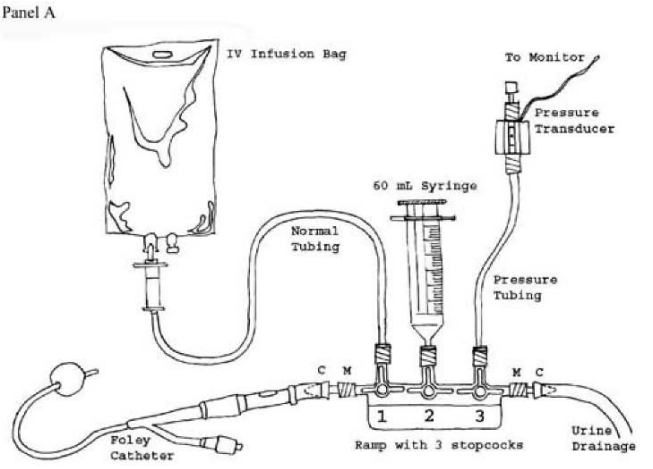
The technique of Cheatham and Safcsak was modified (Fig. 4), as follows. A ramp with three stopcocks is inserted in the drainage tubing connected to a Foley catheter (Fig. 4A). A standard infusion set is connected to a bag of 1,000 ml of normal saline and attached to the first stopcock. A 60-ml syringe is connected to the second stopcock and the third stopcock is connected to a pressure transducer via rigid pressure tubing. The system is flushed with normal saline and the pressure transducer is zeroed at the symphysis pubis (or the midaxillary line when the patient is in complete supine position). Figure 4B shows a picture of the device in a patient with a close-up of the manifold set with conical connectors. (See ESM addendum 4.)

Advantages and disadvantages (Table 1)

It has the same inconveniencies related to a fluid-filled system as described with the Kron, Iberti or Cheatham technique. This technique has the same advantages as the Cheatham technique, with a required nursing time less than 2 min per measurement, a minimized risk of urinary tract infection and sepsis since it is a closed sterile system, the possibility of repeated measurements and reduced cost. Since it is a needle-free system it does not interfere with the culture aspiration port and the risk of injuries is absent. This technique can be used for screening or for monitoring for a longer period of time (2–3 weeks).

The revised closed system repeated measurement technique

In an anuric patient, continuous IAP recordings are possible via the bladder using a closed system connected to the Foley catheter after the culture aspiration port or directly to the Foley catheter using a conical connection piece connected to a standard pressure transducer via pressure tubing (Fig. 5). After initial "calibration" of the system with 50 ml of saline and zeroing at the sypmhysis pubis, the transducer is taped at the symphysis or thigh and a continuous IAP reading can be obtained. Daily calibration can be done in oliguric patients after voiding of rest diuresis.



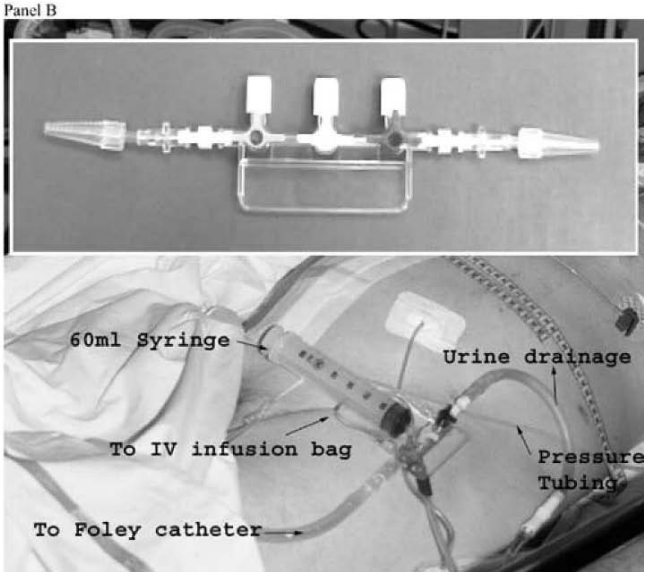


Fig. 4 A A closed needle-free revised method for measurement of intra-abdominal pressure. A standard intravenous infusion set is connected to a bag of 1,000 ml of normal saline and attached to the first stopcock. A 60-ml syringe is connected to the second stopcock and the third stopcock is connected to a pressure transducer via rigid pressure tubing. The system is flushed with normal saline and the pressure transducer is zeroed at the symphysis pubis. To measure IAP, the urinary drainage tubing is clamped distal to the ramp-device, 50 ml of normal saline is aspirated from the IV bag into the syringe and then instilled in the bladder. After opening the stopcocks to the pressure transducer mean IAP can be read from the bedside monitor. See ESM addendum 4 for explanation. **B** Mounted patient view of the device and close up of manifold and conical connection pieces

Conclusion

In conclusion, if one wants to use IVP as estimate for IAP the Cheatham or revised technique is preferred over the Kron or Iberti technique. The revised methods for IAP measurement via the bladder maintain the patient's Foley catheter as a closed system, limiting the risk of infection. Since these are needle-free systems they also avoid the risks of needle-stick injury and overcome the problems of leakage and catheter knick in the method described by Cheatham. They are more cost-effective, and facilitate repeated measurements of IAP.

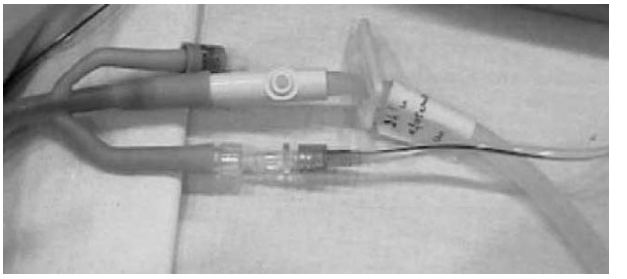


Fig. 5 Close up view of a closed needle-free system for continuous intra-abdominal pressure measurement in an anuric patients, using a conic connection piece (conical connector with female or male lock fitting; B Braun, Melsungen, Germany — Ref. 4896629 or 4438450) connected to a standard pressure transducer via pressure tubing

Stomach

The classic intermittent technique [20]

Background and description

The IAP can also be measured by means of a nasogastric or gastrostomy tube and this method can be used when the patient has no Foley catheter in place, or when accurate bladder pressures are not possible due to the absence of free movement of the bladder wall. In case of bladder trauma, peritoneal adhesions, pelvic haematomas or fractures, abdominal packing, or a neurogenic bladder, IVP may overestimate IAP, and the procedure used for the bladder can then be applied via the stomach [20]. (See ESM addendum 5.)

Advantages and disadvantages (Table 1)

The same inconveniences as with every fluid-filled system apply. Another disadvantage is that gastric pressures might interfere with the migrating motor complex or with nasogastric feeding. Furthermore all air needs to be aspirated from the stomach before measuring IAP, something that is difficult to verify.

The advantages are that it is cheap, does not interfere with urine output, and the risks of infection and needle-stick injuries are absent. This cost-effective technique is ideal for screening.

The semi-continuous technique [21, 22]

Background and description

Sugrue and co-workers assessed the accuracy of measuring simultaneous IVP and IAP via the balloon of a gastric tonometer during laparoscopic cholecystectomy [21]. They found a good correlation between both methods. This technique allows a trend to be obtained. We recently validated these results and found good correlation between the classic gastric method, the tonometer method and IVP [22]. Simultaneous IAPtono and PrCO2 measurement was also possible. (See ESM addendum 6.)

Advantages and disadvantages (Table 1)

Measurement via the tonometer balloon limits the risks and has major advantages over the standard intravesical method: no infection risk and no interference with estimation of urine output. Simultaneous measurement of IAP and PrCO2 is possible; however, only in an intermittent way. Since it is air-filled it has none of the disadvantages associated with fluid-filled systems: no problem with zero-reference, over- or underdamping or body position. A possible disadvantage is the effect on interpretation of IAP values by the migrating motor complex. Recording the "diastolic" value of IAP at end-expiration can solve this problem. Other problems are that a 5-ml glass syringe is needed and that no data are available on effects of enteral feedings on these IAP measurements. This technique could be used for study purposes and clinicians interested in simultaneous CO2 gap and IAP monitoring.

The revised semi-continuous technique

Description

An oesophageal balloon catheter is inserted into the stomach. When the balloon is in the stomach, the whole respiratory IAP pressure wave will be positive and increasing upon inspiration in case of a functional diaphragm. If the balloon is too high in the thorax the pressure will flip from positive to negative on inspiration measuring oesophageal or pleural pressure instead. A standard three-way stopcock is connected to a pressure transducer (Fig. 6A). All air is evacuated from the balloon with a glass syringe and 1–2 ml of air reintroduced to the balloon. The balloon is connected via a "dry" system to the transducer, the transducer itself is NOT classically connected to a pressurized bag and *not* flushed with normal saline in order to avoid air/fluid interactions. The transducer is zeroed to atmosphere and IAP is read end-expiratory. Figure 6B shows a close-up of the oesophageal balloon catheter. (See ESM addendum 7.)

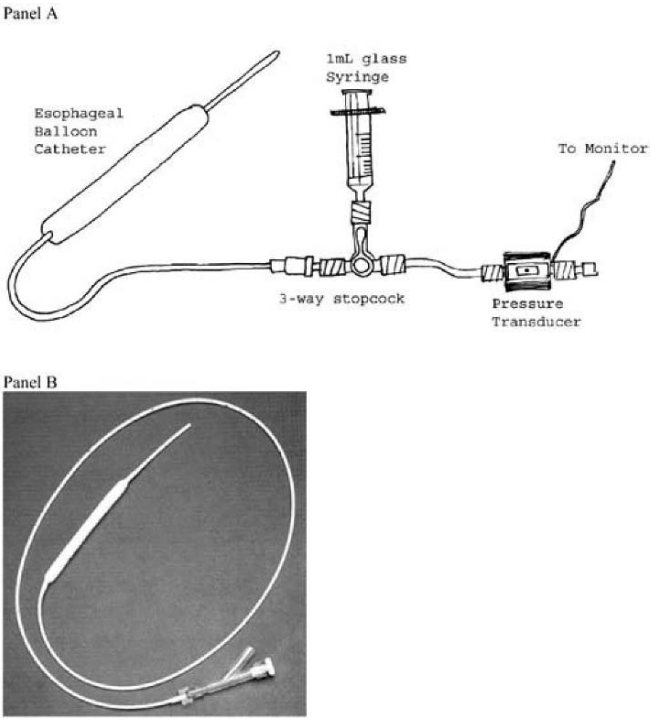


Fig. 6 A An oesophageal balloon catheter is inserted into the stomach (Oesophageal balloon catheter set, adult size with PTFE coated stylet; Ackrad Laboratories, Cranford, N.J., USA — Ref. 47-9005, see at http://www.ackrad.com/products/c-balloon_catheter.cfm or compliance catheter female or male, International Medical Products, Zuthpen, Netherlands, distributed by Allegiance — Ref. 84310). A standard three-way stopcock is connected to the now "nasogastric" tube; one end is connected to a pressure transducer via arterial tubing. All air is evacuated from the balloon with a glass syringe and 1 ml of air reintroduced to the balloon. A glass syringe is recommended to minimize the risk of pulling a negative pressure inside the catheter prior to reintroducing the 1 ml air. The balloon is connected via a "dry" system to the transducer, the transducer itself is *not* classically connected to a pressurized bag and *not* flushed with normal saline in order to avoid air/fluid interactions. The transducer is zeroed to atmosphere and IAP is read end-expiratory. See text for explanation. **B** Close-up view of the oesophageal balloon catheter

Advantages and disadvantages (Table 1)

A disadvantage is that the air in the balloon gets resorbed after a couple of hours (Fig. 7), so that "recalibration" of the balloon is necessary with a 2–5 ml glass syringe for continuous measurement, this might cause inaccurate measurement if the nurse waits too long for recalibration or if the re-instilled volume is not exactly the same as the previous one. It is less time-consuming and has all the advantages of an air-filled system (cfr tonometer). By

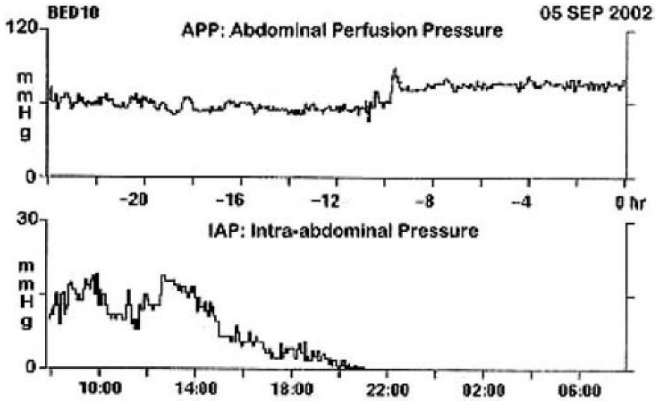


Fig. 7 A trend of 24-h IAP and APP recordings obtained with an oesophageal balloon placed in the stomach (Ackrad). Note the resorption of air after a couple of hours, with loss of IAP signal, confirming the need for recalibration

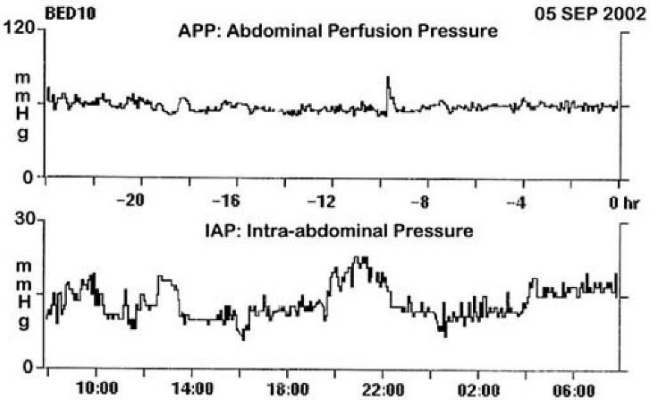


Fig. 8 A continuous trend of 24-h IAP and APP recordings obtained with the Spiegelberg balloon-tipped IAP catheter placed in the stomach. Note the absence of resorption of air due to automated recalibration every hour. Note also the effect of CAPD fluid inflow on IAP. If IAP was measured only twice a day the fluctuations and peak pressures would have been missed

using this technique the cost of IAP is further reduced depending on the catheter used. Moreover, a semi-continuous measurement of IAP as a trend over time is possible. The oesophageal balloon catheter price ranges from €15 (International Medical Systems, The Netherlands) to €55 (Ackrad, USA). This technique is ideal for monitoring for a longer period of time; however, when using multiple tubes the risk of sinusitis or infection needs to be evaluated in the future.

The continuous fully-automated technique

Description: IAP measurement with the air-pouch system

The IAP-catheter is introduced like a nasogastric tube; it is equipped with an air pouch at the tip. The catheter has one lumen that connects the air-pouch with the IAP-monitor and one lumen that takes the guide wire for introduction. The pressure transducer, the electronic hardware, and the device for filling the air-pouch are integrated in the IAP-monitor. Once every hour the IAP-monitor opens the pressure transducer to atmospheric pressure for automatic zero adjustment. The air-pouch is then filled with a volume of 0.1 ml required for accurate pressure transmission. Initial validation in ICU patients and laparoscopic surgery showed good correlation with the standard IVP method [23]. Recently Schachtrupp and co-authors used the same technique to directly measure IAP in a porcine model and found a very good correlation between the air pouch system and direct insufflator pressure (R^2=0.99) with a mean bias of 0.5±2.5 mmHg and small limits of agreement (−4.5 to 5.4 mmHg) [24]. (See ESM addendum 8.)

Advantages and disadvantages (Table 1)

This technique has no major disadvantage except that validation in humans is still in its infant stage. The advantages are those related to other gastric and air-filled methods. In summary, it is simple, fast, accurate, reproducible, and fully automated, so that a real continuous 24-h trend can be obtained (Fig. 8). This technique is not suited for screening, but is best for continuous fully automated monitoring for a long period of time. Since it is less prone to errors and most cost-effective if in place for a longer period of time, this technique has a lot of potential in becoming the future standard for multicentre research purposes.

Conclusion

The revised methods via the stomach have the advantage of being free from interference caused by wrong transducer positions, since the creation of a conductive fluid column is not needed as air is used as the transmitting medium. The last described fully automated technique also gives a continuous tracing of IAP together with abdominal perfusion pressure (APP) in analogy with intracranial pressure and cerebral perfusion pressure, allowing both parameters to be monitored as a trend over time. The APP is calculated by subtracting IAP from the mean arterial blood pressure. Recent data showed the importance of APP as a superior marker for IAH to titrate better the resuscitation of patients with IAH and ACS, hence avoiding end-organ failure and associated morbidity and mortality [2, 25].

Manometry

The classic technique [1, 2, 26]

Description

A quick idea of the IAP can also be obtained in a patient without a pressure transducer connected by using his own urine as the transducing medium, first described by nurse Harrahill [1, 2, 26]. One clamps the Foley catheter just above the urine collection bag. The tubing is then held at a position of 30–40 cm above the symphysis pubis and the clamp is released. The IAP is indicated by the height (in cm) of the urine column from the pubic bone. The meniscus should show respiratory variations. This rapid estimation of IAP can only be done in case of sufficient urine output. In an oliguric patient 50 ml saline can be injected as priming. (See ESM addendum 9.)

Advantages and disadvantages (Table 1)

It has all the inconveniencies that come along with a fluid-filled system as described before. However, since it is needle-free it poses no risks for injuries. It allows repeated measurements, is very inexpensive and fast with minimal manipulation. Since the volume re-instilled into the bladder is not constant raising questions on accuracy and reproducibility, it has limited clinical implications.

The U-tube technique [27]

Description

In a recent animal study, Lee and co-workers compared direct insufflated abdominal pressure with indirect bladder, gastric and inferior vena cava pressures [27]. IVP was measured by both the standard and U-tube technique. With the U-tube technique, the catheter tubing was raised approximately 60 cm above the animal to form a U-tube manometer, and IVP was measured as the height of the meniscus of urine from the pubic symphysis. The authors found a good correlation between the U-tube pressure and other direct and indirect techniques. (See ESM addendum 10.)

Advantages and disadvantages (Table 1)

It has the same advantages and inconveniences as the classic "Harrahill" technique, as with the previous technique the clinical validation is poor. The major advantage of this technique is that the volume re-instilled into the bladder is more stable (but still not well defined), so it can be used as a quick screening method.

The Foleymanometer technique [28]

Description

We recently tested a prototype (Holtech Medical, Copenhagen, Denmark) for IAP measurement using the patients' own urine as pressure transmitting medium [28]. A 50 ml container fitted with a bio-filter for venting is inserted between the Foley catheter and the drainage bag (Fig. 9A). The container fills with urine during drainage; when the container is elevated, the 50 ml of urine flows back into the patient's bladder, and IAP can be read from the position of the meniscus in the clear manometer tube between the container and the Foley catheter (Fig. 9B). We found a good correlation between the IAP obtained via the Foleymanometer and the "gold standard" in 119 paired measurements (R^2=0.71, P<0.0001). The analysis according to Bland and Altman showed that both measurements were almost identical with a mean bias of 0.17±0.8(SD) mmHg (95% CI 0.03–0.3). (See ESM addendum 11.)

Advantages and disadvantages (Table 1)

It has the same inconveniencies and advantages as the other manometry techniques. It allows repeated measurements, is very cost-effective and fast, with minimal manipulation. The great advantage with the Foleymanometer is that the volume re-instilled into the bladder is standardised at 50 ml; therefore, it is preferred over the other manometry techniques. A major drawback is the possibility of occasional blocking of the bio-filter, leading to overestimation of IAP in some cases and the presence of air-bubbles in the manometer tube, producing multiple menisci leading to misinterpretation of IAP. Further refinement and multicentric validation needs to be done before being used in a clinical setting.

Conclusion

The manometry techniques give a rapid and cost-effective idea of the magnitude of IAP and may be as accurate as other direct and indirect techniques. They can easily be done two-hourly together with and without interfering with urine output measurements. Moreover, the risk of infection and needle stick injury is absent. Since they need to be validated in a multicentre setting they are not ready for general clinical usage at the present moment.

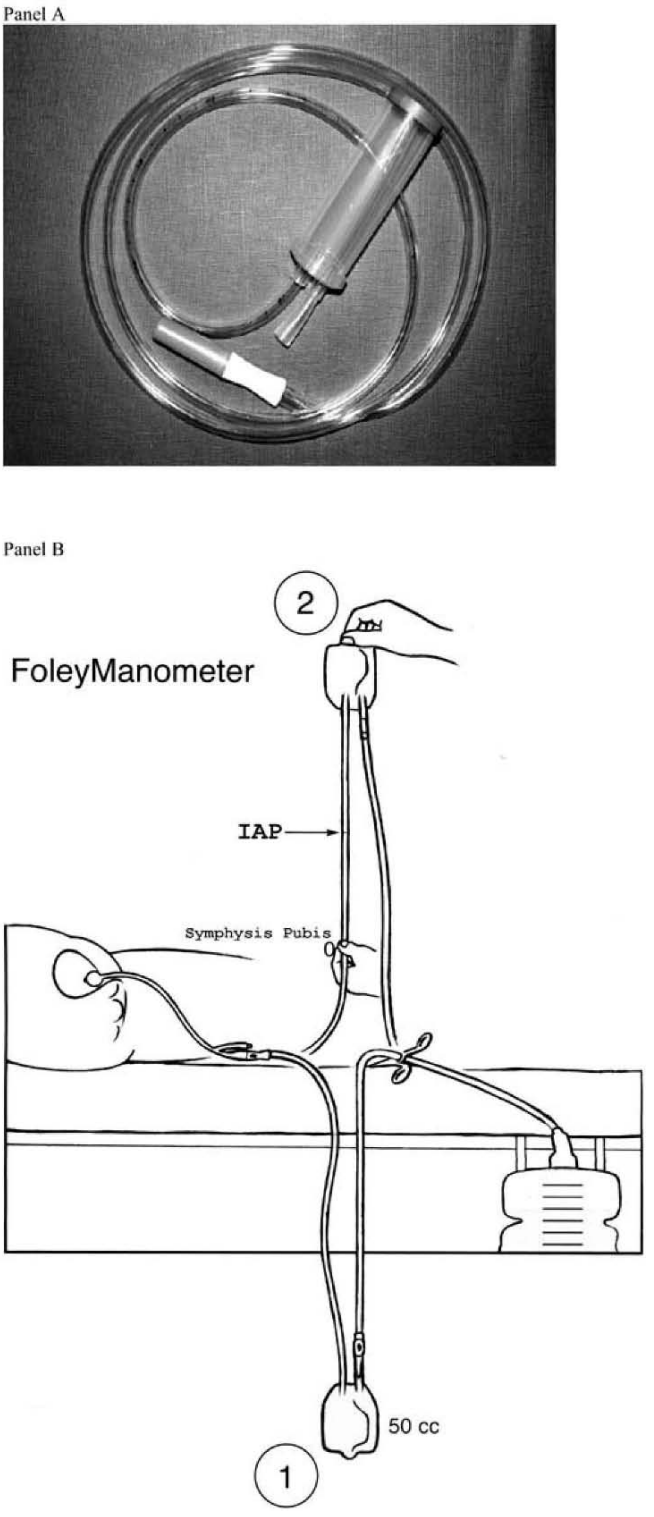


Fig. 9 A The Holtech Foleymanometer: second prototype consists of a 50 ml container fitted with a bio-filter for venting inserted between the Foley catheter and the drainage bag. **B** The use of the Holtech Foleymanometer: schematic drawing. The container fills with urine during drainage (position 1); when the container is elevated (position 2), the 50 ml of urine flows back into the patient's bladder, and IAP can be read from the position of the meniscus in the clear manometer tube between the container and the Foley catheter

Rectal pressure

Description

Rectal pressures are used routinely as estimate for IAP during urodynamic studies to calculate the transmural detrusor muscle pressure as IVP minus IAP [29, 30]. Rectal pressures can be obtained by means of an open rectal catheter with a continuous slow irrigation (1 ml/min), but special fluid-filled balloon catheters are used more routinely, although are more expensive. (See ESM addendum 12.)

Advantages and disadvantages (Table 1)

The major problem with the open catheter is that residual faecal mass can block the catheter-tip opening leading to overestimation of IAP. Other disadvantages of this technique are that it is more difficult, implicates more manipulation, is intermittent, and cannot be used in patients with lower gastro-intestinal bleeding or profound diarrhoea. There is also a great reluctance among nurses to use it. Since it is fluid-filled, it has all the problems associated with a hydrostatic fluid column, but since it is needle-free it decreases patient and healthcare worker infections or injuries. The fluid-filled balloon catheters are more expensive and, even though could theoretically stay in place for a longer period of time, interfere with gastro-intestinal transit and can cause erosions and even necrosis of the anal sphincter and rectal ampulla. Finally these techniques have not been validated in the ICU setting. This technique has no clinical implications in the ICU setting.

Uterine pressure

Description

Basically this technique is mostly done with the same catheters as for the rectal route. Uterine pressures are used routinely by gynaecologists during pregnancy and labour. Most classically a standard so-called "intra-uterine pressure catheter" (IUPC) is used for this purpose [31]. Uterine pressures are mostly obtained by means of a closed special fluid-filled balloon catheter (as for rectal pressure). (See ESM addendum 12.)

Advantages and disadvantages (Table 1)

The major disadvantages of this technique are the same as for rectal pressures: i.e. it is more difficult, implicates more manipulation, is intermittent, and cannot be used on patients with gynaecological bleeding or infection. Since it is also fluid-filled it has all the problems associated with

a hydrostatic fluid column, but is needle-free. Finally, this technique has not been validated in specific ICU patient populations. This technique has no clinical implications in the ICU setting.

Inferior vena cava pressure

Description

The inferior vena cava pressure (IVCP) has been suggested as an estimation for IAP. Basically it uses the same techniques as described previously but applied to an IVC catheter. A normal central venous line is inserted into the inferior vena cava via the left or right femoral vein. The intra-abdominal position of the catheter is confirmed by portable lower abdomen X-ray, and confirmation of a rise in IAP following external abdominal pressure. A three-way stopcock is connected to the distal lumen, one end is connected to a pressure transducer via arterial tubing and the other end is connected to a pressurized infusion bag of 1,000 ml saline. The transducer is zeroed at the midaxillary line with the patient in the supine position and IAP is read end-expiratory as with CVP.

Advantages and disadvantages (Table 1)

The major disadvantage of this technique is the risk of (possible catheter-related) bloodstream infections and septic shock. The initial placement is more time-consuming. It has also the problems inherent to fluid-filled systems and poses potential injury to the patient and healthcare workers. The major advantages are that a continuous trend can be obtained, it does not interfere with urine output, and it could be used in bladder-trauma patients. Finally this technique has not been validated in specific ICU patient populations. In an animal study comparing different methods of indirect IAP measurement, Lacey and co-workers found a good correlation between bladder and inferior vena cava pressure with direct intraperitoneal IAP measurement, but not with gastric, femoral or rectal pressure [29]. Lee and co-workers also found a good correlation in 30 patients during laparoscopy [27]. A recent study in man, comparing superior vena cava pressure (SVCP) with common iliac venous pressure (CIVP) in various conditions of IAP and PEEP showed that the difference between CIVP and SVCP was not affected by the IAP, which implies that CIVP does not reflect IAP correctly [32]. The most likely explanation is the differing anatomy and experimental model used to induce increased IAP in canine studies. In humans both CVIP and SVCP increase as IAP increases [32]. Recently, Joynt and co-workers also found a good correlation between SVCP and IVCP regardless of IAH [33]. This technique has limited implications in the ICU setting.

Microchip transducer-tipped catheters

Description

Different types of catheters tipped with microchip transducers are nowadays available on the market. They can either be placed via the rectal, uterine, vesical or gastric route. These catheters can either have a 360° membrane pressor sensor in the organ (rectum, uterus, bladder, stomach) connected to an external transducer in a reusable cable or they can have a fibre-optic in vivo pressure transducer in the tip of the catheter itself. These catheters provide true zero in-situ calibration. By disconnecting and checking for zero on the monitor, clinicians can instantly validate and check the zero status of the monitor and the transducer [31]. Recently, Schachtrupp and co-workers found a good correlation between IAP calculated be a piezoresistive pressure measurement and direct insufflator pressure (R^2=0.92), with a difference of 1.6±4.8 mmHg; however, the limits of agreement were large (−8 to 11.2 mmHg) [24]. This might have been due to an unknown measurement drift due to the fact that the device cannot be zeroed to the environment when placed intra-abdominally. (See ESM addendum 13.)

Advantages and disadvantages (Table 1)

The major disadvantages of this technique is that it is very expensive, with catheter-price ranging from €1,000 to €1,500. These catheters are said to be re-usable a couple of times after cleaning with soap and water and gas sterilisation, but no data on ICU patients are available. These catheters are mostly used during urodynamic studies and labour for a limited period of time (hours); none of them have been tested in ICU patients for longer periods of time (days to weeks). The major advantages are that a continuous trend can be obtained, it is less time-consuming, and it does not interfere with urine output. This technique has no clinical implications in the ICU setting.

Reproducibility of IAP measurement

As stated previously, the intra-vesical route evolved as the gold standard. However, considerable variability in the measurement technique has been noted and the common pitfalls are briefly addressed below.

1. Malpositioning of the pressure transducer with regard to the symphysis pubis after repositioning of the patient. This may lead to over- and underestimation of IAP, which is commonly seen at changes of nurse shifts.
2. All fluid-filled systems connected to a pressure transducer have their own dynamic response properties

that can create distortions or artefacts in the IAP pressure waveform, leading to signal over- or under-damping [14, 15].

3. It is the most used and validated technique, but with inadequate accuracy and reproducibility. The inaccuracy can come from the presence of air-bubbles in any fluid-filled system leading to over- or underestimation. If the measurement itself is inaccurate, this also implies that it is not reproducible. However, when the pressure transducer position is consistently too high or too low with a fully compliant transducer system of high intrinsic resonant frequency the IAP value obtained will be too low or too high, respectively, but may be reproducible. In order to get an idea of these reproducibility problems with bladder pressure we performed a multicentre snapshot study (four IAP measurements each every 6 h) on a given day [4]. The mean IAP was 10.2±2.7 mmHg, (range 7.6±4 to 12.7±5.7). Analysis according to Bland and Altman showed a global bias of IAP within 24 h (difference between minimum and maximum value) of 5.1±3.8 (SD) mmHg (95% CI 4.3–5.9); the limits of agreement were −2.5 to 12.7 mmHg. The bias differed from centre to centre between 2.4 and 6.2 mmHg, with one outlier bias value as high as 11 mmHg, raising questions as to the reproducibility of the measurement technique used in that centre and making it difficult to compare literature data [4]. The mean coefficient of variation (defined as the standard deviation divided by the mean IAP) was 25%, which is comparable to daily fluctuations in other pressures, like central venous pressure or pulmonary artery occlusion pressure. However, this coefficient ranged from 4% to 66% between centres. Since the literature provides no data on 24-h continuous IAP-measurement in the ICU, it is not possible to determine whether these variations or fluctuations in IAP during one study day were normal or related to the measurement technique used.
4. The bladder "gold standard" measurement techniques reported are not uniform; most authors recommend to inject 50 ml [1, 2], others 0 ml [16], 100 ml [13, 23], 200 ml (data from internet: Brenda Morgan, Clinical Educator, CCTC on http://critcare.lhsc.on.ca/education/abdcompt.html, last revised 2001) or even 250 ml [17] of saline into the bladder. In fact, in the initial article from Iberti and co-workers, data are presented from a canine model without stating the volume instilled in the bladder. The only statement was that "the bladder was continuously emptied between measurements" [16]. In a following study, Iberti and co-workers presented human data stating, "using a sterile technique an average of 250 ml of normal saline was infused through the urinary catheter to gently fill the bladder and eliminate air in the drainage catheter" [17].
5. Conflicting results are reported in the literature regarding the validation of IVP versus directly measured IAP during laparoscopy. In a recent study, Yol and co-workers compared bladder pressure with direct insufflation pressure during laparoscopic cholecystectomy in 40 patients and he found a very good correlation between the two measurements (R=0.973, P<0.0001) [32]. This was also shown by Fusco and co-workers, who compared direct laparoscopic insufflation pressure with bladder pressures measured with bladder volumes of 0, 50, 150 and 200 ml [5]. He found that there was a good correlation across the IAP range from 0 to 25 mmHg between direct and indirect methods with all tested volumes. A bladder volume of 0 ml demonstrated the lowest bias, but when considering only elevated IAPs (25 mmHg) a bladder volume of 50 ml revealed the lowest bias. He concluded that intravesicular pressure closely approximates IAP and that instilling 50 ml of saline improved the accuracy of the bladder pressure in measuring elevated IAPs. However Johna and co-workers recently found that intravesicular pressure did not reflect actual intra-abdominal insufflation pressure (limited up to 15 mmHg) during laparoscopy [34]. He concluded that further research is needed to identify possible variables that may play a role in the relationship between the urinary bladder and abdominal cavity pressures, providing better means for diagnosing ACS. Further reading shows that the methodology of this study was poor.
6. Although many articles have validated IVP against direct insufflation pressures, it is difficult to extrapolate these single observer comparisons in patients undergoing general anesthesia and paralysis to a mixed ICU population of patients not under muscle relaxation as well as subject to other confounding factors (nurse shifts, position, zero reference, etc.). Direct IAP measurement via a laparoscopic insufflator is prone to errors by flow dynamics, resulting in rapid increases in pressure during insufflation. The Verres needle opening can be blocked by tissue or fluid leading to over- or underestimation of IAP and pressures can be influenced by muscle relaxation. Laparoscopy remains an artificial environment, this makes it even more difficult to validate indirect IAP measurement methods.
7. Baseline IAP and the volume instilled in the bladder are important. Gudmundsson and co-workers found recently in an animal study that the IAP increase by instilling Ringer's solution into the abdominal cavity correlated well with intra-vesical pressures [6]. It was also found that IVP as an estimation for IAP is affected by the amount of fluid in the bladder that should not exceed 10–15 ml. If the baseline IAP is lower than 8 mmHg, a 131-ml extra bladder volume is needed to increase IAP by 2 mmHg; however, if baseline IAP is 20 mmHg, only 39-ml extra bladder volume is needed for the same IAP increase [6]. We recently came to the same conclusions: by analysing bladder pressure

volume curves we found that IVP significantly increased depending on the volume instilled. The IVP rose from 4.2±3.2 mmHg at the baseline to 6.9±5 mm Hg with 50 ml and 23.7±16.1 at 300 ml (P<0.0001, ANOVA) [7]. If IVP is used as an estimate for IAP, the volume instilled in the bladder should be between 50 and 100 ml; however, in some patients with a low bladder compliance IVP can be raised at low bladder volumes. Ideally a bladder PV curve should be constructed for each individual patient before using IVP as an estimation for IAP. This study makes it difficult to compare the literature data. It raises not only questions with regard to the previously published definitions and IAP cut-offs, but it also puts the IVP in question as the so-called gold standard. Ideally the bladder should be fully emptied before an IAP measurement, but how can you be really sure?

8. Body position is important. Putting a patient in different body positions has significant effects on IAP (Fig. 10). This is in contradiction with the hypothesis that the abdominal compartment is primarily fluid in character and should follow the law of Pascal, since IAP would then remain constant regardless of body position as fluid is not compressible. The abdomen should in fact be looked at as a "fluidlike" compartment with different components that may influence IVP (the intrinsic weight of the organs, the presence of ascites, the air in the bowel, etc.). Assessment of IAP should, therefore, always be done in the complete supine position. The upright position significantly increases IAP compared with the supine. The effects on IAP being more pronounced in obese patients [35].

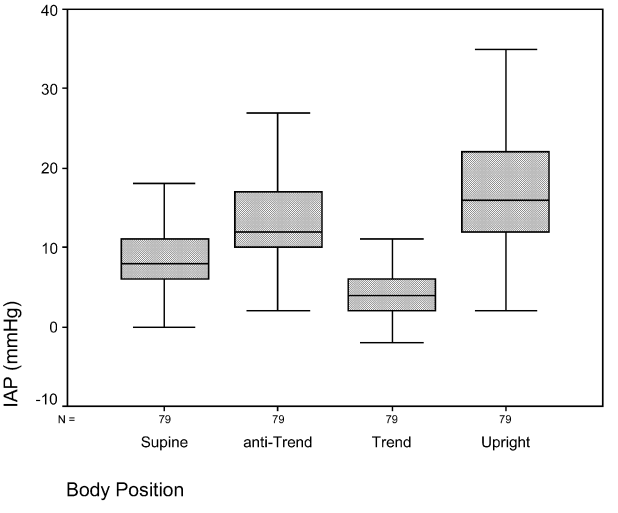


Fig. 10 Boxplot of mean IAP values in different body positions. The IAP was significantly higher in the anti-Trendelenburg and upright position versus the supine, and significantly lower in the Trendelenburg position versus the supine (P<0.0001, one-way Anova)

Many of these drawbacks are not only true for the bladder but are also present when IAP is estimated via other routes. Not much has been studied on the effects of spontaneous breathing, mechanical ventilation, the presence of expiratory muscle activity, auto-PEEP, and curarisation on IAP measurement via the different routes.

Definitions for IAH and ACS stand or fall by the correct measurement of IAP and its reproducibility. Recent literature data put the bladder pressure in question as the so-called gold standard for abdominal pressure [5, 6, 34–36].

Conclusion

This review has undertaken an analysis of the advantages and disadvantages, as well as a cost projection, for each IAP measurement technique and supports the view that: (1) there is no gold standard; (2) it is difficult to compare the different techniques; (3) cost-effectiveness is an issue; (4) IVP can be used as an estimation for IAP as a screening method to identify patients at risk via manometry; (5) IVP can be used as an estimation for IAP for initial follow-up either with the Cheatham or revised bladder technique; (6) for (multicentre) study purposes, surgical patients, trauma patients, patients at risk for IAH and difficult ICU patients, like mechanically ventilated patients with one or more other organ failures (assessed by SOFA score), it is preferable to switch to a continuous method for IAP monitoring via the stomach and focus therapy on optimising IAP and APP.

Acknowledgements I am indebted to my wife, Ms. Bieke Depré, for her patience, advice and technical assistance with the preparation of this manuscript, and to my three sons for providing a quiet writing environment. I also thank Dr. Rao Ivatury and Julia Wendon for their English editing of the manuscript. Part of this work was presented at: the 14th Annual Congress of the European Society of Intensive Care Medicine, Geneva, Switzerland, 30 September–3 October 2001; the 22nd International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium, 19–22 March 2002; the 13th Symposium Intensivmedizin and Intensivpflege, Bremen, Germany, 19–21 February 2003; the 23rd International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium, 18–21 March 2003; the 16th Annual Congress of the European Society of Intensive Care Medicine, Amsterdam, The Netherlands, 5–8 October 2003. This study was supported by Holtech Medical, Denmark (contact Bo Holte at holtech@email.dk). There was no financial support from Holtech other than making the product (Foleymanometer) available, free of charge. This study was supported by Ackrad Medical, USA (contact Charles Noto at cnoto@ackrad.com). There was no financial support from Ackrad other than making five oesophageal balloon catheters available, free of charge. This study was supported by Spiegelberg, Germany (contact Andreas Spiegelberg at info@spiegelberg.de). There was no financial support from Spiegelberg other than making the gastric balloon IAP-catheters and IAP-monitors available for study purposes, free of charge.

References

1. Malbrain MLNG (2001) Intra-abdominal pressure in the Intensive Care Unit: clinical tool or toy? In: Vincent JL (ed) Yearbook of Intensive Care and Emergency Medicine. Springer, Berlin Heidelberg New York, pp 547–585
2. Malbrain MLNG (2002) Abdominal perfusion pressure as a prognostic marker in intra-abdominal hypertension. In: Vincent JL (ed) Yearbook of Intensive Care and Emergency Medicine. Springer, Berlin Heidelberg New York, pp 792–814
3. Pouliart N, Huyghens L (2002) An observational study on intraabdominal pressure in 125 critically ill patients. Crit Care 6 (Suppl 1):S3
4. Malbrain MLNG, for the CIAH study group (2001) Prevalence of intra-abdominal hypertension in the ICU. Intensive Care Med 27 (Suppl 2):S176
5. Fusco MA, Martin RS, Chang MC (2001) Estimation of intra-abdominal pressure by bladder pressure measurement: validity and methodology. J Trauma 50:297–302
6. Gudmundsson FF, Viste A, Gislason H, Svanes K (2002) Comparison of different methods for measuring intra-abdominal pressure. Intensive Care Med 28:509–514
7. Verbrugghe W, Van Mieghem N, Daelemans R, Lins R, Malbrain MLNG (2003) Estimating the optimal bladder volume for intra-abdominal pressure measurement by bladder pressure-volume curves. Critical Care 7(Suppl 2):P184
8. Van Mieghem N, Verbrugghe W, Daelemans R, Lins R, Malbrain MLNG (2003) Can abdominal perimeter be used as an accurate estimation of intra-abdominal pressure? Critical Care 7 (Suppl 2):P183
9. Kirkpatrick AW, Brenneman FD, McLean RF, Rapanos T (2000) Is clinical examination an accurate indicator of raised intra-abdominal pressure in critically injured patients? Can J Surg 43:207–211
10. Sugrue M, Bauman A, Jones F, Bishop G, Flabouris A, Parr M, Stewart A, Hillman K, Deane SA (2002) Clinical examination is an inaccurate predictor of intraabdominal pressure. World J Surg 26:1428–1431
11. Castillo M, Lis RJ, Ulrich H, Rivera G, Hanf C, Kvetan V (1998) Clinical estimate compared to intra-abdominal pressure measurement. Crit Care Med 26 (Suppl 1):78A
12. Platell CF, Hall J, Clarke G, Lawrence-Brown (1990) Intra-abdominal pressure and renal function after surgery to the abdominal aorta. Aust N Z J Surg 60:213–216
13. Kron JL, Harman PK, Nolan SP (1984) The measurement of intra-abdominal pressure as a criterion for abdominal re-exploration. Ann Surg 199:28–30
14. Darovic GO, Vanriper S, Vanriper J (1995) In: Darovic GO (Ed) Hemodynamic monitoring, 2nd edn. WB Saunders, Philadelphia, pp 149–175
15. Kleinman B, Powell S, Kumar P, Gardner RM (1992) The fast flush test measures the dynamic response of the entire blood pressure monitoring system. Anesthesiology 77:1215–1220
16. Iberti TJ, Kelly KM, Gentil DR, Hirsch S, Benjamin E (1987) A simple technique to accurately determine intra-abdominal pressure. Crit Care Med 15:1140–1142
17. Iberti TJ, Lieber CE, Benjamin E (1989) Determination of intra-abdominal pressure using a transurethral bladder catheter: clinical validation of the technique. Anesthesiology 70:47–50
18. Cheatham ML, Safcsak K (1998) Intraabdominal pressure : a revised method for measurement. J Am Coll Surg 186:594–595
19. Sagraves SG; Cheatham ML; Johnson JL; White M; Block EF; Nelson LD (1997) Intravesicular pressure monitoring does not increase the risk of urinary tract or systemic infection. Crit Care Med 27:A48
20. Collee GG, Lomax DM, Ferguson C, Hanson GC (1993) Bedside measurement of intra-abdominal pressure (IAP) via an indwelling naso-gastric tube: clinical validation of the technique. Intensive Care Med 19:478–480
21. Sugrue M, Buist MD, Lee A, Sanchez DJ, Hillman KM (1994) Intra-abdominal pressure measurement using a modified nasogastric tube: description and validation of a new technique. Intensive Care Med 20:588–590
22. Debaveye Y, Bertieaux S, Malbrain M (2000) Simultaneous measurement of intra-abdominal pressure and regional CO2 via a gastric tonometer. Intensive Care Med 26 (Suppl 3):S324
23. Malbrain MLNG (2003) Validation of a novel fully automated continuous method to measure intra-abdominal pressure (IAP). Intensive Care Med 29 (Suppl 1):S73
24. Schachtrupp A, Tons C, Fackeldey V, Hoer J, Reinges M, Schumpelick V (2003) Evaluation of two novel methods for the direct and continuous measurement of intra-abdominal pressure in a porcine model. Intensive Care Med 29:1605–1608
25. Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EFJ (2000) Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. J Trauma 49:621–627
26. Harrahill M (1998) Intra-abdominal pressure monitoring. J Emerg Nurs 24:465–466
27. Lee SL, Anderson JT, Kraut EJ, Wisner DH, Wolfe BM (2002) A simplified approach to the diagnosis of elevated intra-abdominal pressure. J Trauma 52:1169–1172
28. Malbrain MLNG, Leonard M, Delmarcelle D (2002) A novel technique of intra-abdominal pressure measurement: validation of two prototypes. Crit Care 6 (Suppl 1):S2–S3
29. Lacey SR, Bruce J, Brooks SP, Griswald J, Ferguson W, Allen JE, Jewett TC, Karp MP, Cooney DR (1987) The relative merits of various methods of indirect measurement of intra-abdominal pressure as a guide to closure of abdominal wall defects. J Ped Surg 22:1207–1211
30. Shafik A, El-Sharkawy A, Sharaf WM (1997) Direct measurement of intra-abdominal pressure in various conditions. Eur J Surg 163:883–887
31. Dowdle M (1997) Evaluating a new intrauterine pressure catheter. J Reprod Med 42:506–513
32. Yol S, Kartal A, Tavli S, Tatkan Y (1998) Is urinary bladder pressure a sensitive indicator of intra-abdominal pressure? Endoscopy 30:778–780
33. Joynt GM, Gomersall CD, Buckley TA, Oh TE, Young RJ, Freebairn RC (1996) Comparison of intrathoracic and intra-abdominal measurements of central venous pressure. Lancet 347:1155–1157
34. Johna S, Taylor E, Brown C, Zimmerman G (1999) Abdominal compartment syndrome: does intra-cystic pressure reflect actual intra-abdominal pressure? A prospective study in surgical patients. Crit Care 3:135–138
35. Malbrain MLNG, Van Mieghem BN, Verbrugghe W, Daelemans R, Lins R (2003) Effects of different body positions on intra-abdominal pressure and dynamic respiratory compliance. Crit Care 7 (Suppl 2):P179
36. Malbrain MLNG (1999) Abdominal pressure in the critically ill: measurement and clinical relevance. Intensive Care Med 25:1453–1458

Alexandre Toledo Maciel
Jacques Creteur
Jean-Louis Vincent

Tissue capnometry: does the answer lie under the tongue?

Abstract Increases in tissue partial pressure of carbon dioxide (PCO_2) can reflect an abnormal oxygen supply to the cells, so that monitoring tissue PCO_2 may help identify circulatory abnormalities and guide their correction. Gastric tonometry aims at monitoring regional PCO_2 in the stomach, an easily accessible organ that becomes ischemic quite early when the circulatory status is jeopardized. Despite substantial initial enthusiasm, this technique has never been widely implemented due to various technical problems and artifacts during measurement. Experimental studies have suggested that sublingual PCO_2 ($P_{sl}CO_2$) is a reliable marker of tissue perfusion. Clinical studies have demonstrated that high $P_{sl}CO_2$ values and, especially, high gradients between $P_{sl}CO_2$ and arterial PCO_2 ($\Delta P_{sl\text{-}a}CO_2$) are associated with impaired microcirculatory blood flow and a worse prognosis in critically ill patients. Although some questions remain to be answered about sublingual capnometry and its utility, this technique could offer new hope for tissue PCO_2 monitoring in clinical practice.

Keywords Sublingual capnometry · Gastric tonometry · Tissue PCO_2 · Microvascular blood flow · Outcome · Critically ill patients

Introduction

Tissue hypoperfusion is a common pathophysiological process leading to multiple organ dysfunction and death [1–4]. The major objectives in the management of acutely ill patients are to prevent, detect and correct tissue dysoxia as soon as possible to minimize organ damage [5]. Unfortunately, none of the currently available monitoring systems are very reliable at the bedside. Systemic hemodynamic and oxygenation parameters lack sensibility and specificity [5–7], especially in sepsis [8, 9].

The possibility of detecting early signs of tissue hypoperfusion by regional monitoring led to a great interest in gastric tonometry. However, much of the enthusiasm was tempered by technical or artifactual problems and difficulties in demonstrating the utility of gastric tonometry-derived variables as therapeutic guides. Sublingual capnometry has emerged in recent years as a potential alternative to monitoring tissue perfusion without some of the shortcomings that preclude the widespread use of gastric tonometry.

Here we review current knowledge about sublingual capnometry, its applicability and its limitations, as a technique to evaluate organ perfusion in acutely ill patients.

The saga of gastric tonometry

Current hemodynamic monitoring techniques, including the pulmonary artery catheter, are quite invasive and carry a risk of complications [10, 11] and higher costs [12], with controversial benefit [13, 14]. The measurement of arterial lactate concentrations may not reflect early alterations and have their own limitations [7, 15, 16].

Gastric tonometry has raised a lot of interest [17, 18] based on three important concepts: (a) tissue hypercarbia is a marker of mismatch between blood flow and oxygen demand [19]; (b) introduction of a gastric tube is a

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_31, © Springer-Verlag Berlin Heidelberg 2009

common procedure in acutely ill patients and (c) the gut mucosa is exquisitely susceptible to hypoperfusion [20]. A number of studies have indicated that gastric tonometry-derived variables have prognostic value [9, 21, 22]. Changes in gastric mucosal PCO_2 (P_gCO_2) may precede alterations in systemic variables [23–25] and the PCO_2 gap (the difference between P_gCO_2 and arterial PCO_2) may represent a valuable monitoring system [21, 22, 26].

Unfortunately, gastric tonometry has serious limitations, even after the advent of gas tonometry [27, 28], including interruption of enteral feeding and concomitant use of H_2-blockers [28]. All these drawbacks reduce the clinical utility of the stomach as a practical place for routine tissue PCO_2 measurement.

Physiological concepts to interpret tissue partial pressure of carbon dioxide

Blood flow as the main determinant of tissue carbon dioxide content (CCO_2)

Tissue CCO_2 is determined by three variables: arterial CCO_2 (C_aCO_2), regional blood flow and tissue CO_2 production (aerobic or anaerobic). In stable respiratory conditions when C_aCO_2 is constant, tissue CCO_2 reflects the balance between tissue blood flow and local CO_2 production. In low flow states, CCO_2 increases as a result of the "CO_2 stagnation phenomenon" [29], even in the absence of dysoxia. Studies comparing ischemic and hypoxic hypoxia in animal models [30, 31] have demonstrated that the reduction in blood flow is the main determinant of tissue CO_2 accumulation, since even in severe dysoxic conditions induced by pure hypoxic hypoxia (a condition in which blood flow is maintained), CO_2 accumulation has not occurred [31]. However, while mechanistically interesting, the hypoxic hypoxia model is not clinically relevant.

Aerobic and anaerobic production of carbon dioxide

Carbon dioxide production occurs in both aerobic and anaerobic situations [32–35]. Increases in aerobic metabolism are associated with higher CO_2 production by the cells, which is generally associated with parallel increases in blood flow, so that tissue PCO_2 does not increase ("washout phenomenon"). When oxygen delivery decreases and reaches a critical value, aerobiosis can no longer be sustained and anaerobic production of CO_2 by the cells increases as a result of buffering of excess protons by bicarbonate ions and decarboxylation of metabolic intermediates [36]. However, during tissue dysoxia, total CO_2 production may be decreased [37–39] because the fall in aerobic CO_2 production can be greater than the increase in anaerobic CO_2 production. In fact, a distinction between aerobic and anaerobic production of CO_2 in the body is quite difficult [32].

Carbon dioxide content-partial pressure of carbon dioxide relationship

The relation between CCO_2 and PCO_2 follows a curvilinear shape so that changes in PCO_2 are not always associated with similar changes in CCO_2. Some physiological variables can also interfere with this relationship, such as hemoglobin concentration and its oxygen saturation [40], pH and temperature: none of which are of established clinical significance [41, 42].

Monitoring tissue partial pressure of carbon dioxide in sites other than the stomach

Tissue hypercapnia is ubiquitous in shock states. The methodological limitations of gastric tonometry prompted a search for alternative sites of tissue PCO_2 monitoring. Walley et al. [43] proposed, in an experimental model of hemorrhagic shock in pigs, that small bowel (jejunum) tonometry is more accurate than gastric tonometry in detecting gut ischemia, and sigmoid tonometry has been studied as a surrogate monitor of gastrointestinal ischemia, especially useful in aorto-iliac surgery—in which left ischemic colitis is a well known complication [44–46]. Sato et al. [47] demonstrated, in a rodent model of hemorrhagic shock, that the esophagus luminal PCO_2 (P_eCO_2) was a reliable surrogate for the P_gCO_2.

In addition to the gastrointestinal tract, experimental studies have used tonometry to detect hypoperfusion in other places in the body including the brain [48], bladder [49], muscle [50] and peritoneum [51]. However, these sites are not practical for routine use and, in the search for a place in the body where tissue PCO_2 could be easily and rapidly measured in a non-invasive and more practical way, Nakagawa et al. [52] suggested that the sublingual mucosa could be a valuable site.

Relevant aspects of sublingual anatomy and physiology

The sublingual mucosa is a highly vascularized surface supplied by the sublingual arteries, which stem from the lingual arteries, branches of the external carotid arteries. Indeed, in addition to the esophagus, the sublingual region is not part of the splanchnic area. However, alterations in sublingual blood flow may occur in response to feeding, with increased production of saliva by sublingual glands. This process is mediated mainly by the parasympathetic nervous system in response to many factors, including

direct tactile stimulus and as a reflex response to the presence of food in the stomach or proximal intestine.

Sublingual partial pressure of carbon dioxide measurement

Experimental and clinical studies regarding sublingual capnometry have used essentially two different devices: MI-720 CO_2 electrode (Microelectrodes; Londonderry, NH, USA) and CapnoProbe SL Monitoring System (Nellcor; Pleasanton, CA, USA).

MI-720 is a CO_2 electrode that needs to be calibrated in standard gases with known percent values of CO_2 before use. Although not originally designed to be used under the tongue, it is the device that has been used in most relevant experimental studies regarding $P_{sl}CO_2$ measurement [52–54] and also in the first clinical study reported [55]. Weil et al. [55] made some modifications to the device in such a way that it fits better in the human sublingual space and avoids contact with room air, which can interfere badly with measurements.

The CapnoProbe was specially designed for the measurement of $P_{sl}CO_2$ and has been used in most of the clinical studies on this subject [7, 56, 57]. It consists of a disposable $P_{sl}CO_2$ sensor, which is actually a CO_2-sensing optode. The optode comprises a CO_2-permeable silicone capsule filled with a fluorescent dye in a buffer solution, at the distal end of an optical fiber. The fluorescent indicator is excited by light conducted through the optical fiber and changes in the projected light caused by changes in fluorescent emission are monitored by the optical fiber. These changes occur as a consequence of parallel changes in the pH of the solution, which is a result of the presence of CO_2 and formation of carbonic acid (H_2CO_3). Light signals are then transferred via the optical fiber to an instrument where they are converted to a numerical value of PCO_2. If properly placed under the tongue with the mouth shut, exposure to the environmental air and light is minimal. A few minutes are necessary for calibration and equilibration, which are made in a liquid solution with a known concentration of CO_2. The capability range of measurement with this device is from 30 to 150 mmHg.

Current experience with sublingual partial pressure of carbon dioxide measurement

Experimental studies

The first evidence that sublingual capnometry may be useful in the diagnosis and quantitation of circulatory shock came from the work of Nakagawa et al. [52]. These investigators observed, during hemorrhagic and septic shock in rats, that changes in $P_{sl}CO_2$ were parallel to changes in P_gCO_2 and systemic markers of hypoperfusion, such as mean arterial pressure, cardiac index and arterial lactate concentration. It is important to note that the septic shock model used in this study was characterized by a hypodynamic status.

Povoas et al. [53] demonstrated similar phenomena in pigs during bleeding and re-infusion, with a close correlation between P_gCO_2 and $P_{sl}CO_2$ values. In another study in rats [58], hemorrhage resulted in a decrease in blood flow in several organs, including the sublingual region, and these decreases were associated with simultaneous increases in $P_{sl}CO_2$.

As with gut mucosal PCO_2 [59–62], arterial PCO_2 (P_aCO_2) also influences $P_{sl}CO_2$. Pernat et al. [54] showed that acute changes in P_aCO_2 induced by hypo- and hyperventilation in rats influence $P_{sl}CO_2$ under physiological conditions and during hemorrhagic shock. Hence, changes in $P_{sl}CO_2$ should be interpreted in relation to the concurrent P_aCO_2; the gradient ($\Delta P_{sl\text{-}a}CO_2$) rather than $P_{sl}CO_2$ per se must be considered.

Clinical studies

Four clinical studies using sublingual capnometry in critically ill patients have been reported [7, 55–57] (Table 1). Weil et al. [55] reported the first clinical, prospective investigation on sublingual capnometry. These authors measured $P_{sl}CO_2$ and simultaneous values of arterial blood pressure, heart rate and arterial lactate concentrations in 46 patients admitted to the emergency room, intensive care unit (ICU) or trauma service with life-threatening illness or injuries, 26 of whom were considered to be in shock on the basis of a systolic pressure less than 100 mmHg and physical signs of circulatory failure at the time of admission. The authors found higher $P_{sl}CO_2$ values in the shock group and suggested that a $P_{sl}CO_2$ threshold value of 70 mmHg was predictive of the severity of the circulatory failure and the likelihood of hospital survival. Initial $P_{sl}CO_2$ values were highly correlated with arterial lactate concentrations but decreased more promptly during effective treatment, suggesting that decreases in $P_{sl}CO_2$ occur faster and closer to the real time of hemodynamic improvement than arterial lactate concentrations. They concluded that sublingual capnometry was a reliable method for diagnosis and quantitation of severity of circulatory failure in humans.

Marik [56] also measured $P_{sl}CO_2$ in hemodynamically unstable patients during the first 24 h of ICU admission. Initial $\Delta P_{sl\text{-}a}CO_2$ values were statistically higher in non-survivors than in survivors but the $P_{sl}CO_2$ values were not, suggesting that $\Delta P_{sl\text{-}a}CO_2$ is a better prognostic factor than $P_{sl}CO_2$. In a similar study design, Rackow and coworkers [57] also found higher $\Delta P_{sl\text{-}a}CO_2$ in non-survivors than in survivors, but this time measured at 24 h after the start of the study. These authors observed that the correlation between $P_{sl}CO_2$ and the other indexes of tissue

Table 1 Summary of clinical studies using sublingual capnometry

Author(s)/year	Number of patients	Diagnosis	Time of $P_{sl}CO_2$ measurement	$P_{sl}CO_2/\Delta P_{sl\text{-}a}CO_2$ survivors, non-survivors	*p* value
Weil et al, 1999 [55]	46	21 trauma 14 infection 6 cardiac emergency 5 miscellaneous	ICU, ER or TS admission, every 30 min, (total 6 h)	$P_{sl}CO_2$ (admission), 58.4±11.3, 92.6±26.6	<0.001
Marik, 2001 [56]	22	15 severe sepsis/septic shock 7 cardiogenic shock	ICU admission, every 4–6 h, (total 24 h)	$\Delta P_{sl\text{-}a}CO_2$ (admission), 9.2±5.0, 17.8±11.5	0.04
Rackow et al, 2001 [57]	25	19 sepsis 6 cardiac failure	0, 1, 3, 6, 12, 24 h after Swan-Ganz insertion	$\Delta P_{sl\text{-}a}CO_2$ (at 24 h), 14±3, 29±4	<0.05
Marik and Bankov, 2003 [7]	54	21 severe sepsis/septic shock 9 cardiogenic shock 8 major abdominal surgery 8 polytrauma 5 hypovolemic shock 3 severe pancreatitis	0, 4, 8 h after Swan-Ganz insertion	$\Delta P_{sl\text{-}a}CO_2$ (at the time of Swan-Ganz insertion), 19.0±12.8, 35.3±18.3	0.0004

$P_{sl}CO_2$ sublingual partial pressure of carbon dioxide, $\Delta P_{sl\text{-}a}CO_2$ sublingual-arterial partial pressure of carbon dioxide gradient, *ICU* intensive care unit, *ER* emergency room, *TS* trauma service

Table 2 Well-established facts, limitations and unanswered questions about sublingual capnometry

Well-established facts	1. $P_{sl}CO_2$ depends on P_aCO_2, sublingual tissue CO_2 production and regional blood flow
	2. Low blood flow is the main determinant of CO_2 accumulation in tissues
	3. Measurement of $P_{sl}CO_2$ is non-invasive and easily obtained in cooperative or sedated patients
	4. High $\Delta P_{sl\text{-}a}CO_2$ values in critically ill patients predict a poor prognosis
Limitations and questions to be answered	1. Current physiological concepts preclude $\Delta P_{sl\text{-}a}CO_2$ as a sensitive and specific marker of dysoxia
	2. Possible differences in $\Delta P_{sl\text{-}a}CO_2$ patterns in hypodynamic and hyperdynamic shock
	3. Cut-off values between normal and pathological values are hard to define
	4. $\Delta P_{sl\text{-}a}CO_2$-guided therapy has not yet been shown to be beneficial

$P_{sl}CO_2$ sublingual partial pressure of carbon dioxide, P_aCO_2 arterial partial pressure of carbon dioxide, CO_2 carbon dioxide, $\Delta P_{sl\text{-}a}CO_2$ gradient between $P_{sl}CO_2$ and P_aCO_2

perfusion was greater in patients with cardiac failure than with sepsis. Marik and Bankov [7] recently confirmed that $\Delta P_{sl\text{-}a}CO_2$ is a good outcome predictor. They observed that patients with an initial $\Delta P_{sl\text{-}a}CO_2$ higher than 25 mmHg have a high mortality rate. In their study, despite optimization of traditional hemodynamic end points, the $\Delta P_{sl\text{-}a}CO_2$ decreased but remained higher in the non-survivors than in the survivors. When they excluded $\Delta P_{sl\text{-}a}CO_2$ from the analysis, $P_{sl}CO_2$ became the most significant predictor of outcome by multivariate analysis. Based on this, they concluded that, in their study, $P_{sl}CO_2$ alone might be suitable for management, obviating the need for blood gas analysis to calculate $\Delta P_{sl\text{-}a}CO_2$.

By simultaneously monitoring $P_{sl}CO_2$ with Capno-Probe and sublingual microcirculation with the use of the Orthogonal Polarization Spectral imaging technique (Cytoscan, Cytometrics, Philadelphia, PA, USA), our group was able to demonstrate a significant correlation between $P_{sl}CO_2$ and the percentage of perfused sublingual capillaries in 12 septic shock patients [63, 64]. Hence, $\Delta P_{sl\text{-}a}CO_2$ seems to be mainly determined by sublingual microcirculatory blood flow.

Limitations, controversies and unanswered questions

With the currently available data on sublingual capnometry, some questions (Table 2) remain and need proper evaluation and consideration.

Drawbacks of tissue partial pressure of carbon dioxide measurement in the sublingual mucosa

Although more practical than the stomach for measurement of tissue PCO_2, some potential disadvantages need to be discussed. First, since tactile stimuli can increase sublingual blood flow and production of saliva, the presence of the device itself under the tongue can increase sublingual blood flow. Most acutely ill patients are not

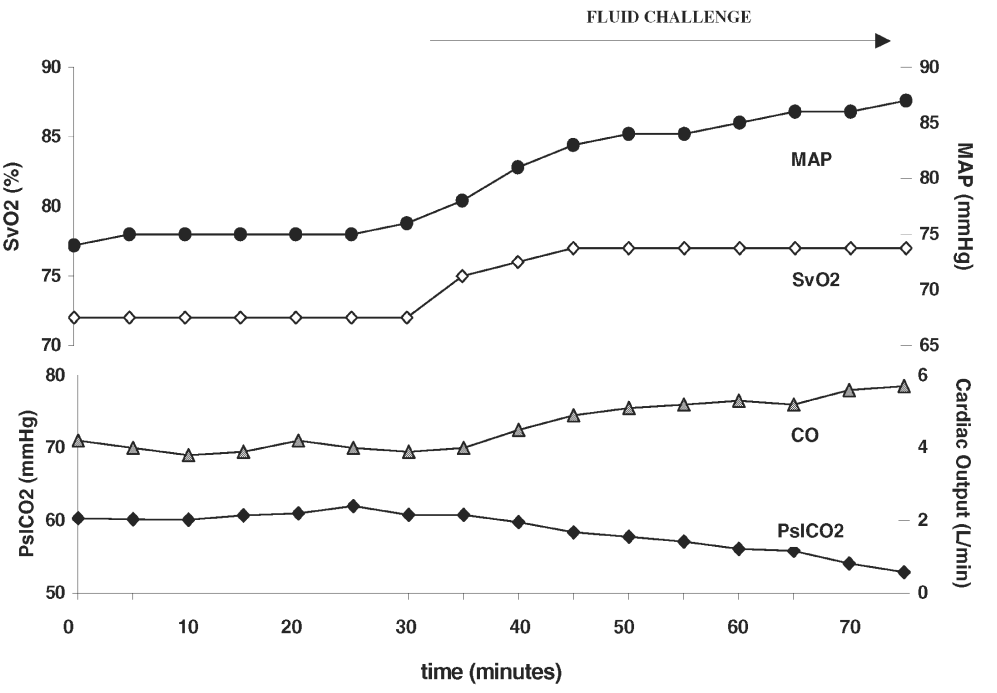


Fig. 1 Results from a 73-year-old woman admitted to the ICU with subarachnoid hemorrhage. Cardiac output was felt to be inadequate in the presence of an increased arterial lactate concentration and a high $P_{sl}CO_2$ (around 60 mmHg). Mean arterial pressure (*MAP*), cardiac output (*CO*), mixed venous oxygen saturation (SvO_2) and sublingual PCO_2 ($P_{sl}CO_2$) were continuously monitored. A fluid challenge resulted in increases in MAP, CO, and SvO_2 and decreases in $P_{sl}CO_2$. Since arterial PCO_2 remained constant (38 mmHg), decreases in the sublingual-arterial PCO_2 gradient ($\Delta P_{sl\text{-}a}CO_2$) were equally significant. Arterial lactate concentration normalized in the subsequent hours

fed orally so that the direct interference of food on sublingual measurement is not a major problem, as it is for gastric tonometry. However, enteral feeding could theoretically interfere indirectly with sublingual blood flow through reflex mechanisms, as previously mentioned. It is important to remember that the sublingual mucosa is sometimes used for drug administration but this should be avoided during sublingual PCO_2 monitoring. In addition, CO_2 production by bacteria of the oral flora and interference of saliva and its composition as well as vomitus in the measurement of the $P_{sl}CO_2$ value are potential areas of concern, but their effects are probably negligible.

The devices clinically available for $P_{sl}CO_2$ measurement measure the value intermittently. However, since $P_{sl}CO_2$ seems to respond fast to changes in hemodynamic conditions, intermittent measurements are not very practical for use in critically ill patients. For this reason, a system that measures $P_{sl}CO_2$ continuously would be more appropriate. This system has already been developed (CapnoProbe SL Model 2000 Sensor; Optical Sensor, MN, USA) but is still not clinically available. Fig. 1 shows an example of the use of this device in a single patient.

Another important aspect of the measurement of tissue PCO_2 in the sublingual mucosa is that, since it is not part of the splanchnic area, elevations in $P_{sl}CO_2$ may not occur as fast as in the stomach in progressive shock states. Hence, it may not serve as a "canary of the body" [65]. In addition, $P_{sl}CO_2$ should always be interpreted in relation to the arterial PCO_2. This latter measurement is subject to bias and imprecisions related to blood gas sampling and analysis, including the pitfalls of the temperature correction of blood gases. Since sublingual and arterial PCO_2 are measured by different equipment and at different temperatures, a methodological error may be introduced [66].

Normal values of sublingual partial pressure of carbon dioxide

There is no large study evaluating the normal value of $P_{sl}CO_2$. Weil et al. [55] measured $P_{sl}CO_2$ in five healthy human volunteers with the MI-720 CO_2 electrode and the range was from 43 to 47 mmHg.

Sublingual partial pressure of carbon dioxide measurement in different types of shock

Most experimental studies on sublingual capnometry have included hypodynamic types of circulatory shock. Even in models of septic shock, the cardiac index started to fall at the beginning of the experiment [52]. This has been a limitation of models using a bolus intravenous injection of bacteria (or endotoxin) [67]. Most of the clinical studies did not evaluate different types of shock separately [7, 55, 56], yet it is possible that different types of shock modify $P_{sl}CO_2$ values in different ways. This may also contribute to the variability in the correlations between $P_{sl}CO_2$ and other markers of tissue perfusion in the various studies, as suggested by Rackow et al. [57].

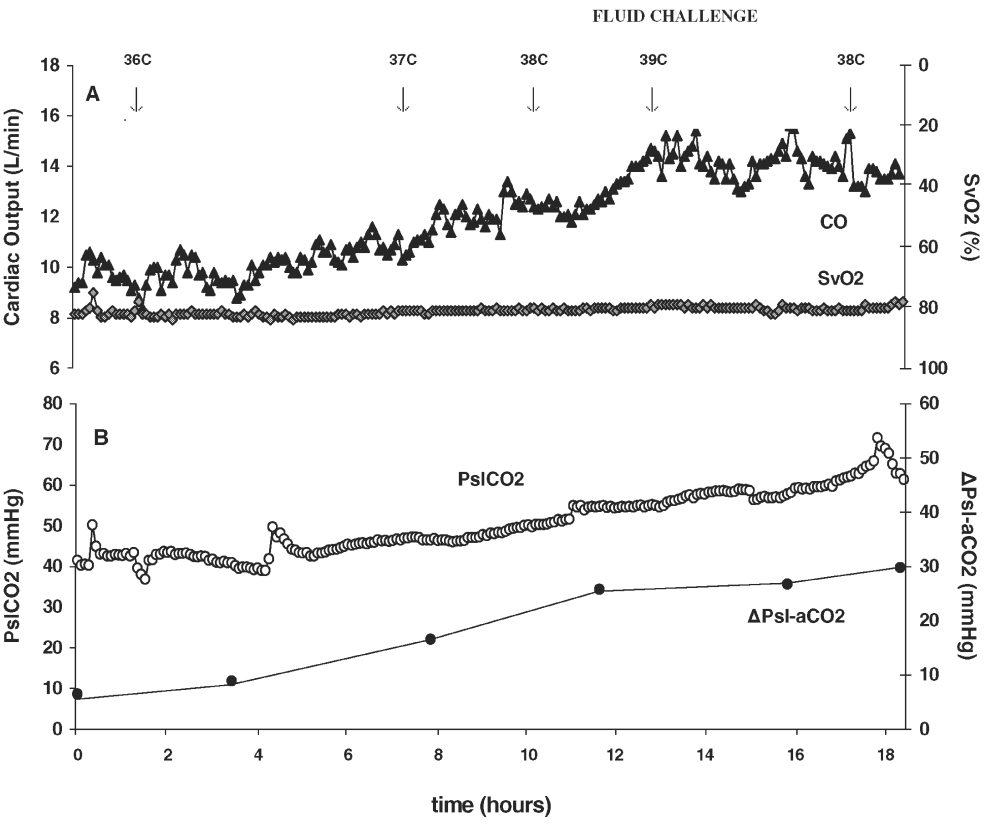


Fig. 2 Results from a 20-year-old man admitted to the ICU with fulminant hepatic failure and severe sepsis, showing a hyperdynamic status. **A** Cardiac output (*CO*) and mixed venous oxygen saturation (SvO_2) were recorded every 5 min. Note the progressive increase in CO and oral temperature (*arrows*) with a stable SvO_2. **B** Continuous sublingual PCO_2 ($P_{sl}CO_2$) monitoring and intermittent sublingual-arterial PCO_2 gradient ($\Delta P_{sl\text{-}a}CO_2$) measurement. Note that although CO increased, $P_{sl}CO_2$ and $\Delta P_{sl\text{-}a}CO_2$ also increased. Arterial lactate concentration was around 2 mmol/l and mean arterial pressure around 65–70 mmHg (no vasoactive agent) throughout the monitoring period. The clinical condition deteriorated in the hours after the end of the monitoring period progressing to septic shock (fungal in origin) and multiple organ failure. The patient died 2 days later

What is the behavior of sublingual partial pressure of carbon dioxide in hyperdynamic sepsis?

We have reported high values of $P_{sl}CO_2$ in hemodynamically stabilized septic shock patients [63, 64], even when cardiac output increased (Fig. 2). The most feasible explanation for increases in $\Delta P_{sl\text{-}a}CO_2$ despite increases in systemic blood flow is compromised microvascular blood flow in patients with sepsis [68–71], including in the sublingual mucosa [63, 72]. Low microvascular blood flow may occur despite high systemic blood flow due to shunts in "weak microcirculatory units" [73, 74] and this is mainly responsible for CO_2 accumulation and increases in $P_{sl}CO_2$ despite the presence of a high cardiac index. Distributive abnormalities of macrocirculatory and microcirculatory blood flow play a key role in the impairment of sepsis-related oxygen extraction [75] and, probably, also in tissue CO_2 accumulation. $P_{sl}CO_2$ seems to correlate well with the microcirculatory alterations reported in sepsis [63, 64], so it could be used as a reliable marker to quantify these alterations.

It is reasonable to speculate that in all types of shock, even in hyperdynamic sepsis, compromised blood flow and impairment in tissue perfusion are a common end point. Hence, tissue PCO_2 is expected to increase in all these situations, whatever the etiology or mechanism. However, dysoxia may occur despite maintained blood flow; adequate perfusion, although essential, is not always a guarantee of normal aerobic cell metabolism, especially in sepsis.

Should treatment be guided by gradients between sublingual partial pressure of carbon dioxide and arterial partial pressure of carbon dioxide?

No study exists on the efficacy of $\Delta P_{sl\text{-}a}CO_2$-guided therapy. A high value for $\Delta P_{sl\text{-}a}CO_2$ suggests a mismatch between blood flow (especially in the microcirculation) and oxygen demand in all types of shock, a situation that usually precedes the occurrence of dysoxia itself and multiple organ failure. However, care must be taken since the literature already has good examples of very promising monitoring techniques, such as pHi measurement, which, although useful as a prognostic index [76, 77], is still controversial as a therapeutic guide, having been shown to be beneficial in some studies [18, 78, 79], but not in others [80, 81]. Since interpretation of $\Delta P_{sl\text{-}a}CO_2$ is not always easy to achieve, the best approach at this moment is to analyze its value in conjunction with the traditional hemodynamic parameters in current use.

Conclusion

Sublingual capnometry has emerged in recent years as a promising technique for non-invasive monitoring of hemodynamic disturbances. Experimental and clinical studies have indicated that: (a) acute and severe reductions in blood flow are associated with significant PCO_2 elevation in virtually all tissues; (b) sublingual tissue is a potential site for measurement of PCO_2 non-invasively, which is the great advantage of this method; (c) P_aCO_2 must be taken into account when interpreting $P_{sl}CO_2$; (d) higher $P_{sl}CO_2$ values and, more specifically, higher $\Delta P_{sl\text{-}a}CO_2$ values correlate with altered sublingual microcirculatory blood flow and an increased risk of death in critically ill patients.

With our current knowledge, some questions and limitations are still present: (a) correct tissue PCO_2 interpretation is not always easy to achieve since some variables can potentially interfere with the measurement, even when it is made in the sublingual mucosa; (b) the sublingual mucosa may not be as susceptible to ischemia as the gastrointestinal tract, so that it may not be compromised so early in progressive shock states; (c) there may be differences in $P_{sl}CO_2$ kinetics in different types of shock; (d) the absence of a "gold standard" monitor of dysoxia to compare with; (e) no well-established normal and pathological $\Delta P_{sl\text{-}a}CO_2$ values; and (f) it is still uncertain if correction of $\Delta P_{sl\text{-}a}CO_2$ improves prognosis. Nevertheless, since $P_{sl}CO_2$ measurement is technically simple and non-invasive, new studies should be encouraged to define the precise role of sublingual PCO_2 measurement in the management of critically ill patients.

References

1. Walley KR, Wood LDH (1992) Shock. In: Hall JB, Schmidt GA, Wood LDH (eds) Principals of critical care. McGraw-Hill, New York, pp 1393–1416
2. Shoemaker WC, Appel PL, Kram HB (1988) Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. Crit Care Med 16:1117–1120
3. Beal AL, Cerra FB (1994) Multiple organ failure in the 1990s. JAMA 271:226–233
4. Deitch EA (1992) Multiple organ failure: pathophysiology and potential future therapy. Ann Surg 216:117–134
5. Consensus conference (1996) Tissue hypoxia: how to detect, how to correct, how to prevent. Am J Respir Crit Care Med 154:1573–1578
6. Russell JA, Phang PT (1994) The oxygen delivery/consumption controversy: approaches to management of the critically ill. Am J Respir Crit Care Med 149:533–537
7. Marik PE, Bankov A (2003) Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. Crit Care Med 31:818–822
8. Marik PE, Varon J (1998) The hemodynamic derangements in sepsis: implications for treatment strategies. Chest 114:854–860
9. Marik PE (1993) Gastric intramucosal pH. A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. Chest 104:225–229
10. Boyd KD, Thomas SJ, Gold J, Boyd AD (1983) A prospective study of complications of pulmonary artery catheterizations in 500 consecutive patients. Chest 84:245–249
11. Rello J, Coll P, Net A, Prats G (1993) Infection of pulmonary artery catheters. Epidemiologic characteristics and multivariate analysis of risk factors. Chest 103:132–136
12. Ramsey SD, Saint S, Sullivan SD, Dey L, Kelley K, Bowdle A (2000) Clinical and economic effects of pulmonary artery catheterization in nonemergent coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 14:113–118
13. Dalen JE, Bone RC (1996) Is it time to pull the pulmonary catheter? JAMA 276:916–918
14. Williams G, Grounds M, Rhodes A (2002) Pulmonary artery catheter. Curr Opin Crit Care 8:251–256
15. De Backer D (2003) Lactic acidosis. Intensive Care Med 29:699–702
16. Hotchkiss RS, Karl IE (1992) Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. JAMA 267:1503–1510
17. Fiddian-Green RG, Baker S (1987) Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. Crit Care Med 15:153–156
18. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J, Klein F, San Roman E, Dorfman B, Shottlender J, Giniger R (1992) Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 339:195–199
19. Johnson BA, Weil MH (1991) Redefining ischemia due to circulatory failure as dual defects of oxygen deficits and of carbon dioxide excesses. Crit Care Med 19:1432–1438
20. Kivilaakso E, Ahonen J, Aronsen KF, Hockerstedt K, Kalima T, Lempinen M, Suoranta H, Vernerson E (1982) Gastric blood flow, tissue gas tension and microvascular changes during hemorrhage-induced stress ulceration in the pig. Am J Surg 143:322–330
21. Hurley R, Chapman MV, Mythen MG (2000) Current status of gastrointestinal tonometry. Curr Opin Crit Care 6:130–135
22. Levy B, Gawalkiewicz P, Vallet B, Briancon S, Nace L, Bollaert PE (2003) Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med 31:474–480
23. Pastores SM, Katz DP, Kvetan V (1996) Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. Am J Gastroenterol 91:1697–1710
24. Fink MP (1993) Adequacy of gut oxygenation in endotoxemia and sepsis. Crit Care Med 21:S4–S8
25. Antonsson JB, Boyle CC, Kruithoff KL, Wang HL, Sacristan E, Rothschild HR, Fink MP (1990) Validation of tonometric measurement of gut intramural pH during endotoxemia and mesenteric occlusion in pigs. Am J Physiol 259:G519–G523
26. Schlichtig R, Mehta N, Gayowski TJ (1996) Tissue-arterial PCO_2 difference is a better marker of ischemia than intramural pH (pHi) or arterial pH-pHi difference. J Crit Care 11:51–56

27. Salzman AL, Strong KE, Wang H, Wollert PS, VanderMeer TJ, Fink MP (1994) Intraluminal balloonless air tonometry: a new method for determination of gastrointestinal mucosal carbon dioxide tension. Crit Care Med 1:126–134
28. Guzman JA, Kruse JA (1996) Development and validation of a technique for continuous monitoring of gastric intramucosal pH. Am J Respir Crit Care Med 153:694–700
29. Teboul JL, Michard F, Richard C (1996) Critical analysis of venoarterial CO_2 gradient as a marker of tissue hypoxia. In: Vincent JL, (ed) Yearbook of intensive care and emergency medicine. Springer, Heidelberg, pp 296–307
30. Neviere R, Chagnon JL, Teboul JL, Vallet B, Wattel F (2002) Small intestine intramucosal $PCO_{(2)}$ and microvascular blood flow during hypoxic and ischemic hypoxia. Crit Care Med 30:379–384
31. Vallet B, Teboul JL, Cain S, Curtis S (2000) Venoarterial $CO_{(2)}$ difference during regional ischemic or hypoxic hypoxia. J Appl Physiol 89:1317–1321
32. Schlichtig R, Heard SO (1999) Sublingual PCO_2 measurement: the nitroglycerin of monitoring? Crit Care Med 27:1380–1381
33. Schlichtig R, Bowles SA (1994) Distinguishing between aerobic and anaerobic appearance of dissolved CO_2 in intestine during low flow. J Appl Physiol 76:2443–2451
34. Rozenfeld RA, Dishart MK, Tonnessen TI, Schlichtig R (1996) Methods for detecting local intestinal ischemic anaerobic metabolic acidosis by PCO_2. J Appl Physiol 81:1834–1842
35. Raza O, Schlichtig R (2000) Metabolic component of intestinal $PCO_{(2)}$ during dysoxia. J Appl Physiol 89:2422–2429
36. Randall HM, Cohen JJ (1966) Anaerobic CO_2 production by dog kidney in vitro. Am J Physiol 211:493–505
37. Mathias DW, Clifford PS, Klopfenstein HS (1988) Mixed venous blood gases are superior to arterial blood gases in assessing acid-base status and oxygenation during acute cardiac tamponade in dogs. J Clin Invest 82:833–838
38. Groeneveld AB, Vermeij CG, Thijs LG (1991) Arterial and mixed venous blood acid-base balance during hypoperfusion with incremental positive end-expiratory pressure in the pig. Anesth Analg 73:576–582
39. Zhang H, Vincent JL (1993) Arteriovenous differences in PCO_2 and pH are good indicators of critical hypoperfusion. Am Rev Respir Dis 148:867–871
40. Jakob SM, Kosonen P, Ruokonen E, Parviainen I, Takala J (1999) The Haldane effect—an alternative explanation for increasing gastric mucosal PCO_2 gradients? Br J Anaesth 83:740–746
41. Hurley R, Mythen MG (2000) The Haldane effect—an explanation for increasing gastric mucosal PCO_2 gradients? Br J Anaesth 85:167–169
42. De Backer D, Creteur J, Vincent JL (2000) The Haldane effect—an explanation for increasing gastric mucosal PCO_2 gradients? Br J Anaesth 85:169
43. Walley KR, Friesen BP, Humer MF, Phang PT (1998) Small bowel tonometry is more accurate than gastric tonometry in detecting gut ischemia. J Appl Physiol 85:1770–1777
44. Fiddian-Green RG, Amelin PM, Herrmann JB, Arous E, Cutler BS, Schiedler M, Wheeler HB, Baker S (1986) Prediction of the development of sigmoid ischemia on the day of aortic operations. Indirect measurements of intramural pH in the colon. Arch Surg 121:654–660
45. Schiedler MG, Cutler BS, Fiddian-Green RG (1987) Sigmoid intramural pH for prediction of ischemic colitis during aortic surgery. A comparison with risk factors and inferior mesenteric artery stump pressures. Arch Surg 122:881–886
46. Klok T, Moll FL, Leusink JA, Theunissen DJ, Gerrits CM, Keijer C, J (1996) The relationship between sigmoidal intramucosal pH and intestinal arterial occlusion during aortic reconstructive surgery. Eur J Vasc Endovasc Surg 11:304–307
47. Sato Y, Weil MH, Tang W, Sun S, Xie J, Bisera J, Hosaka H (1997) Esophageal PCO_2 as a monitor of perfusion failure during hemorrhagic shock. J Appl Physiol 82:558–562
48. Van Hulst RA, Hasan D, Lachmann B (2002) Intracranial pressure, brain PCO_2, PO_2 and pH during hypo- and hyperventilation at constant mean airway pressure in pigs. Intensive Care Med 28:68–73
49. Lang JD Jr, Evans DJ, deFigueiredo LP, Hays S, Mathru M, Kramer GC (1999) A novel approach to monitor tissue perfusion: bladder mucosal PCO_2, PO_2 and pHi during ischemia and reperfusion. J Crit Care 14:93–98
50. Kvarstein G, Mirtaheri P, Tonnessen TI (2004) Detection of ischemia by PCO_2 before adenosine triphosphate declines in skeletal muscle. Crit Care Med 32:232–237
51. Koga I, Stiernstrom H, Christiansson L, Wiklund L (2000) Intraperitoneal tonometry for detection of regional enteric ischaemia. Acta Anaesthesiol Scand 44:985–990
52. Nakagawa Y, Weil MH, Tang W, Sun S, Yamaguchi H, Jin X, Bisera J (1998) Sublingual capnometry for diagnosis and quantitation of circulatory shock. Am J Respir Crit Care Med 157:1838–1843
53. Povoas HP, Weil MH, Tang W, Moran B, Kamohara T, Bisera J (2000) Comparisons between sublingual and gastric tonometry during hemorrhagic shock. Chest 118:1127–1132
54. Pernat A, Weil MH, Tang W, Yamaguchi H, Pernat AM, Sun S, Bisera J (1999) Effects of hyper- and hypoventilation on gastric and sublingual $PCO_{(2)}$. J Appl Physiol 87:933–937
55. Weil MH, Nakagawa Y, Tang W, Sato Y, Ercoli F, Finegan R, Grayman G, Bisera J (1999) Sublingual capnometry: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. Crit Care Med 27:1225–1229
56. Marik PE (2001) Sublingual capnography: a clinical validation study. Chest 120:923–927
57. Rackow EC, O'Neil P, Astiz ME, Carpati CM (2001) Sublingual capnometry and indexes of tissue perfusion in patients with circulatory failure. Chest 120:1633–1638
58. Jin X, Weil MH, Sun S, Tang W, Bisera J, Mason EJ (1998) Decreases in organ blood flows associated with increases in sublingual PCO_2 during hemorrhagic shock. J Appl Physiol 85:2360–2364
59. Creteur J, De Backer D, Vincent JL (1997) Monitoring of gastric mucosal PCO_2 by gas tonometry: in vitro and in vivo validation studies. Anesthesiology 87:504–510
60. Grum CM, Fiddian Green RG, Pittenger GL, Grant BJ, Rothman ED, Dantzker DR (1984) Adequacy of tissue oxygenation in intact dog intestine. J Appl Physiol 56:1065–1069
61. VanderMeer TJ, Wang H, Fink MP (1995) Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. Crit Care Med 23:1217–1226
62. Bernardin G, Lucas P, Hyvernat H, Deloffre P, Mattei M (1999) Influence of alveolar ventilation changes on calculated gastric intramucosal pH and gastric-arterial PCO_2 difference. Intensive Care Med 25:269–273
63. De Backer D, Creteur J, Dubois MJ (2003) Microvascular alterations in patients with circulatory failure. In: Vincent JL (ed) Yearbook of intensive care and emergency medicine. Springer, Heidelberg, pp 535–544

64. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL (2003) Determinant of sublingual PCO_2 in patients with septic shock (abstract). Crit Care Med 31:A116
65. Dantzker DR (1993) The gastrointestinal tract: the canary of the body? JAMA 270:1247–1248
66. Ackland G, Grocott MP, Mythen MG (2000) Understanding gastrointestinal perfusion in critical care: so near and yet so far. Crit Care 4:269–281
67. Deitch EA (1998) Animal models of sepsis and shock: a review and lessons learned. Shock 9:1–11
68. Cryer HM, Garrison RN, Kaebnick HW, Harris PD, Flint LM (1987) Skeletal microcirculatory responses to hyperdynamic Escherichia coli sepsis in unanesthetized rats. Arch Surg 122:86–92
69. Lam C, Tyml K, Martin C, Sibbald W (1994) Microvascular perfusion is impaired in a rat model of normotensive sepsis. J Clin Invest 94:2077–2083
70. Piper RD, Pitt-Hyde M, Li F, Sibbald WJ, Potter RF (1996) Microcirculatory changes in rat skeletal muscle in sepsis. Am J Respir Crit Care Med 154:931–937
71. Farquhar I, Martin CM, Lam C, Potter R, Ellis CG, Sibbald WJ (1996) Decreased capillary density in vivo in bowel mucosa of rats with normotensive sepsis. J Surg Res 61:190–196
72. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166:98–104
73. Ince C, Sinaasappel M (1999) Microcirculatory oxygenation and shunting in sepsis and shock. Crit Care Med 27:1369–1377
74. Zuurbier CJ, van Iterson M, Ince C (1999) Functional heterogeneity of oxygen supply-consumption ratio in the heart. Cardiovasc Res 44:488–497
75. Astiz ME, Rackow EC, Weil MH (1986) Oxygen delivery and utilization during rapidly fatal septic shock in rats. Circ Shock 20:281–290
76. Gutierrez G, Oksenholt RL (1996) Prognostic value of gastric mucosal pH. Réan Urg 5:238–242
77. Doglio GR, Pusajo JF, Egurrola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G (1991) Gastric mucosal pH as a prognostic index of mortality in critically ill patients. Crit Care Med 19:1037–1040
78. Ivatury RR, Simon RJ, Islam S, Fueg A, Rohman M, Stahl WM (1996) A prospective randomized study of end points of resuscitation after major trauma: global oxygen transport indices versus organ-specific gastric mucosal pH. J Am Coll Surg 183:145–154
79. Ivatury RR, Simon RJ, Havriliak D, Garcia C, Greenbarg J, Stahl WM (1995) Gastric mucosal pH and oxygen delivery and oxygen consumption indices in the assessment of adequacy of resuscitation after trauma: a prospective, randomized study. J Trauma 39:128–134
80. Pargger H, Hampl KF, Christen P, Staender S, Scheidegger D (1998) Gastric intramucosal pH-guided therapy in patients after elective repair of infrarenal abdominal aneurysms: is it beneficial? Intensive Care Med 24:769–776
81. Gomersall CD, Joynt GM, Freebairn RC, Hung V, Buckley TA, Oh TE (2000) Resuscitation of critically ill patients based on the results of gastric tonometry: a prospective, randomized, controlled trial. Crit Care Med 28:607–614

Alexandre Lima
Jan Bakker

Noninvasive monitoring of peripheral perfusion

This study was in part supported by materials provided by Hutchinson Technology and a grant from Philips USA. Both authors received a grant US $12,000 from Philips USA and $10,000 from Hutchinson Technology.

Abstract *Background:* Early hemodynamic assessment of global parameters in critically ill patients fails to provide adequate information on tissue perfusion. It requires invasive monitoring and may represent a late intervention initiated mainly in the intensive care unit. Noninvasive monitoring of peripheral perfusion can be a complementary approach that allows very early application throughout the hospital. In addition, as peripheral tissues are sensitive to alterations in perfusion, monitoring of the periphery could be an early marker of tissue hypoperfusion. This review discusses noninvasive methods for monitoring perfusion in peripheral tissues based on clinical signs, body temperature gradient, optical monitoring, transcutaneous oximetry, and sublingual capnometry. *Discussion:* Clinical signs of poor peripheral perfusion consist of a cold, pale, clammy, and mottled skin, associated with an increase in capillary refill time. The temperature gradients peripheral-to-ambient, central-to-peripheral and forearm-to-fingertip skin are validated methods to estimate dynamic variations in skin blood flow. Commonly used optical methods for peripheral monitoring are perfusion index, near-infrared spectroscopy, laser Doppler flowmetry and orthogonal polarization spectroscopy. Continuous noninvasive transcutaneous measurement of oxygen and carbon dioxide tensions can be used to estimate cutaneous blood flow. Sublingual capnometry is a noninvasive alternative for gastric tonometry.

Keywords Body temperature gradient · Hemodynamic assessment · Noninvasive monitoring · Peripheral tissue perfusion · Sublingual capnometry · Transcutaneous oximetry

Introduction

An important goal of hemodynamic monitoring is the early detection of inadequate tissue perfusion and oxygenation to institute prompt therapy and guide resuscitation, avoiding organ damage. In clinical practice tissue oxygenation is frequently assessed by using conventional global measurements such as blood pressure, oxygen derived variables, and blood lactate levels. However, the assessment of global hemodynamic parameters fails to reflect increased blood lactate levels, the imbalance between oxygen demand and oxygen supply, or the status of the microcirculation [1, 2, 3]. In addition, it often requires invasive monitoring techniques that usually limit early initiation, typically after the patient has been admitted to the intensive care unit (ICU).

To address these limitations there have been many attempts to perform measurements of blood flow and oxygenation in peripheral tissues [4, 5]. In circulatory failure blood flow is diverted from the less important tissues (skin, subcutaneous, muscle, gastrointestinal tract) to vital organs (heart, brain, kidneys). Thus monitoring perfusion in these less vital tissues could be an early marker of vital tissue hypoperfusion. Second, the assess-

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_32, © Springer-Verlag Berlin Heidelberg 2009

ment of perfusion in peripheral tissues is more easily obtainable using noninvasive monitoring techniques, thus facilitating earlier initiation.

Monitoring of peripheral perfusion and oxygenation does not need any intravascular catheter, transesophageal probe insertion, blood component analysis or penetration of the skin. Also, it can be performed directly (clinical evaluation and body temperature gradient) or by signal processing (optical monitoring; transcutaneous oximetry; sublingual capnometry). This review discusses several available noninvasive methods to monitor peripheral perfusion and oxygenation (Table 1).

Clinical assessment

During circulatory failure the global decrease in oxygen supply and redistribution of blood flow caused by increased vasoconstriction results in decreased perfusion in organ systems. Some organs, including the brain, heart, and kidney, have vasomotor autoregulation that maintains blood flow in low blood pressure states. However, the cutaneous circulation is deprived of autoregulation, and the sympathetic neurohumoral response predominates, resulting in a decrease in skin perfusion and temperature in these conditions. Skin temperature is measured using the dorsal surface of the examiner hands or fingers because these areas are most sensitive to temperature perception. Patients are considered to have cool extremities if all examined extremities are cool to the examiner, or only the lower extremities are cool despite warm upper extremities, in the absence of peripheral vascular occlusive disease. Clinical signs of poor peripheral perfusion consist of a cold, pale, clammy, and mottled skin, associated with an increase in capillary refill time. In particular, skin temperature and capillary refill time have been advocated as a measure of peripheral perfusion [6, 7, 8, 9, 10, 11].

Capillary refill time (CRT) has been introduced into the assessment of trauma, and a value less than 2 s is considered normal [12]. This is based on the assumption that a delayed return of a normal color after emptying the capillary bed by compression is due to decreased peripheral perfusion. CRT has been validated as a measure of peripheral perfusion with significant variation in children and adults. Schriger and Baraff [8] in a study on a normal population reported that CRT varied with age and sex. It was found that a CRT of 2 s was a normal value for most young children and young adults, but the lowest CRT was substantially higher in healthy women (2.9 s) and in the elderly (4.5 s). Using these normal variations it was further shown that a prolonged CRT did not predict a 450-ml blood loss in adult blood donors or hypovolemic states in patients admitted to the emergency room [10]. Several clinical studies have reported a poor correlation between CRT, heart rate, blood pressure, and cardiac output [6, 7, 10]. However, prolonged CRT in pediatric

Table 1 Measurement methods to study peripheral perfusion (*CRT* capillary refill time, *dTc-p* temperature gradient central-to-peripheral, *dTp-a* temperature gradient peripheral-to-ambient, *Tskin-diff* forearm-to-fingertip skin-temperature gradient, *PFI* peripheral perfusion index, *NIRS* Near-infrared spectroscopy, *Hb* deoxygenated hemoglobin, HbO_2 oxygenated hemoglobin, *HbT* total hemoglobin, StO_2 tissue oxygen saturation, $Cytaa_3$ cytochrome aa_3, *OPS* orthogonal polarization spectroscopy, *FCD* functional capillary density, *LDF* Laser Doppler flowmetry, $PtcO_2$ oxygen partial pressure in the skin, $PtcCO_2$ carbon dioxide partial pressure in the skin, *Tc-index* transcutaneous oxygen index, $PslCO_2$ sublingual tissue PCO_2, $Psl\text{-}aCO_2$ gradient between $PslCO_2$ and arterial PCO_2)

Method	Variable	Advantage	Limitations
Clinical assessment	Warmth and coolness skin CRT	Depends only on physical examination; valuable adjunct for hemodynamic monitoring in circulatory shock	Difficult interpretation in distributive shock
Body temperature gradient	dTc-p dTp-a Tskin-diff	Validated method to estimate dynamic variations in skin blood flow	At least two temperature probes required; does not reflect the variations in real time
Pulse oximetry	PFI	Easily obtainable; reflect real time changes in peripheral blood flow	Not accurate during patient motion
NIRS	Hb, HbO_2, and HbT variations StO_2 $Cytaa_3$	Assessment of oxygenation in all vascular compartments; can be applied to measure regional blood flow and oxygen consumption	Requires specific software to display the variables
OPS	FCD	Direct visualization of the microcirculation	Observer-related bias; semiquantitative measure of perfusion
LDF	Microvascular blood flow	Useful method to evaluate endothelium-dependent vascular responses	Small sampling volume for cutaneous blood flow measurement; does not reflect heterogeneity of blood flow
Transcutaneous oximetry	$PtcO_2/PtcCO_2$ Tc-index	Direct measurement of $PtcO_2/PtcCO_2$; early detection of peripheral hypoperfusion	Necessity to frequently change the sensor position; requires blood gas analysis
Sublingual capnometry	$PslCO_2$ $Psl\text{-}aCO_2$	Direct measurement of tissue PCO_2 noninvasively	Requires blood gas analysis to obtain $PaCO_2$; normal and pathological values not yet defined

patients has been found to be a good predictor of dehydration, reduced stroke volume, and increased blood lactate levels [6, 11]. In adult patients following cardiac surgery no significant relationship between cardiac index and CRT was found during the first 8 h following ICU admission [7].

Distal extremity skin temperature has also been related to the adequacy of the circulation. Kaplan et al. [9] compared distal extremity skin temperature (evaluated by subjective physical examination) with biochemical and hemodynamic markers of hypoperfusion in adult ICU patients. This study found that patients with cold periphery (including septic patients) had lower cardiac output and higher blood lactate levels as a marker of more severe tissue hypoxia. In another study Hasdai et al. [13] showed the importance of the physical examination in determining the prognosis of patients with cardiogenic shock. This study reported the presence of a cold and clammy skin to be an independent predictor of 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction.

The findings of these studies show that skin temperature together with CRT are a valuable adjunct in hemodynamic monitoring during circulatory shock, and should be the first approach to assess critically ill patient. Not much is known about the clinical applicability of these variables after the patient has been admitted to the intensive care unit [14].

Temperature gradients

Since Joly and Weil [15] and Ibsen [16] studied the toe temperature as an indicator of the circulatory shock, body temperature gradients have been used as a parameter of peripheral perfusion. In the presence of a constant environmental temperature a change in the skin temperature is the result of a change in skin blood flow [17]. The temperature gradients peripheral-to-ambient (dTp-a) and central-to-peripheral (dTc-p) can better reflect cutaneous blood flow than the skin temperature itself. Considering a constant environment condition, dTp-a decreases and dTc-p increases during vasoconstriction. The peripheral skin temperature is measured using a regular temperature probe attached to the ventral face of the great toe. This site is more convenient for peripheral temperature measurement because of the negligible local heat production and the distal location from other monitoring devices [18]. The concept of the dTc-p is based on the transfer of heat from the body core to the skin. The heat conduction to the skin by the blood is also controlled by the degree of vasoconstriction of the arterioles and arteriovenous anastomoses. High blood flow causes heat to be conducted from the core to the skin, whereas reduction in blood flow decreases the heat conduction from the core. During vasoconstriction the temperature of the skin falls and the heat conduction from the core decreases, and therefore the central temperature rises and the dTc-p increases. A gradient of 3–7°C occurs in patients with stable hemodynamics [19]. Hypothermia, cold ambient temperature (<20°C) [20], and vasodilatory shock limits the use of dTc-p as an estimate of peripheral perfusion. Forearm-to-fingertip skin-temperature gradient (Tskin-diff) has also been used as an index of peripheral circulation to identify the initiation of thermoregulatory vasoconstriction in patients following surgery [21]. Fingertip temperature is measured with the temperature probe attached to the ventral face of the finger. The use of Tskin-diff is based on assumption that the reference temperature is a skin site exposed to the same ambient temperature as the fingertip. It has been applied in conditions where an ambient temperature is not stable, such as in patients undergoing surgery [21, 22, 23]. A change in ambient temperature therefore affects similarly forearm and fingertip temperature, producing little influence in the gradient. Basically, when vasoconstriction decreases fingertip blood flow, finger skin temperature decreases, and Tskin-diff increases. Experimental studies have suggested a Tskin-diff threshold of 0°C for the initiation of vasoconstriction, and a threshold of 4°C for severe vasoconstriction in anesthetized patients [22, 23].

The body temperature gradient was first applied to assess patients with circulatory shock and to differentiate central heat retention caused by fever from peripheral vasoconstriction [15, 16, 24]. A number of studies have examined the correlation between body temperature gradient and global hemodynamic variables in hypovolemic, septic and cardiogenic shock, but these have produced conflicting results [15, 25, 26, 27, 28, 29, 30, 31]. Henning et al. [28] studied dTp-a in patients with circulatory failure associated with hypovolemia and low cardiac output. An increase in dTp-a to more than 4–6°C over 12 h was observed in survivors, and a good relationship between the lowest dTp-a and the highest blood lactate levels was found in hypovolemic patients at time of admission. In assessing the potential value of dopamine as a therapeutic agent to treat circulatory shock Ruiz et al. [25] showed that survival is associated with an increase in dTp-a of more than 2°C, and that dTp-a is correlated to increases in cardiac output and a reduction in blood lactate levels. In examining the value of dTp-a for assessing peripheral perfusion in cardiogenic shock Vincent et al. [27] found that a cardiac index below 1.8 l/min^{-1} m^{-2} is associated with a decrease in dTp-a below 5°C, and that the increase in dTp-a occurs earlier than the increase in skin oxygen partial pressure during recovery; this correlation was not found in septic shock. No relationship has been observed between dTc-p and cardiac output in adults with diverse causes of shock [31] or in children after open heart surgery [26, 29, 30]. One reason for the inaccurate relationship between body temperature gradient and global hemodynamic parameters could be related to an

unstable environment, as skin temperature depends also on ambient temperature, and the thermoregulatory response is suppressed in anesthetized patients [32]. In addition, global hemodynamic parameters may not be sensitive enough to reflect changes in peripheral blood flow in critically ill patients [33, 34]. Tskin-diff may be an alternative, but its use in these conditions has not yet been defined.

Optical monitoring

Optical methods apply light with different wave lengths directly to tissue components using the scattering characteristics of tissue to assess various states of these tissues [35]. At physiological concentrations the molecules that absorb most light are hemoglobin, myoglobin, cytochrome, melanins, carotenes, and bilirrubin. These substances can be quantified and measured in intact tissues using simple optical methods. The assessment of tissue oxygenation is based on the specific absorption spectrum of oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (Hb) and cytochrome aa_3 ($cytaa_3$). Commonly used optical methods for peripheral monitoring are perfusion index, near-infrared spectroscopy, laser-Doppler flowmetry, and orthogonal polarization spectral.

Peripheral perfusion index

The peripheral perfusion index (PFI) is derived from the photoeletric plesthysmographic signal of pulse oximetry and has been used as a noninvasive measure of peripheral perfusion in critically ill patients [36]. Pulse oximetry is a monitoring technique used in probably every trauma, critically ill and surgical patient. The principle of pulse oximetry is based on two light sources with different wavelengths (660 nm and 940 nm) emitted through the cutaneous vascular bed of a finger or earlobe. The Hb absorbs more light at 660 nm and HbO_2 absorbs more light at 940 nm. A detector at the far side measures the intensity of the transmitted light at each wavelength, and the oxygen saturation is derived by the ratio between the red light (660 nm) and the infrared light (940 nm) absorbed. As other tissues also absorb light, such as connective tissue, bone, and venous blood, the pulse oximetry distinguishes the pulsatile component of arterial blood from the nonpulsatile component of other tissues. Using a two-wavelength system the nonpulsatile component is then discarded, and the pulsatile component is used to calculate the arterial oxygen saturation. The overall hemoglobin concentration can be determined by a third wavelength at 800 nm, with a spectrum that resembles that of both Hb and HbO_2. The resulting variation in intensity of this light can be used to determine the variation in arterial blood volume (pulsatile component). The PFI is calculated as the ratio between the pulsatile component (arterial compartment) and the nonpulsatile component (other tissues) of the light reaching the detector of the pulse oximetry, and it is calculated independently of the patient's oxygen saturation (Fig. 1). A peripheral perfusion alteration is accompanied by variation in the pulsatile component, and because the nonpulsatile component does not change, the ratio changes. As a result the value displayed on the monitor reflects changes in peripheral perfusion.

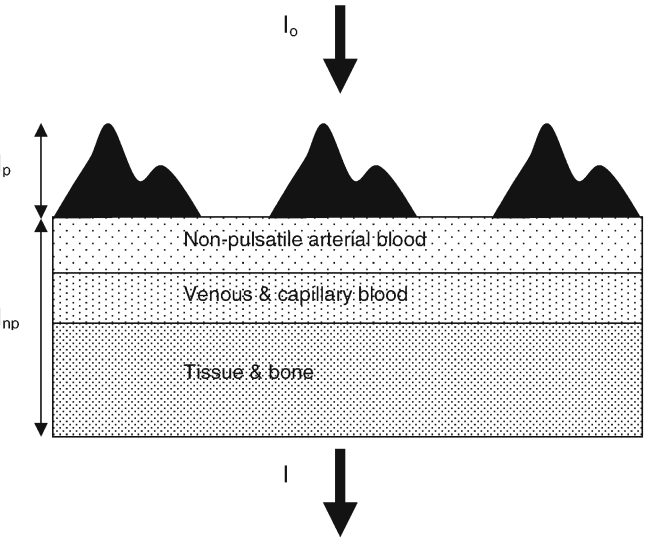


Fig. 1 The pulsation of arterial blood causes a pulsating volume variation. Peripheral perfusion index (*PFI*) is calculated as the ratio between the arterial pulsatile component (I_P) and the nonpulsatile component (I_{NP}). I_0 Source light intensity; I light intensity at the detector

Studies with body temperature gradient suggest that PFI can be a direct indicator of peripheral perfusion. A PFI of 1.4 has been found to be correlated best with hypoperfusion in critically ill patients using normal values in healthy adults [36]. A good relationship between Tskin-diff and PFI is observed in anesthetized patients to identify the initiation of thermoregulatory vasoconstriction [37]. The PFI reflects changes in dTc-p and Tskin-diff and therefore vascular reactivity in adult critically ill patients [36, 38]. Another study has shown that PFI can be used to predict severity of illness in neonates, with a cutoff value of1.24 [39]. The inclusion of PFI into the pulse oximetry signal is a recent advance in clinical monitoring. However, more studies are needed to define its clinical utility.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) offers a technique for continuous, noninvasive, bedside monitoring of tissue

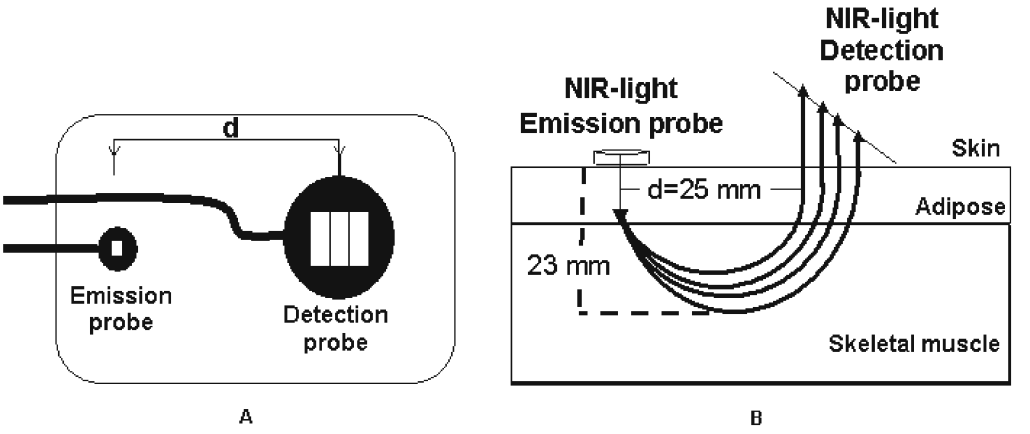


Fig. 2 **A** Diagram of a distal tip of the NIRS optical cable. **B** With 25 mm spacing (*d*) between emission and detection probes, approx. 95% of the detected optical signal is from 23 mm of tissue penetration

oxygenation. As with pulse oximetry, NIRS uses the principles of light transmission and absorption to measure the concentrations of hemoglobin, oxygen saturation (StO_2), and $cytaa_3$ noninvasively in tissues. NIRS has a greater tissue penetration than pulse oximetry and provides a global assessment of oxygenation in all vascular compartments (arterial, venous, and capillary). Tissue penetration is directly related to the spacing between illumination and detection fibers. At 25 mm spacing approx. 95% of the detected optical signal is from a depth of 0 to 23 mm (Fig. 2). NIRS has been used to assess forearm skeletal muscle oxygenation during induced reactive hyperemia in healthy adults and produces reproducible measurements of tissue oxygenation during both arterial and venous occlusive events [40]. Using the venous and arterial occlusion methods NIRS can be applied to measure regional blood flow and oxygen consumption by following the rate of HbO_2 and Hb changes [40, 41, 42]. In the venous occlusion method a pneumatic cuff is inflated to a pressure of approx. 50 mmHg. Such a pressure blocks venous occlusion but does not impede arterial inflow. As a result venous blood volume and pressure increase. NIRS can reflect this change by an increase in HbO_2, Hb, and total hemoglobin. In arterial occlusion method, the pneumatic cuff is inflated to a pressure of approx. 30 mmHg greater than systolic pressure. Such a pressure blocks both venous outflow and arterial inflow. Depletion of local available O_2 is monitored by NIRS as a decrease in HbO_2 and a simultaneous increase in Hb, whereas total Hb remains constant. After release of the occluding cuff a hyperemic response is observed (Fig. 3). Blood volume increases rapidly, resulting in an increase in HbO_2 and a quick washout of Hb. In addition to blood flow and evaluation of HbO_2 and Hb changes, NIRS can assess $cytaa_3$ redox state. $Cytaa_3$ is the final receptor in the oxygen transport chain that reacts with oxygen to form water, and approx. 90% of cellular energy is derived from this reaction. $Cytaa_3$ remains in a reduced state

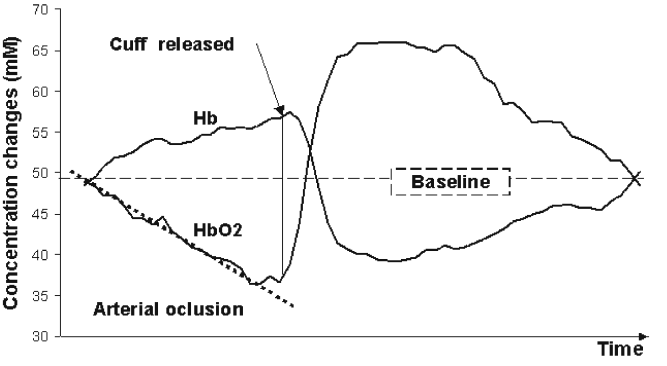


Fig. 3 Quantitative NIRS measurements during arterial occlusion. After release of the occluding cuff blood volume increases rapidly, resulting in an increase in HbO_2 and a quick washout of Hb, followed by a hyperemic response. Oxygen consumption is calculated as the rate of decrease in HbO_2 (*dotted line*)

during hypoxemia. The absorption spectrum of $cytaa_3$ in its reduced state shows a weak peak at 70 nm, whereas the oxygenated form does not. Therefore monitoring changes in its redox state can provide a measure of the adequacy of oxidative metabolism. Despite the potential clinical applications of NIRS, some limitations still exist. The contribution of the $cytaa_3$ signal is small, and its interpretation remains controversial, requiring more rigorous development [43]. There is no a gold standard to which NIRS data can be directly compared, and one of the reasons is that a variety of NIRS equipment is commercially available with different working systems.

In both small- and large-animal models of hemorrhagic shock and resuscitation NIRS has demonstrated sensitivity in detecting skeletal muscle and visceral ischemia [44, 45, 46, 47]. As a noninvasive measure of peripheral perfusion NIRS has been applied in superficial muscles (brachioradialis muscle, deltoid muscle, tibialis anterior) of trauma ICU patients to monitor the adequacy of tissue

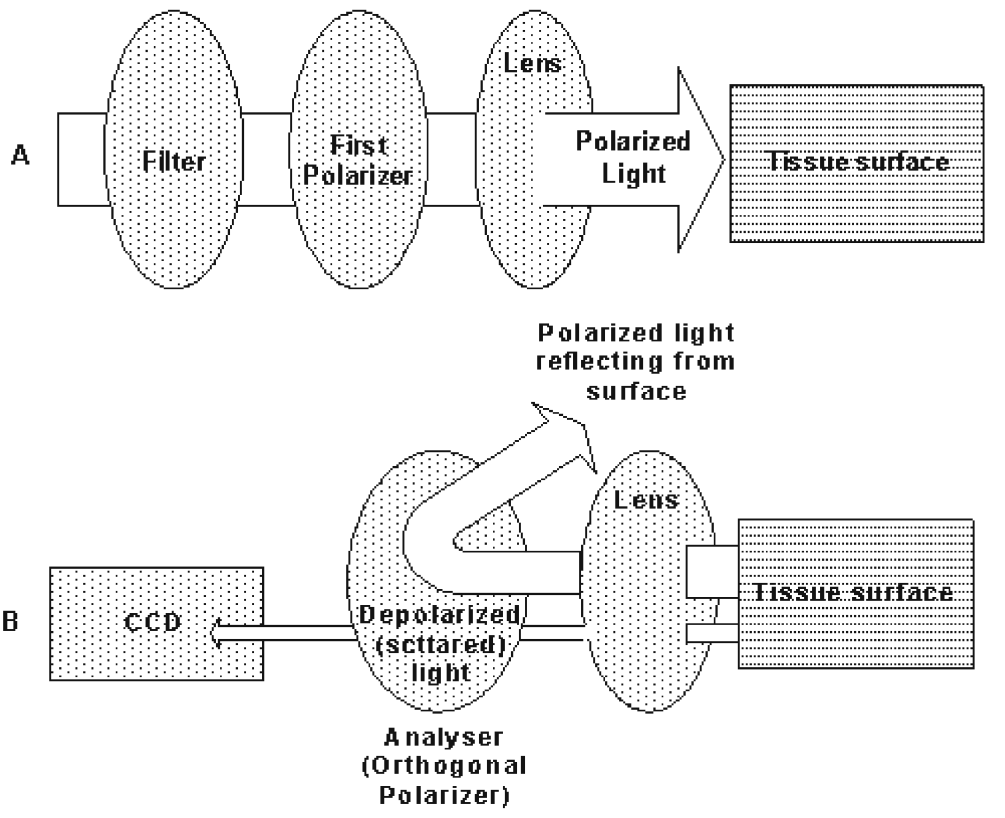


Fig. 4 OPS optical schematic. **A** The light passes through the first polarizer and is reflected back through the lens. **B** The polarized light reflecting from the surface is eliminated, and the depolarized light forms an image of the microcirculation on a videocamera (charge-coupled device, *CCD*)

oxygenation and detect a compartment syndrome [48, 49, 50, 51, 52]. The use of NIRS in deltoid muscle during resuscitation of severe trauma patients has recently been reported [48, 49]. Cairns et al. [49] studied trauma ICU patients and reported a strong association between elevated serum lactate levels and elevated cytaa$_3$ redox state during 12 h of shock resuscitation and development of multiple organ failure. More recently Mckinley et al. [48] showed a good relationship between StO_2, systemic oxygen delivery and lactate in severely trauma patients during and after resuscitation over a period of 24 h. A recent study with septic and nonseptic patients used NIRS to measure both regional blood flow and oxygen consumption after venous occlusion [53]. In this study septic patients had muscular oxygen consumption twice that of nonseptic patients, but oxygen extraction was similar in both groups, emphasizing oxygen extraction dysfunction in sepsis. Another study observed no relationship between forearm blood flow, measured by NIRS, and systemic vascular resistance in septic shock patients [41]. These findings demonstrate the ability of NIRS to reflect microcirculatory dysfunction in skeletal muscle in septic shock. The potential to monitor regional perfusion and oxygenation noninvasively at the bedside makes clinical application of NIRS technology of particular interest in intensive care.

Orthogonal polarization spectral

Orthogonal polarization spectral (OPS) is a noninvasive technique that uses reflected light to produce real-time images of the microcirculation. The technical characteristics of the device have been described elsewhere [54]. Light from a source passes through the first polarizer, and it is directed towards the tissue by a set of lens. As the light reaches the tissue, the depolarized light is reflected back through the lenses to a second polarizer or analyzer and forms an image of the microcirculation on the charge-coupled device, which can be captured through a single videotape (Fig. 4). The technology has been incorporated into a small hand-held video-microscope which can be used in both research and clinical settings. OPS can assess tissue perfusion using the functional capillary density (FCD), i.e., the length of perfused capillaries per observation area (measured as cm/cm^2). FCD is a very sensitive parameter for determining the status of nutritive perfusion to the tissue and it is an indirect measure of oxygen delivery. One of the most easily accessible sites in humans for peripheral perfusion monitoring is the mouth. OPS produces excellent images of the sublingual microcirculation by placing the probe under the tongue. Movement artifacts, semiquantitative measure of perfusion, the presence of various secretions such as saliva and blood, observer-related bias, and inadequacy of sedation

to prevent patients from damaging the device are some of the limitations of the technique.

The use of sublingual tissues with OPS provides information about the dynamics of microcirculatory blood flow, and therefore it can monitor the perfusion during clinical treatment of circulatory shock. It has been used to monitor the effects of improvements in microcirculatory blood flow with dobutamine and nitroglycerin in volume resuscitated septic patients [55, 56]. OPS has been applied in the ICU to study the properties of sublingual microcirculation in both septic shock and cardiogenic shock [2, 56, 57, 58]. In septic patients it has been shown with OPS that microvascular alterations are more severe in patients with a worse outcome, and that these microvascular alterations can be reversed using vasodilators [2]. In patients with cardiac failure and cardiogenic shock the number of small vessels and the density of perfused vessels are lower than in controls, and the proportion of perfused vessels is higher in patients who survived than in patients who did not survive [57]. Using OPS during the time course of treatment of patients with septic shock, Sakr et al. [58] demonstrated that the behavior of the sublingual microcirculation differs between survivors and nonsurvivors. Although alterations in the sublingual microcirculation may not be representative of other microvascular beds, changes in the sublingual circulation evaluated by capnometry during hemorrhagic shock have been related to changes in perfusion of internal organs such as the liver and intestine [59]. Thus OPS could be of use in the monitoring of tissue perfusion.

Laser Doppler flowmetry

Laser Doppler flowmetry (LDF) is a noninvasive, continuous measure of microcirculatory blood flow, and it has been used to measure microcirculatory blood flow in many tissues including neural, muscle, skin, bone, and intestine. The principle of this method is to measure the Doppler shift—the frequency change that light undergoes when reflected by moving objects, such as red blood cells. LDF works by illuminating the tissue under observation with a monochromatic laser from a probe. When the tissue is illuminated, only 3–7% is reflected. The remaining 93–97% of the light is either absorbed by various structures or undergoes scattering. Another optical fiber collects the backscattered light from the tissue and returns it to the monitor (Fig. 5). As a result LDF produces an output signal that is proportional to the microvascular perfusion [60]. Depending on the device and the degree of invasiveness it can be used to assess blood flow in muscle, gastric, rectal, and vagina mucosae. As a noninvasive measure of peripheral blood flow, however, its use is limited to the skin [60]. LDF has been applied to obtain information on the functional state of the skin microcirculation during reactive hyperemia in several conditions,

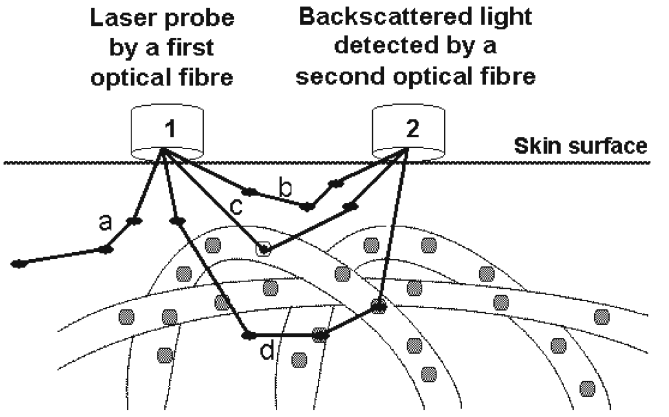


Fig. 5 Schematic diagram of laser Doppler flowmetry. When the tissue is illuminated by a laser source (*1*), 93–97% of the light is either absorbed by various structures or undergoes scattering (*a*, *b*). The remaining 3–7% is reflected by moving red blood cells (*c*, *d*) and returns to the second optical fiber (*2*). Microvascular perfusion is defined as the product of mean red blood cells (*RBC*) velocity and mean RBC concentration in the volume of tissue under illumination from the probe

such as diabetes mellitus, essential hypertension, atherosclerosis, and sepsis [61]. A major limitation of this technique is that it does not take into account the heterogeneity of blood flow as the velocity measurements represent the average of velocities in all vessels of the window studied. In addition, skin blood flow signal varies markedly depending on probe position. No current laser Doppler instrument can present absolute perfusion values (e.g., ml/min per 100 g tissue) and measurements are expressed as perfusion units, which are arbitrary.

LDF is useful in evaluating endothelium-dependent vascular responses in the skin microcirculation during either reactive hyperemia [61, 62] or the noninvasive local application of acetylcholine or sodium nitroprusside [63, 64, 65]. This characteristic of LDF was used in critically ill patients to evaluate endothelial dysfunction in sepsis. Observational studies have shown that the hyperemic response in septic patients is decreased, and a relationship between changes in vasculature tone and severity of sepsis has been described [66, 67, 68]. In addition, restored vasomotion in patients with sepsis evaluated by LDF seems to be associated with a favorable prognosis [67]. The ability of LDF to assess abnormalities of skin blood flow control in sepsis could be of clinical use for early detection of microcirculatory derangements in high-risk patients.

PO_2 and PCO_2 transcutaneous measurements

Continuous noninvasive measurement of oxygen and carbon dioxide tensions is possible because both gases can diffuse through the skin, and thus their partial pres-

sures can be measured in transcutaneous tissue. Normally the skin is not very permeable to gases, but at higher temperatures the ability of the skin to transport gases is improved. Oxygen sensors for transcutaneous electrochemical measurements are based on polarography: a typical amperometric transducer in which the rate of a chemical reaction is detected by the current drained through an electrode. The sensor heats the skin to 43–45°C. The skin surface oxygen tension is increased as a result of three effects: (a) heating the stratum corneum beyond 40°C changes its structure, which allows oxygen to diffuse faster; (b) the local oxygen tension is increased by shifting the oxygen dissociation curve in the heated dermal capillary blood; and (c) by dermal capillary hyperemia. These transcutaneous sensors enable us directly to estimate arterial oxygen pressure (PaO_2) and arterial carbon dioxide pressure ($PaCO_2$), and it has been successfully used for monitoring PaO_2 and $PaCO_2$ in both neonates and in adults [69, 70, 71]. Newborn infant is suitable because of its thin epidermal layer. However, in adults the skin is thicker, and differences in the skin cause the transcutaneous oxygen partial pressure ($PtcO_2$) to be lower than PaO_2. The correlation between $PtcO_2$ and PaO_2 also depends on the adequacy of blood flow. The low blood flow caused by vasoconstriction during shock overcomes the vasodilatory effect of $PtcO_2$ sensor. This causes a mild tissue hypoxia beneath the $PtcO_2$ sensor. The lack of the $PtcO_2$ ability to accurately reflect the PaO_2 in low flow shock enables us to estimate cutaneous blood flow through the relationship between the two variables. Some studies have suggested the use of a transcutaneous oxygen index (tc-index), i.e., the changes in $PtcO_2$ relative to changes in PaO_2 [69, 72, 73, 74, 75]. When blood flow is adequate, $PtcO_2$ and PaO_2 values are almost equal, and the tc-index is close to 1. During low flow shock the $PtcO_2$ drops and becomes dependent on the PaO_2 value, and tc-index decreases. A tc-index greater than 0.7 has been reported to be associated with hemodynamic stability [69, 72, 74, 75]. Transcutaneous carbon dioxide partial pressure ($PtcCO_2$) has been also used as an index of cutaneous blood flow. Differences between $PaCO_2$ and $PtcCO_2$ have been explained by local accumulation of CO_2 in the skin due to hypoperfusion. Because of the diffusion constant of CO_2 is about 20 times greater than O_2, $PtcCO_2$ has been showed to be less sensitive to changes in hemodynamics than $PtcO_2$ [76]. One of the main limitations of this technique is the necessity of blood gas analysis to obtain the tc-index and $PaCO_2$. In addition, the sensor position must be changed every 1–2 h to avoid burns. After each repositioning a period of 15–20 min is required for the next readings, which limits its use in emergency situations.

The ability of $PtcO_2$ to reflect tissue perfusion in critically ill adult patients has been applied using the tc-index. Tremper and Shoemaker [72] found a good correlation (r=0.86) between tc-index and cardiac index in patients with shock. These authors reported that at cardiac index values higher than 2.2 l min^{-1} m^{-2} the tc-index averages 0.79, at 1.5–2.2 l min^{-1} m^{-2} it is 0.48, and at values lower than 1.5 l min^{-1} m^{-2} it is 0.12. However, the relationship between tc-index and cardiac index may not exist in hyperdynamic shock. Reed et al. [75] studied $PtcO_2$ at different cardiac indices. In this study 71 measurements were made in 19 patients, and a low tc-index was seen in 71% of the patients with a cardiac index higher than 4.2l min^{-1} m^{-2}. $PtcO_2$ and $PtcCO_2$ monitoring has been used as an early indicator of tissue hypoxia and subclinical hypovolemia in acutely ill patients [77, 78]. Tatevossian et al. [78] studied 48 severely injured patients during early resuscitation in the emergency department and operating room. The sequential patterns of $PtcO_2$ and $PtcCO_2$ were described throughout initial resuscitation. Nonsurvivors had lower $PtcO_2$ values and higher $PtcCO_2$ values than survivors. These differences were evident even early after the patient's arrival. The authors reported a critical tissue perfusion threshold of $PtcO_2$ 50 mmHg for more than 60 min and $PtcCO_2$ 60 mmHg for more than 30 min. Patients who failed to avoid these critical thresholds had 89% to 100% mortality. This technology has not gained widespread acceptance in clinical practice as the time needed for calibration limits its early use in the emergency department, and critical $PtcO_2$ and $PtcCO_2$ values have not been established.

Sublingual capnometry

Measurement of the tissue-arterial CO_2 tension gradient has been used to reflect the adequacy of tissue perfusion. The gastric and ileal mucosal CO_2 clearance is been the primary reference for measurements of regional PCO_2 gradient during circulatory shock [79]. The regional PCO_2 gradient represents the balance between regional CO_2 production and clearance. During tissue hypoxia CO_2 is produced by hydrogen anions buffered by tissue bicarbonate, which adds to the amount of CO_2 produced by normal oxidative metabolism. The amount of CO_2 produced, either aerobically or because of tissue hypoxia, will be cleared if blood flow is maintained. In low flow states CO_2 increases as a result of stagnation phenomenon [80]. Gastric tonometry is a technique that can be used to assess the adequacy of gut mucosal blood flow to metabolism. The methodological limitations of gastric tonometry required a search for a tissue in which PCO_2 can be measured easily in a noninvasive approach. Comparable decreases in blood flow during circulatory shock have been also demonstrated in the sublingual tissue PCO_2 ($PslCO_2$) [81, 82]. The currently available system for measuring $PslCO_2$ consists of a disposable PCO_2 sensor and a battery powered handheld instrument. The instrument uses fiberoptic technology to transmit light through the sensor placed between the tongue and the

sublingual mucosa. Carbon dioxide diffuses across a semipermeable membrane of the sensor and into a fluorescent dye solution. The dye emits light that is proportional to the amount of CO_2 present. This light intensity is analyzed by the instrument and displayed as a numeric $PslCO_2$ value.

Clinical studies have suggested that $PslCO_2$ is a reliable marker of tissue hypoperfusion [83, 84, 85, 86]. Weil et al. [86] applied $PslCO_2$ in 46 patients with acutely life threatening illness or injuries admitted to the emergency department or ICU. In this study 26 patients with physical signs of circulatory shock and high blood lactate levels had higher $PslCO_2$ values, and a $PslCO_2$ threshold value of 70 mmHg was predictive for the severity of the circulatory failure. Similarly as PCO_2 in the gut mucosal, $PslCO_2$ is also influenced by $PaCO_2$ [87]. Hence the gradient between $PslCO_2$ and $PaCO_2$ (Psl-aCO_2) is more specific for tissue hypoperfusion. This was shown in the study by Marik and Bankov [85] who determined the prognostic value of sublingual capnometry in 54 hemodynamic unstable critically ill patients. In this study Psl-aCO_2 was a sensitive marker for tissue perfusion and a useful endpoint for the titration of goal-directed therapy. Psl-aCO_2 differentiated better than $PslCO_2$ alone between survivors and nonsurvivors, and a difference of more than 25 mmHg indicated a poor prognosis. One limitation of this technique includes the necessity of blood gas analysis to obtain $PaCO_2$. In addition, normal vs. pathological Psl-aCO_2 values are not well defined.

Conclusion

The conventional systemic hemodynamic and oxygenation parameters are neither specific nor sensitive enough to detect regional hypoperfusion. In clinical practice a more complete evaluation of tissue oxygenation can be achieved by adding noninvasive assessment of perfusion in peripheral tissues to global parameters. Noninvasive monitoring of peripheral perfusion could be a complementary approach that allows very early application throughout the hospital, including the emergency department, operating room, and hospital wards. Such approach can be applied using both simple physical examination and new current technologies, as discussed above. Although these methods may reflect variations in peripheral perfusion with certain accuracy, more studies are needed to define the precise role of such methods in the management of the critically ill patients. Finally, evidence for clinical and cost effectiveness of these methods is an important aspect that needs a formal technology assessment.

References

1. Bakker J, Coffernils M, Leon M, Gris P, Vincent J-L (1991) Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest 99:956–962
2. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166:98–104
3. Rady MY, Rivers EP, Nowak RM (1996) Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. Am J Emerg Med 14:218–225
4. Shoemaker WC, Appel PL, Kram HB, Nathan RC, Thompson JL (1988) Multicomponent noninvasive physiologic monitoring of circulatory function. Crit Care Med 16:482–490
5. Siegemund M, van Bommel J, Ince C (1999) Assessment of regional tissue oxygenation. Intensive Care Med 25:1044–1060
6. Tibby SM, Hatherill M, Murdoch IA (1999) Capillary refill and core-peripheral temperature gap as indicators of haemodynamic status in paediatric intensive care patients. Arch Dis Child 80:163–166
7. Bailey JM, Levy JH, Kopel MA, Tobia V, Grabenkort WR (1990) Relationship between clinical evaluation of peripheral perfusion and global hemodynamics in adults after cardiac surgery. Crit Care Med 18:1353–1356
8. Schriger DL, Baraff L (1988) Defining normal capillary refill: variation with age, sex, and temperature. Ann Emerg Med 17:932–935
9. Kaplan LJ, McPartland K, Santora TA, Trooskin SZ (2001) Start with a subjective assessment of skin temperature to identify hypoperfusion in intensive care unit patients. J Trauma 50:620–627
10. Schriger DL, Baraff L (1991) Capillary refill: is it a useful predictor of hypovolemic states? Ann Emerg Med 20:601–605
11. Steiner MJ, DeWalt DA, Byerley JS (2004) Is this child dehydrated? JAMA 291:2746–2754
12. Champion HR, Sacco WJ, Carnazzo AJ, Copes W, Fouty WJ (1981) Trauma score. Crit Care Med 9:672–676
13. Hasdai D, Holmes DR Jr, Califf RM, Thompson TD, Hochman JS, Pfisterer M, Topol EJ (1999) Cardiogenic shock complicating acute myocardial infarction: predictors of death. GUSTO Investigators. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. Am Heart J 138:21–31
14. McGee S, Abernethy WB, III, Simel DL (1999) Is this patient hypovolemic? JAMA 281:1022–1029
15. Joly HR, Weil MH (1969) Temperature of the great toe as an indication of the severity of shock. Circulation 39:131–138
16. Ibsen B (1967) Treatment of shock with vasodilators measuring temperature of the great toe: ten years experience in 150 cases. Dis Chest 52:425
17. Guyton AC (1996) Body temperature, temperature regulation, and fever. In: Guyton AC, Hall JE (eds) Textbook of medical physiology. Saunders, Philadelphia, pp 911–922
18. Ross BA, Brock L, Aynsley-Green A (1969) Observations on central and peripheral temperatures in the understanding and management of shock. Br J Surg 56:877–882

19. Curley FJ, Smyrnios NA (2003) Routine monitoring of critically ill patients. In: Irwin RS, Cerra FB, Rippe JM (eds) Intensive care medicine. Lippincott Williams & Wilkins, New York, pp 250–270
20. Ibsen B (1966) Further observations in the use of air-conditioned rooms in the treatment of hyperthermia and shock. Acta Anaesthesiol Scand Suppl 23:565–570
21. Rubinstein EH, Sessler DI (1990) Skin-surface temperature gradients correlate with fingertip blood flow in humans. Anesthesiology 73:541–545
22. Sessler DI (2003) Skin-temperature gradients are a validated measure of fingertip perfusion. Eur J Appl Physiol 89:401–402
23. House JR, Tipton MJ (2002) Using skin temperature gradients or skin heat flux measurements to determine thresholds of vasoconstriction and vasodilatation. Eur J Appl Physiol 88:141–145
24. Brock L, Skinner JM, Manders JT (1975) Observations on peripheral and central temperatures with particular reference to the occurrence of vasoconstriction. Br J Surg 62:589–595
25. Ruiz CE, Weil MH, Carlson RW (1979) Treatment of circulatory shock with dopamine. Studies on survival. JAMA 242:165–168
26. Ryan CA, Soder CM (1989) Relationship between core/peripheral temperature gradient and central hemodynamics in children after open heart surgery. Crit Care Med 17:638–640
27. Vincent JL, Moraine JJ, van der LP (1988) Toe temperature versus transcutaneous oxygen tension monitoring during acute circulatory failure. Intensive Care Med 14:64–68
28. Henning RJ, Wiener F, Valdes S, Weil MH (1979) Measurement of toe temperature for assessing the severity of acute circulatory failure. Surg Gynecol Obstet 149:1–7
29. Murdoch IA, Qureshi SA, Mitchell A, Huggon IC (1993) Core-peripheral temperature gradient in children: does it reflect clinically important changes in circulatory haemodynamics? Acta Paediatr 82:773–776
30. Butt W, Shann F (1991) Core-peripheral temperature gradient does not predict cardiac output or systemic vascular resistance in children. Anaesth Intensive Care 19:84–87
31. Woods I, Wilkins RG, Edwards JD, Martin PD, Faragher EB (1987) Danger of using core/peripheral temperature gradient as a guide to therapy in shock. Crit Care Med 15:850–852
32. Sessler DI (2000) Perioperative heat balance. Anesthesiology 92:578–596
33. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
34. Vincent JL (1996) End-points of resuscitation: arterial blood pressure, oxygen delivery, blood lactate, or..? Intensive Care Med 22:3–5
35. Flewelling R (2000) Noninvasive optical monitoring. In: Bronzino JD (ed) The biomedical engineering handbook. Springer, Berlin Heidelberg New York, pp 1–10
36. Lima AP, Beelen P, Bakker J (2002) Use of a peripheral perfusion index derived from the pulse oximetry signal as a noninvasive indicator of perfusion. Crit Care Med 30:1210–1213
37. Kurz A, Xiong J, Sessler DI, Dechert M, Noyes K, Belani K (1995) Desflurane reduces the gain of thermoregulatory arteriovenous shunt vasoconstriction in humans. Anesthesiology 83:1212–1219
38. Lima A, Bakker J (2004) The peripheral perfusion index in reactive hyperemia in critically ill patients. Crit Care 8:S27–P53
39. De Felice C, Latini G, Vacca P, Kopotic RJ (2002) The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr 161:561–562
40. Van Beekvelt MC, Colier WN, Wevers RA, Van Engelen BG (2001) Performance of near-infrared spectroscopy in measuring local O (2) consumption and blood flow in skeletal muscle. J Appl Physiol 90:511–519
41. De Blasi RA, Ferrari M, Natali A, Conti G, Mega A, Gasparetto A (1994) Noninvasive measurement of forearm blood flow and oxygen consumption by near-infrared spectroscopy. J Appl Physiol 76:1388–1393
42. Edwards AD, Richardson C, van der ZP, Elwell C, Wyatt JS, Cope M, Delpy DT, Reynolds EO (1993) Measurement of hemoglobin flow and blood flow by near-infrared spectroscopy. J Appl Physiol 75:1884–1889
43. Taylor DE, Simonson SG (1996) Use of near-infrared spectroscopy to monitor tissue oxygenation. New Horiz 4:420–425
44. Rhee P, Langdale L, Mock C, Gentilello LM (1997) Near-infrared spectroscopy: continuous measurement of cytochrome oxidation during hemorrhagic shock. Crit Care Med 25:166–170
45. Puyana JC, Soller BR, Zhang S, Heard SO (1999) Continuous measurement of gut pH with near-infrared spectroscopy during hemorrhagic shock. J Trauma 46:9–15
46. Beilman GJ, Myers D, Cerra FB, Lazaron V, Dahms RA, Conroy MJ, Hammer BE (2001) Near-infrared and nuclear magnetic resonance spectroscopic assessment of tissue energetics in an isolated, perfused canine hind limb model of dysoxia. Shock 15:392–397
47. Crookes BA, Cohn SM, Burton EA, Nelson J, Proctor KG (2004) Noninvasive muscle oxygenation to guide fluid resuscitation after traumatic shock. Surgery 135:662–670
48. McKinley BA, Marvin RG, Cocanour CS, Moore FA (2000) Tissue hemoglobin O2 saturation during resuscitation of traumatic shock monitored using near infrared spectrometry. J Trauma 48:637–642
49. Cairns CB, Moore FA, Haenel JB, Gallea BL, Ortner JP, Rose SJ, Moore EE (1997) Evidence for early supply independent mitochondrial dysfunction in patients developing multiple organ failure after trauma. J Trauma 42:532–536
50. Muellner T, Nikolic A, Schramm W, Vecsei V (1999) New instrument that uses near-infrared spectroscopy for the monitoring of human muscle oxygenation. J Trauma 46:1082–1084
51. Arbabi S, Brundage SI, Gentilello LM (1999) Near-infrared spectroscopy: a potential method for continuous, transcutaneous monitoring for compartmental syndrome in critically injured patients. J Trauma 47:829–833
52. Giannotti G, Cohn SM, Brown M, Varela JE, McKenney MG, Wiseberg JA (2000) Utility of near-infrared spectroscopy in the diagnosis of lower extremity compartment syndrome. J Trauma 48:396–399
53. Girardis M, Rinaldi L, Busani S, Flore I, Mauro S, Pasetto A (2003) Muscle perfusion and oxygen consumption by near-infrared spectroscopy in septic-shock and non-septic-shock patients. Intensive Care Med 29:1173–1176
54. Groner W, Winkelman JW, Harris AG, Ince C, Bouma GJ, Messmer K, Nadeau RG (1999) Orthogonal polarization spectral imaging: a new method for study of the microcirculation. Nat Med 5:1209–1212
55. De Backer D, Dubois MJ, Creteur J, Vincent J-L (2001) Effects of dobutamine on microcirculatory alterations in patients with septic shock. Intensive Care Med 27:S237
56. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360:1395–1396

57. De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL (2004) Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 147:91–99
58. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL (2004) Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 32:1825–1831
59. Jin X, Weil MH, Sun S, Tang W, Bisera J, Mason EJ (1998) Decreases in organ blood flows associated with increases in sublingual PCO2 during hemorrhagic shock. J Appl Physiol 85:2360–2364
60. Schabauer AM, Rooke TW (1994) Cutaneous laser Doppler flowmetry: applications and findings. Mayo Clin Proc 69:564–574
61. Farkas K, Fabian E, Kolossvary E, Jarai Z, Farsang C (2003) Noninvasive assessment of endothelial dysfunction in essential hypertension: comparison of the forearm microvascular reactivity with flow-mediated dilatation of the brachial artery. Int J Angiol 12:224–228
62. Koller A, Kaley G (1990) Role of endothelium in reactive dilation of skeletal muscle arterioles. Am J Physiol 259:H1313–H1316
63. Morris SJ, Shore AC, Tooke JE (1995) Responses of the skin microcirculation to acetylcholine and sodium nitroprusside in patients with NIDDM. Diabetologia 38:1337–1344
64. Warren JB (1994) Nitric oxide and human skin blood flow responses to acetylcholine and ultraviolet light. FASEB J 8:247–251
65. Blaauw J, Graaff R, van Pampus MG, van Doormaal JJ, Smit AJ, Rakhorst G, Aarnoudse JG (2005) Abnormal endothelium-dependent microvascular reactivity in recently preeclamptic women. Obstet Gynecol 105:626–632
66. Hartl WH, Gunther B, Inthorn D, Heberer G (1988) Reactive hyperemia in patients with septic conditions. Surgery 103:440–444
67. Young JD, Cameron EM (1995) Dynamics of skin blood flow in human sepsis. Intensive Care Med 21:669–674
68. Sair M, Etherington PJ, Peter WC, Evans TW (2001) Tissue oxygenation and perfusion in patients with systemic sepsis. Crit Care Med 29:1343–1349
69. Hasibeder W, Haisjackl M, Sparr H, Klaunzer S, Horman C, Salak N, Germann R, Stronegger WJ, Hackl JM (1991) Factors influencing transcutaneous oxygen and carbon dioxide measurements in adult intensive care patients. Intensive Care Med 17:272–275
70. Carter B, Hochmann M, Osborne A, Nisbet A, Campbell N (1995) A comparison of two transcutaneous monitors for the measurement of arterial PO2 and PCO2 in neonates. Anaesth Intensive Care 23:708–714
71. Phan CQ, Tremper KK, Lee SE, Barker SJ (1987) Noninvasive monitoring of carbon dioxide: a comparison of the partial pressure of transcutaneous and end-tidal carbon dioxide with the partial pressure of arterial carbon dioxide. J Clin Monit 3:149–154
72. Tremper KK, Shoemaker WC (1981) Transcutaneous oxygen monitoring of critically ill adults, with and without low flow shock. Crit Care Med 9:706–709
73. Shoemaker WC, Wo CC, Bishop MH, Thangathurai D, Patil RS (1996) Noninvasive hemodynamic monitoring of critical patients in the emergency department. Acad Emerg Med 3:675–681
74. Tremper KK, Barker SJ (1987) Transcutaneous oxygen measurement: experimental studies and adult applications. Int Anesthesiol Clin 25:67–96
75. Reed RL, Maier RV, Landicho D, Kenny MA, Carrico CJ (1985) Correlation of hemodynamic variables with transcutaneous PO2 measurements in critically ill adult patients. J Trauma 25:1045–1053
76. Tremper KK, Shoemaker WC, Shippy CR, Nolan LS (1981) Transcutaneous PCO2 monitoring on adult patients in the ICU and the operating room. Crit Care Med 9:752–755
77. Waxman K, Sadler R, Eisner ME, Applebaum R, Tremper KK, Mason GR (1983) Transcutaneous oxygen monitoring of emergency department patients. Am J Surg 146:35–38
78. Tatevossian RG, Wo CC, Velmahos GC, Demetriades D, Shoemaker WC (2000) Transcutaneous oxygen and CO2 as early warning of tissue hypoxia and hemodynamic shock in critically ill emergency patients. Crit Care Med 28:2248–2253
79. Fiddian-Green RG, Baker S (1987) Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. Crit Care Med 15:153–156
80. De Backer D, Creteur J (2003) Regional hypoxia and partial pressure of carbon dioxide gradients: what is the link? Intensive Care Med 29:2116–2118
81. Nakagawa Y, Weil MH, Tang W, Sun S, Yamaguchi H, Jin X, Bisera J (1998) Sublingual capnometry for diagnosis and quantitation of circulatory shock. Am J Respir Crit Care Med 157:1838–1843
82. Povoas HP, Weil MH, Tang W, Moran B, Kamohara T, Bisera J (2000) Comparisons between sublingual and gastric tonometry during hemorrhagic shock. Chest 118:1127–1132
83. Rackow EC, O'Neil P, Astiz ME, Carpati CM (2001) Sublingual capnometry and indexes of tissue perfusion in patients with circulatory failure. Chest 120:1633–1638
84. Marik PE (2001) Sublingual capnography: a clinical validation study. Chest 120:923–927
85. Marik PE, Bankov A (2003) Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. Crit Care Med 31:818–822
86. Weil MH, Nakagawa Y, Tang W, Sato Y, Ercoli F, Finegan R, Grayman G, Bisera J (1999) Sublingual capnometry: a new noninvasive measurement for diagnosis and quantitation of severity of circulatory shock. Crit Care Med 27:1225–1229
87. Pernat A, Weil MH, Tang W, Yamaguchi H, Pernat AM, Sun S, Bisera J (1999) Effects of hyper- and hypoventilation on gastric and sublingual PCO (2). J Appl Physiol 87:933–937

François Jardin
Antoine Vieillard-Baron

Ultrasonographic examination of the venae cavae

There are two venae cavae in humans. The superior vena cava (SVC) comprises the connection of the left and right brachiocephalic veins and ends on the top of the right atrium, after entering the pericardium. The inferior vena cava (IVC) comprises the connection of the left and right iliac veins and ends on the floor of right atrium, after crossing the diaphragm. Whereas the SVC is an intrathoracic vessel, the IVC is an intraabdominal one, its short intrathoracic part being purely virtual. Both venae cavae provide venous return to the right heart, approx. 25% via the SVC and 75% via IVC [1, 2].

Ultrasonographic examination of the SVC can be performed by a transesophageal approach [3]. To remain open this collapsible vessel requires a distending pressure greater than the critical pressure producing collapse, i.e. its closing pressure. Because lung inflation increases pleural pressure more than right atrial pressure, the distending pressure of the SVC, i.e. right atrial pressure minus pleural pressure, is reduced by lung inflation, and may become insufficient to maintain the vessel open in a hypovolemic patient (Fig. 1). This collapsible vessel can be compared to a "Starling resistor." The influence of SVC zone conditions on respiratory changes in SVC diameter is illustrated with clinical examples in Fig. 2.

We have thus proposed to use the SVC collapsibility index, calculated as maximal expiratory diameter minus minimal inspiratory diameter, divided by maximal expiratory diameter, as an index of fluid responsiveness in mechanically ventilated patients exhibiting circulatory failure [4]. This requires recording of a long-axis view of the vessel using a multiplane transesophageal probe, by coupling motion mode with two-dimensional mode. Our measurements in a group of 66 patients with septic shock as reported in a previous issue, demonstrated that a SVC collapsibility index higher than 36% predicts a positive response to volume expansion, marked by a significant increase in Doppler cardiac output, with 90% sensitivity and 100% specificity [4]. We also found a bimodal distribution for the SVC collapsibility index: most patients exhibited either a partial or complete collapse of the vessel or the absence of significant change in its diameter during inflation. This confirms our hypothesis that the SVC can be compared to a "Starling resistor" which obeys the all-or-nothing law.

Ultrasonographic examination of the IVC can be performed by a transthoracic, subcostal approach [5, 6]. Mea-

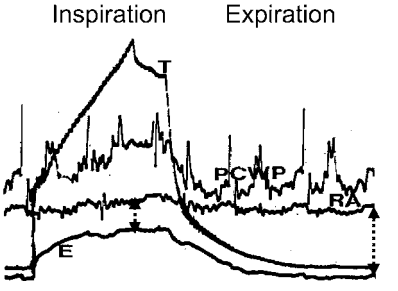


Fig. 1 Simultaneous recordings of tracheal pressure (*T*), pulmonary capillary wedge pressure (*PCWP*), right atrial pressure (*RA*), and esophageal pressure (*E*, as a surrogate for pleural pressure). During lung inflation (inspiration) pleural pressure increases more than right atrial (or central venous) pressure, leading to an inspiratory decrease in venous distending pressure (*arrows*)

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_33, © Springer-Verlag Berlin Heidelberg 2009

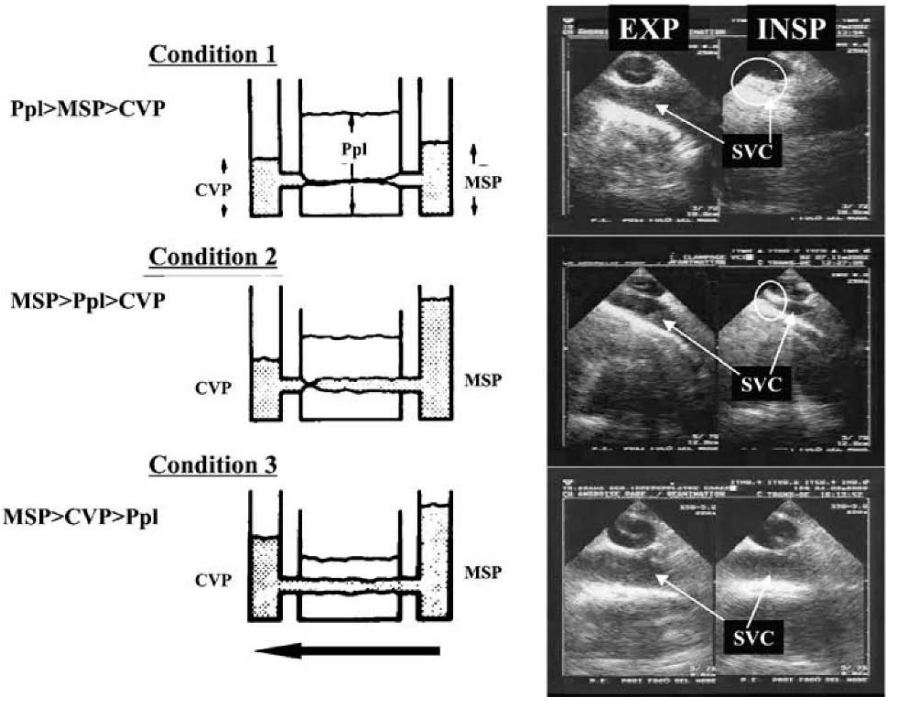


Fig. 2 *Left* Schematic representation of the superior vena cava (*SVC*) as a Starling resistor, with an inflow pressure (the upper body mean systemic pressure, *MSP*), an outflow pressure (the central venous pressure, itCVP), and an external pressure (the pleural pressure, *Ppl*). *Right panel* Cli nical examples illustrating the three zone conditions. *Top panel* (condition 1) Inflow pressure becomes lower than the pleural pressure during lung inflation, which produces a complete collapse of the whole vessel. This setting is illustrated by ultrasonographic examination of the venae cavae in a hypovolemic patient exhibiting low MSP. *Middle panel* (condition 2) the outflow pressure is reduced, and lung inflation produces a localized collapse at entry into the right atrium. This setting is illustrated (*right*) by ultrasonographic examination after clamping of the inferior vena cava during a surgical procedure, a maneuver which suddenly decreases CVP but does not change MSP. *Bottom panel* (condition 3) Outflow pressure is much greater than the external pressure, and the SVC remains fully open during lung inflation. This setting is illustrated (*right*) by ultrasonographic examination of the venae cavae after volume expansion

surement of IVC diameter in different positions has proven useful in separating normal subjects from patients with elevated right atrial pressure [7]. In their famous study of venous return Guyton et al. [8] observed in dogs that negative right atrial pressure from 0 down to –4 mm Hg increases venous return, but then beyond –4mm Hg, further increase in the negative pressure causes no more increase in the venous return. Guyton et al. explained this failure by the collapse of the IVC when entering the thoracic cavity, illustrating the inability of a collapsible vessel to transmit a negative pressure. To our knowledge, the first demonstration of the reality of this phenomenon in humans was provided by our group in asthmatic patients [9] (Fig. 3).

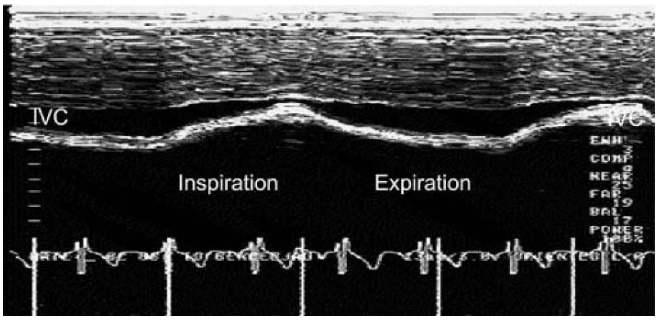


Fig. 3 An example of M mode echocardiography of the inferior vena cava (*IVC*) in spontaneously breathing asthmatic patients. Note the short duration of inspiration, accompanied by a collapse of the vessel, and the increased duration of the expiration (compare Fig. 4, above)

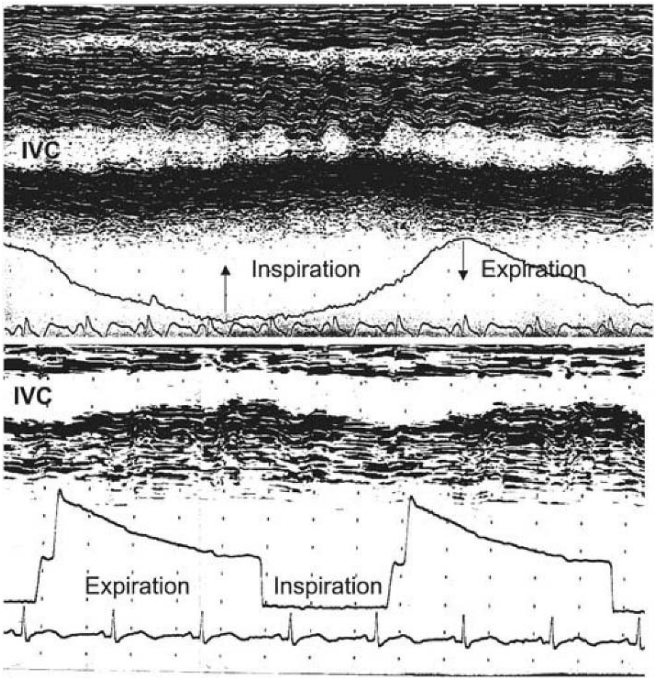


Fig. 4 M mode echocardiography of the inferior vena cava (*IVC*) in a spontaneously breathing healthy volunteer (*above*) and in a mechanically ventilated patient (*below*). Cyclic changes in IVC diameters are opposite, the largest value being observed during expiration in spontaneous breathing, and during inspiration in positive pressure breathing

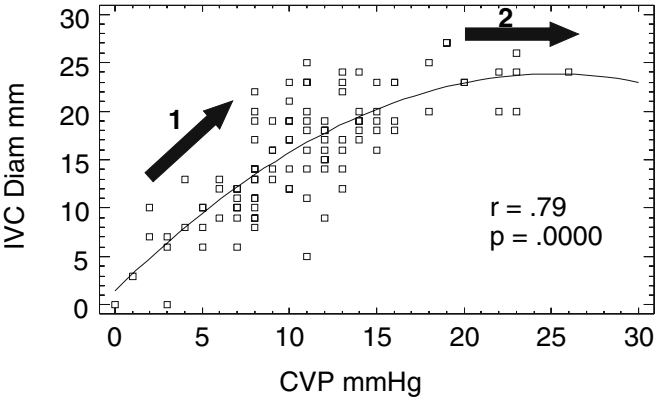


Fig. 5 Simultaneous measurement of central venous pressure (*CVP*) and inferior vena cava diameter (*IVC diam*) recorded at end-expiration in 108 mechanically ventilated patients. The pressure/diameter relationship for the vessel is characterized by an initial ascending part (*arrow 1*), where the index of compliance (slope of diameter/pressure curve) does not change, and a final horizontal part (*arrow 2*), where the index of compliance progressively decreases, reflecting distension

In a healthy subject breathing spontaneously, cyclic changes in pleural pressure, which are transmitted to the right atrial pressure, produce cyclic changes in venous return, with an inspiratory acceleration, inducing an inspiratory decrease in IVC diameter of approx. 50% (Fig. 4, *above*) [5]. This cyclic change in vena cava diameter is abolished, however, when the vessel is dilated because, although some inspiratory increase in venous return persists, the vessel actually stays on the horizontal part of its pressure-diameter relationship (Fig. 5). This is the case when cardiac tamponade [10] or severe right ventricular failure is present [6].

In a mechanically ventilated patient, the inspiratory phase produces an increase in pleural pressure, which is transmitted to the right atrial pressure, thus reducing the venous return. As a result respiratory changes in IVC diameter are reversed, compared with those observed during spontaneous breathing, with an inspiratory increase, and an expiratory decrease (Fig. 4, *below*). However, regarding spontaneous breathing these changes are abolished by vena cava dilatation produced by a high volume status, and/or a high right atrial pressure, the inferior vena cava staying on the horizontal part of its pressure-diameter relationship (Fig. 5). Cyclic respiratory changes in IVC diameter can thus be observed only with a normal or low volume status in a mechanically ventilated patient. In the past, these changes were poorly correlated with atrial pressure during mechanical ventilation [11]. Lack of IVC diameter variation in a mechanically ventilated patient exhibiting circulatory failure rules out the patient's ability to respond fluid in more than 90% of cases [12].

Feissel et al. [12] first proposed the use of cyclic respiratory changes in IVC diameter to detect fluid responsiveness in a mechanically ventilated patient, and their original findings are reported in a recent issue. Expressing respiratory variability in IVC diameter as maximal inspiratory diameter minus minimal expiratory diameter, divided by the average value of the two diameters, they found that a 12% increase in inferior vena cava diameter during lung inflation allowed discrimination between responders and non-responders to volume loading, with a positive predictive value of 93% and a negative predictive value of 92% [12]. The great merit of this work is to propose a noninvasive parameter to evaluate volume loading. Moreover, this echocardiographic measurement is very easy at the bedside, and requires only minimal experience in echocardiography (Fig. 6). The findings of Feissel et al. are confirmed in an identical study by Barbier et al. [13], which appears in the same issue. It remains to be seen whether this index is still reliable in patients with a significant increase in intra-abdominal pressure, which could limit IVC diameter variations.

Another phenomenon occasionally observed in the IVC during mechanical ventilation is backward flow, which is not caused by tricuspid regurgitation but by cyclic compression of the right atrium by lung inflation. Such a sudden compression boosts blood backward from the right atrium to the IVC and does not concern tricuspid valve competency [14]. This backward flow might explain in part the inaccuracy of the thermodilution method in

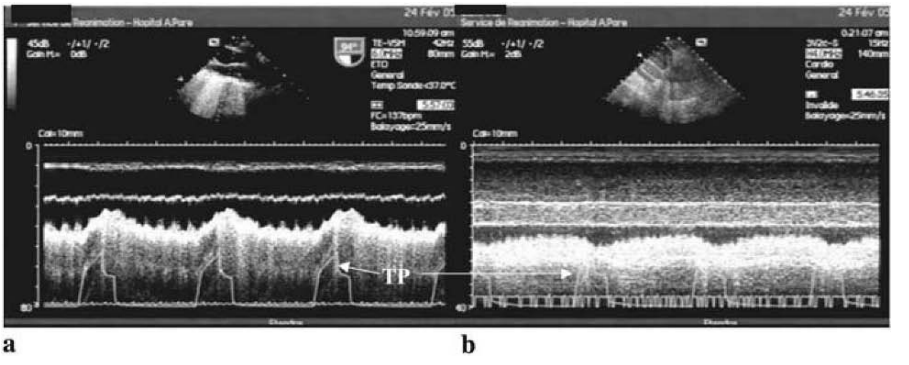


Fig. 6a,b Ultrasonographic examination of the superior (**a**) and inferior (**b**) venae cavae in the same mechanically ventilated patient, who exhibited hypotension. Transesophageal echocardiography demonstrated a partial collapse of the SVC at each inflation, whereas echocardiography by a subcostal approach demonstrated a marked increase in IVC diameter. After blood volume expansion cardiac index significantly increased, hypotension was corrected, and variations in vena cava diameter disappeared. TP: tracheal pressure

measuring cardiac output in mechanically ventilated patients [14].

In conclusion, ultrasonographic examination of the venae cavae provides new and accurate indices of fluid responsiveness in mechanically ventilated patients exhibiting circulatory failure. In our opinion, a complete evaluation of volume status in these patients should include both IVC and SVC examination.

References

1. Mellander S, Johanson B (1968) Control of resistance, exchange and capacitance functions in the peripheral circulation. Pharmacol Rev 20:117–196
2. Rushmer R (1970) Peripheral vascular control. In Rushmer R (ed) Cardiovascular dynamics. WB Saunders, Philadelphia, pp 113–147
3. Vieillard-Baron A, Augarde R, Prin S, Page B, Beauchet A, Jardin F (2001) Influence of superior vena caval zone conditions on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 95:1083–1088
4. Vieillard-Baron A, Chergui K, Rabiller A, Peyrouset O, Page B, Beauchet A, Jardin F (2004) Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. Intensive Care Med 30:1734–1739
5. Mintz G, Kotler M, Parry W, Iskandrian A, Kane S (1981) Real-time inferior vena caval ultrasonography: normal and abnormal findings and its use in assessing right heart function. Circulation 64:1018–1025
6. Moreno F, Hagan A, Holmen J, Pryor A, Strickland R, Castle H (1984) Evaluation of size and dynamics of the inferior vena cava as an index of right-sided cardiac function. Am J Cardiol 52:579–585
7. Nakao S, Come P, McKay R, Ransil B (1987) Effects of positional changes on inferior vena caval size and dynamics and correlations with right-sided cardiac pressures. Am J Cardiol 59:125–132
8. Guyton A, Lindsey A, Abernathy A, Richardson T (1957) Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol 189:609–615
9. Jardin F, Farcot JC, Boisante L, Prost JF, Guéret P, Bourdarias JP (1982) Mechanism of paradoxal pulse in bronchial asthma. Circulation 66:887–894
10. Himelman R, Kircher B, Rockey D, Schiller N (1988) Inferior vena cava plethora with blunted respiratory response: a sensitive echocardiographic sign of cardiac tamponade. J Am Coll Cardiol 12:1470–1477
11. Jue J, Chung W, Schiller N (1992) Does inferior vena cava size predict right atrial pressure in patients receiving mechanical ventilation. J Am Soc Echocardiogr 5:613–619
12. Feissel M, Michard F, Faller JP, Teboul JL (2004) The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med 30:1834–1837
13. Barbier C, Loubières Y, Schmit C, Hayon J, Ricôme JL, Jardin F, Vieillard-Baron A (2004) Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. Intensive Care Med 30:1740–1746
14. Jullien T, Valtier B, Hongnat JM, Dubourg O, Bourdarias JP, Jardin F (1995) Incidence of tricuspid regurgitation and vena caval backward flow in mechanically ventilated patients. A color Doppler and contrast echocardiographic study. Chest 107:488–493

Xavier Monnet
Jean-Louis Teboul

Passive leg raising

Abstract *Objective:* To assess whether the passive leg raising test can help in predicting fluid responsiveness. *Design:* Nonsystematic review of the literature. *Results:* Passive leg raising has been used as an endogenous fluid challenge and tested for predicting the hemodynamic response to fluid in patients with acute circulatory failure. This is now easy to perform at the bedside using methods that allow a real time measurement of systolic blood flow. A passive leg raising induced increase in descending aortic blood flow of at least 10% or in echocardiographic subaortic flow of at least 12% has been shown to predict fluid responsiveness. Importantly, this prediction remains very valuable in patients with cardiac arrhythmias or spontaneous breathing activity. *Conclusions:* Passive leg raising allows reliable prediction of fluid responsiveness even in patients with spontaneous breathing activity or arrhythmias. This test may come to be used increasingly at the bedside since it is easy to perform and effective, provided that its effects are assessed by a real-time measurement of cardiac output.

Keywords Fluid responsiveness · Passive leg raising · Volume expansion · Cardiac preload

Physiological changes in hemodynamics during PLR

Lifting the legs in the event of circulatory collapse is a rescue maneuver that has been used for years by first-aid rescuers. Passive leg raising (PLR) has recently gained interest as a test for monitoring functional hemodynamic and assessing fluid responsiveness since it is a simple way to transiently increase cardiac preload. Lifting the legs passively from the horizontal plane in a lying subject obviously induces a gravitational transfer of blood from the lower part of the body toward the central circulatory compartment and especially toward the cardiac cavities. Using radiolabeled erythrocytes a physiological study in humans demonstrated that the volume of blood contained in the calves was reduced during PLR, a reduction corresponding to the transfer of approx. 150 ml blood [1]. Thus PLR recruits a part of blood contained in the venous reservoir and converts unstressed volume to stressed volume. In turn PLR increases right cardiac preload, likely through an increase in the mean circulatory pressure which is the driving pressure for venous return. If the right ventricle is preload responsive, the increase in systemic venous return results in an increase in right cardiac output and hence in the left ventricular filling. Clinical studies conducted in various hemodynamic conditions have reported an increase in pulmonary artery occlusion pressure [2–5], left ventricular end-diastolic dimension [2, 6], E wave of the mitral flow [2, 3, 7], and left ventricular ejection time [8] during PLR, supporting the evidence that the volume of

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_34,

blood transferred to the heart during PLR is sufficient to increase left cardiac preload. Nonetheless, if the preload reserve of the right heart is limited, the increase in right cardiac preload should not result in an increased flow toward the left ventricle, and thus PLR should not increase left-side preload in such cases. The response to PLR of the markers of right preload (e. g., central venous pressure) and of left preload may therefore differ.

As a result of the increase in left ventricular preload PLR may ultimately result in an increase in cardiac output, depending on the degree of left ventricular preload reserve. Interestingly, Wong and colleagues [9] reported that the increase in stroke volume induced by a 45° leg lifting in healthy subjects was of larger magnitude after withdrawal of 500 ml blood, suggesting that PLR affects cardiac output differently according to the central volume status and thus the degree of cardiac preload reserve. An important point is that the PLR-induced increase in cardiac preload vanishes completely when the legs are returned to horizontal position [5, 8, 10, 11]. Therefore PLR can be considered as a brief and completely reversible "self-volume challenge". It must also be stressed that the effect of PLR on cardiac output—when it occurs—is not always sustained when the leg elevation is prolonged. In septic shock patients capillary leak may account for this attenuation. In a study including critically ill patients with circulatory failure we observed that the increase in the blood flow of the descending thoracic aorta induced by PLR in "preload-dependent" patients occurred in few seconds and was maximal approx. 1 min after starting the PLR maneuver [8]. In patients who did not have a sustained response to PLR the response to volume infusion also was not sustained. Thus the hemodynamic effects of PLR should be assessed during the time frame of 30–90 s after the onset of the test.

Postural changes during PLR are important to consider. If the trunk is in the semirecumbent position before the maneuver, PLR consists in pivoting the entire body, with the legs lifted up and the trunk ultimately in the horizontal position. With this method one would expect that PLR induces the transfer of a larger blood volume than if the trunk is initially lying horizontally since not only the venous blood of the legs but also that contained into the large splanchnic compartment is mobilized in such a case (Fig. 1; Electronic Supplementary Material, ESM). This should increase the total amount of blood that is mobilized during the postural maneuver.

The response to PLR may also depend upon the ability of the venous reservoir to be recruited. In a patient who is vasoconstricted because of hypovolemic/cardiogenic shock the venous reservoir is likely reduced, and the volume recruited by the PLR would be expected to be less. By contrast, in a patient with a vasodilatory state such as septic shock a higher unstressed volume is expected to be recruited by PLR. Based on this hypothesis, PLR should theoretically increase right ventricle preload less in patients with hypovolemic than in those with septic shock. However, in volume-depleted patients with high volume responsiveness even a moderate increase in preload can result in a significant change in cardiac output. In support of this, the increase in cardiac output in normal subjects in response to PLR has been shown to be increased after blood removal [12].

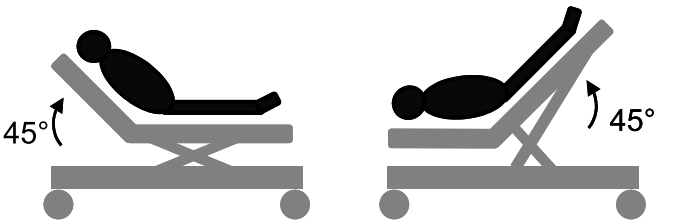


Fig. 1 Postural change during passive leg raising. If at baseline the patient is not lying horizontally but is in semirecumbent position, PLR consists of a simple pivoting of the entire bed. Compared to a case in which the trunk of the patient lies horizontally at baseline, this method is advantageous because (a) it does not change the hip angle, and (b) it may induce the transfer of a larger volume of blood

PLR for testing fluid responsiveness in the critically ill

Facing a hemodynamic failure, the clinician is often tempted to give fluid in order to increase cardiac output by fueling the reservoir in which the heart is pumping. However, fluid administration does not always result in cardiac output enhancement. This comes from the curvilinearity of the Frank–Starling relationship: if the heart is operating on the initial and steep part of the curve, it should have some preload reserve, and any increase in cardiac preload results in an increase in stroke volume. In this case the patient "responds" positively to fluid administration (Fig. 2). In contrast, if the heart is operating on the distal and flat part of the Frank–Starling curve (absence of preload reserve), no significant increase in stroke volume is expected from volume loading. In this case fluid administration may induce harmful effects (e. g., lung inflation, worsening of gas exchange in the case of pulmonary injury, worsening of tissue oxygen transfer) that would not be counterbalanced by any hemodynamic benefit. Thus the need has risen to find diagnostic tools for predicting which shocked patients will respond to fluid administration [13].

Predicting fluid responsiveness solely on the basis of measures of preload must be discouraged. Not only one but a family of Frank–Starling curves rely cardiac preload and stroke volume according to individual factors such as cardiac contractility (Fig. 2). Accordingly, a given value of preload could be associated with preload reserve in patients with normal cardiac contractility but with absence of preload reserve in the case of patients with profoundly

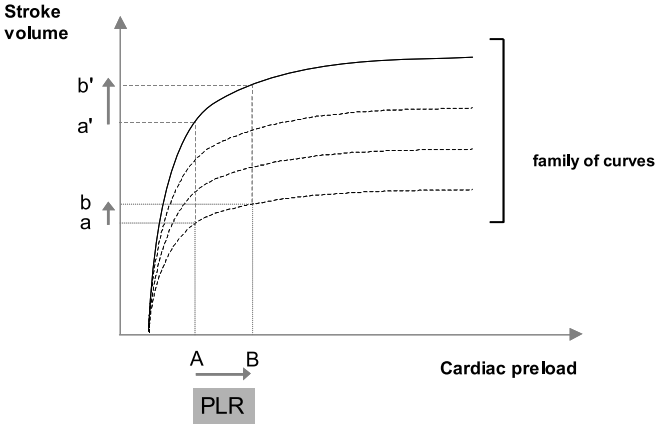


Fig. 2 Challenging the Frank–Starling curve with the passive leg raising (*PLR*). In patients with circulatory failure it is not possible to predict the response to volume administration because not just one but numerous curves rely stroke volume and cardiac preload. PLR induces a change in preload that enables to challenge the relationship. If the increase in cardiac preload occurring during the test (*from A to B*) produces a large increase in stroke volume (*from a' to b'*), preload responsiveness is likely and the patient should respond to fluid administration. If the increase in stroke volume during the test is of small amplitude (*from a to b*), preload responsiveness is unlikely and fluid administration should be avoided

impaired contractility because they are on the steep part of their cardiac function curve. Numerous studies now support the evidence that static measures of cardiac preload are not appropriate to assess preload reserve [14, 15]. In this regard cardiac filling pressures such as central venous pressure and pulmonary artery occlusion pressure cannot differentiate between patients responding and patients not responding to fluid administration [16]. Fluid responsiveness assessment must be rather based on the response to dynamic tests which induce transient changes in cardiac preload [17].

Since mechanical ventilation is able to induce cyclic changes in cardiac preload, the respiratory variation in stroke volume has been proposed to assess preload reserve [17]. Accordingly, the respiratory variations in surrogates of stroke volume such as arterial pulse pressure [18], Doppler subaortic flow [19], pulse contour derived stroke volume [20, 21], descending aortic blood flow [22], and even pulse oximetry wave [23] have been demonstrated to predict fluid responsiveness in the critically ill. Nonetheless, such heart–lung interaction indices can be used in only specific conditions, such as regular sinus cardiac rhythm and full adaptation of the patient to the ventilator as during deep sedation or coma. If not, the irregularity of the cardiac rhythm or of the respiratory cycle also account for variability in stroke volume such that fluid responsiveness can no longer be predicted by the variations in stroke volume [8, 24]. In patients with spontaneous ventilation respiratory variation in the central venous pressure has been proposed as an alternative [25]. Conflicting results have subsequently been reported [24], perhaps because the test is effective only in cases of no forced expiration [26].

PLR is an alternative means to predict the hemodynamic response to fluid administration since it can be used as a "self-volume challenge" at the bedside [27]. In mechanically ventilated patients fully adapted to their ventilator PLR-induced changes in stroke volume have been found to be closely correlated with the changes in stroke volume induced by a subsequent 300 ml colloid infusion [5]. Importantly, the hemodynamic changes induced by PLR are not affected by arrhythmias or by ventilator triggering. Therefore the PLR can be still used in circumstances where heart–lung interaction indices are misleading. In a study including 71 shocked patients monitored by esophageal Doppler we investigated whether the response of descending aortic blood flow to PLR predicts fluid responsiveness [8]. Interestingly, PLR increased the aortic flow time—a marker of left cardiac preload—to the same proportion in both responders and nonresponders, suggesting that this test actually performs as a volume challenge. The changes in the descending aortic blood observed during a PLR test were closely correlated with those induced by the subsequent volume expansion. Moreover, a PLR-induced increase in aortic blood flow by more than 10% predicted a fluid-induced increase in aortic blood flow by more than 15% (i. e., fluid responsiveness) with very good sensitivity and specificity [8] (Fig. 3). In the subgroup of patients fully adapted to their ventilator the response to PLR performed equally to pulse pressure respiratory variation in predicting volume responsiveness [8]. More importantly, in the subgroup of patients who triggered their ventilator or who experienced arrhythmias we found that the aortic blood flow response to PLR to predict fluid responsiveness retained its predictive value while pulse pressure variation was no longer reliable [8]. These findings emphasize the specific interest of PLR under conditions where heart–lung interactions

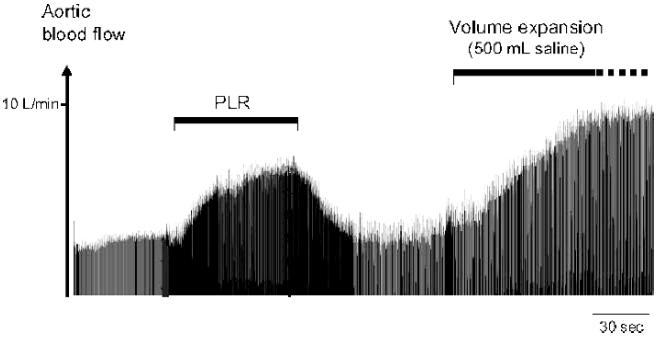


Fig. 3 Typical waveform of aortic blood flow during a passive leg raising (*PLR*) test and volume expansion in a patient with preload reserve. In this patient with an acute circulatory failure the increase in aortic blood flow observed during PLR can predict the positive response to volume expansion

indices cannot be interpretable. Recently two studies performed in patients with spontaneous breathing activity demonstrated that an increase in echocardiographic stroke volume by more than 12% in response to PLR well distinguished between responders and nonresponders to fluid administration [11, 28]. In addition, stroke volume response to PLR performed far better than static ultrasonographic indices of cardiac filling such as left ventricular end-diastolic area and Doppler estimates of left ventricular filling pressure [11].

As with any method for predicting response to fluid administration, the cutoff value found for the PLR effects should not be considered as a magic number. Furthermore, sensitivity and specificity values are not absolute. They should be interpreted differently depending upon the clinical context. For instance, the risk of giving fluid unduly may be more dangerous in patients with acute lung injury or acute respiratory distress syndrome. In these cases the physician should administer fluid if the effects of PLR on the cardiac output estimate are clearly above the proposed cutoff value.

Practical aspects of the PLR test

A simple way to perform PLR is to transfer the patient from the 45° semirecumbent to the PLR position by using the automatic pivotal motion of the patient's bed [8] (Fig. 1; see ESM). In addition to its ease of use, this method allows PLR to be performed rapidly without inducing hip flexion and femoral catheters motion. This is important since such procedures should avoid any pain-induced sympathetic stimulation that can result in erroneous interpretation of the hemodynamic effects of PLR. Accordingly, when performed in such a way, PLR did not increase heart rate, suggesting that no confusing sympathetic alteration occurred during the test [8]. Additionally, keeping the thorax in the horizontal position, and not lower, may avoid the risk of gastric inhalation. Nevertheless, it is reasonable to avoid PLR in patients with head trauma since it can increase the intracerebral pressure. Elastic compression stocking may also alter the venous volume recruited by the PLR [29].

Another important point concerns the conditions that must be fulfilled for correct measurement and interpretation of PLR effects. The first condition is that it be a real-time cardiovascular assessment able to track hemodynamic changes in the time frame of PLR effects, i. e., 30–90 s [30] (see ESM). The second is that the limits of precision in the technique used for assessing the response of cardiac output to PLR be far below the 10–15% increase in cardiac output found as a predicting cutoff [30]. PLR-induced changes in arterial pulse pressure [5, 11], descending aorta blood flow [8, 31], pulse contour-derived stroke volume [32], and pulsed Doppler-derived velocity–time integral [11, 28] have been proposed to be used for this purpose. In patients monitored with esophageal Doppler we found that PLR-induced changes in arterial pulse pressure were less accurate than PLR-induced changes in descending aorta blood flow [8] in predicting fluid responsiveness in critically ill patients. This is probably explained by the fact that the descending aorta blood flow is a more direct estimate of cardiac output than arterial pulse pressure [33]. Given the good sensitivity and specificity values reported in recent clinical studies it is likely that other real-time hemodynamic assessment methods such as transthoracic echocardiography (pulsed Doppler subaortic flow) [11, 28] and pulse contour cardiac output monitor [32] can be also appropriately used for quantifying the short-term hemodynamic response to PLR. The third requirement is to ensure that there is actually a change in preload in response to PLR before trying to determine whether there is an increase in cardiac output or preload. In the case of increase in cardiac preload with PLR the absence of increase in stroke volume should indicate that the patient is not fluid responsive. On the other hand, in the case of insufficient increase in preload with PLR (insufficient volume recruitment) the absence of PLR-induced increase in stroke volume cannot be interpreted. In such cases the PLR cannot be used to predict volume responsiveness. Thus it should be recommended to follow the changes in a marker of cardiac preload as a prerequisite to a correct interpretation of the PLR test [34]. Central venous pressure, duration of the aortic flow measured by esophageal Doppler, or end-diastolic dimensions at echocardiography can be used for this purpose. Finally, the level of the intra-abdominal pressure may be important to consider since it can impede the PLR-induced blood transfer when elevated. This point may be one of those that should be addressed by further studies concerning PLR.

In summary, the physiological effects of PLR consist of an increase in venous return and cardiac preload. The PLR thus acts as a self-volume challenge which is easy-to-perform and completely reversible. It has gained an increasing interest in the field of functional hemodynamic monitoring since it can help to detect fluid responsiveness in critically ill patients even in cases of ventilator spontaneous triggering or cardiac arrhythmias. Its optimal use requires a real-time cardiovascular assessment device able to quantify accurately the short-term hemodynamic response.

References

1. Rutlen DL, Wackers FJ, Zaret BL (1981) Radionuclide assessment of peripheral intravascular capacity: a technique to measure intravascular volume changes in the capacitance circulation in man. Circulation 64:146–152
2. Pozzoli M, Traversi E, Cioffi G, Stenner R, Sanarico M, Tavazzi L (1997) Loading manipulations improve the prognostic value of Doppler evaluation of mitral flow in patients with chronic heart failure. Circulation 95:1222–1230
3. Takagi S, Yokota M, Iwase M, Yoshida J, Hayashi H, Sotobata I, Koide M, Saito H (1989) The important role of left ventricular relaxation and left atrial pressure in the left ventricular filling velocity profile. Am Heart J 118:954–962
4. Rocha P, Lemaigre D, Leroy M, Desfonds P, De Zuttere D, Liot F (1987) Nitroglycerin-induced decrease of carbon monoxide diffusion capacity in acute myocardial infarction reversed by elevating legs. Crit Care Med 15:131–133
5. Boulain T, Achard JM, Teboul JL, Richard C, Perrotin D, Ginies G (2002) Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. Chest 121:1245–1252
6. Kyriakides ZS, Koukoulas A, Paraskevaidis IA, Chrysos D, Tsiapras D, Galiotos C, Kremastinos DT (1994) Does passive leg raising increase cardiac performance? A study using Doppler echocardiography. Int J Cardiol 44:288–293
7. Paelinck BP, van Eck JW, De Hert SG, Gillebert TC (2003) Effects of postural changes on cardiac function in healthy subjects. Eur J Echocardiogr 4:196–201
8. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL (2006) Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med 34:1402–1407
9. Wong DH, O'Connor D, Tremper KK, Zaccari J, Thompson P, Hill D (1989) Changes in cardiac output after acute blood loss and position change in man. Crit Care Med 17:979–983
10. Bertolissi M, Broi UD, Soldano F, Bassi F (2003) Influence of passive leg elevation on the right ventricular function in anaesthetized coronary patients. Crit Care 7:164–170
11. Lamia B, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL (2007) Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. Intensive Care Med 33:1125–1132
12. Wong DH, Tremper KK, Zaccari J, Hajduczek J, Konchigeri HN, Hufstedler SM (1988) Acute cardiovascular response to passive leg raising. Crit Care Med 16:123–125
13. Michard F, Teboul JL (2002) Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 121:2000–2008
14. Bendjelid K, Romand JA (2003) Fluid responsiveness in mechanically ventilated patients: a review of indices used in intensive care. Intensive Care Med 29:352–360
15. Monnet X, Teboul JL (2006) Invasive measures of left ventricular preload. Curr Opin Crit Care 12:235–240
16. Osman D, Ridel C, Ray P, Monnet X, Anguel N, Richard C, Teboul JL (2007) Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. Crit Care Med 35:64–68
17. Pinsky MR, Teboul JL (2005) Assessment of indices of preload and volume responsiveness. Curr Opin Crit Care 11:235–239
18. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138
19. Feissel M, Michard F, Mangin I, Ruyer O, Faller JP, Teboul JL (2001) Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. Chest 119:867–873
20. Berkenstadt H, Margalit N, Hadani M, Friedman Z, Segal E, Villa Y, Perel A (2001) Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. Anesth Analg 92:984–989
21. Reuter DA, Felbinger TW, Schmidt C, Kilger E, Goedje O, Lamm P, Goetz AE (2002) Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. Intensive Care Med 28:392–398
22. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL (2005) Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. Intensive Care Med 31:1195–1201
23. Feissel M, Teboul JL, Merlani P, Badie J, Faller JP, Bendjelid K (2007) Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients. Intensive Care Med 33:993–999
24. Heenen S, De Backer D, Vincent JL (2006) How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? Crit Care 10:R102
25. Magder SA, Goeogiadis G, Tuck C (1992) Respiratory variations in right atrial pressure predict response to fluid challenge. J Crit Care 7:76–85
26. Magder S (2006) Predicting volume responsiveness in spontaneously breathing patients: still a challenging problem. Crit Care 10:165
27. Monnet X, Richard C, Teboul JL (2007) Passive leg raising. In: Vincent JL (ed) Yearbook of intensive care and emergency medicine. Springer, Berlin Heidelberg New York, pp 542–548
28. Maizel J, Airapetian N, Lorne E, Tribouilloy C, Massy Z, Slama M (2007) Diagnosis of central hypovolemia by using passive leg raising. Intensive Care Med 33:1133–1138
29. Zogheib E, Defouilloy C, Mahjoub Y, Cherradi N, Moubarak M, Beloucif S, Dupont H (2007) Modification of hemodynamic effect after passive leg raising test by the use of elastic compression stocking (abstract). Intensive Care Med 33:S72
30. De Backer D (2006) Can passive leg raising be used to guide fluid administration? Crit Care 10:170
31. Lafanechere A, Pene F, Goulenok C, Delahaye A, Mallet V, Choukroun G, Chiche J, Mira J, Cariou A (2006) Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. Crit Care 10:R132
32. Ridel C, Lamia B, Monnet X, Richard C, Teboul JL (2006) Passive leg raising and fluid responsiveness during spontaneous breathing: pulse contour evaluation. Intensive Care Med 32:S81
33. De Backer D, Pinsky MR (2007) Can one predict fluid responsiveness in spontaneously breathing patients? Intensive Care Med 33:1111–1113
34. Antonelli M, Levy M, Andrews PJ, Chastre J, Hudson LD, Manthous C, Meduri GU, Moreno RP, Putensen C, Stewart T, Torres A (2007) Hemodynamic monitoring in shock and implications for management. Intensive Care Med 33:575–590

Sairam Parthasarathy
Martin J. Tobin

Sleep in the intensive care unit

Abstract Abnormalities of sleep are extremely common in critically ill patients, but the mechanisms are poorly understood. About half of total sleep time occurs during the daytime, and circadian rhythm is markedly diminished or lost. Judgments based on inspection consistently overestimate sleep time and do not detect sleep disruption. Accordingly, reliable polygraphic recordings are needed to measure sleep quantity and quality in critically ill patients. Critically ill patients exhibit more frequent arousals and awakenings than is normal, and decreases in rapid eye movement and slow wave sleep. The degree of sleep fragmentation is at least equivalent to that seen in patients with obstructive sleep apnea. About 20% of arousals and awakenings are related to noise, 10% are related to patient care activities, and the cause for the remainder is not known; severity of underlying disease is likely an important factor. Mechanical ventilation can cause sleep disruption, but the precise mechanism has not been defined. Sleep disruption can induce sympathetic activation and elevation of blood pressure, which may contribute to patient morbidity. In healthy subjects, sleep deprivation can decrease immune function and promote negative nitrogen balance. Measures to improve the quantity and quality of sleep in critically ill patients include careful attention to mode of mechanical ventilation, decreasing noise, and sedative agents (although the latter are double-edged swords).

Keywords Sleep · Critical illness · Mechanical ventilation · Artificial respiration · Arousal

Introduction

In his roman-a-clef, "Ravelstein", the Nobel Laureate Saul Bellow [1] describes being admitted to an intensive care unit and receiving mechanical ventilation:

"I was now the dying man. My lungs had failed. A machine did my breathing for me. Unconscious, I had no more idea of death than the dead have. But my head (I assume it was my head) was full of visions, delusions, and hallucinations. These were not dreams or nightmares. Nightmares have an escape hatch...."

Despite the obvious importance of sleep and its desirability in a patient with a serious illness, we know nothing of the visions, hallucinations and dreams experienced by a critically ill patient such as Bellow. Indeed, we know little of the sleep experienced by a critically ill patient. But we do know that sleep is commonly disrupted in critically ill patients [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16], and that sleep disruption may adversely affect patient outcome [8, 17]. In this review, we discuss the nature of sleep disturbances in critically ill patients, potential causes, and possible therapies.

Normal sleep and circadian rhythm

Healthy young adults experience two distinct states of sleep: rapid eye movement (REM) sleep and non-REM (NREM) sleep. REM sleep accounts for about 25% of sleep time and is characterized by episodic bursts of rapid

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_35, © Springer-Verlag Berlin Heidelberg 2009

Table 1 Studies of sleep in critically ill patients

More than 24 h	Number of patients	Patient type	Sleep staging	Arousals and awakenings per hour	Mechanical ventilation (%)
Polysomnography performed over 24 h					
Hilton [2]	10	Medical	Yes	Not listed	Not listed
Aurell [3]	9	Postoperative	Yes	Not listed	Some patients
Gottschlich [4]	11	Burn patients	Yes	>63	100
Cooper [5]	20	Medical	Yes	39	100
Freedman [6]	22	Medical	Yes	>11	100
Valente [7]	24	Head trauma	Yes	Not listed	100
Gabor [8]	7	Medical	Yes	22	100
Polysomnography performed only at nighttime					
Johns [9]	5	Postoperative	Yes	Not listed	Not listed
Orr 10	9	Postoperative	Yes	Not listed	Not listed
Broughton [11]	12	Medical	Yes	>21	NA
Knill [12]	12	Postoperative	Yes	>21	Not listed
Edwards [13]	21	Medical	Yes	Not listed	95
Aaron [14]	6	Medical	Yes	>19	Not listed
Parthasarathy [15]	11	Medical	Yes	58	100
Richards [16]	64	Medical	Not listed	Not listed	0
Polysomnography not performed					
Woods [18]	4	Postoperative			Not listed
Helton [19]	62	Not listed			Not listed
Tweedie [20]	15	Medical and postoperative			80
Kong [21]	60	Medical			100
Hurel [22]	223	Medical and postoperative			0
Freedman [23]	203	Medical and postoperative			0
Simini [24]	162	Medical and postoperative			0
Treggiari [25]	40	Postoperative			0
Walder [26]	17	Postoperative			60
Shilo [27]	8	Medical			50
Olson [28]	843	Medical and postoperative			Not listed
Topf [29]	97	Postoperative			Not listed
Nelson [30]	100	Medical			60
Mundigler [31]	24	Medical and postoperative			100
McKinley [32]	14	Medical and postoperative			0

eye movements, irregularities in respiration and heart rate, and paralysis of major muscle groups with the exception of the diaphragm and upper airway muscles. NREM sleep is divided into four stages (1, 2, 3 and 4). The progression of sleep from stage 1 through to stage 4 is accompanied by a progressive increase in the arousal threshold (the ability to wake in response to a stimulus). Stage 1 occurs at sleep onset and is also a transitional state between sleep stages. Up to 50% of the night is spent in stage 2 sleep, which is characterized by spindles and K complexes on the electroencephalograph (EEG). Progression of stage 2 is accompanied by the gradual appearance of high-voltage slow wave activity on the EEG (greater than 75 μV and less than 2 Hz). When such slow-wave activity exceeds 20% of the time in a 30-s epoch, sleep is categorized as stage 3; when it exceeds 50%, sleep is categorized as stage 4. Slow wave sleep is considered the most restorative. NREM sleep normally cycles with REM sleep every 90 min. The cycling of sleep and wakefulness, in turn, is regulated by a biological clock that operates over a 24-h period (circadian rhythm). In addition to sleep, the biological clock regulates several physiological, behavioral, and biochemical rhythms. Hormone secretion (cortisol, growth hormone), body temperature, immune function, coronary artery muscle tone, and bronchial smooth muscle tone, to name a few, exhibit marked circadian variability.

Abnormalities of sleep in critically ill patients

Just as with ambulatory patients, sleep in critically ill patients is assessed in terms of quantity, distribution over 24 h, and lack of continuity. Also assessed is the type and depth of sleep—rapid eye movement (REM) and non-REM (stages 1, 2, 3 and 4)—and the pattern from day to day in the distribution of sleep over a 24-h period (circadian rhythm). Accurate measurement of sleep quantity and quality requires reliable polygraphic recordings. Judgments based on inspection consistently overestimate sleep time [3] and do not detect sleep disruption [3, 13]. Table 1 classifies research reports on sleep in critically ill patients into studies involving polysomno-

graphic recordings over 24 h [2, 3, 4, 5, 6, 7, 8], polysomnographic recordings during nighttime alone [9, 10, 11, 12, 13, 14, 15, 16], and studies without polysomnographic recordings [18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32]. Also indicated is the type of patient population, whether patients were receiving mechanical ventilation, and whether sleep stages and disruption were adequately reported. Of the 28 studies listed in Table 1, 15 employed polysomnography [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16], and 7 included continuous recordings for 24 h or longer [2, 3, 4, 5, 6, 7, 8]. These studies reveal that almost half of total sleep time in critically ill patients can occur during the daytime [5, 8].

Investigators differ in their conclusions as to whether critically ill patients are sleep deprived. Three groups of investigators found that critically ill patients have a normal or near normal total sleep time, an average of 7–10.4 h a day [4, 5, 6]. Three other groups of investigators found a decrease in total sleep time, 3.6–6.2 h a day [2, 3, 8]. The investigators in one of the studies revealing decreased sleep time had deliberately restricted sedatives and hypnotics [3], although patients received sedatives in the other two studies that revealed sleep deprivation [2, 8]. Even in the studies revealing adequate amounts of sleep, the investigators noted large variations in total sleep time among the patients. Cooper and co-workers found that some patients slept for hardly an hour and other patients for nearly 15 of 24 h [5] (Fig. 1). Total sleep time in the study of Freedman and co-workers varied from 1.7 to 19.4 h [6]**.** Patients falling in the lowest quartile for total sleep time in these studies are clearly suffering from major sleep deprivation. In addition to variation in sleep quality from patient to patient, sleep quality may vary from night to night within a patient as a result of changes in acuity of illness [33], pain, and sedative and analgesic infusions. As such, sleep deprivation occurs in many, if not all, critically ill patients. To achieve better clarification of the frequency and severity of sleep deprivation, longitudinal studies in a large number of patients are needed; it will be essential to control for the effects of sedation, analgesia, and acuity of illness when conducting such studies.

In 11 critically ill patients, Parthasarathy and Tobin [15] noted 19 arousals (abrupt shifts in EEG frequency lasting more than 3 s) and 35 awakenings (EEG features compatible with wakefulness) per hour. Total sleep disruption, 54 arousals and awakenings per hour, was more than twice that seen in healthy individuals similarly instrumented. Cooper and co-workers [5] also reported frequent sleep disruption, with 42 arousals and awakenings per hour, and Gabor and co-workers [8] reported somewhat less frequent disruption, 22 arousals and awakenings per hour. With the exception of the three preceding studies [5, 8, 15], the remaining investigators who obtained EEG recordings in critically ill patients did not specify the sum of arousals and awakenings [3, 7, 9, 10, 16], making it impossible to compare studies in that respect (Table 1). The degree of sleep fragmentation in studies of critically ill patients, however, is equivalent to that in patients with obstructive sleep apnea [34].

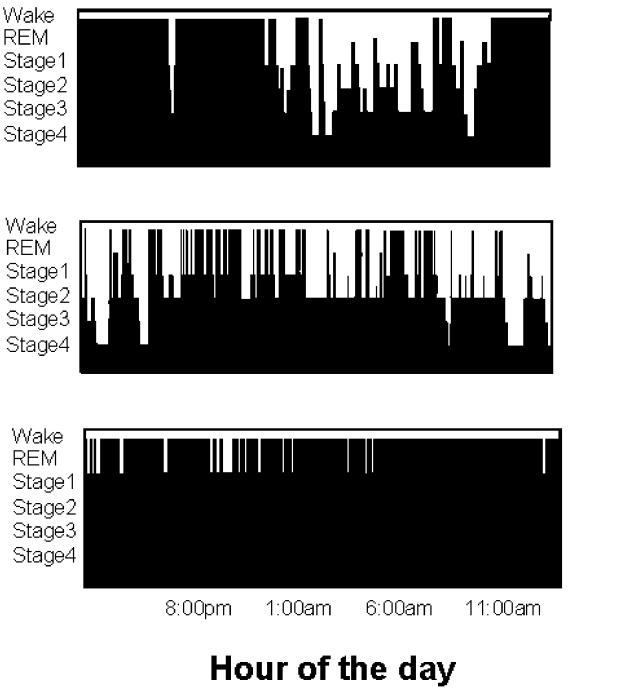


Fig. 1 Sleep stages, along the vertical axis, over a 24-h period in three critically ill patients with disrupted sleep. The hypnogram in patient 1 (*top*) reveals a normal nocturnal sleep pattern. Patients 2 (*middle*) slept for 65% of time, predominantly stages 1 and 2, and wakened repeatedly. Patient 3 (*bottom*) had isolated episodes of stage 1 sleep but was awake for most of 24 h. (Modified from [5] with permission)

Sleep is normally divided into rapid eye movement (REM) and non-REM (NREM) sleep. Critically ill patients spend 6% or less of sleep time in REM sleep as opposed to the normal of 25% [5, 6, 12]. The decrease in REM sleep has been attributed to medications (narcotics) [12], lack of sustained sleep needed to reach REM sleep [6], disturbance of circadian rhythm, underlying disease, and endotoxin release [35, 36]. The reduction in REM sleep might also be an adaptive response to critical illness because REM is a time of sympathetic-parasympathetic imbalance and increased susceptibility to breathing abnormalities. Critically ill patients also experience less of stages 3 and 4 of NREM, which are characterized by stable respiratory control and are devoid of sympathetic-parasympathetic imbalances.

Critically ill patients may not exhibit the EEG features of sleep and wakefulness conventionally seen in ambulatory patients [5]. Cooper and co-workers found that 7 of 20 mechanically ventilated patients were in coma and 5 patients did not exhibit EEG characteristics of stage 2 sleep (spindles or K complexes). Four patients

exhibited pathological wakefulness (a combination of behavioral correlates of wakefulness and EEG features of slow wave sleep), occupying 26–68% of the 24-h recording. Only 8 of the 20 patients demonstrated EEG characteristics of sleep, and even these patients had an average of 39 arousals and awakenings per hour [5] (Fig. 1).

Obtaining reliable EEG recordings is difficult in critically ill patients. Electrical interference (60 Hz) arising from equipment such as infusion pumps or ventilators [37] is common; interference also arises from muscle contractions in agitated patients [38]. To achieve satisfactory EEG signals, which may consist of only a few micro volts, it is necessary to apply electrodes to appropriate areas of the scalp; the skin also requires careful preparation to ensure low contact impedance (preferably less than 5 Ohms). To further minimize interference, all wires between a patient and preamplifier must be as short as possible [37]. Additional challenges in conducting research studies are avoiding a change in sedative medications, curtailing unnecessary visits by hospital personnel, and minimizing agitation.

A few investigators have studied circadian rhythms in critically ill patients. Mundeglier and co-workers [31] measured urinary 6-sulfatoxymelatonin every 4 h over 24 h. Compared with 7 non-septic critically ill patients and 21 healthy volunteers, the amplitude of circadian fluctuation in this melatonin metabolite was markedly lower in 17 critically ill patients suffering from septic shock.

Relationship between sedation and sleep

Critically ill patients are often given sedatives to increase patient comfort, decrease anxiety and agitation, and promote amnesia and sleep [25, 39]. Continuous infusion of sedatives, however, may prolong the duration of mechanical ventilation by 2.5 days and prolong ICU stay by 3.5 days [40]. The effect of sedative agents on the depth of sedation has been rigorously studied [39, 41, 42], although little is known about its effect on sleep quality in critically ill patients [43]. Over a 5-day period, 40 non-intubated critically ill patients were randomized to nocturnal midazolam and propofol [25]. On a 10-point self-rating scale, both groups reported a tendency towards improved sleep quality: from 6.3 to 7.2. The infusions were titrated to achieve a score of 3 or greater on the Ramsay sedation scale (a score of 3 indicates that a patient is asleep but awakens with a brisk response to a glabellar tap or a loud auditory stimulus) [42]. Self-perception of sleep quality was not different for propofol and midazolam (range 0.1–9.7; mean of 7.2). Some patients continued to rate sleep quality close to zero on the fifth day. These data indicate that self-perception of sleep quality can be poor with high dosages of sedatives despite achieving adequate levels of sedation. Severe sleep fragmentation may also occur in mechanically ventilated patients despite sedatives and analgesics [4, 5].

Some of the discrepancies between bedside assessment of sedation and subjective scoring of sleep may reflect known limitations in the Ramsay sedation scale [43]. Kong and co-workers studied the efficacy of midazolam and isoflurane in reducing plasma levels of catecholamines when similar levels of sedation (on the Ramsay scale) were achieved. Although both agents achieved comparable levels of sedation, isoflurane, but not midazolam, lowered the plasma levels of catecholamines from baseline [21]. The persistently elevated catecholamines in the patients receiving midazolam may have produced sleep disruption, although the explanation is no more than a possibility because polysomnography was not performed.

Benzodiazepines, narcotic analgesics, and propofol are commonly used to sedate critically ill patients [39]. Benzodiazepines improve behavioral aspects of sleep. They decrease the time needed to fall asleep, decrease awakenings, increase sleep duration, and increase sleep efficiency (duration of sleep as a percentage of time in bed). Benzodiazepines, however, also increase the number of spindles, increase cortical EEG frequency (at low doses), decrease EEG amplitude and frequency (at high doses), *and* suppress REM and slow wave sleep [44]. Although the clinical importance of these EEG alterations is not totally clear, an ideal hypnotic should not disturb the normal sleep pattern. Narcotics can also suppress REM sleep, cause a dose-dependent slowing of EEG, and suppress slow wave sleep—the most restorative stage of sleep [12, 44, 45]. In sum, a medicated state may resemble sleep on the surface, but may not provide the physiological benefits associated with true sleep.

Factors contributing to sleep disruption

Noise and hospital staff

The level of noise in the ICU ranges from 50 to 75 dB, with peaks of up to 85 dB [8, 26, 46, 47, 48, 49, 50, 51, 52]. This level of noise is comparable to that in a factory (80 dB) or a busy office (70 dB), and is louder than noise in a bedroom (40 dB) [51]. (The decibel scale is logarithmic, and an increase of 10 dB represents a doubling of noise.) When studying the relationship between ICU noise and sleep disruption, investigators commonly attribute arousals to noise when they occur within 3 s of a measurable (greater than 15 dB) increase in noise [5, 6]. In these studies, 11–20% of arousals were attributed to noise [5, 6]. Because critically ill patients have frequent arousals and awakenings (20–68 per hour, Table 1) some arousals may mistakenly be attributed to noise. In a study of healthy volunteers subjected to audio recordings

of ICU noise, a greater than normal number of awakenings and less REM and total sleep time were observed [50, 53]. Findings in healthy subjects, however, may not apply to critically ill patients, who may have a higher arousal threshold secondary to sleep deprivation, sedative agents, or coma.

Gabor and co-workers [8] recorded audio and video signals in synchrony with polysomnography in seven patients receiving mechanical ventilation. Twenty percent of the arousals and awakenings were related to noise peaks, and only 10% were related to patient care activities. The cause of 68% of arousals and awakenings could not be identified [8].

Mechanical ventilation

About 40% of patients in an ICU receive mechanical ventilation [54], but investigations into the precise mechanisms of the effect of mechanical ventilation on sleep are only commencing. Mechanically ventilated patients experience considerable sleep disruption, with as many as 20–63 arousals and awakenings per hour [4, 5, 8]. At first glance, a comparison of mechanically ventilated patients with spontaneously breathing critically ill patients should provide a reasonable method for investigating the effect of mechanical ventilation on sleep (Table 1). Such comparisons might prove misleading for a number of reasons. First, acuity of illness may be greater in ventilated patients than in spontaneously breathing patients. Second, spontaneously breathing patients are vulnerable to obstructive apneas, which will be prevented by an endotracheal tube. Third, factors associated with ventilation, such as masks, tracheal tubes, suctioning, mouth guards, nasogastric tubes, and physical restraints, may contribute to sleep fragmentation [55]. Fourth, sedatives and analgesics are more likely during mechanical ventilation. An attractive way to study the effect of mechanical ventilation on sleep might be to study tracheostomized patients while connected and disconnected from a ventilator over a short time period.

Notwithstanding methodological concerns with the studies, data suggest that the mode of ventilation can influence sleep quality [56, 57]. Meza and co-workers [56] showed that pressure support induces central apneas in healthy subjects during sleep. In a study of 11 critically ill patients during one night of sleep, Parthasarathy and Tobin observed greater sleep fragmentation during pressure support than during assist-control ventilation: 79 versus 54 arousals and awakenings per hour (Fig. 2). Six of the 11 patients developed central apneas during pressure support, but not during assist-control ventilation [15]. Heart failure was more common in the patients who developed apneas than in the patients without apneas: 83% versus 20%. The findings emphasize that research on sleep in critically ill patients needs to be controlled for the ventilator mode. In these 11 patients, the most important determinant of apneas was the difference between PCO_2 during resting breathing and the patient's apnea threshold. When a patient's resting PCO_2 was close to the apnea threshold, central apneas were more likely to develop. The addition of dead space caused a further increase in resting PCO_2 above the apnea threshold and decreased the sum of arousals and awakenings from 83 to 44 events per hour (in the patients who developed central apneas during pressure support). Sleep efficiency (time asleep as a percentage of study duration) increased from 63 to 81% with the addition of dead space (Fig. 2).

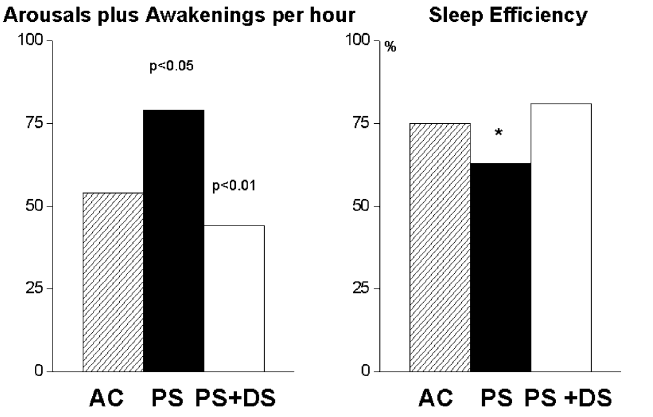


Fig. 2 Sleep fragmentation (*left panel*) and sleep efficiency (*right panel*) during assist-control ventilation and pressure support with and without dead space. Sleep fragmentation, measured as the number of arousals and awakenings, was greater during pressure support (*solid bars*) than during assist-control ventilation (*hatched bars*) or pressure support with dead space (*open bars*). Sleep efficiency (*right panel*) was also lower during pressure support (*solid bars*) than during assist-control ventilation (*hatched bars*) or pressure support with dead space (*open bars*). (Modified from [15] with permission)

Other factors

Factors that contribute to sleep abnormalities in critically ill patients include acute illness [2, 3, 11, 12], pain, light, and patient discomfort [17]. Noxious stimuli that contribute to patient discomfort and arousal include increased respiratory effort [58, 59], hypoxemia [58], and hypercapnia [58]. Swings in intrathoracic pressures are potent stimuli for inducing arousals in healthy subjects [60] and in patients with upper airway resistance syndrome [34].

Clinical implications

Clinical outcomes

Sleep fragmentation may influence morbidity and mortality in critically ill patients. Patients in coma and pa-

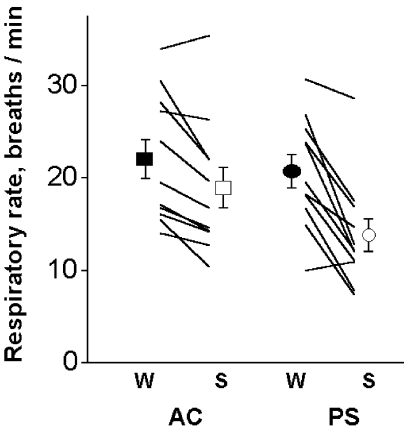


Fig. 3 Respiratory rate during assist-control ventilation (*AC*) and pressure support (*PS*) in 11 critically ill patients. For each mode, the lines connect the mean value for each patient during wakefulness (*W*, *left*) and sleep (*S*, *right*). Compared with wakefulness, group mean respiratory rate was lower during sleep (*closed symbols*) than during wakefulness (*open symbols*). The difference between sleep and wakefulness was greater for pressure support than for assist-control ventilation. (Modified from [15] with permission)

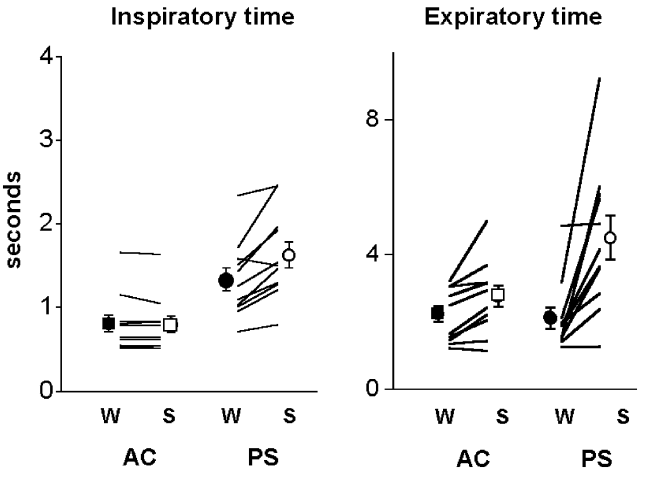


Fig. 4 Inspiratory time (*left panel*) and expiratory time (*right panel)* during assist-control ventilation (*AC*) and pressure support (*PS*) in 11 critically ill patients. The lines connect the mean value for each patient during wakefulness (*W*, *left*) and sleep (*S*, *right*). During pressure support, group mean inspiratory time and expiratory time were greater during sleep (*closed symbols*) than during wakefulness (*open symbols*). The difference between sleep and wakefulness was greater for pressure support than for assist-control ventilation. (Modified from [15] with permission)

tients who lack well-defined EEG characteristics of stage 2 sleep have higher acute physiological scores than do patients with identifiable but fragmented sleep [5]. Some investigators have reported no association between the acuity of illness and sleep disruption [6]. As such, the contribution of acuity of illness to sleep disturbances is unclear. Animal data suggest that sleep deprivation may lead to death [61]. It is thought that death is unlikely to result with sleep deprivation in human subjects [62, 63], but the consequence of sleep deprivation has been studied only in healthy subjects and not in critically ill patients.

Among 24 patients with post-traumatic coma, 5 of 6 patients who had organized sleep patterns survived as opposed to 3 of 7 patients who had low voltage theta-delta or mixed frequency activity without definable features of sleep; functional outcome was also better in the patients with organized sleep patterns [7]. Freedman and co-workers found that 5 of 22 patients exhibited EEG features of mild to moderate encephalopathy before other features of sepsis manifested [6]; none of the non-septic patients demonstrated such EEG features.

Ventilator settings

Physicians typically adjust ventilator settings during the daytime and without knowing whether a patient is asleep or awake. Compared with wakefulness, sleep caused a 33% decrease in respiratory rate during pressure support and a 15% decrease in rate during assist-control (Fig. 3) [15]. The level of pressure support is commonly titrated to respiratory rate, which provides reasonable guidance as to a patient's inspiratory effort [64, 65]. If, however, physicians titrate pressure support to respiratory rate while the patient is asleep, patient effort will increase considerably on awakening.

Changes in ventilator settings are commonly based on arterial blood gas measurements. End-tidal CO_2 was greater in 11 critically ill patients during sleep than during wakefulness: by 11% during pressure support and by 5% during assist-control ventilation. Patients who repeatedly slip in and out of sleep display marked fluctuations in end-tidal CO_2. The coefficient of variation of end-tidal CO_2 was 8.7% during pressure support and 4.7% during assist-control ventilation [15]. In some patients receiving pressure support, end-tidal CO_2 can be as much as 7 mmHg higher during sleep than during wakefulness. Differences in PCO_2 between sleep and wakefulness of this magnitude may cause physicians to change ventilator settings when a change is not necessary. Consequently, under-ventilation or over-ventilation may result [66]. Compared with wakefulness, sleep caused a 23% increase in inspiratory time and a 126% increase in expiratory time in patients receiving pressure support (Fig. 4). The increase in inspiratory time that accompanied change from wakefulness to sleep was also associated with an increase in tidal volume, and the likely accompaniment of hypocapnia may explain the development of apneas during pressure support [67, 68]. These findings indicate that the effect of sleep on breathing pattern and gas exchange has important implications for research on patient-ventilator interaction.

Cardiorespiratory consequences

In ambulatory patients, sleep fragmentation can result in elevations of arterial blood pressure, elevations of urinary and serum catecholamines, arrhythmias, progression of cardiac failure, and even death [69, 70]. Sleep-disordered breathing might cause similar abnormalities in critically ill patients, although direct evidence is lacking. Apneas and hypopneas cause hypoxemia [16], which, in turn, may produce sympathetic activation and arrhythmias in critically ill patients; evidence on this issue, however, is anecdotal [71] and inconclusive [72].

Sleep fragmentation induced by auditory stimuli can increase nocturnal blood pressure in dogs [73]. In patients who have central sleep apnea, the major cause of oscillations in blood pressure is ventilatory oscillations, with a significant contribution from arousals [73]. These investigations [73, 74] suggest that arousals may elevate nocturnal blood pressure, secondary to increases in sympathetic activity, and contribute to cardiovascular complications [75]. Preliminary data suggests that sleep fragmentation in critically ill patients may be associated with elevations in blood pressure [76], but the effect on morbidity and mortality is unknown.

The effect of sleep deprivation [77] on the ventilatory responses to hypoxia and hypercapnia is controversial [78]. Sleep deprivation has long been believed to depress chemoreceptor function [78]. Spengler and colleagues [78], however, recently found that sleep deprivation did not alter the hypercapnic ventilatory response in healthy subjects. The situation in critically ill patients has not been studied. Blunting of the chemoreceptor response can decrease the ability of the respiratory system to compensate for respiratory loads during or after the withdrawal of mechanical ventilation [68].

At least some postoperative patients experience an increase in REM sleep on the third to fourth postoperative day secondary to the earlier suppression of REM sleep by anesthetics and analgesics [12]. Because REM sleep is characterized by unstable breathing patterns and sympathetic-parasympathetic imbalances, the increase in REM sleep in the early postoperative period may aggravate the risk of postoperative atelectasis, pneumonia, hypoxemia, and cardiovascular morbidity.

Neurological consequences

Sleep deprivation may contribute to delirium and agitation [19, 79]. In a study of 62 critically ill patients, Helton and colleagues [19] noted that 24% experienced severe sleep deprivation and 16% experienced moderate deprivation. One third of the patients with severe sleep disruption suffered from delirium, 10% of patients with moderate sleep disruption suffered from delirium, but only 3% of patients with adequate sleep had delirium. The study has limitations. Sleep was assessed at the bedside by nursing staff rather than polysomnography. No intervention was performed, and a cause and effect relationship between sleep deprivation and delirium cannot be inferred. Agitation can cause elevations in plasma catecholamines [21]. Large doses of sedative agents are often used in agitated and delirious patients; when the agitation resolves, however, the sedative agent may remain in adipose tissue and interfere with weaning from mechanical ventilation.

Immunological and metabolic consequences

Sleep deprivation can unfavorably alter immune function [80, 81, 82, 83, 84, 85, 86]. In 42 healthy volunteers, Irwin and co-workers found that sleep deprivation resulted in almost a 50% decrease in natural killer cell activity and a 50% decrease in lymphokine killer cell activity. One night of sleep returned natural killer cell activity to baseline.

Sleep deprivation can promote negative nitrogen balance and increase energy expenditure [62, 63, 87]. In six healthy volunteers, 24 h of sleep deprivation produced a 7% increase in nitrogen excretion. Some subjects experienced as much as a 20% increase in nitrogen excretion. It is not known whether similar changes occur in critically ill patients.

Long-term consequences

Critical illness may have long-term consequences on sleep [22]. When 329 patients were interviewed 6 months after discharge from an ICU, 223 (67%) reported severe alterations in sleep. The lack of a control group makes it impossible to distinguish the role of critical illness from previous health status, underlying medical diagnosis, persistent disability, or other factors.

Strategies to decrease sleep disruption

Gabor and co-workers studied the effect of reducing noise in six healthy volunteers while they slept in an ICU [8]. The average level of noise was 51 dB in an open ICU and 43 dB in an isolated single room (the respective peak levels were 65 and 54 dB). Total sleep time was greater in the isolated room than in the open ICU, 9.5 versus 8.2 h, although the number of arousals and awakenings were virtually identical in the two settings (14 to 15 events per hour) [8]. In six healthy volunteers attempting to sleep in a noisy environment, Wallace and co-workers found that use of earplugs increased REM sleep (20 versus 15%) and decreased REM latency (107 versus 148 min), although the number of awaken-

ings was not affected (25 versus 27 per hour). Because only 20% of sleep fragmentation in critically ill patients appears to be attributable to noise [8], reducing noise in the ICU may be of limited value.

Shilo and co-workers undertook a double blind, placebo-controlled study of melatonin in eight critically ill patients with chronic obstructive pulmonary disease [27]. The authors conclude that melatonin achieved greater sleep time and less fragmentation, although the conclusions are not well supported by the data.

Conclusion

Research into sleep disorders in ambulatory patients over the last 30 years has provided us with a strong set of physiological principles. The time is ripe for applying these principles to critically ill patients. A major challenge, as with most research in critically ill patients, is the difficulty in controlling for confounding influences in order to achieve high fidelity recordings.

References

1. Bellow S (2000) Ravelstein. Penguin, New York, pp 208
2. Hilton BA (1976) Quantity and quality of patients' sleep and sleep-disturbing factors in a respiratory intensive care unit. J Adv Nurs 1:453–468
3. Aurell J, Elmqvist D (1985) Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. BMJ 290:1029–1032
4. Gottschlich MM, Jenkins ME, Mayes T, Khoury J, Kramer M, Warden GD, Kagan RJ (1994) The 1994 Clinical Research Award. A prospective clinical study of the polysomnographic stages of sleep after burn injury. J Burn Care Rehabil 15:486–492
5. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ (2000) Sleep in critically ill patients requiring mechanical ventilation. Chest 117:809–818
6. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ (2001) Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. Am J Respir Crit Care Med 163:451–457
7. Valente M, Placidi F, Oliveira AJ, Bigagli A, Morghen I, Proietti R, Gigli GL (2002) Sleep organization pattern as a prognostic marker at the subacute stage of post-traumatic coma. Clin Neurophysiol 113:1798–1805
8. Gabor JY, Cooper AB, Crombach SA, Lee B, Kadikar N, Bettger HE, Hanly PJ (2003) Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. Am J Respir Crit Care Med 167:708–715
9. Johns MW, Large AA, Masterton JP, Dudley HA (1974) Sleep and delirium after open heart surgery. Br J Surg 61:377–381
10. Orr WC, Stahl ML (1977) Sleep disturbances after open heart surgery. Am J Cardiol 39:196–201
11. Broughton R, Baron R (1978) Sleep patterns in the intensive care unit and on the ward after acute myocardial infarction. Electroencephalogr Clin Neurophysiol 45:348–360
12. Knill RL, Moote CA, Skinner MI, Rose EA (1990) Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. Anesthesiology 73:52–61
13. Edwards GB, Schuring LM (1993) Pilot study: validating staff nurses' observations of sleep and wake states among critically ill patients, using polysomnography. Am J Crit Care 2:125–131
14. Aaron JN, Carlisle CC, Carskadon MA, Meyer TJ, Hill NS, Millman RP (1996) Environmental noise as a cause of sleep disruption in an intermediate respiratory care unit. Sleep 19:707–710
15. Parthasarathy S, Tobin MJ (2002) Effect of ventilator mode on sleep quality in critically ill patients. Am J Respir Crit Care Med 166:1423–1429
16. Richards KC, Anderson WM, Chesson AL Jr, Nagel CL (2002) Sleep-related breathing disorders in patients who are critically ill. J Cardiovasc Nurs 17:42–55
17. Krachman SL, D'Alonzo GE, Criner GJ (1995) Sleep in the intensive care unit. Chest 107:1713–1720
18. Woods NF (1972) Patterns of sleep in postcardiotomy patients. Nurs Res 21:347–352
19. Helton MC, Gordon SH, Nunnery SL (1980) The correlation between sleep deprivation and the intensive care unit syndrome. Heart Lung 9:464–468
20. Tweedie IE, Bell CF, Clegg A, Campbell IT, Minors DS, Waterhouse JM (1989) Retrospective study of temperature rhythms of intensive care patients. Crit Care Med 17:1159–1165
21. Kong KL, Willatts SM, Prys-Roberts C, Harvey JT, Gorman S (1990) Plasma catecholamine concentration during sedation in ventilated patients requiring intensive therapy. Intensive Care Med 16:171–174
22. Hurel D, Loirat P, Saulnier F, Nicolas F, Brivet F (1997) Quality of life 6 months after intensive care: results of a prospective multicenter study using a generic health status scale and a satisfaction scale. Intensive Care Med 23:331–337
23. Freedman NS, Kotzer N, Schwab RJ (1999) Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. Am J Respir Crit Care Med 159:1155–1162
24. Simini B (1999) Patients' perceptions of intensive care. Lancet 354:571–572
25. Treggiari-Venzi M, Borgeat A, Fuchs-Buder T, Gachoud JP, Suter PM (1996) Overnight sedation with midazolam or propofol in the ICU: effects on sleep quality, anxiety and depression. Intensive Care Med 22:1186–1190
26. Walder B, Francioli D, Meyer JJ, Lancon M, Romand JA (2000) Effects of guidelines implementation in a surgical intensive care unit to control nighttime light and noise levels. Crit Care Med 28:2242–2247
27. Shilo L, Dagan Y, Smorjik Y, Weinberg U, Dolev S, Komptel B, Shenkman L (2000) Effect of melatonin on sleep quality of COPD intensive care patients: a pilot study. Chronobiol Int 17:71–76
28. Olson DM, Borel CO, Laskowitz DT, Moore DT, McConnell ES (2001) Quiet time: a nursing intervention to promote sleep in neurocritical care units. Am J Crit Care 10:74–78
29. Topf M, Thompson S (2001) Interactive relationships between hospital patients' noise-induced stress and other stress with sleep. Heart Lung 30:237–243
30. Nelson JE, Meier DE, Oei EJ, Nierman DM, Senzel RS, Manfredi PL, Davis SM, Morrison RS (2001) Self-reported symptom experience of critically ill cancer patients receiving intensive care. Crit Care Med 29:277–282

31. Mundigler G, Delle-Karth G, Koreny M, Zehetgruber M, Steindl-Munda P, Marktl W, Ferti L, Siostrzonek P (2002) Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. Crit Care Med 30:536–540
32. McKinley S, Nagy S, Stein-Parbury J, Bramwell M, Hudson J (2002) Vulnerability and security in seriously ill patients in intensive care. Intensive Crit Care Nurs 18:27–36
33. Parthasarathy S, Tobin MJ (2003) Is sleep disruption related to severity of critical illness (abstract)? Am J Respir Crit Care Med 167:A968
34. Guilleminault C, Partinen M, Quera-Salva MA, Hayes B, Dement WC, Nino-Murcia G (1988) Determinants of daytime sleepiness in obstructive sleep apnea. Chest 94:32–37
35. Young GB, Bolton CF, Austin TW, Archibald YM, Gonder J, Wells GA (1990) The encephalopathy associated with septic illness. Clin Invest Med 13:297–304
36. Trachsel L, Schreiber W, Holsboer F, Pollmacher T (1994) Endotoxin enhances EEG alpha and beta power in human sleep. Sleep 17:132–139
37. Prior PF (1985) EEG monitoring and evoked potentials in brain ischaemia. Br J Anaesth 57:63–81
38. Riker RR, Fraser GL, Simmons LE, Wilkins ML (2001) Validating the sedation agitation scale with the bispectral index and visual analog scale in adult ICU patients after cardiac surgery. Intensive Care Med 27:853–858
39. Kress JP, Pohlman AS, Hall JB (2002) Sedation and analgesia in the intensive care unit. Am J Respir Crit Care Med 166:1024–1028
40. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342:1471–1477
41. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK (2002) The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 166:1338–1344
42. Ramsay MA, Savege TM, Simpson BR, Goodwin R (1974) Controlled sedation with alphaxalone-alphadolone. BMJ 2:656–659
43. Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, Chalfin DB, Masica MF, Bjerke HS, Coplin WM, Crippen DW, Fuchs BD, Kelleher RM, Marik PE, Nasraway SA Jr, Murray MJ, Peruzzi WT, Lumb PD (2002) Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 30:119-141
44. Wauquier A (1993) EEG and neuropharmacology. In: Niedermeyer E and Da Silva FL (eds) Elelctroencephalography. Basic principles, clinical applications, and related fields. Willliams and Wilkins, Baltimore, pp 619–629
45. Sebel PS, Bovill JG, Wauquier A, Rog P (1981) Effects of high-dose fentanyl anesthesia on the electroencephalogram. Anesthesiology 55:203–211
46. Cropp AJ, Woods LA, Raney D, Bredle DL (1994) Name that tone. The proliferation of alarms in the intensive care unit. Chest 105:1217–1220
47. Bentley S, Murphy F, Dudley H (1977) Perceived noise in surgical wards and an intensive care area: an objective analysis. BMJ 2:1503–1506
48. Soutar RL, Wilson JA (1986) Does hospital noise disturb patients? BMJ 292:305
49. Topf M, Davis JE (1993) Critical care unit noise and rapid eye movement (REM) sleep. Heart Lung 22:252–258
50. Topf M (1992) Effects of personal control over hospital noise on sleep. Res Nurs Health 15:19–28
51. Woods NF, Falk SA (1974) Noise stimuli in the acute care area. Nurs Res 23:144–150
52. Kahn DM, Cook TE, Carlisle CC, Nelson DL, Kramer NR, Millman RP (1998) Identification and modification of environmental noise in an ICU setting. Chest 114:535–540
53. Wallace CJ, Robins J, Alvord LS, Walker JM (1999) The effect of earplugs on sleep measures during exposure to simulated intensive care unit noise. Am J Crit Care 8:210–219
54. Esteban A, Anzueto A, Alia I, Gordo F, Apezteguia C, Palizas F, Cide D, Goldwaser R, Soto L, Bugedo G, Rodrigo C, Pimentel J, Raimondi G, Tobin MJ (2000) How is mechanical ventilation employed in the intensive care unit? An international utilization review. Am J Respir Crit Care Med 161:1450–1458
55. Mehta S, Hill NS (2001) Noninvasive ventilation. Am J Respir Crit Care Med 163:540–577
56. Meza S, Mendez M, Ostrowski M, Younes M (1998) Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. J Appl Physiol 85:1929–1940
57. Hotchkiss JR Jr, Adams AB, Stone MK, Dries DJ, Marini JJ, Crooke PS (2002) Oscillations and noise: inherent instability of pressure support ventilation? Am J Respir Crit Care Med 165:47–53
58. Gleeson K, Zwillich CW, White DP (1990) The influence of increasing ventilatory effort on arousal from sleep. Am Rev Respir Dis 142:295–300
59. Preas HL 2nd, Jubran A, Vandivier RW, Reda D, Godin PJ, Banks SM, Tobin MJ, Suffredini AF (2001) Effect of endotoxin on ventilation and breath variability: role of cyclooxygenase pathway. Am J Respir Crit Care Med 164:620–626
60. Issa FG, Sullivan CE (1983) Arousal and breathing responses to airway occlusion in healthy sleeping adults. J Appl Physiol 55:1113–1119
61. Rechtschaffen A, Gilliland MA, Bergmann BM, Winter JB (1983) Physiological correlates of prolonged sleep deprivation in rats. Science 221:182–184
62. Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA (1989) Sleep deprivation in the rat: X. Integration and discussion of the findings. Sleep 12:68–87
63. Bonnet MH (2000) Sleep deprivation. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. Saunders, Philadelphia, pp 53–71
64. Jubran A, Van de Graaff WB, Tobin MJ (1995) Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152:129–136
65. Tobin MJ, Jubran A, Laghi F (2001) Patient-ventilator interaction. Am J Respir Crit Care Med 163:1059–1063
66. Younes M (1994) Mechanisms of respiratory load compensation. In: Dempsey JA, Pack AI (eds) Regulation of breathing. Lung biology in health and disease. Vol. 79. Dekker, New York, pp 867–922
67. Dempsey JA, Skatrud JB (2001) Apnea following mechanical ventilation may be caused by nonchemical neuromechanical influences. Am J Respir Crit Care Med 163:1297–1298
68. Younes M (2001) Apnea following mechanical ventilation may not be caused by neuromechanical influences. Am J Respir Crit Care Med 163:1298–1301

69. Leung RS, Bradley TD (2001) Sleep apnea and cardiovascular disease. Am J Respir Crit Care Med 164:2147–2165
70. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD (2000) Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 102:61–66
71. Wellens HJ, Vermeulen A, Durrer D (1972) Ventricular fibrillation occurring on arousal from sleep by auditory stimuli. Circulation 46:661–665
72. Marin JM, Carrizo SJ, Kogan I (1998) Obstructive sleep apnea and acute myocardial infarction: clinical implications of the association. Sleep 21:809–815
73. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA (1997) Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 99:106–109
74. Trinder J, Merson R, Rosenberg JI, Fitzgerald F, Kleiman J, Douglas Bradley T (2000) Pathophysiological interactions of ventilation, arousals, and blood pressure oscillations during Cheyne-Stokes respiration in patients with heart failure. Am J Respir Crit Care Med 162:808–813
75. Leuenberger U, Jacob E, Sweer L, Waravdekar N, Zwillich C, Sinoway L (1995) Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. J Appl Physiol 79:581–588
76. Parthasarathy S, Laghi F, Jubran A, Tobin MJ (2002) Does ventilator mode influence blood pressure oscillations in critically ill patients (abstract)? Am J Respir Crit Care Med 165:A165
77. Cheshire K, Engelman H, Deary I, Shapiro C, Douglas NJ (1992) Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 152:538–541
78. Spengler C, Shea S (2001) Sleep deprivation per se does not decrease the hypercapnic ventilatory response in humans. Am J Respir Crit Care Med 161:1124–1128
79. McGuire BE, Basten CJ, Ryan CJ, Gallagher J (2000) Intensive care unit syndrome: a dangerous misnomer. Arch Intern Med 160:906–909
80. Irwin M, McClintick J, Costlow C, Fortner M, White J, Gillin JC (1996) Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. FASEB J 10:643–653
81. Dinges DF, Douglas SD, Hamarman S, Zaugg L, Kapoor S (1995) Sleep deprivation and human immune function. Adv Neuroimmunol 5:97–110
82. Dinges DF, Douglas SD, Zaugg L, Campbell DE, McMann JM, Whitehouse WG, Orne EC, Kapoor SC, Icaza E, Orne MT (1994) Leukocytosis and natural killer cell function parallel neurobehavioral fatigue induced by 64 hours of sleep deprivation. J Clin Invest 93:1930–1939
83. Palmblad J, Petrini B, Wasserman J, Akerstedt T (1979) Lymphocyte and granulocyte reactions during sleep deprivation. Psychosom Med 41:273–278
84. Moldofsky H, Lue FA, Davidson JR, Gorczynski R (1989) Effects of sleep deprivation on human immune functions. FASEB J 3:1972–1977
85. Boyum A, Wiik P, Gustavsson E, Veiby OP, Reseland J, Haugen AH, Opstad PK (1996) The effect of strenuous exercise, calorie deficiency and sleep deprivation on white blood cells, plasma immunoglobulins and cytokines. Scand J Immunol 43:228–235
86. Brown R, Pang G, Husband AJ, King MG (1989) Suppression of immunity to influenza virus infection in the respiratory tract following sleep disturbance. Reg Immunol 2:321–325
87. Scrimshaw NS, Habicht JP, Pellet P, Piche ML, Cholakos B (1966) Effects of sleep deprivation and reversal of diurnal activity on protein metabolism of young men. Am J Clin Nutr 19:313–319

J. Luis Noronha
George M. Matuschak

Magnesium in critical illness: metabolism, assessment, and treatment

Introduction

Magnesium is the second most abundant intracellular cation and the fourth most common cation in the body [1]. Its importance as an essential nutrient has been recognized since 1932, when Kruse et al. [2] reported the effects of acute Mg deficiency in rats. Even recently Mg was considered the "forgotten cation" in clinical practice [3]; however, this is no longer the case [4]. Estimates of Mg deficiency range from 20% to 61% [5, 6, 7], while a recent study found that reductions in total serum Mg on admission are associated with increased mortality [8].

Nonetheless, the relevance of such data to intensive care is problematic. Controlled data are lacking on how circulating total Mg concentrations are related to levels of biologically active ionized Mg (Mg^{2+}). Data are likewise sparse concerning the interplay between serum total and ionized Mg levels during specific critical illnesses and their treatment. In particular, the efficacy of therapeutic Mg supplementation on Mg^{2+}, organ function, inflammatory events, and mortality are poorly understood. This lack of information on the biology of Mg contrasts with well established correlations between serum total and ionized calcium (Ca^{2+}) concentrations, manifestations of acute Ca^{2+} deficiency, and the physiological effects of correcting ionized hypocalcemia [9, 10, 11, 12].

This review summarizes key aspects of Mg metabolism in adult intensive care patients, emphasizing the interdependence of Mg homeostasis with that of other cations such as Ca^{2+} and K^{+}. Thereafter we examine the justification for the trend of increasingly frequent measurements of serum total Mg in the critically ill, and how this information is related to emerging data concerning circulating Mg^{2+}. In this context, the limitations of current treatment recommendations for hypomagnesemia in the ICU are analyzed as well as research developments likely to alter our diagnostic and therapeutic algorithms in the near future. The use of therapeutic doses of Mg independent of hypomagnesemia or titration to serum total Mg levels to treat conditions such as preeclampsia and asthma are covered since this is beyond the scope of this review.

Compartmental distribution and metabolism of Mg

The body normally contains 21–28 g Mg [13]. Approximately 53% of total Mg stores are in bone, 27% in muscle, 19% in soft tissues, 0.5% in erythrocytes, and 0.3% in serum [14]. The Mg in muscle, soft tissues, and erythrocytes is considered to be intracellular [1], and mostly bound to chelators such as adenosine triphosphate (ATP), adenosine diphosphate (ADP), proteins, RNA, DNA, and citrate [14]. Although only 5–10% of intracellular Mg is ionized, this fraction is essential for regulating intracellular Mg homeostasis [15] (Fig. 1).

Traditionally, extracellular Mg in serum was considered to be 33% protein bound, 7% complexed to citrate, PO_4^{2-}, and HCO_3^{-} [16], and 55% circulating in the diva-

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_36,

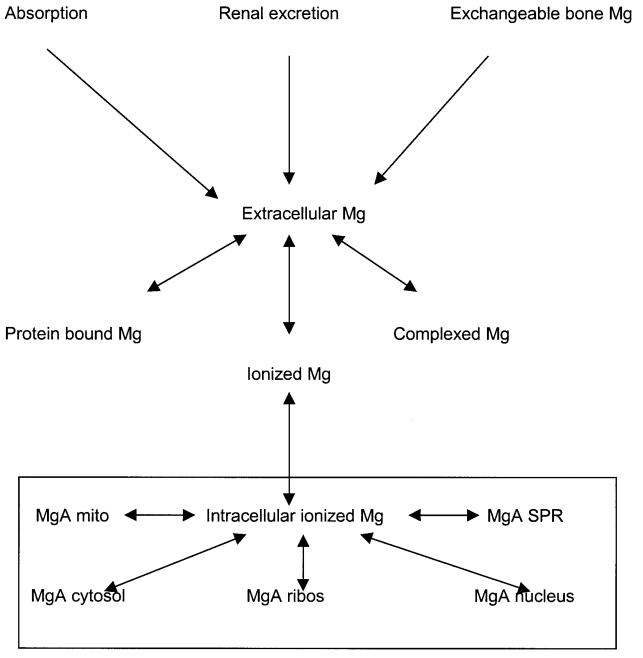


Fig. 1 Mg homeostasis. Extracellular Mg levels are maintained via absorption, renal excretion, and bone contribution. Extracellular Mg comprises protein-bound, complexed, and ionized fractions. Ionized extracellular Mg is in exchanging equilibrium with the intracellular ionized Mg fraction. *MgA cytosol*, *MgA ribos*, *MgA nucleus*, *MgA SPR*, *MgA mito* refer to Mg bound in the cytosol, ribosomes, nucleus, sarcoplasmic reticulum, and mitochondria, respectively

lent ionized form (Mg^{2+}). However, the newer methods of ion-selective Mg electrodes, atomic absorption spectroscopy, and ultrafiltration indicate that serum Mg is 67% ionized, 19% protein bound, and 14% complexed [17]. Standard clinical determinations of serum total Mg reflect all three forms. Of note, protein-bound and complexed Mg are unavailable for most biochemical processes [1]. The important issue of the dynamics of equilibration among the various states of extracellular Mg has not been extensively studied. Since serum contains only 0.3% of total body Mg stores, serum total Mg measurements poorly reflect total body status. Serum total Mg concentrations normally average 1.7–2.3 mg/dl (1.4–2.1 mEq/l) [13], depending on the laboratory and measurement technique. Mg concentrations are commonly expressed in units of milligrams, millimoles, or milliequivalents; for conversion one can use the following formula: 1 g Mg sulfate contains 98 mg= 4.06 mmol=8.12 mEq elemental Mg.

Daily Mg intake in adults normally averages 6–10 mg/kg [18]. Absorption occurs primarily in the jejunum and ileum [19]. Several lines of evidence suggest that absorption involves a transcellular, saturable process involving facilitated diffusion and a passive intercellular mechanism mediated by cationic electrochemical gradients and solvent drag [20]. Although 30–40% of dietary Mg is absorbed [19, 20], factors controlling intestinal absorption are unclear. An inverse curvilinear relationship was shown in healthy volunteers between Mg intake and its fractional absorption ranging from 65% absorption at low intake to 11% at high intake [21]. Thus, estimating the amount of oral Mg salts to correct hypomagnesemia in ICU patients who commonly have ileus and other forms of gastrointestinal dysfunction is problematic. The effects of vitamin D and parathyroid hormone (PTH) on enteral Mg absorption are minor [22].

Renal function is central to Mg homeostasis. Of the approx. 2.4 g Mg filtered per day (i.e., the 77% of total serum Mg that is not protein bound), 5% (120 mg) is normally excreted in the urine [23]. Glomerular filtration and tubular reabsorption both influence renal Mg handling [24]. Specifically, 20–30% of filtered Mg is reabsorbed in the proximal tubule and 60% in the thick ascending loop of Henlé [25]. This is where ionic regulators, hormones, and medications affect Mg excretion. Mg reabsorption in the thick ascending loop of Henlé is linked with NaCl transport and is therefore influenced by tubular flow [24, 25]. Conservation of Mg by normal kidneys during Mg deprivation may decrease fractional excretion to less than 0.5% (12 mg/day) [23]. Conversely, the kidneys increase excretion of Mg to approximate the filtered load during increased intake or excessive Mg administration [26]. During renal failure the fractional excretion of Mg progressively increases, and normal serum total Mg levels are maintained until the later stages when hypermagnesemia supervenes [27].

Mg homeostasis and compensatory mechanisms

Mg homeostasis involves interaction between three organ systems: kidneys, small bowel, and bone (Fig. 1). Acute Mg deprivation increases tubular reabsorption and intestinal absorption [28]. The mechanisms for such compensatory alterations in Mg transport are not fully understood. Several reports indicate a lack of correlation of these alterations with serum total Mg concentrations [29, 30, 31]. In Mg deficient rats a fall in urinary Mg excretion was found to occur without changes in plasma total Mg concentrations [28]. This adaptation was rapid (within 5 h) and specific (without changes in Na^+ or Ca^{2+} reabsorption). If Mg deprivation continues, exchangeable bone Mg starts contributing to extracellular Mg levels [32]. Up to 30% of bone Mg is rapidly exchangeable [33].

The threshold of negative Mg balance that triggers compensatory mechanisms is not known. Even so, ionized intracellular Mg $[Mg^{2+}]_i$ appears to be the ultimate regulatory signal [28]. $[Mg^{2+}]_i$ and intracellular bound Mg are exchangeable and are in equilibrium with extracellular Mg^{2+} [34]. Thus, ionized and bound intracellular

Mg represent buffers whose chief function appears to be maintaining constancy of the intracellular concentration of free $[Mg^{2+}]_i$. In human erythrocytes and other cells an increase in $[Mg^{2+}]_i$ by Mg loading is associated with Mg efflux via the Na^{2+}/Mg^{2+} antiport until $[Mg^{2+}]_i$ is normalized. Furthermore, reductions in $[Mg^{2+}]_i$ stimulate cationic diffusion down a concentration gradient from higher levels of extracellular Mg^{2+} [35, 36]. Consequently, Mg homeostasis is regulated chiefly by $[Mg^{2+}]_i$ which is in equilibrium with both intracellular bound Mg and extracellular Mg^{2+}. Neither the magnitude nor the efficiency of these compensatory mechanisms is known for critically ill patients, in whom counterregulatory hormone release, insulin administration, and de novo renal and gastrointestinal dysfunction are common.

Biochemical, biological, and physiological effects of Mg

Mg is important in physiological processes involving energy storage, transfer, and utilization [13, 37]. Mg complexed to ATP is a substrate for signal-transducing enzymes including phosphatases and phosphokinases on the plasma membrane and within intracellular compartments. Enzymatic reactions involving ATP require Mg^{2+}, which neutralizes the negative charge on ATP to facilitate binding to enzymes and assists hydrolysis of the terminal PO_4^{2-} bond [38]. Intracellular Mg^{2+} regulates intermediary metabolism by activating rate-limiting glycolytic and tricarboxylic acid cycle enzymes [39]. Mg^{2+}-ATPases include Mg^{2+}-(Na^+-K^+) ATPase, Mg^{2+}-(HCO_3^-) ATPase, and Ca^{2+}-Mg^{2+} ATPase, which are involved in Na^+, proton, and Ca^{2+} transport, respectively [40]. Mg indirectly affects protein synthesis by four mechanisms: (a) facilitation of nucleic acid polymerization, (b) enhanced binding of ribosomes to mRNA, (c) acceleration of the synthesis and degradation of DNA, and (d) regulation of protein:DNA interactions and thus transcriptional activity [41, 42]. Adenylate cyclase also requires Mg to generate the intracellular second messenger cAMP [40].

Intracellular Mg^{2+} significantly affects Ca^{2+} and K^+ metabolism. As a divalent cation Mg^{2+} competes with Ca^{2+} for membrane-binding sites and modulates Ca^{2+} binding and release from the sarcoplasmic reticulum [43]. Complementary effects include maintenance of low resting levels of intracellular Ca^{2+}, thereby modulating muscle contraction by noncompetitive inhibition of inositol 1,4,5-triphosphate gated Ca^{2+} channels [44]. Calcium metabolism is controlled chiefly through PTH; substantial evidence indicates that Mg modulates Ca balance by its actions on PTH itself [45]. For example, impaired PTH secretion associated with hypomagnesemia results in hypocalcemia. This is attributed to reduced Mg-dependent activation of adenylate cyclase in parathyroid tissue [46, 47]. Whether Mg deficiency also contributes to skeletal muscle resistance to PTH is controversial [48].

Mg^{2+} regulates K^+ transport via the Na^+-K^+-ATPase system as a cofactor. This action influences Na^+ and K^+ extracellular fluxes, which determine the electrical potential across cell membranes [49]. $[Mg^{2+}]_i$ blocks outward movement of K^+ through K^+ channels in cardiac cells. Decreases in $[Mg^{2+}]_i$ cause excessive outward movement of K^+ even as intracellular K^+ falls, thereby inducing depolarization [50]. This critical role of Mg^{2+} to maintain intracellular K^+ concentrations is termed "inward rectification" [51]. Mg^{2+} deficiency also impairs K^+-Na^+-Cl^- cotransport [52].

In the nervous system Mg has a depressant effect at the synapses; this is related to competition with calcium in the stimulus-secretion coupling processes in transmitter release. The best described of these is presynaptic inhibition of acetylcholine release at the neuromuscular junction [53]. The action of Mg as an anticonvulsant is related to noncompetitive blockade of *N*-methyl-D-aspartate receptors. These are a group of glutamate receptors, stimulation of which leads to excitatory postsynaptic potentials causing seizures [54].

Overall, Mg^{2+} deficiency has the potential to impair oxidative phosphorylation, protein metabolism, and transmembrane electrolyte flux in cardiac and neural tissues.

Assessment of Mg status

Assessing Mg status in the critically ill beyond serum total Mg levels is difficult. No single laboratory test tracks total body Mg stores. In all, three groups of tests are available: (a) estimates of tissue Mg using concentrations in serum, red blood cells, blood mononuclear cells, or muscle; (b) metabolic assessments of Mg balance encompassing isotopic analyses and evaluation of renal Mg excretion and retention, and (c) determination of Mg^{2+} levels which utilize fluorescent probes, nuclear magnetic resonance spectroscopy, or ion-selective electrodes (ISE).

Measuring total Mg concentrations in serum rather than plasma has been preferred because additives such as anticoagulants may be contaminated with Mg or otherwise affect the assay. For example, citrate binds Ca^{2+} as well as Mg^{2+} to affect fluorometric (8-hydroxyquinoline) and colorimetric procedures for Mg estimation [55]. As indicated above, serum total Mg levels reflect Mg^{2+}, the protein-bound Mg fraction, and Mg complexed to anions, and each component of the total value may change independently and in a nonlinear manner with respect to the other Mg fractions.

Most clinical laboratories report serum total Mg concentrations using colorimetric methods with calmagite or methylthymol blue as the chromophore [56]. As men-

tioned above, the chief limitation is that serum concentrations represent only 0.3% of total body Mg content [14]. Moreover, with the exception of bone, serum total Mg concentrations are not correlated with other tissue pools of Mg [57]. As for Ca, normal total Mg levels may coexist with ionized hypomagnesemia and vice versa [58]. Red blood cell Mg determinations have no advantage over serum levels and also are not correlated with other tissue fractions [57]. In normal subjects there is no correlation among Mg levels in mononuclear cells compared with serum or erythrocytes [59]. In a prospective controlled study measuring skeletal muscle Mg concentrations in 32 ICU patients with respiratory failure no correlation was found between serum total and muscle Mg concentrations [60]. Lower muscle Mg levels were associated with reduced intracellular K^+ levels, a higher incidence of ventricular extrasystoles, and a longer ICU stay.

Physiological assessments of Mg balance require steady-state conditions for accurate results, conditions that are infrequent in the critically ill. A 24-h urine collection for renal Mg excretion takes into account the circadian rhythm of cationic urinary losses [61]. However, existence of this rhythm during critical illness is unknown. Even so, a 24-h Mg excretion rate of less than 12 mg/day is acceptable evidence of Mg deficiency in the presence of serum total hypomagnesemia and normal renal function [23]. The Mg tolerance test has been used for many years as a fairly reliable means of assessing total body Mg status in patients at risk of hypomagnesemia [62]. Subjects with normal Mg balance and renal function excrete most of a parenterally administered Mg load within 24 h [28, 62]. A generally accepted protocol includes: (a) a baseline 24-h urine collection for Mg, followed immediately by (b) an infusion of 2.4 mg Mg per kilogram of lean body weight in 50 ml 5% dextrose over 4 h, and (c) a second 24-h urine collection. Differences in Mg content between the two urine collections represent the retained Mg fraction. Retention of more than 20% of administered Mg is suggestive of Mg deficiency, whereas retention of more than 50% is confirmatory [40]. This test is contraindicated when serum creatinine exceeds 200 μmol/l. Furthermore, drugs or conditions producing renal Mg wasting invalidate the results. Using the Mg loading test, serum ionized Mg levels were found to be insensitive markers of Mg deficiency in 44 ICU patients without renal insufficiency [63]. However, confounding variables, such as the use of diuretics, prevent any firm conclusions to be drawn.

A major advance in evaluating Mg deficiency is the ability to measure Mg^{2+}. In 1989 Raju et al. [64] modified the calcium fluoroprobe fura-2 to improve selectivity for Mg^{2+}. The resulting compound furaptra (mag fura-2) exhibits a shift in the peak excitation wavelength for fluorescence when bound to Mg^{2+} or Ca^{2+}. The change in fluorescence corresponds to Mg^{2+} and Ca^{2+} concentrations weighted by their respective dissociation constants. For Mg^{2+}, these probes work well within the cell. Other fluorescent probes for Mg^{2+} have been described [65]. Nuclear magnetic resonance spectroscopy estimates Mg^{2+} noninvasively. Although several isotopes ($^{19}F^-$, $^{25}Mg^{2+}$, and $^{31}P_{-2}$) have been used to estimate Mg^{2+}, the α- and β-phosphate moieties of ATP have been used most frequently [66].

Three ISEs for Mg^{2+} determination are currently available: (a) the NOVA 8 analyzer (NOVA, Waltham, Mass., USA); (b) the Microlyte 6 analyzer (Kone, Espoo, Finland); and (c) the AVL 988/4 analyzer (AVL, Schaffhausen, Switzerland). In May 1993 the United States Food and Drug Administration approved the NOVA 8 electrode for clinical use, and most studies of Mg^{2+} have used the NOVA 8 instrument. These ISEs employ ionophores and neutral carrier-based membranes designed to function in the presence of Ca^{2+} and other cations. Mg^{2+}-specific ISEs yield rapid results on whole blood, plasma, and serum using samples between 100–200 μl. Ionized Mg concentrations in healthy subjects using the NOVA 8 average 0.54–0.67 mmol/l [58, 67]. Serum reference intervals for the Kone and AVL analyzers are 0.47–0.57 mmol/l and 0.55–0.63 mmol/l, respectively [68]. No gender-related differences in Mg^{2+} have been described [67]. To date ISEs have been found to be selective for Mg^{2+}; physiological concentrations of Ca^{2+}, Na^+, K^+, H^+ and NH_4^+ have negligible effects. Therefore the precision of these analyzers is suitable for determining Mg^{2+} in intensive care [67].

The NOVA 8 and AVL analyzers correct signals from the Mg^{2+} electrode for concurrent Ca^{2+}. Calculations of Mg^{2+} and Ca^{2+} are normalized to a pH of 7.4 in the NOVA 8 instrument, which also estimates Na^+, K^+, Ca^{2+}, hematocrit, and pH [69]. The binding capacity and affinity of albumin for Mg^{2+} and Ca^{2+} varies with pH [70]; hence the Mg^{2+} and Ca^{2+} levels are pH dependent. Because of pH changes during specimen storage, measured Mg^{2+} can be reported as the Mg^{2+} at the pH of the blood sample (preferably) or as Mg^{2+} normalized to a pH of 7.4.

Mg deficiency in intensive care

Ideally, Welt and Gitelman's [71] definition of hypomagnesemia as "a reduction in total body magnesium content" defines true Mg deficiency. Unfortunately, this definition of Mg deficiency is not in keeping with commonly available laboratory technology. In spite of its imperfections serum total Mg is still used as the standard for defining hypomagnesemia in intensive care patients.

Clinical manifestations of hypomagnesemia

Most hypomagnesemia in intensive care is asymptomatic. In theory, symptoms and signs occur when the serum total Mg concentrations fall below 1.2 mg/dl (0.5 mmol/l) [72], as summarized below:

- Neuromuscular manifestations
  - Positive Chvostek's sign
  - Positive Trousseau's sign
  - Carpopedal spasm (tetany)
  - Muscle cramps
  - Muscle fasciculations and tremor
  - Muscle weakness
- Neurological manifestations
  - Convulsions
  - Nystagmus
  - Athetoid movements
  - Apathy
  - Delirium
  - Coma
- Cardiac manifestations
  - Supraventricular arrhythmias
  - Ventricular arrhythmias
  - Torsades de pointes
  - Enhanced sensitivity to digitalis intoxication
- Electrolyte disturbances
  - Hypokalemia
  - Hypocalcemia

However, manifestations of hypomagnesemia may depend more on the rate of development of the deficiency, on serum ionized rather than total hypomagnesemia, or on tissue Mg deficits rather than on circulating levels [73]. Consequently symptoms and signs ascribed to Mg deficiency may be absent even with severe hypomagnesemia (serum total Mg levels <0.8 mg/dl) [72]. Such dissociations between serum total Mg levels and clinical findings make it difficult to infer total body Mg deficiency, the need for correction of hypomagnesemia, and the physiological benefit of such correction in individual patients.

Neuromuscular manifestations of hypomagnesemia: relationship to hypocalcemia

Serum total hypomagnesemia is usually corrected because of concerns over neuromuscular irritability (e.g., positive Chvostek's and Trousseau's signs, tremors, fasciculations, and tetany) or weakness [74]. In particular, the possibility of weakness and resultant delays in ventilatory weaning attributable to hypomagnesemia have resulted in the widespread practice of frequent measurements and vigorous normalization of serum total Mg levels in ventilated patients. However, no controlled data support this practice, and its putative physiological benefit to respiratory muscle function remains obscure. Indeed, neuromuscular manifestations of serum total hypomagnesmia may be due more to concomitant hypocalcemia, even though tetany attributable solely to hypomagnesemia can occur independently of reduced serum total Ca levels [75]. Overall, neuromuscular irritability and weakness appear to be related to the combined actions of ionized hypomagnesemia and ionized hypocalcemia on the neuromuscular apparatus. Hypocalcemia does not usually develop until serum total Mg is below 1.2 mg/dl; serum total hypocalcemia occurs in one-third of hypomagnesemic medical ICU patients [76]. Hypocalcemia is usually refractory to Ca repletion unless Mg is first administered [76, 77].

Neurological manifestations of hypomagnesemia

Reported neurological manifestations of hypomagnesemia include convulsions, athetoid movements, nystagmus, apathy, delirium, and coma [40]. As mentioned above, the anticonvulsant effect of Mg appears to be via a voltage-gated antagonist action at the *N*-methyl-D-aspartate receptor [54].

Cardiac electrophysiology, hypomagnesemia, and hypokalemia

The frequency and pathogenesis of cardiac arrhythmias during hypomagnesemia [78] are hard to establish because coexisting hypokalemia is common. Whang et al. [79] reported hypokalemia in 42% of hypomagnesemic patients. Such hypokalemia is also refractory to treatment unless Mg is first repleted [74]. Although Mg per se does not participate in the production of the cardiac action potential [80], Watanabe and Dreifus [81] showed that Mg's effects on cardiac transmembrane potentials varied in perfused rat hearts according to extracellular K^+ levels. Increases or decreases in Mg levels with normal extracellular K^+ concentrations causes minor electrophysiological changes. Alterations in serum total Mg concentrations are unlikely to destabilize sinus rhythm unless accompanied by changes in other cations [80].

Serum total Mg levels below 0.7 mmol/l are associated with electrocardiographic changes indistinguishable from hypokalemia-related effects, including ST segment depression, flattened T waves, and prolongation of PR and QT/QTc intervals [38]. Arrhythmias associated with serum total hypomagnesemia include premature atrial contractions, atrial fibrillation, multifocal atrial tachycar-

dia, premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation [82, 83]. Hypomagnesemia promotes digitalis-induced arrhythmias [84]. The mechanisms are unclear but include: (a) increased myocardial uptake of digoxin, (b) augmented inhibitory action of digoxin on Na^+-K^+-ATPase causing a reduction in intracellular K^+ [82], and (c) loss of the membrane-stabilizing effect Mg^{2+} on the myocardial cell membranes [84]. Mg therapy is recommended for torsades de pointes [85]. Despite these associations of low serum total Mg levels with cardiac electrophysiological changes, purported links between low Mg and arrhythmias do not confirm a cause and effect relationship. Lack of a standard by which to define a Mg-deficient state, coexistence of other electrolyte abnormalities, varying methods of arrhythmia monitoring, and inability to distinguish between spontaneous and drug-induced arrhythmia termination are all factors [80]. Moreover, a prospective uncontrolled study of 23 heart failure patients found no correlation between serum total Mg and myocardial Mg concentrations [86].

Causes of Mg deficiency in intensive care

Singly or combined, Mg deficiency in intensive care has three main causes – (a) reduced intestinal absorption, (b) increased renal losses, and (c) compartmental redistribution, as detailed below.

Gastrointestinal causes include:

- Nutritional disturbances
  - Inadequate intake
  - Mg-free fluids and total parenteral nutrition
  - Refeeding syndrome
- Reduced absorption
  - Malabsorption syndromes
  - Short bowel syndrome
  - Chronic diarrhea
- Increased intestinal losses
  - Intestinal and biliary fistulae
  - Prolonged nasogastric suction
- Pancreatitis

Causes related to renal Mg wasting include:

- Intrinsic tubular defect
  - Interstitial nephropathy
  - Postobstructive diuresis
  - Diuretic phase of ATN
  - Postrenal transplantation
- Drug-induced renal Mg wasting
  - Loop and thiazide diuretics
  - Cisplatin
  - Cyclosporine A
  - Aminoglycosides
  - Amphotericin B
  - Pentamidine and foscarnet
  - Colony-stimulating factor therapy
- Hypophosphatemia
- Hypercalcemia/hypercalciuria

Endocrine causes include:

- Hyperaldosteronism
- Hyperparathyroidism
- Hyperthyroidism
- Syndrome of inappropriate antidiuretic hormone
- Diabetic ketoacidosis
- Alcoholic ketoacidosis

Causes related to the redistribution of Mg include:

- Acute pancreatitis
- Administration of epinephrine
- "Hungry bone" syndrome
- Massive blood transfusion
- Acute respiratory alkalosis

Other causes include:

- Cardiopulmonary bypass
- Severe burns
- Excessive sweating
- Chronic alcoholism and alcoholic withdrawal

Nearly all data concerning hypomagnesemia during critical illness comes from measurements of circulating total Mg. These do not shed light on the causes of Mg deficiency and likely underestimate ionized hypomagnesemia and total body Mg depletion.

Gastrointestinal causes

Prolonged administration of Mg-free parenteral nutrition formulae and other intravenous fluids can precipitate Mg deficiency, especially in patients with preexisting marginal stores of Mg [87]. Vomiting and nasogastric suctioning further contribute to Mg depletion [48], since the Mg content of upper intestinal fluids is about 1 mEq/l. Diarrheal fluids and fistula drainage contain up to 15 mEq/l total Mg ions [88]. Hemorrhagic pancreatitis is an additional cause of acute hypomagnesemia with hypocalcemia due to formation of Mg and Ca fatty acid soaps in sites of tissue necrosis [89].

Renal causes

Renal Mg wasting is traditionally diagnosed when the 24 h urinary Mg excretion exceeds 24 mg in the presence of hypomagnesemia as assessed by serum total Mg levels [23]. Random or "spot" urinary tests for Mg are interesting albeit unvalidated diagnostic tests. Renal Mg wasting has been reported with tubulointerstitial renal diseases, postobstructive diuresis, the diuretic phase of acute tubular necrosis, and following renal transplantation [90]. Since Mg absorption in the thick ascending loop of Henlé depends on the positive transmembrane potential created by NaCl absorption, alterations in NaCl transport by loop diuretics, 0.9% NaCl infusion, or osmotic diuresis promote Mg excretion. Loop diuretics (furosemide, bumetamide, and ethacrynic acid) are potent inhibitors of Mg reabsorption and are a common cause of hypomagnesemia in the ICU. Thiazide diuretics act on the distal tubule, where less than 5% of Mg is absorbed. Short-term administration of thiazides does not produce significant renal Mg wasting, whereas long-term administration may produce substantial Mg deficiency [40].

Several drugs cause excessive renal losses of Mg. Cisplatin causes hypomagnesemia in more than 50% of treated patients [91]; the incidence increases with the cumulative dose. Likewise, aminoglycosides induce magnesuria; 4.5% of 200 patients treated with 400 courses of aminoglycosides developed hypomagnesemia [92]. The total dose of aminoglycoside treatment in these studies varied from 1.3–40 g and recovery from hypomagnesemia varied from 2–8 weeks. A recent prospective study showed ionized hypomagnesemia secondary to renal Mg wasting in cystic fibrosis patients treated with a 2-week course of 33 mg/kg amikacin daily and 250 mg/kg ceftazidime daily [93], although no clinical correlation with ionized hypomagnesemia was performed. Amphotericin B causes mild and reversible hypomagnesemia [94]. Barton et al [94]. reported that reversal of amphotericin B-induced renal Mg wasting could take as long as 1 year following treatment. As with amphotericin B, cyclosporine A causes Mg deficiency secondary to defects in renal tubular function [95]. Parenteral pentamidine has also been implicated in hypomagnesemia secondary to renal Mg wasting [96].

Hypophosphatemia is common during intensive care, particularly in insulin-dependent diabetics and during Gram-negative bacterial sepsis [97]. Although hypophosphatemia promotes magnesuria, the mechanism is unclear [79]. Serum total Mg levels are inversely correlated with the fasting blood sugar level in diabetics in whom glycosuria, ketoaciduria, and hypophosphatemia contribute to renal Mg wasting [98]. Primary [99] and secondary [100] hyperaldosteronism are associated with renal Mg wasting secondary to volume expansion, causing increased tubular flow rates and decreased NaCl reabsorption [99]. The exact mechanism, however, remains controversial. Other hormonal conditions associated with hypomagnesemia are the syndrome of inappropriate antidiuretic hormone secretion [101] and hyperthyroidism [102].

Redistribution of Mg

"Hungry bone syndrome" after parathyroidectomy [103] or diffuse osteoblastic metastasis [104] can result in hypomagnesemic, hypocalcemic tetany from osseous deposition of Mg and Ca. Epinephrine and other β-agonists (e.g., salbutamol) cause transient hypomagnesemia in healthy subjects [105]. This is thought to occur from uptake of Mg into adipose tissue as fatty acids are released. Release of fatty acids into the blood may also lead to the formation of insoluble fatty acid–Mg^{2+} and fatty acid–Ca^{2+} complexes [40]. Massive blood transfusion (>10 U/24 h) may cause hypomagnesemia from the chelating effects of citrate [106]. Hypomagnesemia occurs during and after cardiopulmonary bypass surgery [84, 107]. Potential mechanisms include hemodilution from large-volume infusion of Mg-free fluids, removal of Mg by the bypass pump, and catecholamine-induced intracellular Mg shifts, and binding to free fatty acids [107]. A retrospective study of 30 patients undergoing elective cardiopulmonary bypass surgery demonstrated ionized hypomagnesemia in 73% [108]. Of note, the relationship between Mg^{2+} and Ca^{2+} during CPB was variable, and Ca^{2+} levels did not predict Mg^{2+} levels [108]. Significant hypomagnesemia (i.e., serum total Mg level <1.40±0.15 mEq/l) occurs in up to 30% of alcoholics. Multiple mechanisms are likely, including decreased Mg intake accompanying poor nutritional status, vomiting, chronic pancreatitis-induced steatorrhea, and Mg malabsorption [109].

Collectively, the above data indicate that hypomagnesemia (serum total Mg level <1.5 mEq/l) may have multiple causes in the ICU patient. Even so, three critical questions remain: (a) to what extent does ionized hypomagnesemia parallel reductions in serum total Mg levels and in total body Mg stores? (b) Does Mg replacement to correct levels of serum total Mg also correct ionized hypomagnesemia? (c) Is correction of serum total or ionized hypomagnesemia associated with definable clinical changes in biochemistry, electrophysiology, inflammatory responses or organ function? Until the answers to these questions are forthcoming, we may be spending considerable effort and expense merely to make serum total Mg levels "look better."

Mg, sepsis, and shock

Novel immunoregulatory effects of Mg deficiency and supplementation are increasingly reported [110, 111,

112]. Such data suggest that reductions in circulating and intracellular Mg have important, albeit clinically occult immunomodulatory consequences during severe sepsis and shock states. By enhancing generation of reactive O_2 species [111] and cytokine biosynthesis, hypomagnesemia can promote inflammatory tissue injury [112].

Altura et al. [113] proposed that circulating free Mg^{2+} ions are "natural" Ca^{2+} antagonists that modulate lethal cellular Ca^{2+} entry during shock. Lower Mg^{2+} concentrations have been found to be correlated with efflux of Ca^{2+} from the sarcoplasmic reticulum of frog myocytes over a 0.3- to 3-mmol concentration range of Mg^{2+} [114]. A direct effect of low $[Mg^{2+}]_i$ to increase the voltage-gated calcium current (I_{Ca}) was implicated. Based on this and other reports [115], Mg^{2+} deficiency may promote abnormal cellular Ca^{2+} entry during sepsis; this may in turn increase free cytosolic and mitochondrial Ca^{2+} to cause cell death. In support of this, intracellular Ca^{2+} has been reported to increase as tissue Mg^{2+} levels decline in a rat endotoxic shock model [116]. Concomitant depression of mitochondrial respiration was restored after Mg^{2+} supplementation.

Since considerable intracellular Mg^{2+} is complexed to ATP, sepsis, or ischemia/reperfusion-induced ATP hydrolysis or falls in ATP production release intracellular Mg^{2+} ions. Subsequently $[Mg^{2+}]_i$ concentrations rise, and Mg^{2+} effluxes from cells [115, 117]. Three negative consequences may result: (a) impaired Na^+-K^+ ATPase pump activity, (b) reduced inwardly rectifying K^+ ion channels, and (c) dysfunctional cell membrane and sarcolemmal Ca^{2+} ion channels [61]. These changes may partly account for the increased lethality of endotoxemia seen in rats during hypomagnesemia as well as the protective effects of Mg replacement from endotoxin challenge [118].

Mg^{2+} ions modulate key immunological functions, including macrophage activation, leukocyte adherence, and bactericidal activity [119], granulocyte oxidative burst, lymphocyte proliferation, and endotoxin binding to monocytes [118]. In Mg-deficiency models time-dependent increases are seen in circulating interleukin-1, tumor necrosis factor-α, interferon-γ, substance P, and calcitonin gene related peptide [110, 112, 120]. Such effects may result from altered DNA binding of transcription factors notable for their suppression of inflammatory cytokine gene activation, including the cyclic AMP response element binding protein [42]. Likewise, Mak et al. [121] reported overproduction of nitric oxide in an Mg-deficient rat model. In that report increased nitric oxide production was considered secondary to Mg deficiency-related stimulation of inducible nitric oxide synthase and activation of Ca-sensitive nitric oxide synthase from increased intracellular Ca^{2+}. Cytotoxic effects of NO include those resulting from its combination with superoxide to form peroxynitrite [121]. Inhibition of mitochondrial respiration, interference with the O_2 carrying ability of hemoglobin and myoglobin due to interaction with heme proteins, and inhibition of enzymes containing heme and nonheme iron-sulfur centers all contribute to toxicity [122]. Overall, emerging data showing interrelated links among biochemical, physiological, and immunoregulatory effects of Mg deficiency during sepsis and shock suggest the corollary thesis that titrated Mg supplementation can alter outcomes. Further experimental and clinical data are needed to confirm this notion.

Ionized Mg and intensive care

Serum total Mg levels are not correlated with serum Mg^{2+} in the critically ill because of accompanying variations in plasma protein concentrations, acid-base balance, metabolic derangements, and drugs that affect Mg balance [58, 123]. Külpmann et al. [123] showed that reduced serum total Mg concentrations maymight reflect "pseudohypomagnesemia" from hypoalbuminemia when concomitant Mg^{2+} concentrations are normal. Such findings have led to the suggestion that the terms hypo-, normo-, and hypermagnesemia should be restricted to Mg^{2+} levels. Of note, $[Mg^{2+}]_i$ levels are correlated well with serum Mg^{2+} by ^{31}P-nuclear magnetic resonance spectroscopy [124]. In aortic endothelium $[Mg^{2+}]_i$ levels change within 5 min of increasing extracellular Mg^{2+}, suggesting that extracellular Mg^{2+} dynamically equilibrates with $[Mg^{2+}]_i$ [125]. Additional studies are needed to confirm whether extracellular Mg^{2+} accurately tracks total body Mg balance. In spite of in vitro studies demonstrating the superiority of ionized Mg measurements over total Mg estimations; few studies have attempted to demonstrate the importance of measuring ionized Mg levels in the critical care setting and to examine the correlation of ionized hypomagnesemia with clinical manifestations and outcomes.

Salem et al. [126] measured Mg^{2+} and serum total Mg concentrations in 180 critically ill patients. Serum total Mg values were sensitive (75%) but not specific (38%) in predicting ionized hypomagnesemia. Increased supraventricular and ventricular dysrhythmias, seizures, hypotension, and death were associated with ionized hypomagnesemia (normal range 0.52–0.60 mmol/l). Recently, Huijgen and colleagues [127] evaluated the relationships between serum Mg^{2+}, total body Mg estimated by Mg content in blood mononuclear cells and erythrocytes, serum albumin, and 30-day mortality in 115 critically ill patients. A normal serum Mg^{2+} was found in 71% of patients with total serum hypomagnesemic values. Moreover, neither total nor ionized Mg measurement was correlated with cellular Mg levels or with outcome. With respect to the cardiovascular effects of hypomagnesemia, Kasaoka et al. [128] found that supraventricular and ventricular extrasystoles decreased by 50% and ventricular

tachycardia was abolished by a 0.15 mmol/kg intravenous bolus of Mg sulfate ($MgSO_4$) over 10 min, which increased serum Mg^{2+} from 0.35±0.06 mmol/l to 0.54±0.09 mmol/l. $MgSO_4$ had no effect in patients with a normal serum Mg^{2+}. The ratio of Mg^{2+} to Ca^{2+} as a modulator of vascular tone also increased after intravenous $MgSO_4$ and was thought to contribute to the antiarrhythmic effect. Bertschat et al. [129] determined serum Mg^{2+} levels on days 1, 2, 3, 5, and 7 after myocardial infarction in 42 patients, in addition to concomitant serum total Mg, free fatty acids, Ca^{2+}, and total Ca. Compared with serum total Mg concentrations, Mg^{2+} levels fell on the 1st day of myocardial infarction and were inversely correlated with serum free fatty acids. The ionized hypomagnesemia was attributed to β-adrenergic induced lipolysis and binding of Mg^{2+} by fatty acids. Since the benefit of intravenous $MgSO_4$ during acute myocardial infarction is not established, the authors suggest that serum Mg^{2+} rather than total Mg be measured in coronary care patients, and that those with ionized hypomagnesemia be treated [129].

Frankel et al. [130] noted a poor correlation between serum total and Mg^{2+} values in 113 trauma patients, although injury severity or blood ethanol levels did not predict ionized hypomagnesemia. It has been hypothesized that decreased serum Mg^{2+} levels after trauma result from increases in circulating catecholamines and corticosteroids, and to Mg redistribution within injured tissues [131]. Ionized hypomagnesemia occurs after experimental head trauma [132] and in brain-injured patients [133]. In vivo animal studies have shown that pre- or posttreatment with $MgCl_2$ 15 min after cerebral injury restores brain Mg^{2+} levels, improves motor function [134], attenuates cognitive deficits [135], and reduces cerebral edema [136]. In a traumatic brain injury rat model Bareyre et al. [137] studied serum Mg^{2+} levels 24 h postinjury and neuromotor outcome after 1 and 2 weeks. Supplemental Mg treatment given to rats with ionized hypomagnesemia reduced posttraumatic impairments. No such correlation was found using blood total Mg levels, which did not change postinjury. In other in vivo animal studies Mg treatment has been shown to reduce posttraumatic edema and cortical damage, in association with concomitant changes in gene expression for c-fos, heat shock protein-70, neurotrophins, and cyclooxygenase-2 [136, 138]. In addition to Mg's multiple effects on intermediary metabolism, oxidative phosphorylation, protein synthesis, regulation of membrane permeability to Ca^{2+} and K^+ ions, and potential anti-inflammatory effects, it has also been recently shown in murine cortical cell cultures to be a potent antioxidant to iron-dependent oxidative injury [139]. By increasing the physiologically active ionized Mg fraction, $MgCl_2$ possibly restores the ability of cells to maintain homeostasis [137]. Available data therefore suggest that early measurement of blood ionized Mg levels and supplementation when indicated may be of value in reducing morbidity after head injury or cerebral infarction. The positive data correlating neuromotor outcomes after head injury and correcting ionized hypomagnesemia are currently limited to animal studies only; more investigation needs to be carry out to determine whether the same holds true in human head-injured patients in prospective randomized controlled trials.

Treatment of hypomagnesemia

Treatment recommendations for hypomagnesemia in intensive care are confounded by the lack of controlled clinical data regarding the directional changes in time-matched serum total and ionized Mg levels, particularly in relation to concomitant ionized Ca^{2+}, K^+, and PO_4 concentrations. In addition, renal insufficiency, administration of drugs which promote renal Mg wasting, and varying recommendations for Mg repletion are problematic [140, 141]. An ideal ICU study to clarify these issues would therefore have to first attempt to define the measure of true Mg deficiency (total body, extracellular ionized, etc.) that is correlated with clinical manifestations. The study would further need to control for disturbances in other cations and drugs that interfere with Mg balance and renal function and determine the clinical, biochemical, and hemodynamic effects of correcting Mg deficiency with the ultimate goal of determining patient outcomes.

Nonetheless, several generalizations are appropriate regarding the treatment of Mg deficiency:

- Emergency (intravenous route):
  - 8–12 mmol Mg over 1–2 min
  - 40 mmol Mg over next 5 h
- Severely ill (intravenous or intramuscular route)
  - 40 mmol Mg on day 1
  - 16–24 mmol Mg on days 2–5
- Oral maintenance
  - 12–24 mmol per day

Kidney function must be assessed prior to the initiation of Mg therapy. Since the major route of Mg excretion is via the kidney, significant hypermagnesemia can occur in the setting of compromised renal function. In general, when rapid Mg administration is needed, as for cardiac arrhythmias, the intravenous route is safe. It should, however, be performed with hemodynamic and electrocardiographic monitoring as there may be significant prolongation of intra-atrial and atrioventricular nodal conduction times [142] as well as hypotension. Davies et al. [143] noted hypotension in three patients during

Gram-negative bacteremic sepsis when Mg sulfate ($MgSO_4$) was given using a rapid regimen (8 mmol intravenously over 5 min). The authors did not mention the degree of hypotension that occurred, nor the baseline blood pressure and the use of vasopressors (if any) prior to Mg administration. No hypotension occurred when 48 mmol $MgSO_4$ was infused over 24 h. Such hypotensive responses may reflect the combined effects of sepsis-induced myocardial dysfunction together with Mg infusion-induced reductions in systemic vascular resistance. In the critical care setting treatment recommendations must therefore be tempered with the urgency of replacing Mg deficits. Slower infusions (mentioned below) are appropriate unless cardiac arrhythmias or seizures are present. Slow replacement can be achieved by giving 8–12 g $MgSO_4$ intravenously over 24 h, followed by 4–6 g daily for another 3–4 days [40]. Since up to 50% of administered Mg may be lost in the urine, continuous infusions of Mg or repeated doses may be preferable. However, there are no controlled data with regard to the efficacy of this approach in critically ill patients. Oral Mg salts can be used as maintenance therapy in conditions associated with chronic Mg loss, for example, short or long-term use of diuretics. An initial daily dose of 300–600 mg elemental Mg may be used. The Mg is given in divided doses to decrease its cathartic effect. Significant hypermagnesemia can complicate Mg replacement when the glomerular filtration rate is less than 30 ml/min [13]. Elevation in serum total Mg to levels higher than 2 mmol/l are usually accompanied by symptoms. The effects of increasing rise in serum total Mg levels include hypotension (1.5–2.5 mmol/l), electrocardiographic changes (2.5–5 mmol/l), areflexia (5 mmol/l), respiratory paralysis (7.5 mmol/l), and cardiac arrest (>12.5 mmol/l) [38]. Physiological antagonism of hypermagnesemia with intravenous calcium gluconate can be used until dialysis can be initiated.

With respect to cardiac arrhythmias and ventricular arrhythmias in particular, recommended protocols for Mg treatment are unclear as no large-scale controlled studies comparing replacement regimens, their effects on total vs. ionized Mg levels, and clearcut physiological endpoints have been performed. In general, 2 g $MgSO_4$ constituting 8 mmol intravenously over 1–2 min, followed by an additional 40 mmol over the next 5 h is considered safe and probably effective [141]. As discussed above, an antiarrhythmic dose of 0.15 mmol/kg $MgSO_4$ given as an intravenous bolus over 10 min was used by Kasaoka et al. [128] to correct ionized hypomagnesemia (<0.40 mmol/l). Simultaneous administration of K^+ and Ca may be necessary because concomitant losses of these cations are common in Mg deficiency. Emerging data underscore the lack of a predictable relationship between serum total and ionized Mg levels, either before or after intravenous Mg supplementation. Barrera et al. [144] were unable to predict serum Mg^{2+} levels from serum total Mg values in 33 ICU patients, in whom intravenous treatment with 4.1 mmol (1 g) had no effect on ionized Ca^{2+} or K^+ concentrations, although both serum ionized and total Mg levels were increased.

Summary

Mg metabolism and the important physiological roles of Mg as they relate to the critically ill have been reviewed. However, fundamental aspects of Mg metabolism, assessment of Mg deficiency, and efficacy of treatment of hypomagnesemia, whether total or ionized, remain poorly understood. Although serum total Mg continues to be the most frequently used tool for diagnosing and treating hypomagnesemia, randomized clinical studies are needed to determine whether newer methods of Mg assessment, including the measurement of Mg^{2+}, are superior. Newer insights into the immunomodulatory roles of Mg in vivo, improvements in estimating whole-body and compartmental Mg concentrations, and clearer documentation of the biochemical and physiological effects of correcting hypomagnesemia will undoubtedly assist the intensivist in determining the the rationale and the mode for correcting a low Mg value.

References

1. Elin RJ (1994) Magnesium: the fifth but forgotten electrolyte. Clin Chem 102:616–622
2. Kruse HD, Orent ER, McCollum EV (1932) Studies on magnesium deficiency in animals. I. Symptomatology resulting from Mg deprivation. J Biol Chem 96:519–539
3. Whang R (1987) Routine serum magnesium determination: a continuing unrecognized need. Magnesium 6:1–4
4. Toffaletti J (1995) Physiology and regulation: ionized calcium, magnesium and lactate measurements in critical care settings. Am J Clin Pathol 104 [Suppl 1]:S88–S94
5. Reinhart RA, Desbiens NA (1985) Hypomagnesemia in patients entering the ICU. Crit Care Med 13:506–507
6. Ryzen E, Wagers PW, Singer FR, Rude RK (1985) Magnesium deficiency in a medical ICU population. Crit Care Med 13:19–21
7. Chernow B, Bamberger S, Stoiko M, Vadnais M, Mills S, Hoellrich V, Warshaw AL (1989) Hypomagnesemia in patients in postoperative intensive care. Chest 95:391–397
8. Rubeiz GJ, Thill-Baharozian M, Hardie D, Carlson RW (1993) Association of hypomagnesemia and mortality in acutely ill medical patients. Crit Care Med 21:203–209

9. Drop LJ (1985) Ionized calcium, the heart, and hemodynamic function. Anesth Analg 64:432–451
10. Kost GJ (1993) The significance of ionized calcium in cardiac critical care. Arch Pathol Lab Med 117:890–896
11. Desai TK, Carlson RW, Thill-Baharozian M, Geheb MA (1988) A direct relationship between ionized calcium and arterial pressure among patients in an intensive care unit. Crit Care Med 16:578–582
12. Broner CW, Stidham GL, Westenkirchner DF, Tolley EA (1990) Hypermagnesemia and hypocalcemia as predictors of high mortality in critically ill pediatric patients. Crit Care Med 18:921–928
13. Wacker WEC, Parisi AF (1968) Magnesium metabolism. N Engl J Med 278:658–663
14. Elin RJ (1987) Assessment of magnesium status. Clin Chem 33:1965–1970
15. Günther T (1993) Mechanisms of regulation of Mg efflux and Mg influx. Miner Electrolyte Metab 19:259–265
16. Speich M, Bousquet B, Nicolas G (1981) Reference values for ionized, complexed and protein-bound plasma magnesium in men and women. Clin Chem 27:246–248
17. Altura BT, Altura BM (1994) A method for distinguishing ionized, complexed and protein-bound Mg in normal and diseased subjects. Scand J Clin Lab Invest 54, Suppl 217:83–87
18. Seelig MS (1981) Magnesium requirements in human nutrition. Magnesium Bull 3 [Suppl 1A]:26–47
19. Graham LA, Caessar JJ, Burgen ASV (1960) Gastrointestinal absorption of Mg28 in man. Metabolism 9:646–659
20. Kayne LH, Lee DBN (1993) Intestinal magnesium absorption. Miner Electrolyte Metab 19:210–217
21. Fine KD, Santa Ana CA, Porter JL, Fordtran JS (1991) Intestinal absorption of magnesium from food and supplements. J Clin Invest 88:396–402
22. Hodgkinson A, Marshall DH, Nordin BEC (1979) Vitamin D and magnesium absorption in man. Clin Sci (Colch) 57:121–123
23. Sutton RAL, Domrongkitchaiborn S (1993) Abnormal renal magnesium handling. Miner Electrolyte Metab 19:232–240
24. Quamme GA, Dirks JH (1986) The physiology of renal magnesium handling. Renal Physiol 9:257–269
25. Quamme GA (1989) Control of magnesium transport in the thick ascending limb. Am J Physiol 256:F197–F210
26. Wong NLM, Dirks JH, Quamme GA (1983) Tubular reabsorptive capacity for magnesium in the dog kidney. Am J Physiol 244:F78–F83
27. Coburn JW, Popovtzer MM, Massry SG, Kleeman CR (1969) The physicochemical state and renal handling of divalent ions in chronic renal failure. Arch Intern Med 124:302–311
28. Quamme GA (1993) Laboratory evaluation of magnesium status. Renal function and free intercellular magnesium concentration. Clin Lab Med 13:209–223
29. Dunn MJ, Walser MR (1964) Magnesium depletion in normal man. Metabolism 15:884–895
30. Fitzgerald MG, Fourman P (1956) An experimental study of magnesium deficiency in man. Clin Sci (Colch) 15:635
31. Rude RK, Bethune JR, Singer FR (1980) Renal tubular maximum for magnesium in normal, hypoparathyroid and hyperparathyroid man. J Clin Endocrinol Metab 51:1425
32. Alfrey AC, Miller NL, Trow R (1974) Effect of age and magnesium depletion on bone magnesium pools in rats. J Clin Invest 54:1074–1081
33. Alfrey AC, Miller NL (1973) Bone magnesium pools in uremia. J Clin Invest 52:3019–3027
34. Günther T (1990) Functional compartmentation of intracellular magnesium. In: Sigel H, Sigel A (eds) Metal ions in biological systems, vol 26. Dekker, New York, pp 193–213
35. Quamme GA (1997) Renal magnesium handling: new insights in understanding old problems. Kidney Int 52:1180–1195
36. Beyenbach KW (1990) Transport of magnesium across biological membranes. Magnes Trace Elem 9:223–254
37. Aikawa JK (1981) Magnesium: its biological significance. CRC, Boca Raton
38. Reinhart RA (1988) Magnesium metabolism: a review with special reference to the relationship between intracellular content and serum levels. Arch Intern Med 148:2415–2420
39. Garfinkel L, Garfinkel D (1985) Magnesium regulation of the glycolytic pathway and the enzymes involved. Magnesium 4:60–72
40. Al-Gamadi SMG, Cameron EC, Sutton RAL (1994) Magnesium deficiency: pathophysiologic and clinical overview. Am J Kidney Dis 24:737–752
41. Vernon WB (1988) The role of magnesium in nucleic acid and protein metabolism. Magnesium 7:234–248
42. Schumacher MA, Goodman RH, Brennan RG (2001) The structure of a CREB bZIP.somatostatin CRE complex reveals the basis for selective dimerization and divalent cation-enhanced DNA binding. J Biol Chem 10:35242–35247
43. Ryan MF (1991) The role of magnesium in clinical biochemistry: an overview. Ann Clin Biochem 28:19–26
44. Volpe P, Vezu L (1993) Intracellular magnesium and inositol 1:4,5 triphosphate receptor: molecular mechanisms of interaction, physiology and pharmacology. Magnes Res 6:267–274
45. Rude RK, Oldham SB, Sharpe CF, Singer FR (1978) Parathyroid hormone secretion in magnesium deficiency. J Clin Endocrinol Metab 47:800–806
46. Rude RK, Singer FR (1981) Magnesium deficiency and excess. Annu Rev Med 32:245–259
47. Targovnik JH, Rodman JS, Sherwood LM (1971) Regulation of parathyroid hormone secretion in vitro: quantitative aspects of calcium and magnesium ion control. Endocrinology 88:1477–1482
48. Nadler JL, Rude RK (1995) Disorders of magnesium metabolism. Endocrinol Metab Clin North Am 24:623–641
49. Dyckner T, Wester PO (1984) Intra-/extracellular shifts of potassium after administration of Mg in patients with cardiovascular diseases. Magnesium 3:339–345
50. White RE, Hartzell HC (1989) Magnesium ions in cardiac function. Regulator of ion channels and second messengers. Biochem Pharmacol 38:859–867
51. Vandenberg CA (1987) Inward rectification of a potassium channel in cardiac ventricular cells depends on internal magnesium ions. Proc Natl Acad Sci USA 84:2560–2564
52. Whang R, Whang DD, Ryan MR (1992) Refractory potassium repletion. Arch Intern Med 152:40–45
53. Borzeix MG, Akimjak JP, Charles P, Lenfant M, Cahn R (1994) Effect of magnesium on GABA inhibition-induced convulsions in mice. Effect of three salts. In: Golf S, Dralle D, Vecchiet L (eds) Magnesium 1993. Libbey, London, pp 177–180
54. Mason BA, Standley CA, Irtenkauf SM, Bardicef M, Cotton DB (1994) Magnesium is more efficacious than phenytoin in reducing N-methyl-D-aspartate seizures in rats. Am J Obstet Gynecol 171:999–1002
55. Caddell JL, Erickson M, Byrne PA (1974) Interference from citrate using the titan yellow method and two fluorometric methods for magnesium determination in plasma. Clin Chim Acta 41:435–438
56. Elin RJ (1991) Determination of serum magnesium concentration by clinical laboratories. Magnes Trace Elem 10:60–66
57. Alfrey AC, Miller NL, Butkus D (1974) Evaluation of body magnesium stores. J Lab Clin Med 84:153–162
58. Altura BT, Altura BM (1992) Measurement of ionized magnesium in whole blood, plasma and serum with a new ion-selective electrode in healthy and diseased human subjects. Magnes Trace Elem 10:90–98

59. Elin RJ (1988) Status of the determination of magnesium in mononuclear blood cells in humans. Magnesium 7:300–305
60. Fiaccadori E, Del Canale S, Coffrini E, Melej R, Vitali P, Guariglia A, Borghetti A (1988) Muscle and serum magnesium in pulmonary intensive care unit patients. Crit Care Med 16:751–760
61. Luce GG (1970) Biological rhythms in psychiatry and medicine. Publication no 2088. Public Health Service, Washington
62. Ryzen E, Elbaum N, Singer FR, Rude RK (1985) Parenteral magnesium tolerance testing in the evaluation of magnesium deficiency. Magnesium 4:137–147
63. Hébert P, Mehta N, Wang J, Hindmarsh T, Jones G, Cardinal P (1997) Functional magnesium deficiency in critically ill patients identified using a magnesium-loading test. Crit Care Med 25:749–755
64. Raju B, Murphy E, Levy LA, Hall RD, London RE (1989) A fluorescent indicator for measuring cytosolic free magnesium. Am J Physiol 256:C540–C548
65. Illner H, McGuigan JAS, Lüthi D (1992) Evaluation of Mag-fura-5, the new fluorescent indicator for free magnesium measurements. Pflugers Arch 422:179–184
66. London RE (1991) Methods for measurement of intracellular magnesium: NMR and fluorescence. Annu Rev Physiol 53:241–258
67. Altura BT, Shirey TL, Young CC, Hiti J, Orfano KD, Handwerker M, Altura BM (1992) A new method for the rapid determination of ionized Mg in whole blood, serum and plasma. Methods Find Exp Clin Pharmacol 14:297–304
68. Huijgen HJ, Sanders R, Cecco SA, Rehak NN, Sanders GT, Elin RJ (1999) Serum ionized magnesium: comparison of results obtained with three ion-selective analyzers. Clin Chem Lab Med 37:465–470
69. Anonymous (1997) NOVA 8 reference manual. Nova Biomedical, Waltham
70. Fogh-Andersen N, Bjerrum PJ, Siggaard-Andersen O (1993) Ionic binding, net charge, and Donnan effect of human serum albumin as a function of pH. Clin Chem 39:48–52
71. Welt LG, Gitelman H (1965) Disorders of magnesium metabolism. DM 11:1–32
72. Kingston ME, Al-Siba'i MB, Skooge WC (1986) Clinical manifestations of hypomagnesemia. Crit Care Med 14:950–954
73. Sutton RL, Dirks JH (1991) Disturbances of calcium and magnesium metabolism. In: Brenner BM, Rector FR (ed) The kidney, vol 1, 4th edn. Saunders, Philadelphia, pp 841–887
74. Shills ME (1969) Experimental human magnesium depletion. Medicine (Baltimore) 48:61–85
75. Wacker WEC, Moore FD, Ulmer DD, Vallee BL (1962) Normocalcemic magnesium deficiency tetany. JAMA 180:161–163
76. Ryzen E, Wagers PW, Singer FR, Rude RK (1985) Magnesium deficiency in a medical ICU population. Crit Care Med 13:19–21
77. Abdulrazzaq YM, Smigura FC, Wettrell G (1989) Primary infantile hypomagnesemia; report of two cases and review of literature. Eur J Pediatr 148:459–461
78. Iseri LT, Allen BJ, Brodsky MA (1989) Magnesium therapy of cardiac arrhythmias in critical care medicine. Magnesium 8:299–306
79. Whang R, Oei TO, Aikawa JK, Vannatta J, Fryer A, Markanich M (1984) Predictors of clinical hypomagnesemia. Arch Intern Med 144:1794–1796
80. Keller P, Aronson R (1990) The role of magnesium in cardiac arrhythmias. Prog Cardiovasc Dis 32:433–448
81. Watanabe Y, Dreifus LS (1972) Electrophysiological effects of magnesium and its interaction with potassium. Cardiovasc Res 6:79–88
82. Iseri LT, Freed J, Bures AR (1975) Magnesium deficiency and cardiac disorders. Am J Med 58:837–844
83. Burch GE, Giles TD (1977) The importance of magnesium deficiency in cardiovascular disease. Am Heart J 94:649–657
84. Fawcett WJ, Haxby EJ, Male DA (1999) Magnesium: physiology and pharmacology. Br J Anaesth 83:302–320
85. Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Gottlieb S, Stern S (1988) Treatment of torsade de pointes with magnesium sulfate. Circulation 77:392–397
86. Ralston MA, Murnane MR, Kelley RE, Altschuld R, Unverferth DV, Leier CV (1989) Magnesium content of serum, circulating mononuclear cells, skeletal muscle, and myocardium in congestive heart failure. Circulation 80:573–580
87. Hall RCW, Joffre JR (1973) Hypomagnesemia: physical and psychiatric symptoms. JAMA 224:1749–1751
88. Booth CC, Babouris N, Hanna S, MacIntyre I (1963) Incidence of hypomagnesemia in intestinal malabsorption. BMJ 2:141–144
89. Edmondson HA, Berne CJ, Homann RE, Wertman M (1952) Calcium, potassium, magnesium and amylase disturbances in acute pancreatitis. Am J Med 12:34–42
90. Davis BB, Preuss HG, Murdaugh HV Jr (1975) Hypomagnesemia following the diuresis of post-renal obstruction and renal transplant. Nephron 14:275–280
91. Schilsky RL, Anderson T (1979) Hypomagnesemia and renal magnesium wasting in patients receiving cisplatin. Ann Intern Med 90:929–931
92. Shah GM, Kirschenbaum MA (1991) Renal magnesium wasting associated with therapeutic agents. Miner Electrolyte Metab 17:58–64
93. Von Vigier RO, Truttmann AC, Zindler-Schmocker K, Bettinelli A, Aebischer CC, Wermuth B, Bianchetti MG (2000) Aminoglycosides and renal magnesium homeostasis in humans. Nephrol Dial Transplant 15:822–826
94. Barton CH, Pahl M, Vaziri ND, Cesario T (1984) Renal magnesium wasting associated with amphotericin B therapy. Am J Med 77:471–474
95. Barton CH, Vaziri ND, Martin DC, Choi S, Alikhani S (1987) Hypomagnesemia and renal magnesium wasting in renal transplant recipients receiving cyclosporine. Am J Med 83:693–699
96. Shah GM, Alvarado P, Kirschenbaum MA (1990) Symptomatic hypocalcemia and hypomagnesemia with renal magnesium wasting associated with pentamidine therapy in a patients with AIDS. Am J Med 89:380–382
97. Knochel JP (1977) The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Intern Med 137:203–220
98. Martin HE, Smith K, Wilson ML (1958) The fluid and electrolyte therapy of severe diabetic acidosis and ketosis. Am J Med 24:376–389
99. Delva P, Pastori C, Degan M, Montesi G, Brazzarola P, Lechi A (2000) Intralymphocyte free magnesium with primary aldosteronism. Hypertension 35:113–117
100. Lim P, Jacob E (1972) Magnesium deficiency in liver cirrhosis. Q J Med 41:291–300
101. Hellman ES, Tschudy DP, Bartter FC (1962) Abnormal electrolyte and water metabolism in acute intermittent porphyria. The transient inappropriate secretion of antidiuretic hormone. Am J Med 32:734–746
102. Jones JE, Desper PC, Shane SR, Flink EB (1966) Magnesium metabolism in hyperthyroidism and hypothyroidism. J Clin Invest 45:891–900
103. Davies DR, Friedman M (1966) Complications after parathyroidectomy. Fractures from low calcium and magnesium convulsions. J Bone Joint Surg Br]48:117–126
104. Navarro J, Oster JR, Gkonos PJ, Ruiz JP, Rhamy RK, Perez GO (1991) Tetany induced on separate occasions by administration of potassium and magnesium in a patient with hungry-bone syndrome. Miner Electrolyte Metab 17:340–344

105. Whyte KF, Addis GJ, Whitesmith R, Reid JL (1987) Adrenergic control of plasma magnesium in man. Clin Sci (Colch) 72:135–138
106. McLellan BA, Reid SR, Lane PL (1984) Massive blood transfusion causing hypomagnesemia. Crit Care Med 12:146–147
107. England MR, Gordon G, Salem M, Chernow B (1992) Magnesium administration and dysrhythmia after cardiac surgery. JAMA 268:2395–2402
108. Aziz S, Haigh WG, Van Norman GA, Kenny RJ, Kenny MA (1996) Blood ionized magnesium concentrations during cardiopulmonary bypass and their correlation with other circulating cations. J Card Surg 11:341–347
109. Shane SR, Flink EB (1992) Magnesium deficiency in alcohol addiction and withdrawal. Magnes Trace Elem 10:263–268
110. Weglicki WB, Phillips TM (1992) Pathobiology of magnesium deficiency: a cytokine/neurogenic inflammation hypothesis. Am J Physiol 32:R734–737
111. Weglicki WB, Freedman AM, Bloom S, Atrakchi AH, Cassidy MM, Dickens BF (1992) Antioxidants and the cardiomyopathy of Mg-deficiency. Am J Cardiovasc Pathol 4:210–215
112. Weglicki WB, Phillips TM, Freedman AM, Cassidy MM, Dickens BF (1992) Magnesium-deficiency elevates circulating levels of inflammatory cytokines and endothelin. Mol Cell Biochem 110:169–173
113. Altura BM, Altura BT (1990) Role of magnesium in the pathogenesis of hypertension: relationship to its actions on cardiac and vascular smooth muscle. In: Laragh JH, Brenner BM (ed) Hypertension: pathophysiology, diagnosis and management. Raven, New York, pp 1003–1025
114. White RE, Hartzell HC (1988) Effects of intracellular free magnesium on calcium current in isolated cardiac myocytes. Science 239:778–780
115. Murphy E, Steenbergen C, Levy LS, Raju B, London RE (1989) Cytosolic free magnesium levels in ischemic rat heart. J Biol Chem 264:5622–5627
116. Sayeed MM, Zhu M, Maitra SR (1989) Alterations in cellular calcium and magnesium during circulatory/septic shock. Magnesium 8:179–189
117. Günther T, Ebel H (1990) Membrane transport of magnesium. Metal Ions Biol Syst 26:216–225
118. Salem M, Kasinski N, Munoz R, Chernow B (1995) Progressive magnesium deficiency increases mortality from endotoxin challenge: protective effects of acute magnesium replacement. Crit Care Med 23:108–118
119. Johnson JS, Hand WL, King-Thompson NL (1980) The role of divalent cations in interactions between lymphokines and macrophages. Cell Immunol 53:236–245
120. Weglicki WB, Mak IT, Stafford RE, Dickens BF, Cassidy MM, Phillips TM (1994) Neurogenic peptides and the cardiomyopathy of Mg-deficiency: effects of substance P receptor inhibition. Mol Cell Biochem 130:103–109
121. Mak IT, Komarov AM, Wagner TL, Stafford RE, Dickens BF, Weglicki WB (1996) Enhanced NO production during Mg deficiency and its role in mediating red blood cell glutathione loss. Am J Physiol 271:C385–C390
122. Schmidt HH, Walter U (1994) NO at work. Cell 78:919–925
123. Külpmann WR, Gerlach M (1996) Relationship between ionized and total magnesium in serum. Scand J Clin Lab Invest 56 [Suppl 224]:251–258
124. Altura BM, Altura BT (1996) Role of magnesium in patho-physiological processes and the clinical utility of magnesium ion selective electrodes. Scand J Clin Lab Invest 56 [Suppl 224]:211–234
125. Zhang A, Cheng TPO, Altura BT, Altura BM (1992) Extracellular magnesium regulates intracellular free Mg in vascular smooth muscle cells. Pflugers Arch 421:391–393
126. Salem M, Stacey J, Chernow B (1993) Ionized magnesium values in critically ill patients – a novel ion selective electrode for determining free extracellular magnesium concentrations. Crit Care Med:S256
127. Huijgen HJ, Soesan M, Sanders R, Mairuhu WM, Kesecioglu J, Sander GT (2000) Magnesium levels in critically ill patients: what should we measure? Am J Clin Pathol 114:688–695
128. Kasaoka S, Tsuruta R, Nakashima K, Soejima Y, Miura T, Sadamitsu D, Tateishi A, Maekawa T (1996) Effect of intravenous magnesium sulfate on cardiac arrhythmias in critically ill patients with low serum ionized magnesium. Jpn Circ J 60:871–875
129. Bertschat F, Ising H, Günther T, Jeremias A, Jeremias E (1995) Changes of ionized magnesium and free fatty acids in serum after myocardial infarction. Eur J Clin Chem Clin Biochem 33:553–558
130. Frankel H, Haskell R, Lee SY, Miller D, Rotondo M, Schwab CW (1999) Hypomagnesemia in trauma patients. World J Surg 23:966–969
131. Sawyer RB, Drew MA, Gesink MH, Sawyer KC Jr, Sawyer DC (1970) Post-operative magnesium metabolism. Arch Surg 100:343–348
132. Heath DL, Vink R (1998) Blood-free magnesium concentration declines following graded experimental traumatic brain injury. Scand J Clin Invest 58:161–166
133. Altura BM, Memon ZS, Altura BT, Cracco RQ (1995) Alcohol-associated acute head trauma in human subjects is associated with early deficits in serum ionized Mg and Ca. Alcohol 12:433–437
134. Heath DL, Vink R (1998) Neuroprotective effects of $MgSO_4$ and $MgCl_2$ in closed head injury: a comparative phosphorous NMR study. J Neurotrauma 15:183–189
135. Smith DH, Okiyama K, Gennarelli TA, McIntosh TK (1993) Magnesium and ketamine attenuate cognitive dysfunction following experimental brain injury. Neurosci Lett 157:211–214
136. Kinoshita Y, Ueyuama T, Senba E, Terada T, Nakai K, Itakura T (2001) Expression of c-fos, heat shock protein 70, neurotrophins, and cyclooxygenase-2 mRNA in response to focal cerebral ischemia/reperfusion in rats and their modification by magnesium sulfate. J Neurotrauma 18:435–445
137. Bareyre FM, Saatman KE, Helfaer MA, Sinson G, Weisser JD, Brown AL, McIntosh TK (1999) Alterations in ionized and total blood magnesium after experimental traumatic brain injury: relationship to neurobehavioral outcome and neuroprotective efficacy of magnesium chloride. J Neurochem 73:271–280
138. Feldman Z, Gurevitch B, Artru A, Oppenheim A, Shohami E, Reichenthal E, Shapira Y (1996) Effect of magnesium given 1 hour after head trauma on brain edema and neurological outcome. J Neurosurg 85:131–137
139. Regan RF, Jasper E, Guo Y, Panter SS (1998) The effect of magnesium on oxidative neuronal injury in vitro. J Neurochem 70:77–85
140. James MFM (1991) Magnesium in critical care medicine. Care Crit Ill 7:233–237
141. Iseri LT, Freed J, Bures AR (1975) Magnesium deficiency and cardiac disorders. Am J Med 58:837–846
142. Rasmussen HS, Thomsen PEB (1989) The electrophysiological effects of intravenous magnesium sulfate on human sinus node, atrioventricular node, atrium, and ventricle. Clin Cardiol 12:85–90
143. Davies GE, Cudworth P, Lawler PG (1992) Intravenous magnesium in critically ill patients. Anaesthesia 47:1104
144. Barrera R, Fleischer M, Miletic J, Groeger J (2000) Ionized magnesium supplementation in critically ill patients: comparing ionized and total magnesium. J Crit Care 15:36–40

S. E. Orfanos
I. Mavrommati
I. Korovesi
C. Roussos

Pulmonary endothelium in acute lung injury: from basic science to the critically ill

Abstract *Background:* Pulmonary endothelium is an active organ possessing numerous physiological, immunological, and metabolic functions. These functions may be altered early in acute lung injury (ALI) and further contribute to the development of acute respiratory distress syndrome (ARDS). Pulmonary endothelium is strategically located to filter the entire blood before it enters the systemic circulation; consequently its integrity is essential for the maintenance of adequate homeostasis in both the pulmonary and systemic circulations. Noxious agents that affect pulmonary endothelium induce alterations in hemodynamics and hemofluidity, promote interactions with circulating blood cells, and lead to increased vascular permeability and pulmonary edema formation. *Objective:* We highlight pathogenic mechanisms of pulmonary endothelial injury and their clinical implications in ALI/ARDS patients.

Keywords Endothelium · Lungs · Acute lung injury · Acute respiratory distress syndrome

Introduction

The intimal lining of all blood vessels is composed of a single continuous layer of simple squamous epithelial cells of mesenchymal origin which are called endothelial cells (ECs). In the human lung ECs occupy a surface area of approximately 130 m^2 [1]. Vascular endothelium was considered for many years to be nothing more than a nucleated layer, functioning as a semipermeable barrier that separates blood from the surrounding tissues and, in the lungs, blood from air. However, extensive research over the past 25 years has confirmed that vascular endothelium is a highly specialized metabolically active organ possessing numerous physiological, immunological, and synthetic functions (Table1). The strategic location of the lungs and the tremendous surface area of the pulmonary capillary endothelium allow the latter to filter the entire circulating blood volume before it enters the systemic circulation. Thus pulmonary endothelial functional and structural integrity are essential for adequate pulmonary and systemic cardiovascular homeostasis.

Pulmonary endothelium is a major component of the alveolar-capillary unit; it is therefore vulnerable to injury from noxious agents (mechanical, chemical, or cellular) that are either inhaled or delivered to the lung through the pulmonary circulation and may cause acute lung injury (ALI) in animals and humans (Table 2).

ALI represents a pathological continuum characterized by acute respiratory distress and severe oxygenation impairment, occurring as a consequence of the host response after exposure to noxious external or endogenous agents. The most severe extreme of ALI is the acute respiratory distress syndrome (ARDS), an overt noncardiogenic pulmonary edema that carries high morbidity and mortality

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_37, © Springer-Verlag Berlin Heidelberg 2009

Table 1 Major pulmonary endothelial functions

Synthesis and release of several vasoactive compounds such as angiotensin II, prostacyclin, thromboxane A_2, nitric oxide (NO), and endothelins; regulation of vascular tone
Expression of enzymes such as angiotensin converting enzyme, endothelin converting enzyme, nucleotidases, NO synthase and lipoprotein lipase
Expression of receptors and signal transduction molecules
Cell surface redox activity (transplasma membrane electron transport systems)
Removal and biotransformation of drugs
Regulation of coagulation and thrombolysis; promotion of hemofluidity
Participation in immune reactions
Binding of immune complexes
Interaction with bacteria (phagocytosis) and blood components such as leukocytes and platelets
Expression of adhesion molecules
Production of growth factors
Production of cytokines and chemokines
Production of reactive oxygen species
Barrier function

Table 2 Major agents that cause pulmonary endothelial injury

Endotoxin
Cytokines, chemokines
Activated leukocytes
Proteolytic enzymes
Partially reduced O_2 species
Immune complexes
Microbes (e.g., rickettsial infection)
Hyperoxia
Radiation
Drugs
Ischemia/reperfusion
Hyperlipidemia
Fibrin split products
Actin and actin complexes
Toxins
Mechanical stretch

[2]. ALI/ARDS is caused by an autodestructive inflammatory process characterized by the activation of intrapulmonary and circulating cells and by a tremendous influx of neutrophils (although ARDS occurs in neutropenia) and cytokine production, resulting in a breakdown of the lung barrier and gas exchange functions. ALI pathogenesis is still only partly understood; however, pulmonary endothelium plays a major role by: (a) altering its metabolic activity, thus affecting pulmonary and systemic homeostasis; (b) mediating cell-cell adhesions, especially with neutrophils; and (c) changing its barrier permeability, thus promoting pulmonary edema formation [3].

Pulmonary endothelial functions

The various pulmonary endothelial metabolic properties were identified using isolated perfused lung preparations, in vivo animal studies, and EC culture techniques. It is well recognized now that the pulmonary endothelium possesses numerous enzymes, receptors, and transduction molecules, and that it interacts with other vessel wall constituents and circulating blood cells. Major physiological properties of the pulmonary endothelium include: (a) the promotion of antiaggregation and hemofluidity, (b) an enforced barrier function, and (c) the synthesis, metabolism, or uptake of vasoactive compounds that modulate the systemic (endocrinelike action) and/or pulmonary vascular tone (paracrinelike action) [4, 5]. The latter appears to contribute in the induction of hypoxic pulmonary vasoconstriction (HPV), a unique physiological feature of the pulmonary circulation that maintains proper ventilation/perfusion match and optimizes systemic oxygenation. Although the exact role of EC in HPV is still under investigation, EC-derived vasoactive compounds such as nitric oxide, endothelin (ET) 1, and a yet unidentified agent that may cause Ca^{2+} sensitization in the smooth muscle have been implicated [6]. Consequently, pulmonary endothelial injury is expected to compromise adequate HPV and contribute to the ventilation/perfusion abnormalities seen in ALI/ARDS.

The most important endothelial functions are presented in Table 1. Most of these functions are constitutive while others are induced upon endothelial activation after exposure to proinflammatory stimuli such as endotoxin and/or cytokines. In this respect the activated pulmonary endothelium (a) expresses leukocyte adhesion molecules, (b) produces cytokines, (c) induces changes in vascular integrity and tone, (d) becomes procoagulant, and (e) upregulates HLA molecules [7]. ALI is associated with an intense pulmonary inflammatory response with accumulation of both pro- and anti-inflammatory mediators [8]. If the proinflammatory process dominates, endothelial activation is followed by functional and, at a second stage, structural endothelial injury, leading to alterations in all the above critical metabolic functions that contribute to ARDS pathogenesis. ARDS-related structural endothelial injury has been identified in humans: Postmortem studies of patients who died of sepsis-related ARDS revealed patchy EC swelling and injury [9], while a recent study found circulating ECs to be increased (i.e., increased EC shedding) in sepsis and septic shock, suggesting a widespread endothelial damage that should also include the pulmonary endothelium [10].

Cytokines and pulmonary endothelium

Cytokines are soluble polypeptides serving as chemical messengers between cells; they are involved in processes such as cell growth and differentiation, tissue repair and remodeling, and regulation of the immune response [11]. ECs are both targets and cytokine producers. Among the more than 250 known cytokines, tumor necrosis factor

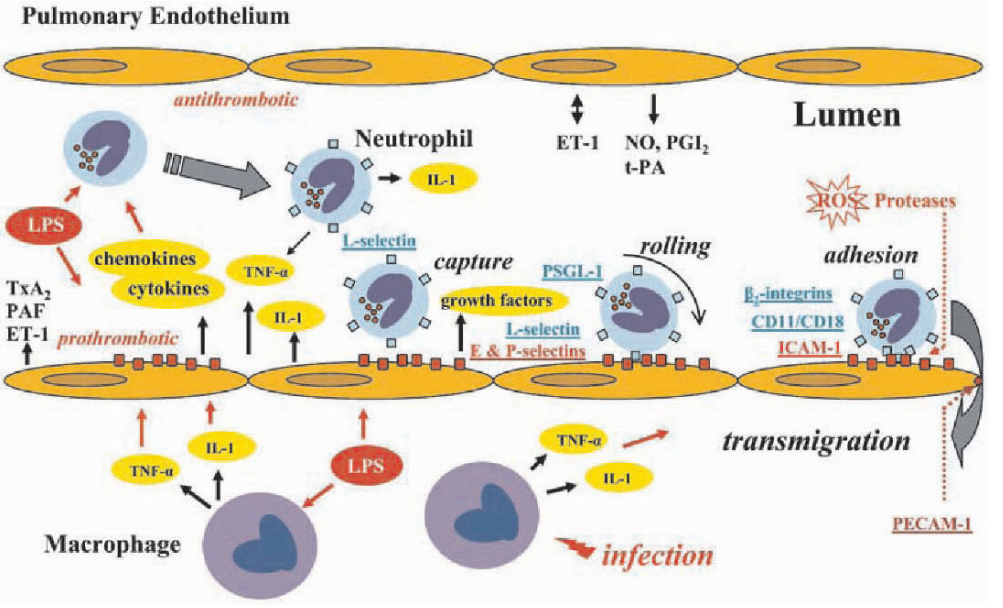


Fig. 1 Schematic illustration demonstrating major endothelial functional properties in the normal lung (upper endothelial cell layer), and mechanisms of pulmonary endothelial injury induced by infection, encompassing many of the major inflammatory interactions among cytokines, macrophages, neutrophils, and pulmonary endothelium. *LPS* Lipopolysaccharide; *TNF-α* tumor necrosis factor-α; *IL-1* interleukin-1; *NO* nitric oxide; *ET-1* endothelin-1; *PGI_2* prostacyclin; *TxA_2* thromboxane A_2; *PAF* platelet-activating factor; *t-PA* tissue plasminogen activator; *ROS* reactive oxygen species; *PSGL-1* P-selectin glycoprotein-1; *ICAM-1* intercellular adhesion molecule-1; *PECAM-1* platelet-endothelial cell adhesion molecule-1. *Underlined* Adhesion molecules; *red arrows* action; *black arrows* synthesis (and uptake for ET-1); *dotted arrows* location

(TNF) α and interleukin (IL) 1 are produced mostly by mononuclear phagocytes, and natural killer cells. In the lung they are mainly produced by activated interstitial and alveolar cells (primarily macrophages), as well as ECs, and have a major role in the early ALI stage. TNF-α and IL-1 share a number of biological properties and markedly amplify each other's biological actions. They act on EC mainly by inducing a functional program that promotes thrombosis and inflammation [12]. Among other things they induce (a) a prothrombotic EC phenotype, (b) the production of several cytokines including chemokines, colony-stimulating factors, IL-6 which has both pro- and anti-inflammatory properties, and IL-1 itself, (c) the production of several autacoids such as prostanoids including prostacyclin (PGI_2) and thromboxane A_2, platelet-activating factor (PAF) and nitric oxide (NO), and (d) the upregulation of adhesion molecules (Fig. 1). All these functions, with the latter being the most important, contribute to ALI/ARDS development [11, 12].

Several animal studies have revealed the pro- or anti-inflammatory contribution of cytokine–EC interaction in the pathogenesis of ALI occurring from different insults. In this respect acid aspiration induced lung injury in rabbits is mediated mainly by neutrophils recruited in the lung by IL-8 and the subsequent endothelial injury [13], while IL-8 also mediates injury from smoke inhalation to both pulmonary endothelium and epithelium in the same animal model [14]. In contrast to this, cardiotrophin-1, a member of the gp130 cytokine family that carries anti-inflammatory properties, appears to attenuate the endotoxin-induced impairment of endothelium-dependent pulmonary vasorelaxation in an ALI ex vivo rat model [15]. Partial liquid ventilation with perflubron decreases serum TNF-α concentrations in a rat acid aspiration model, thus reducing the systemic sequelae of ALI [16]. The above anti-inflammatory phenomenon might be related in part to attenuated leukocyte activation, which would consequently attenuate leukocyte–EC interaction. Interestingly, it has recently been shown that TNF-α installation into the alveolar space sends inflammatory signals to the adjoining capillary endothelium, which in minutes upregulates the expression of the adhesion molecule P-selectin enhancing leukocyte–EC interaction [17].

The cytokine-EC interaction in ALI pathogenesis has also been shown in humans or human tissues. Pulmonary microvascular EC (PMEC) from ARDS patients present an upregulation of TNF-R2 receptors and a higher constitutive production of IL-6 and IL-8 than control PMEC, suggesting either a stronger EC activation occurring during the ALI/ARDS process or that PMEC are constitutively more reactive in subjects who subsequently develop ARDS [18]. Additionally, TNF-α induces IL-8 production by pulmonary EC via the p38 mitogen-activated protein kinase pathway; the underlying mechanism is regulated by the EC redox status, suggesting that anti-oxidant therapy might be of value in the ALI treatment [19].

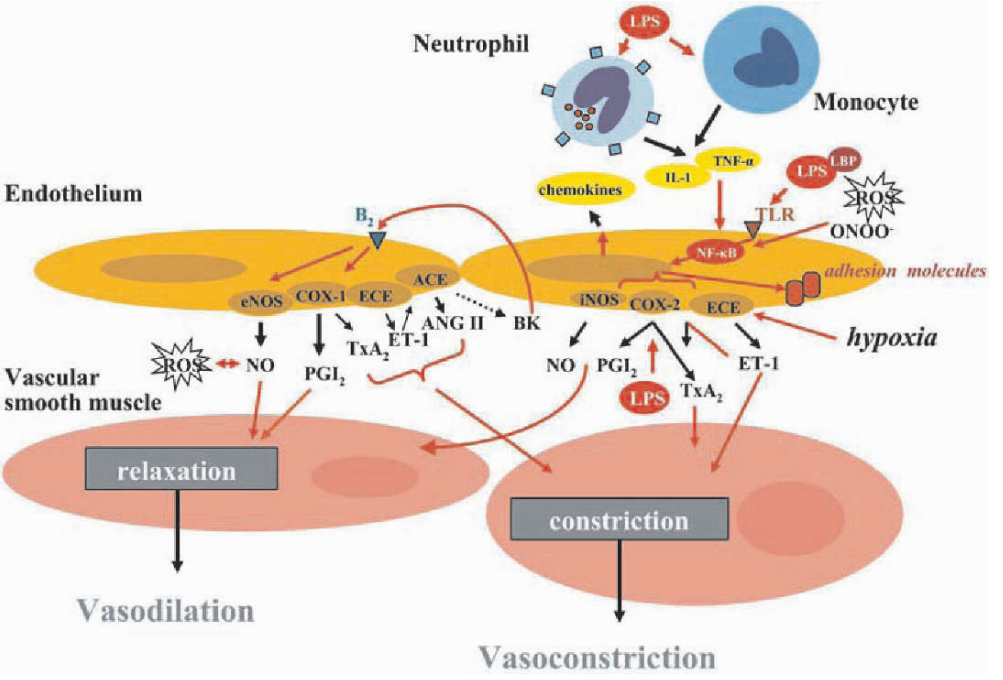


Fig. 2 Schematic illustration of major endothelial–smooth muscle interactions under normal conditions and after endothelial exposure to inflammatory stimuli. Inflammatory stimuli induce vasoactive mediator synthesis via the activation of nuclear factor-κB (*NF-κB*) or other transcription factors. Lipopolysaccharide (*LPS*) activates signaling pathways, leading to NF-κB through binding to Toll-like receptors (*TLR*) on the endothelial surface. TLR responsiveness depends on LPS-binding protein (*LBP*) and other factors. *TNF-α* Tumor necrosis factor-*α*; *IL-1* interleukin-1; *NO* nitric oxide; *ONOO*$^-$ peroxynitrite; *ET-1* endothelin-1; *PGI*$_2$ prostacyclin; *TxA*$_2$ thromboxane A$_2$; *ANG II* angiotensin II; *BK* bradykinin; *ROS* reactive oxygen species; *eNOS* endothelial NO synthase; *iNOS* inducible NO synthase; *COX-1* constitutive cyclooxygenase; *COX-2* inducible cyclooxygenase; *ACE* angiotensin-converting enzyme; *ECE* endothelin-converting enzyme; *B*$_2$ B$_2$ kinin receptor. *Red arrows* Action; *black arrows* synthesis (and uptake for ET-1); *dotted arrow* breakdown

A particular pro-inflammatory process of high clinical importance is the ventilator-induced lung injury (VILI). This highly morbid clinical entity is believed to be caused by excessive mechanical stress that alters epithelial and endothelial barrier properties and stimulates pro-inflammatory responses of several cell types including macrophages and neutrophils [20]. Conventional mechanical ventilation in ARDS patients can induce ventilator-associated lung injury (VALI) that leads to pro-inflammatory cytokine production, attenuated by a protective ventilatory strategy [21]. In this respect "protective" low tidal volumes appear to attenuate epithelial and endothelial injury [estimated by plasma von Willebrand factor (vWF) and permeability to albumin] in a rat model of acid-induced ALI, demonstrating the role of endothelial injury in this pathology [22].

Transcriptional mechanisms in ALI

Transcription factors (i.e., DNA-binding proteins that regulate gene expression) are major components of the molecular mechanism underlying the cytokine-induced EC activation. Among these, nuclear factor-κB (NF-κB) is a crucial factor for the maximal expression of many cytokines involved in ALI pathogenesis. NF-κB enhances the transcription of several genes including cytokines, growth factors, vasoactive mediators, adhesion molecules, immunoreceptors, and acute-phase proteins (Fig. 2) [23]. NF-κB regulates the cytokine-mediated inducibility of adhesion molecules and cytokines in EC [24]. NF-κB activation is the final target of a signal transduction pathway that leads from the cell surface to the nucleous. Numerous inducers have been implicated in NF-κB stimulation including proinflammatory cytokines (mainly TNF-*α* and IL-1), bacterial and viral products [such as lipopolysaccharide (LPS)], and reactive oxygen species (ROS) [23].

ROS at low (subcytotoxic) concentrations function as important signaling molecules, while at higher concentrations they induce cell injury and death (see below) [25]. NF-κB activation is a major redox-sensitive transcription factor: Thiol antioxidants such as *N*-acetylcysteine abolish LPS-induced activation of NF-κB and improve lung function in ARDS patients [23]. Similarly, high intracellular glutathione concentrations inhibit NF-κB activation, an inhibition also induced by high levels of glutathione disulfide, the oxidized form of glutathione [25]. Redox

regulation of NF-κB appears to be complex and mediated by both oxidant and antioxidant mechanisms; it is cell-type specific and in several cases is more facilitatory than causal [23, 25]. Cathecholamines that are often administered in ALI/ARDS subjects also affect NF-κB activation via several mechanisms, including ROS generation [26].

Activation of NF-κB is a critical step in the initiation of neutrophilic inflammation in animals and has been linked to ALI/ARDS pathogenesis. NF-κB activation is inhibited in vivo by treatment with antioxidants, corticosteroids, and the induction of endotoxin tolerance [24]. In a similar respect NF-κB dependent expression of EC adhesion molecules were downregulated by antioxidant treatment [23]. Dexamethasone administration in isolated rat lungs inhibited the TNF-α and IL-1 induced upregulation of pulmonary vascular ET, possibly via NF-κB dependent mechanisms [27]. These findings suggest that a specific NF-κB inhibition would contribute to ALI/ARDS treatment.

Reactive oxygen and nitrogen species

Patients with ARDS are subjected to an oxidant burden that results in molecular/cellular damage and arises from an increased generation of ROS and reactive nitrogen species (RNS) and/or a deficiency of antioxidant defenses. ROS include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH). Various ROS sources such as the mitochondrial respiratory chain, the protease-mediated enzyme xanthine oxidase, the metabolic cascade of arachidonic acid, and the oxidative burst of activated neutrophils are present in ARDS [28]. RNS consist of species such as NO, nitrogen dioxide (NO_2), and peroxynitrite ($ONOO^-$). NO is highly reactive with free radicals; the reaction between NO and O_2^- produces the very powerful and cell toxic $ONOO^-$ [28].

Following the exposure to various inflammatory stimuli, pulmonary endothelial, epithelial, and alveolar macrophages are among the lung cell types that contribute to the production of ROS and RNS, with deleterious effects on pulmonary endothelium [29]. Among other features, oxidant stress alters endothelial barrier function and increases endothelial permeability through activations of protein kinace C, myosin light chain kinase and other signaling pathways [25, 29]. ARDS nonsurvivors reveal higher levels of oxidative stress and damage than survivors as well as histochemical evidence of RNS-modified proteins in the lungs, while the antioxidant protective system in ARDS is severely compromised [28, 29].

Leukocytes and pulmonary endothelium

Pulmonary endothelial-leukocyte interaction is a key step in ALI/ARDS development since alterations in cell-cell adhesion is the initial step in leukocyte migration from the capillaries into the lung parenchyma, and the subsequent inflammatory response. Neutrophils appear to be the key cell type related to pulmonary injury in ALI/ARDS, while eosinophils [30, 31] and macrophages have also been implicated [30, 31, 32]. The latter might be responsible for ALI occurring in neutropenic patients [32].

Neutrophil adhesion to EC is a multistage process and a sine qua non for successful neutrophil migration and extravasation (Fig. 1). The initial phase, neutrophil capture and rolling, is mediated by cell adhesion molecules of the selectin family: L-selectin is constitutively expressed on neutrophils, P-selectin is found on platelets and EC, while E-selectin is expressed solely on EC [32, 33]. P-selectin is expressed within minutes on EC surface after EC activation by stimuli such as histamine, thrombin, bradykinin, leukotriene C_4 or free radicals; P-selectin interacts with neutrophil counterreceptors such as the P-selectin glycoprotein-1. E-selectin is rapidly synthesized by EC after cell activation by cytokines such as TNF-α and IL-1, or endotoxin [33].

The second phase is firm neutrophil adhesion (Fig. 1). It requires the interaction of the β_2 (CD18) integrin family (more specifically the CD11/CD18 integrins) expressed on neutrophils, mainly with the intercellular adhesion molecule (ICAM) 1, a member of the immunoglobulin superfamily expressed on EC [33]. ICAM-1 expression on EC is augmented by inflammatory mediators such as TNF-α, IL-1, γ-interferon, and endotoxin. Although ICAM-1 is constitutively expressed by EC in relatively high levels, it appears that the additional expression induced by cytokines is important for the neutrophil–EC interaction [33]. Oxidant stress promotes neutrophil adhesion [25]. Once neutrophils firmly adhere on the pulmonary endothelial layer, they create a microenviroment for injury, mainly via the production of proteases and ROS (i.e., oxidant burst) that induce cell injury and death. Neutrophil adherence to EC or matrix proteins appears to prime the former for a massive burst lasting 1–3 h in response to stimuli such as TNF-α. Activated EC also generate ROS, contributing in maintaining an oxidant-rich environment at injury site [25].

Neutrophil transmigration through the endothelium is the third phase of the adhesion cascade. It does not necessarily accompany firm adherence and depends on the presence of a chemeotactic gradient and the platelet–EC adhesion molecule 1 (PECAM-1) expressed on EC junctions [33]. ROS appear to increase endothelial permeability, facilitating leukocyte transmigration [25].

A large body of evidence has demonstrated the critical role of the neutrophil interaction with pulmonary endothelium in ALI in animals and humans and has examined potential therapeutic interventions. In this respect the dysfunction of endothelium-dependent and endothelium-independent pulmonary vasorelaxation in an endotoxin-induced ALI rat model is attenuated by

neutrophil depletion [34], while neutralization of CD18 attenuates ALI caused by acid installation in the rabbit [35]. Activated neutrophils, as revealed by elastase and superoxide production, are involved in an oleic acid induced ALI guinea pig model [36], while E-selectin and ICAM-1 play important roles in the bleomycin-induced ALI and the subsequent lung fibrosis, through the induction of neutrophil recruitment in the pulmonary circulation [37, 38]. Pulmonary endothelial P-selectin upregulation appears to play a crucial role in the leukocyte recruitment occurring in the pulmonary microcirculation in a pancreatitis-induced ALI rat model, a process that is possibly related to free radicals generated by xanthine-oxidase released by the injured pancreas. Constitutive pulmonary endothelial ICAM-1 contributes to the pathogenic process [39].

Numerous human studies have been performed focusing on EC–neutrophil interaction indices in ALI in an effort to both investigate the underlying pathogenic mechanisms and possibly provide endothelial markers that could predict ALI/ARDS development or outcome [3]. In this respect granulocyte aggregation occurring in the pulmonary microcirculation after activation by transfusion-derived antibodies or biologically active lipids appears to be involved in transfusion-related ALI in man [40]. Soluble plasma P-selectin was found elevated in ALI patients, especially in those who subsequently died [41], while plasma vWF antigen, soluble ICAM-1, and soluble E-selectin measured in patients at risk for ARDS were elevated in septic but not in trauma subjects [42].

In a different study, plasma soluble (s)L-selectin measured in ARDS at-risk patients were significantly lower in those who subsequently progressed to ARDS than in those who did not or in normal controls. Significant correlations were found between the above low sL-selectin levels and the requirement for ventilation, the degree of respiratory failure, and patient mortality, elucidating the interactions between neutrophils and ECs at the early ARDS stage [43]. Additionally, PMEC purified from ARDS patients who died revealed a significantly higher constitutive expression of ICAM-1 than in control human PMEC. When treated with TNF-α, both cell lines showed a dose-dependent increase in ICAM-1 expression that was significantly higher in the ARDS-derived EC [18]. The question remains, however, of whether the observed stronger EC activation occurred during the ALI/ARDS process, or, more importantly, whether PMEC are constitutively more reactive in subjects who will subsequently develop the syndrome.

A more recent study used the endothelial specific E-selectin promoter to express a selective β_2 CD11/CD18 integrin antagonist in a cell- and inflammation-specific manner. This treatment prevented neutrophil adhesion to human pulmonary artery ECs that had been activated by LPS; it additionally prevented neutrophil sequestration in the lungs and ALI development in mice that had received *Escherichia coli* intraperitoneally. These data suggest that conditionally blocking of β_2 integrin function at sites where the endothelium is activated is feasible and might offer in the future a means of locally preventing neutrophil activation that leads to ALI/ARDS [44].

Pulmonary endothelium and pulmonary vascular permeability

Increased pulmonary vascular permeability is a hallmark of ALI/ARDS pathogenesis since it is a sine qua non for noncardiogenic pulmonary edema formation. ARDS patients exhibit persistent pulmonary endothelial permeability that was revealed in vivo by means of a dual-isotope technique; the severity of vascular permeability appeared related to lung injury score as proposed by Murray et al. [45] and the number of neutrophils in bronchoalveolar lavage [46].

Increased pulmonary endothelial permeability may be induced by ALI-related cytokines, other agents, and via EC cytoskeletal-related mechanisms in response to stimuli such as thrombin or mechanical stretch. For a detailed analysis the reader is referred to [47]. Vascular endothelial growth factor (VEGF) is a potent vascular permeability inducer. VEGF was higher in the plasma of ARDS patients, especially in subsequent nonsurvivors as compared to that from patients at risk of ARDS or controls; VEGF may be another important factor in the pathogenesis of noncardiogenic pulmonary edema in ARDS [48].

Pulmonary endothelium and hemofluidity

ECs possess a sophisticated metabolic machinery of interactive factors that modulates all three components of the hemostatic system: platelet aggregation, blood coagulation, and fibrinolysis [49]. In the healthy lung the combined effect of these factors promotes hemofluidity, while under pathological conditions the injured pulmonary endothelium becomes thrombogenic.

Platelets and pulmonary endothelium

Pulmonary endothelium affects platelet function mainly through the production of the platelet aggregation inhibitors PGI_2 and NO; the production of vWF; the conversion of adenosine diphosphate (which can induce platelet aggregation) to adenosine monophosphate, mediated by the endothelial ectoenzyme adenosine diphoshatase; and the removal of serotonin from the pulmonary circulation [49]. In ALI all the above features may be altered leading to enhanced platelet aggregation. In this respect several agents that could cause ALI, such as oxidative injury generated from reactive oxygen spe-

cies and hyperoxia, alter the synthesis and release of PGI_2 [49], while the pulmonary endothelium-mediated extraction of serotonin is decreased in ARDS patients [50].

Numerous studies have shown that vWF is altered in ALI/ARDS, and that vWF is a sensitive marker denoting the existence of EC injury or activation [3]. vWF is synthesized predominantly by vascular ECs. Markedly elevated levels of plasma vWF were reported in patients with acute respiratory failure 22 years ago [51]; this phenomenon appears to occur in early ALI, prior to significant endothelial damage [52]. Since then investigators have focused on the validity of vWF as a predictor of ARDS development. Elevated plasma vWF in patients with nonpulmonary sepsis had a predictive value for ALI development, especially in patients who had concomitant dysfunction of at least one organ [53]. However, more recent studies confirmed that vWF is increased in ARDS at risk patients, but it does not predict ALI development in a heterogeneous patient population [54, 55].

Pulmonary endothelium and coagulation

Pulmonary endothelium possesses both anticoagulant and procoagulant properties. Antithrombin III (AT III) is a major inhibitor of blood coagulation that inhibits thrombin. EC possess heparinlike glycosaminoglycans and sulfated proteoglycans on their surface that sequester AT III and thrombin from the circulation, facilitating their reaction [49]. Additionally, AT III binding to glycosaminoglycans promotes PGI_2 release [56], a feature that among other things prevents LPS-induced pulmonary vascular injury in rats, possibly by inhibiting lung leukocyte accumulation [57].

Thrombomodulin (TM) is an anticoagulant proteoglycan located on the EC surface. TM reacts with thrombin producing a marked increase in the thrombin-catalyzed activation of protein C, which in turn inactivates coagulation factors VA and VIIIA [49]. Plasma TM is increased in ARDS patients, possibly through proteolytic release from the injured pulmonary endothelium, an event mediated by activated neutrophils [58]. Similarly, plasma TM is increased in preterm infants with respiratory distress syndrome, especially in those treated with mechanical ventilation [59]. The critical role of TM dysfunction on ALI/ARDS development was recently demonstrated by blocking pulmonary endothelial TM in mice by means of glucose oxidase (the H_2O_2 generating enzyme) immunotargeting. This treatment caused lung injury that combined oxidative, prothrombotic, and inflammatory components, characteristic of the ALI/ARDS pathology in humans [60].

Endothelial procoagulant properties under normal conditions are covered by its predominant anticoagulant activity. In this respect the activity of thromboplastin, an EC-associated procoagulant factor, is normally low but can be induced by various ALI-related stimuli such as endotoxin, IL-1, and thrombin [49].

Pulmonary endothelium and fibrinolysis

Pulmonary endothelium is actively involved in the fibrinolytic process, expressing tissue-type (t-PA) and urokinase-type (u-PA) plasminogen activators as well as plasminogen activator inhibitors [49]. The EC fibrinolytic activity appears to be affected by several ALI-related mediators including endotoxin, IL-1, TNF-α, and thrombin [49, 61]. In a more recent study human PMECs isolated from ARDS patients expressed higher procoagulant activity and plasminogen activator inhibitor (PAI) 1 as well as lower fibrinolytic potential (i.e., t-PA/PAI-1) than the controls, confirming the procoagulant pulmonary endothelial profile in ARDS [61].

Pulmonary endothelium-derived vasoactive mediators

Nitric oxide

NO is a free radical (RNS) with a very short half-life and is very unstable in biological systems. NO is formed from L-arginine by NO synthase (NOS). There are three known NOS isoenzymes: (a) neuronal (n) NOS, also expressed in pulmonary arterial smooth muscle cells (SMC), (b) inducible (i) NOS, induced by several pro-inflammatory mediators, which upon expression produces NO at very high rates with profound effects on cardiovascular homeostasis, and (c) endothelial (e) NOS, a constitutive isoenzyme expressed principally in EC (Fig. 2) [62]. The latter is the main isoenzyme involved in vascular tone regulation. Deficiency of L-arginine or the NOS cofactor tetrahydrobiopterin may result in eNOS-generated $O_2^{\bullet -}$ instead of or along with NO, promoting the formation of highly reactive RNS such as $ONOO^-$. NO activates soluble guanylate cyclase, thus producing 3,5-cyclic monophosphate (cGMP) and eliciting cGMP-mediated SMC relaxation and other cell-specific functions [62].

In addition to vascular SMC relaxation, NO inhibits (a) platelet aggregation, (b) leukocyte adhesion, and (c) cellular proliferation [7]. In the pulmonary circulation NO synthesis is reduced under hypoxia, and as such it may modulate HPV [63], a feature that is lost in ARDS. Several studies have reported that NO can in addition exert either pro- or anti-oxidative effects, depending on the type and the quantity of oxygen radicals present; NO can additionally attenuate ARDS-associated lung leak [64]. Therapeutic NO inhalation improves oxygenation in several ALI animal models and in responder ARDS patients, while in addition it inhibits neutrophil activation, platelet adhesion, and the production of inflammatory mediators in the injured lungs [64].

Endothelins

Endothelins (ETs) are the most potent naturally occurring vasoconstrictors. Three isoforms have been identified, ET-1, ET-2, and ET-3 all formed from "big endothelin" by ET-converting enzyme [7]. ET-1 is produced mainly by EC, and its production is induced by several factors including hypoxia, endotoxin, TNF-α, interferon, and epinephrine (Fig. 2) [7]. ET-1 release occurs mainly in the abluminal direction towards SMC, and its signaling is mediated by two distinct receptors, ET_A and ET_B. ET_A is expressed on SMC, signaling vasoconstriction; ET_B is expressed primarily on EC and elicits transient vasodilation by signaling NO and prostaglandin release, revealing a cross-talk between the ET-1 and NO pathways [62]. Similarly, EC activation is characterized by a reciprocal ET-1 and eNOS regulation, with most pro-inflammatory stimuli increasing ET-1 and decreasing eNOS expression [62].

The human lung is an important site for both ET-1 clearance and production: approximately 50% of circulating ET-1 is cleared in a single transpulmonary passage via the ET_B receptor, with a simultaneous equal production [65]. This balance between pulmonary ET-1 clearance and release was found decreased early in ALI, reversing in patients who subsequently recovered [66]. Additionally, plasma ET-1 values are increased in septic patients with and without ARDS [67], possibly contributing to the ALI-associated pulmonary hypertension.

Prostaglandins

Among the several cyclo-oxygenase (COX) products PGI_2 and thromboxane A_2 are probably the most important in ALI. PGI_2 is a potent vasodilator and an important inhibitor of platelet aggregation. Thromboxane A_2 is a potent pulmonary vasoconstrictor secondary to endotoxin infusion; Thromboxane A_2 also increases capillary permeability and platelet aggregation [7]. Prostaglandin E_1 (PGE_1) is another COX product with EC protective properties. As with PGI_2, PGE_1 is a vasodilator and platelet aggregation inhibitor, also impairing neutrophil chemotaxis and macrophage activation [68]. COX products contribute to HPV; however, their vasoactive action varies with the size of the artery and the species involved. A particular role of eicosanoids in several ALI models is their contribution to the regulation of perfusion redistribution that diverts blood flow to healthier lung regions. Pretreatment of rabbits with indomethacin, under partial lung microvascular recruitment, protects against PMA-induced pulmonary endothelial enzyme dysfunction, probably by diverting flow to previously unperfused (i.e., unexposed to PMA) capillaries. Under nearly full microvascular recruitment, the above protective effect of indomethacin is abolished [69]. In a similar respect selective inhibition of the inducible COX isoform protects against the endotoxin-related loss of perfusion redistribution in an oleic acid induced dog ALI model, an effect mediated by PGI_2 [70].

Platelet activating factor

Pulmonary ECs release the phospholipid PAF, a highly reactive mediator that has been reported to cause both vasodilation and vasoconstriction in vivo, depending on its concentration [49]. PAF has been additionally reported to increase lung permeability, to activate platelets, neutrophils, and macrophages and to cause EC release of t-PA and PGI_2. PAF synthesis by EC may be induced by H_2O_2 and other reactive oxygen species [49]. *E. coli* injection in rats induced pulmonary hypertension stimulated by PAF and partly mediated by ET-1; it additionally induced PAF-mediated microvascular injury and leak as well as neutrophil activation-sequestration in the lungs. Pretreatment with a PAF receptor antagonist completely blocked all the above events, suggesting a potential future therapeutic application for this compound [71].

Pulmonary endothelial angiotensin-converting enzyme

Angiotensin-converting enzyme (ACE) hydrolyzes angiotensin I to angiotensin II and breaks down bradykinin [72, 73]. Pulmonary endothelium-bound (PE) ACE has a central role in maintaining adequate local and systemic homeostasis, revealing the dynamic interaction between EC and other cell types schematically shown in Fig. 2. In this respect angiotensin II induces SMC constriction, proliferation, and growth. In contrast to this, bradykinin that escapes ACE inactivation exerts vasodilatory, anti-inflammatory and antithrombotic actions through stimulation of endothelial B_2 kinin receptors, causing the synthesis and release of substances such as NO and PGI_2, generated by eNOS and constitutive COX (COX-1), respectively [73]. PE-ACE pro-inflammatory action is further revealed by the fact that angiotensin II can generate $O_2^{\cdot -}$ via the activation of NADH/NADPH oxidases in EC and SMC [73]. Superoxide anions interact with NO to generate $ONOO^-$, while free radicals from several sources cause molecular and cellular damage and decrease ACE activity [74]. It has recently been proposed that the PE-ACE activity reduction seen in ALI is related to enzyme downregulation, mediated by overproduction of $ONOO^-$ and other ROS/RNS, aimed at reducing oxidant stress in the microenvironment [74]. The role of PE-ACE in lung injury and repair may be more complex since recent investigation provided evidence that ACE possesses characteristics of a signal transduction molecule, involved in EC outside-in signaling [75].

Pulmonary endothelial ACE is an ectoenzyme uniformly distributed throughout the luminal EC surface, with its catalytic site exposed to the blood stream; it is directly accessible to blood-borne substrates, and its activity may be measured in vivo by means of indicator-dilution type techniques [5, 72, 76]. Due to the very high enzyme concentrations in the capillaries, monitoring pulmonary endothelial ACE activity in this type of studies, is in practical terms equal to monitoring pulmonary capillary endothelium-bound (PCEB) ACE activity [72]. This method offers quantifiable indices that may distinguish between abnormalities secondary to endothelial dysfunction per se and decreased pulmonary vascular surface area. PCEB-ACE activity estimations have been recently validated in humans [77].

Plasma soluble ACE (sACE) activity is decreased in ARDS patients [78]. However, in contrast to PCEB-ACE, sACE activity is a surrogate index of pulmonary endothelial function. PCEB-ACE activity reduction is among the earliest signs in various ALI animal models, preceding changes in parameters such as acid-base balance, gas exchange, hemodynamic parameters, increased permeability, and morphological changes at the light and electron-microscopic level. This is the case following administration of bleomycin to rabbits [79], exposure of rabbits to hyperoxia [80], PMA administration to rabbits and dogs [69, 81], and chest irradiation to rabbits [82, 83]. Similarly, pulmonary endothelial ACE activity depression, determined by the decreased pulmonary uptake of an anti-ACE monoclonal antibody, occurs in rats secondary to normoxic lung ischemia/reperfusion [84].

PCEB-ACE activity was estimated in mechanically ventilated patients belonging to high-risk groups for ARDS development and suffering from various degrees of ALI/ARDS [85]. Enzyme activity was expressed as transpulmonary substrate hydrolysis (reflecting enzyme activity per capillary) and as the functional capillary surface area (FCSA) index A_{max}/K_m (reflecting enzyme activity per vascular bed) related to both enzyme quantity and functional integrity [72, 77]. Both indices decreased early during the ALI/ARDS continuum and were inversely related to the lung injury score [45], suggesting that the clinical severity of the syndrome is related to the degree of PCEB-ACE activity depression (i.e., the underlying pulmonary endothelial dysfunction). Further analysis of the FCSA data revealed two different profiles in the A_{max}/K_m vs. cardiac output relationships, probably distinguishing patients with reserves of healthy or mildly injured capillaries from those without; the former had better survival, raising the possibility that FCSA could be of value as an outcome predictor in ARDS [85].

Marshall et al. [86] have recently shown that ACE insertion/deletion polymorphism is associated with the susceptibility and outcome in ARDS, with the DD genotype frequency being increased and associated with mortality in these patients. This first description of a specific allele association with ARDS development suggests a major role for the renin-angiotensin system in the pathophysiology of the syndrome. Although the D allele has been associated with higher ACE activity, this does not necessarily contradict the reported PCEB-ACE activity reduction in ALI/ARDS [85]. The former could affect mostly other lung compartments or, alternatively, the latter might be related to either damaged ECs or to PCEB-ACE downregulation as a host response aimed at reducing local inflammation.

Endothelium-related therapies in ALI/ARDS

Pulmonary endothelial functional and structural alterations are key components of ALI pathogenesis. Consequently EC-related therapies may have beneficial effects in ALI/ARDS. Such therapies should restore adequate endocrine and paracrine EC functions, and protect ECs against harmful insults as well as against pro-inflammatory cell-cell interactions [68, 87]. Several therapeutic interventions, most of them related to endothelium-derived vasoactive (and anti-inflammatory) mediators are already in place, in an effort to improve arterial oxygenation and treat ARDS-related pulmonary hypertension [68]. In this respect inhaled or intravenous PGI_2, inhaled or intravenous (in either native or liposomal form) PGE_1, and, mainly, inhaled NO have been used, with mixed results [68, 87]. Additional agents include antioxidants such as *N*-acetylcysteine and hyperoncotic albumin, and the thromboxane synthetase inhibitor ketoconazole [87]. Several agents already in clinical use for treating pathologies other than ALI, such as ET-1 receptor antagonists, phosphodiesterase inhibitors, and ACE inhibitors might have beneficial effects. For a comprehensive analysis of this topic the reader is referred to [68] and [87]. Throughout this review several experimental studies with future therapeutic potential have been reported. More recent experimental work focus on unmasking EC diversity in an effort to develop means that will target the injured pulmonary endothelium and allow specific drug and/or gene delivery.

Conclusion and future directions

In addition to gas exchange, pulmonary vasculature filters the entire circulating blood before the latter enters the systemic circulation, affecting both local and systemic vascular tones, inflammatory processes, and whole-body homeostasis. Pulmonary circulation possesses two major distinct features: in health it responds to hypoxia with HPV to maintain adequate ventilation/perfusion match; in critical illness pulmonary hypertension may develop, as opposed to the often occurring systemic hypotension. As these responses strongly depend on pulmonary endothelial functional and structural integrity, further under-

standing of the pulmonary endothelial properties will provide insights into ALI pathophysiology and how the latter affects systemic cardiovascular homeostasis. In this respect recent investigations revealed the existence of pulmonary EC heterogeneity that might contribute to ALI pathogenesis: neutrophil adhesion through ICAM-1 induces cytosceletal changes in pulmonary microvascular ECs (where the site of neutrophil emigration) and not in pulmonary arterial ECs [88]. Additionally, Ca^{2+} communication from pulmonary septal capillaries appears to establish a pro-inflammatory state in downstream venular capillaries, probably amplifying lung inflammation [89]. Specific pulmonary ECs that locally enhance or amplify lung injury might be the targets of future genetic or other therapies.

A National Heart, Lung and Blood Institute workshop has recently proposed future research directions in ALI/ARDS [90]. Pulmonary ECs appear to be the first lung cells altered in ALI/ARDS generated by sepsis, trauma, and other systemic conditions. Among other things, EC heterogeneity should be further investigated along with the EC functional changes involving new gene expression or constitutive pathways, the molecular mechanisms that govern pulmonary EC responses, their interaction with alveolar epithelium, and the responses of systemic endothelium in ALI/ARDS. New EC-related therapies targeting pulmonary microvascular inflammation and thrombosis, and the value of newly implanted pulmonary ECs derived by intravenous infusion of bone marrow stem cells should be investigated [90]. In relation to the former, studies of activated protein C administration in ARDS patients are already under way.

In conclusion, pulmonary EC dysfunction is a key component of ALI pathogenesis. Future investigations of pulmonary endothelial dysfunction may provide additional information on ALI pathophysiology, markers that could predict ARDS development or outcome, and new therapeutic approaches.

References

1. Simionescu M (1991) Lung endothelium: structure-function correlates. In: Crystal RG, West JB (eds) The Lung: scientific foundations. Raven, New York, pp 301–331
2. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke A, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R, the Consensus Committee (1994) The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 49:818–824
3. Pittet JF, Mackersie RC, Martin TR, Matthay MA (1997) Biological markers of acute lung injury: prognostic and pathogenic significance. Am J Respir Crit Care Med 155:1187–1205
4. Hassoun PM, Fanburg BL, Junod AF (1991) Metabolic functions. In: Crystal RG, West JB (eds) The lung: scientific foundations. Raven, New York, pp 313–327
5. Orfanos SE, Catravas JD (1993) Metabolic functions of the pulmonary endothelium. In: Yacoub M, Pepper J (eds) Annual review of cardiac surgery, 6th edn. Current Science, London, pp 52–59
6. Aaronson PI, Robertson TP, Ward JPT (2002) Endothelium-derived mediators and hypoxic pulmonary vasoconstriction. Respir Physiol Neurobiol 132:107–120
7. Wort SJ, Evans TW (1999) The role of endothelium in modulating vascular control in sepsis and related conditions. Br Med Bull 55:30–48
8. Park WY, Goodman RB, Steinberg KP, Ruzinski JT, Radella F 2nd, Park DR, Pugin J, Skerrett SJ, Hudson LD, Martin TR (2001) Cytokine balance in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 164:1896–1903
9. Meyrick B (1986) Pathology of the adult respiratory distress syndrome. Crit Care Clin 2:405–428
10. Mutunga M, Fulton B, Bullock R, Batchelor A, Gascoigne A, Gillespie JI, Baudouin SV (2001) Circulating endothelial cells in patients with septic shock. Am J Respir Crit Care Med 163:195–200
11. Oberholzer A, Oberholzer C, Moldawer LL (2000) Cytokine signalling-regulation of the immune response in normal and critically ill states. Crit Care Med 28 [Suppl 4]:N3–N12
12. Mantovani A, Bussolini F, Introna M (1997) Cytokine regulation of endothelial cell function: from molecular level to the bedside. Immunol Today 18:231–239
13. Folkesson HG, Matthay MA, Hebert CA, Broaddus VC (1995) Acid aspiration induced lung injury in rabbits is mediated by interleukin-8 dependent mechanisms. J Clin Invest 96:107–116
14. Laffon M, Pittet JF, Modelska K, Matthay MA, Young DM (1999) Interleukin-8 mediates injury from smoke inhalation to both the lung endothelial and the alveolar epithelial barriers in rabbits. Am J Respir Crit Care Med 160:1443–1449
15. Pulido EJ, Shames BD, Pennica D, O'Leary RM, Bensard DD, Cain BS, McIntyre RC Jr (1999) Cardiotrophin-1 attenuates endotoxin-induced acute lung injury. J Surg Res 84:240–246
16. Kawamae KK, Pristine G, Chiumello D, Tremblay LN, Slutsky AS (2000) Partial liquid ventilation decreases serum tumor necrosis factor-α concentrations in a rat acid aspiration lung injury model. Crit Care Med 28:479–483
17. Kuebler WM, Parthasarathi K, Wang PM, Bhattacharya J (2000) A novel signalling mechanism between gas and blood compartments of the lung. J Clin Invest 105:905–913
18. Grau GE, Mili N, Lou JN, Morel DR, Ricou B, Lucas R, Suter PM (1996) Phenotypic and functional analysis of pulmonary microvascular endothelial cells from patients with acute respiratory distress syndrome. Lab Invest 74:761–770

19. Hashimoto S, Gon Y, Matsumoto K, Takeshita I, Takashi H (2001) N-acetylcysteine attenuates TNF-α induced p38 MAP kinase activation and p38 MAP kinase-mediated IL-8 production by human pulmonary vascular endothelial cells. Br J Pharmacol 132:270–276
20. Matthay MA, Bhattacharya S, Gaver D, Ware LB, Lim LHK, Syrkina O, Eyal F, Hubmayr R (2002) Ventilator-induced lung injury: in vivo and in vitro mechanisms. Am J Physiol Lung Cell Mol Physiol 283:L678–L682
21. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. JAMA 282:54–61
22. Frank JA, Gutierrez JA, Jones KD, Allen L, Dobbs L, Matthay MA (2002) Low tidal volume reduces epithelial and endothelial injury in acid-injured rat lungs. Am J Respir Crit Care Med 165:242–249
23. Fan J, Ye RD, Malik AB (2001) Transcriptional mechanisms of acute lung injury. Am J Physiol Lung Cell Mol Physiol 281:L1037–L1050
24. Blackwell TS, Christman JW (1997) The role of nuclear factor-kappa B in cytokine gene regulation. Am J Respir Cell Mol Biol 17:3–9
25. Lum H, Roebuck KA (2001) Oxidant stress and endothelial cell dysfunction. Am J Physiol Cell Physiol 280:C719–C741
26. Abraham E (2000) NF-κB activation Crit Care Med 28 [Suppl 4]:N100–N104
27. Dschietzig T, Richter C, Pfannenschmidt G, Bartsch C, Laule M, Baumann G, Stangl K (2001) Dexamethasone inhibits stimulation of pulmonary endothelins by pro-inflammatory cytokines: possible involvement of a nuclear factor κB dependent mechanism. Intensive Care Med 27:751–756
28. Quinlan GJ, Upton RL (2002) Oxidant/antioxidant balance in acute respiratory distress syndrome. In: Evans TW, Griffiths MJD, Keogh BF (eds) European respiratory monograph: ARDS, vol 7, monograph 20. European Respiratory Society Journals, Sheffield, pp 33–46
29. Bhatia M, Moochhala S (2004) Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome. J Pathol 202:145–156
30. Haligren R, Samuelson T, Veng P, Modig I (1987) Eosinophil activation in the lung is related to lung damage in adult respiratory distress syndrome. Am Rev Respir Dis 135:639–642
31. Rowen JL, Hyde DM, McDonald RJ (1990) Eosinophils cause acute edematous injury in isolated perfused rat lungs. Am Rev Respir Dis 142:215–220
32. Hasleton PS, Roberts TE (1999) Adult respiratory distress syndrome-an update. Histopathology 34:285–294
33. Albelda SM, Smith CW, Ward PA (1994) Adhesion molecules and inflammatory injury. FASEB J 8:504–512
34. Sheridan BC, McIntyre RC Jr, Moore EE, Meldrum DR, Agrafojo J, Fullerton DA (1997) Neutrophils mediate pulmonary vasomotor dysfunction in endotoxin-induced acute lung injury. J Trauma 42:391–397
35. Folkesson HG, Matthay MA (1997) Inhibition of CD18 or CD11b attenuates acute lung injury after acid instillation in rabbits. J Appl Physiol 82:1743–1750
36. Moriuchi H, Zaha M, Fukumoto T, Yuizono T (1998) Activation of polymorphonuclear leukocytes in oleic acid-induced lung injury. Intensive Care Med 24:709–715
37. Azuma A, Takahashi S, Nose M, Araki K, Araki M, Takahashi T, Hirose M, Kawashima H, Miyasaka M, Kudoh S (2000) Role of E-selectin in bleomycin induced lung fibrosis in mice. Thorax 55:147–152
38. Sato N, Suzuki Y, Nishio K, Suzuki K, Naoki K, Takeshita K, Kudo H, Miyao N, Tsumura H, Serizawa H, Suematsu M, Yamaguchi K (2000) Roles of ICAM-1 for abnormal leukocyte recruitment in the microcirculation of bleomycin-induced fibrotic lung injury. Am J Respir Crit Care Med 161:1681–1688
39. Folch E, Salas A, Panes J, Gelpi E, Roselo-Catafau J, Anderson DC, Navarro S, Pique JM, Fernandez-Cruz L, Closa D (1999) Role of P-selectin and ICAM-1 in pancreatitis-induced lung inflammation in rats. Ann Surg 230:792–799
40. Dry SM, Bechard KM, Milford EL, Churchill WH, Benjamin RJ (1999) The pathology of transfusion-related acute lung injury. Am J Clin Pathol 112:216–221
41. Sakamaki F, Ishizaka A, Handa M, Fujishima S, Urano T, Sayama K, Nakamura H, Kanazawa M, Kawashiro T, Katayama M, Ikeda Y (1995) Soluble form of P-selectin in plasma is elevated in acute lung injury. Am J Respir Crit Care Med 151:1821–1826
42. Moss M, Gillespie MK, Ackerson L, Moore FA, Moore EE, Parsons PE (1996) Endothelial cell activity varies in patients at risk for the adult respiratory distress syndrome. Crit Care Med 24:1782–1786
43. Donelly SC, Haslett C, Dransfield I, Robertson CE, Carter DC, Ross JA, Grant IS, Tedder TF (1994) Role of selectins in development of adult respiratory distress syndrome. Lancet 344:215–219
44. Xu N, Rahman A, Minshall RD, Tiruppathi C, Malik AB (2000) β_2-integrin blockade driven by E-selectin promoter prevents neutrophil sequestration and lung injury in mice. Circ Res 87:254–260
45. Murray JF, Matthay MA, Luce JM, Flick MR (1988) An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720–723
46. Sinclair DG, Braude S, Haslam PL, Evans TW (1994) Pulmonary endothelial permeability in patients with severe lung injury. Clinical correlates and natural history. Chest 106:535–539
47. Dudek SM, Garcia JGN (2001) Cytoskeletal regulation of pulmonary vascular permeability. J Appl Physiol 91:1487–1500
48. Thickett DR, Armstrong L, Christie SJ, Millar AB (2001) Vascular endothelial growth factor may contribute to increased vascular permeability in acute respiratory distress syndrome. Am J Respir Crit Care Med 164:1601–1605
49. Block ER (1992) Pulmonary endothelial cell pathobiology: implications for acute lung injury. Am J Med Sci 304:136–144
50. Morel Dr, Dargent F, Bachmann M, Suter PM, Junod AF (1985) Pulmonary extraction of serotonin and propranolol in patients with adult respiratory distress syndrome. Am Rev Respir Dis 132:479–484
51. Carvalho AC, Bellman SM, Saullo VJ, Quinn D, Zapol WM (1982) Altered factor VIII in acute respiratory failure. N Engl J Med 307:1113–1119
52. Sabharwal AK, Bajaj SP, Ameri A, Tricomi SM, Hyers TM, Dahms TE, Taylor FB, Bajaj MS (1995) Tissue factor pathway inhibitor and von Willebrand factor antigen levels in adult respiratory distress syndrome and in a primate model of sepsis. Am J Respir Crit Care Med 151:758–767
53. Rubin DB, Wiener-Kronish JP, Murray JF, Green DR, Turner J, Luce JM, Montgomery AB, Marks JD, Matthay MA (1990) Elevated von Willebrand factor antigen is an early plasma predictor of acute lung injury in nonpulmonary sepsis syndrome. J Clin Invest 86:474–480
54. Moss M, Ackerson L, Gillespie MK, Moore FA, Moore EE, Parsons PE (1995) Von Willebrand factor antigen levels are not predictive for the adult respiratory distress syndrome. Am J Respir Crit Care Med 151:15–20

55. Bajaj MS, Tricomi SM (1999) Plasma levels of the three endothelial-specific proteins von Willebrand factor, tissue factor pathway inhibitor, and thrombomodulin do not predict the development of acute respiratory distress syndrome. Intensive Care Med 25:1259–1266
56. Fisele B, Lamy M, Thijs LG, Keinecke H-O, Schuster H-P, Matthias FR, Fourrier F, Heinrichs H, Delvos U (1998) Antithrombin III in patients with severe sepsis. A randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. Intensive Care Med 24:663–672
57. Uchiba M, Okajima K (1997) Antithrombin III (AT III) prevents LPS-induced pulmonary vascular injury: a novel biological activity of AT III. Semin Thromb Hemost 23:583–590
58. McGregor IR, Perrie AM, Donnelly SC, Haslett C (1997) Modulation of human endothelial thrombomodulin by neutrophils and their release products. Am J Respir Crit Care Med 155:47–52
59. Distefano G, Romeo MG, Betta P, Rodono A, Amato M (1998) Thrombomodulin serum levels in ventilated preterm babies with respiratory distress syndrome. Eur J Pediatr 157:327–330
60. Christoforidou-Solomidou M, Kennel S, Scherpereel A, Wiewrodt R, Solomides CC, Pietra GG, Murciano JC, Shah SA, Ischiropoulos H, Albelda SM, Muzykantov VR (2002) Vascular immunotargeting of glucose oxidase to the endothelial antigens induces distinct forms of oxidant acute lung injury: targeting to thrombomodulin, but not to PECAM-1, causes pulmonary thrombosis and neutrophil transmigration. Am J Pathol 160:1155–1169
61. Grau GE, de Moerloose P, Bulla O, Lou J, Lei Z, Reber G, Mili N, Morel DR, Suter PM (1997) Haemostatic properties of human pulmonary and cerebral microvascular endothelial cells. Thromb Haemost 77:585–590
62. Mawji IA, Mardsen PA (2003) Perturbations in paracrine control of the circulation: role of the endothelial-derived vasomediators, endothelin-1 and nitric oxide. Microsc Res Tech 60:46–58
63. Liu S, Crawley DE, Barnes PJ, Evans TW (1991) Endothelium derived relaxing factor inhibits hypoxic pulmonary vasoconstriction in rats. Am Rev Respir Dis 143:32–37
64. Hart CM (1999) Nitric oxide in adult lung disease. Chest 115:1407–1417
65. Dupuis J, Stewart DJ, Cernacek P, Gosselin G (1996) Human pulmonary circulation is an important site for both clearance and production of endothelin-1. Circulation 94:1578–1584
66. Langleben D, Demarchie M, Laporta D, Spanier AH, Schlesinger D, Stewart DJ (1993) Endothelin-1 in acute lung injury and the adult respiratory distress syndrome. Am Rev Respir Dis 148: 1646–1650
67. Sanai L, Haynes WG, MacKenzie A, Grant IS, Webb DJ (1996) Endothelin in sepsis and the adult respiratory distress syndrome. Intensive Care Med 22:52–56
68. Moloney ED, Evans TW (2003) Pathophysiology and pharmacological treatment of pulmonary hypertension in acute respiratory distress syndrome. Eur Respir J 21:720–727
69. Chen XL, Orfanos SE, Catravas JD (1992) Effects of indomethacin on PMA-induced pulmonary endothelial enzyme dysfunction in vivo. Am J Physiol 262:L153–L162
70. Gust R, Kozlowski K, Stephenson AH, Schuster DP (1999) Role of cyclooxygenase-2 in oleic acid-induced acute lung injury. Am J Respir Crit Care Med 160:1165–1170
71. Clavijo LC, Carter MB, Matheson PJ, Wills-Frank LA, Wilson MA, Wead WB, Garrison RN (2000) Platelet activating factor and bacteremia-induced pulmonary hypertension. J Surg Res 88:173–180
72. Orfanos SE, Kotanidou K, Roussos C (2002) Pulmonary endothelial angiotensin converting enzyme in lung injury. In: Vincent JL (ed) 2002 Yearbook of intensive care and emergency medicine. Springer, Berlin Heidelberg New York; pp 100–110
73. Linz W, Wohlfart P, Scholkens BA, Malinski T, Wiemer G (1999) Interactions among ACE, kinins and NO. Cardiovasc Res 43:549–561
74. McCloud L, Parkerson JB, Freant L, Hoffman WH, Catravas JD (2004) β-hydroxybutyrate induces acute pulmonary endothelial dysfunction in rabbits. Exp Lung Res 30:193-206
75. Kohlstedt K, Brandes RP, Muller-Esterl W, Busse R, Fleming I (2004) Angiotensin converting enzyme is involved in outside-in signalling in endothelial cells. Circ Res 94:60–67
76. Ryan US, Ryan JW, Whitaker C, Chiu A. (1976) Localization of angiotensin-converting enzyme (kinase II). Immunocytochemistry and immunofluorescence. Tissue Cell 8:125–146
77. Orfanos SE, Langleben D, Khoury J, Schlesinger RD, Dragatakis L, Roussos C, Ryan JW, Catravas JD (1999) Pulmonary capillary endothelium-bound angiotensin converting enzyme activity in humans. Circulation 99:1593–1599
78. Casey L, Krieger B, Kohler J, Rice C, Oparil S, Szidon P (1982) Decreased serum angiotensin converting enzyme in adult respiratory distress syndrome associated with sepsis: a preliminary report. Crit Care Med 9:651–654
79. Lazo JS, Catravas JD, Gillis CN (1981) Reduction in rabbit serum and pulmonary angiotensin converting enzyme after subacute bleomycin treatment. Biochem Pharmacol 30:2577–2584
80. Dobuler KJ, Catravas JD, Gillis CN (1982) Early detection of oxygen-induced lung injury in conscious rabbits: reduced in vivo activity of angiotensin converting enzyme and removal of 5-hydoxytryptamine. Am Rev Respir Dis 126:534–539
81. Ehrhart IC, Orfanos SE, McCloud LL, Sickles DW, Hoffman WF, Catravas JD (1999) Vascular recruitment increases evidence of lung injury. Crit Care Med 27:120–129
82. Orfanos SE, Chen XL, Burch SE, Ryan JW, Chunk AYK, Catravas JD (1994) Radiation-induced early pulmonary endothelial ectoenzyme dysfunction in vivo: effect of indomethacin. Toxicol Appl Pharmacol 124:112–122
83. Catravas JD, Burch SE, Sprulock BO, Mills LR (1988) Early effects of ionising radiation on pulmonary endothelial angiotensin converting enzyme and 5'-nucleotidase, in vivo. Toxicol Appl Pharmacol 94:342–355
84. Atochina EN, Muzykantov VR, Al-Medhi AB, Danilov SM, Fisher AB (1997) Normotoxic lung ischemia/reperfusion accelerates shedding of angiotesin converting enzyme from the pulmonary endothelium. Am J Respir Crit Care Med 156:1114–1119
85. Orfanos SE, Armaganidis A, Glynos C, Psevdi E, Kaltsas P, Sarafidou P, Catravas JD, Dafni UG, Langleben D, Roussos C (2000) Pulmonary capillary endothelium-bound angiotensin converting enzyme activity in acute lung injury. Circulation 102:2011–2018
86. Marshall RP, Webb S, Bellingan GJ, Montgomery HE, Chaudhari B, McAnulty RJ, Humphries SE, Hill MR, Laurent GJ (2002) Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 166:646–650
87. Groeneveld ABJ (2003) Vascular pharmacology of acute lung injury and acute respiratory distress syndrome. Vascul Pharmacol 39:247–256

88. Wang Q, Pfeiffer GR, Stevens T, Doerschuck CM (2002) Lung microvascular and arterial endothelial cells differ in their responses to intercellular adhesion molecule-1 ligation. Am J Respir Crit Care Med 166:872–877

89. Parthasarathi K, Ichimura H, Bhattacharya J (2003) Septal capillaries communicate pro-inflammatory signals to downstream vascular segments in lung (abstract). Am J Respir Crit Care Med 167:A121

90. Matthay MA, Zimmerman GA, Esmon C, Bhattacharya J, Coller B, Doerschuck CM, Floros J, Gimbrone MA Jr, Hoffman E, Hubmayr RD, Leppert M, Matalon S, Munford R, Parsons P, Slutsky AS, Tracey KJ, Ward P, Gail DB, Harabin AL (2003) Future research directions in acute lung injury. Summary of a National Heart, Lung and Blood Institute working group Am J Respir Crit Care Med 167:1027–1035

C. S. A. Macmillan
I. S. Grant
P. J. D. Andrews

Pulmonary and cardiac sequelae of subarachnoid haemorrhage: time for active management?

Abstract Cardiac injury and pulmonary oedema occurring after acute neurological injury have been recognised for more than a century. Catecholamines, released in massive quantities due to hypothalamic stress from subarachnoid haemorrhage (SAH), result in specific myocardial lesions and hydrostatic pressure injury to the pulmonary capillaries causing neurogenic pulmonary oedema (NPO). The acute, reversible cardiac injury ranges from hypokinesis with a normal cardiac index, to low output cardiac failure. Some patients exhibit both catastrophic cardiac failure and NPO, while others exhibit signs of either one or other, or have subclinical evidence of the same.Hypoxia and hypotension are two of the most important insults which influence outcome after acute brain injury. However, despite this, little attention has hitherto been devoted to prevention and reversal of these potentially catastrophic medical complications which occur in patients with SAH. It is not clear which patients with SAH will develop important cardiac and respiratory complications. An active approach to investigation and organ support could provide a window of opportunity to intervene before significant hypoxia and hypotension develop, potentially reducing adverse consequences for the long-term neurological status of the patient. Indeed, there is an argument for all SAH patients to have echocardiography and continuous monitoring of respiratory rate, pulse oximetry, blood pressure and electrocardiogram. In the event of cardio-respiratory compromise developing i.e. cardiogenic shock and/or NPO, full investigation, attentive monitoring and appropriate intervention are required immediately to optimise cardiorespiratory function and allow subsequent definitive management of the SAH.

Keywords Subarachnoid · haemorrhage · Neurogenic pulmonary oedema · Cardiac injury · Critical care Electrocardiogram

Abbreviations *ALI* acute lung injury · *CI* cardiac index · *CK-MB* creatine phosphokinase-myocardial fraction · *CVP* central venous pressure · *ECHO* echocardiogram · *ARDS* acute respiratory distress syndrome · *CPP* cerebral perfusion pressure · *EVLW* extravascular lung water · *HDU* high dependency unit · *ICP* intracranial pressure · *ICU* intensive care unit · *MAP* mean arterial pressure · *MPAP* mean pulmonary artery pressure · *Neuro obs* neuroligical observation/assessment · *NPO* neurogenic pulmonary oedema · *ODM* oesophageal Doppler monitor · *PAC* pulmonary artery catheter · *PAOP* pulmonary artery occlusion pressure · *PAP* pulmonary artery pressure · *PEEP* positive end expiratory pressure · *SAH* subarachnoid haemorrhage · *SBP* systolic blood pressure · *WFNS* World Federation of Neurosurgeons grading for SAH

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_38,

Introduction

Subarachnoid haemorrhage (SAH), which affects predominantly women of working age, has devastating consequences with a mortality exceeding 40% and a morbidity so high that less than 25% make a complete recovery [1]. Improved management over recent years has included optimal timing of surgery [2], endovascular coiling [3]and nimodipine therapy [4, 5, 6]. Recently published recommendations support active intensive care for patients with complications of SAH [7], yet research and clinical resources have focused on other major causes of mortality following SAH – direct pressure effects, rebleed and vasospasm, each of which accounts for a quarter of the deaths. However, in a recent study involving more than 450 SAH patients, medical complications accounted for a similar proportion of deaths [8]. Clearly, there is room for improvement.

Medical complications after SAH have been neglected both in terms of research and their importance to outcome in clinical practice. This review will focus on cardiorespiratory compromise – cardiac dysfunction and pulmonary oedema – associated with acute SAH, where the experience of intensivists may have a crucial influence. Evidence will be assessed to clarify the pathophysiological processes that result in life-threatening clinical deterioration. Treatment options will be reviewed and a evidence-based practical approach to patient management will be discussed.

Medical complications of SAH

The most comprehensive study of medical complications after SAH to date followed 457 adult patients for 3 months after ictus [8]. Patients were recruited between 1987 and 1989, none received a calcium antagonist but corticosteroids were given to 70%, anticonvulsant therapy to 80%, and nearly two-thirds had surgery within 3 days. Complying with current recommendations [7] and practice [9] for 'triple H' therapy, 80% had *H*ypervolaemia (average daily fluid intake during the first 2 weeks was 4.1 l) and over 30% had induced *H*ypertension. In terms of *H*aemodilution, the third '*H*', 30% had 'anaemia'. Medical complications accounted for 23% of deaths. Other deaths were caused by the primary bleed (19%), rebleed (22%) and vasospasm (23%). While little can be done for the primary bleed, much effort has been directed towards reducing the impact of re-bleed and vasospasm, but relatively little has been aimed at identifying the causes, reducing the incidence or improving the management of medical complications. Indeed, not only is a significant proportion of mortality directly attributable to medical complications, but also a significant degree of morbidity as 83% of those who died had a life-threatening medical complication compared to 30% of survivors [8].

The scope of medical complications in these SAH patients was representative of many intensive care patient groups and included renal, hepatic, haematological, metabolic and endocrine dysfunction. However, the most frequent were pulmonary and cardiovascular complications [8]. Cardiac dysfunction is a well-known and frequently reported complication of SAH, most often recognised on the electrocardiogram (ECG) by arrhythmias, including ventricular fibrillation and conduction abnormalities. Cardiac failure is less commonly reported in the literature, but was found in 4% of patients reported by Solenski et.al. This has also been the subject of several studies of cardiac function after SAH [10, 11, 12, 13, 14, 15]. Pulmonary oedema, sometimes severe enough to be life-threatening, was identified in a quarter of patients. As will be discussed later, pulmonary oedema associated with SAH has a different aetiology from the inflammatory response that produces acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS), although SAH can also trigger a systemic inflammatory response leading to this lung pathology.

Cardiac dysfunction and pulmonary oedema may occur together or independently after SAH. Secondary brain injury caused by hypoxia and hypotension – the two most influential factors on poor outcome after acute traumatic brain injury [16] – are situations where intensive care clinicians have arguably the greatest experience and therefore potentially have the most to offer patients. Logical treatment of cardiac and respiratory deterioration requires an understanding of the underlying pathophysiology.

Cardiac injury

Electrical cardiac disturbances

Rhythm and conduction disturbances are almost universal after SAH [17] and have been regularly reported in the last 50 years [18]. Anything from fatal ventricular fibrillation to bradycardia is possible [20]; common findings include QRS, ST segment and T-wave abnormalities, and prolongation of the QT interval [21, 22, 23]. These changes may mimic myocardial infarction or ischaemia on a 12-lead ECG [21], but clinical diagnoses of myocardial infarction have been refuted at post-mortem examination due to lack of coronary artery disease [22, 23, 24]. In survivors of SAH the ECG changes are usually reversible, although they may persist for several weeks [11, 22, 25] and can recur in patients with re-bleed. Experimental evidence may explain these ECG abnormalities. Stimulation of the posterior hypothalamus in cats caused a marked pressor response, multifocal ectopic beats, T wave inversion and S-T segment changes [27]. Hypothalamic stress (from ischaemia and/or pressure) is the common link between SAH and its cardiac sequelae.

Clinical relevance of ECG abnormalities

SAH is almost universally associated with cardiac electrical disturbance [17], but its clinical relevance is questionable. There is no consistent association between ECG abnormalities and the mechanical hypokinesis found on echocardiography, histological cardiac lesions or serum markers of cardiac injury [10, 11, 12, 13, 14, 17]. In relation to brain secondary insults, a low cardiac output with reduced cerebral perfusion could be important to outcome; markers of impending clinical deterioration would thus be helpful.

Arrhythmias make a significant contribution to mortality and most occur within the first week [20, 28]. In monitored patients, rhythm disturbances occurred in 35%, most commonly sinus tachy or bradycardia, and were considered a moderate threat to life. In addition, ventricular arrhythmias such as asystole and fibrillation were recorded [8], with 5% suffering a life-threatening arrhythmia. These ECG abnormalities were not associated with cardiac failure. Arrhythmias causing haemodynamic changes have been detected in more than 40% of patients, and were life-threatening in 10% [8, 20, 29]. ECGs repeated regularly during hospital admission of 37 SAH patients did not reveal any association between abnormalities and outcome [23]. There were conflicting opinions when neurological state was compared with arrhythmias, some finding no association [12, 20, 29] while others concluded the opposite. However, in a recent study of 61 SAH patients with continuous ECG monitoring, poor outcome was associated with tachyarrhythmias and/or cardiac ischaemia, although this did not hold true for individual ECG abnormalities such as T wave changes [17]. Continuous ECG monitoring in an area with immediate cardiac resuscitation facilities could save lives. In terms of neurological outcome, patients with the most to benefit are those with good neurological grades who may suffer a life-threatening arrhythmia.

Virtually every possible static ECG abnormality has been described after SAH, but clinical relevance is uncertain. Electrolyte disturbance of sodium, calcium and potassium do not seem to be relevant to morphology [12, 22, 30], although, not surprisingly, serious arrhythmias occurred in SAH patients with low serum potassium [29]. Increased urinary catecholamine metabolite and plasma cortisol concentrations were significantly associated with tachycardia, large P waves, short PR interval (<0.13 s), peaked or inverted T waves, and prolonged QTc interval [30]. However, this was refuted in a more recent study [25]. Perhaps ECG abnormalities known to be associated with serious arrhythmias, such as an increased QTc interval, should be measured and thus encourage clinicians to increase their vigilance.

Prolongation of the QT interval after SAH is well documented [10, 11, 13, 17, 19, 20, 21, 22, 25, 30]. A more recent measure, QT dispersion (the difference between the longest and shortest QT interval on a standard 12-lead ECG) – which is associated with fatal arrhythmogenic potential [31] – is increased in SAH patients [32, 33]. The exact mechanism for these changes is unclear, but may be related to imbalance of autonomic tone [22, 25], catecholamines [30, 34, 35] or electrolyte disturbance.

Whatever the truth is in relation to ECG changes, clinical course and outcome, the practical relevance may be a delay in surgery to clip or coil aneurysms as a consequence of additional investigations deemed necessary because of such ECG abnormalities. It could be argued that the standard 12-lead ECG should be discounted in relation to risk assessment for anaesthesia for SAH.

Ventricular dysfunction

Mechanical pump failure causing a reduction in cardiac output occurs less frequently than conduction problems, but can be fatal. The aetiology is controversial. Myocardial ‘stunning’ is a term that has been applied to sudden and sometimes unexpected ventricular hypokinesis. Sudden onset of ventricular failure (often hypotensive) with or without pulmonary oedema has been reported in SAH case series [8, 11, 36, 37, 38]. In fact, any acute intracranial pathology may result in a stunned myocardium [39]; endogenous catecholamines are the most likely cause.

Surrogate markers for impaired myocardial function include a reduction in blood pressure and cardiac output, or an increase in pulmonary artery occlusion pressure. Direct evidence of ventricular systolic dysfunction can be obtained using echocardiography or nucleotide ventriculography. There are few studies in the literature because these are relatively new investigative tools, but animal experiments provide some insight. SAH induced in nine dogs resulted in motion abnormalities in each, particularly hypokinesis of the left ventricle, detected by transoesophageal echocardiography [34]. SAH causes similar ventricular dysfunction in patients. Case studies after SAH demonstrate general hypokinesia [11, 40, [41]and reduced ejection fraction [37, 41]. Of 19 SAH patients who had thallium scintigraphy, 6 had areas of reversible reduced uptake, indicating perfusion abnormality [10]. Of 12 patients with SAH, more than half had abnormal ventriculography and echocardiography [13]In a larger series of 45 patients, 4 had ventricular hypokinesis 12, as did 4 of 13 SAH patients in another report [14]. A case series of five SAH patients, all with severe neurogenic pulmonary oedema (NPO), demonstrated low ejection fractions requiring inotropic support. Such cases illustrate that NPO and myocardial wall motion abnormalities can occur concurrently [11], i.e. left ventricular failure, but one does not necessarily follow the other [14]. Wall-motion abnormalities are temporary and normal cardiac function usually returns [10, 11, 13, 14, 41]. In-

terestingly, ventricular dysfunction and ECG changes can occur independently or together [14], but large vessel coronary artery disease has been excluded by angiography as a contributing factor in wall-motion abnormality [13]. This is supported by autopsy [42]; transmural myocardial infarction typically caused by coronary atheroma thrombus was not seen at post-mortem in SAH victims; instead discrete focal lesions occurred [10, 12, 13, 43].

Markers of myocardial cell injury

The myocardium is injured in many patients with SAH; an abnormal increase in plasma creatine phosphokinase-myocardial fraction (CK-MB) concentration is a common finding. The CK-MB was increased in all patients after SAH, but more so in those with echocardiographic evidence of wall-motion abnormalities [14]. More recently, a case series of five SAH patients suffering acute hypotension and NPO was reported [11]. All patients had significantly increased serum CK-MB and wall-motion abnormalities on echocardiography. This pattern has also been described in case reports [40], but there is no association between the increase in CK-MB after SAH and ECG changes [44]. However, there may be an association between cerebral vasospasm after SAH and increased CK-MB [37, 45]. Another marker of cardiac injury, troponin I, was increased in approximately one-fifth of SAH patients, but only a fraction of these had clinically detectable cardiac abnormalities [46]. The reasons for myocardial injury are not clear, but are probably related to hypothalamic stimulation and catecholamine secretion. In animal experiments, stimulation of the midbrain caused myocyte degeneration throughout the heart [27], but most dense in the subendocardium, and surrounded by normal tissue, as is found in SAH patients [47]. Hypothalamic stimulation in cats resulted in cardiac dysfunction and ECG changes similar to those found after SAH. After several hours of stimulation, the hearts had evidence of small haemorrhages and infarcted myocardial fibres with homogeneous cytoplasm, loss of cross striation and loss of nuclei.

Haemodynamic changes

After SAH clinical manifestations of cardiac injury and NPO may occur simultaneously [11, 24, 37, 38, 40, 48, 49] or in isolation [10, 12, 13, 14, 38, 47, 50, 51, 52, 53, 54, 55, 56], depending on the individual's response to the pathophysiological insult [42]. A recent retrospective case series included 16 SAH patients with NPO [48]. All were mechanically ventilated and 4 received vasoactive agents (3 epinephrine and 1 dobutamine) prior to baseline haemodynamic recordings. Their initial mean derivatives included a mean arterial pressure (MAP) of 84 mmHg (range 74–104), mean pulmonary artery pressure (MPAP) 29 mmHg (14–44), CVP 10 mmHg (1–29), PAOP 16 mmHg (5–29), cardiac index (CI) 2.5 $l.min^{-1}m^{-2}$ (1.6–4.5) and a PaO_2:FiO_2 ratio (kPa) of 22 (13–34). The clinical picture was thus one of normal blood pressure, reduced cardiac output and pulmonary oedema diagnosed by chest X-ray findings and hypoxaemia (PaO_2:FiO_2 <40), but with a wide range of PAOP. Most patients had a very low left ventricular stroke work index indicating LVF, but markedly elevated pulmonary vascular resistance implying a pulmonary component in addition to the cardiac aetiology of the NPO. Thus there was a marked variation amongst patients, measured and derived variables being heterogeneous in relation to cardiac and pulmonary lesions.

As the above report shows, NPO occurs in the presence of reduced, normal or increased haemodynamic measures, including PAOP, which ranged from 5 to 29 mmHg at pulmonary artery catheter insertion. It should be noted that insertion of pulmonary catheters in that intensive care unit was not routine, but required the patient to be unstable, for example with hypoxaemia, frank pulmonary oedema or hypotension; five patients had had prior therapy with ephedrine, methoxamine or dobutamine. Another case series of five SAH patients with severe NPO demonstrated a variable cardiac index (1.9–3.0 $l.min^{-1}.\ m^{-2}$), increased PAOP (17–36 mmHg) and reduced ejection fraction (20–35%) on echocardiography with global impairment of the left ventricle [41]. Examining extravascular lung water (EVLW), initial recordings in 21 patients with intracerebral haemorrhage and 4 with SAH showed no difference in PAOP between those with the greatest EVLW and those without increased EVLW (7.8 vs 7.9 mmHg) [54]. Another case report of SAH demonstrated pulmonary oedema, after which a low systemic blood pressure (90/60 mmHg) and high PAOP (22 mmHg) developed, indicating cardiac dysfunction [37]. This was confirmed on cardiac echocardiography and radionuclide ventriculography where a hypokinetic septum and basal segments were associated with a low ejection fraction of approximately 35%. These case series describes small numbers of patients; therefore, caution should be applied when interpreting the results. However, they do illustrate the variable clinical picture at any one point in time.

Other papers demonstrate temporal haemodynamic changes. Although these, too, are drawn from case reports, it is important to acknowledge the cardiovascular changes described, which do not conform to a single clinical picture. A patient with NPO had PAOP values that ranged from 0 to 15 mmHg over a 3-day period with a maximum recorded PAP of 50/17 mmHg [53]. The recordings were infrequent (every 4 h or less), so it is possible that more extreme pressures were missed. Similarly, in a series of four SAH patients who developed NPO

[12], initially normal PAOP values increased to above 16 mmHg. Another patient with SAH developed NPO [55] where the initial right ventricular pressure was 40/2 mmHg and PAOP 0–4 mmHg, although he had several episodes of severe systemic hypertension (up to 410/200 mmHg) with corresponding PAP 110/60 mmHg and PAOP 48 mmHg. Each episode lasted for approximately 5 min before returning to baseline. Other reports confirm rapidly changing PAOP and systemic blood pressure after SAH [57]. These cases underline the rapid and volatile change in pressures that may occur and could easily be missed.

The closest approximation to pulmonary capillary pressure is an estimate somewhere between PAP and PAOP [58]. Indeed, in experimental animals the left ventricular end diastolic pressure exceeded PAP when epinephrine was used to induce pulmonary oedema [59]. The pulmonary veins were the first vessels to develop increased pressure [60]. In response to experimentally induced SAH, the systemic pressure increased, followed by pulmonary venous then pulmonary arterial pressure, with little change in CVP [61]. Resistance in pulmonary veins of rats increases as constrictions or valves within the vessels increase their tone immediately after a blow to the head [62]. Thus pressure increases in the pulmonary veins precede those in the pulmonary capillaries and may not be reflected by PAOP, PAP or CVP [61]. In addition, if the left ventricle fails, it may contribute to the increase in pulmonary venous pressure.

Neurogenic pulmonary oedema

Any factor reducing diffusion across the alveolar-capillary barrier, including interstitial and frank alveolar oedema, will increase the likelihood of hypoxaemia. Post-mortem studies of intracranial pathology recorded an incidence of pulmonary oedema of 46 [63] and 52% [64]. A Minnesota study of sudden deaths found that over 90% of patients with intracranial bleeds had pulmonary oedema [65]. Furthermore, NPO can develop within seconds of a neurological insult. In a series of 56 Vietnam casualties (aged 17–37 years) killed from head wounds, it was found that most had oedema, congestion and haemorrhage of the lungs [66]. Indeed, even 17 of 20 soldiers killed almost instantaneously had these findings at autopsy. Interestingly, casualties with cervical cord transection or massive haemorrhage had normal lungs. The development of NPO requires an adequate systemic circulating volume. Rabbits given epinephrine infusions to induce pulmonary oedema [67] had increased lung-to-body weight ratios and reduced static compliance, but animals rendered hypovolaemic by bleeding prior to epinephrine administration had no evidence of oedema. Similarly, autopsy findings in soldiers with serious head trauma showed no evidence of pulmonary oedema if significant hypovolaemia had occurred [66].

NPO, defined as bilateral pulmonary infiltrates on chest X-ray and reduced PaO_2 not attributable to another cause, was identified in 23% of all SAH patients surviving to reach hospital and was considered to be a threat to life in 6% [8]. This is probably an underestimate because to meet the definitions of severe (life-threatening) pulmonary oedema for the purposes of the study, a pulmonary artery catheter was required to confirm a PAOP>22 mmHg associated with severe impairment of gas exchange (PaO_2 <6.7 kPa with FiO_2 ≥0.4). Pulmonary oedema occurred on days 0–14 but most frequently on day 3, and was associated with increasing age (>30 years), poorer grades (WFNS grading [68]) and day of surgery, but not with 'triple H' therapy, cerebral angiography, past history of cardiac disease, ECG changes or lung disease. The time scale noted also coincides with catecholamine hypersecretion that may last for 10 days or more after SAH [69]. Curiously, hepatic dysfunction was associated with pulmonary oedema [8], perhaps owing to hypoxia or to liver congestion, which has been noted at autopsy [47]. NPO is a serious and common complication after SAH that threatens both survival and good neurological outcome.

Pulmonary oedema fluid

Several investigations into the nature of SAH-induced pulmonary oedema fluid have been conducted to determine if its evolution is hydrostatic (low protein content) or permeable (high protein content) in nature. The ratio of oedema fluid to plasma colloid oncotic pressure separates transudates from exudates. In a study examining pulmonary oedema fluid from multiple causes, left ventricular failure oedema fluid usually had a ratio of <0.6 [49, 70], i.e. a low protein content and therefore hydrostatic in origin. However, in SAH-induced pulmonary oedema, a spectrum of ratios occur. One of the earliest case reports to document this found a high protein content [53], while more recently a study in 12 SAH patients found an increased ratio (>0.7, permeability lesion) in 5 patients and a low ratio (<0.6) in 7 [38]. SAH-induced NPO with a range of protein concentrations requires further explanation because the findings by Smith et al. [38]suggest that some patients have permeability oedema and others hydrostatic oedema. However, there may be only one pathological process at work. Pulmonary oedema developing after SAH is caused by increasing capillary pressures that damage the endothelium and, as the pressure increases further, disrupts the basement membrane causing fluid and protein extravasation [58]. This is supported by animal work where intense pulmonary vascular constriction induced using endothelin produced an increase in pulmonary pressure and EVLW causing

oedema [71]. Microscopic changes have been found in animal experiments using rabbits [72]. When transmural pressures exceeded 40 mmHg, the pulmonary capillary endothelium became disrupted. As the transmural pressure increased further, the basement membranes of the capillaries and alveoli and the alveolar endothelium were also injured to the point where red blood cells, protein and fluid escaped into the alveolar lumen. Thus, oedema fluid is initially low in protein (low permeability, hydrostatic) but, as barriers are disrupted with increasing capillary pressure, the oedema fluid becomes proteinaceous (high permeability). The time course for this is very variable. Patient data are limited and have not examined cardiovascular markers such as PAOP, PAP and central venous pressure (CVP), in relation to hydrostatic and permeability oedema.

Catecholamines as the common link

There is a remarkable similarity between the cardiorespiratory compromise found after SAH and that of phaeochromocytoma crises. Sudden onset of ventricular failure (often hypotensive) with or without pulmonary oedema has been reported in case series of SAH [8, 11, 36, 37, 38] and phaeochromocytoma [73, 74]. Pulmonary oedema [75], cardiogenic shock and arrhythmias are common to both, as is the high concentration of catecholamines [25, 30, 32, 35, 47, 69, 76, 77]. Conclusions from many reports on catecholamines in relation to SAH describe a catecholamine 'storm'. In addition, a recent report has found evidence in SAH patients of prolonged and massive sympathetic nervous activation [69]. A three-fold increase in norepinephrine spill-over into the plasma was detected, which was sustained for at least 10 days, but was normal at the 6-month follow-up.

Catecholamine induced cardiac injury

Experimental evidence linking catecholamines to cardiac injury exists in animals and man. Specific myocardial lesions in animals subjected to infusions of l-norepinephrine [78]are the same as those found in shocked patients treated with epinephrine and l-norepinephrine. In mongrel dogs an increase in plasma catecholamines as a consequence of induced SAH caused specific cardiac lesions on electron microscopy within 4 h of induced SAH [79]. Others have found histological contraction band lesions within 5 min of beginning a catecholamine infusion [80]. Such contraction-band necrosis is unevenly distributed, being most dense at the apex and subendocardial areas of the ventricles [81], i.e. in the regions of heart muscle most responsible for cardiac output.

Focal myocytolysis [82] or myofibrillar degeneration [where dense eosinophilic bands replace the normal striated appearance of the cytoplasm, and the muscle fibres appear as 'empty' sarcolemic sheaths (Fig. 1)] have been described in patients dying from SAH [47] and phaeochromocytoma [73]. Further human post-mortem evidence of myocytolysis and contraction-band necrosis of the heart in neurosurgical patients, including those dying after SAH, has been described by Connor [50], who considered these lesions to be the same as those caused by catecholamines. Furthermore, in a case series of 54 consecutive SAH deaths [42], 42 cadavers (including a 12-year-old boy) had myocardial lesions described as foci of necrotic muscle fibres, haemorrhage and inflammatory cells that were not found in the control group. An interesting finding was that the SAH victims with more variable pulse and blood pressure recorded prior to death (presumably from autonomic fluctuation) were more likely to have myocardial lesions. In addition, hypertensive heart disease was associated with significantly fewer myocardial lesions than SAH victims without hypertensive heart disease. Perhaps patients with hypertensive heart disease are less sensitive to catecholamines and are thus protected from their acute effects. It is not clear if

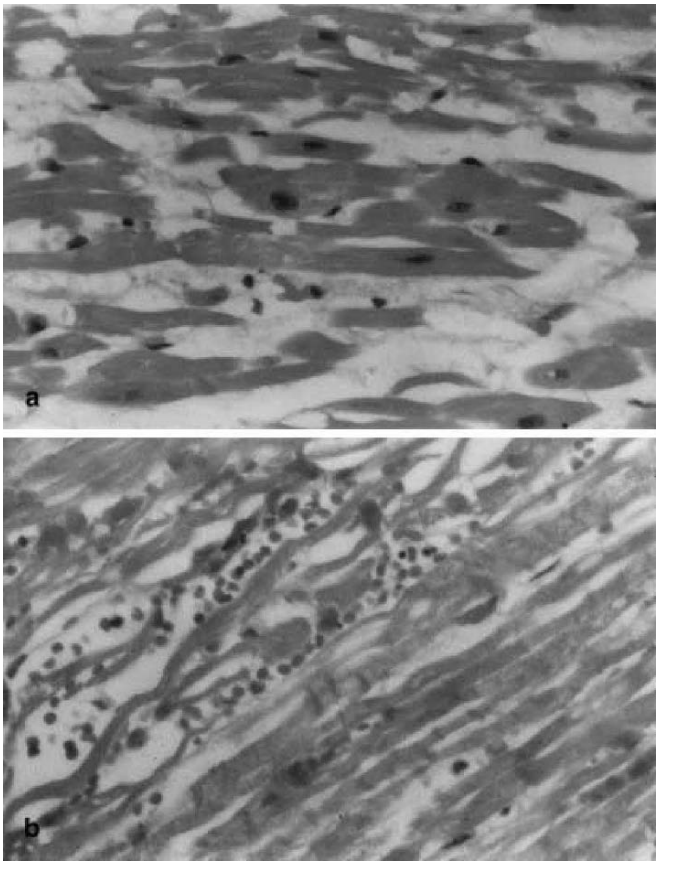


Fig. 1 Histological section (100) of the myocardium demonstrating **a** normal ventricle and **b** myofibrillar degeneration, myocytolysis and inflammatory cell infiltration

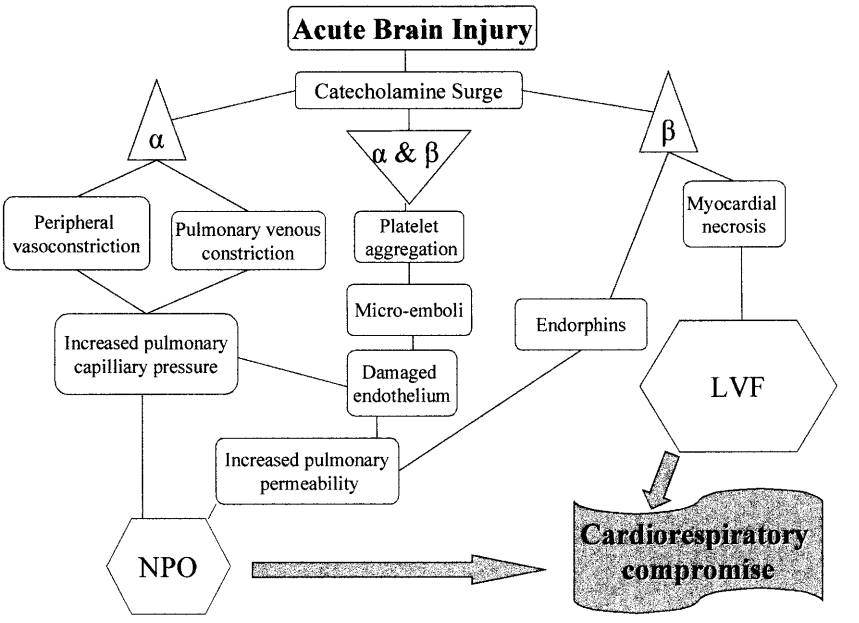


Fig. 2 Subarachnoid haemorrhage can result in sympathetic activation that causes pulmonary oedema and cardiac failure (α alpha-adrenoceptor, β beta-adrenoceptor, *LVF* left ventricular pressure)

anti-hypertensive medication such as beta-blockers or some intrinsic property of the hypertensive myocardium to resist a catecholamine 'storm' play a part. In another SAH post-mortem study, those who died suddenly were compared to those with WFNS grade 5 who subsequently died. NPO was much more common in the 68 sudden-death patients; histological examination of the myocardium was performed in 6 patients which showed contraction band necrosis in every case [28]. Multifocal transmural myocardial injury was the post-mortem finding in most SAH patients, but not in the control group [43]. Catecholamine induced myocardial injury poses challenges for prophylaxis and therapy.

Catecholamine-induced pulmonary oedema

Catecholamines can cause pulmonary oedema. They increase transmural pulmonary vascular pressures [83] by a combination of α- and β-adrenoceptor activation, and cardiac injury (Fig. 2). Frank pulmonary oedema can be induced experimentally by epinephrine infusion [59, 61], or seen clinically in phaeochromocytoma crisis [75, 84, 85, 86]. The largest initial effect is increased pulmonary venous pressure [61]. Pulmonary arterial pressure may then increase and this is *sometimes* reflected in the central venous pressure. A rise in pulmonary capillary pressure was demonstrated in 11 baboons where brain death was induced by acute intracranial hypertension. Between brain injury and death, significant increases in circulating catecholamines occurred, causing an increase in systemic vascular resistance and acute left ventricular failure. In this study mean PAOP increased above the mean PAP in most animals, and more than 70% of blood volume pooled in the lungs. The high pressures within the pulmonary circulation caused pulmonary oedema and alveolar haemorrhage in 4 of the animals [87].

An increase in EVLW, whether extensive enough to result in frank pulmonary oedema or not, reduces compliance [83]. Using the double-indicator dilution method to calculate EVLW in 25 patients with SAH, Tuoho et.al. [54] found a significant positive correlation between increased alveolar-arterial oxygen difference ($AaDO_2$) and increasing EVLW. An increase in EVLW occurs in animal models of raised ICP and massive sympathetic discharge [88, 89]and was proportional to pressures in the pulmonary circulation. The essential physiological phenomenon was the requirement for a massive, but not necessarily prolonged, rise in PAP [88, 90]. Studies in humans during maximum exercise have shown PAP and PAOP to reach maximal mean values of 37 and 21 mmHg, respectively [91]; capillary pressure should fall between the two pressures at approximately 30 mmHg. Pathological states may exceed such pressures. After SAH the increase in catecholamine concentration can occur in seconds and be 1200, 145 and 35 times the normal limit for epinephrine, norepinephrine and dopamine, respectively [92]. Furthermore, epinephrine can remain increased in the circulation for at least 10 days [69]. This could explain why NPO can be seen anytime from ictus up to 14 days [8, 41, 66].

Hypothalamic lesions after SAH

Since catecholamines are responsible for myocardial injury and pulmonary oedema, then the question of what induces the catecholamine release is raised. In a post-mortem study, 49 of 54 patients dying from SAH had microscopic hypothalamic lesions consisting of small-ball haemorrhages and infarctions [42]. Of these, 42 also had the typical myocardial lesions described above. However, in the control group of patients with raised ICP caused by other intracranial pathologies (all with swollen brains), there were no hypothalamic or myocardial lesions. Another group reported hypothalamic and cardiac lesions on post-mortem examinations in patients dying suddenly of SAH [93]. In other reports, patients with SAH had hypothalamic, cardiac and pulmonary lesions [24, 47]. Therefore, a raised ICP per se cannot explain the cardiac and pulmonary injuries, although there is clinical and experimental [34] evidence to support an association between these and hypothalamic lesions.

Ischaemia and/or infarction of the posterior hypothalamus is the most likely initiating event that causes sympathetic activation. In a series of 106 patients dying from SAH, 65 had hypothalamic lesions which had histological evidence of ischaemia, microhaemorrhages, massive haemorrhage or a combination of ischaemia and haemorrhage [94]. Perhaps the close proximity of subarachnoid blood from the ruptured aneurysm influences the fine perforating arteries to the hypothalamus, causing microvascular spasm.

Management

There are two important reasons for being proactive in the treatment of patients with cardiac and/or respiratory complications of SAH. Firstly, secondary brain injury caused by hypoxia and hypotension should be prevented [2]. Secondly, mechanical cardiac dysfunction and NPO are very treatable with potentially good outcomes, despite affected patients appearing moribund [41]

Identifying patients at risk

It is not clear which SAH patients will develop cardiac and respiratory complications, but risk factors include poor neurological grade, age over 30 years, hypertension, ventricular repolarisation abnormalities, and the timing of surgery [8, 33]. These patients may benefit from early intensive monitoring.

Prophylaxis

Regardless of where the trigger zone is within the brain, experimental evidence shows that when acute brain injury occurs, if the cervical cord is transected [47, 61, 66] or if cardiac sympathetic nerves are severed or blocked [95], pulmonary oedema does not develop [27, 93]. Similarly, cardiac lesions do not occur if the cervical cord is transected [27]. Prophylactic pharmacological drugs used to block the effects of the autonomic nervous system, such as α-blockade with phenoxybenzamine, prevented death and pulmonary oedema in rabbits infused with epinephrine [59]. Pharmacological cardiac sympathectomy prevented myocardial injury in baboons killed by a sudden massive increase in ICP [95]. There may be a role for prophylactic intervention to prevent cardiac and pulmonary complications after SAH. Clearly, cord transection is not a therapeutic or prophylactic clinical option, but pharmacological shielding from the catecholamine storm deserves further evaluation.

There are few data from clinical trials, but prophylactic combined α- and β-blockade using phentolamine and propranolol may reduce myocardial injury from catecholamines after SAH [93]. In this study 90 SAH patients presenting within 48 h of ictus and without a history of cardiac disease were randomised to receive both propranolol 80 mg 8 hourly and phentolamine 20 mg 3 hourly, or placebo. There was no difference in the mortality (perhaps because of small numbers) but, at autopsy, focal necrosis of the myocardium was only present in the placebo group, implying a protective cardiac effect. Another report by the same group showed benefit in terms of survival and neurological state in SAH patients given prophylactic phentolamine and propranolol [96]. They surmised this was due to a reduction in complications such as NPO and cardiac lesions. An interesting suggestion that deserves further consideration is stellate ganglion block [66]. A more contemporary therapy that may have benefit is infusion of magnesium, which inhibits catecholamine release and may reduce cerebral vasospasm [97]. These therapies require caution, however, as a reduction in MAP and CPP could result.

Impaired cardiac function

It may be difficult to identify patients with ventricular dysfunction, as the ECG is non-specific [10, 11, 12, 17], while isoenzyme markers of myocardial injury take time to become apparent and may be inconclusive [11, 44]. Once pulmonary oedema and/or cardiac compromise is evident, echocardiography to assess LV function would be useful to guide therapy. In addition, invasive monitoring may produce helpful information, despite the risks [98], as almost any combination of normal and abnormal pulmonary pressures is possible [48], and these may change with time [55]. A new alternative is the oesophageal Doppler monitor, which gives objective and subjective information about left ventricular function and the systemic circulation [99, 100], although not the pulmo-

nary circulation. This method is now used in preference to the pulmonary artery catheter in some intensive care units.

Surprisingly, inotropic support may improve matters, despite catecholamines causing ventricular injury and NPO. In patients with reduced left ventricular work, dobutamine has proved effective [37, 41, 56, 96]. A recent series of SAH patients with pulmonary oedema, increased PAOP and variable cardiac index (but all with low ejection fractions on echocardiography) were treated successfully with dobutamine and a combination of epinephrine and/or norepinephrine (although one patient did also received intra-aortic balloon pump assistance) [41]. This report is not unique. Patients with SAH (or other intracranial pathology) and myocardial impairment treated with dobutamine rapidly normalised their cardiac index, and improved PAOP and ventricular work with consequent benefit to oxygenation [48]. It is difficult to reconcile the fact that endogenous catecholamines cause cardiac and pulmonary complications and that patients may then be treated using similar agents. Perhaps it is the magnitude of the endogenous catecholamine surge that causes the pathology, and thereafter the levels quickly decline, perhaps to the point where catecholamine depletion at the receptor level exists so that low-to-moderate exogenous administration has a beneficial therapeutic effect.

Pulmonary oedema

Traditional management strategies for cardiac failure induced pulmonary oedema, such as positive pressure ventilation and diuretics are often used for SAH patients [48, 101]. Systemic circulating volume overload is, however, not the cause of SAH-associated NPO. The pulmonary circulation may be severely over-loaded [87] as a result of catecholamines shunting blood, so that the systemic circulation is rendered acutely hypovolaemic. Therefore, volume resuscitation may be more appropriate than diuretic therapy to restore circulating volume acutely and optimise right ventricular preload [41].

These clinical reports confirm the potential of functional reversibility of cardiac and pulmonary pathophysiology. Cardiac involvement may be overt or subclinical in a substantial number of SAH patients, and a proactive approach to identify them, for example using echocardiography, with a subsequent increase in the level of monitoring and care would seem appropriate for this relatively young patient group. At the very least, patients exhibiting any clinical evidence of NPO and/or cardiac impairment should have a pulmonary artery catheter or oesophageal Doppler assessment of cardiac function to guide therapy. A guide to management is shown in Fig. 3.

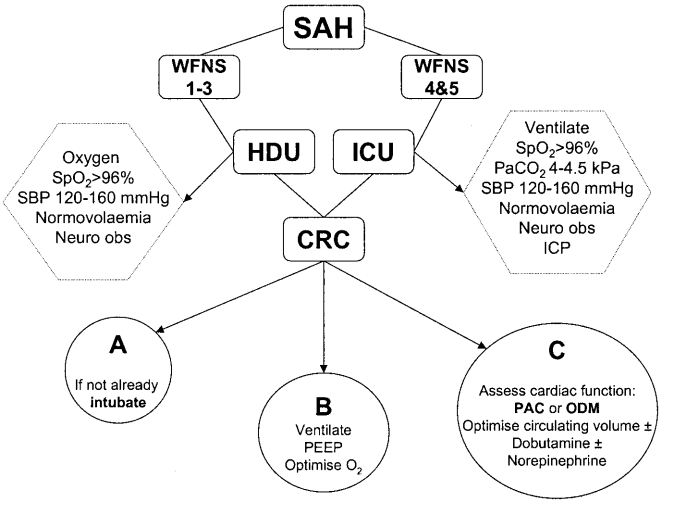


Fig. 3 Management of cardiorespiratory compromise after subarachnoid haemorrhage. Neurogenic pulmonary oedema and cardiac dysfunction can manifest clinically as separate entities or together. They should be considered together as part of a clinical syndrome – 'CRC'- which requires assessment of cardiac function for optimal treatment

Implications for management of brain-stem dead organ donors

Most cadaver organs for transplant in the UK come from patients dying of intracranial catastrophes, i.e. trauma and haemorrhage. Catecholamine-induced myocardial injury (although reversible with time) and pulmonary endothelial injury, with or without gross pulmonary oedema, is not ideal preparation for these organs. In essence, recipients may not be getting the healthy organs that would be predicted from the donor's pre-morbid health. Perhaps management aimed at reducing cardiac and respiratory pathology after SAH should be more aggressive when it becomes clear that the neurological prognosis is hopeless. It may even be appropriate under these circumstances to institute therapies that are organ preserving, such as α- and β-blockade, particularly when cerebral perfusion is no longer a consideration. Some authorities have cautioned against the use of organs from SAH donors because of organ dysfunction, as they do less well than organs from trauma victims [102]. Yet there is such a demand for organs [102] that optimisation of the cadaver until harvest is complete should be a continuing aim [103, 104, 105].

Need for clinical trials

There is a compelling argument for well-conducted trials to be undertaken in order to identify patients who will develop cardiac failure, pulmonary oedema or both.

There is an argument for prevention of catecholamine effects using prophylactic α- and β-blockade, which may reduce the impact of catecholamines on the heart and pulmonary vasculature. However, this needs to be balanced against the need to maintain cerebral perfusion. Once cardiac failure and/or NPO is established, the optimum monitoring and treatment choices need further evaluation. Until a higher priority is given to intensive care aspects for these patients, evidence-based improvements in management cannot happen.

Conclusions

There is substantial clinical and experimental evidence to support the conclusion that catecholamines cause cardiac failure and pulmonary oedema after an acute neurological event such as SAH. The range of symptoms caused by catecholamines should be considered part of a syndrome of cardiorespiratory compromise, so monitoring and therapy can be rationalised (Fig. 3). The subsequent development of hypoxaemia and hypotension, which adds to the neurological insult and may have long-term physical, cognitive and financial consequences for patients and society, could thus be minimised. The intensivist has a major role to play in pre-empting and treating such complications and must aim to improve management for these patients.

References

1. Ingall TJ, Whisnant JP, Wiebers DO O'Fallon WM (1989) Has there been a decline in subarachnoid hemorrhage mortality? Stroke 20:718–724
2. Haley EC, Jr. Kassell NF Torner JC (1992) The International Cooperative Study on the Timing of Aneurysm Surgery. The North American experience. Stroke 23:205–214
3. National CEPOD (2000) Interventional vascular radiology and interventional neurovascular radiology. Callum KG, Whimster F (eds). NCEPOD, London 2000
4. Allen GS, Ahn HS, Preziosi TJ, Battye R, Boone SC, Boone SC, Chou SN, Kelly DL, Weir BK, Crabbe RA, Lavik PJ, Rosenbloom SB, Dorsey FC, Ingram CR, Mellits DE, Bertsch LA, Boisvert DP, Hundley MB, Johnson RK, Strom JA, Transou CR (1983) Cerebral arterial spasm – a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med 308:619–624
5. Pickard JD, Murray GD, Illingworth R, ShawMD, Teasdale GM, Foy PM, Humphrey PR, Lang DA Nelson R, Richards P (1989) Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ 298:636–642
6. Petruk KC, West M, Mohr G, Weir BK, Benoit BG, Gentili F, Disney L, Khan M, Grace M, Holness R (1988) Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. J Neurosurg 68:505–517
7. Mayberg MR, Batjer HH, Dacey R, Diringer M, Haley EC, Heros RC, Sternau LL, Torner J, Adams HPJr, Feinberg W (1994) Guidelines for the management of aneurysmal subarachnoid hemorrhage. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke 25:2315–2328
8. Solenski NJ, Haley ECJ, Kassell NF, Kongable G, Germanson T, Truskowski L Torner JC (1995) Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. Crit Care Med 23:1007–1017
9. Miller JA, Dacey RGJ, Diringer MN (1995) Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. Stroke 26:2260–2266
10. Szabo MD, Crosby G, Hurford WE Strauss HW (1993) Myocardial perfusion following acute subarachnoid hemorrhage in patients with an abnormal electrocardiogram. Anesth Analg 76:253–258
11. Mayer SA, Fink ME, Homma S, Sherman D, LiMandri G, Lennihan L, Solomon RA, Klebanoff LM, Beckford A, Raps EC (1994) Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. Neurology 44:815–820
12. Davies KR, Gelb AW, Manninen PH, Boughner DR Bisnaire D (1991) Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities. BJA 67:58–63
13. Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H Fujiwara A (1994) Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium. J Am Coll Cardiol 24:636–640
14. Pollick C, Cujec B, Parker S Tator C (1988) Left ventricular wall motion abnormalities in subarachnoid hemorrhage: an echocardiographic study. J Am Coll Cardiol 12:600–605
15. Mayer SA, LiMandri G, Sherman D, Lennihan L, Fink ME, Solomon RA, DiTullio M, Klebanoff LM, Beckford AR, Homma S (1995) Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg 83:889–896
16. Gentleman D, Jennett B (1990) Audit of transfer of unconscious head-injured patients to a neurosurgical unit. Lancet 335:330–334
17. Brouwers PJ, Wijdicks EF, Hasan D, Vermeulen M, Wever, EF, Frericks H van Gijn J (1989) Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage. Stroke 20:1162–1167
18. Burch GE, Meyers R Abildskov JA (1954) A new electrocardiographic pattern observed in cerebrovascular accidents. Circulation 9:719–723
19. Marion DW, Segal R Thompson ME (1986) Subarachnoid hemorrhage and the heart. Neurosurgery 18:101–106
20. Andreoli A, di PG, Pinelli G, Grazi P, Tognetti F Testa C (1987) Subarachnoid hemorrhage: frequency and severity of cardiac arrhythmias. A survey of 70 cases studied in the acute phase. Stroke 18:558–564

21. Cropp GJ, Manning GW (1960) Electrocardiographic changes simulating myocardial ischaemia and infarction associated with spontaneous intracranial haemorrhage. Circulation 22:25–38
22. Shuster S (1960) The electrocardiogram in subarachnoid haemorrhage. Br Heart J 22:316–320
23. Galloon S, Rees GA, Briscoe CE, Davies S Kilpatrick GS (1972) Prospective study of electrocardiographic changes associated with subarachnoid haemorrhage. BJA 44:511–516
24. Hammermeister KE, Reichenbach DD (1969) QRS changes, pulmonary edema, and myocardial necrosis associated with subarachnoid hemorrhage. Am Heart J 78:94–100
25. Svigelj V, Grad A Kiauta T (1996) Heart rate variability, norepinephrine and ECG changes in subarachnoid hemorrhage patients. Acta Neur Scand 94:120–126
26. Lanzino G, Kongable GL Kassell NF (1994) Electrocardiographic abnormalities after nontraumatic subarachnoid hemorrhage. J Neurosurg Anesthesiol 6:156–162
27. Melville KI, Blum B, Shister HE, Silver MD (1963) Cardiac ischaemic changes and arrhythmias induced by hypothalamic stimulation. Am J Cardiol 12:781–4
28. Kitahara T, Masuda T Soma K (1993) The etiology of sudden cardiopulmonary arrest in subarachnoid hemorrhage. No Shinkei Geka (Neurological Surgery) 21:781–786
29. di Pasquale G. Pinelli G, Andreoli A, Manini G, Grazi P Tognetti F (1987) Holter detection of cardiac arrhythmias in intracranial subarachnoid hemorrhage. Am J Cardiol 59:596–600
30. Cruickshank JM, Neil-Dwyer G Stott AW (1974) Possible role of catecholamines, corticosteroids, and potassium in production of electrocardiographic abnormalities associated with subarachnoid haemorrhage. Br Heart J 36:697–706
31. Barr CS, Naas A, Freeman M, Lang CC Struthers AD (1994) QT dispersion and sudden unexpected death in chronic heart failure. Lancet 343:327–329
32. Randell T, Tanskanen P, Scheinin M, Kytta J, Ohman J Lindgren L (1999) QT dispersion after subarachnoid hemorrhage. J Neurosurg Anesthesiol 11:163–166
33. Andrews PJD (2000) Medical management of complications following aneurysmal sub-arachnoid haemorrhage. In: Galley HF (ed) Neurological injury. BMJ Books, London, pp 28–38
34. Elrifai AM, Bailes JE, Shih SR, Dianzumba S Brillman J (1996) Characterization of the cardiac effects of acute subarachnoid hemorrhage in dogs. Stroke 27:737–741
35. Grad A, Kiauta T Osredkar J (1991) Effect of elevated plasma norepinephrine on electrocardiographic changes in subarachnoid hemorrhage. Stroke 22:746–749
36. Knudsen K, Abrahamsson J (1995) Antiarrhythmic effects of magnesium sulphate. Report of three cases. Acta Anaesthesiol Scand 39:850–854
37. Schell AR, Shenoy MM, Friedman SA Patel AR (1987) Pulmonary edema associated with subarachnoid hemorrhage. Evidence for a cardiogenic origin. Arch Intern Med 147:591–592
38. Smith WS, Matthay MA (1997) Evidence for a hydrostatic mechanism in human neurogenic pulmonary edema. Chest 111:1326–1333
39. Harari A, Rapin M, Regnier B, Comoy J Caron JP (1976): Normal pulmonary-capillary pressures in the late phase of neurogenic pulmonary oedema. Lancet i:494
40. Raymer K, Choi P (1997) Concurrent subarachnoid haemorrhage and myocardial injury. Can J Anaesth 44:515–519
41. Parr MJ, Finfer SR Morgan MK (1996) Reversible cardiogenic shock complicating subarachnoid haemorrhage. BMJ 313:681–683
42. Doshi R, Neil-Dwyer G (1980) A clinicopathological study of patients following a subarachnoid hemorrhage. J Neurosurg 52:295–301
43. Kolin A, Norris JW (1984) Myocardial damage from acute cerebral lesions. Stroke 15:990–993
44. Rudehill A, Gordon E, Sundqvist K, Sylven C, Wahlgren NG. (1982) A study of ECG abnormalities and myocardial specific enzymes in patients with subarachnoid haemorrhage. Acta Anaesthesiol Scand 26:344–350
45. Fabinyi G, Hunt D McKinley L (1977) Myocardial creatine kinase isoenzyme in serum after subarachnoid haemorrhage. J Neurol Neurosurg Psych 40:818–820
46. Horowitz MB, Willet D Keffer J (1998) The use of cardiac troponin-I (cTnI) to determine the incidence of myocardial ischemia and injury in patients with aneurysmal and presumed aneurysmal subarachnoid hemorrhage. Acta Neurochirurgica 140:87–93
47. Greenhoot JH, Reichenbach DD (1969) Cardiac injury and subarachnoid hemorrhage. A clinical, pathological, and physiological correlation. J Neurosurg 30:521–531
48. Deehan SC, Grant IS (1996) Haemodynamic changes in neurogenic pulmonary oedema: Effect of dobutamine. Intensive Care Med 22:672–676
49. Carlson RW, Schaeffer RC, Jr. Carpio M Weil MH (1981) Edema fluid and coagulation changes during fulminant pulmonary edema. Chest 79:43–49
50. Connor RC (1969) Myocardial damage secondary to brain lesions. Am Heart J 78:145–148
51. Connor RC (1970) Fuchsinophilic degeneration of myocardium in patients with intracranial lesions. Br Heart J 32:81–84
52. Ducker TB (1968) Increased intracranial pressure and pulmonary edema. 1. Clinical study of 11 patients. J Neurosurg 28:112–117
53. Fein IA, Rackow EC (1982) Neurogenic pulmonary edema. Chest 81:318–320
54. Touho H, Karasawa J, Shishido H, Yamada K Yamazaki Y (1989) Neurogenic pulmonary edema in the acute stage of hemorrhagic cerebrovascular disease. Neurosurgery 25: 762–768
55. Wray NP, Nicotra MB (1978) Pathogenesis of neurogenic pulmonary edema. Am Rev Respir Dis 118:783–786
56. Melon E, Bonnet F Lepresle E (1985) Altered capillary permeability in neurogenic pulmonary oedema. Intensive Care Med 11:323–325
57. Wiener F, Carlson RW, Puri VK Weil MH (1983) Mathematical model to study fluid and protein transfer in pulmonary edema in man. Crit Care Med 11:132–141
58. West JB, Mathieu-Costello O (1992) Stress failure of pulmonary capillaries in the intensive care setting. Schweiz Med Wochenschr 122:751–757
59. Siwadlowski W, Aravanis C, Worthen M Luisada AA (1970) Mechanism of adrenalin pulmonary edema and its prevention by narcotics and autonomic blockers. Chest 57:554–557
60. Maron MB (1990) Pulmonary vasoconstriction in a canine model of neurogenic pulmonary edema. J Appl Physiol 68:912–918
61. Ducker TB, Simmons RL (1968) Increased intracranial pressure and pulmonary edema. 2. The hemodynamic response of dogs and monkeys to increased intracranial pressure. J Neurosurg 28:118–123
62. Schraufnagel DE, Patel KR (1990) Sphincters in pulmonary veins. An anatomic study in rats. Am Rev Respir Dis 141:721–726
63. Richards.P (1963) Pulmonary oedema and intracranial lesions. BMJ ii:83
64. Paine R, Smith JR, Howard FA (1952) Pulmonary oedema in patients dying with disease of the central nervous system. JAMA 149: 643–646

65. Schievink WI, Wijdicks EF, Parisi JE, Piepgras DG Whisnant JP (1995) Sudden death from aneurysmal subarachnoid hemorrhage. Neurology 45:871–874
66. Simmons RL, Martin AM, Jr. Heisterkamp CA, III Ducker TB (1969) Respiratory insufficiency in combat casualties. II. Pulmonary edema following head injury. Ann Surg 170:39–44
67. Estanol BV, Marin OS (1975) Cardiac arrhythmias and sudden death in subarachnoid hemorrhage. Stroke 6:382–386
68. Drewes LR (1988) Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid haemorrhage grading scale. J Neurosurg 68:985–986
69. Naredi S, Lambert G, Eden E, Zall S, Runnerstam M, Rydenhag B Friberg P (2000) Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. Stroke 31:901–906
70. Carlson RW, Schaeffer RC, Jr. Michaels SG Weil MH (1979) Pulmonary edema fluid. Spectrum of features in 37 patients. Circulation 60:1161–1169
71. Poulat P, Couture R (1998) Increased pulmonary vascular permeability and oedema induced by intrathecally injected endothelins in rat. Eur J Pharmacol 344:251–259
72. West JB, Mathieu-Costello O (1992) Stress failure of pulmonary capillaries: Role in lung and heart disease. Lancet 340:762–767
73. Kline IK (1961) Myocardial alterations associated with phaeochromocytomas. Am J Pathol 38:539–551
74. Northfield TC (1967) Cardiac complications of phaeochromocytoma. Br Heart J 29:588–593
75. Blom HJ, Karsdorp V, Birnie R Davies G (1987) Phaeochromocytoma as a cause of pulmonary oedema. Anaesthesia 42:646–650
76. Sato K, Masuda T, Kikuno T, Kobayashi A, Ikeda Y, Ohwada T Kikawada R (1990) Left ventricular asynergy and myocardial necrosis accompanied by subarachnoid hemorrhage: contribution of neurogenic pulmonary edema. Jpn J Cardiol 20:359–367
77. Hanley DF, Ulatowski JA (1995) Medical management of aneurysmal subarachnoid hemorrhage. Crit Care Med 23:992–993
78. Szakacs JE, Mehlman B (1960) Pathological changes induced by l-norepinephrine: quantitative aspects. Am J Cardiol 5:619–627
79. Elrifai AM, Bailes JE, Shih SR, Dianzumba S Brillman J (1996) Characterization of the cardiac effects of acute subarachnoid hemorrhage in dogs. Stroke 27:737–741
80. Todd GL, Baroldi G, Pieper GM, Clayton FC Eliot RS (1985) Experimental catecholamine-induced myocardial necrosis. II. Temporal development of isoproterenol-induced contraction band lesions correlated with ECG, hemodynamic and biochemical changes. J Mol Cell Cardiol 17:647–656
81. Todd GL, Baroldi G, Pieper GM, Clayton FC Eliot RS (1985) Experimental catecholamine-induced myocardial necrosis. I. Morphology, quantification and regional distribution of acute contraction band lesions. J Mol Cell Cardiol 17:317–338
82. Schlesinger MJ, Reiner L (1955) Focal myocytolysis of the heart. Am J Pathology 31:443
83. Davidson JT, Charuzi I (1973) Epinephrine-induced changes in the pulmonary pressure-volume curve of the intact and hypovolemic rabbit. Chest 63:250–253
84. Greaves DJ, Barrow PM (1989) Emergency resection of phaeochromocytoma presenting with hyperamylasaemia and pulmonary oedema after abdominal trauma. Anaesthesia 44:841–842
85. Platts JK, Drew PJ Harvey JN (1995) Death from phaeochromocytoma: lessons from a post-mortem survey. JRCPL. 29:299–306
86. Ross EJ, Griffith DN (1989) The clinical presentation of phaeochromocytoma. Q J Med 71:485–496
87. Novitzky D, Wicomb WN, Rose AG, Cooper DK Reichart B (1987) Pathophysiology of pulmonary edema following experimental brain death in the chacma baboon. Ann Thorac Surg 43:288–294
88. Maron MB, Holcomb PH, Dawson CA, Rickaby DA, Clough AV Linehan JH (1994) Edema development and recovery in neurogenic pulmonary edema. J Appl Physiol 77:1155–1163
89. Gupta YK, Chugh A, Kacker V, Mehta VS Tandon PN (1998) Development of neurogenic pulmonary edema at different grades of intracranial pressure in cats. Indian J Physiol Pharmacol 42:71–80
90. Maron MB (1985) A canine model of neurogenic pulmonary edema. J Appl Physiol 59:1019–1025
91. Wagner PD, Gale GE, Moon RE, Torre-Bueno JR, Stolp BW Saltzman HA (1986) Pulmonary gas exchange in humans exercising at sea level and simulated altitude. J Appl Physiol 61:260–270
92. Graf CJ, Rossi NP (1978) Catecholamine response to intracranial hypertension. J Neurosurg 49:862–868
93. Neil-Dwyer G, Walter P, Cruickshank JM, Doshi B O'Gorman P (1978) Effect of propranolol and phentolamine on myocardial necrosis after subarachnoid haemorrhage. BMJ ii:990–992
94. Crompton MR (1963) Hypothalamic lesions following the rupture of cerebral berry aneurysms. Brain 86: 301–318
95. Novitzky D, Wicomb WN, Cooper DK, Rose AG Reichart B (1986) Prevention of myocardial injury during brain death by total cardiac sympathectomy in the Chacma baboon. Ann Thorac Surg 41:520–524
96. Walter P, Neil-Dwyer G Cruickshank JM (1982) Beneficial effects of adrenergic blockade in patients with subarachnoid haemorrhage. BMJ 284:1661–1664
97. Watson VF, Vaughan RS (2001) Magnesium and the anaesthetist. Br J Anaesth CEPD Reviews 1:16–20
98. Rosenwasser RH, Jallo JI, Getch CC Liebman KE (1995) Complications of Swan-Ganz catheterization for hemodynamic monitoring in patients with subarachnoid hemorrhage. Neurosurgery 37:872–875
99. Singer M, Bennett ED (1991) Noninvasive optimization of left ventricular filling using esophageal Doppler. Crit Care Med 19:1132–1137
100. Singer M, Clarke J Bennett ED (1989) Continuous hemodynamic monitoring by esophageal Doppler. Crit Care Med 17: 447–452
101. Lagerkranser M, Pehrsson K Sylven C (1982) Neurogenic pulmonary oedema. A review of the pathophysiology with clinical and therapeutic implications. Acta Medica Scand 212:267–271
102. Cohen B, D'Amaro J, De Meester J Persijn GG (1997) Changing patterns in organ donation in Eurotransplant, 1990–1994. Transplant Int 10:1–6
103. Power BM, Van Heerden PV (1995) The physiological changes associated with brain death–current concepts and implications for treatment of the brain dead organ donor. Anaesth Intensive Care 23:26–36
104. MacLean A, Dunning J (1997) The retrieval of thoracic organs: donor assessment and management. Br Med Bull 53:829–843
105. Bodenham A, Park GR (1989) Care of the multiple organ donor. Intensive Care Med 15:340–348

John G. Laffey
Donall O'Croinin
Paul McLoughlin
Brian P. Kavanagh

Permissive hypercapnia — role in protective lung ventilatory strategies

Abstract 'Permissive hypercapnia' is an inherent element of accepted protective lung ventilation. However, there are no clinical data evaluating the efficacy of hypercapnia per se, independent of ventilator strategy. In the absence of such data, it is necessary to determine whether the potential exists for an active role for hypercapnia, distinct from the demonstrated benefits of reduced lung stretch. In this review, we consider four key issues. *First*, we consider the evidence that protective lung ventilatory strategies improve survival and we explore current paradigms regarding the mechanisms underlying these effects. *Second*, we examine whether hypercapnic acidosis may have effects that are additive to the effects of protective ventilation. *Third,* we consider whether direct elevation of CO_2, in the absence of protective ventilation, is beneficial or deleterious. *Fourth*, we address the current evidence regarding the buffering of hypercapnic acidosis in ARDS. These perspectives reveal that the potential exists for hypercapnia to exert beneficial effects in the clinical context. Direct administration of CO_2 is protective in multiple models of acute lung and systemic injury. Nevertheless, several specific concerns remain regarding the safety of hypercapnia. At present, protective ventilatory strategies that involve hypercapnia are clinically acceptable, provided the clinician is primarily targeting reduced tidal stretch. There are insufficient clinical data to suggest that hypercapnia per se should be independently induced, nor do outcome data exist to support the practice of buffering hypercapnic acidosis. Rapidly advancing basic scientific investigations should better delineate the advantages, disadvantages, and optimal use of hypercapnia in ARDS.

Keywords Hypercapnic acidosis · Mechanical ventilation · Acute lung injury · ARDS · Ventilation-induced lung injury · Buffering

Introduction

'Permissive hypercapnia' is an inherent element of accepted protective lung ventilatory strategies. However, the precise role of hypercapnia remains unclear, with no clinical data comparing the efficacy of protective lung ventilatory strategies in the presence and absence of hypercapnia. Furthermore, it is unlikely that such a trial will be carried out, at least in the medium term. In the absence of such data, it is appropriate to investigate whether the potential exists for an active role for hypercapnia per se, distinct from the demonstrated benefits of reduced lung stretch. This review first considers the evidence that protective lung ventilatory strategies reduce lung injury and improve survival. We examine current paradigms regarding the mechanisms underlying this protective effect, and the passive role presently attributed to hypercapnia. We focus on whether

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_39, © Springer-Verlag Berlin Heidelberg 2009

hypercapnia and/or acidosis may have effects that are distinct from the effects of protective ventilator parameters. In addition, the current status of buffering hypercapnic acidosis is reviewed.

Protective lung ventilatory strategies — current paradigms

It is increasingly clear that mechanical ventilation can potentiate or even cause lung injury and worsen outcome in ARDS patients [1, 2]. The likely mechanisms underlying this 'ventilator associated lung injury' (VALI) are increasingly well characterized [3], and several plausible theories have been proposed. Mechanotrauma, which results from repetitive over-stretching and damage of lung tissue and cyclic recruitment-derecruitment of collapsed areas of lung [4–9], plays a pivotal role (Fig. 1). These effects may be particularly important, because increased mechanical stress may directly activate the cellular and humoral immune response in the lung [8–11], although this is controversial, with conflicting results reported [12]. The potential for intrapulmonary mediators and pathogens to access the systemic circulation is clear from experiments demonstrating translocation of prostaglandins [13], cytokines [14] endotoxin [15], and bacteria [16], across an impaired alveolar-capillary barrier, following high stretch mechanical ventilation. The potential for mechanical ventilation to induce a systemic cytokine response in the clinical context, and for a protective lung ventilation strategy to attenuate this response, has been demonstrated [17]. However, the contribution of cytokine release to the pathogenesis of ventilator induced ALI in the clinical context remains unclear [10, 18].

VALI may be limited by permitting hypoventilation in order to reduce mechanotrauma and the resulting inflammatory effects. This invariably involves a reduction in the tidal volume, and generally leads to an elevation in $PaCO_2$, an approach that has been termed "permissive hypercapnia". These protective lung ventilation strategies

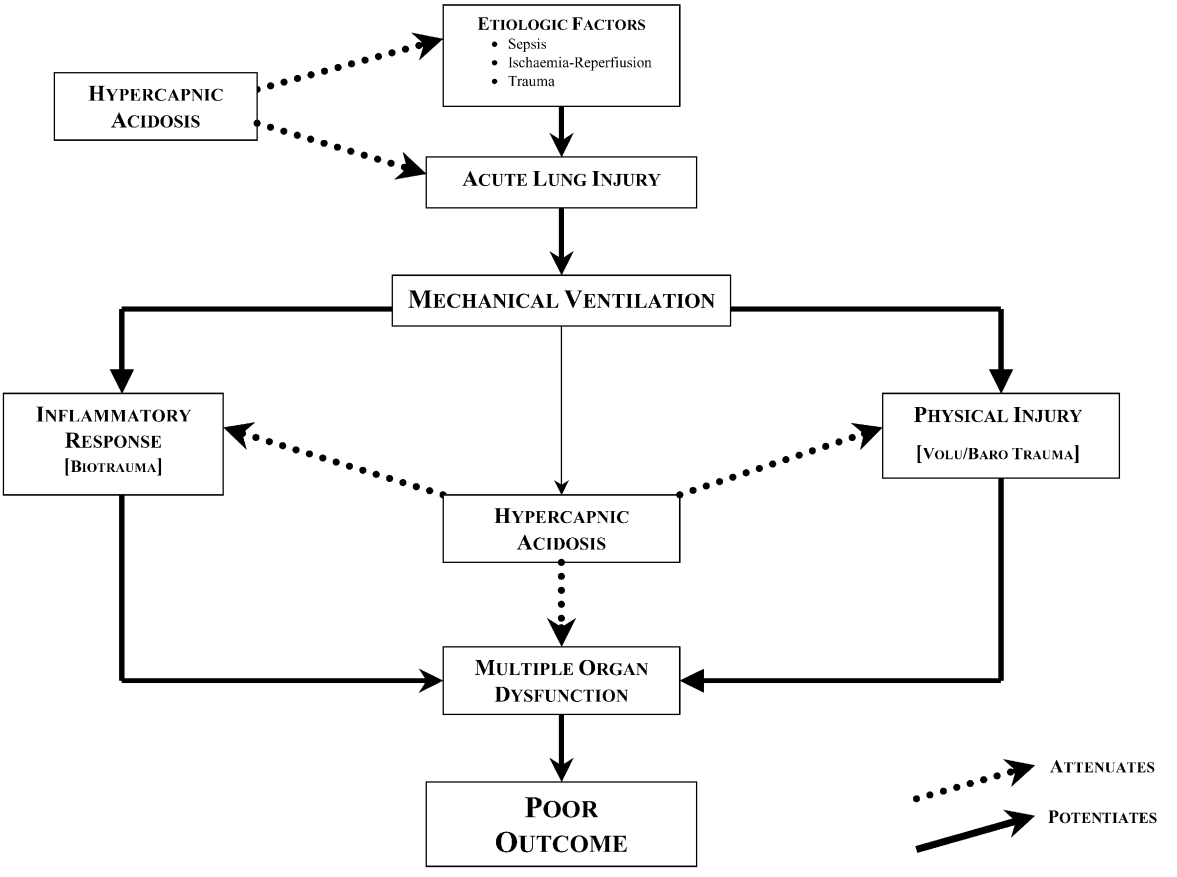


Fig. 1 Mechanical ventilation may contribute to ALI by causing direct physical injury (baro- and/or volutrauma) to the lung and by activating the inflammatory response, which in turn may lead to multiple organ dysfunction and adverse outcome. Hypercapnic acidosis may protect the lung and systemic organs via several mechanisms. These include attenuation of key etiologic factors that lead to ALI, reduction of physical lung damage, inhibition of key aspects of the inflammatory response, and direct protection of systemic organs. *Solid arrows* indicate potentiation of effect; *broken arrows* indicate inhibitory effect

improve survival in acute respiratory distress syndrome (ARDS) patients [1, 19, 20]. The reported levels of $PaCO_2$ and pH (mean maximum $PaCO_2$ 67 torr, mean pH 7.2) in the study of Hickling et al. [19] reflect typical levels observed with institution of this technique. Accordingly, there has been a shift towards greater clinical acceptability of hypercapnia in acute lung injury (ALI) and ARDS. However, current paradigms attribute the protective effect of these ventilatory strategies solely to reductions in lung stretch, with hypercapnia permitted in order to achieve this goal. Accordingly, the potential for hypercapnia to exert clinically important effects in this context has received little attention to date.

Permissive hypercapnia — potential for beneficial effects

Protective ventilatory strategies that involve hypoventilation result in both limitation of tidal volume and elevation of systemic PCO_2. Of course, lung stretch is distinct from elevated PCO_2, and by manipulation of respiratory parameters (frequency, tidal volume, dead-space, inspired CO_2) can to some extent be separately controlled in humans. The ARDSnet study [2] demonstrated that mechanical ventilation of patients with ARDS with a tidal volume of 6 ml kg^{-1} (actually, a complex protocol involving limitation of tidal volume and plateau pressure [21]) resulted in a 25% reduction in mortality when compared with a more traditional tidal volume of 12 ml kg^{-1} and a lower frequency. This study minimized the potential for hypercapnia and instead permitted increased respiratory rates (respiratory frequency of 29 min^{-1}); as a result $PaCO_2$ levels were only modestly elevated, and pH modestly decreased, in the low stretch group. In fact, the need to substantially reduce tidal volumes in order to improve outcome in ARDS patients has recently been questioned [22, 23], and it is increasingly clear that most clinicians (*including expert investigators* [24]) seldom use very low tidal volumes in practice. An acceptance of more moderate tidal volumes, whether by analysis [22], or by observation of actual current practice [25, 26] may reduce the need for — and acceptability of — permissive hypercapnia. Therefore, the context in which elevated CO_2 will be encountered in the future is less likely to be as a passive/permissive accompaniment of 'protective' ventilation.

These issues underscore the necessity for (and difficulty in) consideration of the effects of hypercapnia in isolation. If hypercapnia was proven to have independent benefit, then deliberately elevating $PaCO_2$ could provide an additional advantage over reducing lung stretch. Conversely, in patients managed with conventional permissive hypercapnia, adverse effects of elevated $PaCO_2$ might be concealed by the generally accepted benefits of lessened lung stretch. Because outcome in ICU might be related to systemic injury — as opposed to simply lung injury — it is necessary to examine the effects of hypercapnia on pathophysiologic function in the heart and brain as well as the lung. These issues are further underlined by the fact that hypercapnia has potentially severe adverse effects in some clinical settings, such as critically elevated intracranial pressure.

Clearly, the presence of an acidosis — whether hypercapnic or metabolic — indicates loss of physiologic homeostasis and the presence of disease and/or organ dysfunction. In fact, the extent and severity of acidosis is predictive of adverse outcome in diverse clinical contexts, including cardiac arrest [27, 28] sepsis [29–31] and in the immediate postpartum neonate [32]. However these data indicate an *association* rather than a cause and effect relationship, and do not indicate that acidosis is directly harmful. The systemic haemodynamic effects of hypercapnic acidosis are relatively benign, even as the pH falls to 7.15, with the typical patient experiencing no change or small increases in cardiac output and blood pressure [33, 34]. There is a body of evidence in the critical care literature attesting to the safety of hypercapnic acidosis. In many studies of patients undergoing permissive hypercapnia, a pH of well below 7.2 appeared to have been well tolerated [19, 20, 33, 35–39]. The safety of hypercapnic acidosis is further supported by reports that individuals, both adults [40] and children [41], have survived exposure to extreme levels. Therefore, although acidosis is common in the setting of critical illness, and may herald an adverse prognosis, it is likely that the aetiology of the underlying condition resulting in the acidosis, rather than the acidosis per se, is the key factor [34, 42]. Indeed acidosis may constitute a protective adaptation in the context of cellular stress, and may in fact constitute beneficial effects in the setting of acute organ injury (Table 1) [42].

The potential for hypercapnia to attenuate to the deleterious effects of high stretch mechanical ventilation in the clinical context has recently received strong support in a preliminary communication [43], where Kregenow and co-workers examined mortality as a function of permissive hypercapnia in patients enrolled in the ARDSnet study [2]. Using multivariate logistic regression analysis, and controlling for other co-morbidities and severity of lung injury, they demonstrated that permissive hypercapnia reduced mortality in patients randomized to the higher tidal volume (12 ml kg^{-1}) [43]. However, there was no additional protective effect of permissive hypercapnia in patients randomized to receive the lower tidal volume (6 ml kg^{-1}) [43]. Nevertheless, the potential for hypercapnia to protect against the deleterious effects of mechanical ventilation, is clear (Fig. 1).

Table 1 Published studies of induced hypercapnic acidosis in models of acute organ dysfunction. *ALI* acute lung injury, *IR* ischaemia-reperfusion, K_{fc} capillary filtration coefficient, P_{aw} peak airway pressure, P_{cap} pulmonary capillary pressure, P_{iso} pulmonary capillary isographic pressure, *A-a O_2 gradient* alveolar-arterial oxygen gradient, *BALF* bronchoalveolar lavage fluid, *TNFα* tumour necrosis factor alpha, *NO* nitric oxide, *NMDA* N-methyl-D-aspartate

	Animal model	Injury process	Key findings
Acute lung injury			
Shibata et al. 1998 [44]	Ex vivo isolated perfused (rabbit) lung	1. Lung free radical induced ALI	1. HCA attenuated indices of ALI (K_{fc}, P_{aw}, P_{cap}, P_{iso})
		2. Lung ischemia — reperfusion-induced ALI	2. HCA attenuated indices of ALI (K_{fc}, P_{aw}, P_{cap}, P_{iso})
Laffey et al. 2000 [45]	Ex vivo isolated perfused (rabbit) lung	Lung ischemia — reperfusion	Acidosis attenuated indices of ALI (K_{fc}, P_{aw}, P_{cap}, P_{iso}). Hypercapnic acidosis more protective than metabolic acidosis. Buffering of hypercapnic acidosis abolished protective effect.
Laffey et al. 2000 [46]	In vivo whole animal (rabbit) model	Lung ischemia — reperfusion	HCA attenuated indices of ALI (lung permeability, A-a O_2 gradient, compliance, P_{aw}) and inflammation (BALF TNFα, free radical injury) following unilateral lung IR. Potential mechanisms included attenuation of nitrotyrosine formation, and attenuation of lung apoptosis.
Broccard et al. 2001 [49]	Ex vivo isolated perfused (rabbit) lung	Ventilator-induced high lung stretch	HCA attenuated indices of ALI (lung permeability, BALF protein, K_{fc}). Potential mechanism attenuation of lung NO formation.
Sinclair et al. 2002 [50]	In vivo whole animal (rabbit) model	Ventilator-induced high lung stretch	HCA attenuated indices of ALI (lung permeability, A-a O_2 gradient, compliance, histologic injury) and inflammation (BALF neutrophils).
Laffey et al, 2003 [47]	In vivo whole animal (rat) model	Mesenteric Ischemia-Reperfusion	HCA attenuated indices of ALI (lung permeability, A-a O_2 gradient, compliance, P_{AW}) following Mesenteric IR. HCA was protective if applied following initiation of mesenteric reperfucion, indicating therapeutic potential.
Laffey et al, 2003 [51]	In vivo whole animal (rabbit) model	Ventilator-induced high lung stretch	HCA attenuated (A-a O_2 gradient) while hypocapnic alkalsois worsened (P_{AW}) indices of ALI.
Myocardial Injury			
Nomura et al. 1994 [52]	Ex vivo isolated perfused (neonatal lamb) heart	Myocardial ischemia — reperfusion	HCA improved postischemic myocardial function Metabolic acidosis to an equivalent pH did not improve postischemic function
Kitakaze et al. 1997 [53]	In vivo whole animal (rabbit) model	Myocardial ischemia — reperfusion	Acidosis (hypercapnic and metabolic) during reperfusion decreased myocardial infarct size
Neurologic Injury			
Vannucci et al. 1995 [54]	In vivo whole animal (rat) model	Unilateral common carotid artery occlusion, followed by hypoxia	HCA decreased histologic brain damage Dose response seen with 6% CO_2 more neuroprotective than 9% CO_2
Vannucci et al. 1997 [55]	In vivo whole animal (rat) model	Unilateral common carotid artery occlusion, followed by hypoxia	HCA decreased histologic brain damage Mechanisms may include improved cerebral blood flow and attenuation of NMDA receptor activation.
Vannucci et al. 2001 [73]	In vivo whole animal (rat) model	Unilateral common carotid artery occlusion, followed by hypoxia	Severe HCA (15%CO_2) *worsened* histologic brain damage

Hypercapnia and acidosis — insights from laboratory models

It is not currently feasible to examine the direct effects of hypercapnic acidosis, independent of ventilator strategy, in humans. However, important insights may be gained from evaluation of the direct effects of hypercapnia and acidosis in experimental models of organ injury (Table 1).

Protective effects of hypercapnic acidosis

There is an evolving body of evidence suggesting that hypercapnic acidosis exerts biologically important beneficial effects in experimental models (Table 1). Hypercapnic acidosis directly attenuates both primary [44–46] and secondary [47] ischaemia-reperfusion-induced ALI, without reductions in lung stretch. Hypercapnic acidosis also directly protects against free-radical-induced ALI [44] and endotoxin-induced lung injury independent of ventilation strategy [48]. In addition, hypercapnic acidosis attenuates lung injury induced by excessive lung stretch in both ex vivo [49] and in vivo [50, 51] models, by a surfactant independent mechanism [51].

Hypercapnic acidosis may also protect other vital organs from injury (Table 1). In the heart, reperfusion with a hypercapnic acidotic perfusate potentiates recovery of myocardial function following prolonged ischaemia ex vivo [52] and limits myocardial infarct size for in vivo [53] models. In the brain, hypercapnic acidosis attenuates hypoxic-ischaemic brain injury in the immature rat [54, 55]. Hypercapnic acidosis protects the porcine brain from hypoxia/reoxygenation-induced injury [56]. Hypercapnic acidosis is more effective than comparable degrees of metabolic acidosis in prevention of lipid peroxidation in cortical homogenates [57].

Beneficial effects — acidosis or hypercapnia?

While it is widely accepted that reduction in pH has profound effects on normal tissue function, it is also clear that hypercapnia per se, in the absence of alterations in pH, may exert biologically important physiologic effects distinct from those produced by acidosis. Of potential importance in the context of acute lung injury, hypercapnia per se exerts effects on systemic [58] and pulmonary vascular tone [58, 59] and pulmonary vascular remodeling [60] that are increasingly well characterized. Thus, the protective effects of hypercapnic acidosis may be a function of the acidosis or the hypercapnia per se. This issue is of particular relevance when considering the appropriateness of buffering in the clinical context. If any protective effects of hypercapnic acidosis were found to result from the acidosis, then efforts to buffer a hypercapnic acidosis would lessen such protection and should be discouraged. Conversely, if hypercapnia per se (*and not the acidemia*) were found to be protective, then further research efforts should be directed to finding better buffering strategies in order to maximise the benefits of hypercapnia.

There is increasing evidence that the protective effects of hypercapnic acidosis in ALI appear to be a function of the acidosis, rather than elevated CO_2 per se [45, 61]. Hypercapnia at normal pH caused injury to alveolar epithelial cell monolayers [61] and decreased surfactant protein A function in vitro [62]. In the isolated lung, the protective effect of hypercapnic acidosis in ischaemia reperfusion induced ALI was greatly attenuated if the pH was buffered towards normal [45]. In fact there appeared to be no significant protective effect detectable with buffered hypercapnia (Table 1). Conversely, normocapnic (i.e. metabolic) acidosis attenuates primary ischaemia-reperfusion induced ALI in an ex vivo model, although it is less effective than hypercapnic acidosis in this model [45].

The protective effects of hypercapnic acidosis in models of systemic organ injury also appear to be a function of the acidosis. The myocardial protective effects of hypercapnic acidosis are also seen with metabolic acidosis both in ex vivo [63] and in vivo [53, 64] models. In cortical brain homogenates, the protective effects of hypercapnic acidosis are also seen with metabolic acidosis, albeit to a lesser extent [57]. Metabolic acidosis appears to exert protective effects in other models of organ injury. In the liver, metabolic acidosis delays the onset of cell death in isolated hepatocytes exposed to anoxia[65] and to chemical hypoxia [66, 67]. Correcting the pH to 7.4 abolished the protective effect and in fact accelerated hepatocyte cell death [67]. Finally, isolated renal cortical tubules exposed to anoxia have improved ATP levels on reoxygenation at acidotic — compared with alkalotic — environmental pH levels [65].

Hypercapnic acidosis — underlying mechanisms

The models of ALI and ARDS are not precise representations of the clinical context; indeed most clinical scenarios differ from each other. Therefore, it is important to understand the cellular and biochemical mechanisms underlying the protective effects of hypercapnic acidosis if we are to be able to apply the findings to the bedside, and particularly, to extrapolate the principles to a variety of disease states. Hypercapnic acidosis attenuates key components of the host inflammatory response, including: lung neutrophil recruitment [48], pulmonary and systemic cytokine concentrations [46], cell apoptosis [46, 68], and both free-radical production [44, 45] and free-radical tissue injury [46, 57]. In the brain, hypercapnic acidosis attenuates glutathione depletion and lipid peroxidation [56]. One promising potential mechanism underlying

these protective actions of hypercapnic acidosis is attenuation of the activation of the transcription regulator nuclear factor kappa beta (NF-κB) [69]. NF-kB regulates the expression of several genes involved in inflammatory response and its activation represents a pivotal early step in the activation of the inflammatory response.

Concerns regarding hypercapnia

There are concerns regarding the potential for hypercapnia and/or acidosis to exert deleterious effects that suggest the need for caution when considering its use in the clinical context. The potential for hypercapnic acidosis to exert adverse haemodynamic effects in patients with ARDS is clear [70]. However, the potential for detrimental effects on cardiac output [71] and on the peripheral circulation [72] may be overstated. In addition, beneficial effects of moderate hypercapnia may be counterbalanced by a potential for adverse effects at higher levels. This is supported by the experimental evidence demonstrating that protection from the adverse effects of brain ischaemia was better when the inspired CO_2 was set at 6% rather than at 9% [54]. Of concern, severe hypercapnia produced by 15% CO_2 has been more recently demonstrated to worsen neurologic injury in this context (Table 1) [73]. In isolated hepatocytes, the degree of protection from anoxic injury conferred by a metabolic acidosis was greater at pH 6.9 than at pH 6.6 [65]. Furthermore, acidosis attenuates the neutrophil respiratory burst and superoxide production, which are necessary for neutrophil bactericidal activity [74]. This may impair bacterial killing, resulting in unopposed bacterial proliferation, with deleterious consequences, in patients with sepsis induced ARDS.

There are reports of lung [75] and intestinal [76] injury following induction of metabolic acidosis by hydrochloric acid infusion in whole animal models. However, it is important to recognise that infusion of hyperosmolar solutions of strong acids into whole animal preparations may produce toxic effects close to the infusion site and adverse systemic effects, at least some of which are unrelated to any change in pH [77]. Thus, the effects of infusion of strong acid in any given experiment in vivo is likely to represent the sum of potentially beneficial and adverse actions. This contrasts with the situation with hypercapnic acidosis, which is easy to produce, is well tolerated, and does not produce toxic local effects. In ex vivo experiments, where a changes in pH and/or PCO_2 can be produced independently, and without the need for acid infusion close to the tissue, metabolic acidosis is directly protective against ischaemia-reperfusion induced ALI [45].

Of perhaps more concern is the potential for hypercapnia to increase tissue nitration. Peroxynitrite is a potent free radical produced in vivo largely by the reaction of nitric oxide with superoxide radicals, which are greatly increased in acute inflammatory states [78–80]. Peroxynitrite oxidizes a variety of biomolecules including sulfides, thiols, lipids, nucleic acids, transition metals and selenoproteins [78–80]. These oxidation reactions result in altered cellular function and tissue damage. Peroxynitrite also causes nitration of phenolic amino acid residues in proteins, including tyrosine residues, which leads to alteration of protein function [78, 79, 81, 82]. Two recent in vitro studies demonstrate that increased CO_2 and a reduction in pH below the normal physiological value inhibit oxidation by peroxynitrite while promoting nitration reactions [83, 84]. The potential for hypercapnia to promote the formation of nitration products from peroxynitrite has been clearly demonstrated in recent in vitro experiments [61, 62]. Peroxynitrite-mediated tissue nitration has been suggested to be a key mechanism of tissue damage in inflammatory conditions, including ALI [78, 79, 81, 82].

Finally, an important limitation when extrapolating to the clinical context is the relatively short duration of the ALI models in which hypercapnic acidosis has been studied to date. The common clinical scenario in ARDS patients is that of a more prolonged hypercapnia, during which time the acidosis may be partially, or even completely, compensated. As we have seen, there is reason to believe that the acidosis generated by acute hypercapnia may be the protective factor in acute models of ALI. The need to study the effects of hypercapnia in ALI models of considerably longer duration is therefore clear.

In summary, these findings demonstrate that hypercapnic acidosis, induced by direct administration of CO_2, is protective in multiple models of acute lung and systemic organ injury. These protective effects appear to be a function of the acidosis rather than the hypercapnia per se. While significant concerns remain regarding hypercapnia, in particular, its potential to increase tissue nitration, the potential for hypercapnia to attenuate acute lung and systemic organ injury is clear (Fig. 1).

Hypercapnia — with or without buffering?

Buffering of the acidosis induced by hypercapnia in ARDS patients remains a common, albeit controversial, clinical practice [85, 86]. Buffering with sodium bicarbonate was permitted in the ARDSnet study [2]. The need to examine the effects of buffering a hypercapnic acidosis is emphasised by the fact that both hypercapnia and acidosis per se may exert distinct biologic effects. However, as already discussed, there is evidence that the protective effects of hypercapnic acidosis in ALI are a function of the acidosis, rather than elevated CO_2 per se [45, 61]. In addition, there are specific concerns regarding the use of bicarbonate to correct an acidosis. These

concerns have resulted in the removal of bicarbonate therapy from routine use in cardiac arrest algorithms [87, 88]. The effectiveness of bicarbonate infusion as a buffer is dependent on the ability to excrete CO_2, rendering it less effective in buffering a hypercapnic acidosis. In fact, bicarbonate may further raise systemic CO_2 levels under conditions of reduced alveolar ventilation, such as ARDS [89]. While bicarbonate may correct arterial pH, it may worsen an intracellular acidosis because the CO_2 produced when bicarbonate reacts with metabolic acids diffuses readily across cell membranes, whereas bicarbonate cannot [90]. Bicarbonate may exert detrimental effects when used to buffer a lactic acidosis. The potential for bicarbonate infusion to augment the production of lactic acid has been demonstrated in the experimental and clinical setting [91–97]. Bicarbonate infusion exerted deleterious cardiovascular effects in a model of hypoxia-induced lactic acidosis [93, 94]. The safety of bicarbonate in diabetic patients has also been questioned. Bicarbonate administration slowed the rate of decrease of ketoacids in patients with diabetic ketoacidosis [98]. Of even more concern, bicarbonate administration is associated with a four-fold increase in risk of cerebral oedema in children with diabetic ketoacidosis [99].

The administration of sodium bicarbonate constitutes a significant osmolar load, which may exert independent beneficial effects independent of any associated changes in pH. Osmolar loads, such as hypertonic saline, may improve the haemodynamic profile in hemorrhagic shock [100], attenuate key aspects of the immune response [100–102] and prevent organ injury in experimental models [101–103]. In fact, when compared with an equimolar dose of sodium chloride, bicarbonate administration does not improve the hemodynamic status of critically ill patients who have lactic acidosis [104]. A follow-up study in an in vivo model of lactic acidemia found that bicarbonate exerted haemodynamic effects (mean arterial pressure, cardiac output, left ventricular contractility), which were indistinguishable from those seen in response to an equimolar dose of sodium chloride [105]. These data give cause for concern about the practice of buffering metabolic acidosis, and comparable questions may exist in the setting of hypercapnic acidosis.

There may be a role for the use of buffers, such as the amino alcohol tromethamine (tris-hydroxymethyl aminomethane, THAM), in specific situations where the physiologic effects of hypercapnic acidosis are of concern. THAM penetrates cells easily and can buffer pH changes and simultaneously reduce PCO_2 [106]. Unlike bicarbonate, which requires an open system for CO_2 elimination in order to exert its buffering effect, THAM is effective in a closed or semi-closed system [106]. THAM rapidly restores pH and acid-base regulation in acidaemia caused by CO_2 retention [106]. A common rationale for buffering is to ameliorate the haemodynamic consequences of acidosis. In a small, but carefully performed clinical study in ARDS patients, rapid induction of a hypercapnic acidosis for a two-hour period resulted in significant hemodynamic alterations, including decreased systemic vascular resistance, increased cardiac output, decreased myocardial contractility, decreased mean arterial pressure and increased mean pulmonary arterial pressure [70]. Buffering of the hypercapnic acidosis with THAM rapidly attenuated the haemodynamic alterations and restored myocardial contractility in these patients [70].

In summary, although it is a widely accepted clinical practice, there are no long-term clinical outcome data (e.g., survival, duration of hospital stay) to support the practice of buffering a hypercapnic acidosis. Taken together, the above literature suggests that, in the absence of correcting the primary problem, buffering a hypercapnic acidosis with bicarbonate is not likely to be of benefit. If the clinician elects to buffer a hypercapnic acidosis, the rationale for this practice should be clear (e.g. to ameliorate potentially deleterious haemodynamic consequences of acidosis). THAM may have a role in these clinical situations.

Conclusions

The optimal ventilatory strategy, and the role of 'permissive hypercapnia' in that strategy, is not yet clear. The protective effect of reducing lung stretch in improving outcome in ARDS patients are beyond doubt. There is growing evidence to support the contention that hypercapnic acidosis may contribute to the benefits seen with protective lung ventilation. While direct induction of a hypercapnic acidosis is protective in multiple models of acute lung and systemic organ injury, the potential for hypercapnia to increase peroxynitrite-mediated tissue nitration is of concern and requires further investigation.

At present, ventilatory strategies that involve hypercapnia are clinically acceptable only provided the clinician is primarily targeting reduced tidal stretch. There are insufficient clinical data to suggest that hypercapnia per se should be independently induced, outside the context of a protective ventilatory strategy. Furthermore, the recent questioning of the real benefit of low — versus moderate — tidal volume ventilation for adults with ARDS may result in hypercapnia becoming less acceptable in the ventilatory management of ARDS. If that becomes the case, then the clinical study of hypercapnia will become less feasible in the setting of permissive hypercapnia, and will require the deliberate induction of hypercapnia (i.e., 'therapeutic' hypercapnia). Pre-clinical studies are urgently needed to clarify the advantages, disadvantages, and optimal use of hypercapnia in ARDS.

References

1. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Fihlo G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
2. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
3. Pinhu L, Whitehead T, Evans T, Griffiths M (2003) Ventilator-associated lung injury. Lancet 361:332–340
4. Boussarsar M, Thierry G, Jaber S, Roudot-Thoraval F, Lemaire F, Brochard L (2002) Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. Intensive Care Med 28:406–413
5. Maggiore SM, Jonson B, Richard JC, Jaber S, Lemaire F, Brochard L (2001) Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: comparison with the lower inflection point, oxygenation, and compliance. Am J Respir Crit Care Med 164:795–801
6. Dreyfuss D, Saumon G (1992) Barotrauma is volutrauma, but which volume is the one responsible? Intensive Care Med 18:139–141
7. Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294–323
8. Dreyfuss D, Saumon G (1998) From ventilator-induced lung injury to multiple organ dysfunction? Intensive Care Med 24:102–104
9. Ricard JD, Dreyfuss D, Saumon G (2002) Ventilator-induced lung injury. Curr Opin Crit Care 8:12–20
10. Slutsky AS, Tremblay LN (1998) Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725
11. Tremblay LN, Slutsky AS (1998) Ventilator-induced injury: from barotrauma to biotrauma. Proc Assoc Am Physicians 110:482–488
12. Ricard JD, Dreyfuss D (2001) Cytokines during ventilator-induced lung injury: a word of caution. Anesth Analg 93:251–252
13. Edmonds JF, Berry E, Wyllie JH (1969) Release of prostaglandins caused by distension of the lungs. Br J Surg 56:622–623
14. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS (1997) Injurious ventilatory strategies increase cytokines and c-fos mRNA expression in an isolated rat lung model. J Clin Invest 99:944–952
15. Murphy D, Cregg N, Tremblay L, Engelberts D, Laffey JG, Slutsky AS, Romaschin A, Kavanagh BP (2000) Adverse ventilator strategy causes pulmonary to systemic translocation of endotoxin. Am J Resp Crit Care Med 162:27–33
16. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ (1997) Effect of mechanical ventilation strategy on dissemination of intratracheally instilled Escherichia coli in dogs. Crit Care Med 25:1733–1743
17. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54–61
18. Dreyfuss D, Ricard JD, Saumon G (2003) On the physiologic and clinical relevance of lung-borne cytokines during ventilator-induced lung injury. Am J Respir Crit Care Med 167:1467–1471
19. Hickling KG, Walsh J, Henderson S, Jackson R (1994) Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 22:1568–1578
20. Bidani A, Tzouanakis AE, Cardenas VJ Jr, Zwischenberger JB (1994) Permissive hypercapnia in acute respiratory failure. JAMA 272:957–962
21. Laffey JG, Kavanagh BP (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury (Letter). N Engl J Med 343:812
22. Eichacker PQ, Gerstenberger EP, Banks SM, Cui X, Natanson C (2002) Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. Am J Respir Crit Care Med 166:1510–1514
23. Ricard JD (2003) Are we really reducing tidal volume — and should we? Am J Resp Crit Care Med 167:1297–1298
24. Rubenfeld G, Caldwell E, Hudson L (2001) Publication of study results does not increase use of lung protective ventilation in patients with acute lung injury. Am J Resp Crit Care Med 163:A295
25. Weinert CR, Gross CR, Marinelli WA (2003) Impact of randomized trial results on acute lung injury ventilator therapy in teaching hospitals. Am J Respir Crit Care Med 167:1304–1309
26. Thompson BT, Hayden D, Matthay MA, Brower R, Parsons PE (2001) Clinicians' approaches to mechanical ventilation in acute lung injury and ARDS. Chest 120:1622–1627
27. Jorgensen EO, Holm S (1999) The course of circulatory and cerebral recovery after circulatory arrest: influence of pre-arrest, arrest and post-arrest factors. Resuscitation 42:173–182
28. Suljaga-Pechtel K, Goldberg E, Strickon P, Berger M, Skovron ML (1984) Cardiopulmonary resuscitation in a hospitalized population: prospective study of factors associated with outcome. Resuscitation 12:77–95
29. Balakrishnan I, Crook P, Morris R, Gillespie SH (2000) Early predictors of mortality in pneumococcal bacteraemia. J Infect 40:256–261
30. Mathur NB, Singh A, Sharma VK, Satyanarayana L (1996) Evaluation of risk factors for fatal neonatal sepsis. Indian Pediatr 33:817–822
31. Friedman G, Berlot G, Kahn RJ, Vincent JL (1995) Combined measurements of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis. Crit Care Med 23:1184–1193
32. Anyaegbunam A, Fleischer A, Whitty J, Brustman L, Randolph G, Langer O (1991) Association between umbilical artery cord pH, five-minute Apgar scores and neonatal outcome. Gynecol Obstet Invest 32:220–223
33. Thorens JB, Jolliet P, Ritz M, Chevrolet JC (1996) Effects of rapid permissive hypercapnia on hemodynamics, gas exchange, and oxygen transport and consumption during mechanical ventilation for the acute respiratory distress syndrome. Intensive Care Med 22:182–191
34. Forsythe SM, Schmidt GA (2000) Sodium bicarbonate for the treatment of lactic acidosis. Chest 117:260–267
35. Potkin RT, Swenson ER (1992) Resuscitation from severe acute hypercapnia. Determinants of tolerance and survival. Chest 102:1742–1745
36. Tuxen DV, Williams TJ, Scheinkestel CD, Czarny D, Bowes G (1992) Use of a measurement of pulmonary hyperinflation to control the level of mechanical ventilation in patients with acute severe asthma. Am Rev Respir Dis 146:1136–1142

37. Feihl F, Perret C (1994) Permissive hypercapnia. How permissive should we be? Am J Respir Crit Care Med 150:1722–1737
38. Roupie E, Dambrosio M, Servillo G, Mentec H, el Atrous S, Beydon L, Brun-Buisson C, Lemaire F, Brochard L (1995) Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Respir Crit Care Med 152:121–128
39. Kiely DG, Cargill RI, Lipworth BJ (1996) Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans. Chest 109:1215–1221
40. Slinger P, Blundell PE, Metcalf IR (1997) Management of massive grain aspiration. Anesthesiology 87:993–995
41. Goldstein B, Shannon DC, Todres ID (1990) Supercarbia in children: clinical course and outcome. Crit Care Med 18:166–168
42. Laffey JG, Kavanagh BP (1999) Carbon dioxide and the critically ill — too little of a good thing? (Hypothesis paper). Lancet 354:1283–1286
43. Kregenow DA, Rubenfeld G, Hudson L, Swenson ER (2003) Permissive hypercapnia reduces mortality with 12 ml/kg tidal volumes in acute lung injury. Am J Resp Crit Care Med 167:A616
44. Shibata K, Cregg N, Engelberts D, Takeuchi A, Fedorko L, Kavanagh BP (1998) Hypercapnic acidosis may attenuate acute lung injury by inhibition of endogenous xanthine oxidase. Am J Resp Crit Care Med 158:1578–1584
45. Laffey JG, Engelberts D, Kavanagh BP (2000) Buffering hypercapnic acidosis worsens acute lung injury. Am J Resp Crit Care Med 161:141–146
46. Laffey JG, Tanaka M, Engelberts D, Luo X, Yiang S, Tanswell TK, Post M, Lindsay T, Kavanagh BP (2000) Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. Am J Respir Crit Care Med 162:2287–2294
47. Laffey JG, Jankov R, Engelberts D, Tanswell AK, Post M, Lindsay T, Mullen JB, Romaschin A, Stephens D, McKerlie C, Kavanagh BP (2003) Effects of therapeutic hypercapnia on mesenteric ischemia — reperfusion injury. Am J Respir Crit Care Med: 168:1383–1390
48. Honan D, Laffey JG, Hopkins N, Boylan JF, Mcloughlin P (2002) Therapeutic hypercapnia attenuates endotoxin induced acute lung injury (Abstract). Am J Resp Crit Care Med 165:A383
49. Broccard AF, Hotchkiss JR, Vannay C, Markert M, Sauty A, Feihl F, Schaller M (2001) Protective effects of hypercapnic acidosis on ventilator-induced lung injury. Am J Respir Crit Care Med 164:802–806
50. Sinclair SE, Kregenow DA, Lamm WJ, Starr IR, Chi EY, Hlastala MP (2002) Hypercapnic acidosis is protective in an in vivo model of ventilator-induced lung injury. Am J Respir Crit Care Med 166:403–408
51. Laffey JG, Engelberts D, Duggan M, Veldheuizen R, Lewis J, Kavanagh BP (2003) Carbon dioxide attenuates pulmonary impairment resulting from hyperventilation. Crit Care Med 31:2634–2640
52. Nomura F, Aoki M, Forbess JM, Mayer JE (1994) Effects of hypercarbic acidotic reperfusion on recovery of myocardial function after cardioplegic ischemia in neonatal lambs. Circulation 90:321–327
53. Kitakaze M, Takashima S, Funaya H, Minamino T, Node K, Shinozaki Y, Mori H, Hori M (1997) Temporary acidosis during reperfusion limits myocardial infarct size in dogs. Am J Physiol 272:H2071–H2078
54. Vannucci RC, Towfighi J, Heitjan DF, Brucklacher RM (1995) Carbon dioxide protects the perinatal brain from hypoxic-ischemic damage: an experimental study in the immature rat. Pediatrics 95:868–874
55. Vannucci RC, Brucklacher RM, Vannucci SJ (1997) Effect of carbon dioxide on cerebral metabolism during hypoxia-ischemia in the immature rat. Pediatr Res 42:24–29
56. Barth A, Bauer R, Gedrange T, Walter B, Klinger W, Zwiener U (1998) Influence of hypoxia and hypoxia/hypercapnia upon brain and blood peroxidative and glutathione status in normal weight and growth- restricted newborn piglets. Exp Toxicol Pathol 50:402–410
57. Rehncrona S, Hauge HN, Siesjö BK (1989) Enhancement of iron-catalyzed free radical formation by acidosis in brain homogenates: difference in effect by lactic acid and CO_2. J Cereb Blood Flow Metab 9:65–70
58. Sweeney M, Beddy D, Honner V, Sinnott B, O'Regan RG, McLoughlin P (1998) Effects of changes in pH and CO_2 on pulmonary arterial wall tension are not endothelium dependent. J Appl Physiol 85:2040–2046
59. Sweeney M, O'Regan RG, McLoughlin P (1999) Effects of changes in pH and PCO_2 on wall tension in isolated rat intrapulmonary arteries. Exp Physiol 84:529–539
60. Ooi H, Cadogan E, Sweeney M, Howell K, O'Regan RG, McLoughlin P (2000) Chronic hypercapnia inhibits hypoxic pulmonary vascular remodeling. Am J Physiol Heart Circ Physiol 278:H331–H338
61. Lang JD Jr, Chumley P, Eiserich JP, Estevez A, Bamberg T, Adhami A, Crow J, Freeman BA (2000) Hypercapnia induces injury to alveolar epithelial cells via a nitric oxide-dependent pathway. Am J Physiol Lung Cell Mol Physiol 279:L994–L1002
62. Zhu S, Basiouny KF, Crow JP, Matalon S (2000) Carbon dioxide enhances nitration of surfactant protein A by activated alveolar macrophages. Am J Physiol Lung Cell Mol Physiol 278:L1025–L1031
63. Kitakaze M, Weisfeldt ML, Marban E (1988) Acidosis during early reperfusion prevents myocardial stunning in perfused ferret hearts. J Clin Invest 82:920–927
64. Preckel B, Schlack W, Obal D, Barthel H, Ebel D, Grunert S, Thamer V (1998) Effect of acidotic blood reperfusion on reperfusion injury after coronary artery occlusion in the dog heart. J Cardiovasc Pharmacol 31:179–186
65. Bonventre JV, Cheung JY (1985) Effects of metabolic acidosis on viability of cells exposed to anoxia. Am J Physiol 249:C149–C159
66. Gores GJ, Nieminen AL, Wray BE, Herman B, Lemasters JJ (1989) Intracellular pH during "chemical hypoxia" in cultured rat hepatocytes. Protection by intracellular acidosis against the onset of cell death. J Clin Invest 83:386–396
67. Gores GJ, Nieminen AL, Fleishman KE, Dawson TL, Herman B, Lemasters JJ (1988) Extracellular acidosis delays onset of cell death in ATP-depleted hepatocytes. Am J Physiol 255:C315–C322
68. Xu L, Glassford AJ, Giaccia AJ, Giffard RG (1998) Acidosis reduces neuronal apoptosis. Neuroreport 9:875–879
69. Takeshita K, Suzuki Y, Nishio K, Takeuchi O, Toda K, Kudo H, Miyao N, Ishii M, Sato N, Naoki K, Aoki T, Suzuki K, Hiraoka R, Yamaguchi K (2003) Hypercapnic acidosis attenuates endotoxin-induced nuclear factor-κB activation. Am J Respir Cell Mol Biol 29:124–132

70. Weber T, Tschernich H, Sitzwohl C, Ullrich R, Germann P, Zimpfer M, Sladen RN, Huemer G (2000) Tromethamine buffer modifies the depressant effect of permissive hypercapnia on myocardial contractility in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 162:1361–1365
71. Prys-Roberts C, Kelman GR, Greenbaum R, Robinson RH (1967) Circulatory influences of artificial ventilation during nitrous oxide anaesthesia in man. II. Results: the relative influence of mean intrathoracic pressure and arterial carbon dioxide tension. Br J Anaesth 39:533–548
72. Ebata T, Watanabe Y, Amaha K, Hosaka Y, Takagi S (1991) Haemodynamic changes during the apnoea test for diagnosis of brain death. Can J Anaesth 38:436–440
73. Vannucci RC, Towfighi J, Brucklacher RM, Vannucci SJ (2001) Effect of extreme hypercapnia on hypoxic-ischemic brain damage in the immature rat. Pediatr Res 49:799–803
74. Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H, Chang M, Le AX, Hopf HW, Hunt TK (1997) Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. Arch Surg. 132:991–996
75. Pedoto A, Caruso JE, Nandi J, Oler A, Hoffmann SP, Tassiopoulos AK, McGraw DJ, Camporesi EM, Hakim TS (1999) Acidosis stimulates nitric oxide production and lung damage in rats. Am J Respir Crit Care Med 159:397–402
76. Pedoto A, Nandi J, Oler A, Camporesi EM, Hakim TS, Levine RA (2001) Role of nitric oxide in acidosis-induced intestinal injury in anesthetized rats. J Lab Clin Med 138:270–276
77. Shams H, Peskar BA, Scheid P (1988) Acid infusion elicits thromboxane A2-mediated effects on respiration and pulmonary hemodynamics in the cat. Respir Physiol 71:169–183
78. Beckman JS, Koppenol WH (1996) Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. Am J Physiol 271:C1424–C1437
79. Pryor WA, Squadrito GL (1995) The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide (see comments). Am J Physiol 268:L699–L722
80. Stamler JS (1994) Redox signaling: nitrosylation and related target interactions of nitric oxide. Cell 78:931–936
81. Squadrito GL, Pryor WA (1998) Oxidative chemistry of nitric oxide: the roles of superoxide, peroxynitrite, and carbon dioxide. Free Radic Biol Med 25:392–403
82. van der Vliet A, Eiserich JP, Shigenaga MK, Cross CE (1999) Reactive nitrogen species and tyrosine nitration in the respiratory tract: epiphenomena or a pathobiologic mechanism of disease? Am J Respir Crit Care Med 160:1–9
83. Denicola A, Freeman BA, Trujillo M, Radi R (1996) Peroxynitrite reaction with carbon dioxide/bicarbonate: kinetics and influence on peroxynitrite-mediated oxidations. Arch Biochem Biophys 333:49–58
84. Alvarez B, Ferrer-Sueta G, Freeman BA, Radi R (1999) Kinetics of peroxynitrite reaction with amino acids and human serum albumin. J Biol Chem 274:842–848
85. Tobin MJ (1994) Mechanical ventilation (review). N Engl J Med 330:1056–1061
86. Kollef MH, Schuster DP (1995) The acute respiratory distress syndrome (review). N Engl J Med 332:27–37
87. Levy MM (1998) An evidence-based evaluation of the use of sodium bicarbonate during cardiopulmonary resuscitation. Crit Care Clin 14:457–483
88. Grillo JA, Gonzalez ER (1993) Changes in the pharmacotherapy of CPR. Heart Lung 22:548–553
89. Sun JH, Filley GF, Hord K, Kindig NB, Bartle EJ (1987) Carbicarb: an effective substitute for $NaHCO_3$ for the treatment of acidosis. Surgery 102:835–839
90. Goldsmith DJ, Forni LG, Hilton PJ (1997) Bicarbonate therapy and intracellular acidosis. Clin Sci 93:593–598
91. Abu Romeh S, Tannen RL (1986) Amelioration of hypoxia-induced lactic acidosis by superimposed hypercapnea or hydrochloride acid infusion. Am J Physiol 250:F702–F709
92. Arieff AI, Leach W, Park R, Lazarowitz VC (1982) Systemic effects of $NaHCO_3$ in experimental lactic acidosis in dogs. Am J Physiol 242:F586–F591
93. Graf H, Leach W, Arieff AI (1985) Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science 227:754–756
94. Graf H, Leach W, Arieff AI (1985) Metabolic effects of sodium bicarbonate in hypoxic lactic acidosis in dogs. Am J Physiol 249:F630–F635
95. Benjamin E, Oropello JM, Abalos AM, Hannon EM, Wang JK, Fischer E, Iberti TJ (1994) Effects of acid-base correction on hemodynamics, oxygen dynamics, and resuscitability in severe canine hemorrhagic shock. Crit Care Med 22:1616–1623
96. Rhee KH, Toro LO, McDonald GG, Nunnally RL, Levin DL (1993) Carbicarb, sodium bicarbonate, and sodium chloride in hypoxic lactic acidosis. Effect on arterial blood gases, lactate concentrations, hemodynamic variables, and myocardial intracellular pH. Chest 104:913–918
97. Fraley DS, Adler S, Bruns FJ, Zett B (1980) Stimulation of lactate production by administration of bicarbonate in a patient with a solid neoplasm and lactic acidosis. N Engl J Med 303:1100–1102
98. Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K (1996) Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. J Clin Endocrinol Metab 81:314–320
99. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N (2001) Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 344:264–269
100. Rotstein OD (2000) Novel strategies for immunomodulation after trauma: revisiting hypertonic saline as a resuscitation strategy for hemorrhagic shock. J Trauma 49:580–583
101. Shields CJ, Sookhai S, Winter DC, Dowdall JF, Kingston G, Parfrey N, Wang JH, Kirwan WO, Redmond HP (2001) Attenuation of pancreatitis-induced pulmonary injury by aerosolized hypertonic saline. Surg Infect (Larchmt) 2:215–224
102. Pascual JL, Khwaja KA, Ferri LE, Giannias B, Evans DC, Razek T, Michel RP, Christou NV (2003) Hypertonic saline resuscitation attenuates neutrophil lung sequestration and transmigration by diminishing leukocyte-endothelial interactions in a two-hit model of hemorrhagic shock and infection. J Trauma 54:121–130; discussion 130–132
103. Rizoli SB, Kapus A, Parodo J, Fan J, Rotstein OD (1999) Hypertonic immunomodulation is reversible and accompanied by changes in CD11b expression. J Surg Res 83:130–135
104. Cooper DJ, Walley KR, Wiggs BR, Russell JA (1990) Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. Ann Intern Med 112:492–498
105. Cooper DJ, Herbertson MJ, Werner HA, Walley KR (1993) Bicarbonate does not increase left ventricular contractility duringL-lactic acidemia in pigs. Am Rev Respir Dis 148:317–322
106. Nahas GG, Sutin KM, Fermon C, Streat S, Wiklund L, Wahlander S, Yellin P, Brasch H, Kanchuger M, Capan L, Manne J, Helwig H, Gaab M, Pfenninger E, Wetterberg T, Holmdahl M, Turndorf H (1998) Guidelines for the treatment of acidaemia with THAM. Drugs 55:191–224

François Jardin
Antoine Vieillard-Baron

Right ventricular function and positive pressure ventilation in clinical practice: from hemodynamic subsets to respirator settings

Introduction

When used in patients free of previous cardiorespiratory disease, mechanical ventilation with a normal tidal volume does not have any discernible hemodynamic consequences. Conversely, the presence of a pulmonary disease affecting the bronchial tree, lung parenchyma, or both, may induce extreme conditions for mechanical ventilation. In this setting, an adverse hemodynamic effect may seriously complicate respiratory support.

The drop in cardiac output occurring in extreme conditions of mechanical ventilation is usually attributed to a reduced venous return. But the terms "cardiac output"on the one hand and "venous return" on the other refer to the same phenomenon. From a physiological point of view, such an explanation is insufficient, because reduced venous return may, in the same way, be explained by the drop in cardiac output.

We have been interested for about 30 years in the hemodynamic consequences of mechanical ventilation in ARDS patients, and here we try to summarize our experience in this clinical commentary to enable a logical approach to ventilator settings. The major goal of this approach will be to avoid imposing an excessive load on the rignt ventricle. Our experience was first acquired with right heart catheterization, and later by bedside echocardiography. Recent physiological notes published in the present journal have underscored some of the drawbacks of the invasive method [1, 2] and illustrated the advantage of echocardiography [3]. The clinical results of our respiratory strategy in ARDS has been published recently [4].

The hemodynamic consequences of mechanical ventilation are easy to understand by examining the impact upon the right ventricle of applying a positive airway pressure. On the one hand, cyclic (tidal ventilation) or continuous (PEEP application) changes in transpulmonary pressure produced by respiratory support directly affect RV outflow impedance. On the other hand, cyclic (tidal ventilation) or continuous (PEEP application) increase in pleural pressure produced by respiratory support increases RV effective elastance, a factor limiting diastolic filling.

The "venous return" concept

As established by Guyton, the venous return is promoted by a forward pressure, the mean systemic pressure, and impaired by a backward pressure, the right atrial pressure [5]. For several decades it was believed that positive pressure ventilation, by increasing pleural pressure, decreased the pressure gradient for venous return. In 1991, Fessler et al., working in S. Permutt's group, demonstrated in an experimental study in dogs that positive airway

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_40, © Springer-Verlag Berlin Heidelberg 2009

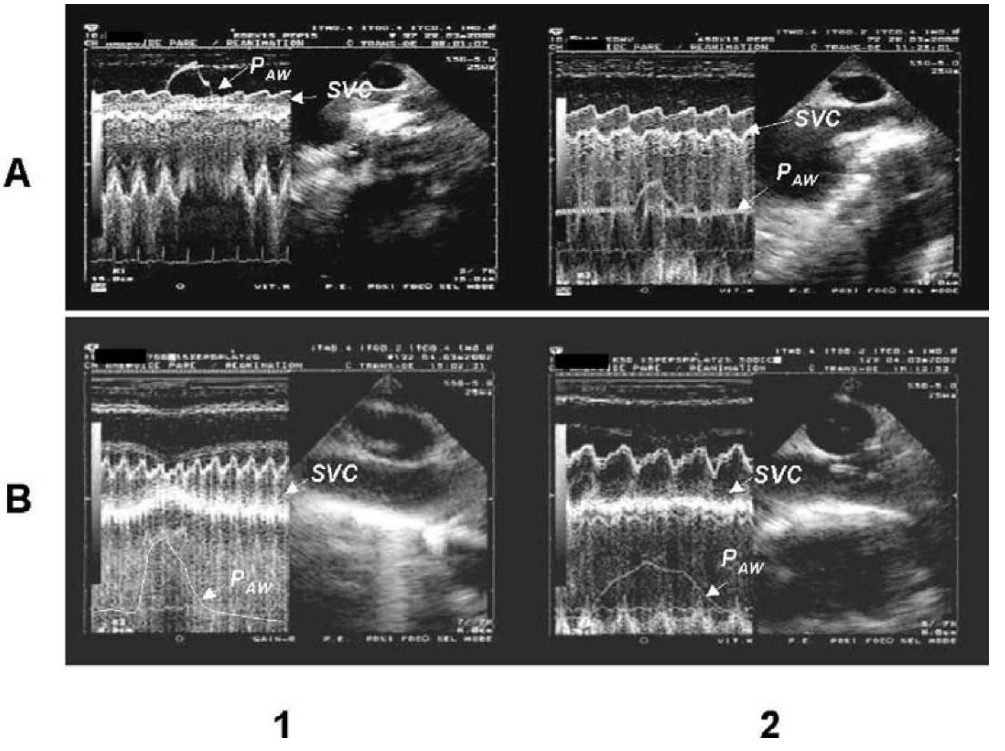


Fig. 1 Transesophageal echocardiographic examination of the superior vena cava (*SVC*) in the *long axis* (with the M-mode study on the *left* and the two-dimensional imaging on the *right* of each record) in two different patients (**A** and **B**). On the left panel (*1*), SVC collapse was observed in these patients during tidal ventilation (airway pressure, P_{AW}, was monitored on the M-mode recording). This collapse was prevented in both patients by blood volume expansion, as illustrated on the right panel (*2*)

pressure did not affect the gradient for venous return, because pleural pressure was transmitted to the same extent to both the mean systemic and right atrial pressures [6]. Van den Berg et al. [7] demonstrated in a recent clinical study that a sustained increase in airway pressure did not decrease venous return because of a concomitant increase in abdominal pressure, an operative mechanism in volume loaded patients, with the inferior vena cava in a zone 3 condition [8]. Also, Fessler et al. observed in another experimental study that venous return was actually reduced by positive pressure ventilation, despite a maintained pressure gradient [9]. They concluded that venous conductance was reduced (or venous resistance was increased) when airway pressure was increased, probably because a collapsible vascular zone was interposed between mean systemic pressure and right atrial pressure [9]. Recently, Jellinek et al. confirmed the validity of this concept in humans, and suggested that liver circulation might constitute this collapsible vascular zone sensitive to pleural pressure transmission throughout the diaphragm [10].

We have also observed another collapsible vascular zone at the level of the thoracic part of the superior vena cava [11]. Placed in a zone 2 condition in a hypovolemic patient, the superior vena cava may partially collapse during tidal ventilation, thus transiently limiting RV filling (Fig. 1, Electronic Supplementary Material Film 1A, B and C). The same phenomenon is not observed at the level of the inferior vena cava, because the thoracic part of this vessel is virtual in humans [11].

Changes in transpulmonary pressure and the impact on right ventricular outflow impedance

Applying the concept of the Starling resistor to the pulmonary circulation, S. Permutt and his co-workers described the relation between the pressures promoting blood flow through the pulmonary circulation [12]. A forward pressure, the pulmonary artery pressure, boosts blood through the pulmonary vascular bed, and a backward pressure, the pulmonary venous pressure, impedes this flow (zone 3 condition). However, alveolar pressure, which directly acts externally on the pulmonary capillary bed, may behave as backward pressure if it rises above venous pressure (zone 2 condition). During tidal volume ventilation, the increase in airway pressure produces an increased zone 2 at the expense of zone 3 (Fig. 2). Thus, during tidal ventilation, alveolar pressure, acting as the backward pressure, impedes pulmonary blood flow. This phenomenon may be important in a mechanically ventilated supine patient. If we assume an average pulmonary venous pressure at the level of the mid-axillary line of 16.5 cmH_2O (12 mmHg), and a 12 cm height between the mid-axillary line and the anterior chest wall, the pulmonary venous pressure in the anterior area of the lungs should be close to 4.5 cmH_2O (i.e., 16.5–12). Thus, in this area, a transpulmonary pressure of 5 cmH_2O would produce a permanent zone 2 condition. Conversely, because of an equal height of 12 cm between the posterior chest wall and the mid-ax-

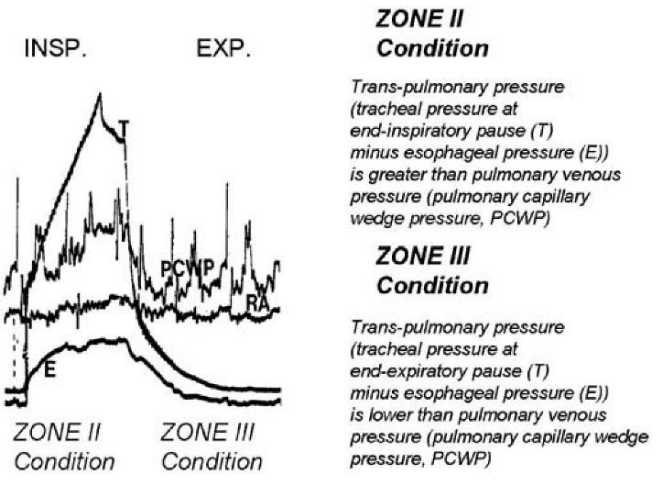


Fig. 2 An example of simultaneous recording of esophageal pressure (*E*), reflecting pleural pressure, right atrial pressure (*RA*), pulmonary capillary wedge pressure (*PCWP*), reflecting pulmonary venous pressure, and tracheal pressure (*T*). During the period of no-flow (end-inspiratory pause and end-expiration), *T* reflects alveolar pressure. Whereas a zone 3 condition is observed at end-expiration (PCWP>T), a zone 2 condition is realized at end-inspiration (T>PCWP). Also note that the increase in *E* during mechanical inspiration is accompanied by a similar increase in PCWP

illary level, dependent areas of the lung are protected against a zone 2 condition.

In fact, it is not alveolar pressure in the strict sense of the term that constitutes backward pressure during tidal ventilation, but alveolar distending pressure (i.e., transpulmonary pressure) as we have recently demonstrated in a clinical study, using chest strapping, a procedure that increases alveolar pressure without a concomitant increase in transpulmonary pressure [13].

By recording simultaneously pulmonary artery and right ventricular pressures in mechanically ventilated patients, we have observed in the past the relation between transpulmonary pressure and right ventricular outflow impedance: when tidal volume is progressively increased, the right ventricle has to develop a more and more elevated pressure to open the pulmonary artery valve (Fig. 3) [14]. We have recently confirmed these results by Doppler analysis of changes in pulmonary artery velocity (Fig. 4, Electronic Supplementary Material Film 2A, B) [13]. Increased transpulmonary pressure during tidal ventilation sharply reduces mean acceleration of blood in the pulmonary artery (Fig. 4), whereas an isolated increase in airway pressure without change in transpulmonary pressure does not affect blood velocity in the pulmonary artery [13].

Indirect evidence of RV afterloading is also provided by the frequency of tricuspid regurgitation during mechanical ventilation [15], which can also be induced by PEEP [16]. An example is given in Fig. 5.

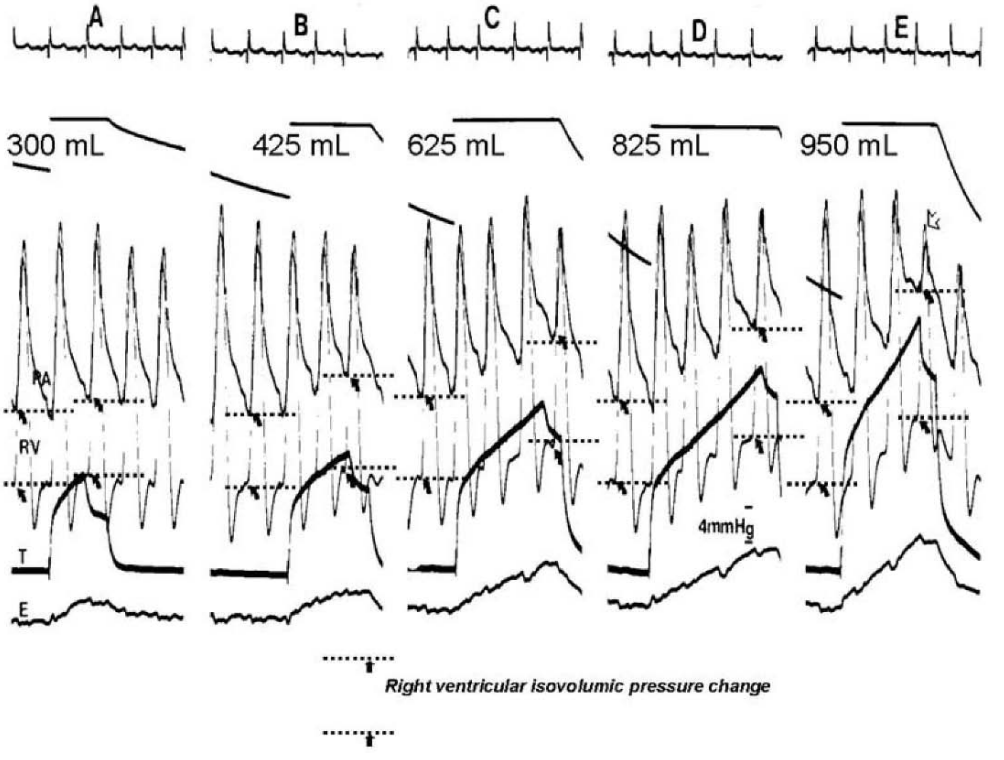


Fig. 3 Simultaneous recordings of expiratory volume (*EV*, ml), pulmonary artery pressure (*PA*, mmHg), right ventricular pressure (*RV*, mmHg), tracheal pressure (*T*, mmHg) and esophageal pressure (*E*, mmHg), during a progressive increase in tidal volume from 300 to 950 ml. This progressive increase in tidal ventilation required a progressive increase in the pressure developed by the RV during its isovolumetric contraction to open the pulmonic valve (i.e., the difference between pulmonary artery diastolic pressure, *small closed arrow*, and right ventricular end-diastolic pressure, *small closed arrow*). Note also that, with the highest tidal volume (*right panel*, *E*), pulmonary artery pulse became negligible (*small open arrow*)

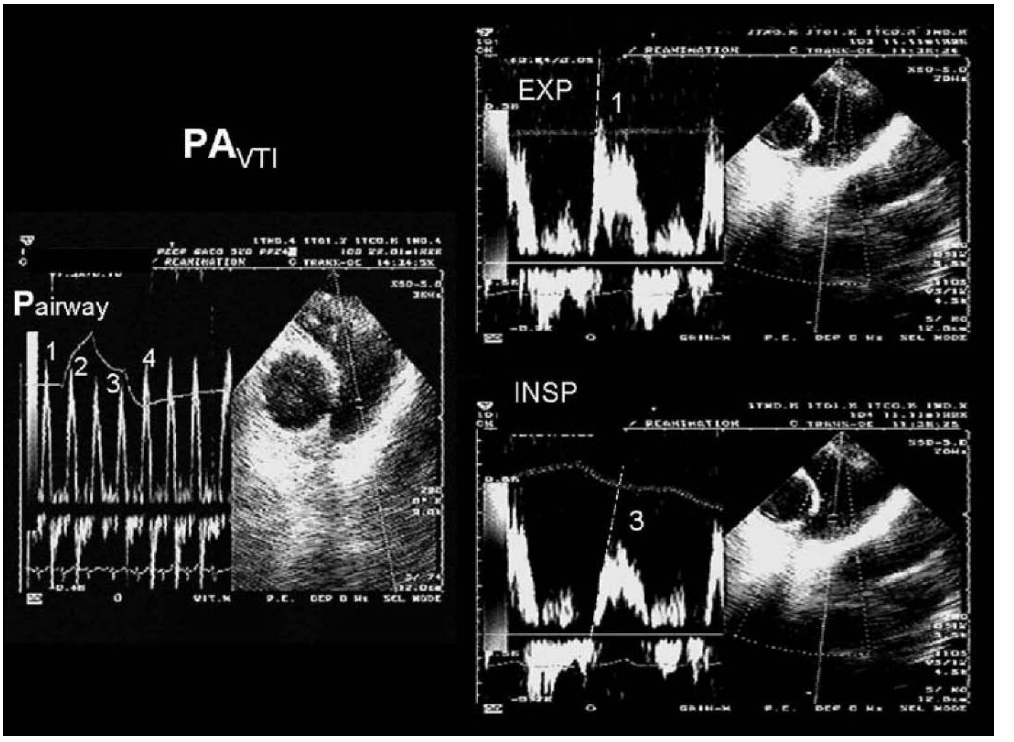


Fig. 4 Cyclic changes in pulmonary artery Doppler flow velocity during tidal ventilation. On the *left panel* these changes are recorded at low speed, illustrating the drop in peak velocity between beat 1 (end-expiratory beat) and beat 2 occurring during the dynamic phase of lung inflation. This drop was accentuated during beat 3, occurring at the end-inspiratory pause, and peak velocity start to return to its baseline value during beat 4, occurring at the onset of expiration. On the *right panel*, recording at high speed demonstrated the associated drop in mean acceleration (i.e., peak velocity divided by acceleration time), which is depicted by the slope of the *broken line* drawn on the initial part of the Doppler profile on beat 1 and beat 3

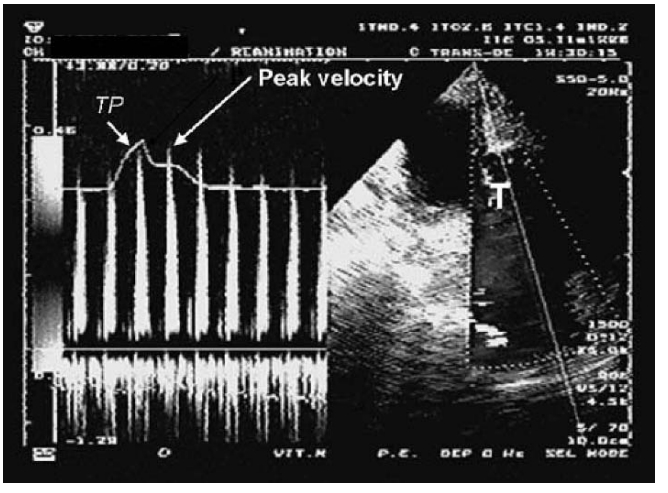


Fig. 5 Examined with a simultaneous recording of tracheal pressure (*TP*), recording of continuous Doppler backward flow velocity at the level of tricuspid valve (*T*) illustrates the increase in peak velocity produced by tidal ventilation

PEEP-related changes in transpulmonary pressure and their hemodynamic impact

In 1975, P. Suter described "best PEEP" as a PEEP resulting in "optimum" oxygen transport in ARDS patients [17]. This PEEP was easy to determine, because it was also associated with the best value of a two-point (quasi-static) compliance of the respiratory system (C_{RS}) [17].

This "best PEEP" was relatively low (8±4 cmH_2O, personal communication from P. Suter). If we assume that changes in C_{RS} in ARDS essentially reflect changes in static compliance of the lung (C_L), we can conclude that the "best PEEP" described by Suter reduced, for a given tidal volume, the required transpulmonary pressure. Thus, a lesser impact of tidal ventilation on right ventricular function should be expected when this PEEP is applied.

This hemodynamic improvement was actually present in Suter's work, where application of the "best PEEP" did not decrease cardiac output despite increased pleural pressure [17]. In accord with Suter's findings, we observed in 1981 that cardiac output was maintained at a low PEEP (<10 cmH_2O), despite pleural pressure increase (–0.6+0.4 mmHg at ZEEP, versus 0.9+1.9 mmHg with PEEP=10 cmH_2O, end-expiratory values) [18]. Conversely, above this PEEP cardiac output fell significantly [18]. Recently, we have corroborated this beneficial hemodynamic effect of a low PEEP by Doppler examination of pulmonary artery flow velocity [19] (Electronic Supplementary Material Film 3A,B).

In Suter's study, C_{RS} was a two-point compliance, calculated as tidal volume divided by plateau pressure minus end-expiratory pressure. The latter was assumed to be external PEEP, because the phenomenon of intrinsic PEEP was unknown at this time. If corrected for intrinsic PEEP [20], which was likely present in ARDS pa-

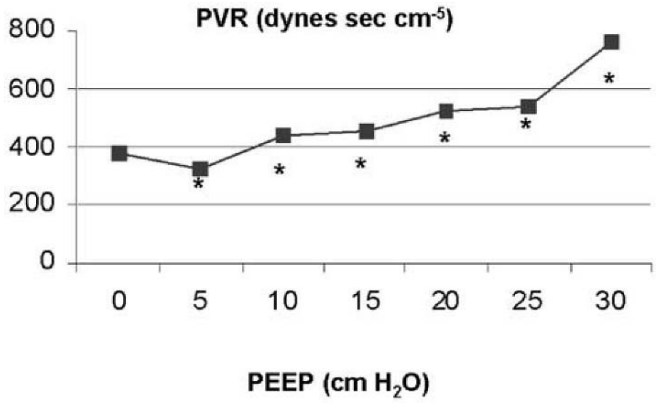


Fig. 6 Average change in pulmonary vascular resistance (*PVR*) during a progressive increase in PEEP in ten ARDS patients studied in 1981 [10]. Error bars are omitted for clarity. PVR was calculated using left ventricular end diastolic pressure measured at end-expiration by the Seldinger method, as reflecting pulmonary venous pressure. Note that PVR was significantly improved at a low PEEP, and was worsened on increasing PEEP above this level (*P<0.05)

tients receiving a high tidal volume (13–15 ml/kg), the C_{RS} in Suter's patients would have probably been unchanged by "best PEEP" application, and the reason for the beneficial hemodynamic effect of this PEEP would probably not be an actual mechanical improvement, permitting reduction in transpulmonary pressure. In the study referred to above [18], we also observed a significant reduction in pulmonary vascular resistance with a low PEEP (between 3 and 8 cmH_2O, Fig. 6). As we have recently emphasized, a "slow compartment" is usually present at a relatively low supportive respiratory rate in ARDS patients, and produces gas trapping [21]. This gas trapping may be responsible for a permanent zone 2 condition in a limited area, and an increased vascular resistance in this specific area. Relieving gas trapping by a low PEEP [21] thus improves blood flow and reduces vascular resistance (Fig. 7).

Effect of an increase in pleural pressure on RV effective diastolic elastance

Pleural pressure is transmitted integrally to the pericardial space [22]. Thus, any increase in pleural pressure induces an increase in pericardial pressure, which limits the distending capacity of the cardiac cavities. During diastole, when pleural pressure is increased, a higher filling pressure is necessary to obtain an adequate end-diastolic volume. We have illustrated in the past the changes in left [18] and right [23] ventricular effective elastance occurring in clinical settings when pleural pressure is progressively increased by raising PEEP, and a schematic representation of theses change is shown in Fig. 8.

As a clinical consequence, a high central venous pressure (>10 mmHg) is required in a mechanically ventilated patient to put the right ventricle on the flat part of its function curve, thus rendering it somewhat insensitive to cyclic change in elastance produced by tidal ventilation

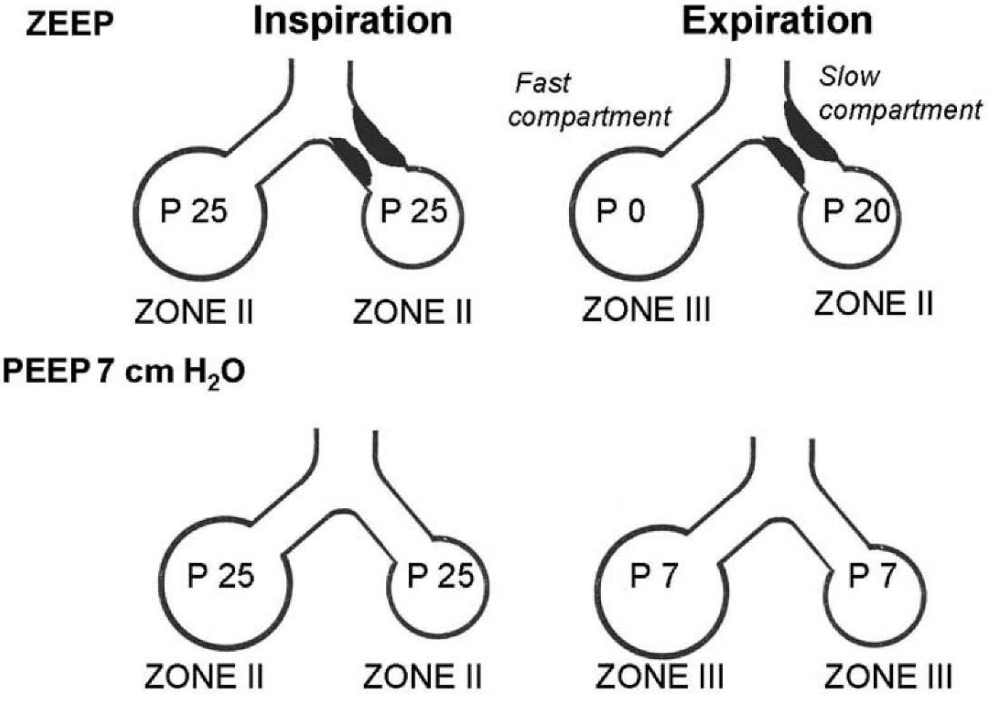


Fig. 7 A schematic representation of the adverse hemodynamic effect of the slow compartment in ARDS. On the *top left panel*, tidal ventilation with ZEEP produces a plateau pressure of 25 cmH_2O, which creates a zone 2 condition. On the *top right panel*, airway pressure in the fast compartment returns to zero at end-expiration with ZEEP, restoring a zone 3 condition, whereas the slow compartment, which cannot empty, is responsible for a permanent zone 2 condition in the corresponding vascular area. On the *bottom panel*, tidal ventilation with PEEP also creates a zone 2 condition (*left*), but the low PEEP of 7 cmH_2O suppresses the slow compartment, so that no zone 2 condition persists at expiration (*right*)

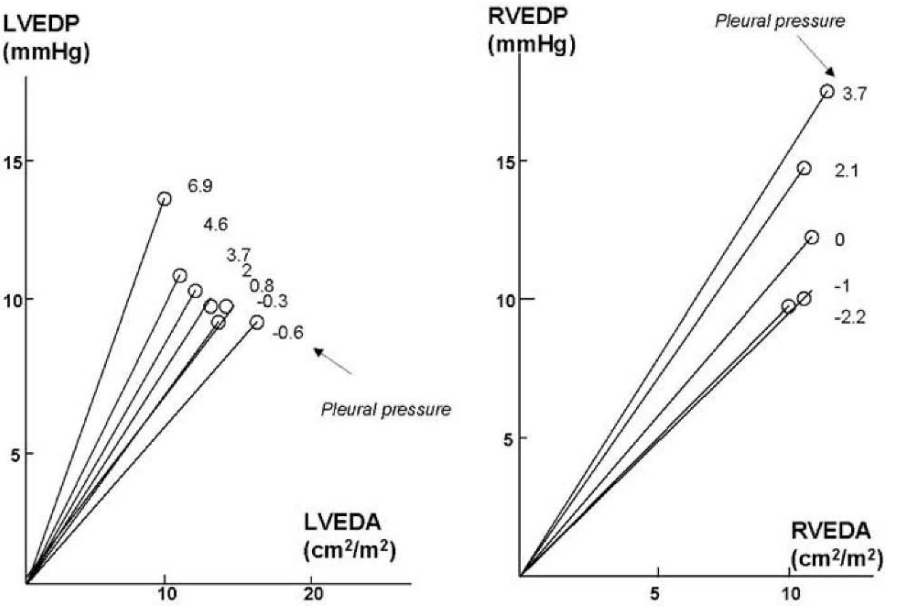


Fig. 8 Simultaneous recording of left ventricular end-diastolic pressure by left ventricular catheterization (*LVEDP*) and right ventricular end-diastolic pressure by right heart catheterization (*RVEDP*) simultaneously with left (*L*) and (*R*) ventricular end-diastolic areas (*EDA*) by two-dimensional echocardiography illustrated the changes in left (*left panel*) and right (*right panel*) ventricular elastance (the slope of the relation) occurring with a progressive increase in pleural pressure produced by a step-by-step application of PEEP. These diagrams were constructed with the data of [18, 23]

[24]. But central venous pressure may be misleading as a monitoring parameter because it is sensitive to venous elastance, which may differ from patient to patient. In our experience, observation of superior vena caval diameter by TEE is fundamental in ensuring that the right ventricle will be on the flat part of its function curve: this is likely the case when cyclic changes in pleural pressure only slightly affect vena caval diameter [11] (Electronic Supplementary Material Films 1A,B,C).

What is the net result of these opposite effects on right ventricular size?

Changes in RV dimensions produced by tidal ventilation or by PEEP application have given apparently conflicting results, some authors emphasizing a reduction in RV dimensions [25], whereas we have demonstrated an increase in RV dimensions [23, 26]. In fact these results are perfectly coherent because, as we have discussed, the two effects of increasing airway pressure have opposite consequences for RV dimensions. Whereas an increase in RV outflow impedance tends to reduce ejection and increase end-diastolic volume (afterload effect, Electronic Supplementary Material Film 4), an increase in RV diastolic elastance tends to reduce end-diastolic volume (preload effect). Thus, the net effect of these opposite actions on RV size is the result of the preponderance of one over the other.

In 1998, Gattinoni et al. [27] introduced a major distinction in the ARDS classification by individualizing, from a mechanical point of view, two different subgroups. Pulmonary ARDS had a markedly reduced C_L, whereas C_W was slightly affected in this subgroup. Extrapulmonary ARDS, on the other hand, had a markedly reduced C_W associated with a relatively preserved C_L. Thus, in pulmonary ARDS, a higher transpulmonary pressure would be required to deliver a given tidal volume. In this setting, one can expect a preeminent afterload effect. Conversely, in extrapulmonary ARDS, a given tidal volume would markedly increase pleural pressure. In this setting, one can expect a preeminent preload effect. Thus, pulmonary ARDS will be subject to RV enlargement with increasing airway pressure, whereas extrapulmonary ARDS will be subject to RV size reduction.

Both effects may also be successively observed in the same patient, with an initial reduction of RV size with a low PEEP, because a concomitant reduction in preload and afterload reduces RV size, and a final enlargement with a higher PEEP, when the increased afterload effect becomes preeminent [23].

Hypercapnia, respiratory rate and RV function

Hypercapnia has been experimentally proved as a deleterious factor for an overloaded RV [28]. With the widespread acceptance of a protective ventilation strategy in clinical practice [29, 30, 31, 32], which requires an airway pressure limitation (plateau pressure <30 cmH_2O), hypercapnia has replaced airway pressure as a direct factor related to acute cor pulmonale in ARDS patients [33, 34]. Clearly, hypercapnia in this setting results from the severity of the disease, but it may only be expressed owing to the new "permissive" respiratory strategy, limiting tidal volume.

Computed tomographic studies in ARDS have illustrated the major reduction in functional alveolar areas observed in this syndrome [35] and have led to the "baby lung" concept. In this concept, ARDS lung is compared to the lung of a baby, admitting only a small tidal volume. Because the respiratory rate of a baby is markedly greater than that of an adult, it has been proposed to limit the level of "permissive" hypecapnia by increasing the respiratory rate [36]. But adult ARDS patients actually exhibited an adult dead space [37], and increasing respiratory rate may produce an adverse intrinsic PEEP [37]. Gas trapping generated by this strategy increased right ventricular outflow impedance [37].

From a hemodynamic point of view, what are the best ventilation strategies in ARDS patients?

First of all, it should be recalled that the differences between cyclic positive airway pressure obtained by tidal ventilation and permanent airway pressure produced by PEEP are profound. Whereas transient increase in inspiratory pressure cannot be adapted because of the fleeting nature of the stress, PEEP induces a steady-state change in cardiovascular conditions, such that altering blood volume by fluid expansion and/or autonomic tone by a vasoactive support usually results in a return to baseline hemodynamic status. However, both interventions may have their own deleterious effects.

In our opinion, a first requirement for a safe mechanical ventilation is to limit transpulmonary pressure. A normal right ventricle may develop a maximal systolic pressure of 30 mmHg. During tidal ventilation, this forward pressure should work against a backward pressure, the transpulmonary pressure. In the past, excessive airway pressure was associated with a high frequency and a marked severity of acute cor pulmonale in ARDS [33]. Airway pressure limitation, which was safely obtained with a medium tidal volume (8 ml/kg of measured body weight) combined with a low PEEP (<10 cmH_2O), has reduced the incidence and clearly improved the prognosis of acute cor pulmonale in ARDS [34]. Additionally, interposing regular periods of ventilation in the prone position, by reversing hydrostatic pressure and its protective effect against a zone 2 situation, might regularly unload the most exposed upper areas of pulmonary vascular bed.

A second requirement for a safe mechanical ventilation is use of a low respiratory rate. The majority of ARDS patients have a localized expiratory flow limitation constituting a "slow compartment" [21], which requires a prolonged expiratory time of 4 s to empty [21]. Additionally, a high respiratory rate produces diffuse expiratory flow limitation and enhances gas trapping [37]. Gas trapping increases both pleural pressure and resistance to flow in the pulmonary vascular bed. However, this requirement is probably not absolute and some increase in respiratory rate may be safe, if it is not associated with intrinsic PEEP [36]. This is the case in a small number of ARDS patients, who exhibit a markedly increased elastic recoil of the lung, associated with a negligible slow compartment. Also instrumental dead space reduction may help to correct excessive hypercapnia [36, 38].

A third requirement for a safe mechanical ventilation is to use at least a low PEEP, thus improving blood flow throughout the pulmonary circulation [19]. As previously stated, the "slow compartment" can not empty with ZEEP when the respiratory rate is greater than 10 breaths/min, because its requires an expiration duration of 4 s [21]. As a result, the airway pressure remains high during the expiratory phase in this area, producing a localized and permanent zone 2. Because a low PEEP is able to reintegrate the "slow compartment" [21], it also permits the return of this area to a zone 3 condition during expiration, and a maximal efficacy of a moderate respiratory rate (15 breaths/min) [2]. This PEEP is actually close to that proposed 25 years ago by P. Suter [17].

Conclusion

The introduction of protective ventilation in 1990 by Hickling has greatly improved ARDS outcome [29]. Unknowingly, this author has also provided better working conditions for the RV, and both are probably in part related [39].

Now, the majority of authors interested in respiratory strategy in ARDS focus on complex mechanical studies to evaluate recruitment. Computed tomography (CT) scanning has been proposed for this purpose [40]. Conversely, few authors are concerned by the impact of the respiratory strategy on pulmonary circulation, and this lack of interest parallels the relative fall from grace of the Swan-Ganz catheter, an inaccurate procedure in mechanically ventilated patients [41]. While lung recruitment appears a justified goal in ARDS treatment, the procedure used for this purpose should remain compatible with the integrity of the pulmonary circulation, also required to obtain recovery [42].

References

1. Pinsky M (2003) Pulmonary artery occlusion pressure. Intensive Care Med 29:19–22
2. Pinsky M (2003) Clinical significance of pulmonary artery occlusion pressure. Intensive Care Med 29:175–178
3. Jardin F (2003) Ventricular interdependence: how does it impact on hemodynamic evaluation in clinical practice? Intensive Care Med 29:361–363

4. Page B, Vieillard-Baron A, Beauchet A, Aegerter Ph, Prin S, Jardin F (2003) Low stretch ventilation strategy in acute respiratory distress syndrome/ 8 years of clinical experience in a single center. Crit Care Med 31:765–769
5. Guyton A, Linsdsey A, Abernathy B, Richardson T (1957) Venous return at various right atrial pressures and the normal venous return curve. Am J Physiol 189:609–615
6. Fessler H, Brower R, Wise R, Premutt S (1991) Effects of positive end-expiratory pressure on the gradient for venous return. Am Rev Respir Dis 145:19–24
7. Van den Berg P, Jansen J, Pinsky M (2002) Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. J Appl Physiol 92:1223–12231
8. Takata M, Wise R, Robotham J (1990) Effects of abdominal pressure on venous return: abdominal vascular zone conditions. J Appl Physiol 69:1961–1972
9. Fessler H, Brower R, Wise R, Permutt S (1992) Effects of positive end-expiratory pressure on the canine venous return curve. Am Rev Respir Dis 146:4–10
10. Jellinek H, Krenn H, Oczenski W, Veit F, Schwartz S, Fitzgerald D (2000) Influence of positive airway pressure on the pressure gradient for venous return in humans. J Appl Physiol 88:926–932
11. Vieillard-Baron A, Augarde R, Prin S, Page B, MD, Beauchet A, Jardin F (2001) Influence of superior vena caval zone conditions on cyclic changes in right ventricular outflow during respiratory support. Anethesiology 95:1083–1088
12. Permutt S, Bromberger-Barnea B, Bane H (1962) Alveolar pressure, pulmonary venous pressure, and the vascular waterfall. Med Thorac 19:239–260
13. Vieillard-Baron A, Loubières Y, Schmitt JM, Page B, Dubourg O, Jardin F (1999) Cyclic changes in right ventricular output impedance during mechanical ventilation. J Appl Physiol 87:1644–1650
14. Jardin F, Brun-Ney D, Cazaux P, Dubourg O, Hardy A, Bourdarias JP (1989) Relation between transpulmonary pressure and right ventricular isovolumetric pressure change during respiratory support. Catheter Cardiovasc Diag 16:215–220
15. Jullien T, Valtier B, Hongnat JM, Dubourg O, Bourdarias JP, Jardin F (1995) Incidence of tricuspid regurgitation and vena caval backward flow in mechanically ventilated patients. A color Doppler and contrast echocardiographic study. Chest 107:488–493
16. Artucio H, Hurtado J, Zimet L, de Paula J, Beron M (1997) PEEP-induced tricuspid regurgitation. Intensive Care Med 23:806–807
17. Suter P, Fairley H, Isenberg M (1975) Optimum end-expiratory airway pressure in patients with acute lung disease. N Engl J Med 292:284–289
18. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP (1981) Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 304:387–392
19. Schmitt JM, Vieillard-Baron A, Augarde R, Prin S, Page B, Jardin F (2001) PEEP titration in ARDS patients: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity. Critical Care Med 29:1154–1158
20. Rossi A, Gottfried B, Zocchi L, Higgs B, Lennox S, Calverley M, Begin P, Grassino A, Milic-Emili J (1985) Measurements of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. The effect of intrinsic positive end-expiratory pressure. Am Rev Respir Dis 131:672–677
21. Vieillard-Baron A, Prin S, Schmitt JM, Augarde R, Page B, Beauchet A, Jardin F (2002) Pressure/volume curves in acute respiratory distress syndrome: clinical demonstration of the influence of expiratory flow limitation on the initial slope. Am J Respir Crit Care Med 165:1107–1112
22. Morgan B, Guntheroth W, Dillard D (1965) Relationship of pericardial pressure to pleural pressure during quiet respiration and cardiac tamponade. Circ Res 26:493–498
23. Jardin F, Brun-Ney D, Hardy A, Aegerter Ph, Beauchet A, Bourdarias JP (1991) Combined thermodilution and two-dimensional echocardiographic evaluation of right ventricular function during respiratory support with PEEP. Chest 99:162–168
24. Jellinek H, Krafft P, Fitzgerald R, Schwartz S, Pinsky M (2000) Right atrial pressure predicts hemodynamic response to apneic positive airway pressure. Crit Care Med 28:672–678
25. Dhainaut JF, Devaux J, Monsallier J, Brunet F, Villemant D, Huyghebaert MF (1986) Mechanism of decreased left ventricular preload during continuous positive pressure ventilation. Chest 90:74–80
26. Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias JP (1990) Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. Anesthesiology 72:966–970
27. Gattinoni L, Pelosi P, Suter P, Pedoto A, Vercesi P, Lissoni A (1998) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? Am J Respir Crit Care Med 158:3–11
28. Rose E, Van Benthuysen K, Jackson T, Tucker C, Kaiser D, Grover R, Weil J (1983) Right ventricular performance during increased afterload impaired by hypercapnic acidosis in conscious dogs. Circ Res 52:76–84
29. Hickling K, Henderson S, Jackson R (1990) Low mortality associated with low volume/pressure-limited ventilation with permissive hypercapnia in severe acute respiratory distress syndrome. Intensive Care Med 16:372–377
30. Amato M, Barbas C, Medeiraos D, Schetino G, Filho L, Kairalla R, Deheinzelin D, Morais C, Fernandes E, Tagaky T, De Carvalho C (1995) Beneficial effect of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. Am J Respir Crit Care Med 152:1835–1846
31. Jardin F, Fellahi JL, Beauchet A, Vieillard-Baron A, Loubières Y, Page B (1999) Improved prognosis of acute respiratory distress syndrome 15 years on. Intensive Care Med 25:936–941
32. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network (2000) N Engl J Med 342:1301–1308
33. Jardin F, Gueret P, Dubourg O, Farcot JC, Margairaz A, Bourdarias JP (1985) Two-dimensional echocardiographic evaluation of right ventricular size and contractility in acute respiratory failure. Crit Care Med 13:952–956
34. Vieillard-Baron A, Schmitt JM, Beauchet A, Augarde R, Prin S, Page B, Jardin F (2001) Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications and prognosis. Crit Care Med 29:1551–1555
35. Gattinoni L, Presenti A, Torresin A, Baglioni S, Rivolta M, Rossi F, Scarani F, Marcolin R, Cappelletti G (1986) Adult respiratory distress syndrome profiles by computed tomography. J Thoracic Imaging 1:25–30

36. Richecoeur J, Q Lu Q, S Vieira, Puybasset L, Kalfon P, Coriat P, Rouby JJ (1998) Expiratory washout versus optimization of mechanical ventilation during permissive hypercapnia in patients with severe acute respiratory distress syndrome. Am J Respir Crit Care Med 160:77–85
37. Vieillard-Baron A, Prin S, Augarde R, Desfonds P, Page B, Beauchet A, MD, Jardin F (2002) Increasing respiratory rate to improve CO_2 clearance during mechanical ventilation is not a panacea in acute respiratory failure. Crit Care Med 30:1407–1412
38. Prin S, Chergui K, Augarde R, Page B, Jardin F, Vieillard-Baron A (2002) Ability and safety of a heated humidifier to control hypercapnic acidosis in severe ARDS. Intensive Care Med 28:1756–1760
39. Scherrer-Crosbie M, Streckenbach S, Zapol W (2001) Acute cor pulmonale in acute respiratory distress syndrome: a dreaded complication of the past? Crit Care Med 29:1641–1642
40. Rouby JJ, Lu Q, Goldstein I (2002) Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 165:1182–1186
41. Jardin F, Bourdarias JP (1995) Right heart catheterization at bedside: a critical view. Intensive Care Med 21:291–295
42. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F (2002) Echo-doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. Am J Respir Crit Care Med 166:1310–1319

Alexandre Mebazaa
Peter Karpati
Estelle Renaud
Lars Algotsson

Acute right ventricular failure—from pathophysiology to new treatments

Abstract The right ventricle (RV) provides sustained low-pressure perfusion of the pulmonary vasculature, but is sensitive to changes in loading conditions and intrinsic contractility. Factors that affect right ventricular preload, afterload or left ventricular function can adversely influence the functioning of the RV, causing ischaemia and right ventricular failure (RVF). As RVF progresses, a pronounced tricuspid regurgitation further decreases cardiac output and worsens organ congestion. This can degenerate into an irreversible vicious cycle.

The effective diagnosis of RVF is optimally performed by a combination of techniques including echocardiography and catheterisation, which can also be used to monitor treatment efficacy. Treatment of RVF focuses on alleviating congestion, improving right ventricular contractility and right coronary artery perfusion and reducing right ventricular afterload. As part of the treatment, inhaled nitric oxide or prostacyclin effectively reduces afterload by vasodilating the pulmonary vasculature. Traditional positive inotropic drugs enhance contractility by increasing the intracellular calcium concentration and oxygen consumption of cardiac myocytes, while vasopressors such as norepinephrine increase arterial blood pressure, which improves cardiac perfusion but increases afterload. A new treatment, the calcium sensitiser, levosimendan, increases cardiac contractility without increasing myocardial oxygen demand, while preserving myocardial relaxation. Furthermore, it increases coronary perfusion and decreases afterload. Conversely, traditional treatments of circulatory failure, such as mechanical ventilation and volume loading, could be harmful in the case of RVF. This review outlines the pathophysiology, diagnosis and treatment of RVF, illustrated with clinical case studies.

Keywords Heart failure · Levosimendan · Vasodilator agents · Inotropic agents · Pathophysiology · Pharmacology

Introduction

Until fairly recently, right ventricular failure (RVF) was a relatively neglected medical condition. The right ventricle (RV) was considered as a moderately passive conduit between the systemic and pulmonary circulations. This belief was supported by studies showing that complete destruction of the right ventricular free wall in dogs had no detectable impairment on overall cardiac performance [1]. However, investigations in the 1970s demonstrated that RVF has significant haemodynamic and cardiac performance effects, as illustrated by Cohen et al.in six patients following a myocardial infarction involving the RV [2]. The patients had severe hypotension, diminished peripheral perfusion and severely impaired pressure generation in the RV, with almost no

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_41,

pressure gradient from the right atrium to the pulmonary artery [2].

Precipitating factors for RVF are common in surgical and medical intensive care units (ICUs). These include increased pulmonary vascular resistance, such as after cardiac transplantation; acute respiratory distress syndrome; the presence of a left ventricular assist device; positive pressure mechanical ventilation and sepsis. There is also a higher incidence of RVF occurring in ICUs than is generally recognised.

Right ventricular failure has a similar incidence to left-sided heart failure, with each affecting about 1 in 20 of the population [3]. Left-sided heart failure is often a chronic, progressive disease with mortality four to eight times greater than that of the age-matched general population [4]. In contrast, the outcome of RVF is largely dependent on the underlying cause, resulting in either an acute or chronic condition. Patients in cardiogenic shock due to an infarction predominantly affecting either the left or right ventricle experience a similar rate of mortality, despite patients with RVF being younger and having a higher prevalence of single vessel disease [5]. Furthermore, ischaemia following a myocardial infarction involving both the right ventricle (RV) and the left, results in a greater risk of mortality than isolated left ventricular ischaemia [6, 7].

The pathophysiology, diagnosis and treatment of RVF in the ICU is associated with some controversy. This review provides an informed opinion on a number of these issues, the effects of some newer treatment options for RVF involving pulmonary vasodilation and enhancing cardiac contraction are described, and their therapeutic benefits are demonstrated in three case studies that are summarised here and described in full in the electronic supplementary material (ESM).

Physiology of the right ventricle and pathophysiology of right ventricular failure

The primary function of the RV is to maintain a low right atrial pressure, optimising venous return and to provide sustained low-pressure perfusion through the lungs. To achieve this, the RV ejects blood quasi-continuously from the right atria to the lungs, continuously emptying the right atria. This 'continuous' ejection is possible because of the favourable characteristics of the pulmonary vascular bed, which is a low pressure, low resistance and high compliance circuit with a pressure gradient of 5 mmHg. Conversely, the left ventricle generates high-pressure pulsatile flow through arterial vessels with low compliance. The right cardiac and pulmonary pressures observed in a healthy spontaneously breathing adult are summarised in Table 1.

The RV is anatomically adapted for the generation of a sustained low-pressure perfusion. It comprises two anatomically and functionally different cavities, termed the sinus and the cone. The sinus generates pressure during systole and the cone regulates this pressure [8]. Right ventricular contraction occurs in three phases; contraction of the papillary muscles, then movement of the right ventricular free wall towards the inter-ventricular septum and, finally, contraction of the left ventricle causes a 'wringing' which further empties the RV. The net effect is pressure generation in the sinus with a peristaltic motion starting at the apex moving towards the cone and, due to the compliance of the upper cone region of the thin-walled RV, the peak pressure is reduced and prolonged. Therefore, ejection into the pulmonary circulation is sustained until the RV has completed its emptying, end-diastolic pressure is minimal and venous return is optimal. Notably, right ventricular preload is determined by both the compliance of the RV and the venous return. The latter depends on the pressure gradient from the periphery to the right atria and the venous resistance. Despite the thin muscular walls of the RV, it adapts to small changes in venous return, such as those occurring during respiration, without altering cavity pressures or volumes. However, larger changes in venous return affect the right ventricular end-diastolic volume.

Table 1 'Normal' right atrial, right ventricular and pulmonary artery pressures for a spontaneously breathing patient

Variable	Value
Right atrial pressure	
Mean	0–7 mmHg
Right ventricular pressure	
Systolic	15–25 mmHg
Diastolic	0–8 mmHg
Pulmonary artery pressure	
Systolic	15–25 mmHg
Diastolic	8–15 mmHg
Mean	10–20 mmHg
Wedge	6–12 mmHg[a]
Pulmonary vascular resistance	100–250 dynes/s per cm^5

[a] Should be less than the pulmonary artery diastolic pressure

Effect of an increase in right ventricular afterload: chronic pulmonary hypertension or acute cor pulmonale

The pressure-volume characteristics for the RV differ markedly from those of the left ventricle (Fig. 1) [9]. The right ventricular pressure-volume loop has a more triangular shape compared with that of the left ventricle, with only brief periods of isovolaemic contraction and relaxation. There is sustained ejection during pressure development that, more importantly, continues during pressure decline. This prolonged low-pressure emptying

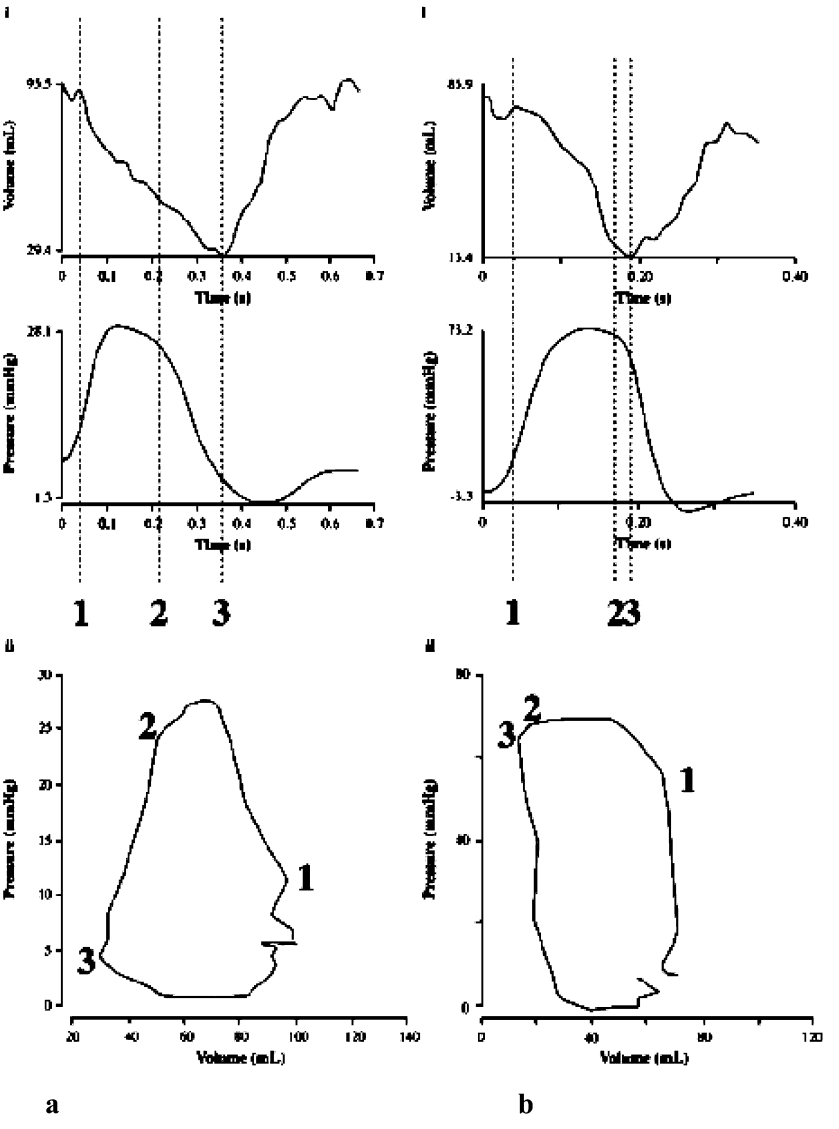


Fig. 1 Pressure and volume changes against time during a contraction cycle (i) and the pressure-volume loop derived from these measurements (ii) are shown for a normal patient (**a**) and for a patient with pulmonary stenosis (**b**). The numbers indicate: 1, the opening of the pulmonary valve marking the start of the ejection phase; 2, the onset of relaxation; 3, the closing of the pulmonary valve marking the end of the ejection phase. In (**a**), the pressure-volume loop is more triangular than that of the left ventricle. Ejection from the right ventricle starts early during the pressure increase and the isovolaemic contraction phase is consequently not well defined. It is interesting to note that ejection continued after the peak pressure during pressure decline (between points 2 and 3). In (**b**), the pressure-volume loop resembles that of the left ventricle. There is a well defined end systolic shoulder and there is no ejection during the pressure decline ([**a**] reproduced from *British Heart Journal* 1988; volume 59, pages 23–30 with permission from BMJ Publishing Group [9]; [**b**] reproduced from *British Heart Journal* 1990; volume 63, pages 45–49, with permission from BMJ Publishing Group [10])

implies that right ventricular emptying is very sensitive to changes in afterload. Thus, in a patient with pulmonary hypertension, the right ventricular pressure-volume loop is not triangular and resembles that of the left ventricle (Fig. 1b) [10]. To compensate, the RV dilates to maintain the stroke volume, though the ejection fraction is reduced [11], and the peristaltic contraction is lost, causing an accelerated increase in pulmonary artery pressure and flow.

The increased afterload also prolongs the isovolaemic contraction phase and ejection time and, therefore, increases myocardial oxygen consumption. Under physiological conditions, there may be increased perfusion of the right coronary artery. However, partial occlusion of the right coronary artery may prevent this compensatory mechanism, resulting in ischaemia [12]. Therefore, in a patient with decreased right coronary artery perfusion, it is important to reduce right ventricular afterload to improve the oxygen supply/demand ratio in the RV to maintain right ventricular function. (This is demonstrated in the first illustrative case study.)

The RV is predominantly perfused by the right coronary artery with supply of some regions by the left anterior descending branch of the left coronary artery. Physiologically, right coronary artery perfusion occurs during both diastole and systole, in contrast to the left coronary artery, that supplies the left ventricular muscle mostly during diastole. However, when pulmonary artery hypertension is present, right coronary artery perfusion occurs quasi-exclusively during diastole, potentially reducing the oxygen supply to the RV during increased oxygen demand.

Acute cor pulmonale relates to a sudden increase in afterload, most often due to a massive pulmonary embo-

lism or acute respiratory distress syndrome in adults [13, 14, 15, 16]. In either setting, right ventricular outflow impedance is suddenly increased, right ventricular ejection is impaired and the RV is enlarged. Thus, both systolic and diastolic function are impaired, which may cause or precipitate circulatory failure in critically ill patients. Acute cor pulmonale is reversible when the cause of increased afterload is removed.

Ventricular interdependence

There is a high degree of ventricular interdependence due to the interaction of the inter-ventricular septum in the contraction of both ventricles, which is pronounced due to the existence of the pericardium [17]. The load on a ventricle is dependent on the passive filling of the contralateral ventricle [18]. The close association between the cardiac cavities can be seen in echocardiography images of the four chambers, such as those shown for the first and the third case studies (Fig. 3 and the ESM) and in recently published papers [14, 16]. Indeed, increases in the end-diastolic volume of the left ventricle are transmitted to the RV by movement of the inter-ventricular septum towards the right cavity, increasing the end-diastolic pressure of the RV [20]. Similarly, when the right ventricular end-diastolic volume is increased, the inter-ventricular septum shifts towards the left cavity during diastole due to the restrictions imposed by the pericardium on the RV as the cavity volume increases. This leftward shift impairs the function of the left ventricle due to the reduction in left ventricular volume, decreasing both left ventricular filling and compliance, manifested as increased muscle stiffness. Thus, in a canine model, ischaemia and acute dilatation of the RV decreased the compliance of the left ventricle, resulting in decreased cardiac output due to a leftward shift in the inter-ventricular septum, which was attenuated by the opening of the pericardium [21].

Ventricular interdependence can also cause RVF during left ventricular assist device support. As the left ventricular assist device unloads the left ventricle, the inter-ventricular septum is shifted left. This alters the right ventricular compliance decreasing force and rate of contraction together with a decreased afterload and increased preload. In a healthy heart, cardiac output may be maintained but, with pre-existing pathology, the decrease in contractility may result in RVF [22]. It is therefore crucial to support right ventricular function during the first days following insertion of a left ventricular assist device.

Vicious cycle of auto-aggravation

Compared to the left ventricle, RVF progresses quickly from compensated to end-stage because of a vicious cycle of auto-aggravation. This is unique to the RV and is not a consequence of isolated left ventricular failure. The elevated right atrial and ventricular end-diastolic pressures eventually lead to an increased right ventricular end-diastolic volume, insufficiency of the tricuspid valve and regurgitation. The tricuspid insufficiency aggravates hepatic and kidney congestion and decreases cardiac output; the heart is, therefore, unable to maintain an adequate function. Thus, the auto-aggravation becomes an irreversible vicious cycle. In addition, decreased venous return to the left ventricle reduces left ventricular preload. This further exacerbates the situation as it causes decreased left ventricular output and systemic blood pressure and hence further impairment of organ perfusion, including the coronary arteries. This ischaemia further diminishes cardiac function and the cycle of worsening output, congestion and ischaemia continues. Therefore, any sign of RVF should result in immediate treatment to avoid the start of the vicious cycle of auto-aggravation.

Diagnosis of right ventricular failure—identifying organ dysfunction

Traditional non-specific approach

The diagnosis of acute RVF in patients in the ICU is complicated by the lack of clinical and biological specific signs. Some biological signs which may be indicative of cardiac dysfunction appear very early during acute RVF. The organs most affected by RVF-induced congestion are the liver and kidneys. Decreased perfusion of the kidneys is manifested as a reduction in both urine output and creatinine clearance. Decreased hepatic perfusion results in increased plasma lactate due to an impaired lactate clearance, a reduction in the synthesis of coagulation factors (observed as a decrease in prothrombin time) and hepatic cytolysis. Interestingly, Fig. 2 and Fig. S1 in the ESM show two examples of the effects of very severe liver and kidney congestion related to RVF.

The sensitivity of conventional chest X-ray techniques to identify changes in right ventricular form is limited by the unusual shape of the RV and the unpredictable manner in which it dilates. Inferential diagnosis may be possible by identification of other radiographic changes, such as the state of the pulmonary circulation and the position of the heart in the chest. Changes in the left ventricle may be apparent on chest X-ray, resulting from the decreased left ventricular preload that is a consequence of RVF.

Echocardiography

Echocardiography is an alternative, more accessible technique for the diagnosis of RVF and for the intermit-

tent repetitive follow-up of the dynamics of therapeutic responses. Its advantage is that a qualitative conclusion can be reached instantaneously. When RVF is secondary to an increase in afterload, the isovolaemic contraction phase and ejection time are prolonged, and increases in pulmonary artery pressure and flow are accelerated. Echocardiography also provides information about the mechanisms of RVF, such as pericardial effusion with or without tamponade, tricuspid insufficiency, pulmonary emboli or right ventricular ischaemia and the resulting acute cor pulmonale [14].

Additionally, echocardiography enables the simultaneous evaluation of left ventricular function, a possible component of the RVF. Due to the geometry and location of the RV, the accuracy and necessity of determining exact right ventricular dimensions remains questionable and an experienced intensivist familiar with performing and evaluating echocardiography is essential. Although echocardiography can be repeated infinitely, the continuous flow of information provided by right heart catheterisation is difficult to reproduce and when technical or human limitations render echocardiography impossible, right heart catheterisation becomes the diagnostic tool of choice.

Pulmonary artery catheterisation

Catheterisation of the pulmonary artery is more invasive but useful to evaluate right ventricular function and confirm the presence of RVF in patients in the ICU. The Swan–Ganz catheter measures both mixed venous oxygen saturation and intravascular pressures or pressure changes in the RV as well as pulmonary artery pressure and pulmonary capillary wedge pressure. Despite difficulties in the interpretation of mean intravascular pressure values, the tracings showing changes in pressure and flow enable the assessment of the impact of treatment on right ventricular function. This cautious interpretation accounts for the almost constant reflux due to the tricuspid insufficiency, which can be observed by central venous and right atrial pressure changes (see Fig. 3 and the illustrative example described in the ESM). Such regurgitation could be used as a hallmark for RVF and as a marker for treatment efficacy.

A more advanced pulmonary catheter, equipped with a fast-response thermistor, is another valuable diagnostic tool enabling clinical assessment of right ventricular volume and haemodynamic parameters by thermodilution. It may also measure cardiac output more precisely even in the presence of tricuspid insufficiency, a particular problem during mechanical ventilation. Indeed, the more widespread introduction of thermodilution techniques to assess pump function has contributed to the recognition of the inherent pathology of RVF. Values for cardiac performance obtained from this technique compare favourably with those using radionucleotides or two-dimensional echocardiography [24, 25].

If a central venous pressure or pulmonary artery catheter is in place, haemodynamic parameters that can aid in the diagnosis of RVF include an increase in right atrial pressure and a decrease in arterial blood pressure, cardiac output and mixed venous oxygen saturation, despite a usually preserved pulmonary artery pressure and pulmonary capillary wedge pressure. For difficult cases, a technique often cited in the literature for the diagnosis of RVF involves the administration of 250 ml of crystalloids or colloids over 10 min [26]. If the patient is suffering from RVF, all the above haemodynamic parameters worsen, including a dramatic increase in right atrial pressure with no change in cardiac output. This test should not be performed in patients who are in acute RVF, as there is a risk of severe aggravation of tricuspid insufficiency and organ congestion after volume loading (see below).

Management of right ventricular failure

The principal therapeutic goals of RVF depend on its underlying aetiology, but generally involve breaking the vicious cycle of reduced cardiac output by restoring adequate oxygen delivery to the myocardium and reducing right ventricular overload. Treatment usually focuses on alleviating congestion, improving right ventricular contractility and/or reducing right ventricular afterload.

When RVF is related to occlusion of the right coronary artery, reperfusion by coronary angioplasty may help restore contractile function to the ischaemic myocardium and improve the clinical outcome [27]. Revascularisation of the right coronary artery may also be prudent when inserting a left ventricular assist device in patients with right coronary artery-associated ischaemia, to avoid subsequent RVF [28]. Patients who have RVF related to atrial fibrillation may benefit from aggressive anti-arrhythmic treatment to improve cardiac output, and temporary pericardiotomy may benefit patients following sternotomy for cardiac surgery.

Volume management

Volume management is a difficult but important task in the treatment of RVF. In very few cases of RVF with normal pulmonary vascular resistance, volume loading may be useful in increasing preload, which increases right ventricular end-diastolic volume and cardiac output [29]. However in the large majority of RVF patients, this compensatory mechanism is potentially limited beyond a mean pulmonary artery pressure of 30 mmHg [30] and therefore caution is warranted when considering volume loading. Volume overload is common during RVF and

volume loading may further dilate the RV, increase tricuspid regurgitation and, consequently, worsen hepatic and renal congestion and RVF. A sharp rise in left- or right-sided filling pressures without a concomitant increase in cardiac output may indicate when further volume loading is detrimental.

In this scenario, fluid withdrawal should be started with diuretics and haemofiltration. If the RV is dilated and the inter-ventricular septum shifted, one should first try diuretics. If this is unsuccessful, haemofiltration is urgently recommended, often under inotropic support.

Pulmonary vasodilators

Systemic therapy

In the presence of elevated pulmonary vascular resistances, vasodilator therapy may reduce right ventricular afterload. This will improve right ventricular function by decreasing right ventricular myocardial oxygen consumption and improving left ventricular filling, which will eventually increase systemic blood pressure and right coronary artery perfusion pressure. This will, in turn, decrease right atrial pressure and organ congestion. Thus, intravenous vasodilators such as nitroglycerin, nitroprusside or prostaglandin E1 may be beneficial in patients with isolated RVF [31, 32]. However, systemic pulmonary vasodilators reverse hypoxic pulmonary vasoconstriction, worsening ventilation-perfusion matching within the lung and decreasing arterial oxygen saturation. Also, they decrease diastolic pressure, resulting in decreased right coronary artery perfusion, which worsens ischaemia [33, 34].

Inhaled therapies

Inhalational vasodilatory agents, such as prostacyclin or its analogues and nitric oxide (NO), have a direct, selective effect on the pulmonary vasculature [23, 35, 36, 37]. NO diffuses into the pulmonary vascular smooth muscle cells, causing vasodilation, and its effects are localised as it rapidly binds to plasma proteins and haemoglobin. Following prolonged administration, rebound pulmonary hypertension has been frequently reported when NO inhalation is suddenly withdrawn [38]. Despite its haemodynamic benefits, a survival advantage for patients with RVF who respond to NO therapy has not been proven [39]. Inhaled sodium nitroprusside, a NO donor drug, is a possible alternative for the future [40].

Beneficial effects of inhaled NO have also been described in the management of RVF associated with a patent foramen ovale. As a patent foramen ovale, together with right-left shunt, is frequently found in patients who have RVF with elevated right atrial pressures, its role in maintaining (or restoring) left ventricular preload, albeit by simultaneously compromising arterial oxygenation, cannot be ignored [41, 42].

An alternative to inhaled NO is inhaled prostacyclin (= prostaglandin I_2). Besides its vasodilator properties, inhaled prostacyclin is the most potent platelet aggregation inhibitor known. Prostacyclin also stimulates endothelial release of NO, and vice versa. A potentially substantial advantage of inhaled, versus intravenous, prostacyclin is that rebound pulmonary hypertension after abrupt discontinuation has so far not been reported. This suggests that, in comparison with inhaled NO, inhaled prostacyclin may treat pulmonary hypertension more effectively. Prostacyclinhas no known toxic effects or active metabolites and it is cheaper than NO, both in terms of the equipment necessary for its administration and the substance itself [43, 44].

Iloprost is the stable carbacyclin derivative of prostacyclin. It has several advantageous properties compared to prostacyclin, including saline solubility, lower viscosity and a significantly longer duration of action with a half-life of 20–30 min and haemodynamic effects that last for 1 h [45].

Contractility enhancing agents

The right ventricular ejection can be directly increased by the insertion of a right ventricular assist device, which may be beneficial for the short-term prophylaxis in patients following cardiac surgery or transplantation, enabling the stunned heart to recover [46].

Positive inotropic agents are also commonly used to improve right ventricular function. Left ventricular contraction assists the ejection from the RV; therefore, inotropic drugs that increase the contraction of the whole heart will improve right ventricular function both by directly enhancing right-sided contractility and by their effects on the entire myocardium. Positive inotropic agents— -adrenoceptor agonists and phosphodiesterase inhibitors—enhance myocardial contractility by increasing the intracellular calcium concentration in both ventricles due to their actions on cAMP [47]. In the treatment of chronic heart failure patients, vasoactive -agonists produce a net increase in cardiac output providing a short-term benefit, but the increased contractility, working against a greater afterload, increases the workload of the heart, resulting in an increase in energy utilisation. Therefore, the oxygen consumption of the myocardium is increased without increasing oxygen supply, which may cause or worsen ischaemia and arrhythmias. Thus, the use of some of these agents has been associated with an increase in long-term mortality [48, 49, 50] and, in the case of dobutamine, tolerance develops after a short time [51]. The treatment of RVF is comparatively short and repeated dosing less common than for chronic heart

failure, therefore tolerance may not be relevant in this setting. However, the effects of sympathomimetics on long-term outcome should perhaps be considered when selecting appropriate treatment for RVF.

A newer class of drugs, the calcium sensitisers, also improve cardiac function by increasing the contraction of the myocardium, but without significantly increasing intracellular calcium levels. Levosimendan, the first calcium sensitiser in clinical use, increases the sensitivity of the cardiac myofilaments to calcium during systole without affecting diastole. The increased calcium sensitivity increases the force and rate of contraction of the myocardium. Moreover, as it only increases systolic calcium sensitivity, it does not affect the relaxation kinetics, in contrast to the traditional inotropic drugs. Hence, levosimendan has no adverse effects on diastolic function [52] and is not associated with a significant increase in myocardial oxygen consumption in patients with chronic heart failure [53], though this result remains to be confirmed.

Levosimendan also induces dilatation of the pulmonary, systemic and coronary vasculature by activation of ATP-sensitive potassium channels resulting in a decreased systemic and pulmonary vascular resistance [54, 55]. This may cause under-perfusion of the myocardium, but the dilation of the coronary arteries results in improved myocardial blood flow [53]. Levosimendan improved haemodynamic performance and decreased the risk of worsening heart failure and mortality in different heart failure populations, compared with dobutamine or placebo [56, 57]. Indeed, all the evidence described comes from studies in patients with chronic heart failure, and the direct effects of levosimendan on RVF are currently unproven. However, from its known effects, including a demonstrated improvement in right ventricular contractile efficiency [53], beneficial effects in RVF may also be expected. The haemodynamic effects of levosimendan may be sustained for days, or even weeks, due to an active metabolite with a half-life of over 3 days [58].

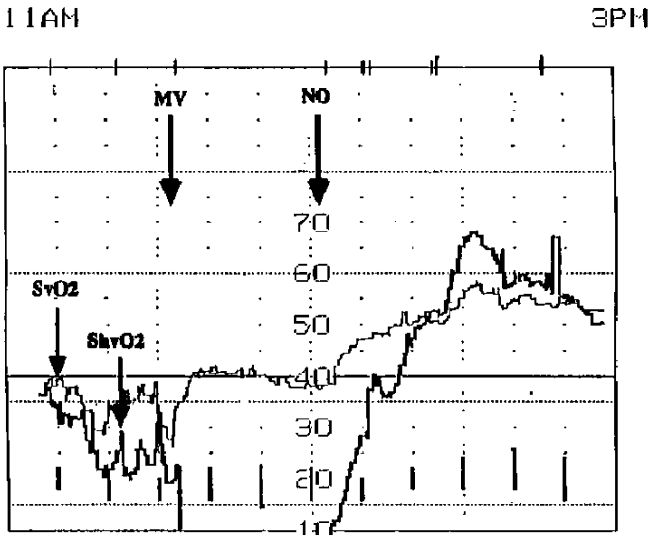


Fig. 2 Mixed venous oxygen saturation (SvO_2) increases and hepatic venous oxygen saturation ($ShvO_2$) decreases in response to the start of mechanical ventilation in a patient with predominantly right-sided congestive heart failure due to increased preload that worsens right ventricular function and hence organ congestion. Following nitric oxide inhalation, $ShvO_2$ increases indicating improved right ventricular function due to decreased preload and relieved liver congestion. *MV* start of mechanical ventilation, *NO* start of nitric oxide inhalation (18 ppm) (reproduced from Gatecel et al., 1995, with permission [23])

Vasopressors

Vasopressors directly increase arterial blood pressure and improve coronary artery perfusion, though also increasing afterload. Their benefits in RVF were pioneered by Prewitt and co-workers and they may be critical in the treatment of RVF, preventing the vicious cycle by improving right coronary artery perfusion and right ventricular contraction [59, 60]. Norepinephrine, a potent -adrenergic-agonist is recommended to improve right coronary artery perfusion pressure and right ventricular function, and it is more effective than phenylephrine, another selective -adrenergic agonist [61]. In patients with septic shock, norepinephrine increased mean arterial pressure, with a moderate increase in mean pulmonary artery pressure, improving right coronary artery perfusion pressure and right ventricular contraction [60]. However, in the case report of sepsis-induced RVF (see below), norepinephrine increased organ perfusion pressure but not cardiac output, and combination with inhaled NO was therefore needed.

Mechanical ventilation

Mechanical ventilation is the usual treatment for shock, however it may worsen RVF as elevated transpulmonary pressures increase right ventricular output impedance and, hence, decrease stroke output. An example of severe hepatic and renal congestion due to subacute RVF markedly aggravated by mechanical ventilation is shown in Fig. 2 [23]. The patient had a low hepatic venous oxygen saturation caused by a high hepatic venous back-pressure that was reducing liver blood flow despite a maintained cardiac output. Due to respiratory fatigue, the patient was mechanically ventilated, which resulted in an improved mixed venous oxygen saturation, from 28 to 40%, related to the decreased respiratory work and, thus, systemic oxygen consumption. However, mechanical ventilation caused an abrupt decrease in hepatic venous oxygen saturation to an undetectable

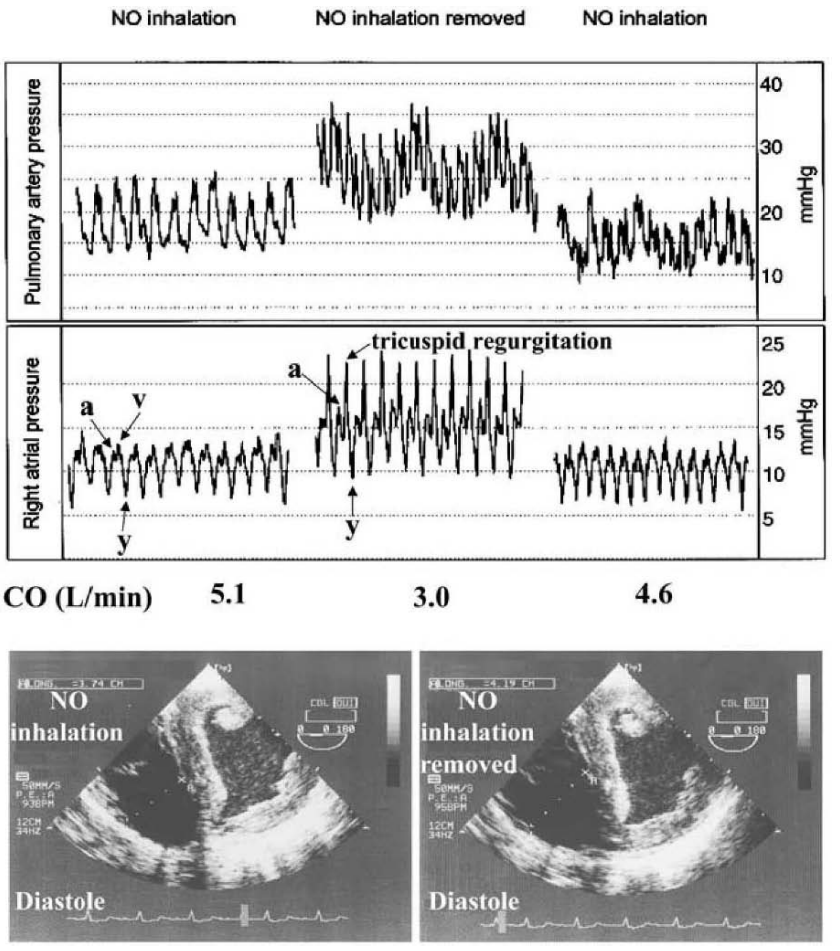


Fig. 3 Patient haemodynamics with and without inhaled nitric oxide (NO). Inhaled NO withdrawal in this patient with ischaemia-induced right ventricular failure increased mean pulmonary artery pressure from 18 to 25 mmHg. During NO inhalation and preserved right ventricular function, right atrial pressure showed 'a' waves (auricular contraction) followed by 'v' waves (passive atrial filling due to venous return) and 'y' waves (beginning of diastole: rapid ventricular filling and passive atrial emptying). When inhaled NO was removed, although pulmonary artery pressure remained in the normal range, the slight increase resulted in a deterioration of right ventricular function and dilation of the right ventricle. Right atrial pressure showed that a tricuspid insufficiency emerged (positive waves) that worsened cardiac output (CO) despite the increase in auricular contraction (increase in 'a' waves). Echocardiography shows the close association between the left and right ventricles separated by the inter-ventricular septum. An enlargement of the right ventricle can be seen, with the end-diastolic diameter increasing from 37 mm to 42 mm when NO inhalation was removed (Reproduced from 2002 Yearbook of Intensive Care and Emergency Medicine, Acute right ventricular failure: physiology and therapy by Renaud E, Karpati P, Mebazaa A, page 211, Fig. 1, and page 212, Fig. 2, 2002, Springer-Verlag, with permission [19])

level, which resulted from worsening RVF related to an increased right ventricular afterload due to positive pressure breathing. Consequently, right atrial pressure was raised, worsening the hepatic congestion. The subsequent use of NO inhalation decreased right ventricular afterload, improved right ventricular function and relieved liver congestion, demonstrated by the rapid increase in hepatic venous oxygen saturation as RVF was successfully controlled.

In summary, although several tools could be used to improve RVF, volume loading and mechanical ventilation should be used with caution because they may precipitate or aggravate RVF.

Illustrative case studies

The treatment of RVF often requires a multi-modal approach with continuous haemodynamic monitoring to observe the patient's progress. Three case studies are summarised below (and described in detail in the ESM) that highlight the diagnosis and treatment of acute RVF with therapy tailored specifically to the patient's diagnosis and haemodynamic status. These cases demonstrate that there are a number of treatment approaches that may result in a successful outcome. The new myocardial contractility-enhancing agents may obviate the use of some agents with a questionable long-term benefit.

Table 2 The treatment of sepsis-induced right ventricular failure with 'traditional' positive inotropic agents: the value of each parameter before and after the corresponding treatment (*DO* dobutamine, *NE* norepinephrine, *NO* inhaled nitric oxide, *VL* volume loading: 250 ml of colloids) had been given

Time	14:00 VL	15:30 VL	16:30 NE	20:30 DO/NO	23:30
HR (bpm)	90	90	90	94	92
BP (mmHg)	96/56	95/49	110/55	130/70	115/68
PAP (mmHg)	35/24	42/28	43/30	46/32	31/21
RAP (mmHg)	12	13	20	16	8
PCWP (mmHg)	12	12	14	15	10
SvO_2 (%)	70	71	65	63	74
CI (l/min per m^2)	2.3	2.3	2.0	1.9	2.8
Lactate (mmol/l)	3.3	3.6	3.8	4.0	4.1

HR heart rate, *BP* arterial blood pressure, *PAP* pulmonary artery pressure, *RAP* right atrial pressure, *PCWP* pulmonary capillary wedge pressure, SvO_2 mixed venous oxygen saturation, *CI* cardiac index

Effects of inhaled nitric oxide on ischaemia-related right ventricular failure following cardiac surgery

A 30-year-old male with acute RVF was treated with inhaled NO, 8 ppm, to reduce the afterload, which rapidly restored haemodynamics. When NO was withdrawn, right atrial pressure increased, cardiac output and arterial blood pressure dropped, there was tricuspid regurgitation and echocardiography showed a severe dilation of the RV (Fig. 3). NO was restored and the patient was weaned from treatment on the 7th postoperative day.

Sepsis-induced right ventricular failure treated with the combination of traditional positive inotropic agents and inhaled nitric oxide

A 55-year-old male had sepsis-induced myocardial dysfunction with a predominant RVF confirmed by echocardiography. Norepinephrine increased blood pressure but could not improve right ventricular function. The patient was subsequently treated with dobutamine, 5 g/kg per min, and inhaled NO, 5 ppm (Table 2). The combination induced a large, rapid and sustained decrease in right atrial pressure, pulmonary capillary wedge pressure was restored, mixed venous oxygen saturation and cardiac index were approaching normal values. A volume loading of 250 ml was given to improve organ perfusion pressure and subsequently the patient was haemodynamically stable and all parameters returned to values towards or within the normal range.

Ischaemia-induced right ventricular failure treated with calcium sensitiser monotherapy

Following coronary artery bypass graft surgery, a 71-year-old male was diagnosed with RVF and treated with levosimendan, 6 g/kg loading dose given over 10 min followed by a 0.1 g/kg per min infusion for 24 h. Four hours after the start of the levosimendan infusion, echocardiograhy showed an improvement in cardiac performance. At 24 h, echocardiography and haemodynamic values were almost restored to normal and the patient reported symptomatic improvement (echocardiography video available in the ESM). This improvement in right ventricular function was related to an improvement in right ventricular contractility and vasodilatory effects on the pulmonary circulation (decrease in pulmonary artery pressure).

Conclusion

It is now evident that the RV plays a pivotal role in haemodynamic homeostasis, and changes in right ventricular function can have profound effects on the pulmonary and systemic circulation. Therefore, it is important that RVF is diagnosed quickly and accurately before it degenerates into the vicious cycle of auto-aggravation with tricuspid deficiency, worsening cardiac ischaemia and multiple organ congestion. Diagnosis should include an assessment of the patient and the use of diagnostic tools that also enable the clinician to follow the progress of treatment.

The management of RVF should focus on restoring right ventricular function with the treatment dictated by the underlying aetiology. The primary cause of RVF should be corrected wherever possible. The right ventricular afterload should be reduced, if necessary, by decreasing the pulmonary artery pressure (e.g. by administering pulmonary vasodilators such as inhaled NO or prostacyclin) and limiting plateau pressure in mechanically ventilated patients, the preload should be increased cautiously with volume loading and an adequate right coronary artery perfusion maintained. Positive inotropic agents have an important role in the treatment of RVF by improving cardiac output and coronary perfusion. However, traditional inotropic drugs increase myocardial contractility by their sympathomimetic action at the expense of increasing myocardial intracellular calcium concentration and oxygen consumption. Calcium sensitisers, specifically levosimendan, enhance contractility without increasing

myocardial oxygen consumption. If the beneficial effects that have been observed in chronic heart failure patients are validated in RVF in clinical studies, this class of agents may represent a valuable addition to the clinician's armamentarium for the management of this condition.

Acknowledgements We would like to acknowledge Professor Didier Payen for his critical review of the paper, Drs. Jan Eskilsson and Ulf Thilèn who performed the echocardiography shown in the ESM at the University Hospital in Lund, Sweden, and Professor Rymer and Dr Boudiaf, who performed the CT scan in Fig. S1 in the ESM.

References

1. Starr I, Jeffers WA, Meade RH (1943) The absence of conspicuous increments of venous pressure after severe damage to the RV of the dog, with discussion of the relation between clinical congestive heart failure and heart disease. Am Heart J 26:291–301
2. Cohen JN, Guiha NH, Broder MJ, Limas CJ (1974) Right ventricular infarction, clinical and hemodynamic features. Am J Cardiol 33:209–214
3. Health Central – General Encyclopaedia – right-sided heart failure http://www.healthcentral.com/mhc/top/000154.cfm. Accessed June 2002
4. Kannel WB, Belanger AJ (1991) Epidemiology of heart failure. Am Heart J 121:951–957
5. Jacobs AK, Leopold JA, Bates E, Mendes LA, Sleeper LA, White H, Davidoff R, Boland J, Modur S, Forman R, Hochman JS (2003) Cardiogenic shock caused by right ventricular infarction: a report from the SHOCK registry. J Am Coll Cardiol 41:1273–1279
6. Mehta SR, Eikelboom JW, Natarajan MK, Diaz R, Yi C, Gibbons RJ, Yusuf S (2001) Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. J Am Coll Cardiol 37:37–43
7. Lupi-Herrera E, Lasses LA, Cosio-Aranda J, Chuquirue-Valenzuela E, Martinez-Sanchez C, Ortiz P, Gonzalez-Pacheco H, Juarez-Herrera U, Rodriguez Mdel C, Vargas-Barron J, Martinez-Rios MA (2002) Acute right ventricular infarction: clinical spectrum, results of reperfusion therapy and short-term prognosis. Coron Artery Dis 13:57–64
8. Stephanazzi J, Guidon-Attali C, Escarment J (1997) Right ventricular function: physiological and pathophysiological features. Ann Fr Anesth Reanim 16:165–186
9. Redington AN, Gray JJ, Hodson ME, Rigby ML, Oldershaw PJ (1988) Characterisation of the normal right ventricular pressure-volume relation by biplane angiography and simultaneous micromanometer pressure measurements. Br Heart J 59:23–30
10. Redington AN, Rigby ML, Shinebourne EA, Oldershaw PJ (1990) Changes in the pressure-volume relation of the right ventricle when its loading conditions are modified. Br Heart J 63:45–49
11. Matthay RA, Arroliga AC, Wiedemann HP, Schulman DS, Mahler DA (1992) Right ventricular function at rest and during exercise in chronic obstructive pulmonary disease. Chest 101:255S–262S
12. Brooks H, Kirk ES, Vokonas PS, Urschel CW, Sonnenblick EH (1971) Performance of the right ventricle under stress: relation to right coronary flow. J Clin Invest 50:2176–2183
13. Vieillard-Baron A, Page B, Augarde R, Prin S, Qandli S, Beauchet A, Dubourg O, Jardin F (2001) Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. Intensive Care Med 27:1481–1486
14. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F (2002) Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. Am J Respir Crit Care Med 166:1310–1319
15. Vieillard-Baron A, Schmitt JM, Augarde R, Fellahi JL, Prin S, Page B, Beauchet A, Jardin F (2001) Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications and prognosis. Crit Care Med 29:1551–1555
16. Jardin F (2003) Ventricular interdependence: how does it impact on hemodynamic evaluation in clinical practice? Intensive Care Med 29:361–363
17. Visner MC, Arentzen CE, O'Conner MJ, Larson EV, Anderson RW (1983) Alterations in left ventricular three-dimensional dynamic geometry and systolic function during acute right ventricular hypertension in the conscious dog. Circulation 67:353–365
18. Goto Y, Yamamoto J, Saito M, Haze K, Sumiyoshi T, Fukami K, Hiramori K (1985) Effects of right ventricular ischemia on left ventricular geometry and the end-diastolic pressure-volume relationship in the dog. Circulation 72:1104–1114
19. Renaud E, Karpati P, Mebazaa A (2002) Acute right ventricular failure: physiology and therapy. In: Vincent J-L (ed) 2002 yearbook of intensive care and emergency medicine Springer, Berlin Heidelberg New York, pp 209–218
20. Taylor RR, Covell JYW, Sonnenblick EH, Ross J (1967) Dependence of ventricular distensibility on filling of the opposite ventricle. Am J Physiol 218:711–718
21. Brookes C, Ravn H, White P, Moeldrup U, Oldershaw P, Redington A (1999) Acute right ventricular dilatation in response to ischemia significantly impairs left ventricular systolic performance. Circulation 100:761–767
22. Santamore WP, Gray LA (1996) Left ventricular contributions to right ventricular systolic function during LVAD support. Ann Thorac Surg 61:350–356
23. Gatecel C, Mebazaa A, Kong R, Guinard N, Kermarrec M, Matéo J, Payen D (1995) Inhaled nitric oxide improves hepatic tissue oxygenation in right ventricular failure: value of hepatic venous oxygen saturation monitoring. Anesthesiology 82:588–590
24. Dhainaut JF, Brunet F, Monsallier JF Villemant D, Devaux JY, Konnon M, De Gournay JM, Armaganidis A, Iotti G, Huyghebaert MF, Lanore JJ (1987) Bedside evaluation of right ventricular performance using a rapid computerized thermodilution method. Crit Care Med 15:148–152
25. Jardin F, Gueret P, Dubourg O, Farcot JC, Margairaz A, Bourdarias J-P (1985) Right ventricular volumes by thermodilution in the adult respiratory distress syndrome. A comparative study using two-dimensional echocardiography as a reference method. Chest 88:34–39
26. Zwissler B (2000) Acute right heart failure. Etiology-pathophysiology-diagnosis-therapy. Anaesthetist 49:788–808

27. Bowers TR, O'Neill WW, Grines C, Pica MC, Safian RD, Goldstein JA (1998) Effect of reperfusion on biventricular function and survival after right ventricular infarction. N Engl J Med 338:933–940
28. Potapov EV, Sodian R, Leobe M, Drew T, Dreysse S, Hetzer R (2001) Revascularization of the occluded right coronary artery during left ventricular assist device implantation. J Heart Lung Transplant 20:918–922
29. Mercat A, Kiehl JLK, Meyer G, Teboul JL, Sors H (1999) Hemodynamics effects of fluid loading in acute massive pulmonary embolism. Crit Care Med 27:540–544
30. Sibbald WJ, Driedger AA (1983) Right ventricular function in acute disease states: pathophysiologic considerations. Crit Care Med 11:339–345
31. Bundgaard H, Boesgaard S, Mortensen SA, Arendrup H, Aldershvile J (1997) Effect of nitroglycerin in patients with increased pulmonary vascular resistance undergoing cardiac transplantation Scand Cardiovasc J 31:339–342
32. Vincent JL, Carlier E, Pinsky MR, Goldstein J, Naeije R, Lejeune P, Brimioulle S, Leclerc JL, Kahn RJ, Primo G (1992) Prostaglandin E1 infusion for right ventricular failure after cardiac transplantation. J Thorac Cardiovasc Surg 103:33–39
33. Packer M (1985) Vasodilator therapy for primary pulmonary hypertension. Limitations and hazards. Ann Intern Med 103:258–270
34. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, Gunther A, Walmrath D, Seeger W, Grimminger F (2002) Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet 360:895–900
35. Langer F, Wendler O, Wilhelm W, Tscholl D, Schafers HJ (2001) Treatment of a case of acute right heart failure by inhalation of iloprost, a long-acting prostacylclin analogue. Eur J Anaestheiol 18:770–773
36. Haraldsson A, Kieler-Jensen N, Ricksten SE (1996) Inhaled prostacyclin for treatment of pulmonary hypertension after cardiac surgery or heart transplantation: a pharmacodynamic study. J Cardiothorac Vasc Anesth 10:864–868
37. Mosquera I, Crespo-Leiro MG, Tabuyo T, Paniagua MJ, Fuente L, Bouzas B, Fojon S, Pastor J, Juffe-Stein A, Castro-Beiras A (2002) Pulmonary hypertension and right ventricular failure after heart transplantation: usefulness of nitric oxide. Transplant Proc 34:166–167
38. Christenson J, Lavoie A, O'Connor M, Bhorade S, Pohlman A, Hall JB (2000) The incidence and pathogenesis of cardiopulmonary deterioration after abrupt withdrawal of inhaled nitric oxide. Am J Respir Crit Care Med 161:1443–1449
39. Borade S, Christenson J, O'Connor M, Lavoie A, Pohlman A, Hall JB (1999) Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med 159:571–579
40. Palhares DB, Figueiredo CS, Moura AJ (1998) Endotracheal inhalatory sodium nitroprusside in severely hypoxic newborns. J Perinat Med 26:219–224
41. De Backer D, Moures JM, Vachiery JL, Leclerc JL, Kahn RJ, Vincent JL (1996) Oxygenation improvement with nitric oxide in right-to-left shunt without significant effects on pulmonary arterial pressure. Chest 110:1361–1363
42. Cholley BP, Guinard N, Mateo J, Payen D (1998) Improvement of extreme hypoxemia during end-stage congenital heart disease using nasal nitric oxide. Anesthesiology 89:1586–1587
43. Lowson SM, Doctor A, Walsh BK, Doorley PA (2002) Inhaled prostacyclin for the treatment of pulmonary hypertension after cardiac surgery. Crit Care Med 30:2762–2764
44. Lowson SM (2002) Inhaled alternatives to nitric oxide. Anesthesiology 96:1504–1513
45. Hoeper MM, Olschewski H, Ghofrani HA, Wilkens H, Winkler J, Borst MM, Niedermeyer J, Fabel H, Seeger W (2000) A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH study group. J Am Coll Cardiol 36:176–182
46. Curtis JJ, McKenney-Knox CA, Wagner-Mann CC (2002) Postcardiotomy centrifugal assist: a single surgeon's experience. Artif Organs 26:994–997
47. Packer M, Leier CV (1987) Survival in congestive heart failure during treatment with drugs with positive inotropic actions. Circulation 75 (Suppl IV): 55–63
48. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, Mallis GI, Sollano JA, Shannon J, Tandon PK, DeMets DL for the PROMISE study Research Group (1991) Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 352:1468–1475
49. The Xamoterol in Severe Heart Failure Study Group (1990) Xamoterol in severe heart failure. Lancet 336:1–6
50. O'Connor CM, Gattis WA, Uretsky BF, Adams KF Jr, McNulty SE, Grossman SH, McKenna WJ, Zannad F, Swedberg K, Gheorghiade M, Califf RM (1999) Continuous intravenous dobut-amine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 138:78–86
51. Unverferth DA, Blanford M, Kates RE, Leier CV (1980) Tolerance to dobutamine after a 72 hour continuous infusion. Am J Med 69:262–266
52. Haikala H, Nissinen E, Etemadzadeh E, Kevijoki J, Linden I-B (1995) Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. J Cardiovasc Pharmacol 25:794–801
53. Ukkonen H, Saraste M, Akkila J, Knuuti MJ, Karanko M, Iida H, Lehikoinen P, Nagren K, Lehtonen L, Voipio-Pulkki LM (2000) Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther 68:522–531
54. Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N (1997) Levosimendan, a novel calcium sensitizer, activates the glibenclamide-sensitive K^+ channel in rat arterial myocytes. Eur J Pharmacol 333:249–259
55. Slawsky MT, Colucci WS, Gottlieb SS (2000) Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 102:2222–2227
56. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L (2002) Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 20:196–202
57. Moiseyev VS, Poder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, Kobalava ZD, Lehtonen LA, Laine T, Nieminen MS, Lie KI (2002) Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J 23:1422–1432

58. Kivikko M, Antila S, Eha J, Lehtonen L, Pentikainen PJ (2002) Pharmacokinetics of levosimendan and its metabolites during and after a 24-hour continuous infusion in patients with sever heart failure. Int J Clin Pharmacol Ther 40:465–471
59. Molloy WD, Lee KY, Girling L, Schick U, Prewitt RM (1984) Treatment of shock in a canine model of pulmonary embolism. Am Rev Respir Dis 130:870–874
60. Ghignone M, Girling L, Prewitt RM (1984) Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. Anesthesiology 60:132–135
61. Hirsch LJ, Rooney MW, Wat SS, Kleinmann B, Mathru M (1991) Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. Chest 100:796–801

M. Piagnerelli
K. Zouaoui Boudjeltia
M. Vanhaeverbeek
J.-L. Vincent

Red blood cell rheology in sepsis

Abstract Changes in red blood cell (RBC) function can contribute to alterations in microcirculatory blood flow and cellular dysoxia in sepsis. Decreases in RBC and neutrophil deformability impair the passage of these cells through the microcirculation. While the role of leukocytes has been the focus of many studies in sepsis, the role of erythrocyte rheological alterations in this syndrome has only recently been investigated. RBC rheology can be influenced by many factors, including alterations in intracellular calcium and adenosine triphosphate (ATP) concentrations, the effects of nitric oxide, a decrease in some RBC membrane components such as sialic acid, and an increase in others such as 2,3 diphosphoglycerate. Other factors include interactions with white blood cells and their products (reactive oxygen species), or the effects of temperature variations. Understanding the mechanisms of altered RBC rheology in sepsis, and the effects on blood flow and oxygen transport, may lead to improved patient management and reductions in morbidity and mortality.

Keywords Erythrocyte · Deformability · Nitric oxide · Sialic acid · Multiple organ failure · Oxygen transport

Introduction

Severe sepsis and septic shock are the commonest causes of death in intensive care units (ICUs), with associated mortality rates of 30–50% [1]. Sepsis is a complex pathophysiological process that involves both alterations in the microcirculation and changes in the biochemical and physiological characteristics of the blood constituents. Microvascular damage plays a crucial role in the impairment of tissue oxygenation that can contribute to multiple organ failure and death [2].

Microcirculatory alterations include slowing of capillary blood flow as a result of decreased perfusion pressure and local arteriolar constriction [2, 3], viscosity alterations [4, 5], and disturbances of red (RBC) and white (WBC) blood cell rheology [6, 7].

Some recent studies [8, 9, 10] have also defined the RBC as a possible oxygen sensor and regulator of vascular tone, opening new perspectives into the pathophysiology of microcirculatory alterations and, perhaps, the treatment of sepsis.

This review evaluates alterations occurring in RBC rheology during sepsis and possible underlying mechanisms. The potential implications of blood transfusion and erythropoietin administration in sepsis will not be discussed.

Major determinants of RBC rheology

Viscosity

Haemorheology is the study of deformation and flow of blood and blood cells. The prime function of blood is transport by flow, and the most important rheological property of blood is its resistance to flow, or viscosity. The definition of viscosity is explained in Fig. 1. Plasma viscosity is about 1.6 times that of water (normal range 1.15–1.35 mPa/s). Blood is a non-Newtonian fluid and

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_42,

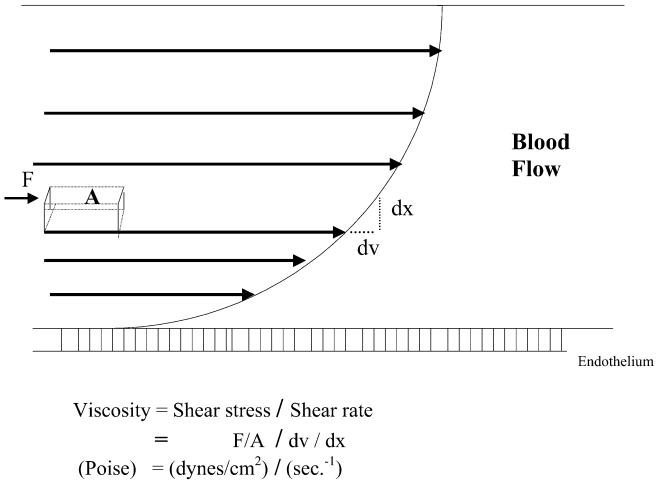


Fig. 1 Blood viscosity. Schematic representation of a vessel lumen. The curved line represents the flow velocity profile in laminar flow. The viscosity (unit: Poise) is expressed as a ratio of shear stress to shear rate, where the shear stress (unit: dynes/cm^2) is the force (*F*) parallel to the direction of flow per unit area of fluid sheared (*A*), and the shear rate (unit: second^{-1}) is the velocity gradient between adjacent layers in laminar flow. [*dv* velocity difference of adjacent fluid laminae, *dx* distance between the fluid laminae (adapted from [5], with permission)]

its viscosity is therefore variable at any given temperature, depending on the shear rate. Haematocrit has a large effect on blood viscosity and blood flow. For example, hyperviscosity syndromes, such as polycythaemia, are associated with profound perfusion problems [11]; in contrast, anaemia favours an increase in cardiac output. In physiological conditions, changes in blood viscosity do not have a pronounced effect on blood flow. However, in low flow states, a reduction in shear rate will cause an increase in viscosity. Blood viscosity, therefore, has the potential to reduce flow under low flow, low shear conditions [3, 4, 5].

When RBCs are added to plasma, blood viscosity increases logarithmically with a linear increase in haematocrit over the range 20–60%. At high shear rates, bulk blood viscosity is low because RBC aggregates are dispersed and deformed into ellipsoids, oriented in parallel with flow streamlines, and with the membrane sliding around its cytoplasm. As shear rates are reduced, blood viscosity rises exponentially. In low flow states, when the shear stress acting on the cell is reduced, the RBC is less deformed; furthermore, the RBCs aggregate to form rouleaux, increasing blood viscosity. In the normal circulation the shear stress is generally sufficient to disperse the rouleaux, allowing RBC deformation and facilitating blood flow [3, 4, 5]. Therefore, the major determinants of whole blood viscosity are shear rate, plasma viscosity, haematocrit, RBC deformability, and RBC aggregation.

It is possible to measure plasma and whole blood viscosity over a wide range of shear rates in a variety of viscometers. Serum viscosity (i.e., plasma viscosity less the effect of fibrinogen) and whole blood viscosity can be measured.

Aggregation

At low shear rates, blood evolves from a low viscosity emulsion to a high viscosity suspension. The electrostatic repulsion of RBC is overcome by the presence of macromolecules which aggregate the cells. In inflammatory states, acute phase proteins (especially fibrinogen and large serum proteins such as a_2 macroglobulin) increase RBC aggregation. Rouleaux of cells bind together in a side-by-side fashion and, together with the continuous uptake of individual cells, networks of larger aggregates are formed.

RBC aggregation is reversible by shear forces. At shear rates of 7–10 s^{-1}, the aggregates in normal blood are dispersed, cells become orientated with flow streamlines, and blood viscosity is reduced as the shear rates increase further. In vitro, this process of aggregation and disaggregation can continue for hours.

In addition to the plasma protein pattern, RBC aggregation is primarily determined by cellular properties; reduction in cell size increases aggregation as does RBC ageing. The haematocrit shows a biphasic effect on red cell aggregation, with a peak effect at around 40–45%.

Conditions of low shear rate in vivo are found primarily in the post-capillary venules. An increase in RBC aggregation would increase blood viscosity at this level [12]. The increased viscosity may promote blood stasis, which may induce local hypoxia and endothelial damage.

There are several methods of estimating RBC aggregation other than low shear rate viscometry, for example, erythrocyte sedimentation rate and direct microscopic observation of aggregation. Microscopic techniques with image analysis have also been developed [13], but the most widely used technique is the light scattering analysis of RBC suspensions that employs light transmission through a RBC suspension to obtain indices of RBC aggregation. This is expressed mainly as the average aggregate size at a certain shear stress.

Deformability

'Cellular deformability' is the term generally used to characterize the RBC's ability to undergo deformation during flow [14]. The deformation response of a RBC to fluid forces is a complex phenomenon that depends on a number of different cell characteristics including membrane material properties [15], cell geometry, and cytoplasmic viscosity [16].

As measures of cellular deformability are dependent on the technique used, quoted values are not comparable.

Methods to measure cellular deformability have been described in detail elsewhere [17, 18]. Briefly, micropipette aspiration provides the most detailed characterization of membrane properties. Single RBCs are aspirated into micropipettes with diameters in the range 1–2 μm; the relationship between the applied negative pressure and the membrane tongue extension is then quantitated. Using ektacytometry, RBCs are subjected to a laminar shear stress field in a cuvette viscometer; the resultant change in cell shape is continuously monitored by laser diffractometry. Unstressed discoid cells generate a circular diffraction pattern. By measuring optical densities at two points along the major and minor axes of the elliptical diffraction pattern, a parameter termed "deformability index" is generated which is a direct measure of cell ellipticity. A numerical value of zero corresponds to nondeformable cells, while increasingly positive values correspond to increasing cellular deformability. The membrane fragmentation assay using the ektacytometer is particularly useful for documenting decreased mechanical integrity of the membrane due to protein defects.

Micropore filtration is limited by the possible occlusion of the filter pores by WBCs [6]. This technique has been replaced by the cell transit analyzer (CTA) as it is insensitive to the presence of WBCs while the passage of individual RBCs are monitored by a computerized system.

Flow cytometry techniques can also be used to appreciate RBC shape, and to study the effect of modifications of osmolality on shape in critically ill patients [19, 20]. The advantage of this technique is that it can provide an easier and more rapid estimation of erythrocyte shape.

RBC Membrane physiology

To undertake oxygen delivery, the RBC must be able to undergo considerable cellular deformation since its diameter (8 μm in humans) far exceeds that of the capillaries (2–3 μm) through which it must pass [14]. The RBC membrane is composed of proteins (52% in weight), lipids (40%), and carbohydrates (8%). Membrane elasticity depends on the structural interactions between the outer plasma membrane and the underlying protein skeleton. The proteins of the RBC membrane are divided into two groups: integral and peripheral (Fig. 2). Integral proteins (glycophorin and Band 3 proteins) are tightly bound to the membrane through hydrophobic interactions lipids in the bilayer [14, 15, 16]. A filamentous network of proteins is anchored to the bilayer by the integral proteins. This network has three principal components: spectrin, actin, and protein 4.1. The peripheral membrane proteins are located on the cytoplasmic surface of the lipid bilayer and can be readily released from the membrane by simple manipulation of the ionic strength of the milieu or variation in the concentrations of other proteins [14].

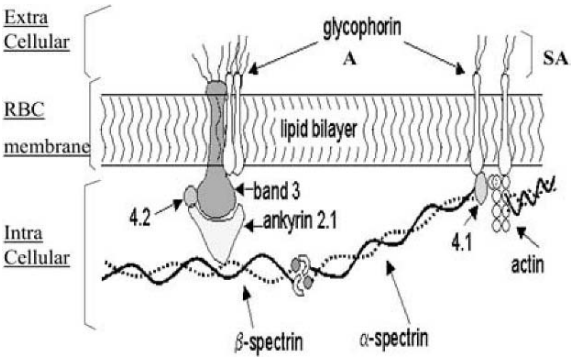


Fig. 2 RBC membrane. Schematic representation of protein orientations in the human RBC. The membrane is composed of a phospholipid membrane bilayer and transmembrane proteins including glycophorin A and Band 3 proteins. Glycophorin A is the major sialoglycoprotein of the RBC. SA bound to glycophorin A is responsible for the negative charge of the RBC membrane. The intracellular compartment (IC) is constituted by spectrin (and subunits), actin, protein 4.1, protein 4.2, and ankyrin

Reversible deformation of the RBC membrane occurs with a change in geometric shape without any change in surface area. With increased deformation, some of the spectrin molecules can attain their maximal linear extension, reaching the limit of reversible deformability [14].

The most abundant and best-studied integral protein of the RBC membrane is glycophorin A. This protein is highly glycosylated, with approximately 60% of its weight being carbohydrate, mostly in the form of 15 O-glycosidically linked tetrasaccharides. The two sialic acid residues (N-acetyl-neuraminic acid; SA) account for the negative electrostatic force on the RBC membrane [14, 15, 16], a necessary feature of the cell's repellent properties. The importance of SA to RBC shape is demonstrated by the observation that neuraminidase-treated cells, which release their membrane SA content, undergo increased aggregation and have a reduced mean curvature [21].

Alterations in microcirculation and blood rheology in sepsis

Sepsis induces profound changes in the microcirculation [2] with loss of capillary density [22], maldistribution of blood flow, increased flow heterogeneity [23], changes in microvascular reactivity [24], and WBC-endothelial cell adhesion and vascular leakage [2].

Microcirculatory dysfunction may be further aggravated by alterations in blood rheology resulting from decreased RBC [2, 6, 12, 25, 26, 27] and WBC deformability [2, 7], RBC aggregation [28, 29] and coagulation disturbances [30]. Interactions with WBCs cause release of oxygen free radicals, stimulating RBC intracellular proteolysis, membrane lipid peroxidation, and nitric oxide

(NO) production. Alterations in RBC membrane (decreased carbohydrate content, alterations of membrane pumps) with increased free calcium concentrations, decreased ATP reserve, and modifications of 2,3 diphosphoglycerate (DPG) concentrations have also been described. Simchon et al. [31] noted that a reduction in RBC deformability in rats led to RBC entrapment in the microcirculation of specific regions (spleen, lung, liver, and femur). This resulted in a reduction in regional blood flow proportional to the number of trapped RBCs.

The role of RBC rheological alterations in sepsis has been investigated relatively recently. Several studies in animals and patients with sepsis have demonstrated decreased RBC deformability, increased aggregation and adhesiveness between WBCs, platelets, and endothelial cells [6, 25, 27, 29, 32]. Moreover, alterations in RBC deformability have been described as an early indicator of infection in trauma patients [33], and as a prognostic factor in canine septic shock [34].

Mechanisms underlying alterations in RBC deformability during sepsis

2,3 diphosphoglycerate (2,3 DPG)

2,3 DPG is one of the most important organic phosphates in the RBC (Fig. 3) as it increases oxygen delivery to the tissues by decreasing the interaction between oxygen and haemoglobin. Hypoxaemia stimulates 2,3 DPG production. Han and colleagues [35] reported an increase in 2,3 DPG in critically ill children, even in the absence of hypoxaemia. This may represent a possible response to illness with increased oxygen unloading to the tissues. However, increased 2,3 DPG can also decrease RBC deformability. Suzuki et al. [36] reported that increasing the 2,3-DPG concentration (by incubating human RBCs with inosine and pyruvate) increased intracellular haemoglobin concentrations (MCHC) and ATP content, and decreased intracellular pH. The deformability of 2,3-DPG-enriched RBC was greatly improved when the MCHC (and thus the internal viscosity) was normalized by suspension in a hypotonic solution, but not when the intracellular pH was altered from 6.5 to 7.5, or when the ATP concentration was adjusted by incubation with various concentrations of adenine, inosine, and glucose (0.6–2.1 mM/cells). Hence, decreased RBC deformability is due in part to the increase in internal viscosity, and in part to the increase in membrane viscoelasticity [36].

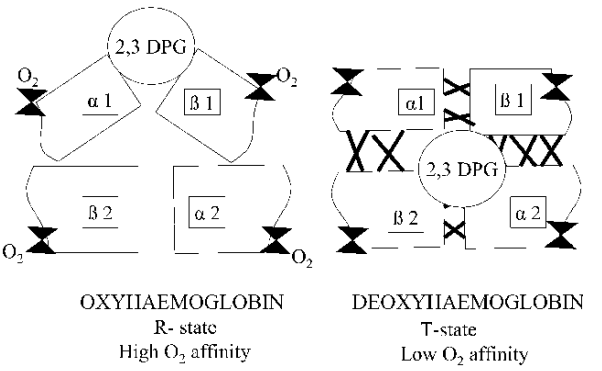


Fig. 3 Role of 2,3 diphosphoglycerate. Diagrammatic representation of the subunit interaction in haemoglobin as O_2 is added. Deoxyhaemoglobin (*right*), with low O_2 affinity, is in the T-state, constrained by salt bridges (*black crosses*) and 2,3 DPG. As O_2 is added in haem (*black double triangles*), the salt bridges are broken (*black dots*), and the 2,3 DPG molecule is expelled, resulting in the R configuration with higher O_2 affinity. As 2,3 DPG lowers the affinity of haemoglobin toward O_2, O_2 transfer from blood to tissues in the microcirculation is increased

Nitric oxide (NO)

RBC and modulation of vascular tone via NO

NO is produced by endothelial cells from L-arginine by constitutive (cNOS) or inducible (iNOS) synthase. In physiological conditions, cNOS plays an essential role in producing small amounts of NO, thus maintaining capillary patency. In sepsis, lipopolysaccharide (LPS) and cytokines such as tumour necrosis factor (TNF) and interferon- (INF-) induce iNOS, resulting in the production of much greater quantities of NO. By its action on vascular smooth muscle, NO causes vasodilatation and increased tissue blood flow, but may also lead to arterial hypotension [37]. In the lung, NO rapidly binds to haemoglobin (T-state, 'tense', low oxygen affinity state, partially nitrosylated), forming a relatively stable haemoglobin-NO complex (R-state, 'relaxed', high oxygen affinity state, ligand-bound). Oxyhaemoglobin (R-state) is thus converted to methaemoglobin and nitrate. NO is released by haemoglobin (R-state) in the peripheral circulation, resulting in opening of the microvasculature [38, 39]. Allosteric transition from the R- to the T-state is triggered by oxygen release in the pre-capillary resistance vessels, which is then followed by release of NO. In the lungs, after eliminating carbon dioxide (CO_2) and H^+, haemoglobin (in the T-state) re-captures oxygen and NO and switches back to the R-state [38, 39].

Sprague and colleagues [40, 41] demonstrated this essential role of RBCs on NO release in isolated perfused rabbit lungs. Based on several observations, they showed that ATP is a key mediator for NO release as RBCs contain large amounts of ATP [42] that are released in response to physiological stimuli [8]. Moreover, ATP stim-

ulates endothelial NO synthesis [43], thereby reducing vascular resistance in isolated lungs; this is prevented by the NO synthase inhibitor NG-nitro-L-arginine methyl ester (L-NAME) [40].

In dogs, ATP is also a mediator of NO release. However, in response to mechanical deformation, dog RBCs release much less ATP than rabbit or human RBCs [41]. This may be related to the much lower ATP concentrations found in dog RBCs compared to rabbits and humans [44].

NO is also a modulator of the membrane properties of RBC although the exact mechanism involved is as yet unclear. By an effect on the membrane RBC Ca^{2+}-ATPase channel, NO may increase free intracellular Ca^{2+} and thus decrease RBC deformability. In blood samples from healthy volunteers, endotoxin induced a significant increase in both intracellular Ca^{2+} concentration (evaluated by a fluorescent membrane probe) and membrane viscosity (anisotropy, evaluated by fluorescence spectrophotometry) [45]. Addition of the NO synthase inhibitor N- monomethyl-arginine (NMA) had no effect in control conditions but prevented the changes induced by endotoxin, suggesting that NO plays a role in intracellular Ca^{2+} homeostasis and erythrocyte membrane deformability in sepsis.

RBCs as producers of NO

Several studies have indicated that RBCs have the capacity to synthesize NO under certain conditions [46, 47]. Jubelin et al. [48] suggested that the RBC possesses all the cellular machinery necessary to synthesize its own NO.

Plasmodium falciparum-infected human RBCs can also produce NO, probably by the activation of iNOS [47]. By this means, RBCs may modulate their membrane deformability and oxygen affinity, and perhaps also contribute to the inflammatory host response by reacting with reactive oxygen species (ROS).

Effect of NO on RBC deformability

Korbut and Gryglewski [49] noted that alterations in deformability of isolated rabbit RBCs depended on the WBC concentration; WBCs decreased RBC deformability when the WBC count was below 1.2 10^6 cells/ml, while higher WBC counts abolished this effect. In the presence of a low WBC count, RBC deformability was increased by NO donors, such as sydnonimine (a metabolite of molsidomine; SIN-1) and sodium nitroprusside, but was reduced by the NO synthase inhibitor L-NAME. In endotoxaemic rats, these same authors [50] noted altered RBC deformability (as measured by shear stress laser diffractometry) associated with increased RBC membrane fragility. L-NAME significantly decreased RBC deformability but did not influence fragility. However, L-NAME administration 10 min prior to endotoxin administration also improved endotoxin-induced fragility. This indicates that NO influences RBC deformability and membrane fragility in the first stages of sepsis, probably by stimulation of cNOS [50].

Bateman et al. [51] recently demonstrated that aminoguanidine, an inhibitor of iNOS, prevented the accumulation of NO within the RBC in a rat model of peritonitis, and also prevented the decrease in RBC deformability. Thus, NO may play a role in modulating the mechanical properties of the RBC in vivo. Whether this is a direct action, with NO interfering with cytoskeletal elements, or indirect, via some intermediate such as peroxynitrite oxidizing cellular proteins [52], is unknown.

RBC calcium (Ca^{2+})

RBC membrane fluidity is dependent upon the maintenance of a normal intracellular Ca^{2+} concentration [53]. This is kept within a narrow range (20–30 nM), some 50,000-fold lower than the external free Ca^{2+} concentration, by a membrane-associated ATPase pump mechanism. In human RBCs, as in most cell types, a rise in cytosolic free Ca^{2+} induces a rapid increase in the potassium permeability by activation of a Ca^{2+}-activated K^+ channel, resulting in membrane hyperpolarization [54].

Increased intracellular Ca^{2+} levels in aged RBC may precipitate their removal from the circulation [53]. Sepsis-associated changes in the RBC membrane may alter pump binding sites, inhibit their function, and disrupt intracellular Ca^{2+} homeostasis [55]. Alterations in the RBC Ca^{2+}-ATPase pump in sepsis remain controversial. Todd and Mollitt [56] reported that intracellular (free cytosolic) RBC Ca^{2+} concentrations (determined by fluorescent spectroscopy) are increased in septic surgical patients as in experimental endotoxemia. RBCs incubated with endotoxin had increased intracellular Ca^{2+} concentrations, but these did not correlate with extracellular Ca^{2+} levels. This phenomenon was not prevented by dantrolene, an inhibitor of intracellular Ca^{2+} release, and only partially prevented by calcium-channel blockade, but it was minimized by adenosine or ATP. It was also partially reversed by post-treatment with ATP, but not with adenosine [56]. These same authors [57] noted in an in vitro study that endotoxin increased intracellular free Ca^{2+} within RBCs but only in the presence of WBCs. Pretreatment of these RBCs with allopurinol (xanthine oxidase inhibitor), superoxide dismutase (free radical scavenger), or pentoxifylline (WBC modulator) significantly limited the rise in intracellular Ca^{2+} concentrations induced by endotoxin.

Ca^{2+} channel blockers are unable to influence the deformability of normal RBCs [58, 59]. In diabetic patients, where intracellular Ca^{2+} are increased, some stud-

ies have demonstrated a beneficial effect of Ca^{2+} channel blockers on RBC deformability, but at concentrations up to ten times higher than those clinically attainable (10^{-8} mol/l) [59]. Further investigations are necessary to fully define the effects of Ca^{2+}-channel blockers on RBC deformability in sepsis.

ATP

RBCs contain millimolar quantities of ATP [44]. These are produced within the cell by membrane-bound glycolytic pathways, and are used to maintain intracellular hydration and electrolyte composition [42]. ATP content is decreased in old RBCs [42], and this is accompanied by a loss of surface membrane SA, which might be a primary factor in the removal of old RBCs by the reticulo-endothelial system.

Bergfeld and Forrester [60] documented that human RBC can release ATP in response to a hypoxic challenge. As ATP binds to receptors on the vascular endothelium, vessel calibre increases and regional blood flow improves [8, 43]. RBCs may act not only as oxygen transporters but also as oxygen sensors able to modify oxygen delivery.

Intracellular RBC ATP levels are decreased in sepsis [56], causing a decrease in energy for the Ca^{2+} RBC membrane pump, thereby increasing RBC intracellular Ca^{2+} and resulting in a decrease in cell deformability. Pretreatment with pentoxifylline may improve RBC deformability through a direct increase in intracellular ATP content [57].

Sialic acid content of the RBC membrane

Decreased RBC SA may be an important mechanism of senescent RBC destruction by the reticulo-endothelial system [61]. Eichelbronner et al. [32] demonstrated that endotoxin promotes adhesion of human RBCs to endothelial cells in vitro, probably by decreasing SA on the RBC membrane, and thereby decreasing the repulsive force between RBCs and the endothelium.

While the effects of SA on RBC aggregation have been well described, the effects of SA on RBC shape remain controversial. We have recently demonstrated a decreased RBC membrane SA content in patients with sepsis that was associated with a modification of RBC shape [62]. Hence, there is a possible link between RBC membrane SA content and RBC shape in sepsis, as is described in other diseases such as diabetes mellitus [63, 64]. Several mechanisms may account for the decrease in SA. There may be increased activity of the SA degrading enzyme, sialidase, either by WBC as has been described in diabetic patients [65], or by the RBC membrane sialidases themselves [66]. Another mechanism could be a direct effect of bacteria upon the RBC [67].

White blood cells (WBC)

Various factors can alter RBC membrane properties including direct contact between RBCs and WBCs [29, 68, 69] or ROS that stimulate intracellular proteolysis and membrane lipid peroxidation [70, 71].

Several studies have reported that WBCs in sepsis have increased rigidity and enhanced aggregation with platelets and RBCs [7, 72, 73]. During inflammation, large numbers of WBCs adhere to or roll along the microvascular endothelium (margination), primarily in the postcapillary venules and only occasionally in the arterioles [13, 29, 74]. In the capillaries, the WBCs usually appear to flow smoothly without rotation. Occasionally, WBCs may impede RBC flow [74]. Berliner et al. [13], using a method involving a slide test and image analysis, demonstrated that both WBC and RBC adhesiveness/aggregation were increased in the peripheral venous blood of septic patients. This phenomenon may impair microvascular flow in sepsis. Moreover, activation of WBCs stimulates multiple mediator networks including the complement, kinin, coagulation and fibrinolytic cascades, along with the release of chemokines, cytokines, soluble receptors, lipid mediators, reactive oxygen species (ROS) and numerous enzymes, including elastase, myeloperoxidase and many proteases [75]. Claster and colleagues [76] demonstrated that ROS released by these activated WBC can attack RBC membranes, causing alterations in lipid and protein structure that may decrease RBC deformability and, ultimately, result in hemolysis. These authors and others also demonstrated a dose-response curve for WBC-mediated lipid peroxidation in RBCs [76, 77].

Reactive oxygen species (ROS)

Sepsis is characterized by increased production of ROS [superoxide anion (O_2^-), hydroxyl radical (OH^-), and hydrogen peroxide H_2O_2)] as well as a decrease in antioxidant defences. Damage occurs when ROS production exceeds the tissues' antioxidant defences [71, 78]. ROS produced by WBCs can also damage haemoglobin and induce haemolysis [76, 77]. Uyesaka et al. [79] demonstrated that RBCs exposed to O_2^- displayed pronounced degradation of membrane proteins (band 3 and spectrin) with formation of new protein bands that can decrease RBC deformability. In sepsis induced by caecal ligation and puncture in rats, Powell et al. [80, 81] demonstrated that the loss of RBC deformability—with increased survival—could be prevented by pre-treatment with the antioxidant a-tocopherol.

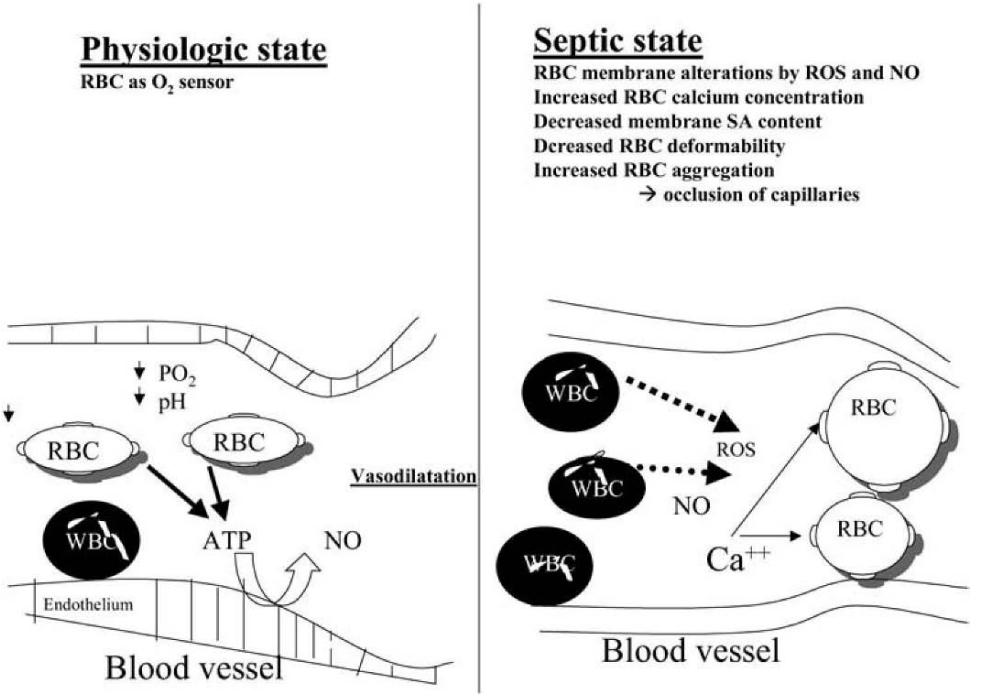


Fig. 4 Schematic relationship between RBCs, WBCs and endothelium. *Left panel:* low PO_2, acidic pH, and decreased RBC deformability lead to ATP liberation from RBCs. These ATP molecules stimulate the endothelial cells to release NO, promoting vasodilatation. *Right panel:* septic conditions with decreased RBC deformability and increased RBC volume with RBC haemolysis. ROS were liberated by the WBC and attack the RBC membrane. The increase in NO induced by sepsis raised the intracellular Ca^{++}. This elevated Ca^{++} impairs the RBC membrane skeleton causing a decline in RBC deformability

Table 1 Some factors influencing RBC deformability

Factor	Potential effects	References
2,3 diphosphoglycerate	Increases tissue O_2 delivery	[35]
	Decreases RBC deformability by increased internal viscosity	[36]
Nitric oxide	Bound by haemoglobin	[37, 38, 39, 40, 41, 42, 43]
	Modulates vascular tone	[39, 40, 41, 43]
	Synthesized by RBC?	[46, 47, 48]
	Modulates RBC membrane properties	[45, 49, 50, 51, 52]
Intracellular calcium	Increased intracellular concentrations by decreased activity of Ca^{++}-ATPase pump	[53, 54, 55, 56, 57]
Adenosine triphosphate	Mediates NO release	[8, 40, 41, 43]
	Maintains intracellular hydration and activity of ionic pumps	[42, 56, 57, 60]
	Released by RBC to improve blood flow	[8, 43, 60]
Sialic acid	Signal recognition for capture by the reticulo-endothelial system.	[61, 64]
	Modifies RBC shape	[62, 63, 64]
	Increases RBC aggregation	[32, 61, 63]
White blood cells	Increase aggregation with RBCs	[7, 13, 29, 68, 69, 72, 73, 74]
	Produce ROS	[70, 71, 75, 76, 77, 79, 80, 81]
Reactive oxygen species (ROS)	Induce degradation of RBC membrane proteins	[71, 76, 77, 78]
	Decrease RBC deformability	[79, 80, 81]
Temperature	Influences in vitro results of RBC deformability	[82, 83, 84, 85]

Effects of temperature

RBC membrane mechanical properties are known to be temperature sensitive. Temperature can have significant effects on RBC deformability. In RBCs from healthy subjects, the elongation index (representing deformability) decreased significantly with a fall in temperature from 37 °C to 5 °C [82]. Artmann and colleagues [83] noted that human RBCs undergo a sudden change from blocking to passing through 1.3±0.2 μm micropipettes at a critical temperature of 36.4±0.3 °C. The authors attributed these findings to an elastomeric transition of haemoglobin from gel-like to fluid, and to an elastomeric transition of membrane proteins such as spectrin [83].

In septic and non-septic rats, Baskurt and Mat [84] noted differences in RBC elongation index only at 37 °C using ektacytometry, while in RBCs from rats incubated with endotoxin (*E. coli*; 75 μg/ml), Jagger et al. [85] not-

ed alterations in RBC deformability measured using the micropipette aspiration technique at 25 °C but not at 37 °C. These authors underline the effect of room temperature measurement on physical membrane properties, which may perhaps exaggerate the differences between normal and perturbed RBCs. The effects of temperature on RBC deformability in sepsis and, in particular, the in vivo relevance of these data clearly require further study. The various factors involved in RBC deformability alterations are summarized in Table 1 and Fig. 4.

Conclusion

Alterations in RBC rheology may contribute to the microvascular injury and impaired oxygen supply seen in sepsis. Multiple factors may be involved including NO and ROS, altered calcium homeostasis, decrease in ATP reserves, increase in intracellular 2,3 DPG, membrane components (sialic acid), and WBC interactions.

Importantly, the RBC is more than an oxygen transporter but also an oxygen sensor and may itself augment blood flow by liberation of ATP and O_2 delivery wherever and whenever the need might arise. New thinking regarding this well-studied cell will lead to a better understanding of the mechanisms of RBC rheological alterations in sepsis and their effect on blood flow and O_2 transport. This may be important in the development of new therapeutic strategies to improve cellular oxygen availability, and thereby reduce organ failure in severe sepsis and septic shock.

References

1. Friedman G, Silva E, Vincent JL (1998) Has the mortality of septic shock changed with time? Crit Care Med 26:2078–2086
2. Hinshaw LB (1996) Sepsis/septic shock: participation of the microcirculation: an abbreviated review. Crit Care Med 24:1072–1078
3. Chien S (1982) Rheology in the microcirculation in normal and low flow states. Adv Shock Res 8:71–80
4. Voerman HJ, Fonk T, Thijs LG (1989) Changes in hemorheology in patients with sepsis or septic shock. Circ Shock 29:219–227
5. Voerman HJ, Groeneveld AB (1989) Blood viscosity and circulatory shock. Intensive Care Med 15:72–78
6. Baskurt OK, Gelmont D, Meiselman HJ (1998) Red blood cell deformability in sepsis. Am J Respir Crit Care Med 157:421–427
7. Yodice PC, Astiz ME, Kurian BM, Lin RY, Rackow EC (1997) Neutrophil rheologic changes in septic shock. Am J Respir Crit Care Med 155:38–42
8. Ellsworth ML, Forrester T, Ellis CG, Dietrich HH (1995) The erythrocyte as a regulator of vascular tone. Am J Physiol 269:H2155–H2161
9. Ellsworth ML (2000) The red blood cell as an oxygen sensor: what is the evidence? Acta Physiol Scand 168:551–559
10. Jagger JE, Bateman RM, Ellsworth ML, Ellis CG (2001) Role of erythrocyte in regulating local O2 delivery mediated by hemoglobin oxygenation. Am J Physiol 280:H2833–H2839
11. Somer T, Meiselman HJ (1993) Disorders of blood viscosity. Ann Med 25:31–39
12. Bishop JJ, Nance PR, Popel AS, Intaglietta M, Johnson PC (2001) Effect of erythrocyte aggregation on velocity profiles in venules. Am J Physiol 280:H222–H236
13. Berliner AS, Shapira I, Rogowski O, Sadees N, Rotstein R, Fusman R, Avitzour D, Cohen S, Arber N, Zeltser D (2000) Combined leukocyte and erythrocyte aggregation in the peripheral venous blood during sepsis. An indication of commonly shared adhesive protein(s). Int J Clin Lab Res 30:27–31
14. Mohandas N (1991) The red blood cell membrane. In: Hoffman R, Benz EJ, Shattil SJ, Furie B, Cohen HJ (eds) Hematology: basis, principles and practice. Churchill-Livingstone, New York, pp 264–269
15. Lux SE (1979) Dissecting the red cell membrane skeleton. Nature 281:426–429
16. Mohandas N, Chasis JA (1993) Red blood cell deformability, membrane material properties and shape: regulation by transmembrane, skeletal and cytosolic proteins and lipids. Semin Hematol 30:171–192
17. Chien S (1977) Principles and techniques for assessing erythrocyte deformability. Blood Cells 3:71–99
18. Mohandas N, Chasis JA, Shohet SB (1983) The influence of membrane skeleton on red cell deformability, membrane material properties, and shape. Semin Hematol 20:225–242
19. Piagnerelli M, Zouaoui Boudjeltia K, Brohee D, Piro P, Vincent JL (2000) Comparison of red cell shape in healthy and septic patients by flow cytometry. Intensive Care Med 26[Suppl 3]: S322 [abstr]
20. Piagnerelli M, Zouaoui Boudjeltia K, Vanhaeverbeek M, Piro P, Vincent JL, Carlier E, Lejeune P (2000) Decrease of red blood cell deformability determined by flow cytometry. Am J Respir Crit Care Med 161:A882 [abstr]
21. Grebe R, Wolff H, Schmid-Schonbein H (1988) Influence of red cell surface charge on red cell membrane curvature. Pflugers Arch 413:77–82
22. Piper RD, Pitt-Hyde M, Li F, Sibbald WJ, Potter RF (1996) Microcirculatory changes in rat skeletal muscle in sepsis. Am J Respir Crit Care Med 154:931–937
23. Lam C, Tyml K, Martin C, Sibbald W (1994) Microvascular perfusion is impaired in a rat model of normotensive sepsis. J Clin Invest 94:2077–2083
24. Tyml K, Yu J, McCormack DG (1998) Capillary and arteriolar responses to local vasodilators are impaired in a rat model of sepsis. J Appl Physiol 84:837–844
25. Astiz ME, DeGent GE, Lin RY, Rackow EC (1995) Microvascular function and rheologic changes in hyperdynamic sepsis. Crit Care Med 23:265–271
26. Powell RJ, Machiedo GW, Rush BFJ (1993) Decreased red blood cell deformability and impaired oxygen utilization during human sepsis. Am Surg 59:65–68
27. Hurd TC, Dasmahapatra KS, Rush BFJ, Machiedo GW (1988) Red blood cell deformability in human and experimental sepsis. Arch Surg 123:217–220

28. Baskurt OK, Temiz A, Meiselman HJ (1997) Red blood cell aggregation in experimental sepsis. J Lab Clin Med 130:183–190
29. Pearson MJ, Lipowsky HH (2000) Influence of erythrocyte aggregation on leukocyte margination in postcapillary venules of rat mesentery. Am J Physiol 279:H1460–H1471
30. Vincent JL (2000) Update on sepsis: pathophysiology and treatment. Acta Clin Belg 55:79–87
31. Simchon S, Jan KM, Chien S (1987) Influence of reduced red cell deformability on regional blood flow. Am J Physiol 253:H898–H903
32. Eichelbronner O, Sielenkamper A, Cepinskas G, Sibbald WJ, Chin-Yee IH (2000) Endotoxin promotes adhesion of human erythrocytes to human vascular endothelial cells under conditions of flow. Crit Care Med 28:1865–1870
33. Langenfeld JE, Livingston DH, Machiedo GW (1991) Red cell deformability is an early indicator of infection. Surgery 110:398–403
34. Chung TW, O'Rear EA, Whitsett TL, Hinshaw LB, Smith MA (1991) Survival factors in a canine septic shock model. Circ Shock 33:178–182
35. Han YY, Murtagh BM, Venkataraman ST (1999) 2,3 diphosphoglycerate increases with critical illness in children. Crit Care Med 27 [Suppl]:A71 [abstr]
36. Suzuki Y, Nakajima T, Shiga T, Maeda N (1990) Influence of 2,3-diphosphoglycerate on the deformability of human erythrocytes. Biochim Biophys Acta 1029:85–90
37. Vincent JL, Zhang H, Szabo C, Preiser JC (2000) Effects of nitric oxide in septic shock. Am J Respir Crit Care Med 161:1781–1785
38. Graf J, Eichelbrönner O, Sibbald WJ (1999) The red blood cell and nitric oxide. In: Vincent JL (ed) Yearbook of intensive care and emergency medicine. Springer, Heidelberg, pp 465–475
39. Jia L, Bonaventura C, Bonaventura J, Stamler JS (1996) S-nitrosohaemoglobin: a dynamic activity of blood involved in vascular control. Nature 380:221–226
40. Sprague RS, Stephenson AH, Dimmitt RA, Weintraub NL, Branch CA, McMurdo L, Lonigro AJ, Weintraub NA (1995) Effect of L-NAME on pressure-flow relationships in isolated rabbit lungs: role of red blood cells. Am J Physiol 269:H1941–H1948
41. Sprague RS, Ellsworth ML, Stephenson AH, Lonigro AJ (1996) ATP: the red blood cell link to NO and local control of the pulmonary circulation. Am J Physiol 271:H2717–H2722
42. Marikovsky Y (1996) The cytoskeleton in ATP-depleted erythrocytes: the effect of shape transformation. Mech Ageing Dev 86:137–144
43. Busse R, Ogilvie A, Pohl U (1988) Vasomotor activity of diadenosine triphosphate and diadenosine tetraphosphate in isolated arteries. Am J Physiol 254:H828–H832
44. Miseta A, Bogner P, Berenyi E, Kellermayer M, Galambos C, Wheatley DN, Cameron IL (1993) Relationship between cellular ATP, potassium, sodium and magnesium concentrations in mammalian and avian erythrocytes. Biochim Biophys Acta 1175:133–139
45. Ismail NH, Cohn EJJ, Mollitt DL (1997) Nitric oxide synthase inhibition negates septic-induced alterations in cytoplasmic calcium homeostasis and membrane dynamics. Am Surg 63:20–23
46. Deliconstantinos G, Villiotou V, Stavrides JC, Salemes N, Gogas J (1995) Nitric oxide and peroxynitrite production by human erythrocytes: a causative factor of toxic anemia in breast cancer patients. Anticancer Res 15:1435–1446
47. Ghigo D, Todde R, Ginsburg H, Costamagna C, Gautret P, Bussolino F, Ulliers D, Giribaldi G, Deharo E, Gabrielli G (1995) Erythrocyte stages of Plasmodium falciparum exhibit a high nitric oxide synthase (NOS) activity and release an NOS-inducing soluble factor. J Exp Med 182:677–688
48. Jubelin BC, Gierman JL (1996) Erythrocytes may synthesize their own nitric oxide. Am J Hypertens 9:1214–1219
49. Korbut R, Gryglewski RJ (1993) Nitric oxide from polymorphonuclear leukocytes modulates red blood cell deformability in vitro. Eur J Pharmacol 234:17–22
50. Starzyk D, Korbut R, Gryglewski RJ (1997) The role of nitric oxide in regulation of deformability of red blood cells in acute phase of endotoxaemia in rats. J Physiol Pharmacol 48:731–735
51. Bateman RM, Jagger JE, Sharpe MD, Ellsworth ML, Mehta S, Ellis CG (2001) Erythrocyte deformability is a nitric oxide-mediated factor in decreased capillary density during sepsis. Am J Physiol 280:H2848–H2856
52. Mallozzi C, Di Stasi AM, Minetti M (1997) Peroxynitrite modulates tyrosine-dependent signal transduction pathway of human erythrocyte band 3. FASEB J 11:1281–1290
53. Shiga T, Sekiya M, Maeda N, Kon K, Okazaki M (1985) Cell age-dependent changes in deformability and calcium accumulation of human erythrocytes. Biochim Biophys Acta 814:289–299
54. Ortiz-Carranza O, Miller ME, Adragna NC, Lauf PK (1997) Alkaline pH and internal calcium increase Na+ and K+ effluxes in LK sheep red blood cells in Cl--free solutions. J Membr Biol 156:287–295
55. Lau YT, Hsieh CC, Liu MS, Hwang TL, Chen MF, Cheng HS (1994) Erythrocyte Ca2+ pump is defective during sepsis. Circ Shock 44:121–125
56. Todd JC, Mollitt DL (1995) Effect of sepsis on erythrocyte intracellular calcium homeostasis. Crit Care Med 23:459–465
57. Todd JC, Mollitt DL (1995) Leukocyte modulation inhibits endotoxin-induced disruption of intracellular calcium homeostasis. J Trauma 39:1148–1151
58. Sowemimo-Coker SO, Debbas NM, Kovacs IB, Turner P (1985) Ex vivo effects of nifedipine, nisoldipine and nitrendipine on filterability of red blood cells from healthy volunteers. Br J Clin Pharmacol 20:152–154
59. Fujita J, Tsuda K, Takeda T, Yu L, Fujimoto S, Kajikawa M, Nishimura M, Mizuno N, Hamamoto Y, Mukai E, Adachi T, Seino Y (1999) Nisoldipine improves the impaired erythrocyte deformability correlating with elevated intracellular free calcium-ion concentration and poor glycaemic control in NIDDM. Br J Clin Pharmacol 47:499–506
60. Bergfeld GR, Forrester T (1992) Release of ATP from human erythrocytes in response to a brief period of hypoxia and hypercapnia. Cardiovasc Res 26:40–47
61. Durocher JR, Payne RC, Conrad ME (1975) Role of sialic acid in erythrocyte survival. Blood 45:11–20
62. Piagnerelli M, Zouaoui Boudjeltia K, Brohee D, Piro P, Carlier E, Vincent JL, Lejeune P, Vanhaeverbeek M (2003) Alterations of red blood cell shape and sialic acid membrane content in septic shock. Crit Care Med (in press)
63. Rogers ME, Williams DT, Niththyananthan R, Rampling MW, Heslop KE, Johnston DG (1992) Decrease in erythrocyte glycophorin sialic acid content is associated with increased erythrocyte aggregation in human diabetes. Clin Sci (Colch) 82:309–313

64. Mazzanti L, Rabini RA, Salvolini E, Tesei M, Martarelli D, Venerando B, Curatola G (1997) Sialic acid, diabetes, and aging: a study on the erythrocyte membrane. Metabolism 46:59–61
65. Chari SN, Nath N (1984) Sialic acid content and sialidase activity of polymorphonuclear leucocytes in diabetes mellitus. Am J Med Sci 288:18–20
66. Chiarini A, Fiorilli A, Di Francesco L, Venerando B, Tettamanti G (1993) Human erythrocyte sialidase is linked to the plasma membrane by a glycosylphosphatidylinositol anchor and partly located on the outer surface. Glycoconj J 10:64–71
67. Milligan TW, Baker CJ, Straus DC, Mattingly SJ (1978) Association of elevated levels of extracellular neuraminidase with clinical isolates of type III group B streptococci. Infect Immun 21:738–746
68. Todd JC, Poulos ND, Davidson LW, Mollitt DL (1993) Role of the leukocyte in endotoxin-induced alterations of the red cell membrane. Second place winner of the Conrad Jobst Award in the Gold Medal paper competition. Am Surg 59:9–12
69. Betticher DC, Keller H, Maly FE, Reinhart WH (1993) The effect of endotoxin and tumour necrosis factor on erythrocyte and leucocyte deformability in vitro. Br J Haematol 83:130–137
70. Machiedo GW, Powell RJ, Rush BFJ, Swislocki NI, Dikdan G (1989) The incidence of decreased red blood cell deformability in sepsis and the association with oxygen free radical damage and multiple-system organ failure. Arch Surg 124:1386–1389
71. Goode HF, Webster NR (1993) Free radicals and antioxidants in sepsis. Crit Care Med 21:1770–1776
72. Drost EM, Kassabian G, Meiselman HJ, Gelmont D, Fisher TC (1999) Increased rigidity and priming of polymorphonuclear leukocytes in sepsis. Am J Respir Crit Care Med 159:1696–1702
73. Kirschenbaum LA, Aziz M, Astiz ME, Saha DC, Rackow EC (2000) Influence of rheologic changes and platelet-neutrophil interactions on cell filtration in sepsis. Am J Respir Crit Care Med 161:1602–1607
74. Schmid-Schonbein GW, Usami S, Skalak R, Chien S (1980) The interaction of leukocytes and erythrocytes in capillary and postcapillary vessels. Microvasc Res 19:45–70
75. Bellingan G (2000) Leukocytes: friend or foe. Intensive Care Med 26[Suppl 1]:S111–S118
76. Claster S, Chiu DT, Quintanilha A, Lubin B (1984) Neutrophils mediate lipid peroxidation in human red cells. Blood 64:1079–1084
77. Davies KJ, Goldberg AL (1987) Oxygen radicals stimulate intracellular proteolysis and lipid peroxidation by independent mechanisms in erythrocytes. J Biol Chem 262:8220–8226
78. Hirayama T, Folmerz P, Hansson R, Jonsson O, Pettersson S, Roberts D, Schersten T (1986) Effect of oxygen free radicals on rabbit and human erythrocytes. Studies on cellular deformability. Scand J Thorac Cardiovasc Surg 20:247–252
79. Uyesaka N, Hasegawa S, Ishioka N, Ishioka R, Shio H, Schechter AN (1992) Effects of superoxide anions on red cell deformability and membrane proteins. Biorheology 29:217–229
80. Powell RJ, Machiedo GW, Rush BFJ, Dikdan G (1991) Oxygen free radicals: effect on red cell deformability in sepsis. Crit Care Med 19:732–735
81. Powell RJ, Machiedo GW, Rush BFJ, Dikdan G (1989) Effect of alpha-tocopherol on red cell deformability and survival in sepsis. Curr Surg 46:380–382
82. Singh M, Stoltz JF (2002) Influence of temperature variation from 5 degrees C to 37 degrees C on aggregation and deformability of erythrocytes. Clin Hemorheol Microcirc 26:1–7
83. Artmann GM, Kelemen C, Porst D, ldt B, Chien S (1998) Temperature transitions of protein properties in human red blood cells. Biophys J 75:3179–3183
84. Baskurt OK, Mat F (2000) Importance of measurement temperature in detecting the alterations of red blood cell aggregation and deformability studied by ektacytometry: a study on experimental sepsis in rats. Clin Hemorheol Microcirc 23:43–49
85. Jagger JE, Ellis CG, Sibbald W, Eichelbrönner O (2001) Measurement temperature plays a pivotal role in the distribution of erythrocyte deformability after LPS. Biorheology 38:439–448

Paul E. Marik
Murugan Raghavan

Stress-hyperglycemia, insulin and immunomodulation in sepsis

Abstract Stress-hyperglycemia and insulin resistance are exceedingly common in critically ill patients, particularly those with sepsis. Multiple pathogenetic mechanisms are responsible for this metabolic syndrome; however, increased release of pro-inflammatory mediators and counter-regulatory hormones may play a pivotal role. Recent data suggests that hyperglycemia may potentiate the pro-inflammatory response while insulin has the opposite effect. Furthermore, emerging evidence suggests that tight glycemic control will improve the outcome of critically ill patients. This paper reviews the pathophysiology of stress hyperglycemia in the critically ill septic patient and outlines a treatment strategy for the management of this disorder.

Keywords Insulin · Glucose · Sepsis · Sepsis syndrome · Critical illness · Insulin resistance · Hyperglycemia

Introduction

In recent decades the reported incidence of sepsis has increased dramatically, largely due to the advancing age of the population, an increased number of invasive procedures being performed and immunosuppressive therapy [1]. In the United States, approximately 750,000 cases of sepsis occur each year, at least 225,000 of which are fatal [2]. Despite the use of antimicrobial agents and advanced life-support care, the case fatality rate for patients with sepsis has remained between 30 and 40% over the past three decades [2, 3].

When the body is challenged by foreign microbial agents homeostatic mechanisms come into play that attempt to rid the body of the foreign agent without damaging the host. This involves the activation of pro- and anti-inflammatory pathways which are tightly controlled and regulated [4]. In most infected persons, the body is able to achieve a balance between pro-inflammatory and anti-inflammatory mediators and homeostasis is restored. In some patients, however, this balance is upset with an excessive pro-inflammatory response resulting in the systemic inflammatory response syndrome (SIRS), multisystem organ dysfunction, and ultimately death [4, 5, 6, 7]. Attempts at down-regulating the pro-inflammatory response with novel agents directed at specific pro-inflammatory mediators has uniformly met with failure [4, 8, 9, 10]. Recent provocative data suggests that tight glycemic control with insulin may the restore the balance between pro-inflammatory and anti-inflammatory mediators and improve the outcome of critically ill patients [11, 12].

In this article we review the physiology of stress hyperglycemia and the immune-modulatory role of insulin in critically ill patients. The reader should be cautioned that many of the studies quoted in our review were performed in non-critically ill patients, many of whom were diabetic. While it is likely that the pathogenetic pathways are similar in both groups of patients, many of these postulates remain unproven in the critical care setting.

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_43, © Springer-Verlag Berlin Heidelberg 2009

Endocrinology of stress

Stress associated with critical illness is characterized by activation of the hypothalamic–pituitary–adrenal (HPA) axis with the release of cortisol from the adrenal gland [13]. Activation of the HPA axis with the release of cortisol is an essential component of the general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis.

In addition to increased cortisol secretion the stress response is characterized by a marked increase in the release of norepinephrine and epinephrine as well as glucagon and growth hormone [14, 15, 16]. Insulin levels are usually normal or decreased, despite peripheral insulin resistance [17, 18, 19]. It has been suggested that insulin release may be suppressed as the result of increased activation of the pancreatic alpha receptors [19]. In addition to causing insulin resistance, interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) inhibit insulin release, an effect which appears to be concentration dependent [20]. The low to normal insulin levels together with insulin resistance in the presence of increased secretion of the counter-regulatory hormones results in stress hyperglycemia (see discussion below).

Glucose transporters and the mechanism of insulin action

Glucose is normally taken up across the cellular membranes by a system of carrier-mediated facilitated transport [21]. Five transporter isoforms exists. Three of the isoforms, GLUT 1, GLUT 2, and GLUT 4, are important for glucose uptake [21]. GLUT 1 can be found in many tissues and is responsible for basal uptake. It has a high affinity for glucose and it ensures transport even under the conditions of hypoglycemia. GLUT 2 mediates uptake and release of glucose by hepatocytes and regulation of glucose-stimulated insulin secretion in pancreas. The GLUT2 transporter ensures that the liver is freely permeable to glucose and that glucose transport is not rate-limiting for hepatic glucose uptake. GLUT 4 isoform is involved in glucose transport in tissues where uptake is mediated by insulin which includes skeletal muscle, cardiac muscle, and adipose tissue. Binding of insulin to cell-surface receptors results in autophosphorylation and activation of an intrinsic tyrosine kinase molecule of the insulin receptor (IR) b-subunit. Activated tyrosine kinase subsequently phosphorylates messenger molecular proteins known as insulin receptor substrates (IRS1 and IRS2). The IRS-1 associates with several proteins including the enzyme phosphatidylinositol (PI) 3-kinase. Physiologically insulin increases glucose uptake into the cell by causing translocation of GLUT 4 from intracellular compartments to the plasma membrane. The signaling enzyme molecule PI-3-kinase is essential for insulin stimulated GLUT 4 translocation [22]. PI-3-kinase also mediates many of the metabolic effects of insulin, including activation of glycogen synthase, protein synthesis, lipogenesis, and the regulation of various genes in insulin-responsive cells including inhibition of phosphoenol pyruvate carboxykinase (PEPCK), the key enzyme of gluconeogenesis.

Mechanisms of stress-induced hyperglycemia and insulin resistance in sepsis

The prevalence of stress hyperglycemia in sepsis and critical illness is difficult to establish due to limited data and variations in the definition of hyperglycemia. Stress hyperglycemia has been previously defined as a plasma glucose above 200 mg/dl [23]; however, in view of the results of the Leuven Intensive Insulin Therapy Trial (see below), stress hyperglycemia should be considered in any critically ill patient with a blood glucose in excess of 110 mg/dl [11]. In a study of septic non-diabetic ICU patients 75% had a baseline blood glucose level above 110 mg/dl [24]. In the Leuven Intensive Insulin Therapy Trial, 12% of patients had a baseline blood glucose above 200 mg/dl; however, 74.5% of patients had a baseline blood glucose above 110 mg/dl, with 97.5% having a recorded blood glucose level above 110 mg/dl sometime during their ICU stay [11].

Changes in whole-body glucose uptake and glucose oxidation in sepsis are complex and may depend on the severity of illness and the stage of the disease. Whole-body glucose uptake and glucose oxidation may be increased in the early stages of sepsis and endotoxemia [25, 26]. This may be the result of cytokine-induced increase in non-insulin mediated glucose uptake by tissues rich in mononuclear phagocytes, including the liver, spleen, ileum, and lung [27, 28]. Enhanced non-insulin mediated glucose uptake appears to result from an increase in the synthesis, concentration or activity of the GLUT1 transporter [29, 30]. With the development of insulin resistance (see below) glucose utilization and oxidation may decrease [25, 31, 32]. Exogenous insulin increases glucose utilization and oxidation; however, non-oxidative disposal (storage) remains impaired [25, 31, 32].

The metabolic milieu in which stress-induced hyperglycemia develops in the critically ill in the absence of pre-existing diabetes mellitus is complex. A combination of several factors, including the presence of excessive counter regulatory hormones such as glucagon, growth hormone, catecholamines, glucocorticoids, and cytokines such as IL-1, IL-6, and TNF-α combined with exogenous administration of catecholamines, dextrose, and nutritional support together with relative insulin deficiency, play an important role [23]. Increased gluconeogenesis combined with hepatic insulin resistance are the major factors

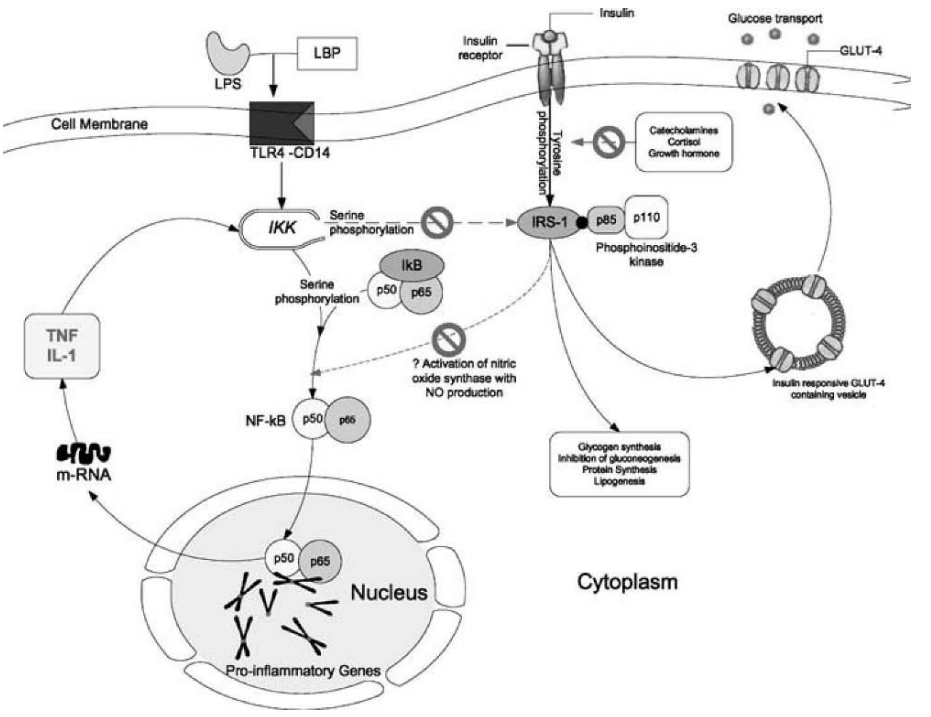


Fig. 1 Postulated interaction between the insulin signaling pathway and activation of the pro-inflammatory cascade in the pathogenesis of stress hyperglycemia of sepsis. *LPS* lipopolysaccharide, *LBP* lipopolysaccharide binding protein, *TLR4* Toll-like receptor 4, *IκB* inhibitor, *IKK* inhibitor κB kinase, *IRS-1*, insulin receptor substrate-1, *IL-1* interleukin-1, *TNF* tumor necrosis factor, *NF-kB* nuclear factor-kappa B

leading to hyperglycemia [33]. Recent human data suggests that hepatic insulin resistence (and PEPCK suppression) remains refractory to intensive insulin therapy [34]. Increased hepatic output of glucose may therefore be more important than peripheral insulin resistance in the genesis of stress hyperglycemia [35]. Gluconeogenic substrates released during stress include lactate, alanine, and glycerol with exogenous glucose failing to suppress gluconeogenesis [16, 36]. Glucagon is the primary hormonal mediator of gluconeogenesis, with septic patients having a significant increase in serum glucagon levels [16]. This effect is mediated by adrenergic stimulation by catecholamines and by cytokines [37]. In addition, cytokines such as TNF-α and IL-1 and catecholamines independently and synergistically promote hepatic glucose production [38, 39].

Sepsis is characterized by marked insulin resistance [19, 25, 31, 32, 40, 41]. The insulin resistance in sepsis is directly proportional to the severity of stress response [19]. During sepsis, insulin induced tyrosine phosphorylation of IRS-1 and subsequent activation of PI-3-kinase is impaired resulting in defective GLUT-4 receptor translocation, diminished glucose uptake, insulin resistance in skeletal muscle, and hepatic insulin resistance [22]. The mechanism whereby sepsis induces these alterations are unknown, but increased levels of TNF-α may play a key role. Aljada and colleagues have demonstrated that in endothelial cells TNF-α causes a reduction of tyrosine phosphorylation and expression of the insulin receptor [42]. TNF-α diminishes insulin-induced IRS-1 tyrosine phosphorylation in hepatocytes and adipocytes and impairs the activation of PI-3 kinase [43, 44, 45, 46]. These alterations of the early steps in insulin action are probably mediated by TNF-α induced IRS-1 serine phosphorylation [43, 46, 47, 48]. Upon serine phosphorylation, IRS1 proteins have a reduced ability to interact with the insulin receptor, to be tyrosine phosphorylated by the insulin receptor and to bind phosphatidylinositol-3 kinase [44, 45].

Recently, Gao and colleagues have demonstrated that activation of the inhibitor κB kinase (IKK) complex is associated with serine phosphorylation of IRS-1 [49]. The IKK is activated by endotoxin via Toll-like receptor 4 (LTR4) as well as by TNF-α and interleukin-1 (IL-1) [50, 51, 52]. The IKK is a serine kinase that controls the activation of nuclear factor-kappa B (NF-κB) a ubiquitous nuclear transcription factor closely associated with the activation of the genes for almost all of the pro-inflammatory mediators [53]. Before activation, NF-κB is bound to inhibitor κB (I κB). This association between I κB and NF-κB results in the cytosolic localiazation of NF-κB. The serine phosphorylation of I κB by the IKK complex results in the degradation of I κB followed by the nuclear translocation of NF κB. The serine phosphorylation of IRS-1 and I κB by IKK may partly explain the insulin resistance noted with activation of the pro-inflammatory cascade (see Fig. 1).

Catecholamines have also been shown to inhibit insulin binding, tyrosine kinase activity, and translocation of GLUT-4 either directly through a receptor or a post-

receptor mechanism [54, 55]. Blockade of α_2 adrenergic receptors has been demonstrated to reduce insulin resistance in septic rats [40]. Glucocorticoids impair insulin mediated glucose uptake in skeletal muscle, by down regulating various signaling proteins with resulting inhibition of translocation of GLUT-4 glucose transporter from its internal membrane stores to the plasma membrane [56]. Growth hormone inhibits the insulin pathway by reducing insulin receptors and impairing its activation through phosphorylation on tyrosine residues [57, 58].

Deleterious effects of hyperglycemia in the critically ill

To some extent the deleterious effects of hyperglycemia in the critically ill are similar to that of actual diabetes, although the time scale obviously differs [59]. Stress hyperglycemia but not pre-existing diabetes has been shown to be associated with a worse outcome following acute myocardial infarction and stroke [60, 61, 62, 63, 64, 65, 66]. The plasma glucose level on admission has been shown to be an independent predictor of prognosis after myocardial infarction [60, 61]. In diabetic patients with acute myocardial infarction, therapy to maintain blood glucose at a level below 215 mg/dl improves outcome [62, 63, 64]. The presence of hyperglycemia following an ischemic or hemorrhagic stroke is associated with a two- to threefold increased mortality and significant impairment in functional recovery [65, 66].

Pro-inflammatory effects

Glucose has been shown to be a powerful pro-inflammatory mediator [67], and tight glucose control below 110 mg/dl with insulin has been shown to exert anti-inflammatory effects in the critically ill patient [68]. The oral administration of 75 g of glucose to healthy volunteers increases reactive oxygen species (ROS) generation by polymorphonuclear leukocytes and mononuclear cells [69]. Similarly, an oral glucose load has been demonstrated to increase plasma IL-8 levels [70]. Chettab and coworkers have demonstrated that hyperglycemia upregulates the IL-8 gene [71]. IL-8 is a potent neutrophil chemoattractant, playing an important role in inflammation [72, 73, 74]. Glucose induces an increase in intranuclear NF-κB, a fall in cytosolic I κB, and an increase in I κB kinase in vivo and in vitro which are pro-inflammatory [75, 76, 77]. Glucose also has been shown to exert pro-thrombotic effects and to increase oxidative stress due to increased lipid peroxidation [78, 79]. Glucose increases the expression and plasma concentration of matrix metalloproteinase-2 (MMP-2) and MMP-9, which aid in spread of inflammation [80]. Acute hyperglycemia reduces endothelial nitric oxide levels, causing abnormal vascular reactivity and organ perfusion [81].

Increased susceptibility to infection

In diabetic patients hyperglycemia has long been known to increase the susceptibility to infections [82]. In critically ill surgical and burn patients tight glycemic control has been demonstrated to reduce the risk of septic morbidity [11, 83, 84, 85]. The in vitro responsiveness of leukocytes stimulated by inflammatory mediators is inversely correlated with glycemic control [86, 87]. Rassias and colleagues demonstrated that tight glycemic control partially prevented the postoperative decrease in neutrophil phagocytic activity [88]. In addition, hyperglycemia has been demonstrated to decrease the oxidative burst of leukocytes [89, 90].

Immune-modulatory role of insulin in sepsis

Besides control of hyperglycemia, insulin has potent acute anti-inflammatory effects. In a group of obese subjects, Dandona and colleagues demonstrated that an infusion of insulin was associated with a significant fall of intranuclear NF-κB, and increase in IκB in mononuclear cells [91]. These changes were associated with a fall in the generation of reactive oxygen species and a fall in the serum levels of soluble intercellular adhesion molecule-1 (sICAM-1), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator inhibitor-1 (PAI-1) [91]. In a similar experiment Aljada et al. demonstrated that insulin decreased expression of the pro-inflammatory transcription factor, early growth response-1 (EGR-1), and this was associated with a significant fall in plasma tissue factor (TF) and PAI-1 levels [92]; thus, while hyperglycemia has pro-thrombotic effects, insulin has anti-thrombotic and fibrinolytic effects by suppressing TF and PAI-1.

One mechanism underlying the anti-inflammatory effect of insulin may be through the release of nitric oxide (NO) from the endothelium. Insulin has been demonstrated to induce an increase in the expression NO synthase (NOS), the enzyme that generates NO [93]. The NO has been demonstrated to down-regulate the expression of endothelial cell adhesion molecules (ECAMs) as well as the pro-inflammatory cytokines [94, 95, 96, 97, 98]. While the anti-inflammatory effects of NO have not been fully delineated, it is thought that NO inhibits the activation of NF-κB. Several authors have demonstrated that NO *S*-nitrosylates a key thiol group in the DNA binding domain of NF-κB p50 and that this is associated with decreased gene transcription and synthesis of NF-κB [96, 99, 100].

NF-κB as a therapeutic target for tight glycemic control

NF-κB is a nuclear transcription factor involved in the regulation of over 150 genes related to inflammation, including TNF-α, IL-1, IL-6, IL-8, cyclooxygenase-2, and inducible nitric oxide synthase [53, 101]. Excessive activation of NF-κB has been identified as a marker of poor prognosis in sepsis [102, 103, 104]. Emerging data suggests that NF-κB may be a therapeutic target for the adjuvant treatment of sepsis [105, 106, 107, 108]. The data cited above suggests that tight glycemic control with insulin may decrease NF-κB activation. This hypothesis is supported by the Leuven Intensive Insulin Therapy Trial in which mannose-binding lectin (MBL) and C-reactive protein (CRP) levels were significantly suppressed by intensive insulin therapy [68].

Intensive insulin therapy in the critically ill

Van Den Berghe et al. in a prospective randomized controlled study involving 1548 patients demonstrated that intensive insulin therapy reduced mortality and morbidity among patients admitted to a surgical critical care unit (the Leuven Intensive Insulin Therapy Trial) [11, 12]. These authors compared an intensive insulin therapy regimen aimed to maintain blood glucose between 80 and 110 mg/dl with conventional treatment in which insulin infusion was only initiated when glucose level was greater than 215 mg/dl and maintenance of glucose between 180 and 200 mg/dl. At 12 months the mortality was 4.6% with the intensive insulin regimen compared with 8.0% in the control group. The benefit was most apparent in patients with greater than 5 days of stay in the intensive care unit. Intensive insulin therapy reduced bloodstream infections by 46%, acute renal failure by 41%, and critical illness poly-neuropathy by 44%. Using multivariate analysis the authors suggested that improved metabolic control, as reflected by normoglycemia, rather than the infused insulin dose per se, was responsible for the beneficial effects of intensive insulin therapy [12]; however, achieving normoglycemia and the administration of insulin are linked, and from the available evidence it appears likely that both factors played a key role in the improved outcome.

The outcome data from the Leuven Intensive Insulin Therapy Trial indicates that there is a dose response curve between the degree of glycemic control and hospital mortality [12] In the long stay patients (>5 days in the ICU) the cumulative hospital mortality was 15% in patients with a mean blood glucose less than 110 mg/dl, 25% in those with a blood glucose between 110 and 150 mg/dl, and 40% in those with a mean blood glucose of greater than 150 mg/dl. In diabetic patients with acute myocardial infarction, therapy to maintain blood glucose at a level below 215 mg/dl improves outcome [62, 63, 64]. This data suggests that even "modest" glycemic control will have an impact on patient outcome. This is very important as in the "real world" it may be very difficult (if not somewhat risky) to attempt to maintain a blood glucose in the range of 80–110 mg/dl. This goal may only be achievable in ICUs with a high nursing-to-patient ratio and close physician supervision. On the other hand, the Leuven study showed that in order to improve morbidity by reducing the incidence of bacteremia, acute renal failure, critical illness polyneuropathy, and transfusion requirements, a blood glucose level of <110 mg/dl was required. Indeed, a blood glucose level of 110–150 mg/dl was not effective on these morbidity measures as compared with >150 mg/d [12]. It is also important to note that in the Leuven Intensive Insulin Therapy Trial all patients received between 200 and 300 g of intravenous glucose on the day of admission followed by parenteral or enteral (or both) nutrition started on the second ICU day. In this study tight early glycemic control was associated with the more rapid improvement of insulin resistance [12]. Based on the results of this study we recommend the initiation of parenteral glucose and enteral nutrition in all ICU patients on the day of ICU admission [109, 110, 111] and the initiation of an insulin infusion in patients with a blood glucose above 150 mg/dl (a threshold of 110 mg/dl may be appropriate in select ICUs). Subcutaneous insulin "sliding scales" are not recommended, at least during the first few days, until the patient's medical condition has stabilized, the blood glucose is well controlled, and the patient has achieved his/her nutritional goal.

Thiazolidinediones are a new class of drugs that are used in the treatment of type-II diabetes mellitus. These drugs reduce insulin resistence through its binding to peroxisome proliferator-activated receptors-λ (PPARλ). Ghanim and colleagues demonstrated that troglitazone caused a significant fall in cellular NF-κB with an increases in I κB in mononuclear cells of diabetic subjects [112]. The changes were associated with a parallel fall in serum levels of TNF-α, sICAM, MCP-1, and PAI-1. While one expects these effects to be useful in chronic situation, it is relevant that these anti-inflammatory were observed within 3–7 days [112, 113]. In an experimental model of acute myocardial infarction, even a single dose of rosiglitazone has been shown to reduce myocardial damage by 50% [114, 115]. Thiazolidinediones may therefore have a role in the metabolic management of patients with sepsis; however, clinical studies are required before these agents can be recommended.

Conclusion

Stress-hyperglycemia and insulin resistance are almost universal findings in patients with sepsis. Multiple pathogenetic mechanisms are responsible for this metabolic

syndrome; however, increased release of pro-inflammatory mediators and counter-regulatory hormones may play a pivotal role. Hyperglycemia per se is pro-inflammatory, whereas insulin has anti-inflammatory properties. Emerging evidence suggests that tight glycemic control with insulin will improve the outcome of critically ill patients.

References

1. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the nited States from 1979 through 2000. N Engl J Med 348:1546–1554
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. Crit Care Med 29:1303–1310
3. Friedman G, Silva E, Vincent JL (1998) Has the mortality of septic shock changed with time? Crit Care Med 26:2078–2086
4. Marik PE, Varon J (2001) Sepsis: state of the art. Dis Mon 47:463–532
5. Bone RC (1996) Sir Isaac Newton, sepsis, SIRS and CARS. Crit Care Med 24:1125–1128
6. Bone RC, Sibbald WJ, Sprung CL (1992) The ACCP-SCCM Consensus Conference on sepsis and organ failure. Chest 101:1481–1483
7. Bone RC, Grodzin CJ, Balk RA (1997) Sepsis: a new hypothesis for pathogenesis of the disease process. Chest 112:235–243
8. Natanson C, Esposito CJ, Banks SM (1998) The sirens' songs of confirmatory sepsis trials: selection bias and sampling error. Crit Care Med 26:1927–1931
9. Eichacker PQ, Parent C, Kalil A, Esposito C, Cui X, Banks SM, Gerstenberger EP, Fitz Y, Danner RL, Natanson C (2002) Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. Am J Respir Crit Care Med 166:1197–1205
10. Dellinger RP (1999) Severe sepsis trials: Why have they failed? Minerva Anestesiol 65:340–345
11. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R (2001) Intensive insulin therapy in critically ill patients. N Engl J Med 345:1359–1367
12. van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P (2003) Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med 31:359–366
13. Marik PE, Zaloga GP (2002) Adrenal insufficiency in the critically ill: a new look at an old problem. Chest 122:1784–1796
14. Hart BB, Stanford GG, Ziegler MG, Lake CR, Chernow B (1989) Catecholamines: study of interspecies variation. Crit Care Med 17:1203–1218
15. van den Berghe G (2002) Neuroendocrine pathobiology of chronic illness. Crit Care Clin 18:509–528
16. Siegel JH, Cerra FB, Coleman B, Giovannini I, Shetye M, Border JR, McMenamy RH (1979) Physiological and metabolic correlations in human sepsis. Invited commentary. Surgery 86:163–193
17. Clowes GH, Martin H, Walji S, Hirsch E, Gazitua R, Goodfellow R (1978) Blood insulin responses to blood glucose levels in high output sepsis and spetic shock. Am J Surg 135:577–583
18. Dahn MS, Jacobs LA, Smith S, Hans B, Lange MP, Mitchell RA, Kirkpatrick JR (1985) The relationship of insulin production to glucose metabolism in severe sepsis. Arch Surg 120:166–172
19. Mizock BA (2001) Alterations in fuel metabolism in critical illness hyperglycemia. Best Pract Res Clin Endocrinol Metab 15:533–551
20. Mehta VK, Hao W, Brooks-Worrell BM, Palmer JP (1994) Low-dose interleukin 1 and tumor necrosis factor individually stimulate insulin release but in combination cause suppression. Eur J Endocrinol 130:208–214
21. Shepard PR, Kahn BB (1999) Glucose transporters and insulin action. Implications for insulin resistance and diabetes mellitus. N Engl J Med 341:248–257
22. Pessin JE, Saltiel AR (2000) Signaling pathways in insulin action: molecular targets of insulin resistance. J Clin Invest 106:165–169
23. McCowen KC, Malhotra A, Bistrian BR (2001) Stress-induced hyperglycemia. Crit Care Clin 17:107–124
24. Frankenfield DC, Omert LA, Badellino MM, Wiles CE, III, Bagley SM, Goodarzi S, Siegel JH (1994) Correlation between measured energy expenditure and clinically obtained variables in trauma and sepsis patients. J Parenter Enteral Nutr 18:398–403
25. Agwunobi AO, Reid C, Maycock P, Little RA, Carlson GL (2000) Insulin resistance and substrate utilization in human endotoxemia. J Clin Endocrinol Metab 85:3770–3778
26. Gelb AW, Bayona NA, Wilson JX, Cechetto DF (2002) Propofol anesthesia compared to awake reduces infarct size in rats. Anesthesiol 96:1183–1190
27. Sakurai Y, Zhang XJ, Wolfe RR (1996) TNF directly stimulates glucose uptake and leucine oxidation and inhibits FFA flux in conscious dogs. Am J Physiol 270:E864–E872
28. Lang CH, Dobrescu C (1991) Gram-negative infection increases noninsulin-mediated glucose disposal. Endocrinology 128:645–653
29. Meszaros K, Lang CH, Bagby GJ, Spitzer JJ (1987) Tumor necrosis factor increases in vivo glucose utilization of macrophage-rich tissues. Biochem Biophys Res Commun 149:1–6
30. Bird TA, Davies A, Baldwin SA, Saklatvala J (1990) Interleukin 1 stimulates hexose transport in fibroblasts by increasing the expression of glucose transporters. J Biol Chem 265:13578–13583
31. Green CJ, Campbell IT, O'Sullivan E, Underhill S, McLaren DP, Hipkin LJ, MacDonald IA, Russell J (1995) Septic patients in multiple organ failure can oxidize infused glucose, but non-oxidative disposal (storage) is impaired. Clin Sci 89:601–609
32. Saeed M, Carlson GL, Little RA, Irving MH (1999) Selective impairment of glucose storage in human sepsis. Br J Surg 86:813–821
33. Mizock BA (1997) Alterations in fuel metabolism in critical illness. Hyperglycemia. In: Ober KP (ed) Endocrinology of critical disease. Humana Press, Totawa, New Jersey, pp 197–297

34. Mesotten D, Delhanty PJ, Vanderhoydonc F, Hardman KV, Weekers F, Baxter RC, Van den BG (2002) Regulation of insulin-like growth factor binding protein-1 during protracted critical illness. J Clin Endocrinol Metab 87:5516–5523
35. Jeevanandam M, Young DH, Schiller WR (1990) Glucose turnover, oxidation, and indices of recycling in severely traumatized patients. J Trauma 30:582–589
36. Cerra FB (1987) Hypermetabolism, organ failure, and metabolic support. Surgery 101:1–14
37. Wolfe RR (1997) Substrate utilization/insulin resistance in sepsis/trauma. Baillieres Clin Endocrinol Metab 11:645–657
38. Petit F, Bagby GJ, Lang CH (1995) Tumor necrosis factor mediates zymosan-induced increase in glucose flux and insulin resistance. Am J Physiol 268:E219–E228
39. Roh MS, Moldawer LL, Ekman LG, Dinarello CA, Bistrian BR, Jeevanandam M, Brennan MF (1986) Stimulatory effect of interleukin-1 upon hepatic metabolism. Metabolism 35:419–424
40. Lang CH (1992) Sepsis-induced insulin resistance in rats is mediated by a beta-adrenergic mechanism. Am J Physiol 263:E703–E711
41. Chambrier C, Laville M, Rhzioual BK, Odeon M, Bouletreau P, Beylot M (2000) Insulin sensitivity of glucose and fat metabolism in severe sepsis. Clin Sci 99:321–328
42. Aljada A, Ghanim H, Assian E, Dandona P (2002) Tumor necrosis factor-alpha inhibits insulin-induced increase in endothelial nitric oxide synthase and reduces insulin receptor content and phosphorylation in human aortic endothelial cells. Metabolism 51:487–491
43. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM (1996) IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 271:665–668
44. Kanety H, Feinstein R, Papa MZ, Hemi R, Karasik A (1995) Tumor necrosis factor alpha-induced phosphorylation of insulin receptor substrate-1 (IRS-1). Possible mechanism for suppression of insulin-stimulated tyrosine phosphorylation of IRS-1. J Biol Chem 270:23780–23784
45. Paz K, Hemi R, LeRoith D, Karasik A, Elhanany E, Kanety H, Zick Y (1997) A molecular basis for insulin resistance. Elevated serine/threonine phosphorylation of IRS-1 and IRS-2 inhibits their binding to the juxtamembrane region of the insulin receptor and impairs their ability to undergo insulin-induced tyrosine phosphorylation. J Biol Chem 272:29911–29918
46. Nunes AL, Carvalheira JB, Carvalho CR, Brenelli SL, Saad MJ (2001) Tissue-specific regulation of early steps in insulin action in septic rats. Life Sci 69:2103–2112
47. Hotamisligil GS, Budavari A, Murray D, Spiegelman BM (1994) Reduced tyrosine kinase activity of the insulin receptor in obesity-diabetes. Central role of tumor necrosis factor-alpha. J Clin Invest 94:1543–9
48. Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM (1994) Tumor necrosis factor alpha inhibits signaling from the insulin receptor. Proc Natl Acad Sci USA 91:4854–4858
49. Gao Z, Hwang D, Bataille F, Lefevre M, York D, Quon MJ, Ye J (2002) Serine phosphorylation of insulin receptor substrate 1 by inhibitor kappa B kinase complex. J Biol Chem 277:48115–48121
50. Gay NJ, Keith FJ (1991) Drosophila Toll and IL-1 receptor. Nature 351:355–356
51. Belvin MP, Anderson KV (1996) A conserved signaling pathway: the Drosophila toll-dorsal pathway. Annu Rev Cell Develop Biol 12:393–416
52. Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, Takeda K, Akira S (1999) Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. J Immunol 162:3749–3752
53. Barnes PJ, Karin M (1997) Nuclear factor-kB-A pivotal transcription factor in chronic inflammatory diseases. N Engl J Med 336:1066–1071
54. Chiasson JL, Shikama H, Chu DT, Exton JH (1981) Inhibitory effect of epinephrine on insulin-stimulated glucose uptake by rat skeletal muscle. J Clin Invest 68:706–713
55. Haring H, Kirsch D, Obermaier B, Ermel B, Machicao F (1986) Decreased tyrosine kinase activity of insulin receptor isolated from rat adipocytes rendered insulin-resistant by catecholamine treatment in vitro. Biochem J 234:59–66
56. Dimitriadis G, Leighton B, Parry-Billings M, Sasson S, Young M, Krause U, Bevan S, Piva T, Wegener G, Newsholme EA (1997) Effects of glucocorticoid excess on the sensitivity of glucose transport and metabolism to insulin in rat skeletal muscle. Biochem J 321:707–712
57. Smith TR, Elmendorf JS, David TS, Turinsky J (1997) Growth hormone-induced insulin resistance: role of the insulin receptor, IRS-1, GLUT-1, and GLUT-4. Am J Physiol 272:E1071–E1079
58. Dominici FP, Cifone D, Bartke A, Turyn D (1999) Alterations in the early steps of the insulin-signaling system in skeletal muscle of GH-transgenic mice. Am J Physiol 277:E447–E454
59. Khaodhiar L, McCowen K, Bistrian B (1999) Perioperative hyperglycemia, infection or risk? Curr Opin Clin Nutr Metab Care 2:79–82
60. Norhammar AM, Ryden L, Malmberg K (1999) Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. Diabetes Care 22:1827–1831
61. Zindrou D, Taylor KM, Bagger JP (2001) Admission plasma glucose: an independent risk factor in nondiabetic women after coronary artery bypass grafting. Diabetes Care 24:1634–1639
62. Malmberg K, Norhammar A, Wedel H, Ryden L (1999) Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation 99:2626–26232
63. Malmberg K (1997) Prospective randomised study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. Br Med J 314:1512–1515
64. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L (1995) Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 26:57–65

65. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC (2001) Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 32:2426–2432
66. Woo J, Lam CW, Kay R, Wong AH, Teoh R, Nicholls MG (1990) The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. Arch Neurol 47:1174–1177
67. Dandona P, Aljada A, Bandyopadhyay A (2003) The potential therapeutic role of insulin in acute myocardial infarction in patients admitted to intensive care and in those with unspecified hyperglycemia. Diabetes Care 26:516–519
68. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, van den Berghe G (2003) Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. J Clin Endocrinol Metab 88:1082–1088
69. Mohanty P, Hamouda W, Garg R, Aljada A, Ghanim H, Dandona P (2000) Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. J Clin Endocrinol Metab 85:2970–2973
70. Straczkowski M, Dzienis-Straczkowska S, Stepien A, Kowalska I, Szelachowska M, Kinalska I (2002) Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-alpha system. J Clin Endocrinol Metab 87:4602–4606
71. Chettab K, Zibara K, Belaiba SR, McGregor JL (2002) Acute hyperglycaemia induces changes in the transcription levels of 4 major genes in human endothelial cells: macroarrays-based expression analysis. Thromb Haemost 87:141–148
72. Standiford TJ, Kunkel SL, Greenberger MJ, Laichalk LL, Strieter RM (1996) Expression and regulation of chemokines in bacterial pneumonia. J Leukoc Biol 59:24–28
73. Hack CE, Aarden LA, Thijs LG (1997) Role of cytokines in sepsis. Adv Immunol 66:101–195
74. Multz AS, Cohen R (2003) Systemic response to pneumonia in the critically ill patient. Semin Resp Infect 18:68–71
75. Aljada A, Ghanim H, Mohanty P, Hofmeyer D, Tripathy D, Dandona P (2002) Glucose activates nuclear factor kappa B pathway in mononuclear cells (MNC) and induces an increase in p47phox. subunit in MNC membranes [Abstract]. Diabetes 51 (Suppl 2):A537
76. Yorek MA, Dunlap JA (2002) Effect of increased concentration of D-glucose or L-fucose on monocyte adhesion to endothelial cell monolayers and activation of nuclear factor-kappaB. Metabolism 51:225–234
77. Guha M, Bai W, Nadler JL, Natarajan R (2000) Molecular mechanisms of tumor necrosis factor alpha gene expression in monocytic cells via hyperglycemia-induced oxidant stress-dependent and -independent pathways. J Biol Chem 275:17728–17739
78. Ceriello A, Bortolotti N, Motz E, Pieri C, Marra M, Tonutti L, Lizzio S, Feletto F, Catone B, Taboga C (1999) Meal-induced oxidative stress and low-density lipoprotein oxidation in diabetes: the possible role of hyperglycemia. Metabolism 48:1503–1508
79. Ceriello A (1993) Coagulation activation in diabetes mellitus: the role of hyperglycaemia and therapeutic prospects. Diabetologia 36:1119–1125
80. Aljada A, Ghanim H, Mohanty P, Syed T, Dandona P (2003) Glucose intake induces an increase in AP-1 and Egr-1 in mononuclear cells and plasma matrix metalloproteinases and tissue factor (TF) concentrations. J Clin Endocrinol Metab
81. Giugliano D, Marfella R, Coppola L, Verrazzo G, Acampora R, Giunta R, Nappo F, Lucarelli C, D'Onofrio F (1997) Vascular effects of acute hyperglycemia in humans are reversed by L-arginine. Evidence for reduced availability of nitric oxide during hyperglycemia. Circulation 95:1783–1790
82. Pozzilli P, Leslie RD (1994) Infections and diabetes: mechanisms and prospects for prevention. Diabet Med 11:935–941
83. Mowlavi A, Andrews K, Milner S, Herndon DN, Heggers JP (2000) The effects of hyperglycemia on skin graft survival in the burn patient. Ann Plast Surg 45:629–632
84. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A (1999) Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 67:352–360
85. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A (1997) Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann Thorac Surg 63:356–361
86. McManus LM, Bloodworth RC, Prihoda TJ, Blodgett JL, Pinckard RN (2001) Agonist-dependent failure of neutrophil function in diabetes correlates with extent of hyperglycemia. J Leukoc Biol 70:395–404
87. Evans TW (2001) Hemodynamic and metabolic therapy in critically ill patients. N Engl J Med 345:1417–1418
88. Rassias AJ, Marrin CA, Arruda J, Whalen PK, Beach M, Yeager MP (1999) Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. Anesth Analg 88:1011–1016
89. Nielson CP, Hindson DA (1989) Inhibition of polymorphonuclear leukocyte respiratory burst by elevated glucose concentrations in vitro. Diabetes 38:1031–1035
90. Kwoun MO, Ling PR, Lydon E, Imrich A, Qu Z, Palombo J, Bistrian BR (1997) Immunologic effects of acute hyperglycemia in nondiabetic rats. J Parenter Enteral Nutr 21:91–95
91. Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S (2001) Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? J Clin Endocrinol Metab 86:3257–3265
92. Aljada A, Ghanim H, Mohanty P, Kapur N, Dandona P (2002) Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. J Clin Endocrinol Metab 87:1419–1422
93. Aljada A, Dandona P (2000) Effect of insulin on human aortic endothelial nitric oxide synthase. Metabolism 49:147–150
94. Peng HB, Spiecker M, Liao JK (1998) Inducible nitric oxide: an autoregulatory feedback inhibitor of vascular inflammation. J Immunol 161:1970–1976
95. Spiecker M, Darius H, Kaboth K, Hubner F, Liao JK (1998) Differential regulation of endothelial cell adhesion molecule expression by nitric oxide donors and antioxidants. J Leukoc Biol 63:732–739

96. Spiecker M, Peng HB, Liao JK (1997) Inhibition of endothelial vascular cell adhesion molecule-1 expression by nitric oxide involves the induction and nuclear translocation of IkappaBalpha. J Biol Chem 272:30969–30974
97. Meldrum DR, McIntyre RC, Sheridan BC, Cleveland JC Jr, Fullerton DA, Harken AH (1997) L-arginine decreases alveolar macrophage proinflammatory monokine production during acute lung injury by a nitric oxide synthase-dependent mechanism. J Trauma 43:888–893
98. Laroux FS, Lefer DJ, Kawachi S, Scalia R, Cockrell AS, Gray L, van der Heyde H, Hoffman JM, Grisham MB (2000) Role of nitric oxide in the regulation of acute and chronic inflammation. Antioxidants Redox Signaling 2:391–396
99. Torre A de la, Schroeder RA, Punzalan C, Kuo PC (1999) Endotoxin-mediated S-nitrosylation of p50 alters NF-kappa B-dependent gene transcription in ANA-1 murine macrophages. J Immunol 162:4101–4108
100. Walley KR, McDonald TE, Higashimoto Y, Hayashi S (1999) Modulation of proinflammatory cytokines by nitric oxide in murine acute lung injury. Am J Respir Crit Care Med 160:698–704
101. Pahl HL (1999) Activators and target genes of rel/NF-kappaB transcription factors. Oncogene 18:6853–6866
102. Bohrer H, Qiu F, Zimmermann T, Zhang Y, Jllmer T, Mannel D, Bottiger BW, Stern DM, Waldherr R, Saeger HD, Ziegler R, Bierhaus A, Martin E, Nawroth PP (1997) Role of NFkappaB in the mortality of sepsis. J Clin Invest 100:972–985
103. Arnalich F, Garcia-Palomero E, Lopez J, Jimenez M, Madero R, Renart J, Vazquez JJ, Montiel C (2000) Predictive value of nuclear factor kappaB activity and plasma cytokine levels in patients with sepsis. Infect Immunol 68:1942–1945
104. Paterson RL, Galley HF, Dhillon JK, Webster NR (2000) Increased nuclear factor kappa B activation in critically ill patients who die. Crit Care Med 28:1047–1051
105. Marik PE (2002) Nuclear factor-kappaB inhibition in sepsis: steroids versus specific nuclear factor-kappaB inhibitors? Crit Care Med 30:2393–2394
106. Christman JW, Lancaster LH, Blackwell TS (1998) Nuclear factor kappa B: a pivotal role in the systemic inflammatory response syndrome and new target for therapy. Intensive Care Med 24:1131–1138
107. Fink MP (2003) Nulcear factor-kB: Is it a therapeutic target for the adjuvant treatment of sepsis. Crit Care Med 31:2400–2402
108. Liu SF, Ye X, Malik AB (1999) Inhibition of NF-kappaB activation by pyrrolidine dithiocarbamate prevents In vivo expression of proinflammatory genes. Circulation 100:1330–1337
109. Marik PE, Zaloga G (2003) Gastric vs post-pyloric feeding? A systematic review. Intensive Care Med
110. Marik PE, Zaloga GP (2001) Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med 29:2264–2270
111. Marik PE, Pinsky MR (2003) Death by total parenteral nutrition. Intensive Care Med 29:867–869
112. Ghanim H, Garg R, Aljada A, Mohanty P, Kumbkarni Y, Assian E, Hamouda W, Dandona P (2001) Suppression of nuclear factor-kappaB and stimulation of inhibitor kappaB by troglitazone: evidence for an anti-inflammatory effect and a potential antiatherosclerotic effect in the obese. J Clin Endocrinol Metab 86:1306–1312
113. Aljada A, Garg R, Ghanim H, Mohanty P, Hamouda W, Assian E, Dandona P (2001) Nuclear factor-kappaB suppressive and inhibitor-kappaB stimulatory effects of troglitazone in obese patients with type 2 diabetes: evidence of an antiinflammatory action? J Clin Endocrinol Metab 86:3250–3256
114. Yue Tl TL, Chen J, Bao W, Narayanan PK, Bril A, Jiang W, Lysko PG, Gu JL, Boyce R, Zimmerman DM, Hart TK, Buckingham RE, Ohlstein EH (2001) In vivo myocardial protection from ischemia/reperfusion injury by the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone. Circulation 104:2588–2594
115. Wayman NS, Hattori Y, McDonald MC, Mota-Filipe H, Cuzzocrea S, Pisano B, Chatterjee PK, Thiemermann C (2002) Ligands of the peroxisome proliferator-activated receptors (PPAR-gamma and PPAR-alpha) reduce myocardial infarct size. FASEB J 16:1027–1040

Ioanna Dimopoulou
Stylianos Tsagarakis

Hypothalamic-pituitary dysfunction in critically ill patients with traumatic and nontraumatic brain injury

Abstract *Background:* A significant number of studies have shown that critically ill patients with brain injury (BI) frequently exhibit abnormal pituitary hormonal responses during the immediate postinjury period. *Discussion:* The elucidation of endocrine alterations depends on the criteria used, the diagnostic tests applied, and the timing of testing in relation to BI. The pattern of the detected hormonal abnormalities shows considerable variability. Altered endocrine responses are due mostly to hypothalamic changes rather than to pituitary dysfunction. Several studies have examined the correlation between hormonal alterations and BI severity, but the results are inconsistent. Furthermore, it remains currently unclear whether and how pituitary abnormalities adversely affect the clinical course of BI patients during the period of critical illness. On the basis of current knowledge, with the exception of clinically significant relative adrenal deficiency and diabetes insipidus, the other endocrine alterations do not seem to require any therapeutic intervention in severely ill BI patients. It is also uncertain whether hormonal abnormalities detected in the early post-BI period persist for the rest of these patients' lives. *Conclusions:* In view of current evidence indicating a high incidence of pituitary dysfunction even years following BI it is recommended that repetition of endocrine evaluation should be performed during the rehabilitation phase in all patients.

Keywords Brain injury · Critical illness · Endocrine alterations · Treatment · Outcome · Recovery

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in young adults [1]. Nontraumatic brain injury (BI) includes ischemic stroke, intracerebral hemorrhage, and aneurysmal subarachnoid hemorrhage (SAH) and constitutes a major public-health burden [2]. Advanced life support in the intensive care unit may be needed in a number of BI patients [3].

Pituitary function is an important regulator of a variety of adaptive responses that allow survival during critical states of any type. The mechanisms regulating pituitary hormone secretion are located within the hypothalamus and the brainstem; consequently acute BI as a result of trauma, stroke, or aneurysmal SAH more than any other type of severe illness might be expected to modify the neuroendocrine responses. Autopsy studies show that more than two-third of patients dying of severe head injury have structural abnormalities in the hypothalamic-pituitary region [4]. Therefore it is not surprising that over the past few years pituitary dysfunction has been increasingly reported in patients with TBI [5, 6, 7].

In this review we first briefly discuss the anatomy of the hypothalamic-pituitary axis and the pathophysiology of pituitary dysfunction along with the endocrinology of the normal stress response. Thereafter we outline the existing data regarding the frequency and pattern of pituitary dysfunction in critically ill patients with TBI and

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_44,

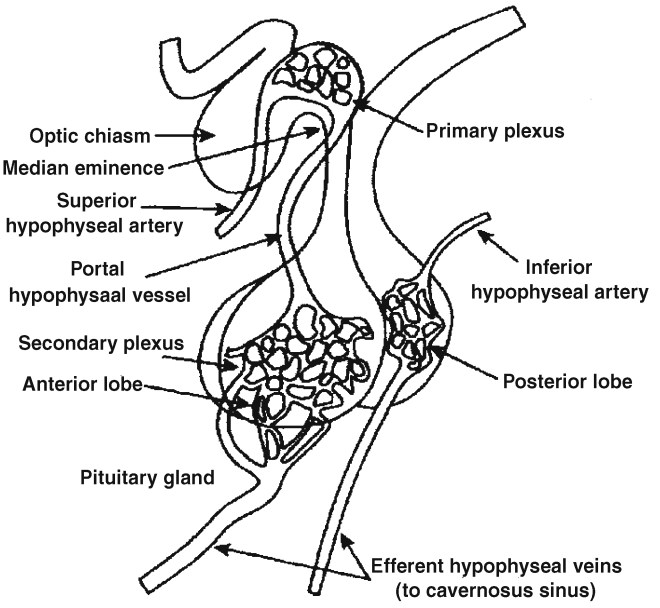


Fig. 1 Anatomy of the hypothalamic-pituitary axis [8]

nontraumatic BI and the clinical relevance of these abnormalities. For this the PubMed search strategy "brain injury and endocrine alterations" was used. Case reports and investigations with a small number of patients (less than five) were excluded.

Anatomy of the hypothalamic-pituitary axis and pathophysiology of pituitary dysfunction following brain injury

The anatomy of the axis is shown in Fig. 1 [8]. The hypothalamus is a structure formed by the anterior and inferior parts of the walls of the third ventricle. It is attached to the pituitary via the stalk, which is derived from the median eminence, a region of the floor of the third ventricle. The median eminence receives the endings of hypothalamic neurons, which produce releasing and inhibiting factors controlling the function of the anterior pituitary lobe. The pituitary is constructed by two parts, the anterior lobe, or adenohypophysis, and the posterior lobe, or neurohypophysis. The adenohypophysis is divided into three regions: (a) the pars distalis, which comprises the major portion of the anterior lobe, (b) the pars intermedia, and (c) the pars tuberalis. The blood supply of the hypothalamus is provided from small branches of all arteries of the circle of Willis. Arterial supply to the anterior pituitary lobe, median eminence, and stalk is derived from paired superior hypophyseal arteries. These arteries form the primary vascular plexus, and converge into venules to form the long and short hypophyseal portal veins. These veins descend to the pars tuberalis and pars distalis of the anterior lobe, where a secondary plexus of sinusoidal capillaries is formed. The long portal veins pass through the diaphragma sella, being thus vulnerable to mechanical compression from brain or pituitary swelling or direct stalk injury. In contrast, the short portal veins originate below the diaphragma sella. Thus the anterior pituitary lobe, particularly its lateral aspects, receives its blood supply indirectly after passage through the median eminence and portal vessels. Consequently any interruption of the portal vessels can result in anterior pituitary dysfunction. In contrast, the neurohypophysis receives a direct arterial blood supply from the inferior hypophyseal arteries.

There are several ways by which BI may adversely affect pituitary function. Direct or indirect (i.e., diffuse brain swelling) mechanical trauma to the hypothalamus, pituitary gland, stalk or vessels is one possible explanation [4, 5, 6]. Functional alterations may also affect pituitary hormone levels. In this context, drugs (opiates, sedatives, antiepileptics, or corticosteroids) have been implicated [9, 10]. During acute BI cytokines, such as tumor necrosis factor α, interleukin 1, and interleukin 6, are produced in large amounts [11]. These may influence hormone levels by exerting stimulatory and/or inhibitory effects [12]. Finally, pituitary dysfunction has been linked to secondary cerebral insults, including hypotension and hypoxemia [13].

Endocrinology of the normal stress response

The endocrinology of the normal stress response is presented in Fig. 2 [14, 15]. The body reacts to hostile conditions by complex physiological and behavioral central nervous system and peripheral adaptive responses. The brain, particularly the hippocampus and amygdala, is intimately involved in the stress response. The stress response is mediated mainly by the sympathoadrenal system (SAS), which includes the sympathetic nervous system (SNS) and the adrenal medulla, and by the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis and the SAS are functionally related. Activation of SAS results to secretion of epinephrine and norepinephrine from the adrenal medulla and to an increased production of interleukin 6. Activation of the HPA axis involves increased secretion in the hypothalamus of corticotropin-releasing hormone (CRH) and arginine vasopressin, which enhances CRH activity. CRH stimulates the production of corticotropin (ACTH), causing the adrenal cortex to produce more cortisol and dehydroepiadnrosterone; in addition, CRH activates the SAS and SNS. During stress the growth, reproductive and thyroid axes are inhibited at many levels. Glucocorticoids suppress the secretion of growth hormone (GH) and thyroid-stimulating hormone (TSH) and exert an inhibitory effect on the pituitary gonadotrophs and the gonads [16]. These adaptations are initially protective for the human body, how-

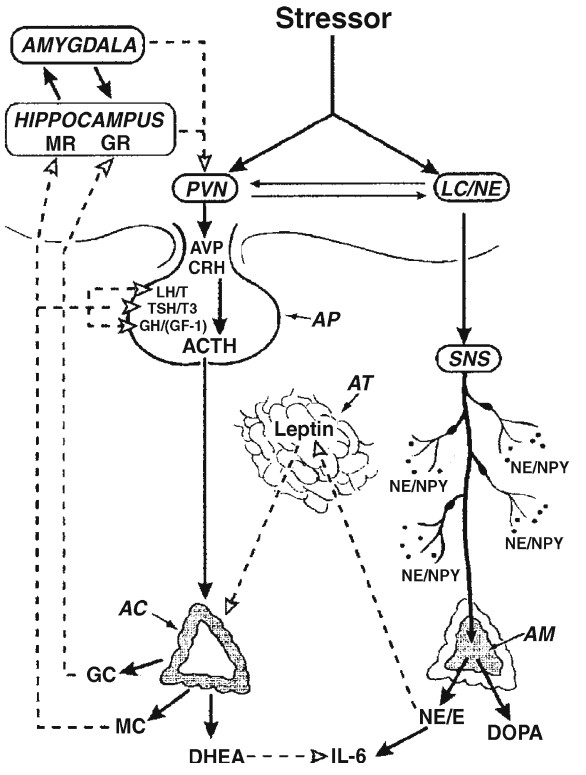


Fig. 2 Endocrinology of the normal stress response. *Straight lines* Stimulation; *dashed lines* inhibition; *PVN* paraventricular nucleus; *AVP* arginine vasopressin; *CRH* corticotropin-releasing hormone; *ACTH* corticotropin; *AP* anterior pituitary; *AC* adrenal cortex; *GC* glucocorticoids; *MC* mineralocorticoids; *DHEA* dehydroepieandrosterone; *LH/T* luteinizing hormone/testosterone; *TSH/T_3* thyrotropin/triiodothyronine; *GH/IGF-1* growth hormone/insulin-like growth factor 1; *MR* mineralocorticoid receptors; *GR* glucocorticoid receptors; *LC/NE* locus ceruleus/norepinephrine; *SNS* sympathetic nervous system; *NPY* neuropeptide Y; *AM* adrenal medulla; *E* epinephrine; *IL-6* interleukin-6; *AT* adipose tissue [14, 15]

ever, if inadequate or excessive they may damage health, causing endocrine, metabolic, autoimmune, and psychiatric disturbances [14, 15, 16].

Anterior pituitary dysfunction in brain injury

Anterior pituitary dysfunction in critically ill patients with TBI

In recent years TBI has been increasingly recognized as a cause of neuroendocrine dysfunction [5, 6]. For example, TBI is considered as one of the causes of adult-onset hypopituitarism [7]. Several studies have investigated the anterior pituitary function in TBI patients during the period of critical illness (Table 1) [17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39].

HPA axis

The HPA axis status is probably the most extensively investigated endocrine function in acute or critically ill TBI patients [18, 20, 27, 31, 32, 34, 35, 36, 37, 38, 39]. Normally patients present with high cortisol levels [18, 20, 28, 32, 34, 35]. These may persist up to 15 days after the trauma [35] and are essential in maintaining vascular tone and endothelial integrity and in potentiating the vasoconstrictor actions of catecholamines [40]. Initially the increase in cortisol is mediated by ACTH [34]. Later other substances, possibly cytokines or catecholamines, act as mediators [12]. The diurnal variation in cortisol may be preserved or abolished [18, 39]. The administration of dexamethasone results in a decrease in plasma cortisol, suggesting an intact negative feedback control mechanism [18].

Studies examining the associations between cortisol dynamics, severity of TBI and outcome prediction have yielded controversial results. Some investigations infer that higher cortisol values are associated with more severe head trauma and with a worse clinical outcome [18, 28, 32, 34], whereas others find lower cortisol values in the most severely injured patients having brainstem dysfunction [20] or in brain-dead victims [41]. Other studies found no correlations between baseline cortisol and TBI severity [35, 37].

The adequacy of cortisol secretion in critical illness, including TBI, remains a diagnostic challenge. This is due mainly to the fact that the normal ranges for baseline or stimulated cortisol levels remain poorly defined. Also, there is much debate on which stimulation test should be used for diagnosis [9, 40]. Assays for serum cortisol measure the total hormone concentration (serum free cortisol plus the protein bound fraction of cortisol). It is believed that free cortisol is responsible for the physiological actions of the hormone. Moreover, it is well known that 90% of circulating cortisol is bound to proteins (corticosteroid-binding globulin and albumin), which both decline in critical illness. Thus in severe illness free cortisol may be a better indicator of adrenal function [42]. On the other hand, measurement of free cortisol is not easily available; thus total cortisol concentration remains the most suitable marker of adrenal function.

Despite the above difficulties some studies have examined relative adrenal dysfunction in critically ill TBI patients (Table 2) [36, 37, 38, 43]. In one of our studies we used the low-dose (1 μg) ACTH stimulation test [43]. This dose of ACTH is similar to the amounts of pituitary ACTH produced under intense stress stimulation [44]. An inadequate adrenal response to this dose indicates that the affected individual is not able to produce adequate amounts of cortisol whenever the need arises. However, the test that we applied indicates adrenal inability to mount a normal cortisol response and does not necessarily

Table 1 Studies on anterior pituitary function in patients with traumatic brain injury during the period of critical illness (*BS* brainstem, *CBG* corticosteroid binding-globulin, *F* cortisol, *GT* gonadotropic, *HPA* hypothalamic pituitary adrenal, *ICP* intracranial pressure, *LT* lactotropic, *NE* norepinephrine, *SNS* sympathetic nervous system, *ST* somatotropic, *TBI* traumatic brain injury, *TH* thyroid)

Reference	*n*	Axes tested	Main findings
Fleischer et al. [17]	15	TH, GT	Central hypothyroidism/gonadism
Steinbock and Thompson [18]	49	HPA	Diurnal rhythm of F altered, high F levels, correlations with TBI severity
King et al. [19]	6	TH, GT, ST, LT	No trends in hormone levels
Feibel et al. [20]	14	HPA	F depends on ICP level and BS function
Matsuura et al. [21]	30	TH, LT	Hormone levels relate to TBI severity
Woolf et al. [22]	54	GT	Frequent hypogonadism, mostly transient
Woolf et al. [23]	31	HPA, GT	Hypogonadism relates to SNS activity
Clark et al. [24]	33	GT, LT	Persistent, central hypogonadism
Woolf et al. [25]	66	TH	TH dysfunction relates to outcome
Chiolero et al. [26]	35	TH	High incidence of TH dysfunction
Chiolero et al. [27]	36	TH, HPA, GT, ST, LT	Hormone levels relate to TBI severity
Woolf et al. [28]	120	HPA	High F associated with bad outcome
Ziegler et al. [29]	23	TH	TH dysfunction correlated with NE
Gottardis et al. [30]	10	TH, ST	Hormone levels predict prognosis
Hackl et al. [31]	21	TH, HPA, GT, ST, LT	Hormones do not predict outcome
Pentelenyi [32]	81	HPA, ST	High F associated with fatal outcome
Mocchegiani et al. [33]	31	TH	TH function weakly associated with survival
Koiv et al. [34]	55	HPA	HPA activity relates to prognosis
Della Corte et al. [35]	22	TH, HPA, ST, LT	Hormonal responses linked to outcome
Hoen et al. [36]	34	HPA	Frequently impaired adrenal reserve
Dimopoulou et al. [37]	34	TH, HPA, GT, ST, LT	High incidence of endocrine alterations
Agha et al. [38]	50	TH, HPA, GT, ST, LT	High incidence of endocrine alterations
Savaridas et al. [39]	9	HPA	High free F, low CBG

Table 2 Results of studies investigating relative adrenal dysfunction in TBI patients during the period of critical illness (*GST* glucagon stimulation test, *hCRH* human corticotrophin-releasing hormone, *HDST* high-dose stimulation test, *LDST* low-dose stimulation test, *TBI* traumatic brain injury)

Reference	*n*	Study entry postinjury	Diagnostic test	Definition of relative adrenal dysfunction	Incidence of relative adrenal dysfunction (%)
Hohen et al. [36]	34	6–63 h	HDST	Increment in cortisol <9 μg/dl	47
Dimopoulou et al. [37]	34	9–60 days	hCRH	Peak cortisol <20 μg/dl	24
Agha et al. [38]	50	7–20 days	GST	Peak cortisol <450 nmol/l	16
Dimopoulou et al. [43]	40	7–60 days	LDST	Peak cortisol <18 μg/dl	15

demonstrate a central defect in the HPA axis. For this reason and to localize the site of HPA axis dysfunction in TBI patients human CRH was applied, and it was found that a subset of patients fail to augment ACTH appropriately in response to human CRH, suggesting a central defect, i.e., hypothalamic-pituitary failure. However, the majority showed increased ACTH after human CRH, indicating primary adrenal dysfunction as the most common cause of inadequate cortisol responses in this clinical setting [43].

Taken together these data indicate that at least on in ten patients with acute TBI develops inadequate HPA function. It seems that in the majority of patients this dysregulation is reminiscent of the relative adrenal insufficiency that presents in a substantial proportion of patients with severe illness. However, it should be mentioned that in a subset of patients HPA dysfunction is centrally mediated. These cases are most likely the result of TBI.

Somatotropic axis

Early after TBI basal plasma GH is within normal limits [30] or high [19, 27, 31]. Insulin-like growth factor 1 has been shown to be normal, or low [37]. However, the adequacy of GH reserve is best investigated by dynamic testing [45]. Agha and coworkers [38] evaluated 50 critically ill TBI patients. The somatotropic axis was assessed by stimulation with glucagon, and the cutoff of 5 ng/ml was selected as a normal response. Nine patients (18%) had GH deficiency. A recent study from our group enrolled 34 TBI patients. GH production was assessed by stimulation with growth hormone releasing hormone (GHRH). We showed that three patients (9%) had partial GH deficiency, defined by a peak GH level between 3 and 5 ng/ml [37].

Some studies have examined the correlation between GH response to provocative tests and prognosis or clinical outcome in the early post-TBI period. However, the reported results are conflicting. For example, it has been shown that the administration of GHRH in comatose TBI

Table 3 Studies on anterior pituitary function in patients with nontraumatic brain injury (*BI*) during the period of critical illness (*CBG* corticosteroid binding-globulin, *HPA* hypothalamic pituitary adrenal, *ICH* itracerebral hemorrhage, *ICP* intracranial pressure, *IS* ischemic stroke, *LT* lactotropic, *SAH* subarachnoid hemorrhage, *TH* thyroid)

References	Type of BI	*n*	Axes tested	Main findings
Feibel et al. [20]	ICH	9	HPA	Cortisol levels depend on ICP and brainstem function
Savaridas et al. [39]	Aneurysmal SAH	6	HPA	High free cortisol, low CBG
Schwarz et al. [47]	IS	22	HPA, TH, LT	Profound endocrine changes, central regulation impaired
Dimopoulou et al. [48]	ICH	3	HPA	High incidence of impaired adrenal reserve, no association with outcome
	IS	17		
	Aneurysmal SAH	4		

survivors entails a significant increase in GH; in contrast, nonsurvivors had no such augmented GH levels [30]. In another investigation a paradoxical rise in GH after glucose loading was observed only in patients with more severe TBI [19]. A subsequent study showed a higher peak GH response to GHRH in patients who had a poor long-term outcome [35].

Gonadotropic-lactotropic axes

TBI produces a profound decrease in testosterone along with low basal follicle-stimulating hormone and luteinizing hormone which develops shortly after injury and deteriorates during the subsequent days [17, 22, 23, 24, 31]. The incidence of hypogonadism in critically ill TBI patients is variable, ranging from 24% to 80% [37, 38]. In a subset of patients testosterone levels normalize within 3–6 months after injury [24]. The magnitude of the decline in testosterone is correlated with head trauma severity in some studies [24, 37, 38] but not in others [22]. The pituitary-ovarian axis is comparably depressed [22].

Several studies attempted to elucidate the mechanisms of hypogonadism in TBI. Clark et al. [46] analyzed the pulse frequency and amplitude of luteinizing hormone in men and found that the former was normal whereas the latter was reduced. The authors concluded that a central dysfunction rather than primary gonadal impairment accounts for hypogonadism after TBI. They suggested that a possible explanation for the reduction in luteinizing hormone pulse amplitude is impaired delivery of gonadotropin-releasing hormone to the anterior pituitary as a consequence of increased intracranial pressure causing stalk compression. The hypothalamic etiology for hypogonadotrophic hypogonadism is further supported by studies showing normal or exaggerated luteinizing hormone and follicle-stimulating hormone responses to releasing factors [17, 22, 31, 37].

Prolactin (PRL) may increase [19, 21, 37, 38], remain normal [35], or decrease [31] in acute TBI. Baseline PRL is correlated with head trauma severity, as expressed by the Glasgow Coma Scale score [38] or the intracranial pressure levels [27]. The PRL responses to GHRH may be of prognostic significance; PRL is higher in TBI patients with a favorable outcome than in those with a poor clinical course [35]. Furthermore, PRL responses to thyrotropin-releasing hormone (TRH) may reflect TBI severity; responses are attenuated in patients with severe head injury [21].

Thyroid axis

Thyroid dysfunction occurs following TBI at an incidence ranging from 4% to 15% [37, 38]. TSH may be normal [19, 26, 33] or low [17, 27, 35], triiodothyronine (T_3) is low [17, 25, 26, 29, 30, 31, 33, 35] and total or free thyroxine (T_4) may be normal [30, 35] or low [17, 25, 26, 29]. Reverse T_3 usually increases [26, 29, 31, 33]. These findings suggest a low T_3 and/or a low T_4 syndrome. Changes in T_3 and reverse T_3 appear immediately after trauma [25] and can persist for at least 2 weeks [35]. Thyroid dysfunction has been shown to be reversible [17]. According to some studies basal thyroidal hormones reflect head trauma severity and predict outcome [17, 25, 26, 33]; thus patients with the greatest neurological dysfunction and a bad ultimate outcome have the lowest T_4 and T_3 levels [25]. However, others have failed to support these associations [35]. Dynamic testing may be of value in predicting clinical outcome; the TSH response after stimulation with TRH has been shown to be absent only in patients having a poor outcome [30, 35].

Anterior pituitary dysfunction in critically ill patients with nontraumatic BI

Pituitary function in critically ill patients with nontraumatic BI has received less systematic attention (Table 3) [20, 39, 47, 48].

Stroke (ischemic stroke and intracerebral hemorrhage)

Evidence that stroke is associated with endocrine dysfunction comes primarily from studies investigating noncritically ill patients with acute stroke. Most research has focused on HPA axis activity showing high cortisol

responses [49], disturbed diurnal cortisol rhythm [50], and reduced suppressibility of serum cortisol by dexamethasone [51]. Several other abnormalities have been reported, such as thyroid function suppression [52], hypogonadism [53, 54], and low insulin-like growth factor 1 [55].

Critically ill stroke patients may also experience hormonal dysfunction. A recent study evaluated 22 patients with acute space occupying hemispheric ischemic stroke on admission in the ICU and on days 3, 5, 7, and 9. Plasma levels of PRL, TSH, total and free T_4, total T_3, ACTH, and cortisol were measured; furthermore, on day 3 a TRH stimulation test was performed. The authors found abnormally low cortisol and ACTH concentrations, high PRL, and slightly suppressed thyroid function throughout the observation period. TRH stimulation of plasma TSH and PRL was low. The diurnal rhythm of cortisol was abolished [47]. Our group examined the HPA axis function in 20 critical care patients with stroke. We found that two patients had blunted cortisol responses following dynamic stimulation. Hypoadrenalism was associated with a higher mortality rate, although it did not constitute an independent outcome predictor [48].

Aneurysmal SAH

The concept of SAH-induced hormonal alterations is supported by a study performed in noncritically ill patients with acute SAH. Baseline cortisol was high in all patients, gonadal hormones were within normal ranges, and hyperprolactinemia was present in 14%. Thyroid function abnormalities consisted of high TSH (14%), low T_3 (14%), and low T_4 (6%) [56]. Recent evidence suggests that hormonal abnormalities are frequent in long-term SAH survivors [57, 58, 59, 60], with GH or gonadal deficiencies predominating [57, 58, 60]. This pattern is similar to that in survivors of TBI, suggesting that GH and/or gonadotropin function is more fragile than the other axes, and that the pattern of endocrine abnormalities is unrelated to the type of BI [58, 61].

Data on hormonal changes in critically ill patients with aneurysmal SAH are sparse. A recent study investigated cotisol dynamics in six mechanically ventilated SAH patients. Total cortisol and corticosteroid-binding globulin were measured in the morning and evening, while free cortisol was calculated. In three patients the diurnal variation in total cortisol was abolished. All patients had total cortisol levels within the accepted reference range for nonstressed individuals. However, all patients had low corticosteroid-binding globulin and normal free cortisol. The authors concluded that critically ill SAH patients have no evidence of cortisol depletion [39].

Posterior pituitary dysfunction in brain injury

A normal function of the posterior pituitary is crucial for water homeostasis. Posterior pituitary dysfunction is a well-recognized complication of traumatic BI, but there are only scarce data in patients with SAH [62]. Inadequate antidiuretic hormone (ADH) secretion results in diabetes insipidus (DI). The most reliable data regarding the prevalence and natural course of posttraumatic DI have been published recently by Agha et al. [62]; they reported a prevalence of DI in the immediate period following TBI of 21.6%. In this series the occurrence of DI was related to the severity of the traumatic insult, but it was unrelated to the development of anterior pituitary abnormalities. In most cases posttraumatic DI was transient. A prospective study by Agha et al. [63] reported that 9 of 13 patients who had DI in the acute posttraumatic phase recovered by 6 months, and one additional patient recovered by 12 months. Interestingly, the majority of patients with permanent DI had only partial vasopressin deficiency.

Apart from hypernatremic dehydration induced by ADH deficiency, hyponatremia also develops in a substantial proportion of patients during the acute period of BI due to an inappropriate release of ADH (syndrome of inappropriate antidiuretic hormone, SIADH) as a result of damage to the pituitary stalk or the posterior pituitary. The reported prevalence of this abnormality varies form 2.3% to 36%. As a rule SIADH induced by TBI is transient [63].

Clinical implications of pituitary function alterations in brain injury

It has been stated that the importance of delineating pituitary function during the early phase of traumatic or nontraumatic BI is threefold: (a) to detect abnormalities that hamper recovery of these patients during the critical phase of their illness, (b) to obtain prognostic information for patients' morbidity and mortality rates, and (c) to diagnose pituitary hormone deficiencies that may persist later in life at an early stage.

Pituitary function and impaired recovery

As in other critical states, it is not clear whether hormone deficiencies discovered during the acute phase of BI are adaptive or detrimental [64]. Suppression of the hypothalamic-pituitary-gonadal axis may be appropriate to downregulate the production of anabolic androgens to conserve utilization of metabolic substrates by the less vital organs. On the other hand, loss of the sex steroids with their anabolic properties might be expected to affect wound healing and convalescence [65]. The changes in the thyroid axis have been interpreted as an attempt to

reduce energy expenditure and are generally believed to be adaptive for the individual [66]. Although not widely accepted [6, 61], some studies suggest that both gonadal and thyroid endocrine abnormalities are transient in critically ill TBI patients [17, 22, 23, 24]; thus it is questionable whether they should be treated. Similarly, the GH deficiency state observed during the acute phase in some patients with BI does not seem to require medical intervention. A large multicenter study showed that the administration of high doses of GH in critically ill patients, instead of improving outcome, doubled mortality [67]. Thus GH supplementation is not currently recommended during the acute phase of critical illness of any type. However, diminished GH secretion persisting later in life may be harmful since GH is beneficial on the net protein balance, bone mineral density, well-being, and cardiac and immune function [68].

In contrast, independently of its cause, the inability to mount an adequate cortisol response may increase the risk of death during severe illness, especially in patients with multiple organ failure and hemodynamic instability [10, 40]. On the other hand, no strict biochemical criteria for "normal" serum cortisol concentrations in critically ill patients are currently available [9, 10, 69]. Consequently, baseline or stimulated cortisol levels in deciding when to treat patients need further assessment. It should be noted that a recent large, randomized, placebo-control study showed that the early administration of pharmacological doses of methylprednisolone is not beneficial in patients with TBI injury. In fact this treatment was associated with a significant rise in risk of death within 2 weeks [70]. Therefore it is recommended that in the presence of clinically significant functional hypoadrenalism only physiological doses of steroid replacement be applied.

The same is true for posterior pituitary dysfunction occurring as a result of BI. Untreated DI leads to polyuria. Since in the early post-TBI period water intake may be inadequate due to impaired cognition, polyuria can lead to hypernatremic dehydration with increased morbidity and impairment of recovery, a condition that is reversible with appropriate treatment with desmopressin and maintenance of fluid balance. Similarly, recognition and treatment of SIADH is important as hyponatremia increases the risk of cerebral edema and is associated with increased morbidity and mortality in BI patients.

Pituitary function and prognosis

The relevance of pituitary hormonal changes to patients' morbidity and mortality remains controversial. Some studies infer that basal hormones and/or hormonal responses to provocative tests serve as markers of head trauma severity. As a consequence such associations might be useful in establishing early prognosis in TBI patients. However, other studies have failed to confirm these relationships. The relationship between pituitary dysfunction and long-term functional outcome is also controversial; one study showed that a good neurological recovery is more common in patients without hormonal abnormalities [13], while a recent investigation did not support this finding [61].

Early detection of persistent pituitary function abnormalities

A number of recent reports have examined the incidence and type of hormonal deficiencies in short or long-term survivors of BI. These studies suggest that subjects with a history of BI frequently develop pituitary dysfunction. The time-course of these anterior pituitary function abnormalities is currently unclear. One possibility is that these abnormalities occur in the early postinjury period; another possibility is that they appear progressively during the years following the acute insult. However, based on the data presented in this review pituitary dysfunction occurring in the early phase of BI consists of a mixture of pathophysiologically different changes. Thus most hormonal deficiencies observed during the early phase of BI follow the same course as in almost all critical states, and therefore it is difficult to discern a separate effect attributed to structural neuroendocrine damage. Even in those patients presenting with altered pituitary function tests during the early phase it is currently unclear whether these changes are permanent or reversible. Therefore and given the high prevalence of pituitary deficits in BI survivors it is strongly recommended that the management of these patients routinely include a complete neuroendocrine reevaluation at their recovery phase.

Conclusions

In critically ill BI patients abnormal pituitary endocrine responses are due principally to hypothalamic changes. Several studies have examined the correlation between these hormonal alterations and BI severity, but the results are inconsistent. It remains currently unclear whether and how pituitary abnormalities adversely affect the clinical course of BI patients during the period of critical illness. With the exception of clinically significant relative adrenal deficiency and DI, the other endocrine alterations do not seem to require any therapeutic intervention in severely ill BI patients. It is also uncertain whether endocrine abnormalities detected in the early post-BI period persist for the rest of these patients' lives. In view of current evidence indicating a high incidence of pituitary dysfunction even years following BI it is recommended that repetition of endocrine evaluation be performed during the rehabilitation phase in all patients.

References

1. Marik PE, Varon J, Trask T (2002) Management of head trauma. Chest 122:699–711
2. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P (2003) Stroke. Lancet 362:1211–1224
3. Fahy BG, Sivaraman V (2002) Current concepts in neurocritical care. Anesthesiol Clin North America 20:441–462
4. Crompton MR (1971) Hypothalamic lesions following closed head injury. Brain 94:165–172
5. Edwards OM, Clark JD (1986) Post-traumatic hypopituitarism. Six cases and review of the literature. Medicine (Baltimore) 65:281–290
6. Benvega S, Campenni A, Ruggeri RM, Trimarchi F (2000) Clinical Review 113. Hypopituitarism secondary to head trauma. J Clin Endocrinol Metab 85:1353–1361
7. Lamberts SWJ, de Herder WW, van der Lely AJ (1998) Pituitary insufficiency. Lancet 352:127–134
8. Amar AP, Weiss MH (2003) Pituitary anatomy and physiology. Neurosurg Clin N Am 13:11–23
9. Oelkers W (1996) Adrenal insufficiency. N Engl J Med 335:1206–1212
10. Cooper MS, Stewart PM (2003) Corticosteroid insufficiency in acutely ill patients. N Engl J Med 348:727–734
11. McKeating EG, Andrews PJD (1998) Cytokines and adhesion molecules in acute brain injury. Br J Anaesth 80:77–84
12. Bornstein SR, Chroussos GP (1999) Clinical review 104. Adrenocorticotropin (ACTH)- and non-ACTH-mediated regulation of the adrenal cortex: neural and immune inputs. J Clin Endocrinol Metab 84:1729–1736
13. Kelly DF, Gaw Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C (2000) Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J Neurosurg 93:743–752
14. Chroussos GP (2000) The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuroendocrine and target tissue-related causes. Int J Obes Relat Metab Disord 24:S50–S55
15. Vanltallie TB (2002) Stress: a risk factor for serious illness. Metabolism 51 [Suppl 1]:40–45
16. Charmandari E, Tsigos C, Chrousos G (2005) Endocrinology of the stress response. Annu Rev Physiol 67:259–284
17. Fleischer AS, Rudman DR, Payne NS, Tindall GT (1978) Hypothalamic hypothyroidism and hypogonadism in prolonged traumatic coma. J Neurosurg 49:650–657
18. Steinbok P, Thompson G (1979) Serum cortisol abnormalities after craniocerebral trauma. Neurosurgery 5:559–565
19. King LR, Knowles HC, McLaurin RL, Brielmaier J, Perisutti G, Piziak VK (1981) Pituitary response to head injury. Neurosurgery 9:229–235
20. Feibel J, Kelly M, Lee L, Woolf P (1983) Loss of adrenocortical suppression after acute brain injury: role of increased intracranial pressure and brain stem function. J Clin Endocrinol Metab 57:1245–1250
21. Matsuura H, Nakazawa S, Wakabayashi I (1985) Thyrotropin-releasing hormone provocative release of prolactin and thyrotropin in acute head injury. Neurosurgery 16:791–795
22. Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M (1985) Transient hypogonadotropic hypogonadism caused by critical illness. J Clin Endocrinol Metab 60:444–450
23. Woolf PD, Hamill RW, McDonald JV, Lee LA, Kelly M (1986) Transient hypogonadotrophic hypogonadism after head trauma: effects on steroid precursors and correlation with sympathetic nervous system activity. Clin Endocrinol (Oxf) 25:265–274
24. Clark JD, Raggatt PR, Edwards OM (1988) Hypothalamic hypogonadism following major head injury. Clin Endocrinol (Oxf) 29:153–165
25. Woolf PD, Lee LA, Hamill RW, McDonald JV (1988) Thyroid test abnormalities in traumatic brain injury: correlation with neurologic impairment and sympathetic nervous system activation. Am J Med 84:201–208
26. Chiolero RL, Lemarchand-Beraud T, Schutz Y, de Tribolet N, Bayer-Berger M, Freeman J (1988) Thyroid function in severely traumatized patients with or without head injury. Acta Endocrinol (Copenh) 117:80–86
27. Chiolero R, Lemarchand T, Schutz Y, de Tribolet N, Felber JP, Freeman J, Jequier E (1988) Plasma pituitary hormone levels in severe trauma with or without head injury. J Trauma 28:1368–1374
28. Woolf PD, Cox C, Kelly M, Nichols D, McDonald JV, Hamill RW (1990) The adrenocortical response to brain injury: correlation with the severity of neurologic dysfunction, effects of intoxication, and patient outcome. Alcohol Clin Exp Res 14:917–921
29. Ziegler MG, Morrissey EC, Marshall LF (1990) Catecholamine and thyroid hormones in traumatic injury. Crit Care Med 18:253–258
30. Gottardis M, Nigitsch C, Schmutzhard E, Neumann M, Putensen C, Hackl JM, Koller W (1990) The secretion of human growth hormone stimulated by human growth hormone releasing factor following severe cranio-cerebral trauma. Intensive Care Med 16:163–166
31. Hackl JM, Gottardis M, Wieser C, Rumpl E, Stadler C, Schwarz S, Monkayo R (1991) Endocrine abnormalities in severe traumatic brain injury-a cue to prognosis in severe craniocerebral trauma? Intensive Care Med 17:25–29
32. Pentelenyi T (1992) Significance of endocrine studies in the general assessment and prediction of fatal outcome in head injury. Acta Neurochir Suppl 55:21–24
33. Mocchegiani E, Imberti R, Testasecca D, Zandri M, Santarelli L, Fabris N (1995) Thyroid and thymic endocrine function and survival in severely traumatized patients with or without head injury. Intensive Care Med 21:334–341
34. Koiv L, Merisalu E, Zilmer K, Tomberg T, Kaasik AE (1997) Changes of sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in patients with head injury. Acta Neurol Scand 96:52–58
35. Della Corte F, Mancini A, Valle D, Gallizzi F, Carducci P, Mignani V, De Marinis L (1998) Provocative hypothalamopituitary axis tests in severe head injury: correlations with severity and prognosis. Crit Care Med 26:1419–1426
36. Hoen S, Asehnoune K, Brailly-Tabart S, Mazoit JX, Benhamou D, Moine P, Edouard AR (2002) Cortisol response to corticotropin stimulation in trauma patients: influence of hemorrhagic shock. Anesthesiology 97:807–813
37. Dimopoulou I, Tsagarakis S, Theodorakopoulou M, Douka E, Zervou M, Kouyialis AT, Thalassinos N, Roussos C (2004) Endocrine abnormalities in critical care patients with moderate-to-severe head trauma: incidence, pattern and predisposing factors. Intensive Care Med 30:1051–1057
38. Agha A, Rogers B, Mylotte D, Taleb F, Tormey W, Phillips J, Thompson CJ (2004) Neuroendocrine dysfunction in the acute phase of traumatic brain injury. Clin Endocrinol (Oxf) 60:584–591
39. Savaridas T, Andrews PJD, Harris B (2004) Cortisol dynamics following acute severe brain injury. Intensive Care Med 30:1479–1483
40. Lamberts SWJ, Bruining HA, de Jong FH (1997) Drug therapy: corticosteroid therapy in severe illness. N Engl J Med 337:1285–1292

41. Dimopoulou I, Tsagarakis S, Anthi A, Milou E, Ilias I, Stavrakaki K, Charalambidis C, Tzanela M, Orfanos S, Mandragos K, Thalassinos N, Roussos C (2003) High incidence of decreased cortisol reserve in brain-dead potential organ donors. Crit Care Med 31:1113–1117
42. Hamrahian AH, Oseni TS, Arafah B (2004) Measurements of serum free cortisol in critically ill patients. N Engl J Med 350:1629–1638
43. Dimopoulou I, Tsagarakis S, Kouyialis AT, Roussou P, Assithianakis G, Christoforaki M, Ilias I, Sakas DE, Thalassinos N, Roussos C (2004) Hypothalamic-pituitary-adrenal dysfunction in critically ill patients with traumatic brain injury: incidence, pathophysiology, and relationship to vasopressor dependence and peripheral interleukin-6 levels. Crit Care Med 32:404–408
44. Dickstein G, Shechner C, Nicholson WE, Rosner I, Shen-Orr Z, Adawi F, Lahav M (1991) Adrenocorticotropin stimulation test: effects of basal cortisol level, time of day, and suggested new sensitive low dose test. J Clin Endocrinol Metab 72:773–778
45. Stavrou S, Kleinberg DL (2001) Diagnosis and management of growth hormone deficiency in adults. Endocrinol Metab Clin North Am 30:545–563
46. Clark JDA, Raggatt PR, Edwards OM (1992) Abnormalities of the hypothalamo-pituitary-gonadal axis after head injury. Clin Endocrinol (Oxf) 36:481–485
47. Schwarz S, Schwab S, Klinga K, Maser-Gluth C, Bettendorf M (2003) Neuroendocrine changes in patients with acute space occupying ischemic stroke. J Neurol Neurosurg Psychiatry 74:725–727
48. Dimopoulou I, Tsagarakis S, Douka E, Zervou M, Kouyialis AT, Dafni U, Thalassinos N, Roussos C (2004) The low-dose corticotropin stimulation test in acute traumatic and non-traumatic brain injury: incidence of hypo-responsiveness and relationship to outcome. Intensive Care Med 30:1216–1219
49. Fassbender K, Schmidt R, Mossner R, Daffertshofer M, Hennerici M (1994) Pattern of activation of the hypothalamic-pituitary-adrenal axis in acute stroke. Relation to acute confusional state, extent of brain damage, and clinical outcome. Stroke 25:1105–1108
50. Johansson A, Ahren B, Nasman B, Carlstrom K, Olsson T (2000) Cortisol axis abnormalities early after stroke—relationships to cytokines and leptin. J Intern Med 247:179–187
51. Olsson T, Marklund N, Gustafson Y, Nasman B (1992) Abnormalities at different levels of the hypothalamic-pituitary-adrenocortical axis early after stroke. Stroke 23:1573–1576
52. Hagg E, Asplund K, Eriksson S, Lithner F, Strand T, Wester PO (1986) Serum thyroid-stimulating hormone in cerebrovascular disease. Acta Med Scand 219:53–58
53. Pepper GM, Koenigsberg R, Zito JL, Deutsch S (1993) Alterations of serum pituitary hormone levels in postmenopausal women with stroke. Stroke 24:805–808
54. Jeppesen LL, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS, Winther K (1996) Decreased serum testosterone in men with acute ischemic stroke. Arterioscler Thromb Vasc Biol 16:749–754
55. Schwab S, Spranger M, Krempien S, Hacke W, Bettendorf M (1997) Plasma insulin-like growth factor I and IGF binding protein 3 levels in patients with acute cerebral ischemic injury. Stroke 28:1744–1748
56. Mangieri P, Suzuki K, Ferreira M, Domingues L, Casulari LA (2003) Evaluation of pituitary and thyroid hormones in patients with subarachnoid hemorrhage due to ruptured intracranial aneurysm. Arq Neuropsiquiatr 61:14–19
57. Brandt L, Saveland H, Valdenmarsson S, Sjoholm H, Reinstrup P (2004) Fatigue after aneurysmal subarachnoid hemorrhage evaluated by pituitary function and 3D-CBF. Acta Neurol Scand 109:91–96
58. Aimaretti G, Ambrosio MR, Di Somma C, Fusco A, Cannavo S, Gasperi M, Scaroni C, De Marinis L, Benvega S, Degli Uberti EC, Lombardi G, Mantero F, Martino E, Giordano G, Ghigo E (2004) Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. Clin Endocrinol (Oxf) 61:320–326
59. Kreitschmann-Andermahr I, Hoff C, Saller B, Niggemeier S, Pruemper S, Hutter BO, Rohde V, Gressner A, Matern S, Gilsbach JM (2004) Prevalence of pituitary deficiency in patients after aneurysmal subarachnoid hemorrhage. J Clin Endocrinol Metab 89:4986–4992
60. Dimopoulou I, Kouyialis AT, Tzanella M, Armaganidis A, Thalassinos N, Sakas DE, Tsagarakis S (2004) High incidence of neuroendocrine dysfunction in long-term survivors of aneurysmal subarachnoid hemorrhage. Stroke 35:2884–2889
61. Bondanelli M, De Marinis L, Ambrosio MR, Monesi M, Valle D, Zatelli MC, Fusco A, Bianchi A, Farneti M, Degli Uberti EC (2004) Occurrence of pituitary dysfunction following traumatic brain injury. J Neurotrauma 21:685–696
62. Agha A, Thornton E, O'Kelly P, Tormey W, Phillips J, Thompson CJ (2004) Posterior pituitary dysfunction after traumatic brain injury. J Clin Endocrinol Metab 89:5987–5992
63. Agha A, Sherlock M, Phillips J, Tormey W, Thompson CJ (2005) The natural history of post-traumatic neurohypophysial dysfunction. Eur J Endocrinol 152:371–377
64. Van den Berghe G (2000) Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 143: 1–13
65. Spratt DI (2001) Altered gonadal steroidogenesis in critical illness: is treatment with anabolic steroids indicated? Baillieres Best Pract Res Clin Endocrinol Metab 15:479–494
66. Stathatos N, Levetan C, Burman KD, Wartofsky L (2001) The controversy of the treatment of critically ill patients with thyroid hormone. Baillieres Best Pract Res Clin Endocrinol Metab 15:465–478
67. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ (1999) Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 341:785–792
68. Carroll PV (2001) Treatment with growth hormone and insulin like growth factor-I in critical illness. Baillieres Best Pract Res Clin Endocrinol Metab 15:435–451
69. Ligtenberg JJM, Zijlstra JG (2004) The relative adrenal insufficiency syndrome revisited: which patients will benefit from low-dose steroids? Curr Opin Crit Care 10:456–460
70. CRASH trial collaborators (2204) Effect of intravenous corticosteroids on death within 14 days in 10.008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 364:1321–1328

Pierre Squara

Matching total body oxygen consumption and delivery: a crucial objective?

Abstract The strength of the rationale for incorporating total body oxygen consumption (VO_2) and delivery (DO_2) into our decision making strategies contrasts with the absence of demonstrated benefits of bedside calculations in clinical practice. This situation mandates a careful reappraisal of the theoretical limitations of bedside calculations of DO_2 and VO_2, including a re-evaluation of the clinical situations in which these calculations are valid. Three levels of complexity can be distinguished when analysing a patient's hemodynamic status: 1) simple cases where investigations can be limited to clinical monitoring, including lactate changes over time; 2) intermediate situations requiring invasive investigations in which continuous monitoring of VO_2-related variables such as cardiac output and mixed venous oxygen saturation often provide enough information to guide clinical decision; and 3) complex situations where assessment of VO_2 and VO_2/DO_2 analysis might be recommended. Although studies that support such recommendations are limited they are based on a widely accepted physiological model. VO_2 and DO_2 analysis is also limited by theoretical and technical difficulties. In this article, we discuss the validity of these limitations in the bedside assessment of VO_2 and DO_2, and review data supporting the use of VO_2/DO_2 analysis in the clinical evaluation of complex cases.

Introduction

Regardless of the cause of shock, failure to rapidly restore adequate status leads to impaired mitochondrial O_2 uptake and dysoxia. Significant O_2 uptake due to nonoxidative systems may occur only when dysoxia has resolved, as these systems have lower affinity for oxygen than do oxidative systems [1, 2, 3]. A reasonable assumption therefore is that below a critical level, VO_2 is inversely correlated to the risk of cell dysfunction and to the severity of shock. Once a substantial amount of cell necrosis has occurred, organ function recovery is not always possible even when an adequate VO_2 is restored. In a large population of shock of various origins it has been shown that a VO_2 value below that expected is the one most strongly related to death [4]. Thus early VO_2 adaptation to tissue needs should be the major treatment goal in patients with shock [5, 6]. The contrast between this strong rationale and the lack of consensus that bedside VO_2 assessment is beneficial in practice mandates a careful reappraisal of our means to match VO_2 and needs.

The VO_2/DO_2 relationship

The physiological model

In both isolated cells [7, 8, 9] and whole organisms [10, 11, 12] a biphasic relationship between O_2 use and resources has been established. When DO_2 is higher than a threshold value, VO_2 remains stable (O_2 supply independency) because the O_2 extraction rate of oxygen ($EO_2=VO_2/DO_2$) changes proportionally. When DO_2 falls below this threshold, a proportional increase in EO_2

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_45,

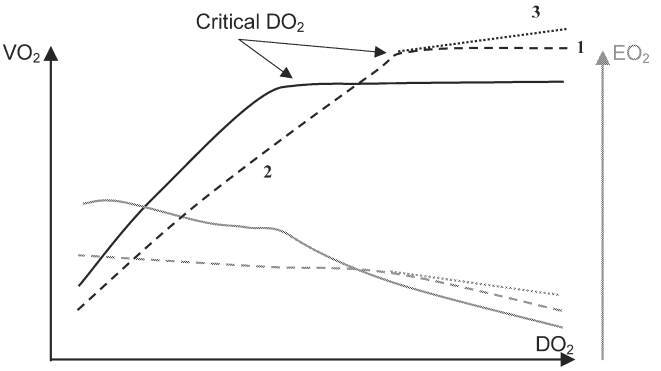


Fig. 1 Pathophysiological changes in the VO_2/DO_2 relationship. *Solid black line* Normal relationship; *dotted lines* abnormal relationships *1* increased VO_2 needs; *2* impaired EO_2; *3* other mechanisms (see text). *Gray curves* Corresponding EO_2/DO_2 relationships

cannot be maintained, and the VO_2 linearly drops to zero (O_2 supply dependency). The inflection point between the two slopes is accepted as indicating the critical level of DO_2 (Fig. 1). The O_2 supply dependency is associated with an increase in blood lactate concentration denoting possible activation of the anaerobic pathway [11, 13, 14, 15].

Assessment of the VO_2/DO_2 relationship is a theoretical means of evaluating the gap between actual VO_2 and needed VO_2. A DO_2 challenge can be performed easily at the bedside by increasing cardiac output (CO) [16], increasing low hemoglobin concentration (Hb) [11, 17], or increasing low SaO_2 [18]. When DO_2 increases, an increase in VO_2 argues for inadequate O_2 supply. In contrast, a stable VO_2 value when DO_2 increases suggests either that VO_2 matches needs when associated with decreasing lactate levels [11, 13, 14, 15], or that VO_2 is limited by other mechanisms than O_2 supply, when associated with increasing lactate levels [19, 20, 21].

Although VO_2 can be calculated by spirometry or indirect calorimetry, the reverse Fick method using a pulmonary artery catheter (PAC) is the most popular method for assessing the VO_2/DO_2 relationship in clinical practice. DO_2 is the arterial oxygen delivery calculated as the product of CO by arterial oxygen content (CaO_2). VO_2 can be calculated as the product of CO by the arteriovenous oxygen difference in oxygen contents ($Ca{-}vO_2{=}CaO_2{-}CvO_2$).

"Patho-physiological" changes

Two mechanisms delay achievement of the VO_2 plateau and account for a rightward shift in the critical DO_2 point (Fig. 1). When VO_2 needs are excessive (uncoupling and/or increased metabolic activity), the VO_2 plateau is reached at a higher level of VO_2 [22, 23]. When O_2 tissue diffusion is impaired (impaired microcirculation and/or impaired O_2 mitochondrial use), the slope of the dependent part of the VO_2/DO_2 relationship is decreased [24, 25, 26].

Three other mechanisms result in an increase in VO_2 as DO_2 increases beyond the critical point, so that a slight upward slope, usually of less than 5%, replaces the expected VO_2 plateau. Although more difficult, identification of the critical DO_2 inflection point remains possible when these mechanisms are operative, because the slope of the VO_2/DO_2 dependency segment ranges from 20% to 50% [27]. The first mechanism occurs during a DO_2 challenge involving an increase in CO because the VO_2 needs of kidneys [28], stomach [29], and muscle [30] increase in direct proportion to flow. Furthermore, infusion of inotropic agents increases myocardial O_2 consumption [11, 15, 27]. Another mechanism is additional oxygen uptake due to nonmitochondrial oxidase systems when dysoxia has resolved [1, 31]. The last mechanism, conformance, is a decrease in the cells' metabolic needs in response to a gradual decline in available O_2. Although secondary to a chronic change, this phenomenon has been observed in acute situations [32], and recovery from conformance may account for progressive increase in metabolic needs [33].

The spurious "pathological" supply dependency

A controversy arose in the 1980s from several studies on the acute respiratory distress syndrome and/or sepsis in which the expected VO_2 plateau was not observed in patients who were recovering from shock and had high DO_2 values [34, 35, 36, 37]. This was interpreted as evidence of "pathological O_2 supply dependency" possibly related to a hidden oxygen deficit contributing to multiorgan failure and death. However, increasing DO_2 to supranormal values was beneficial in some studies [38, 39, 40, 41] but not in others [42, 43]. Furthermore, it has been suggested this so-called "pathological supply dependency" results from spurious upsloping of the VO_2/DO_2 relationship due to mathematical coupling of measurement errors when using a PAC because in some studies simultaneous and independent assessments of VO_2 demonstrated a plateau [12, 44, 45, 46].

Methodological limitations of VO_2/DO_2 relationship assessment

The formulas of $VO_2{=}CO{\times}[Hb{\times}1.36{\times}(SaO_2{-}SvO_2)]$ and $DO_2{=}CO{\times}SaO_2{\times}Hb{\times}1.36$, where blood gases are neglected, shows that VO_2 and DO_2 share three variables: Hb, SaO_2, and CO (plus height and weight if CO is indexed). It is therefore necessary to study the impact of these shared variables on the VO_2/DO_2 relationship.

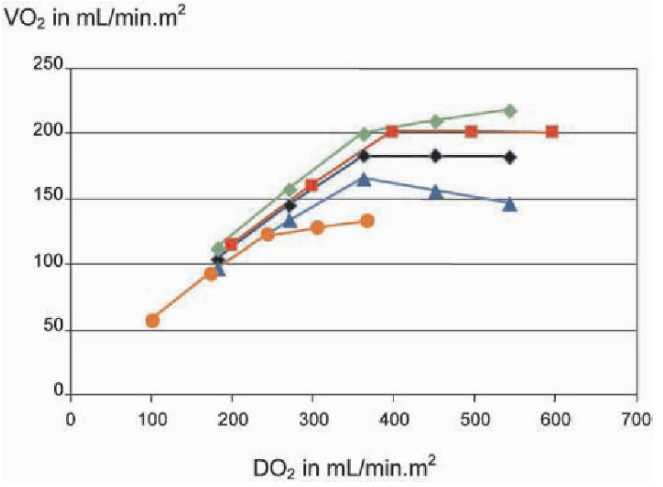


Fig. 2 Effect of systematic errors in the VO_2/DO_2 relationship. *Black curve* A hypothetical patient. The critical DO_2 is reached at the third point. *Red curve* Systematic 10% overestimation of CO, Hb, or $CavO_2$; *blue curve* systematic 10% overestimation of SvO_2 with no error in SaO_2; *green curve* systematic 10% underestimation of SvO_2 with no error in SaO_2; *orange curve* 0.5 l/min absolute underestimation of CO

Systematic measurement errors

Systematic relative errors in Hb, CO, height, or weight measurements do not modify the shape of the curve because all points are changed proportionally (Fig. 2). Even if VO_2 and DO_2 values are over- or underestimated, the critical DO_2 is identified at the same moment during a DO_2 challenge. From the formulae it is easy to understand that the shape of the VO_2/DO_2 relationship can only change when there is an absolute error in CO (with upsloping of the VO_2 plateau when CO is underestimated), or when errors of different magnitude occur in SvO_2 and SaO_2 values (with upsloping of the VO_2 plateau when SvO_2 is selectively underestimated or SaO_2 selectively overestimated).

Most sources of CO error such as tricuspid regurgitation and left-to-right shunting are more likely to create a relative systematic error [47]. The most likely systematic source of absolute underestimation of CO is underestimation of left ventricle output related to the fact that the bronchial circulation is disregarded when DO_2 and VO_2 are calculated from right ventricular output. Bronchial blood flow may increase by 200% in injured lungs [48]. We can speculate that the magnitude of the error is relatively constant and dependent on lung injury severity and on lung oxygen consumption. However, even when lung oxygen consumption reaches 20% of the total VO_2, the spurious slope ranges from 4% to 6%.

Absolute underestimation of SvO_2 as compared to SaO_2 is possible only if venous sampling is repeatedly flawed, which can occur in practice only when HbO_2 saturation is not measured but calculated from PO_2 [49]. Aspiration of capillary blood when mixed venous blood is sampled too quickly or with an inflated balloon leads to CvO_2 overestimation with a downsloping VO_2 plateau.

Random measurement errors

In clinical practice, when all analyzers are properly calibrated, random error is the most likely type of error. Although the combined variability of within-patient, between-patient, between-device, and between-day measurements may be large, it is of no assistance for estimating the effect of random errors on the VO_2/DO_2 relationship determined using one device on one day in one patient. Within-patient variability (S_d) is much smaller. Here we consider the 95% confidence interval (95%CI, which is $\pm 2S_d$) for S_d. The S_d value for hemodynamic variables should be reassessed in the light of recent changes in devices. With current continuous CO calculators, variability is lower than previously reported [44, 50, 51] because there is no manual intervention and because more than three measurements are averaged. We assume a mean error of 0 and a 95%CI of 10% [52]. The 95%CI of hemoglobin measurements can been estimated at 2% [53], and the 95%CI of HbO_2 saturation at 4% [54]. The global impact of these random errors on VO_2 is 18% (range −9 to +9%). This 95%CI obtained using PAC is close to values obtained when VO_2 is assessed by indirect calorimetry (95%CI=10%, range [−7 to +3%] [55]. Then random measurement errors may affect absolute values of variables but the VO_2 plateau starts at the same point of the DO_2 challenge as for exact values (Fig. 3). Therefore the clinical conclusion remains the same.

Mathematical coupling of data

Archie [56] emphasized mathematical coupling of data when the relationship between two variables having one or more common components is being assessed. Caution is required in distinguishing between "mathematical" coupling and "other" couplings. All biological variables coming from the same patient may be dependent on one another due to overt or hidden couplings. Any pertinent information provided by two variables derives exclusively from their (a) mean, (b) variability, and (c) associative function. Thus mathematical coupling, if present, is a classical form of the relationship between two conventional variables. It remains worthwhile to study the relationship between two variables if the underlying medical question makes sense, regardless of whether coupling is clearly present.

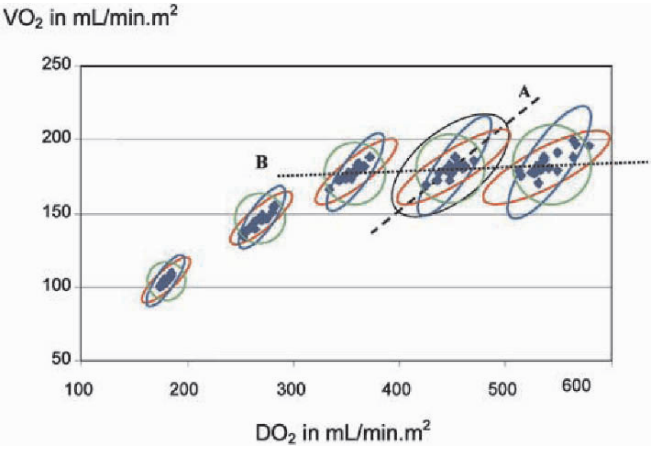


Fig. 3 Mathematical coupling in the VO_2/DO_2 relationship. *Black points* show 20 examples of the effect of random errors in our hypothetical experiment assuming a 95%CI of 10%, 2%, and 4% for CO, Hb, and $SavO_2$ measurements, respectively. The biphasic shape of the curve remains easy to identify. In the *red*, *blue*, and *green* areas the 95%CI of measured values increased to 20% for CO (or Hb), 10% for SaO_2, and 10% for SvO_2, respectively. *A* Global area and slope of mathematical coupling of all random errors. *B* Slope of the VO_2/DO_2 relationship

Mathematical coupling of random measurement errors

In contrast, mathematical coupling of measurement errors supplies no information of interest [6, 46, 57, 58]. When VO_2 and DO_2 are calculated from the same values of CO, Hb, and SaO_2, mathematical coupling of random error for each common variable linearly extends the dispersion of each VO_2/DO_2 point. The slope of each axis of variation depends on the associative functions between variables: 0.33 for CO, 1 for SaO_2, and 0 for SvO_2 because this is not a common variable. The combination of random errors for all components therefore creates an area of dispersion around the correct value that combines all specific variable axes (Fig. 3). Depending on the magnitude of possible error in each common variable, the global slope usually varies from 0.25 to 0.50. This global slope determines the statistical area of dispersion of measured values around the correct value of a single VO_2/DO_2 point (slope A in Fig. 3). It should not be confused with the slope of the plateau joining two consecutive points (slope B in Fig. 3), for which the probabilities of upward shifting and of downward shifting are similar.

These probabilities are similar but not exactly equal because the areas of dispersion around the exact value slope upwards and enlarge when DO_2 increases. Therefore the average B slope of many experiments is expected to be slightly positive. Calculation of a reliability coefficient (R_D) allows appropriate weighting of this slope and recalculation of the true relationship [57, 58]. Figure 3 provides an intuitive understanding of what R_D means. When the distance between two points increases (large DO_2 range) and when measurement variability decreases (small area of distribution), R_D tends to one and the impact of mathematical coupling of measurement errors tends to zero.

The final impact of mathematical coupling varies across experiments but can be very low. Using very large measurement errors, Stratton et al. [58] calculated that the impact of measurement errors (random effect plus mathematical coupling) on a VO_2 plateau gave an averaged slope of 0.06±0.05. This variability may account for a spurious slope between –0.04 and +0.16 [59, 60], in keeping with published studies [12, 44, 45, 46]. However, if this simulation were performed using the actual best variability, as shown in our hypothetical patient, the mean slope of the VO_2 plateau would be 0.007±0.05. This variability may account for a spurious slope between –0.10 and +0.10. The mathematical coupling of error is then negligible compared with the effect of random errors.

The use of empirical regression models

It thus makes sense to plot VO_2 against DO_2 to identify the critical DO_2 value in a specific situation. Obtaining more than two measurements can smooth the curve [59, 60]. However, the use of linear regression to calculate the VO_2/DO_2 slope raises several concerns. It is not possible to use simple models to characterize the VO_2/DO_2 relationship when the well-established physiological model predicts a biphasic curve [37]. Testing two different regression models to identify the biphasic shape of the curve requires that the inflection point be identified. The best pair of equations could be determined by testing all possible pairs of equations for all possible inflection points and by selecting the best pair of equations based on its minimum sum of residual sums of squares [61, 62].

Another concern arises because linear regression analyses are based on the minimum sum of squared residuals. The residual is the difference, for each x value, between observed and calculated y values on the x-axis. Therefore this model assumes that x values are correct (independent variable), or at least that the error on the x-axis is small compared to the error on the y-axis. This prerequisite is not met for the VO_2/DO_2 relationship even when DO_2 and VO_2 are measured independently. This is another source of spurious upsloping (Fig. 4). Because DO_2 is presumed to increase proportionally with time during a DO_2 challenge, using time as the actual independent variable is more appropriate (Figs. 4, 5). Additionally, the error in VO_2 is usually proportional to the VO_2 value; therefore the residuals of the regression line are not randomly distributed. Thus, when analyzing a family of regression lines from several patients, a more appropriate approach is a weighted linear regression model that also allows handling of between-patient variability [44, 63].

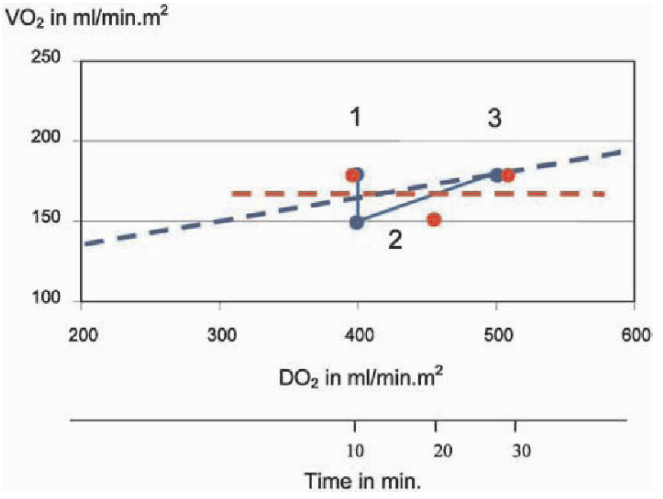


Fig. 4 Spurious upsloping due to an error in DO_2. *Points 1, 2, and 3* Three successive points of a VO_2/DO_2 plateau with a measurement error in point 2. The regression line between these three points shows a positive relationship (*blue dotted line*). This does not take into account the fact that during a DO_2 challenge DO_2 is expected to increase steadily. When time is used as the independent variable, the relationship is flat (*red dotted line*)

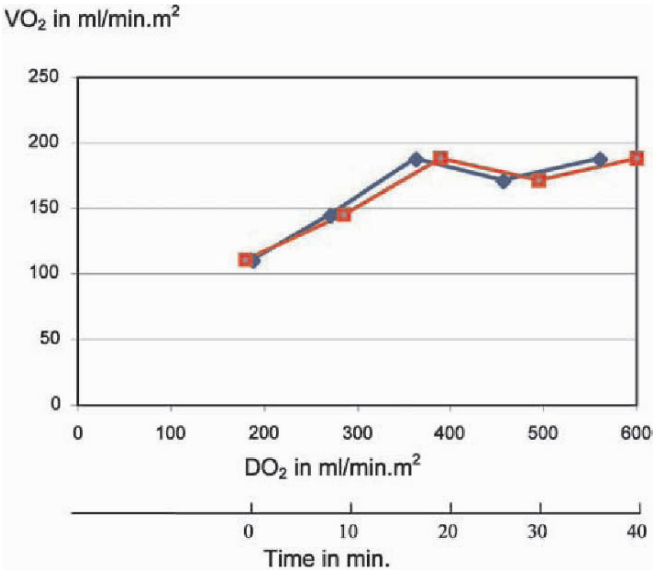


Fig. 5 Combination of the VO_2/DO_2 relationship and of the VO_2/time relationship in one random experiment in our hypothetical model, using the same random errors as in Fig. 3. For this figure DO_2 increased linearly with time. This helps to identify the critical VO_2 point and eliminates the possible effect of mathematical coupling of error

The impact of pooling data

Some studies of goal-oriented strategies for improving DO_2 and VO_2 found no improvement in survival but pooled patients with different disease processes, different metabolic needs, and different stages of shock [42, 43]. In contrast, the strategies were successful in studies investigating only postoperative surgical patients [18, 39, 41, 64, 65, 66, 67, 68], or patients who had a variety of diseases but were all included at the very early stage of shock [23, 69, 70]. Thus, the most conspicuous difference between studies that did and did not find better survival is heterogeneity vs. homogeneity of circulatory disorder characteristics in the study populations [71].

Analysis of the VO_2/DO_2 relationship on pooled data from several patients is also likely to show a spurious positive slope, for three reasons. Firstly, a large increase in mathematical coupling of errors is expected because the coefficient of variation for each measurement increases due to variability across patients, devices, and days [57]. Secondly, pooled data are likely to come from a mix of patients with inadequate resuscitation, adequate resuscitation, and relapsing shock. Thus with pooled data a substantial proportion of patients may have hidden dysoxia with physiological VO_2/DO_2 dependency. Thirdly, pooled data are also likely to come from patients with different metabolic needs. After circulatory shock critical DO_2 may vary from 8 to 21 ml/kg depending on the cause of the shock [22, 62, 72]. Even in comparable patients, differences in oxygen deficits, sedation, and/or activities may account for substantial differences in metabolic needs [73]. Therefore even if all patients are adequately resuscitated, analysis of pooled data from different levels of the VO_2 plateau results in a slope without any relevance. Thus it is more appropriate to average the slopes of each individual patient [44, 46].

Other means for matching VO_2 and needs

Although most of the limitations to the DO_2/VO_2 relationship can be corrected and/or optimized, matching VO_2 and needs by ensuring that a VO_2 plateau has been reached remains difficult. Considerable effort has been expended to develop alternatives. Three levels of clinical complexity can be distinguished.

1. Clinical improvement is a good indicator of adequate resuscitation [74]. In practice, VO_2 needs are usually met by decreasing metabolic needs, optimizing the hematocrit and SaO_2 level, and increasing blood flow empirically, until the clinical status improves. This situation does not require invasive hemodynamic investigations. A clear improvement in blood lactate clearance is also a good, minimally invasive, indicator of adequate resuscitation [74]. The blood lactate concentration alone fails to discriminate between dysoxia and aerobiosis [75, 76]. Although more reliable [4, 74, 77, 78], the time course of lactate levels is not an ideal marker. Lactate limitations have been recently reviewed by De Backer [76]. Diabetus mellitus, liver dysfunction, tissue reperfusion, catecholamine infusion, cellular metabolic alter-

ations, and inhibition of pyruvate dehydrogenase can result in a marked increase in blood lactate concentrations despite an improvement in tissue dysoxia. In these more complex situations where a clear clinical improvement and a normalization of blood lactate cannot be obtained, an evaluation of the adequacy of tissue oxygenation is required.

2) Some investigators have recommended that DO_2 be increased to supranormal values, greater than the usual critical level, without paying much attention to VO_2. This simplification of the method based on the VO_2/DO_2 relationship was associated with favorable outcomes in homogeneous population of high-risk surgery patients [18, 39, 41, 64, 67, 79], cardiogenic shock following myocardial infarction [69], and acute respiratory failure [23, 60] but failed to verify beneficial effects after onset of organ failure [67], or when different causes of shock were pooled [23, 60]. Other studies argue that sequential DO_2 and VO_2 calculations can be advantageously replaced by continuous measurement of CO [80] and/or SvO_2 [81]. More recently a clinical algorithm including $ScvO_2$ monitoring in patients with sepsis was shown to be clinically beneficial [70]. The use of these variables allows continuous comparison between measured values and targeted values.

However, targeting a preestablished value for DO_2, CO, or SvO_2 does not prove that these values meet the needs of an individual patient [22]. These preestablished targets are derived from normal findings or from survivors in selected populations of patients. The determination of the needed value of one given variable must take into consideration the limitation of other variables which are specific to the patient, his past history, the actual pathological event, the delay before onset of shock, and often the recent therapeutic interventions. Intuitive evaluation of the needed value for each variable in each specific case requires considerable expertise. Misinterpretation of PAC-related information and heterogeneity in the medical decision process is frequent [42, 43]. Even for experts the intuitive evaluation of needs may be subject to errors [22]. In some conditions, such as coronary disease, efforts to increase CO to "normalize" the cardiac index to more than 2.5 l min^{-1} m^{-2} or the SvO_2 value to more than 70% can be harmful. In addition, there is some evidence that an excessive O_2 supply may be deleterious, either via the useless metabolic cost of an excessive increase in DO_2 or via activation of nonoxidative systems. Failure to consider the latter two mechanisms may also explain the poor results obtained in studies targeting nonspecific "supranormal" values of DO_2 in heterogeneous populations of patients [42, 43] Thus treatment efforts should be limited to what is necessary (not less but not more).

3. All hemodynamic variables are interrelated, and the VO_2 value is the final result. Ensuring that VO_2 meets tissue needs is the best means of ensuring that global hemodynamic status is adequate [4]. VO_2, whether calculated by spirometry, indirect calorimetry, or using a PAC, is equal to needs when a plateau is reached in the VO_2/DO_2 relationship. No other relationship between two variables allows a clear identification of an inflection point between anaerobiosis and aerobiosis. The shape of the CO/SvO_2 relationship or the CO/EO_2 relationship is bi-curvilinear and similar to the DO_2/EO_2 relationship shown in Fig. 1. The inflexion point is much more difficult to identify.

Needs can also be estimated as the sum of VO_2 at basal metabolism, as indicated by age- and gender-specific normative data, and of other metabolic needs, as evaluated roughly based on a number of factors such as body temperature, which changes VO_2 needs by ±13% for each degree above or below 37°C. Depending on metabolic conditions, VO_2 needs usually vary from 0.7- to 3-fold of basal metabolism. The two latter methods can be combined. When the VO_2 plateau is reached at a value close to the estimated value, the patient's needs are probably met. Handling the large amount of information required to assess O_2 needs can be difficult [82, 83, 84], and computer assistance may be helpful (http://www.hemodyn.com) [4, 85].

Practical implications

The rationale for incorporating the VO_2/DO_2 relationship in our clinical management strategies is confirmed by several studies in which most of the limiting factors listed above were avoided [19, 20, 21]. In contrast, the chances of survival are very small in patients whose DO_2 and VO_2 fail to increase with treatment despite evidence of an oxygen deficit [19, 20, 21]. Thus, reaching the critical DO_2 ensuring that VO_2 needs are met is a crucial objective even if these two variables are calculated or intuitively estimated. To increase the likelihood of identifying clinical benefits related to bedside VO_2-guided therapy we suggest a number of practical guidelines.

Selection of early stage of shock states

Shock responds better to hemodynamic resuscitation in the early stages [70]. Although the final objective is to provide enough oxygen to each cell, there is some evidence that rapidly achieving a sufficient total body VO_2 is a prerequisite. Late-stage shock is a far more complex situation involving not only the macro- and microcirculation but also cell metabolism and the consequences of cell necrosis, which cannot be corrected by hemodynamic resuscitation alone.

Matching VO_2 with needs is the first objective

In most situations targeting a clinical improvement, a decrease in lactate level, or a preestablished value for CO or SvO_2 or both is an acceptable means of intuitively reaching an adequate VO_2. In complex situations, by plotting VO_2/DO_2 over time during a DO_2 challenge, the critical DO_2 value can be evaluated rapidly as the inflection area on the curve, and resuscitation efforts can then be limited to what is necessary. Because the critical DO_2 value can be determined visually with a 95%CI of 20%, it is reasonable to limit DO_2 to its observed critical value +20%. When lactate remains high despite evidence that a VO_2 plateau has been reached, there is no argument that increasing DO_2 further is beneficial [19, 20, 21]. Continuous efforts to decrease O_2 demand and to improve the microcirculation may be more appropriate [86, 87]. Combined analysis of the VO_2/DO_2 and VO_2/time relationships provide the most useful means of eliminating the effects of mathematical coupling of errors and the theoretical limitations due to DO_2 variability in the regression line derivations. A mild upsloping of the VO_2 plateau (slope <10%) should not be confounded with O_2 dependency. When necessary, the critical DO_2 point can be determined more accurately using the method developed by John-Alder and Bennet [61].

To reach this objective the best compromise must be identified, based on metabolic cost

In the case of persistent O_2 supply dependency the first way to match VO_2 and needs is to decrease the needs. Hyperthermia, acute respiratory failure, and/or pain increase VO_2 needs sharply. Antipyretic drugs [88], sedation [89], and mechanical ventilation [90] often produce a 50% decrease in VO_2 needs. This has exactly the same favorable effect as doubling the CO or doubling the EO_2.

When VO_2 needs have been lowered as much as possible, because $VO_2=EO_2\times DO_2$, matching VO_2 and needs implies to increase EO_2 or DO_2. Improving EO_2 must be always considered first, although this rarely produces a rapid VO_2 increase. Treating infection, excessive sedation, or excessive water retention, for example, may increase EO_2 [70]. Finally, when the only possibility is to increase DO_2, clinicians must choose among various means that presumably differ in their caloric effects. Arterial vasodilatation improves DO_2 and decreases myocardial O_2 requirements. In contrast, inotropic agents and vasoconstrictors have major caloric effects. Whatever the method used, a metabolic price must be paid for improving VO_2 and DO_2 to the critical values. This metabolic cost (a part of the total VO_2 requirement) must also be limited to what is strictly necessary.

Conclusion

Whereas there is a strong rationale for incorporating VO_2 into our early goal-oriented management strategies, proof that this improves patient survival is lacking. However, this should not lead to discontinuation of bedside VO_2 assessment, because no studies have been designed specifically to evaluate the potential benefits of rapidly increasing VO_2 to the specific value required by each individual patient at a given point in time. The present review is a call for such a study.

Acknowledgements The author thanks Dr. Hervé Mentec, Pr. Jean Daniel Chiche, and Pr. Didier Payen for their critical review of the manuscript.

References

1. Cain SM (1984) Supply dependency of oxygen uptake in ARDS: myth or reality? Am J Med Sci 288:119–124
2. Schumacker P, Cain S (1987) The concept of critical oxygen delivery. Intensive Care Med 13:223–229
3. Cain SM, Curtis SE (1991) Experimental models of pathologic oxygen supply dependency. Crit Care Med 19:603–612
4. Squara P, Journois D, Formela F, Dhainaut J, Sollet JP, Bleichner G (1994) Value of elementary, calculated and modeled hemodynamic variables. J Crit Care 9:223–235
5. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, Cunningham KF, Russell JA, Walley KR (1993) Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA 270:1724–1730
6. Russell JA, Phang PT (1994) The oxygen delivery/consumption controversy. Approaches to management of the critically ill. Am J Respir Crit Care Med 149:533–537
7. Kennedy FG, Jones DP (1986) Oxygen dependence of mitochondrial function in isolated rat cardiac myocytes. Am J Physiol 250:C374–C383
8. Vallet B, Curtis SE, Guery B, Mangalaboyi J, Menager P, Cain SM, Chopin C, Dupuis BA (1995) ATP-sensitive K+ channel blockade impairs O2 extraction during progressive ischemia in pig hindlimb. J Appl Physiol 79:2035–2042
9. Guery BP, Mangalaboyi J, Menager P, Mordon S, Vallet B, Chopin C (1999) Redox status of cytochrome a,a3: a noninvasive indicator of dysoxia in regional hypoxic or ischemic hypoxia. Crit Care Med 27:576–582
10. Cain SM (1975) Oxygen delivery and utilization in dogs with a sublethal dose of cobalt chloride. J Appl Physiol 38:20–25

11. Gilbert EM, Haupt MT, Mandanas RY, Huaringa AJ, Carlson RW (1986) The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. Am Rev Respir Dis 134:873–878
12. Hanique G, Dugernier T, Laterre PF, Dougnac A, Roeseler J, Reynaert MS (1994) Significance of pathologic oxygen supply dependency in critically ill patients: comparison between measured and calculated methods. Intensive Care Med 20:12–18
13. Haupt MT, Gilbert EM, Carlson RW (1985) Fluid loading increases oxygen consumption in septic patients with lactic acidosis. Am Rev Respir Dis 131:912–916
14. Kruse JA, Haupt MT, Puri VK, Carlson RW (1990) Lactate levels as predictors of the relationship between oxygen delivery and consumption in ARDS. Chest 98:959–962
15. Vincent JL, Roman A, De Backer D, Kahn RJ (1990) Oxygen uptake/supply dependency. Effects of short-term dobutamine infusion. Am Rev Respir Dis 142:2–7
16. De Backer D, Berre J, Moraine JJ, Melot C, Vanfraechem J, Vincent JL (1996) Effects of dobutamine on the relationship between oxygen consumption and delivery in healthy volunteers: comparison with sodium nitroprusside. Clin Sci (Lond) 90:105–111
17. Ronco JJ, Phang PT, Walley KR, Wiggs B, Fenwick JC, Russell JA (1991) Oxygen consumption is independent of changes in oxygen delivery in severe adult respiratory distress syndrome. Am Rev Respir Dis 143:1267–1273
18. Ziegler DW, Wright JG, Choban PS, Flancbaum L (1997) A prospective randomized trial of preoperative "optimization" of cardiac function in patients undergoing elective peripheral vascular surgery. Surgery 122:584–592
19. Ronco JJ, Fenwick JC, Wiggs BR, Phang PT, Russell JA, Tweeddale MG (1993) Oxygen consumption is independent of increases in oxygen delivery by dobutamine in septic patients who have normal or increased plasma lactate. Am Rev Respir Dis 147:25–31
20. Vallet B, Chopin C, Curtis SE, Dupuis BA, Fourrier F, Mehdaoui H, LeRoy B, Rime A, Santre C, Herbecq P et al (1993) Prognostic value of the dobutamine test in patients with sepsis syndrome and normal lactate values: a prospective, multicenter study. Crit Care Med 21:1868–1875
21. Rhodes A, Lamb FJ, Malagon I, Newman PJ, Grounds RM, Bennett ED (1999) A prospective study of the use of a dobutamine stress test to identify outcome in patients with sepsis, severe sepsis, or septic shock. Crit Care Med 27:2361–2366
22. Mohsenifar Z, Goldbach P, Tashkin DP, Campisi DJ (1983) Relationship between O2 delivery and O2 consumption in the adult respiratory distress syndrome. Chest 84:267–271
23. Bihari D, Smithies M, Gimson A, Tinker J (1987) The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. N Engl J Med 317:397–403
24. Nelson DP, Beyer C, Samsel RW, Wood LD, Schumacker PT (1987) Pathological supply dependence of O2 uptake during bacteremia in dogs. J Appl Physiol 63:1487–1492
25. Schumacker PT, Samsel RW (1989) Analysis of oxygen delivery and uptake relationships in the Krogh tissue model. J Appl Physiol 67:1234–1244
26. Gutierrez G, Marini C, Acero AL, Lund N (1990) Skeletal muscle PO2 during hypoxemia and isovolemic anemia. J Appl Physiol 68:2047–2053
27. De Backer D, Moraine JJ, Berre J, Kahn RJ, Vincent JL (1994) Effects of dobutamine on oxygen consumption in septic patients. Direct versus indirect determinations. Am J Respir Crit Care Med 150:95–100
28. Jeppsson A, Ekroth R, Friberg P, Kirno K, Milocco I, Nilsson F, Svensson S (2000) Renal effects of amino acid infusion in cardiac surgery. J Cardiothorac Vasc Anesth 14:51–55
29. Jacobson E (1963) Effects of histamine, acetylcholine, and norepinephrine on gastric vascular resistance. AM J Physiol 204:1013–1017
30. Duran W, Renkin E (1974) Oxygen consumption and blood flow in resting mamalians skeletal muscles. Am J Physiol 226:173–177
31. McCord J (1985) Oxygen-derived free radicals in post ischemic tissue injury. N Engl J Med 312:159–161
32. Schumacker PT, Chandel N, Agusti AG (1993) Oxygen conformance of cellular respiration in hepatocytes. Am J Physiol 265:L395–L402
33. Schumacker PT, Soble JS, Feldman T (1994) Oxygen delivery and uptake relationships in patients with aortic stenosis. Am J Respir Crit Care Med 149:1123–1131
34. Powers SR Jr, Mannal R, Neclerio M, English M, Marr C, Leather R, Ueda H, Williams G, Custead W, Dutton R (1973) Physiologic consequences of positive end-expiratory pressure (PEEP) ventilation. Ann Surg 178:265–272
35. Danek SJ, Lynch JP, Weg JG, Dantzker DR (1980) The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. Am Rev Respir Dis 122:387–395
36. Gutierrez G, Pohil RJ (1986) Oxygen consumption is linearly related to O2 supply in critically ill patients. J Crit Care 1:45–53
37. Clarke C, Edwards JD, Nightingale P, Mortimer AJ, Morris J (1991) Persistence of supply dependency of oxygen uptake at high levels of delivery in adult respiratory distress syndrome. Crit Care Med 19:497–502
38. Shoemaker W (1987) Relation of oxygen transport patterns to the pathophysiology and therapy of shock states. Intensive Care Med 13:230–243
39. Shoemaker W, Appel P, Kram H, Waxman K, Lee T (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 94:1176–1186
40. Shoemaker W (1989) Shock states: pathophysiology, monitoring, outcome, prediction and therapy. In: Shoemaker W (ed) Textbook of critical care. Saunders, Philadelphia, pp 977–993
41. Edwards J, Brown G, Nightingale P, et al (1989) Use of survivors' cardiorespiratory values as therapeutic goals in septic shock. Crit Care Med 17:1098–1103
42. Hayes MA, Timmings AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717–1722
43. Gattinoni L, Brazzi L, Pelozzi P (1995) A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025–1032
44. Phang PT, Cunningham KF, Ronco JJ, Wiggs BR, Russell JA (1994) Mathematical coupling explains dependence of oxygen consumption on oxygen delivery in ARDS. Am J Respir Crit Care Med 150:318–323
45. Mira J, Fabre J, Baigorr iF, Coste J, Annat G, Artigas A, Nitenberg G, Dhainaut J (1994) Lack of oxygen supply dependency in patients with severe sepsis. A study of oxygen delivery increased by military antishock trouser and dobutamine. Chest 106:1524–1531
46. Granton JT, Walley KR, Phang PT, Russell JA, Lichtenstein S (1998) Assessment of three methods to reduce the influence of mathematical coupling on oxygen consumption and delivery relationships. Chest 113:1347–1355
47. Perret C, Tagan D, Feihl F, Marini J (1996) Measuring Cardiac output: sources of error. In: The pulmonary artery catheter in critical care: a concise handbook. Arnette Blackwell, Cambridge p 109

48. Lakshminarayan S, Bernard S, Polissar NL, Glenny RW (1999) Pulmonary and bronchial circulatory responses to segmental lung injury. J Appl Physiol 87:1931–1936
49. Nierman DM, Schechter CB (1994) Mixed venous O2 saturation: measured by co-oximetry versus calculated from PVO2. J Clin Monit 10:39–44
50. Stetz CW, Miller RG, Kelly GE, Raffin TA (1982) Reliability of the thermodilution method in the determination of cardiac output in clinical practice. Am Rev Respir Dis 126:1001–1004
51. Rubini A, Del Monte D, Catena V, Attar I, Cesaro M, Soranzo D, Rattazzi G, Alati GL (1995) Cardiac output measurement by the thermodilution method: an in vitro test of accuracy of three commercially available automatic cardiac output computers. Intensive Care Med 21:154–158
52. Le Tulzo Y, Belghith M, Seguin P, Dall'Ava J, Monchi M, Thomas R, Dhainaut JF (1996) Reproducibility of thermodilution cardiac output determination in critically ill patients: comparison between bolus and continuous method. J Clin Monit 12:379–385
53. Picard F, Gicquel C, Marnet L, Guesnu M, Levy J (1999) Preliminary evaluation of the new hemotology analyser COULTER GEN-S in a university hospital. Clin Chem Lab Med 37 (6)
54. Scuderi PE, MacGregor DA, Bowton DL, Harris LC, Anderson R, James RL (1993) Performance characteristics and interanalyzer variability of PO2 measurements using tonometered human blood. Am Rev Respir Dis 147:1354–1359
55. Ronco J, Phang T (1991) Validation of an indirect calorimeter to measure oxygen consumption in critically ill patients. J Crit Care 6:36–41
56. Archie JP (1981) Mathematic coupling of data. Ann Surg 193:296–303
57. Moreno LF, Stratton HH, Newell JC, Feustel PJ (1986) Mathematical coupling of data: correction of a common error for linear calculations. J Appl Physiol 60:335–343
58. Stratton HH, Feustel PJ, Newell JC (1987) Regression of calculated variables in the presence of shared measurement error. J Appl Physiol 62:2083–2093
59. Dorinsky PM, Costello JL, Gadek JE (1988) Relationships of oxygen uptake and oxygen delivery in respiratory failure not due to the adult respiratory distress syndrome. Chest 93:1013–1019
60. Hankeln K, Gronemeyer R, Held A, Bohmert F (1991) Use of continuous noninvasive measurement of oxygen consumption in patients with adult respiratory distress syndrome following shock of various etiologies. Crit Care Med 19:642–649
61. John-Alder H, Bennet A (1981) Thermal dependence of endurance and locomotory energetics in a lizard. Am J Physiol 241:R342–R349
62. Komatsu T, Shibutani K, Okamoto K, Kumar V, Kubal K, Sanchala V, Lees DE (1987) Critical level of oxygen delivery after cardiopulmonary bypass. Crit Care Med 15:194–197
63. Feldman H (1988) Families of lines: random effects in linear regression analysis. J Appl Physiol 64:1721–1732
64. Boyd O, Grounds RM, Bennett ED (1993) A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 270:2699–2707
65. Yu M, Burchell S, Hasaniya NW, Takanishi DM, Myers SA, Takiguchi SA (1998) Relationship of mortality to increasing oxygen delivery in patients >or=50 years of age: a prospective, randomized trial. Crit Care Med 26:1011–1019
66. Wilson J, Woods I, Fawcett J, Whall R, Dibb W, Morris C, McManus E (1999) Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. BMJ 318:1099–1103
67. Kern JW, Shoemaker WC (2002) Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med 30:1686–1692
68. Fenwick E, Wilson J, Sculpher M, Claxton K (2002) Pre-operative optimisation employing dopexamine or adrenaline for patients undergoing major elective surgery: a cost-effectiveness analysis. Intensive Care Med 28:599–608
69. Creamer JE, Edwards JD, Nightingale P (1990) Hemodynamic and oxygen transport variables in cardiogenic shock secondary to acute myocardial infarction, and response to treatment. Am J Cardiol 65:1297–1300
70. Rivers E, Nguyen B, Havstat D, Ressler J, Muzzin A, Knoblish B, Peterson E, Tomlanovitch M (2001) Early goal-directed theraphy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
71. Pinsky M (1994) Beyond global oxygen supply-demand relations: in search of measures of dysoxia. Intensive Care Med 20:1–3
72. Shibutani K, Komatsu T, Kubal K, Sanchala V, Kumar V, Bizzarri DV (1983) Critical level of oxygen delivery in anesthetized man. Crit Care Med 11:640–643
73. Weissman C, Kemper M (1991) The oxygen uptake-oxygen delivery relationship during ICU interventions. Chest 99:430–435
74. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL (1991) Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest 99:956–962
75. Curtis SE, Cain SM (1992) Regional and systemic oxygen delivery/uptake relations and lactate flux in hyperdynamic, endotoxin-treated dogs. Am Rev Respir Dis 145:348–354
76. De Backer D (2003) Lactic acidosis. Intensive Care Med 29:699–702
77. Vincent J, Dufaye P, Berre J, Leeman M, De Gaute J, Kahn R (1983) Serial lactate determination during circulatory shock. Crit Care Med 11:449–451
78. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL (1996) Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 171:221–226
79. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 90:1052–1059
80. Mihm FG, Gettinger A, Hanson CW, 3rd, Gilbert HC, Stover EP, Vender JS, Beerle B, Haddow G (1998) A multicenter evaluation of a new continuous cardiac output pulmonary artery catheter system. Crit Care Med 26:1346–1350
81. Armaganidis A, Dhainaut JF, Billard JL, Klouche K, Mira JP, Brunet F, Dinh-Xuan AT, Dall'Ava-Santucci J (1994) Accuracy assessment for three fiberoptic pulmonary artery catheters for SvO2 monitoring. Intensive Care Med 20:484–488
82. Iberti T, Fischer E, Leibowitz A, Panacek E, Silverstein E, Albertson T (1990) A multicenter study of physician's knowledge of the pulmonary artery catheter. JAMA 12:2933–2940
83. Gnaegi A, Feihl F, Perret C (1997) Intensive care physicians' insufficient knowledge of right heart catheterization at the bedside: time to act? Crit Care Med 25:213–220
84. Squara P, Bennett D, Perret C (2002) Pulmonary artery catheter: does the problem lie in the users? Chest 121:2009–2015

85. Squara P, Dhainaut J, Lamy M, Perret C, Larbuisson R, Poli S, Armaganidis A, de Gournay J, Bleichner G (1989) Computer assistance for hemodynamic evaluation. J Crit Care 4:273–282
86. Kirov MY, Evgenov OV, Evgenov NV, Egorina EM, Sovershaev MA, Sveinbjornsson B, Nedashkovsky EV, Bjertnaes LJ (2001) Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. Crit Care Med 29:1860–1867
87. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, Zandstra DF (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360:1395–1366
88. Gozzoli V, Treggiari MM, Kleger GR, Roux-Lombard P, Fathi M, Pichard C, Romand JA (2004) Randomized trial of the effect of antipyresis by metamizol, propacetamol or external cooling on metabolism, hemodynamics and inflammatory response. Intensive Care Med 30:401–407
89. Bruder N, Lassegue D, Pelissier D, Graziani N, Francois G (1994) Energy expenditure and withdrawal of sedation in severe head-injured patients. Crit Care Med 22:1114–1119
90. Miwa K, Mitsuoka M, Takamori S, Hayashi A, Shirouzu K (2003) Continuous monitoring of oxygen consumption in patients undergoing weaning from mechanical ventilation. Respiration 70:623–630

Brian P. Kavanagh
L. Joanne Meyer

Normalizing physiological variables in acute illness: five reasons for caution

B.P.K. is funded by the Canadian Institutes of Health Research and the Ontario Ministry of Science and Technology.

Introduction

Acute illness is accompanied by the development of abnormal physiology. The development and severity of illness, as well as recovery, is paralleled by changes in the physiological variables that clinicians commonly monitor. Several factors may prompt clinicians to address and treat the variables in isolation from addressing the underlying disease. This article explores why clinicians may target and attempt to normalize abnormal physiological variables and identifies five reasons why such an approach can be hazardous.

Physiological parameters and illness

The evolution of many illnesses usually follows predictable patterns. For example, septic shock, an acute syndrome that is perhaps emblematic of critical care medicine and has a high mortality, commonly follows a foreseeable trajectory from localized to generalized infection, progressive hemodynamic deterioration, multiple organ dysfunction and, in over 30% of patients, death [1]. The cardiovascular changes associated with this syndrome typically include tachycardia and decreased blood pressure and usually an increase in cardiac output.

There are several reasons why clinicians monitor and attempt to correct such physiological variables in the acutely ill. First, in some highly specific situations this approach appears to work. Indeed, although seriously questioned [2, 3], randomized controlled clinical trials have suggested improvement in survival associated with rigorous control of plasma glucose in postoperative adult cardiac surgical patients [4] or more rapid resuscitation of patients with recently diagnosed septic shock [1]. Second, traditionally physiology has been the basis for assessment and treatment in critically ill patients, where monitoring directs how therapy is applied [5]. Although ongoing developments of molecular medicine and evidence-based medicine may alter how patients are treated in the future, the "physiological" approach, i.e., treatment based on physiological monitoring, has been a cornerstone of teaching in critical care medicine for decades [6]. Third, the extent to which physiological variables differ from normal values indicates how ill the patient is. This is important because clinicians know well that disease severity is an important indicator of ultimate outcome, and the assessment of severity is largely based on the degree to which the measured variables (e.g., perturbations of the cardiovascular, respiratory, and acid-base systems) differ from normal values. Indeed such impressions have been validated by numerous scoring systems that incorporate the extent of physiological derangement and predict outcomes

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_46, © Springer-Verlag Berlin Heidelberg 2009

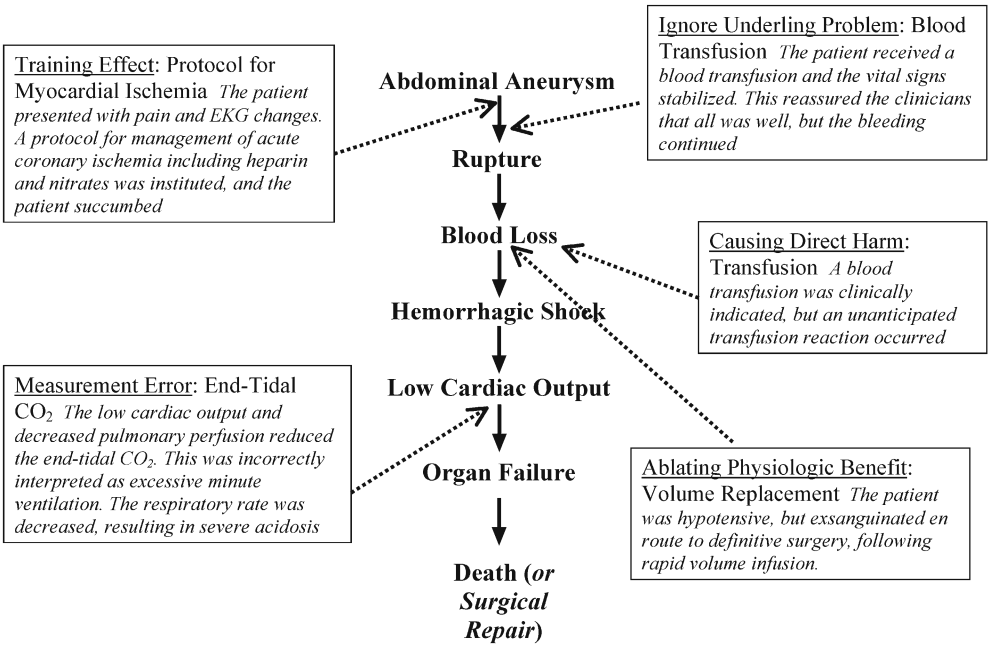


Fig. 1 An example of an acute illness state: hemorrhagic shock resulting from a ruptured abdominal aortic aneurysm. This flowchart illustrates how, using the five identified erroneous approaches, clinicians may intervene but direct therapy inappropriately

in populations of critically ill adults [7, 8] and children [9]. Fourth, beyond linking the initial degree of physiological derangement with severity of illness at the outset, established data have documented a close association between the sequential changes in physiological abnormalities and prognosis from acute illness [10]. Finally, in the same way that increasing deviation of variables from normal values reflects worsening of disease and poor prognosis, the converse is also true; normalization of abnormal variables parallels disease resolution and may be the principal objective evidence that a patient's condition is improving.

Despite this rationale the approach is imperfect and sometimes has disastrous results. A recent randomized controlled trial of nitric oxide synthase inhibition in septic shock was designed with simple pathophysiological rationale [11]; although the drug was effective in correcting the blood pressure and reversing shock [12], mortality was increased, not decreased [11]. Indeed, more comprehensive consideration, including attention to the critical importance of myocardial function in sepsis, might have predicted such a response [13, 14]. This vivid example illustrates the need for reflection about simplistic physiological rationale vs. demonstration of actual outcome benefit, and the potential for error associated with the former.

Normalization as a therapeutic endpoint

Based on the above considerations it is understandable why clinicians would instinctively focus on attempting to normalize abnormal physiological variables in patients who are acutely ill. Although several studies have demonstrated adverse effects of increasing levels of physiological support to supranormal levels (e.g., oxygen delivery [15], endocrine replacement [16]), clinicians may not appreciate dangers that may be associated with adjustment of variables to normal levels. We outline in this contribution five principles by which targeting and attempting to normalize physiological variables in acutely ill patients can lead to harm. These principles are illustrated by published examples and suggest global approaches for avoidance of such complications. An illustrated outline is provided in Fig. 1, focusing on the potential harm associated with correcting variables in a patient with ruptured abdominal aneurysm.

Ignoring the underlying problem

Classical approaches to treating acute illness involve provision of supportive care while at the same time addressing the primary problem. There are clearly some derangements in physiological variables, for example, severe hypoxemia, which are inherently life-threatening and must therefore be immediately treated. However, the clinician cannot be content with the return of measured variables to normal but must consider the underlying cause of the derangement. Failure to do so can result in significant harm to the patient.

Consider a patient presenting with severe hypovolemic shock from a massive gastrointestinal hemorrhage. Initial management may include fluids, blood products, and potentially vasopressors. It is gratifying to see the blood pressure climb to normal levels with the supportive care. It would be catastrophic, however, if one did not continue with definitive management of the bleeding. Similarly, a

patient with pyonephrosis from an obstructed ureter could develop septic shock and all the physiological derangements that occur with multiorgan dysfunction. The variables can look much better with usual critical care support (e.g., mechanical ventilation, fluids, vasopressors), but the patient is unlikely to improve overall without appropriate abscess drainage. In both situations it is obvious that the management of the patient requires both supportive care in addition to measures directed at the underlying cause.

Consider also each individual parameter monitored in the critical care unit. Derangements in any variable can have a myriad of causes. For example, pulse oximetry may inform the clinician about a potentially important change in a key physiological parameter, oxygen saturation. Desaturation can have any of numerous underlying causes, each requiring specific therapy. Such concerns are reflected in an editorial commentary on the intraoperative use of pulse oximetry wherein Fairley [17] wrote, "As the blindfolded anesthetist walks unknowingly towards the cliff of hypoxia.... the protective hand of the pulse oximeter sentry stops him from falling over the edge. The oximeter will not tell him why.... or the direction back."

Inducing harm

It has long seemed logical to clinicians that in acutely ill patients the restoration of vital functions to normal levels would result in reduced imposition on the physiological reserve and increase the probability, and the rapidity, of recovery [18]. In terms of transfusion of red blood cells, the rationale—representing conventional thinking up to 5 years ago—was that the increased O_2 delivery to tissues resulting from transfusion would permit greater O_2 consumption at the cellular level, and that this would translate into better outcome. Although simplistic, such concepts have long provided the impetus for "topping up" hemoglobin levels in acutely ill patients [19, 20].

In fact, this specific intervention—red cell transfusion—has been subjected to several important clinical studies, with unexpected results [21, 22]. To test the acute effects of red cell transfusion on tissue oxygenation, Marik and Sibbald [21] transfused patients suffering from systemic sepsis who were mildly anemic. Several important lessons were learned. First, global O_2 consumption was not increased when directly measured, despite indirect estimation suggesting the contrary. Second, at a local tissue level the majority of the transfusions resulted in adverse, not beneficial, changes in the oxygenation status. This was detected using gastric tonometry, a technique that assesses the O_2 supply-demand status of the vulnerable mucosal cells that line the stomach. In addition, the age of the transfused red cells was predictive of the degree of mucosal dysoxia, raising the possibility that storage duration, well within ranges common in North America, resulted in dysfunctional red cells.

While the pathophysiological responses to stored red cells are of mechanistic interest, a subsequent clinical study has provided important outcome data that may mandate changes in practice [22]. This study demonstrated that transfusion, even to a modest hemoglobin concentration, does not improve the status of anemic patients who are acutely ill in the intensive care unit; in fact subgroup analysis suggests that it may increase mortality [22], perhaps due to leukocyte-mediated actions [23] or altered volume status. Other examples exist where treatment aimed at normalizing variables can result in adverse outcome. For example, rapid correction of serum sodium concentration in cases of hyponatremia can result in brainstem destruction from central pontine myelinolysis [24]; conversely, rapid normalization of hyperosmolar states, such a hyperosmolar coma and diabetic ketoacidosis, can result in accelerated cerebral edema, with devastating consequences. In preterm infants the targeting of normal, not high, levels of oxygenation with low amounts of supplemental O_2 was hypothesized to improve neurodevelopment [25]. The hypothesis, although apparently soundly constructed, turned out to be false [25], and the approach instead of helping caused harm, resulting in an increased incidence of chronic lung disease. Finally, it is now apparent that the high tidal volumes associated with frankly lowered $PaCO_2$ towards or below normal levels in patients with acute respiratory distress syndrome (ARDS) are associated with increased mortality [26, 27, 28]; indeed alternative approaches to management of ARDS have been proposed [29, 30].

Ablation of physiological benefit

Whereas abnormal physiological variables always suggest an abnormal milieu or disease state, this does not mean that all abnormal variables are directly causing harm. Indeed, in some situations abnormal variables (e.g., mild hypotension) may benefit the patient.

Resuscitation of trauma victims who have developed hypotension due to blood loss has traditionally followed the "A, B, C" (i.e., airway, breathing, circulation) approach [31, 32]. In this scenario the patient's airway is controlled, breathing assured, and the depleted circulating volume is restored, all in rapid succession. However, the idea that circulating volume should be rapidly restored has undergone reevaluation during the past decade. Indeed, a randomized controlled trial in hypotensive trauma patients suggested that delayed correction of depleted circulating volume, as compared with the traditional immediate correction, leads to superior outcome in terms of survival and duration of hospital stay [33].

How could such an approach be beneficial? The results of that study suggest that hypotension in such a population [33], although reflecting severe depletion of circulating volume, is in fact protective because it reduces the

propensity for ongoing bleeding. The idea is supported by direct experimental evidence [34, 35]. Thus although it is not suggested that prolonged or severe hypotension is beneficial per se, or is even sustainable, the data do indicate that rapid volume correction without first attending to the sources of bleeding may be associated with elevated systemic blood pressure, reinitiating or increasing blood loss, and escalating the risk of death from hemorrhage [33]. Thus in this specific context and perhaps in others, for example, ruptured aortic aneurysm, temporary hypotension is protective.

There are other examples whereby an abnormal parameter is protective. It has been suggested that acidemia, the presence of a pH in the extracellular fluid that is lower than normal, may protect against the ongoing production of endogenous organic acids such as lactic and keto acids [36] as well as augmenting release of oxygen from hemoglobin [37, 38]. In diabetic ketoacidosis the standard approach is to provide insulin and careful rehydration, with assiduous attention to osmolality and electrolyte abnormalities. Administration of insulin addresses the generation of ketoacids, the fundamental biochemical disorder in this syndrome, and that as the ketoacids are cleared a major component of the acidemia resolves. In some circumstances clinicians have opted for treating the pH per se by buffering with intravenous bicarbonate. Significant concerns have arisen with this approach, however, with the evolving awareness that bicarbonate therapy may worsen, not improve, cerebral oxygenation in this condition [39]. Indeed, a clinical trial has demonstrated that such therapy does not help in treating the underlying condition; on the contrary, buffering the pH reverses resolution of the underlying ketoacidosis [40]. The same approach to normalizing pH has also been in another acute illness, septic shock [41]. Here the important findings were that buffering the pH did not improve either the cardiovascular performance, or the effectiveness of the vasoactive drugs being used [41].

Although not translated into the clinical setting, several laboratory studies suggest that abnormal physiology may have protective effects (e.g., hyperpyrexia in sepsis [42], and hyperosmolarity [43] and hypercapnia [44] in reperfusion injury). It has recently been suggested that multiple organ dysfunction in the context of critical illness represents a protective adaptive response rather than a set of circumstances to be aggressively prevented or reversed [45]. It was further argued that such organ dysfunction represents an effort on the part of the body to cope with on-going critical illness, and that attempts to correct this pathophysiological state could therefore result in harm [45].

Generation of associated errors

Medical error has been the focus of intense recent interest. In hospitalized patients error is an important source of morbidity and mortality, with 75% of errors being associated with "diagnostic mishaps" and 70% occurring in acute care settings [46]. An important type of error is misinterpretation of data, and when monitoring the acutely ill errors in the acquisition or interpretation of data can certainly mislead. Many examples of errors in monitoring have been described, and in many cases these result in a cascade of events that lead to significant patient harm [47].

We present an example in which experienced clinicians were misled by an incorrectly placed central vascular catheter; in this example, the response to subsequent therapy compounded the misimpression that catheter placement was correct, and that the therapy was effective [48]. The patient was assessed in the emergency room and was noted to be cyanosed, febrile, and hypotensive. The clinicians diagnosed septic shock in a patient with cyanotic cardiac disease, performed a procedure to insert a catheter into the femoral artery for monitoring purposes, and commenced infusion of a vasoconstrictor agent. The initial response, elevation in intravascular pressure in response to the therapy, appeared gratifying. However, the patient deteriorated, and upon placement of an additional central vascular catheter, which was placed in a central artery, it became obvious that the initial catheter had been placed in a vein instead of an artery. The error was detected because the waveforms of the two intravascular pressures were different. However, the error was possible because of the conditions presented. The patient had severe tricuspid valve regurgitation, and in the setting of systemic hypotension and cyanosis this resulted in severely elevated venous pressures being mistaken for arterial pressures. The error was compounded, however, because the response to therapy being sought, elevation in systemic arterial pressure, appeared to be obtained, but in fact the elevation was that of venous pressure. Thus instead of providing cardiovascular support with increased arterial pressure the therapy was compromising the heart, reducing forward flow, and increasing backward regurgitant flow. This is an example in which experienced clinicians were deceived by assumption of correct monitoring placement, a false assumption that was compounded by an apparent beneficial response to administered medication [48].

Training effect

The "science" of medicine involves understanding the processes and mechanisms of sickness. Such insight should enable clinicians to adapt to altered circumstances within the context of an illness and in addition to translate knowledge and techniques from one illness state to another. While we often consider why research findings are "lost in translation" between scientific research and patient benefit [49, 50], we may not consider how appropriate it is

to translate findings from one illness context to another. Examples of translation include application of positive airways pressure to sleep apnea instead of its original use in acute respiratory failure [51], the use of a therapy that was originally thought to act on the coagulation pathway (e.g., activated protein C) to treatment of sepsis [52], and high frequency oscillatory ventilation, developed originally for treatment of neonatal respiratory failure, and now being studied in adults with ARDS [53, 54]. Such translation of treatment modalities from one disease state or population to another presupposes that the clinician understands the mechanisms of action in the original disease as well as the mechanisms of action and risk-benefit profile in the subsequent disease. In fact, although physiological insight is continuously evolving and would be necessary to predict successful "knowledge transfer" from one situation to another, there is often a major gap between physiological expectation, as predicted by the clinician, and the results of careful context-specific physiological evaluation. Thus certain interventions that may seem to make sense from past experience may ultimately be detrimental when used in an alternative context.

We present an example of a traditional therapy, hyperventilation, almost certainly highly effective in incipient brainstem herniation but harmful when translated to other patients with brain trauma in the absence of cerebral hyperemia. It has been known for decades that hyperventilation reduces intracranial pressure [55], and in subsequent years it became apparent that this could be used to clinical advantage. In incipient brainstem herniation the intracranial pressure is critically elevated, and the compliance characteristic of the solid cranium and the flexible brain are such that whereas a slight increase in pressure results in herniation and brain death, a slight reduction prevents herniation at that time. Many such patients are the victims of head trauma; indeed, almost all patients with significant head injury serious enough to require intensive care or neurosurgical intervention have at least some degree of elevated intracranial pressure. However, because acute hyperventilation is accepted practice in conditions in which intracranial pressure is most dangerous, it became commonplace to institute the same therapy in the presence of intracranial hypertension, of lesser severity. Unfortunately, this assumed the "benefits" of hyperventilation (i.e., reduction in elevated intracranial pressure, prevention of brainstem herniation) in patients in whom such factors were not important. Conversely, whereas the disadvantages of hyperventilation (i.e., focal ischemia due to vasoconstriction, diminished release of O_2 from circulating hemoglobin, and potentially increased local O_2 demand) appear minimal when weighed against impending death or irreversible brain damage, they may not be minimal when weighed against no benefit. Indeed a randomized controlled trial demonstrated that prophylactic hyperventilation in patients with severe head trauma increased the incidence of long-term CNS disability [56].

Targeting variables: balancing theory, physiology, and outcome

The above account, with examples selected to support the particular points in question, requires balance; while balance is needed, in practice it is difficult. The clinician faces many problems in balancing among the issues he thinks he understands, those he does understand, and those for which he can provide evidence of benefit. Indeed the situation is even more complex because over time the response of some illness states changes. For example, goal-directed therapy in early septic shock may decrease mortality [1], but extending the notion of normalization to pharmacological supranormalization applied in later phases of the same illness can cause harm [15]. In another important condition common in the critically ill, acute respiratory distress syndrome, attempts to recruit lung volume, while successful in early stages of the disease, appear to be far less successful in more established disease [57]. Finally, hyperventilation, while harmful if applied globally to patients with severe head injury [56], may help a small number of patients with intracranial hypertension due to cerebral hyperemia.

The above clinical trials [1, 4, 22, 26, 33] are presented in a simplistic manner. While simplicity has the advantage of clarity, it ignores both the complex nature of the trials and the disease entities involved. Indeed it is important to note that several detailed critiques have generated significant debate about the interpretation and incorporation of clinical studies into practice [2, 30, 58, 59, 60].

Conclusion

Multiple examples of therapies exist in the acute care setting that are based on physiological principles, and that involve monitoring and titrating against physiological endpoints. Many such approaches either have been directly responsible for saving lives in acutely ill patients or have reflected such management strategies. Nonetheless, clinicians recognize that following physiological principles is not the same as normalizing all physiological variables. To illustrate this distinction, and the dangers associated with the latter, we have identified five patterns, with examples of each, whereby such an approach can lead to harm. As knowledge advances, clinicians will integrate evidence-based information, mechanistic knowledge, and evolving error prevention strategies to incorporate advances in monitoring technology for provision of optimal patient care.

Acknowledgements The authors acknowledge Drs. Deborah Cook and Arthur Slutsky for their insightful comments.

References

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
2. Finney SJ, Zekveld C, Elia A, Evans TW (2003) Glucose control and mortality in critically ill patients. JAMA 290:2041–2047
3. Natanson C, Danner RL (2002) Early goal-directed therapy reduced mortality and multiorgan dysfunction in severe sepsis or septic shock. ACP J Club 136:90
4. Berghe G van den, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R (2001) Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359–1367
5. Colice GL (1998) A historical perspective on intensive care monitoring. In: Tobin MJ (ed) Principles and practice of intensive care monitoring. McGraw Hill, New York, pp 1–31
6. Ibsen B (1999) Intensive therapy: background and development. A history of critical care and hyperbaric oxygen therapy as documented in the international anesthesiologiy clinics 37:1–14
7. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
8. Peres Bota D, Melot C, Lopes Ferreira F, Nguyen Ba V, Vincent JL (2002) The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction. Intensive Care Med 28:1619–1624
9. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastien B, Cotting J, Gottesman R, Joffe A, Pfenninger J, Hubert P, Lacroix J, Leclerc F (2003) Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet 362:192–197
10. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL (2001) Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286:1754–1758
11. Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S, Brockway M, Anzueto A, Holzapfel L, Breen D, Silverman MS, Takala J, Donaldson J, Arneson C, Grove G, Grossman S, Grover R (2004) Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. Crit Care Med 32:21–30
12. Watson D, Grover R, Anzueto A, Lorente J, Smithies M, Bellomo R, Guntupalli K, Grossman S, Donaldson J, Le Gall JR (2004) Cardiovascular effects of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) in patients with septic shock: results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). Crit Care Med 32:13–20
13. Cohen RI, Shapir Y, Davis A, Loona R, Scharf SM (2000) Comparison between selective and nonselective nitric oxide synthase inhibition and phenylephrine in normal and endotoxic swine. Crit Care Med 28:3257–3267
14. Barrington KJ, Etches PC, Schulz R, Talbot JA, Graham AJ, Pearson RJ, Cheung PY (2000) The hemodynamic effects of inhaled nitric oxide and endogenous nitric oxide synthesis blockade in newborn piglets during infusion of heat-killed group B streptococci. Crit Care Med 28:800–808
15. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717–1722
16. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ (1999) Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 341:785–792
17. Fairley HB (1989) Changing perspectives in monitoring oxygenation. Anesthesiology 70:2–4
18. Shoemaker WC, Sullivan MJ, Wo CCJ (2000) Hemodynamic evaluation and management of acute illnesses in the emergency department. Textbook of Critical Care 258–272
19. Czer LS, Shoemaker WC (1978) Optimal hematocrit value in critically ill postoperative patients. Surg Gynecol Obstet 147:363–368
20. Shoemaker WC, Bryan-Brown CW (1973) Resuscitation and immediate care of the critically ill and injured patient. Semin Drug Treat 3:249–267
21. Marik PE, Sibbald WJ (1993) Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA 269:3024–3029
22. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E (1999) A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med 340:409–417
23. Hebert PC, Fergusson D, Blajchman MA, Wells GA, Kmetic A, Coyle D, Heddle N, Germain M, Goldman M, Toye B, Schweitzer I, vanWalraven C, Devine D, Sher GD (2003) Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA 289:1941–1949
24. Lundbom N, Laurila O, Laurila S (1993) Central pontine myelinolysis after correction of chronic hyponatraemia. Lancet 342:247–248
25. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM (2003) Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 349:959–967
26. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Fihlo G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
27. Hickling KG, Walsh J, Henderson S, Jackson R (1994) Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit. Care Med. 22:1568–1578
28. Hickling KG, Wright T, Laubscher K, Town IG, Tie A, Graham P, Monteath J, A'Court G (1998) Extreme hypoventilation reduces ventilator-induced lung injury during ventilation with low positive end-expiratory pressure in saline-lavaged rabbits. Crit Care Med 26:1690–1697
29. Marini JJ, Gattinoni L (2004) Ventilatory management of acute respiratory distress syndrome: a consensus of two. Crit Care Med 32:250–255
30. Dreyfuss D, Saumon G (2002) Evidence-based medicine or fuzzy logic: what is best for ARDS management? Intensive Care Med 28:230–234
31. Trauma Life Support Committee, National Association of Emergency Medical Technicians in cooperation with Committee on Trauma, American College of Surgeons (1995) Prehospital trauma life support instructors' manual, 3rd edn. Mosby, St. Louis
32. American College of Surgeons (1997) Advanced trauma life support for doctors, 6th edn. American College of Surgeons, Chicago
33. Bickell WH, Wall MJ, Pepe PE, Martin RR, Ginger VF, Allen MK, Mattox KL (1994) Immediate versus delayed fluid resuscitation for hypotensive patients with pentrating torso injuries. N Engl J Med 331:1105–1109

34. Dronen SC, Stern SA, Wang X, Stanley M (1993) A comparison of the response of near-fatal acute hemorrhage models with and without a vascular injury to rapid volume expansion. Am J Emerg Med 11:331–335
35. Stern SA, Dronen SC, Birrer P, Wang X (1993) Effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. Ann Emerg Med 22:155–163
36. Hood VL, Tannen RL (1998) Protection of acid-base balance by pH regulation of acid production. N Engl J Med 339:819–826
37. Laffey JG, Kavanagh BP (2002) Hypocapnia. N Engl J Med 347:43–53
38. Laffey JG, Kavanagh BP (1999) Carbon dioxide and the critically ill—too little of a good thing? (hypothesis paper). Lancet 354:1283–1286
39. Bureau MA, Begin R, Berthiaume Y, Shapcott D, Khoury K, Gagnon N (1980) Cerebral hypoxia from bicarbonate infusion in diabetic acidosis. J Pediatr 96:968–973
40. Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K (1996) Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. J Clin Endocrinol Metab 81:314–320
41. Cooper DJ, Walley KR, Wiggs BR, Russell JA (1990) Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. Ann Intern Med 112:492–498
42. Jiang Q, Cross AS, Singh IS, Chen TT, Viscardi RM, Hasday JD (2000) Febrile core temperature is essential for optimal host defense in bacterial peritonitis. Infect Immun 68:1265–1270
43. Rizoli SB, Kapus A, Parodo J, Rotstein OD (1999) Hypertonicity prevents lipopolysaccharide-stimulated CD11b/CD18 expression in human neutrophils in vitro: role for p38 inhibition. J Trauma 46:794–798
44. Shibata K, Cregg N, Engelberts D, Takeuchi A, Fedorko L, Kavanagh BP (1998) Hypercapnic acidosis may attenuate acute lung injury by inhibition of endogenous xanthine oxidase. Am J Respir Crit Care Med 158:1578–1584
45. Singer M, De Santis V, Vitale D, Jeffcoate W (2004) Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet 364:545–548
46. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, Hebert L, Newhouse JP, Weiler PC, Hiatt H (1991) The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med 324:377–384
47. Deyo RA (2002) Cascade effects of medical technology. Annu Rev Public Health 23:23–44
48. Gilron I, Magder S (1995) Monitoring complication due to a pulsatile femoral vein from tricuspid regurgitation. Can J Anaesth 42:141–143
49. Wolpert HA, Anderson BJ (2001) Metabolic control matters: Why is the message lost in the translation? The need for realistic goal-setting in diabetes care. Diabetes Care 24:1301–1303
50. Lenfant C (2003) Shattuck lecture-clinical research to clinical practice-lost in translation? N Engl J Med 349:868–874
51. Sullivan CE, Issa FG, Berthon-Jones M, Eves L (1981) Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet I:862–865
52. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709
53. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, Carlin B, Lowson S, Granton J (2002) High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 166:801–808
54. Froese AB (1997) High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! Crit Care Med 25:906–908
55. Lundberg N, Kjallquist A, Bien C (1959) Reduction of increased intracranial pressure by hyperventilation. A therapeutic aid in neurological surgery. Acta Psychiatr Scand 34 [Suppl 139]:1–64
56. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF (1991) Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized trial. J. Neurosurg. 75:731–739
57. Grasso S, Mascia L, Del Turco M, Malacarne P, Giunta F, Brochard L, Slutsky AS, Marco Ranieri V (2002) Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. Anesthesiology 96:795–802
58. Silverman HJ, Miller FG (2004) Control group selection in critical care randomized controlled trials evaluating interventional strategies: an ethical assessment. Crit Care Med 32:852–857
59. Miller FG, Silverman HJ (2004) The ethical relevance of the standard of care in the design of clinical trials. Am J Respir Crit Care Med 169:562–564
60. Eichacker PQ, Gerstenberger EP, Banks SM, Cui X, Natanson C (2002) Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. Am J Respir Crit Care Med 166:1510–1514

Shane M. Tibby
Andrew Durward

Interpretation of the echocardiographic pressure gradient across a pulmonary artery band in the setting of a univentricular heart

Introduction

Pulmonary artery (PA) banding has been established as a palliative surgical technique for congenital heart defects for over 50 years [1]. With the advent of earlier corrective surgery, the indications for PA banding have changed over time [2, 3]. Currently these include: (a) limitation of pulmonary blood flow in the setting of an excessive left-to-right shunt; (b) regulation of pulmonary blood flow in the univentricular circulation; and (c) a training procedure for the left ventricle prior to conversion to the systemic pumping chamber (late presentation of D-transposition of the great arteries, or prior to a double-switch procedure with L-transposition).

From a physiological perspective the goals of PA banding in conditions (a) and (b) are threefold:

1. To protect the pulmonary arteries from hypertrophy and the development of irreversible pulmonary vascular disease. This phenomenon is thought to be both pressure- and flow mediated [4].
2. To regulate the pulmonary to systemic flow ratio (Qp:Qs) in the setting of a univentricular heart, and minimize the risk of developing inadequate systemic and coronary blood flow.
3. To prevent the development of congestive heart failure from an excessive total cardiac output (Qp plus Qs).

This article primarily considers PA banding and its interpretation in the setting of a univentricular heart. For simplicity sake, we assume complete mixing of venous return in the systemic ventricle, and an absence of streaming. In addition, we do not discuss limitations in echocardiographic measurements using the Doppler principle or the Bernouilli equation (as these can be found in any major textbook), but instead assume that such measurements are made correctly.

Assessment of the adequacy of banding

The importance of accurate assessment of PA band tightness is highlighted by the fact that undiagnosed loose bands are associated with a higher mortality [5]. The commonest bedside method for assessing the adequacy of a PA band involves echocardiographic estimation of the pressure drop across the band, via the modified Bernoulli equation, in tandem with measurement of arterial oxygen saturations using pulse oximetry [2, 6]. This provides a measure of the degree of protection from pressure effects on the pulmonary vasculature (via the band gradient), and an estimate of Qp:Qs (from the arterial oxygen saturation). Optimal band tightness in the univentricular setting is thought to be represented by an estimated pressure drop of the order of 40–60 mmHg, with arterial oxygen saturations in the range of 75–85% [3, 7]. Several publications have highlighted the value of concurrent assessment of parameters such as acid-base status, arterial blood lactate measurements, urine output and chest X-ray, but this is by no means universal [3, 8].

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_47,

Limitations of this method

Unfortunately, this may be an oversimplification, as there are many factors which can confound interpretation of both band gradient and arterial oxygen saturation.

Band gradient

The mean pressure drop across a PA band is a function of the flow through the band and the resistance of the band itself (pressure drop = flow × resistance). This means that a low resistance band receiving high flow may yield the same pressure drop as a high resistance band with low flow; thus, when interpreting a band gradient, it is necessary to consider concurrently *all* factors which contribute to flow through the band, including the following: total cardiac output; the ratio of systemic to pulmonary flow (Qp:Qs); systemic vascular resistance; band resistance; and the resistance of the pulmonary vasculature distal to the band (the latter two may be regarded functionally as being in series). These factors are represented in Fig. 1.

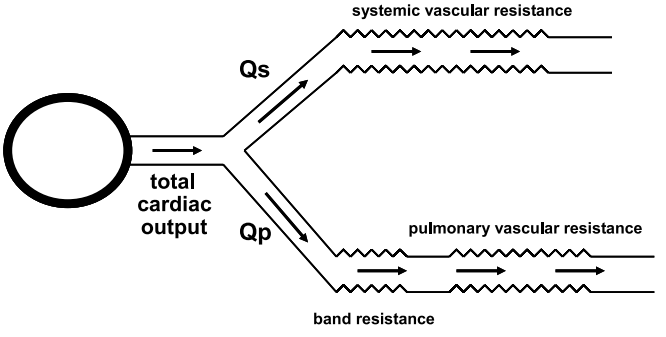


Fig. 1 Variables which influence the pressure gradient across the pulmonary arterial band. *Qp*, pulmonary blood flow; *Qs*, systemic blood flow

Arterial oxygen saturations

For a univentricular heart with common mixing, arterial saturations are a function of both the proportionate inflow from the various venous sources (systemic, pulmonary, coronary and thebesian) and their oxygen saturations. Fig. 2 shows two hypothetical situations that may produce identical arterial oxygen saturations. (For ease of demonstration coronary and thebesian venous blood flow is ignored, and pulmonary venous blood is considered to be fully saturated.) Fig. 2a shows an "ideal" situation with a Qp:Qs of 1:1, resulting in an arterial saturation of 80%. Fig. 2b shows overcirculation, with a Qp:Qs of 3:1. In this setting, inadequate systemic flow has resulted in a reduction in the mixed venous saturation, the net result also yielding an arterial saturation of 80%. The limitation of arterial saturation as an estimate of Qp:Qs is well documented in the intensive care management of patients with hypoplastic left heart syndrome [9–11]. The importance of concurrent measurement of the mixed venous saturation has been highlighted in this setting. Typically this is expressed in terms of the arteriovenous oxygen saturation difference.

Incorporating arteriovenous oxygen saturation difference into band assessment

We suggest that postoperative assessment following PA band placement could be improved by considering the arteriovenous oxygen saturation difference in conjunction with the band gradient. The theoretical relationship between these two variables is shown in Fig. 3, which was constructed by application of the Fick principle, shunt and vascular resistance equations (Table 1) to a hypothetical patient. For simplicity sake, we made several haemodynamic assumptions, including: complete mixing (i. e. a true univentricular heart); absence of intracardiac

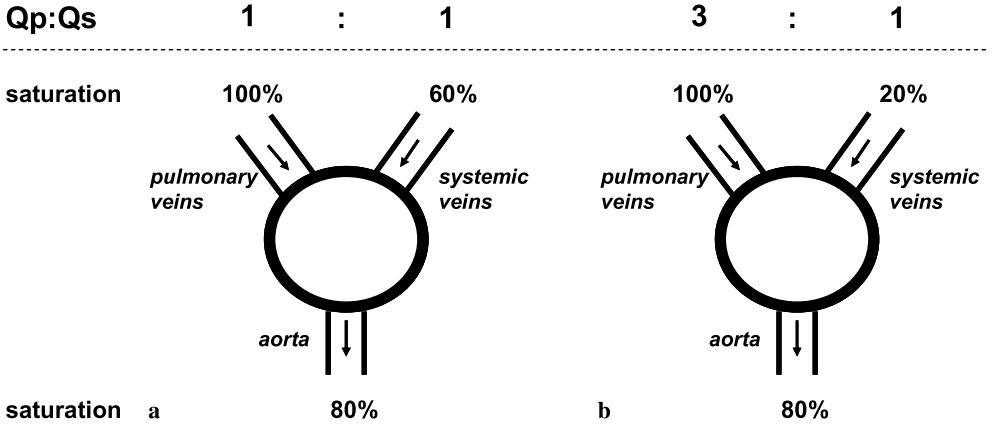


Fig. 2 a,b Limitation of the arterial oxygen saturation as an estimate of pulmonary to systemic flow ratio (*Qp:Qs*)

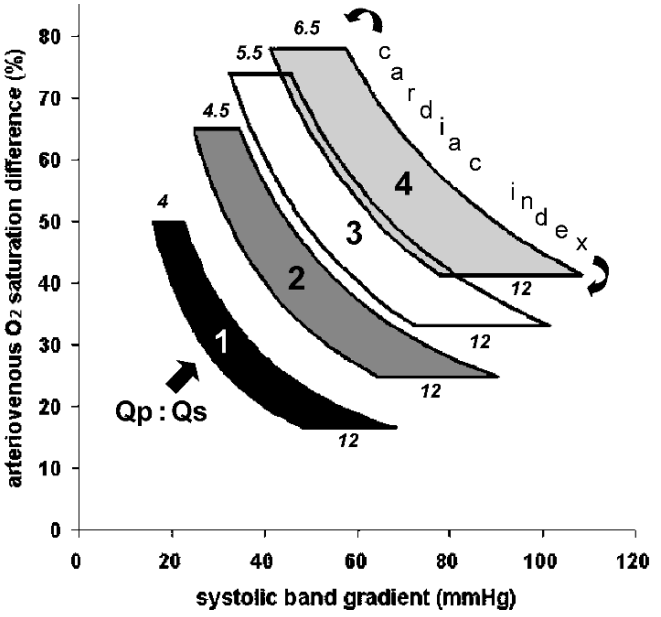


Fig. 3 Theoretical relationship between systolic pressure drop across the pulmonary arterial band and the arteriovenous oxygen saturation difference. Haemodynamic assumptions include: complete intracardiac mixing; oxygen consumption of 160 ml/min m^{-2}; haemoglobin of 120 gm/l; pulmonary venous oxygen saturation of 100%; and constant systemic and pulmonary vascular resistances (the latter being distal to the band). Four regions of "iso-shunt" are shown, with Qp:Qs ranging from 1 to 4. Total cardiac index (systemic plus pulmonary) is measured in litres per minute per square metre, and may vary within each iso-shunt region. Low cardiac index is associated with higher arteriovenous oxygen saturation differences and smaller band gradients occurring towards the top of the iso-shunt blocks, whereas higher cardiac index occurs with smaller arteriovenous oxygen saturation differences and larger band gradients

streaming of blood; oxygen consumption at the lower limit for age (160 ml/min m^{-2}); haemoglobin of 120 g/l; pulmonary venous saturations of 100%; and constant systemic and pulmonary vascular resistances. (Here pulmonary resistance refers to that which is distal to the band.)

Superimposed on the diagram are blocks which represent potential areas of constant shunt (Qp:Qs). The width of these blocks was chosen by considering the upper and lower limits for band resistance that may occur with an error of ± 1 mm when applying the Trussler formula to infants [12]. (If we assume laminar flow, then band resistance is proportional to band radius to the fourth power; and an error of ± 1 mm in the Trussler-derived band circumference will alter the band radius by ± circumference/2π, resulting in a potential variation in resistance of approximately 30% for infants from 2 to 5 kg.) If band resistance is known, we can calculate the mean pressure drop across the PA band for a given cardiac output and Qp:Qs, which is related to the systolic pressure drop by a factor of one third (given that mean blood pressure = diastolic pressure plus one-third pulse pressure, and that diastolic pressure is likely to be equal on either side of the band). Because it is pressure drop that we are estimating, the absolute values for systolic and diastolic pressures in this setting are irrelevant.

This produces a relationship between band gradient and arteriovenous oxygen saturation difference incorporating a variety of shunts and a range of total (pulmonary plus systemic) cardiac output (Fig. 3). Within each iso-shunt block, it can be seen that low total cardiac output occurs towards the upper portion and is associated with a higher arteriovenous difference. Conversely, cardiac output increases, and arteriovenous difference decreases as one progresses towards the lower end of each iso-shunt block.

Limitations of this method

The number of assumptions (and hence unmeasured variables) means that this diagram cannot be used to estimate Qp:Qs in individual patients, as a unique diagram must be constructed for every different combination of oxygen consumption, pulmonary venous oxygen saturation, haemoglobin concentration and systemic and pulmonary

Table 1 Haemodynamic formulae. VO_2, oxygen consumption (ml/min m^{-2}); CaO_2, arterial oxygen content (ml/l); $C_{MV}O_2$, mixed venous oxygen content; *Hgb*, haemoglobin concentration (g/l); SaO_2, arterial oxygen saturation; PaO_2, partial pressure of dissolved oxygen; $S_{Ao}O_2$, aortic oxygen saturation; $S_{MV}O_2$, mixed venous oxygen saturation; $S_{PV}O_2$, pulmonary venous oxygen saturation; $S_{PA}O_2$, pulmonary arterial oxygen saturation

Parameter	Formula
Fick's principle	Cardiac index = $VO_2/(CaO_2–C_{MV}O_2)$
Oxygen content	$CaO_2 = (1.34 \times Hgb \times SaO_2) + (PaO_2 \times 0.003)$
Pulmonary to systemic flow ratio	$Qp:Qs = S_{Ao}O_2 – S_{MV}O_2/S_{PV}O_2 – S_{PA}O_2$
Vascular resistance index	VRI = 79.9 × pressure drop/cardiac index

Units of measurement: cardiac index, l/min m^{-2}; vascular resistance index, dyn-s/cm^5 m^{-2}

Table 2 Hypothetical scenarios demonstrating the inconsistency of the relationship between arterial oxygen saturation, band gradient and degree of shunt (*Qp:Qs*). In this case a high Qp:Qs is differentiated from an optimal Qp:Qs on the basis of the arteriovenous oxygen saturation difference. *Ao*, aortic; *MV*, mixed venous; *PV*, pulmonary venous; *PA*, pulmonary arterial

Scenario	Band resistance dyn-s/cm^5 m^{-2}	Band gradient mean (mm Hg)	Band systolic pressure drop (mm Hg)	Cardiac index (l/min m^{-2})				Oxygen saturation (%)				Arteriovenous difference (%)
				Pulmonary	Systemic	Total	Qp:Qs	Ao	MV	PV	PA	
1 A	428	26.7	80	4.98	1.42	6.40	3.5 : 1	80	10	100	80	70
1 B	428	26.7	80	4.98	3.32	8.29	1.5 : 1	80	50	100	80	30
2 A	161	10.0	30	4.98	1.42	6.40	3.5 : 1	80	10	100	80	70
2 B	161	10.0	30	4.98	3.32	8.29	1.5 : 1	80	50	100	80	30

vascular resistances. In addition, the diagram has been simplified such that the blocks of Qp:Qs ratios represent whole numbers only; inclusion of smaller increments (Qp:Qs of 1.5, 2.5, etc.) would result in a degree of overlap that would render the diagram uninterpretable.

Our calculations utilise oxygen saturations from mixed venous blood, whereas in clinical practice central venous oxygen saturations are usually obtained. Consistent with other authors, we recommend that the superior vena caval site be used, as the haemodynamic assumptions remain valid [13, 14].

Lastly, the calculations refer to placement of a single, central pulmonary artery band, and not to the placement of bilateral (right and left pulmonary artery) banding that is utilised as part of the hybrid procedure for hypoplastic left heart syndrome [15]; however, Fig. 3 does illustrate two important points:

1. For a given band gradient, larger Qp:Qs values are associated with higher arteriovenous oxygen differences.
2. Higher band gradients are likely to be associated with larger shunts, which is counterintuitive to traditional teaching.

This can be illustrated further by considering two typical clinical scenarios. A patient with a measured arterial oxygen saturation of 80% and a systolic band gradient of 80 mmHg is likely to be interpreted as having an adequate band (scenario 1), whereas a patient with the same oxygen saturation but band gradient of 30 mmHg may be interpreted as having a band that is too loose (scenario 2). In reality, neither assumption may be true, as shown in Table 2. Scenarios 1A and 1B demonstrate that the high band gradient may occur with either an elevated or an optimal Qp:Qs. In the former, the high band gradient is occurring because of high flow through the pulmonary circuit (which may be due to an elevated systemic vascular resistance), and the "adequate" arterial saturations of 80% are occurring because the mixed venous saturations are very low (10%). The two situations are readily differentiated by comparing the arteriovenous oxygen saturation differences. In scenario 2, the lower band gradient is a function of decreased band resistance (a looser band). Similar to scenario 1, markedly different Qp:Qs are possible because of an altered ratio of systemic vascular resistance to the pulmonary vascular resistance distal to the band; again, these may manifest identical arterial oxygen saturations but can be differentiated by the arteriovenous oxygen saturation difference.

The requirement for central venous blood sampling means that this technique is not practical for all patients following PA banding. In addition, it may take some time for post-operative haemodynamic equilibrium to be achieved; thus, it may be unwise to interpret adequacy of PA banding with this method in the early post-operative period (0–12 h). However, the technique may be of most benefit (a) in the intermediate post-operative period, (b) for patients who are unable to be successfully weaned from mechanical ventilation and (c) for those with ongoing heart failure. It also underlines the importance of adopting a wider physiological perspective, rather than interpreting a haemodynamic parameters in isolation.

References

1. Muller WH Jr, Danimann JF Jr (1952) The treatment of certain congenital malformations of the heart by the creation of pulmonic stenosis to reduce pulmonary hypertension and excessive pulmonary blood flow; a preliminary report. Surg Gynecol Obstet 95:213–219
2. Corno AF (2005) Pulmonary artery banding. Swiss Med Wkly 135:515–519
3. Plunkett M, Laks H. Pulmonary Artery Banding. E-medicine http://www.emedicine.com/ped/topic2900.htm accessed 28 March 2007
4. Granton JT, Rabinovitch M (2002) Pulmonary arterial hypertension in congenital heart disease. Cardiol Clin 20:441–457
5. Pinho P, von Oppell UO, Brink J, Hewitson J (1997) Pulmonary artery banding: adequacy and long-term outcome. Eur J Cardiothorac Surg 11:105–111
6. Fyfe DA, Currie PJ, Seward JB, Tajik AJ, Reeder GS, Mair DD, Hagler DJ (1984) Continuous-wave Doppler determination of the pressure gradient across pulmonary artery bands: hemodynamic correlation in 20 patients. Mayo Clin Proc 59:744–750
7. Wernovsky G, Bove EL (1998) Single ventricle lesions. In: Chang AC, Hanley FL, Wernovsky G, Wessel DL (eds) Pediatric cardiac intensive care. Lippincott Williams and Wilkins, Philadelphia, pp 275–276
8. Corno AF (2000) Revised pulmonary artery banding. Ann Thorac Surg 69:1295–1296
9. Barnea O, Austin EH, Richman B, Santamore WP (1994) Balancing the circulation: theoretic optimization of pulmonary/systemic flow ratio in hypoplastic left heart syndrome. J Am Coll Cardiol 24:1376–1381
10. Charpie JR, Dekeon MK, Goldberg CS, Mosca RS, Bove EL, Kulik TJ (2001) Postoperative hemodynamics after Norwood palliation for hypoplastic left heart syndrome. Am J Cardiol 87:198–202
11. Taeed R, Schwartz SM, Pearl JM, Raake JL, Beekman RH III, Manning PB, Nelson DP (2001) Unrecognized pulmonary venous desaturation early after Norwood palliation confounds Gp:Gs assessment and compromises oxygen delivery. Circulation 103:2699–2704
12. Albus RA, Trusler GA, Izukawa T, Williams WG (1984) Pulmonary artery banding. J Thorac Cardiovasc Surg 88:645–653
13. Rivers EP, Ander DS, Powell D (2001) Central venous oxygen saturation monitoring in the critically ill patient. Curr Opin Crit Care 7:204–211
14. Li J, Zhang G, McCrindle BW, Holtby H, Humpl T, Cai S, Caldarone CA, Redington AN, Van Arsdell GS (2007) Profiles of hemodynamics and oxygen transport derived by using continuous measured oxygen consumption after the Norwood procedure. J Thorac Cardiovasc Surg 133:441–448
15. Akintuerk H, Michel-Behnke I, Valeske K, Mueller M, Thul J, Bauer J, Hagel KJ, Kreuder J, Vogt P, Schranz D (2003) Stenting of the arterial duct and banding of the pulmonary arteries: basis for combined Norwood stage I and II repair in hypoplastic left heart. Circulation 105:1099–1103

Theodoros Vassilakopoulos

Ventilator-induced diaphragm dysfunction: the clinical relevance of animal models

Abstract Experimental evidence suggests that controlled mechanical ventilation (CMV) can induce dysfunction of the diaphragm, resulting in an early-onset and progressive decrease in diaphragmatic force-generating capacity, called ventilator-induced diaphragmatic dysfunction (VIDD). The mechanisms of VIDD are not fully elucidated, but include muscle atrophy (resulting from lysosomal, calpain, caspase and proteasome activation), oxidative stress, structural injury (disrupted myofibrils, increased numbers of lipid vacuoles, and abnormally small and disrupted mitochondria), myofiber remodeling and mitochondrial dysfunction. The major clinical implication of the VIDD is to limit the use of CMV to the extent possible. Partial (assisted) modes of ventilatory support should be used whenever feasible, since these modes attenuate the deleterious effects of mechanical ventilation on respiratory muscles.

Keywords Mechanical ventilation · Complications · Disuse atrophy · Weaning · Diaphragm

Introduction

Controlled mechanical ventilation (CMV) is a mode of ventilatory support where the respiratory muscles are not contracting and the ventilator takes full responsibility for inflating the respiratory system. Animal studies suggest that CMV can induce dysfunction of the diaphragm, resulting in decreased force-generating capacity, called ventilator-induced diaphragmatic dysfunction (VIDD) [1].

The frequency of CMV use cannot be determined with certainty. The international mechanical ventilation study group reported that 13% of mechanically ventilated patients receive a neuromuscular blocker for 8% of the total days of ventilatory support [2]. In these patients full ventilatory support is mandatory. There are additional patients who are on full ventilator support without receiving neuromuscular blockers (e.g. traumatic brain injury patients, postoperative neurosurgical patients, comatose patients, and patients with status epilepticus on barbiturate coma to suppress seizure activity). Thus, a significant proportion of mechanically ventilated patients are on full ventilator support and could be potentially vulnerable to VIDD.

The mechanisms of this dysfunction and the clinical relevance for mechanically ventilated patients will be the subject of this review.

Evidence from animal models

Diaphragmatic force and endurance following CMV

Measurements in intact animals

Controlled mechanical ventilation leads to decreased diaphragmatic force-generating capacity in various animal species. In the intact diaphragm studied in vivo, transdiaphragmatic pressure (Pdi) generation upon phrenic nerve stimulation declines at all stimulation frequencies (20–100 Hz) (Fig. ESM 1) [3–6]. The decline ensues early (1 day in rabbits [5], 3 days in piglets [4, 6]) and is progressive, Pdi decreasing to 63% of the control value after 1 day of CMV and to 49% of the control value after 3 days of CMV in rabbits [5]. Within a few days (3 days in rabbits, 3–5 days in piglets, 11 days in baboons) the

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_48, © Springer-Verlag Berlin Heidelberg 2009

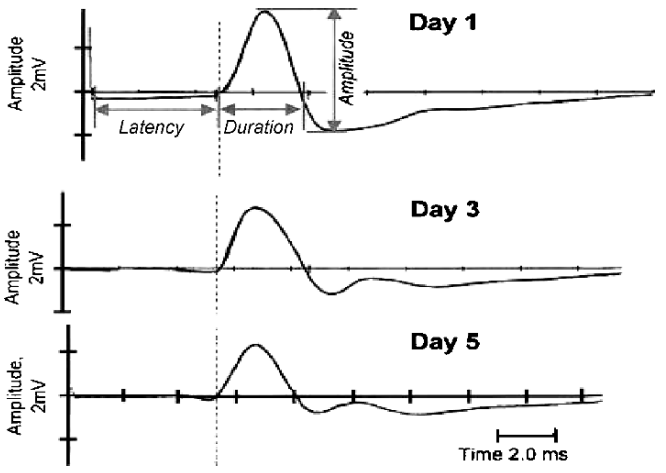


Fig. 1 The evoked compound muscle action potential (*CMAP*) tracings of the diaphragm upon electrical stimulation of the phrenic nerves in vivo from one piglet on days 1, 3 and 5 of CMV. The time from the stimulus to the onset of CMAP (*Latency*) does not change after 3-5 days of CMV, whereas the amplitude of CMAP is progressively reduced. From reference [4] with permission. This indicates that the neural and neuromuscular transmission are not affected when VIDD develops and that the contractile dysfunction resides within the diaphragmatic myofibers

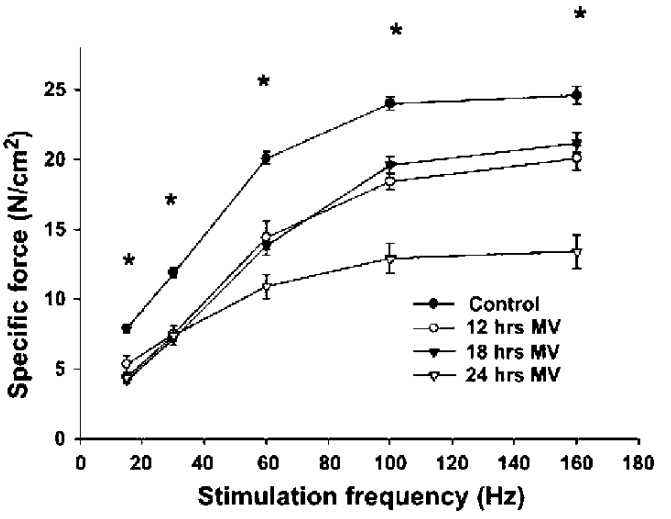


Fig. 2 Effects of prolonged CMV on the diaphragmatic force–frequency response in vitro in rats. Values are means ± SE. Compared with control, CMV (all durations) resulted in a significant ($*p < 0.05$) reduction in diaphragmatic specific force production at all stimulation frequencies. From reference [8] with permission. Please note that the decline in force is progressive, worsening as the duration of CMV is prolonged

pressure generating capacity of the diaphragm declines by 35–50%. The endurance of the diaphragm is also compromised [3].

The decreased force-generating capacity ensuing with CMV is not due to changes in lung volume [6] or to changes in abdominal compliance [3, 4]. Neural and neuromuscular transmission remain intact, as evidenced by the lack of changes in phrenic nerve conduction (latency) and the stable response to repetitive stimulation of the phrenic nerve [4] (Fig. 1). In contrast, the compound muscle action potential (CMAP) declines progressively, suggesting that excitation/contraction coupling or membrane depolarization may be involved (Fig. 1) [4]. Thus, the CMV-induced impairment in the diaphragmatic force-generating capacity appears to reside within the myofibers.

In vitro measurements

The isometric (both twitch and tetanic) tension development by isolated diaphragmatic strips in vitro [7–10] confirm the in vivo findings and suggest that the decline in contractility is an early (12 h) and progressive phenomenon (Fig. 2) [8], the isometric force declining by 30–50% after 1–3 days of CMV in rats. The force–velocity relationship of the diaphragm also changes, the maximum shortening velocity increasing after CMV [11] (Fig. ESM 2; for details and implications see the ESM text).

The effects of CMV on diaphragm in vitro fatigability are controversial (see ESM).

Pathophysiology

Muscle atrophy

CMV leads to diaphragmatic atrophy [7, 9, 10, 12]. Ventilator-induced atrophy [13] develops rapidly (as early as 12 h after the institution of CMV [14]) and is more pronounced in the diaphragm, which atrophies earlier than the peripheral skeletal muscles that are also inactive during CMV [7, 9, 12]. Two days of CMV with PEEP (2 cmH_2O) induced atrophy in rabbits [10], whereas 3 days of CMV without PEEP were inadequate to induce atrophy [5], which suggests that the rapidity of atrophy development might be augmented with the use of PEEP. The increased lung volume at the end of expiration with the use of PEEP would put the passive diaphragm in a relatively shortened position, and skeletal muscles atrophy faster in the shortened position [15, 16].

The decreased volume of the cytoplasm (atrophy) was observed in the presence of decreased number of myonuclei (skeletal muscle cells are multinucleated cells and theoretically a single myonucleus can sustain the necessary gene expression for a limited area of the cytoplasm, a relationship known as the myonuclear domain [17]), so that the myonuclear domain remains constant [14]. This decrease in myonuclear content was mediated by caspase-3-dependent increased apoptosis, which was evident as early as 6 h after the onset of CMV [14]. Both the apoptosis and the atrophy were attenuated with caspase-3 inhibition [14].

Atrophy can result from decreased protein synthesis, increased proteolysis or both. Six hours of CMV in rats

decreased the in vivo rate of mixed muscle protein synthesis (an average synthesis rate for all muscle proteins) by 30% and the rate of myosin heavy chain protein synthesis by 65%, both of which persisted throughout 18 h of CMV [18]. In addition, 24 h of CMV suppressed the mRNA levels of insulin-like growth factor (IGF)-1, which stimulates protein synthesis [19]. Thus, CMV decreases protein synthesis in the diaphragm.

Increased proteolysis has been documented in diaphragm strips of animals subjected to 18 h of CMV [12]. All systems of proteases that mammalian cells have for intracellular proteolysis (the lysosomal proteases, the calpains, the caspases and the proteasome system) [20]), are activated after CMV [12, 14, 21]. Calpains do not fully degrade, but only partially cleave proteins in vivo (Fig. ESM 3). This renders the proteins amenable to the proteasome [13]. The stimulus for calpain activation in not known, but calcium elevation in the cell is prerequisite. The reduced (mRNA) levels of sarcoplasmatic reticulum calcium ATPase (the enzyme that removes calcium from the sarcoplasm) secondary to 24 h of CMV [22] may contribute to calpain activation. The lysosomal proteases such as cathepsin B are also activated secondary to CMV [21]. Caspases are proteases that can degrade proteins and especially complexes of actin and myosin [20, 23]. Upregulation of caspase-3 expression has been documented in the diaphragm secondary to CMV [14]. Caspase-3 can be activated by oxidative stress, increased intracellular calcium and increased calpain activity [20].

Using the proteasome inhibitor lactacystin, Shanely et al. [12] showed that the proteasome is involved in the augmented proteolysis of the diaphragm strips from CMV animals. The proteasome is a multi-subunit multi-catalytic

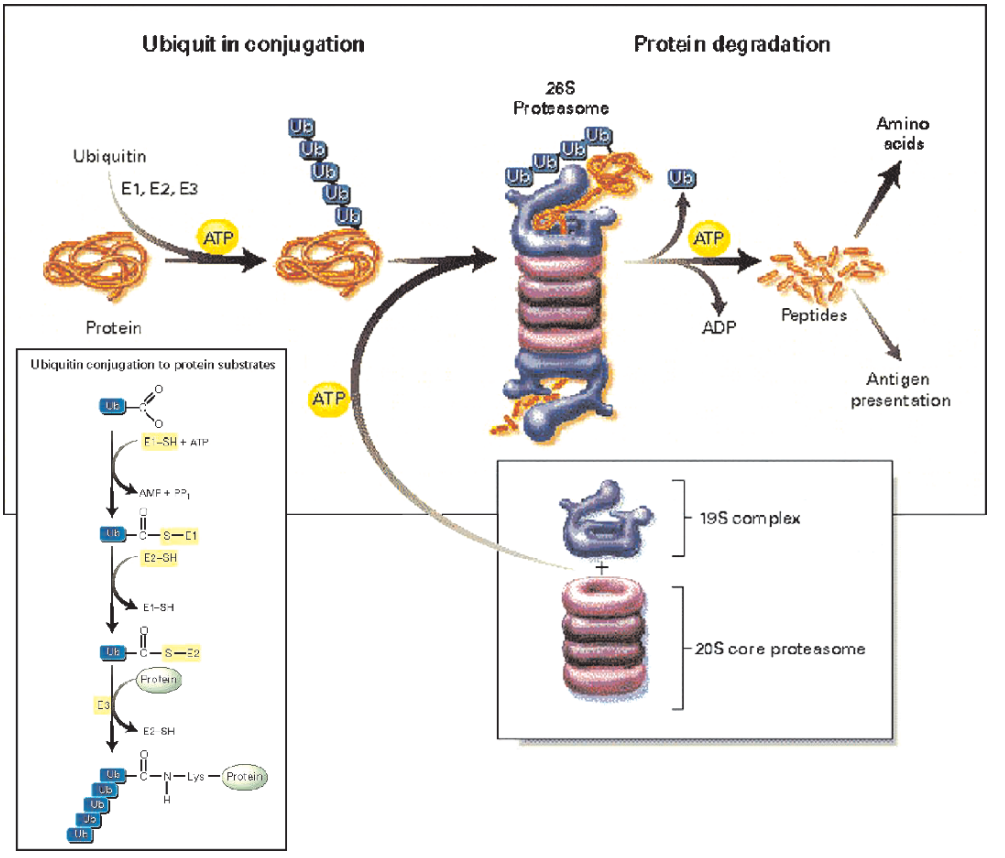


Fig. 3 The ubiquitin–proteasome pathway of proteolysis. Proteins degraded by the ubiquitin–proteasome pathway are first conjugated to ubiquitin (*Ub*). The process of linking ubiquitin to lysine residues in proteins destined for degradation (inlet) involves the activation of ubiquitin by the E1 enzyme in an ATP-dependent reaction. Activated ubiquitin is transferred to an E2 carrier protein and then to the substrate protein, a reaction catalyzed by an E3 enzyme (E3 ligase). This process is repeated as multiple ubiquitin molecules are added to form a ubiquitin chain. In ATP-dependent reactions, ubiquitin-conjugated proteins are recognized and bound by the 19S complex, which releases the ubiquitin chain and catalyzes the entry of the protein into the 20S core proteasome. Degradation occurs in the 26S core proteasome, which contains multiple proteolytic sites within its two central rings. Peptides produced by the proteasome are released and rapidly degraded to amino acids by peptidases in the cytoplasm or transported to the endoplasmic reticulum and used in the presentation of class I antigens. The ubiquitin is not degraded but is released and reused. *SH* denotes sulfhydryl, PP_1 pyrophosphate, and *ATP*, *ADP* adenosine tri- and diphosphate respectively. From reference [25] with permission

complex that exists in two major forms (Fig. 3): the core 20S proteasome can be free or bound to a pair of 19S regulators to form the 26S proteasome, which degrades (in an ATP-dependent manner) proteins covalently bound to a polyubiquitin protein chain (ubiquitinated proteins). The binding of ubiquitin to protein substrates requires the ubiquitin-activating enzyme (E1), which utilizes ATP-derived energy to form a covalent link with a ubiquitin protein, followed by transfer of the active ubiquitin moiety to a ubiquitin-conjugating enzyme (E2) and finally transfer of this ubiquitin to the protein to be degraded via a ubiquitin ligase (E3). Accordingly, CMV increases the level of ubiquitin–protein conjugates in the diaphragm [24] that are the substrates of the 26S proteasome (Fig. 3) [25]. Furthermore, key enzymes involved in the function of ubiquitin–proteasome pathway are upregulated in the diaphragm, such as the skeletal muscle-specific ubiquitin ligases (E3 enzymes) muscle atrophy F-box (MAFbx/Atrogin-1) [24, 26, 27] and muscle ring finger-1 (MuRF1) [24, 27]. However, not all mRNAs of the ubiquitin–proteasome pathway are upregulated in the diaphragm, since no change was found for the ubiquitin-conjugating enzyme $E2_{14k}$, or the polyubiquitin secondary to 12 h of CMV [24]. The relatively short period of CMV (12 h) may have been inadequate for the upregulation of these components of the ubiquitin–proteasome pathway. In any case, increased protein ubiquitination in the diaphragm secondary to CMV did not require increased expression of all components of the ubiquitin-proteasome pathway.

Interestingly, Shanely et al. showed that CMV resulted in 500% increase in the 20S proteasome activity [28], which is specialized in degrading proteins oxidized by reactive oxygen species. Oxidative damage of a protein results in its partial unfolding, exposing hidden hydrophobic residues (Fig. ESM 4) [29, 30]. Therefore, an oxidized protein does not need to be further modified by ubiquitin conjugation to confer a hydrophobic patch, nor does it require energy from ATP hydrolysis to unfold.

Oxidative stress

CMV is associated with augmented oxidative stress in the diaphragm, as indirectly evidenced by the rise in protein oxidation (elevated protein carbonyls [12]; Fig. 4) and lipid peroxidation (elevated 8-isoprostane [12], total lipid hydroperoxides [27, 28] and thiobarbituric reactive substance content [6]) and directly shown by the increased emissions of dichlorofluorescein (a molecule that fluoresces upon reacting with reactive oxygen species within cells) when diaphragmatic strips from CMV-treated animals are incubated in vitro with the dye [31]. The onset of oxidative injury is rapid, occurring within 6 h after the institution of CMV in rats [28], and is long-lasting, being present after 3 days of CMV in piglets [6].

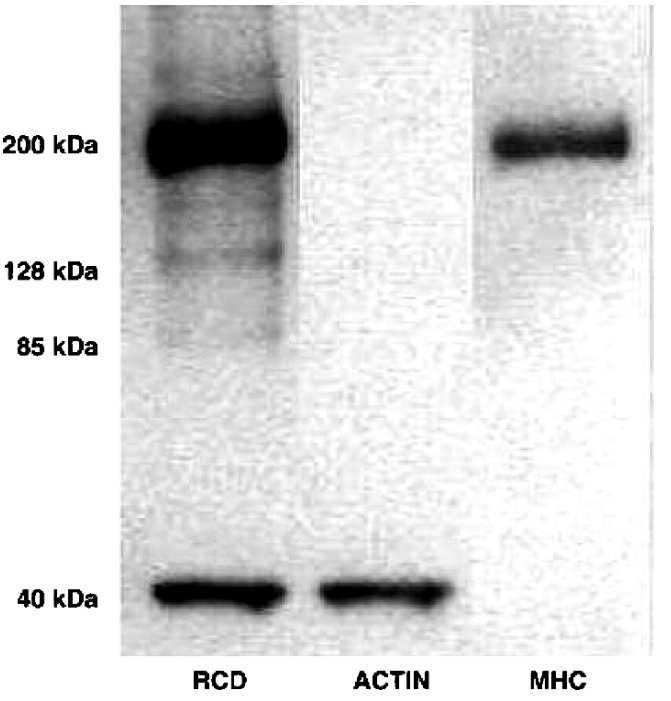


Fig. 4 Illustration of Western blots using monoclonal antibodies to identify oxidized proteins with molecular masses of 200–40 kDa. *Left lane:* Reactive carbonyl derivatives (*RCD*), which are the footprints of protein modifications induced by oxidative stress in insoluble proteins isolated from the diaphragm of an animal exposed to CMV for 18 h. *Middle* and *right lanes:* The same membrane stripped of the 2,4-dinitrophyenylhydrazone antibody (the antibody recognizing RCD was removed) and then sequentially re-probed with monoclonal antibodies specific for rat skeletal muscle actin and all myosin heavy chain (*MHC*) isoforms. From reference [28] with permission

The response of antioxidant enzymes in the diaphragm to CMV is controversial and the mechanisms of oxidative stress generation remain elusive (for both see ESM).

Oxidative stress can modify proteins involved in energetics, excitation–contraction coupling, intracellular calcium regulation and force generation [32]. CMV-induced diaphragmatic protein oxidation was evident in proteins with molecular masses of about 200, 128, 85, and 40 kDa [28]. These findings raise the possibility that actin (40 kDa) and/or myosin (200 kDa) undergo oxidative modification during CMV (Fig. 4), which would be expected to compromise diaphragm contractility. This intriguing possibility awaits confirmation by more specific identification of the modified proteins.

Oxidative stress and especially the lipid peroxidation product 4-hydroxy-2-nonenal (produced in the diaphragm under conditions such as sepsis or resistive loading [33]) can reduce the activity of plasma membrane calcium ATPase [34]. This would retard calcium removal from the diaphragmatic myofibers and would contribute to calcium accumulation and calpain activation [20]. Oxidative stress could also injure various intracellular structures (organelles).

Structural injury

Structural abnormalities of different subcellular components of diaphragm myofibers progressively develop after 2–3 days of CMV in rabbits (Fig. ESM 5) [5, 11, 35]. The changes consisted of disrupted myofibrils, increased numbers of lipid vacuoles in the sarcoplasm, and abnormally small mitochondria containing focal membrane disruptions. Similar alterations were observed in the external intercostal muscles of ventilated animals [35] but not in the hindlimb muscle [5]. The structural abnormalities have detrimental effects on diaphragmatic contractility. The number of abnormal myofibrils is inversely related to the force output of the diaphragm [5]. The mechanisms of injury have not been elucidated, but may involve activation of calpains, which have the ability to degrade several sarcomeric proteins and direct cellular injury secondary to augmented oxidative stress [1].

Muscle fiber remodeling

Muscle fibers are classified as either slow-twitch (type I) or fast-twitch (type II) based on their myosin heavy chain (MHC) isoform content (in increasing order of maximum shortening velocity, MHC isoforms are I, IIa, IIx and IIb) [36]. Muscles can modify their MHC phenotype in two ways: preferential atrophy/hypertrophy of fibers containing a specific MHC isoform and actual transformation from one fiber type to another. Both short-term [12, 22] and long-term [9] CMV result in significant modifications of the MHC phenotype in rats. Within 12 and 18 h of CMV both type I and II fibers are reduced in size [12, 14], yet type II fibers exhibit much greater reduction [12], and within 24 h of mechanical ventilation the transcript levels of the MHC 2A and 2B isoforms are decreased by ~20% [22], consistent with the preferential atrophy observed in the above-mentioned studies. This modification of the MHC phenotype could contribute to the force decline of the diaphragm, since the force produced by slow fibers is less than the force produced by fast fibers [37], but at the same time could explain the increased fatigue resistance observed [38], (though this result is not uniform in all studies), since type I fibers have higher oxidative capacity and thus endurance than type II fibers. However, prolonged (44–93 h) CMV in rats results in a different pattern of MHC phenotype modification, with decreased number of type I fibers and increases in fast MHC isoforms mainly within hybrid fibers (fibers co-expressing both slow and fast isoforms) [9]. This slow-to-fast transformation does not compromise diaphragmatic contractility per se, but reduces diaphragmatic endurance, since fewer slow-twitch fatigue-resistant fibers are available. The basis of this different response is not known, but may be related to the ventilatory strategy or the duration of CMV (< 24 h vs. 44–93 h). Despite similar respiratory rates, the tidal volume and thus the degree of phasic diaphragmatic shortening was double in the study of Shanely et al. [12] (1 ml/100 g body weight) compared to the tidal volume used by Yang et al. [9] (0.5 ml/100 g body weight). In contrast, the degree of tonic diaphragmatic shortening imposed by positive end-expiratory pressure (PEEP) was much greater in the study of Yang et al. [9] (PEEP = 4 cmH_2O) than in the study of Shanely et al. [12] (PEEP = 1 cmH_2O). Whether different ventilatory patterns result in different fiber type transformations is not known. Interestingly, in limb muscles the duration of inactivity influences the fiber type transformation observed. Whereas short-term inactivity results in fast-to-slow transformation (similar to short-term mechanical ventilation), longer inactivity results in slow-to-fast transformation. Although the duration of inactivity was much longer (6 weeks) in limb muscles, the diaphragm might exhibit much faster adaptation to inactivity, since it is continuously contracting throughout life with much higher duty cycles (duration of contraction relative to relaxation) than the limb muscles. In rabbits, 2 days of CMV resulted in atrophy of the respiratory muscles and in decreased cross-sectional area of type IIa and IIb fibers but not type I fibers (fast-to-slow transformation), with no change in their proportion [10], whereas 3 days of mechanical ventilation did not affect the cross-sectional areas of slow and fast fibers but resulted in a decrease in the proportion of the fast MHC2X isoform (a form of fast-to-slow transformation) [5]. The differences might be attributed to the presence of PEEP (2 cmH_2O in [10], 0 cmH_2O in [5]) or to the episodes of breakthrough diaphragmatic activity observed [5].

Interestingly, 24 h of CMV in rats resulted in changes in the mRNA expression of the myogenic regulatory transcription factors myoD (myogenic determination gene D) (decrease) and myogenin (increase) with a consequent decrease in the myoD/myogenin ratio [22]. These transcription factors bind to the promoter of many skeletal muscle-specific genes and drive myoblast determination and differentiation during embryogenesis, but may also influence fiber type transformation in the adult muscle. The levels of myoD are significantly greater in fast than in slow muscle fibers, myogenin is preferentially located in slow fibers, and their ratio is highly correlated with muscle fiber phenotype. Whether this correlation is causal is debated [39]. In the diaphragm, the deletion of MyoD resulted in a shift in MHC phenotype from MHC IIb toward the slower MHC IIa and IIx (fast to slow transformation), associated with decreased force-generating capacity [40]. Thus, the decreased myoD/myogenin ratio in the diaphragm secondary to 24 h of CMV [22] might contribute to the observed fast-to-slow fiber type transformation.

Remodeling could also lead to reduced optimal diaphragmatic length [7, 9] (see ESM).

Drugs

Anesthetics should be excluded as causes of VIDD, since studies that used appropriate controls (to the extent feasible, i.e. a group of anesthetized spontaneously breathing animals) concluded that the decreased contractility was due to the effects of mechanical ventilation per se (and not to anesthetic use) [5].

Neuromuscular blockers [3, 9] cannot solely account for the decreased contractility secondary to CMV, since decreased contractility was also observed in studies that did not use these drugs [5, 8]. However, the effects of 24 h of CMV and aminosteroidal neuromuscular blockers (rocuronium) are synergistic in depressing diaphragm contractility, in inducing atrophy of type IIx/b fibers and in upregulating the ubiquitin ligase (E3) MuRF1 (but not the E3 MAFbx/Atrogin-1) [27], a synergism not observed with different doses of benzylisoquinoline neuromuscular blockers (cisatracurium) [41].

Metabolic enzymes and mitochondrial function

The changes documented after CMV are not dramatic (see ESM).

Clinical relevance

Evidence for VIDD in humans

Although there is no definite evidence of VIDD in humans, several intriguing data suggest that it is a clinical relevant phenomenon. The twitch transdiaphragmatic pressure elicited by magnetic stimulation of the phrenic nerves was reduced in mechanically ventilated patients [42] and in patients ready to undergo weaning trials [43] compared to normal subjects. This is not specific evidence for the presence of VIDD, since other factors leading to muscle weakness in the ICU may have contributed. Diaphragmatic atrophy was documented (by ultrasound) in a tetraplegic patient after prolonged CMV [44]. However, denervation removes neurotrophic influences for the muscle, which is not the case for VIDD. Retrospective analysis of postmortem data obtained in neonates who received ventilatory assistance for 12 days or more immediately before death documented diffuse diaphragmatic myofiber atrophy (small myofibers with rounded outlines), not present in extradiaphragmatic muscles [45]. Furthermore, preliminary data suggest that brain-dead organ donors (with an intact circulation) who underwent CMV for 18–72 h exhibit reduced cross-sectional area (i.e. atrophy) of both slow and fast diaphragmatic fibers (by 40% and 36% respectively) compared to matched control patients subjected to surgery for resection of solitary pulmonary nodules (receiving CMV for less than 2 h) [46]. The ubiquitin–proteasome pathway was implicated in the development of atrophy, since both the ubiquitin–protein conjugates and the mRNA levels of the E3 ligases MAFbx/Atrogin-1 and MuRF1 were upregulated in the diaphragms of brain-dead patients receiving CMV [47].

Clinical context

VIDD should be suspected in patients who fail to wean after a period of CMV. The weaning failure is related to respiratory muscle weakness. Other causes of respiratory muscle weakness should be ruled out [48]. However, the above-mentioned conditions may coexist with VIDD.

VIDD prevention

Ventilatory strategy

Since data in humans are lacking, suggestions are based on animal models and speculations. The time spent in CMV must be curtailed to the extent possible, especially in older individuals, since the effects of aging and CMV are additive [49]. Although CMV induced similar losses (24%) in diaphragmatic isometric tension in both young and old animals, the combined effects of aging and CMV resulted in a 34% decrement in diaphragmatic isometric tension compared to young control animals.

When feasible, partial support modes should be used. Recent studies raise the possibility of partial support modes in conditions traditionally considered as indications for CMV such as ALI/ARDS [50, 51]. In an animal model, assisted (flow-triggered pressure-limited) mechanical ventilation from the onset of ventilator support resulted in attenuation of the force loss induced by CMV (Fig. 5) [26]. Thus, it stands to reason that preserving diaphragmatic contractions during mechanical ventilation should attenuate the force loss induced by CMV, though other forms of partial ventilatory support (pressure support, SIMV) have not been experimentally tested. It should be stressed that these suggestions may be valid in the absence of sepsis, since during sepsis in rats (albeit of short duration, 4 h), CMV protects the diaphragm from injury [52].

Assisted modes or even noninvasive mechanical ventilation in hypercapnic COPD [53–55] can be an alternative strategy in patients who experience weaning failure after a spontaneous breathing trial or after extubation and who may be ventilated using CMV [56], a strategy based on the premise that respiratory muscle fatigue (requiring rest to recover) is the cause of weaning failure [57, 58]. This is because the load that the respiratory muscles of patients who fail to wean are facing is increased to the range that would predictably produce fatigue of the respiratory muscles [59], if patients were allowed

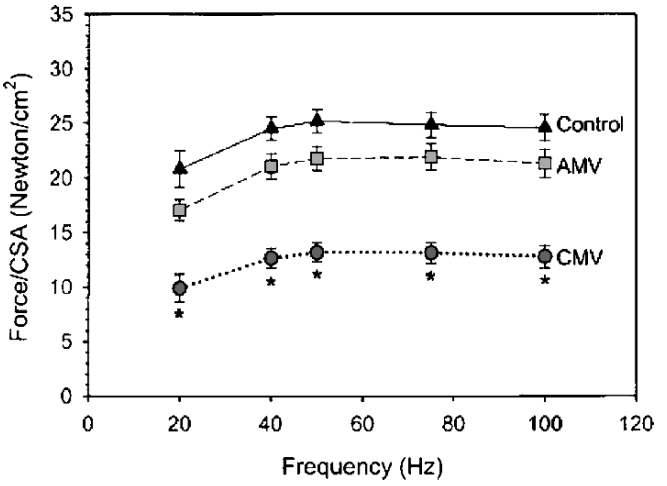


Fig. 5 Diaphragmatic tetanic force at various stimulation frequencies in control circumstances, assisted mechanical ventilation (*AMV*), and controlled mechanical ventilation (*CMV*) in rats. Values are mean ± SE. * $p < 0.01$, CMV versus control and AMV. *CSA*, cross-sectional area. From reference [26] with permission

to continue spontaneous breathing without ventilator assistance. Recent evidence, however, does not support the existence of low-frequency fatigue (the type of fatigue that is long-lasting, taking more than 24 h to recover) in patients who fail to wean despite the excessive respiratory muscle load [43]. This is because physicians have adopted criteria of spontaneous breathing trial failure and termination of unassisted breathing, which lead them to put patients back on the ventilator before the development of low-frequency respiratory muscle fatigue. Thus, no reason exists to completely unload the respiratory muscles with CMV for fatigue reversal if weaning is terminated based on predefined criteria [56].

Intermittent diaphragmatic contractions

When CMV is inevitable, short periods of diaphragmatic activity have been suggested as a preventive countermeasure. This could be achieved with either phrenic nerve stimulation or short periods of intermittent spontaneous breathing. Only 30 min of pacing of one hemidiaphragm each day attenuated atrophy in this hemidiaphragm during prolonged CMV in a tetraplegic patient compared to the non-paced hemidiaphragm [44]. In rats subjected to 24 h of CMV, either 5 min or 60 min of spontaneous breathing every 6 h did not preserve diaphragm force. Rats receiving CMV developed reduced cross-sectional areas of type I and type IIx/b diaphragmatic fibers, which was not observed in intermittently spontaneously breathing rats, yet no difference was observed in the cross-sectional areas between the CMV rats and the intermittently spontaneously breathing rats [60]. Whether more frequent or longer intervals of spontaneous breathing might be more effective in preventing VIDD awaits experimental proof.

Pharmacological approaches

Antioxidant supplementation could decrease the oxidative stress and thus could attenuate VIDD. Accordingly, when rats were administered the antioxidant Trolox (an analogue of vitamin E) from the onset of CMV, its detrimental effects on contractility (Fig. 6) and proteolysis were prevented [61].

A similar approach is adopted by nature itself! Various dormant animals immobilized for prolonged periods of time prevent muscle atrophy through a decrease in metabolic rate that reduces formation of reactive oxygen species and through a concomitant rise in antioxidant enzymes [62, 63]. Interestingly, a combination of vitamins E and C administered to critically ill surgical (mostly trauma) patients was effective in reducing the duration of mechanical ventilation compared to nonsupplemented patients [64]. It is tempting to speculate that part of this beneficial effect was mediated by preventing VIDD. Thus, when CMV is used, concurrent administration of antioxidants seems justified, since a recent meta-analysis suggests that they are beneficial in critical care patients [65].

Administration of leupeptin (an inhibitor of lysosomal proteases and calpain) at the beginning of CMV prevented the development of diaphragmatic contractile dysfunction and atrophy [21] in experimental animals. This raises the possibility of future clinical trials of protease inhibitors in patients to prevent VIDD.

Recovery from VIDD

There is no established or experimentally tested therapy for VIDD. Theoretically, resumption of spontaneous

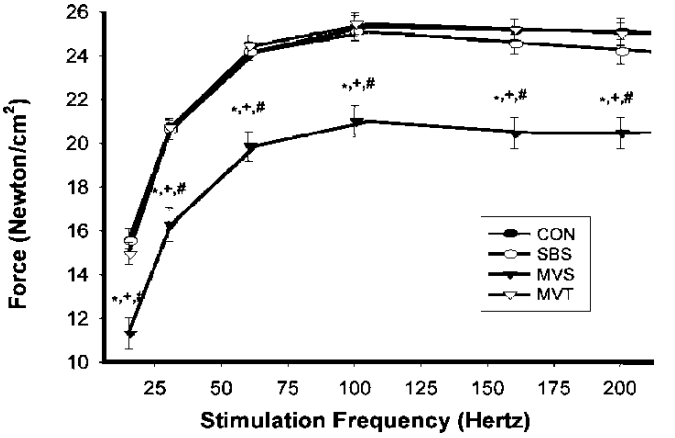


Fig. 6 Force–frequency curves of in vitro diaphragm strips from control rats (*CON*), spontaneously breathing animals (*SBS*), mechanically ventilated animals (*MVS*), and mechanically ventilated animals receiving Trolox (*MVT*). Values represent means ± SEM. * Significantly different from CON group, $p < 0.05$; $^{+}$ significantly different from SBS group, $p < 0.05$; $^{\#}$ significantly different from MVT group, $p < 0.05$. From reference [61] with permission

breathing would retrain the respiratory muscles, yet the time course of recovery of normal function is unknown. A major concern is that diaphragm disuse associated with CMV would increase its susceptibility to subsequent contraction-induced injury, once respiratory efforts are resumed, similar to other skeletal muscles [66]. Rats receiving 24 h of CMV exhibited 26% decline in maximal specific diaphragmatic force with no apparent injury to the cell membrane or evidence of inflammation [67]. Resumption of spontaneous breathing for 2 h in these rats did not exacerbate contractile dysfunction or induce membrane injury or macrophage invasion [67]. However, reloading was associated with increased myeloperoxidase activity and neutrophil infiltration in the diaphragm, which is expected to cause injury at a later time point, should reloading be continued [67]. Further studies are needed to elucidate the recovery response of the diaphragm that has developed VIDD to the resumption of spontaneous respiratory muscle activity.

Summary and conclusion

In recent years researchers have discovered that mechanical ventilation can damage previously injured lungs [68]. Mechanical ventilation can also damage the previously normal respiratory muscles. CMV imposes a unique form of skeletal muscle disuse: the diaphragm is simultaneously unloaded, electrically quiescent, and phasically shortened by cyclical lung inflation, or tonically shortened when PEEP is used. Recent microarray analysis identified 354 differentially expressed gene products in the diaphragms of animals subjected to CMV compared to control animals [69]. Intense research is required to unravel the mechanisms of VIDD and discover ways to translate this knowledge into clinical benefit.

The respiratory muscles are not an inert mechanical pump that can be "light-heartedly" substituted by the ventilator. The respiratory muscles should remain active because they are plastic, and vulnerable.

References

1. Vassilakopoulos T, Petrof BJ (2004) Ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 169:336–341
2. Arroliga A, Frutos-Vivar F, Hall J, Esteban A, Apezteguia C, Soto L, Anzueto A (2005) Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. Chest 128:496–506
3. Anzueto A, Peters JI, Tobin MJ, de los SR, Seidenfeld JJ, Moore G, Cox WJ, Coalson JJ (1997) Effects of prolonged controlled mechanical ventilation on diaphragmatic function in healthy adult baboons. Crit Care Med 25:1187–1190
4. Radell PJ, Remahl S, Nichols DG, Eriksson LI (2002) Effects of prolonged mechanical ventilation and inactivity on piglet diaphragm function. Intensive Care Med 28:358–364
5. Sassoon CS, Caiozzo VJ, Manka A, Sieck GC (2002) Altered diaphragm contractile properties with controlled mechanical ventilation. J Appl Physiol 92:2585–2595
6. Jaber S, Sebbane M, Koechlin C, Hayot M, Capdevila X, Eledjam JJ, Prefaut C, Ramonatxo M, Matecki S (2005) Effects of short vs. prolonged mechanical ventilation on antioxidant systems in piglet diaphragm. Intensive Care Med 31:1427–1433
7. Le Bourdelles G, Viires N, Boczkowski J, Seta N, Pavlovic D, Aubier M (1994) Effects of mechanical ventilation on diaphragmatic contractile properties in rats. Am J Respir Crit Care Med 149:1539–1544
8. Powers SK, Shanely RA, Coombes JS, Koesterer TJ, McKenzie M, Van Gammeren D, Cicale M, Dodd SL (2002) Mechanical ventilation results in progressive contractile dysfunction in the diaphragm. J Appl Physiol 92:1851–1858
9. Yang L, Luo J, Bourdon J, Lin MC, Gottfried SB, Petrof BJ (2002) Controlled mechanical ventilation leads to remodeling of the rat diaphragm. Am J Respir Crit Care Med 166:1135–1140
10. Capdevila X, Lopez S, Bernard N, Rabischong E, Ramonatxo M, Martinazzo G, Prefaut C (2003) Effects of controlled mechanical ventilation on respiratory muscle contractile properties in rabbits. Intensive Care Med 29:103–110
11. Zhu E, Sassoon CS, Nelson R, Pham HT, Zhu L, Baker MJ, Caiozzo VJ (2005) Early effects of mechanical ventilation on isotonic contractile properties and MAF-box gene expression in the diaphragm. J Appl Physiol 99:747–756
12. Shanely RA, Zergeroglu MA, Lennon SL, Sugiura T, Yimlamai T, Enns D, Belcastro A, Powers SK (2002) Mechanical ventilation-induced diaphragmatic atrophy is associated with oxidative injury and increased proteolytic activity. Am J Respir Crit Care Med 166:1369–1374
13. Hussain SN, Vassilakopoulos T (2002) Ventilator-induced cachexia. Am J Respir Crit Care Med 166:1307–1308
14. McClung JM, Kavazis AN, Deruisseau KC, Falk DJ, Deering MA, Lee Y, Sugiura T, Powers SK (2007) Caspase-3 regulation of diaphragm myonuclear domain during mechanical ventilation-induced atrophy. Am J Respir Crit Care Med 175:150–159
15. Jarvinen MJ, Einola SA, Virtanen EO (1992) Effect of the position of immobilization upon the tensile properties of the rat gastrocnemius muscle. Arch Phys Med Rehabil 73:253–257
16. Jokl P, Konstadt S (1983) The effect of limb immobilization on muscle function and protein composition. Clin Orthop Relat Res 222–229
17. Allen DL, Roy RR, Edgerton VR (1999) Myonuclear domains in muscle adaptation and disease. Muscle Nerve 22:1350–1360
18. Shanely RA, Van Gammeren D, Deruisseau KC, Zergeroglu AM, McKenzie MJ, Yarasheski KE, Powers SK (2004) Mechanical ventilation depresses protein synthesis in the rat diaphragm. Am J Respir Crit Care Med 170:994–999
19. Gayan-Ramirez G, De Paepe K, Cadot P, Decramer M (2003) Detrimental effects of short-term mechanical ventilation on diaphragm function and IGF-I mRNA in rats. Intensive Care Med 29:825–833
20. Powers SK, Kavazis AN, Deruisseau KC (2005) Mechanisms of disuse muscle atrophy: role of oxidative stress. Am J Physiol Regul Integr Comp Physiol 288:R337–R344

21. Maes K, Testelmans D, Powers S, Decramer M, Gayan-Ramirez G (2007) Leupeptin inhibits ventilator-induced diaphragm dysfunction in rats. Am J Respir Crit Care Med 175:1134–1138
22. Racz GZ, Gayan-Ramirez G, Testelmans D, Cadot P, De Paepe K, Zador E, Wuytack F, Decramer M (2003) Early changes in rat diaphragm biology with mechanical ventilation. Am J Respir Crit Care Med 168:297–304
23. Du J, Wang X, Miereles C, Bailey JL, Debigare R, Zheng B, Price SR, Mitch WE (2004) Activation of caspase-3 is an initial step triggering accelerated muscle proteolysis in catabolic conditions. J Clin Invest 113:115–123
24. Deruisseau KC, Kavazis AN, Deering MA, Falk DJ, Van Gammeren D, Yimlamai T, Ordway GA, Powers SK (2005) Mechanical ventilation induces alterations of the ubiquitin–proteasome pathway in the diaphragm. J Appl Physiol 98:1314–1321
25. Mitch WE, Goldberg AL (1996) Mechanisms of muscle wasting. The role of the ubiquitin–proteasome pathway. N Engl J Med 335:1897–1905
26. Sassoon CS, Zhu E, Caiozzo VJ (2004) Assist–control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 170:626–632
27. Testelmans D, Maes K, Wouters P, Gosselin N, Deruisseau K, Powers S, Sciot R, Decramer M, Gayan-Ramirez G (2006) Rocuronium exacerbates mechanical ventilation-induced diaphragm dysfunction in rats. Crit Care Med 34:3018–3023
28. Zergeroglu MA, McKenzie MJ, Shanely RA, Van Gammeren D, Deruisseau KC, Powers SK (2003) Mechanical ventilation-induced oxidative stress in the diaphragm. J Appl Physiol 95:1116–1124
29. Shringarpure R, Grune T, Davies KJ (2001) Protein oxidation and 20S proteasome-dependent proteolysis in mammalian cells. Cell Mol Life Sci 58:1442–1450
30. Davies KJ (2001) Degradation of oxidized proteins by the 20S proteasome. Biochimie 83:301–310
31. Falk DJ, Deruisseau KC, Van Gammeren DL, Deering MA, Kavazis AN, Powers SK (2006) Mechanical ventilation promotes redox status alterations in the diaphragm. J Appl Physiol 101:1017–1024
32. Reid MB (2001) Invited Review: Redox modulation of skeletal muscle contraction: what we know and what we don't. J Appl Physiol 90:724–731
33. Hussain SN, Matar G, Barreiro E, Florian M, Divangahi M, Vassilakopoulos T (2006) Modifications of proteins by 4-hydroxy-2-nonenal in the ventilatory muscles of rats. Am J Physiol Lung Cell Mol Physiol 290:L996–1003
34. Siems W, Capuozzo E, Lucano A, Salerno C, Crifo C (2003) High sensitivity of plasma membrane ion transport ATPases from human neutrophils towards 4-hydroxy-2,3-trans-nonenal. Life Sci 73:2583–2590
35. Bernard N, Matecki S, Py G, Lopez S, Mercier J, Capdevila X (2003) Effects of prolonged mechanical ventilation on respiratory muscle ultrastructure and mitochondrial respiration in rabbits. Intensive Care Med 29:111–118
36. Bottinelli R (2001) Functional heterogeneity of mammalian single muscle fibres: do myosin isoforms tell the whole story? Pflugers Arch 443:6–17
37. Geiger PC, Cody MJ, Macken RL, Sieck GC (2000) Maximum specific force depends on myosin heavy chain content in rat diaphragm muscle fibers. J Appl Physiol 89:695–703
38. Shanely RA, Coombes JS, Zergeroglu AM, Webb AI, Powers SK (2003) Short-duration mechanical ventilation enhances diaphragmatic fatigue resistance but impairs force production. Chest 123:195–201
39. Talmadge RJ (2000) Myosin heavy chain isoform expression following reduced neuromuscular activity: potential regulatory mechanisms. Muscle Nerve 23:661–679
40. Staib JL, Swoap SJ, Powers SK (2002) Diaphragm contractile dysfunction in MyoD gene-inactivated mice. Am J Physiol Regul Integr Comp Physiol 283:R583–R590
41. Testelmans D, Maes K, Wouters P, Powers SK, Decramer M, Gayan-Ramirez G (2007) Infusions of rocuronium and cisatracurium exert different effects on rat diaphragm function. Intensive Care Med 33:872–879
42. Watson AC, Hughes PD, Louise HM, Hart N, Ware RJ, Wendon J, Green M, Moxham J (2001) Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Crit Care Med 29:1325–1331
43. Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, Tobin MJ (2003) Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med 167:120–127
44. Ayas NT, McCool FD, Gore R, Lieberman SL, Brown R (1999) Prevention of human diaphragm atrophy with short periods of electrical stimulation. Am J Respir Crit Care Med 159:2018–2020
45. Knisely AS, Leal SM, Singer DB (1988) Abnormalities of diaphragmatic muscle in neonates with ventilated lungs. J Pediatr 113:1074–1077
46. Levine S, Nguyen T, BSE, Friscia M, Kaiser LR, Shrager JB (2006) Ventilator-induced atrophy in human diaphragm myofibers. Proc Am Thorac Soc [Abstract] 3:A27
47. Nguyen T, Friscia M, Kaiser LR, Shrager JB, Levine S (2006) Ventilator–induced proteolysis in human diaphragm myofibers. Proc Am Thorac Soc [Abstract] 3:A259
48. Deem S, Lee CM, Curtis JR (2003) Acquired neuromuscular disorders in the intensive care unit. Am J Respir Crit Care Med 168:735–739
49. Criswell DS, Shanely RA, Betters JJ, McKenzie MJ, Sellman JE, Van Gammeren DL, Powers SK (2003) Cumulative effects of aging and mechanical ventilation on in vitro diaphragm function. Chest 124:2302–2308
50. Zakynthinos SG, Vassilakopoulos T, Daniil Z, Zakynthinos E, Koutsoukos E, Katsouyianni K, Roussos C (1997) Pressure support ventilation in adult respiratory distress syndrome: short-term effects of a servocontrolled mode. J Crit Care 12:161–172
51. Putensen C, Zech S, Wrigge H, Zinserling J, Stuber F, Von Spiegel T, Mutz N (2001) Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 164:43–49
52. Ebihara S, Hussain SN, Danialou G, Cho WK, Gottfried SB, Petrof BJ (2002) Mechanical ventilation protects against diaphragm injury in sepsis: interaction of oxidative and mechanical stresses. Am J Respir Crit Care Med 165:221–228
53. Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, Beltrame F, Navalesi P (2005) Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med 33:2465–2470
54. Ferrer M, Esquinas A, Arancibia F, Bauer TT, Gonzalez G, Carrillo A, Rodriguez-Roisin R, Torres A (2003) Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. Am J Respir Crit Care Med 168:70–76

55. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A (2006) Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med 173:164–170
56. Vassilakopoulos T, Zakynthinos S, Roussos C (2005) Bench-to-bedside review: Weaning failure – should we rest the respiratory muscles with controlled mechanical ventilation? Crit Care 10:204
57. Vassilakopoulos T, Zakynthinos S, Roussos C (1996) Respiratory muscles and weaning failure. Eur Respir J 9:2383–2400
58. Vassilakopoulos T, Roussos C, Zakynthinos S (1999) Weaning from mechanical ventilation. J Crit Care 14:39–62
59. Vassilakopoulos T, Zakynthinos S, Roussos C (1998) The tension-time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. Am J Respir Crit Care Med 158:378–385
60. Gayan-Ramirez G, Testelmans D, Maes K, Racz GZ, Cadot P, Zador E, Wuytack F, Decramer M (2005) Intermittent spontaneous breathing protects the rat diaphragm from mechanical ventilation effects. Crit Care Med 33:2804–2809
61. Betters JL, Criswell DS, Shanely RA, Van Gammeren D, Falk D, Deruisseau KC, Deering M, Yimlamai T, Powers SK (2004) Trolox attenuates mechanical ventilation-induced diaphragmatic dysfunction and proteolysis. Am J Respir Crit Care Med 170:1179–1184
62. Grundy JE, Storey KB (1998) Antioxidant defenses and lipid peroxidation damage in estivating toads, *Scaphiopus couchii*. J Comp Physiol [B] 168:132–142
63. Hudson NJ, Franklin CE (2002) Maintaining muscle mass during extended disuse: aestivating frogs as a model species. J Exp Biol 205:2297–2303
64. Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, Radella F, Garcia I, Maier RV (2002) Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg 236:814–822
65. Heyland D (2005) Antioxidant nutrients:a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med 31:327–337
66. Vijayan K, Thompson JL, Norenberg KM, Fitts RH, Riley DA (2001) Fiber-type susceptibility to eccentric contraction-induced damage of hindlimb-unloaded rat AL muscles. J Appl Physiol 90:770–776
67. Van Gammeren D, Falk DJ, Deruisseau KC, Sellman JE, Decramer M, Powers SK (2005) Reloading the diaphragm following mechanical ventilation does not promote injury. Chest 127:2204–2210
68. International consensus conferences in intensive care medicine: Ventilator-associated lung injury in ARDS. This official conference report was cosponsored by the American Thoracic Society, The European Society of Intensive Care Medicine, and The Societe de Reanimation de Langue Francaise, and was approved by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 160:2118–2124
69. Deruisseau KC, Shanely RA, Akunuri N, Hamilton MT, Van Gammeren D, Zergeroglu AM, McKenzie M, Powers SK (2005) Diaphragm unloading via controlled mechanical ventilation alters the gene expression profile. Am J Respir Crit Care Med 172:1267–1275

Caroline Créput
Lionel Galicier
Sophie Buyse
Elie Azoulay

Understanding organ dysfunction in hemophagocytic lymphohistiocytosis

Abstract *Objective:* This review aims to help critical care clinicians maintain a high level of suspicion regarding the diagnosis of Hemophagocytic Histiolymphocytosis (HLH). It describes the clinical and laboratory features of HLH, outlines its pathophysiology and reviews the most frequent etiologies related to HLH. Prognostic factors and therapeutic options are also reported. *Data sources:* Review of the literature. *Results:* The diagnosis of HLH relies on the association of clinical abnormalities and hemophagocytosis in bone marrow, spleen, or lymph node specimens. Liver, pulmonary, renal, cardiac and skin involvement may occur at various degrees possibly leading to multiple organ failure. Three main etiologies can be found, namely infections, lymphoproliferative diseases, or connective tissue diseases. Immune deficiency is often retrieved. Mortality can be as high as 50%. Although clinically mimicking severe sepsis, HLH has a distinct pathophysiology on which specific therapy is based. Early diagnosis and treatment is mandatory to increase the chances of survival. *Conclusion:* The comprehensive management of severe HLH requires the involvement of a multidisciplinary team in order to determine the best therapeutic strategy and to identify the underlying cause.

Keywords Hemophagocytosis · Histiocytosis · Langerhans cells · Th1 Cytokines activation · Cytopenia · Autoimmune disease

Introduction

Hemophagocytosis describes the pathological finding of activated macrophages engulfing erythrocytes, leukocytes, platelets, and their precursor cells. This phenomenon is an important finding in patients with hemophagocytic syndrome, more properly referred to as hemophagocytic lymphohistiocytosis (HLH).

Hemophagocytic lymphohistiocytosis is a distinct clinical entity characterized by fever, pancytopenia, splenomegaly, and the pathological finding of hemophagocytosis in bone marrow and other tissues. The syndrome, also referred to as "histiocytic medullary reticulosis," was first described in 1939 as a condition characterized by a fever, a rapid decline in general health, peripheral lymph node enlargement, pancytopenia, and histiocyte proliferation in the bone marrow with a fatal outcome [1]. Forty years later, Risdall et al. used the term "reactive hemophagocytic syndrome" to designate an inappropriate immune response to viral infection leading to uncontrolled proliferation of benign histiocytes with hemophagocytosis and symptoms matching those described by Scott and Robb-Smith [1]. Subsequently, additional cases related to viral infection were reported [3–5], and hemophagocytic syndrome was described in association with other diseases, including malignancies and systemic connective tissue diseases [6–8].

Hemophagocytic lymphohistiocytosis is a life-threatening condition which may be difficult to distinguish from severe sepsis [9]. A simple clinical approach may be helpful to appraise the diagnosis of HLH. Along this line, autopsy studies suggest that HLH may be underrecognized

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_49, © Springer-Verlag Berlin Heidelberg 2009

Table 1 Diagnostic guidelines for hemophagocytic lymphohistiocytosis. The diagnosis of hemophagocytic lymphohistiocytosis can be established by fulfilling five of the eight criteria. *NK*, natural killer. (From [37])

Clinical criteria
Fever (> 7 days)
Splenomegaly
Laboratory criteria
Bicytopenia without marrow hypoplasia, including:
Hemoglobin < 9 g/l
Platelet count < 100.10 × 9 mm^3
Neutrophil count < 1.10 × 9/mm^3
Hypertriglyceridemia (3.0 mmol/l, fasting value)
and/or hypofibrinemia (< 1.5 g/l)
Hyperferritinemia (> 500 ug/l)
Low/absent NK cell activity
Increased soluble CD 25 levels (> 2400 IU/ml)
Histological criteria
Hemophagocytosis

in intensive care unit (ICU) patients [10, 11]. On the other hand, incidence of HLH may be overestimated. Indeed, studies in critically ill septic patients with cytopenia report an incidence of HLH in marrow smears between 0.8 and 4% [10, 12]; however, these studies are often difficult to interpret as no cytological results from relevant control populations are available. Moreover, criteria for the definite diagnosis of HLH were not met, suggesting that although hemophagocytosis was identified, diagnosis of HLH remained doubtful [13].

Several criteria sets have recently been developed for the diagnosis of HLH. In the latest HLH-2004 protocol, a recent revision of diagnostic criteria suggests that HLH diagnosis can be established if five of the eight following diagnostic criteria are fulfilled: (a) fever; (b) splenomegaly; (c) bicytopenia; (d) hypertriglyceridemia (> 3.0 mmol/l fasting value), and/or hypofibrinogenemia (< 1.5 g/l); (e) hemophagocytosis; (f) low or absent natural killer (NK) cell activity; (g) hyperferritinemia (> 500 ug/l); and (h) and increased soluble CD-25 levels (> 2400 IU/ml; Table 1).

This review aims to help critical care clinicians maintain a high level of suspicion regarding the diagnosis of HLH. It describes the clinical and laboratory features of HLH, outlines its pathophysiology, and reviews the most frequent etiologies related to HLH. Prognostic factors and therapeutic options are also reported.

Clinical and laboratory features

The clinical and laboratory features of HLH are nonspecific and may be difficult to separate from those of the underlying disease; however, HLH should be considered routinely in patients with unexplained and atypical multiple organ failure [12]. Diagnosis of HLH relies on clinical, laboratory, and histological findings. Clinical and laboratory manifestations were proposed by the Histiocyte Society and are listed in Table 1. Acute onset with high-grade fever is the rule. Rapid weight loss may occur [14, 15]. Overall, macrophage and T-lymphocyte proliferation and activation in the reticuloendothelial system manifest as peripheral lymphadenopathy (35% of patients) and as enlargement of the liver and spleen (50% of patients) [16, 17]. Clotting disorders may lead to bleeding, and liver involvement may manifest as jaundice and portal hypertension. Pulmonary infiltrates are found in 20–30% of patients [18]. Cardiac or renal involvement may occur. Skin abnormalities are noted in 20% of patients [17], with the most common patterns being rash, erythema, and purpura. Of central nervous system manifestations, encephalopathy, meningitis, and seizures are the most commonly reported [19]. In severe cases, mechanical ventilation is required because of alterations in consciousness. Multiple organ failures may occur. Table 2 reports usual causes in connective-tissue diseases associated with HLH.

Laboratory tests can assist in the diagnosis of HLH. The most prominent laboratory abnormalities noted are cytopenia, which may be profound. Cytopenia results from both hemophagocytosis in the bone marrow and depression of hematopoiesis by cytokines such as interferon-γ (IFN-γ), tumoral necrosis factor-α (TNF-α), and interleukin 1-β (IL-1β) [20]. All patients have anemia, which is usually nonregenerative. Serum chemistry findings may suggest hemolysis, with hyperbilirubinemia and elevation of lactate dehydrogenase. Thrombocytopenia is almost

Table 2 Causes of reactive hemophagocytic lymphohistiocytosis (*HLH*) in published series. (Adapted from [78])

Associated disorders with HLH	Prevalence (%)
Viral infections	29.1
HSV	2.9
EBV	6.9
CMV	10.5
HIV	8.8
Other infections	20.6
Bacteria	31.1
Parasites/fungi	5.2
Mycobacteria	2.3
Lymphoma	19.9
Other hematological malignancies	8.2
Solid cancer	1.6
Systemic disease[a]	7.2
Lupus	
Still's disease	
Rheumatoid arthritis	
Sarcoidosis	
Scleroderma	
Mixed connective tissue disease	
Sjögren's syndrome	
Hereditary	6.2
No identified cause	18.0

Clinical features may be difficult to differentiate from those of the underlying systemic disease

[a] Diseases are set in order of frequency according to Dhote et al. [70]

consistently present, occurs early in the course of the disease, and is usually profound. Leukopenia is less common, less severe, and occurs later in the course of the syndrome. Overall, three of every four patients have pancytopenia and all have bicytopenia. Serum ferritin elevation is the rule [21, 22], the most likely mechanism being IL-1β elevation [23]. Serum ferritin levels may correlate with disease activity and outcome under treatment. Hypertriglyceridemia is an extremely common finding that is ascribable to lipoprotein lipase inhibition by TNF-α [24, 25].

Coagulation disorders are present in most patients. The most common pattern is isolated fibrin deficiency due to liver dysfunction and, above all, plasminogen and factor-X activation by IL-1β [26, 27]. More rarely, disseminated intravascular coagulation (DIC) develops as a result of IFN-γ and TNF-α overproduction. The DIC is associated with high mortality [2, 24]. Liver dysfunction (cytolysis and cholestasis) is frequently reported [28, 29]. IFN-γ contributes to the development of cholestasis [30]. In addition, colony-stimulating factor (CSF), together with Fas/Fas-ligand interaction in response to IFN-γ overproduction, contribute to cause apoptosis and liver damage. IFN-γ elevation also leads to hypoalbuminemia [31].

Renal failure is often reported at the advanced stage of HLH and is related to abnormally high concentrations of nephrotoxic interleukin-6 (IL-6) in serum [32]. Renal biopsy usually shows tiny glomerular lesions [33, 34]. Markers for inflammation are markedly elevated. Many other nonspecific laboratory abnormalities may be found, such as hypo- or hypergammaglobulinemia, a positive Coombs test, or hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion [35].

Cytology and histology

The pathological hallmark of HLH is a proliferation of activated macrophages (histiocytes) engulfing blood cells and their precursors (Fig. 1). This proliferation is found in the reticuloendothelial system (bone marrow, lymph nodes, spleen, and liver) and occasionally affects other sites, such as the skin. Cytological examination of bone marrow smears is the best investigation for confirming HLH, although normal findings, do not rule out the diagnosis. Cellularity is usually normal for all three lines at an early stage. Hypocellularity with reduced granulopoiesis and erythropoiesis may be present [2]. Hyperplasia of the megacaryocyte line with good maturation initially is the rule. Hemophagocytosis in bone marrow occurs not only in HLH, but also in hemolytic diseases and other hematological disorders; therefore, hemophagocytosis does not indicate a diagnosis of HLH unless other clinical and laboratory features of the syndrome are present also [10].

Histological examination of bone marrow biopsies may be less effective in establishing the diagnosis of HLH than examination of bone marrow smears. Nevertheless, bone marrow biopsy may show an underlying hematological disorder or infectious process, as in tuberculosis for example [16]. Liver histology is abnormal in 50% of patients with HLH. Findings may consist of nonspecific histiocytic infiltration of the sinusoid capillaries and portal tracts and/or hepatocyte necrosis [36]. In a study of 30 patients with HLH and liver dysfunction, de Kerguenec and coworkers consistently found sinusoid dilation and hemophagocytosis, with liver biopsy identifying the underlying disease in 50% of cases [28]. Examination of spleen specimens may show red pulp expansion with hemophagocytosis, as well as lymphocyte depletion in white pulp. In HLH, histological examination of spleen sections may also identify the etiology of the process. In lymph node specimens, histiocytic infiltration is more meaningful when found in the sinusoids than in the cortical or paracortical area. Lymphocyte depletion with atrophic germinal centers is an extremely rare pattern. When lymph node architecture

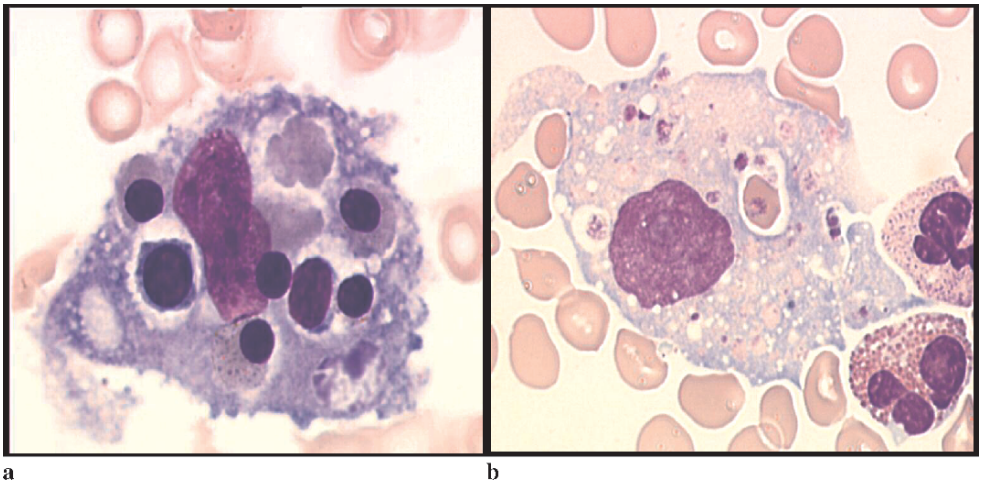


Fig. 1 Evidence of hemophagocytosis on histological samples. Hematoxylin-eosin stain of bone marrow sample shows histiocytes, phagocytosing erythroblasts, and lymphocytes. **a** Hematoxylin-eosin stain of bone marrow sample shows phagocytic cells with engulfed erythrocytes and platelets. **b** Hematoxylin-eosin stain of bone marrow sample shows phagocytic cells with engulfed erythrocytes and platelets

a b

is not invaded by a tumoral proliferation, its structure is usually normal, although vessel proliferation may be present.

Etiologies

Viral infections, other infections, autoimmune disorders, and underlying malignancy are the most common triggers for reactive HLH (Table 2). In adults, acquired (reactive) HLH is commonly associated with immune deficiency, which should be looked for routinely.

Viral infections

Although many viruses can trigger HLH, herpes viruses account for more than 50% of cases of virus-associated HLH [37]. Epstein–Barr virus (EBV) is the most common triggering agent for HLH. The HLH associated with primary EBV infection is more common in young children than in other age groups and may be fatal, most notably in immunocompromised individuals [37]. The diagnosis rests on serology, MNI test, and PCR detection of viral DNA in serum. Cytomegalovirus (CMV) contributes 30–50% of all cases of virus-associated HLH and should be sought routinely, as specific treatment is available [38]. Herpes simplex virus (HSV) [39], and parvovirus [40] are common triggers of HLH. Cases associated with adenovirus [41], hepatitis viruses [42], rubella, respiratory syncytial virus, and coxsackie [43] have been reported. Post-mortem analyses in patients dying after severe avian influenza A (H5N1) infection have also revealed hemophagocytosis [44]. Human immunodeficiency virus (HIV) alone or in the presence of other opportunistic or nonopportunistic infections, or malignancies (e.g., Hodgkin's lymphoma and Castleman's disease), has been associated with hemophagocytic syndrome [45].

Bacterial infections

Although pyogenic infections have been reported in association with HLH, the link is poorly documented. In contrast, stronger evidence exists to support a relation with intracellular bacteria (mycobacteria, mycoplasma, *Rickettsia* sp., *Legionella* sp., *Chlamydia* sp., *Brucella* sp., and *Borrellia* sp.) [46, 47].

Fungal and parasitic infections

Histoplasmosis is the most common fungal infection found in association with HLH [48, 49]. Leishmaniasis is akin to an animal model of hemophagocytosis [50, 51]. HLH has been reported during malaria attacks due to *Plasmodium falciparum* and in *Babesia*-related infections. More rarely, disseminated strongyloidiasis, *Pneumocystis jiroveci* infection [52], aspergillosis [53], toxoplasmosis, cryptococcosis, and candidiasis [54] have been described in association with HLH.

Lymphoproliferative diseases

In non-immunocompromised patients, the first malignancy to be found associated with HLH is T-cell lymphoma [55], above all when the trigger is identified as EBV [56]. Hodgkin's disease is the second malignancy associated with HLH [37, 57, 58]. B-cell lymphoma and intravascular lymphoma may also be associated with HLH, more particularly in Asians [59]. The EBV-induced lymphomas, transplant-recipient lymphomas, and lymphomas in HIV-infected patients are associated with a higher risk of HLH [60]. Human herpes virus 8 (HHV-8) is associated with several distinct lymphoproliferative disorders [61–63]. The HLH triggered by HHV-8 is extremely rare but has been reported in associated lymphoproliferative disorders as well as in immunocompromised patients. Conditions rarely reported in association with HLH include acute T-cell or NK leukemia [64, 65].

Systemic diseases

Occurrence of HLH during connective disease course may be related to the systemic disease activity, to infection, or rarely to lymphoma [66–69]. In a study by Dhote et al. among 26 patients with systemic diseases and HLH, the diagnoses were systemic lupus erythematosus ($n = 14$), Still's disease ($n = 4$), rheumatoid arthritis ($n = 2$), polyarteritis nodosa ($n = 2$), Kawasaki disease ($n = 1$), mixed connective tissue disease ($n = 1$), sarcoidosis ($n = 1$), and Sjögren syndrome ($n = 1$). In 15 patients, HLH was triggered by active infection (viral, $n = 3$; bacterial, $n = 10$; mycobacterial, $n = 1$; and *Aspergillus*, $n = 1$), which required a reduction in the immunosuppressive regimen. Only Lupus or Still's disease were directly responsible for HLH (in 9 patients), which required intensification of immunosuppressive regimens [70].

Pathophysiology

Genetic defects in familial HLH: keys to HLH pathophysiology

Studies of genetic HLH have provided valuable insight into the mechanisms of host defense and the pathophysiology of acquired (reactive) HLH. The clinical and laboratory features of primary HLH are identical to those of reactive HLH, except for occurrence in childhood, greater

frequency, and severity of neurological involvement, and higher rates of fatal primary viral infections.

Genetic (primary) HLH is inherited in an autosomal or X-linked manner and can be divided into two subgroups: familial HLH (FHLH), in which the clinical syndrome of HLH is the only manifestation; and the immune deficiencies Chédiak–Higashi syndrome (CHS1), Griscelli syndrome (GS2), and X-linked proliferative syndrome (XLP), which have distinctive clinical features besides the sporadic, though frequent, development of HLH [37].

Since 1999, several genetic loci related to the activity of perforin and granzyme granule have been associated with genetic hemophagocytic syndrome, thus explaining the impaired or absent function of NK cells and cytotoxic T cells characteristic of the disease. The cytotoxic activity of NK cells and of CD8+ T-cell lymphocytes (CTL) is mediated by the release of cytolytic granules (containing large amounts of perforin, granzymes, and other serin-like proteases) via the immunological synapse to the target cell [71]. In genetic HLH, mutations impair the cytotoxic activity of CTL and NK cells without modifying their activation capacity or cytokine secretion. Most of the mutations affect the cytoplasmic granules in cytotoxic cells, altering either the effectors they contain (perforin) or their ability to migrate to the cell membrane [71]. This impairment may remain asymptomatic until the cytokine system is stimulated, when paradoxical inefficient overactivation reveals the illness.

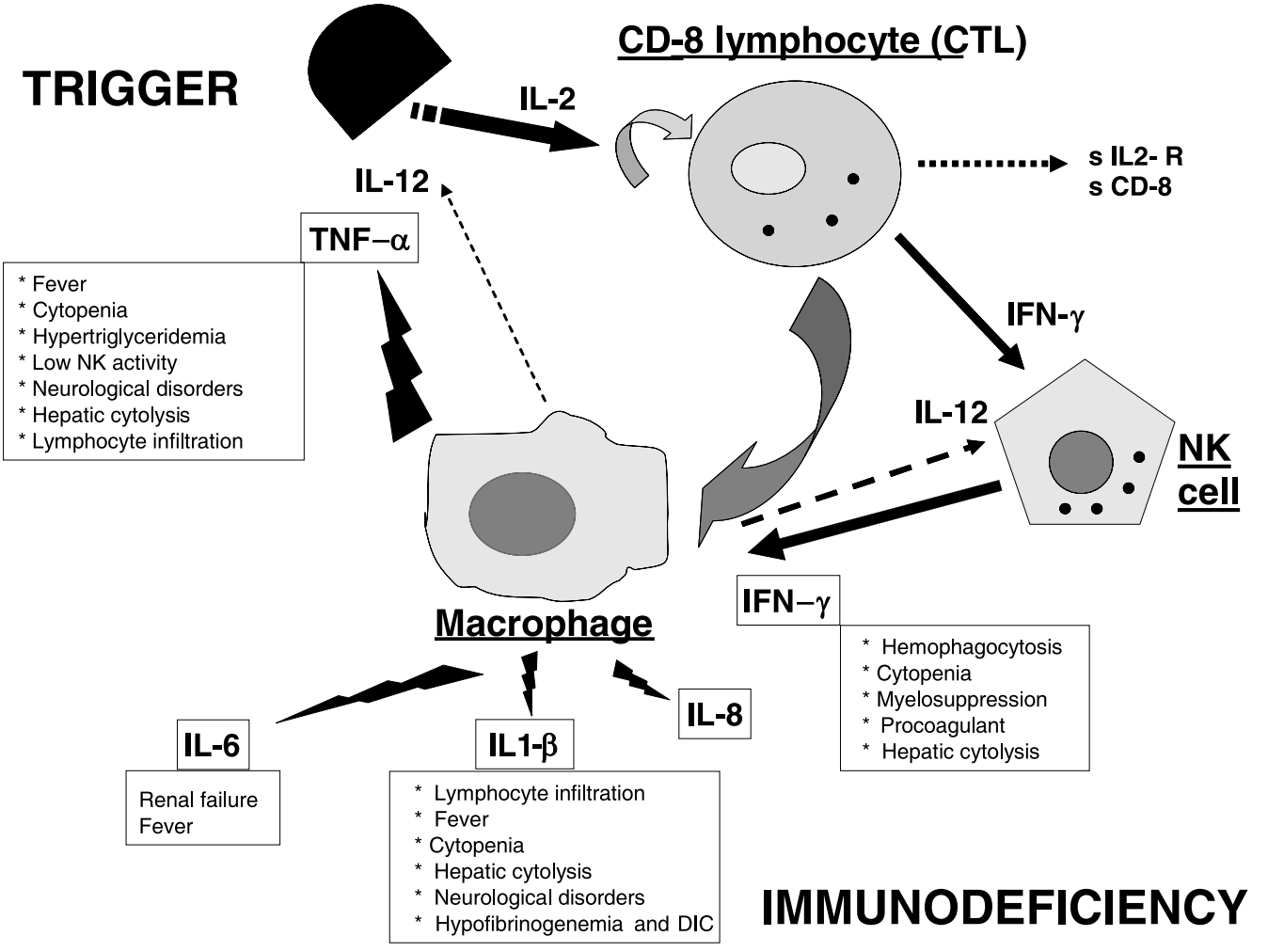


Fig. 2 Immunopathological mechanisms in hemophagocytic lymphohistiocytosis: clinical effects of Th1 activation loop and cytokines production. Activation of CD-8 T lymphocytes results in clonal proliferation and activation of NK cells, with production of high levels of activating cytokines. Elaboration of TNF-α and other cytokines causes fever and systemic illness. TNF-α and IFN-γ production contribute to macrophage activation with resulting hemophagocytosis. *TNF-α*, tumor necrosis factor alpha; *IFN-γ*, interferon-gamma; *IL1-β*, interleukin-1 beta; *IL-2*, interleukin-2; *IL-6*, interleukin-6; *IL-8*, interleukin-8; *IL-12*, interleukin-12; *sCD-8*, soluble cluster of differentiation 8; *NK cell*, natural killer cell

Uncontrolled TH1 response and defective cytotoxic function: key points to reactive HLH pathophysiology

In reactive HLH, there is an overwhelming activation of normal T cells and macrophage which cause clinical and biological alterations: cooperation among triggered histiocytes, macrophages, CTL, and NK cells is at the hub of HLH, where evidence of a cytotoxic response, including Th1 response and cytotoxic cell overactivation, soon becomes apparent (Fig. 2) [72].

Infection with a virus or intracellular pathogen normally induces a Th1 response in which cytotoxic Th1 cells and macrophage cooperate to increase the efficiency of the CTL system and the capacity of macrophage to proliferate. The antigen-presenting cells promote CTL and NK cells expansion and activation via the secretion of interleukin-12 (IL-12) and TNF-α. In turn, the cytotoxic cells release increased amounts of IFN-γ, TNF-α, and macrophage colony-stimulating factor (M-CSF). In HLH, this loop is amplified continuously, leading to the lymphohistiocytic proliferation responsible for the tumoral syndrome, and to the cytokine storm responsible for the other clinical and laboratory features (Fig. 2).

Activation manifests predominantly as a Th1 cytotoxic response with elevated serum levels of IFN-γ, IL-12, IL-2, M-CSF [73, 74], and Fas ligand [75], reflecting the Th1/Th2 imbalance (Fig. 2). The CTL upregulates activation markers such as CD-25 (alpha-chain of the IL-2 receptor), HLA-DR, and Fas [76]. The serum also contains high levels of the macrophage-produced monokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), TNF-α, and granulocyte colony-stimulating factor (G-CSF) [77, 78], as well as of coagulation factors (V, VII, IX, and X) and transferrin. Paradoxically, there is a tendency to peripheral CD8+ lymphocytopenia as a result of tissue infiltration by these cells [74, 79].

Linkage between HLH and infection

The linkage between HLH and infection is complex, as an infection may trigger the development of HLH or complicate the course of HLH. Infection accounts directly for half the deaths in patients with HLH [37]. Clinical immune deficiency complicating HLH results not only from neutropenia, but also from anergy in Th1 cells associated with increased levels of cytokines such as IFN-γ. Infection complicating HLH probably reflects acquired impairments of similar nature. Immune deficiency has been reported in 40–60% of cases of HLH: The main causes of acquired immune deficiency were HIV infection [80] and immunosuppressive treatment for systemic diseases [81] or transplantation [82].

Linkage between HLH and lymphoproliferation

Reactive HLH secondary to EBV-related or T-cell lymphoproliferative disease seems to be independent from a triggering factor. Indeed, uncontrolled transcription of messenger RNA for INF-γ in lymphoid T-cells [83] or of TNF-α in EBV+ lymphoid cells [84] has been documented in such cases. In addition, supernatant from T-EBV cell cultures induce macrophagic differentiation of monocyte lines [56]; thus, some lymphoid proliferations can trigger and perpetuate the Th1 activation and loop via a paracrine effect.

Prognostic factors and mortality

The overall mortality rate from HLH ranges across studies from 22 to 59% (Table 3). The HLH related to hematological malignancies or EBV infection carries a higher mortality rate than cases related to viruses or

Table 3 Mortality rates and risk factors for death reported in studies of patients with hemophagocytic lymphohistiocytosis

Reference	No. of cases	Deaths	
		Number	Percentage
[2] Risdall RJ et al.	19	5	26
[14] Dinarello CA et al.	23	7	30
[24] Dinarello CA et al.	40	18	45
[79] Fujinara F et al.	23	5	22
[67] al Eid W et al.	34	20	59
[55] Jaffe ES et al.	26	10	38
		Clinical prognostic factors	
		Age > 30 years	
		Pre-existing disease	
		No lymphadenopathy	
		History of corticosteroid therapy	
		Biological prognostic factors	
		High bilirubin level	
		High alkaline phosphatase levels	
		High TNF-α concentrations	
		IFN-γ > 30 IU	
		sIL-2-R > 10,000	

intracellular bacteria. In fatal HLH, death usually occurs during the first 4–8 weeks, from multiple organ failure, bleeding, or sepsis. In a retrospective study of 34 cases of HLH, Kaito et al. found that factors predicting death were: (a) age older than 30 years; (b) nature of the underlying disease; (c) hemoglobin level < 10 g/dl; (d) platelet count < 100,000/mm^3; (e) ferritin level > 500 μg/l; or (f) bilirubin or alkaline phosphatase elevation [85]. In adults with active systemic disease and HLH, Dhote et al. did identify the following factors as being associated with death: absence of lymphadenopathy at diagnosis; corticosteroid treatment at diagnosis; and thrombocytopenia [70]; however, some of the prognostic factors identified in both studies are actually considered to be diagnostic criteria. It is thus likely that the outcome of patients with proper HLH was affected in these studies. In some studies, the time of etoposide administration was the main determinant of long-term survival. This effect was particularly marked for EBV-associated HLH. Imashuku et al. reported that survival was 90% in patients given etoposide within the first 4 weeks compared with only 56% in those treated later [86–88].

Therapeutic options

Supportive care

Comprehensive ICU management is needed to support organ function, to apply specific measures aiming to control the symptoms, to identify and treat the underlying cause of HLH, to prevent its recurrence, and also to manage infectious complications. Special attention should be given to correcting coagulation disorders, by transfusing platelets, plasma, and fibrinogen, as appropriate. Fluid and electrolyte balance must be restored and renal replacement therapy given, if needed. Vasoactive drugs may be needed to maintain cardiac function and hemodynamics and assisted ventilation to treat acute respiratory insufficiency. Anemia and neurological disorders may require additional treatment. Antibiotic and antifungal agents should be given as needed to treat infectious complications.

The underlying cause should be treated as soon as it is identified. Antiviral agents have been reported as beneficial in patients with herpes simplex virus, varicella zoster virus, or cytomegalovirus infection [89, 90], but not in HLH associated with EBV, herpes human virus 8, or herpes human virus 6. As soon as infection is ruled out, immediate treatment of lymphoproliferative or systemic disease, along with empiric or prophylactic anti-infectious agents, is essential to control both HLH and its trigger; however, lymphoma may be difficult to detect, as severe hemophagocytosis may develop despite a small tumor burden. The diagnosis may require invasive procedures such as bone marrow or lymph node biopsy, liver biopsy, or splenectomy. In the absence of specific etiological treatment, hemophagocytosis relapses a few days or weeks after the symptomatic treatment.

Measures targeted specifically at HLH

Hemophagocytic lymphohistiocytosis is a highly fatal disease if untreated. Severe HLH should be treated promptly after symptom onset. In less severe forms, investigations for a cause can be performed first, albeit rapidly, as sudden worsening may occur at any time. Life-threatening hyperinflammation, caused by excessive levels of cytokines, can be treated by corticosteroids.

In patients without underlying systemic diseases, etoposide combined with corticosteroid therapy is now the treatment of reference for HLH [86]. Etoposide (VP-16) is a cytotoxic drug that targets the enzyme topoisomerase-2. Although nonspecific, etoposide selectively targets the monocyte line. Etoposide was reported to benefit patients with HLH nearly 10 years ago and was subsequently proven effective in several studies [37, 86]. In patients with severe HLH, etoposide should be administered immediately and acts rapidly, within 24–48 h. Its efficacy far outweighs the risk of secondary leukemia and transient worsening of the neutropenia. Etoposide has been proved superior over intravenous immunoglobulins and cyclosporine in patients with EBV-induced HLH [88, 91]. Moreover, times to treatment was associated with outcome [86]. Once HLH control is achieved, the appropriateness of continuing etoposide therapy must be determined according to the underlying cause.

In patients with infection-related HLH, intravenous immunoglobulin has some chance of success, only if used early [72]; however, intravenous immunoglobulin combined with steroids is thought to be inferior to an etoposide-containing regimen [73].

In case of HLH secondary to lymphoproliferative diseases, treatment should target malignant lymphocytes using combined chemotherapy regimens (which all include corticosteroids). Addition of etoposide in this setting is questionable as it may add some medullar or mucosal toxicity.

In patients with systemic diseases, such as lupus or Still's disease, corticosteroid therapy is the reference [92]. When complementary immunosuppressive treatment is needed, cyclosporine is often the best choice [81, 93, 94]. In patients with Still's disease, TNF-α antagonists (etanercept and infliximab) have generated interest because TNF-α plays a key role in the pathophysiology of both HLH and Still's disease [24, 95].

Conclusion

In conclusion, the diagnosis of HLH relies on the association of clinical abnormalities (fever, splenomegaly, pancy-

topenia) and hemophagocytosis in bone marrow, spleen, or lymph node specimens. Liver, pulmonary, renal, cardiac, and skin involvement may occur at various degrees possibly leading to multiple organ failure. Three main associated etiologies can be found, namely infections (viral, bacterial, fungal, or parasitic), lymphoproliferative diseases, or connective tissue diseases. Immune deficiency is often retrieved. Although clinically mimicking severe sepsis, HLH has a distinct pathophysiology on which specific therapy is based. The comprehensive management of severe HLH requires the involvement of a multidisciplinary team in order to determine the best therapeutic strategy and to identify the underlying cause. The high mortality in patients with no etiological diagnosis warrants aggressive investigations and treatment. Studies are needed to identify whether early administration of etoposide reverses organ failure and decreases mortality in critically ill patients with HLH.

Acknowledgements. The authors thank M.T. Daniel for her contribution to iconography preparation and A. Wolfe for her help with the manuscript.

References

1. Scott R, Robb-Smith A (1939) Histiocytic medullary reticulosis. Lancet 2:194–198
2. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH Jr, Simmons RL, Brunning RD (1979) Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer 44:993–1002
3. Cohen RA, Hutter JJ Jr, Boxer MA, Goldman DS (1980) Histiocytic medullary reticulosis associated with acute Epstein–Barr (EB) virus infection. Am J Pediatr Hematol Oncol 2:245–248
4. McKenna RW, Risdall RJ, Brunning RD (1981) Virus associated hemophagocytic syndrome. Hum Pathol 12:395–398
5. Wilson ER, Malluh A, Stagno S, Crist WM (1981) Fatal Epstein–Barr virus-associated hemophagocytic syndrome. J Pediatr 98:260–262
6. Ezdinli EZ, Kucuk O, Chedid A, Sinclair TF, Thomas K, Singh S, Sarpel S, Jovanovic L (1986) Hypogammaglobulinemia and hemophagocytic syndrome associated with lymphoproliferative disorders. Cancer 57:1024–1037
7. Liang DC, Chu ML, Shih CC (1986) Reactive histiocytosis in acute lymphoblastic leukemia and non-Hodgkin's lymphoma. Cancer 58:1289–1284
8. March LM, Webb J, Eckstein RP (1986) Cytophagic panniculitis. Aust N Z J Med 16:397–401
9. Gauvin F, Toledano B, Champagne J, Lacroix J (2000) Reactive hemophagocytic syndrome presenting as a component of multiple organ dysfunction syndrome. Crit Care Med 28:3341–3345
10. Strauss R, Neureiter D, Westenburger B, Wehler M, Kirchner T, Hahn EG (2004) Multifactorial risk analysis of bone marrow histiocytic hyperplasia with hemophagocytosis in critically ill medical patients: a postmortem clinicopathologic analysis. Crit Care Med 32:1316–1321
11. Nahum E, Ben-Ari J, Stain J, Schonfeld T (2000) Hemophagocytic lymphohistiocytic syndrome: unrecognized cause of multiple organ failure. Pediatr Crit Care Med 1:51–54
12. Stephan F, Thioliere B, Verdy E, Tulliez M (1997) Role of hemophagocytic histiocytosis in the etiology of thrombocytopenia in patients with sepsis syndrome or septic shock. Clin Infect Dis 25:1159–1164
13. Grom AA (2003) Macrophage activation syndrome and reactive hemophagocytic lymphohistiocytosis: The same entities? Curr Opin Rheumatol 15:587–590
14. Dinarello CA, Wolff SM (1993) The role of interleukin-1 in disease. N Engl J Med 328:106–113
15. Dinarello CA, Cannon JG (1993) Cytokine measurements in septic shock. Ann Intern Med 119:853–854
16. Reiner AP, Spivak JL (1988) Hematophagic histiocytosis. A report of 23 new patients and a review of the literature. Medicine (Baltimore) 67:369–388
17. Shirono K, Tsuda H (1995) Virus-associated haemophagocytic syndrome in previously healthy adults. Eur J Haematol 55:240–244
18. Ohta H, Yumara-Yagi K, Sakata N, Inoue M, Kawa-Ha K (1994) Capillary leak syndrome in patients with hemophagocytic lymphohistiocytosis. Acta Paediatr 83:1113–1114
19. Honig LS, Snipes GJ, Vogel H, Horoupian DS (1991) Sensorimotor neuropathy in hemophagocytosis syndrome. Acta Neurol Scand 84:316–320
20. Hanada T, Ono I, Iinuma S, Nagai Y (1989) Pure red cell aplasia in association with virus associated haemophagocytic syndrome (VAHS). Br J Haematol 73:570–571
21. Koduri PR, Carandang G, DeMarais P, Patel AR (1995) Hyperferritinemia in reactive hemophagocytic syndrome report of four adult cases. Am J Hematol 49:247–249
22. Esumi N, Ikushima S, Todo S, Imashuku S (1987) Hyperferritinemia in malignant histiocytosis and virus-associated hemophagocytic syndrome. N Engl J Med 316:346–347
23. Esumi N, Ikushima S, Hibi S, Todo S, Imashuku S (1988) High serum ferritin level as a marker of malignant histiocytosis and virus-associated hemophagocytic syndrome. Cancer 61:2071–2076
24. Dinarello CA, Gelfand JA, Wolff SM (1993) Anticytokine strategies in the treatment of the systemic inflammatory response syndrome. J Am Med Assoc 269:1829–1835
25. Henter JI, Carlson LA, Soder O, Nilsson-Ehle P, Elinder G (1991) Lipoprotein alterations and plasma lipoprotein lipase reduction in familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand 80:675–681
26. Ooe K (1992) Pathogenesis and clinical significance of hemophagocytic syndrome: hypothesis. Pediatr Pathol 12:309–312
27. McClure PD, Strachan P, Saunders EF (1974) Hypofibrinogenemia and thrombocytopenia in familial hemophagocytic reticulosis. J Pediatr 85:67–70
28. de Kerguenec C, Hillaire S, Molinie V, Gardin C, Degott C, Erlinger S, Valla D (2001) Hepatic manifestations of hemophagocytic syndrome: a study of 30 cases. Am J Gastroenterol 96:852–857
29. Billiau AD, Roskams T, Van Damme-Lombaerts R, Matthys P, Wouters C (2005) Macrophage activation syndrome: characteristic findings on liver biopsy illustrating the key role of activated, IFN-gamma-producing lymphocytes and IL-6- and TNF-alpha-producing macrophages. Blood 105:1648–1651
30. Whiting JF, Green RM, Rosenbluth AB, Gollan JL (1995) Tumor necrosis factor-alpha decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis. Hepatology 22:1273–1278

31. Iso ON, Hashimoto N, Tanaka A, Sunaga S, Oka T, Kurokawa K, Watanabe T (1998) Cytokine-induced hypoalbuminemia in a patient with hemophagocytic syndrome: direct in vitro evidence for the role of tumor necrosis factor-alpha. Dig Dis Sci 43:67–73
32. Weber J, Yang JC, Topalian SL, Parkinson DR, Schwartzentruber DS, Ettinghausen SE, Gunn H, Mixon A, Kim H, Cole D et al. (1993) Phase I trial of subcutaneous interleukin-6 in patients with advanced malignancies. J Clin Oncol 11:499–506
33. Braun MC, Cohn RA, Kletzel M (1996) Nephrotic syndrome accompanying familial hemophagocytic syndrome. J Pediatr Hematol Oncol 18:195–197
34. Thaunat O, Delahousse M, Fakhouri F, Martinez F, Stephan JL, Noel LH, Karras A (2006) Nephrotic syndrome associated with hemophagocytic syndrome. Kidney Int 69:1892–1898
35. Chubachi A, Miura I, Hatano Y, Ohshima A, Nishinari T, Miura AB (1995) Syndrome of inappropriate secretion of antidiuretic hormone in patients with lymphoma-associated hemophagocytic syndrome. Ann Hematol 70:53–55
36. Favara BE (1996) Histopathology of the liver in histiocytosis syndromes. Pediatr Pathol Lab Med 16:413–433
37. Janka GE (2007) Hemophagocytic syndromes. Blood Rev 21:245–253
38. Danish EH, Dahms BB, Kumar ML (1985) Cytomegalovirus-associated hemophagocytic syndrome. Pediatrics 75:280–283
39. Lasserre M, Huguet C, Terno O (1993) Acute severe herpes simplex hepatitis with virus-associated hemophagocytic syndrome in an immunocompetent adult. J Hepatol 18:256–257
40. Boruchoff SE, Woda BA, Pihan GA, Durbin WA, Burstein D, Blacklow NR (1990) Parvovirus B19-associated hemophagocytic syndrome. Arch Intern Med 150:897–899
41. Morimoto A, Teramura T, Asazuma Y, Mukoyama A, Imashuku S (2003) Hemophagocytic syndrome associated with severe adenoviral pneumonia: usefulness of real-time polymerase chain reaction for diagnosis. Int J Hematol 77:295–298
42. Kyoda K, Nakamura S, Machi T, Kitagawa S, Ohtake S, Matsuda T (1998) Acute hepatitis A virus infection-associated hemophagocytic syndrome. Am J Gastroenterol 93:1187–1188
43. Guerin C, Pozzetto B, Berthoux F (1989) Hemophagocytic syndrome associated with coxsackie virus A 9 infection in a non-immunosuppressed adult. Intensive Care Med 15:547–548
44. Henter JI, Chow CB, Leung CW, Lau YL (2006) Cytotoxic therapy for severe avian influenza A (H5N1) infection. Lancet 367:870–873
45. Chen TL, Wong WW, Chiou TJ (2003) Hemophagocytic syndrome: an unusual manifestation of acute human immunodeficiency virus infection. Int J Hematol 78:450–452
46. Baraldes MA, Domingo P, Gonzalez MJ, Aventin A, Coll P (1998) Tuberculosis-associated hemophagocytic syndrome in patients with acquired immunodeficiency syndrome. Arch Intern Med 158:194–195
47. Yang WK, Fu LS, Lan JL, Shen GH, Chou G, Tseng CF, Chi CS (2003) Mycobacterium avium complex-associated hemophagocytic syndrome in systemic lupus erythematosus patient: report of one case. Lupus 12:312–316
48. Masri K, Mahon N, Rosario A, Mirza I, Keys TF, Ratliff NB, Starling RC (2003) Reactive hemophagocytic syndrome associated with disseminated histoplasmosis in a heart transplant recipient. J Heart Lung Transplant 22:487–491
49. Kumar N, Jain S, Singh ZN (2000) Disseminated histoplasmosis with reactive hemophagocytosis: aspiration cytology findings in two cases. Diagn Cytopathol 23:422–424
50. Kontopoulou T, Tsaousis G, Vaidakis E, Fanourgiakis P, Michalakeas E, Trigoni E, Samarkos M (2002) Hemophagocytic syndrome in association with visceral leishmaniasis. Am J Med 113:439–440
51. Tapisiz A, Belet N, Ciftci E, Ince E, Dogru U (2007) Hemophagocytic lymphohistiocytosis associated with visceral leishmaniasis. J Trop Pediatr 11:11
52. Taillan B, Ferrari E, Heudier P, Fuzibet JG, Dujardin P (1991) Hemophagocytic syndrome in pneumocystosis. Presse Med 20:1456–1457 [in French]
53. Garcia Escudero A, Benitez Moya JM, Lag Asturiano E (2000) Hemophagocytic syndrome and invasive aspergillosis in a patient with Churg-Strauss vasculitis. Med Clin (Barc) 115:598 [in Spanish]
54. Bhatia S, Bauer F, Bilgrami SA (2003) Candidiasis-associated hemophagocytic lymphohistiocytosis in a patient infected with human immunodeficiency virus. Clin Infect Dis 37:e161–e166
55. Jaffe ES, Costa J, Fauci AS, Cossman J, Tsokos M (1983) Malignant lymphoma and erythrophagocytosis simulating malignant histiocytosis. Am J Med 75:741–749
56. Chuang HC, Lay JD, Hsieh WC, Su IJ (2007) Pathogenesis and mechanism of disease progression from hemophagocytic lymphohistiocytosis to Epstein–Barr virus-associated T-cell lymphoma: nuclear factor-kappa B pathway as a potential therapeutic target. Cancer Sci 98:1281–1287
57. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI (1998) Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 12:435–444
58. Kojima H, Takei N, Mukai Y, Hasegawa Y, Suzukawa K, Nagata M, Noguchi M, Mori N, Nagasawa T (2003) Hemophagocytic syndrome as the primary clinical symptom of Hodgkin's disease. Ann Hematol 82:53–56
59. Aouba A, Lambotte O, Vasiliu V, Divine M, Valensi F, Varet B, Bazarbachi A, Hermine O (2004) Hemophagocytic syndrome as a presenting sign of transformation of smoldering to acute adult T-cell leukemia/lymphoma: efficacy of antiretroviral and interferon therapy. Am J Hematol 76:187–189
60. Srichaikul T, Punyagupta S, Mongkolsritrakul W, Jidpugdeebodin S (2004) EBV and hemophagocytic syndrome: analysis of 3 cases, with speculation on clinical features, therapy and role of EBV. J Med Assoc Thai 87:974–983
61. Fardet L, Blum L, Kerob D, Agbalika F, Galicier L, Dupuy A, Lafaurie M, Meignin V, Morel P, Lebbe C (2003) Human herpesvirus 8-associated hemophagocytic lymphohistiocytosis in human immunodeficiency virus-infected patients. Clin Infect Dis 37:285–291
62. Seliem RM, Griffith RC, Harris NL, Beheshti J, Schiffman FJ, Longtine J, Kutok J, Ferry JA (2007) HHV-8+, EBV+ multicentric plasmablastic microlymphoma in an HIV+ Man: the spectrum of HHV-8+ lymphoproliferative disorders expands. Am J Surg Pathol 31:1439–1445
63. Li CF, Ye H, Liu H, Du MQ, Chuang SS (2006) Fatal HHV-8-associated hemophagocytic syndrome in an HIV-negative immunocompetent patient with plasmablastic variant of multicentric Castleman disease (plasmablastic microlymphoma). Am J Surg Pathol 30:123–127

64. Okuda T, Sakamoto S, Deguchi T, Misawa S, Kashima K, Yoshihara T, Ikushima S, Hibi S, Imashuku S (1991) Hemophagocytic syndrome associated with aggressive natural killer cell leukemia. Am J Hematol 38:321–323
65. Ma L, Bandarchi B, Glusac EJ (2005) Fatal subcutaneous panniculitis-like T-cell lymphoma with interface change and dermal mucin, a dead ringer for lupus erythematosus. J Cutan Pathol 32:360–365
66. Palazzi DL, McClain KL, Kaplan SL (2003) Hemophagocytic syndrome after Kawasaki disease. Pediatr Infect Dis J 22:663–666
67. al-Eid W, al-Jefri A, Bahabri S, al-Mayouf S (2000) Hemophagocytosis complicating Kawasaki disease. Pediatr Hematol Oncol 17:323–329
68. Okada M, Suzuki K, Hidaka T, Shinohara T, Kataharada K, Matsumoto M, Takada K, Ohsuzu F (2001) Hemophagocytic syndrome in systemic lupus erythematosus. Intern Med 40:1263–1264
69. Sekigawa I, Suzuki J, Nawata M, Ikeda K, Koike M, Iida N, Hashimoto H, Oshimi K (2001) Hemophagocytosis in autoimmune disease. Clin Exp Rheumatol 19:333–338
70. Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, Dupond JL, Larroche C, Piette AM, Mechenstock D, Ziza JM, Arlaud J, Labussiere AS, Desvaux A, Baty V, Blanche P, Schaeffer A, Piette JC, Guillevin L, Boissonnas A, Christoforov B (2003) Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature review. Arthritis Rheum 49:633–639
71. Menasche G, Feldmann J, Fischer A, Basile Gde S (2005) Primary hemophagocytic syndromes point to a direct link between lymphocyte cytotoxicity and homeostasis. Immunol Rev 203:165–179
72. Egeler RM, Shapiro R, Loechelt B, Filipovich A (1996) Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol 18:340–345
73. Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, Matsuda Y, Ohta H, Fujisaki H, Kobayashi M, Sakata N, Kawa-Ha K, Okada S, Tawa A (1997) Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. Blood 89:4100–4103
74. Akashi K, Hayashi S, Gondo H, Mizuno S, Harada M, Tamura K, Yamasaki K, Shibuya T, Uike N, Okamura T et al. (1994) Involvement of interferon-gamma and macrophage colony-stimulating factor in pathogenesis of haemophagocytic lymphohistiocytosis in adults. Br J Haematol 87:243–250
75. Hasegawa D, Kojima S, Tatsumi E, Hayakawa A, Kosaka Y, Nakamura H, Sako M, Osugi Y, Nagata S, Sano K (1998) Elevation of the serum Fas ligand in patients with hemophagocytic syndrome and Diamond-Blackfan anemia. Blood 91:2793–2799
76. Imashuku S, Hibi S, Sako M, Ishida Y, Mugishima H, Chen J, Tsunematsu Y (1995) Soluble interleukin-2 receptor: a useful prognostic factor for patients with hemophagocytic lymphohistiocytosis. Blood 86:4706–4707
77. Imashuku S, Hibi S (1991) Cytokines in hemophagocytic syndrome. Br J Haematol 77:438–440
78. Henter JI, Elinder G, Soder O, Hansson M, Andersson B, Andersson U (1991) Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. Blood 78:2918–2922
79. Fujiwara F, Hibi S, Imashuku S (1993) Hypercytokinemia in hemophagocytic syndrome. Am J Pediatr Hematol Oncol 15:92–98
80. Castilletti C, Preziosi R, Bernardini G, Caterini A, Gomes V, Calcaterra S, Carletti F, Capobianchi MR, Armignacco O (2004) Hemophagocytic syndrome in a patient with acute human immunodeficiency virus infection. Clin Infect Dis 38:1792–1793
81. Lambotte O, Khellaf M, Harmouche H, Bader-Meunier B, Manceron V, Goujard C, Amoura Z, Godeau B, Piette JC, Delfraissy JF (2006) Characteristics and long-term outcome of 15 episodes of systemic lupus erythematosus-associated hemophagocytic syndrome. Medicine (Baltimore) 85:169–182
82. Karras A, Thervet E, Legendre C (2004) Hemophagocytic syndrome in renal transplant recipients: report of 17 cases and review of literature. Transplantation 77:238–243
83. Lin MT, Chang HM, Huang CJ, Chen WL, Lin CY, Lin CY, Chuang SS (2007) Massive expansion of EBV+ monoclonal T cells with CD5 down regulation in EBV-associated haemophagocytic lymphohistiocytosis. J Clin Pathol 60:101–103
84. Chuang HC, Lay JD, Chuang SE, Hsieh WC, Chang Y, Su IJ (2007) Epstein–Barr virus (EBV) latent membrane protein-1 down-regulates tumor necrosis factor-alpha (TNF-alpha) receptor-1 and confers resistance to TNF-alpha-induced apoptosis in T cells: implication for the progression to T-cell lymphoma in EBV-associated hemophagocytic syndrome. Am J Pathol 170:1607–1617
85. Kaito K, Kobayashi M, Katayama T, Otsubo H, Ogasawara Y, Sekita T, Saeki A, Sakamoto M, Nishiwaki K, Masuoka H, Shimada T, Yoshida M, Hosoya T (1997) Prognostic factors of hemophagocytic syndrome in adults: analysis of 34 cases. Eur J Haematol 59:247–253
86. Imashuku S (2000) Advances in the management of hemophagocytic lymphohistiocytosis. Int J Hematol 72:1–11
87. Imashuku S, Hibi S, Tabata Y, Todo S (1999) Hemophagocytic syndrome in five patients with Epstein–Barr virus negative B-cell lymphoma. Cancer 85:2298–2300
88. Imashuku S, Kuriyama K, Sakai R, Nakao Y, Masuda S, Yasuda N, Kawano F, Yakushijin K, Miyagawa A, Nakao T, Teramura T, Tabata Y, Morimoto A, Hibi S (2003) Treatment of Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) in young adults: a report from the HLH study center. Med Pediatr Oncol 41:103–109
89. Hardikar W, Pang K, Al-Hebbi H, Curtis N, Couper R (2006) Successful treatment of cytomegalovirus-associated haemophagocytic syndrome following paediatric orthotopic liver transplantation. J Paediatr Child Health 42:389–391
90. Ramasamy K, Lim ZY, Savvas M, Salisbury JR, Dokal I, Mufti GJ, Pagliuca A (2006) Disseminated herpes virus (HSV-2) infection with rhabdomyolysis and hemophagocytic lymphohistiocytosis in a patient with bone marrow failure syndrome. Ann Hematol 85:629–630
91. Imashuku S, Hibi S, Ohara T, Iwai A, Sako M, Kato M, Arakawa H, Sotomatsu M, Kataoka S, Asami K, Hasegawa D, Kosaka Y, Sano K, Igarashi N, Maruhashi K, Ichimi R, Kawasaki H, Maeda N, Tanizawa A, Arai K, Abe T, Hisakawa H, Miyashita H, Henter JI (1999) Effective control of Epstein–Barr virus-related hemophagocytic lymphohistiocytosis with immunochemotherapy. Histiocyte Society. Blood 93:1869–1874

92. Papo T, Andre MH, Amoura Z, Lortholary O, Tribout B, Guillevin L, Piette JC (1999) The spectrum of reactive hemophagocytic syndrome in systemic lupus erythematosus. J Rheumatol 26:927–930
93. Ravelli A, Viola S, Benedetti F de, Magni-Manzoni S, Tzialla C, Martini A (2001) Dramatic efficacy of cyclosporine A in macrophage activation syndrome. Clin Exp Rheumatol 19:108
94. Ravelli A (2002) Macrophage activation syndrome. Curr Opin Rheumatol 14:548–552
95. Henzan T, Nagafuji K, Tsukamoto H, Miyamoto T, Gondo H, Imashuku S, Harada M (2006) Success with infliximab in treating refractory hemophagocytic lymphohistiocytosis. Am J Hematol 81:59–61

Claude Perret
Jean-François Enrico

Manipulating afterload for the treatment of acute heart failure

A historical summary

For decades, digitalis and diuretics presented as the mainstay of the conventional treatment of heart failure. In the late 1960s, however, the use of positive inotropic agents was reconsidered on account of several studies demonstrating a poor hemodynamic response to digitalis and arrhythmogenic effects in patients with coronary disease. The beneficial effect of diuretics in relieving pulmonary congestion and acute pulmonary edema was clearly established. But, it was also shown that excessive use could be deleterious, leading to electrolyte imbalance, hypovolemia, low cardiac output and shock.

Before the introduction of bedside hemodynamic investigation in the early 1970s, the assessment of ventricular performance in man was essentially clinical and radiological. In patients with acute left ventricular failure, successive chest X-rays were used to demonstrate a reduction in cardiac size or a clearing of pulmonary congestion. In view of the usefulness of assessing ventricular function in experimental animals by relating filling pressure to ventricular performance during volume expansion, it was thought that a similar approach in man might be of interest. But the method appeared not to be convenient due to reflex adjustments to the change in blood volume.

In 1964, an important paper, by John Ross and Eugene Braunwald, was published in *Circulation* [1] describing a new method to evaluate left ventricular function by increasing resistance to ventricular ejection. They investigated the ventricular response to graded infusions of angiotensin in patients with and without clinical evidence of impaired left ventricular function. The method used consisted in simultaneous measurements of left ventricular pressure, obtained by transseptal left heart catheterization, and cardiac output determined by the indicator-dilution technique. It was thus possible to construct individual function curves while relating stroke work to filling pressure and to compare the response to a progressive increase in resistance to ventricular ejection. It appeared that, in patients with normal or near normal left ventricular function, there was a steep increase in ventricular stroke work with small elevations in left ventricular end-diastolic pressure. By contrast, in patients with signs of a markedly depressed functional capacity, the initial limb of the curve was flat or even descending, demonstrating a fall in cardiac index and stroke volume as the arterial blood pressure and left ventricular filling pressure rose.

This study was of primary importance for understanding heart function in disease. It demonstrated that the left ventricular response to increased resistance to ejection was highly dependent of its function: in

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_50, © Springer-Verlag Berlin Heidelberg 2009

normal hearts stroke work increased with the augmented afterload so that stroke volume was maintained constant; by contrast, in severely depressed hearts, stroke volume decreased with any increase in aortic pressure. Surprisingly, this new concept did not give rise to the potential implications it contained for clinicians and apparently none raised the question: if an increase in resistance to ventricular ejection worsens ventricular performance, might its reduction be used to improve this?

Our personal experience with vasodilators for the treatment of severe acute left ventricular failure began in the early 1960s, with an erroneous diagnosis. It concerned a 60-year-old patient who was hospitalized in the ICU of the university medical department for severe acute pulmonary edema. Upon admission, he was tachypneic and cyanotic. Blood pressure was extremely unstable oscillating between 150 and 240 mmHg of systolic and 100 and 140 of diastolic pressures. There were signs of intense peripheral vasoconstriction with a cold and clammy skin. Electrocardiogram showed sinus tachycardia with frequent supraventricular ectopic beats and diffuse T wave inversions. Chest X-ray demonstrated marked pulmonary venous congestion and enlarged cardiac silhouette. The patient was immediately treated with high concentrations of oxygen, diuretics and digitalis. The response was poor. Hypertension and tachypnea persisted with signs of clinical shock.

A pheochromocytoma was suspected and an intravenous infusion of phentolamine, an agent with adrenergic and sympathetic blockade properties, was initiated in an attempt to correct hypertension. The drug produced an immediate and dramatic clinical improvement: peripheral signs of shock subsided, blood pressure progressively normalized and pulmonary venous congestion improved. The infusion was progressively discontinued and the patient recovered uneventfully. The beneficial response to phentolamine with a positive test for catecholamines in a sample of urine collected during the hypertensive crisis made likely the diagnosis of pheochromocytoma but all subsequent urinary tests were negative. The diagnosis could not be confirmed and the excessive excretion of urinary catecholamines was attributed to an intense and temporary drive in sympathetic activity related to acute left ventricular failure.

The surprising benefit obtained with phentolamine infusion in a patient with acute pulmonary edema lead us to investigate further the role of vasodilation in left ventricular failure [2]. Seven patients were studied, five of whom had a history of acute myocardial infarction. All were admitted to the intensive care unit for refractory acute pulmonary edema, associated with hypertension in six. Arterial blood gas analysis with repeated lactate determinations were used as an index of severity of the patient's condition. Upon admission, all patients demonstrated marked hypoxemia in spite of oxygen therapy (SaO_2: 56–76%) and severe metabolic acidosis (pH: 7.08–7.33) with a mean lactate concentration of 6.4 mEq/l, indicative of severe tissue anoxia. Phentolamine was administered by a constant infusion at a dose varying between 5 and 20 mg/h. The response was rapid, characterized by the disappearance of pulmonary edema, the normalization of arterial blood and central venous pressures and the complete correction of lactic acidosis in a few hours. The series was extended to include finally a total of 15 patients with the same clinical and metabolic response [3]. All patients survived.

These results attested to an important improvement in tissue perfusion after vasodilator administration and were attributed to a decreased systolic load due to the fall in systemic resistance combined with better distribution of peripheral perfusion following the relief of excessive adrenergic vasoconstriction.

As a matter of fact, Taylor et al. [4] had already investigated the circulatory effects of the acute intravenous injection of phentolamine in normal subjects and in patients with hypertensive disease. The intravenous administration of 5 mg of the drug was shown to produce a prompt reduction in systemic vascular resistance. This resulted in a rapid fall in systemic blood pressure associated with a significant increase in heart rate and cardiac output without large or consistent changes in stroke volume. The response was essentially the same in both groups of subjects, although the time course of their response was different, being significantly slower in the hypertensive group. It was concluded that the predominant vascular activity of phentolamine was to cause a direct relaxation of vascular smooth muscle on the resistance vessels of the systemic circulation. The drug also developed a moderate antagonism to circulating catecholamines with a weak sympathetic blocking activity.

Considering the circulatory effects of phentolamine observed in normal subjects, it could be assumed that such a vasodilation in patients with acute left ventricular failure would be of particular benefit. It had been previously shown that the onset of pump failure was associated with two "compensatory" mechanisms: a reflex vasoconstriction in systemic vessels causing an increase in left ventricular workload and myocardial oxygen demand and a redistribution of blood volume towards the heart and the lungs. It could then be assumed that pharmacological vasodilation would improve ventricular ejection and possibly produce a shift of blood from the lungs to the periphery by reducing venous tone.

These hypotheses were fully confirmed by Majid, Sharma and Taylor in an article published in the *Lancet* [5] a few months after our initial presentation. In a series of 12 patients with severe acute or subacute left ventricular failure due to ischemic heart disease, phentolamine

was administered by intravenous infusion. The initial dose was 5 mg/min for 1 min followed by a dose adjusted in each subject to reduce the supine mean systemic arterial pressure by approximately 25 mmHg. The fall in blood pressure produced rapid relief of dyspnea associated with a progressive clearing in pulmonary edema and a significant reduction of heart size, as we had described. But most interesting was the hemodynamic response observed in the group of patients with severe heart failure: phentolamine infusion produced a rapid and substantial reduction in left ventricular end-diastolic and pulmonary-artery mean pressures associated with an increase in stroke volume and cardiac output. These benefits in ventricular performance were attributed essentially to two mechanisms: the reduction in cardiac pressure load obtained by lowering the raised vascular resistance and an increase in the capacity of the peripheral vessels, particularly the veins, which reduced the volume of blood in the dilated heart. A reflex increase in sympathetic activity secondary to the fall in systemic blood pressure could not be definitively discarded. But the absence of significant change in heart rate made an increase in inotropic activity unlikely.

This study was the first to use sophisticated left and right catheterization techniques to measure the response of cardiac output and filling pressures to peripheral vasodilation. It demonstrated the therapeutic value of reducing systemic vascular resistance in patients with severe left ventricular failure. It showed that relief of the workload of a failing heart could provide significant clinical benefit with apparently no hazard to the cerebral and coronary circulations.

During the early 1970s, several studies demonstrated that the incidence and severity of left ventricular failure complicating acute myocardial infarction were directly related to the extent of ventricular mass necrosis. Consequently the ideal therapy would minimize myocardial oxygen demand and raise oxygen delivery to the ischemic area. On a theoretical basis, one could expect that phentolamine, as well as other vasodilators, might improve heart pump function without interfering adversely with the myocardial oxygen metabolism.

In 1973, Kelly et al. [6] used phentolamine to decrease arterial blood pressure in 11 hypertensive patients with acute myocardial infarction and left ventricular dysfunction. Six had a history of chronic hypertension confirmed by ophthalmoscopy and electrocardiographic signs of left ventricular hypertrophy. The remaining five had no previous history of hypertension. The hemodynamic response to low doses of phentolamine was similar to those previously described with a significant decline in arterial and pulmonary capillary wedge pressures and a concomitant increase in cardiac index. Interestingly, as stroke work index and heart rate were unchanged, the rate-pressure time product thought to be a reasonable index of myocardial oxygen consumption decreased significantly in the group with acute hypertension. The conclusion was that, in such conditions of acute hypertension, reduction of left ventricular afterload might offer advantages over current therapy for left ventricular dysfunction.

A few months later another clinical investigation was published in the same journal by Chatterjee et al. [7] from the group of Cedars-Sinai Medical Center in Los Angeles, describing the hemodynamic and metabolic responses to vasodilator therapy in patients with acute myocardial infarction. Thirty-eight patients were examined and were divided in three groups according to the severity of left ventricular failure estimated on the initial level of pulmonary capillary wedge pressure and stroke work index. In group III (15 patients) all had clinical evidence of left ventricular failure, 14 had frank pulmonary edema and 8 had clinical features of shock. In 11 patients, phentolamine was used: 5 mg were administered intravenously in the first minute then at a rate of 0.1–0.2 mg/min. In the remaining 27 patients, sodium nitroprusside was infused at a rate of 16–200 μg/min. The infusion of the vasodilator was gradually increased until the mean arterial blood pressure decreased by not more than 20 mmHg or when there was a significant decrease in pulmonary capillary wedge pressure. Pressures and cardiac output were measured with a balloon-tip triple lumen catheter using the thermodilution technique. Coronary sinus flow was determined by the constant infusion technique. The myocardial extraction ratio for lactate was calculated from arterial and coronary sinus blood samples.

The study showed that the hemodynamic response to phentolamine or nitroprusside was identical to that reported previously. But it also demonstrated that the benefit in heart performance was greater in those patients with the most severely depressed cardiac function. The functional improvement was obtained without any increase in metabolic cost. Myocardial oxygen demand either remained unchanged or even, in some cases, fell and myocardial lactate extraction did not decrease. Therefore, it appeared that vasodilator therapy might well play an important role in the treatment of pump failure following myocardial infarction.

These expectations were confirmed in another hemodynamic study performed in a series of 15 patients with acute myocardial infarction [8]. It was shown that with a dose of 10 mg/h, phentolamine could be used in normotensive patients without adverse effects; the fall of mean arterial blood pressure was less than 15 mmHg and was associated with a significant increase in cardiac output and a substantial reduction in right and left filling pressures. The overall clinical course appeared surprisingly good with a mortality rate of 13% in a group of high-risk patients.

In conclusion, for years the therapy of congestive heart failure had focused on trying to influence the factors which at that time were recognized as the determinants of myocardial function, such as reducing the diastolic filling of the ventricle with diuretics or increasing its contractility with inotropic drugs. In the early 1960s, several studies demonstrated that the diseased left ventricle was highly dependent on peripheral vascular factors, which had been hitherto relatively neglected. In the normal heart, an increased impedance to ventricular ejection was well tolerated and did not change stroke volume. In the presence of left ventricular dysfunction, an enhanced impedance could lead to a decrease in cardiac output with an increase in ventricular volume and pressure. This abnormal response appeared of particular importance when it was shown that heart failure itself produced an arteriolar vasoconstriction and different alterations in vascular wall structure, which increased impedance to ventricular outflow and thus further deteriorated ventricular performance. The pharmacological reduction of impedance with the use of vasodilator drugs led to a new approach. It has proved to be a most important adjunction in the management of both acute and chronic heart failure [9].

References

1. Ross J, Braunwald E (1964) The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. Circulation 29:739–749
2. Enrico JF, Poli S, Grandjean T, Perret C (1971) Utilité de la phentolamine dans le traitement de l'oedème pulmonaire aigu. Schweiz Med Wochenschr 9:325–328
3. Enrico JF, Poli S, Perret C (1971) La phentolamine dans le traitement de l'oedème aigu "réfractaire". Bull Physio-Path Respir 7:1319–1340
4. Taylor SH, Sutherland GR, MacKenzie GJ, Staunton HP, Donald KW (1965) The circulatory effects of intravenous phentolamine in man. Circulation 31:741–754
5. Majid PA, Sharma B, Taylor SH (1971) Phentolamine for vasodilator treatment of severe heart failure. Lancet 2:719–724
6. Kelly DT, Delgado CE, Taylor DR, Pitt B, Ross RS (1973) Use of phentolamine in acute myocardial infarction associated with hypertension and left ventricular failure. Circulation 47:729–735
7. Chatterjee K, Parmley WW, Ganz W, Forrester J, Walinsky P, Crexells C, Swan HJC (1973) Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. Circulation 48:1183–1193
8. Perret C, Gardaz JP, Reynaert M, Grimbert F, Enrico JF (1975) Phentolamine for vasodilator therapy in left ventricular failure complicating acute myocardial infarction. Haemodynamic study. Br Heart J 37:640–646
9. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary (2001). Circulation 104:2996–3007

Waldemar G. Johanson
Lisa L. Dever

Nosocomial pneumonia

Abstract Nosocomial pneumonia, or terminal pneumonia as it was formerly called, results from the repetitive microaspiration of contaminated oropharyngeal secretions into the lungs in the presence of impaired host defenses. This pathophysiologic sequence was suggested by the observations of Osler but clarified by the seminal work of Rouby and colleagues. The enormous impact of antimicrobial agents on the organisms responsible for nosocomial pneumonias was first identified by Kneeland and Price who found that organisms of the normal pharyngeal flora virtually disappeared in terminal pneumonias following administration of these drugs, being replaced by gram-negative bacilli. The remarkable susceptibility of seriously ill patients to becoming colonized by exogenous organisms, even in the absence of antimicrobial therapy, was shown by Johanson et al. These factors, antibiotics and the change in bacterial binding receptors in the airways associated with illness, lead to infections caused by exogenous organisms that are frequently resistant to antimicrobial agents. Clinical findings that usually identify patients with respiratory infections are unreliable for the diagnosis of nosocomial pneumonias as shown by Andrews et al. Invasive techniques, especially the protected specimen brush (PSB) technique, avoid contamination of the specimen by proximal secretions and accurately reflect the bacterial burden of the lung, as first shown by Chastre et al. Quantitation of such specimens serves as an excellent proxy for direct cultures of the lung and are the current gold standard for diagnosis.

Keywords Nosocomial pneumonia · Protected specimen brush · Aspiration

Introduction

The development of pneumonia in patients who are already seriously ill with a different process is not a new phenomenon but one that has long been recognized with the phrase "Pneumonia is the old man's friend" – the implication being that pneumonia is the mode of exit from this worldly life when continued existence becomes problematic. Sir William Osler honed his world-renowned clinical skills at the autopsy table where he had the opportunity to correlate his clinical findings directly with anatomical findings, an opportunity very largely lost to today's physicians, at least in the United States. In his classic text, "The Principles and Practice of Medicine" [1], Osler discusses at length the differences between lobar pneumonia and forms of pneumonia that occurred in other settings such as complications of other diseases, post-operatively, especially following ether anesthesia, or as in so-called "terminal pneumonias".

He thought that no physician could miss the diagnosis of lobar pneumonia, based on the presenting signs and symptoms, even without a chest radiograph. In contrast, the other forms of pneumonia were easily overlooked, leading to Osler's comment that there was a much great-

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_51, © Springer-Verlag Berlin Heidelberg 2009

er incidence of terminal pneumonia in the autopsy room than on the wards. These pneumonias were lobular initially, consisting of an intense neutrophilic inflammatory exudate centered on a small bronchiole located in a dependent portion of the lung. This infection was then, and still is today, caused by the microaspiration of small quantities of contaminated oropharyngeal secretions in the presence of host defenses that are unable to eliminate the challenge. We will review two aspects of these infections; the pathophysiology and the methods of diagnosis in the midst of confounding factors.

Pathophysiology of nosocomial pneumonia

It is now understood that nosocomial pneumonia is usually initiated by colonization of the upper respiratory tract by potentially pathogenic bacteria. Secretions contaminated by these bacteria are aspirated in small quantities into the lungs–around the cuff of an endotracheal tube if present. The lung's antibacterial defenses try to inactivate this bacterial bolus. If these defenses are successful, pneumonia will not result. If they are unsuccessful, infection occurs, beginning as bronchiolitis and progressing to bronchopneumonia that may extend to involve adjacent regions of lung in a confluent pneumonia with or without abscess formation. Osler [1] understood the outlines of this process when he wrote about ether weakening the lining of the lungs to allow postoperative pneumonias to develop.

Studies of the pathophysiology of complex clinical processes are usually difficult and the work of any one group of investigators is often incomplete. Every now and then a particularly important study is completed that brings much of the field into focus. Such was the case with the paper published in 1992 by Rouby et al. [2]. These investigators utilized a French law that enables researchers to perform an autopsy shortly after the patient's death to obtain specimens for research if not expressly forbidden by the patient. They performed a bedside thoracotomy and removed either the left or right lung of 83 patients who died while receiving mechanical ventilation for respiratory failure. The removed lungs were serially sectioned so that five to ten samples were obtained from each bronchopulmonary segment for histologic examination. Additional sections from each lobe were submitted for microbiologic study. In 69 of the 83 patients a bronchoalveolar lavage (BAL) procedure had been performed within 48 h prior to death as part of a prospective study of pneumonias. Thus, the key features that make this such an important study are (1) a large sample size; (2) prospective data collection for some elements; (3) meticulous pathologic techniques, especially serial sectioning of the lungs and (4) sampling performed immediately after death.

Infection was found in 60 of 83 (72%) lungs and occurred predominantly in dependent lung segments indicating the aspirational nature of this process. Stages of severity from bronchiolitis alone, to bronchopneumonia, to lung abscess were readily recognized and lesions at varying stages usually co-existed in the same lung, suggesting a recurring process. Foci of infection were widely dispersed among areas of either normal lung or lung tissue involved with other pathologic processes such as diffuse alveolar damage. Without serial sectioning, many foci of infection would have been missed and the patient wrongly categorized as uninfected. The correlation between microbiologic results and histology was imperfect but illuminating (Table 1). In general, higher bacterial counts were associated with more advanced lesions of infection, i.e. bronchopneumonia and abscess. No microbial growth was observed in lobes free of infectious lesions histologically. However, 30–40% of lobes that showed infectious lesions had no bacterial growth but over 90% of these patients were receiving intravenous antibiotics.

These findings indicate that nosocomial bronchopneumonia occurs in most patients undergoing prolonged mechanical ventilation, when defined by histologic criteria. Foci of bronchopneumonia may become sterile either as a result of successful host defenses or the effect of powerful antibiotics, or both. Alternatively, progressive lung infection with systemic manifestations results if host defenses, with or without antibiotics, are unable to rise to the challenge posed by colonization of distal airways [3]. The source of organisms that colonize the distal airways remains somewhat controversial, with some investigators finding that colonization of the stomach precedes colonization of the airways [4]. In most cases, colonization of the stomach is the result of swallowing contaminated secretions [5]. Airway colonization by *Pseudomonas aeruginosa* and related organisms seems to differ from the usual pattern with colonization of the distal airways occurring first, before any more proximal site [6]. That may be because receptors to bind *P. aeruginosa* are more readily available in the trachea and more distal sites. Alternatively, it may suggest that colonization is the result of aerosol contamination by *P. aeruginosa* and other organisms that thrive in water, such as *Serratia marcescens*.

Many studies of nosocomial pneumonia have failed to reproduce one or another of the key features of the Rouby study. Most are readily explained by a careful evaluation of the data and study design. For example, many studies have found a lower prevalence of pneumonia–in some cases much lower. As Rouby et al. [2] pointed out, the prevalence they found was due to serial sectioning of the lungs, enabling them to identify small focal lesions that would have been missed by the less rigorous sampling techniques that are generally used. Some have suggested that sterile inflammatory lesions cannot be bacterial pneumonias and argue that a histologic gold standard overestimates the incidence of pneu-

Table 1 Correlation of lung histology and microbiology [2]

Histologic grading of severity	Number of lobes	Quantitative colony counts in lung tissue (cfu/g)		
		No growth	$<10^3$ Colonies	$\geq 10^3$ Colonies
No infection	43	43 (100%)	0	0
Bronchiolitis	20	6 (30%)	14 (70%)	0
Bronchopneumonia	15	6 (40%)	4 (27%)	5 (33%)
Confluent pneumonia	18	7 (39%)	5 (28%)	6 (33%)
Total	96	62	23	11

Table 2 Post-mortem culture results in the pre-antibiotic era [7]

Organism	Bronchopneumonia (n =109)		No bronchopneumonia (n =98)	
	Lung isolates (%)	Nasopharyngeal colonization (%)	Lung isolates (%)	Nasopharyngeal colonization (%)
Streptococcus pneumoniae	37	78	11	39
Group A streptococci	7	80	6	50
Haemophilus influenzae	21	78	4	20
Staphylococcus aureus	41	58	24	44

monia. However, sterile lesions usually co-exist with other lesions with positive cultures. As with the presence of positive cultures in regions that do not show histologic pneumonias, these findings are likely explained by sampling errors induced by the focal nature of this process.

Historical perspective

Colonization, or the persistence of a bacterial species at a particular site over time, is a root cause of nosocomial pneumonia. The upper airways of healthy individuals contain a limited bacterial flora, including a number that are potentially pathogenic. In fact, the organisms that we regard as being highly pathogenic for the respiratory tract, such as *Streptococcus pneumoniae*, are members of the normal flora. In the pre-antibiotic era, these were the organisms that caused pneumonia, whether nosocomial or community-acquired.

Smillie and Duerschner [7] reported, in 1947, their findings in an autopsy study of 109 subjects with terminal pneumonia and 98 people who died but did not have pneumonia at post-mortem. Specimens of peripheral lung and nasopharyngeal swabs were cultured (Table 2). These results were interpreted as showing that terminal bronchopneumonias were caused by organisms that were members of the normal nasopharyngeal flora and that colonization of the upper respiratory tract with the same organisms found in the lungs was readily demonstrated at the time of autopsy. Nasopharyngeal colonization was also common among patients who did not have pneumonia. The role of *Staphylococcus aureus* was uncertain, primarily because it so often colonized the nasopharynx of patients who did not have pneumonia. Gram-negative bacilli (GNB) were found in "some" patients, but were not felt to play an important role.

By 1960 the situation had changed dramatically. Kneeland and Price [8] duplicated the earlier study in an autopsy series of 200 consecutive patients; 110 were found to have terminal, or nosocomial, pneumonia. The authors compared the causative organisms to those reported by Smillie and Duerschner [7] 10 years earlier (Table 3). Clearly, an enormous shift in the bacteria associated with nosocomial pneumonia had occurred in this 10-year period. Kneeland and Price [8] were far more convinced about the pathogenicity of *S. aureus* than had been their predecessors, thinking that it was "probably a pathogen". This impression was influenced by the impact of the influenza pandemic in the late 1950s. Pneumonias due to normal flora, e.g. *S. pneumoniae, H. influenzae*, and Group A streptococci, were seen only in patients who had not received antimicrobial therapy.

The reason for the predominance of the normal flora organisms as the cause of pneumonia is simply that they are more pathogenic for the lungs than other organisms. However, serious illness or surgery causes a shift in the availability of receptors for other bacterial species in the respiratory tract so that colonization by GNB, *S. aureus* and other organisms may occur. In 1969, Johanson et al. [9] reported that the pharyngeal flora of hospitalized, ill patients underwent a dramatic and swift alteration. GNB that rarely colonized the throats of healthy individuals appeared quickly in throat swabs of sick patients, with their prevalence being proportional to the severity of illness. Antibiotics alone were not responsible. For exam-

Table 3 Etiologies of terminal pneumonia, 1947 and 1957

Organism	1946–47 [7] (*n* =109; %)	1956–57 [8] (*n* =110; %)
Streptococcus pneumoniae	37	6
Group A streptococci	7	0
Haemophilus influenzae	21	4
Staphylococcus aureus	41	50
Pseudomonas aeruginosa	0	24
Klebsiella pneumoniae	0	25
Other Gram-negative bacilli	"Some"	19

ple, GNB colonization ranged from 0–2% among hospitalized patients who were not physically ill (psychiatry patients) and non-hospitalized healthy people, but was found in 62% of moribund patients in the absence of antibiotic therapy. Antibiotic therapy increased GNB colonization to 80% in the latter patients. This study showed that underlying disease was an important determinant of GNB colonization in addition to antibiotic therapy.

Seriously ill patients are remarkably susceptible to acquiring exogenous organisms from their environment, a susceptibility not shared by healthy individuals. Antibiotics, either given to the patient or present in the patient's environment, cause strong pressure on the bacterial flora and select resistant strains. Trouillet et al. [10] analyzed the factors associated with potentially drug-resistant (PDR) bacteria in nosocomial pneumonias and found that prior antibiotic therapy, prior broad spectrum antibiotic use and the duration of mechanical ventilation were each associated with an increasing prevalence of PDR infections. Pneumonias that occurred early in the hospital course or before antibiotics had been given were usually caused by antibiotic-susceptible organisms.

It is fortunate that members of the normal bacterial flora of the respiratory tract have remained susceptible to most antibiotics so that administration of almost any antibiotic leads to the swift elimination of these organisms. The result of these two factors, the change in bacterial binding sites in the airways and the elimination of the normal flora by antibiotics, is that the airways of sick individuals become colonized by organisms that are not normally present, such as GNB. However, members of the normal flora are acquiring antimicrobial genes in greater numbers. Clinicians soon may be faced with the specter of pneumonias caused by normal flora organisms that are resistant to common, if not all, antibiotics. Given the greater pathogenicity of these organisms, such a resistance pattern could potentially recreate the pre-antibiotic era.

Diagnosis of nosocomial pneumonia

The shortcomings of a histologic gold standard have led to a variety of studies exploring the usefulness of surrogate measures. Osler, of course, relied entirely on his findings at autopsy to make the diagnosis of terminal, or nosocomial, pneumonia. In the absence of antibiotics, the evolution of pneumonia follows a predictable histologic course that is closely correlated with quantitative microbiologic findings in both experimental animals and humans. Following the inoculation of pathogenic bacteria into the lungs resident alveolar macrophages phagocytose and kill the invading bacteria. If they are unable to do so, neutrophils are recruited from the blood into alveolar spaces, a sequence that has been known for over 100 years [11]. This process begins in the region of terminal bronchioles because of the rapid increase in cross-sectional area of the airways at that level with the resultant deposition of inhaled materials. Inflammation spreads quickly to adjacent alveoli if not contained. In acute situations, and in the absence of antibiotics, recognizable foci of bronchopneumonia require bacterial densities of approximately 10^4 cfu/g [12]. Confluent pneumonias are associated with approximately 10^7 cfu/g and abscesses even greater numbers. However, the association between histology and quantitative microbiology becomes much less tight over time as lung defenses kill organisms and the milieu of the consolidated lung no longer supports bacterial multiplication [13].

Nevertheless, histologic findings remain the principal "gold standard" for nosocomial pneumonia, even though regarded as unreliable by some investigators, due to poor agreement among multiple reviewers [14]. Factors that contribute to uncertainty about the recognition of pneumonia histologically include the presence of underlying lung disease, especially diffuse alveolar damage and pulmonary edema, and certain systemic processes, notably marked leukopenia. However, the major confounding factor is antibiotic therapy that has the capacity to sterilize pneumonic lesions long before they resolve histologically leading to the often-observed disparity between histology and microbiology and limiting the usefulness of histology as a gold standard. At least that problem is well understood. The problem that is not understood is the extent of histologic pneumonia that must be present to be important clinically. Since aspiration presumably occurs on a daily basis in mechanically ventilated patients, new foci of potential bronchopneumonia are being initiated every day. Within a few days, there are foci at the stage of bronchiolitis, some at the early broncho-

pneumonia stage and perhaps others at the confluent stage. How many of what types of lesions are necessary to produce clinical signs of pneumonia is not known.

A number of investigators have examined the relationship between histologic evidence of nosocomial pneumonia and clinical signs of infection. Andrews and coworkers [15] studied 24 patients who died while enrolled in a prospective study of acute respiratory failure. Multiple sections through both lungs were examined by a pathologist who was blinded to the clinical history of the patient. Similarly, clinicians made the determination of whether or not pneumonia was present at the time of the patient's death based on the clinical findings while blinded to the pathologic findings. Foci of bronchopneumonia were found in 14 (58%) patients in at least one lung segment and these were classified as having histologic pneumonias. Only 9 of these 14 patients (64%) were classified by the clinicians as having clinical pneumonia at the time of death. Similarly, two of ten patients (20%) who had only diffuse alveolar damage without pneumonia histologically were diagnosed clinically as having pneumonia. These findings have been reproduced in a number of studies [16, 17, 18] and it is clear that clinical findings are not reliable indicators of the presence or absence of histologic pneumonia in mechanically ventilated patients, especially those with ARDS.

Since nosocomial pneumonia is caused by the presence of bacteria in normally sterile regions of the lungs, it seems obvious that appropriate cultures should provide a useful surrogate for a histologic diagnostic standard. The value of expectorated sputum, analogous to a tracheal aspirate in an intubated patient for this purpose, has been debated for nearly 100 years [19, 20]. Sputum has the great advantages of ready availability and lack of expense. However, colonization of proximal airways, including the oropharynx, with multiple species of bacteria causes contamination of specimens passing through, so that potentially pathogenic bacteria are present in expectorated sputum or tracheal aspirates from most patients, whether or not they have pneumonia.

An often-overlooked aspect of sputum or tracheal aspirates as a source of material is the handling of the specimen. A previous generation of physicians was taught to inspect the sample carefully, preferably in a petri dish, and to select the most purulent portion with sterile scissors or a loop. Another recommended approach was to have the patient rinse his mouth with sterile water prior to expectoration [21, 22] or to wash the specimen repeatedly with sterile water in a container [23]. This was shown to remove a significant number of oral bacteria in subsequent culture, presumably from the surface of the specimen. Another technique is to homogenize the sample as is done for quantitative cultures. It is believed that organisms present in sputum at high concentrations are more likely to be important than those present at low concentrations. An organism present in sputum at a concentration of 10^5cfu/ml or more has long been believed to be the cause of community-acquired pneumonia [23], a notion based on the premise that pneumonias were caused by single organisms.

The protected specimen brush (PSB) technique is a highly selective approach to the sampling of secretions in the distal airways while avoiding contamination by proximal secretions [24]. Chastre et al. [25] performed a landmark study in 26 patients who died while receiving mechanical ventilation. While ventilation was continued, bronchoscopy was performed and PSB samples were obtained from the anterior segment of the left lower lobe (LLL). A mini-thoracotomy was then performed and multiple samples of lung tissue were obtained from the same segment for histology and quantitative cultures. Six patients had histologic pneumonias in the anterior segment of the LLL, 20 did not. Lung tissue cultures yielded 10^4 cfu/g or more of lung tissue in all six patients with pneumonia. In four (67%) patients these infections were polymicrobial with multiple organisms present at concentrations of 10^4 cfu/g or more. Interestingly, none of these four patients had received antibiotics in the week before their death and the predominant organisms were members of the normal oropharyngeal flora, such as *S. pneumoniae*. In the two pneumonia patients who had received antibiotics, the predominant organisms were *P. aeruginosa* and *Proteus mirabilis*. Overall there was a highly significant correlation between lung tissue cultures and PSB cultures. A cut-off value for the PSB of 10^3 cfu/ml identified all patients with pneumonia. As expected, some patients whose PSB cultures yielded 10^3 cfu/ml or more did not have pneumonia in the anterior segment of the LLL.

The Rouby study would predict that a focal pneumonia would have been found in a nearby segment [2]. This is a drawback of the sampling strategy used by Chastre et al. [25]. A total of 30 organisms were recovered from cultures of lung tissue from the 26 patients while 51 organisms were recovered from PSB samples. Virtually all of the excess PSB yield was accounted for by GNB and fungi, suggesting that contamination by proximal colonizing organisms was an additional contributing factor to the discrepancy between PSB and tissue cultures. Nevertheless, this study showed that the PSB technique closely reflects the bacterial burden of the lung segment sampled and that a quantitative value of 10^3 cfu/ml or more provides a reliable cut-off to identify patients with pneumonia. Selection of an anterior segment may explain the relatively low prevalence of pneumonia in this study. Overall, this study showed that PSB samples do meet the objective of finding a usable surrogate for the histologic gold standard.

It is important to understand the mechanics of PSB sampling. The PSB samples approximately 0.001 ml of secretions. Virtually all investigators who have utilized this technique have placed the PSB in 1.0 ml of sterile water or saline for vigorous shaking or vortexing. Sam-

ples of this 1.0 ml are then plated in various dilutions. A final result of 10^3 cfu/ml would indicate that the original material sampled in the airway contained a concentration of bacteria of 10^6 cfu/ml. Many studies have verified these findings and have found that bronchoalveolar lavage (BAL) provides similar information although with a cut-off value of 10^4 cfu/ml or more [26, 27, 28, 29]. Studies that have failed to support the findings of Chastre et al. [25] generally suffer from one or more critical faults, the most important of which is failure to account for antibiotic therapy appropriately. It has become clear that changes in therapy within 72 h of invasive sampling renders the results unpredictable and often not interpretable [30]. A second consideration is the failure to match histologic and PSB samples sources closely. Several recent studies have reported that quantitative cultures of tracheal aspirates have greater sensitivity than more invasive PSB or BAL samples [31, 32]. This would be expected from the pathophysiology of these infections, in which colonization precedes infection and many more organisms colonize proximal ways than cause pneumonia. The specificity of BAL and PSB remain greater than that of tracheal aspirates [31, 32]. These findings have been reproduced in a non-human primate model of respiratory failure as well [33].

Attempts to diagnose pneumonia by non-microbiologic techniques have been generally unsuccessful. Elastin fragments have been identified in the sputum of patients with pneumonias caused by GNB [34, 35]. The source of the elastin is presumably necrosis of alveolar walls or airways, but it is not found in the sputum of patients with other types of pneumonia and, hence, has limited usefulness. Endotoxin is also found in the sputum of patients with GNB pneumonias but it may be difficult to distinguish colonization from infection [36, 37]. Various antigens unique to organisms found in the lungs, such as pneumococcal polysaccharide capsular material, confirm the fact that the organism is present but do not distinguish between colonization and infection.

Summary

Critically ill patients are remarkably susceptible to colonization by exogenous bacteria which, in the hospital environment, are often antibiotic-resistant. Differences in hospital environments account for the widely varying bacterial etiologies among different hospitals and the necessity of knowing current antibiotic susceptibility patterns for each hospital. PSB and BAL provide useful surrogates for histology in the diagnosis of nosocomial pneumonia as long as certain precautions are followed. Most important is the avoidance of obtaining cultures shortly after changing antibiotics. Finally, the pathophysiology of nosocomial pneumonia as explained by Rouby and colleagues [2] provides a framework for the understanding of this process that is extremely useful in the interpretation of new research findings.

References

1. Osler W (1909) The principles and practice of medicine, 7th edn. Appleton, New York London
2. Rouby JJ, Martin De Lassale E, Poete P, Nicolas MH, Bodin L, Jarlier V, Le Charpentier Y, Grosset J, Viars P (1992) Nosocomial bronchopneumonia in the critically ill. Histologic and bacteriologic aspects. Am Rev Respir Dis 146:1059–1066
3. Delclaux C, Roupie E, Blot F, Brochard L, Lemaire F, Brun-Buisson C (1997) Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: incidence and diagnosis. Am J Respir Crit Care Med 156:1092–1098
4. Du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A (1982) Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of post operative colonization of the airway. Lancet 1:242–245
5. Bonten MJ, Gaillard CA (1995) Ventilator-associated pneumonia: do the bacteria come from the stomach?. Neth J Med. 46:1–3
6. Talon D, Mulin B, Rouget C, Bailly P, Thouverez M, Viel JF (1998) Risks and routes for ventilator-associated pneumonia with Pseudomonas aeruginosa. Am J Respir Crit Care Med 157:978–984
7. Smillie WG, Duerschner DR (1947) The epidemiology of terminal pneumonia: II. The selectivity of nasopharyngeal bacteria in invasion of the lungs. Am J Hygiene 45:13–18
8. Kneeland YJ, Price KM (1960) Antibiotics and terminal pneumonia. Am J Med 29:967–979
9. Johanson WG Jr, Pierce AK, Sanford JP (1969) Changing pharyngeal bacterial flora of hospitalized patients. N Engl J Med 281:1137–1140
10. Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC, Gibert C (1998) Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 157:531–539
11. Wadsworth A (1904) Experimental studies on the etiology of acute pneumonitis. Am J Med Sci 127:851–877
12. Coalson JJ (1995) The pathology of nosocomial pneumonia. Clin Chest Med 16:13–28
13. Wood WB Jr, Smith MR (1950) Host-parasite relationships in experimental pneumonia due to pneumococcus type III. J Exp Med 92:85–99
14. Corley DE, Kirtland SH, Winterbauer RH, Hammar SP, Dail DH, Bauermeister DE, Bolen JW (1997) Reproducibility of the histologic diagnosis of pneumonia among a panel of four pathologists: analysis of a gold standard. Chest 112:458–465
15. Andrews CP, Coalson JJ, Smith JD, Johanson WG Jr (1981) Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. Chest 80:254–258

16. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR (1986) Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 133:792–796
17. Jimenez P, Torres A, Rodriguez-Roisin R, de la Bellacasa JP, Aznar R, Gatell JM, Agusti-Vidal A (1989) Incidence and etiology of pneumonia acquired during mechanical ventilation. Crit Care Med 17:882–885
18. Torres A, Aznar R, Gatell JM, Jimenez P, Gonzalez J, Ferrer A, Celis R, Rodriguez-Roisin R (1990) Incidence, risk and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. Am Rev Respir Dis 142:523–528
19. Luestcher JA (1906) A bacteriologic and clinical study of the nontuberculous infections of the respiratory tract, with special reference to sputum cultures as a means of diagnosis. Arch Intern Med 16:657–680
20. Coster JF, Barrett-Connor E (1972) The nonvalue of sputum culture in the diagnosis of pneumonia. Am Rev Respir Dis 105:139–140
21. Monroe PW, Muchmore HG, Felton FG, Pirtle JK (1969) Quantitation of microorganisms in sputum. Appl Microbiol 18:214–220
22. Pirtle JK, Monroe PW, Smalley TK, Mohr JA, Rhoades ER (1969) Diagnostic and therapeutic advantages of serial quantitative cultures of fresh sputum in acute bacterial pneumonia. Am Rev Respir Dis 100:831–838
23. Saadah HA, Nasr FL, Shagoury ME (1980) Washed sputum gram stain and culture in pneumonia: a practical tool for the clinician. J Okla State Med Assoc 73:354–359
24. Wimberley NW, Bass JB Jr, Boyd BW, Kirkpatrick MB, Serio RA, Pollock HM (1982) Use of a bronchoscopic protected catheter brush for the diagnosis of pulmonary infections. Chest 81:556–562
25. Chastre J, Viau F, Brun P, Pierre J, Dauge MC, Bouchama A, Akesbi A, Gibert C (1984) Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. Am Rev Respir Dis 130:924–929
26. Chastre J, Fagon JY, Bornet-Lecso M, Calvat S, Dombret MC, al Khani R, Basset F, Gibert C (1995) Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 52:231–240
27. Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C (1996) Nosocomial pneumonia and mortality among patients in intensive care units. JAMA 275:866–869
28. Barreiro B, Dorca J, Manresa F, Catala I, Esteban L, Verdaguer R, Gudiol F (1996) Protected bronchoalveolar lavage in the diagnosis of ventilator-associated pneumonia. Eur Respir J 9:1500–1507
29. Gerbeaux P, Ledoray V, Boussuges A, Molenat F, Jean P, Sainty JM (1998) Diagnosis of nosocomial pneumonia in mechanically ventilated patients: repeatability of the bronchoalveolar lavage. Am J Respir Crit Care Med 157:76–80
30. Ruiz M, Torres A, Ewig S, Marcos MA, Alcon A, Lledo R, Asenjo MA, Maldonaldo A (2000) Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. Am J Respir. Crit Care Med 162:119–125
31. el-Ebiary M, Torres A, Gonzalez J, de la Bellacasa JP, Garcia C, Jimenez de Anta MT, Ferrer M, Rodriguez-Roisin R (1993) Quantitative cultures of endotracheal aspirates for the diagnosis of ventilator-associated pneumonia. Am Rev Respir Dis 148:1552–1557
32. Marquette CH, Georges H, Wallet F, Ramon P, Saulnier F, Neviere R, Mathieu D, Rime A, Tonnel AB (1993) Diagnostic efficiency of endotracheal aspirates with quantitative bacterial cultures in intubated patients with suspected pneumonia. Comparison with the protected specimen brush. Am Rev Respir Dis 148:138–144
33. Johanson WG Jr, Seidenfeld J, Gomez P, Santos R, Coalson JJ (1988) Bacteriologic diagnosis of nosocomial pneumonia following protracted mechanical ventilation. Am Rev Respir Dis 137:259–264
34. Salata RA, Lederman MM, Shlaes DM, Jacobs MR, Eckstein E, Tweardy D, Toossi Z, Chmielewski R, Marino J, King CH, Graham RC, Ellner JJ (1987) Diagnosis of nosocomial pneumonia in intubated, intensive care unit patients. Am Rev Respir Dis 135:426–432
35. el-Ebiary M, Torres A, Gonzalez J, Martos A, Puig de la Bellacasa J, Ferrer M, Rodriguez-Roisin R (1995) Use of elastin fibre detection in the diagnosis of ventilator associated pneumonia. Thorax 50:14–17
36. Kollef MH, Eisenberg PR, Ohlendorf MF, Wick MR (1996) The accuracy of elevated concentrations of endotoxin in bronchoalveolar lavage fluid for the rapid diagnosis of gram-negative pneumonia. Am J Respir Crit Care Med 154:1020–1028
37. Nys M, Ledoux D, Canivet JL, De Mol P, Lamy M, Damas P (2000) Correlation between endotoxin level and bacterial count in bronchoalveolar lavage fluid of ventilated patients. Crit Care Med 28:2825–2830

Konrad J. Falke

The introduction of positive endexpiratory pressure into mechanical ventilation: a retrospective

Continuous positive pressure breathing consisting of a pressure in the airways above the atmospheric level during spontaneous inspiration and expiration was used in the treatment of pulmonary edema and severe pneumonia even before World War II [1]. Positive endexpiratory airway pressure was also very commonly used in the experimental laboratory in any open chest preparation in order to prevent expiratory lung collapse. An important precondition for the introduction of positive endexpiratory pressure (PEEP) in conjunction with mechanical ventilation was established by the experiments of Cournand et al. in 1948 [2]. They found, however, that, compared to mechanical ventilation with ambient endexpiratory pressure, mechanical ventilation with PEEP was associated with a marked decrease in cardiac output due to reduced venous return of blood to the heart. Possible negative circulatory effects were the major concern in the early phase of clinical application of positive endexpiratory pressure.

PEEP in conjunction with mechanical ventilation as it is used today first became possible with the introduction of the Engström mechanical ventilator in Sweden in the mid-1950s. This machine already had an attachment which allowed endexpiratory pressure to be increased above the atmospheric level. Presumably this option was added by the inventors in order to prevent endexpiratory lung collapse during open chest surgery. The first reported clinically important use of PEEP was undertaken in the cardiac catheterization laboratory of the University Hospital in Zürich, Switzerland, by Bühlmann, Gattiker, and Hossli, who published their work in the *Schweizer Medizinische Wochenschrift* in 1964 [3]. They demonstrated very impressively in patients with mitral valve disease that mechanical ventilation with continuous positive airway pressure led to a marked decrease in the pulmonary capillary wedge pressure despite the increase in alveolar pressure. This reflected the decrease in pulmonary vascular and cardiac transmural pressures which occurs when endexpiratory airway pressure is increased—a phenomenon which was elucidated years later by many studies, an example being the work of Qvist et al. in 1975 [4]. Bühlmann and his colleagues already found in their patients that continuous positive airway pressure ventilation led to improved mixed venous oxygen saturation despite a decrease in cardiac output, indicating a reduction in pulmonary right-to-left shunt and an improvement in arterial oxygenation. However, because they could not measure arterial blood gases at that time, they did not recognize the clinical significance of this finding.

The first clinical evidence that PEEP increases lung volume in correlation with an improvement in arterial oxygenation was established by Frumin et al. in 1959 [5] in anesthetized patients, although they too could only rely on O_2 saturation measurements. They explained the positive effect of PEEP on the alveolar arterial O_2 difference by a possible recruitment of closed alveolar gas spaces. They hypothesized that intermittent alveolar collapse with maintained perfusion might take place during endexpiration, a phenomenon which they called "shunt in time" being reduced by the use of PEEP. (Much later this was supported by the finding of marked swings of Pa_{O_2} during the respiratory cycle in left atrial blood, especially if large tidal volumes and low respiratory frequencies were used (present author's unpublished observation, 1971).

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_52, © Springer-Verlag Berlin Heidelberg 2009

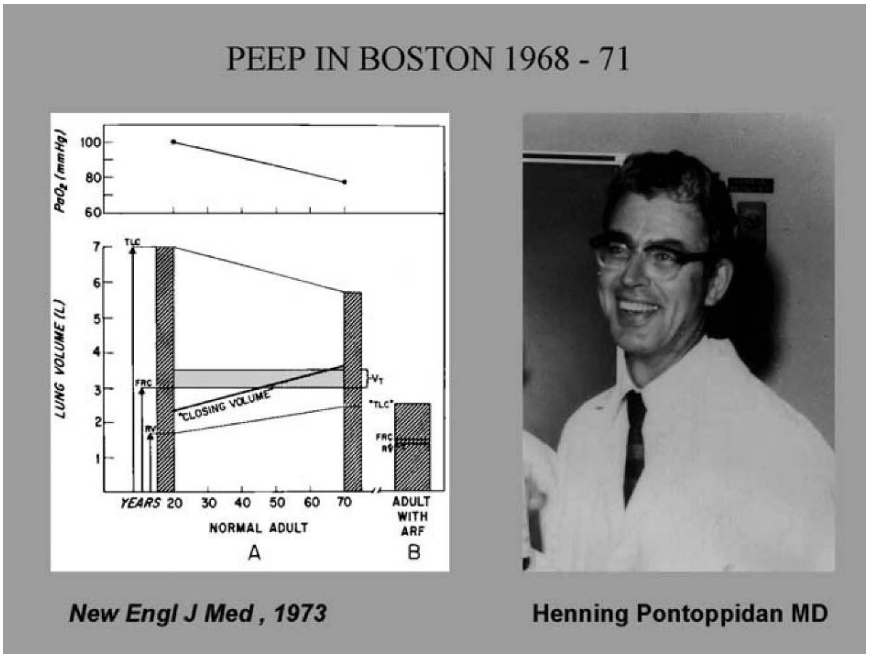


Fig. 1 Henning Pontoppidan M.D., Professor and Director of the Respiratory Intensive Care Unit at the Massachusetts General Hospital, Harvard Medical School, in Boston in 1971. The graph shows his view of the changes in Pa_{O_2} and lung volumes with age (*A*) and with acute lung disease (*B*) based on the measurements of FRC using helium dilution carried out in 1969–71 at the Massachusetts General Hospital [13]. This was later characterized by Gattinoni and Pesenti [17] as the so-called "baby lung" in ARDS patients

Hence, it was not until the mid-1960s, when Thomas Petty in Denver had learned how to determine arterial blood gases, that the potential of mechanical ventilation with PEEP to improve arterial oxygenation was recognized [6]. Petty and his colleagues first used an Engström anesthesia mechanical ventilator equipped with a device to produce PEEP. They discovered that in mechanically ventilated patients with hypoxic acute respiratory failure, which they termed "adult respiratory distress syndrome" (ARDS), the addition of PEEP was capable of relieving severe life-threatening hypoxemia with cyanosis. Their famous paper [7], published in the *Lancet* in 1967 (after being rejected by three major US journals!), became a milestone in the evolution of respiratory intensive care medicine. The news spread very quickly, and in spring of 1969 a group of enthusiastic clinical researchers under the direction of Henning Pontoppidan (Fig. 1) and Myron B. Laver (Fig. 2) started to further investigate mechanical ventilation with PEEP in patients with severe acute lung disease [8]. Meanwhile, McIntyre et al. [9] had studied and published first results on using 5 cmH_2O PEEP in five patients with acute lung disease. Both studies showed marked improvements in arterial Po_2. McIntyre et al. [9], who had studied the addition of 5 cmH_2O PEEP, did not find a decrease in cardiac output, whereas Kumar et al. [8], using 13 cmH_2O, showed a decrease in cardiac output averaging 15% of control.

On the basis of H.K. Beecher's (1933!) finding of collapsed pulmonary gas spaces after upper abdominal surgery [10] and of the already mentioned investigations by Frumin et al. [5], Henning Pontoppidan at the Massachusetts General Hospital in Boston hypothesized that the impaired pulmonary oxygenation in acute lung disease might be due to reduced lung volume or functional residual capacity (FRC), and that the improvement in arterial oxygenation with PEEP, which could indeed be quite dramatic, should correlate with changes in the FRC. Hence the group in Boston went on to investigate how the stepwise increase of PEEP from zero to 5 and 10 and further on to 15 cmH_2O would lead to an increase in the FRC and an associated improvement in Pa_{O_2} [11]. They also hypothesized that if recruitment of closed gas spaces in the lung takes place, this should be associated with an improvement in lung compliance. They found that this was indeed true; however, if the so-called dynamic or semistatic pulmonary compliance ($C=V_T/P_{AW\ insp-exp}$) was determined, it was found that this parameter would only increase with lower levels of PEEP—with higher levels lung and total thoracic compliance would fall, indicating overdistention of pulmonary gas spaces (Fig. 3) [11, 12]. In fact, they found that lung volume (FRC) was markedly decreased in ARDS, and on the basis of their findings on compliance they proposed that PEEP improves arterial oxygenation by recruitment of collapsed alveoli [11, 13]. However, they were surprised that improvements in Pa_{O_2} could go along with a decrease in compliance (Fig. 3). Today we understand that recruitment and overdistention of pulmonary gas spaces may take place simultaneously.

While the early PEEP studies in Boston were coming to an end, Peter Suter and Berrie Fairley in San Francisco had also started working on the interactions of PEEP and compliance. They found that if mechanical ventilation takes place within the pulmonary pressure/volume range associated with maximum compliance, the negative effect of PEEP on cardiac output is at its minimum.

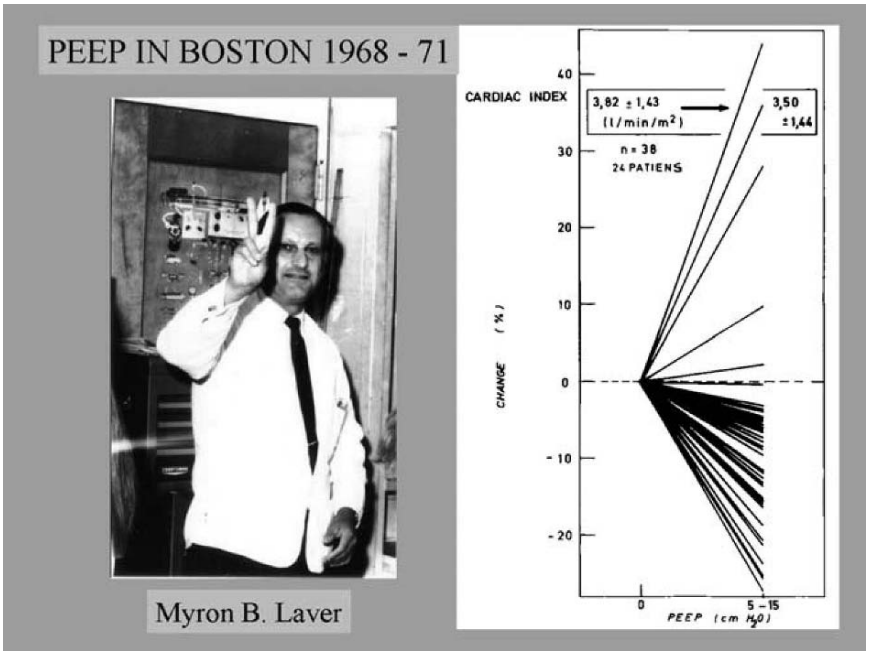


Fig. 2 Myron B. Laver MD as Professor at the Department of Anesthesia at the Massachusetts General Hospital in Boston around 1970. Later he became chairman at the Department of Anaesthesia at the Kantonsspital in Basel. He was very enthusiastic about the hemodynamic effects of PEEP, especially in cardiogenic pulmonary edema. He believed that PEEP should improve cardiac output due to reductions in pre- and afterload if left ventricular function is compromised. The graph shows all the measurements of cardiac output carried out by Kumar et al. [8] and Falke et al. [11]. M. Laver used to tell the story of the trumpet player whose cardiac angina was relieved when he played his trumpet, presumably due to the continuous positive airway/thoracic pressure applied. Today we know that PEEP usually does not increase cardiac output, but due to its decreasing effect on pre- and afterload, reducing myocardial wall stress, it may improve left ventricular function

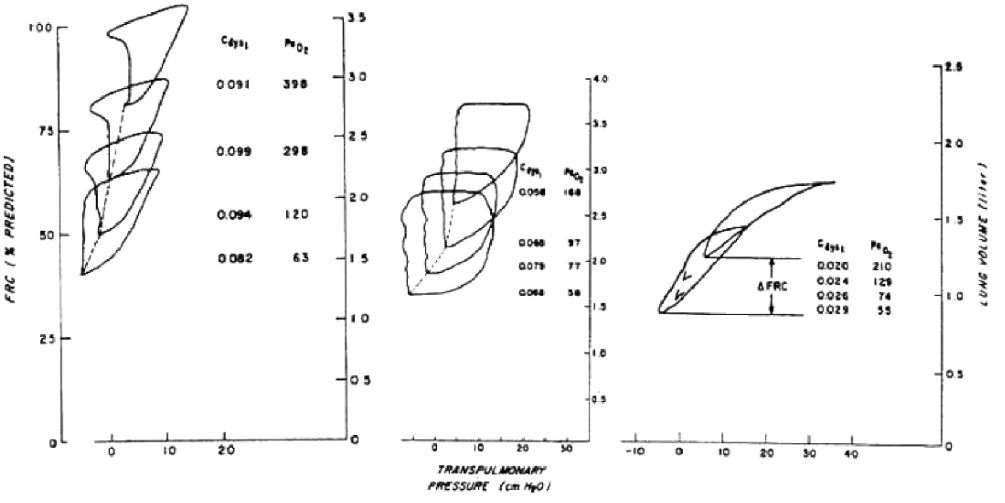


Fig. 3 Pressure–volume loops with four levels of endexpiratory pressure (zero, 5, 10 and 15 cmH_2O) in three patients with ARDS [11]. The *horizontal axis* represents the transpulmonary pressure and the *vertical axis* the lung volume in liters or percent of predicted. The FRC was measured with helium dilution technique, the ΔFRC and the pressure–volume loops were determined using pneumotachography. These examples all show increasing lung compliance in the lower parts and decreasing lung compliance in the upper parts of the pressure–volume relationships, the latter indicating overdistention of the lungs. Nevertheless PaO2 improved with all levels of PEEP

In fact, in their group of patients the level of PEEP which led to the best compliance coincided with the maximum O_2 transport (cardiac output × arterial O_2 content). They called this level of PEEP "best PEEP" [14]. In a later study they demonstrated that the combination of large tidal volumes with high levels of PEEP led to marked falls in compliance, indicating that such combinations of ventilator settings could be detrimental to lung function parameters [15].

The various studies by Falke et al. and Suter et al. clearly showed more than 20 years ago that in ARDS patients lung volume and compliance are markedly reduced, and that mechanical ventilation with high tidal volumes applied on top of PEEP may lead to overdistention of the lungs. Even at that time the conclusion should have been that *low* tidal volumes adjusted to the *low* lung volume in combination with relatively high PEEP are the settings of the ventilator which can be expected to be least detrimental to lung function. In fact, in the early 1970s MyronB. Laver had proposed the use of low tidal volumes together with relatively high PEEP and high respiratory frequencies, a type of mechanical ventilatory support which he called "pressure panting." However, at that time our attempts to lower tidal volumes in mechanically ventilated patients already suffering from severely compromised pulmonary oxygenation were inhibited by the observation that the Pa_{O_2} would fall even further. This anecdotal observation was recently confirmed by the US ARDS Network study on low versus high tidal volume. After 1980 pulmonary CT scanning of critically ill patients was introduced by Rommelsheim [16]. This new diagnostic approach helped to improve our understanding of the pathophysiological scenario of ARDS, which was very well characterized by Gattinoni and Pesenti in 1987 [17] as the so-called "baby lung concept." Subsequently it became obvious that overdistention of the lungs as indicated by a decreased compliance could be extremely harmful, contributing to what it is now called "ventilator-induced or ventilator-associated lung injury." Another voice in the wilderness came from Theodor Kolobow and colleagues in 1980, who developed the most consistent strategy of lung-protective respiratory support, advocating "extracorporeal gas exchange with low frequency (pressure limited) mechanical ventilation" [18]. Most recently, it was firmly established by the already mentioned large multicenter trial that low tidal volume in conjunction with PEEP is the only suitable approach by which to prevent iatrogenic lung injury [19]. Although today we believe we have evidence that mechanical ventilation is best tolerated if it takes place in between the lower and the upper inflection points of the static pressure volume relationship of the diseased lungs, the question of how to determine the optimal level of PEEP is still disputed.

References

1. Barach AL, Martin J, Eckman M (1938) Positive pressure respiration and its application to the treatment of pulmonary edema. Ann Intern Med 1:754–795
2. Cournand A, Motley HL, Werko L, Richards DW (1948) Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 152:162–174
3. Bühlmann A, Gattiker H, Hossli G (1964) Die Behandlung des Lungenödems mit Überdruckbeatmung. Schweiz Med Wochenschr 44:1547–1551
4. Qvist J, Pontoppidan H, Wilson RS, Lowenstein E, Laver MB (1975) Hemodynamic responses to mechamical ventilation with PEEP: the effect of hypervolemia. Anesthesiology 1:45–55
5. Frumin JM, Bergman NA, Holaday DA, Rackow H, Salanitre E (1959) Alveolar-arterial O_2 differences during artficial respiration in man. J Appl Physiol 14:694–700
6. Petty TL (2001) In the cards was ARDS. Am J Respir Crit Care Med 163:602–603
7. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults, Lancet 2:319–323
8. Kumar A, Falke KJ, Geffin B, Aldredge CF, Laver MB, Lowenstein E, Pontoppidan H (1970) Continuous positive-pressure ventilation in acute respiratory failure. N Engl J Med 283:1430–1436
9. McIntyre RW, Laws AK, Rachmandran PR (1969) Positive expiratory pressure plateau: improved gas exchange during mechanical ventilation. Can Anaesth Soc J 16:477–486
10. Beecher HK (1933) Effect of laparotomy on lung volume. Demonstration of a new type of pulmonary collapse. J Clin Invest 12: 651–658
11. Falke KJ, Pontoppidan H, Kumar A, Leith DE, Geffin B, Laver MB (1972) Ventilation with end-expiratory pressure in acute lung disease. J Clin Invest 51:2315–2323
12. Falke KJ (1980) Do changes in lung compliance allow the determination of "optimal PEEP"? Anaesthesist 4:165–168
13. Pontoppidan H, Geffin B, Lowenstein E (1972) Acute respiratory failure in the adult. N Engl J Med 287:690–8, 743–52, 799–806
14. Suter PM, Fairley HB, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284–289
15. Suter PM, Fairley HB, Isenberg MD (1978) Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. Chest 73:158–162
16. Rommelsheim K, Lackner K, Westhofen P, Distelmaier W, Hirt S (1983) Respiratory distress syndrome of the adult in the computer tomograph. Anasth Intensivther Notfallmed 18:59–64
17. Gattinoni L, Pesenti A (1987) ARDS the nonhomogeneous lung: facts and hypothesis". Int Crit Care Digest 6:1–4
18. Kolobow T, Pesenti A, Solca ME, Gattinoni L (1980) A new approach to the prevention and treatment of acute pulmonary insufficiency. Int J Artif Organs 3:86–93
19. The ARDS Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308

Björn Jonson

Elastic pressure-volume curves in acute lung injury and acute respiratory distress syndrome

This work was supported by the Swedish Medical Research Council (02872) and by the Swedish Heart Lung Foundation

Abstract *Background:* The principal features of elastic pressure-volume curves of lungs or the respiratory system (P_{el}/V curves) recorded during reexpansion of collapsed lungs and subsequent deflation have been known since the 1950s. In acute respiratory failure and acute respiratory distress syndrome such curves have recently attracted increasing interest because new knowledge can be acquired from them, and because such curves may be useful as guidelines in setting the ventilator so as to avoid ventilator-induced lung injury. *Discussion:* This article reviews recording methods, underlying physiology and utility of P_{el}/V curves in research and clinical work.

Keywords Monitoring · Respiratory physiology · Mechanics

Introduction

The relationship between elastic recoil pressure and volume (P_{el}/V) when a collapsed isolated lung in health is reinflated was studied as early as the 1950s by Mead et al. [1] and Radford [2]. They observed that lung units "pop open" during the irregular reexpansion of the lung, and that the elastic recoil pressure during inflation with air is much higher than during emptying (Fig. 1). Emptying occurred more uniformly over the lung. They explained that one reason for the higher elastic pressure during insufflation is that a particular volume was shared by fewer open lung units than emptying. When the lung was inflated with saline, no hysteresis was observed. Obviously surface forces have a large influence on the P_{el}/V curves, a fact that was later misinterpreted, as is discussed below. The seminal study by Mead et al. [1] demonstrates that some basic concepts relating to collapse/recruitment of lung units and the P_{el}/V loop were known and understood as early as the 1950s! Development with respect to measurement technique and mathematical analysis, understanding of physiology, and clinical utility of the P_{el}/V curve has progressed since that time, as is described in this review.

Technical development with respect to intensive care medicine

The development of the specialty of intensive care medicine that took off in the early 1970s was closely linked to new facilities for recording physiological events. Dynamic pressure volume loops were recorded in patients with acute severe respiratory failure in a study by Falke et al. in 1972 [3]. The supersyringe introduced by Harf et al. [4] in 1975 was an innovation of great significance and

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_53, © Springer-Verlag Berlin Heidelberg 2009

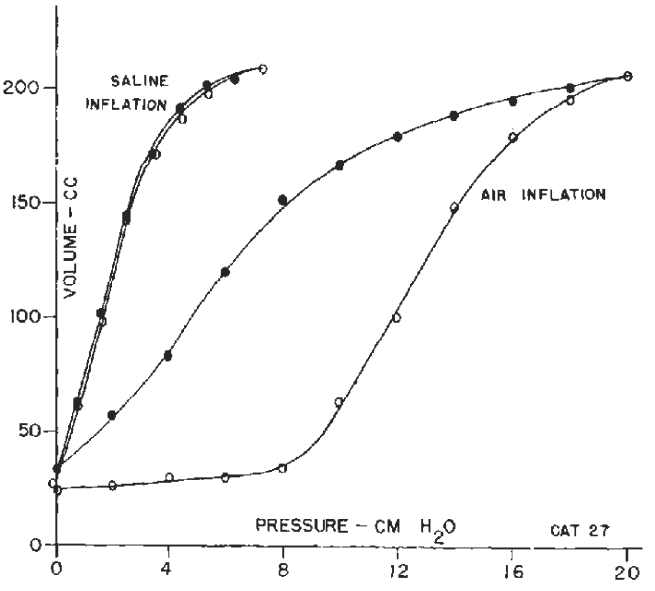


Fig. 1 Pressure-volume loops from an isolated cat lung that was reinflated from a degassed state, with air and with saline [2]

enabled more detailed studies of static P_{el}/V loops. The ServoVentilator 900 first marketed in 1971 comprised transducers for airway pressure and flow allowing studies of mechanics without disconnection of the patient from the ventilator [5]. Much later this facility was used for recording static P_{el}/V curves based upon the flow interruption method [6, 7, 8, 9]. This method uses interruption of study breaths at varying volume. The study breaths are separated by some ordinary breaths and are followed by a pause during which static P_{el} is measured. A potential problem with this method is the assumption that end-expiratory volume remains constant following each exhalation. Recruitment during the larger breaths causes an error if the recruited volume is not lost during the interposed normal breaths.

The constant inspiratory flow or the pulse method for recording inspiratory P_{el}/V curves was introduced by Suratt and Owens [10] in 1980. Compliance of the respiratory system was accurately calculated by dividing the constant flow rate (L/s) by the rate of pressure increase (cmH_2O/s). A low inspiratory flow rate minimized the importance of resistance. By applying the complementary principle to measure resistance and subtracting the resistive pressure to obtain P_{el} Servillo et al. [11] showed that dynamic P_{el}/V curves, which are equivalent to static P_{el}/V curves, could be determined in a few seconds in critically sick patients. Finally, implementing sinusoidal flow modulation a computer-controlled ServoVentilator 900 (ServoVentilator 900C, Siemens-Elema, Solna) allowed fully automated recording of inspiratory and now also expiratory P_{el}/V curves in less than 0.5 min [12, 13, 14].

Gas exchange may cause artifacts in P_{el}/V recordings [15]. During insufflation the CO_2 and O_2 exchanged roughly balance each other. During recording of expiratory P_{el}/V curves only O_2 uptake continues. This leads to a volume loss not detected by integration of flow rate at airway opening. To reduce the artifact caused by gas exchange the time for expiration should be minimized. This is carried out both with the flow interruption technique for static curves and with the low flow modulation technique for dynamic curves. Gattinoni et al. [16] have underlined how artifacts may affect P_{el}/V recordings, and how they may be corrected. Still the exchange of O_2, CO_2, heat, and humidity can be avoided completely only using body plethysmography, which is applicable only in experimental work [8].

During recording of dynamic expiratory P_{el}/V curves flow limitation often occurs towards the end of expiration down to the elastic equilibrium volume. Then resistance depends upon driving pressure and increases towards infinity at low volumes. When resistance has no defined value, the subtraction of resistive pressure is not feasible. If flow rate is reduced to very low values, flow limitation occurs only very late during expiration. However, problems related to gas exchange increase if expiration is exceedingly prolonged.

A mathematical description of the P_{el}/V curve facilitates objective analysis of results. A model by Venegas et al. [17] describes with four parameters a sigmoid that is symmetrical with respect to one upper and one lower curvilinear segment without a liner segment between them. However, an inspiratory P_{el}/V curve is often characterized by a linear segment between the upper and lower nonlinear segments (Fig. 2). Furthermore, the upper and lower segments represent different physiological phenomena. There is hardly any reason to assume that they are symmetrical, and in reality they are not. The algorithm of Venegas et al. can be improved by adding one more coefficient to allow nonsymmetrical upper and lower segments [18]. A six-parameter model was developed to allow a comprehensive description of a nonsymmetrical curve with a middle, strictly linear segment [19, 20]. Four parameters describe the coordinates of the linear segment and the two others the minimum and maximum volumes at which compliance of the extrapolated curve would fall to zero. The parameters of the noncontinuous, nonlinear equation are calculated with a numerical method available, for example, in Excel (Microsoft, Redmond, Wash., USA). A precise mathematical description of the curve is normally obtained (Fig. 2)

In contexts in which the detailed shape of the P_{el}/V curve is an issue the six-parameter model has obvious advantages. In other situations the four-parameter model may well serve its purpose. In spite of an excellent fit one needs to be warned against uncritical physiological interpretation of the parameters of any equation. Although

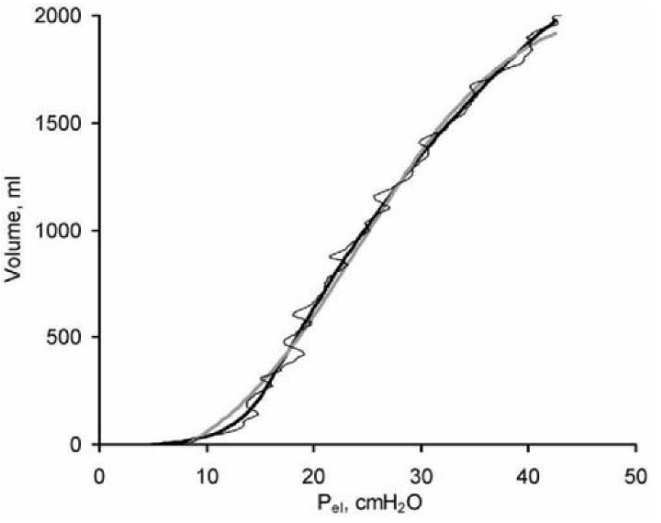


Fig. 2 *Thin line* Elastic P_{el}/V curve recorded with the low flow inflation method; *smooth black line* curve according to Svantesson et al. [19, 20]; *gray line* curve according to Venegas et al. [17] The symmetrical nature of the latter implies that the curvature is exaggerated in the upper segment and underestimated in the lower. Obviously both fits have very high R^2 values

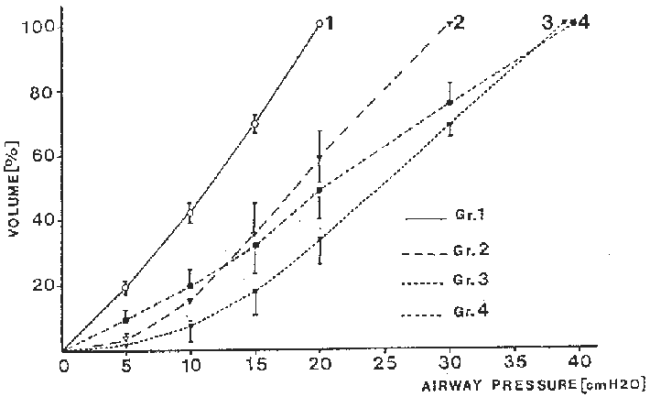


Fig. 3 Inspiratory P_{el}/V curves from patients with nearly normal chest radiography (*1*), early progressive ALI/ARDS (*2*, *3*), and late-stage ARDS (*4*). (From Matamis et al. [21])

the parameters were originally based upon physiological concepts, the values, for example, for lower (LIP) and upper (UIP) inflection points have complex physiological significance, as is discussed below.

Physiology

In the pioneering study by Falke et al. [3] dynamic P_{el}/V loops from different levels of positive end-expiratory pressure (PEEP) showed that recruitment was maintained by PEEP. Furthermore, increasing compliance during insufflation, later referred to as the LIP, was considered to represent recruitment of terminal airspaces. When PEEP was increased from 10 to 15 cmH_2O, compliance fell as a sign of "overdistension of open alveoli."

Using the supersyringe Matamis et al. [21] in 1984 presented static P_{el}/V loops from patients at varying stages of acute respiratory failure and acute lung injury/acute respiratory distress syndrome (ALI/ARDS; Fig. 3). In acute stages high hysteresis indicated alveolar flooding. A pressure higher than LIP and above the zone of inflection was suggested as a guideline to set PEEP on the basis of observations of improved oxygenation when this was implemented. In late stages compliance and hysteresis were low and LIP was no longer evident; fibrotic changes had occurred. These observations and the interpretations are still of great significance.

As early as 1975 Suter et al. [22] suggested that by choosing an optimum PEEP the tidal volume could be confined within the part of the P_{el}/V curve with highest

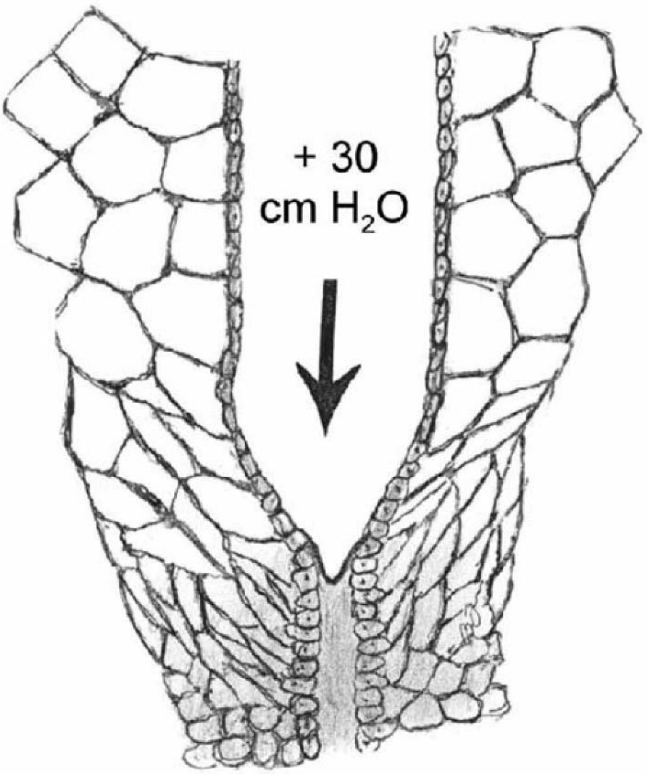


Fig. 4 Illustration of shear forces in the zone of lung opening, caused by stretching of densely distributed alveolar membranes, obliquely attached to bronchiolar basal membranes [26]. "At a transpulmonary pressure of 30 cmH_2O the pressure tending to expand an atelectatic region surrounded by a fully expanded lung would be approximately 140 cmH_2O" [25]

compliance. This was later underlined by Roupie et al. [23]. The rationale would be to avoid derecruitment of lung below the LIP and overdistension above the UIP. In the first controlled study showing that lung-protective ventilation was associated with increased survival in

ARDS patients PEEP was set above the pressure at LIP to avoid derecruitment while plateau pressure was not higher than PEEP plus 20 cmH_2O in order to avoid hyperinflation and barotrauma [24].

A basic concept in today's lung-protective ventilation goes back to 1970 when Mead et al. [25] and later Jonson [26] and explained that shear leads to extremely high local forces when a collapsed lung zone is recruited (Fig. 4).

In ALI/ARDS it has repeatedly been shown that recruitment is not limited to a narrow zone of pressure. Rather, it is a phenomenon that continues to high transpulmonary pressures [27, 28, 29, 30, 31]. The notation by Frazer et al. [29] that sequential opening of the lung contributes to an increased value of the slope of the inspiratory P_{el}/V curve was later underpinned in theoretical studies [32, 33, 34]. Obviously volume change in a lung that undergoes recruitment reflects both distension of open units and recruitment of previously closed lung units when they "pop open": $\Delta V=(\Delta V_{distension}+\Delta V_{recruitment})$. Accordingly, recruitment contributes to compliance, C: $C=(\Delta V_{distension}+\Delta V_{recruitment})/\Delta P_{el}$. It is noteworthy that a concept established by Mead et al. [1] in 1957 and so clearly demonstrated in the prominent articles referred to needed to be reiterated. Elegant experimental and clinical computed tomography studies have recently confirmed finally that recruitment is a process that continues throughout the insufflation to high airway pressures [28, 30]. The effect of continuing recruitment makes a single P_{el}/V curve difficult to interpret. The LIP reflects rather the onset of recruitment. The UIP may indicate the gradual cessation of recruitment rather than overdistension of the lung. It is worth pointing out that in patients with early severe acute lung injury the particularly high compliance corresponding to the steep part of the pressure-volume curve probably represents ongoing recruitment rather than an open lung. Titration of best PEEP should not be determined from compliance read from inspiratory P_{el}/V curves.

In ARDS the P_{el}/V curve is dependent upon the volume history immediately preceding the recording [35]. Also in health this may be the case particularly in swine [36, 37]. Also in healthy anesthetized and paralyzed humans derecruitment of lung units occurring at zero airway pressure is reversed by a deep insufflation [38, 39]. P_{el}/V curves performed before and after a recruitment maneuver are suitable for studying such phenomena. On the other hand, a standardized volume history, for example, a recruitment maneuver, is recommended to allow comparisons of P_{el}/V curves observed in different groups or situations.

Enhanced information has since long been obtained by recording multiple P_{el}/V curves at different levels of PEEP [3, 40]. The 1973 studies by Glaister et al. [40] of isolated dog lungs illustrate important principles which are actually applied in clinical studies (Fig. 5) [41]. In a

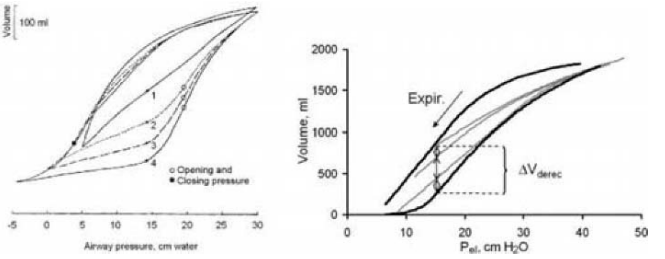


Fig. 5 It took 30 years to go from dog lungs [40] to ARDS patients [41]. A family of inspiratory P_{el}/V curves shows derecruitment at low expiratory airway pressure (ΔV_{derec}). The inspiratory curves merge at high pressures because of recruitment. Expiratory curves follow a common trajectory

study of ARDS by Ranieri et al. [42] showed in 1994 that recruitment at different PEEP levels can be studied using multiple inspiratory P_{el}/V curves.

Jonson et al. [13] studied a group of patients with ALI using the computer-controlled ventilator in a mode that allows alignment of successive pressure-volume curves to the elastic equilibrium volume. Full recovery of volume loss caused by derecruitment during a single expiration at zero PEEP occurred during the following insufflation only after pressure was higher than 35 cmH_2O. It was confirmed that the LIP indicated nothing more than onset of recruitment, and that compliance was increased during the process of recruitment.

The progressive derecruitment for each step of lower PEEP below 15 cmH_2O was quantified by recording a family of inspiratory P_{el}/V curves in ALI/ARDS [20, 43]. In the modestly large groups of patients derecruitment was about equally large for each step of lower PEEP. Later a larger series indicated that this is not always the case (unpublished). Figure 5 shows an example in which derecruitment occurred mainly between 5 and 10 cmH_2O. As is commonly observed, the merging inspiratory curves show that recruitment continued to about 40 cmH_2O.

In dogs with oleic acid induced ARDS Pelosi et al. [30] gave a solid demonstration of the relationship between the inspiratory P_{el}/V curve and recruitment as observed with computed tomography. Recruitment had just started at the LIP; it was prominent over the linear part of the P_{el}/V curve and continued to pressures above 40 cmH_2O. In an accompanying study of ARDS patients the same group showed a similarly wide range of opening pressure [28]. Closing pressures were widely distributed, but closing occurred in general at much lower pressures than opening. These data confirm previous conclusions drawn on the basis of P_{el}/V curve recordings. Accordingly, the information obtained from an inspiratory curve recorded from zero pressure is limited, while a family of P_{el}/V curves indicates the distribution of both opening and closing pressures of the lungs. This information is at-

tainable at the bedside without any other equipment than a computer-controlled ventilator.

Recording of expiratory P_{el}/V curves is an alternative way to enhance information. The physiological significance of an expiratory P_{el}/V curve recorded from a pressure high enough to recruit the lung must then be considered. In its upper segment, before derecruitment has begun, it reflects elastic properties of the respiratory system. At lower pressures, when derecruitment has started, it is also influenced by expulsion of gas from collapsing lung units. Accordingly, the expiratory P_{el}/V curve is in principle affected by the same physiological factors as the inspiratory curve. Furthermore, in its lower part dynamic airway compression and flow limitation are sometimes additional factors making analysis of dynamic expiratory P_{el}/V curves difficult. In any case, as collapse of lung units and flow limitation affects mainly the lower part of the expiratory curve, this curve gives a better indication of elastic properties than the inspiratory curve.

Various characteristics reflecting shape of the expiratory P_{el}/V curve have been suggested as indicators of closure of lung units and even as guidelines for setting PEEP [29, 40, 44]. However, this curve reflects a physiology as complex as the inspiratory curve. Overinterpretation, as that of the inspiratory LIP, should not be repeated.

Another aspect is that the expiratory P_{el}/V curve recorded from a pressure high enough to recruit the lung shows the highest volume that can be maintained at each pressure level. It may accordingly be regarded as a reference for other P_{el}/V curves. Benito et al. [45] showed as early as 1985 how expiratory compliance increases when measured after insufflations to higher and higher volumes. The hypothesis was confirmed that opening of previously closed units continues to occur, and that the increase in compliance reflects sequential opening of more units. Rimensberger et al. [46, 47] showed the usefulness of the expiratory curve recorded from a high pressure as a reference for P_{el}/V loops recorded under tidal volume ventilation (Fig. 6). While the inspiratory P_{el}/V curve is affected by continuing recruitment over a wide range of pressure, the expiratory P_{el}/V curve is affected by alveolar collapse only in its lower part. This was very recently emphasized in an elegant study by Downie et al. [48].

As shown in Fig. 5, the inspiratory curve recorded from the highest PEEP level falls closest to the expiratory curve. However, even the P_{el}/V curve recorded from a PEEP of 15 cmH_2O falls below the expiratory curve recorded from 50 cmH_2O. This may reflect collapse of some lung units above this pressure or by other factors (see below).

In ARDS the hysteresis of P_{el}/Vloops is reduced by PEEP because it attenuates collapse of lung units [49]. Static P_{el}/V loops show minimal hysteresis under conditions when lung closure and reopening does not occur, either in health [6, 8, 12] or in disease [50]. These observations motivate reassessment of the common model of lung surfactant film hysteresis as an important source of P_{el}/V hysteresis of the lung. An even greater misconception related to surfactant and closure of lung units involves Laplace's law of elastic spheres. As Prange [51] notes, "The Y-tube model of alveolar inflation and the bunch-of-grapes model of alveolar anatomy deserves a place, not in our minds and textbooks, but in the museum of wrong ideas."

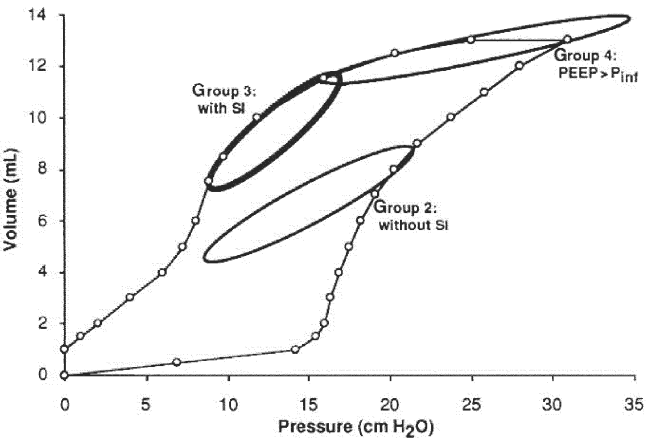


Fig. 6 Schematic drawing illustrating how in an ARDS animal model a large P_{el}/V loop was recorded from zero to 35 cmH_2O. *Group 3* Ventilated at moderate PEEP after a recruitment maneuver, showing less damage than other groups. The P_{el}/V loop over the tidal volume was in this group situated at the expiratory limb of the large loop. (From [46])

Hysteresis of dynamic P_{el}/V curves is caused in a complex way by resistance, viscoelastic behavior, and differences between closing and opening pressure of lung units. Even at low flow rates during recording of dynamic P_{el}/V loops and after subtraction of resistive pressure dynamic and static loops differ slightly because of viscoelastic phenomena in healthy pigs [12]. More data from patient studies are needed for proper interpretation of hysteresis of dynamic loops.

Utility of P_{el}/V curves in research and in the clinic

For about 50 years the recording of P_{el}/V curves has contributed to the understanding of the physiology of healthy and diseased lungs. At present we have come to the knowledge that a family of P_{el}/V curves estimate how much volume is lost by derecruitment for each step of lower PEEP, and how recruitment successively occurs with increasing pressures during insufflation (Fig. 5). Accordingly, P_{el}/V curves have given us substantial knowledge about the pathophysiology in ALI/ARDS with regards to the phenomenon of lung collapse and reopening. As this phenomenon is probably linked to ventilator-

induced lung injury, the knowledge obtained through P_{el}/V curves is one of the keys to improved treatment of patients with ALI/ARDS. Studies based upon recording of P_{el}/V curves have demonstrated how the maintenance of recruitment depends upon PEEP, tidal volume, and recruitment maneuvers [42, 52, 53]. Thus the lungs may be well recruited even at low tidal volume ventilation if PEEP is adequately high. In a proper context therefore PEEP is a major component of the open lung concept. How should this knowledge be applied to a particular patient?

In patients with ALI/ARDS a distinct LIP of an inspiratory P_{el}/V curve recorded from zero pressure indicates that derecruitment and recruitment are a threat with respect to ventilator-associated lung injury. PEEP should then be used and set at some value above the pressure at LIP. This strategy has long been applied [21, 23, 42] but has only recently been associated with improved outcome in a controlled study by Amato et al. [24]. As in the latter study, the setting of PEEP in relation to the LIP was not the only component of the tested strategy; a role of the P_{el}/V curve may be argued. Experimental evidence suggest that the role of PEEP in a lung protective strategy is important [54]. The P_{el}/V curve is used in only rather few centers, mainly in those with scientific interest in the topic. To tailor ventilation to the changing pathophysiology of the individual patient with respect to tidal volume, respiratory rate, and PEEP one would need the detailed information of multiple P_{el}/V curves or loops aligned to a common volume axis. In ALI/ARDS this should be repeatedly obtained to follow the course of the disease. Studies in both animal models and in patients show that this is feasible using computer-controlled ventilators [13, 14, 47, 55]. The recently released Hamilton Galileo Gold Ventilator represents a step forward (Hamilton Medical, Rhäzüns, Switzerland). When systems fulfilling the demands on versatility become generally available, it will be possible to develop new strategies and test them in large series of patients in multicenter studies. Only then it will be possible to define the optimal use of P_{el}/V curves for improving ventilation so as to avoid ventilator-induced lung damage.

References

1. Mead J, Whittenberger JL, Radford EP (1957) Surface tension as a factor in pulmonary volume-pressure hysteresis. J Appl Physiol 10:191–196
2. Radford EP (1957) Recent studies of the mechanical properties of mammalian lungs. In: Remington JW (ed) Tissue elasticity American Physiological Society Washington, pp 177–190
3. Falke KJ, Pontoppidan H, Kumar A, Leith DE, Geffin B, Laver MB (1972) Ventilation with end-expiratory pressure in acute lung disease. J Clin Invest 51:2315–2323
4. Harf A, Lemaire F, Lorino H, Atlan G (1975) Étude de la Méchanique Ventilatoire: application à la Ventilation Artificielle. Bull Physiopathol Respir (Nancy) 11:709–728
5. Ingelstedt S, Jonson B, Nordström L, Olsson SG (1972) A servo-controlled ventilator measuring expired minute volume, airway flow and pressure. Acta Anaesthesiol Scand Suppl 47:7–27
6. Jonson B, Beydon L, Brauer K, Månsson C, Valind S, Grytzell H (1993) Mechanics of respiratory system in healthy anesthetized humans with emphasis on viscoelastic properties. J Appl Physiol 75:132–140
7. Similowski T, Levy P, Corbeil C, Albala M, Pariente R, Derenne JP, Bates JH, Jonson B, Milic-Emili J (1989) Viscoelastic behavior of lung and chest wall in dogs determined by flow interruption. J Appl Physiol 67:2219–2229
8. Svantesson C, John J, Taskar V, Evander E, Jonson B (1996) Respiratory mechanics in rabbits ventilated with different tidal volumes. Respir Physiol 106:307–316
9. Bates JH, Brown KA, Kochi T (1989) Respiratory mechanics in the normal dog determined by expiratory flow interruption. J Appl Physiol 67:2276–2285
10. Suratt PM, Owens D (1981) A pulse method of measuring respiratory system compliance in ventilated patients. Chest 80:34–38
11. Servillo G, Svantesson C, Beydon L, Roupie E, Brochard L, Lemaire F, Jonson B (1997) Pressure-volume curves in acute respiratory failure: automated low flow inflation versus occlusion. Am J Respir Crit Care Med 155:1629–1636
12. Bitzén U, Drefeldt B, Niklason L, Jonson B (2004) Dynamic elastic pressure-volume loops in healthy pigs recorded with inspiratory and expiratory sinusoidal flow modulation. Relationship to static pressure-volume loops. Intensive Care Med 30:481–488
13. Jonson B, Richard JC, Straus C, Mancebo J, Lemaire F, Brochard L (1999) Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. Am J Respir Crit Care Med 159:1172–1178
14. Svantesson C, Drefeldt B, Sigurdsson S, Larsson A, Brochard L, Jonson B (1999) A single computer-controlled mechanical insufflation allows determination of the pressure-volume relationship of the respiratory system. J Clin Monit Comput 15:9–16
15. Dall'Ava Santucci J, Dhainaut JF (1990) Effect of gas exchange on hysteresis of respiratory pressure-volume curves. J Appl Physiol 69:2317–2318
16. Gattinoni L, Mascheroni D, Basilico E, Foti G, Pesenti A, Avalli L (1987) Volume/pressure curve of total respiratory system in paralysed patients: artefacts and correction factors. Intensive Care Med 13:19–25
17. Venegas JG, Harris RS, Simon BA (1998) A comprehensive equation for the pulmonary pressure-volume curve. J Appl Physiol 84:389–395
18. Heller H, Brandt S, Scuster K-D (2002) Development of an algorithm for improving the description of the pulmonary pressure-volume curve. J Appl Physiol 92:1770–1771
19. Svantesson C DB, Sigurdsson S, Larsson A, Brochard L, Jonson B (1999) A single computer-controlled mechanical insufflation allows determination of the pressure-volume relationship of the respiratory system. J Clin Monit Comput:9–16

20. Maggiore SM, Jonson B, Richard JC, Jaber S, Lemaire F, Brochard L (2001) Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury. Comparison with the lower inflection point, oxygenation, and compliance. Am J Respir Crit Care Med 164:795–801
21. Matamis D, Lemaire F, Harf A, Brun-Buisson C, Ansquer JC, Atlan G (1984) Total respiratory pressure-volume curves in the adult respiratory distress syndrome. Chest 86:58–66
22. Suter PM, Fairley B, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284–289
23. Roupie E, Dambrosio M, Servillo G, Mentec H, el Atrous S, Beydon L, Brun-Buisson C, Lemaire F, Brochard L (1995) Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Respir Crit Care Med 152:121–128
24. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
25. Mead J, Takishima T, Leith D (1970) Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 28:596–608
26. Jonson B (1982) In: Prakash O (ed) Applied physiology in clinical respiratory care. Nijhoff, The Hague, pp 123–139
27. Cheng W, DeLong DS, Franz GN, Petsonk EL, Frazer DG (1995) Contribution of opening and closing of lung units to lung hysteresis. Respir Physiol 102:205–215
28. Crotti S, Mascheroni D, Caironi P, Pelosi P, Ronzoni G, Mondino M, Marini JJ, Gattinoni L (2001) Recruitment and derecruitment during acute respiratory failure: a clinical study. Am J Respir Crit Care Med 164:131–140
29. Frazer DG, Weber KC, Franz GN (1985) Evidence of sequential opening and closing of lung units during inflation-deflation of excised rat lungs. Respir Physiol 61:277–288
30. Pelosi P, Goldner M, McKibben A, Adams A, Eccher G, Caironi P, Losappio S, Gattinoni L, Marini JJ (2001) Recruitment and derecruitment during acute respiratory failure: an experimental study. Am J Respir Crit Care Med 164:122–130
31. Smaldone GC, Mitzner W, Itoh H (1983) Role of alveolar recruitment in lung inflation: influence on pressure-volume hysteresis. J Appl Physiol 55:1321–1332
32. Jonson B, Svantesson C (1999) Elastic pressure-volume curves: what information do they convey? Thorax 54:82–87
33. Hickling KG (2001) Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. Am J Respir Crit Care Med 163:69–78
34. Hickling KG (1998) The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. Am J Respir Crit Care Med 158:194–202
35. Takeuchi M, Sedeek KA, Schettino GP, Suchodolski K, Kacmarek RM (2001) Peak pressure during volume history and pressure-volume curve measurement affects analysis. Am J Respir Crit Care Med 164:1225–1230
36. De Robertis E, Liu JM, Blomquist S, Dahm PL, Thörne J, Jonson B (2001) Elastic properties of the lung and the chest wall in young and adult healthy pigs. Eur Respir J 17:703–711
37. Liu JM, De Robertis E, Blomquist S, Dahm PL, Svantesson C, Jonson B (1999) Elastic pressure-volume curves of the respiratory system reveal a high tendency to lung collapse in young pigs. Intensive Care Med 25:1140–1146
38. Svantesson C, Sigurdsson S, Larsson A, Jonson B (1998) Effects of recruitment of collapsed lung units on the elastic pressure-volume relationship in anaesthetised healthy adults. Acta Anaesthesiol Scand 42:1149–1156
39. Sigurdsson S, Svantesson C, Larsson A, Jonson B (2000) Elastic pressure-volume curves indicate derecruitment after a single deep expiration in anaesthetised and muscle-relaxed healthy man. Acta Anaesthesiol Scand 44:980–984
40. Glaister DH, Schroter RC, Sudlow MF, Milic-Emili J (1973) Bulk elastic properties of excised lungs and the effect of a transpulmonary pressure gradient. Respir Physiol 17:347–364
41. Aboab J, Kouatchet A, Drefeldt B, Niklason L, Brochard L, Jonson B (2003) Multiple inspiratory-expiratory Pel/V loops in patients with ARDS (abstract). Intensive Care Med 29:S81
42. Ranieri VM, Giuliani R, Fiore T, Dambrosio M, Milic-Emili J (1994) Volume-pressure curve of the respiratory system predicts effects of PEEP in ARDS: "occlusion" versus "constant flow" technique. Am J Respir Crit Care Med 149:19–27
43. De Robertis E, Servillo G, Tufano R, Jonson B (2001) Aspiration of dead space allows isocapnic low tidal volume ventilation in acute lung injury. Relationships to gas exchange and mechanics. Intensive Care Med 27:1496–1503
44. Ingimarsson J, Björklund LJ, Larsson A, Werner O (2001) The pressure at the lower inflexion point has no relation to airway collapse in surfactant-treated premature lambs. Acta Anaesthesiol Scand 45:690–695
45. Benito S, Lemaire F, Mankikian B, Harf A (1985) Total respiratory compliance as a function of lung volume in patients with mechanical ventilation. Intensive Care Med 11:76–79
46. Rimensberger PC, Pristine G, Mullen BM, Cox PN, Slutsky AS (1999) Lung recruitment during small tidal volume ventilation allows minimal positive end-expiratory pressure without augmenting lung injury. Crit Care Med 27:1940–1945
47. Rimensberger PC, Cox PN, Frndova H, Bryan AC (1999) The open lung during small tidal volume ventilation: concepts of recruitment and "optimal" positive end-expiratory pressure. Crit Care Med 27:1946–1952
48. Downie JM, Nam AJ, Brett AS (2004) Pressure-volume curve does not predict steady-state lung volume in canine lavage lung model. Am J Respir Crit Care Med 169:957–962
49. Dall'ava-Santucci J, Armaganidis A, Brunet F, Dhainaut JF, Nouira S, Morisseau D, Lockhart A (1990) Mechanical effects of PEEP in patients with adult respiratory distress syndrome. J Appl Physiol 68:843–848
50. 50 Beydon L, Svantesson C, Brauer K, Lemaire F, Jonson B (1996) Respiratory mechanics in patients ventilated for critical lung disease. Eur Respir J 9:262–273
51. Prange HD (2003) Laplace's law and the alveolus: a misconception of anatomy and a misapplication of physics. Adv Physiol Educ 27:34–40
52. Richard JC, Brochard L, Vandelet P, Breton L, Maggiore SM, Jonson B, Clabault K, Leroy J, Bonmarchand G (2003) Respective effects of end-expiratory and end-inspiratory pressures on alveolar recruitment in acute lung injury. Crit Care Med 31:89–92

53. Richard JC, Maggiore SM, Jonson B, Mancebo J, Lemaire F, Brochard L (2001) Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver. Am J Respir Crit Care Med 163:1609–1613

54. Takeuchi M, Goddon S, Dolhnikoff M, Shimaoka M, Hess D, Amato MB, Kacmarek RM (2002) Set positive end-expiratory pressure during protective ventilation affects lung injury. Anesthesiology 97:682–692

55. Rimensberger PC, Pache JC, McKerlie C, Frndova H, Cox PN (2000) Lung recruitment and lung volume maintenance: a strategy for improving oxygenation and preventing lung injury during both conventional mechanical ventilation and high-frequency oscillation. Intensive Care Med 26:745–455

Luciano Gattinoni
Antonio Pesenti

The concept of "baby lung"

Abstract *Background:* The "baby lung" concept originated as an offspring of computed tomography examinations which showed in most patients with acute lung injury/acute respiratory distress syndrome that the normally aerated tissue has the dimensions of the lung of a 5- to 6-year-old child (300–500 g aerated tissue). *Discussion:* The respiratory system compliance is linearly related to the "baby lung" dimensions, suggesting that the acute respiratory distress syndrome lung is not "stiff" but instead small, with nearly normal intrinsic elasticity. Initially we taught that the "baby lung" is a distinct anatomical structure, in the nondependent lung regions. However, the density redistribution in prone position shows that the "baby lung" is a functional and not an anatomical concept. This provides a rational for "gentle lung treatment" and a background to explain concepts such as baro- and volutrauma. *Conclusions:* From a physiological perspective the "baby lung" helps to understand ventilator-induced lung injury. In this context, what appears dangerous is not the V_T/kg ratio but instead the V_T/"baby lung" ratio. The practical message is straightforward: the smaller the "baby lung," the greater is the potential for unsafe mechanical ventilation.

Keywords Acute respiratory distress syndrome · Baby lung · Baro-/volutrauma · Mechanical ventilation · Respiratory system compliance · Ventilator-induced lung injury

Introduction

Adult respiratory distress syndrome (ARDS) was first described in 1967 [1]. It is worth rereading the original paper as it clearly outlines the basic physiopathology and management problems which continue to be a matter of scientific debate. The 12 patients described there had ARDS of pulmonary and extrapulmonary origin, some with fluid overload and shock. Positive end-expiratory pressure (PEEP) was applied in five of them (three survived) and zero end-expiratory pressure (ZEEP) in the remaining seven (two survived). Respiratory system compliance ranged from 5 to 16 ml/cmH_2O, all patients were hypoxemic, and PCO_2 ranged from 22 to 69 mmHg. At autopsy the lungs were heavy (average 2110 g), and microscopic examination revealed areas of alveolar atelectasis, interstitial and alveolar hemorrhage and edema, dilated and congested capillaries. Interestingly, PEEP was described as a "buying time maneuver," preventing alveolar collapse at end-expiration.

How does the "baby lung" fit into this framework? The concept was introduced in the middle 1980s [2], but before discussing its place a brief history of the ARDS physiopathology and treatment is necessary. Some of the "new" concepts are nothing more than rediscoveries. Often, as new knowledge progresses, old knowledge is abandoned or forgotten.

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_54,

From the 1970s to the middle 1980s

To understand the progress of research in this period it is important to realize that the ultimate, undisputed target in ARDS patients was to maintain normal arterial PCO_2 and PO_2. Maintaining normal PCO_2 was not considered a problem, as it was common to use high pressure and volume ventilation, with tidal volume (V_T) even exceeding 20 ml/kg. Actually the recommended standard care was V_T between 12 and 15 ml/kg [3]. The most common side effects were pneumothorax and pulmonary hyperinflation, collectively termed barotrauma [4, 5].

To improve PaO_2 the key maneuver, after the report by Ashbaugh et al. [1], was to apply PEEP. To investigate its mechanism Falke et al. [6] first tested the effect of increasing PEEP from 0 to 15 cmH_2O in ten patients with ARDS. PEEP improved PaO_2 linearly, and the putative mechanism was the prevention of alveolar end-expiratory collapse and/or airway closure. That study reported a decrease in lung compliance with high PEEP and variable hemodynamic responses, as in some patients cardiac output rose and in others it fell. It is important to recall that at that time the major concern with PEEP was the possible hemodynamic impairment caused by the increase in intrathoracic pressure.

In 1975 Suter et al. [7] published their investigation on the "optimum PEEP." For the first time the relationship between lung mechanics and hemodynamics was approached in a structured fashion. Defining optimum PEEP as that which achieves not the best PaO_2 but the best oxygen transport (cardiac output × oxygen content), they found it to be associated with the highest compliance of the respiratory system. The hypothesis that was successfully tested, explicitly stated by the authors, is that the best compliance indicates that recruitment prevails over alveolar overdistension.

It is impossible to cite all the subsequent reports dealing with this concept, but in our opinion those that have introduced a new view of the problem were the ones by Lemaire et al. [8] and Kirby et al. [9] Lemaire et al. [8] suggested that the "minimal PEEP" to keep the lung open is 2 cmH_2O higher than the lower inflection point on the inflation limb of the volume pressure curve [8]. At the other end of the spectrum stood Kirby et al. [9] who proposed the "super PEEP" concept, defined as the pressure that maximally reduces shunt (down to 20% at 20 torr) [9]. For many years beginning in the middle 1970s the overall picture can be summarized as follows: ARDS lungs were regarded as homogeneously heavy and stiff. To achieve normal PCO_2 high volume and pressure ventilation was required, and to ensure normal oxygenation high FIO_2 and PEEP were necessary, although the criteria for selecting PEEP were elusive. At that time the recognized side effects were ventilation-induced barotrauma, and the major concern was the hemodynamic impairment due to PEEP and high FIO_2.

A new perspective was opened by Hill et al. [10] who described the successful treatment of a young trauma patient with long-term membrane lung oxygenation. This led the National Institutes of Health in the United States to sponsor the first multicenter randomized trial on ARDS [11]: 42 patients were randomized to extracorporeal membrane oxygenation (ECMO) and 48 to conventional care. Overall mortality in both groups was near 90%. To highlight the thinking at that time it is worth noting that both groups were treated with high-volume/pressure ventilation, and that the only difference was the lower FIO_2 in the group receiving extracorporeal membrane oxygenation.

At about the same time, after extensive experimental work showing that it was possible to control breathing by extracorporeal removal of CO_2 [12, 13, 14], we began to treat severe ARDS patients with this technique [15], the aim being to provide "lung rest" avoiding high-volume/pressure mechanical ventilation [16]. With this technique we could dissociate CO_2 removal and oxygenation; the first was achieved with a low-flow venovenous extracorporeal membrane lung and the second by apneic oxygenation through the natural lungs which were kept substantially immobile, being ventilated with only 3/5 bpm. At that time we had no scientific rationale for the "lung rest," except for the clinical observation of severe traumatic damage induced by high-volume/pressure ventilation. With extracorporeal CO_2 removal the gas exchange targets were again, as in the early 1970s, normal PCO_2 and normal PO_2.

Middle 1980s: the "baby lung" concept

Surprisingly the first reports on computed tomography (CT) examinations appeared only in the middle 1980s [17, 18, 19]. CT dramatically changed our view of ARDS [20]. What was considered a "homogeneous lung," as usually shown by anteroposterior radiography, appeared non-homogeneous on CT, with the densities concentrated primarily in the most dependent regions (Fig. 1). When we began a quantitative assessment of CT images, which measures the amount of normally aerated, poorly aerated, overinflated, and nonaerated tissue, we found that the amount of normally aerated tissue, measured at end-expiration, was in the order of 200–500 g in severe ARDS, i.e., roughly equivalent to the normally aerated tissue of a healthy boy of 5/6 years. From this finding came the concept of "baby lung," as an offspring of CT examinations [2].

As expected, the amount of nonaerated tissue was correlated with the degree of hypoxemia, the shunt fraction, and pulmonary hypertension. What was absolutely new, however, was the finding that respiratory compliance was well correlated only with the amount of normally aerated tissue and not with the amount of nonaerated tissue

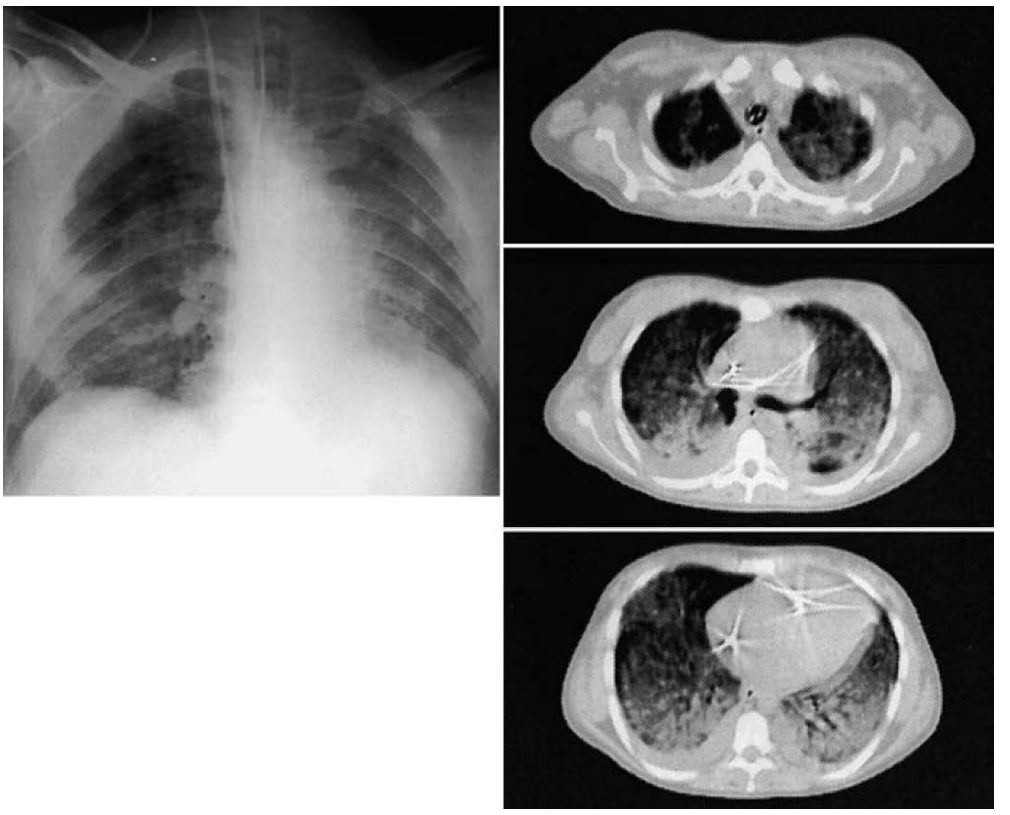


Fig. 1 Anteroposterior chest radiography (*right*) and CT—apex, hilum, and base—(*left*) in ARDS from sepsis, taken at 5 cmH_2O end-expiratory pressure. Chest radiography shows diffuse ground glass opacification, sparing the right upper lung. CT shows inhomogeneous disease and both the craniocaudal and sternovertebral gradients. (From Gattinoni et al. [20])

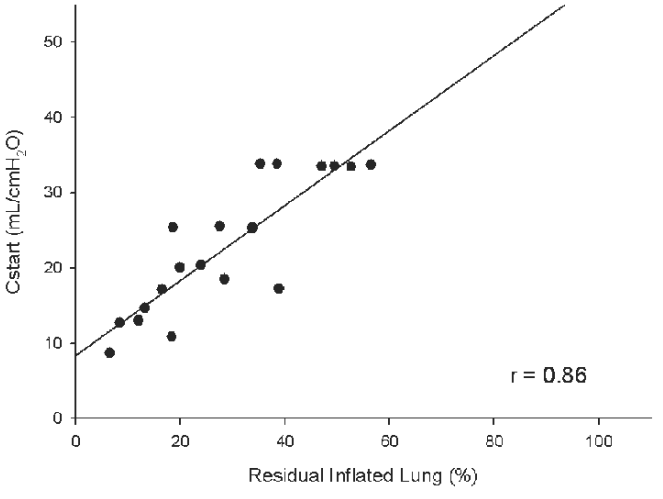


Fig. 2 Starting compliance (*Cstart*) as a function of residual inflated lung expressed as percentage of the expected normal lung volume. (Redrawn from Gattinoni et al. [22])

[21]. In other words, compliance appears to "measure" the dimension of the "baby lung" [22] (Fig. 2). We then discovered that the ARDS lung is not "stiff" at all, but small, and that the elasticity of the residual inflated lung is nearly normal, as indicated by the specific tissue compliance (compliance/normally aerated tissue) [21, 23].

When we first elaborated these concepts, we believed that the "baby lung" was a healthy anatomical structure, located in the nondependent regions of the original lungs. This model helped account for the disaster observed during high-volume and pressure mechanical ventilation. It was easily understandable that ventilating the lung of a healthy child with, for example, 1000 ml V_T, would destroy it. The relationship between the "baby lung" size and compliance explained why, on quite a large ARDS population with similar gas exchange impairment (referred to our hospital for extracorporeal support), only the patients with compliance below 20 ml/cmH_2O ("baby lung" approx. 20% of the original lung) actually received extracorporeal assistance while the others, with similar gas exchange but better compliance, could be treated with alternative methods [16]. Moreover, the "baby lung" concept fitted neatly with the concept of volutrauma (straining of the "baby lung") introduced by Dreyfuss et al. [24]. This helped provide a solid rational basis for trying to achieve "lung rest."

As soon as we realized that the "baby lung" was located primarily in the nondependent lung regions, we started to use the prone position. The goal was to improve oxygenation by increasing perfusion of the anatomical "baby lung," which was expected to be dependent in the prone position. Oxygenation did actually improve in the majority of patients. However, when we examined CT images in the prone position to confirm the theory [25], we found that the

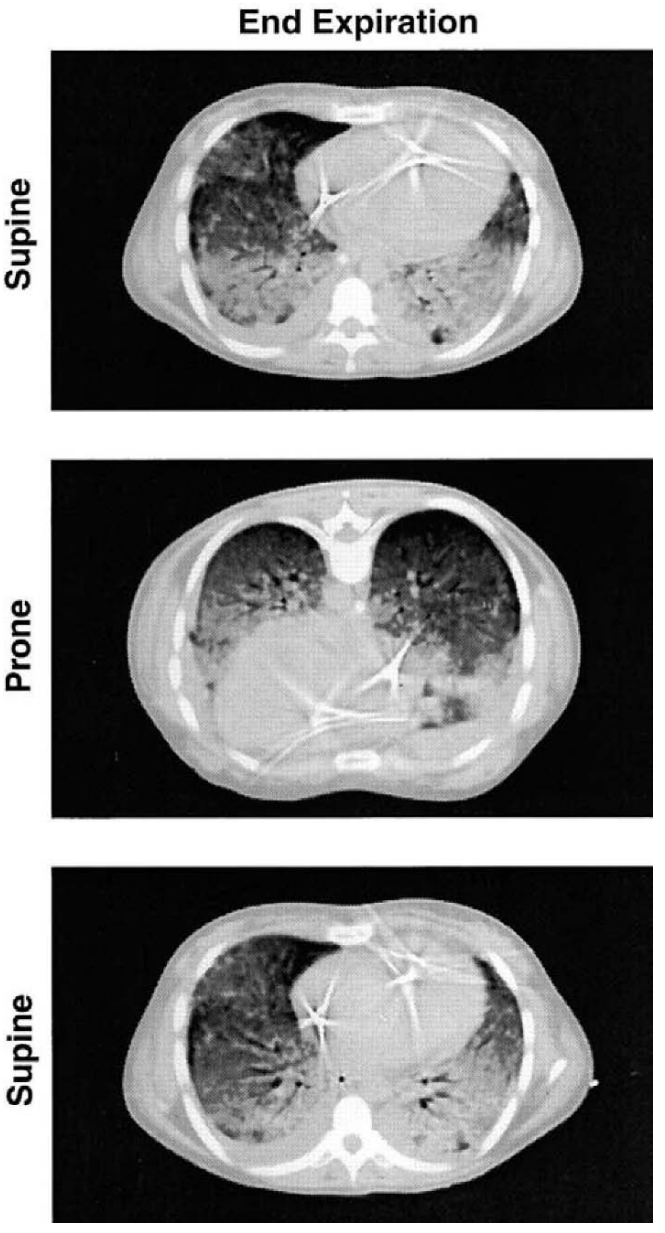


Fig. 3 CT of ARDS lung in supine (*upper*), prone (*middle*), and return to supine position (*lower*). The images were taken at end expiration and 10 cmH_2O PEEP. Note how gravity-dependent densities shift from dorsal to ventral within minutes when the patient is turned prone. (From Gattinoni et al. [20])

densities were redistributed in the dependent lung [26], thus demolishing the notion of the "baby lung" as a discrete, healthy anatomical structure (Fig. 3).

From "baby lung" to "sponge lung"

To understand the mechanism of lung density redistribution in the prone position we applied regional analysis, studying the lung composition along the sternum-vertebral axis [26, 27]. The main findings can be summarized as follows: all the lung parenchyma in ARDS is involved by the disease process, and the edema is evenly distributed from the sternum to the vertebra, i.e., not gravitationally, as observed previously [28, 29] and after [30, 31] ex vivo and in experimental animals. The increased lung weight, due to the accumulated edema, raises the hydrostatic pressures transmitted throughout the lung, which we called superimposed pressure. Consequently the gas in the dependent lung regions is squeezed out by the heavy lung parenchyma above (Fig. 4). The densities in the dependent lung regions are in fact due not to an increase in the amount of edema but to a loss of alveolar gases, as the result of the compressive gravitational forces, including the heart weight [32, 33].

This model, which Bone [34] called "sponge lung," accounts, although not completely, for the redistribution of the lung densities in prone position: the superimposed hydrostatic pressure is reversed, and the ventral regions instead of the dorsal are compressed [35]. The sponge lung also partly explains the mechanism of PEEP: to keep open the most dependent lung regions PEEP must be greater than the superimposed pressure [23]. Unfortunately, this unavoidably leads to overdistension of the lung regions with lower superimposed pressure (Fig. 4). That superimposed pressure is the main cause of collapse was inferred from the human studies cited above and, years later, was directly confirmed experimentally in animals [36] although this view was challenged [37, 38]. In the context of "sponge lung" the "baby lung" still has value if considered from a functional, not an anatomical, perspective. In a broad sense the "baby lung" concept can be applied to any kind of ARDS as every patient has a reduced amount of normally aerated tissue.

The sponge lung model, however, implies different considerations. It assumes that the edema is evenly distributed throughout the lung parenchyma. While this is likely when the noxious stimulus leading to ARDS originates from the blood, i.e., all the lung parenchyma is exposed as in extrapulmonary ARDS, the picture may differ when the noxious stimulus comes from the airways, and distribution may possibly be nonhomogeneous (as in pulmonary ARDS) [39, 40]. This, however, remains to be verified, although CT differences between pulmonary and extrapulmonary ARDS have been reported [41, 42].

The "baby lung" at end-inspiration

New information was obtained, with further refinement of the model, when not only end-expiration but also end-inspiration was explored. We found that during inspiration part of the lung is recruited [43]. This has been shown in humans and in experimental animals both with [36, 44] and without CT [45]. These findings suggest the follow-

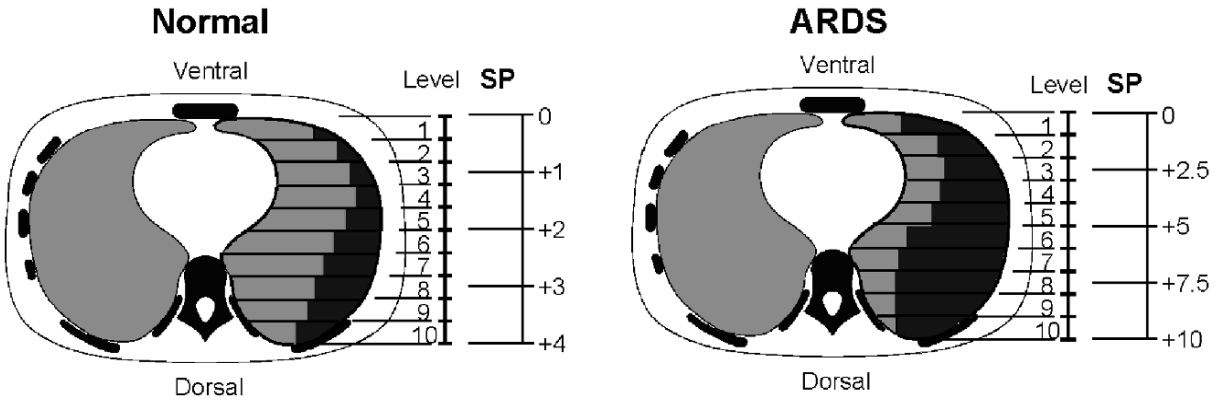


Fig. 4 Schema representation of sponge model. In ARDS the "tissue," likely edema in the early phase, is almost doubled in each lung level compared with normal, indicating the nongravitational distribution of edema. The increased mass, however, causes an increased superimposed pressure (*SP*; cmH_2O), which in turn leads to a "gas squeezing" from the most dependent lung regions. Superimposed pressure is expressed as cmH_2O. (The values are taken from Pelosi et al. [27])

ing scheme (Fig. 5): the opening pressures are widely and normally distributed throughout the lung parenchyma both in humans and in experimental models, with the mode between 20 and 25 cmH_2O of airway pressure. Some lung regions, however—usually the most dependent—may require opening pressure up to 45 cmH_2O. It follows that during inspiration new tissue continuously opens to the plateau pressure. Of course, if the plateau pressure is limited, say, to 25 cmH_2O, all collapsed tissue with a higher opening pressure stays closed throughout the entire respiratory cycle. At end-expiration the PEEP, if adequate, can keep open only the lung regions that were already opened by the plateau pressure [36, 44].

CT examinations at end-inspiration did in fact clearly focus the relationship between the end-expiratory and end-inspiratory pressures, which may be relevant and are discussed below in the context of the lung protective strategy. During inspiration the "baby lung" augments its own parenchyma through newly recruited tissue up to the inspiratory plateau pressure. This complicates the interpretation of the pressure/volume curve. In fact the amount of tissue explored between end-expiration and end-inspiration in ARDS is not the same as in the normal lung which simply inflates. In ARDS during inspiration the "baby lung" gains both gas and tissue, and the gas volume/pressure curve is similar to the recruitment/pressure curve [20].

The "baby lung" and the protective lung strategy: changing the goals

As discussed above, the concept of "baby lung" fully justified the goal of lung rest. With extracorporeal CO_2 removal we were able to fully provide lung rest, but at the price of the side effects of extracorporeal circulation (primarily bleeding). In the 1990s Hickling et al. [46] introduced low V_T ventilation to "rest the lung." This technique, referred to as "permissive hypercapnia," to underline the price paid for resting the lung, had been used with success in asthma patients [47]. In our opinion, however, *the real "revolution" was not the use of low tidal volume but the change of the goal*. For nearly 20 years this had been normal gas exchange, but from the 1990s the accepted target became gentle lung treatment while maintaining adequate oxygenation and accepting high PCO_2 [48].

The "baby lung" and "VILI"

Anatomical and physiological basis of ventilator-induced lung injury

We recently reviewed the physical and biological triggers of ventilator-induced lung injury (VILI) [49] and briefly discuss them now in relation to the "baby lung." The lung's fibrous skeleton is the structure that bears the forces applied by mechanical ventilation. The skeleton consists of two fiber systems: an axial system which is anchored to the hilum and runs along the branching airways down to the alveolar ducts, and a peripheral system which is anchored to the visceral pleural that goes centripetally down into the lung to the acini. The two systems are linked at the level of the alveoli and form a continuum, the lung skeleton [50]. The anatomical units of the system are extensible elastin and inextensible collagen which is "folded" in the lung resting position (Fig. 6, left panel). The lung cells (epithelial and endothelial) do not bear the force directly but are anchored (via integrins) to the fibrous skeleton and must accommodate their shape when the skeleton is distended. The limits of distension are of course dictated by the inextensible collagen fibers, which work as a "stop-length" system. When the collagen fibers are fully unfolded, the lungs reach their maximal volume (total lung capacity) and further elongation is

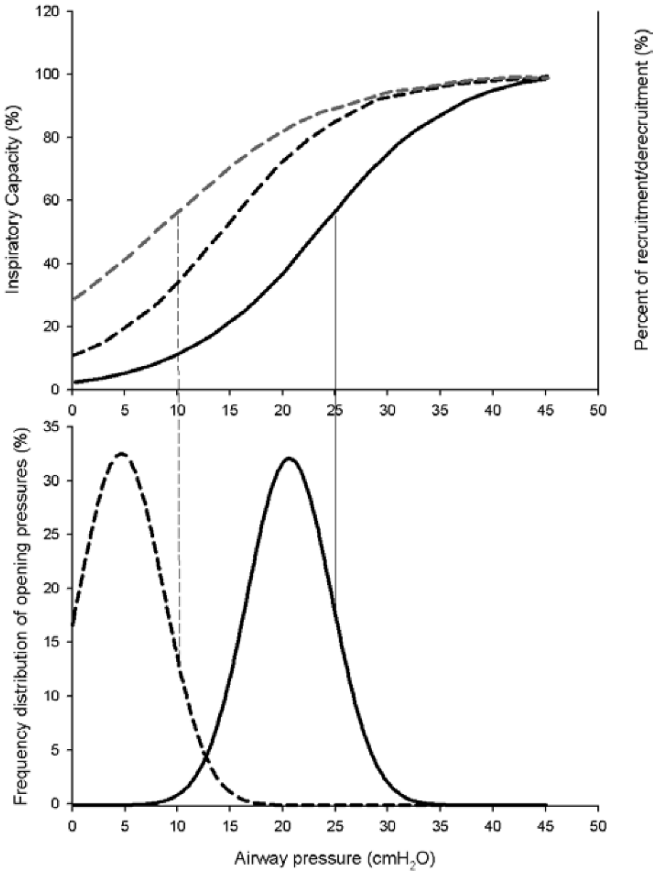


Fig. 5 *Upper* Percentage of inspiratory capacity (*black lines*; *solid black line* also percentage of recruitment) and percentage of derecruitment (*dashed gray line*) as function of airway pressure. *Lower* Frequency distribution of opening pressure as function of airway pressure (*solid line*) and of closing pressure (*dashed line*). *Vertical lines* Example of airway pressures used during mechanical ventilation, plateau pressure 25 cmH_2O (*solid line*) and PEEP 10 cmH_2O (*dashed line*). At 25 cmH2O airway pressure nearly 60% inspiratory capacity, 40% of lung units are still closed. At 10 cmH_2O PEEP nearly 35% undergoes opening and closing. (Data from Crotti et al. [44])

prevented (Fig. 6, right panel). This is true for the whole lung as well as for each lung region, which has its own "total regional maximal capacity."

When a force is applied by the ventilator, the fibers of the lung skeleton develop an internal tension (spatial molecular rearrangement), equal to but opposite the pressure applied to the fibers. The applied pressure is not the airway pressure but the transpulmonary pressure (PL), i.e., the airway pressure minus the pleural pressure. The fiber tension is called "stress." In an elastic structure such as the lung skeleton, the stress is associated with elongation (ΔL) of the fibers from their resting position (L_0), and this is called "strain" ($\Delta L/L_0$). Stress and strain, indeed, are two faces of the same coin, and are linked as follows: *stress=K* × *strain*, where K is Young's module of the material [51].

If the stress exceeds the tensile properties of the collagen fibers up to "stress at rupture," the lung undergoes the classical "barotrauma." When the strain, without reaching the levels of physical rupture, is unphysiological (volutrauma), the macrophages, endothelial, and epithelial cells anchored to the lung skeleton are stretched abnormally [52, 53, 54, 55, 56, 57], the mechanosensors are activated [58, 59, 60], cytokines are produced [61, 62, 63], and full-blown inflammation develops [64].

Stress and strain in the "baby lung"

From this perspective, VILI is nothing more than the global/regional excessive stress and strain applied to the "baby lung." The rough equivalent of the stress in the whole lung is the PL, while the equivalent of the strain is the change in the size of the lung from its resting position, i.e., the ratio of V_T to the size of the "baby lung" at end-expiration (ZEEP): *PL(i.e. stress)=K* × *[(V_T/baby lung)] (i.e. strain)*. The link between stress and strain, K, is the specific lung elastance (E_{spec}=*PL/V_T* × *"baby lung"*), which is the pressure at which the "baby lung" (end-expiratory lung volume) doubles in size, i.e., when V_T/"baby lung"=1.

The issue is more complicated (but the overall concept does not change) when PEEP is applied. In fact, the effects of PEEP are twofold. On the one hand, PEEP may overdistend the already open lung, increasing stress and strain (i.e., the numerator of above equation increases). On the other hand, PEEP may keep open new lung portions, increasing the resting end expiratory lung volume (i.e., the denominator of the above equation increases, stress/strain decreases). The final effect should be detected in every patient, who may show varying amounts of recruitable lung.

We do not know the safe limits of mechanical ventilation, but they can be discussed against a physiological and anatomical background. In the normal lung doubling the resting volume occurs at approx. 80% of total lung capacity, and at this level of strain (V_T/end-expiratory lung volume=1) most of the collagen fibers are unfolded, and PL equals the specific elastance, which is normally 12.5 cmH_2O. We found that specific elastance in the "baby lung" is near normal [21, 23]. If so, considering the upper limits of physiological strain between 0.8 and 1 as "safe" (although we do not know), the "safe" PL should not exceed the specific elastance (approx. 12–13 cmH_2O).

To prevent VILI, by applying stress and strain within physiological limits, we must take the V_T/"baby lung" ratio, not the V_T/kg ratio. For example, in a 70-kg ARDS patient the "baby lung" dimension may be highly variable, say 200, 400, or even 800 ml. A 6 ml/kg V_T [65] applied to these different "baby lungs" would result in three different sets of global [stress and strain], i.e., [26.3 cmH_2O and 2.1], [13.1 cmH_2O and 1.1],

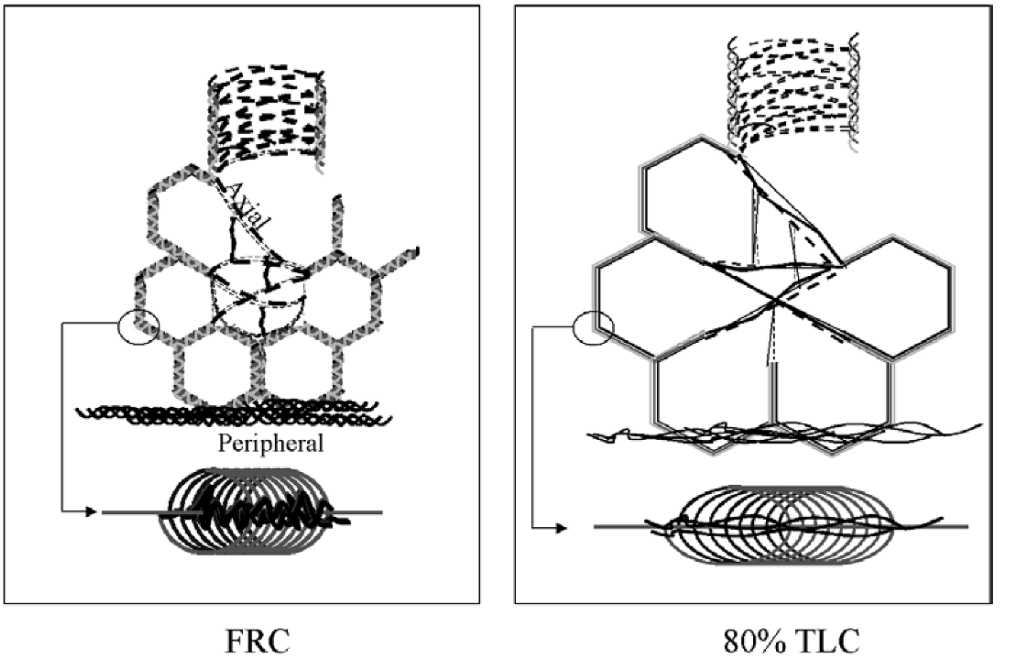


Fig. 6 Disposition of fibers in an acinus. The particular shows the association of elastic fibers (spring) and collagen fibers (string). *Left* Relaxed state (*FRC*); *right* 80% TLC state. (Modified from Weibel [67])

[6.6 cmH_2O and 0.5] respectively. Only the third set is within physiological limits.

If we eventually verify (work is in progress) that E_{spec} is constant or within narrow limits in ARDS, knowing either the PL or the "baby lung" dimension will be sufficient to tailor stress and strain, so that they remain within physiological limits. Unfortunately, none of the variables needed to estimate stress and strain are measured routinely in the ICU.

So far we have considered PL as a single value, but in fact it changes along the vertical axis of the lung. In supine position the PL gradient is steeper than in prone position [26]. This suggests that strain and stress are distributed more evenly in the prone position, and this is the rationale for its application in ARDS, independently of gas exchange, as we recently observed experimentally [66].

Conclusion

The "baby lung" is a model, with all the limits inherent to models. However, it is useful for the interpretation of both physiopathology and treatment. The "baby lung" is actually the "small" lung open at end-expiration; it may become larger during inspiration due to newly recruited tissue, according to the recruitment-pressure curve and the opening pressure distribution. The "baby lung" is not healthy but it is aerated. Its specific elastance, however, is usually near-normal. The smaller the "baby lung," the greater the potential for VILI. Barotrauma (PL, stress) and the volutrauma-biotrauma (V_T/end-expiratory lung volume, strain) are linked to the "baby lung" by the following relationship, which clearly indicates that the smaller the "baby lung" the greater the stress/strain: $PL=E_{spec}\times(V_T/baby\ lung)$. The final message is straightforward: Treat the "baby lung" gently. Low PL, low V_T, and prone position are the means to hand today.

Acknowledgements We cannot list individually, but we are deeply indebted to the hundreds of incredible persons who have worked, contributed, and discussed with us over the past 30 years. Without them we could not have reached any result, great or small. Intensive care is founded not only on a "great idea" but on near-paranoid attention to detail and understanding of the minute-by-minute changes in patients' physiology.

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet II:319–323
2. Gattinoni L, Pesenti A (1987) ARDS: the non-homogeneous lung; facts and hypothesis. Intensive Crit Care Dig 6:1–4
3. Pontoppidan H, Geffin B, Lowenstein E (1972) Acute respiratory failure in the adult. III. N Engl J Med 287:799–806
4. Kumar A, Pontoppidan H, Falke KJ et al (1973) Pulmonary barotrauma during mechanical ventilation. Crit Care Med 1:181–186
5. Baeza OR, Wagner RB, Lowery BD (1975) Pulmonary hyperinflation. A form of barotrauma during mechanical ventilation. J Thorac Cardiovasc Surg 70:790–805

6. Falke KJ, Pontoppidan H, Kumar A et al (1972) Ventilation with end-expiratory pressure in acute lung disease. J Clin Invest 51:2315–2323
7. Suter PM, Fairley B, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284–289
8. Lemaire F, Harf A, Simonneau G et al (1981) [Gas exchange, static pressure-volume curve and positive-pressure ventilation at the end of expiration. Study of 16 cases of acute respiratory insufficiency in adults]. Ann Anesthesiol Fr 22:435–441
9. Kirby RR, Downs JB, Civetta JM et al (1975) High level positive end expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 67:156–163
10. Hill JD, O'Brien TG, Murray JJ et al (1972) Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. N Engl J Med 286:629–634
11. Zapol WM, Snider MT, Hill JD et al (1979) Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 242:2193–2196
12. Kolobow T, Gattinoni L, Tomlinson TA, Pierce JE (1977) Control of breathing using an extracorporeal membrane lung. Anesthesiology 46:138–141
13. Kolobow T, Gattinoni L, Tomlinson T, Pierce JE (1978) An alternative to breathing. J Thorac Cardiovasc Surg 75:261–266
14. Gattinoni L, Kolobow T, Tomlinson T et al (1978) Control of intermittent positive pressure breathing (IPPB) by extracorporeal removal of carbon dioxide. Br J Anaesth 50:753–758
15. Gattinoni L, Agostoni A, Pesenti A et al (1980) Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO_2. Lancet II:292–294
16. Gattinoni L, Pesenti A, Mascheroni D et al (1986) Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 256:881–886
17. Rommelsheim K, Lackner K, Westhofen P et al (1983) [Respiratory distress syndrome of the adult in the computer tomograph]. Anasth Intensivther Notfallmed 18:59–64
18. Maunder RJ, Shuman WP, McHugh JW et al (1986) Preservation of normal lung regions in the adult respiratory distress syndrome. Analysis by computed tomography. JAMA 255:2463–2465
19. Gattinoni L, Mascheroni D, Torresin A et al (1986) Morphological response to positive end expiratory pressure in acute respiratory failure. Computerized tomography study. Intensive Care Med 12:137–142
20. Gattinoni L, Caironi P, Pelosi P, Goodman LR (2001) What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 164:1701–1711
21. Gattinoni L, Pesenti A, Avalli L et al (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. Am Rev Respir Dis 136:730–736
22. Gattinoni L, Pesenti A, Baglioni S et al (1988) Inflammatory pulmonary edema and positive end-expiratory pressure: correlations between imaging and physiologic studies. J Thorac Imaging 3:59–64
23. Gattinoni L, D'Andrea L, Pelosi P et al (1993) Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. JAMA 269:2122–2127
24. Dreyfuss D, Soler P, Basset G, Saumon G (1988) High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137:1159–1164
25. Langer M, Mascheroni D, Marcolin R, Gattinoni L (1988) The prone position in ARDS patients. A clinical study. Chest 94:103–107
26. Gattinoni L, Pelosi P, Vitale G et al (1991) Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. Anesthesiology 74:15–23
27. Pelosi P, D'Andrea L, Vitale G et al (1994) Vertical gradient of regional lung inflation in adult respiratory distress syndrome. Am J Respir Crit Care Med 149:8–13
28. Jones T, Jones HA, Rhodes CG et al (1976) Distribution of extravascular fluid volumes in isolated perfused lungs measured with H215O. J Clin Invest 57:706–713
29. Hales CA, Kanarek DJ, Ahluwalia B et al (1981) Regional edema formation in isolated perfused dog lungs. Circ Res 48:121–127
30. Sandiford P, Province MA, Schuster DP (1995) Distribution of regional density and vascular permeability in the adult respiratory distress syndrome. Am J Respir Crit Care Med 151:737–742
31. Quintel M, Pelosi P, Caironi P et al (2004) An increase of abdominal pressure increases pulmonary edema in oleic acid-induced lung injury. Am J Respir Crit Care Med 169:534–541
32. Albert RK, Hubmayr RD (2000) The prone position eliminates compression of the lungs by the heart. Am J Respir Crit Care Med 161:1660–1665
33. Malbouisson LM, Busch CJ, Puybasset L et al (2000) Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group. Am J Respir Crit Care Med 161:2005–2012
34. Bone RC (1993) The ARDS lung. New insights from computed tomography. JAMA 269:2134–2135
35. Gattinoni L, Pelosi P, Valenza F, Mascheroni D (1994) Patient positioning in acute respiratory failure. In: Tobin MJ (ed) Principle and practice of mechanical ventilation. McGraw-Hill, New York, pp 1067–1076
36. Pelosi P, Goldner M, McKibben A et al (2001) Recruitment and derecruitment during acute respiratory failure: an experimental study. Am J Respir Crit Care Med 164:122–130
37. Martynowicz MA, Minor TA, Walters BJ, Hubmayr RD (1999) Regional expansion of oleic acid-injured lungs. Am J Respir Crit Care Med 160:250–258
38. Wilson TA, Anafi RC, Hubmayr RD (2001) Mechanics of edematous lungs. J Appl Physiol 90:2088–2093
39. Gattinoni L, Pelosi P, Suter PM et al (1998) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? Am J Respir Crit Care Med 158:3–11
40. Ranieri VM, Brienza N, Santostasi S et al (1997) Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. Am J Respir Crit Care Med 156:1082–1091
41. Goodman LR, Fumagalli R, Tagliabue P et al (1999) Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: CT, clinical, and functional correlations. Radiology 213:545–552
42. Desai SR, Wells AU, Suntharalingam G et al (2001) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary injury: a comparative CT study. Radiology 218:689–693
43. Gattinoni L, Pelosi P, Crotti S, Valenza F (1995) Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 151:1807–1814
44. Crotti S, Mascheroni D, Caironi P et al (2001) Recruitment and derecruitment during acute respiratory failure: a clinical study. Am J Respir Crit Care Med 164:131–140

45. Jonson B, Richard JC, Straus C et al (1999) Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. Am J Respir Crit Care Med 159:1172–1178
46. Hickling KG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16:372–377
47. Darioli R, Perret C (1984) Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 129:385–387
48. Pesenti A (1990) Target blood gases during ARDS ventilatory management. Intensive Care Med 16:349–351
49. Gattinoni L, Carlesso E, Cadringher P et al (2003) Physical and biological triggers of ventilator-induced lung injury and its prevention. Eur Respir J Suppl 47:15s-25s
50. Weibel ER (1986) Functional morphology of lung parenchyma. In: American Physiological Society (ed) Handbook of physiology a critical, comprehensive presentation of physiological knowledge and concepts. Waverly, Baltimore, pp 89–111
51. Wilson TA (1986) Solid mechanics. In: American Physiological Society (ed) Handbook of physiology a critical, comprehensive presentation of physiological knowledge and concepts. Waverly, Baltimore, pp 35–39
52. Dos Santos CC, Slutsky AS (2000) Invited review: mechanisms of ventilator-induced lung injury: a perspective. J Appl Physiol 89:1645–1655
53. Pugin J, Dunn I, Jolliet P et al (1998) Activation of human macrophages by mechanical ventilation in vitro. Am J Physiol 275:L1040–L1050
54. Edwards YS (2001) Stretch stimulation: its effects on alveolar type II cell function in the lung. Comp Biochem Physiol A Mol Integr Physiol 129:245–260
55. Vlahakis NE, Hubmayr RD (2000) Invited review: plasma membrane stress failure in alveolar epithelial cells. J Appl Physiol 89:2490–2496
56. Vlahakis NE, Hubmayr RD (2003) Response of alveolar cells to mechanical stress. Curr Opin Crit Care 9:2–8
57. Vlahakis NE, Schroeder MA, Pagano RE, Hubmayr RD (2001) Deformation-induced lipid trafficking in alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 280:L938–L946
58. Liu M, Tanswell AK, Post M (1999) Mechanical force-induced signal transduction in lung cells. Am J Physiol 277:L667–L683
59. Uhlig S (2002) Ventilation-induced lung injury and mechanotransduction: stretching it too far? Am J Physiol Lung Cell Mol Physiol 282:L892–L896
60. Pugin J (2003) Molecular mechanisms of lung cell activation induced by cyclic stretch. Crit Care Med 31:S200–S206
61. Haseneen NA, Vaday GG, Zucker S, Foda HD (2003) Mechanical stretch induces MMP-2 release and activation in lung endothelium: role of EMMPRIN Am J Physiol Lung Cell Mol Physiol 284:L541–L547
62. Yamamoto H, Teramoto H, Uetani K et al (2002) Cyclic stretch upregulates interleukin-8 and transforming growth factor-beta1 production through a protein kinase C-dependent pathway in alveolar epithelial cells. Respirology 7:103–109
63. Vlahakis NE, Schroeder MA, Limper AH, Hubmayr RD (1999) Stretch induces cytokine release by alveolar epithelial cells in vitro. Am J Physiol 277:L167–L173
64. Belperio JA, Keane MP, Burdick MD et al (2002) Critical role for CXCR2 and CXCR2 ligands during the pathogenesis of ventilator-induced lung injury. J Clin Invest 110:1703–1716
65. Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
66. Valenza F, Guglielmi M, Maffioletti M et al (2005) Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? Crit Care Med 33:361–367
67. Weibel ER (1984) The pathway for oxygen structure and function in the mammalian respiratory system. Harvard University Press, Cambridge

Göran Hedenstierna
Lennart Edmark

The effects of anesthesia and muscle paralysis on the respiratory system

Abstract *Background:* Oxygenation is impaired in almost all subjects during anesthesia, and hypoxemia for shorter or longer periods is a common finding. Moreover, postoperative lung complications occur in 3–10% after elective abdominal surgery and more in emergency operations. *Discussion:* Rapid collapse of alveoli on induction of anesthesia and more widespread closure of airways seem to explain the oxygenation impairment and may also contribute to postoperative pulmonary infection. Causative mechanisms to atelectasis and airway closure seem to be loss of respiratory muscle tone and gas resorption. *Conclusion:* Avoiding high inspired oxygen fractions during both induction and maintenance of anesthesia prevents or reduces atelectasis, while intermittent "vital capacity" maneuvers recruit atelectatic lung regions.

Keywords Anesthesia · Mechanical ventilation · Atelectasis · Airway closure · Shunt

Introduction

Anesthesia during mechanical ventilation is administered to 10–15 million patients per year in the countries of the European Union. A frequent finding is impaired oxygenation, despite the administration of 30–40% oxygen in the inspired gas. Increased alveolar-arterial oxygen tension difference ($P_{A\text{-}a}O_2$) is therefore seen in 90% or more of anesthetized patients [1]. This holds true for all anesthetic regimes, whether intravenous or inhalational agents are used, and whether the patient is breathing spontaneously or is ventilated mechanically [2]. Moreover, postoperative pulmonary complications occur in 3–10% of patients undergoing elective abdominal surgery [3, 4], and more in emergency surgery. To what extent postoperative complications are caused by a respiratory dysfunction during anesthesia is not clear. However, atelectasis that develops during anesthesia remains in the postoperative period, and impairment in arterial oxygenation and decrease in forced spirometry are correlated with the size of the atelectasis [5]. Moreover, in view of the large number of anesthesias that are given in the Western world even a moderate complication rate will have considerable social and economic consequences.

This review examines the morphological and functional causes of impaired oxygenation that is regularly seen during anesthesia and mechanical ventilation.

Gas exchange

Shunt, as calculated from arterial, mixed venous, and alveolar PO_2 [6], increases from 1–2% in the waking subject to 8–10% in the anesthetized patient [1]. The standard shunt equation is based on the assumption of two populations of alveoli, those that are "ideally" perfused in proportion to their ventilation and those that are perfused but not at all ventilated (the shunt). However, the lung does not contain two populations of alveoli only. There are a number of units with less ventilation than perfusion, with low ventilation-perfusion ratios ("low V_A/Q regions"), as well as units that are ventilated in excess of

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_55, © Springer-Verlag Berlin Heidelberg 2009

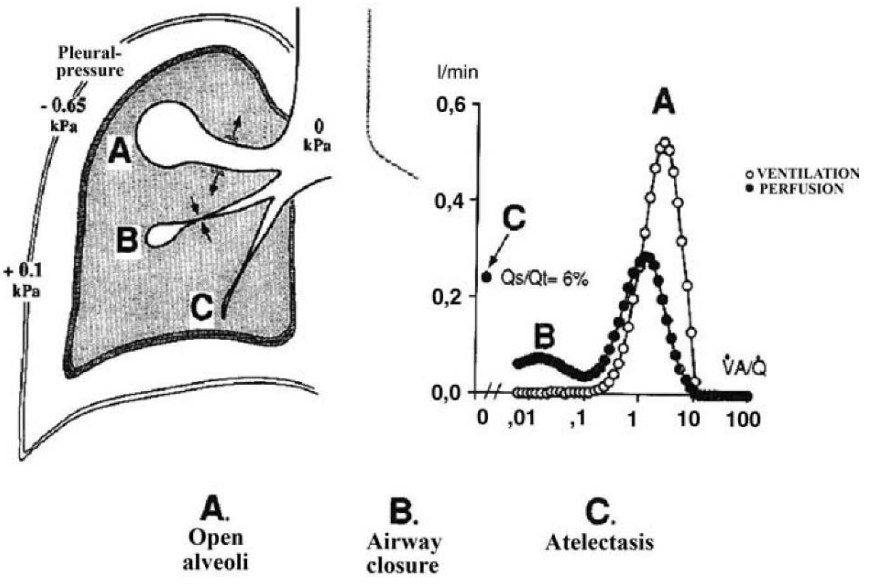


Fig. 1 *Right* Ventilation-perfusion matching (V_A/Q) in an anesthetized subject. Note the large normal mode centered on a V_A/Q ratio of 1, as well as a low V_A/Q mode with V_A/Q ratios between 0.01 and 0.1, and finally shunt (V_A/Q=0). *Left* The morphological and functional correlates with intermittent airway closure explaining low V_A/Q and atelectasis explaining the shunt

their perfusion ("high V_A/Q regions"). Perfusion of low V_A/Q regions also impedes the oxygenation of blood and to a varying extent is included in the calculated "shunt." The shunt, as measured by the standard oxygen technique, should therefore rather be called "venous admixture" [1]. A good correlation between venous admixture and the sum of "true" shunt and perfusion of "low V_A/Q regions" was seen in a study of 45 anesthetized subjects [7].

The extent by which venous admixture includes low V_A/Q regions depends on the inspired oxygen fraction (FIO_2). The higher it is, the less of low V_A/Q is included. However, with high FIO_2 the regions with low V_A/Q collapse because of gas adsorption and be transformed to shunt regions [8, 9].

A more detailed picture of the distribution of V_A/Q ratios with no need to change FIO_2 can be obtained by the multiple inert gas elimination technique [10]. This technique is based on the infusion of a number of inert gases (usually six) in a vein and the calculations of the retention (arterial/mixed venous concentration ratio) and excretion (mixed expired/mixed venous concentration ratio) of each gas. The ratios, together with the measured solubilities of the inert gases, enable the construction of a virtually continuous distribution of ventilation and perfusion against V_A/Q ratios.

When this technique is applied to the anesthesia setting, a major finding is increased dispersion of V_A/Q with the appearance of low V_A/Q ratios. Thus there is impaired matching of ventilation and perfusion during anesthesia with regions that are poorly ventilated in relation to their perfusion. Another major observation is the appearance of true shunt of around 8%, but frequently exceeding 20% [11, 12, 13]. Figure 1 presents an example of a V_A/Q distribution. Thus there seem to be at least two major functional causes of impaired oxygenation during anesthesia, low V_A/Q and true shunt. The morphological correlates are be discussed below.

Hypoxic pulmonary vasoconstriction

Attenuation of hypoxic pulmonary vasoconstriction (HPV) is frequently considered a mechanism of impaired gas exchange during anesthesia. Most inhalational anesthetics inhibit HPV in isolated lung preparations [14]. However, no such effect has been seen with intravenous anesthetics (barbiturates) [15]. Results from human studies vary, reasonably explained by the complexity of the experiment that causes several variables to change at the same time. In studies with no gross changes in cardiac output the inhalational anesthetics isoflurane and halothane depress the HPV response by 50% at twice the minimum alveolar concentration [16]. The HPV response acts efficiently both in the atelectatic lung (where HPV seems to be more important than mechanical kinking of vessels) and during ventilation with hypoxic gases [17].

The breathing of pure oxygen may increase the shunt by promoting alveolar collapse [18]. High FIO_2 may also increase shunt by increasing alveolar PO_2 and thus attenuate the HPV response [16]. Similarly, pulmonary hypertension counters HPV, presumably by requiring higher muscle force to constrict a vessel.

It should also be emphasized that attenuation of the HPV response cannot be the only disturbance during anesthesia to cause gas exchange impairment. If there were no corresponding ventilatory impediment, loss of pulmonary vascular tone would be of no significance since adequate gas exchange would still occur. Loss of HPV can only aggravate an existing V_A/Q mismatch.

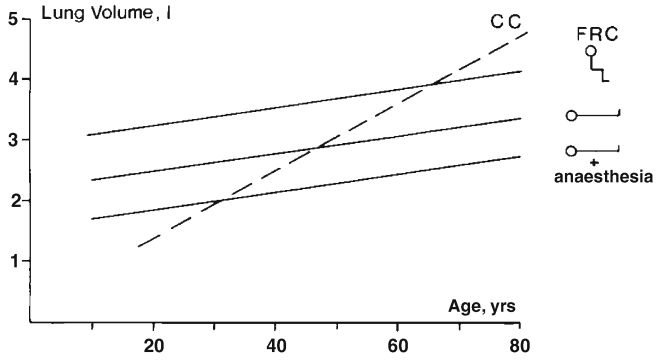


Fig. 2 Functional residual capacity (*FRC*) and closing capacity (*CC*, the lung volume at which airways begin to close during expiration). Note the decrease in FRC from sitting or standing to supine and the further decrease with anesthesia. Note also the slight increase in volumes with age, an effect of loss of elastic tissue in the lung (as well as elsewhere in the body). Note also the much faster increase in CC with age, making airway closure more common in elderly. Airway closure during a breath occurs at ages of 30 years and more in the supine anesthetized subject

Lung volume and respiratory mechanics

The resting lung volume (functional residual capacity, FRC) is reduced by 0.8–1.0 l by changing body position from upright to supine, and there is another decrease by 0.4–0.5 l when anesthesia is induced [19]. The end-expiratory lung volume is thus reduced from approx. 3.5 to 2 l, the latter being close or equal to residual volume. When one tries to breathe voluntarily at that level, one realizes the difficulty in doing so! The decrease seems to be related to loss of respiratory muscle tone, shifting the balance between the elastic recoil force of the lung and the outward forces of the chest wall to a lower chest and lung volume [20, 21]. Maintenance of muscle tone, such as during ketamine anesthesia, does not reduce FRC [22]. The effect of body position and anesthesia on FRC is shown in Fig. 2. As seen here, FRC increases with age. This is dealt with below.

Compliance of the respiratory system (lungs and chest wall) is also reduced during anesthesia, from a mean of 95 to 60 ml/cmH_2O [23]. This may be due mainly to decreased lung compliance [23]. Rehder and coworkers [24] ruled out direct effects of the anesthetic on the lung tissue, and it is more likely that the fall in compliance is a consequence of the reduced FRC. This promotes airway closure and atelectasis, as is discussed below.

The resistance of the respiratory system and of the lungs has also been measured, showing considerable increase during both spontaneous breathing and mechanical ventilation [23, 24]. However, studies on resistance during anesthesia have been hampered by different experimental conditions during the awake and the anesthetized conditions. Thus studies that enables comparison of resistance under both isovolume and isoflow conditions are still lacking. It is rather likely that the increased lung resistance merely reflects the reduced FRC.

Atelectasis

In their classical study in 1963 Bendixen and coworkers [25] proposed "a concept of atelectasis" as a cause of impaired oxygenation during anesthesia. They had observed a subsequent decrease in compliance of the respiratory system and a similar subsequent decrease in arterial oxygenation in both anesthetized humans and experimental animals. This was interpreted as the formation of atelectasis. However, other research groups who were unable to reproduce their findings noted a more rapid fall in compliance and PaO_2 on induction of anesthesia. Moreover, atelectasis could not be shown by conventional chest radiography.

In the middle 1980s new observations were made that may explain the altered function of the lung during anesthesia. Using computed tomography (CT) with transverse exposures of the chest Brismar and coworkers [26] demonstrated prompt development of densities in dependent regions of both lungs during anesthesia. Similar densities had previously been seen in anesthetized infants [27]. Morphological studies of these densities in various animals supported the diagnosis of atelectasis [28]. An example of atelectasis as shown by CT is shown in Fig. 3.

Atelectasis appears in around 90% of patients who are anesthetized [7]. It occurs both during spontaneous breathing and after muscle paralysis and regardless of whether intravenous or inhalational anesthetics are used [2]. The atelectatic area on CT slice near the diaphragm is generally approx. 5–6% of the total lung area but can easily exceed 15–20%. It should also be remembered that the amount of tissue that is collapsed is even larger, the atelectatic area comprising mainly lung tissue whereas the aerated lung consists only of 20–40% tissue, the rest being air. Thus 15–20% of the lung is regularly collapsed at the base of the lung during uneventful anesthesia—before any surgery has been done! Abdominal surgery adds only little to the atelectasis, but it can remain for several days in the postoperative period [5]. It is likely to be a focus of infection and may contribute to pulmonary complications [29]. One should also note that after thoracic surgery and cardiopulmonary bypass more than 50% of the lung can remain collapsed even several hours after surgery [30]. The amount of atelectasis decreases towards the apex, which is mostly spared (fully aerated).

There is a weak correlation between the size of the atelectasis and body weight or body mass index [31], obese patients showing larger atelectatic areas than lean ones. While this was expected, it came as a surprise that the atelectasis is independent of age, with children and young persons showing as much atelectasis as elderly patients [7]. Another unexpected observation was that

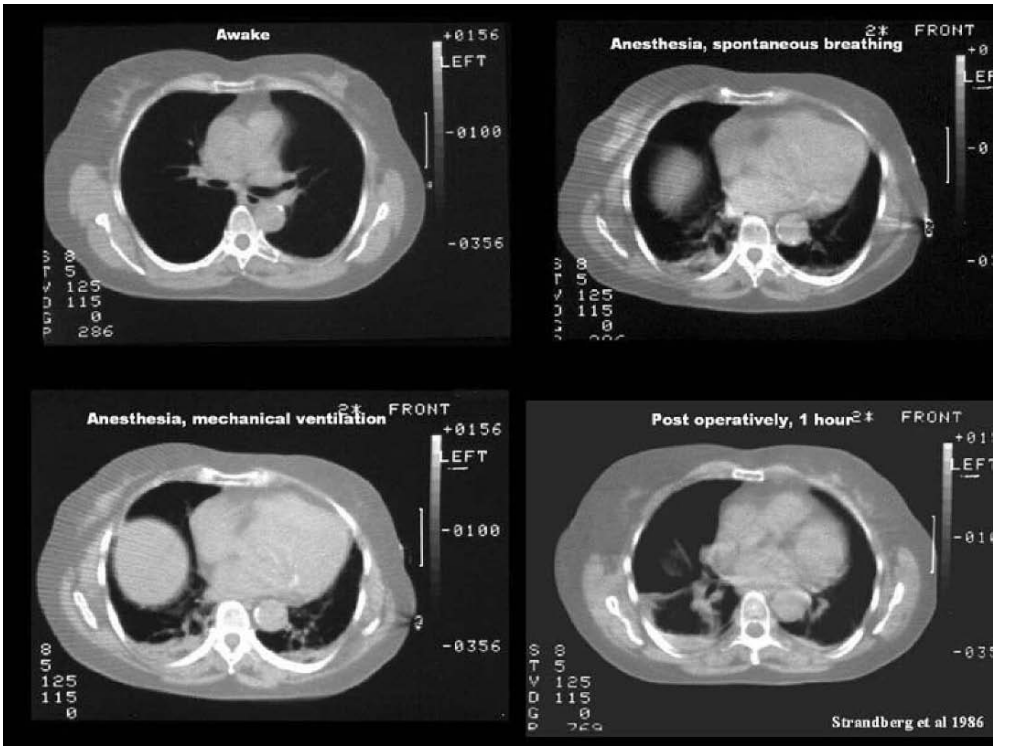


Fig. 3 Computed tomography in a subject when awake (*upper left*), during anesthesia with spontaneous breathing (*upper right*), after muscle paralysis (*lower left*), and 1 h postoperatively (*lower right*). Note the appearance of atelectasis already during spontaneous breathing during anesthesia with a slight further increase with mechanical ventilation (mainly explained by the end-expiratory exposure in the paralyzed subject whereas during spontaneous breathing the exposure covers most of the breath). Note also that the anesthesia-induced atelectasis remains for some time in the postoperative period. The *large gray area* in the middle of the right lung field (to the left in the CT image) is the diaphragm and liver that have been moved cranially during anesthesia. (Redrawn from [23])

patients with chronic obstructive lung disease show less, or even no, atelectasis during the 45 min of anesthesia of study [32]. The mechanism that prevents the lung from collapsing is not clear, but it may be airway closure occurring before alveolar collapse takes place or an altered balance between the chest wall and the lung that counters a decrease in the lung dimensions.

There is a good correlation between the amount of atelectasis and pulmonary shunt as measured by the multiple inert gas elimination technique. The regression equation based on 45 patients studied during inhalational anesthesia has been calculated as: shunt=0.8 ×atelectasis +1.7 (r=0.81, p<0.01), with atelectasis as a percentage of the lung area just above the diaphragm on CT and shunt as a percentage of cardiac output. Interestingly, shunt did not increase with age [7]. Combining CT and single photon emission computed tomography confirms the distribution of shunt and its location within the atelectatic area [33] (Fig. 4).

Airway closure

In addition to atelectasis, intermittent closure of airways can be expected to reduce the ventilation of dependent lung regions. Such lung regions may then become "low V_A/Q" units if perfusion is maintained or not reduced to the same extent as ventilation. Airway closure increases with age [34] (see also Fig. 2) as does the perfusion to "low V_A/Q" regions [7]. Since anesthesia causes an FRC reduction by 0.4–0.5 l [35], it may be anticipated that airway closure becomes even more prominent in the anesthetized subject. There is accumulating evidence that this is indeed the case [36, 37, 38]. The reduced ventilation in the lower half of the lung just above the atelectasis that can be seen in Fig. 4 is thus reasonably explained by airway closure. It can also be seen that ventilation is smaller than perfusion, causing "low V_A/Q" regions. These contribute to impaired oxygenation during the anesthesia.

As much as 74% of the impaired arterial oxygenation can be explained by atelectasis and airway closure taken together, according to the equation [39]: P_aO_2 (mmHg)= 218–22 ×ln atelectasis (cm^2)–0.06 (CV–ERV) (ml)

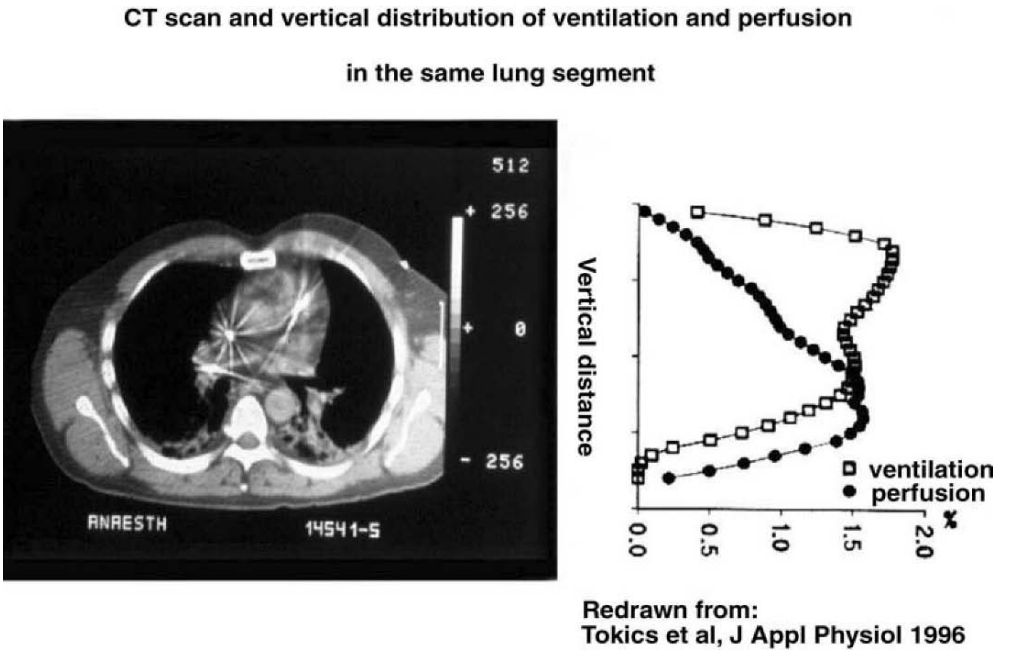


Fig. 4 Transverse computed tomography with atelectasis visible in the dependent parts of both lungs (*left*) and corresponding vertical distributions of ventilation and lung blood flow by isotope technique (single photon emission computed tomography, *right*) in an anesthetized subject. Note that ventilation is distributed preferentially to upper lung regions, contrary to what is normally seen in the waking subject. Note also the decreasing ventilation in the lower part and the complete cessation of ventilation in the bottom, corresponding to the atelectatic area. Perfusion, on the other hand, increases down the lung, except for the bottom-most region where a decrease is seen (so-called "zone IV"). (Redrawn from [28])

(r=0.86, p<0.001) where (CV−ERV) indicates the amount of airway closure occurring above FRC, CV is closing volume, and ERV is expiratory reserve volume. A simple three-compartment lung model can thus be constructed to explain oxygenation impairment during anesthesia. The model consists of one compartment with "normal" ventilation and perfusion, one with airway closure that impedes ventilation, and one of collapsed lung with no ventilation at all. This is shown in Fig. 1 together with the subsequent impact on the V_A/Q distribution.

Anesthesia vs. muscle paralysis

How much of the lung function impairment is produced by the anesthetic and how much by the muscle paralysis? Interestingly, the anesthetic per se causes a fall in FRC despite the maintenance of spontaneous breathing [20, 40]. The addition of muscle paralysis does not produce a further drop in FRC. Since airway closure and atelectasis depends on the lung volume the findings suggest that most of the impairment is caused by the anesthesia per se [2]. Figure 3 shows the appearance of atelectasis during spontaneous breathing with no significant increase with muscle paralysis. However, there may be a difference between spontaneous and mechanical ventilation; that is, the spontaneous breath may have a different effect on the aeration of the lung than the mechanically delivered. The diaphragm during the active respiration moves with the dorsal, dependent part making the largest excursions whereas during passive ventilation the anterior, nondependent part is pushed away more than other regions [41]. The spontaneous breath may therefore recruit collapsed tissue in the bottom of the lung better than the mechanical breath. The CT sequence in Fig. 3 does not provide substantial support to this, and it may be that any positive effect is that recruited tissue stays open with spontaneous breathing whereas slow derecruitment occurs with mechanical breaths. This remains to be tested.

Anesthesia vs. acute respiratory distress syndrome

Hallmarks of acute respiratory failure and its most severe form, acute respiratory distress syndrome (ARDS), are hypoxemia, reduced respiratory compliance, and atelectasis/consolidation as seen on CT of the lung [42, 43]. There are indeed qualitative similarities between anesthesia and ARDS, however with much more severe changes in ARDS. Widespread but mainly dependent lung regions collapse under their own weight, causing atelectasis. In addition, alveoli may become fluid filled. However, can it be that the treatment of ARDS per se adds to the atelectasis? This is indeed rather likely. Loss of

muscle tone, as caused by muscle relaxants, anesthetics, and sedatives, and the use of high oxygen concentration in inspired gas are the prerequisites to produce atelectasis in the lung healthy subject during anesthesia. This is common treatment in ARDS and certainly adds to the collapse and consolidation caused by the disease itself. Maintenance of muscle tone and modest use of supplemental oxygen may be a better approach to treatment than abuse of muscle depressants and oxygen. There is hardly any confirmation of beneficial effects of supranormal oxygen tension in blood, but it is frequently seen in the treatment of ARDS!

Prevention of atelectasis during anesthesia

There are several interventions that can help prevent atelectasis or even reopen collapsed tissue. These are discussed below.

PEEP

The application of 10 cmH_2O positive end-expiratory pressure (PEEP) has been tested in several studies and been shown consistently to reopen collapsed lung tissue. This is more likely an effect of increased inspiratory airway pressure than of PEEP per se [26, 44]. However, some atelectasis persists in most patients. Whether further increase in the PEEP level reopens this tissue was not analyzed in these studies. PEEP, however, appears not to be the ideal procedure. First, shunt is not reduced proportionately, and arterial oxygenation may not improve significantly. Hewlett and coworkers [45] warned as early as 1974 of the "indiscriminate use of PEEP in routine anesthesia." The persistence of shunt may be explained by a redistribution of blood flow towards more dependent parts of the lungs when intrathoracic pressure is increased by PEEP. Under such circumstances any persisting atelectasis in the bottom of the lung receives a larger share of the pulmonary blood flow than without PEEP [46]. Also, increased intrathoracic pressure impedes venous return and decreases cardiac output. This results in a lower venous oxygen tension for a given oxygen uptake and reduces arterial oxygen tension [8]. Second, the lung recollapses rapidly after discontinuation of PEEP. Within 1 min after cessation of PEEP the collapse is as large as it was before the application of PEEP [26].

Maintenance of muscle tone

The use of an anesthetic that allows maintenance of respiratory muscle tone prevents the formation of atelectasis. Ketamine does not impair muscle tone and does not cause atelectasis. This is the only anesthetic so far tested that does not cause collapse. However, if muscle relaxation is required, atelectasis appears as with other anesthetics [22]. Another attempt is to restore respiratory muscle tone by pacing of the diaphragm. This was tested by applying phrenic nerve stimulation, which did reduce the atelectatic area [47]. The effect, however, was small, and this technique is certainly too complicated to be used as a routine during anesthesia and surgery.

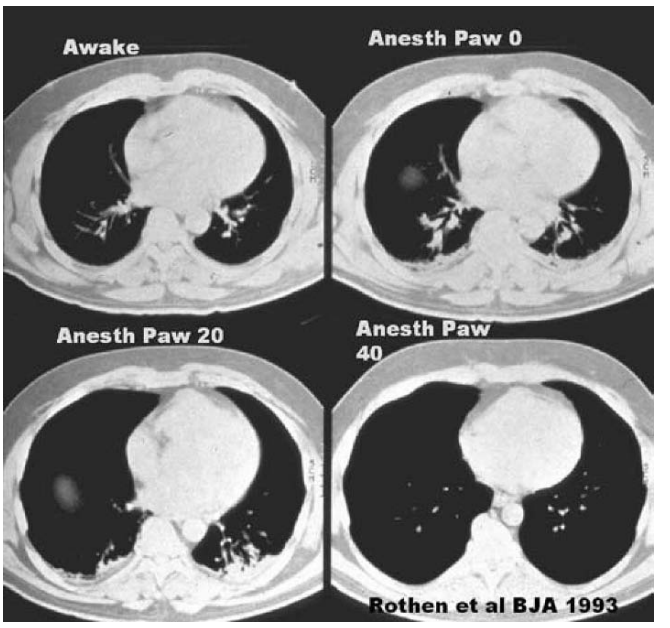


Fig. 5 Computed tomography in a patient awake (*left upper*) during anesthesia at zero airway pressure (*Paw*), i.e., after a normal expiration (*right upper*), after an inflation to Paw 20 (*left lower*) and 40 cmH_2O (*right lower*) and a breath hold of 15 s. Note the appearance of atelectasis in the dorsal part of the lungs during anesthesia and the persistence of the atelecatsis even with inflation to 20 cmH_2O. Not until Paw was increased to 30 cmH2O did some of the atelectasis reopen. A Paw of 40 cmH_2O was required to open up all atelectasis (From [48] with permission from the publisher)

Recruitment maneuvers

The use of a sigh maneuver, or a double tidal volume, has been advocated to reopen any collapsed lung tissue [48]. However, the atelectasis is not decreased by tidal volume or by a sigh up to an airway pressure of 20 cmH_2O. Not until an airway pressure of 30 cmH_2O is reached does the atelectasis decrease to approximately one-half the initial size. Complete reopening of all collapsed lung tissue requires an inflation pressure of 40 cmH_2O (Fig. 5) [48]. Such a large inflation corresponds to a maximum spontaneous inspiration and can thus be called a vital capacity maneuver.

Because the vital capacity maneuver may result in adverse cardiovascular events, the dynamics in resolving atelectasis during such a procedure was analyzed [49]. It

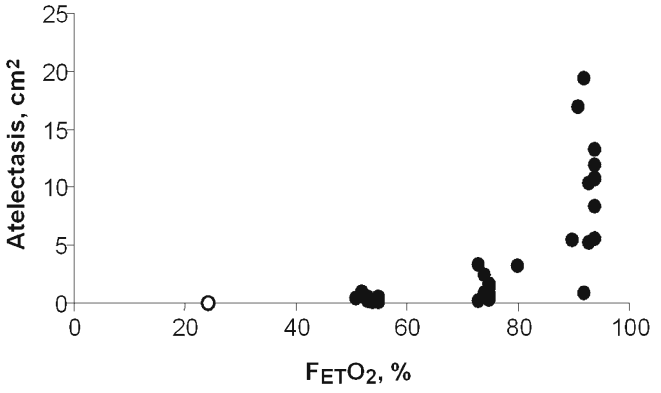


Fig. 6 Atelectasis near the diaphragm in individual patients (*filled circles*) after induction of anesthesia and a period of apnea in relation to their endtidal O_2 concentration ($F_{ET}O_2$) just before the period of apnea. The results are compared with data (*open circle*) [51] in which subjects were ventilated with 30% oxygen in nitrogen (From [52] with permission from the publisher)

was found that in adults with healthy lungs inflation of the lungs to +40 cmH_2O maintained for no more than 7–8 s may reexpand all previously collapsed lung tissue.

Minimizing gas resorption

Ventilation of the lungs with pure oxygen after a vital capacity maneuver that had reopened previously collapsed lung tissue has been shown to result in a rapid reappearance of the atelectasis [50]. If, on the other hand, 40% O_2 in nitrogen is used for ventilation of the lungs, atelectasis reappears slowly, and 40 min after the vital capacity maneuver only 20% of the initial atelectasis has reappeared. Thus ventilation during anesthesia should be carried out with a moderate FIO_2, for example., 0.3–0.4, and be increased only if arterial oxygenation is compromised.

The striking effects of oxygen during anesthesia raised the question of whether the preoxygenation during induction of anesthesia affects atelectasis formation. The breathing of 100% O_2 for only a few minutes before and during the commencement of anesthesia increases the safety margin in the event of a difficult intubation of the airway with prolonged apnea. However, there proves to be a prize for this. Avoidance of the preoxygenation procedure (ventilation with 30% O_2) eliminates atelectasis formation during the induction and subsequent anesthesia [51]. In a recent study, 12 patients breathed 100% O_2 during the induction of anesthesia, 12 80% O_2, and 12 60% O_2 [52]. Atelectasis appeared in all patients on 100% O_2 and was much less in the 80% O_2 group and almost absent in the 60% O_2 group (Fig. 6).

Preliminary data from our own experiments show that with induction of anesthesia during 100% preoxygenation atelectasis occurs within 7 min and continues to increase in extent for at least another 7 min. Very little was seen after 4 min, suggesting that there is a narrow time window after the induction and the intubation of the airway when no collapse yet has occurred, and that might be prevented by a deep breath with more modest oxygen concentration, the make-up gas being nitrogen. That rather subtle changes in the preoxygenation procedure and anesthesia regime can prevent substantial atelectasis formation with potential decrease in postoperative lung complications is likely but requires further study.

In summary, rapid collapse of alveoli on induction of anesthesia and more widespread closure of airways seem to explain oxygenation impairment during anesthesia. They may also contribute to postoperative pulmonary infection. Causative mechanisms seem to be a loss of respiratory muscle tone and gas resorption. Avoiding high inspired oxygen fractions during both induction and maintenance of anesthesia prevents or reduces atelectasis, while intermittent "vital capacity" maneuvers recruit atelectatic lung regions.

References

1. Nunn JF (1993) Nunn's applied respiratory physiology, 4th edn. Heinemann, Oxford
2. Strandberg Å, Tokics L, Brismar B, Lundquist H, Hedenstierna G (1986) Atelectasis during anesthesia and in the postoperative period. Acta Anaesthesiol Scand 30:154–158
3. McAlister FA, Bertsch K, Man J, Bradley J, Jacka M (2005) Incidence of and risk factors for pulmonary complications after nonthoracic surgery. Am J Respir Crit Care Med 171:514–547
4. Squadrone V, Coha M, Cerutti E, Schellino MM, Biolino P, Occella P, Belloni G, Vilianis G, Fiore G, Cavallo F, Ranieri VM, Piedmont Intensive Care Units Network (PICUN) (2005) Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. JAMA 293:589–595
5. Lindberg P, Gunnarsson L, Tokics L, Secher E, Lundquist H, Brismar B, Hedenstierna G (1992) Atelectasis, gas exchange and lung function in the postoperative period. Acta Anaesthesiol Scand 36:546–553
6. Berggren SM (1942) The oxygen deficit of arterial blood caused by nonventilating parts of the lung. Acta Physiol Scand Suppl 2
7. Gunnarsson L, Tokics L, Gustavsson H, Hedenstierna G (1991) Influence of age on atelectasis formation and gas exchange impairment during general anesthesia. Br J Anaesth 66:423–432
8. West JB (1977) State of the art: Ventilation-perfusion relationships. Am Rev Respir Dis 116:919–943
9. Dantzker DR, Wagner PD, West JB (1975) Instability of lung units with low V_A/Q ratios during O_2 breathing. J Appl Physiol 38:886–895

10. Wagner PD, Saltzman HA, West JB (1974) Measurement of continuous distributions of ventilation-perfusion ratios: theory. J Appl Physiol 36:588–599
11. Rehder K, Knopp TJ, Sessler AD, Didier EP (1979) Ventilation-perfusion relationship in young healthy awake and anesthetized-paralyzed man. J Appl Physiol 47:745–753
12. Prutow RJ, Dueck R, Davies NJH, Clausen J (1982) Shunt development in young adult surgical patients due to inhalation anesthesia. Anesthesiology 57:A477
13. Bindslev L, Hedenstierna G, Santesson J, Gotlieb I, Carvallhas A (1981) Ventilation-perfusion distribution during inhalation anaesthesia. Effect of spontaneous breathing, mechanical ventilation and positive end-expiratory pressure. Acta Anaesthesiol Scand 25:360–371
14. Sykes MK, Loh L, Seed RF, Kafer ER, Chakrabarti NK (1972) The effects of inhalational anaesthetics on hypoxic pulmonary vasoconstriction and pulmonary vascular resistance in the perfused lungs of the dog and cat. Br J Anaesth 44:776–788
15. Bjertnaes LJ (1977) Hypoxia induced vasoconstriction in isolated perfused lungs exposed to injectable or inhalational anaeshtetics. Acta Anaesthesiol Scand 21:133–147
16. Marshall BE (1989) Effects of anesthetics on pulmonary gas exchange. In: Stanley TH, Sperry RJ (eds) Anesthesia and the lung. Kluwer, London, pp 117–125
17. Miller FL, Chen L, Malmkvist G et al (1989) Mechanical factors do not influence blood flow distribution in atelectasis. Anesthesiology 70:481–488
18. Dantzker DR, Wagner PD, West JB (1975) Instability of lung units with low VA/Q ratios during O2 breathing. J Appl Physiol 38:886–895
19. Wahba RWM (1991) Perioperative functional residual capacity. Can J Anaesth 38:384–400
20. Westbrook PR, Stubbs SE, Sessler AD, Rehder K, Hyatt RE (1973) Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. J Appl Physiol 34:81–86
21. Tusiewicz K, Bryan AC, Froese AB (1977) Contributions of changing rib cage diaphragm interactions to the ventilatory depression of halothane anesthesia. Anesthesiology 47:327–337
22. Tokics L, Strandberg A, Brismar B, Lundquist H, Hedenstierna G (1987) Computerized tomography of the chest and gas exchange measurements during ketamine anaesthesia. Acta Anaesthesiol Scand 31:684–692
23. Don H (1977) The mechanical properties of the respiratory system during anesthesia. Int Anesthesiol Clin 15:113–136
24. Rehder K, Sessler AD, Marsh HM (1975–1976) General anesthesia and the lung. In: Murray JF (ed) Lung disease state of the art. American Lung Association, New York, pp 367–389
25. Bendixen HH, Hedley-Whyte J, Laver MB (1963) Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: a concept of atelectasis. N Engl J Med 269:991–996
26. Brismar B, Hedenstierna G, Lundquist H, Strandberg A, Svensson L, Tokics L (1985) Pulmonary densities during anesthesia with muscular relaxation: a proposal of atelectasis. Anesthesiology 62:422–428
27. Damgaard Pedersen K, Qvist T (1980) Pediatric pulmonary CT-scanning. Anesthesia-induced changes. Pediatr Radiol 9:145–148
28. Hedenstierna G, Lundquist H, Lundh B, Tokics L, Strandberg A, Brismar B, Frostell C (1989) Pulmonary densities during anaesthesia. An experimental study on lung histology and gas exchange. Eur Respir J 2:528–535
29. Kaam AH van, Lachmann RA, Hertig E, De Jaegere A, van Iwaarden F, Noorduyn LA, Kok JH, Haitsma JJ, Lachmann B (2004) Reducing atelectasis attenuates becterial growth and translocation in experimental pneumonia. Am J Respir Crit Care Med 169:1046–1053
30. Tenling A, Hachenberg T, Tydén H, Wegenius G, Hedenstierna G (1998) Atelectasis and gas exchange after cardiac surgery. Anesthesiology 89:371–378
31. Strandberg Å, Tokics L, Brismar B, Lundquist H, Hedenstierna G (1987) Constitutional factors promoting development of atelectasis during anesthesia. Acta Anaesthesiol Scand 31:21–24
32. Gunnarsson L, Tokics L, Lundquist H, Brismar B, Strandberg Å, Berg B, Hedenstierna G (1991) Chronic obstructive pulmonary disease and anesthesia: formation of atelectasis and gas exchange impairment. Eur Respir J 4:1106–1116
33. Tokics L, Hedenstierna G, Svensson L, Brismar B, Cederlund T, Lundquist H, Strandberg A (1996) V/Q distribution and correlation to atelectasis in anesthetized paralyzed humans. J Appl Physiol 81:1822–1833
34. Leblanc P, Ruff F, Milic-Emili J (1970) Effects of age and body position on "airway closure" in man. J Appl Physiol 28:448–451
35. Wahba RWM (1991) Perioperative functional residual capacity. Can J Anaesth 38:384–400
36. Hedenstierna G, McCarthy G, Bergstrom M (1976) Airway closure during mechanical ventilation. Anesthesiology 44:114–123
37. Juno P, Marsh M, Knopp TJ, Rehder K (1978) Closing capacity in awake and anesthetized-paralyzed man. J Appl Physiol 44:238–244
38. Dueck R, Prutow RJ, Davies NJH, Clausen J, Davidson TM (1988) The lung volume at which shunting occurs with inhalation anesthesia. Anesthesiology 69:854–861
39. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G (1998) Airway closure, atelectasis and gas exchange during general anaesthesia. Br J Anaesth 81:681–686
40. Hedenstierna G, Jarnberg PO, Gottlieb I (1981) Thoracic gas volume measured by body plethysmography during anesthesia and muscle paralysis: description and validation of a method. Anesthesiology 55:439–443
41. Froese AB, Bryan CH (1974) Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242–255
42. Gattinoni L, Pesenti A, Bombino M et al (1988). Relationships between lung computed tomographic.density, gas exchange, and PEEP in acute respiratory failure. Anesthesiology 69:824–832
43. Puybasset L, Cluzel P, Chao N et al (1998) A computed tomography scan assessment of regional lung volume in acute lung injury. The CT Scan ARDS Study Group. Am J Respir Crit Care Med 158:1644–1655
44. Tokics L, Hedenstierna G, Strandberg A, Brismar B, Lundquist H (1987) Lung collapse and gas exchange during general anesthesia: Effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. Anesthesiology 66:157–167
45. Hewlett AM, Hulands GH, Nunn JF, Milledge JS (1974) Functional residual capacity during anesthesia III: Artificial ventilation. Br J Anaesth 46:495–503
46. West JB, Dollery CT, Naimark A (1964) Distribution of blood flow in isolated lung: relations to vascular and alveolar pressure. J Appl Physiol 19:13–24

47. Hedenstierna G, Tokics L, Lundquist H, Andersson T, Strandberg Å, Brismar B (1994) Phrenic Nerve Stimulation during Halothane Anesthesia. Anesthesiology 80:751–760
48. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G (1993) Re-expansion of atelectasis during general anesthesia: a computed tomography study. Br J Anaesth 71:788–795
49. Rothen HU, Neumann P, Berglund JE, Valtysson J, Magnusson A, Hedenstierna G (1999) Dynamics of re-expansion of atelectasis during general anaesthesia. Br J Anaesth 82:551–556
50. Rothen HU, Sporre B, Engberg G, Wegenius G, Hogman M, Hedenstierna G (1995) Influence of gas composition on recurrence of atelectasis after a re-expansion maneuver during general anesthesia. Anesthesiology 82:832–842
51. Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G (1995) Prevention of atelectasis during general anesthesia. Lancet 345:1387–1391
52. Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G (2003) Optimal oxygen concentration during induction of general anesthesia. Anesthesiology 98:28–33

Sophie Lanone
Camille Taillé
Jorge Boczkowski
Michel Aubier

Diaphragmatic fatigue during sepsis and septic shock

The diaphragm is the primary muscle of respiration, and severe dysfunction of the diaphragm, consisting of decreased maximal force production and increased susceptibility to fatigue, has been documented in animal models of sepsis. A large number of studies have examined the effects of endotoxemia and other sepsis models on diaphragm contractility in spontaneously breathing animals.

Introduction

In the United States sepsis annually affects 700,000 people and accounts for about 210,000 deaths. Respiratory failure has long been known to be a frequent occurrence of this pathological condition and to represent a major contributor to the high associated mortality [1]. This contribution discusses of the effects of sepsis and septic shock on respiratory muscle function and focuses on some of the possible mechanisms involved in the genesis of these effects.

For nearly a century sepsis has been defined as the systemic host response to infection. A consensus definition was formulated a decade ago [2], and the list of symptoms has recently been updated [3]. Sepsis is now defined as infection with evidence of systemic inflammation, with at least two of the following: increased or decreased temperature or leukocyte count, tachycardia, and rapid breathing. In this context septic shock is defined as a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes [3]. Interestingly, the spectrum of responsible micro-organisms seems to have shifted from Gram-negative bacteria in the late 1970s to Gram-positive ones at present [4]. This is an important fact to point out since studies evaluating the effects of sepsis and septic shock on respiratory muscle function have been performed in animal models of sepsis, where Gram-negative bacteria have mainly been used as the infectious agent.

Respiratory muscle dysfunction during sepsis

Twenty years ago Hussain and associates [5] first demonstrated in spontaneously breathing dogs that endotoxic shock resulted in respiratory muscle fatigue, which in turn was the main factor responsible for respiratory failure and death in this experimental model of septic shock (*Escherichia coli* administration). Occurrence of respiratory muscle dysfunction in endotoxic shock has also been reported by our laboratory in mechanically ventilated rats [6]. In this study we observed decreased diaphragmatic strength restricted to the transdiaphragmatic pressure (Pdi) generated at high frequencies of phrenic nerve stimulation (50 and 100 Hz) while both twitch and low frequency Pdi and muscle relaxation rate remained unchanged. Endurance capacity of the diaphragm was curtailed in endotoxemic animals. Contractile dysfunction was associated with a decreased diaphragmatic resting membrane potential. This phenomenon, which has been reported in critically ill patients with various diseases [7] and in septic animal models [8], could impair action potential generation resulting in failure of neuromuscular transmission due to a postsynaptic membrane depolarization and an impaired propagation of electrical excitation along diaphragmatic fibers.

A major common point between the two studies cited above is that blood pressure was significantly reduced in

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_56, © Springer-Verlag Berlin Heidelberg 2009

septic animals. It is well known that blood pressure is a major determinant of muscle metabolic substrate delivery and contractile function. The results of Hussain and coworkers [5] are very similar to those reported by Aubier and coworkers [9] in nonseptic hypotensive spontaneously breathing dogs. The similarity in findings raises the question of the role of hypotension in the pathophysiology of the immediate effects of sepsis on respiratory muscle function, which could be of particular importance in the context of septic shock.

Murphy and associates [10] evaluated the role of Gram-positive bacterial products in muscle dysfunction in 4-week-old piglets. These authors investigated in spontaneously breathing animals the effects on diaphragmatic strength of a continuous infusion of group B streptococcus at a level that caused a decrease in cardiac output, but which avoided hypotension. Diaphragmatic strength was evaluated by measuring Pdi generated during bilateral phrenic stimulation. The main result of this study was that Pdi remained unchanged in septic animals over a 4-h period. However, another study from the same laboratory [10] showed that increasing the dose of streptococcus while avoiding significant hypotension resulted in a transitory but significant decrease in diaphragmatic strength. Hurtado and coworkers [11] investigated the role of hypotension in peripheral muscle dysfunction during sepsis. These authors evaluated the effects of a similar level of septic and nonseptic hypotension on peripheral muscle metabolism and strength generation in rabbits. Blood pressure decreased by approx. 22% of baseline values in both groups of animals. This study showed that by the end of the experiment (180 min after the onset of hypotension) hind-limb force was significantly reduced in septic animals for all the frequencies of stimulation. However, a similar reduction was observed in nonseptic animals. Taken together, these studies suggest that both hypotension and bacterial products make individual contributions to the genesis of the immediate deleterious effects of sepsis on respiratory muscle function. It is unclear whether septic hypotension has none, additive, or synergic effects (in terms of diaphragm dysfunction) with respect to nonseptic hypotension. To our knowledge, no data are available in the literature examining at the same time both septic and nonseptic hypotension. One can imagine that an animal model supporting both septic and nonseptic hypotension would be extremely difficult to manage.

Once the first reports on the immediate effects of sepsis on respiratory muscle function were published, investigators began to be interested also by the consequences of septic processes lasting several days. Using an in vivo rat model we evaluated the modifications in diaphragmatic function 3 days after *Streptococcus pneumoniae* injection [12] and 2 days after inoculation of *E. coli* endotoxin [13]. Both inoculations were performed subcutaneously, and both models of sepsis were nonlethal, with no change in blood pressure, serum electrolytes and acid-base status. The results of these studies were similar: 2 or 3 days of experimental sepsis in rats impaired diaphragmatic function without affecting muscle mass or histology. Contractile force in response to phrenic stimulation was reduced without a concomitant decrease in the electrical activity of the muscle. Muscle relaxation rate was prolonged, and the diaphragms of septic animals fatigued rapidly in response to a stimulation regimen that was without effect on the diaphragms of control animals.

Similar results were reported by Shindoh and coworkers [14] in *E. coli* endotoxin-inoculated hamsters. More recently Krause and coworkers [15] and Matzcuzak and collaborators [16] showed a decreased diaphragmatic force in experimental models of pancreatitis, suggesting that patients suffering from such disease may be susceptible to respiratory muscle failure. Finally, Drew and associates [17] examined the effects of a chronic infection lasting several weeks, visceral leishmaniasis, on the function of the diaphragm and the peripheral muscles soleus and plantaris. Muscular function was assessed in vitro. Infected animals (intracardiac inoculation of *Leishmania donovani* amastigotes) were maintained for 7–12 weeks until advanced disease characterized by anorexia, weight loss, and weakness was evident. Body weight and the mass of the diaphragm, soleus, and plantaris were reduced in septic animals. Absolute contractile force of the diaphragm and soleus muscles was moderately reduced, and only to the extent that muscle mass was decreased. Force normalized to muscle mass or cross-sectional area was not impaired. In contrast, the force of the plantaris, a fast twitch muscle, was severely reduced even after correcting for loss of muscle mass. The effects of leishmaniasis on the diaphragm and soleus muscles did not differ from those of semistarvation with equivalent weight loss, but these models of sepsis produced much greater loss in plantaris force than occurred with semistarvation.

To summarize, the last 20 years have brought multiple evidence and some explanation regarding the occurrence of severe dysfunction of the diaphragm in animal models of sepsis, dysfunction consisting in decreased maximal force production, and an increased susceptibility to fatigue.

Mechanisms of respiratory muscle dysfunction during sepsis

The underlying mechanisms of respiratory muscle dysfunction occurring during the early phase and after several days of sepsis are certainly different. They encompass energetic and metabolic components as well as the implication of mediators such as prostaglandins, cytokines, reactive oxygen species (ROS), and nitric oxide [18].

Energetics

From a general point of view respiratory muscle dysfunction is thought to occur when blood supply of energetic subtracts to the muscle is not sufficient to meet the muscle's metabolic needs [19]. The efficiency of energy minus uptake by these muscles depends mainly upon the total blood flow that reaches them, the conditions of perfusion of the microvascular network, and the ability of muscle cells to utilize metabolic substrates. All of these processes can be altered by the septic condition.

The septic state is characterized by generalized blood flow misdistribution among the different organs including the respiratory muscles. However, this phenomenon is modulated by the degree of contractile activity. Either immediately or lately after the beginning of the septic process, blood flow decreases if the diaphragm is at rest [5] and increases if it contracts [20]. The increase in respiratory muscles blood flow during septic shock can reach dramatic levels, resulting in reduced blood flow to the brain, gastrointestinal tract, and other skeletal muscles [5]. It is predictable that in this state the function of the vital organs other than the respiratory muscles is compromised. However, in spite of this finding the values for diaphragmatic blood flow observed during septic shock are much lower than the maximum reported in normotensive conditions [5]. Therefore, although diaphragmatic blood flow is significantly increased during sepsis, a septic-induced limitation to the maximal blood flow is operational. This limitation can occur at the microcirculatory level. Using an in vivo experimental model in rats we have shown that the number of perfused-diaphragmatic capillaries decreases significantly after *E. coli* endotoxin inoculation [21]. In addition to the microcirculatory limitation in metabolic substrates delivery to the respiratory muscles, the ability of muscle cells to utilize metabolic substrates is compromised in sepsis. *E. coli* endotoxin inoculation in rats induces an impairment in diaphragmatic mitochondrial respiration associated with an increased production of hydrogen peroxide [22, 23], secondary to induction of the inducible isoform of nitric oxide synthase (NOS II) in the muscle (see below).

For many years it has been recognized that the septic process is the result of extensive triggering of the body defense mechanisms by the invading micro-organisms and their products. Studies performed in the past 15 years have shown that respiratory muscle dysfunction during sepsis can be attributed to the actions of endogenously produced mediators, such as prostaglandins, cytokines, ROS, and NO.

Mediators

Several studies indicate that prostaglandins play a role in the development of peripheral skeletal muscle dysfunction during sepsis [24]. Elevated prostaglandin E_2 levels have been found in peripheral muscles of septic animals [25, 26], and pharmacological inhibition of prostaglandins synthesis has been shown to protect septic animals from peripheral skeletal muscle impairment [24]. In a similar line, we have found that the cyclooxygenase inhibitor indomethacin prevents the reduction in diaphragmatic strength found in *E. coli* endotoxemic animals [13]. In addition, this agent prevents peripheral muscles atrophy. Similar results have been reported by Murphy and coworkers [27] in septic piglets. The latter study found that systemic administration of thromboxane A_2 mimics the reduction in diaphragmatic strength observed in septic animals.

Among cytokines tumor necrosis factor (TNF) α has received substantial attention in the context of the septic process. In vitro studies show a dose-dependent decrease in diaphragmatic strength elicited by incubation of muscular fibers with murine or human TNF-α [28], with a synergistic effect of interleukin-1β on diaphragmatic contractility [29]. Furthermore, in vivo TNF-α induced a significant decrease in diaphragmatic force in dogs beginning 4 h after administration [30]. Inoculation of rats with *E. coli* endotoxin induced TNF-α mRNA expression in the diaphragm along with a decreased force [31], and pretreatment of the animals with an anti-murine TNF-α antibody prevented the deterioration in diaphragmatic contractile properties [31]. Together these findings suggest that TNF-α induces a decrease in diaphragmatic force generation. Different mechanisms may explain the effects of TNF-α on diaphragmatic contractility. Wilcox and coworkers [32] showed a role of prostaglandins and Reid and associated [33] demonstrated that TNF-α decreases force by blunting the response of muscle myofilaments to calcium activation. Whether these effects are mediated directly by TNF-α or indirectly by the induction of molecules such as ROS or NO (see below) warrants further investigation.

Reactive oxygen species

ROS are produced by all aerobic organisms as a consequence of oxygen consumption and cell respiration. They play a role of intracellular mediators at physiological concentrations, but in stress situations increasing production of ROS can lead to cellular injury. During sepsis the rate of ROS produced by respiratory muscles increases, releasing a large amount of superoxide anion, hydroxyl radical, and hydrogen peroxide [34]. This enhanced ROS production derives from different cellular compartments: one part of these ROS depends on mitochondrial chain respiration impairment following hemodynamic failure [35] while another part comes from sepsis-activated constitutive skeletal muscle NAD(P)H oxidase [36]. The participation of ROS in septic dia-

phragmatic failure has been clearly demonstrated in experimental models by the protective effect of antioxidant treatments, such as *N*-acetylcysteine [13], catalase, and superoxide dismutase [14]. Among the different ROS superoxide anion and hydroxyl radical are the two species that play the central role in reducing fibers calcium sensitivity and altering contractile protein capacity [37]. ROS reduce skeletal muscle force-generating capacity by inhibiting mitochondrial oxygen consumption, especially during ADP-stimulated (state 3) diaphragm mitochondrial oxygen utilization [23]. In septic patients an association has been found between antioxidant depletion, mitochondrial dysfunction and organ failure and outcome [38], underlying the importance of oxidative stress in generating energetic failure. Oxidants can structurally alter other, different components of excitation-contraction coupling system: T-tubules, sarcoplasmic reticulum calcium ATPase, and head of myosin oxidation (leading to inhibition of actin-myosin binding). Protein oxidation in skeletal muscle comes early during sepsis and is significantly correlated to the decline in mitochondrial respiration. Moreover, oxidized proteins are more sensitive to degradation. Proteolysis takes part to the development of muscular weakness observed in sepsis. Finally, myoglobin oxidation decreases oxygen storage capacity of the muscle.

Nitric oxide and its metabolites

NO is a secondary messenger molecule which participates in numerous biological processes, including vasodilatation, neurotransmission, and bronchodilatation. NO is synthesized by a group of enzymes referred to as NOS which are responsible of the conversion of L-arginine to L-citrulline and NO in presence of oxygen. Three NOS isoforms (I–III) have been identified so far, and they all are expressed in respiratory muscles, particularly in diaphragm [39, 40, 41]. In animal models of sepsis it has been extensively demonstrated that NOS II expression is induced in the diaphragm, both at mRNA and protein levels, with a resultant increase in NO production [41, 42, 43]. Several lines of evidence suggest that impaired diaphragmatic contractility is a result of NO overproduction during sepsis. Boczkowski et al. [41] were the first to propose a link between in vivo induction of diaphragmatic NOS II and its involvement in the genesis of diaphragmatic contractile dysfunction after *E. coli* endotoxin inoculation in rats. First, this study showed that the time course of NOS II induction in diaphragmatic myocytes and that of the decrease in diaphragmatic force are similar, and, second, that inhibition of NO synthesis by either N^{ω}-monomethyl-L-arginine (L-NMMA), an inhibitor of NOS activity, or dexamethasone, an inhibitor of NOS II induction, significantly improves the decrease in diaphragmatic force observed in endotoxemic animals. Similar results have been reported by El-Dwairi et al. [44] using *S*-methylisothiourea as NOS activity inhibitor. In an attempt to define the exact role of the different NOS isoforms in lipopolysaccharide (LPS) induced diaphragmatic contractile injury, two studies by Comtois and collaborators [45, 46] investigated their role in genetically engineered mice, knockouts (KO) for either NOS II or NOS I. Taken together, the findings of these studies suggest that both NOS I and NOS II isoforms play protective roles in attenuating LPS-induced reduction in diaphragmatic contractile function, despite leading, respectively, to a decreased and an increased NO synthesis. Interestingly, another study in NOS II KO mice [47], showed that LPS injection induces less tyrosine nitration than in wild-type mice, although deficiency for NOS I or NOS III does not affect this protein modification. This points out the great importance of the environment in which NO is synthesized. However, the mechanism(s) by which NO participates in the alteration of diaphragmatic contractile function remain(s) to be determined.

NO by itself has a deleterious effect on mitochondrial respiration, with the inhibition of several enzymes such as aconitase and cytochrome oxidase [48, 49]. This effect of NO may contribute to poor oxygen extraction observed in sepsis and thus participate in altered muscular function. Moreover, NO can produce its deleterious effects by its reaction with superoxide anion to form peroxynitrite anion ($ONOO^-$), a very strong oxidizing agent [50], which targets various molecules such as thiols, lipids, and proteins containing aromatic amino acids, and irreversibly inhibits several mitochondrial enzymes such as aconitase, NADH and succinate dehydrogenases, and superoxide dismutase [51, 52, 53]. Several authors have described peroxynitrite formation in the diaphragm of endotoxemic animals [41, 44, 47], mainly in the mitochondrial and membrane fractions of LPS-treated rats diaphragm [47], a treatment with L-NMMA leading to a diminished nitration of diaphragmatic mitochondrial proteins [22]. Finally, studies on the role of peroxynitrite on diaphragmatic contractile function show that in vitro exposure of muscular samples to peroxynitrite itself or peroxynitrite-generating agents leads to a decreased force generation [54]. It must be pointed out, however, that exogenously generated peroxynitrite, considering its short half-life at physiological pH [55], may not react in the same way as endogenously produced peroxynitrite. The exact relationship between peroxynitrite generation and contractile function impairment is not entirely clear, but one possible explanation lies in the oxidating and nitrating properties of peroxynitrite which can lead to the alteration of proteins involved in the contractile process, such as actin [56] and the sarcoplasmic reticulum Ca^{2+}-ATPase [57].

One mediator of interest could be cGMP, as it is widely known that NO activates the soluble guanylyl cyclase, leading to cyclic GMP synthesis [58]. Kobzik et al. [40] demonstrated that agents able to increase intra-

cellular cGMP content, such as 8-bromo cGMP, reverse the protective effect of NOS inhibitors on muscular force. However, in another study [41], activation of guanylyl cyclase observed in diaphragmatic muscle after LPS inoculation showed a biphasic time course; early activation appeared to be due to NO synthesized by NOS II, while late activation was independent of NO. Thus the exact role of cGMP in mediating the effects of NO in sepsis-induced diaphragmatic contractile dysfunction still remains to be elucidated. Finally, the pharmacological approach used by several authors brings some insights to better understand the exact role that NO could play in the alteration of respiratory muscle function. Inhibition of NOS activity, by administration of the NOS inhibitor N^{ϕ}-nitro-L-arginine methylester leads to a protection against the reduction in myofiber calcium sensitivity observed in endotoxemic rats [37]. Moreover, administration of L-NMMA, another NOS inhibitor, significantly reduces LPS-induced diaphragm sarcolemmal injury and alters resting membrane potential in rats [43]. This could have a direct effect on muscular function. It is important to mention in this context a study by Ebihara and coworkers [59] which determined the impact of mechanical ventilation on rat diaphragm sarcolemnal injury, NOS II expression, and oxidative stress during endotoxemia. These authors demonstrated that starting ventilation at the time of infusing endotoxin into rats partially prevents the impaired diaphragmatic contractility due to sepsis. Mechanical ventilation also prevented the injury to the sarcolemma of diaphragmatic cells [59], but surprisingly did not reduce the increase in expression of NOS II. This should not lead us to the conclusion that nitric oxide and oxidative stress are less important than in the context of muscle injury caused by sepsis. Indeed, in the same study [59], using an in vitro system to independently modulate oxidative and mechanical stresses, the authors demonstrated that these two factors act in a synergistic fashion to favor the occurrence of sarcolemmal injury.

Conclusion

There is no doubt that sepsis impairs the function of respiratory muscles. This impairment is observed soon after the onset of the septic process and may be still present after several weeks, depending on the duration of the infectious aggression. The precocious dysfunction is strongly related to the hypotension that can be present in this condition. In contrast, the later effects (days to weeks) appear to be independent of hemodynamic alterations and are connected to pathophysiological processes that need some time (days to weeks) to develop. From an integrated point of view it is possible to postulate that sepsis impairs respiratory muscle function by acting at two levels. The first is by disturbances at different steps of the chain of muscular energy supply: blood flow and metabolic substrate extraction and utilization. The second is a direct impairment of the contractile process. These effects of sepsis are probably the result of the action of septic mediators. The result is a complex series of effects on the respiratory muscles that have the potential for profound clinical consequences. Despite the recent advances in the field much remains to be learned, and several questions are still unresolved. Answers to these questions will allow the clinicians to better manage respiratory failure in septic patients and particularly the mechanical ventilation procedure. Recommendations for the use of mechanical ventilation during sepsis will depend substantially on the clinical status of the patient. Putting the respiratory muscles at rest when they are fatigued has been shown to be beneficial at least during the weaning process of mechanical ventilation. However, resting the respiratory muscles by mechanical ventilation could also be deleterious. The decision as to mechanical ventilation during sepsis should therefore be based on the respiratory as well as circulating parameters, both leading to respiratory failure.

References

1. Montgomery AB, Stager MA, Carrico CJ, Hudson LD (1985) Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 132:485–489
2. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knauss WA, Schein RMH, Sibbald WJ (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 101:1644–1655
3. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 31:1250–1256
4. Annane D, Bellissant E, Cavaillon JM (2005) Septic shock. Lancet 365:63–78
5. Hussain SNA, Simkus G, Roussos C (1985) Respiratory muscle fatigue: a cause of ventilatory muscle failure in septic shock. J Appl Physiol 58:2033–2040
6. Leon A, Boczkowski J, Dureuil B, Desmonts JM, Aubier M (1992) Effects of endotoxic shock on diaphragmatic function in mechanically ventilated rats. J Appl Physiol 72:1466–1472
7. Cunningham JN Jr, Carter NW, Rector FC Jr, Seldin DW (1971) Resting transmembrane potential difference of skeletal muscle in normal subjects and severely ill patients. J Clin Invest 50:49–59
8. Illner HP, Shires GT (1981) Membrane defect and energy status of rabbit skeletal muscle cells in sepsis and septic shock. Arch Surg 116:1302–1305

9. Aubier M, Trippenbach T, Roussos C (1981) Respiratory muscle failure during cardiogenic shock. J Appl Physiol 51:499–508
10. Murphy TD, Mayock DE, Standaert TA, Gibson RL, Woodrum DE (1992) Group B streptococcus has no effect on piglet diaphragmatic force generation. Am Rev Respir Dis 145:471–475
11. Hurtado FJ, Gutierrez AM, Silva N, Fernandez E, Khan AE, Gutierrez G (1992) Role of tissue hypoxia as the mechanism of lactic acidosis during E. coli endotoxemia. J Appl Physiol 72:1895–1901
12. Boczkowski J, Dureuil B, Branger C, Pavlovic D, Murciano D, Pariente R, Aubier M (1988) Effects of sepsis on diaphragmatic function in rats. Am Rev Respir. Dis 138:260–265
13. Boczkowski J, Dureuil B, Pariente R, Aubier M (1990) Preventive effects of indomethacin on diaphragmatic contractile alterations in endotoxemic rats. Am Rev Respir Dis 142:193–198
14. Shindoh C, Dimarco A, Nethery D, Supinski G (1992) Effect of PEG-Superoxide dismutase on the diaphragmatic response to endotoxin. Am Rev Respir Dis 145:1350–1354
15. Krause KM, Moody MR, Andrade FH, Taylor AA, Miller CC, 3rd, Kobzik L, Reid MB (1998) Peritonitis causes diaphragm weakness in rats. Am J Respir Crit Care Med 157:1277–1282
16. Matuszczak Y, Viires N, Allamedin H, Aubier M, Desmonts JM, Dureuil B (1999) Alteration in diaphragmatic function induced by acute necrotizing pancreatitis in a rodent model. Am J Respir Crit Care Med 160:1623–1628
17. Drew JS, Farkas GA, Pearson RD, Rochester DF (1988) Effects of a chronic wasting infection on skeletal muscle size and contractile properties. J Appl Physiol 64:460–465
18. Hussain S (1998) Respiratory muscle dysfunction in sepsis. Mol Cell Biochem 179:125–134
19. Supinski G (1986) Contol of respiratory muscles blood flow. Am Rev. Respir Dis 134:1078–1079
20. Ferguson JL, Spitzer JJ, Miller HI (1978) Effects of endotoxin on regional blood flow in the unanesthetized guinea pig. J Surg Res 25:236–243
21. Boczkowski J, Vicaut E, Aubier M (1992) In vivo effects of Escherichia coli endotoxemia on diaphragmatic microcirculation in rats. J Appl Physiol 72:2219–2224
22. Boczkowski J, Lisdero CL, Lanone S, Samb A, Carreras MC, Boveris A, Aubier M, Poderoso JJ (1999) Endogenous peroxynitrite mediates mitochondrial dysfunction in rat diaphragm during endotoxemia. FASEB J 13:1637–1646
23. Callahan L, Stofan D, Szweda L, Nethery D, Supinski G (2001) Free radicals alter maximal diaphragmatic mitochondrial oxygen consumption in endotoxin-induced sepsis. Free Radic Biol Med 30:129–138
24. Ruff RL, Secrist D (1984) Inhibitors of prostaglandin synthesis or cathepsin B prevent muscle wasting due to sepsis in the rat. J Clin Invest 73:1483–1486
25. Turinsky J, Loegering DJ (1985) Prostaglandin E2 and muscle protein turnover in Pseudomonas aeruginosa sepsis. Biochim Biophys Acta 840:137–140
26. Hasselgren PO, Talamini M, LaFrance R, James JH, Peters JC, Fischer JE (1985) Effect of indomethacin on proteolysis in septic muscle. Ann Surg 202:557–562
27. Murphy TD, Gibson RL, Standaert TA, Woodrum DE (1995) Diaphragmatic failure during group B streptococcal sepsis in piglets: the role of thromboxane A2. J Appl Physiol 78:491–498
28. Hopkins PM (1996) Human recombinant TNF alpha affects rat diaphragm muscle in vitro. Intensive Care Med 22:359–362
29. Wilcox PG, Bressler B (1992) Effects of tumor necrosis factor α on in vitro hamster diaphragm contractility (abstract). Am Rev Respir Dis 145:A457
30. Wakai Y, Wilcox P, Cooper J, Walley K, Road J (1991) The effect of tumor necrosis factor α: TNFα on diaphragmatic contractility in anesthetized dogs (abstract). Am Rev Respir Dis 143:A560
31. Shindoh C, Hida W, Ohkawara Y, Yamauchi K, Ohno I, Takishima T, Shirato K (1995) TNF-alpha mRNA expression in diaphragm muscle after endotoxin administration. Am J Respir Crit Care Med 152:1690–1696
32. Wilcox P, Milliken C, Bressler B (1996) High-dose tumor necrosis factor alpha produces an impairment of hamster diaphragm contractility. Attenuation with a prostaglandin inhibitor. Am J Respir Crit Care. Med 153:1611–1615
33. Reid MB, Lannergren J, Westerblad H (2002) Respiratory and limb muscle weakness induced by tumor necrosis factor-alpha: involvement of muscle myofilaments. Am J Respir Crit Care Med 166:479–484
34. Nethery D, DiMarco A, Stofan D, Supinski G (1999) Sepsis increases contraction-related generation of reactive oxygen species in the diaphragm. J Appl Physiol 87:1279–1286
35. Poderoso JJ, Peralta J, Lisdero C, Carreras M, Radisic M, Schopfer F, Cadenas E, Boveris A (1998) Nitric oxide regulates oxygen uptake and hydrogen peroxide release by the isolated beating rat heart. Am J Physiol 274:C112–C119
36. Javesghani D, Magder SA, Barreiro E, Quinn MT, Hussain SN (2002) Molecular characterization of a superoxide-generating NAD(P)H oxidase in the ventilatory muscles. Am J Respir Crit Care Med 165:412–418
37. Callahan L, Nethery D, Stofan D, DiMarco A, Supinski G (2001) Free radical-induced contractile protein dysfunction in endotoxin-induced sepsis. Am J Respir Cell Mol Biol 24:210–217
38. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies N, Cooper C, singer M (2002) Association between mitochondrial dysfunction and severity and outcome of septic shock. The Lancet 360:219–223
39. El Dwairi Q, Guo Y, Comtois A, Zhu E, Greenwood MT, Bredt DS, Hussain SNA (1998) Ontogenesis of nitric oxide synthases in the ventilatory muscles. Am J Respir Cell Mol Biol 18:844–852
40. Kobzik L, Reid MB, Bredt DS, Stamler JS (1994) Nitric oxide in skeletal muscle. Nature 372:546–548
41. Boczkowski J, Lanone S, Ungureanu-Longrois D, Danialou G, Fournier T, Aubier M (1996) Induction of diaphragmatic nitric oxide synthase after endotoxin administration in rats: role on diaphragmatic contractile dysfunction. J Clin Invest 98:1550–1559
42. Hussain S, Giaid A, El Dawiri Q, Sakkal D, Hattori R, Guo Y (1997) Expression of nitric oxide synthases and GTP cyclohydrolase I in the ventilatory and limb muscles during endotoxemia. Am J Respir Cell Mol Biol 17:173–180
43. Lin M-C, Ebihara S, El Dwairi Q, Hussain SNA, Yang L, Gottfried SB, Comtois A, Petrof BJ (1998) Diaphragm sarcolemnal injury is induced by sepsis and alleviated by nitric oxide synthase inhibition. Am J Respir Crit Care Med 158:1656–1663
44. El Dwairi Q, Comtois A, Guo Y, Hussain SN (1998) Endotoxin-induced skeletal muscle contractile dysfunction: contribution of nitric oxide synthases. Am J Physiol 274:C770–C779
45. Comtois A, El-Dwairi Q, Laubach V, Hussain S (1999) Lipopolysaccharide-induced diaphragmatic contractile dysfunction in mice lacking the inducible nitric oxide synthase. Am J Respir Crit Care Med 159:1975–1980
46. Comtois A, Barreiro E, Huang P, Marette A, Perrault M, Hussain S (2001) Lipopolysaccharide-induced diaphragmatic contractile dysfunction and sarcolemmal injury in mice lacking the neuronal nitric oxide synthase. Am J Respir Crit Care Med 163:977–982
47. Barreiro E, Comtois A, Gea J, Laubach V, Hussain S (2002) Protein tyrosine nitration in the ventilatory muscles. Role of nitric oxide synthases. Am J Respir Cell Mol Biol 26:438–446

48. Kobzik L, Stringer B, Balligand JL, Reid MB, Stamler JS (1995) Endothelial type nitric oxide synthase in skeletal muscle fibers: mitochondrial relationships. Biochem Biophys Res Commun 211:375–381
49. Cleeter MWJ, Cooper JM, Darley-Usmar VM, Moncada S, Schapira AHV (1994) Reversible inhibition of cytochrome c oxidase, the terminal enzyme of the mitochondrial respiratory chain, by nitric oxide. FEBS Lett 345:50–54
50. Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA (1990) Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci USA 87:1620–1624
51. Radi R, Rodriguez M, Castro L, Telleri R (1994) Inhibition of mitochondrial electron transport by peroxynitrite. Arch Biochem Biophys 308:89–95
52. Ischiropoulos H, Zhu L, Chen J, Tsai M, Martin JC, Smith CD, S. BJ (1992) Peroxynitrite-mediated tyrosine nitration catalyzed by superoxide dismutase. Arch Biochem Biophys 298:431–437
53. Poderoso JJ, Carreras MC, Lisdero C, Riobo N, Schopfer F, Boveris A (1996) Nitric oxide inhibits electron transfer and increases superoxide radical production in rat heart mitochondria and submitochondrial particles. Arch Biochem Biophys 328:85–92
54. Supinski G, Stofan D, Callahan LA, Nethery D, Nosek TM, DiMarco A (1999) Peroxynitrite induces contractile dysfunction and lipid peroxidation in the diaphragm. J Appl Physiol 87:783–791
55. Brunelli L, Crow JP, Beckman JS (1995) The comparative toxicity of nitric oxide and peroxynitrite to Escherichia coli. Arch Biochem Biophys 316:327–334
56. Hantler PD, Gratzer WB (1975) Effects of specific chemical modification of actin. Eur J Biochem 60:67–72
57. Viner RI, Hühmer AFR, Bigelow DJ, Schöneich C (1996) The oxidative inactivation of sarcoplasmic reticulum Ca 2+-ATPase by peroxynitrite. Free Radic Res 24:243–259
58. Moncada S, Higgs A (1993) The L-arginine-nitric oxide pathway. N Engl J Med 329:2002–2012
59. Ebihara S, Hussain S, Danialou G, Cho W, Gottfried S, Petrof B (2002) Mechanical ventilation protects against diaphragm injury in sepsis. Interaction of oxidative and mechanical stresses. Am J Respir Crit Care Med 165:221–228

Jean-Roger Le Gall

The use of severity scores in the intensive care unit

Background

Around 1980 several intensivists decided to score the severity of ICU patients in order to compare the populations and evaluate the results. The outcome of intensive care depends on several factors present on the first day in the ICU and on the patient's course under ICU therapy. The severity scores comprise usually two parts: the score itself and a probability model. The score itself is a number (the highest number, the highest severity). The probability model is an equation giving the probability of hospital death of the patients. This seminal comprise two parts: the classification of the scores and their practical use.

Classification of the severity scores

Many severity scores have been published but only a few are used. Most scores are calculated from data collected on the first ICU day; these include the Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), and Mortality Prediction Model (MPM). Others are repetitive and collect data every day throughout the ICU stay or for the first 3 days; these include the Organ System Failure (OSF), Organ Dysfunction and Infection System (ODIN), Sequential Organ Failure Assessment (SOFA), Multiple Organs Dysfunction Score (MODS), Logistic Organ Dysfunction (LOD) model, and Three-Day Recalibrating ICU Outcomes (TRIOS).

First-day ICU severity scores

Subjective scores

These scores are established by a panel of experts who choose the variables and assign a weight to each variable based on their personal opinion. For each variable a range of normality is defined, with a score of 0 within this range. The more abnormal the result, the higher the weight that is given, from 0 to 4 points. The total number of points constitutes the score. The most commonly used scoring system is APACHE II [1]. This includes variables such as age, preexisting diseases, and 12 acute physiological variables. This yields a probability of hospital death depending on the main diagnosis.

Objective scores

Development of a multipurpose probability model requires that a large database be compiled using data from many ICUs. Variables collected can generally be classified into four groups: age, comorbidities, physiological abnormalities, and acute diagnoses. Some systems have introduced variables designed to decrease the lead-time bias. The principal outcome for each of the systems is vital status at hospital discharge. Other outcome measures (e.g., vital status 28 days after hospital discharge or quality, life among long-term survivors) can also be modeled. Logistic regression modeling techniques, smoothing methods, and clinical judgment are used to select variables, determine ranges, and assign weights. All of the systems result in a logistic regression model that estimates the risk of death. In chronological order of

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_57, © Springer-Verlag Berlin Heidelberg 2009

publication the main objective scores are APACHE III [2], the SAPS II [3], and the MPM II [4].

APACHE III. This score uses largely the same variables as APACHE II but a different way in which to collect the neurological data, no longer using the Glasgow Coma Score. It adds particularly two important variables: the patient's origin and the lead-time bias. The acute diagnosis is taken into account; one diagnosis must be preferred.

SAPS II and the expanded SAPS II. The same technique was used to construct SAPS II. The database, however, was established from European and North American ICUs, and the acute diagnosis were not included. The authors considered it too difficult to select a single diagnosis for an ICU patient. As for other scoring systems the discrimination and particularly the calibration of the SAPS II model does not fit when applied to a new population. The model can be adapted to a country or a specific population by a customization process or by expansion of the model through the addition of new variables. For example, a revision of SAPS II has been proposed by Aergerter et al. [5]. Retrospective analysis of 33,471 prospectively collected multicenter data was performed in 32 ICUs located in the Paris aera. They developed two logistic regression models. The second one reevaluated items of SAPS II and integration of the preadmission location and chronic comorbidity. Another proposal was recently made by Le Gall et al. [6]. From a database of 77,490 admissions in 106 French ICUs they added six admission variables to SAPS II: age, sex, length of the ICU hospital stay, patient location before ICU, clinical category, and whether drug overdose was present. The statistical qualities of the expanded SAPS II are much better than those of the original and even the customized SAPS II. The original SAPS II mortality prediction model is outdated and needs to be adapted to current ICU populations. The original SAPS II may be used to score the ICU patients' severity. But to calculate the standardized mortality ratio or the ICU performance measure it is now necessary to use the expanded SAPS II Adding simple data, routinely collected, to the original SAPS II led to better calibration, discrimination, and uniformity-of-fit of the model. The statistical qualities of the expanded SAPS II are much better than those of the original and the customized SAPS II. Above all, the expanded SAPS II is easy to obtain from the existing databases. It is now the simplest system for precisely measuring ICU performance and comparing performance over years.

MPM II. In the case of the MPM II one has not a score but a model giving directly the probability of hospital death. This uses chronic health status, acute diagnosis, a few physiological variables, and some other variables including mechanical ventilation. The database is the same as that for the SAPS II. Four models have been proposed: MPM II at admission and at 24, 48, and 78 h.

SAPS 3. A worldwide database of 19,577 patients was used to develop SAPS III. It comprises three parts: chronic variables, acute variables including the sepsis and its characteristics, and physiology. The calculated probability of ICU and hospital death emerges by adding diagnoses to the model. Evaluation of ICU performance is adapted to each ICU according to its case-mix [7, 8].

Repetitive scores

Subjective scores

OSF. Data on five organ failures are included in the OSF system [9]. The main prognostic factors are the number and duration of these failures. Mortality is close to 100% when three organs failures persist for 5 days or longer.

ODIN. Fagon et al. [10] proposed the ODIN system in 1993. This includes data on six organ failures plus one infection and differentiates prognosis according to the type of failures.

SOFA. Published in 1998 by Vincent et al. [11], the SOFA subjective score was evaluated on 1,449 patients. Data on six failures are scored on a scale of 0–4. One failure plus a respiratory failure indicate the lowest mortality; all the other combinations yield a mortality between 65% and 74%. Subsequent analyses have considered the maximal score plus the maximal change and have shown that the latter has a lower prognostic value than the former.

Objective scores

MODS. In 1995 Marshall et al. [12] examined the definitional criteria of organ failures proposed in the literature and tested these criteria in a population of 692 patients. The result of their work, the MODS, comprises a score based on six failures each scored from 0 to 4. This considers the time of occurrence of each failure; respiratory failure was found to be the first (1.8±4.7 days) and hepatic failure the last (4.7±5.5 days). They showed that mortality depends non only on the admission score but also on course.

LOD model. This model based on the LOD is the only one based on logistic regression. From a European North American database 12 variables were tested and 6 organ failures defined [13]. The originality of the model is to give to each dysfunction a weight of 0–5 points. Severe neurological, cardiovascular, and renal failures are scored

5, severe respiratory failure 3, and severe hepatic failure 1. The model has been tested over time. The difference between the LOD scores on day 3 and day 1 is highly predictive of the hospital outcome.

TRIOS. A composite score using daily SAPS II and LOD score for predicting hospital hospitality in ICU patients hospitalized for more 72 h was proposed by Timsit et al. [14] in 2001. This TRIOS composite score has excellent statistical qualities and may be used for research purposes.

Model validation

Model performance must be demonstrated in a sample of patients independent of that used to develop the models. Validation samples have been assembled either by collecting data on a new cohort of patients or by randomly splitting an available database into two portions—one used to develop the model and the other to validate it [15].

Model calibration

Calibration evaluates the degree of correspondence between the estimated probabilities of mortality produced by a model and the actual mortality experienced by patients. Calibration can be statistically evaluated using formal goodness-of-fit tests [16]. What information does the assessment of calibration provide? If a model estimates that a set of patients have a probability of hospital mortality of 0.38, this means that among 100 such patients 38 would be expected to die and 62 to live. When the observed number of deaths is close to the number predicted by the model, it is considered to be well calibrated.

To test calibration formally patients are rank-ordered according to their probability of mortality and grouped into range-defined strata. Typically ten such strata are formed, each containing approximately the same number of patients (called "risk deciles"). To obtain the predicted number of deaths in a stratum, the probabilities of mortality for all patients in that stratum are summed. Formal goodness-of-fit testing compares the observed with the predicted number of deaths and the observed with the predicted number of survivors in each stratum of patients. The resulting value can be used to determine whether the combined discrepancy between observed and predicted outcome across all strata is within sampling variability. If differences are large, the model does not correctly reflect the outcome in that cohort of patients.

Model discrimination

Discrimination uses the area under the receiver operating characteristic (ROC) curve to evaluate the ability of a model to distinguish patients who die from patients who live, based on the estimated probabilities of mortality. To construct the ROC curve [17] a sequence of probability cutoff points is specified, and a 2×2 classification table of predicted and observed outcome is constructed for each cutoff. For example, if the cutoff is set at 0.35, any patient whose probability of mortality is 0.35 or higher would be predicted to die, whereas any patient whose probability is less than 0.35 would be predicted to live. Observed mortality is noted for each patient and from the resulting 2×2 table the false-positive and true-positive rates are determined. All these pairs of rates for the sequence of cutoff points are then plotted, resulting in the visual presentation of the ROC curve. The higher the true-positive rate is relative to the false-positive rate, the greater is the area under the ROC curve.

Interpretation of the area under the ROC curve is quite simple. If the entire sample were divided into patients who lived and patients who died, and each patient who lived were paired with each patient who died, there would be $n_1 \times n_0$ such pairs (where n_1 is the number of patients who lived and n_0 is the number who died). The area under the ROC curve is the proportion of the total number of pairs in which the model resulted in a higher probability for the patient who died than the patient who lived. Clearly, if the value is in the neighborhood of 0.50, the model performs no better than the flip of a coin. Developers of models are usually not satisfied unless the ROC area of a model exceeds 0.70.

Comparison of the models

Comparison provided by the developers

The latest generation of models (APACHE III, SAPS II, MPM II) have been evaluated by the developers. Ideally information would be available on calibration and discrimination in both the developmental and the validation samples. Except for the physiology component of APACHE III the system was developed using the entire sample, and therefore no independent validation sample results are reported in the publication which presents the system. Reported discrimination power of all three systems was excellent. In the total sample the area under the ROC curve was 0.90for APACHE III, 0.88 for SAPS II, and 0.84, 0.84, 0.81, and 0.79 for $MPM_{0,}$ MPM_{24}, MPM_{48}, and MPM_{72}, respectively, in the developmental samples. For SAPS II the area under the ROC curve was 0.86 in the validation sample and 0.82, 0.84, 0.80, and 0.75 in the validation samples for the four models of the MPM II. Information for evaluating the goodness-of-fit of APACHE III has been not reported. The calibration of the models in the SAPS II and MPM II systems indicated that all of the models fit the data well, as reflected by the close correspondence between the observed and predicted out-

comes across the entire range of probabilities. Calibration was excellent in the developmental samples for all of the SAPS II and MPM II models, and close correspondence between observed and predicted numbers of deaths was noted in the independent validation sample as well.

The qualities of models over time

The case-mix does not remain the same as the therapies evolve over time, and the selection of patients admitted to ICUs may differ over time, and therefore published scoring systems become obsolete. Usually the ROC curves remain good, but the validation, when the scores are applied to other populations, is poor. Depending on the score it may be useful to customize it to the respective population. To compare patient groups in a clinical study it is not necessary to charge the score used. For instance the SAPS II continues to be used in many scientific publications. To evaluate the performance of an ICU it is better to customize the score. There are two ways in which to do this: change the probability equation or the weight of each variable [18], or add new variables, which requires a further collection of data.

Practical use of the scores

Scoring systems have been proposed in use for individual patient prediction to evaluate the performance of ICUs and for therapeutic trials. In general, proposed uses for scores or probabilities can be considered at both the individual patient level and the aggregate level. That is, one may use a score to make a statement about groups of patients. Serious consequences may arise depending on the action that one takes in response to such a statement, and therefore a conservative approach to the application of scores to individuals is necessary. After all the careful research that has produced the various severity scoring systems, the uses to which they can be appropriately be put are still not universally agreed [19]

Prediction for individuals patients

The systems can be used either to determine objective risk of death or in a clinical assessment. Meyer et al. [20] showed that among the patients who were predicted by both methods to die, more than 40% of actually survived. They concluded that no method is reliable for predicting the mortality of surgical ICU patients. This illustrates the confusion that exists between interpreting an estimated probability of mortality and predicting whether a given patient will live or die. A good severity system provides an accurate estimate of the number of patients predicted to die among a group of similar patients; however, it does not provide a prediction of which particular patients will in fact die. Using a well-calibrated severity model, we can reasonably expect that approx. 75% of patients with a probability of mortality of 0.75 will die, but we cannot know in advance which of those patients will be among the 25% who will live. Furthermore, these 25% will not have falsified the odds but will have confirmed the validity of the probabilities.

The possibility that clinical decisions can be augmented by having an objective (although not always more accurate) assessment of a patient's severity of illness is appealing. Physicians are interested in severity systems for individual patients as an adjunct to their informed but subjective opinion. Using these tools as part of the decision-making process is reasonable and prudent. Using these tools to dictate individual patient decisions is not appropriate. Decisions will and should remain the responsibility of the individual physician and should be based on a number of criteria, one of which is severity as estimated by a well calibrated scoring system.

Evaluation of ICU performance

Using the APACHE II system Knaus et al. [21] calculated the probabilities of hospital mortality in a sample of 16,622 consecutive patients from 42 ICUs and compared this to the actual outcome. They observed that the ratio of observed to predicted number of deaths varied from 0.67 to 1.21 across ICUs. That is, in some ICUs the observed mortality was lower than predicted by the models, and in some it was higher. Similarly, using the SAPS II system Le Gall et al. [22] compared the probabilities of hospital mortality and actual outcome in ICUs in several countries. They found that the ratio varied across countries from 0.74 to 1.31, with some countries having a lower number of deaths that predicted and some a higher number.

One cannot conclude from these findings, however that clinical performance in different ICUs or different countries is necessarily below par when the observed mortality is higher than predicted, or that it is necessarily above par when the observed mortality is lower than predicted. To use these ratios effectively one must know the extent to which they are affected by factors others than clinical performance. These ratios are most effectively interpreted as indicators that one should look more deeply into the situation in the various ICUs to identify factors associated with the observed mortality differential. These probabilities by themselves do not effectively control for all of the differences that may have an impact on outcome. They cannot control for differences in patient mix or for disparities in available technical and therapeutic resources. Neither can they control for administrative differences or the level or organization of support staffing (e.g., beds per nurse). Only after taking such factors into consideration can meaningful evaluations and comparisons be made.

Therapeutic trials

As a specific case in point, this discussion is oriented toward therapeutic trials for sepsis, but the issues involved can be applied to clinical trials involving any disease or condition and any proposed new therapy. While some authors [23] have stressed the importance of preexisting comorbidity for prognosis of septicemia in critically ill patients, others [24] have shown by multivariate analysis that using the initial score, cause (urosepsis or other), and treatment location prior to ICU admission provides the greatest degree of discrimination (ROC=0.82) of patients by risk of hospital death.

A complex model has been published for sepsis derived from a large database using physiology, primary disease, previous intensive care, age, clinical history of cirrhosis, and other variables [25]. This is proposed for use in clinical trials in which sepsis is the sole disorder of interest. However, the database from which the model was developed defined disease spectrum and inclusion criteria in a manner that may differ from that specified for a proposed trial of a new therapy for sepsis. In general it is unlikely that the precise inclusion or exclusion criteria for a specific trial were in used in compiling the original database from which a model was developed. Nor is it reasonable to expect that a large, general medical/surgical database would contain all of the information for addressing all the requirements of current and future trials. Although this should not deter one from the use of such models, it should make investigators wary of comparisons between the predicted mortality rate given by a model derived from a large database and the observed mortality rate in a precisely defined group. The probability can be used to stratify patients by level of severity at the onset of the trial, but conclusions about observed and predicted outcome should be drawn with care.

In a critique of scoring systems Loirat [26] suggested using a simpler tool without assigned weights for acute diseases. Such a disease-independent assessment of severity could be used to derive a disease-specific model using one-half of the patients in a control group. The model would be applied to the patients in the other one-half of the control group and the patients in the treatment group, and comparisons of observed and predicted outcome between the two groups could be made to evaluate the success of the treatment.

It must also be noted that the present general models have all been developed for use at very specific time periods, either at admission to the ICU (MPM_0), during the first 24 h of the ICU stay (SAPS II, APACHE III), or at three 24-h time points of the ICU stay (MPM_{24}, MPM_{48}, MPM_{72}). These models are not automatically transferable for use in stratifying patients at time of randomization in a clinical trial if this time point lies outside the time limits during which the models were intended to be applied. Research is necessary to confirm that severity at the time of randomization is accurately measured by these models (i.e., to confirm that they are well calibrated at the intended time period).

Conclusion

In an editorial Selker [27] stated that the desirable characteristics of risk-adjusted mortality predictors are that they be time-insensitive predictive instruments, based on the first minutes of hospital presentation, not affected by whether a patient is hospitalized, based on data collected in the usual care of patients, calibrated with a high degree of precision, integrated into computer systems, independent of the diagnosis-related groups system, and open for inspection and testing. These criteria are probably utopian, and the ideal scoring systems remains to be discovered. The available ICU scoring systems reviewed in this article are, however, based on rigorous research and have reported excellent calibration and discrimination.

Regarding the critical point of view we wish to stress the following: SAPS 3 seems very promising. It is currently the most recent and sophisticated model. The original models may be used to score patients' severity and make comparison of severity over years. The customized models are easy to obtain from the existing databases. The expanded SAPS II, simple to obtain from the existing data bases, may be used to compare performances over time.

References

1. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
2. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A (1991) The APACHE III prognostic system: risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100:1619–1636
3. Le Gall J-R, Lemeshow S, Saulnier F (1994) A new Simplified Acute Physiology Score (SAPS II) based in European/North American multicenter study. JAMA 270:2957–2963

4. Lemeshow S, Klar J, Teres D, Avrunin JS, Gehlbach SH, Rapoport J, Rue (1994) Mortality probability models for patients in the intensive care unit for 48 or 72 hours: a prospective multicenter study. Crit Care Med 22:1351–1358
5. Aergerter P, Boumendil A, Retbi A, Minvielle E, Dervaux B, Guidet B (2005) SAPS II revisited. Intensive Care Med 31:416–423
6. Le Gall JR, Neumann A, Hemery F, Bleriot JP, Fulgencio JP, Garrigues B, Gouzes C, Lepage E, Moine P, Villers D (2005) Mortality prediction using the SAPS II: an update for French ICUs. Critical Care Med 9:R645–R652
7. Metnitz PGH, Moreno RP, Almeida E, Jordan B, Bauer P, Abizanda-Campos R, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR on behalf of the SAPS 3 investigators (2005) SAPS 3 – From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. Intensive Care Med 31:1336–1344
8. Moreno RP, Metnitz PGH, Almeida E, Jordan B, Bauer P, Abizanda-Campos R, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR on behalf of the SAPS 3 investigators (2005) SAPS 3 – From evaluation of the patient to evaluation of the intensive care unit. Part 2. Objectives, methods and cohort description. Intensive Care Med 31:1345–1355
9. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) Prognosis in acute organ-system failure. Arch Surg 202:685–693
10. Fagon JY, Chastre J, Novara A, Medioni P, Gibert C (1993) Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the ODIN model. Intensive Care Med 19:137–144
11. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S (1998) Use of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med 26:1793–1890
12. Marshall J, Cook DJ, Christou NU, Bernard GR, Sprung CL, Sibbald WJ (1995) Multiple organ dysfunction score: a reliable description of a complex clinical outcome. Crit Care Med 23:1638–1652
13. Le Gall J-R, Klar J, Lemeshow S, Saulnier F, Alberti C (1996) The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. JAMA 276:802–810
14. Timsit JF, Fosse JP, Troché G, De Lassence A, Alberti C, Garrouste-Orgeas M, Azoulay E, Chevret S, Moine P, Cohen Y (2001) Accuracy of a composite score using daily SAPS II and LOD scores for predicting hospital mortality in ICU patients hospitalized for more than 72 h. Intensive Care Med 27:1012–1021
15. Lemeshow S, Le Gall JR (1994) Modeling the severity of illness of ICU patients. JAMA 272:1049–1055
16. Hosmer DW, Lemeshow S (1989) Applied logistic regression. Wiley, New York
17. Hanley JA, Mc Neil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143:29–36
18. Le Gall J-R, Lemeshow S, Leleu G, Klar J, Huillard J, Montserra R, Teres D, Artigas A for Intensive Care Unit Scoring Group (1995) Customized probability models for early severe sepsis adult intensive care patients. JAMA 273:644–650
19. Teres D, Lemeshow S (1994) Why severity models should be used with caution. Crit Care Clin 10:93–110
20. Meyer AA, Messick WJ, Young R, Backer CC, Fakhry S, Muakkassa F, Rutherford EJ, Napolitano LM, Rutledge R (1992) Prospective comparison of clinical judgement and APACHE II score in predicting the outcome in critically ill surgical patients. J Trauma 32:747–753
21. Knaus WA, Wagner DP, Zimmerman JE, Draper EA (1993) Variation in mortality and length of stay in intensive care units. Ann Intern Med 118:753–761
22. Le Gall J-R, Artigas A, Lemeshow S, Saulnier F, Avrunin J (1993) Une comparaison internationale des unités de réanimation (abstract). Reanimation Soins Intensifs Med Urgence 6:656
23. Pittet D, Thievent B, Wenzel RC, Gurman G, Sutter PM (1993) Importance of preexisting comorbidities for prognosis of septicemia in critically ill patients. Intensive Care Med 19:265–272
24. Knaus WA, Sun X, Nystrom Pr, Wagner DP (1992) Evaluation of definitions for sepsis. Chest 101:1656–1662
25. Knaus WA, Harrel FE, Fisher CJ Jr, Wagner DP, Opal SM, Sadoff JC, Draper EA, Walawander CA, Conboy K, Grasela TH (1993) The clinical evaluation of new drugs for sepsis: a prospective study design based on survival analysis. JAMA 270:1233–1241
26. Loirat P (1994) Critique of existing scoring systems: admission scores. Reanation Soins Intensifs Med Urgence 3:173–175
27. Selker HP (1993) Systems for comparing actual and predicted mortality rates: characteristics to promote cooperation in improving hospital care. Ann Intern Med 118:820–822

Jean-Louis Vincent
Daniel De Backer

Oxygen transport—the oxygen delivery controversy

Introduction

Most cellular activities require energy in the form of oxygen, primarily obtained from the degradation of adenosine triphosphate (ATP) and other high-energy compounds. Oxygen must be present in sufficient amounts in the mitochondria to maintain effective concentrations of ATP in the electron transport system. Cells have to perform a series of activities essential for survival, including membrane transport, growth, cellular repair and maintenance processes. In addition, cells often have facultative functions such as contractility, electrolyte or protein transport, motility and various biosynthetic activities. If oxygen availability is limited, cellular oxygen consumption may fall and become supply-dependent. Facultative functions are the first to be altered, leading to organ dysfunction. If the situation becomes more serious, obligatory functions can no longer be maintained and irreversible alterations may occur.

It is thus fundamental to maintain sufficient oxygen availability to the cell; the hypoxic cell is doomed to become dysfunctional and to die. Maintenance of adequate oxygen delivery (DO_2) is essential to preserve organ function, as a low DO_2 is a direct path to organ failure and death.

The concept of oxygen delivery

The amount of oxygen available to the cell is determined by a number of central and peripheral factors. Central factors are related to the adequacy of cardiorespiratory function (cardiac index and PaO_2) and hemoglobin concentration, according to the formula given in Table 1. Peripheral factors are related to the redistribution of cardiac output to the various organs and to regulation of the microcirculation. The latter mechanism is primarily determined by the autonomic control of vascular tone and local microvascular responses and to the degree of affinity of the hemoglobin molecule for oxygen. Among the central factors, cardiac output is the most important determinant of DO_2 (Table 1). Indeed, a fall in hemoglobin concentration or arterial oxygen saturation (SaO_2) can be compensated for by an increase in cardiac output, whereas the opposite is not true. Likewise, to increase DO_2, SaO_2 is normally close to 100% and the hemoglobin concentration cannot change acutely. In addition, blood transfusions do not systematically increase DO_2, because cardiac output usually decreases as a result of the associated increase in blood viscosity. Hence, cardiac output must constantly adapt to the oxygen needs of the body in physiological conditions.

Peripheral factors can be substantially altered in inflammatory conditions (including sepsis), where local

Table 1 The determinants of oxygen delivery, oxygen consumption and oxygen extraction

Oxygen delivery (DO_2) = CI x Hb x SaO_2 x C x 10
Oxygen consumption (VO_2) = CI x CaO_2 – CvO_2×10 (neglecting the dissolved oxygen) = CI x Hb x (SaO_2–SvO_2) x C
Oxygen extraction (O_2ER) = VO_2/DO_2 = (CaO_2-CvO_2)/CaO_2 (neglecting the dissolved oxygen) = (SaO_2–SvO_2)/SaO_2

CO cardiac output, *Hb* hemoglobin concentration, SaO_2 arterial oxygen saturation, SvO_2 mixed venous oxygen saturation, *C* constant value: representing the amount of oxygen bound to 1 g of Hb (this value is usually 1.34 or 1.39)

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_58, © Springer-Verlag Berlin Heidelberg 2009

control of vascular tone may be altered, the formation of microthrombi may shut down some capillaries and the development of edema may contribute to altering the distribution of blood flow. Changes in the oxygen affinity of hemoglobin can also influence the peripheral delivery of oxygen. Importantly, the oxygen extraction capabilities of the tissues are primarily determined by the matching of microvascular blood flow to microregional oxygen demand, a heterogeneity of capillary perfusion leading to oxygen consumption (VO_2)/DO_2 mismatch [1] and hence alterations in oxygen extraction [1, 2].

Back to basics—the relationship between oxygen consumption and oxygen delivery and the concept of oxygen consumption/oxygen delivery dependency

The animal experiments by Cain [3], Schumacker [4] and others [5, 6, 7, 8, 9, 10, 11, 12] provided the fundamental data to characterize the relationship between VO_2 and DO_2. VO_2 is independent of DO_2 over a wide range of values, because oxygen extraction can readily adapt to the changes in DO_2. Hence, when DO_2 is acutely reduced by a decrease in blood flow (cardiac output), in hemoglobin concentration (anemia) or in hemoglobin oxygen saturation (hypoxemia), oxygen extraction increases (mixed venous oxygen saturation [SvO_2] decreases) and VO_2 remains stable for a long time. It is only when DO_2 falls below a critically low value (DO_2crit), that VO_2 starts to fall. An abrupt increase in blood lactate concentration then occurs, indicating the development of anaerobic metabolism (Fig. 1).

Low flow (hypovolemic, cardiogenic and obstructive types of shock), anemic and hypoxic hypoxia are characterized by a decreased DO_2 but preserved oxygen extraction ratio (O_2ER, the ratio of DO_2 to VO_2) so that the DO_2crit remains normal. In distributive shock, the oxygen extraction capabilities are altered so that the critical O_2ER is typically decreased. These situations are typically associated with an increased DO_2crit, and in these conditions VO_2 can become dependent on DO_2 even when the latter is normal or elevated. These observations have been made after endotoxin administration [13] as well after injection of live bacteria [14]. Taken together, these observations help to characterize the four principal types of circulatory shock (Fig. 2). Admittedly, this classification is somewhat simplistic as several types of alteration may coexist, in particular in cardiogenic shock [15].

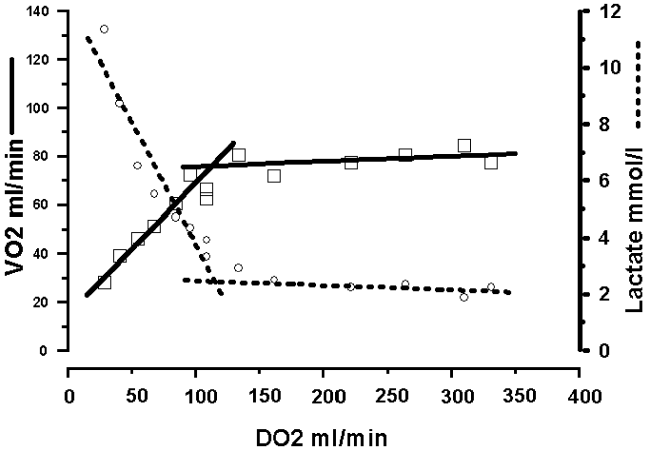


Fig. 1 Relationship between oxygen consumption (VO_2) and oxygen delivery (DO_2) when DO_2 is acutely reduced by tamponade or hemorrhage in anesthetized animals (data pooled from several studies). Note that blood lactate levels increase as soon as DO_2 falls below a critically low value (DO_2crit)

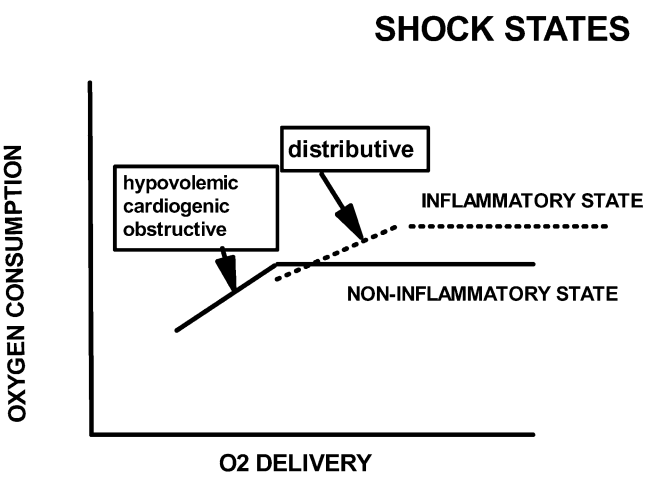


Fig. 2 Schematic representation of the four types of acute circulatory failure. Importantly, several types of shock may coexist

The clinical controversies

There are at least two controversies in the human application of these physiological data. One surrounds the concept of 'non-physiological' VO_2/DO_2 dependency, and the other the need to increase DO_2 to supranormal values.

The first controversy—'non-physiological' oxygen consumption/oxygen delivery dependency

Early human studies [16, 17, 18] suggested that patients with the acute respiratory distress syndrome (ARDS) may have VO_2/DO_2 dependency. However, these studies had methodological problems in that pooled data were obtained from the patients.

Subsequent investigations indicated that VO_2/DO_2 dependency may occur in some individuals but not others. Some studies related the phenomenon to hyperlactatemia,

as VO_2 increased when DO_2 was increased with i.v. fluids or vasoactive agents in patients with high lactate concentrations but not in those with normal lactate concentrations [19, 20, 21, 22]. Bihari et al. [23] related the VO_2/DO_2 dependency phenomenon to survival, as they observed that a prostacyclin infusion was associated with an increase in VO_2 primarily in non-survivors.

Several groups of investigators have challenged these concepts on the basis of various arguments.

First argument: limitations of blood lactate concentrations

The use of blood lactate concentrations in some of these studies may not faithfully identify patients with VO_2/DO_2 dependency. Moreover, elevated blood lactate concentrations do not necessarily reflect anaerobic metabolism secondary to cellular hypoxia. Other mechanisms, including increased glycolysis, altered lactate clearance and abnormal pyruvate metabolism may contribute to the hyperlactatemia observed in septic states.

Response: It is true that hyperlactatemia alone is not sufficient to affirm the presence of VO_2/DO_2 dependency, but should complement the clinical signs of altered tissue perfusion. After all, the VO_2/DO_2 phenomenon is a hallmark of acute circulatory failure (shock). Even though the limitations of blood lactate concentrations must be well understood [24], increased lactate concentrations remain a reliable prognostic indicator, actually superior to DO_2 and VO_2 values [25].

Second argument: mathematical coupling of data

There are important methodological problems in the assessment of VO_2/DO_2 relationships. Most studies evaluating the relationship between VO_2 and DO_2 have calculated VO_2 and DO_2 from the same variables, i.e., cardiac output, hemoglobin concentrations and SaO_2, thus resulting in mathematical coupling of data. Some have argued that VO_2 should be 'measured' from the expired gas analysis rather than 'calculated'. Importantly, the VO_2/DO_2 dependency phenomenon has never been reported when indirect calorimetry has been used to determine VO_2 independently.

Response: Possible methodological problems cannot be neglected. However, the determination of VO_2 by direct measurement may not be better for several reasons. First, even though people sometimes refer to 'calculated versus measured', they overlook the fact that VO_2 is always calculated as flow (blood flow or gas flow) times oxygen content difference (between arterial and venous blood or between inspired and expired gases). In fact, the formula used to 'calculate' VO_2 by indirect calorimetry is quite complex. Second, indirect calorimetry has its own

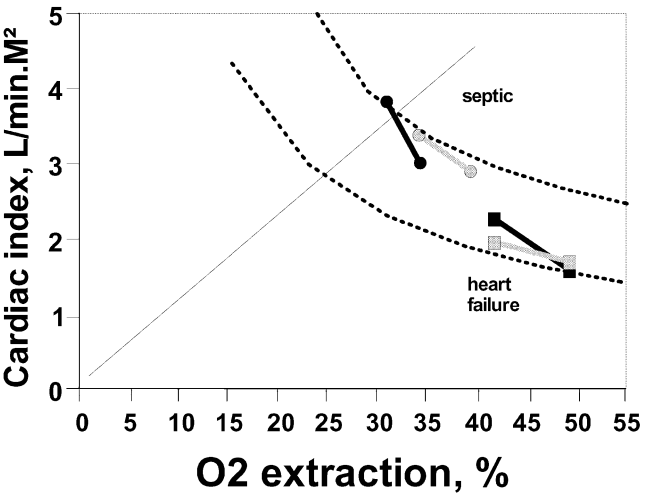


Fig. 3 Cardiac index/oxygen extraction ratio (O_2ER) diagram during a short-term dobutamine infusion indicating oxygen consumption (VO_2)/oxygen delivery (DO_2) dependency in patients with increased lactate levels (*black bars*) but not in those with normal lactate levels (*gray bars*) (data from [22]). The line of reference refers to the physiological response to exercise. The *curved dotted lines* represent isopleths of various levels of VO_2. If VO_2 remains stable and is independent of DO_2, data points on the diagram move parallel to the VO_2 isopleths; if there is VO_2/DO_2 dependency, data points will cross VO_2 isopleths

limitations and sources of error, especially when high FiO_2 are required. Also indirect calorimetry is a cumbersome method; it takes time to prepare and is not easily accessible in urgent conditions. Hence, patients studied with this technique have usually been stabilized. In such stable patients, no VO_2/DO_2 dependency phenomenon could be documented by either method [26].

The importance of methodological problems is probably less serious than sometimes considered. First, a complex analysis by Stratton et al. [27] revealed that the methodological problems due to estimations of VO_2 and DO_2 are probably of minor magnitude when the increase in DO_2 is significant. Second, different responses have been reported in various groups of patients including survivors versus non-survivors [23], patients with or without hyperlactatemia [20, 21, 22] and hemodynamically stable or unstable patients [28]. The changes in DO_2 were similar in the two groups so that the risk of mathematical coupling was not limited to the group with VO_2/DO_2 dependency. Third, similar observations have been made using the cardiac index/O_2ER relationship, which does not have any problem with mathematical coupling of data (Fig. 3).

Third argument: the thermogenic effects of catecholamines

Dobutamine has been used to disclose the VO_2/DO_2 dependency phenomenon [22], but this catecholamine may increase VO_2 in all individuals. The mechanisms involve, in part, increased cellular metabolism primarily under the influence of beta-adrenergic stimulation and, in part, the increase in blood flow that is associated with increased cardiac work and increased oxygen demand by the heart and organs like the kidney and the liver, whose needs are proportional to the blood flow. Importantly, these metabolic effects may vary according to the individual [29].

Response: the thermogenic effects of catecholamines cannot be neglected, but are relatively limited for dobutamine [26, 30] and less significant than for epinephrine. Moreover, a study comparing the effects of dobutamine to those of sodium nitroprusside in volunteers indicated a similar increase in VO_2 with the two molecules [31]; hence this phenomenon is probably limited.

Fourth argument: observations made in dying patients

Such studies performed in anesthetized animals can hardly be reproduced in humans, where an acute reduction in DO_2 would be unethical in most situations. However, Ronco and collaborators [32] did demonstrate the same phenomenon in dying patients in whom life support treatment was withdrawn. Importantly, they showed that the VO_2/DO_2 dependency phenomenon appeared only at very low DO_2 values, thus indicating that the phenomenon may occur only in extreme conditions.

Response: although very interesting these observations made in patients in the final stages of the disease process may not apply to all critically ill patients.

So can VO_2/DO_2 dependency exist in patients? On the basis of these observations, one can conclude that:

1. VO_2/DO_2 dependency does NOT exist globally in stable, critically ill patients, even in those with sepsis or ARDS [33].
2. VO_2/DO_2 dependency DOES exist in severe cases of circulatory shock, when blood flow is significantly reduced.
3. VO_2/DO_2 dependency MAY exist globally in patients with septic shock and perhaps regionally in patients with severe sepsis. However, global measurements are not precise enough to guide therapy effectively and regional measurements cannot be obtained routinely in critically ill patients. Thus it remains difficult to define where the limit can be drawn.

The second controversy: supranormal oxygen delivery versus the regional versus the 'individual' approach

The supranormal oxygen delivery approach

If inadequate tissue oxygenation can result in organ failure, one might suggest creating and maintaining supranormal DO_2 values for all patients at risk of complications, to ensure sufficient cellular oxygen availability. This idea is based on the observation that those who do well usually have higher DO_2 values than those who develop complications. Using these values in survivors as reference values, William Shoemaker and his colleagues [34] suggested that this strategy of achieving supranormal DO_2 (to at least 600 ml/min per m^2) may result in better outcomes. Although this approach may have merits in some populations [35, 36], it has several problems. First, it may be true that patients with a high cardiac output and DO_2 are more likely to survive, but this may simply be a marker of their physiological reserve. In other words, it may be that survivors are more likely to be able to generate a higher cardiac output, whereas patients who are elderly or with severe cardiorespiratory compromise may not be able to generate a high cardiac output and innately have a higher risk of death. Second, calculation of DO_2 (and other derived variables) is not only complex but prone to errors. Every primary variable is approximated and multiplying the values carries the risk of amplifying these errors. Third, and most importantly, increasing DO_2 to supranormal values in all patients 'at risk' may be helpful to some, but harmful to others. Pouring fluids and adrenergic agents into patients who do not need them can be expected to be harmful. Hence the benefit to some patients may be largely outweighed by the detrimental effects on others. Stated bluntly, this concept is an oversimplification of a complex phenomenon. When applied to a mixed group of critically ill patients, such strategies have been shown to be ineffective [37] and may even be harmful, especially if high doses of dobutamine are administered [38].

The regional approach

Unfortunately, global determinations of DO_2 and VO_2 may not be sensitive enough to be clinically relevant. Importantly, they may fail to detect regional perfusion abnormalities. In particular, the splanchnic circulation is thought to be important and regional measurements have shown the VO_2/DO_2 dependency phenomenon in the hepatosplanchnic circulation. De Backer et al. evaluated hepatosplanchnic VO_2/DO_2 relationships by the introduction of a catheter into the suprahepatic vein [39]. Some patients demonstrated regional VO_2/DO_2 dependency and others did not, although there were no differences in clinical or biochemical parameters (Fig. 4).

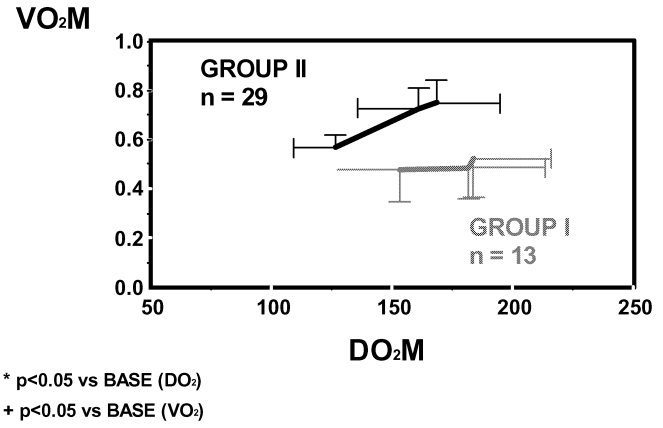


Fig. 4 Regional oxygen consumption (VO_2)/oxygen delivery (DO_2) relationship in the splanchnic circulation in patients with severe sepsis. Group I: patients with gradient between mixed venous and hepatic venous oxygen saturation lower than or equal to 10%. Group II: patients with gradient between mixed venous and hepatic venous oxygen saturation higher than 10%. Data are presented as means ± SEM. (adapted from [39] with permission). *VO_2M* and *DO_2M* refer to mesenteric VO_2 and DO_2, respectively

Unfortunately, these measurements are not easily accessible, so limiting the application of a common monitoring technique. The use of a dobutamine infusion using gastric tonometry may help to identify patients who may have such a phenomenon [40].

The individualized approach

Many investigators prefer a titrated, individualized approach, with the aim of classifying patients by careful clinical evaluation and paraclinical tests including measurements of cardiac index, SvO_2, blood lactate concentrations and, perhaps, regional PCO_2. This requires a complete understanding of the pathophysiological alterations.

To evaluate the relationship between VO_2 and DO_2 in a simplified way, one may construct a cardiac index/O_2ER diagram [41] (Fig. 3). The study of such variables also avoids cumbersome calculations, as cardiac index is a primary variable and O_2ER can be very simply calculated (Table 1). However, in most cases, SvO_2 or even central venous oxygen saturation ($ScvO_2$) alone may suffice. Rivers et al. [42], using oxygen saturation in the superior vena cava as a guide, showed that early goal-directed therapy could result in significantly lower mortality rates in patients with severe sepsis and septic shock. Likewise, Polonen et al. [43] found that this approach shortened hospital stays and reduced the degree of organ dysfunction at the time of hospital discharge in cardiac surgery patients. Hence, in addition to standard clinical evaluation, repeated measurements of blood lactate and SvO_2 may be helpful. Measurement of base excess may also be used to assess the imbalance between oxygen supply and delivery by quantifying the metabolic acidosis that results from the anaerobic metabolism [44]. However, as with blood lactate levels, there are many causes of metabolic acidosis and, hence, an abnormal base excess in critically ill patients (including renal failure, ketoacidosis, convulsions, etc.), and its interpretation may not be straightforward. The proper evaluation of the critically ill patient thus requires the integration of several factors, including measurement of DO_2, urine output, blood lactate concentrations, base excess, SvO_2 and, maybe, some indices of regional perfusion such as gastric tonometry. If there is doubt, a DO_2 challenge may be performed to rule out VO_2/DO_2 dependency, but the errors in measurements may sometimes lead to inadequate interpretation.

Conclusions

The relationship between VO_2/DO_2 remains an important concept, even though its application to guide therapy may be too simplistic. Discussion of this important area leads us back to simple but important recommendations:

- Patients with signs of poor tissue perfusion, such as arterial hypotension, slow capillary refill, oliguria or high blood lactate concentrations, may benefit from further administration of fluid and/or inotropic agents like dobutamine.
- Monitoring of SvO_2 represents a simplification that may be helpful, and algorithms may be constructed to guide therapy along with these measurements.
- Although one may argue that lactate concentrations reflect other cellular abnormalities than anaerobic metabolism secondary to hypoxia, the time course of lactate levels remain valuable, so that increased lactate levels should indicate an alarm signal.
- In the absence of notable renal failure, measuring base deficit may provide a useful indication of inadequate oxygenation.

Whatever the cause of shock, maintaining adequate tissue oxygenation is critical. In the evaluation of tissue oxygenation none of the available monitors alone is ideal, and decisions regarding the need for strategies to increase and maintain oxygen delivery must thus be based on the combined interpretation of repeated measurements of clinical, biochemical and oxygenation parameters.

References

1. Humer MF, Phang PT, Friesen BP, Allard MF, Goddard CM, Walley KR (1996) Heterogeneity of gut capillary transit times and impaired gut oxygen extraction in endotoxemic pigs. J Appl Physiol 81:895–904
2. Ellis CG, Bateman RM, Sharpe MD, Sibbald WJ, Gill R (2002) Effect of a maldistribution of microvascular blood flow on capillary O(2) extraction in sepsis. Am J Physiol Heart Circ Physiol 282:H156–H164
3. Cain SM (1977) Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. J Appl Physiol 42:228–234
4. Schumacker PT, Cain SM (1987) The concept of a critical oxygen delivery. Intensive Care Med 13:223–229
5. Van der Linden P, Gilbart E, Engelman E, Schmartz D, Vincent JL (1991) Effects of anesthetic agents on systemic critical O_2 delivery. J Appl Physiol 71:83–93
6. Van der Linden P, Gilbart E, Paques P, Simon C, Vincent JL (1993) Influence of hematocrit on tissue O_2 extraction capabilities in anesthetized dogs during acute hemorrhage. Am J Physiol 264:H1942–H1947
7. Rock P, Beattie C, Kimball AW, Nyhan DP, Chen BB, Fehr DM, Derrer SA, Parker SD, Murray PA (1990) Halothane alters the oxygen consumption-oxygen delivery relationship compared with conscious state. Anesthesiology 73:1186–1197
8. Cilley RE, Scharenberg AM, Bongiorno PF, Guire KE, Barlett RH (1991) Low oxygen delivery produced by anemia, hypoxia and low cardiac output. J Surg Res 51:425–433
9. Schlichtig R, Kramer DJ, Pinsky MR (1991) Flow redistribution during progressive hemorrhage is a determinant of critical O_2 delivery. J Appl Physiol 70:169–178
10. De Backer D, Roman A, Van der Linden P, Armistead C, Schiltz G, Vincent JL (1992) The effects of balloon filling into the inferior vena cava on the VO_2/DO_2 relationship. J Crit Care 7:167–173
11. Zhang H, Spapen H, Benlabed M, Vincent JL (1993) Systemic oxygen extraction can be improved during repeated episodes of cardiac tamponade. J Crit Care 8:93–99
12. Zhang H, Vincent JL (1993) Arteriovenous differences in PCO_2 and pH are good indicators of critical hypoperfusion. Am Rev Respir Dis 148:867–871
13. Zhang H, Vincent JL (1993) Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. Circ Shock 40:168–176
14. Nelson DP, Beyer C, Samsel RW, Wood LDH, Schumacker PT (1987) Pathological supply dependence of O_2 uptake during bacteremia in dogs. J Appl Physiol 63:1487–1492
15. Lim N, Dubois MJ, De Backer D, Vincent JL (2003) Do all nonsurvivors of cardiogenic shock die with a low cardiac index? Chest 124:1885–1891
16. Powers SR Jr, Mannal R, Neclerio M, English M, Marr C, Leather R, Ueda H, Williams G, Custead W, Dutton R (1973) Physiologic consequences of positive end-expiratory pressure (PEEP) ventilation. Ann Surg 178:265–272
17. Mohsenifar Z, Goldbach P, Tashkin DP, Campisi DJ (1983) Relationship between O_2 delivery and O_2 consumption in the adult respiratory distress syndrome. Chest 84:267–271
18. Danek S, Lynch JP, Weg JG, Dantzker DR (1980) The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. Am Rev Respir Dis 122:387–395
19. Bakker J, Vincent JL (1991) The oxygen supply dependency phenomenon is associated with increased blood lactate levels. J Crit Care 6:152–159
20. Haupt MT, Gilbert EM, Carlson RW (1985) Fluid loading increases oxygen consumption in septic patients with lactic acidosis. Am Rev Respir Dis 131:912–916
21. Gilbert EM, Haupt MT, Mandanas RY, Huaringa AJ, Carlson RW (1986) The effect of fluid loading, blood transfusion and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. Am Rev Respir Dis 134:873–878
22. Vincent JL, Roman A, De Backer D, Kahn RJ (1990) Oxygen uptake/supply dependency: effects of short-term dobutamine infusion. Am Rev Respir Dis 142:2–8
23. Bihari D, Smithies M, Gimson A, Tinker J (1987) The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. N Engl J Med 317:397–403
24. De Backer D (2003) Lactic acidosis. Intensive Care Med 29:699–702
25. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL (1991) Blood lactate levels are superior to oxygen derived variables in predicting outcome in human septic shock. Chest 99:956–962
26. De Backer D, Moraine JJ, Berré J, Kahn RJ, Vincent JL (1994) Effects of dobutamine on oxygen consumption in septic patients: Direct vs indirect determinations. Am J Respir Crit Care Med 150:95–100
27. Stratton HH, Feustel PJ, Newell JC (1987) Regression of calculated variables in the presence of shared measurement error. J Appl Physiol 62:2083–2093
28. Friedman G, De Backer D, Shahla M, Vincent JL (1998) Oxygen supply dependency is a hallmark of septic shock. Intensive Care Med 24:118–123
29. Teboul JL, Annane D, Thuillez C, Depret J, Bellissant E, Richard C (1992) Effects of cardiovascular drugs on oxygen consumption/oxygen delivery relationship in patients with congestive heart failure. Chest 101:1582–1587
30. Gutierrez G, Clark C, Brown SD, Price K, Ortiz L, Nelson C (1994) Effect of dobutamine on oxygen consumption and gastric mucosal pH in septic patients. Am J Respir Crit Care Med 150:324–329
31. De Backer D, Berre J, Moraine JJ, Melot C, Vanfraechem J, Vincent JL (1996) Effects of dobutamine on the relationship between oxygen consumption and delivery in healthy volunteers: comparison with sodium nitroprusside. Clin Sci 90:105–111
32. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, Cunningham KF, Russell JA, Walley KR (1993) Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA 270:1724–1730
33. De Backer D, Vincent JL (1995) VO_2-DO_2 relationships are altered in some critically ill patients. Semin Respir Crit Care Med 16:394–402
34. Shoemaker WC, Appel PL, Waxman K, Schwartz S, Chang P (1982) Clinical trial of survivors' cardiorespiratory patterns as therapeutic goals in critically ill postoperative patients. Crit Care Med 10:398–403
35. Yu M, Levy MM, Smith P, Takiguchi SA, Miyasaki A, Myers SA (1993) Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: a prospective, randomized, controlled study. Crit Care Med 21:830–838
36. Lobo SM, Salgado PF, Castillo VG, Borim AA, Polachini CA, Palchetti JC, Brienzi SL, de Oliveira GG (2000) Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 28:3396–3404
37. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R (1995) A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025–1032

38. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717–1722
39. De Backer D, Creteur J, Noordally O, Smail N, Gulbis B, Vincent JL (1998) Does hepatosplanchnic VO_2/DO_2 dependency exist in critically ill patients. Am J Respir Crit Care Med 157:1219–1225
40. Creteur J, De Backer D, Vincent JL (1999) A dobutamine test can disclose hepato-splanchnic hypoperfusion in septic patients. Am J Respir Crit Care Med 160:839–845
41. Vincent JL (1996) Determination of O_2 delivery and consumption vs cardiac index vs oxygen extraction ratio. Crit Care Clin 12:995–1006
42. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
43. Polonen P, Ruokonen E, Hippelainen M, Poyhonen M, Takala J (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 90:1052–1059
44. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, Bennett ED (2001) Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med 27:74–83

Suveer Singh
Timothy W. Evans

Organ dysfunction during sepsis

Abstract *Background:* Multiple organ dysfunction syndrome is the commonest reason for sepsis-associated mortality. *Discussion:* In the 40 years since it was first described understanding of its pathophysiology has improved, and novel methodologies for monitoring and severity of illness scoring have emerged. These, together with the development of systematic strategies for managing organ dysfunction in sepsis, and potentially effective new therapeutic interventions, should assist in reducing sepsis-associated mortality. *Conclusion:* These historical developments are discussed, and the reader is directed to these references for further guidance.

Keywords Multiple organ dysfunction syndrome · Sepsis · Microvascular dysfunction · Cytopathic hypoxia · Bioenergetic failure · Scoring system

Introduction

Sepsis: historical perspective

The term sepsis is derived from the Greek word *sepsin*, which means 'to make putrid'. Early descriptions of disease mediated by "small invisible creatures" were made in the second century B.C., and the concepts of contagion and isolation of diseased individuals followed. Despite attempts at prevention pan-epidemic infections have caused the deaths of millions of persons throughout history. The first documented observations of living bacteria were made by van Leeuwenhoek in 1674 and classification of bacterial morphology in the early nineteenth century. However, the relationship between infectious disease, its aetiology, and its pathogenesis remained elusive.

The principles of disinfection and anti-septic practices pioneered by Semmelweis and later by Lister were adopted only several decades later. The importance of the host response to infection was first described in the 1880s and classified separately in terms of cell-mediated and humoral immunity. The subsequent use of drug anti-metabolites to ameliorate the effects of syphilis at the turn of the century, and the discovery of antibiotic sulphonamides, moulds and vaccination, led to a revolution in the treatment and prevention of infection. It was believed that these developments had the potential of eradicating sepsis from the modern age, but the problems of changing disease patterns and antibiotic resistance dampened early ambitions and sepsis has remained a formidable problem in many areas of medical practice.

Sepsis and multiple organ dysfunction: epidemiology

Sepsis, the host response to an infectious process, is termed severe when complicated by predefined organ system dysfunction [1]. Together, the systemic inflammatory response syndrome (SIRS), sepsis and septic shock have been termed the 'sepsis syndromes' [1, 2, 3]. The

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_59, © Springer-Verlag Berlin Heidelberg 2009

nature of infectious organisms associated with sepsis is changing. Thus, whilst Gram-negative bacteria were traditionally responsible for the majority of hospital-acquired infections, Gram-positive organisms (30–50% of cases) and multidrug-resistant bacteria or fungi (25%) are now more common [4, 5]. Moreover, the burden of sepsis-related disease is also rising; from 82.7 to 240.4 cases per 100,000 population in the United States and to 51 cases per 100,000 population (1997 figures) in the United Kingdom, where 27.1% of adult ICU admissions had severe sepsis in the first 24 h [6].

Severe sepsis and shock are characterised by tissue hypoperfusion, cellular hypoxia and metabolic dysfunction. Consequently the majority of patients with SIRS and its sequelae who fail to survive succumb to multiple organ dysfunction syndrome (MODS). Multiple organ failure (i.e. demonstrable failure of two or more organs) within the ICU was first documented in 1977. Bacterial sepsis was aetiologically significant in 69% of the cases described [7]. Indeed, the onset of MODS, synonymous with multiple organ system failure, was thought originally to follow a temporal sequence (lung, liver, gastric mucosa and kidney) [8]. Moreover, whilst strongly linked to uncontrolled infection (in particular intra-abdominal), it is now recognised that MODS can occur independently of sepsis. The commonest manifestation of MODS is acute lung injury, defined by refractory hypoxaemia attributable to high permeability pulmonary oedema [9]. Its extreme manifestation, the acute respiratory distress syndrome (ARDS), occurs in more than 40% of patients with sepsis and severe sepsis [6, 10].

There has been an evolution in the appreciation of mechanisms that result in sepsis and subsequent MODS. Thus, initially, a link between infections, which were recognised and treated and their inflammatory consequences was not appreciated. Indeed, progression to MODS, in spite of evidence of clearing of infection, nurtured the hypothesis of the body's response to infection associated systemic inflammation (by now autonomous from the initial infection) as being crucial to outcome. The process of increasing understanding of sepsis-associated MODS has required a number of key components, namely: (a) defining the biophysiological pathways arising from a systemic inflammatory insult, (b) clear epidemiological definitions of the spectrum of sepsis syndromes (often misused terms), (c) understanding the pathophysiological processes of the clinically apparent systemic disturbances during early and later stages and (d) testing different therapeutic approaches, directed at specific implicated inflammatory markers or at abnormal physiological parameters. Many therapeutic 'bedside' approaches have been proven wrong, yet providing insights into further 'bench' studies.

In summary, the sepsis syndromes and their sequelae, specifically MODS, represent the leading cause of death in adult general ICUs, with an associated mortality of 30–45%, consumption of 45% of ICU and 33% of hospital bed days and an estimated cost of $16.7 billion [6, 11].

Pathophysiology of MODS in sepsis

It is unknown why sepsis progresses to MODS in only certain individuals, or what the exact pathway is that leads to this. If the inflammatory process that characterises the systemic response to infectious pathogens becomes self-sustaining and progressive, organ dysfunction ensues. An extraordinarily complex and intricate cascade of inflammatory mediators, extra- and intracellular cell signalling pathways is activated. Prevailing wisdom suggests that these result in either microvascular dysregulation and/or mitochondrial dysfunction (so-called cytopathic hypoxia). These processes result in tissue hypoperfusion, and a further cascade of biochemico-physical alterations culminating in MODS [12].

Microvascular dysfunction

Early in the course of sepsis cardiac output (CO) rises to maintain blood pressure and organ perfusion in the face of reduced peripheral vascular resistance (hyperdynamic sepsis). As sepsis progresses, cardiac output is frequently reduced (so-called hypodynamic sepsis), which has a poor prognosis. Cardiac dysfunction per se is apparent in up to 44% of critically ill septic patients, with the aetiological agents suspected to be circulating depressant factors. Myocardial function tends to recover in survivors, and the prognostic significance of dysfunction in sepsis remains debatable [13]. Redistribution of capillary blood flow has been demonstrated in both animal models and in clinical sepsis [14, 15]. The use of investigatory tools such as intravital videomicroscopy, now applicable in the clinical setting, has provided evidence of simultaneous structural and functional abnormalities in sepsis, strengthening the association between tissue hypoperfusion and organ dysfunction. However, contradictory evidence from animal studies suggests that such hypoperfusion does not invariably lead to organ dysfunction and death.

Cytopathic hypoxia

Elevated tissue oxygen levels have been demonstrated in animals during experimental sepsis and in human skeletal muscle, suggesting that cellular inefficiency of oxygen utilisation rather than a failure of oxygen delivery (DO_2) to tissues occurs in sepsis. By contrast, in cardiogenic shock tissue oxygen is reduced [16, 17]. Tissue oxygen consumption occurs normally principally through ATP production by oxidative phosphorylation in mitochondria. Reduced ATP concentrations in skeletal muscle during

sepsis are associated with increasing severity of, and poor outcome from, septic shock [18]. The pathophysiological consequences of both regional flow alterations and mitochondrial dysfunction undoubtedly co-exist in the septic state, but do not appear to lead to significant histopathological correlates detectable at post-mortem examination.

Inflammatory cytokines in sepsis

The development of sequential organ failure in critically ill patients with sepsis is strongly predictive of mortality. However, the mechanisms involved in the dynamic interaction between different organ systems are dictated by the intricate interplay of haemodynamics, oxygen transport and metabolic disturbances. Genetic predisposition is almost certainly relevant in upregulating the expression of inflammatory mediators [e.g. tumour necrosis factor (TNF), interleukin (IL) 1, IL-8, triggering receptor on myeloid cells 1, high mobility group box 1), thereby influencing adversely the anti-/pro-inflammatory balance. Genetic predisposition seems more important for some infectious diseases such as meningococcaemia, but polymorphisms such as for TNF-α gene promoter can play a more general role in susceptibility to septic shock associated mortality [19]. Neuroendocrine systems and prothrombotic pathways (e.g. tissue factor) are activated with downregulation of fibrinolytic systems (i.e. anti-thrombin III, activated protein C and tissue factor pathway inhibitor) [20]. Inflammatory mediators TNF, IL-1, nitric oxide and reactive oxygen species are believed to disrupt communication pathways between organs which precedes organ failure [21]. Indeed, epithelial dysfunction has been proposed as a final common pathway for organ dysfunction in sepsis [22]. The tight junctions between these cells are affected in experimental models of sepsis. This may be particularly relevant in the gastrointestinal tract, which has been variously proposed as the 'seat of sepsis' and the 'motor of multiple organ failure' [23, 24]. Bacterial translocation (i.e. direct transcellular transport of microbes from the enterocytes to the submucosal layer) across a permeable intestinal luminal mucosa into the splanchnic circulation has been proposed as the initiator and propagator of sepsis following a remote insult. Mechanisms for this mucosal injury are multifactorial, including reduced intestinal blood flow and tissue hypoxia. Impaired hepatic clearance of toxins may also be relevant [25, 26, 27].

The prevailing theories of sepsis as an uncontrolled inflammatory response, which have been based on extensive animal studies, do not necessarily reflect the human clinical pattern. They used relatively large doses of bacteria or endotoxin and mortality was therefore the result of a 'cytokine storm', that if blocked improved survival. Meningococcaemia is perhaps the only human form of sepsis in which circulating levels of TNF-α are high and correlated with mortality [28]. Furthermore, there is much evidence of immune suppression during sepsis. Anergy (a state of non-responsiveness to antigen) through lymphocyte apoptosis has been demonstrable in vivo, and from autopsy studies of patients dying from sepsis [29]. Cellular hibernation or 'stunning' as occurs during myocardial ischaemia has been postulated as a mechanism for sepsis-associated MODS based on the notable findings of discordance between histological findings and the degree of organ dysfunction from patients who died of sepsis [30].

An emerging concept is the variable immune response during sepsis; from hyperimmune to hypoimmune, depending on factors that include virulence of the organism, size of the inoculum, pre-existing co-morbidity, genetic polymorphisms in candidate genes and the inflammatory insults during the course of sepsis. Therefore it is perhaps too simplistic to consider an overactive immune system as the reason for sepsis and associated MODS but rather a dynamic state where a severely compromised immune system might prevent adequate eradication of pathogens [29].

Clinical relevance of organ dysfunction: severity of illness scoring systems

Scoring systems as risk prediction tools rely on acute derangements in acute physiological parameters which are numerically assigned by degree and aggregated. Such generic (as distinct from disease-specific) scoring systems are best exemplified by the Acute Physiology and Chronic Health Evaluation (APACHE) system [31] which has led to the development of a number of other organ-based failure scores [32, 33, 34, 35].

Perhaps the most widely applied in current practice is the Sequential Organ Failure Assessment Score (SOFA, previously called the Sepsis-Related Organ Failure Assessment). Daily SOFA scores provide an important physiological tracking system for the dynamic course of critically ill patients with sepsis. Whilst not designed for mortality prediction, worse scores are strongly associated with mortality [36]; the mean and highest SOFA scores are predictors of poor prognosis, whilst a worsening of SOFA within the first 48 h predicts the likelihood of mortality 50% or higher [37]. However, whether organ-based scoring systems direct the timing, degree and duration of appropriate interventions to prevent MODS in sepsis is uncertain.

Detecting organ dysfunction in sepsis

Continuous monitoring of clinical and physiological variables, recognition of the significance of any changes in monitored parameters, and an appropriate response, are

the cornerstones and defining characteristic of modern-day intensive care medicine. Electrocardiographic, peripheral temperature (as an indicator of shock or its response) [38], non-invasive oxygen saturations [39], arterial blood gas, end tidal CO_2, metabolism (i.e. lactate), central venous, and cardiac output monitoring have become routine in practice. Specific organ system monitoring can guide management in certain circumstances such as intracranial pressure monitoring in traumatic head injury [40], whilst other more novel techniques such as gastric tonometry, and hepatic blood flow devices are under evaluation in the setting of sepsis [41].

Metabolic monitoring

Hyperlactataemia is multifactorial in origin. Nevertheless, there is a good relationship in sepsis between lactic acidosis, organ failure and poor outcome [42]. Indeed, blood lactate sampling is established and now recommended as an important parameter for monitoring in international guidelines on the management of severe sepsis [43].

Cardiac output monitoring

The history of the development of flow-directed, balloon-tipped, pulmonary artery catheters (PAC) saw them adopt a pivotal role in continuous bedside cardiopulmonary monitoring, and coincidently propagated the value of central venous catheters [44, 45, 46]. However, the SUPPORT [47] investigators identified an increased odds ratio for mortality and resource utilisation with the use of the PAC, even after adjustment for treatment selection bias. The 'attributable' morbidity associated with PAC use was thought more likely due to misinterpretation of the values thereby derived than to physical complications on insertion [48]. However, such work has led to the development of a number of other monitoring devices utilising arterial waveform analysis (i.e. pulse contour cardiac output, lithium dilution cardiac output), oesophageal Doppler and bioimpedance. Whilst all are relatively less invasive than the PAC, none provides the additional information about the pulmonary circulation. By contrast, the use of echocardiography is becoming more widespread in assessing cardiac function in sepsis [49, 50, 51, 52].

Mixed venous oxygen saturation

The value of reduced mixed venous oxygen tensions/saturations sampled from indwelling PACs as an accurate reflection of inadequate DO_2 due to reduced CO in cardiorespiratory failure was first demonstrated in patients undergoing cardiac surgery in whom a close correlation between venous oxygen saturation, CO and outcome was demonstrated [53]. Central venous oxygen saturation is now regarded as a crucial physiological surrogate for identifying and directing the correction of 'hidden' oxygen debt [54, 55, 56].

Management of organ dysfunction in sepsis

The principles of management of severe sepsis and associated organ dysfunction have evolved concomitantly with an increasing evidence base. Some critical concepts and studies that have helped this development are discussed below.

Diagnosis, source control and anti-microbial therapy

Early diagnosis of infection, 'source control' and appropriate anti-microbial treatment have been reported as crucial to outcome in sepsis for many years [57]. By contrast, up to eight-fold higher mortality is observed in prospective cohort studies of antibiotic misuse [58, 59], while inadequate surgical source control predicts MODS and increases mortality [7, 60].

Resuscitation-fluid management

Prompt and adequate haemodynamic resuscitation in patients with severe sepsis is pivotal in preventing progression to MODS and death. International recommendations suggest achieving a central venous pressure of 8–12 mmHg (or 12–15 mmHg in mechanically ventilated patients [56]. Which type of fluid replacement (i.e. crystalloid vs. colloid or albumin) to administer is more contentious [61, 62, 63], although a recent position statement by the American Thoracic Society is helpful in this regards [64].

Haemodynamic goals in sepsis

Fluid resuscitation in septic shock is directed at achieving adequate tissue perfusion and oxygenation, thereby overcoming tissue oxygen 'debt' which relates in part to inadequate DO_2. However, an early demonstration that dobutamine and adequate volume resuscitation improve DO_2 (and oxygen consumption, VO_2) as well as haemodynamic parameters post-operatively [65, 66, 67] was not reproduced in patients with sepsis-induced organ failures. Indeed, a strategy of goal directed supranormal oxygen delivery (cardiac index $4.5\,l\,min^{-1}\,m^{-2}$, $DO_2 > 60\,ml\,min^{-1}\,m^{-2}$, $VO_2 > 170\,ml\,min^{-1}\,m^{-2}$) using dobutamine in volume resuscitated critically ill patients increased mortality (54%) compared to controls (34%) [68]. In fact, the dobutamine-'driven' patients did not increase

Table 1 Diagnostic criteria for sepsis and associated organ dysfunction in adults. Adapted from [2]: infection (documented or suspected—a pathological process induced by a micro-organism) and some of the following variables

General	
Temperature	$< 36\,^{\circ}C$ or $> 38.3\,^{\circ}C$ (core temperature)
Heart rate	$> 90\,min^{-1}$ (or > 2 SD above the normal value)
Tachypnoea	
Altered mental status	
Significant oedema or positive fluid balance	> 20 ml/kg over 24 h)
Plasma glucose	> 120 mg/dl (7.7 mmol/l) if not diabetic
Inflammatory	
White blood cell count	$12{,}000\,\mu l^{-1}$ or $< 4000\,\mu l^{-1}$ (or > 10% immature forms)
Plasma C-reactive protein	> 2 SD above normal
Plasma procalcitonin	> 2 SD above normal
Haemodynamic	
Arterial hypotension	Systolic blood pressure < 90 mmHg, mean arterial blood pressure < 70, or fall in systolic blood pressure > 40 mmHg below normal)
Mixed venous oxygen saturation	< 70%
Cardiac index	$< 3.5\,l\,min^{-1}\,m^{-2}$
Organ dysfunction	
PaO_2/FIO_2 ratio	< 300 mmHg or 40 kPa
Urine output	$< 0.5\,ml\,kg^{-1}\,h^{-1}$ for at least 2 h
Creatinine increase	> 0.5 mg/dl
International normalised ratio	> 1.5 or activated partial thromboplastin time > 60 s
Ileus	
Platelet count	< 100,000/μl
Plasma bilirubin	> 4 mg/dl or 70 mmol/l
Tissue perfusion	
Plasma lactate	> 1 mmol/l
Decreased capillary refill or mottling	

their VO_2 beyond those of adequately volume resuscitated controls. A second study with similar outcomes [69] helped to establish a number of facts. First, patients with sepsis and septic shock who can improve their haemodynamic indices through adequate fluid resuscitation are likely to do better than those who do not. Second, supranormal targets for DO_2/VO_2 are at best unnecessary, and at worst increase mortality. Third, a beneficial response to fluid resuscitation is more likely in the acute phase, before established critical illness. Thus patients with severe sepsis and septic shock resuscitated to standard haemodynamic goals, who additionally achieve central venous oxygen saturation of 70% or higher within the first 6 h by fluid resuscitation, red cell transfusion to a haematocrit of 30%, and/or dobutamine (up to $20\,\mu g\,kg^{-1}\,min^{-1}$) display significantly lower 30- and 60-day mortality rates [56].

Ventilatory strategies

In those patients with sepsis who develop acute lung injury and require mechanical ventilatory support low tidal volumes (approx. 6 ml/kg) and inspiratory plateau pressures below $30\,cmH_2O$ should be used where possible. Such recommendations have emerged from animal studies [70, 71] and a retrospective analysis of patients with ARDS, which demonstrated that pressure-limited ventilation with so-called permissive hypercapnia reduced hospital mortality compared with APACHE II predictions (18.6% vs. 37.8%) [72]. It was, however, the pivotal ARDSnet study that demonstrated a 9% absolute mortality reduction (31% vs. 39.8% for controls) in patients with ARDS randomised to receive a tidal volume of 6 ml/kg with plateau pressure limited to less than $30\,cmH_2O$ [73]. By contrast, higher positive end expiratory pressures, prone positioning and the use of inhaled nitric oxide and surfactant have demonstrated only short-term improvements in oxygenation. The results of a large randomised controlled trial of steroid therapy in late stage ARDS based upon an encouraging single-centre study are awaited [74].

Management of renal dysfunction

The importance of maintaining regional perfusion in sepsis is increasingly recognised, not least the hepatosplanchnic circulation. Since the first experiences of arteriovenous haemofiltration in anuric intensive care patients with fluid overload resistant to diuretics in the 1970s [75], acute renal failure in the critically ill has been recognised to be of multifactorial aetiology. Hypotension, nephrotoxic drug insults, sepsis and preceding renal dysfunction may all be relevant [76]. Acute renal failure is an independent risk factor for mortality in the critically ill, which varies from 45% to 70% when associated with sepsis [77, 78]. Factors predicting a poor outcome are advanced age, altered pre-

Table 2 The Sequential Organ failure Assessment score (*MAP* mean arterial blood pressure, *Nor* norepinephrine, *Dop* dopamine, *Dob* dobutamine, *Epi* epinephrine; FIO_2 fraction of inspired oxygen, *GCS* Glasgow Coma Scale score) (adapted from [31])

	0	1	2	3	4
Respiratory: PaO_2/FIO_2 ratio	> 400	≤ 400	≤ 300	≤ 200[c]	≤ 100[c]
Coagulation: platelets ($\times 10^3$ µl^{-1})[a]	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver: bilirubin (mg dl^{-1})[a]	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	> 12.0
Cardiovascular: hypotension	No hypotension	MAP < 70 mmHg	Dop ≤ 5 or Dob any dose[d]	Dop > 5, Epi ≤ 0.1 or Nor ≤ 0.1[d]	Dop ≥ 15, Epi > 0.1 or Nor > 0.1[d]
Central nervous system: GCS	15	13–14	10–12	6–9	< 6
Renal: creatinine (mg dl^{-1}) or daily urine output (ml)[a]	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9or < 500	> 5 or < 200

[a] To convert bilirubin from mg dl^{-1} multiply by 17.1
[b] To convert mg dl^{-1} to µmol^{-1} multiply by 88.4
[c] Values are with respiratory support
[d] Adrenergic agents administered for 1 h or longer (doses as µg kg^{-1} min^{-1})

vious health status, later onset of acute renal failure, sepsis, oliguria and severity of illness [79]. The use of low-dose dopamine has been shown to be ineffective in halting the progression to acute renal failure in the critically ill [80, 81]. Daily intermittent haemodialysis is better than alternate-day haemofiltration in critically ill patients who require renal replacement therapy, improving the time to resolution and survival at 14 days [82]. Continuous renal replacement therapy has equivalent outcomes to intermittent renal replacement therapy for acute renal failure in critical illness, although the former may offer easier management of fluid balance in the haemodynamically unstable septic patient. Whether higher doses (i.e. ultrafiltration rates 35–45 vs. 20 ml kg^{-1} h^{-1}) of continuous renal replacement therapy confer a survival advantage in acute renal failure awaits corroboration [83].

Metabolic management

Impaired adrenoceptor responsiveness has long been recognised in endotoxic shock, partially reversible by corticosteroids [84, 85]. However, high doses of steroids (methylprednisolone 30 mg/kg or dexamethasone), administered on day 1 of septic shock failed to show an outcome benefit in two multicentre randomised controlled trial in the 1980s, with the abandonment of empirical steroid treatment, except for those with demonstrable adrenocortical insufficiency [86, 87, 88]. However, later work employing the prospective characterisation of the adrenal status of patients in septic shock, through the use of a 250 µg ACTH stimulation test, into so-called responders (proposed unimpaired adrenocortical axis) and non-responders (proposed relative adrenocortical insufficiency) proved more encouraging. Thus non-responders randomised to 50 mg hydrocortisone every 6 h plus 50 µg oral fludrocortisone for 7 days displayed a significantly better 28-day vasopressor-withdrawal effect and survival advantage than those receiving placebo [89]. Overall survival between the hydrocortisone and placebo groups was not statistically different [90]. An ongoing trial (EUROCORTICUS) aims to address previous findings and investigate the risk-benefit ratio of low-dose steroids in non-refractory septic shock.

Glycaemic control, whilst avoiding potentially deleterious episodes of hypoglycaemia, plays an important role in outcomes of sepsis-associated organ failures and mortality. Tight glucose control (4.4–6.1 mmol/l) compared with standard care confers significant survival advantage in post-operative cardiac surgery patients. Multiple-organ failure with a proven focus of sepsis was also decreased [91]. Recent studies further support tight but less stringent control of blood glucose in critically ill patients (8.0 mmol/l or less) but suggest that glucose control, rather than insulin dose per se, is more important in determining outcome [92].

Anti-thrombotic strategies

The inflammatory response in severe sepsis is integrally related to procoagulant activity and endothelial activation. Protein C is activated by complexing with thrombin and endothelial cell thrombomodulin. Activated protein C (APC) then modulates inflammation, coagulation and endothelial cell function. A deficiency of APC and lower levels of protein C activity in sepsis are correlated with higher mortality rates [93, 94]. The PROWESS trial of drotrecogin alfa (activated) (recombinant human APC, rhAPC) showed that patients with severe sepsis who were randomised to 96-h infusions of rhAPC (24 µg kg^{-1} h^{-1}) within 24 h of inclusion had significantly lower 28-day all-cause mortality vs. placebo (24.7% vs. 30.8% respectively). The incidence of serious bleeding was higher in the

Table 3 Management guidelines for 'early' (the initial few hours following suspected sepsis) and 'late' (the period beyond the first few hours of severe sepsis) severe sepsis and septic shock (*ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *APACHE* Acute Physiology and Chronic Health Evaluation, *MODS* multiple organ dysfunction syndrome) (adapted from [38])

Early sepsis
Investigations
Diagnosis
Elevated serum lactate
Microbiological cultures before anti-microbial therapy is initiated
Two or more blood cultures (percutaneously and vascular access)
Therapy
Initial resuscitation
Begin resuscitation immediately in patients with hypotension
Early goals
Central venous pressure: 8–12 mmHg
Mean arterial blood pressure: $\geq$ 65 mmHg and < 90 mmHg
Urine output: $\geq$ 0.5 ml kg^{-1} h
Central venous oxygen saturation or mixed venous saturation: $\geq$ 70%
During the first 6 h if goals not achieved with CVP of 8–12 mmHg
Transfuse packed red blood cells to hmt $\geq$ 30%, and/or
Dobutamine infusion to achieve goals
Antibiotic therapy
Intravenous antibiotic therapy *within the first hour* of recognition of severe sepsis, *after* appropriate cultures
Consider local microbiology susceptibility patterns in guiding treatment regimens
Reassess anti-microbial regimens after 48–72 h aiming to de-escalate empirical broad spectrum regimens, at the earliest opportunity
Source control measures
As soon as possible
Consider measures that are definitive but minimise physiological disturbance, e.g. percutaneous vs. surgical drainage of an abscess
Low threshold for suspecting and replacing intravascular access devices promptly
Late sepsis[a]
Investigations
Antibiotic therapy: as for early sepsis
Source control: as for early sepsis
Therapy
Fluid therapy
Crystalloid or colloid
Fluid challenges based on response and tolerance
Vasopressors
When an appropriate fluid challenge fails to restore adequate mean arterial pressure and organ perfusion
Vasopressor therapy may also be required transiently to sustain life and maintain perfusion
Norepinephrine (or dopamine)
Inotropic support
If a low CO persists despite adequate initial resuscitation
Dobutamine, epinephrine or dopamine will all increase CO. If used in the presence of low mean arterial pressure, consider combination with a vasopressor
Steroids
Intravenous corticosteroids: hydrocortisone 200–300 mg/day, for 7 days in patients with fluid-resuscitated, vasopressor-dependent septic shock
Those with a positive response to an ACTH stimulation test can discontinue therapy
Recombinant human activated protein C
Consider in patients with APACHE II $\geq$ 25, sepsis-induced MODS, septic shock, or sepsis-induced ARDS and without contraindications
Blood transfusion
Red blood cell transfusion when haemoglobin decreases to 7.0 g/dl to achieve a target of 7.0–9.0 g/dl
Only when early resuscitation is complete, and in the absence of significant coronary artery disease, acute haemorrhage, or lactic acidosis
Mechanical ventilation of sepsis-induced ALI/ARDS
Avoid high tidal volumes coupled with high plateau pressures
Aim to reduce tidal volumes to $\sim$ 6 ml.kg^{-1} of lean body weight and end inspiratory plateau pressure < 30 cmH_2O
Permissive hypercapnia allowable
Adjunctive strategies
Prone ARDS patients or utilise selective pulmonary vasodilators (i.e. Inhaled NO) for short term improvements in oxygenation, if requiring potentially injurious levels of FIO_2 or plateau pressure

[a] Management guidelines, once initial resuscitation/evaluation of the early sepsis strategies above have been fulfilled, but not mutually exclusive

Table 3 (*continued*)

> 30° semi-recumbent position to prevent ventilator associated pneumonia, unless contraindicated
Weaning
Use a weaning protocol and daily spontaneous breathing trial to evaluate for ventilation discontinuation
Sedation, analgesia, and neuromuscular blockade in sepsis
Use sedation protocols. Use standardised sedation scores, and retitrate daily to the minimum necessary dose
If necessary, retitrate neuromuscular blockers daily and monitor the depth of blockade
Glucose control
Maintain blood glucose < 150 mg/dl (8.3 mmol) following initial stabilisation
Renal replacement
Continuous veno-venous haemofiltration is equivalent to intermittent veno-venous haemofiltration, but offers easier management in haemodynamically unstable septic patients
Deep vein thrombosis prophylaxis
Use low-dose unfractionated heparin, low molecular weight heparin
Stress ulcer prophylaxis
Histamine (H_2) receptor blockers or alternatively proton pump inhibitors
Advanced care planning
Describe likely outcomes and realistic expectations

rhAPC group (3.5% vs. 2.0%, $p = 0.06$) [95], and it seems that sicker patients (APACHE II>25) benefit most from this therapy [96]. The effect was not reproduced in a large scale trial of anti-thrombin III in severe sepsis (mortality 38.9%, anti-thrombin group vs. 38.7% for placebo group) in spite of favourable indications from preclinical and phase II trials [97], in this sense mirroring experience with many other putative therapeutic interventions (i.e. anti-endotoxin, anti-TNF and nitric oxide synthase inhibition) trialled in patients with sepsis over many years [98, 99, 100, 101, 102, 103, 104, 105, 106, 107]. This failure (PROWESS notwithstanding) of new pharmacological therapies and immunotherapies in patients with sepsis may in part reflect the complexity of mechanisms leading to organ dysfunction and the consequent heterogeneity of the patient population. Whether new definitions are needed that may identify critically ill patients more likely to respond to novel therapies remains unclear [106].

Other strategies

Blood transfusion requirements in the critically ill have evolved from reports of its beneficial use dating back to 1935 and the appreciation of its value in improving tissue DO_2 in early resuscitation [108]. However, the Transfusion in Critical Care Trial demonstrated that a conservative strategy employing a hemoglobin threshold of 7.0 g/dl (to maintain hemoglobin between 7 and 9 g/dl) is not associated with higher mortality than with a liberal transfusion protocol (i.e. threshold 10 g/dl), previously accepted as standard practice. However, only 6% of patients enrolled had sepsis, and in patients with ischaemic cardiac disease a higher threshold was recommended [109]. The optimal haemoglobin levels of specific groups of critically ill patients are therefore as yet unstudied, and the value of recombinant erythropoietin remains unclear.

Stress-ulcer prophylaxis to prevent clinically important bleeding from the gastrointestinal tract in critically ill patients is well established, and the predisposing factors (i.e. coagulopathy, hypotension and mechanical ventilation) are frequently present in patients with sepsis [110]. However, relatively small percentages of patients develop clinically important bleeding from recent observational studies. Moreover, the pursuit of early enteral nutrition where possible, together with a trend to an increased incidence of ventilator associated pneumonia by H_2 antagonists/proton pump inhibitors, means that identifying subgroups of patients who may benefit most from stress ulcer prophylaxis remains difficult.

Conclusions

Multiple organ dysfunction complicating sepsis remains the commonest cause of mortality in the ICU. However, its mechanisms remain unknown, and the results of pathological autopsy studies show no correlation with degree of organ dysfunction or with specific causes of death. Nevertheless, these mechanisms continue to be unravelled, alongside emerging genetic predisposing targets. Moreover, the concept of a variable immune status, which can be tracked during sepsis and modulated, provides an increasing number of potential new therapeutic targets. A body of evidence accrued over decades reemphasises the fundamental importance of early recognition of physiological surrogates of tissue dysoxia in reducing associated organ dysfunction. Local and International clinical strategies, through a phased approach of the development of evidenced-based guidelines (incorporating proven strategies in sepsis), their implementation and evaluation, have undertaken the challenge of effecting improved survival in this patient population.

References

1. Members of the American College of Chest Physicians/Society of Crit Care Med Consensus Conference Committee: American College of Chest Physicians/Society of Crit Care Med Consensus conference (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20:864–874
2. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, SCCM/ESICM/ACCP/ATS/SIS (2003) 2001 International Sepsis Definitions Conference. Crit Care Med 31:1250–1256
3. Brun-Buisson C (2000) The epidemiology of the systemic inflammatory response. Intensive Care Med 26 [Suppl 1]:S64–S74
4. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348:1546–1554
5. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B (2003) Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med 168:165–172
6. Padkin A, Goldfrad C, Brady AR, Young D, Black N, Rowan K (2003) Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales, and Northern Ireland. Crit Care Med 31:2332–2338
7. Eiseman B, Beart R, Norton L (1977) Multiple organ failure. Surg Gynecol Obstet 144:323–326
8. Fry DE, Pearlstein L, Fulton RL, Polk HC Jr (1980) Multiple system organ failure. Arch Surg 115:136–140
9. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, LeGall JR, Morris A, Spragg R (1994) The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824
10. Milberg JA, Davis DR, Steinberg KP, Hudson LD (1995) Improved survival of patients with acute respiratory distress syndrome 1983–1993. JAMA 273:306–309
11. Angus DC, Musthafa AA, Clermont G, Griffin MF, Linde-Zwirble WT, Dremsizov TT, Pinsky MR (2001) Quality-adjusted survival in the first year after the acute respiratory distress syndrome. Am J Respir Crit Care Med 163:1389–1394
12. Fink MP, Evans TW (2002) Mechanisms of organ dysfunction in critical illness: report from a round table conference held in Brussels. Intensive Care Med 28:369–375
13. Parrillo JE, Burch C, Shelhamer JH, Parker MM, Natanson C, Schuette W (1985) A circulating myocardial depressant substance in humans with septic shock. Septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. J Clin Invest 76:1539–1553
14. Lam C, Tyml K, Martin C, Sibbald W (1994) Microvascular perfusion is impaired in a rat model of normotensive sepsis. J Clin Invest 94:2077–2083
15. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL (2004) Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 32:1825–1831
16. Fink MP (2002) Bench-to-bedside review: cytopathic hypoxia. Crit Care 6:491–499
17. Sair M, Etherington PJ, Winlove CP, Evans TW (2001) Tissue oxygenation and perfusion in human skeletal muscle in patients with systemic sepsis. Crit Care Med 29:1343–1349
18. Brealey D, Brand M, Hargreaves I, Heales S, Land J, Smolenski R, Davies NA, Cooper CE, Singer M (2002) Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet 360:219–223
19. Mira JP, Cariou A, Grall F, Delclaux C, Losser MR, Heshmati F, Cheval C, Monchi M, Teboul JL, Riche F, Leleu G, Arbibe L, Mignon A, Delpech M, Dhainaut JF (1999) Association of TNF2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. JAMA 282:561–568
20. Levi M, Ten Cate H (1999) Disseminated intravascular coagulation. N Engl J Med 341:586–592
21. Godin PJ, Buchman TG (1996) Uncoupling of biological oscillators: a complementary hypothesis concerning the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med 24:1107–1116
22. Fink MP (2005) Epithelial barrier dysfunction: a unifying theme to explain the pathogenesis of multiple organ dysfunction at the cellular level. Crit Care Clin 21:177–196
23. Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV (1986) Multiple-organ-failure syndrome: the gastrointestinal tract-the motor of MOF. Arch Surg 121:197–201
24. Fine J, Frank ED, Rutenberg SH, Schweinburg FB (1959) The bacterial factor in traumatic shock. N Engl J Med 260:214–220
25. Chiu CJ, McArdle AH, Brown R, Scott HJ, Gurd FN (1970) Intestinal mucosal lesion in low-flow states. A morphological, hemodynamic, and metabolic appraisal. Arch Surg 101:478–483
26. Fink MP, Antonsson JB, Wang HL, Rothschild HR (1991) Increased intestinal permeability in endotoxic pigs. Mesenteric hypoperfusion as an etiologic factor. Arch Surg 126:211–218
27. Matuschak GM, Rinaldo JE (1988) Organ interaction in the adult respiratory distress syndrome during sepsis: role of the liver in host defence. Chest 94:400–406
28. Hatherill M, Tibby SM, Turner C, Ratnavel N, Murdoch IA (2000) Procalcitonin and cytokine levels: relationship to organ failure and mortality in pediatric septic shock. Crit Care Med 28:2591–2594
29. Hotchkiss RS, Karl IE (2003) The pathophysiology and treatment of sepsis. N Engl J Med 348:138–150
30. Hotchkiss RS, Swanson PE, Freeman BD, et al (1999) Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med 27:1230–1251
31. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) Prognosis in acute organ-system failure. Ann Surg 202:685–693

32. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
33. Lemeshow S, Klar J, Teres D, Avrunin JS, Gehlbach SH, Rapoport J, Rue M (1994) Mortality probability models for patients in the intensive care unit for 48 or 72 hours: a prospective, multicenter study. Crit Care Med 22:1351–1358
34. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A (1991) The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100:1619–1636
35. Moreno R, Morais P (1997) Outcome prediction in intensive care: results of a prospective, multicentre Portuguese study. Intensive Care Med 23:177–186
36. Moreno R, Vincent JL, Matos R, Mendonca A, Cantraine F, Thijs L, Takala J, Sprung C, Antonelli M, Bruining H, Willatts S (1999) The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Intensive Care Med 25:686–696
37. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL (2001) Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286:1754–1758
38. Joly HR, Weil MH (1969) Temperature of the great toe as an indication of the severity of shock. Circulation 39:131–138
39. Yoshiya I, Shimada Y, Tanaka K (1980) Spectrophotometric monitoring of arterial oxygen saturation at the fingertip. Med Biol Eng Comput 18:27–32
40. Lundberg N, Troupp H, Lorin H (1965) Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. J Neurosurg 22:581–590
41. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J (1992) Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 339:195–199
42. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL (1996) Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 171:221–226
43. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32:858–873
44. Khalil HH, Richardson TQ, Guyton AC (1966) Measurement of cardiac output by thermal dilution and direct Fick method in dogs. J Appl Physiol 21:1131–1135
45. Branthwaite MA, Bradley RD (1968) Measurement of cardiac output by thermal dilution in man. J Appl Physiol 24:434–438
46. Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D (1970) Catheterisation of the heart in man with use of a flow directed balloon-tipped catheter. N Engl J Med 283:447–451
47. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ Jr, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA (1996) The effectiveness of right heart catheterisation in the initial care of critically ill patients. SUPPORT investigators. JAMA 276:889–897
48. Matthay MA, Chatterjee K (1988) Bedside catheterisation of the pulmonary artery: risks compared with benefits. Ann Intern Med 109:826–834
49. Linton RA, Band DM, Haire KM (1993) A new method of measuring cardiac output in man using lithium dilution. Br J Anaesth 71:262–266
50. Orme RM, L'EPigott DW, Mihm FG (2004) Measurement of cardiac output by transpulmonary arterial thermodilution using a long radial artery catheter. A comparison with intermittent pulmonary artery thermodilution. Anaesthesia 59:590–594
51. Singer M, Clarke J, Bennett ED (1989) Continuous haemodynamic monitoring by esophageal Doppler. Crit Care Med 17:447–452
52. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F (2003) Hemodynamic instability in sepsis: bedside assessment by Doppler echocardiography. Am J Respir Crit Care Med 168:1270–1276
53. Armstrong RF, Walker JS, Andrew DS, Cobbe SM, Cohen SL, Lincoln JC (1978) Continuous monitoring of mixed venous oxygen tension (PvO2) in cardiorespiratory disorders. Lancet I:632–634
54. Reinhart K, Kuhn HJ, Hartog C, Bredle DL (2004) Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. Intensive Care Med 30:1572–1578
55. Rady MY, Rivers EP, Nowak RM (1996) Resuscitation of the critically ill in the ED: responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. Am J Emerg Med 14:218–25
56. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
57. Weil MH, Shubin H, Biddle M (1964) Shock caused by Gram-negative organisms: analysis of 169 cases. Ann Intern Med 60:384–400
58. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH (2000) The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 118:146–155
59. MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L, Barchuk W (2004) Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 38:284–288
60. MacLean LD, Mulligan WG, McLean APH, Duff JH (1967) Patterns of septic shock in man—a detailed study of 56 patients. Ann Surg 166:543–562
61. Cochrane Injuries Group Albumin Reviewers (1998) Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ 317:235–240
62. Choi PT, Yip G, Quinonez LG, Cook DJ (1999) Crystalloids vs. colloids in fluid resuscitation: a systematic review. Crit Care Med 27:200–210
63. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247–2256
64. American Thoracic Society (2004) Evidence based colloid use in the critically ill. American Thoracic Society consensus statement. Am J Respir Crit Care Med 170:1247–1259
65. Shoemaker WC, Appel PL, Kram HB (1986) Hemodynamic and oxygen transport effects in critically ill general surgical patients. Crit Care Med 14:1032–1037

66. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients. Chest 94:1176–1186
67. Boyd O, Grounds RM, Bennett ED (1993) A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high risk surgical patients. JAMA 270:2699–2707
68. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330:1717–1722
69. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R (1995) A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025–1032
70. Webb HH, Tierney DF (1974) Experimental pulmonary oedema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 110:556–565
71. Dreyfuss D, Soler P, Basset G, Saumon G (1988) High Inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137:1159–1164
72. Hickling KG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16:372–377
73. Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
74. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, Tolley EA (1998) Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomised controlled trial. JAMA 280:159–165
75. Kramer P, Kaufhold G, Grone HJ, Wigger W, Rieger J, Matthaei D, Stokke T, Burchardi H, Scheler F (1980) Management of anuric intensive care patients with arteriovenous hemofiltration. Int J Artif Organs 3:225–230
76. Rasmussen HH, Ibels LS (1982) Acute renal failure; a multivariate analysis of causes and risk factors. Am J Med 73:211–218
77. Levy EM, Viscoli CM, Horowitz RI (1996) The effect of acute renal failure on mortality: a cohort analysis. JAMA 275:1489–1494
78. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29:1303–1310
79. Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ (1996) Acute renal failure in intensive are units-causes, outcome, and prognostic factors for hospital mortality. Crit Care Med 24:192–198
80. Goldberg LI, Mcdonald RH, Zimmerman AM (1963) Sodium diuresis produced by dopamine in patients with congestive heart failure. N Engl J Med 263:1060–1064
81. Australia and New Zealand Intensive Care Society (ANZICS) Clinical Trials group (2000) Low dose dopamaine in patients with early renal dysfunction: a placebo-controlled randomised trial. Lancet 356:2139–2143
82. Schiffl H, Lang SM, Fischer R (2002) Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 346:305–310
83. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G (2000) Effects of different doses in continuous venovenous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 356:26–30
84. Weil MH, Shubin H, Biddle M (1964) Shock caused by Gram-negative micro-organisms: analysis of 169 cases. Ann Intern Med 60:384–400
85. Schumer W (1976) Steroids in the treatment of clinical septic shock. Ann Surg 184:333–341
86. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA (1987) A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317:653–658
87. Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, Duncan RC, Tendler MD, Karpf M (1984) The effects of high-dose corticosteroids in patients with septic shock. N Engl J Med 311:1137–1143
88. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A (1998) Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 26:645–650
89. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E (2000) A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 283:1038–1045
90. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862–871
91. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R (2001) Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359–1367
92. Finney SJ, Zekveld C, Elia A, Evans TW (2003) Glucose control and mortality in critically ill patients. JAMA 2041–2047
93. Levi M, ten Cate B (1999) Disseminated intravascular coagulation. N Engl J Med 341:586–592
94. Yan SB, Helterbrand JD, Hartman DL, Wright TJ, Bernard GR (2001) Low levels of protein C are associated with poor outcomes in sepsis. Chest 120:915–922
95. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group (2001) Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709
96. Vincent JL (2003) Effects of drotrecogin alfa (activated) on organ dysfunction in the PROWESS Trial. Crit Care Med 31:834–840
97. Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Penzes I, Kubler A, Knaub S, Keinecke HO, Heinrichs H, Schindel F, Juers M, Bone RC, Opal SM; KyberSept Trial Study Group (2001) Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 286:1869–1878
98. Ziegler EJ, McCutchan JA, Fierer J, Glauser MP, Sadoff JC, Douglas H, Braude AI (1982) Treatment of gram-negative bacteremia and shock with human anti-serum to a mutant Escherichia coli. N Engl J Med 307:1225–1230

99. Ziegler EJ, Fisher CJ Jr, Sprung CL, Straube RC, Sadoff JC, Foulke GE, Wortel CH, Fink MP, Dellinger RP, Teng NN; HA-1A Sepsis Study Group (1991) Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomised, double blind placebo controlled trial. N Engl J Med 324:429–436
100. Greenman RL, Schein RM, Martin MA, Wenzel RP, MacIntyre NR, Emmanuel G, Chmel H, Kohler RB, McCarthy M, Plouffe J; XOMA Sepsis Study Group (1991) A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. JAMA 266:1097–1102
101. Abraham E, Wunderink R, Silverman H, Perl TM, Nasraway S, Levy H, Bone R, Wenzel RP, Balk R, Allred R (1995) Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. JAMA 273:934–941
102. Cohen J, Carlet J (1996) INTERSEPT: an international, multicenter, placebo-controlled trial of monoclonal antibody to human tumor necrosis factor-alpha in patients with sepsis. International Sepsis Trial Study Group. Crit Care Med 24:1431–1440
103. Abraham E, Anzueto A, Gutierrez G, Tessler S, San Pedro G, Wunderink R, Dal Nogare A, Nasraway S, Berman S, Cooney R, Levy H, Baughman R, Rumbak M, Light RB, Poole L, Allred R, Constant J, Pennington J, Porter S (1998) Double blind randomised controlled trial of monoclonal antibody to human tumor necrosis factor in the treatment of septic shock. NORASEPT II Study Group. Lancet 351:929–933
104. Panacek EA, Marshall JC, Albertson TE, Johnson DH, Johnson S, MacArthur RD, Miller M, Barchuk WT, Fischkoff S, Kaul M, Teoh L, Van Meter L, Daum L, Lemeshow S, Hicklin G, Doig C; Monoclonal Anti-TNF Randomized Controlled Sepsis Study Investigators (2004) Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. Crit Care Med 32:2173–2182
105. Marshall JC (2003) Much stuff as dreams are made on: mediator directed therapy in sepsis. Nat Rev Drug Discov 2:391–395
106. Abraham E, Matthay MA, Dinarello CA, Vincent JL, Cohen J, Opal SM, Glauser M, Parsons P, Fisher CJ Jr, Repine JE (2000) Consensus conference definitions for sepsis, septic shock, acute lung injury, and acute respiratory distress syndrome: time for a reevaluation. Crit Care Med 28:232–235
107. Lopez A, Lorente JA, Steingrub J, Bakker J, McLuckie A, Willatts S, Brockway M, Anzueto A, Holzapfel L, Breen D, Silverman MS, Takala J, Donaldson J, Arneson C, Grove G, Grossman S, Grover R (2004) Multiple-center, randomised placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. Crit Care Med 32:21–30
108. Marriott HL, Kerwick A (1935) Continuous drip blood transfusion. Lancet 1:977–981
109. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E; Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group (1999) A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 340:409–17 (erratum: 340:1056)
110. Cook D, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, Peters S, Rutledge F, Griffith L, McLellan A, Wood G, Kirby A (1998) The Canadian Critical Care Trials Group. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. N Engl J Med 338:791–797

Lorraine N. Tremblay
Arthur S. Slutsky

Ventilator-induced lung injury: from the bench to the bedside

Introduction

Once upon a time the existence of ventilator-induced lung injury (VILI) was debated. After all, most patients with lung dysfunction requiring mechanical ventilation had other potential causes of lung injury, and many patients appeared to tolerate mechanical ventilation for prolonged periods without any adverse sequelae. However, as a result of numerous studies over the past century, and especially during the past 20 years it is now generally accepted that mechanical ventilation per se can initiate as well as exacerbate lung injury and contribute to patient morbidity and mortality. This review examines the seminal bench and bedside studies that contributed to our current understanding of VILI, and that form the basis for current recommendations for mechanical ventilation of the critically ill. Figure 1 schematically depicts a timeline of bench to bedside research on VILI. Included in this review are many of the most frequently cited studies (with the number of citations, *N*, from the Institute for Science Information Citation Index as of August 2005 included in parentheses), as well as those studies which the authors feel have had a particularly significant impact on subsequent research and/or clinical practice.

Brief overview of the early years: air leaks, surfactant dysfunction, and "respirator lung"

As early as the 1700s investigators raised concerns that inflation of the lung with positive pressure ventilation could potentially damage the lungs and produce air leaks (for an excellent historical review see [1]). In 1887 Champneys [2] reported that lung rupture and cervical emphysema ensue if the lungs of dead infants are subjected to pressures of 20–80 mmHg. In 1939 Macklin [3] (Number of citations, *N*=467) published a frequently cited study demonstrating that excessive alveolar distension produces rupture at the junction of the alveolar wall and vascular sheath, allowing air to track along the bronchovascular sheath into the mediastinum and subcutaneous tissues or to rupture into the pleural or peritoneal spaces. Given that the development of air leaks appeared to be related to the use of high airway pressures, the term "barotrauma" was applied.

In addition to air leaks, laboratory investigations also demonstrated that mechanical ventilation can adversely affect lung compliance and surfactant function. Greenfield et al. [4] (*N*=115) showed that ventilation of dog lungs with large tidal volume (V_t; generated with a peak inspiratory pressure, PIP, of 36–32 cmH_2O) for 2 h produces surfactant dysfunction, and Faridy et al. [5] (*N*=178) observed in an ex vivo dog lung model that the addition of positive end expiratory pressure (PEEP) attenuates ventilation-induced increases in surface tension.

Early investigators also made a number of important observations. For example, in 1949 Fowler [6] (*N*=325)

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_60, © Springer-Verlag Berlin Heidelberg 2009

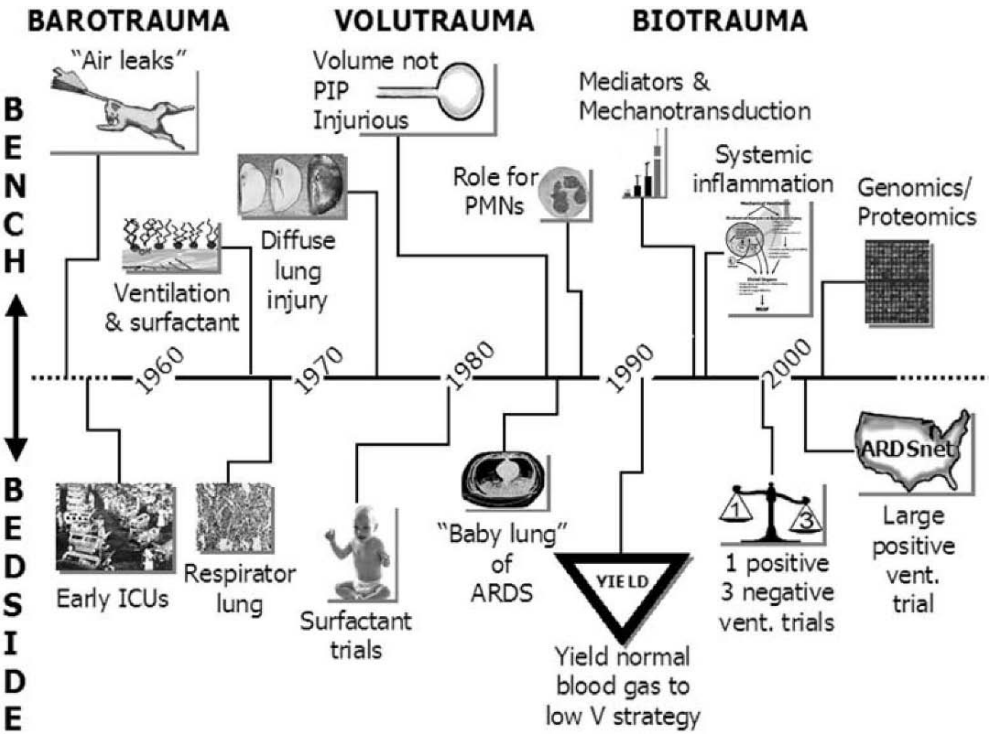


Fig. 1 Time line illustrating a number of the seminal basic science (*top*) and clinical (*bottom*) observations that have influenced our understanding of ventilator-induced lung injury and have changed ventilatory support of critically ill patients over the years

published a key observation that would be revisited in later studies of VILI: the fact that ventilation in lungs is not uniform, particularly in the presence of underlying lung disease. Mead et al. [7] (*N*=584) published an often cited paper examining the forces acting on alveoli within the lung. They illustrated that although uniform force proportional to the transalveolar pressure acts on adjacent alveoli in a uniformly expanded lung, the traction forces exerted by adjacent expanded alveoli on the walls of a collapsed alveolus can greatly exceed transpulmonary pressure (e.g., exceed 140 cmH_2O) due to interdependence.

On the clinical front the use of mechanical ventilation as a supportive therapy outside the operating theater became increasingly widespread in the aftermath of the polio epidemics of the 1950s, and the term "respirator lung" started being applied to autopsy findings of diffuse alveolar damage (dense pulmonary cellular infiltrates, pulmonary edema, and hyaline membranes) in critically ill patients who had required ventilation with high airway pressures prior to death. Indeed, when Ashbaugh et al. [8] (*N*=1193) submitted their landmark paper in 1967 on acute respiratory distress (ARDS) in adults, one reviewer purportedly dismissed this "new" syndrome as simply a manifestation of VILI [9].

Recognizing that it would be impossible in the clinical arena to dissect out the contribution of ventilator-induced injury from lung injury due to other causes, investigators turned to the bench.

Seminal bench studies on ventilator-induced injury

The initial challenge tackled by investigators was determining whether mechanical ventilation per se could produce diffuse lung injury (i.e., "respirator lung"), and if so, what ventilatory parameters (e.g., V_t, end-expiratory pressure) were responsible.

Can mechanical ventilation produce lung injury other than air leaks, and at what ventilatory settings?

A landmark paper examining this question was published by Webb and Tierney [10] (*N*=374) in 1974 entitled "Experimental pulmonary-edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure." Realizing that "some patients with ARDS may require pressures of 40–80 cmH_2O," Webb and Tierney set out to determine whether the "only complications of these pressures involve lung rupture with interstitial emphysema or pneumothorax." Their study design consisted of ventilating rats with normal lungs with PIP values of 14, 30, or 45 cmH_2O without PEEP, as well as with PIP of 30 or 45 cmH_2O and 10 cmH_2O of PEEP. In order to maintain similar $PaCO_2$ with the various ventilation strategies the dead space of the ventilatory circuit was altered.

This seminal study had several key findings. First, in keeping with prior studies, Webb and Tierney demonstrated that ventilation of normal lungs with low pressures

(PIP 14 cmH_2O) does not cause significant injury. Second, they dramatically showed that ventilation with high pressures (30 or 45 cmH_2O) produces perivascular edema, and that ventilation at high airway pressures (45 cmH_2O) without PEEP leads to severe lung injury (gross pulmonary edema, severe hypoxia) as well as death within 35 min. Third, they showed that PEEP confers protection from alveolar edema due to high inspiratory pressure ventilation.

Based on the results of this study, Webb and Tierney put forth a number of precepts that future research would validate: (a) that lungs from patients with ARDS have some "normal alveoli scattered among collapsed or fluid-filled alveoli, and that although the flooded alveoli "may be protected from over inflation... we are concerned that the normal alveoli may be over inflated and damaged," (b) that "tissue disruption secondary to a high inspiratory pressure is probably not the mechanism of the changes we observed," and (c) that surfactant dysfunction with certain ventilatory strategies likely contributed to the development of lung injury. Prophetically, they concluded with the comment that the results "have influenced our management of patients requiring ventilatory assistance. We avoid the use of high inspiratory pressure positive pressure breathing, especially if the end-expiratory volume is low, as for example in patients with ARDS..." and "in such situations we strive to avoid high inspiratory pressures, use a low frequency, and apply PEEP" (quite similar to current recommendations decades later).

However, the study by Webb and Tierney (and other animal studies to follow) had a number of significant limitations. As would subsequently become even more apparent, different species have different susceptibility to VILI (i.e., small species are generally more susceptible). Therefore it remained uncertain whether the bench findings were applicable to humans. Second, the period of ventilation in this study was only approx. 60 min (N.B. short periods of ventilation are a limitation of most bench studies). As such, it remained unclear whether the results were applicable to the lung injury found with longer periods of ventilation. Third, hemodynamic parameters were not measured or controlled between groups and lung volumes (e.g., V_t, end-inspiratory volume) were not measured. Thus it remained unclear whether other factors (e.g., hypotensive shock) may have contributed to the lung injury. Finally, the study did not dissect out the mechanisms responsible for high inspiratory pressure VILI.

What ventilatory parameters are injurious and how?

In a series of eloquently designed experiments Dreyfuss and colleagues [11, 12, 13] explored which of the many parameters of mechanical ventilation (e.g., V_t, PIP, end expiratory lung volume) is responsible for the development of pulmonary edema, and whether the physiological changes seen with injurious ventilation are associated with any ultrastructural changes (as assessed by electron microscopy). In their 1985 paper Dreyfuss et al. [11] demonstrated that high pressure (PIP 45 cmH_2O) ventilation of rat lungs in vivo increases extravascular water and lung albumin uptake rapidly (within 5 min of ventilation), and that with longer periods of ventilation (up to 20 min) a progressive increase in lung injury occurs (i.e., endothelial cell detachment and blebs progressing to diffuse injury including denudation of the epithelial basement membrane, interstitial and alveolar edema with hyaline membranes and cell debris) [11] (*N*=364). This study illustrated that injurious ventilation of normal lungs could not only produce ultrastructural cellular damage, but that this injury occurs within *minutes* of initiating an injurious ventilation strategy.

Dreyfuss et al. [12] (*N*=503) also explored whether it was the high airway pressure per se or the resulting lung volume that leads to VILI and pulmonary edema. In order to differentiate the effect of airway pressure from that of lung volume rats were subjected to one of the following five ventilatory strategies: (a) low PIP (7 cmH_2O) resulting in relatively low V_t (13 ml/kg); (b) high PIP (45 cmH_2O) resulting in high V_t (40 ml/kg); (c) high PIP (45 cmH_2O) and 10 cmH_2O PEEP (V_t 25 ml/kg); (d) high PIP (45 cmH_2O) but restricted V_t (19 ml/kg, produced by using a thoracoabdominal binder to limit chest wall excursion); and (e) negative inspiratory pressure (using a mini-iron lung) and high V_t (44 ml/kg). The key finding of this study was that high V_t ventilation, irrespective of airway pressure, produces severe lung injury characterized by pulmonary edema, increased alveolar-capillary permeability, and structural abnormalities. In contrast, ventilation with lower V_t, irrespective of airway pressure, does not produce ultrastructural changes or signs of alveolar edema or hemorrhage. In addition, PEEP once again was found to be "protective," as the presence of PEEP prevented pulmonary epithelial damage and alveolar edema and significantly reduced interstitial edema and endothelial cell changes. As a result of this study (and several confirmatory studies in other models, see [13]), researchers began to focus in on "volutrauma" (i.e., injury due to lung volume which is proportional to the transmural pressure gradient across the alveolus) rather than "barotrauma" (injury due to airway pressure) as the predominant injurious ventilatory parameter. These results agreed with Bouhuys' [14] observation in *Nature* in 1969 that musicians playing the trumpet repetitively develop pressures at the airway opening of approx. 150 cmH_2O without developing lung injury. Further laboratory studies showed that ventilation with either high V_t or high end-inspiratory lung volume is detrimental [13].

Meanwhile, other investigators such as West et al. [15] and Parker et al. [16, 17] focused on the injurious forces acting on the opposite side of the thin (<0.4 μm) alveolar

capillary interface, i.e., the endothelial surface. Using isolated perfused rabbit lungs, West et al. [15] (*N*=230) examined the role of three of the major forces acting on the pulmonary capillary wall (circumferential tension due to transmural pressure, surface tension of the alveolus, and longitudinal tension due to lung inflation) and demonstrated that at high lung volume or with high perfusion pressure, capillary stress failure greatly increases.

Multiple investigators also explored the relationship between PEEP and VILI (including what level of PEEP is associated with reduced alveolar edema, surfactant dysfunction, histological injury, and improved gas exchange). Studies showed that in experimental models in which excessive lung distension could occur with high PEEP (e.g., open chest models or ex vivo lungs), high PEEP worsened lung edema. However, with in vivo models in which lung volume was restricted by the chest wall, high PEEP resulted in cardiovascular compromise and was associated with either increased or decreased pulmonary edema. The particular level of PEEP that was injurious appeared to depend on a number of factors including the experimental model, animal species, and end-inspiratory lung volume (with similar PEEP leading to more adverse sequelae in ex vivo models, smaller species or with large lung volumes) [13].

Conversely, ventilation without PEEP did not appear to cause significant injury, provided low airway pressure/physiological V_t was used in normal lungs in vivo (i.e., with intact negative pleural pressure to maintain end-expiratory lung volume) for short periods of time. However, ventilation with low PEEP or no PEEP in ex vivo lungs, or lungs with surfactant dysfunction (such as occurs with high V_t ventilation) was associated with lung injury and dysfunction. For example, in an ex vivo rat lung model Muscedere et al. [18] (*N*=332) illustrated that ventilation using PEEP below the inflection point of the pressure-volume curve resulted in significant distal airway injury and reduced lung compliance as compared to the minimal injury found if PEEP greater than the inflection point was used. These studies led to a new concept in VILI—"atelectrauma" (injury from repetitive opening and collapse of distal lung units due to insufficient end-expiratory lung volume) [19] (*N*=46).

Factors that predispose to ventilator-induced lung injury

Multiple bench studies have also identified a number of factors (such as underlying lung disease, systemic inflammation, surfactant dysfunction, aspiration, pulmonary edema, extremes of age, heterogeneous lung ventilation) that increase the susceptibility of lungs to injury by mechanical ventilation. Often a synergistic interaction was found between mechanical ventilation and a preexisting lung abnormality. For example, in isolated perfused rabbit lungs Hernandez et al. [20] (*N*=63) demonstrated that, individually, oleic acid or ventilation with PIP of 25 cmH_2O has negligible effects on lung capillary filtration coefficients. However, when the insults are combined, severe lung injury (pulmonary edema, hyaline membranes, and extensive alveolar hemorrhage) ensue. Similarly, they found that age or surfactant inactivation predisposes to increased injury with subsequent mechanical ventilation [21, 22], and Dreyfuss et al. [23] (*N*=93) demonstrated a synergistic interaction between high volume ventilation (V_t 45 ml/kg) and pretreatment of rats with α-naphthylthiourea (a drug that increases alveolar capillary permeability and edema). Of the various factors studied particular attention was paid to surfactant dysfunction, given its prevalence in both neonatal respiratory distress and in adult lung disorders such as aspiration and lung sepsis (for review see [24]).

Several explanations have been put forth as to why such preexisting lung abnormalities increase the susceptibility to mechanical VILI. First, for structural disruption to occur the magnitude of force applied must exceed the resilience of the underlying lung parenchyma. Thus it follows that factors that either increase the forces applied to regions of the lung (e.g., surfactant dysfunction, heterogeneous ventilation due to atelectasis and flooded alveoli, repetitive opening and collapse of alveoli) or weaken lung tissue (such as age, inflammation) predispose to injury. In addition, factors that prime the inflammatory response or inhibit tissue healing also increase the lung's susceptibility to VILI [25], as does genetic predisposition. It is thought that the interaction of mechanical ventilation with other coexisting lung abnormalities is one explanation as to why identical ventilation settings produce VILI in some individuals but not all.

Is the mechanism of ventilator-induced injury due solely to physical disruption due to excessive force?

Most of the investigations cited above suggest physical disruption of the lung (e.g., capillary stress failure by alveolar overdistension) as one mechanism whereby mechanical ventilation produces lung injury. However, evidence of a potentially important role for ventilator-induced molecular and cell-mediated events in the pathogenesis of ventilator-induced injury soon began to emerge.

In 1983 Hamilton et al. [26] (*N*=263) published a study showing a benefit of high-frequency oscillation (i.e., using 15 Hz, V_t 1.5 ml/kg; mean airway pressure 15 cmH_2O) compared to "conventional" ventilation (using PIP 25 cmH_2O; PEEP 6 cmH_2O) in surfactant depleted rabbits. In this study the authors found significantly better lung function with fewer signs of histological lung injury in the high-frequency oscillation study group than in the conventional ventilation group. On further analysis, however, the investigators noted the presence of granu-

locyte infiltration in the alveoli and interstitium of the rabbits in the conventional ventilation group. To determine whether the granulocytes had a significant role in producing ventilation related lung injury Kawano et al. [27] (*N*=126) repeated the study using both neutrophil-depleted rabbits and neutrophil-depleted rabbits in which the granulocytes were reintroduced. They found that in contrast to rabbits with neutrophils, the neutrophil-depleted rabbits did not develop significant lung injury (changes in oxygenation, vascular permeability, hyaline membranes or granulocyte infiltration) with conventional ventilation. However, when neutrophils were reinfused into the neutrophil depleted rabbits, lung dysfunction ensued. Thus lung injury due to surfactant dysfunction/VILI in this model was not due simply to structural disruption but was mediated in large part by granulocytes.

Other investigators have observed that ventilation of lungs can increase levels of inflammatory mediators within the lungs, and that treatment with blockers of inflammatory mediators can reduce ventilator associated lung injury. For example, Tremblay et al. [28] (*N*=364) found increased bronchoalveolar lavage levels of several inflammatory mediators—including tumor necrosis factor (TNF) α, interleukin (IL) 6, and IL10—in ex vivo rat lungs subjected to injurious ventilation strategies. The same investigators in another report [29] (*N*=75) coined the term "biotrauma" to encompass this new field of investigation of molecular and cell mediated mechanisms of VILI. Supportive of this hypothesis, investigators such as Narimanbekov and Rozycki [30] (*N*=52) demonstrated that use of cytokine modulators can reduced lung dysfunction following mechanical ventilation. Administration of an IL-1 receptor antagonist prior to initiation of the injurious ventilation strategy in surfactant depleted rabbits reduced the severity of lung injury (bronchoalveolar lavage levels of polymorphonuclear cells, elastase, and albumin) produced by hyperoxia and 8 h of ventilation with 24 cmH_2O PIP. Of note, in this study the use of IL-1 receptor antagonist (RA) did not significantly improve either lung compliance or oxygenation. Other investigators, however, have demonstrated reduced ventilator associated lung injury as well as reduced ventilator-associated systemic abnormalities (such as increased gut permeability) using mediators such as anti-TNF or transgenic mice strains (for a concise summary of these studies see [31]).

Numerous subsequent studies have revealed species and model-specific differences with regards to levels of multiple mediators (including cytokines, receptors, ion channels, proteases, and extracellular components such as collagen/laminin) as well as a role for various cell types in addition to neutrophils in mediating the ventilator associated inflammatory response (e.g., type II pneumocytes, macrophages). Studies have also suggested that mechanotransduction (the conversion of externally applied forces on cells into activation of various cell signaling pathways and alterations in gene expression or cell structure) plays a role in VILI, and multiple stretch-activated signal transduction pathways (e.g., mitogen-activated protein kinases, stretch-sensitive ion channels, integrin receptors) have been identified. In a seminal study using an isolated perfused rat lung model Parker et al. [16] (*N*=51) abrogated the increase in microvascular permeability due to high PIP ventilation (20 and 30 cmH_2O) with gadolinium (an inhibitor of endothelial stretch-activated cation channels). In a subsequent study Parker et al. [17] demonstrated in the same model that inhibition of phosphotyrosine kinase increases the susceptibility of the lungs to high PIP injury; in contrast, inhibition of tyrosine kinase attenuates lung injury. The results of these studies lent further support to the contention that ventilation-induced changes in microvascular permeability is actively modulated by a molecular response to ventilation rather than simply a result of passive structural failure of the alveolar capillary membrane.

Not surprisingly, significant debate has ensued and continues as to the relative contribution of physical disruption vs. biotrauma in the pathogenesis of ventilator-induced injury [32, 33].

Is ventilator-induced injury limited to the lung?

Early investigators appreciated that in addition to lung injury, mechanical ventilation can also have adverse systemic sequelae including death from tension pneumothorax, or hypotension and impaired renal function secondary to high PEEP. In recent years experimental evidence has emerged that mechanical ventilation may also produce numerous other systemic sequelae. For example, Kolobow et al. [34] (*N*=378) compared the effect in sheep of ventilation with prolonged high V_t (50–70 ml/kg, PIP 50 cmH_2O) to that with low V_t (10 ml/kg, PIP 15–20 cmH_2O) . Interestingly, they found that all sheep subjected to the high V_t strategy died with multiple organ system dysfunction within 48 h.

In 1998 we hypothesized that biotrauma and the translocation of mediators can lead to the development of multisystem organ dysfunction [35] (*N*=185). Supportive of this hypothesis, several investigators have demonstrated that the increased alveolar capillary membrane permeability observed with high V_t ventilation allows translocation of various alveolar inflammatory mediators or bacteria into the systemic circulation. For example, using in an isolated perfused lung model von Bethmann et al. [36] (*N*=122) showed that high V_t ventilation produces increased levels of TNFα and IL6 in the perfusate; and in an acid aspiration rat model Chiumello et al. observed increased serum TNF-a levels in the group ventilated with zero PEEP and high V_t [37] (*N*=130). Similarly, using an in vivo dog model Nahum et al. [38] (*N*=85) demonstrated translocation of *Escherichia coli* from the lungs into the

bloodstream of most dogs ventilated with high V_t and low PEEP (transpulmonary pressure of 35, equivalent to 76 ml/kg, 3 cmH_2O PEEP). In contrast, bacterial translocation was only found in one of six dogs ventilated at the same end-inspiratory pressure (35 cmH_2O) and 10 cmH_2O PEEP, and in none of the dogs ventilated with V_t 15 ml/kg and 3 cmH_2O PEEP. Subsequent studies have provided further evidence of ventilation-induced "spillover" of a number of other intra-alveolar pathogens (e.g., *Klebsiella* [39], LPS [40]) and inflammatory mediators into the circulation. In addition, recent studies have shown that ventilatory strategy can also have a wide range of effects on remote organs, including increased ileal permeability [41], increased renal and small intestine apoptosis [42], changes in the peripheral immune response and host susceptibility to infection, and the development of systemic capillary leak [32, 43].

Strengths and weakness of the bench studies

As alluded to above, bench studies have a number of limitations that prevent direct extrapolation to the clinical arena. Although in vitro and ex vivo models are indispensable for addressing questions regarding the effect of cell stretch or ventilation on particular cells or signal transduction pathways in the absence of confounding systemic sequelae (such as hypotension due to high mean pleural pressure), the findings from such models may not be representative of the events occurring in vivo. In addition, although animal models may minimize differences between study participants, there are genetic and species-specific susceptibilities and responses to certain stimuli which may or may not be representative of the human response. Furthermore, with few exceptions the majority of laboratory studies of VILI to date have involved only brief periods of ventilation (hours) and used fairly extreme ventilatory settings to produce injury, leading some to question the clinical relevance of such studies.

Seminal *bedside* studies on ventilation-induced lung injury

From a clinician's perspective the key question is whether VILI contributes to patient morbidity and mortality, and if so, how can it be avoided. Although underlying lung injury is known to be a confounding factor present in many patients on ventilatory support, the laboratory studies have suggested that, if anything, this places the patients at increased risk of VILI as: (a) these patients often require higher pressure/volume to oxygenate/ventilate, and (b) many of these patients have factors known to increase susceptibility to VILI (such as surfactant dysfunction, malnutrition, endotoxemia).

In a series of publications Gattinoni et al. used computed tomography to demonstrate the effect of different ventilation strategies on the lungs of patients with acute lung injury (ALI). In a highly cited study Gattinoni et al. [44] (*N*=318) examined the effect of ventilation with different levels of PEEP (5, 10, and 15 cmH_2O) on lung compliance, lung volumes (as measured by helium dilution), and the computed tomographic appearance of the lungs in 20 patients with ALI. The key finding of this study was the visual evidence that lung inflation in ALI is extremely heterogeneous, with dependent regions being flooded or atelectatic, and often only a low volume of aerated nondependent lung. In addition, ventilation in these patients with ALI appears to be distributed principally to this low volume of aerated nondependent lung with relatively normal compliance (which the authors termed "baby lung," due to its low volume) [44, 45]. These computed tomography studies also suggested that the pressure-volume curve of the patients is representative of only the healthy aerated zones of the lung, and that optimal lung recruitment (i.e., opening up of lung units without significant overdistension) coincides with the PEEP at which optimal lung compliance was measured. Thus, in keeping with the speculations of Webb and Tierney [10] and others decades earlier, the studies by Gattinoni et al. demonstrated how mechanical ventilation of heterogeneously injured lungs with even relatively low V_t can produce significant regional overdistension. For example, in a lung with only 25% of alveoli ventilated, a ventilator set to deliver a V_t of 10 ml/kg would actually deliver approx. 40 ml/kg to the patient's "baby lungs"—a volume associated with significant lung injury in laboratory studies.

Based on the above, and mounting experimental evidence of potential adverse sequelae of mechanical ventilation with greater than physiological volumes, clinical investigators began to question whether mechanical ventilation using "conventional" V_t of 10–15 ml/kg to maintain normal arterial oxygenation and ventilation is necessary or harmful, particularly in patients with ARDS and "baby" lungs. After all, in patients with status asthmaticus a ventilatory approach that uses lower peak pressures and allows higher $PaCO_2$, a technique termed "controlled hypoventilation," appeared to be well tolerated and associated with improved outcomes [46, 47].

In 1990 Hickling et al. [48] (*N*=368) published a landmark study showing that the use of a "protective" ventilation strategy that limits PIP (<40 or <30 cmH_2O if possible, corresponding to V_t of 4–7 ml/kg) and allowed hypercapnia and a slight deterioration in oxygenation, appeared to reduce mortality by 60% in 70 patients with severe ARDS compared to mortality predicted by Acute Physiology and Chronic Health Evaluation II score (i.e., 16% vs. 40%). This seminal study suggested a promising new approach for ventilation in ARDS. A major weakness of the study, however, was the absence of a concurrent

control group. In addition, the study was only a retrospective case series from a single institution, which despite showing an apparent survival advantage did not observe a difference in either gas exchange or signs of lung injury between survivors and nonsurvivors. These weaknesses, however, do not diminish the importance of this study which helped to change the prevailing philosophy at the time that normal arterial blood gases should be a major goal of ventilatory support.

To circumvent the inherent limitations of retrospective and nonrandomized trials, prospective randomized trials examined whether a ventilation strategy with lower vs. higher lung volume improves patient outcome. In 1995 Amato et al. [49] (*N*=238) published a positive trial that further fueled debate. In this study 28 patients with ARDS were randomized to either a low V_t/high PEEP strategy (V_t <6 ml/kg, PIP<40 cmH_2O, permissive hypercapnia, PEEP 15–20 cmH_2O, and a goal of a plateau pressure, P_{plat}, <30 cmH_2O) or a high V_t strategy (V_t 12 ml/kg, PEEP 6–8 cmH_2O, P_{plat} of approx. 46 cmH_2O). The low V_t strategy was associated with improved survival (40% relative reduction in mortality at 28 days). The benefits of the low V_t/high PEEP strategy were confirmed by extending the study to 53 patients at which point the study was stopped because an interim analysis revealed a significant survival difference (28-day mortality of 38% with the low volume/high PEEP strategy vs. 71% with the high V_t strategy; p<0.001) [50] (*N*=678). In addition to a survival advantage, at 28 days more patients in the "protective" ventilation strategy arm had been weaned from ventilation (66% vs. 29%), and there was a lower incidence of barotrauma (7% vs. 42%). However, the Amato et al. study was criticized for having higher than predicted mortality in the control group. Furthermore, three other small prospective randomized trials failed to find a survival advantage of low vs. high V_t ventilation strategy [51, 52, 53] (*N*=258, 182, 102, respectively). These smaller negative trials, however, were criticized for having only a small difference in V_t between study groups, insufficient statistical power to detect a difference, the presence of uncorrected acidosis in the low volume arms, as well as the fact that the conventional ventilation arms in all the negative trials had a P_{plat} less than 32 cmH_2O (i.e., had relatively low end-inspiratory lung volumes more in keeping with ventilatory strategies found to be noninjurious in laboratory studies).

To overcome the limitations of these small studies the National Institutes of Health (NIH) sponsored a consortium (ARDSNet) to carry out a large multicenter prospective randomized trial in which patients with ALI or ARDS were randomized to either: (a) "traditional" V_t of 12 ml/kg predicted body weight (using a formula based on gender and height rather than actual weight) and a P_{plat} of 50 cmH_2O or lower, or (b) V_t of 6 ml/kg predicted body weight and a P_{plat} of 30 cmH_2O or lower [54] (*N*=1027). Although the study was conceived with a patient population of approx. 1000, the trial was stopped early after an interim analysis revealed a 22% relative survival advantage with the low V_t strategy (n=861; mortality of 31% vs. 39.8%). In addition to improved survival, patients in the low V_t strategy were also found to have more days free of ventilatory support during the 28 days following randomization (12±11 vs. 10±11). Of note, the mean P_{plat} s of the low and high V_t strategy were 25±6 vs. 33±8 cmH_2O respectively (a greater difference between groups than that of the small, negative trials). Furthermore, in keeping with the animal studies suggesting that ventilation affect systemic inflammation, the low V_t strategy also resulted in lower plasma IL-6 levels (on day 3) as well as fewer nonpulmonary organ failures (circulatory, renal, coagulation).

Subsequent reports, however, have brought to light a number of caveats regarding the ARDSNet study. First, some have argued that the study demonstrated the increased mortality of a high V_t strategy resulting in a high P_{plat} (33 cmH_2O) rather than a survival advantage to using V_t of 6 ml/kg. Of note, the P_{plat} in all of the smaller negative studies was less than 32 cmH_2O in both study groups (i.e., control and less injurious ventilation strategy groups). Second, it has been argued that those in the low V_t group may have developed higher auto-PEEP than those in the conventional ventilation group due to the high respiratory rates used [55]. As such, the survival advantage may have been due to higher PEEP rather that low V_t and/or end-inspiratory lung volume (although the results of a more recent trial argue against this [56]). Third, the study population was restricted to patients with ALI or ARDS and the exclusion criteria included patients with severe chronic respiratory disease, morbid obesity, burns, a contraindication to hypercapnia or hypoxia (such as increased intracranial pressure or sickle cell disease) or a predicted 6 month mortality of more than 50%. Thus the study findings cannot be directly extrapolated to the excluded patient populations or to patients with less injured or normal lungs. Fourth, the low V_t group developed hypercapnia and received bicarbonate to treat acidosis (note: bicarbonate was not used in the smaller negative trials). Thus it is unclear to what extent bicarbonate contributed to the survival difference. Fifth, the higher number of ventilator-free days was due to reduced mortality (i.e., no significant difference was found in ventilator-free days among survivors between the two groups). Nevertheless, despite these limitations this study was the only large interventional study in decades in ARDS patients to show a significant reduction in mortality, and certainly was in keeping with the plethora of laboratory studies showing that high volume lung ventilation strategies are deleterious. Thus this study provided a new "gold standard" ventilation strategy for patients with ARDS or ALI.

Another seminal study in patients that also supported the experimental evidence that ventilation strategy can

have systemic effects on the host inflammatory response was published by Ranieri and colleagues [57] (*N*=360) in 1999. This study, entitled the "Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome—a randomized controlled trial," examined whether a lung protective ventilation strategy in patients with ARDS reduces their pulmonary and systemic inflammatory cytokine response. Fifty-one ARDS patients who had been ventilated for less than 8 h were randomized to either "control" ventilation (V_t 11 ml/kg to produce normal $PaCO_2$) and PEEP (6 cmH_2O) producing best improvement in PaO_2 without worsening hemodynamics; P_{plat} 31 cmH_2O) or V_t and PEEP based on the pressure-volume curve (V_t 7 ml/kg, PEEP 15 cmH_2O, P_{plat} 25 cmH_2O). In the 44 patients who completed the study the concentration of inflammatory mediators 36 h after randomization was found to rise significantly in the control group (i.e., bronchoalveolar lavage levels of IL-1β and IL-6 and as well as bronchoalveolar lavage and plasma levels of TNF-α, IL-6, TNF-α receptors, and IL-1 RA) whereas in patients in the lung-protective strategy group a reduction in bronchoalveolar lavage concentrations of polymorphonuclear cells, IL-1β, TNF-α, IL-8, IL-6, TNF-α receptors, IL-1 RA, and in plasma concentration of IL-6, IL-1 RA, and a TNF-α receptor was found. Of note, this study was not designed to address whether these changes in inflammatory mediators resulted in improved survival or long-term outcomes (i.e., the ventilation protocols were only set for 36–40 h post inclusion, and organ failure and mortality were not primary outcomes). However, a post-hoc analysis revealed more ventilator-free days (over 28 days) in the lung protective group, and a number of subsequent clinical studies have also demonstrated ventilation strategy dependent changes in systemic inflammatory mediators (including the previously discussed NIH trial [54, 58]). Of importance, although there appeared to be an association between mediator levels and patient outcome in several studies, a cause and effect relationship has never been demonstrated.

Recently the NIH consortium published the results of yet another large trial comparing the effect of high vs. low PEEP on lung injury and survival in patients with ARDS. In this study 549 patients with ALI or ARDS were randomized to ventilation with V_t of 6 ml/kg, P_{plat} of less than 30 cmH_2O, and PEEP of either 8.3±3.2 or 13.2±3.5 cmH_2O [56]. The study was stopped early due to futility when an interim analysis revealed no significant differences in either mortality or ventilator-free days in the 28-day period following randomization. Thus, key clinical questions including how much PEEP is ideal, and what is the best way to determine optimal PEEP remain unanswered.

Similarly, to date most of the other promising interventions found to reduce lung injury and improve outcome in animal studies (e.g., prone positioning, surfactant supplementation, nitric oxide, lung recruitment maneuvers) have not been found significantly to improve patient survival or outcome in adult intensive care patients [59, 60, 61, 62]. As such, ongoing investigations at both the bench and bedside continue in the hopes of addressing the reasons for the discrepancies and better understanding the complex interactions of ventilation with the lung/whole organism.

In summary, the study of VILI over the past century exemplifies the "bench to bedside and back to the bench" research approach. This review discusses several of the seminal studies that led to our current understanding of VILI. Understanding these studies is helpful for interpreting and applying current guidelines for ventilation as well as appreciating the need for further studies at both the bench and the bedside to define the precise mechanisms of injury and develop novel approaches to further reduce or abrogate ventilator-induced injury.

References

1. Baker AB (1971) Artificial respiration, the history of an idea. Med Hist 15:336–351
2. Champneys FH (1887) Expiratory cervical emphysema, that is, emphysema of the neck occurring during labour and during violent expiratory efforts. In: Experimental researches in artificial respiration in stillborn children, and allied subjects. Lewis, London
3. Macklin CC (1939) Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum. Arch Intern Med 64:913–926
4. Greenfield LJ, Ebert PA, Benson DW (1964) Effect of positive pressure ventilation on surface tension properties of lung extracts. Anesthesiology 25:312–316
5. Faridy EE, Permutt S, Riley RL (1966) Effect of ventilation on surface forces in excised dogs' lungs. J Appl Physiol 21:1453–1462
6. Fowler WS (1949) Lung function studies 3. Uneven pulmonary ventilation in normal subjects and in patients with pulmonary disease. J Appl Physiol 2:283–299
7. Mead J, Takishima T, Leith D (1970) Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 28:596–608
8. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE (1967) Acute respiratory distress in adults. Lancet II:319–323
9. Evans T, Cranshaw J (2003) Lung Injury. In: Fink M, Hayes M, Soni N (ed) Classic papers in critical care. Bladon, Oxfordshire, pp 31–58
10. Webb HH, Tierney DF (1974) Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 110:556–565

11. Dreyfuss D, Basset G, Soler P, Saumon G (1985) Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 132:880–884
12. Dreyfuss D, Soler P, Basset G, Saumon G (1988) High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137:1159–1164
13. Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 157:294–323
14. Bouhuys A (1969) Physiology and musical instruments. Nature 221:1199–1204
15. West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R (1991) Stress failure in pulmonary capillaries. J Appl Physiol 70:1731–1742
16. Parker JC, Ivey CL, Tucker JA (1998) Gadolinium prevents high airway pressure-induced permeability increases in isolated rat lungs. J Appl Physiol 84:1113–1118
17. Parker JC, Ivey CL, Tucker A (1998) Phosphotyrosine phosphatase and tyrosine kinase inhibition modulate airway pressure-induced lung injury. J Appl Physiol 85:1753–1761
18. Muscedere JG, Mullen JB, Gan K, Slutsky AS (1994) Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 149:1327–1334
19. Slutsky AS (1999) Lung injury caused by mechanical ventilation. Chest 116:9S-15S
20. Hernandez LA, Coker PJ, May S, Thompson AL, Parker JC (1990) Mechanical ventilation increases microvascular permeability in oleic acid-injured lungs. J Appl Physiol 69:2057–2061
21. Coker PJ, Hernandez LA, Peevy KJ, Adkins K, Parker JC (1992) Increased sensitivity to mechanical ventilation after surfactant inactivation in young rabbit lungs. Crit Care Med 20:635–640
22. Adkins WK, Hernandez LA, Coker PJ, Buchanan B, Parker JC (1991) Age effects susceptibility to pulmonary barotrauma in rabbits. Crit Care Med 19:390–393
23. Dreyfuss D, Soler P, Saumon G (1995) Mechanical ventilation-induced pulmonary edema. Interaction with previous lung alterations. Am J Respir Crit Care Med 151:1568–1575
24. Verbrugge SJ, Lachmann B (1998) Mechanisms of ventilation-induced lung injury and its prevention: role of surfactant. Appli Cardiopulm Pathophysiol 7:173–198
25. Vlahakis NE, Hubmayr RD (2005) Cellular stress failure in ventilator injured lungs. Am J Respir Crit Care Med 171:1328–1342
26. Hamilton PP, Onayemi A, Smyth JA, Gillan JE, Cutz E, Froese AB, Bryan AC (1983) Comparison of conventional and high-frequency ventilation: oxygenation and lung pathology. J Appl Physiol 55:131–138
27. Kawano T, Mori S, Cybulsky M, Burger R, Ballin A, Cutz E, Bryan AC (1987) Effect of granulocyte depletion in a ventilated surfactant-depleted lung. J Appl Physiol 62:27–33
28. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS (1997) Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 99:944–952
29. Tremblay LN, Slutsky AS (1998) Ventilator-induced injury: from barotrauma to biotrauma. Proc Assoc Am Physicians 110:482–488
30. Narimanbekov IO, Rozycki HJ (1995) Effect of IL-1 blockade on inflammatory manifestations of acute ventilator-induced lung injury in a rabbit model. Exp Lung Res 21:239–254
31. Uhlig S, Uhlig U (2004) Pharmacological interventions in ventilator-induced lung injury. Trends Pharmacol Sci 25:592–600
32. Plotz FB, Slutsky AS, van Vught AJ, Heijnen CJ (2004) Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses. Intensive Care Med 30:1865–1872
33. Dreyfuss D, Rouby JJ (2004) Mechanical ventilation-induced lung release of cytokines: a key for the future or pandora's box? Anesthesiology 101:1–3
34. Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, Joris M (1987) Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. Am Rev Respir Dis 135:312–315
35. Slutsky AS, Tremblay LN (1998) Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725
36. Bethmann AN von, Brasch F, Nusing R, Vogt K, Volk HD, Muller KM, Wendel A, Uhlig S (1998) Hyperventilation induces release of cytokines from perfused mouse lung. Am J Respir Crit Care Med 157:263–272
37. Chiumello D, Pristine G, Slutsky AS (1999) Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med 160:109–116
38. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ (1997) Effect of mechanical ventilation strategy on dissemination of intratracheally instilled Escherichia coli in dogs. Crit Care Med 25:1733–1743
39. Verbrugge SJ, Sorm V, van't Veen A, Mouton JW, Gommers D, Lachmann B (1998) Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental Klebsiella pneumoniae inoculation. Intensive Care Med 24:172–177
40. Murphy DB, Cregg N, Tremblay L, Engelberts D, Laffey JG, Slutsky AS, Romaschin A, Kavanagh BP (2000) Adverse ventilatory strategy causes pulmonary-to-systemic translocation of endotoxin. Am J Respir Crit Care Med 162:27–33
41. Guery BP, Welsh DA, Viget NB, Robriquet L, Fialdes P, Mason CM, Beaucaire G, Bagby GJ, Neviere R (2003) Ventilation-induced lung injury is associated with an increase in gut permeability. Shock 19:559–563
42. Imai Y, Parodo J, Kajikawa O, de PM, Fischer S, Edwards V, Cutz E, Liu M, Keshavjee S, Martin TR, Marshall JC, Ranieri VM, Slutsky AS (2003) Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 289:2104–2112
43. Choi WI, Quinn DA, Park KM, Moufarrej RK, Jafari B, Syrkina O, Bonventre JV, Hales CA (2003) Systemic microvascular leak in an in vivo rat model of ventilator-induced lung injury. Am J Respir Crit Care Med 167:1627–1632
44. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. Am Rev Respir Dis 136:730–736
45. Gattinoni L, Mascheroni D, Torresin A, Marcolin R, Fumagalli R, Vesconi S, Rossi GP, Rossi F, Baglioni S, Bassi F (1986) Morphological response to positive end expiratory pressure in acute respiratory failure. Computerized tomography study. Intensive Care Med 12:137–142
46. Menitove SM, Goldring RM (1983) Combined ventilator and bicarbonate strategy in the management of status asthmaticus. Am J Med 74:898–901
47. Darioli R, Perret C (1984) Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 129:385–387

48. Hickling KG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16:372–377
49. Amato MB, Barbas CS, Medeiros DM, Schettino GP, Lorenzi FG, Kairalla RA, Deheinzelin D, Morais C, Fernandes EO, Takagaki TY (1995) Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med 152:1835–1846
50. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR (1998) Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 338:347–354
51. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, Mazer CD, McLean RF, Rogovein TS, Schouten BD, Todd TR, Slutsky AS (1998) Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. N Engl J Med 338:355–361
52. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, Clementi E, Mancebo J, Factor P, Matamis D, Ranieri M, Blanch L, Rodi G, Mentec H, Dreyfuss D, Ferrer M, Brun-Buisson C, Tobin M, Lemaire F (1998) Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 158:1831–1838
53. Brower RG, Shanholtz CB, Fessler HE, Shade DM, White P Jr, Wiener CM, Teeter JG, Dodd-o JM, Almog Y, Piantadosi S (1999) Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med 27:1492–1498
54. Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308
55. Durante G de, del Turco M, Rustichini L, Cosimini P, Giunta F, Hudson LD, Slutsky AS, Ranieri VM (2002) ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 165:1271–1274
56. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327–336
57. Ranieri VM, Suter PM, Tortorella C, De TR, Dayer JM, Brienza A, Bruno F, Slutsky AS (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA 282:54–61
58. Parsons PE, Matthay MA, Ware LB, Eisner MD (2005) Elevated plasma levels of soluble TNF receptors are associated with morbidity and mortality in patients with acute lung injury. Am J Physiol Lung Cell Mol Physiol 288:L426–L431
59. Spragg RG, Lewis JF, Walmrath H, Johannigman J, Bellingan G, Laterre P, Witte WC, Richards GA, Rippin G, Rathgeb F, Hafner D, Taut FJH, Seeger W (2004) Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. N Engl J Med 351:884–892
60. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, Malacrida R, Di GP, Fumagalli R, Pelosi P, Brazzi L, Latini R (2001) Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 345:568–573
61. Guerin C, Gaillard S, Lemasson S, Ayzac L, Girard R, Beuret P, Palmier B, Le QV, Sirodot M, Rosselli S, Cadiergue V, Sainty JM, Barbe P, Combourieu E, Debatty D, Rouffineau J, Ezingeard E, Millet O, Guelon D, Rodriguez L, Martin O, Renault A, Sibille JP, Kaidomar M (2004) Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. JAMA 292:2379–2387
62. Kallet RH (2004) Evidence-based management of acute lung injury and acute respiratory distress syndrome. Respir Care 49:793–809

Martin J. Tobin

Remembrance of weaning past: the seminal papers

Abstract The approach to ventilator weaning has changed considerably over the past 30 years. Change has resulted from research in three areas: pathophysiology, weaning-predictor testing, and weaning techniques. Physiology research illuminated the mechanisms of weaning failure. It also uncovered markers of weaning success. Through more reliable prediction, patients whose weaning would have been tedious in the 1970s are now weaned more rapidly. The weaning story offers several lessons in metascience: importance of creativity, the asking of heretical questions, serendipity, mental-set psychology, cross-fertilization, and the hazards of precocity. Weaning research also illustrates how Kuhnian normal (me-too) science dominates any field. Making the next quantum leap in weaning will depend on spending less time on normal science and more on the raising (and testing) of maverick ideas.

Keywords Mechanical ventilation · Weaning · Pathophysiology · Control of breathing · Respiratory muscles · Diagnostic testing · Monitoring · Randomized clinical trials · Metascience · Serendipity · Cross-fertilization

In the world of ideas, *seminal* refers to a thought pregnant with consequences. In science, to a paper that fostered new research. When judging a paper as seminal, a distinction arises between scientific and humanistic literature [1]. Whereas humanistic writing can retain interest centuries later (permanence), scientific literature is cumulative: a new paper that provides a better solution to a problem supersedes older papers. Researchers are prone to regard the latest paper more influential – a phenomenon known as "supersedure."

Is there a yardstick for rating a paper as seminal? Understandably, some use citation counts [2]. Scientometricians, however, have long recognized that authors often fail to cite the most ground-breaking work [3] and frequently cite papers of limited intellectual fiber or originality. Between 1961 and 1975, Watson and Crick's paper on DNA [4] was cited at one-hundredth the frequency of Lowry's report on a reagent for measuring protein [5]. The phenomenon of under-citation is known as "obliteration by incorporation" [6]. I say all this to justify my own subjective selection of seminal papers on weaning.

In writing on weaning history, the goal and hazards are clear. A mere chronicle of facts would be banal. Instead, the goal is to understand how events unfolded. A historian of science should keep one eye focused on contingencies faced by researchers of the day, while turning the other to subsequent developments. But there's the rub. It is impossible to capture accurately the minds of researchers who did not know what was going to happen next. Aware of the denouement, a historian is prone to exaggerate the rationality of those steps taken by researchers that were later proven correct. And to smugly list follies committed by other researchers.

My canvas contains only broad-brush strokes. Many contributions deserving pointillistic attention are omitted. At the end, I dilate on metascientific lessons offered by weaning research. That goal also influences my choice of seminal papers.

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_61,

Prologue

All discussion of modern ventilation dates to early-1950s Scandinavia [7]: Bjorn Ibsen's introduction of positive-pressure ventilation during the Copenhagen polio epidemic [8]; Carl-Gunnar Engström's first volume-oriented ventilator [9]; and Eric Nilsson's (1915–2004) management of barbiturate overdose [10]. Two Danes who earned their stripes bagging polio victims, Henrik Bendixin (1923–2004) and Henning Pontoppidan, later pioneered ventilator management in the United States [11]. After founding the first respiratory intensive care unit in the USA (at Massachusetts General Hospital) in 1961, they conducted much ventilator research [11].

In 1965, Bendixin, Pontoppidan and colleagues published the first textbook in the field, *Respiratory Care*. Its goal was to improve patient care "through the clinical application of the principles of respiratory physiology" [12]. At that time, the Boston unit was ventilating about 400 patients a year. Few were ventilated for longer than 2 days without a tracheotomy [13]: "It is our practice to limit endotracheal intubation to approximately forty-eight hours" [12]. The Bostonians articulated a principle that still holds: "To know the proper timing and rate of weaning from the respirator requires considerable judgment and experience. As a rule, weaning should start as soon as possible" [12].

Research over the ensuing 40 years can be divided into three areas: timing and prediction of weaning outcome, weaning techniques, and pathophysiology. To help readers see how findings in one area cross-fertilized research in other areas, I have broken discussion of each subfield into two phases.

Predictor tests, phase I (1968–1983)

Weaning research begins with the development of diagnostic tests to identify the earliest time a patient might be safely disconnected from the ventilator. The first reports, from Pontoppidan's group (1968, 1972) [14, 15], are limited to abstracts. Thus, Sahn and Lakshminarayan's 1973 report [16] is the first detailed study. In 100 patients, they found that minute ventilation (< 10 l/min) and maximal inspiratory pressure (> 30 cmH_2O) "correlated well with the ability to discontinue mechanical ventilation."

In 1983, Tahvanainen and colleagues [17] reported on 47 patients who had been weaned to an intermittent mandatory ventilation (IMV) rate of zero. Minute ventilation, maximal inspiratory pressure, vital capacity and dead space did not differentiate between patients who required reintubation and the rest.

The Tahvanainen paper represented a major advance. Unlike Sahn and Lakshminarayan, who did not express results as statistical quantities, they presented complete two-by-two tables (true positives, true negatives, false positives, false negatives) for all variables. They, however, based conclusions about diagnostic-test reliability on chi-square comparisons of group means. Neither group used expressions such as sensitivity or specificity to judge a test's reliability.

Weaning techniques, phase I (1965–1988)

The 1960s approach to weaning is given in Bendixin's book: "weaning is started by taking the patient off the respirator for three to four minutes every half hour and, if this is tolerated, by gradually increasing the period off the respirator as rapidly as is tolerated" [12]. In 1977, Egan advised: "When the patient can breathe unassisted around the clock, and is moving a reasonable amount of air without undue effort, and can walk for short distances consistent with his general physical condition, and when ventilation is satisfactory and stable by blood gas values, it is time to consider removal of the endotracheal tube" [18].

Compared with the preceding tedium, no imagination is needed to see how nurses and therapists regarded dialing an IMV rate as a major advance [19]. And by the mid-1980s, IMV was triumphant: being used for more than 90% of weaning attempts in the US [20]. Europe was little different. In 1988, Lemaire wrote: "Despite the lack of evidence that IMV shortens the weaning period, IMV is extensively used in the majority of ICUs" [21].

Pathophysiology, phase I (1977–1989)

Throughout the 1970s, authors emphasized the challenge posed by difficult-to-wean patients. But attempts to elucidate underlying mechanisms were almost non-existent. An exception was a 1977 study by Henning, Shubin and Weil [22]. Using esophageal-balloon catheters, these investigators made detailed measurements of work of breathing. Ventilator-dependent patients had higher work readings. The mechanism, however, was not clear. In particular, dynamic pulmonary compliance was equivalent to that in weaning-success patients.

In 1982, Cohen, Roussos, Macklem and colleagues [23] reported electromyographic recordings in difficult-to-wean patients. Six patients developed power-spectral features of diaphragmatic fatigue. Electromyographic abnormalities were accompanied by abdominal paradox (inward motion during inspiration) and respiratory alternans (alternating predominance of rib-cage and abdominal breathing) (Fig. 1).

For the first time, there was a framework with which to investigate weaning pathophysiology. Attention turned from the lungs per se to the respiratory muscle pump. In 2006, this seems a trivial turn. In 1982, it was revolutionary. Most provocative was the suggestion that simple physical signs, paradox and alternans, could detect fatigue

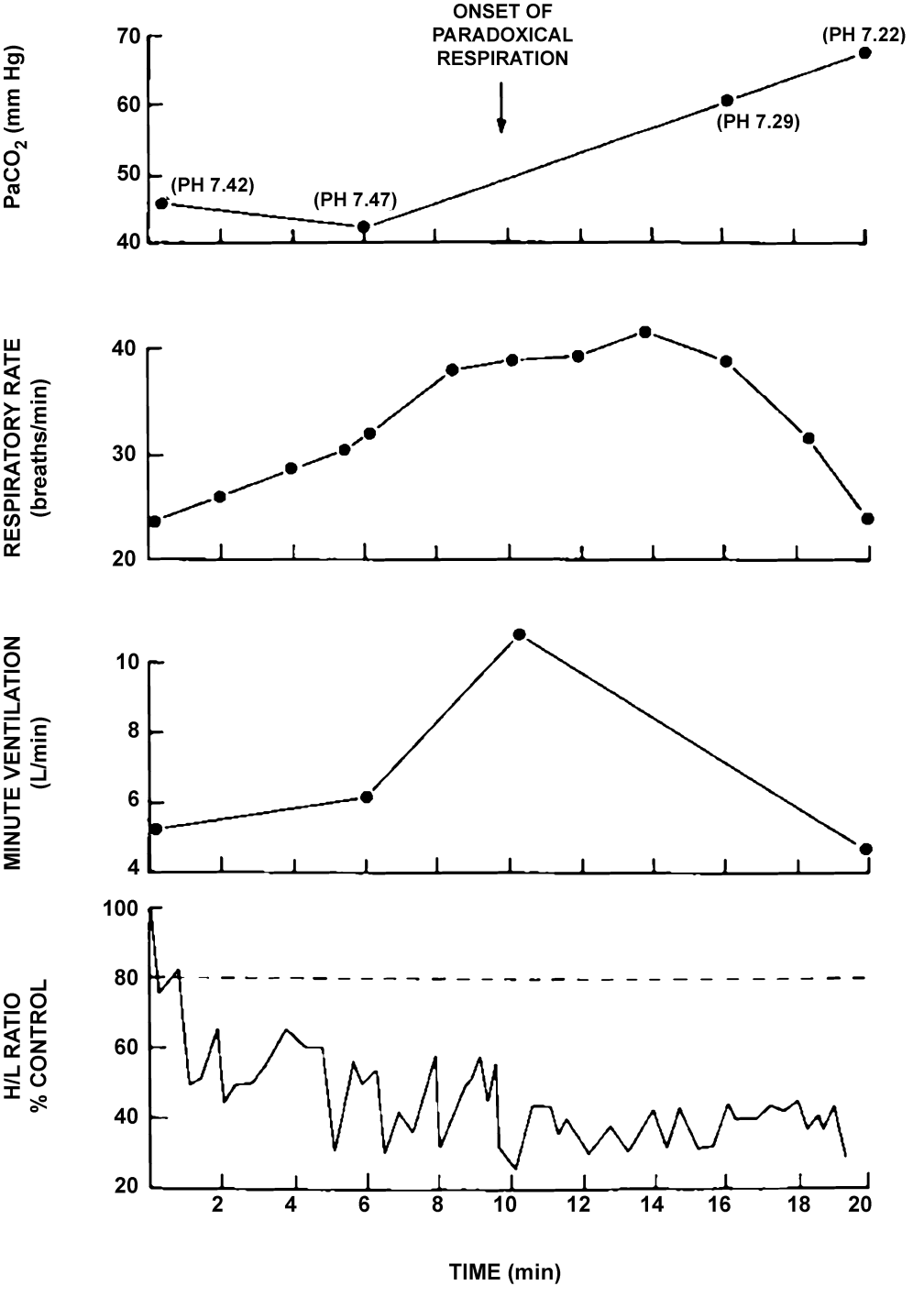


Fig. 1 Sequence of changes in arterial carbon dioxide tension ($PaCO_2$), respiratory rate, minute ventilation, and high/low (H/L) ratio of power spectrum of the diaphragmatic electromyogram in a patient who failed a weaning trial. Ventilator discontinuation was followed by an immediate change in the high/low ratio, followed by a slow increase in respiratory rate, then abdominal paradox (and alternans), and finally hypercapnia. (From Cohen et al. [23])

and provide a means for minute-by-minute monitoring of weaning progression. But Cohen [23] did not attempt to quantify chest-wall motion.

Stirred by these findings, we used inductive plethysmography to obtain quantitative indices of chest-wall motion [24]. Abnormal motion, however, turned out to be common in both success and failure patients [24]. Moreover, motion did not worsen over time in weaning-failure patients, suggesting it did not reflect fatigue (a negation subsequently confirmed [25]).

Although our study was undertaken to quantify chest-wall motion, we also analyzed breathing pattern (since the data were available) [26]. We expected acute hypercapnia to result from a fall in respiratory drive, whereas drive

rose. Rather, 81% of the variance in $PaCO_2$ was accounted for by development of rapid shallow breathing [26]. Alveolar–arterial oxygen gradient did not widen. These findings suggested a number of mechanisms were unlikely to cause weaning failure: respiratory center depression, respiratory muscle fatigue, and ventilation–perfusion abnormality [26]. Instead, rapid shallow breathing dominated.

Before 1986, several investigators had reported that tidal volume and respiratory frequency did not discriminate between weaning-success and weaning-failure patients [15, 17, 19, 27]. Since 1986, researchers have repeatedly confirmed their discriminatory power [28]. How could such a striking distinction have gone undetected? In previous studies, we had documented considerable breath-to-breath variability in breath components, and thus used large breath samples in our breathing-pattern studies [29, 30] (Fig. 2). Most importantly, we believed that subtle differences in breathing pattern could yield as much pathophysiologic insight as data generated by more sophisticated methodology. In the mid-1980s, physicians did not focus on respiratory rate. Rate was a nursing measurement, along with charting of temperature and

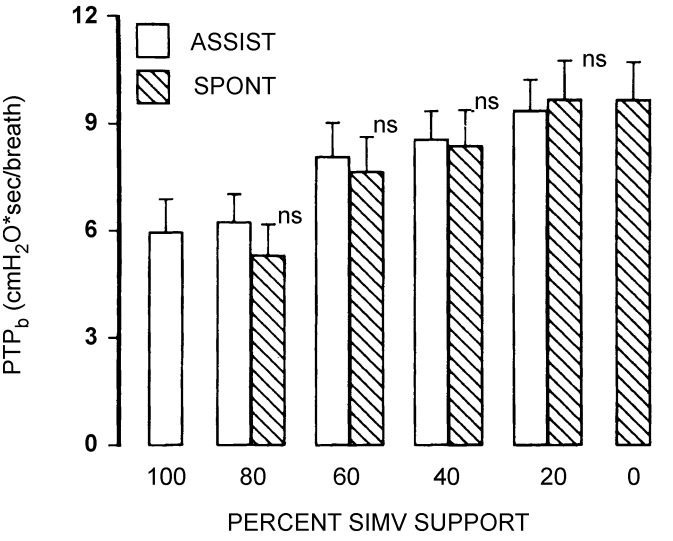


Fig. 3 Inspiratory pressure-time product per breath for assisted, mandatory breaths (*open bars*) and intervening spontaneous breaths (*cross-hatched bars*). Patient effort was equivalent for mandatory and spontaneous breaths at every level of synchronized intermittent mechanical ventilation (*SIMV*). (From Marini et al. [33])

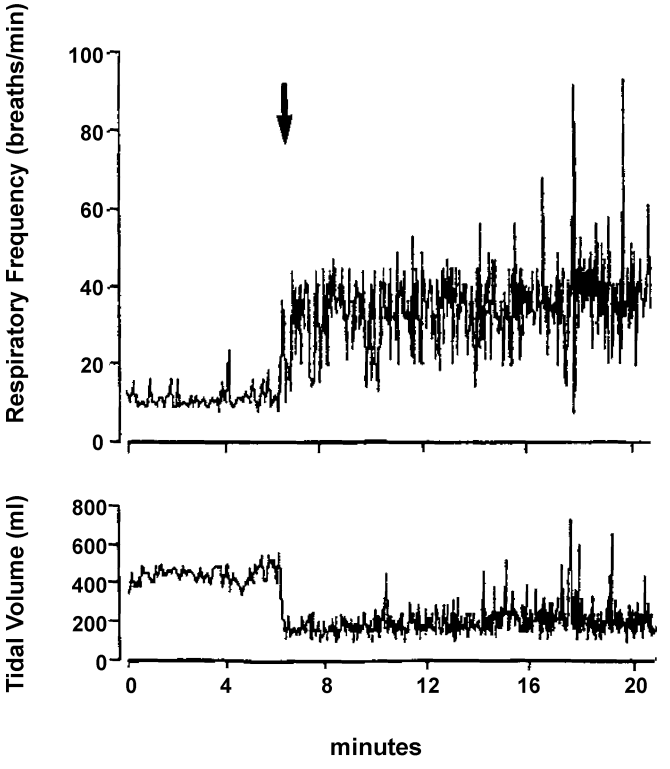


Fig. 2 A time-series, breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. Discontinuation of ventilator support (*arrow*) resulted in almost immediate rapid shallow breathing. Note the marked breath-to-breath variability in the data. (From Tobin et al. [26])

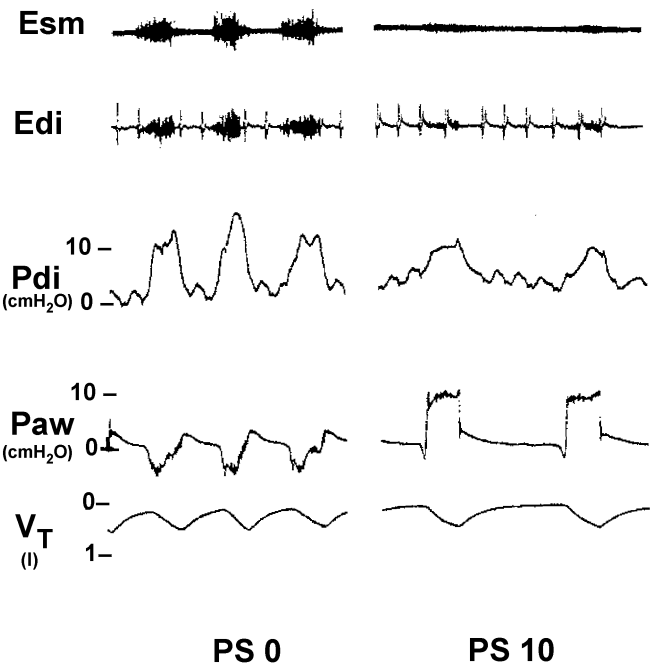


Fig. 4 Electromyographic recordings of the sternomastoid muscle (*Esm*) and diaphragm (*Edi*), transdiaphragmatic pressure (*Pdi*), airway pressure (*Paw*), and tidal volume (V_T) in a ventilator-supported patient. Compared with 0, pressure support of 10 cmH_2O decreased (but did not abolish) sternomastoid and diaphragmatic electrical activity, decreased Pdi, increased V_T, and slowed respiratory rate. (From Brochard et al. [35])

number of bowel motions [31]. And bedside spirometers measured total minute ventilation – spontaneous tidal volume did not become part of bedside testing until the 1990s [31].

Research into patient–ventilator interaction also advanced (weaning) understanding. In 1985, Marini and colleagues reported that subjects receiving assist-control ventilation performed half as much work as done by the ventilator [32]. This was heresy. It had been dogma that connecting a patient to a ventilator lessened work to near zero. In 1988, Marini reported that patient effort was virtually the same during mandatory IMV breaths as during the intervening spontaneous breaths (Fig. 3) [33]. This was blasphemy. By the late 1980s, IMV had been deified as the nonpareil weaning technique [20].

The importance of rigorous evaluation was recognized by the time pressure support was launched. In 1987 and 1989, Brochard, Lemaire, Harf and colleagues reported recordings of transdiaphragmatic pressure, electromyography, and work of breathing (Fig. 4) [34, 35]. Armed with such data, they delineated the pressure-support level that avoided fatigue but still maintained diaphragmatic activity. These studies ensured that misunderstanding about a mode's ability to assuage work, as with IMV, did not recur.

Predictor tests, phase II (1985 and after)

The mid-1980s saw a flurry of reports on airway occlusion pressure ($P_{0.1}$). Herrera (1985) [36], Sassoon (1987) [37] and colleagues reported that low $P_{0.1}$ (low respiratory drive) was superior to conventional tests in predicting weaning success.

Montgomery, Pierson and colleagues [38] reported that $P_{0.1}$ was reliable only when expressed as ratio of $P_{0.1}$ during CO_2 stimulation to baseline $P_{0.1}$. These authors were the first to discuss results in terms of sensitivity and specificity. They noted that ventilatory response to CO_2 was higher in success patients, "although overlap occurred indicating that this predictor could neither be 100 percent sensitive or specific" [38]. In contrast, ratio of $P_{0.1}$ during CO_2 stimulation to baseline $P_{0.1}$ "separated all weaning failure patients from all those who succeeded and was thus, a completely specific and sensitive test."

The quotations are revelatory. They portray a mindset where a test is judged reliable only if it attains 100% sensitivity and 100% specificity. The authors made no distinction between desirability of high sensitivity versus high specificity [38]. This monolithic orientation pervades to this day.

In 1986, Milic-Emili [39] proposed an index that integrated several respiratory muscle characteristics. We followed his suggestion, and developed the CROP index, which integrated *c*ompliance, *r*ate, *o*xygenation, and (maximal inspiratory) *p*ressure [40]. CROP proved superior to conventional tests. Cognizant that rapid shallow breathing was the dominant finding in our 1986 pathophysiology study [26], we quantified this phenomenon as frequency-to-tidal volume ratio (f/V_T). This test proved superior to all others [40].

The 1991 f/V_T paper [40] is typically cited as the source for usefulness of rapid shallow breathing in weaning prediction. In reality, this paper has much less intellectual content than our 1986 pathophysiological study [26]. The merit of the 1991 paper was its experimental design. First, all studies up to then involved post-hoc data analysis (which inflates test reliability). Instead, we first determined threshold values for each predictor test in a "training-data set", and then investigated reliability in a prospective "validation-data set." Second, clinicians were blinded to CROP and f/V_T. Third, results were expressed in terms of sensitivity, specificity, positive-predictive value, negative-predictive value, and receiver-operating-characteristic (ROC) curves [40].

Since 1991, f/V_T has been evaluated in more than 25 studies [41]. Unfortunately, many authors have not complied with the canons for diagnostic-test evaluation, grounded on Bayes' theorem. In particular, many have ignored conditional independence, pre-test probability, test-referral bias, and spectrum bias – each of which can corrupt reported measures of test reliability [41].

Pathophysiology, phase II (1989 and after)

The multiple inert-gas technique paints vivid pictures of pulmonary gas exchange. This technique enabled Torres, Rodriguez-Roisin and colleagues (1989) [42] to show that acute hypercapnia and ventilation–perfusion maldistribution in weaning-failure patients results from rapid shallow breathing. Using the same technique, Beydon, Harf, Lemaire and colleagues (1991) [43] confirmed shallow breathing as the major cause of ventilation–perfusion maldistribution. Years later, we studied tissue gas exchange using mixed-venous oxygen saturation [44]. Saturation fell progressively in failure patients consequent to a relative decrease in convective oxygen transport combined with an increase in tissue oxygen extraction.

In a series of studies, Bates, Rossi, Milic-Emili and colleagues [45, 46, 47, 48] used the rapid airway-occlusion technique to characterize respiratory mechanics. Through inventive mathematical modeling, they partitioned the relative roles of ohmic resistance, viscoelastic behavior, and time-constant inhomogeneity. The main abnormality in ventilator-dependent patients resulted from airway resistance, with less contribution from time-constant inhomogeneities and abnormal viscoelastic behavior of the lung. Chest-wall contribution was negligible. With this methodology, it was possible to find out whether severe

disturbance of mechanics made weaning failure little more than enactment of a predestined state.

In 1997, we found that passive respiratory mechanics were severely disturbed in patients who failed subsequent weaning, but no worse than in patients who weaned successfully [49]. This contrasted with findings during an ensuing 30–60-min T-tube trial. Inspiratory effort was much higher in weaning-failure patients consequent to marked increases in resistance, elastance and auto-PEEP [50]. That mechanics were markedly worse in failure patients during the weaning trial, but equivalent to those in success patients immediately beforehand, indicated that some mechanism associated with spontaneous breathing caused the abnormalities. That mechanism is still unidentified.

More deranged mechanics in failure patients was confirmed by Vassilakopoulos et al. [51]. They studied a group of patients at two points: shortly after failing a T-tube trial, and about 9 days later, shortly before successful extubation. Over this interval, airway resistance and auto-PEEP decreased substantially. Multiple logistic regression uncovered two determinants of weaning failure: tension–time index and f/V_T.

After the 1982 Cohen study [23], the role of muscle fatigue in weaning failure was not reexamined directly until 1994. Goldstone, Moxham and Green [52] reported slowing of maximum relaxation rate (of transdiaphragmatic pressure), a harbinger for fatigue, in failure patients but not in success patients. Stimulating the phrenic nerves and recording transdiaphragmatic pressure provides the most direct measure of diaphragmatic fatigue. Using this technique, we were surprised to find that not even one weaning-failure patient developed fatigue [53]. Related analyses disclosed why. Failure patients became progressively distressed during the trial, leading clinicians to reinstate ventilator support before patients had breathed long enough to develop fatigue. That is, monitoring clinical signs of distress provides sufficient warning to avoid fatigue.

Weaning techniques, phase II (1994 and after)

The year 1994 ushered in a new era of weaning research: Brochard and colleagues published the first randomized controlled trial (RCT) [54]. They randomized 109 difficult-to-wean patients to T-tube trials, IMV, or pressure support. At 21 days, ventilator dependency was less with pressure support than with other techniques. This report was revolutionary. Its main message was that steps chosen for weaning influenced duration of ventilator dependency. Second, 76% of 456 patients entered into the study passed the first T-tube trial (without "weaning"). Third, a 2-hr limit was imposed on T-tube trials; back then, trials often lasted 24 h [55, 56].

The major contribution of RCTs to clinical research is the elimination of susceptibility bias, a source of major disparity in baseline states of compared groups. "Beyond this achievement," notes Feinstein [57], "randomization itself makes no other scientific contribution". Despite the name, use of control groups is not limited to RCTs. Investigators studying weaning-failure pathophysiology have commonly included success patients as controls.

Knowledge gained through research depends ultimately on the ingenuity of the hypothesis under interrogation. RCTs are typically designed by research groups. Committees are hardly renowned for maverick ideas. So questions subjected to RCT testing are characterized by their sameness. Our 1995 RCT copied the general design of the Brochard trial, though we specified different steps [58]. T-tube trials proved superior to pressure support. The different outcomes in the two RCTs primarily reflected different steps in the algorithms of the two studies [54, 58].

In 1997, Ely et al. [59] borrowed two steps from previous studies: measurement of f/V_T (and other predictors), followed by a T-tube trial. The two-step approach achieved faster weaning than usual care. This study has since been portrayed as a comparison of weaning-by-protocol versus usual care. But this portrayal flouts a fundamental requirement for sound science: need for internal validity. Of patients in the usual-care arm, 76% were managed with IMV [59]. Not one protocol patient was so managed. To conclude that protocols are superior, weaning methods need to be the same in the protocol and usual-care arms.

Lessons in metascience

It would be naïve to regard the weaning story as a microcosm of the entire scientific process. Nonetheless, it offers several metascientific lessons.

The steam in science's engine is the novel question. Medical practice today depends on what questions our predecessors asked. But questions are not there for the picking, like apples on a tree. People have to formulate them. The reason why one researcher makes greater contributions to science than an equally talented coeval is courage to raise antinomial questions [60]. To think the unthinkable. As did Marini, when he suspected that ventilated patients might be performing prodigious respiratory work, and that IMV was largely ineffectual [32, 33]. But getting heresies published is not easy – the acceptance date on Marini's 1995 paper provides a clue to that effect.

Being too novel poses other problems. The 1977 report by Henning, Shubin, and Weil incorporated the most advanced scientific techniques [22]. But others did not build on their findings. The paper's sophistication was about a decade ahead of its time. Yes, researchers live in constant dread of being pipped at the post. But if they arrive before the zeitgeist, others cannot build on their

work. The most famous example is Gregor Mendel's paper in 1866 [61]. Not for another thirty years did general biological theory find a slot in which to fit the abbot's discovery [6].

Allied to discovery is serendipity. We did not set out to show that rapid shallow breathing is a hallmark of weaning failure [26]. Rather, our motivation was to quantify rib cage–abdominal motion [24]. But serendipity per se does not produce discoveries [60]. Instead, it produces opportunities for making discoveries. The person making the serendipitous connection is already primed to appreciate its significance. "Luck favors only the prepared mind," mused Pasteur.

Before the mid-1980s, rapid shallow breathing went unheeded by weaning researchers [15, 17, 19, 27, 37]. After it was pronounced a hallmark of weaning failure, the connection was reported over and over again [28]. The switch from non-detection to repeated confirmation is a consequence of *mental set* (as labeled by psychology researchers). Mental set describes the set of beliefs that determines what a person perceives (the prepared mind). With a mental set, a goal (detecting rapid shallow breathing) selects and shapes what it is a researcher sees. Without a mental set, the obvious becomes invisible. The researcher is distracted and blinded by a blizzard of other possible observations. In his magisterial history of the Scientific Revolution, Herbert Butterfield (1900–1979) [62] concluded, "of all forms of mental activity, the most difficult to induce ... is the art of handling the same bundle of data as before, but placing them in a new system of relations with one another by giving them a different framework, all of which virtually means putting on a different kind of thinking-cap for a moment."

The mid-1980s opened a new chapter in the weaning story. Like elsewhere in critical care, greater emphasis was placed on RCTs – in the belief that this was the only science that improved patient outcome. The purpose of science, however, is to enhance *understanding*, not simply accumulate facts [60]. Facts generated through research improve patient outcome only if they enhance physician understanding. Tanenbaum [63] undertook an ethnographic study of how clinicians think. For only a small fraction of time did clinicians engage in probabilistic reasoning – based on results of RCTs. The vast majority of reasoning involved models with moving parts, like heart valves – the type of understanding gained through physiology research.

Few seminal advances in the *understanding* of weaning originated in RCTs. Take weaning techniques. It was Marini's study of patient–ventilator interaction that highlighted the limitations of IMV [33]. Brochard's group, already steeped in pathophysiology methods [34, 35], built on Marini's understanding and undertook the first RCT [54]. The blending of different research disciplines among the Parisians exemplifies how cross-fertilization leads to scientific progress. New ideas rarely arise out of the blue. More often, they represent novel combinations of existing ideas [60]. To make a connection, a researcher has to traverse interdisciplinary boundaries. For the Parisians, this involved combining knowledge gained through physiology research with knowledge of trial design. Cognitive psychologists view cross-fertilization as a major source of mental creativity [60].

The introduction of f/V_T as a weaning-predictor test provides another example of cross-fertilization. For years before the 1991 report [40], we had been studying control of breathing in various settings – including weaning failure [26, 29, 30]. Independently, we had a specific interest in ICU monitoring [31]. Monitoring fundamentally boils down to the serial application of diagnostic tests. An understanding of the principles of diagnostic testing (garnered through expertise in monitoring) combined with immersion in physiology research gave birth to the f/V_T test [40].

The framework posited by Thomas Kuhn (1922–1996) in *The Structure of Scientific Revolutions* helps select which papers were seminal in advancing a field [64]. Kuhn averred that inquiry is dominated by long periods of *normal science*, punctured intermittently by sharp revolutions (*paradigm shifts*). Normal science, quantified by the amount of me-too research, makes few demands on an individual's intellect and psyche [60]. Kuhn concluded, "Few people who are not actually practitioners of a mature science realize how much mop-up work" there is to do. And, "Mopping-up operations are what engage most scientists throughout their careers" [64]. The seminal advances in weaning *understanding* (and thus management) resulted from pathophysiology research on respiratory muscles and breathing pattern [23, 26, 32, 33, 34], and cross-fertilization between pathophysiology research and fundamentals of diagnostic testing [40] and principles of RCT design [54]. The many RCTs published after the first [54] fit the category of *normal science*: they help with the dotting of i's and crossing of t's. But they have not seeded ideas on how to make the next quantum leap in this field.

Conclusion

As long as ventilators are used, the impetus for greater understanding of weaning will continue. We do a better job of weaning easy patients than in the 1970s, but more complex patients populate today's units. As a practicing intensivist, nothing taxes my intellect more than the difficult-to-wean patient. I know of no problem where connoisseurship of the individual intensivist has a greater influence on patient wellbeing and outcome.

Acknowledgements. Supported by a Merit Review grant from the Veterans Administration Research Service and by the National Institute of Health (RO1 NR008782).

References

1. Kronick DA (1962) A history of scientific and technical periodicals: the origins and development of the scientific and technological press 1665–1790. Scarecrow Press, New York, pp 16–17
2. Tremblay LN, Slutsky AS (2006) Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med 32:24–33
3. Garfield E (1998) From citation indexes to infometrics: is the tail now wagging the dog? Libri 48:67–80
4. Watson JD, Crick FH (1953) Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. Nature 171:737–738
5. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the Folin phenol reagent. J Biol Chem 193:265–275
6. Kronick DA (1985) The literature of the life sciences: reading, writing, research. Philadelphia: ISI Press: 1, 66
7. Colice GL (2006) Historical perspective on the development of mechanical ventilation. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. McGraw-Hill, New York, pp 1–36
8. Ibsen B (1952) The anesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen. Proc R Soc Med 47:72–74
9. Bjork VO, Engstrom CG (1955) The treatment of ventilatory insufficiency after pulmonary resection with tracheostomy and prolonged artificial ventilation. J Thorac Surg 30:356–367
10. Nilsson E (1951) On treatment of barbiturate poisoning; a modified clinical aspect. Acta Med Scand Suppl 253:1–127
11. Pontoppidan H (2003) The development of respiratory care and the respiratory intensive care unit (RICU): a written oral history. In: Ritz RJ (ed) This is no humbug! Reminiscences from the Department of Anesthesia at the Massachusetts General Hospital – a history. Massachusetts General Hospital, Boston, pp 151–177
12. Bendixin HH, Egbert LD, Hedley-Whyte J, Laver MB, Pontoppidan H (1965) Respiratory Care. Mosby, St Louis, pp 149–150
13. Harrison GA, Tonkin JP (1968) Prolonged (therapeutic) endotracheal intubation. Br J Anaesth 40:241–249
14. Berry PR, Pontoppidan H (1968) Oxygen consumption and blood gas exchange during controlled and spontaneous ventilation in patients with respiratory failure. Anesthesiology 29:177–178
15. Browne AGR, Pontoppidan H, Chiang H, Geffin B, Wilson R (1972) Physiological criteria for weaning patients from prolonged mechanical ventilation. Abstracts of scientific papers, Annual meeting of the American Society of Anesthesiologists, pp 69–70
16. Sahn SA, Lakshminarayan S (1973) Bedside criteria for discontinuation of mechanical ventilation. Chest 63:1002–1005
17. Tahvanainen J, Salmenpera M, Nikki P (1983) Extubation criteria after weaning from intermittent mandatory ventilation and continuous positive airway pressure. Crit Care Med 11:702–707
18. Egan DF (1977) Fundamentals of respiratory therapy. 3rd ed. Mosby, St Louis, pp 456–458
19. Downs JB, Klein EF Jr, Desautels D, Modell JH, Kirby RR (1973) Intermittent mandatory ventilation: a new approach to weaning patients from mechanical ventilators. Chest 64:331–335
20. Venus B, Smith RA, Mathru M (1987) National survey of methods and criteria used for weaning from mechanical ventilation. Crit Care Med 15:530–533
21. Lemaire F (1988) Weaning from mechanical ventilation. In: Ledingham I McA, editor. Recent advances in critical care medicine. Churchill Livingstone, New York, pp 15–30
22. Henning RJ, Shubin H, Weil MH (1977) The measurement of the work of breathing for the clinical assessment of ventilator dependence. Crit Care Med 5:264–268
23. Cohen CA, Zagelbaum G, Gross D, Roussos C, Macklem PT (1982) Clinical manifestations of inspiratory muscle fatigue. Am J Med 73:308–316
24. Tobin MJ, Guenther SM, Perez W, Lodato RF, Mador MJ, Allen SJ, Dantzker DR (1987) Konno–Mead analysis of ribcage–abdominal motion during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis 135:1320–1328
25. Tobin MJ, Perez W, Guenther SM, Lodato RF, Dantzker DR (1987) Does rib cage–abdominal paradox signify respiratory muscle fatigue? J Appl Physiol 63:851–860
26. Tobin MJ, Perez W, Guenther SM, Semmes BJ, Mador MJ, Allen SJ, Lodato RF, Dantzker DR (1986) The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am Rev Respir Dis 134:1111–1118
27. Gilbert R, Auchincloss JH Jr, Peppi D, Ashutosh K (1974) The first few hours off a respirator. Chest 65:152–157
28. Tobin MJ, Jubran A (2006) Weaning from mechanical ventilation. In: Tobin MJ (ed) Principles and practice of mechanical ventilation. McGraw-Hill New York, pp 1185–1220
29. Tobin MJ, Chadha TS, Jenouri G, Birch SJ, Gazeroglu HB, Sackner MA (1983) Breathing patterns. 2. Diseased subjects. Chest 84:286–294
30. Tobin MJ, Jenouri G, Birch S, Lind B, Gonzalez H, Ahmed T, Sackner MA (1983) Effect of positive end-expiratory pressure on breathing patterns of normal subjects and intubated patients with respiratory failure. Crit Care Med 11:859–867
31. Tobin MJ (1988) State-of-the-art: Respiratory monitoring in the intensive care unit. Am Rev Respir Dis 138:1625–1642
32. Marini JJ, Capps JS, Culver BH (1985) The inspiratory work of breathing during assisted mechanical ventilation. Chest 87:612–618
33. Marini JJ, Smith TC, Lamb VJ (1988) External work output and force generation during synchronized intermittent mechanical ventilation. Effect of machine assistance on breathing effort. Am Rev Respir Dis 138:1169–1179
34. Brochard L, Pluskwa F, Lemaire F (1987) Improved efficacy of spontaneous breathing with inspiratory pressure support. Am Rev Respir Dis 136:411–415
35. Brochard L, Harf A, Lorino H, Lemaire F (1989) Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. Am Rev Respir Dis 139:513–521
36. Herrera M, Blasco J, Venegas J, Barba R, Doblas A, Marquez E (1985) Mouth occlusion pressure (P0.1) in acute respiratory failure. Intensive Care Med 11:134–139
37. Sassoon CS, Te TT, Mahutte CK, Light RW (1987) Airway occlusion pressure. An important indicator for successful weaning in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 135:107–113
38. Montgomery AB, Holle RH, Neagley SR, Pierson DJ, Schoene RB (1987) Prediction of successful ventilator weaning using airway occlusion pressure and hypercapnic challenge. Chest 91:496–499
39. Milic-Emili J (1986) Is weaning an art or a science? Am Rev Respir Dis 134:1107–1108
40. Yang KL, Tobin MJ (1991) A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med 324:1445–1450

41. Tobin MJ, Jubran A (2006) Variable performance of weaning-predictor tests: role of Bayes' theorem and spectrum and test-referral bias (submitted for publication)
42. Torres A, Reyes A, Roca J, Wagner PD, Rodriguez-Roisin R (1989) Ventilation–perfusion mismatching in chronic obstructive pulmonary disease during ventilator weaning. Am Rev Respir Dis 140:1246–1250
43. Beydon L, Cinotti L, Rekik N, Radermacher P, Adnot S, Meignan M, Harf A, Lemaire F (1991) Changes in the distribution of ventilation and perfusion associated with separation from mechanical ventilation in patients with obstructive pulmonary disease. Anesthesiology 75:730–738
44. Jubran A, Mathru M, Dries D, Tobin MJ (1998) Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. Am J Respir Crit Care Med 158:1763–1769
45. Bates JH, Baconnier P, Milic-Emili J (1988) A theoretical analysis of interrupter technique for measuring respiratory mechanics. J Appl Physiol 64:2204–2214
46. Polese G, Rossi A, Appendini L, Brandi G, Bates JH, Brandolese R (1991) Partitioning of respiratory mechanics in mechanically ventilated patients. J Appl Physiol 71:2425–2433
47. Guerin C, Coussa ML, Eissa NT, Corbeil C, Chasse M, Braidy J, Matar N, Milic-Emili J (1993) Lung and chest wall mechanics in mechanically ventilated COPD patients. J Appl Physiol 74:1570–1580
48. Tantucci C, Corbeil C, Chasse M, Braidy J, Matar N, Milic-Emili J (1991) Flow resistance in patients with chronic obstructive pulmonary disease in acute respiratory failure. Effects of flow and volume. Am Rev Respir Dis 144:384–389
49. Jubran A, Tobin MJ (1997) Passive mechanics of lung and chest wall in patients who failed or succeeded in trials of weaning. Am J Respir Crit Care Med 155:916–921
50. Jubran A, Tobin MJ (1997) Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. Am J Respir Crit Care Med 155:906–915
51. Vassilakopoulos T, Zakynthinos S, Roussos C (1998) The tension–time index and the frequency/tidal volume ratio are the major pathophysiologic determinants of weaning failure and success. Am J Respir Crit Care Med 158:378–385
52. Goldstone JC, Green M, Moxham J (1994) Maximum relaxation rate of the diaphragm during weaning from mechanical ventilation. Thorax 49:54–60
53. Laghi F, Cattapan SE, Jubran A, Parthasarathy S, Warshawsky P, Choi YS, Tobin MJ (2003) Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med 167:120–127
54. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, Gasparetto A, Lemaire F (1994) Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 150:896–903
55. Krieger BP, Ershowsky PF, Becker DA, Gazeroglu HB (1989) Evaluation of conventional criteria for predicting successful weaning from mechanical ventilatory support in elderly patients. Crit Care Med 17:858–861
56. Thorens JB, Kaelin RM, Jolliet P, Chevrolet JC (1995) Influence of the quality of nursing on the duration of weaning from mechanical ventilation in patients with chronic obstructive pulmonary disease. Crit Care Med 23:1807–1815
57. Feinstein AR (1987) The intellectual crisis in clinical science: medaled models and muddled mettle. Perspect Biol Med 30:215–230
58. Esteban A, Frutos F, Tobin MJ, Alia I, Solsona JF, Valverdu I, Fernandez R, de La Cal MA, Benito S, Tomas R (1995) A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 332:345–350
59. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF (1996) Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 335:1864–1869
60. Ziman J (2000) Real science: what it is, and what it means. Cambridge University Press, Cambridge, pp 182–245
61. Mendel G (1866) Versuche über Pflanzenhybriden (Experiments on plant hybrids). Verhandl Naturforsch Ver Brunn, Bd IV für das Jahr 1865, Abhandl:3–47
62. Butterfield H (1949) The origins of modern science 1300–1800. Bell, London, p 1
63. Tanenbaum SJ (1994) Knowing and acting in medical practice: the epistemological politics of outcomes research. J Health Politics, Policy and Law 19:27–44
64. Kuhn TS (1962) The structure of scientific revolutions, 3rd edn. University of Chicago Press, Chicago, p 24

François Feihl
Alain F. Broccard

Interactions between respiration and systemic hemodynamics. Part I: basic concepts

Abstract The topic of cardiorespiratory interactions is of extreme importance to the practicing intensivist. It also has a reputation for being intellectually challenging, due in part to the enormous volume of relevant, at times contradictory literature. Another source of difficulty is the need to simultaneously consider the interrelated functioning of several organ systems (not necessarily limited to the heart and lung), in other words, to adopt a systemic (as opposed to analytic) point of view. We believe that the proper understanding of a few simple physiological concepts is of great help in organizing knowledge in this field. The first part of this review will be devoted to demonstrating this point. The second part, to be published in a coming issue of *Intensive Care Medicine*, will apply these concepts to clinical situations. We hope that this text will be of some use, especially to intensivists in training, to demystify a field that many find intimidating.

Keywords Heart-lung interactions · Cardiovascular issues in the ICU · Cardiovascular monitoring · Mechanical ventilation, complications · Mechanical ventilation, weaning

Historical note

The earliest description of cardiorespiratory interactions may be traced back to the first invasive measurement of arterial blood pressure, carried out by Stephen Hales. In the early eighteenth century, this renowned English physiologist inserted a glass tube into the carotid artery of a mare and noted that the height of the column of blood fluctuated with the animal's respiratory efforts. Hales did not stop at describing these fluctuations, but he also theorized on the possible effects of respiration on venous return [1]. Many of the concepts which underly our current understanding of cardiorespiratory interactions were already in place at the start of the twentieth century. For example, the idea that the fall in pleural pressure could impede left ventricular ejection during inspiration was put forward by Donders in 1853, and Riegel mentioned the potential role of this mechanism in the pathogenesis of pulsus paradoxus in 1903 [1].

However, the diffusion and extension of this new knowledge had to await the need for practical applications. The first one arose during World War II, when the US Air Force sought to enhance the ability of its pilots to fly at very high altitude in airplanes with unpressurized cockpits. In these conditions, hypoxia was the limiting factor. It was calculated that every 5 cm H_2O of pressure

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_62, © Springer-Verlag Berlin Heidelberg 2009

added selectively to the face mask supplying the pilot with 100% oxygen would increase the maximal tolerable altitude by 1,000 feet [1, 2]. To clarify the possible adverse effects of such positive pressure breathing, the US Air Force sponsored studies by several groups of prominent physiologists, in particular Rahn and Fenn as well as Carr and Essex. These studies clearly described the effects of pressure breathing on intramural vascular pressures and cardiac output [2–4]. In the late 1940s, seminal work conducted by Cournand and colleagues at Columbia University demonstrated the major role of a reduction in right ventricular transmural filling pressure in the depression of cardiac output caused by positive pressure mechanical inflation (Fig. 1) [5]. In the following years, Guyton provided a theoretical framework of particular relevance to these observations [6]. This framework remains important to our present understanding of cardiorespiratory interactions. It will now be shortly presented.

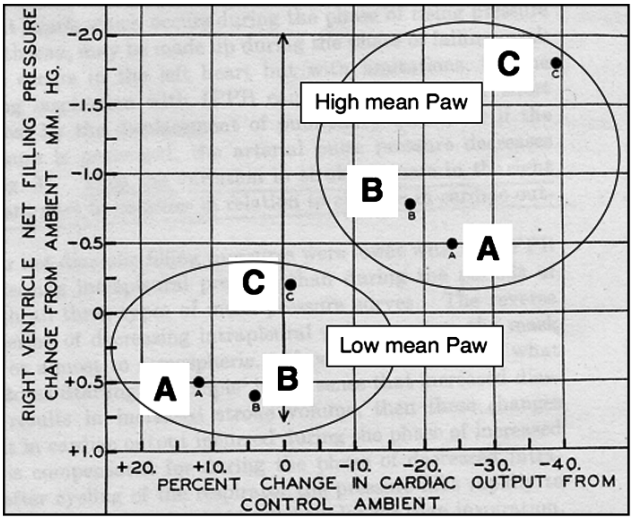


Fig. 1 Some of Cournand's original data showing a direct relationship between the effects of intermittent positive pressure breathing (IPPB) on right ventricular filling pressure and on cardiac output. *A*, *B*, and *C* designate three individual patients, with two data points for each. The right ventricle was catheterized. IPPB was administered via a face mask. Due to the presence of a therapeutic pneumothorax, pleural pressure could be easily obtained. In stable ventilatory conditions, right ventricular end-diastolic pressure and pleural pressure (both measured relative to atmosphere) were averaged over one full respiratory cycle, and the difference of these two values indicated right ventricular net filling (i.e., transmural) pressure. Cardiac output was measured with the direct Fick method. The *abscissa* indicates the change in cardiac output observed when switching from spontaneous breathing (SB, i.e., ambient pressure in face mask) to IPPB, expressed in % of the baseline value in SB. The *ordinate* shows the concomitant change in right ventricular end-diastolic transmural pressure (in mm Hg). Note the inverted scale of both axes. The 3 points on the *upper right part of the plot* (which indicate that a large decrease in transmural filling pressure was associated with a marked depression of cardiac output) were obtained when switching from SB to a pattern of IPPB with a high I/E ratio (>1) and some positive end-expiratory pressure (3 cm H_2O), thus inducing a relatively large increase in mean airway pressure (P_{aw}). The group of 3 points on the *lower left* correspond to a switch from SB to IPPB with an I/E ratio <1 and no positive end-expiratory pressure, a pattern which raised mean P_{aw} to a lesser extent, and neither decreased transmural filling pressure nor depressed cardiac output. Reproduced from [5], with permission from the American Physiological Society

Guyton's description of integrated cardiocirculatory function

Venous return curve

The term *capacitance* vessels designates the highly distensible vessels of the circulatory system, in practice largely the veins (Chap. 10 of [6]). The veins, and especially the small veins [7], contain the major fraction—approximately 70%—of the total systemic blood volume. They are not only highly distensible, but also contain substantial volume even when their transmural pressure is near zero, that is, they have a large *unstressed volume*. Magder [8, 9] has proposed a representation of venous capacitance as a reservoir drained through an opening in the side rather than the bottom (Fig. 2a). The liquid below the opening represents the unstressed volume, which cannot escape from the system. The amount of liquid above the opening is the *stressed volume*, which alone generates a pressure known as the *mean systemic filling pressure* (MSFP). The blood flow from the reservoir to the heart, i.e., the flow of venous return (Q_{RV}), is governed by the equation

$$Q_{RV} = (\mathrm{MSFP} - \mathrm{RAP})/R_v \quad (1)$$

where MSFP and RAP (right atrial pressure) are measured *relative to atmosphere*, and R_v is the resistance to venous return. Thus, the numerator of Eq. 1 is the pressure gradient which drives venous return. If MSFP and R_v remain constant, it can be seen from Eq. 1, that Q_{RV} must increase when RAP decreases. However, if RAP is lowered below a *critical pressure* (P_{crit}) normally close to atmospheric, the transmural pressure of the great veins at the thoracic inlet becomes negative, leading to their collapse which prevents any further increase in Q_{RV} (flow-limitation). From this overall state of affairs, it results that the relationship between Q_{RV} and RAP *at constant MSFP* has the shape depicted by curve 1 in Fig. 2b. Guyton has coined the term *venous return curve* for this relationship. His classical experiments in dogs where right ventricular bypass was used to uncouple venous return from cardiac output have provided a strong support for this model. In particular, the linearity of the venous return curve for values of RAP above P_{crit} has been confirmed[1] [10]. *The venous return*

[1] A minor departure of experimental data from Eq. 1, the junction of the horizontal and steep part of actual venous return curves is smooth rather than angular, suggesting a distribution rather than a unique value of P_{crit}.

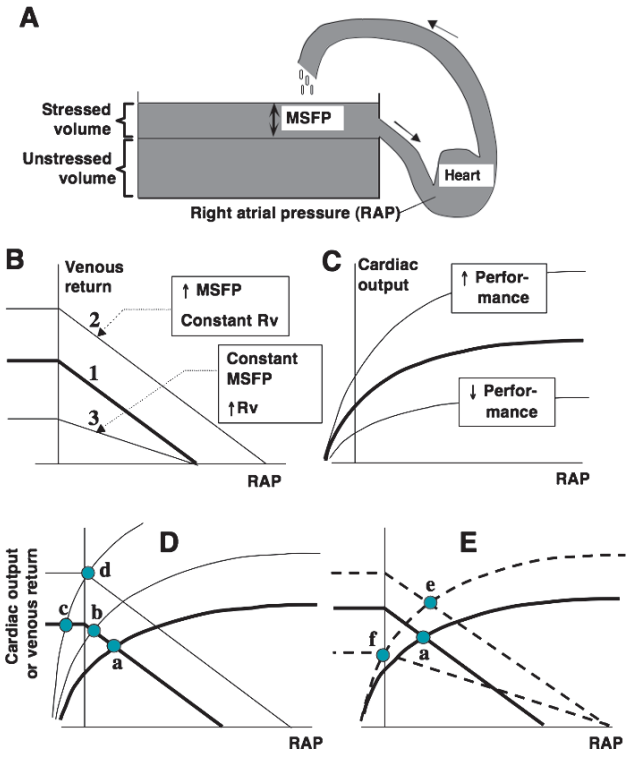


Fig. 2 Interactions of venous return and cardiac function. **a** Magder's representation of the circulatory system. Modified from [8], with permission. MSFP mean systemic filling pressure. Detailed explanations in the text (beginning of Sect. "Venous return curve"). **b** Venous return curves (later part of Sect. "Venous return curve"). **c** cardiac function curves (Sect. "Cardiac function curve"). **d** Guyton's graphical analysis of cardiac output regulation (Sect. "Graphical analysis of cardiac output/venous return"). **e** Potential effects of generalized venoconstriction on cardiac output (last paragraph of Sect. "Graphical analysis of cardiac output/venous return"). In panels **b–e**, RAP designates right atrial pressure *relative to atmosphere*

curve intercepts the horizontal axis at a pressure value equal to MSFP. This statement implies that RAP equals MSFP in circulatory arrest, forming the basis for the experimental measurement of MSFP. At constant P_{crit} and R_v, any increase in MSFP, whether due to an augmentation of the total blood volume in the capacitance vessels or to a transfer of blood from the unstressed to the stressed volume (the latter often resulting from venoconstriction due to adrenergic stimulation), translates into an "rightward" shift[2] of the venous return curve (Fig. 2b, curve 2). Conversely, hypovolemia, whether absolute or relative (i.e., reduced venous tone leading to increased venous compliance and transfer of blood from the stressed to the unstressed volume) would shift the venous return curve "leftwards" (not shown on Fig. 2b). Finally, let us note that the slope of the linear part above *Pcrit* is inversely related to R_v (Fig. 2b, curve 3)[3] .

Cardiac function curve

In Guyton's representation, the cardiac function curve is a plot of cardiac output against the *intramural* RAP (Fig. 2c). As such, it is "a composite function curve for the entire segment of the circulatory system between the input of the heart and its output, including, of course, both sides of the heart as well as the pulmonary circulatory system" (Chap. 8 of [6]). The position of the cardiac function curve depends on, and in fact integrates, all aspects of cardiac pump performance, including the diastolic function, contractility and afterload of both ventricles, as well as heart rate.

Let us insist that, despite *transmural* pressure being a better index of cardiac preload, the RAP depicted in Fig. 2c is *intramural* pressure, i.e., measured relative to atmosphere, as is the case for the venous return curve in Fig. 2b. Why this is so will become clear in an instant.

Graphical analysis of cardiac output/venous return

Both the venous return and the cardiac function curves express flow as a function of *intramural* RAP, and may therefore be superimposed on the same plot (Fig. 2d). *Over any time frame longer than a few heartbeats, cardiac output must equal venous return,* i.e., the heart can only pump what it receives from the periphery. Thus, systemic blood flow is indicated by the intersection of the cardiac output and venous return curves, which is designated as the *operating point* of the circulatory system for specific states of vascular and cardiac function. In spite of its simplicity, this representation has considerable heuristic value for the integrated analysis of cardiovascular events. For example, an instantaneous increase in cardiac output cannot influence MSFP because of the large compliance of capacitance vessels. Therefore, the only way that an augmentation of ventricular performance may cause a steady increase of venous return is by lowering RAP (Fig. 2d, operating point displaced from a to b). When RAP decreases below P_{crit}, the operating point becomes located on the horizontal part of the venous return curve, so that circulatory flow becomes independent of cardiac function (Fig. 2d, point c) although it may

[2] "Rightward" is enclosed in quotes for the following reason: with a true rightward shift of the venous return curve, i.e., a horizontal translation in the narrow geometric sense, P_{crit} would increase and maximal venous return would not change. This would not be consistent with the differences between curves 1 and 2 shown in Fig. 2b.

[3] R_v is not a simple function of venous geometry and blood rheology, but depends in addition, and nonintuitively, on the distribution of blood flow between parallel vascular beds of different time constants [11]. Hence, its designation as resistance to venous return rather than venous resistance.

increase if peripheral determinants of venous return change in the appropriate direction (for example if MSFP is augmented and the venous return curve is shifted "rightwards" following i.v. fluid administration, Fig. 2d, point d).

We have so far ignored potential changes in the resistance to venous return (R_v). For example, venoconstriction induced by a sympatho-adrenergic discharge may both reduce venous compliance (thus increasing MSFP) and augment R_v (thus "flattening" the oblique part of the venous return curve, see end of Sect. "Venous return curve" and Fig. 2b). The net impact on the position of the operating point, and thus on cardiac output, then depends on the balance between these two conflicting influences, as shown in Fig. 2e, where the plain curves represent the baseline state (operating point a), and the dashed curves, the effects of sympatho-adrenergic stimulation, assuming either a small (point e) or large (f) increase in R_v for the same change in MSFP.

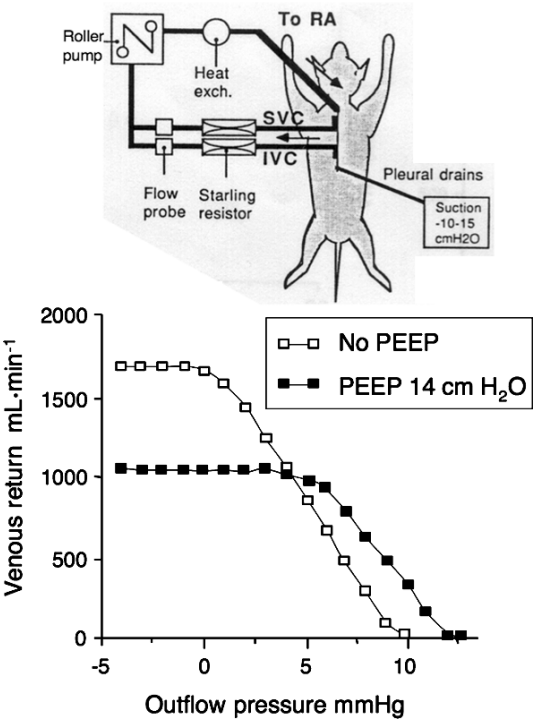


Fig. 3 Effects of PEEP on the venous return curve in closed-chest canines. Dogs were anesthetized, intubated and ventilated. By ways of cannulas placed in both venae cavae, venous return was drained through Starling resistors (i.e., collapsible tubes enclosed in an airtight chamber to allow control of their extramural pressure), and pumped back into the right atrium (*RA*) with a roller pump (*upper part of the figure*). The pump rotating speed was set so as to maintain a negative intramural pressure within the collapsible tubes. In such conditions, the pump forwarded into the heart and circulation whatever amount of blood came through the Starling resistors, independent of heart function (i.e., venous return would be uncoupled from heart function). By adjusting the extramural pressure around the collapsible tubes, outflow pressure for venous return (the equivalent of right atrial pressure in the intact organism) could be set at any desired value, and the resulting venous outflow was then measured. In this way, the venous return curves shown in the *lower part of the figure* were constructed at two different PEEP levels, after surgical closure of the chest (from [25] with permission). These data are discussed in detail in Sect. "Respiration and venous return". Outflow pressure is measured *relative to atmosphere*

Three caveats

The graphical analysis presented above is conceptually quite useful, as we hope to demonstrate in subsequent sections. However, it may be a source of confusion if incompletely understood. The *first confusion* arises if it is not clearly noted that the *intramural* RAP *relative to atmosphere* is being used throughout. Thus, the Guytonian cardiac function curve is shifted to the left or to the right by a decrease or an increase in extramural (intrathoracic) pressure (Sect. "Contact interactions of the heart and lungs" in Part I and Sect. "Effects of PEEP on cardiac output" in Part II). The *second confusion* relates to the intellectual habit of considering a variable plotted in abscissa as necessarily independent. For example, it is commonly considered that i.v. fluid loading increases cardiac filling pressures (thus RAP), hence cardiac preload, hence cardiac output. Considering Fig. 2b which predicts that venous return should decrease with a increasing RAP, one might feel faced with a conundrum. The solution is of course that vascular filling first increases MSFP, which augments venous return, which increases cardiac preload and filling pressures. In such conditions, MSFP must always increase more than RAP does,[4] otherwise venous return could not be augmented. In general, RAP can only be independently controlled if the heart is uncoupled from venous return by interposing an external bypass circuit, as Guyton (Sect. "Venous return curve") and others (Sect. "Contact interactions of the heart and lungs", Figs. 3, 4) have done experimentally. In the intact organism, by contrast, RAP is no more an independent variable than are venous return or cardiac output. The *third confusion* consists in a semantic ambiguity of the expression "venous return", which designates either the *flow* of venous return (in liters of blood per minute) or the *physiological function* depicted by the venous return curve. In the case of the heart, such ambiguity does not exist (i.e., usual terminology always clearly distinguishes heart function from cardiac output).

[4]By considering Fig. 2d, the geometrically-minded reader might note that intravascular volume expansion, translated into a "rightward" shift of the venous return curve, necessarily leads to a smaller increase in RAP than in MSFP if the heart operates on the ascending part of its function curve (i.e., if cardiac output is preload-dependent).

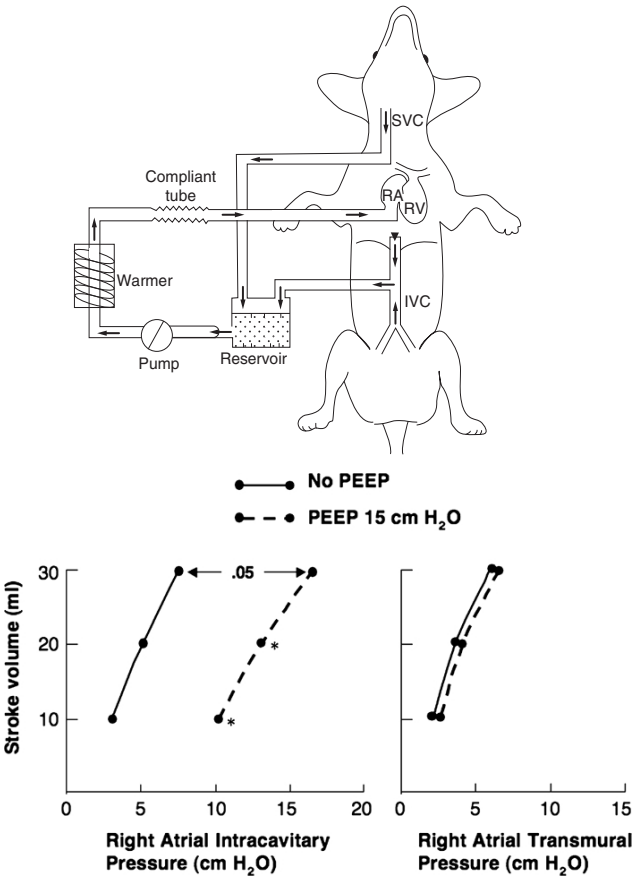


Fig. 4 Effects of PEEP on the cardiac function curve in closed-chest canines. Dogs were anesthetized, intubated and ventilated. Venous return was drained through caval cannulae into a large volume reservoir (2 l), then forwarded to the right atrium (*RA*) by means of a roller pump (*upper part of the figure*). Contrary to the setup shown in Fig. 3, there were no Starling resistors in the circuit (the compliant tube served only to reduce the pressure oscillations generated by the pump). Here, the controlled variable was pump output, which determined ventricular filling. Changing pump output would induce concomitant changes in cardiac output and right atrial pressure. Due to the buffering effect of the reservoir, these modifications would not depend on the particular value of venous return flow (i.e., cardiac function would be uncoupled from venous return function). In this way, cardiac output curves were constructed at different PEEP levels, after surgical closure of the chest (*lower part of the figure*). Surface pressure over the heart was measured with specialized flat sensors, to allow the calculation of right atrial transmural pressure. Left atrial pressure, also measured in these experiments, is not shown for simplicity (from [28] with permission). Right atrial pressure is measured relative to atmosphere in the *left-hand part*, and relative to extramural pressure in the *right-hand part of the figure* These data are discussed in detail in Sect. "Contact interactions of the heart and lungs"

Cardiorespiratory interactions in transient versus steady state

Whenever considering the interactions of respiration with the function of other organs, it is important to bear in mind the distinction between *transient* and *steady state* effects [12]. Transient effects refer either to periodic changes induced by the inspiratory/expiratory cycle (*phasic effects*) or to unsustained effects of various respiratory maneuvers. Due to the short duration, their mechanisms are of a primarily mechanical nature. Steady state effects indicate the impact of sustained alterations of respiratory conditions, such as the institution of positive end-expiratory pressure (PEEP) in a mechanically ventilated patient. Steady state effects depend both on mechanical and on neurohumoral factors (for example the neural regulation of venous compliance, resistance to venous return and cardiac contractility, Fig. 2e).

A caveat is here in order. In the steady state, venous return is methodologically very hard to dissociate from cardiac function. Again, the construction of a complete venous return curve is impossible without bypassing the right ventricle with an external circuit, and a similar remark applies to the cardiac function curve (Sects. "Venous return curve", "Cardiac function curve"). For these reasons, there is an understandable lack of human data on steady state cardiorespiratory interactions. Furthermore, most available experimental studies have been carried out in animals with normal lungs, and have focused on the effects of high PEEP levels ($\geq$15 cm H_2O) while ignoring those related to tidal inflation. Extrapolation of such data to the clinical setting must therefore be done with some caution.

Respiration and venous return

Transient effects of practical importance will be discussed in later Sects. (6.1–6.4 in Part II). Here, we shall restrict ourselves to the description of steady state effects. Most of the available relevant studies have been focused on the impact of a steady increase in intrathoracic pressure as effected by positive end-expiratory airway pressure (PEEP).

For decades, it has been conventional wisdom that an essential mechanism whereby PEEP depresses cardiac output consists in the transmission of the elevated mean intrathoracic pressure into the right atrium, which raises intramural RAP and so decreases the pressure gradient for venous return [6, 13]. The assumption that other determinants of venous return remain unaltered by PEEP was implicit in this reasoning, but is now contradicted by several lines of evidence.

Two independent groups have reported that PEEP levels of up to 15 [14] or 20 cm H_2O [15], while clearly depressing cardiac output, caused identical increases in RAP and MSFP, so that the pressure gradient for venous return was invariant, a finding confirmed more recently in humans [16]. The mechanisms involved a transfer of capacitance blood from the unstressed to the stressed volume [15], due to enhancement of venous tone

mediated in part by sympatho-adrenergic activation [14], akin to changes noted earlier in hypotension produced by hemorrhage [17] or local manipulation of the carotid sinus [18, 19]. Furthermore, the depression of cardiac output by PEEP was amplified by alpha adrenergic blockade [20]. These data indicate that the reflex matching of the increased RAP by an equivalent increase in MSFP is an important facet of cardiovascular adaptation to PEEP. Part of the PEEP-induced augmentation of MSFP could also be due to purely mechanical factors, such as the translocation of blood from the pulmonary to the systemic capacitance vessels [21–23] or the increase in abdominal pressure (due to diaphragmatic descent) which compresses the splanchnic part of the venous reservoir [24].

Although the MSFP–RAP gradient remained constant, cardiac output was clearly depressed in the aforementioned studies, implying that PEEP modified either the resistance to venous return (R_v) or the critical pressure (P_{crit}). This issue was handled in further experiments by Fessler and coworkers [25], who constructed true venous return curves with and without 10 cm H_2O PEEP in closed-chest dogs equipped with a external circuit which bypassed the right ventricle. The main results of this unique study are shown in Fig. 3; PEEP somewhat flattened the portion of the curve to the right of the critical point indicating slightly augmented values of R_v, as also found by Nanas et al. [15]. PEEP also increased P_{crit} and sharply depressed the plateau, indicating a decrease in the maximal value of venous return. These effects might be understood if expansion of the lung by PEEP distorted venous geometry, for example, at the entrance of the venae cavae into the thorax [26], or further upstream in the portal circulation (i.e., compression of the liver by diaphragmatic descent [27]).

In short, the available evidence indicates that PEEP interferes with systemic venous return in a manner more complicated than by just raising RAP. It is important to note that all the aforementioned actions of PEEP must be modulated by the volemic status, although detailed experimental data are scant on this point. In particular, hypovolemia is likely to blunt or even entirely prevent the compensatory rise in MSFP. Conversely, repletion of intravascular volume might make the systemic veins less susceptible to compression, thus minimizing the effects of PEEP on R_v and P_{crit}, as shown in the case of the porcine hepatic circulation [27].

Respiration and cardiac function

Contact interactions of the heart and lungs

Considering that RAP is measured relative to atmosphere and assuming that respiration should not alter the relationship of *transmural* filling pressure to cardiac output, Guyton predicted that changes in intrathoracic pressure (ITP) would cause parallel shifts of the cardiac function curve (i.e., cardiac output plotted against *intramural* RAP) along the pressure axis (Chap. 24 of [6]). This hypothesis was verified by Marini and coworkers [28] (Fig. 4, lower left) in anesthetized, mechanically ventilated canines, using a bypass circuit from the great veins to the right atrium in order to control the inflow of blood into the heart (Fig. 4, upper part). To allow the most accurate measurement of transmural filling pressures, epicardial fluid-filled flat sensors were positioned over the left and right ventricles. In these experiments, the plots of cardiac output versus *transmural* RAP or left atrial pressure (LAP) were not modified by PEEP levels of up to 15 cm H_2O, indicating little modulation of ventricular function per se by these ventilatory conditions, consistent with results by other investigators [29] (Fig. 4, lower right). In the former study, there was evidence that lung inflation "compressed the heart", i.e., imposed a progressive external constraint mediated by local surface pressure on the epicardium, which increased with increasing heart volume. This constraint appeared local and independent of global ITP, since it was not removed by opening the chest and could be elicited by the selective inflation of basal lung segments [30]. The concept of heart compression by the inflated lung is consistent with the small heart size typically observed on chest films in acute asthma. Via dynamic hyperinflation, it could also explain the increase in RAP and pulmonary artery occlusion pressure (PAOP) observed on mild exercise as well as voluntary hyperventilation in patients with obstructive lung disease uncomplicated by pulmonary hypertension or overt heart failure [31].

Ventricular interdependence and left ventricular diastolic function

The right (RV) and left ventricle (LV) are mechanically coupled, because they share a common septum and circumferential fibers, and the expansion of both is constrained by a common pericardium. For these reasons, the diastolic filling of one chamber has direct influence on the geometry and stiffness of the other, a phenomenon known as *direct (or parallel) ventricular diastolic interdependence* [32].

With phasic respiration, the end-diastolic volumes of both ventricles tend to change in opposite directions [33]. Spontaneous inspiration augments venous return, thus increasing RV filling, which in turn makes the LV stiffer, thus impeding its filling [33, 34]. Lung inflation with positive airway pressure tends to act in an inverse fashion [35, 36]. These mechanisms imply phasic changes in the diastolic properties of the ventricles. They underly in part the respiratory fluctuations of arterial pressure to be described below, although an equally important role is

being played in that respect by *series interdependence* (the propagation of changes in RV output to LV output, due to the series arrangement of both ventricles) [37].[5]

Encroachment of a dilated RV on LV filling as a steady, rather than transient effect may result from extreme hyperinflation, such as associated with PEEP levels in excess of 20 cm H_2O [40], or when more moderate increases of ITP and lung volume are superimposed on either an obstructed pulmonary circulation or a failing RV [41]. In these cases, the primum movens is the acute increase in RV afterload, with consequent RV dilatation.

Ventricular afterload

Defined as the force opposing ejection,[6] ventricular afterload is represented by the level of *transmural* pressure, in the course of systole, within either the aortic root (LV afterload) or the pulmonary artery trunk (RV afterload) The transmural rather than the intraluminal pressure must be considered [44, 45], because these great vessels as well as the ventricles are exposed to an extramural pressure (i.e., ITP) which is usually non atmospheric. The mechanisms whereby respiration interacts with LV and RV afterload are different.

LV afterload

At the onset of spontaneous inspiration, the intraluminal pressure in the aortic root decreases less than does ITP, due to the connection of this vessel with extrathoracic arteries. As a result, aortic transmural pressure increases. With spontaneous breathing therefore, LV afterload is greater in inspiration than in expiration [46–48]. A symmetrical chain of events leads to a reduced LV afterload in the course of a transient increase in ITP, such as with positive pressure inflation of the lungs. Steady increases in ITP, as effected with PEEP, similarly unload the LV with potentially beneficial consequences in presence of left heart failure, as described in greater detail below (Sect. "Effects of PEEP on cardiac output" in Part II). Conversely, patients with obstructive sleep apnea have bouts of greatly negative ITP which increase LV afterload, thus contributing to LV hypertrophy [49].

RV afterload

A seminal paper by Permutt [50] shows that RV afterload is highly dependent on and increases with the proportion of lung tissue in West zone 1 or 2, as opposed to zone 3 conditions. Zones 1 or 2 exist whenever the extraluminal pressure of alveolar capillaries (which is close to alveolar pressure, P_A) exceeds the intraluminal value, leading to vessel compression. In zone 3 by contrast, intraluminal capillary pressure exceeds P_A. For hydrostatic reasons, zones 1 and 2 are more likely to occur in nondependent parts of the lung. Furthermore, respiratory changes in the intraluminal pressure of alveolar capillaries tend to track changes in ITP[7] and thus to decrease more than does P_A during a spontaneous inspiration and to increase less than does PA on inflation of the lung with positive pressure. Thus, any increase in lung volume, whether in the context of spontaneous [51] or mechanically assisted breathing [45], has the potential to promote the formation of zones 1 and 2 at the expense of zone 3, and thus to increase RV afterload. These considerations are of high clinical relevance, notably concerning the possible induction or aggravation of acute cor pulmonale by mechanical ventilation, as described below (Sect. "Mechanical ventilation and acute cor pulmonale" in Part II).

Myocardial contractility

Some studies have indicated that lung inflation by PEEP could trigger the humoral release of one or several cardiodepressor agents [52, 53]. However, as we have already seen, biventricular Starling curves were not depressed by PEEP (Fig. 4, right). Furthermore, work in both animals and humans, using various methodologies to measure the size of cardiac chambers, consistently failed to indicate any influence of PEEP on the relationship of ventricular preload to stroke output, stroke work, or end-systolic ventricular pressure [40, 41, 54, 55]. Finally, experimental studies have shown that end-systolic elastance, a recognized load-invariant index of contractility, remained constant at levels of PEEP up to 15 cm H_2O [55, 56], even when possible adrenergic reflexes were suppressed with beta-blockade [55]. In short, a steady state increase in ITP

[5] A further factor which modulates the impact of respiration on LV filling is the influence of lung inflation on pulmonary blood volume and pulmonary venous outflow. Experiments in isolated lungs [38, 39] have indicated that, whether actuated by positive airway or negative pleural pressure, an increase in lung volume can "squeeze" blood out of the pulmonary vascular bed, provided that intra-alveolar vessels are filled at end-expiration, which usually requires a left atrial pressure >3–5 mmHg (more rigorously, West zone 3 conditions, see Sect. "RV afterload" for definition of West zones, and detailed discussion of this issue in [39].

[6] A useful simplification. More rigorously, ventricular afterload is defined as the systolic wall stress (σ), linked to transmural ejection pressure (P), chamber radius (r), and wall thickness (h) by the Laplace relationship $\sigma = P \times r/h$ [42]. Ejection pressure is in turn linked to arterial impedance, which measures the degree to which the arterial system opposes pulsatile blood flow [43].

[7] This is because the alveolar capillaries are in continuity with the pulmonary artery trunk, where intraluminal pressure decreases when ITP decreases, and increases when ITP increases.

and lung volume, as effected by PEEP, does not appear to directly depress myocardial contractility.

Myocardial perfusion and ischemia

Whether in specific conditions PEEP could indirectly alter myocardial contractility by inducing myocardial ischemia remains largely unresolved [57, 58]. Many studies have indicated that clinically relevant levels of PEEP can decrease myocardial blood flow. In the LV, afterload and preload are concomitantly reduced, leading to diminished systolic wall stress and O_2 demand, with an unpredictable net effect on the adequacy of myocardial O_2 supply [59, 60]. In a dog model of acute ischemic LV failure induced by embolization of the left coronary artery with microspheres, the institution of 15 cm H_2O PEEP had no impact on ischemic myocardial metabolism assessed by lactate extraction [61]. In the RV by contrast, PEEP has a greater potential to upset the balance between O_2 supply and demand, due to its ability to increase afterload. Indeed, two canine studies have shown that the institution of PEEP aggravates the RV dysfunction induced by ligation of the right coronary artery [41, 62]. In one of them, PEEP also caused an extension of myocardial necrosis in the area at risk [62].

There is evidence that negative ITP can induce or aggravate LV myocardial ischemia, likely by increasing LV afterload in the presence of insufficient coronary reserve. Scharf and colleagues [63] found that patients with coronary artery disease developed LV dyskinesis during a Mueller maneuver with an inspiratory effort of −20 to −30 cm H_2O. These changes were not seen in patients with normal coronary arteries. Negative ITP of this magnitude can occur during weaning from mechanical ventilation, at times inducing LV dysfunction possibly due to LV ischemia and responsible for weaning failure (Part II, Sect. "Weaning failure from cardiovascular origin").

Acknowledgments We warmly thank the reviewers for their contribution to this text, in the form of numerous thoughtful, in depth, and very constructive comments.

References

1. Wise RA (1994) Historical perspectives on the mechanical interactions of respiration and circulation. In: Perret C (ed) Les interactions cardio-pulmonaires. Arnette, Paris, pp 3–15
2. Farhi LE (1990) World War II and respiratory physiology: the view from Rochester, New York. J Appl Physiol 69:1565–1570
3. Carr DT, Essex HE (1945) Certain effects of positive pressure respiration on the circulatory and respiratory systems. Am Heart J 8:53–72
4. Otis AB, Rahn H, Brontman M, Mullins LJ, Fenn WO (1946) Ballistocardiographic study of changes in cardiac output due to respiration. J Clin Invest 25:413–421
5. Cournand A, Motley HL, Werko L, Richards DW (1948) Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol 152:162–174
6. Guyton AC, Jones CE, Coleman TG (1973) Circulatory physiology: cardiac output and its regulation. Saunders, Philadelphia
7. Rothe CF (1983) Venous system: physiology of the capacitance vessels. In: Shepherd JT, Abboud FM (eds) Handbook of physiology: the cardiovascular system vol. 3: peripheral circulation and organ blood flow, Part 1. American Physiological Society, Bethesda, pp 397–452
8. Magder S (1994) Venous return and cardiac output. In: Perret C, Feihl F (eds) Les interactions cardio-pulmonaires. Arnette, Paris, pp 29–36
9. Magder S (2006) Point: the classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct. J Appl Physiol 101:1523–1525
10. Guyton AC, Lindsey AW, Abernathy B, Langston JB (1958) Mechanism of increased venous return and cardiac output caused by epinephrine. Am J Physiol 192:126–130
11. Caldini P, Permutt S, Waddell JA, Riley RL (1974) Effect of epinephrine on pressure, flow, and volume relationships in the systemic circulation of dogs. Circ Res 34:606–623
12. Fessler HE (1997) Heart-lung interactions: applications in the critically ill. (Review) (105 refs). Eur Respir J 10:226–237
13. Qvist J, Pontoppidan H, Wilson RS, Lowenstein E, Laver MB (1975) Hemodynamic response to mechanical ventilation with PEEP: the effect of hypervolemia. Anesthesiology 42:45–55
14. Fessler HE, Brower RG, Wise RA, Permutt S (1991) Effects of positive end-expiratory pressure on the gradient for venous return. Am Rev Respir Dis 143:19–24
15. Nanas S, Magder S (1992) Adaptations of the peripheral circulation to PEEP. Am Rev Respir Dis 146:688–693
16. Jellinek H, Krenn H, Oczenski W, Veit F, Schwarz S, Fitzgerald RD (2000) Influence of positive airway pressure on the pressure gradient for venous return in humans. J Appl Physiol 88:926–932
17. Rothe CF, Drees JA (1976) Vascular capacitance and fluid shifts in dogs during prolonged hemorrhagic hypotension. Circ Res 38:347–356
18. Shoukas AA, Sagawa K (1973) Control of total systemic vascular capacity by the carotid sinus baroreceptor reflex. Circ Res 33:22–33
19. Deschamps A, Magder S (1992) Baroreflex control of regional capacitance and blood flow distribution with or without alpha-adrenergic blockade. Am J Physiol 263(6 Pt 2):H1755–H1763
20. Scharf SM, Ingram RH (1977) Influence of abdominal pressure and sympathetic vasoconstriction on the cardiovascular response to positive end-expiratory pressure. Am Rev Respir Dis 116:661–670
21. Mitzner W, Goldberg H, Lichtenstein S (1976) Effect of thoracic blood volume changes on steady state cardiac output. Circ Res 38:255–261
22. Risoe C, Hall C, Smiseth OA (1991) Splanchnic vascular capacitance and positive end-expiratory pressure in dogs. J Appl Physiol 70:818–824

23. Peters J, Hecker B, Neuser D, Schaden W (1993) Regional blood volume distribution during positive and negative airway pressure breathing in supine humans. J Appl Physiol 75:1740–1747
24. Van Den Berg PCM, Jansen JRC, Pinsky MR (2002) Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. J Appl Physiol 92:1223–1231
25. Fessler HE, Brower RG, Wise RA, Permutt S (1992) Effects of positive end-expiratory pressure on the canine venous return curve. Am Rev Respir Dis 146:4–10
26. Fessler HE, Brower RG, Shapiro EP, Permutt S (1993) Effects of positive end-expiratory pressure and body position on pressure in the thoracic great veins. Am Rev Respir Dis 148:1657–1664
27. Brienza N, Revelly JP, Ayuse T, Robotham JL (1995) Effects of PEEP on liver arterial and venous blood flows. Am J Respir Crit Care Med 152:504–510
28. Marini JJ, Culver BH, Butler J (1981) Effect of positive end-expiratory pressure on canine ventricular function curves. J Appl Physiol 51:1367–1374
29. Wise RA, Robotham JL, Bromberger-Barnea B, Permutt S (1981) Effect of PEEP on left ventricular function in right-heart-bypassed dogs. J Appl Physiol 51:541–546
30. Marini JJ, Culver BH, Butler J (1981) Mechanical effect of lung distention with positive pressure on cardiac function. Am Rev Respir Dis 124:382–386
31. Butler J, Schrijen F, Henriquez A, Polu JM, Albert RK (1988) Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. Am Rev Respir Dis 138:350–354
32. Janicki JS, Weber KT (1980) Factors influencing the diastolic pressure–volume relation of the cardiac ventricles. [Review] [44 refs]. Fed Proc 39:133–140
33. Scharf SM (1992) Cardiopulmonary interactions. In: Scharf SM (ed) Cardiopulmonary physiology in critical care. Marcel Dekker, New York, pp 333–355
34. Kim BH, Ishida Y, Tsuneoka Y, Matsubara N, Hiraoka T, Takeda H, Inoue M, Kamada T, Kimura K, Kozuka T (1987) Effects of spontaneous respiration on right and left ventricular function: evaluation by respiratory and ECG gated radionuclide ventriculography. J Nucl Med 28:173–177
35. Santamore WP, Heckman JL, Bove AA (1983) Cardiovascular changes from expiration to inspiration during IPPV. Am J Physiol 245:H307–H312
36. Mitchell JR, Whitelaw WA, Sas R, Smith ER, Tyberg JV, Belenkie I (2005) RV filling modulates LV function by direct ventricular interaction during mechanical ventilation. Am J Physiol 289:H549–H557
37. Olsen CO, Tyson GS, Maier GW, Spratt JA, Davis JW, Rankin JS (1983) Dynamic ventricular interaction in the conscious dog. Circ Res 52:85–104
38. Permutt S, Howell JB, Proctor DF, Riley RL (1961) Effect of lung inflation on static pressure–volume characteristics of pulmonary vessels. J Appl Physiol 16:64–70
39. Brower R, Wise RA, Hassapoyannes C, Bromberger-Barnea B, Permutt S (1985) Effect of lung inflation on lung blood volume and pulmonary venous flow. J Appl Physiol 58:954–963
40. Jardin F, Farcot JC, Boisante L, Curien N, Margairaz A, Bourdarias JP (1981) Influence of positive end-expiratory pressure on left ventricular performance. N Engl J Med 304:387–392
41. Schulman DS, Biondi JW, Zohgbi S, Cecchetti A, Zaret BL, Soufer R (1992) Left ventricular diastolic function during positive end-expiratory pressure. Impact of right ventricular ischemia and ventricular interaction. Am Rev Respir Dis 145:515–521
42. Opie L (1997) Ventricular function, Chap. 12. In: Opie L (ed) The heart: physiology, from cell to circulation. Lippincott-Raven, Philadelphia, pp 391–420
43. Nichols WW, O'Rourke MF (1990) Vascular impedance. McDonald's blood flow in arteries, Chap. 11. Edward Arnold, London, pp 283–329
44. Scharf SM, Brown R, Tow DE, Parisi AF (1979) Cardiac effects of increased lung volume and decreased pleural pressure in man. J Appl Physiol 47:257–262
45. Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias JP (1990) Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. Anesthesiology 72:966–970
46. Buda AJ, Pinsky MR, Ingels NB Jr, Daughters GT 2nd, Stinson EB, Alderman EL (1979) Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 301:453–459
47. Pinsky MR, Summer WR, Wise RA, Permutt S, Bromberger-Barnea B (1983) Augmentation of cardiac function by elevation of intrathoracic pressure. J Appl Physiol 54:950–955
48. Peters J, Kindred MK, Robotham JL (1988) Transient analysis of cardiopulmonary interactions. II. Systolic events. J Appl Physiol 64:1518–1526
49. Naughton MT, Bradley TD (1998) Sleep apnea in congestive heart failure. Clin Chest Med 19:99–113
50. Permutt S, Bromberger-Barnea B, Bane HN (1962) Alveolar Pressure, pulmnary venous pressure, and the vascular waterfall. Med Thorac 19:239–260
51. Jardin F, Farcot JC, Boisante L, Prost JF, Gueret P, Bourdarias JP (1982) Mechanism of paradoxic pulse in bronchial asthma. Circulation 66:887–894
52. Manny J, Grindlinger G, Mathe AA, Hechtman HB (1978) Positive end-expiratory pressure, lung stretch, and decreased myocardial contractility. Surgery 84:127–133
53. Grindlinger GA, Manny J, Justice R, Dunham B, Shepro D, Hechtman HB (1979) Presence of negative inotropic agents in canine plasma during positive end-expiratory pressure. Circ Res 45:460–467
54. Calvin JE, Driedger AA, Sibbald WJ (1981) Positive end-expiratory pressure (PEEP) does not depress left ventricular function in patients with pulmonary edema. Am Rev Respir Dis 124:121–128
55. Johnston WE, Vinten-Johansen J, Santamore WP, Case LD, Little WC (1989) Mechanism of reduced cardiac output during positive end-expiratory pressure in the dog. Am Rev Respir Dis 140:1257–1264
56. Crottogini AJ, Willshaw P, Barra JG, Breitbart GJ, Pichel RH (1988) End-systolic pressure-volume relationships in dogs during ventilation with PEEP. Am J Physiol 254(4 Pt 2):H664–H670
57. Scharf SM (2001) Ventilatory support in the failing heart. In: Scharf SM, Pinsky MR, Magder S (eds) Respiratory-circulatory interactions in health and disease. Marcel Dekker, New York, pp 519–550
58. Fessler HE (2001) Mechanical ventilation with PEEP. In: Scharf SM, Pinsky MR, Magder S (eds) Respiratory-circulatory interactions in health and disease. Marcel Dekker, New York, pp 807–836
59. Tucker HJ, Murray JF (1973) Effects of end-expiratory pressure on organ blood flow in normal and diseased dogs. J Appl Physiol 34:573–577
60. Hevroy O, Grundnes O, Bjertnaes L, Mjos OD (1989) Myocardial blood flow and oxygen consumption during positive end-expiratory pressure ventilation at different levels of cardiac inotropy and frequency. Crit Care Med 17:48–52

61. Hevroy O, Reikeras O, Grundnes O, Mjos OD (1988) Cardiovascular effects of positive end-expiratory pressure during acute left ventricular failure in dogs. Clin Physiol 8:287–301

62. Johnston WE, Vinten-Johansen J, Shugart HE, Santamore WP (1992) Positive end-expiratory pressure potentiates the severity of canine right ventricular ischemia-reperfusion injury. Am J Physiol 262(1 Pt 2):H168–H176

63. Scharf SM, Bianco JA, Tow DE, Brown R (1981) The effects of large negative intrathoracic pressure on left ventricular function in patients with coronary artery disease. Circulation 63:871–875

François Feihl
Alain F. Broccard

Interactions between respiration and systemic hemodynamics. Part II: practical implications in critical care

Abstract In Part I of this review, we have covered basic concepts regarding cardiorespiratory interactions. Here, we put this theoretical framework to practical use. We describe mechanisms underlying Kussmaul's sign and pulsus paradoxus. We review the literature on the use of respiratory variations of blood pressure to evaluate volume status. We show the possibilities of attaining the latter aim by investigating with ultrasonography how the geometry of great veins fluctuates with respiration. We provide a Guytonian analysis of the effects of PEEP on cardiac output. We terminate with some remarks on the potential of positive pressure breathing to induce acute cor pulmonale, and on the cardiovascular mechanisms that at times may underly the failure to wean a patient from the ventilator.

Clinical correlates

Kussmaul's sign

Kussmaul's sign is a paradoxical increase in RAP during inspiration. Although first described in constrictive pericarditis, it occurs most frequently in severe right-sided heart failure of any cause [1]. Whether due to pericardial constraint or due to dilation of the ventricular chamber to the limit of distensibility, an abnormally high impedance to right ventricular (RV) diastolic filling is a prerequisite for the appearance of Kussmaul's sign. The traditional explanation is that the rigid RV cannot accommodate the inspiratory increase of venous return [1]. However, if venous return increased solely as a response to the fall in intrathoracic pressure (ITP), RAP measured relative to atmosphere could never become elevated above its end-expiratory value (otherwise, venous return would fall, a contradiction in terms) [2]. Work by Takata and colleagues [3] has shown that an absolute requirement for the occurrence of Kussmaul's sign is an inspiratory increase in abdominal pressure, induced by diaphragmatic descent and presumably raising mean systemic filling pressure (MSFP).

Pulsus paradoxus

In healthy humans breathing spontaneously, the systolic arterial pressure falls slightly (by less than 10 mmHg) in inspiration. It is now well accepted that this phenomenon reflects an inspiratory fall of left ventricular (LV) stroke volume due to diastolic ventricular interdependence (Part I, Section "Respiration and cardiac function") [4].

As originally described by Kussmaul in 1873, pulsus paradoxus referred to the inspiratory disappearance of the radial pulse in patients with tuberculous pericarditis [2, 5].

M.R. Pinsky et al. (eds.), *Applied Physiology in Intensive Care Medicine*,
DOI: 10.1007/978-3-642-01769-8_63,

In its present definition, this term designates an abnormally large fall (>10 mmHg) in systolic arterial blood pressure during spontaneous inspiration. Pulsus paradoxus is a frequent symptom of cardiac tamponade [6] and acute severe asthma [7, 8]. It may be observed as well in other forms of airway obstruction and in hypovolemia. There are occasional reports of pulsus paradoxus in massive pleural effusion [9], pulmonary embolism [10], anaphylactic shock [11], strangulated diaphragmatic hernia [12], and tricuspid atresia [13].

As already suspected by Dornhorst 50 years ago [14], the main mechanism of pulsus paradoxus in cardiac tamponade is a massive amplification of parallel diastolic ventricular interdependence, due to a much tighter mechanical coupling of the cardiac chambers when compressed within a tense, pressurized pericardium [6]. Thus, pulsus paradoxus in experimental tamponade disappeared following extracorporeal bypass of the RV [15]. Accordingly, pulsus paradoxus is minimal or absent in tamponade associated with atrial septal defect, a condition in which RV and LV fillings are no longer competitive [16]. For somewhat less clear reasons, tamponade may also fail to cause pulsus paradoxus in presence of concomitant LV dysfunction [17].

The mechanism of pulsus paradoxus in acute severe asthma differs somewhat from that in tamponade. Jardin and colleagues [7] studied patients admitted to an intensive care unit for acute severe asthma, using 2D echography and invasive hemodynamic monitoring. They found that exaggerated parallel diastolic interdependence, although clearly present in view of the respiratory changes in ventricular end-diastolic volumes and septal geometry, did not suffice to explain the concomitant pulsus paradoxus, because RV stroke volume appeared to fall, rather than increase in inspiration. They concluded that, with severe hyperinflation of the lung, inspiration augmented RV afterload sufficiently to depress RV output, hence LV preload. In other words, pulsus paradoxus in acute severe asthma is an exaggerated form of series (in addition to parallel) ventricular interdependence (Part I, Section "Respiration and cardiac function").

Respiratory fluctuations of vascular pressures for the evaluation of preload-sensitivity at the bedside

When peripheral perfusion is inadequate, a basic question facing the clinician is whether any improvement is to be expected from expansion of the intravascular volume. This is equivalent to asking whether the heart operates on the steep portion (i.e., preload-sensitive cardiac output), or on the plateau of its function curve (preload-insensitive). Little help can be expected in that respect from single determinations of RAP and pulmonary artery occlusion pressure (PAOP), as provided by the Swan-Ganz catheter [18–20]. An essential, although not the only reason is that the PAOP and RAP are intramural rather than true filling (i.e., transmural) pressures [21]. Taking readings at end-expiration is not a foolproof solution, due to frequent active expiration (Fig. 1) [22]. This latter problem may be suspected by abdominal wall palpation to assess for expiratory contraction of abdominal muscles. It may also be detected by observing the respiratory fluctuations of bladder pressure [23]. Also, trends in PAOP and RAP following i.v. fluid administration may be more informative than single measurements [24], an approach which however entails the risk of volume overload. A substitute to fluid challenge devoid of the latter risk might consist in observing the hemodynamic impact of passive leg raising, a maneuver which translocates peripheral blood towards the thorax, and thus may augment cardiac preload [25–27]. Finally, the easily measured respiratory fluctuations of arterial blood pressure and RAP may convey useful information on preload-sensitivity.

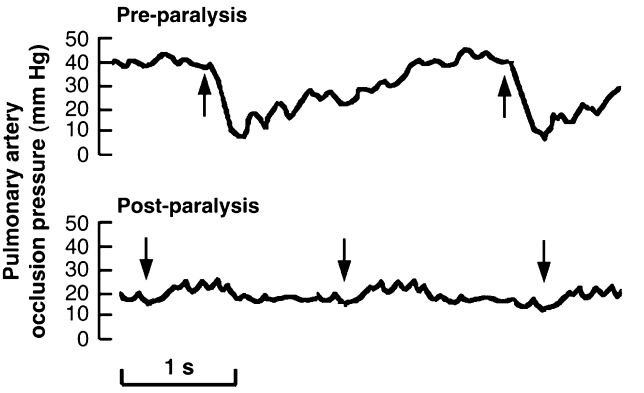


Fig. 1 Impact of active expiration on readings of pulmonary artery occlusion pressure (PAOP) made at end-expiration. In this example obtained in a ventilated patient, the effect is evident from the comparison of recordings made before (upper trace) and after administration of a neuromuscular blocking agent (lower trace). *Arrows* indicate end-expiration. Before paralysis, active inspiration causes a rapid drop in vascular pressure, the transition from end-inspiration to the begin of expiration cannot be recognized, and active expiration is manifested by a progressive increase, reaching a maximum at end-expiration, where the PAOP reads 42 mmHg. After paralysis, passive inflation by the ventilator causes the vascular pressure to increase above the end-expiratory value, which now reads 20 mmHg. In this case, uncritical reading of the upper trace would lead to considerable overestimation of the true PAOP. The wavelets seen on the upper trace might be cardiogenic oscillations (*a* and *v* waves, compatible with a heart rate of approximately 150/min), or artefacts. Modified from [22], with permission

In the course of a ventilator-delivered positive pressure breath, the systolic blood pressure transiently increases relative to the stable level obtained in a prolonged expiratory pause (Fig. 2, Δup), and then decreases below that level (Fig. 2, Δdown). The Δup reflects the transient augmentation of LV stroke volume related both to diminished afterload and enhanced pulmonary venous return (blood "squeezed out of the lungs") [28–30]. The Δdown is

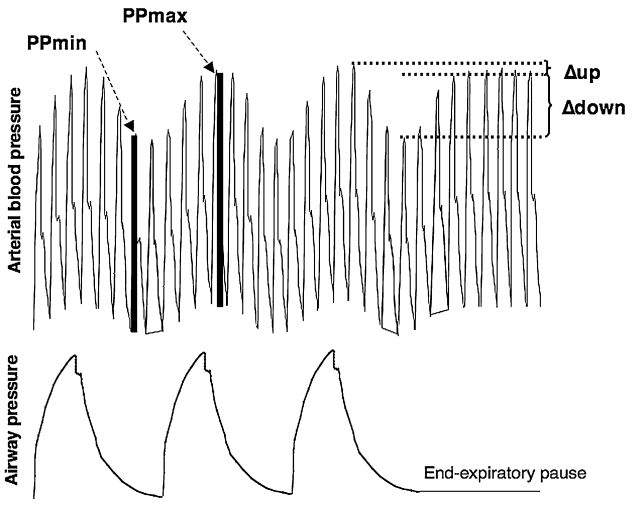


Fig. 2 Respiratory variations of arterial blood pressure in a sedated patient on volume-controlled mechanical ventilation. In such conditions, the respiratory fluctuations of either systolic (**Δ**up and **Δ**down) or pulse pressure (PP_{max} and PP_{min}) may be used to detect hypovolemia and so determine the need for intravascular volume expansion. The first method requires an end-expiratory pause of sufficient duration for systolic blood pressure to stabilize, to obtain a reference level from which to measure **Δ**up and **Δ**down as indicated. PP_{max} and PP_{min} can be obtained without interrupting ventilation. A high value of either **Δ**down or **ΔPP** (=PP_{max}–PP_{min}) indicates hypovolemia. Detailed explanations in "Respiratory fluctuations of vascular pressures"

caused by the subsequent reduction of LV preload and stroke volume, which takes place in exhalation as the inspiratory depression of RV preload and output propagates to pulmonary venous return with a time lag of a few heartbeats [29]. Thus, preload-insensitivity of the heart should be associated with a blunting or disappearance of the Δdown. The Δup would be less reliable in that respect due to the potential influence of changing LV afterload. This concept has been validated experimentally [31–33]. Two small clinical studies demonstrated a superiority of the Δdown, compared with either PAOP or echographic estimates of LV size, for predicting the response of cardiac output to a fluid challenge in mechanically ventilated postoperative [34] or severely septic patients [19].

A variation of the Δdown approach, which has been similarly validated consists in quantifying the variations of pulse pressure (ΔPP) induced by a positive pressure breath (Fig. 2) [20, 35]. The respiratory fluctuations in the amplitude of the plethysmographic pulse wave (obtained non-invasively from pulse oxymetry) have been used to the same effect [36]. A practical problem with all these methods is the potential confounding influence of cardiac arrythmias, increased abdominal pressure [37], and changes in vascular tone or ventilatory conditions. Indeed, the aforementioned validation studies were carried out in heavily sedated patients ventilated in controlled mode with relatively large tidal volumes (≥8 ml/kg) [19, 20, 34]. It is not clear that similar results would be obtained with smaller tidal volumes [38–40]. A possible answer to this critique has been proposed in the form of applying a succession of three mechanical breaths of progressively increasing plateau pressure and quantifying the effect on systolic blood pressure [41]. We must finally underscore that these methods lose most of their validity with the presence of active inspiratory or expiratory effort, whether in the course of mechanically assisted or spontaneous breathing [25, 26, 42].

With spontaneous breathing, Magder et al. [43] have suggested that the lack of an inspiratory drop in RAP is indicative of an overfilled, non-compliant heart lying on the flat part of its function curve, and therefore predicts the lack of volume responsiveness of cardiac output.

Respiratory fluctuations of great veins geometry

The transmural pressure versus volume relationship of the venae cavae is nonlinear, with a steep slope at low distension and a plateau at full repletion [44]. Thus, one would expect that phasic changes in transmural pressure would more readily translate into respiratory variations in cross-sectional size when imposed on a partially empty vessel (hypovolemia), as opposed to a fully repleted one (normo or hypervolemia). Based on this rationale, the phasic changes in caval diameters, as evaluated from echocardiography, have been proposed as non-invasive indices of intravascular volume status [44–50].

In man, the IVC runs almost entirely intraabdominal, i.e., it enters the right atrium immediately after crossing the diaphragm. Thus, its extramural pressure is abdominal pressure (Pabd), while its intramural pressure lies close to RAP. In the course of a spontaneous inspiration, Pabd increases (diaphragmatic descent) while RAP decreases (transmission of pleural pressure swing), leading to an inspiratory diminution of transmural pressure. The latter, however, only causes the IVC diameter to shrink if the vessel is not fully repleted (i.e., if it operates on the steep part rather than the plateau of its transmural pressure/diameter relationship). Quantified in various ways with transthoracic echocardiography, the inspiratory decrease of IVC diameter has been used to characterize volume status in the course of hemodialysis for end-stage renal disease [45, 46]. In the ICU, we are aware of no similar application in spontaneously breathing subjects. In contrast with spontaneous breathing, positive pressure inflation is expected to dilate an incompletely filled IVC, because the positive swing of pleural pressure is fully transmitted to RAP, but only partially to Pabd, thus causing an inspiratory increase of IVC transmural pressure. Two studies have found that the amplitude of phasic changes in IVC geometry, as measured with transthoracic echocardiography, were highly predictive of cardiac output response to a fluid challenge in sedated septic shock patients ventilated in controlled mode [47, 48]. Although

not documented so far, respiratory fluctuations in IVC diameter are likely to depend not only on volemia, but also on respiratory pattern, prevailing level of mean Pabd, and right ventricular function, as is the case for ΔPP and Δdown.

In contrast to the IVC, the superior vena cava (SVC) runs mainly intrathoracic, so that its extramural pressure is close to pleural pressure. In hypovolemic conditions, positive pressure inflation may transiently create zone 2 conditions (intraluminal pressure <Ppl[1]) in this vessel, leading to its partial inspiratory collapse [49]. Phasic variations of SVC diameter have been found to correlate well with fluid responsiveness of cardiac output in septic patients on controlled mechanical ventilation [50]. This index of hypovolemia has been advocated as superior to that based on IVC diameter [44], notably because it is not influenced by Pabd. In contrast with the IVC, however, the SVC can only be echographically imaged via the transesophageal, but not the transthoracic route.

Effects of PEEP on cardiac output

The effects of PEEP on cardiac output are modulated by a variety of factors, the understanding of which is greatly facilitated by the Guytonian representation of venous return-cardiac function interactions (i.e., Fig. 2d in Part I). In Fig. 3, the venous return curves labeled "ZEEP" (zero end-expiratory pressure) and "PEEP" have been taken from the data presented above [51] (Fig. 3 in Part I). The venous return curve labeled "PEEP + volume" has been drawn under the assumptions that intravascular volume expansion under PEEP would increase MSFP, with little effect on either Rv or Pcrit (Chapter 12 of [52]). Figure 3a depicts events associated with normal cardiac function: the cardiac function curve under ZEEP is steep (Fig. 4 in Part I) and intersects the corresponding venous return curve at point 1 located slightly on the right of and below the critical point [53]. PEEP effects a shift to the right of the cardiac function curve (Fig. 4, lower left, in Part I) and of the critical point by approximately the same amount (equal to the increase in ITP), while depressing the maximal venous return. Under PEEP, the operating point becomes located on the plateau of the new venous return curve (point 2), showing not only that cardiac output must decrease, but also that it becomes insensitive to changes in cardiac function (point 3). In these conditions, volume expansion is mandatory to restore systemic blood flow (point 4), whereas PEEP superimposed on hypovolemia may lead to cardiovascular collapse (point 4a), as is well known to clinicians [54].

Figure 3b shows the possible effects of PEEP in presence of LV failure. Under ZEEP, the cardiac function

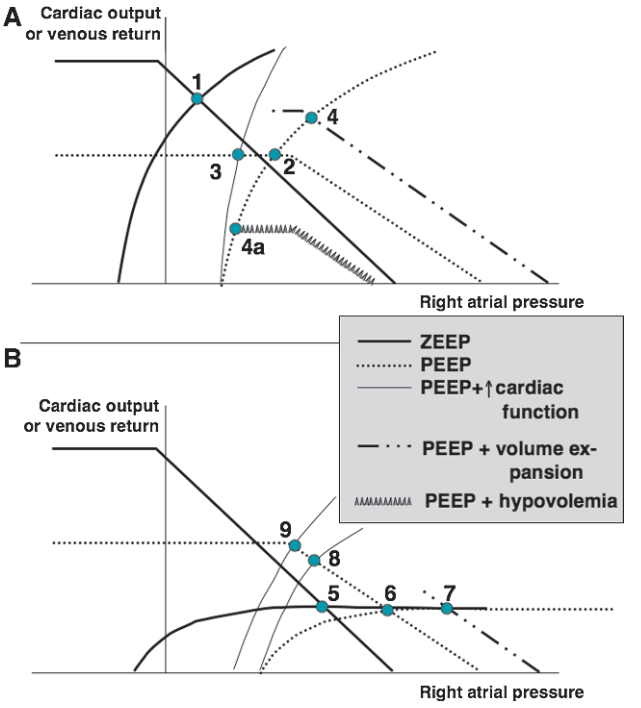


Fig. 3 Various possible effects of PEEP on cardiac output, illustrated with Guyton's graphical analysis: **a** with normal cardiac function, **b** with depressed cardiac function. In both panels **a** and **b**, right atrial pressure is measured relative to atmosphere, i.e., it represents the intracavitary pressure. This is the reason why PEEP shifts the cardiac function curve to the right (see left lower part of Fig. 4 in Part I). PEEP shifts the venous return curve as shown in Fig. 3 of Part I, i.e., the zero flow intercept (which is MSFP) and the critical pressure (Pcrit, at the intersection of the oblique and plateau parts) are increased by approximately equal amounts, while the maximal venous return (height of the plateau part) is depressed. Volume expansion shifts the venous return curve "rightwards" (see Footnote 2 in Part I), whereas hypovolemia has the opposite effect. Pcrit is not affected by changes in volemia. Further explanations in the text ("Effects of PEEP on cardiac output")

curve is so depressed that the operating point is located on its plateau (point 5) and remains so under PEEP if cardiac function is not simultaneously altered, i.e., if the cardiac function curve is merely shifted to the right (point 6). In these conditions, systemic blood flow cannot be increased by volume expansion (point 7). With a failing LV, however, cardiac function becomes sensitive to changes in LV afterload. Reduction of the latter by PEEP or continuous positive airway pressure (CPAP), therefore may cause cardiac output to increase (point 8) [55, 56], or at least to be better preserved [57–59] in normo- or hypervolemic patients with a failing left heart, compared to those with normal LV function.

It is worth noting that PEEP reduces the afterload of the failing LV by increasing LV extramural pressure at all phases of the respiratory cycle, not only at end-expiration. This is especially true when spontaneous inspiratory efforts occur in the context of pulmonary edema: PEEP or

[1]In analogy with West lung zones, see Part I, Section "Respiration and cardiac function; RV afterload".

CPAP then improve lung mechanics, thereby attenuating the negative inspiratory swings of ITP [59]. Another interesting observation has been made by Huberfeld and colleagues [60], who found in volume loaded sedated pigs that a substantial surface pressure existed on the dilated heart under ZEEP. Application of CPAP in these conditions decreased pericardial pressure, in spite of increasing esophageal pressure (Fig. 4). This paradox was explained by the lower heart size which followed afterload reduction by CPAP. In Fig. 3b, this phenomenon would translate into a shift to the left of the cardiac function curve, with a further increase in cardiac output (point 9). These considerations form in part the basis for the beneficial hemodynamic effects of CPAP or mechanical ventilation with PEEP in LV failure [59, 61–65]. However, a limit would be set to these benefits by the concomitant reduction of maximal venous return. Accordingly, clinical experience has shown that moderate levels of end-expiratory pressure (5–10 cm H_2O) are optimal in these conditions.

Of course, Fig. 3 is an oversimplified representation of two idealized extremes in continuous spectrum of actual situations. However, it is certainly necessary to evaluate in each patient whether he/she stands closer to panel A or B. Such evaluation essentially requires integrated clinical and pathophysiological thinking. Some help may come from observing the phasic fluctuations of arterial pressure or great veins geometry (see previous two sections).

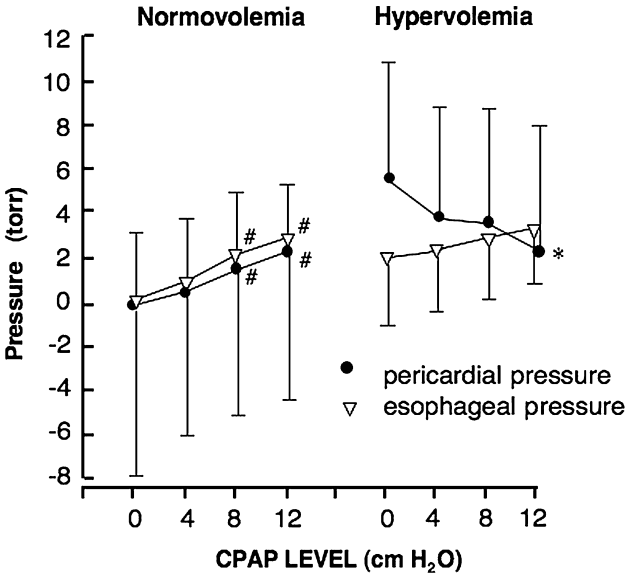


Fig. 4 Differential effects of continuous positive airway pressure (CPAP) on esophageal and pericardial pressure in normovolemic and hypervolemic pigs. Pigs were chronically instrumented with pressure sensors in the pericardial space. On the day of experiment a pressure sensor was inserted into the esophagus. The animals were intubated and connected to a high flow CPAP system. Esophageal (Pes) and pericardial pressure (Pper) were measured synchronously at end-diastole, at various CPAP levels, before (normovolemia) and after volume expansion with i.v. hetastarch (35 ml/kg, hypervolemia). In normovolemia, Pper and Pes track each other. In hypervolemia and without CPAP, Pper exceeds Pes, due to the contact pressure exerted by the lung on the surface of the dilated heart. The progressive institution of CPAP reduces the afterload of the left ventricle (LV), with the following consequences: a smaller LV, a lower global size of the heart, hence release of contact pressure exerted by the lung and finally reduction of Pper. Pes, measured away from the lung surface, increases with CPAP, independent of heart size. From [60], with permission

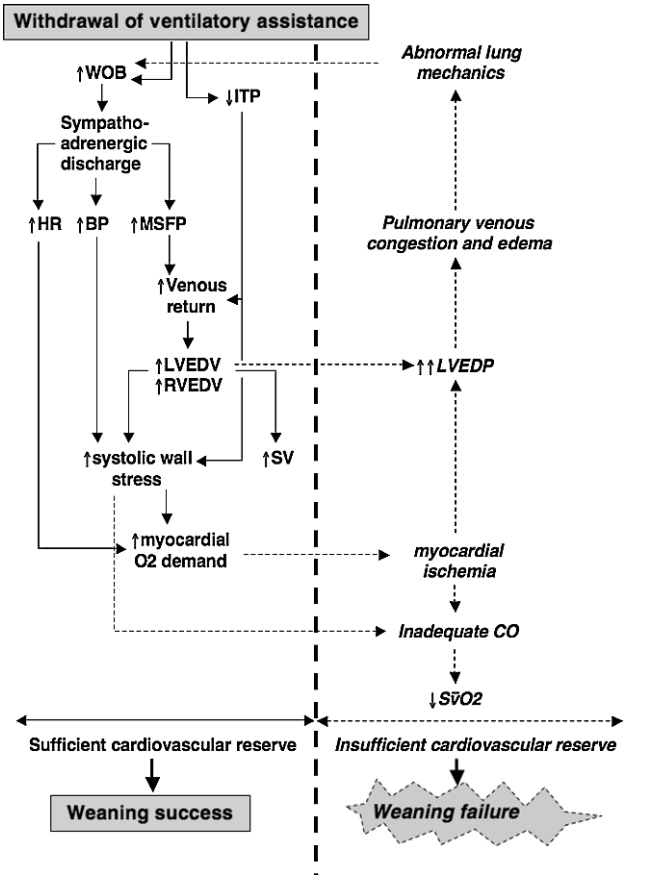


Fig. 5 Cardiovascular mechanisms of weaning failure. The obligatory cardiovascular effects of withdrawing mechanical assistance (linked by *plain arrows*) are depicted on the left of the *thick vertical dashed line*. The *dashed arrows* point to potential consequences in presence of insufficient cardiovascular reserve. *BP* blood pressure, *CO* cardiac output, *HR* heart rate, *ITP* intrathoracic pressure, *MSFP* mean systemic filling pressure, *LVEDV* left ventricular end-diastolic volume, *LVEDP* left ventricular end-diastolic pressure, *RVEDV* right ventricular end-diastolic volume, *SV* stroke volume, $S\bar{v}O_2$ mixed venous oxygen saturation, *WOB* work of breathing. Upstream effects on the lung and downstream effects on peripheral oxygenation are not necessarily linked: depending on circumstances, one or the other may predominate, or both may occur concomitantly More explanations in "Weaning failure from cardiovascular origin"

Mechanical ventilation and acute cor pulmonale

Acute pulmonary hypertension and associated RV failure (acute cor pulmonale, ACP) are frequent findings in patients on mechanical ventilation for respiratory failure, especially ARDS. An important role in this setting is now attributed to mechanical ventilation itself, which in addition to promoting alveolar-capillary injury, acts by direct mechanical augmentation of RV afterload in the inflation period, leading to RV dilation, abnormal septal motion and low cardiac output [66, 67] (Part I, Section "Ventricular afterload"). Especially when combined with high inflation pressures, ACP in ARDS is associated with a high mortality [68]. One might speculate that the improved mortality seen when patients with ARDS receive smaller tidal volumes [69] may be due in part to improved RV function.

It is essential for clinicians to understand that, in patients with ARDS, a major cause of ventilator-induced hypotension may not be venous return impairment but increased RV afterload. Echography is required to confirm this mechanism, and the correct treatment in this case is primarily a reduction in inflation pressures, especially plateau pressure.

Weaning failure from cardiovascular origin

The switch from assisted to spontaneous breathing stresses the cardiovascular system, akin to an exercise test [70]. As depicted in the left part of Fig. 5. weaning activates the sympathoadrenergic system, with predictable consequences on heart rate and blood pressure. Due to venoconstriction and associated reduction in venous compliance, MSFP increases. At the same time, the mean ITP falls, thus increasing LV afterload (Part I, Section "Ventricular afterload"), to which the failing heart is oversensitive. Furthermore, venous return is boosted, leading to increased right and left ventricular end-diastolic volumes. These chains of events augment the myocardial O_2 demand. A prerequisite to successful weaning is therefore that the heart be able to cope with this situation. With diminished cardiovascular reserve (right hand part of Fig. 5), myocardial ischemia may appear [71], and left ventricular filling pressure may increase disproportionately [72]. The upstream consequences on the lung [72] and downstream consequences on O_2 transport [73] then initiate vicious circles which culminate in florid cardiorespiratory failure and the need to resume mechanical ventilation. Such considerations are of paramount importance when evaluating patients who are difficult to wean [74].

Conclusion

Cardiorespiratory interactions are encountered daily in the clinical practice of critical care. Much of our understanding in this area rests on fundamental knowledge acquired decades ago. These concepts have then been enriched by technological advance, notably the advent and ever greater performance of echocardiography, and are likely to keep evolving as new methods of investigation become available, such as cardiorespiratory-resolved magnetic resonance imaging [75]. We hope to have convinced the reader that understanding cardiorespiratory interactions is not only of academic, but also of practical importance for his or her training as an intensivist. The concepts covered in the present review are essential to the proper use of mechanical ventilatory assistance. Furthermore, they have been put to use in the last decade in order to promote a less invasive approach to hemodynamic monitoring, an area in which progress may be expected in the near future.

Acknowledgments We warmly thank the reviewers for their contribution to this text, in the form of numerous thoughtful, in depth, and very constructive comments.

References

1. O'Rourke RA, Silverman ME, Schlant RC (1994) Chap 10: general examination of the patient. In: Schlant RC, Wayne Alexander R (eds) The heart, arteries and veins. McGraw-Hill, New York, p 240
2. Fessler HE (1997) Heart-lung interactions: applications in the critically ill (review). Eur Respir J 10:226–237
3. Takata M, Beloucif S, Shimada M, Robotham JL (1992) Superior and inferior vena caval flows during respiration: pathogenesis of Kussmaul's sign. Am J Physiol 262:H763–H770
4. Scharf SM (1992) Cardiopulmonary interactions. In: Scharf SM (ed) Cardiopulmonary physiology in critical care. Marcel Dekker, New York, pp 333–355
5. Wise RA (1994) Historical perspectives on the mechanical interactions of respiration and circulation. In: Perret C (ed) Les interactions cardio-pulmonaires. Arnette, Paris, pp 3–15
6. Reddy PS, Curtiss EI (1990) Cardiac tamponade. Cardiol Clin 8:627–637
7. Jardin F, Farcot JC, Boisante L, Prost JF, Gueret P, Bourdarias JP (1982) Mechanism of paradoxic pulse in bronchial asthma. Circulation 66:887–894
8. Blaustein AS, Risser TA, Weiss JW, Parker JA, Holman BL, McFadden ER (1986) Mechanisms of pulsus paradoxus during resistive respiratory loading and asthma. J Am Coll Cardiol 8:529–536

9. Vaska K, Wann LS, Sagar K, Klopfenstein HS (1992) Pleural effusion as a cause of right ventricular diastolic collapse. Circulation 86:609–617
10. Silverman HJ, Haponik EF (1986) Pulsus paradoxus in pulmonary embolism: reversal with thrombolytic therapy. Crit Care Med 14:165–166
11. Ward GL, Heiselman DE, White LJ (1992) Pulsus paradoxus in anaphylactic shock due to urokinase administration. Chest 101:589
12. Hooper TL, Lawson RA (1986) Volvulus of the stomach—an unusual cause of pulsus paradoxus. Postgrad Med J 62:377–379
13. Baum VC, Tarnoff H, Hoffman JI (1980) Pulsus paradoxus in a patient with tricuspid atresia and hypoplastic right heart. Circulation 62:651–652
14. Dornhorst AC, Howard P, Leathart GL (1952) Pulsus paradoxus. Lancet 1:746–748
15. Shabetai R, Fowler NO, Guntheroth WG (1970) The hemodynamics of cardiac tamponade and constrictive pericarditis. Am J Cardiol 26:480–489
16. Winer HE, Kronzon I (1979) Absence of paradoxical pulse in patients with cardiac tamponade and atrial septal defects. Am J Cardiol 44:378–380
17. Hoit BD, Gabel M, Fowler NO (1990) Cardiac tamponade in left ventricular dysfunction. Circulation 82:1370–1376
18. Diebel L, Wilson RF, Heins J, Larky H, Warsow K, Wilson S (1994) End-diastolic volume versus pulmonary artery wedge pressure in evaluating cardiac preload in trauma patients. J Trauma 37:950–955
19. Tavernier B, Makhotine O, Lebuffe G, Dupont J, Scherpereel P (1998) Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. Anesthesiology 89:1313–1321
20. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138
21. Pinsky MR (2003) Pulmonary artery occlusion pressure. Intensive Care Med 29:19–22
22. Hoyt JD, Leatherman JW (1997) Interpretation of the pulmonary artery occlusion pressure in mechanically ventilated patients with large respiratory excursions in intrathoracic pressure. Intensive Care Med 23:1125–1131
23. Qureshi AS, Shapiro RS, Leatherman JW (2007) Use of bladder pressure to correct for the effect of expiratory muscle activity on central venous pressure. Intensive Care Med 33:1907–1912
24. Feihl F, Perret C (1995) Right heart catheterization at bedside: a note of cautious optimism (comment). Intensive Care Med 21:296–298
25. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL (2006) Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med 34:1402–1407
26. De Backer D, Pinsky MR (2007) Can one predict fluid responsiveness in spontaneously breathing patients? Intensive Care Med 33:1111–1113
27. Monnet X, Teboul JL (2008) Passive leg raising. Intensive Care Med 34:659–663
28. Brower R, Wise RA, Hassapoyannes C, Bromberger-Barnea B, Permutt S (1985) Effect of lung inflation on lung blood volume and pulmonary venous flow. J Appl Physiol 58:954–963
29. Jardin F, Farcot JC, Gueret P, Prost JF, Ozier Y, Bourdarias JP (1983) Cyclic changes in arterial pulse during respiratory support. Circulation 68:266–274
30. Vieillard-Baron A, Chergui K, Augarde R, Prin S, Page B, Beauchet A, Jardin F (2003) Cyclic changes in arterial pulse during respiratory support revisited by Doppler echocardiography. Am J Respir Crit Care Med 168:671–676
31. Perel A, Pizov R, Cotev S (1987) Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesiology 67:498–502
32. Pizov R, Ya'ari Y, Perel A (1989) The arterial pressure waveform during acute ventricular failure and synchronized external chest compression. Anesth Analg 68:150–156
33. Pizov R, Cohen M, Weiss Y, Segal E, Cotev S, Perel A (1996) Positive end-expiratory pressure-induced hemodynamic changes are reflected in the arterial pressure waveform. Crit Care Med 24:1381–1387
34. Coriat P, Vrillon M, Perel A, Baron JF, Le Bret F, Saada M, Viars P (1994) A comparison of systolic blood pressure variations and echocardiographic estimates of end-diastolic left ventricular size in patients after aortic surgery (see comments). Anesth Analg 78:46–53
35. Michard F, Chemla D, Richard C, Wysocki M, Pinsky MR, Lecarpentier Y, Teboul JL (1999) Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. Am J Respir Crit Care Med 159:935–939
36. Feissel M, Teboul JL, Merlani P, Badie J, Faller JP, Bendjelid K (2007) Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients. Intensive Care Med 33:993–999
37. Duperret S, Lhuillier F, Piriou V, Vivier E, Metton O, Branche P, Annat G, Bendjelid K, Viale JP (2007) Increased intra-abdominal pressure affects respiratory variations in arterial pressure in normovolaemic and hypovolaemic mechanically ventilated healthy pigs. Intensive Care Med 33:163–171
38. Szold A, Pizov R, Segal E, Perel A (1989) The effect of tidal volume and intravascular volume state on systolic pressure variation in ventilated dogs. Intensive Care Med 15:368–371
39. Reuter DA, Bayerlein J, Goepfert MS, Weis FC, Kilger E, Lamm P, Goetz AE (2003) Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. Intensive Care Med 29:476–480
40. Renner J, Cavus E, Meybohm P, Tonner P, Steinfath M, Scholz J, Lutter G, Bein B (2007) Stroke volume variation during hemorrhage and after fluid loading: impact of different tidal volumes. Acta Anaesthesiol Scand 51:538–544
41. Preisman S, Kogan S, Berkenstadt H, Perel A (2005) Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators. Br J Anaesth 95:746–755
42. Soubrier S, Saulnier F, Hubert H, Delour P, Lenci H, Onimus T, Nseir S, Durocher A (2007) Can dynamic indicators help the prediction of fluid responsiveness in spontaneously breathing critically ill patients? Intensive Care Med 33:1117–1124
43. Magder S, Georgiadis G, Cheong T (1992) Respiratory variations in right atrial pressure predict the response to fluid challenge. J Crit Care 7:76–85
44. Charron C, Caille V, Jardin F, Vieillard-Baron A (2006) Echocardiographic measurement of fluid responsiveness. Curr Opin Crit Care 12:249–254

45. Mandelbaum A, Ritz E (1996) Vena cava diameter measurement for estimation of dry weight in haemodialysis patients. Nephrol Dial Transplant 11(Suppl 2):24–27
46. Haciomeroglu P, Ozkaya O, Gunal N, Baysal K (2007) Venous collapsibility index changes in children on dialysis. Nephrology (Carlton) 12:135–139
47. Feissel M, Michard F, Faller JP, Teboul JL (2004) The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med 30:1834–1837
48. Barbier C, Loubieres Y, Schmit C, Hayon J, Ricome JL, Jardin F, Vieillard-Baron A (2004) Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. Intensive Care Med 30:1740–1746
49. Vieillard-Baron A, Augarde R, Prin S, Page B, Beauchet A, Jardin F (2001) Influence of superior vena caval zone condition on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 95:1083–1088
50. Vieillard-Baron A, Chergui K, Rabiller A, Peyrouset O, Page B, Beauchet A, Jardin F (2004) Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. Intensive Care Med 30:1734–1739
51. Fessler HE, Brower RG, Wise RA, Permutt S (1992) Effects of positive end-expiratory pressure on the canine venous return curve. Am Rev Respir Dis 146:4–10
52. Guyton AC, Jones CE, Coleman TG (1973) Circulatory physiology: cardiac output and its regulation. W. B. Saunders Company, Philadelphia
53. Guyton AC (1955) Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev 35:123–129
54. Qvist J, Pontoppidan H, Wilson RS, Lowenstein E, Laver MB (1975) Hemodynamic response to mechanical ventilation with PEEP: the effect of hypervolemia. Anesthesiology 42:45–55
55. Grace MP, Greenbaum DM (1982) Cardiac performance in response to PEEP in patients with cardiac dysfunction. Crit Care Med 10:358–360
56. Bradley TD, Holloway RM, McLaughlin PR, Ross BL, Walters J, Liu PP (1992) Cardiac output response to continuous positive airway pressure in congestive heart failure. Am Rev Respir Dis 145(2 Pt 1):377–382
57. Rasanen J, Heikkila J, Downs J, Nikki P, Vaisanen I, Viitanen A (1985) Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema. Am J Cardiol 55:296–300
58. Naughton MT, Rahman MA, Hara K, Floras JS, Bradley TD (1995) Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. Circulation 91:1725–1731
59. Lenique F, Habis M, Lofaso F, Dubois-Rande JL, Harf A, Brochard L (1997) Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. Am J Respir Crit Care Med 155:500–505
60. Huberfeld SI, Genovese J, Tarasiuk A, Scharf SM (1995) Effect of CPAP on pericardial pressure and respiratory system mechanics in pigs. Am J Respir Crit Care Med 152:142–147
61. Pinsky MR, Summer WR, Wise RA, Permutt S, Bromberger-Barnea B (1983) Augmentation of cardiac function by elevation of intrathoracic pressure. J Appl Physiol 54:950–955
62. Rasanen J, Vaisanen IT, Heikkila J, Nikki P (1985) Acute myocardial infarction complicated by left ventricular dysfunction and respiratory failure. The effects of continuous positive airway pressure. Chest 87:158–162
63. Genovese J, Huberfeld S, Tarasiuk A, Moskowitz M, Scharf SM (1995) Effects of CPAP on cardiac output in pigs with pacing-induced congestive heart failure. Am J Respir Crit Care Med 152:1847–1853
64. Mehta S, Liu PP, Fitzgerald FS, Allidina YK, Douglas Bradley T (2000) Effects of continuous positive airway pressure on cardiac volumes in patients with ischemic and dilated cardiomyopathy. Am J Respir Crit Care Med 161:128–134
65. Scharf SM (2001) Ventilatory support in the failing heart. In: Scharf SM, Pinsky MR, Magder S (eds) Respiratory-circulatory interactions in health and disease. Marcel Dekker, New York, pp 519–550
66. Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias JP (1990) Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. Anesthesiology 72:966–970
67. Vieillard-Baron A, Loubieres Y, Schmitt JM, Page B, Dubourg O, Jardin F (1999) Cyclic changes in right ventricular output impedance during mechanical ventilation. J Appl Physiol 87:1644–1650
68. Jardin F, Vieillard-Baron A (2007) Is there a safe plateau pressure in ARDS? The right heart only knows. Intensive Care Med 33:444–447
69. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 342:1301–1308
70. Pinsky MR (2000) Breathing as exercise: the cardiovascular response to weaning from mechanical ventilation (comment). Intensive Care Med 26:1164–1166
71. Hurford WE, Lynch KE, Strauss HW, Lowenstein E, Zapol WM (1991) Myocardial perfusion as assessed by thallium–201 scintigraphy during the discontinuation of mechanical ventilation in ventilator-dependent patients. Anesthesiology 74:1007–1016
72. Lemaire F, Teboul JL, Cinotti L, Giotto G, Abrouk F, Steg G, Macquin-Mavier I, Zapol WM (1988) Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 69:171–179
73. Jubran A, Mathru M, Dries D, Tobin MJ (1998) Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. Am J Respir Crit Care Med 158:1763–1769
74. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Vieillard-Baron A, Welte T (2007) Weaning from mechanical ventilation. Eur Respir J 29:1033–1056
75. Thompson RB, McVeigh ER (2006) Cardiorespiratory-resolved magnetic resonance imaging: measuring respiratory modulation of cardiac function. Magn Reson Med 56:1301–1310

Index