Board Review Series

PHYSIOLOGY

Cases and Problems

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- *Most revelent information for courses and USMLE Step I*
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- *Thought-provoking questions with complete explanations*
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Contents

Cellular and Autonomic Physiology

Case 1

Permeability and Simple Diffusion

Case

Four solutes were studied with respect to their permeability and rate of diffusion in a lipid bilayer. Table 1–1 shows the molecular radius and oil-water partition coefficient of each of the four solutes. Use the information in the table to answer the following questions about diffusion coefficient, permeability, and rate of diffusion.

▼ **Table 1–1.** Molecular Radii and Oil-water Partition Coefficients of Four Solutes

Solute	Molecular Radius, Å	Oil-water Partition Coefficient
A	20	1.0
B	20	2.0
C	40	1.0
D	40	0.5

QUESTIONS

1. What equation describes the diffusion coefficient for a solute? What is the relationship between molecular radius and diffusion coefficient?

2. What equation relates permeability to diffusion coefficient? What is the relationship between molecular radius and permeability?

3. What is the relationship between oil-water partition coefficient and permeability? What are the units of the partition coefficient? How is the partition coefficient measured?

4. Of the four solutes shown in Table 1–1, which has the highest permeability in the lipid bilayer?

5. Of the four solutes shown in Table 1–1, which has the lowest permeability in the lipid bilayer?

6. Two solutions with different concentrations of Solute A are separated by a lipid bilayer that has a surface area of 1 cm^2. The concentration of Solute A in one solution is 20 mmol/ml, the concentration of Solute A in the other solution is 10 mmol/ml, and the permeability of the lipid bilayer to Solute A is 5×10^{-5} cm/sec. What is the direction and net rate of diffusion of Solute A across the lipid bilayer?

7. If the surface area of the lipid bilayer in Question 6 is doubled, what is the net rate of diffusion of Solute A?

8. If all conditions are identical to those described for Question 6, except that Solute A is replaced by Solute B, what is the net rate of diffusion of Solute B?

9. If all conditions are identical to those described for Question 8, except that the concentration of Solute B in the 20 mmol/ml solution is doubled to 40 mmol/ml, what is the net rate of diffusion of Solute B?

ANSWERS AND EXPLANATIONS

1. The Stokes-Einstein equation describes the **diffusion coefficient** as follows:

$$D = \frac{K\,T}{6\,\pi\,r\,\eta}$$

where

D = diffusion coefficient

K = Boltzmann's constant

T = absolute temperature (K)

r = molecular radius

η = viscosity of the medium

The equation states that there is an inverse relationship between molecular radius and diffusion coefficient. Thus, small solutes have high diffusion coefficients, and large solutes have low diffusion coefficients.

2. **Permeability** is related to the diffusion coefficient as follows:

$$P = \frac{K\,D}{\Delta x}$$

where

P = permeability

K = partition coefficient

D = diffusion coefficient

Δx = membrane thickness

The equation states that permeability (P) is directly correlated with the diffusion coefficient (D). Furthermore, because the diffusion coefficient is inversely correlated with molecular radius, permeability is also inversely correlated with molecular radius. As the molecular radius increases, both the diffusion coefficient and permeability decrease.

One potential point of confusion is that in the equation for permeability, K represents the partition coefficient (discussed in the next question); in the equation for diffusion coefficient, K represents Boltzmann's constant.

3. The oil-water **partition coefficient** ("K" in the permeability equation) describes the solubility of a solute in oil relative to its solubility in water. The higher the partition coefficient of a solute, the higher its oil or lipid solubility and the more readily it dissolves in a lipid bilayer. The relationship between the oil-water partition coefficient and permeability is described in the equation for permeability (see Question 2): the higher the partition coefficient of the solute, the higher its permeability in a lipid bilayer.

The partition coefficient is a dimensionless number (meaning that it has no units). It is measured by determining the concentration of solute in an oil phase relative to its concentration in an aqueous phase and expressing the two values as a ratio. When expressed as a ratio, the units of concentration cancel each other.

4. As already discussed, permeability in a lipid bilayer is inversely correlated with molecular size and directly correlated with partition coefficient. Thus, a small solute with a high partition coefficient (i.e., high lipid solubility) has the highest permeability, and a large solute with a low partition coefficient has the lowest permeability.

   Table 1–1 shows that among the four solutes, Solute B has the highest permeability because it has the smallest size and the highest partition coefficient. Solutes C and D have lower permeabilities than Solute A based on their larger molecular radii and their equal or lower partition coefficients.

5. Of the four solutes, Solute D has the lowest permeability because it has a large molecular size and the lowest partition coefficient.

6. This question asked you to calculate the net rate of diffusion of Solute A, which is described by **Fick's law of diffusion:**

   $$\mathbf{J = P\,A\,(C_1 - C_2)}$$

   where

   J = net rate of diffusion (mmol/sec)

   P = permeability (cm/sec)

   A = surface area (cm^2)

   C_1 = concentration in solution 1 (mmol/ml)

   C_2 = concentration in solution 2 (mmol/ml)

   In words, the equation states that the net rate of diffusion (also called **flux,** or **flow**) is directly correlated with the permeability of the solute in the membrane, the surface area available for diffusion, and the difference in concentration across the membrane. The net rate of diffusion of Solute A is:

   $$\begin{aligned} J &= 5 \times 10^{-5}\ \text{cm/sec} \times 1\ \text{cm}^2 \times (20\ \text{mmol/ml} - 10\ \text{mmol/ml}) \\ &= 5 \times 10^{-5}\ \text{cm/sec} \times 1\ \text{cm}^2 \times (10\ \text{mmol/ml}) \\ &= 5 \times 10^{-5}\ \text{cm/sec} \times 1\ \text{cm}^2 \times (10\ \text{mmol/cm}^3) \\ &= 5 \times 10^{-4}\ \text{mmol/sec, from high to low concentration} \end{aligned}$$

   Note that there is one very useful trick in this calculation: 1 ml $\approx$ 1 cm^3.

7. If the surface area doubles, and all other conditions remain the same, the net rate of diffusion of Solute A doubles (i.e., to 1×10^{-3} mmol/sec).

8. Because Solute B has the same molecular radius as Solute A, but twice the oil-water partition coefficient, the permeability and the net rate of diffusion of Solute B

must be twice those of Solute A. Therefore, the permeability of Solute B is 1×10^{-4} cm/sec, and the net rate of diffusion of Solute B is 1×10^{-3} mmol/sec.

9. If the higher concentration of Solute B is doubled, then the net rate of diffusion increases to 3×10^{-3} mmol/sec, or threefold, as shown in the following calculation:

$$\begin{aligned} J &= 1 \times 10^{-4} \text{ cm/sec} \times 1 \text{ cm}^2 \times (40 \text{ mmol/ml} - 10 \text{ mmol/ml}) \\ &= 1 \times 10^{-4} \text{ cm/sec} \times 1 \text{ cm}^2 \times (30 \text{ mmol/ml}) \\ &= 1 \times 10^{-4} \text{ cm/sec} \times 1 \text{ cm}^2 \times (30 \text{ mmol/cm}^3) \\ &= 3 \times 10^{-3} \text{ mmol/sec} \end{aligned}$$

If you thought that the diffusion rate would double (rather than triple), remember that the net rate of diffusion is directly related to the *difference* in concentration across the membrane; the *difference* in concentration is tripled.

Key topics

- Diffusion coefficient
- Fick's law of diffusion
- Flux
- Partition coefficient
- Permeability
- Stokes-Einstein equation

Case 2

Osmolarity, Osmotic Pressure, and Osmosis

Case

The information shown in Table 1–2 pertains to six different solutions.

▼ **Table 1–2.** Comparison of Six Solutions

Solution	Solute	Concentration	g	σ
1	Urea	1 mmol/L	1.0	0
2	NaCl	1 mmol/L	1.85	0.5
3	NaCl	2 mmol/L	1.85	0.5
4	KCl	1 mmol/L	1.85	0.4
5	Sucrose	1 mmol/L	1.0	0.8
6	Albumin	1 mmol/L	1.0	1.0

g, osmotic coefficient; σ, reflection coefficient.

QUESTIONS

1. What is osmolarity, and how is it calculated?

2. What is osmosis? What is the driving force for osmosis?

3. What is osmotic pressure, and how is it calculated? What is effective osmotic pressure, and how is it calculated?

4. Calculate the osmolarity and effective osmotic pressure of each solution listed in Table 1–2 at 37°C. For 37°C, RT = 25.45 L-atm/mol, or 0.0245 L-atm/mmol.

5. Which, if any, of the solutions are isosmotic?

6. Which solution is hyperosmotic with respect to all of the other solutions?

7. Which solution is hypotonic with respect to all of the other solutions?

8. A semipermeable membrane is placed between Solution 1 and Solution 6. What is the difference in effective osmotic pressure between the two solutions? Draw a diagram that shows how water will flow between the two solutions and how the volume of each solution will change with time.

9. If the hydraulic conductance, or filtration coefficient (K_f), of the membrane in Question 8 is 0.01 ml/min-atm, what is the rate of water flow across the membrane?

10. Mannitol is a large sugar that does not dissociate in solution. A semipermeable membrane separates two solutions of mannitol. One solution has a mannitol concentration of 10 mmol/L, and the other has a mannitol concentration of 1 mmol/L. The filtration coefficient of the membrane is 0.5 ml/min-atm, and water flow across the membrane is measured as 0.1 ml/min. What is the reflection coefficient of mannitol for this membrane?

ANSWERS AND EXPLANATIONS

1. **Osmolarity** is the concentration of osmotically active particles in a solution. It is calculated as the product of solute concentration (e.g., in mmol/L) times the number of particles per mole in solution (i.e., whether the solute dissociates in solution). The extent of this dissociation is described by an **osmotic coefficient** called **"g."** If the solute does not dissociate, g = 1.0. If the solute dissociates into two particles, g = 2.0, and so forth. For example, for solutes such as urea or sucrose, g = 1.0 because these solutes do not dissociate in solution. On the other hand, for NaCl, g ≈ 2.0 because NaCl dissociates into two particles in solution, Na^+ and Cl^-. With this last example, it is important to note that Na^+ and Cl^- ions may interact in solution, making g slightly less than the theoretical, ideal value of 2.0. [Instead of "g," some texts use "n" to designate the theoretical number of particles in solution and "Φ" to indicate the extent of deviation from ideal (i.e., the extent that the ions interact in solution); according to this terminology, $n \times \Phi = g$.]

   Osmolarity = g C

   where

   g = number of particles/mol in solution (in some texts, $g = n \times \Phi$)

   C = concentration (e.g., mmol/L)

   Two solutions that have the same calculated osmolarity are called **isosmotic.** If the calculated osmolarity of two solutions is different, then the solution with the higher osmolarity is **hyperosmotic** and the solution with the lower osmolarity is **hyposmotic.**

2. **Osmosis** is the flow of water between two solutions separated by a semipermeable membrane caused by a difference in solute concentration. The driving force for osmosis is a difference in **osmotic pressure** caused by the presence of solute. Initially, it may be surprising that the presence of solute can cause a pressure, which is explained as follows. Solute particles in a solution interact with pores in the membrane and, in so doing, lower the hydrostatic pressure of the solution. The higher the solute concentration, the higher the osmotic pressure (see Question 3) and the lower the hydrostatic pressure (because of the interaction of solute with pores in the membrane). Thus, if two solutions have different solute concentrations, then their osmotic and hydrostatic pressures are also different; the difference in pressure causes water flow across the membrane (i.e., osmosis).

3. The **osmotic pressure** of a solution is described by the **van't Hoff equation:**

   π = g C RT

   where

   π = osmotic pressure [atmospheres (atm)]

   g = number of particles/mol in solution

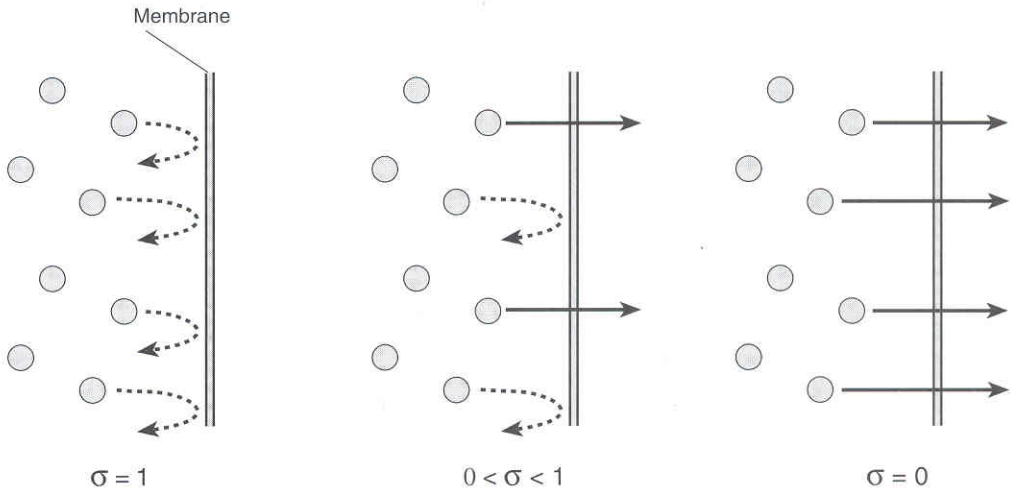
   C = concentration (e.g., mmol/L)

   R = gas constant (0.082 L-atm/mol-K)

   T = absolute temperature (K)

In words, the van't Hoff equation states that the osmotic pressure of a solution depends on the concentration of osmotically active solute particles. The concentration of solute particles is converted to a pressure by multiplying it by the gas constant and the absolute temperature.

The concept of **"effective" osmotic pressure** involves a slight modification of the van't Hoff equation. Effective osmotic pressure depends on *both* the concentration of solute particles *and* the extent to which the solute crosses the membrane. The extent to which a particular solute crosses a particular membrane is expressed by a dimensionless factor called the **reflection coefficient (σ).** The value of the reflection coefficient can vary from 0 to 1.0 (Figure 1–1). When $\sigma = 1.0$, the membrane is completely impermeable to the solute; the solute remains in the original solution and exerts its full osmotic pressure. When $\sigma = 0$, the membrane is freely permeable to the solute; solute diffuses across the membrane and down its concentration gradient until the concentrations in both solutions are equal. In this case, where $\sigma = 0$, the solutions on either side of the membrane have the same osmotic pressure because they have the same solute concentration; there is no difference in effective osmotic pressure across the membrane, and no osmosis of water occurs. When σ is between 0 and 1, the membrane is somewhat permeable to the solute; the effective osmotic pressure lies somewhere between its maximal value and 0.



▲ **Figure 1–1.** Reflection coefficient. σ, reflection coefficient.

Thus, to calculate the **effective osmotic pressure (π_{eff}),** the van't Hoff equation for osmotic pressure is modified by the value for σ, as follows:

$$\pi_{eff} = g\ C\ \sigma\ RT$$

where

π_{eff} = effective osmotic pressure (atm)
g = number of particles/mol in solution
C = concentration (e.g., mmol/L)
R = gas constant (0.082 L-atm/mol-K)
T = absolute temperature (K)
σ = reflection coefficient (no units; varies from 0 to 1)

Isotonic solutions have the same effective osmotic pressure. When isotonic solutions are placed on either side of a semipermeable membrane, there is no difference in effective osmotic pressure across the membrane, no driving force for osmosis, and no water flow.

If two solutions have different effective osmotic pressures, then the one with the higher effective osmotic pressure is **hypertonic,** and the one with the lower effective osmotic pressure is **hypotonic.** If these solutions are placed on either side of a semipermeable membrane, then an osmotic pressure difference is present. This osmotic pressure difference is the driving force for water flow. Water flows from the hypotonic solution (with the lower effective osmotic pressure and the higher hydrostatic pressure) into the hypertonic solution (with the higher effective osmotic pressure and the lower hydrostatic pressure).

4. See Table 1–3.

▼ **Table 1–3.** Calculated Values of Osmolarity and Effective Osmotic Pressure of Six Solutions

Solution	Osmolarity (mOsm/L)	Effective Osmotic Pressure (atm)
1	1	0
2	1.85	0.0227
3	3.7	0.0453
4	1.85	0.0181
5	1	0.0196
6	1	0.0245

5. Solutions with the same calculated osmolarity are **isosmotic.** Therefore, Solutions 1, 5, and 6 are isosmotic with respect to each other. Solutions 2 and 4 are isosmotic with respect to each other.

6. Solution 3 has the highest calculated osmolarity. Therefore, it is hyperosmotic with respect to the other solutions.

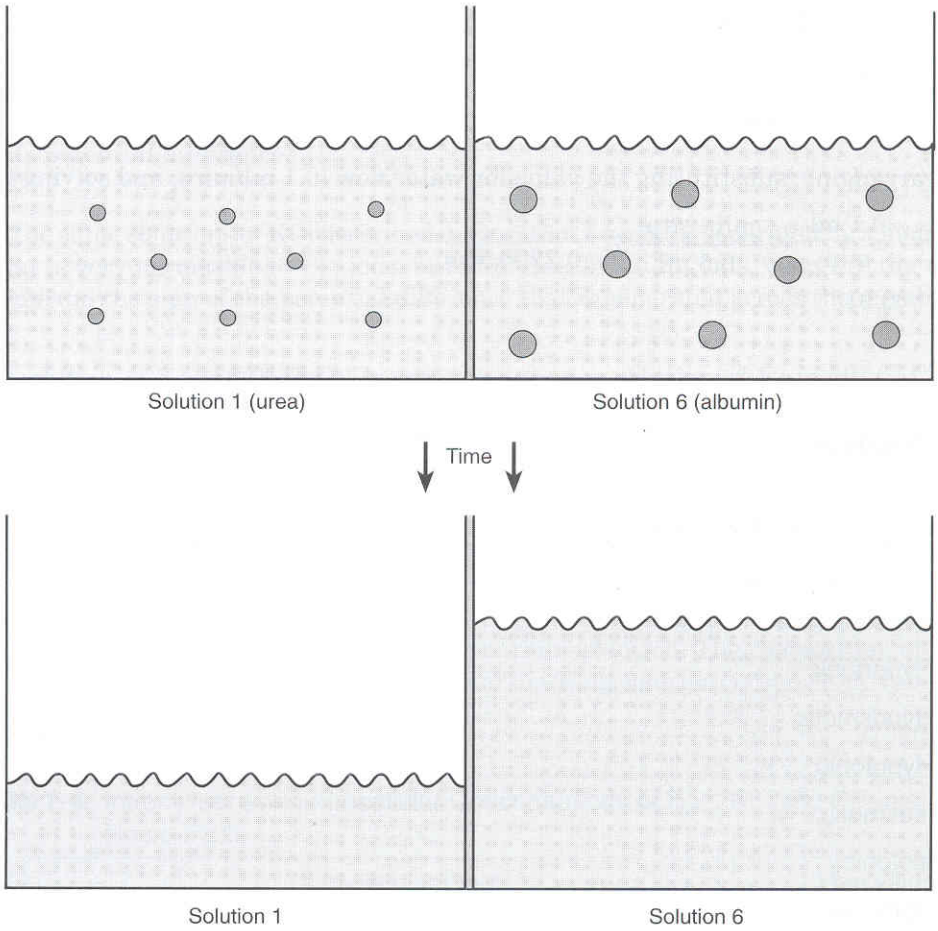
7. According to our calculations, Solution 1 is hypotonic with respect to the other solutions because it has the lowest effective osmotic pressure (zero). But why zero? Shouldn't the urea particles in Solution 1 exert *some* osmotic pressure? The answer lies in the reflection coefficient of urea, which is zero: because the membrane is freely permeable to urea, urea diffuses down its concentration gradient until the concentrations of urea on both sides of the membrane are equal. At this point of equal concentration, urea exerts no "effective" osmotic pressure.

8. Solution 1 is 1 mmol/L urea, with an osmolarity of 1 mOsm/L and an effective osmotic pressure of 0. Solution 6 is 1 mmol/L albumin, with an osmolarity of 1 mOsm/L and an effective osmotic pressure of 0.0245 atm. According to the previous discussion, these two solutions are *isosmotic* because they have the same osmolarity. However, they are *not isotonic* because they have different effective osmotic pressures.

Solution 1 (urea) has the lower effective osmotic pressure and is hypotonic. Solution 6 (albumin) has the higher effective osmotic pressure and is hypertonic. The effective osmotic pressure difference ($\Delta\pi_{eff}$) is the difference between the effective osmotic pressure of Solution 6 and that of Solution 1:

$$\begin{aligned}\Delta\pi_{eff} &= \pi_{eff}\,(\text{Solution 6}) - \pi_{eff}\,(\text{Solution 1})\\ &= 0.0245\ \text{atm} - 0\ \text{atm}\\ &= 0.0245\ \text{atm}\end{aligned}$$

If the two solutions are separated by a semipermeable membrane, water flows by osmosis from the hypotonic urea solution into the hypertonic albumin solution. With time, as a result of this water flow, the volume of the urea solution decreases and the volume of the albumin solution increases, as shown in Figure 1–2.



▲ **Figure 1–2.** Osmotic water flow between a 1 mmol/L solution of urea and a 1 mmol/L solution of albumin. Water flows from the hypotonic urea solution into the hypertonic albumin solution.

9. **Osmotic water flow** across a membrane is the product of the osmotic driving force ($\Delta\pi_{eff}$) and the water permeability of the membrane, which is called the hydraulic conductance, or **filtration coefficient (K_f).** In this question, K_f is given as 0.01 ml/min-atm, and $\Delta\pi_{eff}$ was calculated in Question 8 as 0.0245 atm.

$$\begin{aligned}\text{Water flow} &= K_f \times \Delta\pi_{eff} \\ &= 0.1 \text{ ml/min-atm} \times 0.0245 \text{ atm} \\ &= 0.00245 \text{ ml/min}\end{aligned}$$

10. This question is approached by using the relationship between water flow, hydraulic conductance (K_f), and difference in effective osmotic pressure that was introduced in Question 9. For each mannitol solution, $\pi_{eff} = \sigma\ g\ C\ RT$. Therefore, the difference in effective osmotic pressure between the two mannitol solutions ($\Delta\pi_{eff}$) is:

$$\begin{aligned}\Delta\pi_{eff} &= \sigma\ g\ \Delta C\ RT \\ \Delta\pi_{eff} &= \sigma \times 1 \times (10 \text{ mmol/L} - 1 \text{ mmol/L}) \times 0.0245 \text{ L-atm/mmol} \\ &= \sigma \times 0.2205 \text{ atm}\end{aligned}$$

Now, substituting this value for $\Delta\pi_{eff}$ into the expression for water flow:

$$\begin{aligned}\text{Water flow} &= K_f \times \Delta\pi_{eff} \\ &= K_f \times \sigma \times 0.2205 \text{ atm}\end{aligned}$$

Rearranging, substituting the value for water flow (0.1 ml/min), and solving for σ:

$$\sigma = \frac{0.1 \text{ ml}}{\text{min}} \times \frac{\text{min}-\text{atm}}{0.5 \text{ ml}} \times \frac{}{0.2205 \text{ atm}}$$

$$= 0.91$$

Key topics

- Effective osmotic pressure (π_{eff})
- Filtration coefficient (K_f)
- Hyperosmotic
- Hypertonic
- Hyposmotic
- Hypotonic
- Isosmotic
- Isotonic
- Osmolarity
- Osmosis
- Osmotic coefficient
- Osmotic pressure (π)
- Reflection coefficient (σ)
- Van't Hoff equation

Case 3

Nernst Equation and Equilibrium Potentials

Case

This case will guide you through the principles underlying diffusion potentials and electrochemical equilibrium.

QUESTIONS

1. A solution of 100 mmol/L KCl is separated from a solution of 10 mmol/L KCl by a membrane that is very permeable to K^+ ions, but impermeable to Cl^- ions. What are the magnitude and the direction (sign) of the potential difference that will be generated across this membrane? (Assume that 2.3 RT/F = 60 mV.) Will the concentration of K^+ in either solution change as a result of the process that generates this potential difference?

2. If the same solutions of KCl described in Question 1 are now separated by a membrane that is very permeable to Cl^- ions, but impermeable to K^+ ions, what are the magnitude and the sign of the potential difference that is generated across the membrane?

3. A solution of 5 mmol/L $CaCl_2$ is separated from a solution of 1 μmol/L $CaCl_2$ by a membrane that is selectively permeable to Ca^{2+}, but is impermeable to Cl^-. What are the magnitude and the sign of the potential difference that is generated across the membrane?

4. A nerve fiber is placed in a bathing solution whose composition is similar to extracellular fluid. After the preparation equilibrates at 37°C, a microelectrode inserted into the nerve fiber records a potential difference across the nerve membrane as 70 mV, cell interior negative with respect to the bathing solution. The composition of the intracellular fluid and the extracellular fluid (bathing solution) is shown in Table 1–4.

▼ **Table 1–4.** Intracelluar and Extracellular Concentrations of Na^+, K^+, and Cl^- in a Nerve Fiber

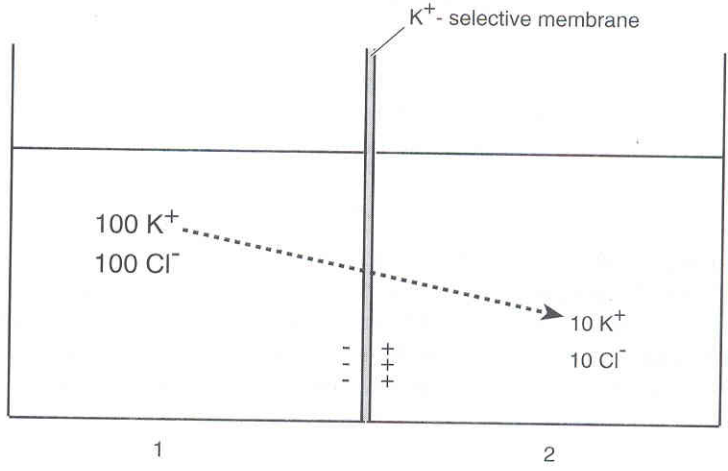
Ion	Intracellular Fluid	Extracellular Fluid
Na^+	30 mmol/L	140 mmol/L
K^+	100 mmol/L	4 mmol/L
Cl^-	5 mmol/L	100 mmol/L

Assuming that 2.3 RT/F = 60 mV at 37°C, which ion is closest to electrochemical equilibrium? What can be concluded about the relative conductance of the nerve membrane to Na^+, K^+, and Cl^- under these conditions?

ANSWERS AND EXPLANATIONS

1. Two solutions that have different concentrations of KCl are separated by a membrane that is permeable to K^+, but not to Cl^-. Since in solution, KCl dissociates into K^+ and Cl^- ions, there is also a concentration gradient for K^+ and Cl^- across the membrane. Each ion would "like" to diffuse down its concentration gradient. However, the membrane is permeable only to K^+. Thus, K^+ ions diffuse across the membrane from high concentration to low concentration, but Cl^- ions do not follow. As a result of this diffusion, net positive charge is carried across the membrane, creating a potential difference (**K^+ diffusion potential**), as shown in Figure 1–3. The buildup of positive charge at the membrane retards further diffusion of K^+ (positive is repelled by positive). Eventually, sufficient positive charge builds up at the membrane to exactly counterbalance the tendency of K^+ to diffuse down its concentration gradient. This condition, called **electrochemical equilibrium,** occurs when the chemical and electrical driving forces on an ion (in this case, K^+) are equal and opposite and no further net diffusion of the ion occurs.

   Very few K^+ ions need to diffuse to establish electrochemical equilibrium. Because very few K^+ ions are involved, the process does not change the concentration of K^+ in the bulk solutions. Stated differently, because of the prompt generation of the K^+ diffusion potential, K^+ does *not* diffuse until the two solutions have equal concentrations of K^+ (as would occur with diffusion of an uncharged solute).



▲ **Figure 1–3.** K^+ diffusion potential.

The **Nernst equation** is used to calculate the magnitude of the potential difference generated by the diffusion of a single permeant ion (in this case, K^+). Thus, the Nernst equation is used to calculate the **equilibrium potential** of an ion for a given concentration difference across the membrane, assuming that the membrane is permeable only to that ion.

$$E = -\frac{2.3\ RT}{z\ F} \log_{10} \frac{[C_1]}{[C_2]}$$

where

E = equilibrium potential (mV)

2.3 RT/F = constants (60 mV at 37°C)

z = charge on diffusing ion (including sign)

C_1 = concentration of the diffusing ion in one solution (mmol/L)

C_2 = concentration of the diffusing ion in the other solution (mmol/L)

Now, to answer the question. What are the magnitude and the direction (sign) of the potential difference that is generated by the diffusion of K^+ ions down a concentration gradient of this magnitude? Stated differently, what is the K^+ equilibrium potential for this concentration difference? In practice, calculations involving the Nernst equation can be streamlined. Because these problems involve a logarithmic function, all signs in the calculation can be omitted, and the equation can be solved for the *absolute value* of the potential difference. For convenience, always put the higher concentration in the numerator and the lower concentration in the denominator. The correct sign of the potential difference is then determined intuitively, as illustrated in this question.

The higher K^+ concentration is 100 mmol/L, the lower K^+ concentration is 10 mmol/L, 2.3 RT/F is 60 mV at 37°C, and z for K^+ is +1. Because we are determining the **K^+ equilibrium potential** in this problem, "E" is denoted as E_{K^+}. Remember that we agreed to omit all signs in the calculation and to determine the final sign intuitively later.

$$E_{K^+} = \frac{60 \text{ mV}}{1} \times \log_{10} \frac{100 \text{ mmol/L}}{10 \text{ mmol/L}}$$

$$= 60 \text{ mV} \times \log_{10} 10$$

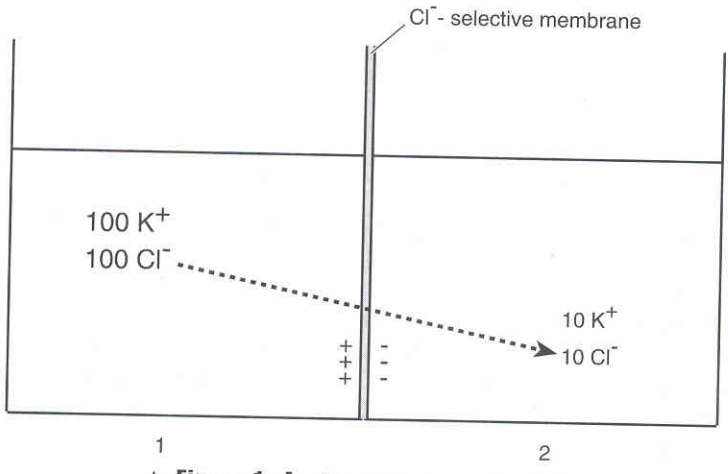
$$= 60 \text{ mV} \times 1$$

$$= 60 \text{ mV (absolute value of the equilibrium potential)}$$

To determine the direction (sign) of the equilibrium potential, see Figure 1–3. Which way does K^+ diffuse to create this potential difference? It diffuses from high concentration (Solution 1) to low concentration (Solution 2). Positive charge accumulates near the membrane in Solution 2; negative charge remains behind at the membrane in Solution 1. Thus, the potential difference (or the K^+ equilibrium potential) is 60 mV, with Solution 1 negative with respect to Solution 2. (Or, stated differently, the potential difference is 60 mV, with Solution 2 positive with respect to Solution 1.)

2. All conditions are the same as for Question 1, except that the membrane is permeable to Cl^- and impermeable to K^+. Again, both K^+ and Cl^- ions have a large concentration gradient across the membrane, and both ions would "like" to diffuse down that concentration gradient. However, now only Cl^- can diffuse. Cl^- diffuses from the solution that has the higher concentration to the solution that has the lower concentration, carrying a net negative charge across the membrane and generating a **Cl^- diffusion potential,** as shown in Figure 1–4. As negative charge builds up at the membrane, it prevents further net diffusion of Cl^- (negative repels negative). At electrochemical equilibrium, the tendency for Cl^- to diffuse down its concentration gradient is exactly counterbalanced by the potential difference that is generated. In other words, the chemical and electrical driving forces on Cl^- are equal and

opposite. Again, very few Cl^- ions need to diffuse to create this potential difference; therefore, the process does not change the Cl^- concentrations of the bulk solutions.



▲ **Figure 1–4.** Cl^- diffusion potential.

This time, we are using the Nernst equation to calculate the **Cl^- equilibrium potential** (E_{Cl^-}). The absolute value of the equilibrium potential is calculated by placing the higher Cl^- concentration in the numerator, the lower Cl^- concentration in the denominator, and ignoring all signs.

$$E_{Cl^-} = \frac{60 \text{ mV}}{1} \times \log_{10} \frac{100 \text{ mmol/L}}{10 \text{ mmol/L}}$$
$$= 60 \text{ mV} \times \log_{10} 10$$
$$= 60 \text{ mV} \times 1$$
$$= 60 \text{ mV (absolute value of the equilibrium potential)}$$

The sign of the potential difference is determined intuitively from Figure 1–4. Cl^- diffuses from high concentration in Solution 1 to low concentration in Solution 2. As a result, negative charge accumulates near the membrane in Solution 2, and positive charge remains behind at the membrane in Solution 1. Thus, the Cl^- equilibrium potential (E_{Cl^-}) is 60 mV, with Solution 2 negative with respect to Solution 1.

3. This problem is a variation on those you solved in Questions 1 and 2. There is a concentration gradient for $CaCl_2$ across a membrane that is selectively permeable to Ca^{2+} ions. You are asked to calculate the **Ca^{2+} equilibrium potential** for the stated concentration gradient (i.e., the potential difference that would exactly counterbalance the tendency for Ca^{2+} to diffuse down its concentration gradient). Ca^{2+} ions diffuse from high concentration to low concentration, and each ion carries two positive charges. Again, the absolute value of the equilibrium potential is calculated by placing the higher Ca^{2+} concentration in the numerator, the lower Ca^{2+} concentration in the denominator, and ignoring all signs. Remember that for Ca^{2+}, z is +2.

$$E_{Ca^{2+}} = \frac{60\ mV}{2} \times \log_{10} \frac{5\ mmol/L}{1\ \mu mol/L}$$

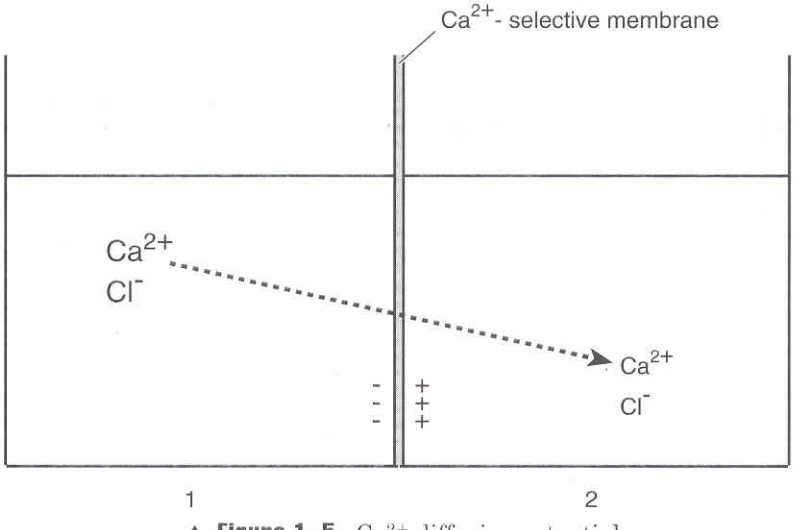
$$= 30\ mV \times \log_{10} \frac{5 \times 10^{-3}\ mol/L}{1 \times 10^{-6}\ mol/L}$$

$$= 30\ mV \times \log_{10} 5 \times 10^{3}\ mol/L$$

$$= 30\ mV \times 3.699$$

$$= 111\ mV$$

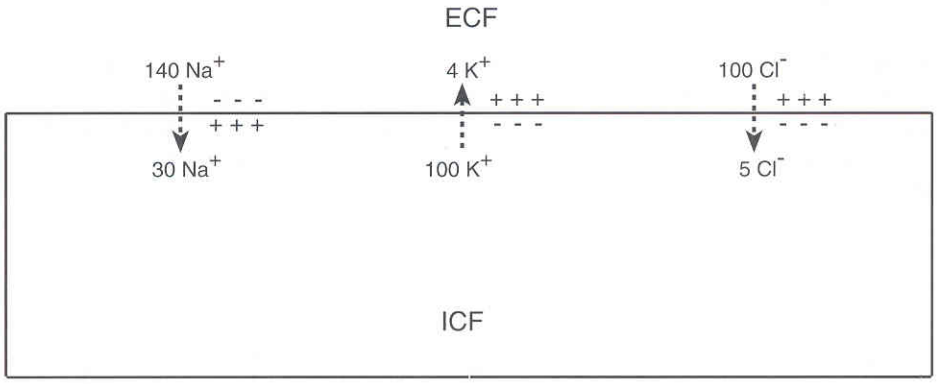
The sign of the equilibrium potential is determined intuitively from Figure 1–5. Ca^{2+} diffuses from high concentration in Solution 1 to low concentration in Solution 2, carrying positive charge across the membrane and leaving negative charge behind. Thus, the equilibrium potential for Ca^{2+} is 111 mV, with Solution 1 negative with respect to Solution 2.



▲ **Figure 1–5.** Ca^{2+} diffusion potential.

4. The problem gives the intracellular and extracellular concentrations of Na^+, K^+, and Cl^- and the measured membrane potential of a nerve fiber. The question asks which ion is closest to electrochemical equilibrium under these conditions. Indirectly, you are being asked which ion has the highest permeability or conductance in the membrane. The approach is to first calculate the equilibrium potential for each ion at the stated concentration gradient. (As before, use the Nernst equation to calculate the absolute value of the equilibrium potential, and determine the sign intuitively). Then, compare the *calculated* equilibrium potentials with the *actual* measured membrane potential. If the calculated equilibrium potential for an ion is close or equal to the measured membrane potential, then that ion is close to (or at) electrochemical equilibrium; that ion must have a high permeability or conductance. If the equilibrium potential for an ion is far from the measured membrane potential, then that ion is far from electrochemical equilibrium and must have a low permeability or conductance.

Figure 1–6 shows the nerve fiber and the concentrations of the three ions in the intracellular fluid and extracellular fluid. The sign of the equilibrium potential for each ion (determined intuitively) is superimposed on the nerve membrane in its correct orientation. It is important to know that membrane potentials and equilibrium potentials are always expressed as intracellular potential with respect to extracellular potential. For example, in this question, the membrane potential is 70 mV, cell interior negative; by convention, that is called −70 mV.



▲ **Figure 1–6.** Orientation of equilibrium potentials for Na^+, K^+, and Cl^- in a nerve fiber.

Now the equilibrium potential for each ion can be calculated with the Nernst equation. Figure 1–6 can be referenced for the signs.

$$E_{Na^+} = \frac{60 \text{ mV}}{1} \times \log_{10} \frac{140 \text{ mmol/L}}{30 \text{ mmol/L}}$$
$$= 60 \text{ mV} \times \log_{10} 4.67$$
$$= 60 \text{ mV} \times 0.669$$
$$= 40 \text{ mV (or } +40 \text{ mV, cell interior positive)}$$

$$E_{K^+} = \frac{60 \text{ mV}}{1} \times \log_{10} \frac{100 \text{ mmol/L}}{4 \text{ mmol/L}}$$
$$= 60 \text{ mV} \times \log_{10} 25$$
$$= 60 \text{ mV} \times 1.40$$
$$= 84 \text{ mV (or } -84 \text{ mV, cell interior negative)}$$

$$E_{Cl^-} = \frac{60 \text{ mV}}{1} \times \log_{10} \frac{100 \text{ mmol/L}}{5 \text{ mmol/L}}$$
$$= 60 \text{ mV} \times \log_{10} 20$$
$$= 60 \text{ mV} \times 1.3$$
$$= 78 \text{ mV (or } -78 \text{ mV, cell interior negative)}$$

These calculations are interpreted as follows. The equilibrium potential for Na^+ at the stated concentration gradient is +40 mV. In other words, for Na^+ to be at electrochemical equilibrium, the membrane potential must be +40 mV. However, the actual membrane potential of −70 mV is far from that value. Thus, we can conclude that Na^+, because it is far from electrochemical equilibrium, must have a low conductance or permeability. For K^+ to be at electrochemical equilibrium, the mem-

brane potential must be −84 mV. The actual membrane potential is reasonably close, at −70 mV. Thus, we can conclude that K^+ is close to electrochemical equilibrium. The ion closest to electrochemical equilibrium is Cl^-; its calculated equilibrium potential of −78 mV is closest to the measured membrane potential of −70 mV. Thus, the conductance of the nerve cell membrane to Cl^- is highest, the conductance to K^+ is next highest, and the conductance to Na^+ is the lowest.

Key topics

- Conductance
- Diffusion potential
- Electrochemical equilibrium
- Equilibrium potential
- Membrane potential
- Nernst equation
- Permeability

Case 4

Primary Hypokalemic Periodic Paralysis

Case

Jimmy Jaworski is a 16-year-old sprinter on the high school track team. Recently, after he completed his events, he felt extremely weak, and his legs became "like rubber." Eating, especially carbohydrates, made him feel worse. After the most recent meet, he was unable to walk and had to be carried from the track on a stretcher. His parents were very alarmed and made an appointment for Jimmy to be evaluated by his pediatrician. As part of the workup, the pediatrician measured Jimmy's serum K^+ concentration, which was normal (4.5 mEq/L). However, because the pediatrician suspected a connection with K^+, the measurement was repeated immediately after a strenuous exercise treadmill test. After the treadmill test, Jimmy's serum K^+ was alarmingly low (2.2 mEq/L). Jimmy was diagnosed as having an inherited disorder called primary hypokalemic periodic paralysis and subsequently was treated with K^+ supplementation.

QUESTIONS

1. What is the normal distribution of K^+ between intracellular fluid and extracellular fluid? Where is most of the K^+ located? What is the concentration of K^+ in intracellular fluid and extracellular fluid?

2. What major factors can alter the distribution of K^+ between intracellular fluid and extracellular fluid?

3. What is the relationship between the serum K^+ concentration and the resting membrane potential of excitable cells (e.g, nerve, skeletal muscle)?

4. How does a decrease in serum K^+ concentration alter the resting membrane potential of skeletal muscle?

5. Propose a mechanism whereby a decrease in the serum K^+ concentration could lead to skeletal muscle weakness.

6. Why did Jimmy's weakness occur *after* exercise? Why did eating carbohydrates exacerbate (worsen) the weakness?

7. How would K^+ supplementation be expected to improve Jimmy's condition?

8. Another inherited disorder, called primary *hyper*kalemic periodic paralysis, involves an initial period of spontaneous muscle contractions (spasms), followed by prolonged muscle weakness. Using your knowledge of the ionic basis for the skeletal muscle action potential, propose a mechanism whereby an *increase* in the serum K^+ concentration could lead to spontaneous contractions followed by prolonged weakness.

ANSWERS AND EXPLANATIONS

1. Most of the body's K^+ is located in the intracellular fluid; K^+ is the major intracellular cation. The intracellular concentration of K^+ ($\approx$ 120 mEq/L) is more than 20 times that of extracellular K^+ (4.5 mEq/L). This asymmetrical distribution of K^+ is maintained by the Na^+-K^+ adenosine triphosphatase (ATPase) that is present in all cell membranes. The Na^+-K^+ ATPase, using ATP as its energy source, actively transports K^+ from extracellular fluid to intracellular fluid against an electrochemical gradient, thus maintaining the high intracellular K^+ concentration.

2. Several factors, including hormones and drugs, can alter the distribution of K^+ between intracellular fluid and extracellular fluid. Such a redistribution is called a **K^+ shift** to signify that K^+ has *shifted* from extracellular fluid to intracellular fluid or from intracellular fluid to extracellular fluid. Because the normal concentration of K^+ in the extracellular fluid is low, K^+ shifts can cause profound changes in the concentration of K^+ in the extracellular fluid or in the serum.

   The major factors that cause K^+ to shift *into* cells (from extracellular fluid to intracellular fluid) are **insulin,** β-adrenergic agonists (e.g., epinephrine, norepinephrine), and alkalemia. The major factors that cause K^+ to shift *out* of cells (from intracellular fluid to extracellular fluid) are lack of insulin, β-adrenergic antagonists, **exercise,** hyperosmolarity, cell lysis, and acidemia. Therefore, insulin and β-adrenergic agonists cause K^+ to shift from extracellular fluid to intracellular fluid and may cause a decrease in serum K^+ concentration (hypokalemia). Conversely, lack of insulin, β-adrenergic antagonists, exercise, hyperosmolarity, or cell lysis cause K^+ to shift from intracellular fluid to extracellular fluid and may cause an increase in serum K^+ concentration (hyperkalemia).

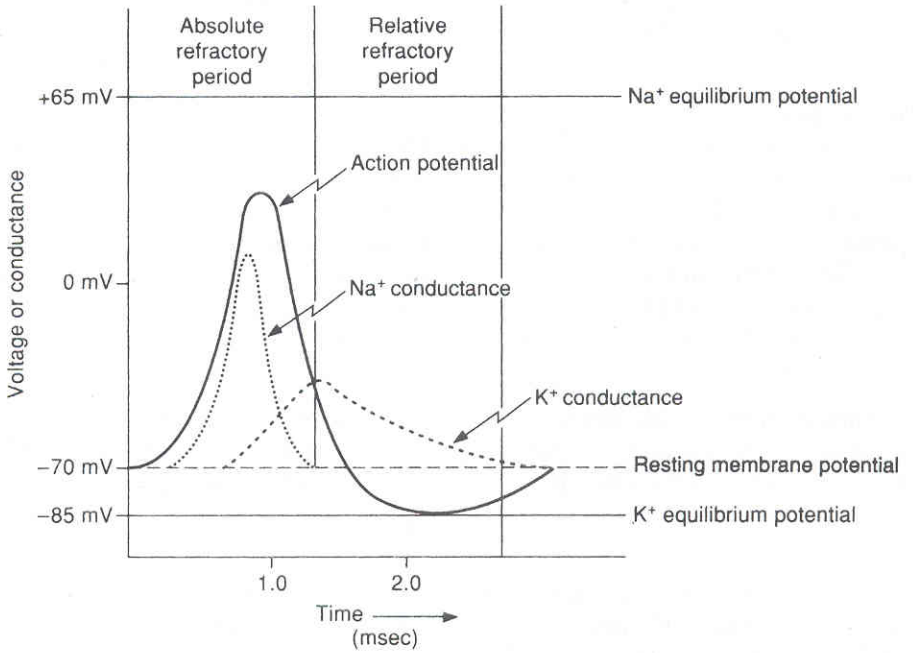
3. At rest (i.e., between action potentials), nerve and skeletal muscle membranes have a high permeability or conductance to K^+. There is also a large concentration gradient for K^+ across cell membranes created by the Na^+-K^+ ATPase (i.e., high K^+ concentration in intracellular fluid and low K^+ concentration in extracellular fluid). The large chemical driving force, coupled with the high conductance to K^+ causes K^+ to diffuse from intracellular fluid to extracellular fluid. As discussed in Case 3, this process generates an inside-negative potential difference, or K^+ diffusion potential, which is the basis for the **resting membrane potential.** The resting membrane potential approaches the **K^+ equilibrium potential** (calculated with the Nernst equation for a given K^+ concentration gradient) because the resting K^+ conductance is very high.

   Changes in the serum (extracellular fluid) K^+ concentration alter the K^+ equilibrium potential, and consequently, the resting membrane potential. The lower the serum K^+ concentration, the greater the K^+ concentration gradient across the membrane, and the more negative (hyperpolarized) the K^+ equilibrium potential. The more negative the K^+ equilibrium potential, the more negative the resting membrane potential. Conversely, the higher the serum K^+ concentration, the smaller the K^+ concentration gradient, and the less negative the K^+ equilibrium potential and the resting membrane potential.

4. Essentially, this question has been answered: as the concentration of K^+ in the serum decreases, the resting membrane potential of skeletal muscle becomes more

negative (hyperpolarized). Thus, the lower the serum K^+ concentration, the larger the K^+ concentration gradient across the cell membrane, and the larger and more negative the K^+ equilibrium potential. Because the K^+ conductance of skeletal muscle is very high at rest, the membrane potential is driven toward this more negative K^+ equilibrium potential.

5. To answer this question about why Jimmy was weak, it is necessary to understand the events that are responsible for action potentials in skeletal muscle. Figure 1–7 shows a single action potential superimposed by the relative conductances to K^+ and Na^+.



▲ **Figure 1–7.** Nerve action potential and associated changes in Na^+ and K^+ conductance. (Reprinted with permission from Costanzo LS: *Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 12.)

The **action potential** in skeletal muscle is a very rapid event (lasting approximately 1 msec) and is composed of depolarization (the upstroke) followed by repolarization. The resting membrane potential is approximately −70 mV (cell negative). Because of the high conductance to K^+, the resting membrane potential approaches the K^+ equilibrium potential, as described earlier. At rest, the conductance to Na^+ is low; therefore, the resting membrane potential is far from the Na^+ equilibrium potential. The action potential is initiated when inward current (positive charge entering the muscle cell) depolarizes the muscle cell membrane. This inward current is usually the result of current spread from action potentials at neighboring sites. If the muscle membrane is depolarized to the **threshold potential** (approximately −60 mV), activation gates on voltage-gated Na^+ channels rapidly open. As a result, the Na^+ conductance increases and becomes even higher than the K^+ conductance. This rapid increase in Na^+ conductance produces an inward Na^+ current that further depolarizes the membrane potential toward the Na^+ equilibrium potential, which constitutes the **upstroke of the action potential.** The upstroke is followed

by repolarization to the resting membrane potential. Repolarization is caused by two slower events: closure of inactivation gates on the Na^+ channels (leading to closure of the Na^+ channels and decreased Na^+ conductance) and increased K^+ conductance, which drives the membrane potential back toward the K^+ equilibrium potential.

Now, to use these concepts and answer the question of why Jimmy's decreased serum K^+ concentration led to his skeletal muscle weakness. Decreased serum K^+ concentration increased the negativity of both the K^+ equilibrium potential and the resting membrane potential, as already discussed. Because the resting membrane potential was further from the threshold potential, more inward current was required to depolarize the membrane to threshold to initiate the upstroke of the action potential. In other words, firing action potentials became more difficult. Without action potentials, Jimmy's skeletal muscle could not contract, and as a result, his muscles felt weak and "rubbery."

6. We can speculate about why Jimmy's periodic paralysis occurred *after* extreme exercise, and why it was exacerbated by eating carbohydrates. By mechanisms that are not completely understood, exercise causes K^+ to shift from intracellular fluid to extracellular fluid. It may also lead to a transient local increase in the K^+ concentration of extracellular fluid. (Incidentally, this local increase in K^+ concentration is one of the factors that causes an increase in muscle blood flow during exercise). Normally, after exercise, K^+ is reaccumulated in skeletal muscle cells. Because of his inherited disorder, in Jimmy, this reaccumulation of K^+ was exaggerated and led to hypokalemia.

Ingestion of carbohydrates exacerbated his muscle weakness because glucose stimulates insulin secretion. Insulin is a major factor that causes uptake of K^+ into cells. This insulin-dependent K^+ uptake augmented the postexercise K^+ uptake and caused further hypokalemia.

7. K^+ supplementation provided more K^+ to the extracellular fluid, which offset the exaggerated uptake of K^+ into muscle cells that occurred after exercise. Once the pediatrician understood the physiologic basis for Jimmy's problem (too much K^+ shifting into cells after exercise), sufficient K^+ could be supplemented to prevent the serum K^+ from decreasing.

8. Another disorder, primary *hyper*kalemic periodic paralysis, also leads to skeletal muscle weakness. However, in this disorder, the weakness is preceded by muscle spasms. This pattern is also explained by events of the muscle action potential.

The initial muscle spasms (hyperactivity) can be understood from our earlier discussion. When the serum K^+ concentration increases (**hyperkalemia**), the K^+ equilibrium potential and the resting membrane potential become less negative (depolarized). The resting membrane potential is moved closer to threshold potential and, as a result, less inward current is required to initiate the upstroke of the action potential.

It is more difficult to understand why the initial phase of muscle hyperactivity is followed by prolonged weakness. If the muscle membrane potential is closer to threshold, won't it continue to fire away? Actually, no. The explanation lies in the behavior of the two sets of gates on the **Na^+ channels.** Activation gates on Na^+ channels *open* in response to depolarization; these gates are responsible for the upstroke

of the action potential. However, inactivation gates on the Na^+ channel *close* in response to depolarization, albeit more slowly than the activation gates open. Therefore, in response to prolonged depolarization (as in hyperkalemia), the inactivation gates close and remain closed. When the inactivation gates are closed, the Na^+ channels are closed, regardless of the position of the activation gates. For the upstroke of the action potential to occur, both sets of gates on the Na^+ channels must be open; if the inactivation gates are closed, no action potentials can occur.

Key topics

- Action potential
- Activation gates
- β-Adrenergic agonists (epinephrine, norepinephrine)
- Depolarization
- Exercise
- Hyperpolarization
- Inactivation gates
- Insulin
- Inward current
- K^+ distribution
- K^+ equilibrium potential
- K^+ shifts
- Na^+ channels
- Outward current
- Repolarization
- Resting membrane potential
- Threshold potential
- Upstroke

Case 5

Epidural Anesthesia: Effect of Lidocaine on Nerve Action Potentials

Case

Sue McKnight, a healthy 27-year-old woman, was pregnant with her first child. The pregnancy was completely normal. However, as the delivery date approached, Sue became increasingly fearful of the pain associated with a vaginal delivery. Her mother and five sisters had told her horror stories about their experiences with labor and delivery. Sue discussed these fears with her obstetrician, who reassured her that she would be a good candidate for epidural anesthesia. The obstetrician explained that during this procedure, lidocaine, a local anesthetic, is injected into the epidural space around the lumbar spinal cord. The anesthetic drug prevents pain by blocking action potentials in the sensory nerve fibers that serve the pelvis and perineum. Sue was comforted by this information and decided to politely excuse herself from further conversations with "helpful" relatives. Sue went into labor on her due date. She received an epidural anesthetic midway through her 10-hour labor and delivered an 8 lb 10 oz boy with virtually no pain. She reported to her mother and sisters that epidural anesthesia is "the greatest thing since sliced bread."

QUESTIONS

1. Lidocaine and other local anesthetic agents block action potentials in nerve fibers by binding to specific ion channels. At low concentration, these drugs decrease the rate of rise of the upstroke of the action potential. At higher concentrations, they prevent the occurrence of action potentials altogether. Based on this information and your knowledge of the ionic basis of the action potential, which ion channel would you conclude is blocked by lidocaine?

2. Lidocaine is a weak base with a pK of 7.9. At physiologic pH, is lidocaine primarily in its charged or uncharged form?

3. Lidocaine blocks ion channels by binding to receptors from the *intracellular* side of the channel. Therefore, to act, lidocaine must cross the nerve cell membrane. Using this information, if the pH of the epidural space were to decrease from 7.4 to 7.0 (becomes more acidic), would drug activity increase, decrease, or be unchanged?

4. Based on your knowledge of how nerve action potentials are propagated, how would you expect lidocaine to alter the conduction of the action potential along a nerve fiber?

ANSWERS AND EXPLANATIONS

1. To determine which ion channel is blocked by lidocaine, it is necessary to review which ion channels are important in nerve function. At **rest** (i.e., between action potentials), the conductance to K^+ and Cl^- is high, mediated respectively, by K^+ and Cl^- channels in the nerve membrane. Thus, the resting membrane potential is driven toward the K^+ and Cl^- equilibrium potentials. During the **upstroke** of the nerve action potential, **voltage-gated Na^+ channels** are most important. These channels open in response to depolarization, and this opening leads to further depolarization toward the Na^+ equilibrium potential. During **repolarization,** the voltage-gated Na^+ channels close and K^+ channels open; as a result, the nerve membrane is repolarized back toward the resting membrane potential.

   Lidocaine and other **local anesthetic agents** block voltage-gated Na^+ channels in the nerve membrane. At low concentrations, this blockade results in a slower rate of rise (dV/dt) of the upstroke of the action potential. At higher concentrations, the upstroke is prevented altogether, and no action potentials can occur.

2. According to the Brønsted-Lowry nomenclature for weak acids, the proton donor is called HA and the proton acceptor is called A^-. With weak bases (e.g., lidocaine), the proton donor has a net positive charge and is called BH^+; the proton acceptor is called B. Because the pK of lidocaine (a weak base) is 7.9, the predominant form of lidocaine at physiologic pH (7.4) is BH^+, with its net positive charge. This can be confirmed with the **Henderson-Hasselbalch equation,** which is used to calculate the relative concentrations of BH^+ and B at a given pH as follows:

$$pH = pK + \log \frac{B}{BH^+}$$

   Physiologic pH is 7.4, and the pK of lidocaine is 7.9. Thus:

$$7.4 = 7.9 + \log \frac{B}{BH^+}$$

$$-0.5 = \log \frac{B}{BH^+}$$

$$0.316 = B/BH^+$$

   or

$$BH^+/B = 3.16$$

   In words, at physiologic pH, the concentration of BH^+ (with its net positive charge) is approximately three times the concentration of B (uncharged).

3. As discussed in Question 2, the BH^+ form of lidocaine has a net positive charge, and the B form of lidocaine is uncharged. You were told that lidocaine must cross the lipid bilayer of the nerve membrane to act from the intracellular side of the Na^+ channel. Because the uncharged (B) form of lidocaine is more lipophilic than the positively charged (BH^+) form, it crosses the nerve cell membrane more readily. Thus,

at physiologic pH, although the positively charged (BH^+) form is predominant (see Question 2), it is the uncharged form that enters the nerve fiber.

If the pH of the epidural space decreases to 7.0, the equilibrium shifts toward the BH^+ form, again demonstrated by the Henderson-Hasselbalch equation.

$$pH = pK + \log \frac{B}{BH^+}$$

$$7.0 = 7.9 + \log \frac{B}{BH^+}$$

$$-0.9 = \log \frac{B}{BH^+}$$

$$0.126 = B/BH^+$$

or

$$BH^+/B = 7.94$$

At this more acidic pH, the amount of the charged form of lidocaine is now approximately eight times that of the uncharged form. When the pH is more acidic, *less* of the permeant, uncharged form of the drug is present. Thus, access of the drug to its intracellular site of action is impaired, and the drug is *less* effective.

4. Action potentials are propagated (e.g., along sensory nerve axons) by the spread of local currents from active depolarized regions (i.e., regions that are firing action potentials) to adjacent inactive regions. These local depolarizing currents are caused by the **inward Na^+ current** of the upstroke of the action potential. When lidocaine blocks voltage-gated Na^+ channels, the inward Na^+ current of the upstroke of the action potential does not occur. Thus, propagation of the action potential, which depends on this depolarizing inward current, is also prevented.

Key topics

- Action potential
- Henderson-Hasselbalch equation
- Lidocaine
- Lipid solubility
- Local anesthetics
- Local currents
- Propagation of action potentials
- Upstroke of action potential
- Weak acids
- Weak bases

Case 6

Myasthenia Gravis: Neuromuscular Transmission

Case

Wendy Chu is a 23-year-old photographer for a busy local newspaper. Over the last 8 months, she experienced "strange" symptoms. She had severe eyestrain when she read for longer than 15 minutes. She became tired when she chewed her food, brushed her teeth, or dried her hair; and she had extreme fatigue on the job. Despite her strong work ethic, Wendy had to excuse herself from several "shoots" because she simply could not carry the heavy equipment. Wendy is not a complainer, but she began to worry about these vague symptoms.

She was evaluated by her physician, who suspected myasthenia gravis. While awaiting the results of a serum antibody test, the physician initiated a trial of pyridostigmine, an acetylcholinesterase inhibitor. Wendy immediately felt better while taking the drug; her strength returned to almost normal. Meanwhile, the results of the antibody test were positive, confirming the diagnosis of myasthenia gravis.

QUESTIONS

1. What steps are involved in neuromuscular transmission?

2. What antibody was measured in Wendy's serum? Against what protein is this antibody directed?

3. Using your description of neuromuscular transmission, explain why severe muscle weakness (e.g., ocular, jaw) occurs in myasthenia gravis.

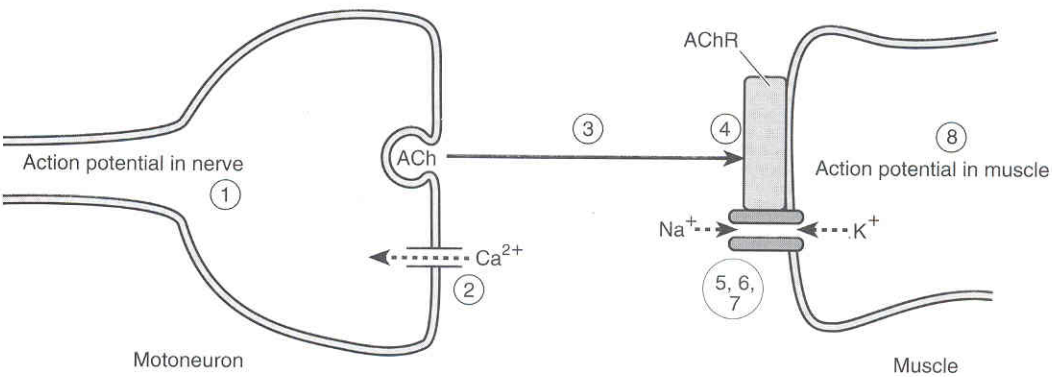
4. Why does pyridostigmine, an acetylcholinesterase inhibitor, improve muscle strength in myasthenia gravis?

5. Consider the following drugs that act at various steps in neuromuscular transmission. What is the action of each drug, and which drugs are *contraindicated* in myasthenia gravis?

   Botulinus toxin
   Curare
   Neostigmine
   Hemicholinium

ANSWERS AND EXPLANATIONS

1. **Neuromuscular transmission** is the process whereby an action potential in a motoneuron produces an action potential in the muscle fibers that it innervates. The steps in neuromuscular transmission, shown in Figure 1–8, are as follows: (1) An action potential is propagated down the motoneuron until the presynaptic terminal is depolarized. (2) Depolarization of the presynaptic terminal causes voltage-gated Ca^{2+} channels to open, and Ca^{2+} flows into the nerve terminal. (3) Uptake of Ca^{2+} into the nerve terminal causes exocytosis of stored acetylcholine (ACh) into the synaptic cleft. (4) ACh diffuses across the synaptic cleft to the muscle end plate, where it binds to **nicotinic ACh receptors (AChR).** (5) The nicotinic AChR is also an ion channel for Na^+ and K^+. When ACh binds to the receptor, the channel opens. (6) Opening of the channel causes both Na^+ and K^+ to flow down their respective electrochemical gradients. As a result, depolarization occurs. (7) This depolarization, called the **end plate potential,** spreads to neighboring regions of the muscle fiber. (8) Finally, the muscle fibers are depolarized to threshold and fire action potentials. Through this elaborate sequence of events, an action potential in the motoneuron causes an action potential in the muscle fibers that it innervates.



▲ **Figure 1–8.** Steps in neuromuscular transmission. The numbers correspond to the steps discussed in the text. *ACh,* acetylcholine; *AChR,* ACh receptor.

2. Wendy's physician suspected myasthenia gravis and measured serum levels of an antibody to the **nicotinic AChR.** Accordingly, the antibody is called AChR-ab.

3. In myasthenia gravis, abnormal antibodies to AChR (AChR-ab) are produced, circulate in the blood, and bind to nicotinic receptors on the muscle end plates. When antibodies are bound to AChR, the receptors are not available to be activated by ACh that is released physiologically from motoneurons. Thus, while normal action potentials occur in the motoneurons and ACh is released normally, the ACh cannot cause depolarization of muscle end plates. Without depolarization of muscle end plates, there can be no action potentials or contraction in the muscle.

4. After ACh binds to and activates AChR on the muscle end plate, it is degraded by **acetylcholinesterase,** an enzyme that is also present on the muscle end plate. This degradative step, whose byproducts are choline and acetate, terminates the action

of ACh on the muscle fiber. Choline is taken up into the motoneuron terminal and recycled into the synthesis of more ACh.

Pyridostigmine is an **acetylcholinesterase inhibitor** that binds to acetylcholinesterase and thereby prevents binding and degradation of ACh at the muscle end plate. In the treatment of myasthenia gravis, pyridostigmine prevents degradation of ACh, increases its synaptic concentration, and prolongs its action. The longer the muscle end plate is exposed to high concentrations of ACh, the greater the likelihood that action potentials and contraction in the muscle will occur.

5. In principle, any drug that interferes with any step in neuromuscular transmission is contraindicated in myasthenia gravis. **Botulinus toxin** blocks the release of ACh from motoneuron terminals, and therefore, causes total blockade of neuromuscular transmission; it is contraindicated in myasthenia gravis. **Curare,** a competitive inhibitor of ACh for the AChR on the muscle end plate, prevents depolarization of the muscle fiber; it is contraindicated. **Neostigmine** is an acetylcholinesterase inhibitor that is related to pyridostigmine and is used to *treat* myasthenia gravis by preventing ACh degradation. **Hemicholinium** blocks the reuptake of choline into motoneuron terminals, thereby depleting stores of ACh; it is contraindicated.

Key topics

- Acetylcholine (ACh)
- Acetylcholine receptors (AChR)
- Acetylcholinesterase
- Acetylcholinesterase inhibitor
- Botulinus toxin
- Curare
- End plate potential
- Hemicholinium
- Muscle (motor) end plate
- Myasthenia gravis
- Neostigmine
- Neuromuscular transmission
- Nicotinic receptors
- Pyridostigmine

Case 7

Pheochromocytoma: Effects of Catecholamines

Case

Helen Ames is a 51-year-old homemaker who experienced what she thought were severe menopausal symptoms. These awful "attacks" were becoming more frequent. Her heart raced and pounded; she had a throbbing headache and visual disturbances; she felt hot, but her hands and feet were cold; and she was nauseated, sometimes to the point of vomiting. Mrs. Ames called her physician, who agreed that the symptoms were probably menopausal and prescribed hormone replacement therapy over the phone. Mrs. Ames took the hormones (a combination of estrogen and progesterone), but they did not relieve her symptoms. The attacks were occurring almost daily. She made an appointment with her physician.

In the physician's office, Mrs. Ames' blood pressure was severely elevated at 200/110, and her heart rate was increased at 110 beats/min. To rule out a pheochromocytoma (a rare tumor of the adrenal medulla), the physician ordered a 24-hour urine measurement of 3-methoxy-4-hydroxymandelic acid (VMA). To his surprise, the results of the 24-hour urinary VMA test were positive, a finding that provided nearly conclusive evidence of a pheochromocytoma. A computerized tomographic scan confirmed that Mrs. Ames had a 3-cm mass on her right adrenal gland. While awaiting surgery to remove the tumor, she was given phenoxybenzamine, an α_1-adrenergic antagonist. After an appropriate dosage of phenoxybenzamine was established, she was also given a low dose of propranolol, a β-adrenergic antagonist. She was cleared for surgery when the medications had decreased her blood pressure to 140/90.

QUESTIONS

1. What is the relationship of the adrenal medulla to the autonomic nervous system?

2. What hormones are secreted by a pheochromocytoma?

3. Why does an elevated urinary level of VMA (a metabolite of epinephrine and norepinephrine) suggest the presence of a pheochromocytoma? Why is it necessary to do a 24-hour measurement of VMA, rather than a spot-urine test?

4. In view of the pathophysiology of pheochromocytoma, explain Mrs. Ames' symptoms, specifically, her increased heart rate, pounding heart, cold hands and feet, visual disturbances, and nausea and vomiting. What receptors are involved in each of these symptoms?

5. Why are two values reported for arterial pressure, and what is the significance of each value? Why were both the systolic and the diastolic blood pressures elevated?

6. Is there a plausible explanation for the fact that Mrs. Ames felt hot, even though her hands and feet were cold?

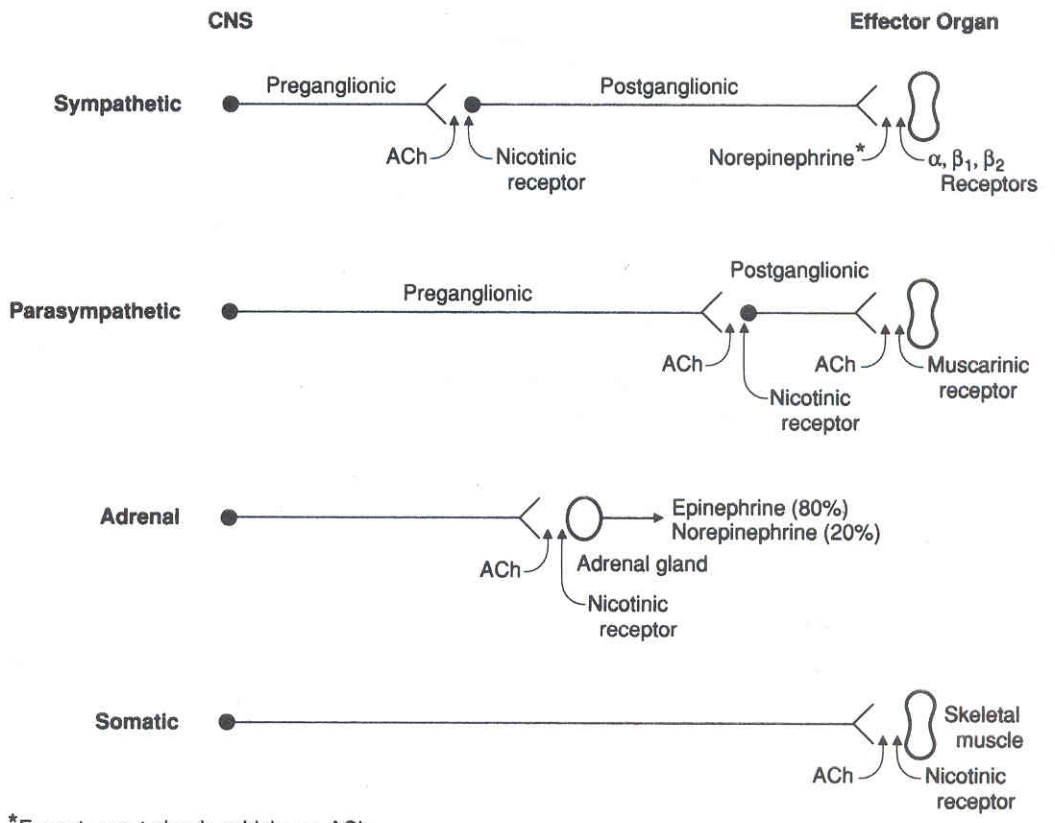
7. How did phenoxybenzamine lower Mrs. Ames' blood pressure?

8. After the dosage of phenoxybenzamine was established, what was achieved by adding a low dose of propranolol?

9. What might have happened if Mrs. Ames had been given propranolol alone?

ANSWERS AND EXPLANATIONS

1. The **adrenal medulla** is a specialized ganglion of the **sympathetic division** of the autonomic nervous system. The preganglionic neurons have their cell bodies in the thoracic spinal cord. Axons of these preganglionic neurons travel in the greater splanchnic nerve to the adrenal medulla, where they synapse on **chromaffin cells** and release the neurotransmitter acetylcholine. When stimulated, chromaffin cells (the postsynaptic unit) secrete catecholamines (epinephrine and norepinephrine) into the circulation (Figure 1–9).



▲ **Figure 1–9.** Organization of the autonomic nervous system. *ACh,* acetylcholine; *CNS,* central nervous system. (Reprinted with permission from Costanzo LS: *Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 34.)

2. A pheochromocytoma is a tumor of the adrenal medulla gland that secretes large quantities of **epinephrine** and **norepinephrine.** As with the normal adrenal medulla, the greater secretory component is epinephrine (80%) and the lesser component is norepinephrine (20%).

3. **3-Methoxy-4-hydroxymandelic acid (VMA)** is a major metabolite of both epinephrine and norepinephrine. When epinephrine and norepinephrine are degraded by the enzymes catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO), the final metabolic product is VMA, which is excreted in urine. Thus, when

a pheochromocytoma produces large quantities of epinephrine and norepinephrine, urinary excretion of VMA is increased.

A 24-hour urine sample is necessary because the tumor secretes its hormones in bursts, or pulses; a single spot-urine sample might "miss" large secretory bursts of the hormones.

4. All of Mrs. Ames' symptoms can be explained in terms of the actions of catecholamines on the various organ systems (Table 1–5). In the **heart,** catecholamines have three major effects, each mediated by a **β_1 receptor:** increased heart rate; increased contractility, or force of contraction; and increased conduction velocity through the atrioventricular node. In Mrs. Ames, excess amounts of catecholamines caused the sensation that her heart was racing (increased heart rate) and pounding (increased contractility). In **blood vessels,** primarily arterioles, catecholamines cause vasoconstriction in most vascular beds (e.g., cutaneous and splanchnic) through **α_1 receptors.** Vasoconstriction of cutaneous blood vessels leads to decreased cutaneous blood flow and cold skin, especially in the feet and hands. In blood vessels of skeletal muscle, however, catecholamines cause the opposite effect (vasodilation) through **β_2 receptors.** The effects on vision are explained by sympathetic effects on the **eye muscles.** In the radial muscle of the iris, catecholamines cause contraction (β_1 receptor); in the ciliary muscle, catecholamines cause dilation (β_2 receptor). The **gastrointestinal** effects of catecholamines include relaxation of the smooth muscle wall of the gastrointestinal tract (α_2 and β_2 receptors); contraction of the gastrointestinal sphincters (α_1 receptors); and increased production of saliva (β_1 receptors). The coordinated actions on the muscle wall and sphincters slow the motility of chyme through the gastrointestinal tract, and may lead to nausea and even vomiting.

▼ **Table 1–5.** Effect of the Autonomic Nervous System on Organ Systems

Organ	Sympathetic Action	Sympathetic Receptor	Parasympathetic Action (receptors are muscarinic)
Heart	↑ heart rate	β_1	↓ heart rate
	↑ contractility	β_1	↓ contractility (atria)
	↑ AV node conduction	β_1	↓ AV node conduction
Vascular smooth muscle	Constricts blood vessels in skin; splanchnic	α_1	—
	Dilates blood vessels in skeletal muscle	β_2	—
Gastrointestinal tract	↓ motility	α_2, β_2	↑ motility
	Constricts sphincters	α_1	Relaxes sphincters
Bronchioles	Dilates bronchiolar smooth muscle	β_2	Constricts bronchiolar smooth muscle
Male sex organs	Ejaculation	α	Erection
Bladder	Relaxes bladder wall	β_2	Contracts bladder wall
	Constricts sphincter	α_1	Relaxes sphincter
Sweat glands	↑ sweating	Muscarinic (sympathetic cholinergic)	—
Kidney	↑ renin secretion	β_1	—
Fat cells	↑ lipolysis	β_1	—

AV = atrioventricular. (Reprinted with permission from Costanzo LS: *Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 37.)

5. Mrs. Ames' blood pressure was reported as 200/110. (Normal blood pressure is 120/80.) The two numbers refer, respectively, to systolic arterial pressure and diastolic arterial pressure. Arterial pressure is not expressed as a single value because systemic arterial pressure changes over the course of the cardiac cycle. **Systolic pressure** is the highest value for arterial pressure and is measured just after blood is ejected from the left ventricle into the large arteries (i.e., systole). **Diastolic pressure** is the lowest value for arterial pressure and is measured when the ventricle is relaxed and blood is flowing from the arteries to the veins and back to the heart (i.e., diastole).

   In Mrs. Ames' case, both systolic and diastolic pressures were significantly elevated. These elevations are explained by the effects of excess catecholamines on the heart and blood vessels that have already been discussed. Catecholamines increase both heart rate and contractility. These two effects combine to produce an increase in cardiac output (the volume of blood ejected from the ventricle per minute). An increase in cardiac output means that, during systole, a greater blood volume is ejected into the arteries. This increase in arterial volume is reflected in a higher systolic pressure. In addition, catecholamines cause constriction of arterioles in many vascular beds. This constriction has the effect of "holding" more blood on the arterial side of the circulation, which increases both systolic and diastolic pressures.

   The preceding explanation of the effects of catecholamines on the heart and blood vessels may be somewhat misleading because it suggests that these effects are entirely independent. They are not independent, but interact as follows. As described earlier, the vasoconstrictor effect of catecholamines in several vascular beds causes an increase in **total peripheral resistance (TPR),** which increases systemic arterial pressure. Systemic arterial pressure is the **afterload** of the left ventricle (i.e., the pressure against which the left ventricle must eject blood). An increase in systemic arterial pressure, or afterload, means that the left ventricle must work harder to eject blood. As a result, the effects of catecholamines to increase cardiac output are partially, or even completely, offset by the increase in afterload.

6. As already discussed, Mrs. Ames' hands and feet were cold because catecholamines cause arteriolar vasoconstriction in the cutaneous circulation. However, why would she *feel* hot? The answer lies in the role of the cutaneous circulation in dissipating the heat generated by metabolism. Normally, heat is removed from the body through responses directed by the hypothalamus. These responses include *decreased* sympathetic outflow to the cutaneous blood vessels, resulting in vasodilation. Warm blood from the body core is shunted to the skin surface, where heat is then dissipated by convection and radiation. When a pheochromocytoma is present, the large quantities of circulating catecholamines cancel or override this cutaneous vasodilatory response. As a result, the body retains heat from metabolism that should have been dissipated.

7. Phenoxybenzamine, an **α_1-adrenergic antagonist,** inhibits all effects of catecholamines that are mediated through α_1 receptors. These effects include vasoconstriction of cutaneous and splanchnic blood vessels; contraction of the sphincters of the gastrointestinal tract; and contraction of the radial muscle of the iris. As discussed earlier, one of the major reasons that Mrs. Ames' systolic and diastolic blood pressures were so high was that excess catecholamines caused vasoconstriction of arterioles (increased TPR). When this vasoconstriction was blocked by an α_1-adre-

nergic antagonist, TPR was decreased, and both diastolic and systolic blood pressures were decreased.

8. Once treatment with the α_1-adrenergic antagonist was established, low doses of propranolol, a **β-adrenergic antagonist,** could be administered to reduce blood pressure further. The drugs were intentionally given in this sequence because of the effects of high levels of catecholamines on the heart and blood vessels. Recall that constriction of arterioles by catecholamines increases arterial pressure (afterload). One effect of this increased afterload is that it is more difficult for the left ventricle to eject blood. Thus, increased afterload offsets the other effects of catecholamines to increase cardiac output.

   Once Mrs. Ames' afterload was reduced by the α_1-adrenergic antagonist, the work of the left ventricle was reduced, and it was easier for the ventricle to eject blood. At this point, the effects of excess catecholamines to increase cardiac output (through increased heart rate and contractility) would have become evident. In other words, Mrs. Ames' blood pressure may have remained elevated, even in the presence of an α_1-adrenergic antagonist. Addition of propranolol, a β-adrenergic antagonist, blocked the effects of excess catecholamines on heart rate and contractility and further reduced her blood pressure.

9. It would have been dangerous to give Mrs. Ames a β-adrenergic antagonist (e.g., propranolol) without also giving her an α_1-adrenergic antagonist. As we have already discussed, excess circulating catecholamines caused vasoconstriction of her arterioles and increased her arterial pressure (afterload). Increased afterload made it more difficult for the ventricles to eject blood. The action of catecholamines to increase contractility through cardiac β_1 receptors partially offset this difficulty. If Mrs. Ames' cardiac β_1 receptors had been blocked by propranolol (without the assistance of phenoxybenzamine to lower TPR and afterload), her heart might not have been able to eject enough blood to serve the metabolic needs of her tissues (cardiac failure).

Key topics

- Adrenal medulla
- Catechol-*O*-methyltransferase (COMT)
- Chromaffin cells
- Diastolic pressure
- Epinephrine
- 3-Methoxy-4-hydroxymandelic acid (VMA)
- Monoamine oxidase (MAO)
- Norepinephrine
- Phenoxybenzamine
- Pheochromocytoma
- Propranolol
- α_1 Receptors
- α_2 Receptors
- β_1 Receptors
- β_2 Receptors
- Systolic pressure
- Total peripheral resistance (TPR)

Case 8

Shy-Drager Syndrome: Central Autonomic Failure

Case

Ben Garcia was a 54-year-old executive with a large, thriving investment company. He was well regarded among his clients as the consummate professional. He and his wife of 32 years had two children, both of whom were college graduates. Life was great until Mr. Garcia found, to his embarrassment, that he was occasionally impotent. His wife teased him gently about "getting old." However, his impotence rapidly progressed from "occasional" to "frequent" to "every time." Additionally, Mr. Garcia was experiencing urinary problems. He felt enormous urgency to urinate, but had difficulty producing a urinary stream. His embarrassment (because of the nature of his symptoms), combined with his busy schedule, kept him from seeking medical attention. It wasn't until he arose from bed one morning and fainted that he made an appointment with his physician. By the time he saw his physician, he had been feeling dizzy every morning for a month and had an array of symptoms that convinced him that something was terribly wrong. In addition to impotence, urinary difficulties, and dizziness when he stood up, he had double vision, indigestion, diarrhea, and heat intolerance.

Mr. Garcia was referred to a neurologist who, based on the global nature of his symptoms and the results of a specific ocular test, diagnosed him as having Shy-Drager syndrome, a rare, progressive disease of the central autonomic nervous system. Shy-Drager syndrome is associated with degeneration of preganglionic neurons of the intermediolateral cell column of the spinal cord, autonomic ganglia in the periphery, and autonomic centers in the hypothalamus. As a result, both the sympathetic and parasympathetic divisions of the autonomic nervous system are profoundly impaired.

As part of his treatment, Mr. Garcia was instructed to elevate his head during sleep and to wear support stockings to prevent blood from pooling in his veins. He also took an aldosterone analogue to increase his blood volume. Each of these measures was an attempt to ameliorate the dizziness and fainting he experienced when he stood up. Mr. Garcia and his family understood that the treatments were palliative and that there was no cure for his degenerative disease. He died at home at 58 years of age, 4 years after the onset of his symptoms.

QUESTIONS

1. Which organ systems or bodily functions would you expect to be adversely affected by degeneration of the central autonomic nervous system?

2. As experienced by Mr. Garcia, often the earliest symptom of Shy-Drager syndrome is impotence. Describe the normal autonomic control of male sexual response, and explain why it is impaired in patients who have central autonomic failure.

3. Describe the autonomic control of micturition, including the functions of the detrusor muscle and the sphincters of the bladder. Why did Mr. Garcia experience urinary urgency, but was then unable to void normally?

4. Why was Mr. Garcia heat-intolerant?

5. The ocular test involved instilling methacholine (a cholinergic muscarinic agonist) into the conjunctival sac. In Mr. Garcia, methacholine caused exaggerated miosis (constriction of the pupil caused by contraction of the circular muscle of the iris). Is there a plausible explanation for why his response to methacholine was greater than that of a healthy person?

6. The hallmark of Shy-Drager syndrome is orthostatic hypotension (a decrease in blood pressure that occurs when a person stands up). When a healthy person stands up, orthostatic hypotension does not occur because autonomic reflexes operate to maintain a constant arterial pressure. What are the reflex responses that prevent orthostatic hypotension in healthy individuals, and why were these responses impaired in Mr. Garcia?

7. Support stockings prevent blood from pooling in the leg veins. How would these stockings have been helpful in alleviating Mr. Garcia's orthostatic hypotension?

8. Aldosterone and its analogues produce an increase in extracellular fluid volume. How did the aldosterone analogue help to alleviate Mr. Garcia's orthostatic hypotension?

9. Name three classes of drugs that would have been *absolutely contraindicated* in Mr. Garcia's case.

ANSWERS AND EXPLANATIONS

1. The autonomic nervous system controls the function of virtually every organ system and every bodily function, usually as a result of an interplay between the sympathetic and parasympathetic divisions. (See Table 1–5 in Case 7 to review autonomic control of organ system functions.) Central failure of the autonomic nervous system, as seen in Shy-Drager syndrome, would be predicted to adversely affect every organ system. This failure affects control of arterial blood pressure; function of the bronchioles, which regulate the flow of air into the lungs; motility, secretion, digestive, and absorptive functions of the gastrointestinal tract; filling and emptying of the bladder; male sexual response, including erection and ejaculation; function of the eye muscles that control near and far vision; activity of the sweat glands involved in thermoregulation; and metabolic functions of the liver and adipose tissue. It is difficult to imagine a more comprehensive list of bodily functions, and it is easy to appreciate why Mr. Garcia was so sick.

2. The male sexual response consists of erection and ejaculation. **Erection** is under parasympathetic control (muscarinic receptors), which causes the venous sinuses of the corpus cavernosa to fill with blood and the penis to become erect. **Ejaculation** is under sympathetic control (α receptors), which causes the ischiocavernosa and bulbocavernosa muscles to contract.

3. The detrusor muscle of the bladder wall is composed of smooth muscle that has both sympathetic (β_2 receptors) and parasympathetic (muscarinic receptors) innervation. The internal sphincter of the bladder is also composed of smooth muscle, with both sympathetic (α_1 receptors) and parasympathetic (muscarinic receptors) innervation. The external sphincter is skeletal muscle, which is under trained voluntary control.

   Normal bladder function has two phases: filling and emptying (micturition). When the **bladder is filling** with urine, **sympathetic** control dominates. The detrusor muscle relaxes (sympathetic β_2 receptors), and the internal sphincter contracts (sympathetic α_1 receptors). When the bladder is full, mechanoreceptors in the wall sense the fullness and relay this information to the spinal cord and then to the brain stem, where the micturition reflex is coordinated. During **micturition,** or emptying, **parasympathetic** control dominates. The detrusor muscle contracts (parasympathetic muscarinic receptors), and the internal sphincter relaxes (parasympathetic muscarinic receptors), allowing the bladder to empty.

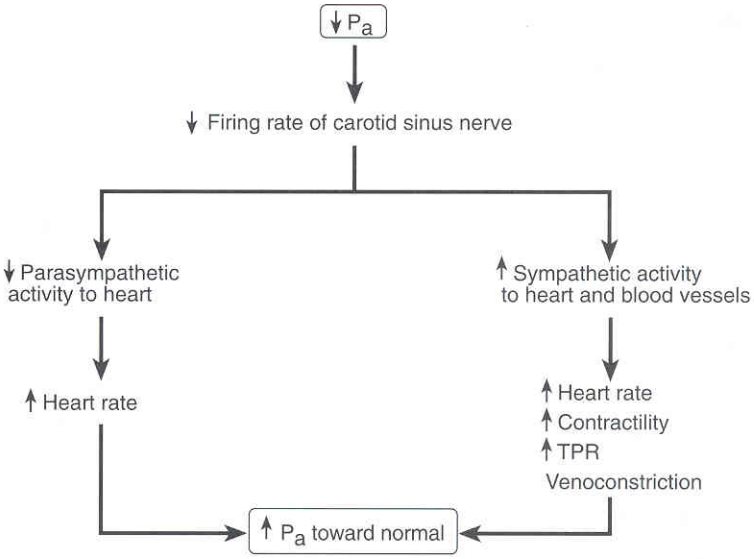
   In Mr. Garcia, both sympathetic control (filling) and parasympathetic control (emptying) of the bladder were impaired. Because of the loss of sympathetic control, his bladder did not fill normally, and he felt urinary urgency when his bladder contained a small amount of urine. Because of the loss of parasympathetic control, his bladder could not contract forcefully enough to produce a normal urinary stream.

4. **Thermoregulatory sweat glands** are controlled by the sympathetic nervous system. This sympathetic innervation is unusual in that postganglionic neurons innervating the sweat glands release acetylcholine (i.e., they are sympathetic *cholinergic* fibers). [In contrast, most sympathetic postganglionic neurons release norepinephrine (i.e., they are sympathetic *adrenergic* fibers)]. In keeping with this unusual feature, the receptors on sweat glands are the *cholinergic* muscarinic type.

As the name suggests, thermoregulatory sweating is important for dissipation of the heat generated by metabolism, especially when the ambient temperature is high. Loss of sympathetic innervation in Shy-Drager syndrome led to impairment of thermoregulatory sweating and caused heat intolerance.

5. The ocular test involved instilling a cholinergic muscarinic agonist into the eye. In healthy persons, the cholinergic agonist methacholine produces **miosis** (constriction of the pupil) by causing the circular muscle of the iris to contract. In Mr. Garcia, the miosis response was exaggerated. Why would he have an *exaggerated* parasympathetic cholinergic response when his central parasympathetic nervous system was impaired? The answer involves the sensitivity of cholinergic receptors on the circular muscle of the iris. Without normal parasympathetic innervation, the receptors are upregulated (i.e., increased number of receptors), a condition called **denervation hypersensitivity.** Thus, when an exogenous cholinergic agonist (e.g., methacholine) was instilled in Mr. Garcia's eyes, it caused a larger than usual miosis response.

6. When a healthy person stands up suddenly, blood pools in the veins of the legs, and there is a transient decrease in arterial blood pressure. This decrease is only transient because it is detected and immediately corrected by reflexes involving the sympathetic and parasympathetic nervous systems (**baroreceptor reflex**). For this reflex to occur, information about blood pressure must be relayed from baroreceptors in the carotid sinus to specific brain stem centers. These brain stem centers orchestrate an increase in sympathetic outflow to the heart and blood vessels and a decrease in parasympathetic outflow to the heart (Figure 1–10). The sympathetic and parasympathetic effects include an increase in heart rate and contractility, which combine to produce an increase in cardiac output; constriction of arterioles, with a resultant increase in total peripheral resistance; and venoconstriction, which increases venous return to the heart. These effects, in combination, restore arterial pressure to its normal set-point value. The responses occur so quickly that healthy persons are unaware of them, or may be briefly aware of an increase in heart rate.



▲ **Figure 1–10.** Responses of the baroreceptor reflex to a decrease in mean arterial pressure. P_a, arterial pressure; *TPR*, total peripheral resistance.

In Mr. Garcia, the baroreceptor reflex was severely impaired because of central damage to the sympathetic and parasympathetic nervous systems. When he stood up, his arterial pressure fell (**orthostatic hypotension**) and could not be corrected by autonomic reflexes. He felt dizzy and fainted because the sustained decrease in arterial pressure caused a decrease in cerebral blood flow.

7. Support stockings constrict the veins in the legs and prevent the venous pooling of blood that initiates an orthostatic decrease in blood pressure.

8. **Aldosterone** and its analogues increase the reabsorption of Na^+ in the kidney and thereby increase both extracellular fluid volume and blood volume. Because most of the blood volume is contained in the veins, an increase in total blood volume leads to an increase in venous blood volume and venous return, which produces an increase in cardiac output and arterial pressure.

9. Mr. Garcia's disease involved loss of both sympathetic and parasympathetic control of his organ systems. Any drug that would further antagonize either sympathetic or parasympathetic activity (e.g., inhibition of autonomic receptors on the end organs) would have exacerbated his problems. Your list might include α-adrenergic receptor antagonists (e.g., phenoxybenzamine), β-adrenergic receptor antagonists (e.g., propranolol), muscarinic receptor antagonists (e.g., atropine), and nicotinic receptor antagonists (e.g., curare). [Recall that nicotinic receptors are present on postsynaptic neurons in both sympathetic and parasympathetic ganglia.]

Key topics

- α-Adrenergic receptors
- β-Adrenergic receptors
- Aldosterone
- Autonomic nervous system
- Baroreceptor reflex
- Ejaculation
- Erection
- Micturition
- Miosis
- Muscarinic receptors
- Nicotinic receptors
- Orthostatic hypotension
- Parasympathetic nervous system
- Regulation of arterial pressure
- Sympathetic nervous system
- Thermoregulatory sweat glands

Cardiovascular Physiology

Case 9

Essential Cardiovascular Calculations

Case

This case is designed to take you through important basic calculations involving the cardiovascular system. Use the information provided in Table 2–1 to answer the questions. Part of the challenge in answering these questions will be in deciding which information you need in order to perform each calculation. Good luck!

▼ **Table 2–1.** Cardiovascular Values for Case 9

Parameter	Value
Systolic pressure (aorta)	124 mm Hg
Diastolic pressure (aorta)	82 mm Hg
R-R interval	800 msec
Left ventricular end-diastolic volume	140 ml
Left ventricular end-systolic volume	70 ml
Mean pulmonary artery pressure	15 mm Hg
Right atrial pressure	2 mm Hg
Left atrial pressure	5 mm Hg
O_2 consumption (whole body)	250 ml/min
O_2 content of systemic arterial blood	0.20 ml O_2/ml blood
O_2 content of pulmonary arterial blood	0.152 ml O_2/ml blood

R-R interval, time between R waves on the electrocardiogram.

QUESTIONS

1. Mean arterial pressure is not the simple average of systolic and diastolic pressures. Why not? How is mean arterial pressure estimated? From the information given in Table 2–1, calculate the mean arterial pressure in this case.

2. Calculate the stroke volume, cardiac output, and ejection fraction of the left ventricle.

3. Calculate cardiac output using the Fick principle.

4. What is the definition of total peripheral resistance (TPR)? What equation describes the relationship between TPR, arterial pressure, and cardiac output? What is the value of TPR in this case?

5. How is pulmonary vascular resistance calculated? What is the value of pulmonary vascular resistance in this case? Compare the calculated values for pulmonary vascular resistance and TPR, and explain any difference in the two values.

6. What is total blood flow (in ml/min) through *all* of the pulmonary capillaries?

7. What is total blood flow (in ml/min) through *all* of the systemic arteries?

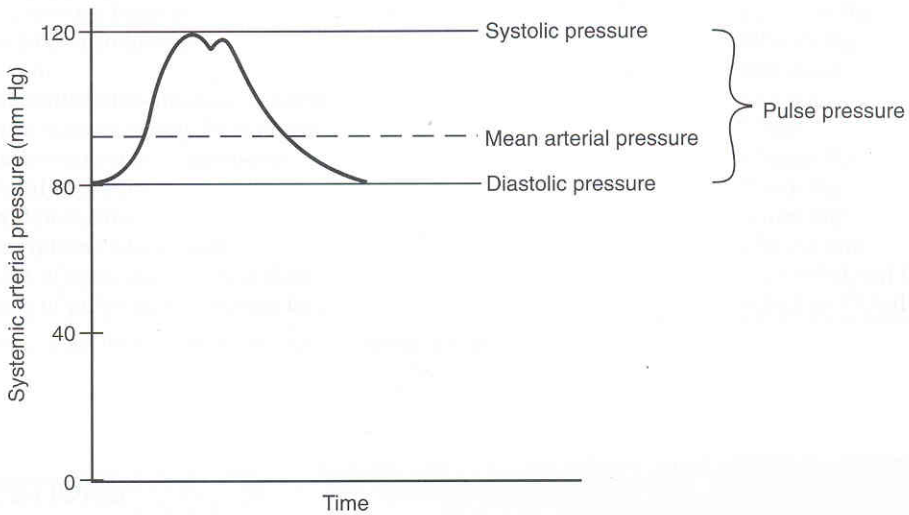
8. What information, in addition to that provided in Table 2–1, is needed to calculate the resistance of the renal vasculature?

9. If the diameter of the aorta is 20 mm, what is the velocity of aortic blood flow? Would you expect the velocity of blood flow in systemic capillaries to be higher, lower, or the same as the velocity of blood flow in the aorta?

ANSWERS AND EXPLANATIONS

1. Systemic arterial pressure is not a single value because arterial pressure varies over the course of each cardiac cycle. Its highest value is **systolic pressure,** which is measured just after blood is ejected from the left ventricle into the aorta (i.e., systole). Its lowest value is **diastolic pressure,** which is measured as blood flows from the arteries into the veins and back to the heart (i.e., diastole).

Mean arterial pressure cannot be calculated as the simple average of systolic and diastolic pressures because averaging does not take into account the fact that a greater fraction of each cardiac cycle is spent in diastole (approximately two-thirds) than in systole (approximately one-third). Thus, *mean* arterial pressure is closer to diastolic pressure than to systolic pressure. Figure 2–1 shows an arterial pressure tracing over a single cardiac cycle. The difference between systolic pressure and diastolic pressure is called **pulse pressure.**



▲ **Figure 2–1.** Systemic arterial pressure during the cardiac cycle.

Although this approach is impractical, mean arterial pressure can be determined by measuring the area under the arterial pressure curve. Alternatively, mean arterial pressure can be estimated as follows:

Mean arterial pressure = diastolic pressure + 1/3 pulse pressure

where

Diastolic pressure = lowest value for arterial pressure in a cardiac cycle
Systolic pressure = highest value for arterial pressure in a cardiac cycle
Pulse pressure = systolic pressure − diastolic pressure

Therefore, in this case:

Mean arterial pressure = 82 mm Hg + 1/3 (124 mm Hg − 82 mm Hg)
= 82 mm Hg + 1/3 (42 mm Hg)
= 82 mm Hg + 14 mm Hg
= 96 mm

2. These calculations concern the cardiac output of the left ventricle. The basic relationships are as follows:

Stroke volume = end-diastolic volume − end-systolic volume

where

Stroke volume = volume ejected by the ventricle during systole (ml)
End-diastolic volume = volume in the ventricle before ejection (ml)
End-systolic volume = volume in the ventricle after ejection (ml)

Cardiac output = stroke volume × heart rate

where

Cardiac output = volume ejected by the ventricle per minute (ml/min)
Stroke volume = volume ejected by the ventricle (ml)
Heart rate = beats/min

Ejection fraction = stroke volume/end-diastolic volume

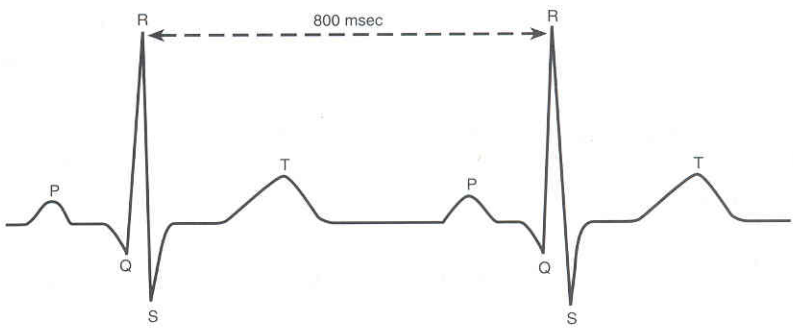
where

Ejection fraction = fraction of the end-diastolic volume ejected in one stroke

Now we can use these basic equations to calculate stroke volume, cardiac output, and ejection fraction in this case.

Stroke volume = left ventricular end-diastolic volume
− left ventricular end-systolic volume
= 140 ml − 70 ml
= 70 ml

Cardiac output is the volume ejected by the left ventricle per minute. It is calculated as the product of stroke volume (determined to be 70 ml) and heart rate. Heart rate is not given in Table 2–1, but it can be calculated from the R-R interval. "R" is the R wave on the electrocardiogram and represents electrical activation of the ventricles. The R-R interval is the time elapsed from one R wave to the next (Figure 2–2). It is also called **cycle length** (i.e., time elapsed in one cardiac cycle).



▲ **Figure 2–2.** The electrocardiogram measured from lead II. The interval between R waves is the cycle length.

Cycle length can be used to calculate heart rate as follows:

$$\begin{aligned}\text{Heart rate} &= 1/\text{cycle length}\\ &= 1/800 \text{ msec}\\ &= 1/0.8 \text{ sec}\\ &= 1.25 \text{ beats/sec}\\ &= 75 \text{ beats/min}\end{aligned}$$

$$\begin{aligned}\text{Cardiac output} &= \text{stroke volume} \times \text{heart rate}\\ &= 70 \text{ ml} \times 75 \text{ beats/min}\\ &= 5250 \text{ ml/min}\end{aligned}$$

$$\begin{aligned}\text{Ejection fraction} &= \text{stroke volume/end-diastolic volume}\\ &= 70 \text{ ml}/140 \text{ ml}\\ &= 0.5, \text{ or } 50\%\end{aligned}$$

3. As shown in Question 2, we *calculate* cardiac output as the product of stroke volume and heart rate. However, we *measure* cardiac output by the **Fick principle of conservation of mass.** The Fick principle for measuring cardiac output employs two basic assumptions: (1) Pulmonary blood flow (the cardiac output of the right ventricle) equals systemic blood flow (the cardiac output of the left ventricle) in the steady state. (2) The rate of O_2 utilization by the body is equal to the difference between the amount of O_2 leaving the lungs in pulmonary venous blood and the amount of O_2 returning to the lungs in pulmonary arterial blood. This relationship can be stated mathematically as follows:

$$\begin{aligned}O_2 \text{ consumption} = &\ \text{cardiac output} \times [O_2]_{\text{pulmonary vein}}\\ &- \text{cardiac output} \times [O_2]_{\text{pulmonary artery}}\end{aligned}$$

Rearranging to solve for cardiac output:

$$\textbf{Cardiac output} = \frac{\textbf{O}_2 \textbf{ consumption}}{[O_2]_{\text{pulmonary vein}} - [O_2]_{\text{pulmonary artery}}}$$

where

Cardiac output = cardiac output (ml/min)

O_2 consumption = O_2 consumption by the body (ml O_2/min)

$[O_2]_{\text{pulmonary vein}}$ = O_2 content of pulmonary venous blood (ml O_2/ml blood)

$[O_2]_{\text{pulmonary artery}}$ = O_2 content of pulmonary arterial blood (ml O_2/ml blood)

In this case, cardiac output can be calculated by substituting values from Table 2–1. To find the appropriate values in the table, recall that systemic arterial blood is equivalent to pulmonary venous blood.

$$\begin{aligned}\text{Cardiac output} &= \frac{250 \text{ ml/min}}{0.20 \text{ ml } O_2/\text{ml blood} - 0.152 \text{ ml } O_2/\text{ml blood}}\\ &= \frac{250 \text{ ml/min}}{0.048 \text{ ml } O_2/\text{ml blood}}\\ &= 5208 \text{ ml/min}\end{aligned}$$

Thus, the value for cardiac output measured by the Fick principle (5208 ml/min) is very close to the value of 5250 ml/min calculated as the product of stroke volume and heart rate in Question 2.

4. **TPR** is the collective resistance to blood flow that is provided by all of the blood vessels on the *systemic* side of the circulation. These blood vessels include the aorta, large and small arteries, arterioles, capillaries, venules, veins, and vena cava. Most of this resistance resides in the **arterioles.**

The fundamental equation of the cardiovascular system relates blood flow, blood pressure, and resistance. The relationship is analogous to the one that relates current (I), voltage (V), and resistance (R) in electrical circuits as expressed by **Ohm's law** ($I = \Delta V/R$). Blood flow is analogous to current flow, blood pressure is analogous to voltage, and hemodynamic resistance is analogous to electrical resistance. Thus, the equation for blood flow is:

$$\mathbf{Q = \Delta P/R}$$

or, rearranging and solving for R,

$$\mathbf{R = \Delta P/Q}$$

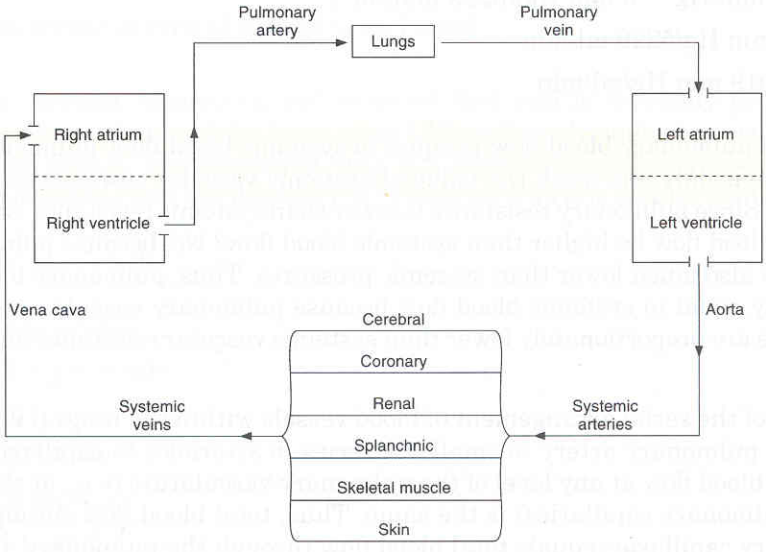
where

Q = blood flow (ml/min)

ΔP = pressure difference (mm Hg)

R = resistance (mm Hg/ml/min)

Therefore, to calculate *total* peripheral resistance (TPR), it is necessary to know the *total* blood flow through the systemic circulation (i.e., cardiac output of the left ventricle) and the pressure difference across the *entire* systemic circulation. In solving this problem, it may be helpful to visualize the organization and circuitry of the cardiovascular system (Figure 2–3).



▲ **Figure 2–3.** Circuitry of the cardiovascular system. (Reprinted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 71.)

Cardiac output was calculated by different methods in Questions 2 and 3 as 5250 ml/min and 5208 ml/min, respectively. These values are similar, and we can (arbitrarily) take the average value (5229 ml/min) to represent cardiac output. The pressure difference across the systemic circulation (ΔP) is the difference in pressure at the inflow and outflow points. Inflow pressure is aortic pressure, and outflow pressure is right atrial pressure. In Question 1, mean aortic pressure was calculated as 96 mm Hg. Right atrial pressure is given in Table 2–1 as 2 mm Hg. Thus, ΔP across the systemic circulation is 96 mm Hg − 2 mm Hg, or 94 mm Hg. Resistance (R), which represents TPR, is:

$R = \Delta P/Q$

or

TPR = (mean arterial pressure − right atrial pressure)/cardiac output

= (96 mm Hg − 2 mm Hg)/5229 ml/min

= 94 mm Hg/5229 ml/min

= 0.018 mm Hg/ml/min

5. Pulmonary vascular resistance is calculated in the same way that TPR was calculated in Question 4. We need to know the values for pulmonary blood flow (cardiac output of the right ventricle) and the pressure difference across the pulmonary circulation. To determine pulmonary blood flow, it is necessary to understand that the left and right sides of the heart operate in series (i.e., blood flows sequentially from the left heart to the right heart and back to the left heart). Thus, in the steady state, the cardiac output of the right ventricle (pulmonary blood flow) equals the cardiac output of the left ventricle, or 5229 ml/min. The pressure difference across the pulmonary circulation is inflow pressure minus outflow pressure. The inflow pressure is mean pulmonary artery pressure (15 mm Hg), and the outflow pressure is left atrial pressure (5 mm Hg). Thus, **pulmonary vascular resistance** is:

$R = \Delta P/Q$

= (mean pulmonary artery pressure − left atrial pressure)/cardiac output

= (15 mm Hg − 5 mm Hg)/5229 ml/min

= 10 mm Hg/5229 ml/min

= 0.0019 mm Hg/ml/min

Although pulmonary blood flow is equal to systemic blood flow, pulmonary vascular resistance is only one-tenth the value of systemic vascular resistances. How is this possible? Since pulmonary resistance is lower than systemic resistance, shouldn't pulmonary blood flow be higher than systemic blood flow? No, because pulmonary pressures are also much lower than systemic pressures. Thus, pulmonary blood flow can be exactly equal to systemic blood flow because pulmonary vascular resistance and pressures are proportionately lower than systemic vascular resistance and pressures.

6. Because of the serial arrangement of blood vessels within the lungs (i.e., blood flows from the pulmonary artery to smaller arteries to arterioles to capillaries to veins), the total blood flow at any level of the pulmonary vasculature (e.g., at the level of all of the pulmonary capillaries) is the same. Thus, total blood flow through *all* of the pulmonary capillaries equals total blood flow through the pulmonary artery, which is the cardiac output of the right ventricle, or 5229 ml/min.

7. This question addresses the same issue as Question 6, but in terms of the systemic circulation. Because of the serial arrangement of blood vessels in the systemic circulation (i.e., blood flows from the aorta to smaller arteries to arterioles, and so forth), the total blood flow at any level of the systemic vasculature (e.g., at the level of all of the arteries) is the same. Thus, total blood flow through *all* of the systemic arteries equals the cardiac output of the left ventricle, or 5229 ml/min.

8. The principles that were used to determine TPR (or to determine pulmonary vascular resistance) can also be used to calculate the vascular resistance of individual organs (e.g., kidney). Recall how the pressure, flow, resistance relationship was rearranged to solve for resistance: $R = \Delta P/Q$. R can also represent the resistance of the blood vessels in an individual organ (e.g., kidney), ΔP can represent the pressure difference across the organ's vasculature (e.g., for the kidney, the pressure in the renal artery minus the pressure in the renal vein), and Q can represent the organ's blood flow (e.g., renal blood flow).

   Actually, none of the information needed to calculate renal vascular resistance is available in Table 2–1 or from the previous calculations. Renal arterial pressure is close, but not exactly equal, to mean arterial pressure that was calculated for the aorta in Question 1. The mean pressure in large "downstream" arteries is slightly lower than the pressure in the aorta. (It must be lower in order for blood to flow in the right direction, i.e., from the aorta to the distal arteries.) Like the pressure in any large vein, renal venous pressure must be slightly higher than right atrial pressure. Because of the parallel arrangement of arteries off the aorta, renal blood flow is only a fraction of total systemic blood flow.

9. The **velocity of blood flow** is the rate of linear displacement of blood per unit time:

   $$\mathbf{v = Q/A}$$

   where

   v = linear velocity of blood (cm/min)

   Q = blood flow (ml/min)

   A = cross-sectional area of a blood vessel (cm^2)

   In words, velocity is proportional to blood flow and is inversely proportional to the cross-sectional area of the blood vessel. Blood flow through the aorta is total systemic blood flow, or cardiac output, which is 5229 ml/min. The cross-sectional area can be calculated from the diameter of the aorta, which is 20 mm (radius, 10 mm).

   $$v = \frac{Q}{\pi r^2}$$

   $$= \frac{5229 \text{ ml/min}}{3.14 \times (10 \text{ mm})^2}$$

   $$= \frac{5229 \text{ ml/min}}{3.14 \times 1 \text{ cm}^2}$$

   $$= \frac{5229 \text{ cm}^3\text{/min}}{3.14 \text{ cm}^2}$$

   $$= 1665 \text{ cm/min}$$

Based on the inverse relationship between velocity and radius of blood vessels, the velocity of blood flow should be lower in *all* of the capillaries than in the aorta. (Of course, a single capillary has a smaller radius than the aorta, but *all* of the capillaries have a larger collective radius and cross-sectional area than the aorta.)

Key topics

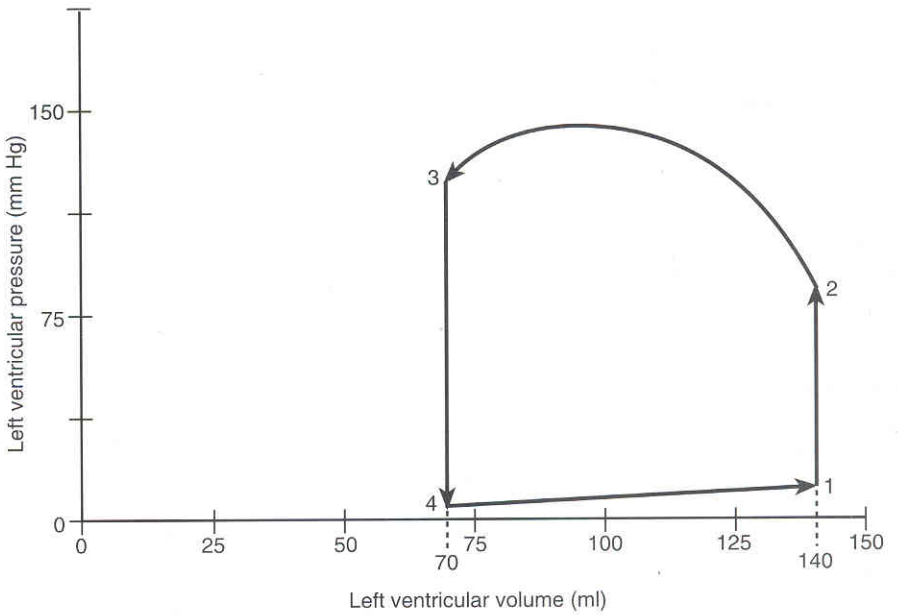
- Cardiac output
- Cycle length
- Diastolic pressure
- Ejection fraction
- Electrocardiogram (ECG)
- Fick principle of conservation of mass
- Heart rate
- Mean arterial pressure
- Pressure, blood flow, resistance relationship
- Pulmonary vascular resistance
- Pulse pressure
- R-R interval
- Stroke volume
- Systolic pressure
- Total peripheral resistance (TPR), or systemic vascular resistance
- Velocity of blood flow

Case 10

Ventricular Pressure–Volume Loops

Case

Figure 2–4 shows a pressure–volume loop for the left ventricle. This loop shows the relationship between left ventricular pressure (in mm Hg) and left ventricular volume (in ml) over a single cardiac cycle. Use Figure 2–4 to answer the following questions.



▲ **Figure 2–4.** Left ventricular pressure–volume loop. (Adapted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 86.)

QUESTIONS

1. Describe the events that occur in the four segments between numbered points on the pressure–volume loop (e.g., 1 → 2, 2 → 3). Correlate each segment with events in the cardiac cycle.

2. According to Figure 2–4, what is the value for left ventricular end-diastolic volume? What is the value for end-systolic volume?

3. What is the approximate value for stroke volume? What is the approximate value for ejection fraction?

4. Which portion, or portions, of the pressure–volume loop correspond to diastole? To systole?

5. Which portions of the pressure–volume loop are isovolumetric?

6. At which numbered point does the aortic valve open? At which numbered point does the aortic valve close? At which numbered point does the mitral valve open?

7. At which numbered point, or during which segment, would the first heart sound be heard?

8. At which numbered point, or during which segment, would the second heart sound be heard?

9. Superimpose a new pressure–volume loop to illustrate the effect of an increase in left ventricular end-diastolic volume (i.e., increased preload). What is the effect on stroke volume?

10. Superimpose a new pressure–volume loop to illustrate the effect of an increase in contractility. What is the effect on end-systolic volume? What is the effect on ejection fraction?

11. Superimpose a new pressure–volume loop to illustrate the effect of an increase in aortic pressure (i.e., increased afterload). What is the effect on end-systolic volume? What is the effect on ejection fraction?

ANSWERS AND EXPLANATIONS

1. Figure 2–4 shows a single left ventricular cycle of contraction, ejection of blood, relaxation, and filling (to begin another cycle). This figure can be used to describe the events as follows. **1 → 2 is isovolumetric contraction.** During this phase, the ventricle (which was previously filled from the atrium) is contracting. Contraction causes a steep increase in ventricular pressure. However, because the aortic valve is closed, no blood is ejected and left ventricular volume remains constant (i.e., is isovolumetric). **2 → 3 is ventricular ejection.** The ventricle is still contracting, causing ventricular pressure to increase further. The aortic valve is now open, and blood is ejected from the left ventricle, which causes ventricular volume to decrease. **3 → 4 is isovolumetric relaxation.** The left ventricle relaxes, and ventricular pressure decreases. Both the aortic and the mitral valves are closed, and ventricular volume remains constant. **4 → 1 is ventricular filling.** The left ventricle is still relaxed, but now the mitral valve is open and the ventricle is filling with blood from the atrium. Because the ventricle is relaxed, ventricular pressure increases only slightly as ventricular volume increases.

2. **End-diastolic volume** is the volume present in the ventricle after filling is complete, but before any blood is ejected into the aorta. Therefore, end-diastolic volume is present at points 1 and 2 (approximately 140 ml). **End-systolic volume** is the volume that remains in the left ventricle after ejection is complete, but before the ventricle fills again (i.e., the volume at points 3 and 4, which is approximately 70 ml).

3. **Stroke volume** is the volume ejected during systole (ventricular ejection). Thus, stroke volume is represented by the ***width* of the pressure–volume loop,** or approximately 70 ml (140 ml − 70 ml). **Ejection fraction** is stroke volume expressed as a fraction of end-diastolic volume (i.e., stroke volume/end-diastolic volume), or 70 ml/140 ml, or 0.5 (50%).

4. **Diastole** is the portion of the cardiac cycle when the ventricle is relaxed (i.e., is not contracting). Diastole corresponds to segments 3 → 4 (isovolumetric relaxation) and 4 → 1 (ventricular filling). **Systole** is the portion of the cardiac cycle when the ventricle is contracting. Thus, systole corresponds to segments 1 → 2 (isovolumetric contraction) and 2 → 3 (ventricular ejection).

5. By definition, **isovolumetric** portions of the ventricular cycle are those in which ventricular volume is constant (i.e., the ventricle is neither filling with blood nor ejecting blood). Isovolumetric segments are 1 → 2 and 3 → 4.

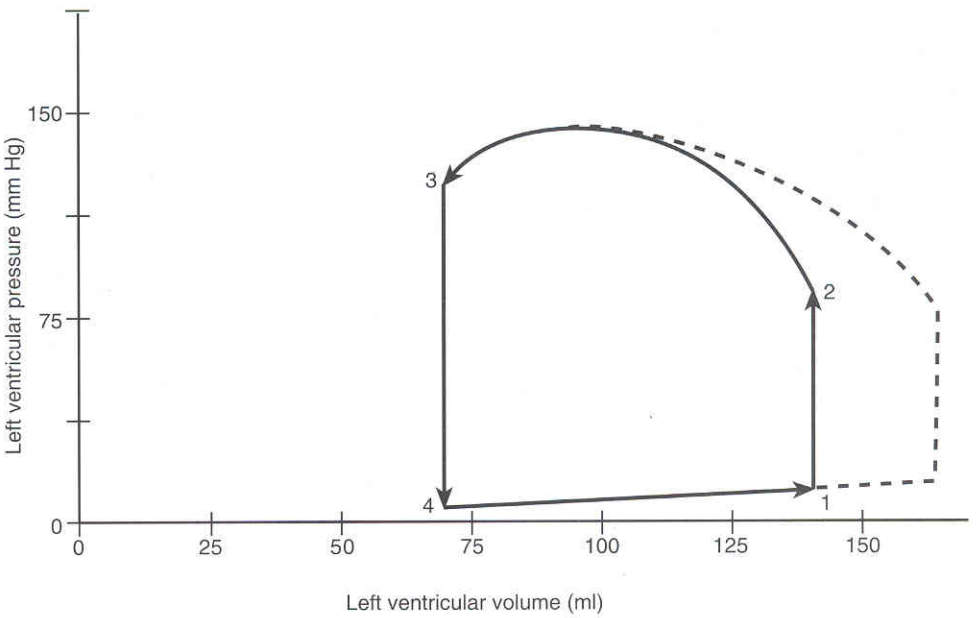
6. The **aortic valve** opens at point 2, when ventricular pressure exceeds aortic pressure. Opening of the aortic valve is followed immediately by ejection of blood and a decrease in ventricular volume. The aortic valve closes at point 3, and ejection of blood ceases. The **mitral valve** (the atrioventricular valve of the left heart) opens at point 4, and ventricular filling begins.

7. The **first heart sound** corresponds to closure of the atrioventricular valves. This

closure occurs at the end of ventricular filling and just before contraction of the ventricle. Thus, the first heart sound occurs at point 1.

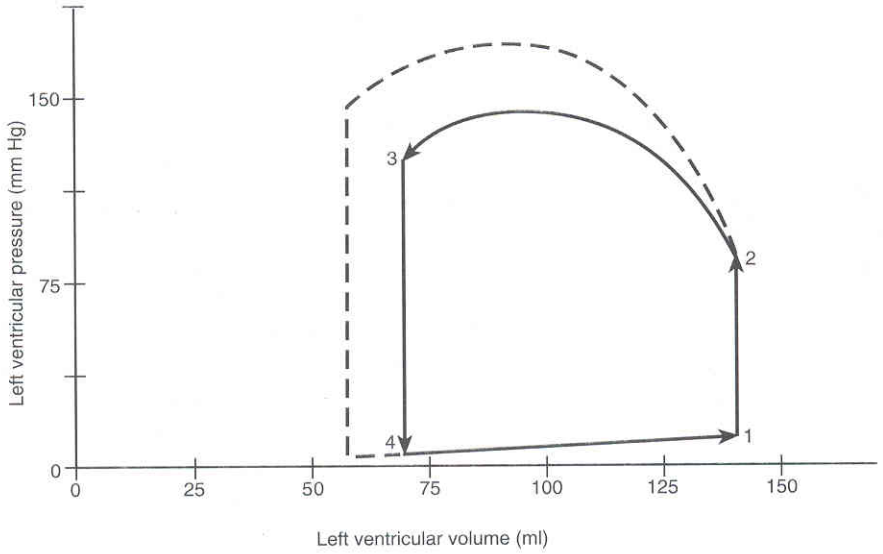
8. The **second heart sound** corresponds to closure of the aortic valve, at point 3.

9. End-diastolic volume (**preload**) is the volume of blood contained in the ventricle just before contraction. Therefore, an increase in ventricular end-diastolic volume (e.g., produced by an infusion of saline) means the ventricle has filled to a greater volume during diastole. In Figure 2–5, point 1 shifts to the right to represent the increased end-diastolic volume. The **Frank-Starling relationship** for the ventricle states that the greater the end-diastolic volume, the greater the stroke volume. Therefore, without any change in contractility, an increase in end-diastolic volume causes an increase in stroke volume, as evidenced by increased width of the pressure–volume loop.



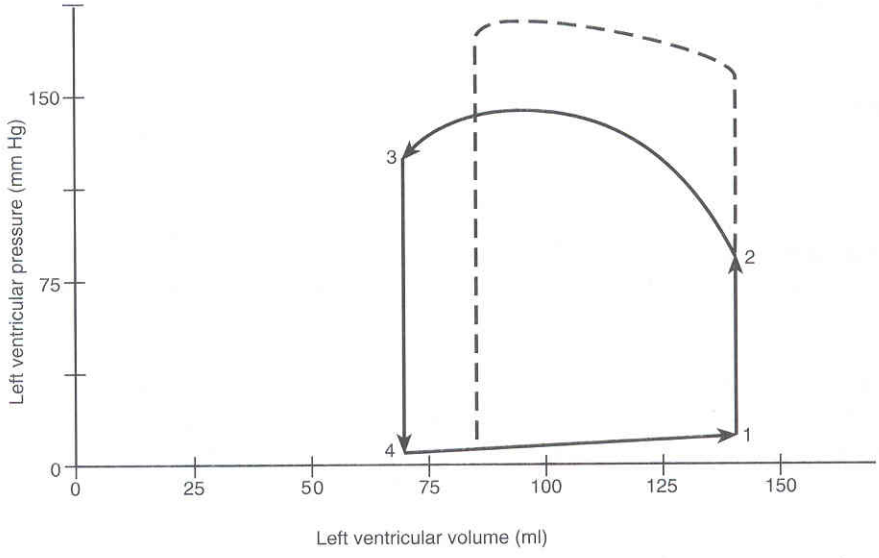
▲ **Figure 2–5.** Effect of an increase in preload on the left ventricular pressure–volume loop. (Adapted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 86.)

10. **Contractility (inotropy)** is the intrinsic ability of myocardial fibers to develop tension at a given muscle length (i.e., at a given end-diastolic volume). Contractility is directly correlated with the **intracellular Ca^{2+} concentration,** which dictates how many cross-bridges cycle and, therefore, how much tension is generated. When contractility is increased (e.g., by positive inotropic agents, such as norepinephrine or digitalis), the ventricle can develop greater tension and pressure during systole. As a result, stroke volume increases (Figure 2–6) and less blood remains in the ventricle after ejection. Therefore, end-systolic volume decreases. Because ejection fraction is stroke volume expressed as a fraction of end-diastolic volume, if stroke volume increases and end-diastolic volume is unchanged, ejection fraction must have increased.



▲ **Figure 2–6.** Effect of an increase in contractility on the left ventricular pressure–volume loop. (Adapted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 86.)

11. **Afterload** is the pressure against which the ventricles must eject blood. Afterload of the left ventricle is aortic pressure. To open the aortic valve and eject blood, left ventricular pressure must increase to a level greater than aortic pressure. Thus, if afterload increases, the left ventricle must work harder than usual to overcome this higher pressure. Figure 2–7 shows the consequences of an increase in afterload. During isovolumetric contraction (1 → 2) and ventricular ejection (2 → 3), ventricular pressure increases to a higher level than normal. Because of the increased afterload, stroke volume is compromised, more blood remains in the left ventricle after ejection, and end-systolic volume is increased. Because stroke volume decreases and end-diastolic volume is unchanged, ejection fraction must have decreased.



▲ **Figure 2–7.** Effect of an increase in afterload on the left ventricular pressure–volume loop. (Adapted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 86.)

Key topics

- Afterload
- Aortic valve
- Atrioventricular valves
- Cardiac cycle
- Contractility
- Ejection fraction
- End-diastolic volume
- End-systolic volume
- Heart sounds
- Mitral valve
- Preload
- Stroke volume
- Ventricular pressure–volume loops

Case 11

Responses to Changes in Posture

Case

Joslin Chambers is a 27-year-old assistant manager at a discount department store. One morning, she awakened from a deep sleep and realized that she was more than an hour late for work. She panicked, momentarily regretting her late-night socializing, and then jumped out of bed. Briefly, she felt light-headed and thought she might faint. She had the sensation that her heart was "racing." Had she not been so late for work, she would have returned to bed. As she walked toward the bathroom, she noticed that her light-headedness dissipated. The rest of her day was uneventful.

QUESTIONS

1. When Joslin moved rapidly from a supine (lying) position to a standing position, there was a brief, initial decrease in arterial pressure that caused her light-headedness. Describe the sequence of events that produced this transient fall in arterial pressure.

2. Why did the decrease in arterial pressure cause Joslin to feel light-headed?

3. Joslin's light-headedness was transient because a reflex was initiated that rapidly restored arterial pressure to normal. Describe the specific effects of this reflex on heart rate, myocardial contractility, total peripheral resistance (TPR), and capacitance of the veins. What receptors are involved in each of these responses?

4. How does each component of the reflex (e.g., the effect on heart rate) help to restore arterial pressure? (Hint: It may help to write the equation that relates arterial pressure, cardiac output, and TPR.)

5. In addition to the reflex correction of blood pressure, the fact that Joslin walked to the bathroom helped return her arterial pressure to normal. How did walking help?

ANSWERS AND EXPLANATIONS

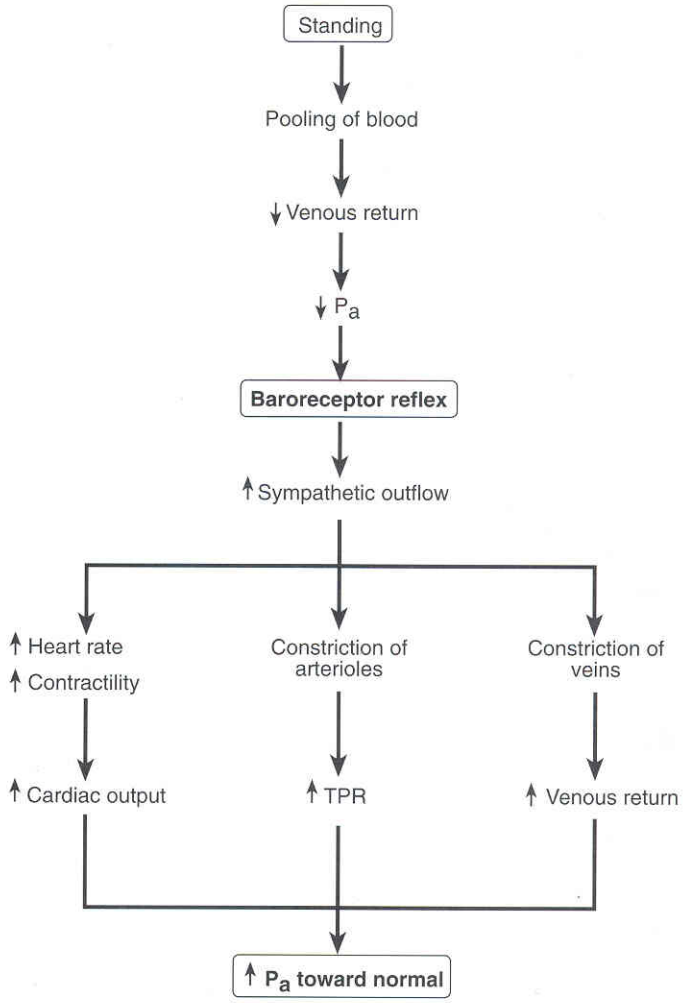
1. **Orthostatic hypotension** is the phenomenon whereby arterial pressure decreases when one stands up. When a person suddenly moves from a supine (lying) position to a standing position, blood pools in the veins of the legs. (Because the capacitance, or compliance, of the veins is high, they can hold large volumes of blood.) This pooling decreases venous return to the heart, which decreases cardiac output by the **Frank-Starling mechanism.** (The Frank-Starling mechanism describes the relationship between venous return and cardiac output. Increases in venous return lead to increases in end-diastolic volume. Up to a point, increases in end-diastolic volume lead to increases in cardiac output. Conversely, decreases in venous return lead to decreases in cardiac output.) Because arterial pressure is affected by the volume of blood in the arteries, a decrease in cardiac output (i.e., less blood is pumped into the arterial system) causes a decrease in arterial pressure.

2. When Joslin stood up quickly, she felt light-headed because a brief period of cerebral ischemia occurred as a result of the decrease in arterial pressure. The autoregulatory range for **cerebral blood flow** is 60–140 mm Hg. In other words, cerebral blood flow is maintained constant as long as arterial pressure is greater than 60 mm Hg and less than 140 mm Hg. When Joslin stood up, her arterial pressure briefly decreased below this critical autoregulatory range. As a result, cerebral blood flow decreased, and she felt light-headed.

3. Baroreceptors located in the carotid sinus and the aortic arch sensed the decrease in arterial pressure. The **baroreceptor reflex** then orchestrated a series of compensatory responses, including increased sympathetic outflow to the heart and blood vessels. There are four consequences of this increased sympathetic outflow:

   - Increased heart rate (the sensation of a racing heart), a **positive chronotropic effect** mediated by β_1-adrenergic receptors in the sinoatrial node
   - Increased contractility of the ventricles, a **positive inotropic effect** mediated by β_1-adrenergic receptors in the ventricular muscle
   - Increased **arteriolar constriction,** mediated by α_1-adrenergic receptors on vascular smooth muscle of the arterioles
   - Increased **venoconstriction,** mediated by α_1-adrenergic receptors on vascular smooth muscle of the veins

4. All of the components of the baroreceptor reflex contributed to the restoration of Joslin's arterial pressure (Figure 2–8).



▲ **Figure 2–8.** Cardiovascular responses in a person moving suddenly from a supine to a standing position. P_a, arterial pressure; *TPR*, total peripheral resistance.

These contributions can be appreciated by reviewing the relationship between arterial pressure, cardiac output, and TPR:

$$\mathbf{P_a = \text{cardiac output} \times \text{TPR}}$$

where

P_a = mean arterial pressure

Cardiac output = volume of blood ejected from the left ventricle/min

TPR = total peripheral resistance

In words, arterial pressure depends on the volume of blood pumped into the arteries from the left ventricle and the resistance of the arterioles. (It may be helpful to think of arteriolar resistance as "holding" blood on the arterial side of the circulation.)

Now, using the equation, consider how each portion of the baroreceptor reflex helped to restore Joslin's arterial pressure back to normal. The increased heart rate

and contractility combined to produce an increase in cardiac output. The increased cardiac output caused an increase in arterial pressure. The increased arteriolar constriction produced an increase in TPR, which also increased arterial pressure. Finally, venoconstriction led to decreased capacitance of the veins, which increased venous return to the heart and cardiac output (by the Frank-Starling mechanism).

5. As Joslin walked toward the bathroom, the muscular activity compressed the veins in her legs and decreased venous capacitance (i.e., the volume of blood the veins can hold). This effect, combined with sympathetic venoconstriction, increased venous return to the heart and cardiac output.

Key topics

- Arterial blood pressure (P_a)
- Autoregulation
- Baroreceptor reflex
- Carotid sinus baroreceptors
- Cardiac output
- Cerebral blood flow
- Chronotropic effects
- Contractility
- Frank-Starling mechanism
- Inotropic effects
- Orthostatic hypotension
- Parasympathetic nervous system
- Pressure, blood flow, resistance relationship
- α or α_1 Receptors
- β or β_1 Receptors
- Stroke volume
- Sympathetic nervous system

Case 12

Cardiovascular Responses to Exercise

Case

Cassandra Farias is a 34-year-old dietician at an academic medical center. She believes in the importance of a healthy lifestyle and was intrigued when the division of cardiology recruited healthy female volunteers for a study on the cardiovascular responses to exercise. Cassandra met the study criteria (i.e., 25–40 years old, no medications, normal weight for height, normal blood pressure), and she was selected for participation.

Control measurements were taken of Cassandra's blood pressure, heart rate, and arterial and venous P_{O_2}; her stroke volume was estimated. Cassandra then walked on the treadmill for 30 minutes at 3 miles per hour. Her blood pressure and heart rate were monitored continuously, and her arterial and venous P_{O_2} were measured at the end of the exercise period (Table 2–2).

▼ **Table 2–2.** Cassandra's Cardiovascular Responses to Exercise

Parameter	Control (pre-exercise)	Exercise
Systolic blood pressure	110 mm Hg	145 mm Hg
Diastolic blood pressure	70 mm Hg	70 mm Hg
Heart rate	75 beats/min	130 beats/min
Stroke volume (estimated)	80 ml	110 ml
Arterial P_{O_2}	100 mm Hg	100 mm Hg
Venous P_{O_2}	40 mm Hg	25 mm Hg

QUESTIONS

1. To set the stage for the following questions, describe the cardiovascular responses to moderate exercise, including the roles of the autonomic nervous system and local control of blood flow in skeletal muscle. What is the ultimate "purpose" of these cardiovascular responses?

2. What were Cassandra's mean arterial pressure and pulse pressure for the control and exercise periods, respectively?

3. What was her cardiac output for the control and exercise periods, respectively? Of the two factors that contribute to cardiac output (stroke volume and heart rate), which factor made the greater contribution to the increase in cardiac output that was seen when Cassandra exercised, or do these factors have equal weight?

4. What is the significance of the observed change in pulse pressure?

5. Why was systolic pressure increased during exercise? Why did diastolic pressure remain unchanged?

6. If Cassandra had been taking propranolol (a β-adrenergic antagonist), how might the responses to exercise have been different? Would her "exercise tolerance" have increased, decreased, or remained the same?

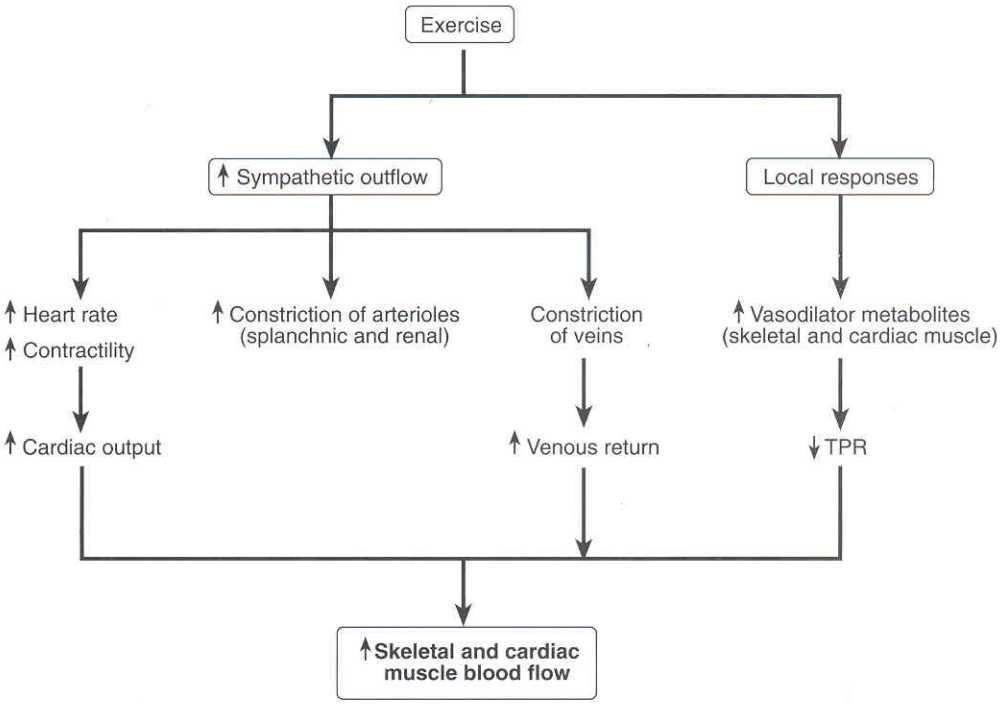
7. Early in the exercise period, Cassandra's skin was cool to the touch. However, at the peak of exercise, her skin was flushed and very warm to the touch. What mechanisms were responsible for these changes in skin color and temperature as the exercise progressed?

8. Arterial and venous P_{O_2} were measured before and after exercise. Explain why venous P_{O_2} decreased, but arterial P_{O_2} did not.

ANSWERS AND EXPLANATIONS

1. The "goal" of the cardiovascular responses to exercise is to **increase O_2 delivery** to muscles that are working harder (skeletal and cardiac muscle). The major mechanism for providing this additional O_2 is increased blood flow to the exercising skeletal muscle and the myocardium.

In principle, blood flow in an organ can be increased in two ways: (1) Total blood flow (cardiac output) can increase, which also increases blood flow to individual organs. (2) Blood flow can be redistributed so that the percentage of total flow to some organs is increased at the expense of other organs. During exercise, both of these mechanisms are utilized: cardiac output increases significantly (through increases in heart rate and stroke volume), *and* blood flow is redistributed to skeletal muscle and myocardium, so that these tissues receive a greater percentage of the (increased) cardiac output. Figure 2–9 summarizes these responses.



▲ **Figure 2–9.** Cardiovascular responses to exercise. *TPR*, total peripheral resistance.

At the initiation of exercise, muscle mechanoreceptors and chemoreceptors trigger reflexes that send afferent signals to the cerebral motor cortex. The cerebral cortex then directs responses that include **increased sympathetic outflow** to the heart and blood vessels. (1) In the heart, increased sympathetic activity, through activation of **β_1 receptors,** produces an **increase in heart rate** and an **increase in contractility.** The increase in contractility results in increased stroke volume. Together with increased heart rate, this increased stroke volume produces an increase in cardiac output. (Recall that cardiac output = stroke volume × heart rate.) (2) In addition, increased sympathetic activity, through **α_1 receptors,** produces **arteriolar**

constriction in some vascular beds (e.g., splanchnic, renal) and venoconstriction. (3) **Venoconstriction** (combined with compression of the veins by the squeezing action of skeletal muscle) increases venous return to the heart. Increased venous return is an essential component of the response to exercise; it provides the increased blood volume that is needed to produce the increase in cardiac output (**Frank-Starling mechanism**).

In addition to these central responses that are orchestrated by the sympathetic nervous system, **local responses** occur in skeletal and cardiac muscle to increase their blood flow. In skeletal muscle, as the metabolic rate increases, metabolites such as lactate, K^+, nitric oxide, and adenosine are generated. These metabolites produce vasodilation of skeletal muscle arterioles, thereby increasing local blood flow. This local vasodilation in skeletal muscle is so prominent that it is responsible for an overall ***decrease* in total peripheral resistance (TPR).** (If these local responses in skeletal muscle did not occur, TPR would have *increased* as a result of sympathetic vasoconstriction.) Local responses also dominate in the myocardium, where they are primarily mediated by adenosine and decreased P_{O_2} and cause vasodilation and increased coronary blood flow.

2. Recall the calculations of pulse pressure and mean arterial pressure from Case 9:

Pulse pressure = systolic pressure − diastolic pressure

Mean arterial pressure = diastolic pressure + 1/3 pulse pressure

During the control period, Cassandra's **pulse pressure** was *40 mm Hg* (110 mm Hg − 70 mm Hg). During exercise, her pulse pressure increased to *75 mm Hg* (145 mm Hg − 70 mm Hg). During the control period, **mean arterial pressure** was *83 mm Hg* [70 mm Hg + 1/3 (40 mm Hg)]. During the exercise period, mean arterial pressure increased to *95 mm Hg* [70 mm Hg + 1/3 (75 mm Hg)]. You may wish to add this data on pulse pressure and mean arterial pressure to the data provided in Table 2–2.

3. Cardiac output is the product of stroke volume and heart rate, as discussed in Case 9:

Cardiac output = stroke volume × heart rate

Thus, in the control period, Cassandra's cardiac output was *6 L/min* (80 ml/beat × 75 beats/min = 6000 ml/min, or 6 L/min). During exercise, her cardiac output increased dramatically to *14.3 L/min* (110 ml/beat × 130 beats/min = 14,300 ml/min, or 14.3 L/min). Again, you may wish to add these values to the data in Table 2–2.

To determine whether stroke volume or heart rate made the greater contribution to the increase in cardiac output, it is helpful to evaluate the observed changes on a percentage basis. In other words, during exercise, how much did cardiac output, stroke volume, and heart rate change as a percentage of their control values? Cardiac output increased from a control value of 6 L/min to 14.3 L/min during exercise. Thus, cardiac output increased by 8.3 L (14.3 L/min − 6 L/min = 8.3 L/min), or 138% above the control value (8.3 L/min/6 L/min = 1.38). Stroke volume increased from 80 ml/beat to 110 ml/beat, an increase of 30 ml/beat, or 38% above the control value. Heart rate increased from 75 beats/min to 130 beats/min, or 73% above the control value. Thus, the dramatic increase in cardiac output has two components, increased

stroke volume and increased heart rate, and the increase in heart rate is the more significant factor.

4. Cassandra's **pulse pressure,** the difference between systolic and diastolic pressures, increased from a control value of 40 mm Hg to 75 mm Hg during exercise. To understand what this change means, consider what the pulse pressure represents. Because of the large amount of elastic tissue in the arterial walls, they are relatively stiff and noncompliant. (Yes! Compliance is the inverse of elastance.) Therefore, during systole, when blood is rapidly ejected from the left ventricle into the systemic arteries, arterial pressure increases rapidly from its lowest value (diastolic pressure) to its highest value (systolic pressure). The magnitude of this increase in pressure (i.e., pulse pressure) depends on the volume of blood ejected from the ventricle (**stroke volume**) and the compliance of the arteries. Cassandra's pulse pressure increased during exercise because her stroke volume increased.

5. The explanation for the increase in **systolic pressure** is the same as the explanation for the increase in pulse pressure: a larger stroke volume was ejected into the arteries during systole.

   On the other hand, **diastolic pressure** was *not* increased, which may be surprising. However, think about what diastolic pressure represents: it is the pressure in the arteries while the heart is relaxed (in diastole) and blood is flowing from the arteries to the veins and back to the heart. During exercise, more blood is ejected into the arterial system during systole (i.e., cardiac output is increased), but this blood returns to the veins and eventually to the heart (i.e., venous return is also increased). You might be wondering whether diastolic pressure would actually *decrease* during exercise because of the overall decrease in TPR. In fact, the effect of the decrease in TPR is offset by the increase in stroke volume, and diastolic pressure usually remains unchanged, or may decrease slightly.

6. **Propranolol** is a β-adrenergic receptor antagonist. Propranolol blocks β_1 receptors that mediate the sympathetic increases in heart rate and contractility. Recall that these effects on heart rate and contractility were the major mechanisms underlying Cassandra's increased cardiac output. Furthermore, increased cardiac output was a major mechanism for increasing O_2 delivery during exercise. Therefore, had Cassandra been taking propranolol, her exercise tolerance would have been significantly reduced.

7. **Cutaneous blood flow** exhibits a biphasic response to exercise. Early in exercise, vasoconstriction of cutaneous arterioles occurs as a result of the activation of sympathetic α_1 receptors. Blood flow is shunted away from the skin, and the skin is cool. As exercise progresses, body temperature increases secondary to increased O_2 consumption, and sympathetic centers controlling cutaneous blood flow in the anterior hypothalamus are inhibited. This selective inhibition of sympathetic activity produces vasodilation in cutaneous arterioles. As a result, warmed blood is shunted from the body core to venous plexus near the skin surface, as evidenced by redness and warmth of the skin.

8. Cassandra's skeletal and cardiac muscle performed increased work and used more O_2 during exercise than at rest. To help meet the increased demand for O_2, her skeletal and cardiac muscles extracted more O_2 from arterial blood. As a result, the P_{O_2}

of venous blood was lower than normal; the normal P_{O_2} of venous blood is 40 mm Hg, and Cassandra's venous P_{O_2} was 25 mm Hg. (In the respiratory portion of your course, you will appreciate that this increased extraction of O_2 is accomplished by a **right shift** of the **O_2-hemoglobin dissociation curve.** Right shifts of this curve are produced by increased temperature, increased P_{CO_2}, and decreased pH, all of which are consequences of an increased metabolic rate.) Thus, in addition to increased blood flow, which delivered more O_2 to the exercising muscles, more O_2 was extracted from the blood.

Now for a puzzling question. If Cassandra's venous P_{O_2} was decreased, shouldn't her arterial P_{O_2} also have been decreased? No, not if O_2 exchange in the lungs restored the P_{O_2} of the blood to its normal arterial value of 100 mm Hg. Systemic venous blood enters the right side of the heart and is pumped to the lungs for oxygenation. In Cassandra's case, even though this venous blood had a lower P_{O_2} than normal, the diffusion of O_2 from alveolar gas was rapid enough to raise P_{O_2} to its normal arterial value (100 mm Hg). This blood then left the lungs through the pulmonary vein, entered the left side of the heart, and became systemic arterial blood. (You may be correctly thinking that people with lung diseases that interfere with O_2 diffusion might not be able to restore their arterial P_{O_2} to the normal value of 100 mm Hg, especially during exercise, when more O_2 is extracted by the exercising tissues.)

Key topics

- Adenosine
- Cardiac output
- Cutaneous blood flow
- Exercise
- Frank-Starling mechanism
- Local control of muscle blood flow
- Local metabolites
- Mean arterial pressure
- Nitric oxide
- O_2 extraction
- O_2-hemoglobin dissociation curve
- Propranolol
- Pulse pressure
- α_1 Receptors
- β_1 Receptors
- Right shift of the O_2-hemoglobin dissociation curve
- Total peripheral resistance (TPR)

Case 13

Renovascular Hypertension: The Renin-Angiotensin-Aldosterone System

Case

Stewart Hanna is a 58-year-old partner in a real estate firm. Over the years, the pressures of the job have taken their toll. Mr. Hanna has smoked two packs of filtered cigarettes a day for 40 years. He tries to watch his diet, but "required" business lunches and cocktail hours have driven his weight up to 210 lb. (He is 5 feet, 9 inches tall.) He recently separated from his wife of 35 years and is dating a much younger woman. Suddenly realizing how out of shape he had become, he made an appointment for a physical examination.

In his physician's office, Mr. Hanna's blood pressure was 180/125 (normal, 120/80). The physician heard a continuous abdominal bruit (sound). Because of Mr. Hanna's elevated blood pressure and the bruit, the physician drew a venous blood sample to determine plasma renin levels. After receiving the results, the physician ordered an additional test called a differential renal vein renin. Mr. Hanna's plasma renin activity was 10 ng/ml/hr (normal, 0.9–3.3 ng/ml/hr). His differential renal vein renin (left to right) was 1.6 (normal is 1.0).

The test results were consistent with left renal artery stenosis. Mr. Hanna was scheduled for a renal arteriogram, which showed 80% occlusion of the left renal artery as a result of severe atherosclerotic disease. A balloon angioplasty was performed immediately to clear the occlusion. Mr. Hanna's blood pressure was expected to return to normal after the procedure. He was ordered to stop smoking, follow a low-fat diet, exercise regularly, and undergo periodic physical examinations.

QUESTIONS

1. How did occlusion of Mr. Hanna's left renal artery lead to an increase in plasma renin activity?

2. How did the increase in plasma renin activity cause an elevation in Mr. Hanna's arterial blood pressure (called renovascular hypertension)?

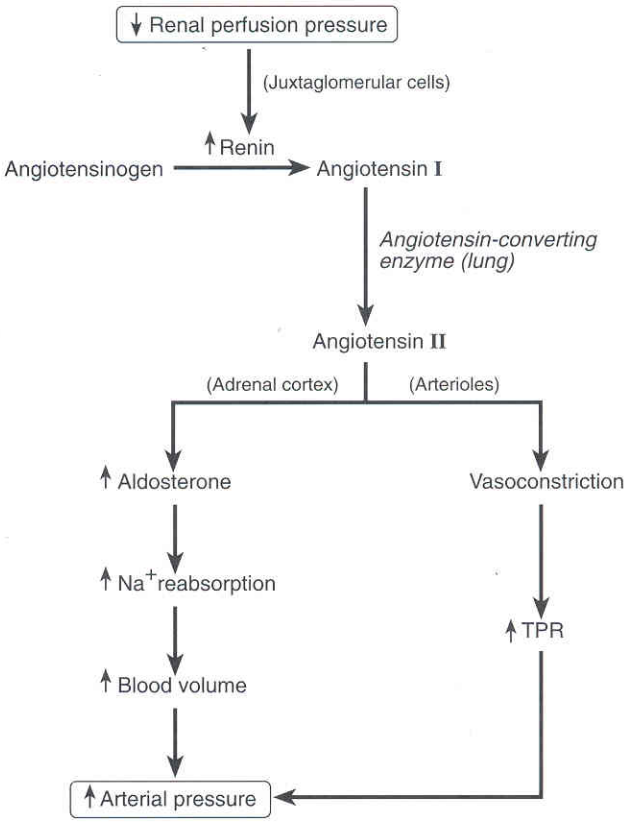
3. The differential renal vein renin measurement involves determining the renin level in venous blood from each kidney. In healthy persons, the renal vein renin level from each kidney is approximately the same; therefore, the ratio of left to right renin is 1.0. In Mr. Hanna, this ratio was elevated to 1.6. Although it is not apparent, the elevation of the ratio actually had two components: (1) his left renal vein renin was increased and (2) his right renal vein renin was decreased. Why was renin secretion increased in the left kidney and decreased in the right kidney?

4. The abdominal bruit was caused by turbulent blood flow through the stenosed (narrowed) left renal artery. Why did narrowing of the artery cause renal blood flow to become turbulent?

5. If the balloon angioplasty was not successful, Mr. Hanna would be treated with an angiotensin-converting enzyme (ACE) inhibitor (e.g., captopril). What is the rationale for using ACE inhibitors to treat hypertension caused by renal artery stenosis?

ANSWERS AND EXPLANATIONS

1. Atherosclerotic disease caused occlusion (narrowing) of Mr. Hanna's left renal artery. This occlusion caused a **decrease in renal perfusion pressure,** which then stimulated renin secretion from the kidney's **juxtaglomerular cells** (Figure 2–10). Increased quantities of renin, secreted by Mr. Hanna's left kidney, entered renal venous blood and then the systemic circulation.



▲ **Figure 2–10.** The renin-angiotensin II-aldosterone system. *TPR,* total peripheral resistance.

2. **Renin** is an enzyme that catalyzes the conversion of angiotensinogen (renin substrate) to angiotensin I. **Angiotensin I** is then converted, primarily in the lungs, to **angiotensin II,** which has several biologic actions. The first action of angiotensin II is to stimulate the synthesis and secretion of **aldosterone** by the adrenal cortex; aldosterone increases renal Na^+ reabsorption, extracellular fluid volume, and blood volume. The second action of angiotensin II is to cause vasoconstriction of arterioles; this vasoconstriction increases total peripheral resistance (TPR). In Mr. Hanna, the increase in blood volume (which increased venous return and cardiac output) combined with the increase in TPR to produce an increase in his arterial pressure. (Recall from Case 9 that P_a = cardiac output × TPR.)

Mr. Hanna had **renovascular hypertension,** in which his left kidney incorrectly sensed low arterial pressure. Because his left renal artery was stenosed, there

was a decrease in left renal perfusion pressure that activated the renin-angiotensin II-aldosterone system and produced an increase in arterial pressure above normal.

3. In the question, you were told that the ratio of left to right renin was elevated for two reasons: (1) increased renin secretion by the left kidney and (2) decreased renin secretion by the right kidney.

   Based on the earlier discussion, it is relatively easy to state why left renal renin secretion was increased: narrowing of the *left* renal artery led to decreased *left* renal perfusion pressure and increased *left* renal renin secretion.

   But how can we explain *decreased* renin secretion by the right kidney? The answer lies in the response of the normal right kidney to the increased arterial pressure (that resulted from stenosis of the left renal artery). The right kidney "saw" increased arterial pressure, and responded appropriately by decreasing its renin secretion.

4. Narrowing of the left renal artery resulted in **turbulent blood flow,** which made a sound called a **bruit.** The probability of turbulence is given by **Reynold's number:**

$$\textbf{Reynold's number} = \frac{\rho\, d\, v}{\eta}$$

   where

   ρ = density of blood

   d = diameter of the blood vessel

   v = velocity of blood flow

   η = viscosity of blood

   The higher the Reynold's number, the higher the probably of turbulent blood flow. In general, a Reynold's number greater than 2000 predicts turbulence. Initially, the relationship between blood vessel size and turbulence is puzzling. Diameter (d) is in the numerator. If a blood vessel narrows and its diameter decreases, shouldn't Reynold's number also decrease, making turbulence *less* likely? What is "hidden" in the Reynold's number equation is the relationship between velocity of blood flow and radius of the blood vessel. Recall the equation for **velocity of blood flow** from Case 9:

   $v = Q/A$

   where v is velocity, Q is blood flow, and A is area, or πr^2. Thus, velocity, which appears in the numerator of the Reynold's number equation, is *inversely correlated* with radius to the second power (r^2). Diameter, which also appears in the numerator, is *directly correlated* with radius to the first power. In other words, because of the greater second-power dependence on velocity, Reynold's number increases as vessel radius decreases.

5. The reason why angiotensin-converting enzyme **(ACE) inhibitors** successfully lower arterial pressure in renovascular hypertension should be evident from the etiology of the elevated blood pressure. In Mr. Hanna's case, unilateral renal artery stenosis led to increased plasma renin activity, which led to increased levels of an-

giotensin II. Angiotensin II caused the increase in arterial pressure, both directly, by vasoconstriction, and indirectly, through the actions of aldosterone. Blocking the production of angiotensin II by inhibiting ACE activity interrupts this sequence of events.

Key topics

- Aldosterone
- Angiotensin II
- Angiotensin-converting enzyme (ACE)
- ACE inhibitors
- Arterial blood pressure
- Bruit
- Captopril
- Plasma renin activity
- Renin-angiotensin II-aldosterone system
- Renovascular hypertension
- Reynold's number
- Turbulent blood flow
- Velocity of blood flow

Case 14

Hypovolemic Shock: Regulation of Blood Pressure

Case

Mavis Byrne is a 78-year-old widow who was brought to the emergency room one evening by her sister. Early in the day, Mrs. Byrne had seen bright red blood in her stool, which she attributed to hemorrhoids. She continued with her daily activities: she cleaned her house in the morning, had lunch with friends, and volunteered in the afternoon as a "hugger" in the newborn intensive care unit. However, the bleeding continued all day, and by dinnertime, she could no longer ignore it. Mrs. Byrne does not smoke or drink alcoholic beverages. She takes aspirin, as needed, for arthritis, sometimes up to 10 tablets daily.

In the emergency room, Mrs. Byrne was light-headed, pale, cold, and very anxious. Her hematocrit was 29% (normal for women, 36%–46%). Table 2–3 shows her blood pressure and heart rate in the lying (supine) and upright (standing) positions.

▼ **Table 2–3.** Mrs. Byrne's Blood Pressure and Heart Rate

Parameter	Lying down (supine)	Upright (standing)
Blood pressure	90/60	75/45
Heart rate	105 beats/min	135 beats/min

An infusion of normal saline was started, and a blood sample was drawn to be typed and cross-matched to prepare for a blood transfusion. A colonoscopy showed that the bleeding came from herniations in the colonic wall, called diverticula. (When arteries in the colon wall rupture, bleeding can be quite vigorous.) By the time of the colonoscopy, the bleeding had stopped spontaneously. Because of the quantity of blood lost, Mrs. Byrne received two units of whole blood and was admitted for observation. The physicians were prepared to insert a bladder catheter to allow continuous monitoring of urine output. However, by the next morning, her normal color had returned, she was no longer light-headed, and her blood pressure, both lying and standing, had returned to normal. No additional treatment or monitoring was needed. Mrs. Byrne was discharged to the care of her sister and advised to "take it easy."

QUESTIONS

1. What is the definition of circulatory shock? What are the major causes?

2. After the gastrointestinal blood loss, what sequence of events led to Mrs. Byrne's decreased arterial pressure?

3. Why was Mrs. Byrne's arterial pressure lower in the upright position than in the lying (supine) position?

4. Mrs. Byrne's heart rate was elevated (105 beats/min) when she was supine. Why? Why was her heart rate even more elevated (135 beats/min) when she was upright?

5. If central venous pressure and pulmonary capillary wedge pressure had been measured, would you expect their values to have been increased, decreased, or the same as in a healthy person?

6. What is hematocrit? Why was Mrs. Byrne's hematocrit decreased, and why was this decrease potentially dangerous?

7. Why was her skin pale and cold?

8. If Mrs. Byrne's urinary Na^+ excretion had been measured, would you expect it to be higher, lower, or the same as that of a healthy person? Why?

9. How was the saline infusion expected to help her condition?

10. Why did the physicians consider monitoring her urine output? How do prostaglandins "protect" renal blood flow after a hemorrhage? In this regard, why was it dangerous that Mrs. Byrne had been taking aspirin?

11. Had her blood loss been more severe, Mrs. Byrne might have received a low dose of dopamine, which has selective actions in various vascular beds. In cerebral, cardiac, renal, and mesenteric vascular beds, dopamine is a vasodilator; in muscle and cutaneous vascular beds, dopamine is a vasoconstrictor. Why is low-dose dopamine helpful in the treatment of hypovolemic shock?

ANSWERS AND EXPLANATIONS

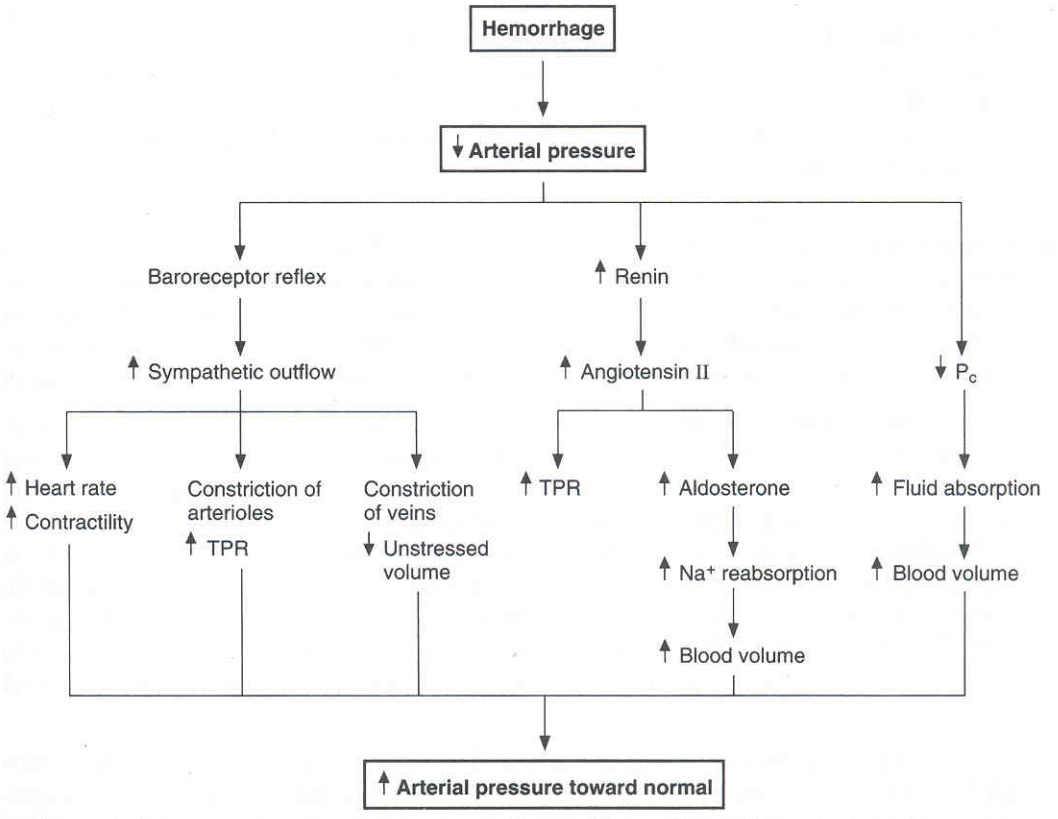
1. **Shock** (or circulatory shock) is a condition in which decreased blood flow causes decreased tissue perfusion and O_2 delivery. Untreated, shock can lead to impaired tissue and cellular metabolism and, ultimately, death.

   In categorizing the causes of shock, it is helpful to consider the components of the cardiovascular system that determine blood flow to the tissues: the heart (the pump), the blood vessels, and the volume of blood in the system. Shock can be caused by a failure of, or deficit in, any of these components. **Hypovolemic shock** occurs when circulating blood volume is decreased because of loss of whole blood (hemorrhagic shock), loss of plasma volume (e.g., burn), or loss of fluid and electrolytes (e.g., vomiting, diarrhea). **Cardiogenic shock** is caused by myocardial impairment (e.g., myocardial infarction, congestive heart failure). **Mechanical obstruction to blood flow** can occur anywhere in the circulatory system and cause a local decrease in blood flow. **Neurogenic shock** (e.g., deep general anesthesia, spinal anesthesia, spinal cord injury) involves loss of vasomotor tone, which leads to venous pooling of blood. **Septic or anaphylactic shock** involves increased filtration across capillary walls, which leads to decreased circulating blood volume.

2. Mrs. Byrne had a gastrointestinal hemorrhage and lost a significant volume of whole blood. How did this blood loss lead to decreased arterial pressure? Although it is tempting to picture blood pouring out of the arteries as the direct cause of her decreased arterial pressure, this explanation is an oversimplification. A number of intervening steps are involved. Recall that because the capacitance of the veins is high, most of the blood volume is contained in the veins, not in the arteries. Therefore, when a hemorrhage occurs, most of the blood volume that is lost comes from the veins. A decrease in venous volume leads to a decrease in venous return to the heart and a decrease in end-diastolic volume (preload). A decrease in end-diastolic volume leads to a decrease in cardiac output by the **Frank-Starling mechanism** (the length–tension relationship for the ventricles). A decrease in cardiac output leads to a decrease in arterial pressure, as expressed by the familiar relationship: Arterial pressure = cardiac output × total peripheral resistance (symbolically, P_a = cardiac output × TPR). Thus, after blood loss, the fundamental problem is decreased venous volume and venous return, leading to decreased cardiac output. In textbooks, you will see references to **"filling pressure,"** "venous filling pressure," or "cardiac filling pressure." All of these terms refer to the relationships between venous volume, venous return, cardiac output, and (ultimately) arterial pressure.

3. Mrs. Byrne's arterial pressure was lower in the upright position than in the supine position (**orthostatic hypotension**) because when she was upright, blood pooled in the veins of her legs and her venous return was further compromised. As a result, end-diastolic volume was further reduced, which led to further reductions in cardiac output and arterial pressure.

4. Asking why Mrs. Byrne's heart rate was elevated brings us to the larger issues of **compensatory responses to hemorrhage.** Essentially, decreased arterial pressure triggers several compensatory mechanisms that attempt to restore blood pressure to normal (Figure 2–11).



▲ **Figure 2–11.** Cardiovascular responses to hemorrhage. P_c, capillary hydrostatic pressure; *TPR,* total peripheral resistance. (Reprinted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 108.)

Two major mechanisms are activated in response to decreased arterial pressure: (1) the baroreceptor reflex and (2) the renin-angiotensin II-aldosterone system (discussed in Question 8).

In the **baroreceptor reflex,** sympathetic outflow to the heart and blood vessels is increased. As a result, heart rate and contractility increase and cause an increase in cardiac output. There is arteriolar constriction, which increases TPR, and there is venoconstriction, which increases venous return. Looking once again at the equation for arterial pressure (P_a = cardiac output × TPR), you can appreciate how each of these changes works to restore arterial pressure toward normal.

Mrs. Byrne's heart rate was more elevated in the upright position than in the supine position because her arterial blood pressure was lower when she was upright (venous pooling). Therefore, the baroreceptor mechanism was more strongly stimulated, and sympathetic stimulation of the heart and blood vessels (including the increase in heart rate) was exaggerated.

5. **Central venous pressure** is measured in the vena cava. Its value is related to the volume of blood in the veins and is approximately equal to right atrial pressure. **Pulmonary capillary wedge pressure** is measured by advancing a catheter through the pulmonary artery until it "wedges" in the artery's smallest branch. At that point, the catheter senses pulmonary capillary pressure, which is nearly equal to left atrial pressure.

Thus, central venous pressure estimates right atrial pressure, and pulmonary capillary wedge pressure estimates left atrial pressure. The values reflect end-diastolic volume, or preload, of the right and left ventricles, respectively. Had they been measured, Mrs. Byrne's central venous pressure and pulmonary capillary wedge pressure both would have been *decreased* because of the loss of blood volume from the venous side of the circulation.

6. **Hematocrit** is the fraction (or percentage) of blood volume occupied by red blood cells; the remaining fraction of whole blood is plasma, which is mostly water. A decrease in hematocrit can be caused by any number of factors, including blood loss, decreased red blood cell production, increased red blood cell destruction, or an increase in plasma volume without an accompanying increase in red blood cell volume.

   In Mrs. Byrne's case, the decreased hematocrit was probably secondary to hemorrhage of whole blood. But, wait a minute! You may be asking: If *whole* blood was lost from the gastrointestinal tract, why would hematocrit be changed (reasoning that red blood cells and plasma were lost proportionately)? In the first hours after hemorrhage, it is true that hematocrit is unchanged. However, as plasma volume is restored [as a result of increased aldosterone levels (see the answer to Question 8), increased capillary absorption of fluid, and the infusion of saline], plasma volume increases, but red blood cell volume does not. (It takes about 7 days for a stem cell to become a mature red blood cell.) Therefore, Mrs. Byrne's hematocrit was decreased by *dilution.*

   A decrease in hematocrit is dangerous because red blood cells contain **hemoglobin,** the O_2-carrying protein of blood. Thus, after a hemorrhage, there are two potentially lethal consequences for **O_2 delivery** to the tissues: the decrease in blood flow to the tissues (i.e., decreased cardiac output) and the decreased O_2-carrying capacity of the blood (decreased hematocrit).

7. Mrs. Byrne's pale, cold skin is typical of the response to hemorrhage, reflecting vasoconstriction of cutaneous arterioles. As the baroreceptor reflex was initiated in response to decreased arterial pressure (see Question 4), sympathetic vasoconstriction of arterioles occurred in many vascular beds, including the skin. Cutaneous vasoconstriction particularly makes sense as it allows the body to increase arterial pressure and redirect blood flow to more vital organs, (e.g., brain, heart).

8. If **urinary Na^+ excretion** had been measured, it likely would have been *decreased.* The reason for this decreased Na^+ excretion is activation of the **renin-angiotensin II-aldosterone** system in response to decreased arterial pressure. Increased levels of **aldosterone** cause increased Na^+ reabsorption in the late distal tubule and collecting duct of the kidney (i.e., decreased Na^+ excretion). This mechanism is designed to increase the amount of Na^+ in extracellular fluid, which increases extracellular fluid volume and blood volume. Increased blood volume leads to increased venous return, increased cardiac output, and ultimately, increased arterial pressure.

9. In an attempt to restore venous return and cardiac output, Mrs. Byrne received an infusion of saline to increase her extracellular fluid volume and blood volume. The saline infusion accomplished a result similar to the body's endogenous aldosterone, only faster.

10. A critical element in the response to hemorrhage, and one that may determine the outcome for the patient, is the "balancing act" between vasoconstriction in some organs (e.g., kidney) and maintaining blood flow in those organs. Increased sympathetic activity and increased angiotensin II both produce vasoconstriction and an increase in TPR, which is important to the body's attempt to restore arterial pressure (recall that P_a = cardiac output × TPR). However, vasoconstriction, by increasing resistance, decreases blood flow in the involved organs.

Of particular note is the kidney, where both sympathetic activity and angiotensin II cause arteriolar vasoconstriction. If unopposed, this vasoconstriction can compromise **renal blood flow,** producing renal failure and even death. Thus, had Mrs. Byrne not recovered so quickly, it would have been important to monitor her urine output as an indicator of renal perfusion and renal function.

Notice the word "unopposed" in the previous paragraph. Perhaps this word led you to question whether there are endogenous "modulators" of the vasoconstricting effects of sympathetic activity and angiotensin II in the kidneys. Yes, there are! **Prostaglandins** serve this modulatory role. Both sympathetic activity and angiotensin II cause increased local production of prostaglandin E_2 and prostaglandin I_2, which are renal vasodilators. Thus, the vasoconstrictive effects of sympathetic activity and angiotensin II are offset by the vasodilatory effects of endogenous prostaglandins. Renal blood flow is thereby protected and maintained in high vasoconstrictor states, such as hemorrhage.

The confounding and potentially harmful issue with Mrs. Byrne was her use of large amounts of aspirin for her arthritis. Aspirin, a **nonsteroidal anti-inflammatory drug (NSAID),** is a cyclooxygenase inhibitor that blocks prostaglandin synthesis. Therefore, Mrs. Byrne was at risk for developing renal failure if her ingestion of aspirin prevented the protective, vasodilatory effects of prostaglandins.

11. Mrs. Byrne's physicians were prepared to administer a low dose of **dopamine** if her blood pressure and blood flow (as reflected in the color returning to her skin) had not been corrected. Dopamine, a precursor of norepinephrine, has its own vasoactive properties, as explained in the question. Low doses of dopamine selectively dilate arterioles in critical organs (i.e., heart, brain, kidney) and selectively constrict arterioles in less critical organs (e.g., skeletal muscle, skin), thus redirecting blood flow where it is most needed. In particular, the kidneys, which might otherwise be vasoconstricted as a result of increased sympathetic activity and angiotensin II, may be spared by the vasodilatory actions of dopamine.

Key topics

- Aldosterone
- Anaphylactic shock
- Arterial pressure, regulation
- Baroreceptor reflex
- Cardiac filling pressure, or filling pressure
- Cardiogenic shock
- Central venous pressure
- Dopamine
- End-diastolic volume
- Frank-Starling mechanism
- Glomerular filtration rate (GFR)
- Hematocrit
- Hemoglobin
- Hemorrhage
- Hypovolemic shock
- Neurogenic shock
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- O_2 delivery
- Orthostatic fall in arterial pressure (orthostasis)
- Prostaglandins
- Pulmonary capillary wedge pressure
- Renal blood flow
- Renin-angiotensin II-aldosterone system
- Septic shock
- Shock, or circulatory shock

Case 15

Primary Pulmonary Hypertension: Right Ventricular Failure

Case

At the time of her death, Celia Lukas was a 38-year-old homemaker and mother of three children, 15, 14, and 12 years of age. She had an associate's degree in computer programming from a community college, but had not worked outside the home since the birth of her first child. Keeping house and driving the children to activities kept her very busy. To stay in shape, she took aerobics classes at the local community center. The first sign that Celia was ill was vague: she fatigued easily. However, within 6 months, Celia was short of breath (dyspnea), both at rest and when she exercised, and she had swelling in her legs and feet. She made an appointment to see her physician.

On physical examination, Celia's jugular veins were distended, her liver was enlarged (hepatomegaly), and she had ascites in her peritoneal cavity and edema in her legs. A fourth heart sound was audible over her right ventricle. The physician was very concerned and immediately scheduled Celia for a chest x-ray, an electrocardiogram (ECG), and a cardiac catheterization.

The chest x-ray showed enlargement of the right ventricle and prominent pulmonary arteries. The ECG findings were consistent with right ventricular hypertrophy. The results of cardiac catheterization are shown in Table 2–4.

▼ **Table 2–4.** Results of Celia's Cardiac Catheterization

Pressure	Value
Mean pulmonary artery pressure	35 mm Hg (normal, 15 mm Hg)
Right ventricular pressure	Increased
Right atrial pressure	Increased
Pulmonary capillary wedge pressure	Normal

Consulting physicians in cardiology and pulmonology concluded that Celia had primary pulmonary hypertension, a rare type of pulmonary hypertension that is caused by diffuse pathologic changes in the pulmonary arteries. These abnormalities lead to increased pulmonary vascular resistance and pulmonary hypertension, which causes right ventricular failure (cor pulmonale). Celia was treated with vasodilator drugs, but they were not effective. Her name was added to a list of patients awaiting a heart–lung transplant. However, she died of right heart failure before a transplant could be performed.

QUESTIONS

1. Why did increased pulmonary vascular resistance cause an increase in pulmonary artery pressure (pulmonary hypertension)?

2. What values are needed to calculate pulmonary vascular resistance?

3. Discuss the concept of "afterload" of the ventricles. What is the afterload of the left ventricle? What is the afterload of the right ventricle? What is the effect of increased afterload on stroke volume, cardiac output, ejection fraction, and end-systolic volume? How did Celia's increased pulmonary artery pressure lead to right ventricular failure?

4. In the context of Celia's right ventricular failure, explain the data from the cardiac catheterization.

5. Why does right ventricular failure cause right ventricular hypertrophy? (Hint: Use the law of Laplace to answer this question.)

6. Increased systemic venous pressure and jugular vein distension are the sine qua non (defining characteristics) of right ventricular failure. Why were Celia's jugular veins distended?

7. During what portion of the cardiac cycle is the fourth heart sound heard? What is the meaning of an audible fourth heart sound?

8. Why did right ventricular failure lead to edema on the systemic side of the circulation (e.g., ascites, edema in the legs)? Discuss the Starling forces involved. Would you expect pulmonary edema to be present in right ventricular failure?

9. Celia very much wanted to attend a family reunion in Denver. Her physicians told her that the trip was *absolutely contraindicated* because of Denver's high altitude. Why is ascent to high altitude so dangerous in a person with pulmonary hypertension? (Knowledge of pulmonary physiology is necessary to answer this question.)

10. The physician hoped that vasodilator drugs would improve Celia's condition. What was the physician's reasoning?

ANSWERS AND EXPLANATIONS

1. To explain why **increased pulmonary vascular resistance** (caused by intrinsic pathology of the small pulmonary arteries) led to increased pulmonary artery pressure, it is necessary to think about the relationship between pressure, flow, and resistance. Recall this relationship from Case 9: ΔP = blood flow × resistance. Mathematically, it is easy to see that if blood flow (in this case, pulmonary blood flow) is constant and resistance of the blood vessels increases, then ΔP, the pressure difference between the pulmonary artery and the pulmonary vein, must increase. ΔP could increase because pressure in the pulmonary artery increases *or* because pressure in the pulmonary vein decreases. (Note, however, that a decrease in pulmonary vein pressure would have little impact on ΔP because its value is normally very low.)

   In Celia, ΔP increased because her pulmonary arterial pressure increased. As pulmonary vascular resistance increased, resistance to blood flow increased, and blood "backed up" proximal to the pulmonary microcirculation into the pulmonary arteries. Increased blood volume in the pulmonary arteries caused increased pressure.

2. **Pulmonary vascular resistance** is calculated by rearranging the equation for the pressure, flow, resistance relationship. ΔP = blood flow × resistance; thus, resistance = ΔP/blood flow. ΔP is the pressure difference between the pulmonary artery and the pulmonary vein. Pulmonary blood flow is equal to the cardiac output of the right ventricle, which in the steady state, is equal to the cardiac output of the left ventricle. Thus, the values needed to calculate pulmonary vascular resistance are pulmonary artery pressure, pulmonary vein pressure (or left atrial pressure), and cardiac output.

3. Afterload of the ventricles is the pressure against which the ventricles must eject blood. **Afterload of the left ventricle** is aortic pressure. **Afterload of the right ventricle** is pulmonary artery pressure. For blood to be ejected during systole, left ventricular pressure must increase above aortic pressure, and right ventricular pressure must increase above pulmonary artery pressure.

   Celia's increased pulmonary artery pressure had a devastating effect on the function of her right ventricle. Much more work was required to develop the pressure required to open the pulmonic valve and eject blood into the pulmonary artery. As a result, right ventricular stroke volume, cardiac output, and ejection fraction were decreased. Right ventricular end-systolic volume was increased, as blood that should have been ejected into the pulmonary artery remained in the right ventricle. (Celia had **cor pulmonale,** or right ventricular failure secondary to pulmonary hypertension.)

4. Celia's **cardiac catheterization** showed that her pulmonary artery pressure was increased, her right ventricular pressure and right atrial pressure were increased, and her pulmonary capillary wedge pressure was normal. The increased pulmonary artery pressure (the cause of Celia's right ventricular failure) has already been discussed: pulmonary artery pressure increased secondary to increased pulmonary vascular resistance. Right ventricular pressure increased because more blood than usual remained in the ventricle after systolic ejection. As right ventricular pressure increased, it was more difficult for blood to move from the right atrium to the right ventricle; as a result, right atrial volume and pressure also increased. Pulmonary capillary wedge pressure (*left* atrial pressure) was normal, suggesting that there was no failure on the left side of the heart.

5. Right ventricular failure led to **right ventricular hypertrophy** (evident from Celia's chest x-ray and ECG) because her right ventricle was required to perform increased work against an increased afterload. The right ventricular wall thickens (hypertrophies) as an adaptive mechanism for performing more work. This adaptive response is explained by the **law of Laplace** for a sphere (a sphere being the approximate shape of the heart):

$$P = \frac{2\,H\,T}{r}$$

where

P = ventricular pressure

H = ventricular wall thickness (height)

T = wall tension

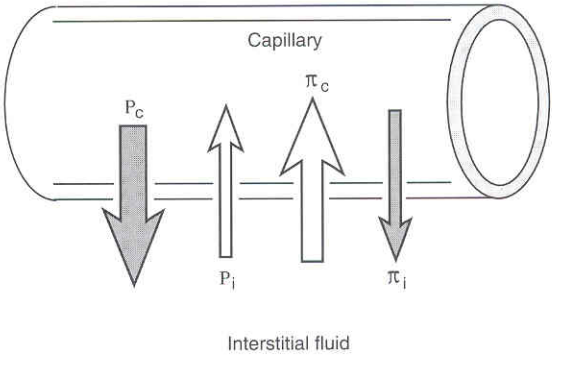
r = radius of the ventricle

Thus, ventricular pressure correlates directly with developed wall tension and wall thickness, and inversely with radius. The thicker the ventricular wall, the greater the pressure that can be developed at a given tension. Celia's right ventricle hypertrophied adaptively so that it could develop the higher pressures required to eject blood against the increased pulmonary artery pressure.

6. Celia's jugular veins were distended with blood because right ventricular failure caused blood to back up into the right ventricle, and then into the right atrium and the systemic veins.

7. A **fourth heart sound** is not normally audible in adults. However, it may occur in **ventricular hypertrophy,** where ventricular compliance is decreased. During filling of a less compliant ventricle, blood flow produces noise (the fourth heart sound). Thus, when it is present, the fourth heart sound is heard during atrial systole.

8. As already explained, right ventricular failure caused blood to back up into the systemic veins, which increased systemic venous pressure. The **Starling forces** that determine fluid movement across capillary walls can be used to explain why edema would form on the systemic side of the circulation (e.g., ascites, edema in the legs) when systemic venous pressure is increased (Figure 2–12).



▲ **Figure 2–12.** Starling pressures across the capillary wall. P_c, capillary hydrostatic pressure; P_i, interstitial hydrostatic pressure; π_c, capillary oncotic pressure; π_i, interstitial oncotic pressure.

There are four Starling pressures (or forces) across the capillary wall: capillary hydrostatic pressure (P_c), capillary oncotic pressure (π_c), interstitial hydrostatic pressure (P_i), and interstitial oncotic pressure (π_i). As shown in Figure 2–12, P_c and π_i favor filtration of fluid out of the capillary, and π_c and P_i favor absorption of fluid into the capillary. In most capillary beds, the Starling pressures are such that there is a small net filtration of fluid that is returned to the circulation by the lymphatics.

Edema occurs when filtration of fluid increases and exceeds the capacity of the lymphatics to return it to the circulation. The question, then, is why there was increased filtration of fluid in Celia's case (assuming that her lymphatic function was normal). The answer lies in her increased systemic venous pressure, which caused an increase in capillary hydrostatic pressure (P_c). Increases in P_c *favor* filtration.

Pulmonary edema would *not* be expected to occur in right ventricular failure. Pulmonary edema occurs in *left* ventricular failure, where blood backs up into the left atrium and pulmonary veins. An increase in pulmonary venous pressure then leads to increased pulmonary capillary hydrostatic pressure and increased filtration of fluid into the pulmonary interstitium. Celia's left atrial pressure (estimated by pulmonary capillary wedge pressure) was normal, suggesting that she did not have left ventricular failure; thus, pulmonary venous pressure is not expected to have been elevated and pulmonary edema is not expected to have occurred.

9. At **high altitude,** barometric pressure is decreased, resulting in decreased partial pressure of atmospheric gases, such as O_2. If Celia had traveled to Denver, she would have breathed air with a lower P_{O_2} than the air at sea level. Such **alveolar hypoxia** produces vasoconstriction in the pulmonary circulation (normally a protective mechanism in the lungs that diverts blood flow away from hypoxic areas). Celia's pulmonary vascular resistance was already abnormally elevated as a result of her intrinsic disease. So-called **hypoxic vasoconstriction** at high altitude would have further increased her pulmonary vascular resistance and pulmonary arterial pressure, and further increased the afterload on her right ventricle. (Incidentally, hypoxic vasoconstriction is unique to the lungs. Other vascular beds *dilate* in response to hypoxia.)

10. The physician hoped that vasodilator drugs would dilate pulmonary arterioles and decrease Celia's pulmonary vascular resistance and pulmonary arterial pressure, thus lowering the afterload of the right ventricle.

Key topics

- Afterload
- Ascites
- Cardiac catheterization
- Cor pulmonale
- Edema
- Fourth heart sound
- High altitude
- Hypoxic vasoconstriction
- Law of Laplace
- Lymph, or lymphatic, vessels
- Pulmonary capillary wedge pressure
- Pulmonary edema
- Pulmonary hypertension
- Pulmonary vascular resistance
- Right heart, or right ventricular, failure
- Right ventricular hypertrophy
- Starling forces, or pressures

Case 16

Myocardial Infarction: Left Ventricular Failure

Case

Marvin Zimmerman is a 52-year-old construction manager who is significantly overweight. Despite his physician's repeated admonitions, Marvin ate a rich diet that included red meats and high-calorie desserts. Marvin also enjoyed unwinding with a few beers each evening. He joked with the guys, "I guess I'm a heart attack waiting to happen." He had occasional chest pains (angina) that were relieved by nitroglycerin.

The evening of his myocardial infarction, Marvin went to bed early because he wasn't feeling well. He awakened at 2:00 A.M. with crushing pressure in his chest and pain radiating down his left arm that was not relieved by nitroglycerin. He was nauseated and sweating profusely. He also had difficulty breathing (dyspnea), especially when he was recumbent (orthopnea). His breathing was "noisy." Marvin's wife called 911, and paramedics arrived promptly and transported him to the nearest hospital.

In the emergency room, Marvin's blood pressure was 105/80. Inspiratory rales were present, consistent with pulmonary edema, and his skin was cold and clammy. Sequential electrocardiograms and serum levels of cardiac enzymes (creatine phosphokinase and lactate dehydrogenase) suggested a left ventricular wall myocardial infarction. Pulmonary capillary wedge pressure, obtained during cardiac catheterization, was 30 mm Hg (normal, 5 mm Hg). His ejection fraction, measured with two-dimensional echocardiography, was 0.35 (normal, 0.55).

Marvin was transferred to the coronary intensive care unit. He was treated with a thrombolytic agent to prevent another myocardial infarction, digitalis (a positive inotropic agent), and furosemide (a loop diuretic). After 7 days in the hospital, he was sent home on a strict, low-fat, low-Na^+ diet.

QUESTIONS

1. Marvin had a left ventricular wall infarction secondary to myocardial ischemia. This damage to the left ventricle compromised its function as a pump; the left ventricle could no longer generate enough pressure to eject blood normally. Draw the normal Frank-Starling relationship for the left ventricle. Superimpose a second curve showing the Frank-Starling relationship after the myocardial infarction, and use this relationship to predict changes in stroke volume and cardiac output.

2. Which information provided in the case tells you that Marvin's stroke volume was decreased?

3. What is the meaning of Marvin's decreased ejection fraction?

4. Why was Marvin's pulmonary capillary wedge pressure increased?

5. Why did pulmonary edema develop? (In your explanation, discuss the Starling forces involved.) Why is pulmonary edema so dangerous?

6. Why did Marvin have dyspnea and orthopnea?

7. Why was Marvin's skin cold and clammy?

8. What was the rationale for treating Marvin with a positive inotropic agent, such as digitalis? (Hint: See Figure 2–13, which shows the Frank-Starling relationship.)

9. What was the rationale for treating Marvin with furosemide (a loop diuretic)?

10. A medical student in the coronary intensive care unit asked whether Marvin should also be treated with propranolol (a β-adrenergic antagonist). The student reasoned that propranolol would reduce the myocardial O_2 requirement and possibly prevent another infarction. Why does propranolol decrease the myocardial O_2 requirement? The attending physician pointed out that there could be a risk associated with the use of propranolol. What is this risk?

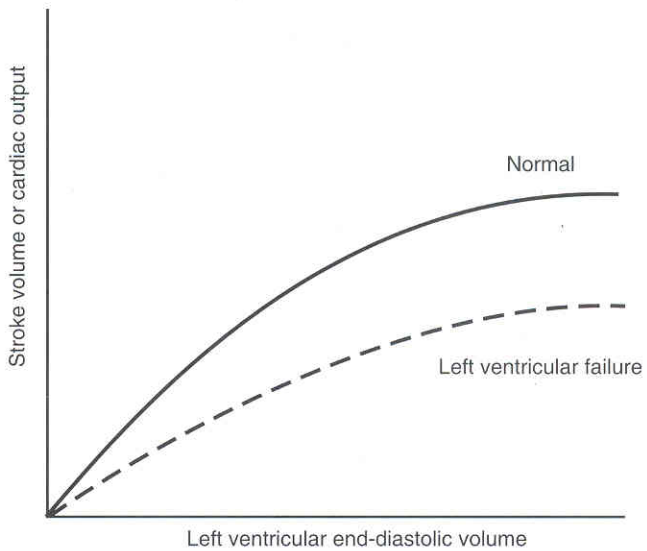
11. Why was Marvin sent home on a low-Na^+ diet?

ANSWERS AND EXPLANATIONS

1. The **Frank-Starling relationship** for the ventricle states that stroke volume and cardiac output increase with increased ventricular end-diastolic volume (Figure 2–13). Applied to the left ventricle, the volume of blood ejected in systole depends on the volume present in the ventricle at the end of diastolic filling (i.e., preload).

   The underlying physiologic principle of the Frank-Starling relationship is the **length–tension relationship for ventricular muscle.** Analogous to the length–tension relationship in skeletal muscle, sarcomere length (which is set by end-diastolic volume) determines the degree of overlap of thick and thin filaments. The degree of overlap determines the *possibility* of cross-bridge formation and cycling. The number of cross-bridges that *actually* cycle then depends on the intracellular Ca^{2+} concentration. Thus, two factors determine how much tension is generated by the ventricle: muscle length (i.e., extent of overlap of thick and thin filaments) and intracellular Ca^{2+} concentration.

   In ventricular failure, contractility decreases and the intrinsic ability of the myocardial fibers to produce tension is impaired; thus, for a given end-diastolic volume, stroke volume and cardiac output are decreased.



▲ **Figure 2–13.** Effect of ventricular failure on the Frank-Starling relationship.

2. Several pieces of information are consistent with decreased left ventricular stroke volume, including increased pulmonary capillary wedge pressure (discussed in the answer to Question 4) and decreased ejection fraction (discussed in the answer to Question 3).

   However, the most specific information indicating that Marvin's stroke volume was decreased was his decreased pulse pressure. Recall that **pulse pressure** is the difference between systolic and diastolic blood pressure. Marvin's systolic pressure was 105 mm Hg, and his diastolic pressure was 80 mm Hg; therefore, his pulse pressure was only 25 mm Hg. (Normal arterial pressure is 120/80, with a pulse pressure of 40 mm Hg.) Stroke volume is an important determinant of pulse pressure: the blood

volume ejected from the ventricle in systole causes arterial pressure to increase from its lowest value (diastolic pressure) to its highest value (systolic pressure). Thus, Marvin's decreased stroke volume resulted in a decreased pulse pressure.

3. Ejection fraction = stroke volume/end-diastolic volume; in other words, ejection fraction is the fraction of the end-diastolic volume that is ejected during systole. **Ejection fraction** is related to **contractility,** which is decreased in ventricular failure. Marvin's stroke volume was only 0.35 (35%) compared with the normal value of 0.55 (55%).

4. **Pulmonary capillary wedge pressure** is an estimate of left atrial pressure. It is measured by advancing a cannula through the pulmonary artery until it lodges ("wedges") in its smallest branches. At that point, the cannula senses pulmonary capillary pressure, which is nearly equal to **left atrial pressure.**

   Marvin's pulmonary capillary wedge pressure was increased because his left atrial pressure was increased. His left atrial pressure was increased secondary to decreased left ventricular stroke volume and ejection fraction. Following ejection, more blood than normal remained behind in the left ventricle; as a result, left ventricular pressure and left atrial pressure both increased.

5. The decrease in left ventricular ejection fraction caused blood to "back up" in the left side of the heart, increasing left ventricular and left atrial pressures. The increase in left atrial pressure led to increased pulmonary venous pressure. The increase in pulmonary venous pressure led to increased pulmonary capillary hydrostatic pressure (P_c), which is the major Starling force favoring filtration of fluid into the pulmonary interstitium (see Case 15 and Figure 2–12).

   When the filtration of fluid exceeded the capacity of Marvin's pulmonary lymphatics to remove the fluid, **pulmonary edema** occurred. Initially, the excess fluid accumulated in the interstitial space, but eventually, it also "flooded" the alveoli.

   Pulmonary edema is dangerous because it compromises gas exchange in the lungs. This discussion is more the venue of pulmonary physiology. Briefly, pulmonary edema increases the diffusion distance for O_2. When the diffusion distance increases, there is decreased diffusion of O_2 from alveolar gas into pulmonary capillary blood. In addition, pulmonary blood flow is shunted away from alveoli that are filled with fluid rather than with air (i.e., hypoxic vasoconstriction). As a result, there is impaired oxygenation of pulmonary capillary blood, which causes **hypoxemia** (decreased P_{O_2} of arterial blood). Hypoxemia is an important cause of **hypoxia** (decreased O_2 delivery to the tissues).

6. If you are a first-year medical student, you may need to look up the terms "dyspnea" and "orthopnea."

   Dyspnea is the sensation of difficult breathing. The etiology of dyspnea in pulmonary edema is not entirely clear, but the following factors play a role: (1) Juxtacapillary (J) receptors are stimulated by the accumulation of interstitial fluid, and trigger reflexes that stimulate rapid, shallow breathing. (2) Bronchial congestion stimulates the production of mucus. As a result, resistance of the bronchi is increased, causing wheezing and respiratory distress (called "cardiac asthma," referring to the

left ventricular failure that produced the pulmonary edema). (3) Accumulation of edema fluid leads to decreased pulmonary compliance, which increases the work of breathing.

Orthopnea is dyspnea that is precipitated by lying down. When a person lies down, venous return from the lower extremities back to the heart is increased. In left ventricular failure, increased venous return compounds the pulmonary venous congestion that is already present.

7. Marvin's skin was cold and clammy because the stress of the myocardial infarction produced a massive outpouring of **catecholamines** (epinephrine and norepinephrine) from the adrenal medulla. The circulating catecholamines activated **α_1-adrenergic receptors** in cutaneous vascular beds and reduced cutaneous blood flow.

8. As already discussed, damage to the left ventricle (secondary to the myocardial infarction) led to decreased contractility, decreased stroke volume, and decreased cardiac output for a given end-diastolic volume. Consider the Frank-Starling relationships that you constructed for Question 1. The curve for ventricular failure is lower than the curve for a normal ventricle, reflecting decreased contractility, stroke volume, and cardiac output. **Positive inotropic agents,** such as **digitalis,** increase contractility by increasing intracellular Ca^{2+} concentration. Digitalis was expected to increase contractility and return the Frank-Starling relationship toward that seen in a normal ventricle.

9. One of the most dangerous aspects of Marvin's condition was the increased pulmonary venous pressure that caused his pulmonary edema. (As already discussed, the cardiac output of the left ventricle was impaired, and blood backed up into the pulmonary veins.) Therefore, one therapeutic strategy was to reduce venous blood volume by reducing extracellular fluid volume. **Loop diuretics,** such as **furosemide,** are potent inhibitors of Na^+ reabsorption in the renal thick ascending limb; when Na^+ reabsorption is inhibited, Na^+ excretion increases. The resulting decrease in extracellular Na^+ content leads to decreased extracellular fluid volume and blood volume.

10. Propranolol, a **β-adrenergic antagonist,** reduces myocardial O_2 requirement by blocking β_1 receptors in the sinoatrial node and ventricular muscle. Normally, these β_1 receptors mediate increases in heart rate and contractility, which increase cardiac output. Cardiac output is part of the "work" of the heart, and this work requires O_2. Therefore, antagonizing β_1 receptors with propranolol decreases heart rate, contractility, cardiac output, and myocardial O_2 consumption.

Perhaps you've anticipated the potential risk involved in treating Marvin with a β-adrenergic antagonist. Propranolol would further decrease his already compromised cardiac output.

11. Extracellular fluid volume is determined by extracellular Na^+ content. A **low-Na^+ diet** was recommended to reduce extracellular fluid volume and blood volume, and to prevent subsequent episodes of pulmonary edema (similar to the idea of treating Marvin with a diuretic).

Key topics

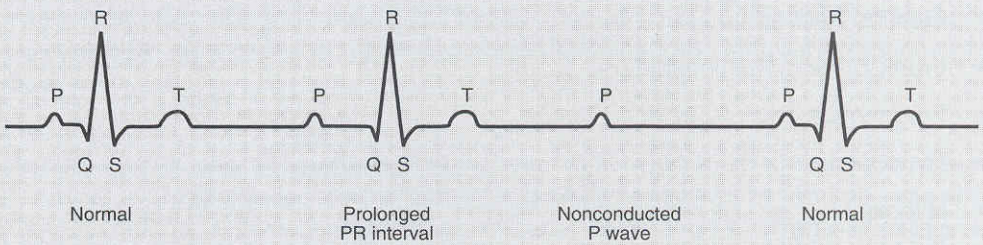
- β-Adrenergic antagonist
- Contractility
- Cutaneous blood flow
- Digitalis, or cardiac glycosides
- Dyspnea
- Ejection fraction
- Frank-Starling relationship
- Furosemide
- Hypoxemia
- Hypoxia
- Left heart failure
- Left ventricular failure
- Loop diuretics
- Orthopnea
- Positive inotropism
- Propranolol
- Pulmonary capillary wedge pressure
- Pulmonary edema
- Pulse pressure
- Starling forces

Case 17

Atrioventricular Conduction Block

Case

Charles Doucette, who is 68 years old, retired from a middle management position in the automotive industry following an acute myocardial infarction. He was recovering in a local hospital, where the physicians closely monitored his electrocardiogram (ECG) [Figure 2–14].



▲ **Figure 2–14.** Effect of atrioventricular conduction block on the electrocardiogram

Mr. Doucette's PR intervals were longer than normal. Although his QRS complexes had a normal configuration, there were occasional P waves that were not followed by QRS complexes (nonconducted P waves). He fainted twice in the hospital. The physicians believed that the myocardial infarction caused a block in his atrioventricular (AV) conducting system. While they were discussing the possibility of treating him with atropine, his ECG returned to normal. Mr. Doucette had no more fainting episodes, and he was sent home without further treatment.

QUESTIONS

1. What does the PR interval on the ECG represent? What units are used to express the PR interval? What is the normal value?

2. What does the term "conduction velocity" mean, as applied to myocardial tissue? What is the normal conduction velocity through the AV node? How does conduction velocity in the AV node compare with conduction velocity in other portions of the heart?

3. How does AV nodal conduction velocity correlate with PR interval? Why were Mr. Doucette's PR intervals longer than normal?

4. What does the QRS complex on the ECG represent? What is implied in the information that the QRS complexes on Mr. Doucette's ECG had a normal configuration?

5. How is it possible to have P waves that are not followed by QRS complexes? Explain this phenomenon in light of a presumed decreased AV node conduction velocity.

6. Why did Mr. Doucette faint?

7. How might atropine have helped Mr. Doucette?

ANSWERS AND EXPLANATIONS

1. The **PR interval** on the ECG represents the time from initial depolarization of the atria to initial depolarization of the ventricles (i.e., beginning of the P wave to beginning of the R wave). Therefore, the PR interval includes the P wave (atrial depolarization) and the PR segment, an isoelectric portion of the ECG that corresponds to conduction through the AV node. Because PR interval is a *time,* its units are given in seconds (sec) or milliseconds (msec). You may have needed to look up the normal value for PR interval, which is 120–200 msec (average, 160 msec).

2. **Conduction velocity,** as applied to myocardial tissue, has the same meaning that it has in nerve or skeletal muscle. It is the speed at which action potentials are propagated within the tissue from one site to the next. Thus, the units for conduction velocity are distance/time [e.g., meters/seconds (m/sec)]. Conduction velocity in the AV is the slowest of all of the myocardial tissues (0.01–0.05 m/sec). Compare this value in the AV node with the much faster conduction velocities in atria and ventricles (1 m/sec) and in His-Purkinje tissue (2–4 m/sec).

   The slow conduction velocity through the AV node, or **AV delay,** has a physiologic purpose: it ensures that the ventricles will not be activated "too soon" after the atria are activated, thus allowing adequate time for ventricular filling prior to ventricular contraction.

3. The slower the conduction velocity through the AV node, the longer the PR interval (because the length of the PR segment is increased). Conversely, the faster the conduction velocity through the AV node, the shorter the PR interval. Mr. Doucette's PR intervals were longer than normal because the conduction velocity through the AV node was decreased, presumably because of tissue damage caused by the myocardial infarction.

4. The **QRS complex** on the ECG corresponds to electrical activation of the ventricles. The normal configuration of Mr. Doucette's QRS complexes implies that his ventricles were activated in the normal sequence (i.e., the spread of activation was from the AV node through the bundle of His to the ventricular muscle).

5. Mr. Doucette's ECG showed some P waves that were not followed by QRS complexes. AV nodal conduction was slowed so much that some impulses were not conducted *at all* from atria to ventricles. This observation is consistent with increased AV delay and increased PR interval.

6. Mr. Doucette fainted because his arterial pressure was decreased, which caused a decrease in cerebral blood flow. The decrease in arterial pressure is likely related to the absent QRS complexes on the ECG. Each cardiac cycle without a QRS complex is a cardiac cycle in which electrical activation of the ventricles did not occur. If the ventricles were not activated electrically, they did not contract; if they did not contract, they did not eject blood, and mean arterial pressure decreased.

7. The rationale for treating Mr. Doucette with atropine is based on the effect of the

parasympathetic nervous system on conduction velocity in the AV node. Parasympathetic nerves innervating the AV node release acetylcholine, which activates muscarinic receptors and decreases AV node conduction velocity. Therefore, atropine (a muscarinic receptor antagonist) opposes this parasympathetic effect and increases AV node conduction velocity.

Key topics

- Atropine
- Atrioventricular (AV) node
- AV delay
- Conduction velocity
- Electrocardiogram
- Muscarinic receptors
- P wave
- Parasympathetic nervous system
- PR interval
- PR segment
- QRS complex

Respiratory Physiology

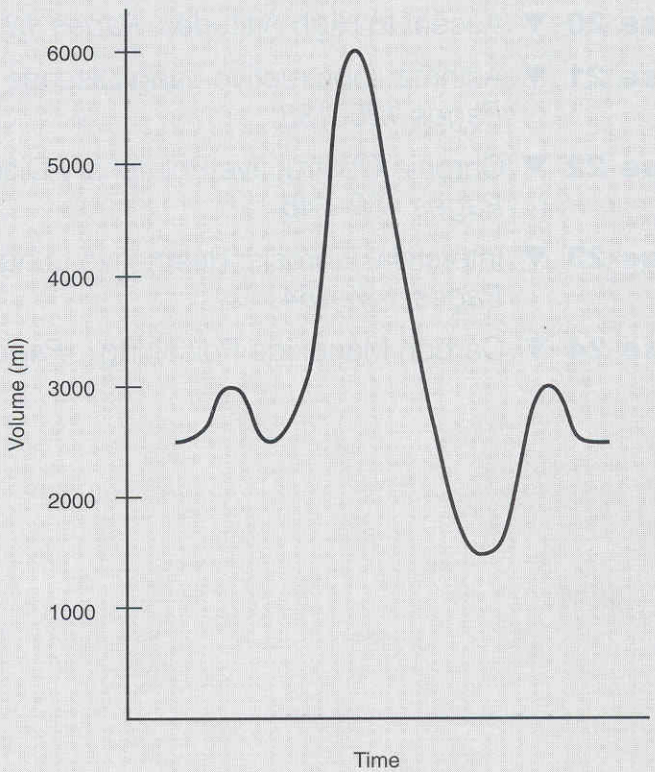
Case 18

Essential Respiratory Calculations: Lung Volumes, Dead Space, and Alveolar Ventilation

Case

This case will guide you through some of the important, basic calculations involving the respiratory system. Use the information provided to answer the questions.

Figure 3–1 shows a record from a person breathing into and out of a spirometer. The volume displaced by the spirometer's bell is recorded on calibrated paper. The person took one normal breath followed by a maximal inhalation, a maximal exhalation, and another normal breath. (The volume remaining in the lungs after maximal expiration is not measurable by spirometry and was determined by other techniques.)



▲ **Figure 3–1.** Spirometry diagram showing a tidal breath, followed by maximal inspiration and maximal expiration.

▼ **Table 3–1.** Respiratory Values for Case 18

Breathing rate	12 breaths/min
Pa_{CO_2} (arterial P_{CO_2})	40 mm Hg
Pa_{O_2} (arterial P_{O_2})	100 mm Hg
PE_{CO_2} (P_{CO_2} in expired air)	30 mm Hg
PI_{O_2} (P_{O_2} in humidified inspired air)	150 mm Hg
PI_{CO_2} (P_{CO_2} in inspired air)	0
$\dot{V}_{CO_2}$ (rate of CO_2 production)	200 ml/min
$\dot{V}_{O_2}$ (rate of O_2 consumption)	250 ml/min

P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen.

QUESTIONS

1. Using the information provided in Table 3–1 and Figure 3–1, what are the values for tidal volume, inspiratory capacity, expiratory reserve volume, functional residual capacity, vital capacity, and total lung capacity? (Hint: It may be helpful to label the spirometry diagram with the names of the lung volumes and capacities.)

2. What is the name of the volume remaining in the lungs after maximal expiration that is not measurable by spirometry? What other lung volumes or capacities are not measurable by spirometry?

3. What is the meaning of the term "physiologic dead space"? What assumptions are made in calculating the physiologic dead space? What is the volume of the physiologic dead space in this case?

4. What is the value for minute ventilation?

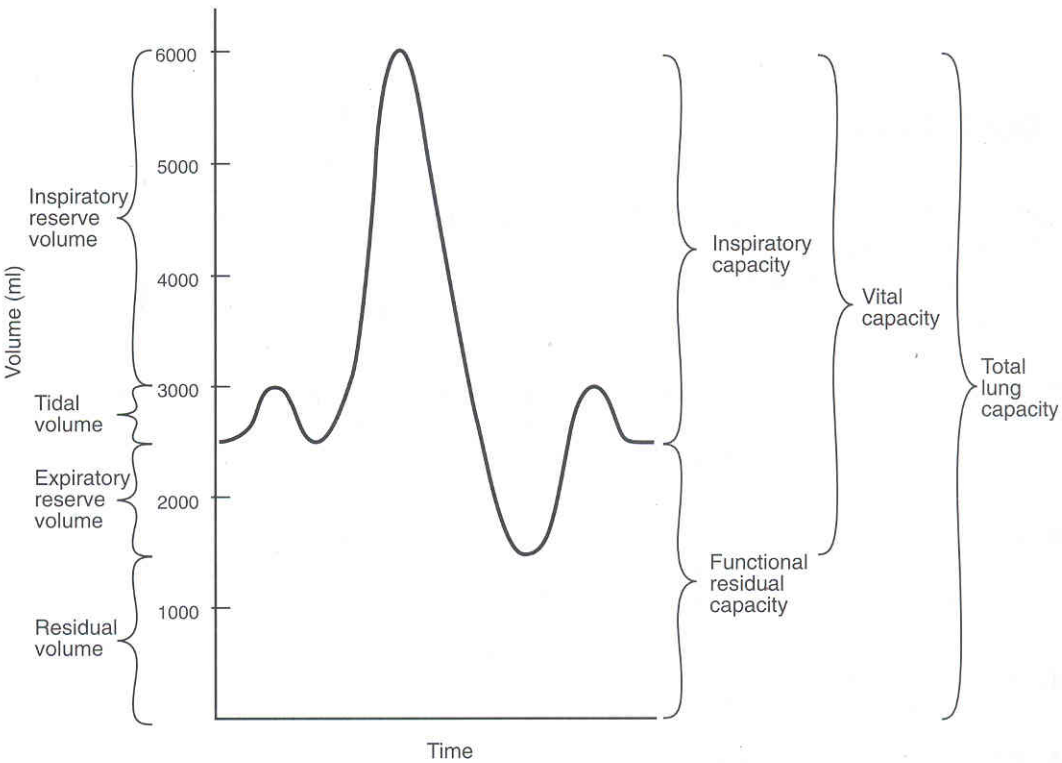
5. What is the value for alveolar ventilation?

6. What is the alveolar ventilation equation? Use this equation to calculate alveolar partial pressure of carbon dioxide (PA_{CO_2}) in this case.

7. What is the value for alveolar partial pressure of oxygen (PA_{O_2})?

ANSWERS AND EXPLANATIONS

1. Static **lung volumes** (except for residual volume) are measured by **spirometry.** They include the tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume. **Lung capacities** include two or more lung volumes. If you began by labeling the lung volumes and capacities shown in Figure 3–2 and Table 3–2, then determining the numerical values should be a straightforward exercise.



▲ **Figure 3–2.** Spirometry diagram labeled with lung volumes and capacities.

▼ **Table 3–2.** Lung Volumes and Capacities in Case 18

Tidal volume	500 ml
Inspiratory capacity	3500 ml
Expiratory reserve volume	1000 ml
Functional residual capacity	2500 ml
Vital capacity	4500 ml
Total lung capacity	6000 ml

2. The volume remaining in the lungs after maximal expiration is called the **residual volume.** This volume is not measurable by spirometry. Therefore, any lung volume or capacity that includes the residual volume is also not measurable by spirometry (i.e., functional residual capacity, total lung capacity).

3. **Physiologic dead space** is the volume of air in the lungs that does not participate in gas exchange (i.e., it is "*dead*"). Physiologic dead space has two components: (1) anatomic dead space, which is the volume of conducting airways; and (2) functional dead space, which is alveoli that do not participate in gas exchange (i.e., alveoli that are ventilated, but are not perfused by pulmonary capillary blood). By comparing the physiologic dead space with the tidal volume, it is possible to estimate how much ventilation is "wasted."

The volume of the physiologic dead space is estimated with a method based on the P_{CO_2} of expired air (PE_{CO_2}) that applies to the following three assumptions. (1) There is no CO_2 in inspired air (i.e., $PI_{CO_2} = 0$). (2) The physiologic dead space does not participate in gas exchange; therefore, it does not contribute any CO_2 to expired air. (3) All of the CO_2 in expired air comes from the exchange of CO_2 in functioning alveoli.

When discussing physiologic dead space, it is helpful to consider two examples, one in which there is *no* physiologic dead space and the other in which *some* degree of physiologic dead space is present. If there is *no* physiologic dead space, PE_{CO_2} should equal the P_{CO_2} in alveolar air (PA_{CO_2}). If there *is* a physiologic dead space present, then PE_{CO_2} will be "diluted" by air expired from the dead space (air that contains no CO_2), and PE_{CO_2} will be less than PA_{CO_2}.

One problem in comparing the P_{CO_2} of alveolar and expired air is that alveolar air cannot be sampled directly; in other words, we cannot measure PA_{CO_2}. This problem can be solved, however, because alveolar gas normally equilibrates with pulmonary capillary blood (which becomes systemic arterial blood). Thus, by measuring arterial P_{CO_2} (Pa_{CO_2}), we can determine PA_{CO_2}. Using the foregoing assumptions, **physiologic dead space** is calculated as follows:

$$\mathbf{V_D = V_T \times \frac{Pa_{CO_2} - PE_{CO_2}}{Pa_{CO_2}}}$$

where

V_D = physiologic dead space (ml)

V_T = tidal volume (ml)

Pa_{CO_2} = P_{CO_2} of arterial blood (mm Hg)

PE_{CO_2} = P_{CO_2} of expired air (mm Hg)

In words, physiologic dead space is the tidal volume multiplied by a fraction that expresses the dilution of alveolar P_{CO_2} by dead-space air.

We have all of the values we need to calculate the physiologic dead space in this case. Tidal volume was determined from spirometry, and the values for Pa_{CO_2} and PE_{CO_2} are given in the case data.

$$V_D = V_T \times \frac{Pa_{CO_2} - PE_{CO_2}}{Pa_{CO_2}}$$

$$= 500 \text{ ml} \times \frac{40 \text{ mm Hg} - 30 \text{ mm Hg}}{40 \text{ mm Hg}}$$

$$= 500 \text{ ml} \times 0.25$$

$$= 125 \text{ ml}$$

Thus, in the tidal volume of 500 ml, 125 ml occupied the physiologic dead space (i.e., the conducting airways and nonfunctional alveoli). In other words, 125 ml was "wasted" in lung spaces that cannot participate in gas exchange.

4. **Minute ventilation** is the tidal volume multiplied by the number of breaths per minute. In this case:

$$\textbf{Minute ventilation} = V_T \times \textbf{breaths/min}$$
$$= 500 \text{ ml} \times 12/\text{min}$$
$$= 6000 \text{ ml/min}$$

5. **Alveolar ventilation ($\dot{V}_A$)** is minute ventilation corrected for physiologic dead space, or:

$$\dot{V}_A = (V_T - V_D) \times \textbf{breaths/min}$$

where

$\dot{V}_A$ = alveolar ventilation (ml/min)

V_T = tidal volume (ml)

V_D = physiologic dead space (ml)

In this case, tidal volume was determined by spirometry (500 ml), and physiologic dead space was calculated in the previous question (125 ml). Thus, alveolar ventilation is:

$$\dot{V}_A = (500 \text{ ml} - 125 \text{ ml}) \times 12 \text{ breaths/min}$$
$$= 375 \text{ ml} \times 12 \text{ breaths/min}$$
$$= 4500 \text{ ml/min}$$

6. In considering these questions about alveolar ventilation and alveolar P_{CO_2}, perhaps you wondered what alveolar ventilation has to do with alveolar P_{CO_2}. The answer is everything! The fundamental relationship in respiratory physiology is an inverse correlation between alveolar ventilation (the volume of air reaching functional alveoli per minute) and alveolar P_{CO_2}. If CO_2 production is constant, the higher the alveolar ventilation, the more CO_2 expired and the lower the alveolar P_{CO_2}. Conversely, the lower the alveolar ventilation, the less CO_2 expired and the higher the alveolar P_{CO_2}. This relationship is expressed by the **alveolar ventilation equation:**

$$\dot{V}_A = \frac{\dot{V}_{CO_2} \times K}{PA_{CO_2}}$$

Rearranging to solve for PA_{CO_2}:

$$PA_{CO_2} = \frac{\dot{V}_{CO_2} \times K}{\dot{V}_A}$$

where

$P_{A_{CO_2}}$ = alveolar P_{CO_2}
$\dot{V}_A$ = alveolar ventilation
$\dot{V}_{CO_2}$ = rate of CO_2 production (ml/min)
K = constant (863 mm Hg)

The constant (K) requires a brief explanation. The value for K is 863 mm Hg under conditions of BTPS, when $\dot{V}_A$ and $\dot{V}_{CO_2}$ are expressed in the same units (e.g., ml/min). BTPS refers to body temperature (310 K), ambient pressure (760 mm Hg), and gas saturated with water vapor.

Now, let's calculate the value for $P_{A_{CO_2}}$. The rate of CO_2 production was given (200 ml/min), and alveolar ventilation was calculated in the previous question (4500 ml/min).

$$P_{A_{CO_2}} = \frac{200 \text{ ml/min}}{4500 \text{ ml/min}} \times 863 \text{ mm Hg}$$
$$= 38.4 \text{ mm Hg}$$

7. Because we cannot sample alveolar gas, we cannot directly measure $P_{A_{O_2}}$. However, we can use the following approach to estimate its value. $P_{A_{O_2}}$ is determined by the balance between removal of O_2 from alveolar gas (to meet the body's demands for O_2) and replenishment of O_2 by alveolar ventilation. Therefore, if O_2 consumption is constant, alveolar P_{O_2} is determined by alveolar ventilation (just as alveolar P_{CO_2} is determined by alveolar ventilation).

This relationship is expressed by the **alveolar gas equation,** which incorporates the factors that determine $P_{A_{O_2}}$ [including partial pressure of O_2 in inspired air ($P_{I_{O_2}}$)], $P_{A_{CO_2}}$ (which reflects alveolar ventilation, as explained earlier), and respiratory quotient (R, the ratio of CO_2 production to O_2 consumption):

$$\mathbf{P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R}}$$

where

$P_{A_{O_2}}$ = alveolar P_{O_2} (mm Hg)
$P_{I_{O_2}}$ = P_{O_2} in inspired air (mm Hg)
$P_{A_{CO_2}}$ = alveolar P_{CO_2} (mm Hg)
R = respiratory quotient (ratio of CO_2 production to O_2 consumption)

In this case, the value for $P_{I_{O_2}}$ (150 mm Hg) was given, the value for $P_{A_{CO_2}}$ (38.4 mm Hg) was calculated in the previous question, and the value for respiratory quotient can be calculated as the rate of CO_2 production (200 ml/min) divided by the rate of O_2 consumption (250 ml/min), or 0.8.

$$P_{A_{O_2}} = 150 \text{ mm Hg} - \frac{38.4 \text{ mm Hg}}{0.8}$$
$$= 150 \text{ mm Hg} - 48 \text{ mm Hg}$$
$$= 102 \text{ mm Hg}$$

Key topics

- Alveolar gas equation
- Alveolar ventilation
- Alveolar ventilation equation
- Anatomic dead space
- Expiratory reserve volume
- Functional residual capacity
- Inspiratory capacity
- Inspiratory reserve volume
- Minute ventilation
- Physiologic dead space
- Residual volume
- Respiratory quotient
- Spirometry
- Tidal volume
- Total lung capacity
- Vital capacity

Case 19

Essential Respiratory Calculations: Gases and Gas Exchange

Case

Using O_2 as an example, this case guides you through important, basic calculations involving partial pressures of gases and concentrations of gases in solutions such as blood. Use the information provided in Table 3–3 to answer the questions.

▼ **Table 3–3.** Respiratory Values for Case 19

P_B (barometric pressure)	760 mm Hg (at sea level)
PH_2O (water vapor pressure)	47 mm Hg at 37°C
FI_{O_2} (fractional concentration of O_2 in inspired air)	0.21 (or 21%)
PA_{O_2} (alveolar P_{O_2})	100 mm Hg
Solubility of O_2 in blood	0.003 ml O_2/100 ml blood/mm Hg
Hemoglobin concentration of blood	15 g/dl
O_2-binding capacity of blood	20.1 ml O_2/100 ml blood
% saturation	98%

P_{O_2}, partial pressure of oxygen.

QUESTIONS

1. What is the partial pressure of O_2 (P_{O_2}) in dry air at sea level?

2. When inspired air enters the trachea, it is saturated with water vapor (humidified). What is the P_{O_2} of humidified tracheal air at sea level?

3. The value for alveolar P_{O_2} (PA_{O_2}) is given as 100 mm Hg. Assuming complete equilibration of O_2 across the alveolar–pulmonary capillary barrier, what is the value for P_{O_2} in pulmonary capillary blood? How does this equilibration occur? What is the concentration of dissolved O_2 in that blood?

4. The total O_2 content of blood includes dissolved O_2 and O_2 bound to hemoglobin (O_2-hemoglobin). What is the total O_2 content of the blood in this case? What fraction of the total O_2 content is O_2-hemoglobin?

5. If the hemoglobin concentration is reduced from 15 g/dl to 9 g/dl, how would this reduction alter the amount of O_2-hemoglobin? How would it alter the amount of dissolved O_2? How would it alter the total O_2 content of blood?

6. If alveolar P_{O_2} is reduced from 100 mm Hg to 50 mm Hg, how would this reduction alter pulmonary capillary P_{O_2}? How would it alter the concentration of dissolved O_2 in pulmonary capillary blood? How would it alter the total O_2 content?

ANSWERS AND EXPLANATIONS

1. **Dalton's law of partial pressures** states that the partial pressure of a gas in a mixture of gases (e.g., in atmospheric air) is the pressure that the gas would exert if it occupied the total volume of the mixture. Therefore, partial pressure is the total pressure (e.g., atmospheric pressure) multiplied by the fractional concentration of the gas:

   $$\mathbf{Px = P_B \times F}$$

   where

   Px = partial pressure of the gas (mm Hg)

   P_B = barometric pressure (mm Hg)

   F = fractional concentration of the gas (no units)

   Thus, the P_{O_2} in dry air at a barometric pressure of 760 mm Hg is:

   $$P_{O_2} = 760 \text{ mm Hg} \times 0.21$$
   $$= 159.6 \text{ mm Hg}$$

2. When inspired air is humidified in the trachea, water vapor becomes an obligatory component of the gas mixture. To calculate the P_{O_2} of humidified air, barometric pressure must be corrected for water vapor pressure:

   $$\mathbf{Px = (P_B - P_{H_2O}) \times F}$$

   where

   Px = partial pressure of the gas in humidified air (mm Hg)

   P_B = barometric pressure (mm Hg)

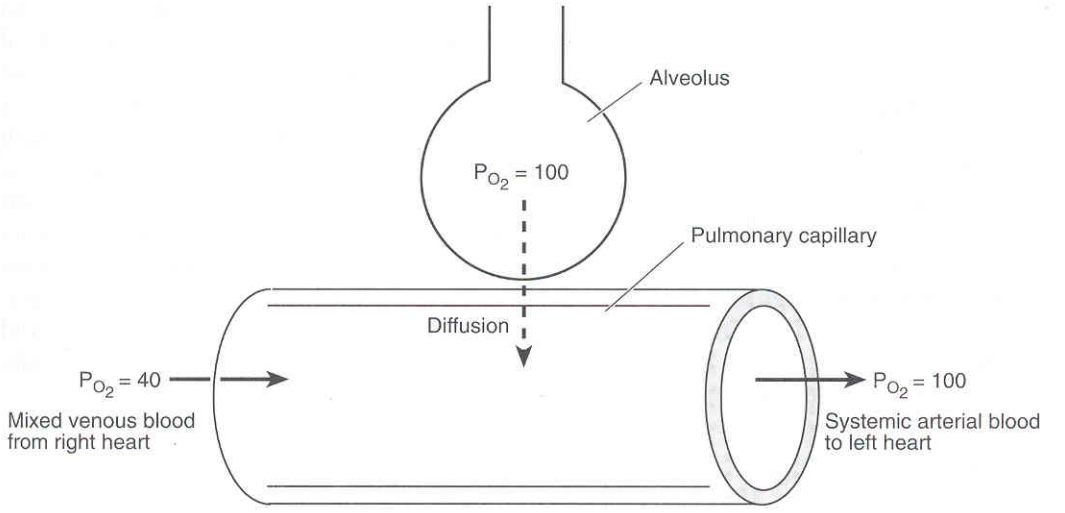
   F = fractional concentration of the gas (no units)

   P_{H_2O} = water vapor pressure (47 mm Hg at 37°C)

   Thus, the P_{O_2} of humidified tracheal air is:

   $$P_{O_2} = (760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 0.21$$
   $$= 149.7 \text{ mm Hg}$$

3. Normally, pulmonary capillary blood equilibrates almost completely with alveolar gas. Therefore, if alveolar gas has a P_{O_2} of 100 mm Hg, pulmonary capillary blood will also have a P_{O_2} of 100 mm Hg, which occurs as follows. O_2 is transferred from alveolar gas into pulmonary capillary blood by **simple diffusion.** The driving force for this diffusion is the partial pressure difference for O_2 between alveolar gas and pulmonary capillary blood (Figure 3–3).



▲ **Figure 3–3.** Diffusion of O_2 from alveolar gas into pulmonary capillary blood. P_{O_2}, partial pressure of oxygen.

Mixed venous blood from the right side of the heart enters the pulmonary capillaries with a relatively low P_{O_2} (approximately 40 mm Hg). Alveolar gas has a much higher P_{O_2} (approximately 100 mm Hg). Thus, initially, there is a large partial pressure gradient (driving force) for diffusion of O_2 from alveolar gas into the pulmonary capillary. O_2 diffuses into the blood until the P_{O_2} of pulmonary capillary blood is equal to the P_{O_2} of alveolar gas (100 mm Hg). Once equilibration has occurred, there is no longer a driving force for further diffusion of O_2. This equilibrated blood leaves the pulmonary capillaries, enters the left side of the heart, and becomes systemic arterial blood.

According to **Henry's law,** the *concentration* of dissolved O_2 depends on the partial pressure of O_2 in the liquid phase (e.g., blood) and the solubility of O_2 in that liquid:

Cx = Px × solubility

where

Cx = concentration of dissolved gas (ml gas/100 ml blood)

Px = partial pressure of the gas (mm Hg)

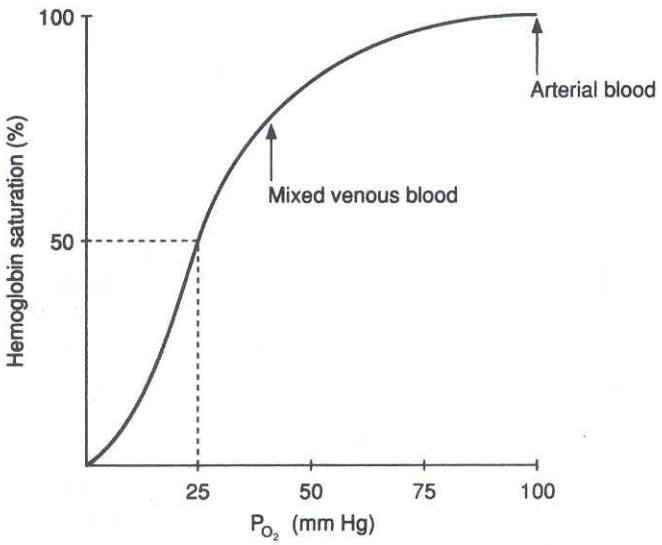
Solubility = solubility of gas in blood (ml gas/100 ml blood/mm Hg)

As discussed earlier, the P_{O_2} of pulmonary capillary blood is 100 mm Hg. The solubility of O_2 is given in the case as 0.003 ml O_2/100 ml blood/mm Hg. Thus:

$$\text{Dissolved } [O_2] = 100 \text{ mm Hg} \times 0.003 \text{ ml } O_2/100 \text{ ml blood/mm Hg}$$
$$= 0.3 \text{ ml } O_2/100 \text{ ml blood}$$

4. The **O_2 content of blood** includes dissolved O_2 and O_2 bound to hemoglobin. In the previous question, we discussed the dissolved form of O_2 (which depends on P_{O_2} and the solubility of O_2 in blood) and calculated its value.

Now, what determines the amount of O_2 present as **O_2-hemoglobin** (the bound form)? The amount of O_2-hemoglobin depends on the hemoglobin concentration of the blood, the O_2-binding capacity of the hemoglobin (i.e., the maximum amount of O_2 that can be bound), and the percent saturation of hemoglobin by O_2. This last point is very important! The hemoglobin molecule has four subunits, each of which can bind one molecule of O_2, for a total of four O_2 molecules per hemoglobin. Thus, 100% saturation means four O_2 molecules per hemoglobin, 75% saturation means three O_2 molecules per hemoglobin, and so forth. The percent saturation of hemoglobin depends on the P_{O_2} of the blood, as described by the **O_2-hemoglobin dissociation curve** (Figure 3–4). When P_{O_2} is 100 mm Hg, hemoglobin is 100% saturated; when P_{O_2} is 50 mm Hg, hemoglobin is approximately 85% saturated; and when P_{O_2} is 25 mm Hg, hemoglobin is 50% saturated. (The P_{O_2} at which hemoglobin is 50% saturated is called the **P_{50}**.)



▲ **Figure 3–4.** O_2-hemoglobin dissociation curve. P_{O_2}, partial pressure of oxygen. (Reprinted with permission from Costanzo LS: *BRS Physiology*, 2nd ed. Baltimore, Williams & Wilkins, 1998, p 135.)

Thus, the amount of O_2 bound to hemoglobin is calculated by multiplying the O_2-binding capacity of hemoglobin times the percent saturation, both of which are given in the case.

$$\begin{aligned} O_2\text{-hemoglobin} &= O_2\text{-binding capacity} \times \% \text{ saturation} \\ &= 20.1 \text{ ml } O_2/100 \text{ ml blood} \times 98\% \\ &= 19.7 \text{ ml } O_2/100 \text{ ml blood} \end{aligned}$$

Finally, the total O_2 content is the sum of dissolved O_2 and O_2-hemoglobin:

$$\begin{aligned} \text{Total } O_2 \text{ content} &= \text{dissolved } O_2 + O_2\text{-hemoglobin} \\ &= 0.3 \text{ ml } O_2/100 \text{ blood} + 19.7 \text{ ml } O_2/100 \text{ ml blood} \\ &= 20.0 \text{ ml } O_2/100 \text{ ml blood} \end{aligned}$$

O_2-hemoglobin is 98% of the total O_2 content (i.e., 19.7/20.0).

5. If the hemoglobin concentration is 9 g/dl instead of 15 g/dl, the O_2 content of blood is reduced because the O_2-hemoglobin component is reduced. What is the new value for the total O_2 content? In the previous calculation of O_2-hemoglobin content, we didn't use the hemoglobin concentration because the O_2-binding capacity of the blood was given (20.1 ml O_2/100 ml). To determine the effect of a reduction in hemoglobin concentration on the O_2-hemoglobin content, we simply need to calculate how such a change will alter the O_2-binding capacity (i.e., in this case, it will be reduced to 9/15 of the original O_2-binding capacity).

$$\begin{aligned} O_2\text{-binding capacity} &= 9/15 \times 20.1 \text{ ml } O_2/100 \text{ ml blood} \\ &= 12.1 \text{ ml } O_2/100 \text{ ml blood} \end{aligned}$$

Now we can calculate the amount of O_2 bound to hemoglobin, assuming that percent saturation is not affected by a reduction in hemoglobin concentration:

$$\begin{aligned} O_2\text{-hemoglobin} &= O_2\text{-binding capacity} \times \% \text{ saturation} \\ &= 12.1 \text{ ml } O_2/100 \text{ ml blood} \times 98\% \\ &= 11.9 \text{ ml } O_2/100 \text{ ml blood} \end{aligned}$$

We know that the total O_2 content is the sum of O_2-hemoglobin and dissolved O_2. We also know that O_2-hemoglobin is quantitatively much more important than dissolved O_2 and that O_2-hemoglobin is decreased by a decrease in hemoglobin concentration (discussed earlier). However, might dissolved O_2 also be altered by such a change in hemoglobin concentration, perhaps because of a change in P_{O_2}? The answer is that, if anything, P_{O_2} will be slightly increased. (If less O_2 is bound to hemoglobin because less hemoglobin is available, then more O_2 will be free in solution.) However, normally, the contribution of dissolved O_2 to total O_2 content is so small that it is insignificant. For this reason, we can safely use the original value for dissolved O_2 (0.3 ml O_2/100 ml blood) that we calculated in Question 3. Therefore, total O_2 content at a reduced hemoglobin concentration of 9 g/dl is:

$$\begin{aligned} \text{Total } O_2 \text{ content} &= O_2\text{-hemoglobin} + \text{dissolved } O_2 \\ &= 11.9 \text{ ml } O_2/100 \text{ ml blood} + 0.3 \text{ ml } O_2/100 \text{ ml blood} \\ &= 12.2 \text{ ml } O_2/100 \text{ ml blood} \end{aligned}$$

Such a reduction in hemoglobin concentration (e.g., as occurs in **anemia**) has a profound effect on the O_2 content of the blood; the total O_2 content is reduced to 60% of normal (i.e., 12.2/20.0)!

6. If alveolar P_{O_2} is 50 mm Hg and O_2 equilibration is assumed to be normal, then pulmonary capillary P_{O_2} is also 50 mm Hg. The dissolved O_2 concentration is the P_{O_2} multiplied by the solubility of O_2 in blood, or:

$$\begin{aligned} \text{Dissolved } [O_2] &= 50 \text{ mm Hg} \times 0.003 \text{ ml } O_2/100 \text{ ml blood/mm Hg} \\ &= 0.15 \text{ ml } O_2/100 \text{ ml blood} \end{aligned}$$

What about the amount of O_2 that is bound to hemoglobin? Will it be altered if P_{O_2} is reduced to 50 mm Hg? Recall that the amount of O_2 bound to hemoglobin depends on the O_2-binding capacity, hemoglobin concentration, the number of available binding sites, and the percent saturation of hemoglobin by O_2. When the P_{O_2} is 50 mm Hg, the percent saturation is reduced, which reduces the amount of O_2

bound to hemoglobin. Using the O_2-hemoglobin dissociation curve (see Figure 3–4), the percent saturation at a P_{O_2} of 50 mm Hg can be estimated to be approximately 85%.

$$\begin{aligned} O_2\text{-hemoglobin} &= O_2\text{-binding capacity of blood} \times \% \text{ saturation} \\ &= 20.1 \text{ ml } O_2/100 \text{ ml blood} \times 85\% \\ &= 17.1 \text{ ml } O_2/100 \text{ ml blood} \end{aligned}$$

Using these calculated values of dissolved O_2 and O_2-hemoglobin, the total O_2 content at a P_{O_2} of 50 mm Hg is:

$$\begin{aligned} \text{Total } O_2 \text{ content} &= \text{dissolved } O_2 + O_2\text{-hemoglobin} \\ &= 0.15 \text{ ml } O_2/100 \text{ ml blood} + 17.1 \text{ ml } O_2/100 \text{ ml blood} \\ &= 17.3 \text{ ml } O_2/100 \text{ ml blood} \end{aligned}$$

Thus, at a P_{O_2} of 50 mm Hg (assuming a normal hemoglobin concentration and normal O_2-binding capacity), the total amount of O_2 in blood is severely reduced compared with normal, *primarily* because the amount of O_2 bound to hemoglobin is reduced. (The change in dissolved O_2 makes little difference.)

Key topics

- Dalton's law of partial pressures
- Diffusion
- O_2-binding capacity
- O_2 content of blood
- O_2-hemoglobin
- Partial pressure
- P_{50}
- Percent saturation

Case 20

Ascent to High Altitude

Case

Dan Hsieh celebrated his graduation from college by joining a mountain climbing expedition in the Swiss Alps. Dan is in excellent physical condition: he runs 3–5 miles daily, and he played intramural soccer, volleyball, and rugby throughout college. At the insistence of his parents, Dan underwent a complete medical examination before the climb, which he passed with flying colors. He was off to the Alps!

QUESTIONS

1. Mont Blanc, the highest elevation in the Swiss Alps, is 15,771 feet above sea level. The barometric pressure on Mont Blanc is approximately 420 mm Hg. (The barometric pressure at sea level is 760 mm Hg.) What is the fractional concentration of O_2 (FI_{O_2}) in atmospheric air on Mont Blanc? What is the partial pressure of oxygen (P_{O_2}) of humidified air on Mont Blanc? How does this value of P_{O_2} compare with the P_{O_2} of humidified air at sea level?

2. At his physical examination (performed at sea level), Dan's arterial P_{O_2} (Pa_{O_2}) was 100 mm Hg. If Dan's Pa_{O_2} had been measured when he arrived on Mont Blanc, it would have been approximately 50 mm Hg. Why would his Pa_{O_2} be decreased at the higher elevation? What was Dan's alveolar P_{O_2} (PA_{O_2}) on Mont Blanc?

3. Predict whether each of the following parameters would be increased, decreased, or unchanged on Mont Blanc. Explain why each of the predicted changes would occur.
   a. Breathing rate
   b. Percent saturation of hemoglobin
   c. P_{O_2} at which hemoglobin is 50% saturated (P_{50})
   d. Pulmonary artery pressure

4. If Dan's arterial P_{CO_2} (Pa_{CO_2}) had been measured on Mont Blanc, would it have been increased, decreased, or unchanged compared with normal? Why? If you predicted a change in Pa_{CO_2}, what effect would this change have had on arterial pH? What acid–base disorder would it have caused?

5. The climbers were encouraged to breathe from tanks of 100% O_2. What is the P_{O_2} of 100% humidified O_2 on Mont Blanc? What effect would breathing 100% O_2 have had on Dan's Pa_{O_2}? What effect would it have had on his breathing rate?

6. Dan's physician suggested that Dan take acetazolamide, a carbonic anhydrase inhibitor, prophylactically. Which of the responses and changes that you predicted in Questions 3 and 4 would have been eliminated or offset if Dan took acetazolamide?

ANSWERS AND EXPLANATIONS

1. Although the barometric pressure on Mont Blanc is much lower than that at sea level, the FI_{O_2} is the same (0.21, or 21%). We calculate the P_{O_2} in humidified air by correcting the barometric pressure (PB) for water vapor pressure (PH_2O), and then multiplying this figure by FI_{O_2} (as described in Case 19).

$$P_{O_2}\text{ (Mont Blanc)} = (PB - PH_2O) \times FI_{O_2}$$
$$= (420\text{ mm Hg} - 47\text{ mm Hg}) \times 0.21$$
$$= 78.3\text{ mm Hg}$$

$$P_{O_2}\text{ (sea level)} = (PB - PH_2O) \times FI_{O_2}$$
$$= (760\text{ mm Hg} - 47\text{ mm Hg}) \times 0.21$$
$$= 149.7\text{ mm Hg}$$

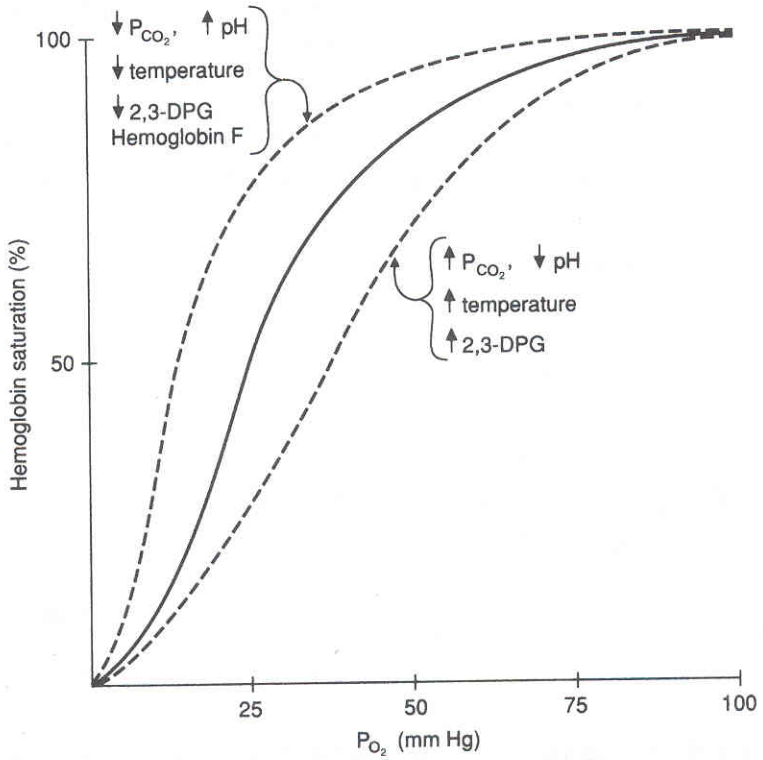
Thus, the P_{O_2} of humidified air on Mont Blanc is much lower than the P_{O_2} of humidified air at sea level because of the lower barometric pressure at the higher altitude.

2. Dan's Pa_{O_2} would be greatly reduced (**hypoxemia**) on Mont Blanc because, as demonstrated in the previous question, the air he breathed on Mont Blanc had a much lower P_{O_2} (78.3 mm Hg) than the air he breathed at sea level (149.7 mm Hg).

Such a decrease in inspired P_{O_2} would be reflected in a decreased alveolar P_{O_2} (PA_{O_2}). How can we estimate what his PA_{O_2} might have been? One approach is to assume that O_2 equilibrates between alveolar gas and pulmonary capillary blood (systemic arterial blood). If Dan's measured Pa_{O_2} was 50 mm Hg, then his PA_{O_2} can be assumed to be 50 mm Hg.

3. On Mont Blanc, the following changes are predicted:
   a. Dan's breathing rate would be *increased* (**hyperventilation**) because decreased Pa_{O_2} stimulates **peripheral chemoreceptors** in the carotid bodies located near the bifurcation of the common carotid arteries. When **Pa_{O_2} is less than 60 mm Hg,** these chemoreceptors are strongly stimulated. This information is then relayed to medullary respiratory centers that direct an increase in breathing rate. In other words, the body is calling for more O_2!

   b. **Percent saturation of hemoglobin** would be *decreased* because Pa_{O_2} is decreased. Figure 3–5 shows the effect of P_{O_2} on percent saturation of hemoglobin.



▲ **Figure 3–5.** Changes in the O_2-hemoglobin dissociation curve showing the effects of partial pressure of carbon dioxide (P_{CO_2}), pH, temperature, 2,3-diphosphoglycerate (DPG), and fetal hemoglobin (*hemoglobin F*). P_{O_2}, partial pressure of oxygen. (Reprinted with permission from Costanzo LS: *BRS Physiology*, 2nd ed. Baltimore, Williams & Wilkins, 1998, p 137.)

In Figure 3–5, the solid line shows the normal O_2-hemoglobin relationship that was discussed in Case 19. At a Pa_{O_2} of 50 mm Hg, hemoglobin would be approximately 85% saturated, which would significantly decrease the total O_2 content of Dan's blood and compromise O_2 delivery to his tissues.

c. P_{50} would be *increased* because there is a **right shift** of the O_2-hemoglobin curve on ascent to high altitude. This right shift occurs because hypoxemia stimulates the synthesis of **2,3-diphosphoglycerate (DPG).** 2,3-DPG binds to hemoglobin and decreases its affinity for O_2. This **decreased affinity** is a helpful adaptation at high altitude that facilitates unloading of O_2 in the tissues.

Notice also the effect of the right shift on percent saturation; at a P_{O_2} of 50 mm Hg, hemoglobin is approximately 75% saturated on the right-shifted curve, which is less than the 85% saturation we estimated from the normal curve.

d. Pulmonary artery pressure would be *increased* because alveolar hypoxia causes vasoconstriction of pulmonary arterioles (**hypoxic vasoconstriction**). Vasoconstriction leads to increased pulmonary vascular resistance, which increases pulmonary arterial pressure. (Recall from cardiovascular physiology that arterial pressure = blood flow × resistance.) Hypoxic vasoconstriction is a unique phenomenon in the lungs that shunts blood flow away from hypoxic regions; in other tissues, hypoxia is vasodilatory.

4. Dan's Pa_{CO_2} would have been *decreased* secondary to hyperventilation. As discussed earlier, hypoxemia (Pa_{O_2}, 50 mm Hg) stimulated Dan's peripheral chemoreceptors and increased his breathing rate (hyperventilation). Hyperventilation drives off extra CO_2 from the lungs and causes a decrease in arterial P_{CO_2}. (Recall from Case 18 that, if CO_2 production is constant, arterial P_{CO_2} is determined by alveolar ventilation.)

   Decreased Pa_{CO_2} causes an increase in arterial pH, according to the **Henderson-Hasselbalch equation,** which states that:

$$\mathbf{pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2}}}$$

   where

   pH = $-\log_{10} [H^+]$

   6.1 = pK of HCO_3^-/CO_2 buffer

   HCO_3^- = HCO_3^- concentration of arterial blood

   P_{CO_2} = P_{CO_2} of arterial blood

   The acid–base disorder that is caused by hyperventilation is **respiratory alkalosis.** As the name implies, the alkaline blood pH results from a respiratory problem (in this case, hyperventilation that produced a decreased P_{CO_2}).

5. To calculate the P_{O_2} of 100% O_2 saturated with water vapor, we use the same approach that was described in Question 1. Note that FI_{O_2} is now 1.0 (or 100%). Thus:

$$\begin{aligned} P_{O_2} &= (P_B - P_{H_2O}) \times 1.0 \\ &= (420 \text{ mm Hg} - 47 \text{ mm Hg}) \times 1.0 \\ &= 373 \text{ mm Hg} \end{aligned}$$

   Thus, breathing 100% O_2 would be expected to increase the P_{O_2} of Dan's inspired air to 373 mm Hg, which would be expected to increase his alveolar and arterial P_{O_2}. According to the O_2-hemoglobin curve, such an increase in arterial P_{O_2} would increase the percent saturation of hemoglobin and thereby increase O_2 delivery to Dan's tissues. Dan would no longer be hypoxemic, there would no longer be a hypoxemic stimulation of peripheral chemoreceptors, and his breathing rate would return to normal.

6. **Acetazolamide,** a carbonic anhydrase inhibitor, inhibits renal HCO_3^- reabsorption and increases HCO_3^- excretion in the urine. Increased urinary HCO_3^- excretion leads to decreased HCO_3^- concentration in the blood (**metabolic acidosis**).

   Dan's physician suggested that he take acetazolamide to produce a mild metabolic acidosis that would offset or negate the respiratory alkalosis caused by hyperventilation. The Henderson-Hasselbalch equation shows how this offset occurs:

$$pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2}}$$

   Hypoxemia causes hyperventilation by stimulating peripheral chemoreceptors. Hyperventilation causes a decrease in P_{CO_2} that, by decreasing the denominator of the

Henderson-Hasselbalch equation, causes an increase in blood pH. Acetazolamide causes a decrease in blood HCO_3^- concentration, which decreases the numerator in the Henderson-Hasselbalch equation. If the numerator (HCO_3^-) and the denominator (P_{CO_2}) decrease to the same extent, then the pH is normalized.

Of all of the responses predicted to occur at high altitude, the only one that would be offset by acetazolamide is the increased blood pH. Dan would still be breathing air with a low P_{O_2}. Thus, he would still have a low Pa_{O_2} and a low percent saturation, and he would still be hyperventilating secondary to hypoxemia.

Key topics

- Acetazolamide
- 2,3-Diphosphoglycerate (DPG)
- Henderson-Hasselbalch equation
- High altitude
- Hyperventilation
- Hypoxemia
- Hypoxic vasoconstriction
- Metabolic acidosis
- O_2-hemoglobin
- O_2-hemoglobin dissociation curve
- P_{50}
- Peripheral chemoreceptors
- Respiratory alkalosis
- Right shift of the O_2-hemoglobin curve

Case 21

Asthma: Obstructive Lung Disease

Case

Ralph Grundy was a 43-year-old lineman for a Midwestern power company. He was married and the father of four children who were 24, 22, 21, and 18 years of age. Ralph had a history of asthma since childhood. His asthma attacks, which were characterized by wheezing and shortness of breath, were often precipitated by high pollen levels and cold weather. He used an inhaled bronchodilator (albuterol, a β_2-adrenergic agonist) to treat the attacks. At the time of his death, Ralph had been trying desperately to get "inside" work. His asthma attacks were becoming more frequent and more severe, and he had been taken to the emergency room five times in the past year.

Three days before his death, Ralph had an upper respiratory infection, with nasal and chest congestion and a fever of 101.8°F. He was exhausted from "just trying to breathe," and the bronchodilator inhaler wasn't working. On the third day of the illness, Ralph's oldest son took him to the emergency room of the local community hospital. He had inspiratory and expiratory wheezes and was in severe respiratory distress. Table 3–4 shows the information obtained when he arrived at the emergency room at 4 P.M.

▼ **Table 3–4.** Ralph's Respiratory Values at 4 P.M.

Respiratory rate	30 breaths/min (normal, 12–15)
FI_{O_2} (fractional concentration of O_2)	0.21 (room air)
pH	7.48 (normal, 7.4)
Pa_{O_2} (arterial P_{O_2})	55 mm Hg (normal, 100 mm Hg)
Pa_{CO_2} (arterial P_{CO_2})	32 mm Hg (normal, 40 mm Hg)

The emergency room staff treated Ralph with an inhaled bronchodilator and had him breathe 50% O_2 (FI_{O_2}, 0.5). At 6 P.M., his condition had not improved; in fact, it had worsened, and Ralph was obtunded (sleepy and inattentive). Before proceeding with more aggressive treatment (e.g., anti-inflammatory drugs and intubation), the emergency room staff obtained a second set of measurements (Table 3–5).

▼ **Table 3–5.** Ralph's Respiratory Values at 6 P.M.

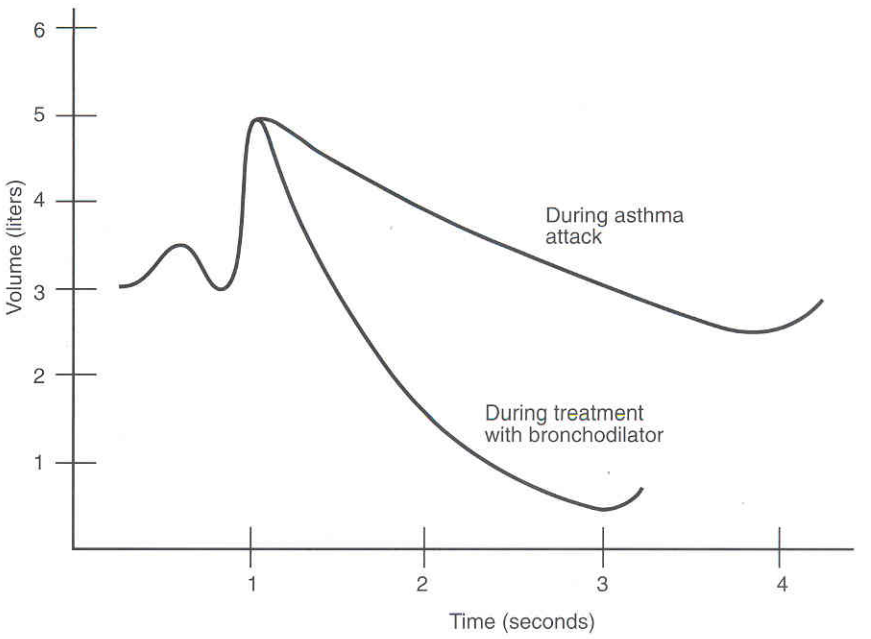
Respiratory rate	8 breaths/min
FI_{O_2} (fractional concentration of O_2)	0.5
pH	7.02 (normal, 7.4)
Pa_{O_2} (arterial P_{O_2})	45 mm Hg (normal, 100 mm Hg)
Pa_{CO_2} (arterial P_{CO_2})	80 mm Hg (normal, 40 mm Hg)

Ralph died before aggressive treatment could be initiated. At autopsy, his airways were almost totally occluded by mucus plugs.

QUESTIONS

1. Asthma is an obstructive disease in which the airways narrow, increasing the resistance to airflow into and out of the lungs. What are the relationships between airflow, resistance, and airway diameter? Use equations to support your answers.

2. Figure 3–6 shows the results of pulmonary function tests performed on Ralph during an asthma attack the previous year. For the test, Ralph first took a normal tidal breath, then a maximal inspiration, followed by maximal expiration. The test was repeated after he inhaled a bronchodilator, a β_2-adrenergic agonist.



▲ **Figure 3–6.** Lung volumes during forced expiration during an asthma attack and during treatment with an inhaled bronchodilator.

What was Ralph's tidal volume? What was his forced vital capacity (FVC) during the asthma attack and after treatment with the bronchodilator? What was his FEV_1 (volume expired in the first second of forced expiration) during the attack and after bronchodilator treatment? What was Ralph's FEV_1/FVC during the attack and after treatment? What is the significance of the changes in FVC, FEV_1, and FEV_1/FVC that were produced by the bronchodilator?

3. What effect did Ralph's asthma have on residual volume and functional residual capacity (FRC)?

4. Why was Ralph exhausted from "just trying to breathe"? How does obstructive lung disease increase the work of breathing?

5. Why was Ralph's arterial P_{O_2} (Pa_{O_2}) decreased at 4 P.M.? [Hint: Consider how changes in the ventilation–perfusion ($\dot{V}/\dot{Q}$) ratio might alter Pa_{O_2}.]

6. What is an A–a gradient, and what is its significance? What was Ralph's A–a gradient at 4 P.M.? (Assume that his respiratory quotient was 0.8.)

7. Why was Ralph hyperventilating at 4 P.M.? Why was his arterial P_{CO_2} (Pa_{CO_2}) decreased (compared with normal)? What acid–base abnormality did he have at 4 P.M.?

8. What was Ralph's A–a gradient at 6 P.M.? (Assume that his respiratory quotient remained at 0.8.) What is the significance of the change in A–a gradient that occurred between 4 P.M. and 6 P.M.?

9. Why was Ralph's Pa_{CO_2} increased at 6 P.M.? What acid–base abnormality did he have at that time? Why was he obtunded?

ANSWERS AND EXPLANATIONS

1. **Airway resistance** is inversely correlated with airway diameter or **radius.** As the radius of an airway increases, resistance to airflow decreases, according to **Poiseuille's law:**

$$R = \frac{8 \eta l}{\pi r^4}$$

where

R = resistance of the airway

η = viscosity of inspired air

l = length of the airway

r = radius of the airway

This relationship, which is especially powerful because of the fourth-power dependence on radius, should be familiar from cardiovascular physiology.

Airflow is inversely proportional to airway resistance, according to the now familiar relationship between flow, pressure, and resistance:

$$Q = \frac{\Delta P}{R}$$

where

Q = airflow (L/min)

ΔP = pressure difference (mm Hg or cm H_2O)

R = airway resistance (cm H_2O/L/sec)

Thus, airflow (Q) is directly proportional to the pressure difference (ΔP) between the inlet and the outlet of the airway (e.g., between the mouth and the alveoli) and inversely proportional to the resistance of the airway (R). The pressure difference is the *driving force* for airflow; resistance is the *impediment* to airflow.

By combining the relationships for airway radius, resistance, and airflow, we conclude that the larger the radius of the airway, the smaller the resistance and the higher the airflow. Conversely, the smaller the radius, the larger the resistance and the lower the airflow.

Note that, although the resistance of a single airway is inversely correlated with its radius, the **medium-sized bronchi** are actually the site of highest airway resistance in the intact respiratory system (even though it seems that the smallest airways should have the highest resistance). This apparent discrepancy is explained by the parallel arrangement of the small airways. When resistances are arranged in parallel, the total resistance is lower than the individual resistances.

2. **Tidal volume** is the volume inspired and expired during normal breathing. Forced vital capacity (**FVC**) is the volume that can be forcibly expired after a maximal inspiration. **FEV_1** is the volume expired in the first second of the forced expiration. **FEV_1/FVC** is the fraction of FVC expired in the first second. In healthy people, FEV_1/FVC is approximately 0.8 (or 80%); in other words, normally, most of the vital capacity is expired in the first second of forced expiration (Table 3–6).

▼ **Table 3–6.** Ralph's Lung Volumes and Capacities During an Asthma Attack and During Treatment With a Bronchodilator

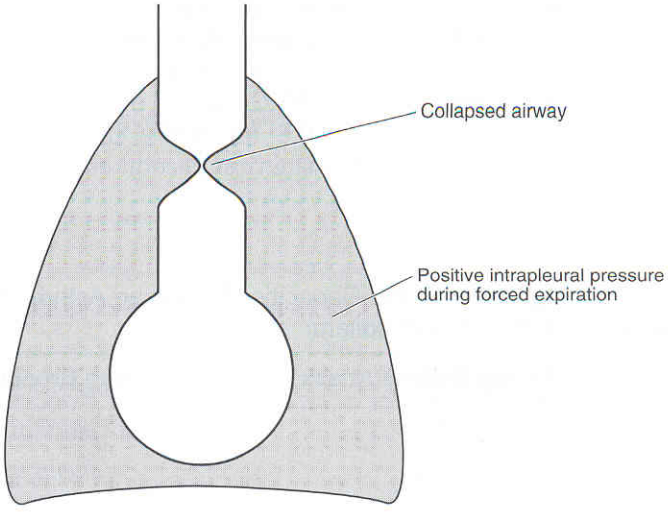
	During Asthma Attack	During Bronchodilator Treatment
Tidal volume	0.5 L	0.5 L
FVC	2.5 L	4.5 L
FEV_1	1.2 L	3.5 L
FEV_1/FVC	0.48	0.78

FVC, forced vital capacity; *FEV_1*, volume expired in the first second of forced expiration.

Ralph had asthma, an **obstructive disease** that is characterized by inflammation and narrowing of the airways. This narrowing (i.e., decreased airway radius) led to **increased resistance** and decreased airflow, as discussed in the previous question. Ralph's **wheezes** were the sounds produced when he expired forcibly through these narrowed airways.

In asthma, the airways are narrowed for three major reasons: (1) hyperresponsiveness of bronchial smooth muscle to a variety of stimuli, which causes bronchospasm and **bronchoconstriction** during an attack; (2) thickening and edema of the bronchial walls secondary to **inflammation;** and (3) increased production of bronchial **mucus** that obstructs the airways. The first mechanism (bronchoconstriction) can be reversed by administering bronchodilator drugs, such as **β_2-adrenergic agonists** (e.g., albuterol).

Increases in airway resistance, such as those seen in asthma, lead to *decreases in all expiratory parameters,* including FVC, FEV_1, and FEV_1/FVC. The higher the airway resistance, the more difficult it is to expire air from the lungs. Airway resistance is especially increased during *forced* expiration, when intrapleural pressure becomes positive and tends to compress, or even close, the airways (Figure 3–7). Therefore, FVC decreases during an asthma attack because the airways close prematurely during expiration. One result of this **premature closure of the airways** is that air that should have been expired remains in the lungs (**air trapping**).



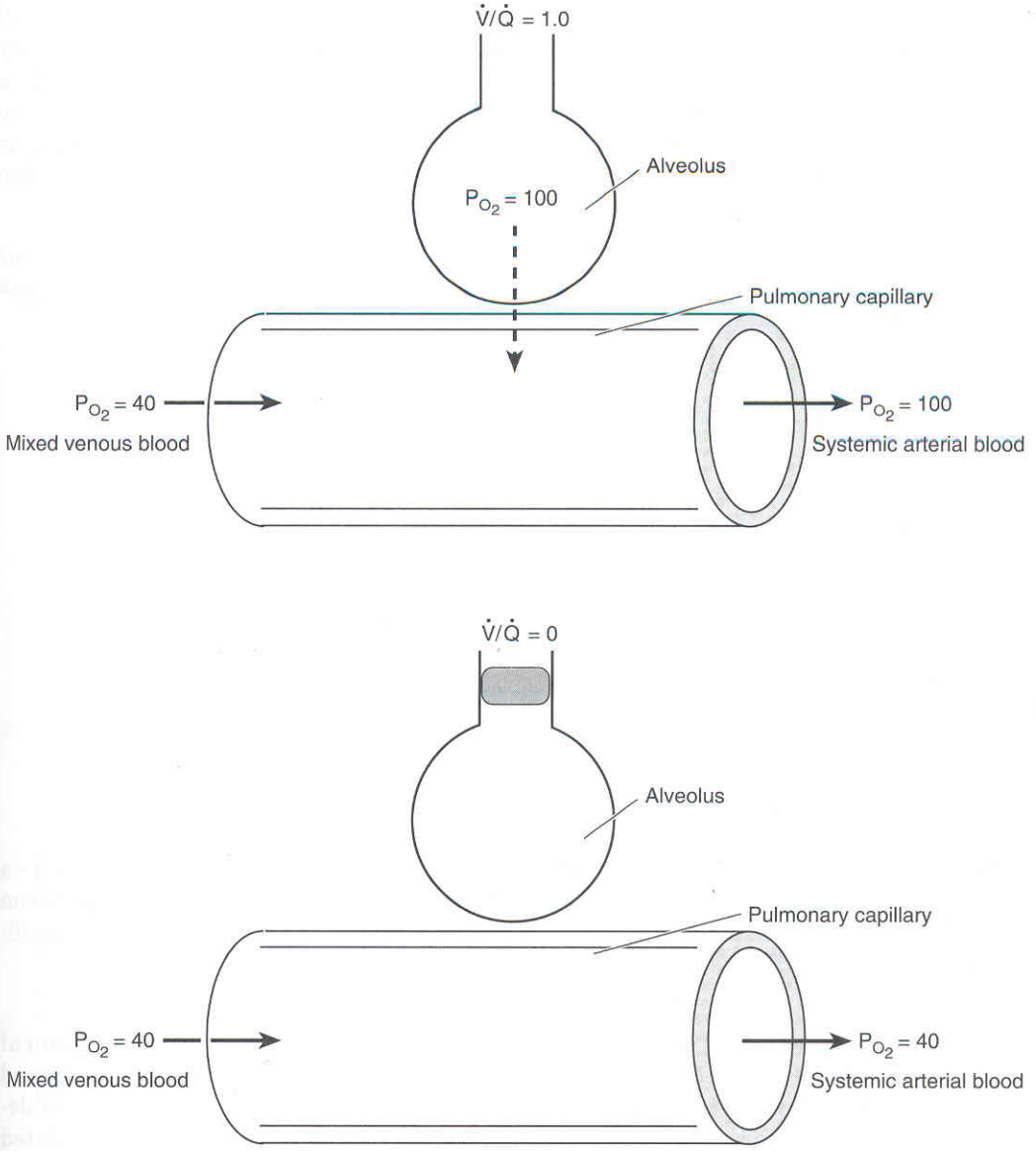
▲ **Figure 3–7.** Airway collapse during forced expiration as a result of positive intrapleural pressure.

The inhaled **bronchodilator** relaxed Ralph's airways, increasing their radii and decreasing their resistance to airflow. The decrease in airway resistance improved Ralph's expiratory functions, as evidenced by the increased FEV_1 and FEV_1/FVC. Also, because his airways did not close prematurely, his FVC was increased.

3. Ralph's asthma was associated with increased airway resistance, which compromised his expiratory functions. As a result, air that should have been expired remained in the lungs, increasing his residual volume and his **functional residual capacity (FRC).** Recall that FRC is the resting, or equilibrium, position of the lungs (i.e., the volume in the lungs between breaths). Because Ralph's FRC was increased, his normal "tidal" breathing had to occur at higher lung volumes.

4. The work of breathing is determined by how much pressure change is required to move air into and out of the lungs. In obstructive lung diseases, such as asthma, the **work of breathing** is increased for two reasons. (1) A person with asthma breathes at higher lung volumes (because of the higher FRC), as discussed earlier. During *inspiration,* a person with asthma must lower intrathoracic pressure more than a healthy person to bring air into the lungs; thus, more work is required during inspiration. (2) During *expiration,* because airway resistance is increased, higher pressures must be created to force air out of the lungs; this greater expiratory effort requires the use of accessory muscles. (In healthy people, expiration is passive and does not require the assistance of accessory muscles.) Increased work of breathing is reflected in higher rates of O_2 consumption and CO_2 production.

5. Recall the **ventilation–perfusion ($\dot{V}/\dot{Q}$) relationship** in the lungs. Ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) are normally matched such that ventilated alveoli lie in close proximity to perfused capillaries. This $\dot{V}/\dot{Q}$ matching (i.e., $\dot{V}/\dot{Q} = 1.0$) allows O_2 exchange to proceed normally (as shown in the upper portion of Figure 3–8). O_2 diffuses from alveolar gas into pulmonary capillary blood until alveolar P_{O_2} and pulmonary capillary P_{O_2} are equal (normally 100 mm Hg).



▲ **Figure 3–8.** Effect of airway obstruction on ventilation–perfusion ($\dot{V}/\dot{Q}$) ratio and O_2 exchange. P_{O_2}, partial pressure of oxygen.

Ralph's arterial P_{O_2} (Pa_{O_2}) was decreased (**hypoxemia**) because he had a **$\dot{V}/\dot{Q}$ defect** (or mismatch). Bronchoconstriction and obstruction of some airways prevented adequate ventilation of some regions of his lungs. In these unventilated regions, fresh air, with its supply of O_2, did not reach the alveoli for gas exchange. Therefore, the pulmonary capillary blood that perfused these unventilated alveoli was not oxygenated. As shown in the lower portion of Figure 3–8, the P_{O_2} of the blood in these capillaries remained the same as that of mixed venous blood. This portion of the pulmonary blood flow is called a **shunt** because the blood flow bypasses ventilated alveoli and is not oxygenated. Ralph's pulmonary venous blood (which becomes systemic arterial blood) was a mixture of blood from well-ventilated and poorly ventilated regions of the lungs; therefore, his systemic arterial blood had a P_{O_2} of less than 100 mm Hg.

6. The **A–a gradient** is the difference between alveolar P_{O_2} (PA_{O_2}, or "A") and arterial P_{O_2} (Pa_{O_2}, or "a"). The A–a gradient tells us whether O_2 is equilibrating normally between alveolar gas and pulmonary capillary blood. For example, the normal A–a gradient is close to zero because O_2 equilibrates almost perfectly: PA_{O_2} and Pa_{O_2} are equal, or nearly equal. However, if a $\dot{V}/\dot{Q}$ defect (or mismatch) occurs, then Pa_{O_2} is less than PA_{O_2} and the A–a gradient is larger than zero. The greater the disturbance in O_2 exchange, the larger the A–a gradient.

The A–a gradient is determined by measuring "a" (the P_{O_2} of arterial blood, or Pa_{O_2}) and calculating "A" (the P_{O_2} of alveolar gas, or PA_{O_2}) with the **alveolar gas equation** (described in Case 18). Therefore, at 4 P.M.:

$$\text{"a"} = 55 \text{ mm Hg}$$

$$\text{"A"} = PI_{O_2} - \frac{PA_{CO_2}}{R}$$

$$= (P_B - P_{H_2O}) \times FI_{O_2} - \frac{PA_{CO_2}}{R}$$

$$= (760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 0.21 - \frac{32 \text{ mm Hg}}{0.8}$$

$$= 150 \text{ mm Hg} - \frac{32 \text{ mm Hg}}{0.8}$$

$$= 110 \text{ mm Hg}$$

$$\text{A–a} = 110 \text{ mm Hg} - 55 \text{ mm Hg}$$

$$= 55 \text{ mm Hg}$$

Compared with a healthy person, whose A–a gradient is close to zero, Ralph's A–a gradient was greatly increased. In other words, O_2 could not equilibrate between alveolar gas and pulmonary capillary blood because of Ralph's **$\dot{V}/\dot{Q}$ defect** (specifically, a *decreased* $\dot{V}/\dot{Q}$ ratio).

7. Ralph was hyperventilating at 4 P.M. because **hypoxemia** stimulated **peripheral chemoreceptors** located in the carotid bodies. This stimulation led to an increased breathing rate (hyperventilation). At 4 P.M., Ralph's arterial P_{CO_2} (Pa_{CO_2}) was decreased *secondary* to the hyperventilation. (Recall that Pa_{CO_2} is inversely correlated with alveolar ventilation.) This decrease in Pa_{CO_2} caused an acid–base disorder called **respiratory alkalosis.** The pH of arterial blood is determined by the ratio of HCO_3^- to CO_2, as described by the **Henderson-Hasselbalch equation:**

$$\mathbf{pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2}}}$$

where

pH = $-\log_{10}[H^+]$

6.1 = pK of the HCO_3^-/CO_2 buffer

HCO_3^- = HCO_3^- concentration of arterial blood

P_{CO_2} = P_{CO_2} of arterial blood

The decrease in P_{CO_2} (secondary to hyperventilation) decreased the denominator of the Henderson-Hasselbalch equation and, consequently, increased the pH of Ralph's arterial blood (i.e., respiratory alkalosis).

8. At 6 P.M., Ralph's A–a gradient was as follows (note that FI_{O_2} was increased from 0.21 to 0.5, or 50%):

$$\text{"a"} = 45 \text{ mm Hg}$$

$$\text{"A"} = PI_{O_2} - \frac{PA_{CO_2}}{R}$$

$$= (760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 0.5 - \frac{80 \text{ mm Hg}}{0.8}$$

$$= 357 \text{ mm Hg} - 100 \text{ mm Hg}$$

$$= 257 \text{ mm Hg}$$

$$A\text{–}a = 257 \text{ mm Hg} - 45 \text{ mm Hg}$$

$$= 212 \text{ mm Hg}$$

Ralph's A–a gradient had increased further at 6 P.M.! Increasing FI_{O_2} to 0.5 caused Ralph's alveolar P_{O_2} ("A") to increase from 110 mm Hg to 257 mm Hg. However, this change did not improve Ralph's blood oxygenation. In fact, at 6 P.M., his arterial P_{O_2}("a") had decreased further, to 45 mm Hg. The fact that Ralph's A–a gradient widened (or increased) suggests that even more regions of his lungs were receiving inadequate ventilation; as a result, the $\dot{V}/\dot{Q}$ defect was even greater.

9. At 6 P.M., Ralph's Pa_{CO_2} was 80 mm Hg. This value was significantly elevated compared with both the normal value of 40 mm Hg and Ralph's value at 4 P.M. (which was lower than normal). We have already discussed why Ralph's Pa_{CO_2} was reduced at 4 P.M. (i.e., he was hyperventilating secondary to hypoxemia). The dramatic increase in Ralph's arterial P_{CO_2} between 4 P.M. and 6 P.M. reflects significant worsening of his condition. Undoubtedly, Ralph's airways had become more obstructed (a suspicion that was confirmed at autopsy), his work of breathing was further increased, he was hypoventilating, and he could not eliminate the CO_2 that his body produced. Retention of CO_2 elevated his Pa_{CO_2} and caused **respiratory acidosis,** as predicted by the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2}}$$

The increase in P_{CO_2} (in the denominator) caused his arterial pH to decrease to 7.01 (respiratory acidosis). Ralph was obtunded as a result of the narcotic effect of high P_{CO_2}.

Key topics

- A–a gradient
- β_2-Adrenergic agonists
- Airflow, pressure, resistance relationship
- Airway resistance
- Albuterol
- Asthma
- Bronchoconstriction
- Bronchodilator drugs
- Forced expiratory volume (FEV)
- Forced vital capacity (FVC)
- Functional residual capacity (FRC)
- Hyperventilation
- Hypoventilation
- Hypoxemia
- Obstructive pulmonary disease
- Peripheral chemoreceptors
- Poiseuille's law
- Respiratory acidosis
- Respiratory alkalosis
- Tidal volume
- Ventilation–perfusion ($\dot{V}/\dot{Q}$) defect, or mismatch
- $\dot{V}/\dot{Q}$ ratio
- FEV_1
- FEV_1/FVC

Case 22

Chronic Obstructive Pulmonary Disease

Case

Bernice Betweiler is a 73-year-old retired seamstress who has never been married. She worked in the alterations department of a men's clothier for 48 years. Bernice is a chain smoker. On the job, she was never found without a cigarette hanging from her lips. When her employer announced that smoking would no longer be allowed in the store, Bernice retired. Since her retirement 3 years ago, Bernice has not been feeling well. She fatigues easily, even with light exertion. She has shortness of breath and recently has begun to sleep on two pillows. However, despite these problems, she has refused to stop smoking.

Bernice made an appointment with her physician, who noted a prolonged expiratory phase in her breathing, expiratory wheezes, and increased anteroposterior chest diameter. Her nail beds were cyanotic, and she had moderate pitting edema of her ankles. Based on these observations and the results of laboratory and pulmonary tests, the physician concluded that Bernice has a combination of emphysema and bronchitis, called chronic obstructive pulmonary disease (COPD), which resulted from her long history of smoking.

The results of pulmonary function and laboratory tests are shown in Tables 3–7 and 3–8, respectively.

▼ Table 3–7. Bernice's Pulmonary Function Tests

Vital capacity	Decreased
Residual volume	Increased
Functional residual capacity	Increased
Expiratory flow rate	Decreased

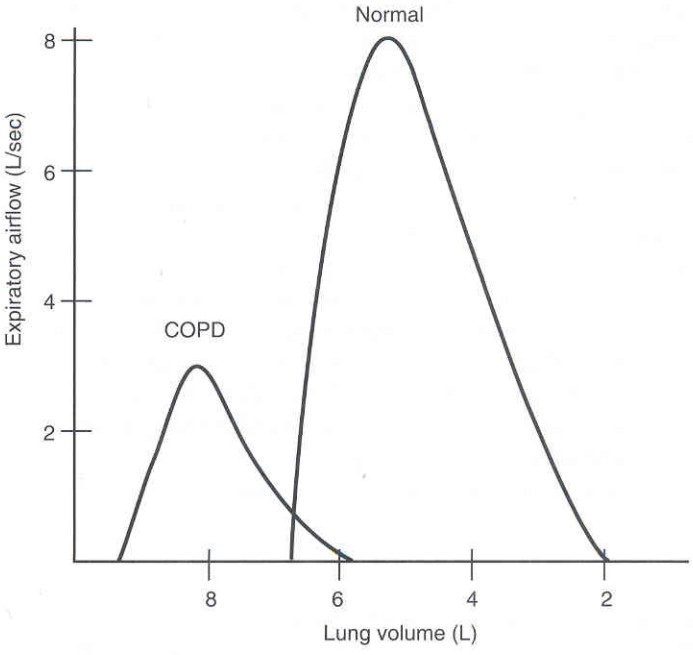
▼ Table 3–8. Bernice's Laboratory Values

Hemoglobin	14.5 g/dl (normal for women, 12–15 g/dl)
Pa_{O_2} (arterial P_{O_2})	48 mm Hg (normal, 100 mm Hg)
O_2 saturation	78% (normal, 98%–100%)
Pa_{CO_2} (arterial P_{CO_2})	69 mm Hg (normal, 40 mm Hg)
HCO_3^-	34 mEq/L (normal, 24 mEq/L)

QUESTIONS

1. Bernice's chronic bronchitis is associated with inflammation of the airways and hypersecretion of mucus, which led to obstruction of her airways and increased airway resistance. Her emphysema is associated with loss of alveolar–capillary units and decreased lung elasticity. How do these changes in airway resistance and lung elasticity explain the results of Bernice's pulmonary function tests?

2. The curves in Figure 3–9 show expiratory airflow during *forced expiration* in a healthy person and in a person with COPD. Each subject first inspired maximally (not shown) and then expired forcibly. The curves show the expiratory flow rates and lung volumes during forced expiration.



▲ **Figure 3–9.** Expiratory flow rate during forced expiration in healthy people and in patients with chronic obstructive pulmonary disease (*COPD*).

What is the value for forced vital capacity (FVC) in the healthy person and the person with COPD? What is the value for peak expiratory flow rate in each person? What is the value for residual volume in each person?

3. How is Bernice's increased anteroposterior (AP) chest diameter explained by the results of her pulmonary function tests and by your answers to Question 1?

4. Why does Bernice have a decrease in arterial P_{O_2} (Pa_{O_2})?

5. Why is her percent O_2 saturation decreased, and what are the implications for O_2 delivery to the tissues?

6. Why are Bernice's nail beds cyanotic (blue)?

7. Bernice's hemoglobin concentration is normal. If her hemoglobin concentration had been decreased, would that have altered her Pa_{O_2}? If so, in what direction?

8. Why does Bernice have an increase in arterial P_{CO_2} (Pa_{CO_2})?

9. What is Bernice's arterial pH? (Assume that the CO_2 concentration of arterial blood is $P_{CO_2} \times 0.03$.) What acid–base disorder does she have, and what is the cause? Why is her HCO_3^- concentration increased?

10. How does respiratory acidosis alter the delivery of O_2 to the tissues? (Think about the effect of CO_2 on the O_2-hemoglobin dissociation curve.) Is this effect helpful or harmful?

11. Why does Bernice have ankle edema? (Hint: Think sequentially, starting with her lungs.)

ANSWERS AND EXPLANATIONS

1. The pulmonary function tests showed that Bernice had increased residual volume, increased functional residual capacity (FRC), decreased vital capacity, and decreased expiratory flow rate. Recall that **residual volume** is the volume that remains in the lungs after forced maximal expiration; **FRC** is the volume that remains in the lungs after expiration of a normal tidal volume. Two components of Bernice's disease led to these pulmonary changes: increased resistance of her airways and decreased elasticity of her lung tissues.

The **bronchitic** component of Bernice's pulmonary disease caused narrowing and obstruction of her airways. The resulting **increased resistance** of the airways caused a decrease in airflow, especially during expiration. Because the expiratory phase was compromised, air was trapped in the lungs and residual volume was increased. Because FRC includes residual volume, FRC was also increased.

The **emphysematous** component of Bernice's disease caused **decreased elasticity** of her lung tissues, which also compromised expiration. To understand how lung elasticity is related to expiratory function, it is necessary to recall that elastance is inversely correlated with compliance (where compliance = volume/pressure). To illustrate the relationship between elastance and compliance, consider two rubber bands, one thick and one thin. The thick rubber band has a large amount of elastic "tissue;" thus, it has high elastance and high elastic recoil strength, but low compliance. The thin rubber band has a smaller amount of elastic "tissue;" thus, it has lower elastance and lower elastic recoil strength, but high compliance. In emphysema, there is loss of elastic tissue in the lung structures; as a result, elastance is decreased and **compliance is increased.** These changes in elastance and compliance have two important implications for the expiratory functions of the lungs: (1) Normal expiration is driven by elastic recoil forces that compress the air in the lungs, increase alveolar pressure, and drive the air out of the lungs. When elastic tissue is lost, elastic recoil force is decreased and expiration is impaired. (2) Normally, the airways are kept open during expiration by radial traction. This traction is created by elastic recoil forces acting on the airway walls. When elastic recoil strength decreases, the airways are deprived of this radial traction. As a result, they may collapse and close during expiration. When the airways collapse, expiration ends "early," and air that should have been expired is trapped in the lungs.

One consequence of air being trapped in the lungs, which increases the residual volume, is that the **vital capacity is decreased.** (Recall from Case 18 that vital capacity is the maximal volume of air that can be inspired above the residual volume.) Because the residual volume occupies a greater fraction of total lung capacity, it encroaches on and decreases the vital capacity.

2. To answer these numerical questions, first note that the curves show expiratory airflow as a function of lung volume. Each person has just inspired maximally. The curves show the lung volume and airflow during the forced expiration that follows.

The *healthy person* inspired maximally to a lung volume of 6.8 L, and then started the forced expiration. During expiration, the peak (maximal) expiratory flow rate was 8 L/sec. At the completion of the forced expiration, 2 L remained in the lungs. Thus, the healthy person's residual volume was 2 L, and his FVC (the total volume expired) was 4.8 L (6.8 L − 2 L).

The *person with COPD* inspired maximally to a lung volume of 9.3 L, and then started the forced expiration. The peak expiratory flow rate was much less than in the healthy person (3 L/sec). At the completion of the forced expiration, 5.8 L remained in the lungs. Thus, the person with COPD had a higher residual volume (5.8 L) and a lower FVC [3.5 L (9.3 L − 5.8 L)] than the healthy person.

3. Bernice's anteroposterior (AP) chest diameter was increased because her expiratory functions were compromised. As a result, Bernice had **air trapping,** increased residual volume, and increased FRC. Because of air trapping and increased FRC, people with COPD have **barrel-shaped chests** and are said to "breathe at higher lung volumes."

4. Bernice's arterial P_{O_2} (Pa_{O_2}) was 48 mm Hg, much lower than the normal value of 100 mm Hg. In other words, she was **hypoxemic.** Recall that a normal value of Pa_{O_2} indicates normal oxygenation of blood in the lungs. Normal oxygenation requires $\dot{V}/\dot{Q}$ matching, whereby ventilated alveoli lie in close proximity to perfused capillaries. Bernice had a **$\dot{V}/\dot{Q}$ defect** as a result of impaired ventilation. A portion of her pulmonary blood flow perfused lung regions that were not ventilated (**intrapulmonary shunt**). Those regions had a **decreased $\dot{V}/\dot{Q}$ ratio.** In other words, the denominator ($\dot{Q}$) became relatively higher than the numerator ($\dot{V}$). The blood serving these lung regions could not be oxygenated. This poorly oxygenated blood from shunt regions mixed with blood from regions of the lung that were well oxygenated. As a result, the overall P_{O_2} of blood leaving the lungs (and becoming systemic arterial blood) was decreased.

5. The **percent saturation** of hemoglobin was reduced because Bernice's P_{O_2} was reduced. Recall the important relationship between P_{O_2} and percent saturation from the discussion of the O_2-hemoglobin dissociation curve in Case 20 (see Figure 3–5).

   According to the curve, percent saturation is approximately 80% at an arterial P_{O_2} of 48 mm Hg. This number is in good agreement with Bernice's measured value of 78%. This percent saturation is clearly *reduced* from the normal value of 100%, and it corresponds to about three O_2 molecules per hemoglobin molecule (rather than the normal four O_2 molecules per hemoglobin molecule). Such a change would impair O_2 delivery to the tissues because the O_2 content of the blood is largely dependent on the amount of O_2 bound to hemoglobin. Thus, at 78% saturation, the delivery and content of O_2 are approximately 78% of normal. (Recall that dissolved O_2, the other form of O_2 in blood, contributes little to the total O_2 content.)

6. Bernice's nail beds were **cyanotic** (they had a dusky blue appearance) because there was an increased concentration of **deoxygenated hemoglobin** in her blood. This deoxygenated hemoglobin was visible in capillary beds near the skin surface. Oxygenated hemoglobin is red; deoxygenated hemoglobin is blue. Because Bernice's P_{O_2} was decreased, she had a decreased percent saturation of hemoglobin. With less hemoglobin present in the oxygenated form, more hemoglobin was present in the deoxygenated form. As a result, the blood appeared blue rather than red.

7. You may have thought that a decrease in hemoglobin concentration automatically means there is a decrease in Pa_{O_2}; however, this is not the case. Although decreased hemoglobin causes decreased O_2 *content* of blood (because the total amount of O_2

bound to hemoglobin is decreased), Pa_{O_2} is determined by the *free,* unbound O_2 (see Case 19), which is not directly affected by the hemoglobin concentration.

8. Bernice's Pa_{CO_2} was increased (**hypercapnia**) because she could not eliminate all of the CO_2 that her tissues produced. The hypercapnia was caused by the **$\dot{V}/\dot{Q}$ defect** that resulted from COPD. We already discussed how a $\dot{V}/\dot{Q}$ defect can cause hypoxemia. The explanation for CO_2 retention is a variation on this theme. We said that Bernice's hypoxemia occurred because a portion of her pulmonary blood flow perfused nonventilated regions of the lung, that those regions had a decreased $\dot{V}/\dot{Q}$ ratio, and that a portion of the blood flow was not oxygenated (i.e., intrapulmonary shunt). What about the CO_2 that is present in the shunted blood? This CO_2 cannot be transferred into alveolar gas to be expired because those regions are not ventilated. Thus, in regions of the lung that are perfused but not ventilated, CO_2 cannot be transferred into alveolar gas and expired. This CO_2 is retained in the body and causes an increased Pa_{CO_2}.

9. Bernice had **respiratory acidosis** secondary to CO_2 retention. Her arterial pH can be calculated with the **Henderson-Hasselbalch equation** as follows:

$$pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2} \times 0.03}$$

$$= 6.1 + \log \frac{34 \text{ mM}}{69 \text{ mm Hg} \times 0.03}$$

$$= 6.1 + \log \frac{34 \text{ mM}}{2.07 \text{ mM}}$$

$$= 6.1 + 1.22$$

$$= 7.32$$

An arterial pH of 7.32 is considered **acidemia** because it is lower than the normal pH of 7.4. Bernice had acidemia secondary to an elevated P_{CO_2}, which increased the denominator of the Henderson-Hasselbalch equation.

Bernice's HCO_3^- concentration was increased because she has *chronic* respiratory acidosis, in which **renal compensation** occurs. The renal compensation for respiratory acidosis is increased reabsorption of HCO_3^- (a process that is aided by the high level of P_{CO_2}). When HCO_3^- reabsorption increases, the blood HCO_3^- concentration increases. This increase in HCO_3^- concentration is "compensatory" in the sense that it helps to restore normal arterial pH. Amazingly, although Bernice had a severely elevated Pa_{CO_2}, her pH was only *slightly* acidic. This is explained by the fact that her HCO_3^- concentration was also elevated, almost to the same extent as her P_{CO_2}. As a result, the ratio of HCO_3^- to CO_2 was nearly normal, and her pH was nearly normal.

10. The only "good news" for Bernice is that her increased P_{CO_2} caused a **right shift** of the O_2-hemoglobin dissociation curve (see Figure 3–5). Increases in P_{CO_2} (and acidosis) cause a decrease in the affinity of hemoglobin for O_2 (**Bohr effect**), which appears as a right shift of the curve. For a given value of P_{O_2}, the percent saturation of hemoglobin is decreased. In Bernice's case, the right shift was helpful; al-

though the O_2 content of her blood was significantly decreased (secondary to hypoxemia), the **decreased affinity** made it easier for hemoglobin to unload O_2 in the tissues. The "bad news" is that the right shift with its decreased affinity also made it more difficult to load O_2 in the lungs.

11. The "hint " in the question suggests that Bernice had edema on the systemic side of the circulation (in the ankles) because of problems in her lungs. In patients with COPD, pulmonary artery pressure is often elevated secondary to **increased pulmonary vascular resistance.** Pulmonary vascular resistance is increased for two reasons: (1) COPD is associated with loss of alveolar–capillary units. The loss of capillary beds increases pulmonary resistance. (2) Alveolar hypoxia (secondary to hypoventilation) causes **hypoxic vasoconstriction.** The increased pulmonary vascular resistance leads to increased pulmonary artery pressure, which is the afterload of the right ventricle. Increased afterload on the right ventricle causes **decreased cardiac output,** or **cor pulmonale** (right ventricular failure secondary to pulmonary hypertension). Blood that is not ejected from the right ventricle "backs up" into the right atrium and the systemic veins. Increased systemic venous pressure increases capillary hydrostatic pressure, leading to increased filtration of fluid into the interstitium (**edema**).

Although hypoxic vasoconstriction (discussed earlier) is "bad" in the sense that it causes pulmonary hypertension and subsequent right ventricular failure, it is "good" in the sense that it is attempting to improve $\dot{V}/\dot{Q}$ matching. Poorly ventilated regions of the lung are hypoxic; this hypoxia causes vasoconstriction of nearby arterioles and directs blood flow away from regions where gas exchange cannot possibly occur. Therefore, this process attempts to redirect (or shunt) blood flow to regions that are ventilated.

A final note on this case: patients with COPD are classified as "pink puffers" (type A) or "blue bloaters" (type B), depending on whether their disease is primarily emphysema (pink puffers) or bronchitis (blue bloaters). Bernice is a **blue bloater:** she has severe hypoxemia with cyanosis, hypercapnia, right ventricular failure, and systemic edema. **Pink puffers** are tachypneic (have an increased breathing rate), have mild hypoxemia, and are hypocapnic or normocapnic.

Key topics

- Anteroposterior (AP) chest diameter
- Bohr effect
- Bronchitis
- Chronic obstructive pulmonary disease (COPD)
- Compliance
- Cor pulmonale
- Cyanosis
- Elastance
- Emphysema
- Functional residual capacity (FRC)
- Heart failure
- Henderson-Hasselbalch equation
- Hypercapnia
- Hypoxemia
- Hypoxic vasoconstriction
- Peak expiratory flow rate
- Percent saturation
- Physiologic dead space
- Physiologic shunt
- Pulmonary hypertension
- Pulmonary vascular resistance
- Residual volume
- Respiratory acidosis
- Right ventricular failure
- Right shift of the O_2-hemoglobin dissociation curve
- Ventilation–perfusion ($\dot{V}/\dot{Q}$) defect
- $\dot{V}/\dot{Q}$ ratio

Case 23

Interstitial Fibrosis: Restrictive Lung Disease

Case

Simone Paciocco, a 42-year-old wife and mother of two teenagers, was diagnosed 3 years ago with diffuse interstitial pulmonary fibrosis. As much as possible, Simone has tried to continue her normal activities, which include working as an assistant manager at a bank. However, keeping up with the demands of day-to-day life has become increasingly difficult. Simone tires easily and can no longer climb a flight of stairs without becoming extremely short of breath. She is being closely followed by her physician, a pulmonologist.

Tables 3–9 and 3–10 show the information obtained at a recent physical examination.

▼ Table 3–9. Simone's Arterial Blood Gases at Rest

Pa_{O_2} (arterial P_{O_2})	76 mm Hg (normal, 100 mm Hg)
Pa_{CO_2} (arterial P_{CO_2})	37 mm Hg (normal, 40 mm Hg)
% saturation	97% (normal, 95%–100%)

▼ Table 3–10. Results of Simone's Pulmonary Function Tests at Rest

Total lung capacity	Decreased
Functional residual capacity	Decreased
Residual volume	Decreased
DL_{CO}	Decreased
FEV_1/FVC	Increased

DL_{CO}, lung diffusing capacity; *FEV_1*, volume expired in the first second of forced expiration; *FVC*, forced vital capacity.

After these results were obtained at rest, Simone was asked to exercise on a stair climber. After only 2 minutes, she became extremely fatigued and had to discontinue the test. The arterial blood gas measurements were repeated, with the following results (Table 3–11).

▼ Table 3–11. Simone's Arterial Blood Gases During Exercise

Pa_{O_2} (arterial P_{O_2})	62 mm Hg (normal, 100 mm Hg)
Pa_{CO_2} (arterial P_{CO_2})	36 mm Hg (normal, 40 mm Hg)
% saturation	90%

QUESTIONS

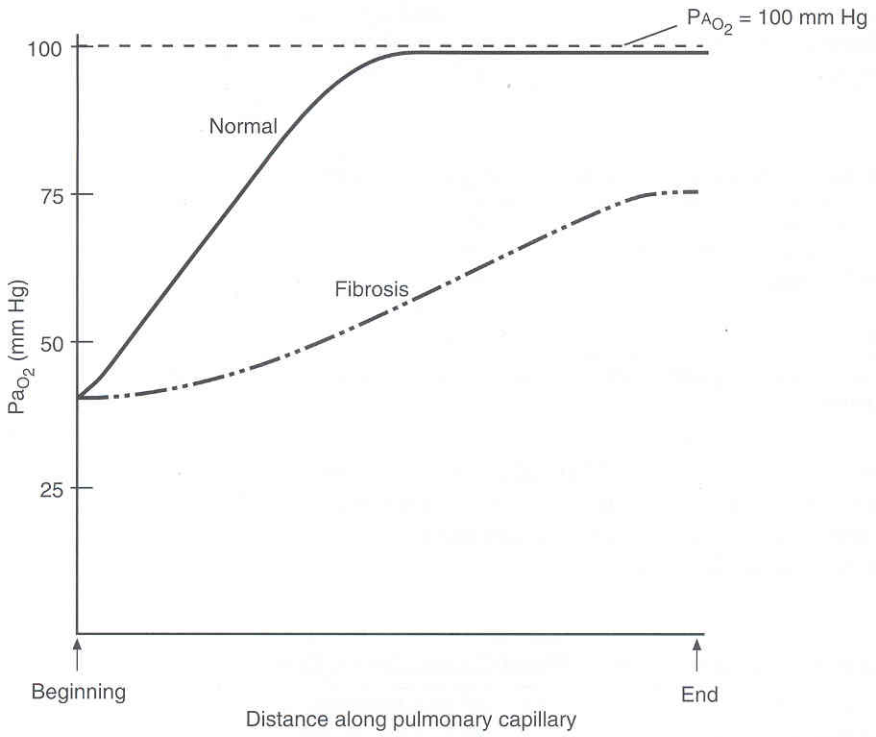
1. Diffuse interstitial fibrosis is a restrictive pulmonary disease characterized by decreased compliance of lung tissues. Use this information to explain Simone's

decreased total lung capacity, decreased functional residual capacity (FRC), and decreased residual volume at rest. Why was there an increase in her FEV_1/FVC [fraction of the forced vital capacity (FVC) expired in the first second of expiration]?

2. Lung diffusing capacity (DL) is measured with carbon monoxide. Why CO? What is the meaning of Simone's decreased DL_{CO}?

3. In addition to changes in lung compliance, diffuse interstitial fibrosis is also characterized by thickening of alveolar membranes. Use this information to explain Simone's decreased arterial P_{O_2} (Pa_{O_2}) at rest.

4. Use Figure 3–10 to explain why O_2 exchange between alveolar gas and pulmonary capillary blood in healthy people is considered a "perfusion-limited" process. In fibrosis, why does O_2 exchange convert to a "diffusion-limited" process? How does this conversion affect Pa_{O_2}?



▲ **Figure 3–10.** O_2 diffusion along the length of the pulmonary capillary in healthy people and patients with fibrosis. PA_{O_2}, partial pressure of oxygen in alveolar gas; Pa_{O_2}, partial pressure of oxygen in arterial blood.

5. What was the total O_2 content of Simone's blood while she was at rest? Assume that the O_2-binding capacity of her blood was 1.34 ml O_2/g hemoglobin, her hemoglobin concentration was 15 g/dl, and the solubility of O_2 in blood is 0.003 ml O_2/100 ml blood/mm Hg.

6. While exercising on the stair climber, Simone's Pa_{O_2} decreased even further, to 62 mm Hg. Propose a mechanism for this further decrease in Pa_{O_2}.

7. Why did the percent saturation of hemoglobin in Simone's blood decrease (from 97% to 90%) when she exercised? How did the decrease in percent saturation affect Simone's exercise tolerance?

8. Simone was hypoxemic (i.e., she had a decreased Pa_{O_2}). However, she was not hypercapnic (i.e., she did not have CO_2 retention or an increased Pa_{CO_2}). In fact, at 37 mm Hg, her Pa_{CO_2} was slightly lower than normal. Simone clearly has a problem with O_2 exchange, but she doesn't seem to have a problem with CO_2 exchange. How can hypoxemia occur in the absence of hypercapnia?

ANSWERS AND EXPLANATIONS

1. Simone had decreased total lung capacity, decreased FRC, and decreased residual volume. In explaining these findings, it is important to understand that **restrictive** pulmonary diseases (e.g., interstitial fibrosis) are associated with **decreased compliance** of lung tissues. Because the lungs are stiff and noncompliant, greater changes in pulmonary pressures and greater effort are needed to expand the lungs during inspiration. As a result, *all* lung volumes and capacities are compromised (or decreased).

   Simone's **FEV_1/FVC** (the fraction expired in the first second of forced expiration) was *increased,* however. This finding may be surprising. Recall, however, that the airways are normally held open by elastic forces in lung tissues. The greater the elastance of the lung tissues, the greater the elastic forces that tether the airways open. Thus, in fibrosis and other restrictive diseases in which compliance is decreased and **elastance is increased,** the airways are more dilated than normal. (In fibrotic lungs, the dilated airways, surrounded by scar tissue, have a characteristic **honeycomb** appearance.) The increased airway diameter results in decreased resistance to airflow, which is evidenced by an increased FEV_1/FVC. Although FVC (like the other lung volumes and capacities) is decreased, the fraction expired in the first second actually can be increased.

2. **D_L** is measured with **CO** as follows. In the single-breath method, a subject maximally inspires air containing CO, holds his breath for 10 seconds, and then expires. The amount of CO that is transferred from alveolar gas into pulmonary capillary blood is measured to assess the diffusion characteristics of the alveolar–pulmonary capillary barrier.

   Why use CO? Why not use some other gas? CO is used because it is **diffusion-limited** (i.e., its transfer from alveolar gas into pulmonary capillary blood depends *solely* on the diffusion process). To understand this point, recall two important principles concerning the diffusion of gases: (1) The partial pressure of a gas in solution depends on the concentration of free, unbound gas. (2) The diffusion of gas is driven by a difference in partial pressure. In the **single-breath method,** the partial pressure of CO in alveolar gas is very high and the partial pressure of CO in pulmonary capillary blood is initially zero. (Normally, we have no CO in our blood.) Thus, the partial pressure gradient across the alveolar–pulmonary capillary barrier is initially very high. The gradient remains high, even after CO begins to diffuse from alveolar gas into the blood, because CO binds avidly to hemoglobin in the blood, forming carboxyhemoglobin. Binding of CO to hemoglobin keeps both the free, unbound CO concentration and the partial pressure of CO in the blood low. Thus, the **driving force for CO diffusion is maintained** along the length of the pulmonary capillary. Consequently (because the driving force for CO diffusion never dissipates), the amount of CO that is transferred from alveolar gas into pulmonary capillary blood depends solely on the diffusion characteristics of the alveolar–pulmonary barrier (e.g., its thickness).

   Simone's $D_{L_{CO}}$ was decreased because interstitial fibrosis is associated with **thickening of the alveolar walls.** This thickening increases the diffusion distance for gases such as CO and O_2 and decreases the total amount of gas that can be transferred across the alveolar wall.

3. At rest, Simone's Pa_{O_2} was 76 mm Hg, which is lower than the normal value (100 mm Hg). Before we discuss why Simone's Pa_{O_2} was decreased, let's consider how the

value of 100 mm Hg is achieved in healthy people. Equilibration of O_2 occurs across the alveolar–pulmonary capillary barrier as follows. O_2 diffuses readily from alveolar gas into pulmonary capillary blood, driven by its partial pressure gradient, until the P_{O_2} of the blood equals that of alveolar gas (approximately 100 mm Hg). Thus, the normal equilibration process results in a Pa_{O_2} of 100 mm Hg.

In Simone's case, however, perfect equilibration of O_2 was impossible: thickening of the alveolar walls impaired O_2 diffusion (as detected in a decreased DL_{CO}), and Pa_{O_2} could not become equal to alveolar P_{O_2} (PA_{O_2}).

4. Figure 3–10 shows the relationship between arterial P_{O_2} (Pa_{O_2}) and distance, or length, along the pulmonary capillary. For reference, alveolar P_{O_2} (PA_{O_2}) is represented by the dashed horizontal line at 100 mm Hg.

The curve for healthy people (**normal**) shows how O_2 equilibrates across the alveolar–pulmonary capillary barrier, as described in Question 3. Mixed venous blood enters the pulmonary capillary with a P_{O_2} of 40 mm Hg. At the beginning of the capillary, there is a large partial pressure gradient for O_2 diffusion because the P_{O_2} of alveolar gas is much higher than that of mixed venous blood. O_2 readily diffuses down this partial pressure gradient, from alveolar gas into the pulmonary capillary blood. Initially, as O_2 enters the capillary, it binds to hemoglobin, which keeps the capillary P_{O_2} low and maintains the partial pressure gradient for O_2 diffusion. However, after all of the binding sites on hemoglobin are occupied, the P_{O_2} of the blood rapidly increases and becomes equal to the PA_{O_2}. This equilibration point occurs approximately one-third of the distance along the capillary. From that point on, no further net diffusion of O_2 can occur because there is no longer a partial pressure gradient or a driving force. Blood leaves the capillary and becomes systemic arterial blood with a Pa_{O_2} equal to PA_{O_2} (100 mm Hg). In healthy people, this process is described as **perfusion-limited** because equilibration of O_2 occurs *early* along the length of the pulmonary capillary. The only way to increase the amount of O_2 transferred into the blood is to provide more blood flow, or *perfusion.*

In patients with **fibrosis,** let's presume (for the sake of discussion) that mixed venous blood enters the pulmonary capillary at the same P_{O_2} as in healthy people (40 mm Hg). Thus, the driving force for O_2 diffusion is initially identical to that of healthy people. However, in fibrotic lungs, O_2 diffusion is severely impaired because of thickening of the alveolar walls. As a result, the rate of O_2 diffusion is much lower than in normal lungs. Although P_{O_2} gradually increases along the length of the capillary, O_2 never equilibrates. The blood that leaves the pulmonary capillary (to become systemic arterial blood) has a much lower P_{O_2} than alveolar gas (in Simone's case, 76 mm Hg). Thus, in fibrosis, there is **diffusion-limited** O_2 exchange. The partial pressure gradient for O_2 is maintained along the entire length of the pulmonary capillary, and equilibration never occurs. (For purposes of discussion, mixed venous blood was shown entering the pulmonary capillary with a normal P_{O_2} of 40 mm Hg. However, because the disease process decreases Pa_{O_2}, it is expected that venous P_{O_2} would eventually be decreased as well. This simplification does not detract from the major point of the question.)

5. The **total O_2 content** of blood has two components: (1) free, dissolved O_2 and (2) O_2-hemoglobin. By now, you know that **O_2-hemoglobin** is by far the greater contributor to total O_2 content. However, to be thorough, let's calculate both dissolved and bound O_2 for Simone at rest, as described in Case 19.

$$\begin{aligned}\text{Dissolved } O_2 &= P_{O_2} \times \text{solubility}\\ &= 76 \text{ mm Hg} \times 0.003 \text{ ml } O_2/100 \text{ blood/mm Hg}\\ &= 0.23 \text{ ml } O_2/100 \text{ ml blood}\end{aligned}$$

$$\begin{aligned}O_2\text{-hemoglobin} &= O_2\text{-binding capacity} \times \%\text{ saturation}\\ &= (\text{hemoglobin concentration} \times O_2\text{-binding capacity})\\ &\quad \times \%\text{ saturation}\\ &= (15 \text{ g/dl} \times 1.34 \text{ ml } O_2/\text{g hemoglobin}) \times \%\text{ saturation}\\ &= 20.1 \text{ ml } O_2/100 \text{ ml blood} \times 97\%\\ &= 19.5 \text{ ml } O_2/100 \text{ ml blood}\end{aligned}$$

$$\begin{aligned}\text{Total } O_2 \text{ content} &= \text{dissolved } O_2 + O_2\text{-hemoglobin}\\ &= 0.23 \text{ ml } O_2/100 \text{ ml blood} + 19.5 \text{ ml } O_2/100 \text{ ml blood}\\ &= 19.7 \text{ ml } O_2/100 \text{ ml blood}\end{aligned}$$

6. You were asked to suggest possible reasons why Simone's Pa_{O_2} decreased further when she exercised. Worsening of hypoxemia during exercise is typical in pulmonary fibrosis. We know that thickening of the alveolar walls compromises O_2 diffusion and lowered Simone's Pa_{O_2} at rest. But why should O_2 exchange *worsen* during exercise? Perhaps, based on the discussions of the importance of ventilation–perfusion ($\dot{V}/\dot{Q}$) matching in this chapter, you wondered whether exercise might induce a $\dot{V}/\dot{Q}$ defect in fibrosis. Good thinking!

During exercise, we expect both ventilation and perfusion (cardiac output) to increase to meet the body's greater demand for O_2. However, in fibrosis, these increases in ventilation and cardiac output are limited, and because of the limitations, hypoxemia worsens with exercise. Because of the restrictive nature of fibrosis, it is difficult for patients to increase their tidal volume as a mechanism for increasing ventilation; instead, they tend to increase breathing rate. This rapid, shallow breathing **increases dead space ventilation.** Increasing dead space causes a **$\dot{V}/\dot{Q}$ defect** and worsens hypoxemia. Also in fibrosis, there are associated increases in pulmonary vascular resistance, which increase afterload on the heart and limit the increase in cardiac output. The limited increase in cardiac output and tissue blood flow results in ***increased* tissue extraction of O_2,** which decreases venous P_{O_2}. Thus, when patients with fibrosis exercise, the mixed venous blood entering the lungs has a P_{O_2} that is lower than at rest. This lower "starting point," coupled with the diffusion defect already discussed, causes arterial blood to have an *even lower P_{O_2} during exercise* than at rest.

7. Simone's percent saturation was further decreased during exercise because her Pa_{O_2} was further decreased. The **O_2-hemoglobin curve** (discussed in Case 19) describes the relationship between percent O_2 saturation of hemoglobin and P_{O_2} (see Figure 3–4). At a P_{O_2} of 100 mm Hg, hemoglobin is 100% saturated (four O_2 molecules per hemoglobin molecule). At a P_{O_2} of 76 mm Hg (Simone at rest), hemoglobin is approximately 97% saturated. At a P_{O_2} of 62 mm Hg (Simone during exercise), hemoglobin is approximately 90% saturated.

Because her percent saturation was decreased, the total O_2 content of Simone's blood was lower during exercise than at rest. How did this change affect O_2 delivery

to the tissues? O_2 delivery is the product of blood flow (cardiac output) and O_2 content of the blood. Although Simone's cardiac output was undoubtedly increased during exercise (but less than in a healthy person), her O_2 content was decreased because the amount of O_2 bound to hemoglobin was decreased. Given the increased O_2 requirement of the body during exercise, it is not surprising that O_2 delivery to the tissues was insufficient to meet the demand (i.e., Simone's exercise tolerance was very poor).

8. Although Simone has a problem with O_2 exchange and is hypoxemic (she has a decreased Pa_{O_2}), she does not seem to have a problem with CO_2 exchange. That is, she is not hypercapnic (she does not have an increased Pa_{CO_2}). In fact, both at rest and during exercise, Simone's Pa_{CO_2} was slightly lower than the normal value of 40 mm Hg. This pattern is common in patients with respiratory diseases: *hypoxemia occurs without hypercapnia.* But why?

Consider the sequence of events in Simone's lungs that created this pattern of arterial blood gases. The fibrotic disease affected some, but not all, regions of her lungs. The diseased regions had thickening of the alveolar walls and the diffusion barrier for O_2 and CO_2. The diffusion problem caused hypoxemia (decreased Pa_{O_2}) and may have briefly caused hypercapnia (increased Pa_{CO_2}). However, because the **central chemoreceptors** are exquisitely sensitive to small changes in P_{CO_2}, they responded to hypercapnia by increasing the ventilation rate. The increase in alveolar ventilation in healthy regions of the lungs eliminated excess CO_2 that was retained in unhealthy regions. In other words, by increasing alveolar ventilation, healthy regions of the lungs could compensate for unhealthy regions with respect to CO_2 exchange. As a result, Simone's P_{CO_2} returned to normal. Later in the course of her disease, **hypercapnia** *may* develop if she does not have enough healthy lung tissue to compensate for the unhealthy tissue, or if the **work of breathing** becomes so great that she cannot increase her alveolar ventilation sufficiently.

At this point, you may legitimately ask: If increased alveolar ventilation can rid the body of excess CO_2 that is retained by unhealthy regions of the lungs, why can't increased alveolar ventilation also correct the hypoxia? The answer lies in the characteristics of the O_2-hemoglobin curve. Increased alveolar ventilation does little to increase the total O_2 content of blood in healthy regions of the lung because of the saturation properties of hemoglobin. Once hemoglobin is 100% saturated (i.e., four O_2 molecules per hemoglobin molecule), further O_2 diffusion increases the P_{O_2} of the pulmonary capillary blood until it equals the P_{O_2} of alveolar gas. Once equilibration occurs, there is no further diffusion of O_2. The O_2 added to this blood is mostly in the dissolved form, which adds little to total O_2 content. Furthermore, well-oxygenated blood from healthy regions of the lung is always mixing with, and being diluted by, poorly oxygenated blood from unhealthy regions. As a result, the Pa_{O_2} of the mixture will always be lower than normal.

Another question may arise from this discussion: Can the degree of hyperventilation be so great that the patient actually becomes hypocapnic (has decreased Pa_{CO_2})? Absolutely! In fact, Simone's Pa_{CO_2} is slightly lower than normal. If Pa_{O_2} is low enough to stimulate the **peripheral chemoreceptors** (i.e., < 60 mm Hg), hyperventilation occurs, even greater amounts of CO_2 are expired by healthy regions of the lung, and Pa_{CO_2} falls below the normal value of 40 mm Hg.

In summary, it is not uncommon for a patient with lung disease to pass through three stages of abnormal arterial blood gases: (1) mild hypoxemia with normocapnia; (2) more severe hypoxemia ($Pa_{O_2} < 60$ mm Hg) with hypocapnia, which results

in respiratory alkalosis; and (3) severe hypoxemia with hypercapnia, which results in respiratory acidosis. At this point in her disease, Simone is somewhere between the first and the second stage.

Key topics

- Carbon monoxide
- Carboxyhemoglobin
- Central chemoreceptors
- Compliance
- Diffusion-limited gas exchange
- DL_{CO}
- Elastance
- Elastic recoil
- FEV_1
- FEV_1/FVC
- Hypercapnia
- Hypocapnia
- Hypoxemia
- Hypoxia
- Lung diffus ing capacity (DL)
- O_2 content of blood
- O_2 delivery to tissues
- O_2-hemoglobin dissociation curve
- Perfusion-limited gas exchange
- Peripheral chemoreceptors
- Pulmonary fibrosis
- Respiratory acidosis
- Respiratory alkalosis
- Restrictive lung disease
- Single-breath method
- Ventilation–perfusion ($\dot{V}/\dot{Q}$) defect
- $\dot{V}/\dot{Q}$ ratio
- Work of breathing

Case 24

Carbon Monoxide Poisoning

Case

Herman Neiswander is a 65-year-old retired landscape architect in northern Wisconsin. One cold January morning, he decided to warm his car in the garage. Forty minutes later, Mr. Neiswander's wife found him slumped in the front seat of the car, confused and breathing rapidly. He was taken to a nearby emergency department, where he was diagnosed with acute carbon monoxide poisoning and given 100% O_2 to breathe. An arterial blood sample had an unusual cherry-red color. The values obtained in the blood sample are shown in Table 3–12.

▼ **Table 3–12.** Mr. Neiswander's Arterial Blood Gases

Pa_{O_2} (arterial P_{O_2})	660 mm Hg (normal, 100 mm Hg, room air)
Pa_{CO_2} (arterial P_{CO_2})	36 mm Hg (normal, 40 mm Hg)
% saturation	50% (normal, 95%–100%)

QUESTIONS

1. In healthy people, the percent O_2 saturation of hemoglobin in arterial blood is 95%–100%. Why was Mr. Neiswander's O_2 saturation reduced to 50%?

2. What percentage of the heme groups on his hemoglobin were bound to carbon monoxide (CO)?

3. Draw a normal O_2-hemoglobin dissociation curve, and superimpose the O_2-hemoglobin dissociation curve that would have been obtained on Mr. Neiswander in the emergency department. What effect did CO poisoning have on his O_2-binding capacity? What effect did CO poisoning have on the affinity of hemoglobin for O_2?

4. How did CO poisoning alter O_2 delivery to Mr. Neiswander's tissues?

5. What was the rationale for giving Mr. Neiswander 100% O_2 to breathe?

6. In healthy people breathing room air, arterial P_{O_2} (Pa_{O_2}) is approximately 100 mm Hg. Mr. Neiswander had a Pa_{O_2} of 660 mm Hg while breathing 100% O_2. How is a value of 660 mm Hg possible? [Hint: There is a calculation that will help you to determine whether this value makes sense. For that calculation, assume that Mr. Neiswander's respiratory quotient (CO_2 production/O_2 consumption) was 0.8.]

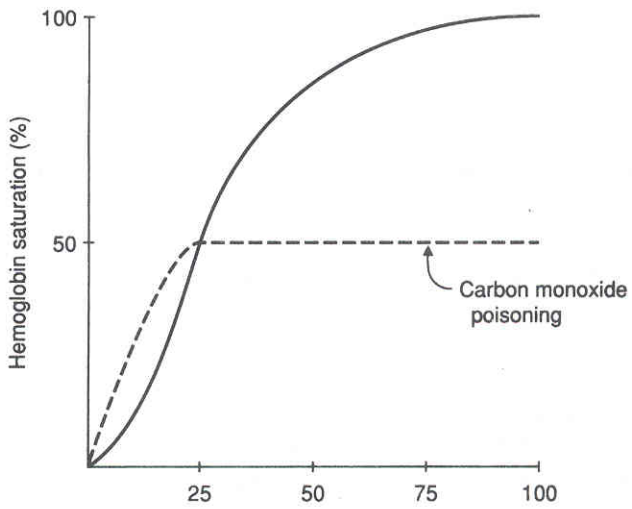
7. What is an A–a gradient? What physiologic process does the presence or absence of an A–a gradient reflect? What was the value of Mr. Neiswander's A–a gradient while he was breathing 100% O_2? What interpretation can your offer for this value?

ANSWERS AND EXPLANATIONS

1. Mr. Neiswander's **percent saturation** was only 50% (normal, 95%–100%) because CO occupied O_2-binding sites on hemoglobin. In fact, CO binds avidly to hemoglobin, with an affinity that is more than 200 times that of O_2. Thus, heme groups that should be bound to O_2 were instead bound to CO. Hemoglobin that is bound to CO is called **carboxyhemoglobin** and has a characteristic **cherry-red color.**

2. Because the percent saturation of O_2 was 50%, we can conclude that the remaining 50% of the heme sites were occupied by CO.

3. In the presence of CO, the O_2-hemoglobin dissociation curve is altered (Figure 3–11). The maximum percent saturation of hemoglobin was decreased (in Mr. Neiswander's case, to 50%), resulting in **decreased O_2-binding capacity.** A **left shift** of the curve also occurred because of a conformational change in the hemoglobin molecule caused by binding of CO. This conformational change increased the affinity of hemoglobin for the *remaining* bound O_2.



▲ **Figure 3–11.** Effect of carbon monoxide on the O_2-hemoglobin dissociation curve. P_{O_2}, partial pressure of oxygen. (Reprinted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 138.)

4. **O_2 delivery** to the tissues is the product of blood flow (cardiac output) and O_2 content of the blood, as follows:

O_2 delivery = cardiac output × O_2 content of blood

The O_2 content of blood is the sum of dissolved O_2 and O_2 bound to hemoglobin. Of these two components, O_2-hemoglobin is, by far, the most important. In Mr. Neiswander's case, O_2 delivery to the tissues was significantly reduced for two reasons: (1) CO occupied O_2-binding sites on hemoglobin, decreasing the total amount

of O_2 carried on hemoglobin in the blood. (2) The remaining heme sites (those not occupied by CO) bound O_2 with a higher affinity (consistent with a left shift of the O_2-hemoglobin curve). This increase in affinity made it more difficult to unload O_2 in the tissues. These two effects of CO combined to cause severe O_2 deprivation in the tissues (**hypoxia**).

5. Mr. Neiswander was given **100% O_2** to breathe for two reasons: (1) to competitively displace as much CO from hemoglobin as possible and (2) to increase the dissolved O_2 content in his blood. As you have learned, dissolved O_2 normally contributes little to the total O_2 content of blood. However, in CO poisoning, the O_2-carrying capacity of hemoglobin is severely reduced (in this case, by 50%), and dissolved O_2 becomes, by default, relatively more significant. By increasing the fraction of O_2 in inspired air to 100% (room air is 21% O_2), the P_{O_2} in Mr. Neiswander's alveolar gas and arterial blood will be increased, which will increase the dissolved O_2 content (dissolved $O_2 = P_{O_2} \times$ solubility of O_2 in blood).

6. While Mr. Neiswander was breathing 100% O_2, the measured value for Pa_{O_2} was strikingly high (660 mm Hg). Because pulmonary capillary blood normally equilibrates with alveolar gas, arterial P_{O_2} (Pa_{O_2}) should be equal to alveolar P_{O_2} (PA_{O_2}). Therefore, the question that we really need to answer is: *Why was the PA_{O_2} 660 mm Hg?*

   The **alveolar gas equation** is used to calculate the expected value for PA_{O_2} (as described in Case 18). For the alveolar gas equation, we need to know the values for P_{O_2} of inspired air (PI_{O_2}), PA_{CO_2}, and respiratory quotient. PI_{O_2} is calculated from the barometric pressure (corrected for water vapor pressure) and the fraction of O_2 in inspired air (FI_{O_2}). In Mr. Neiswander's case, FI_{O_2} is 1.0, or 100%. PA_{CO_2} is equal to Pa_{CO_2}, which is given. The respiratory quotient is 0.8. Thus:

$$PI_{O_2} = (PB - PH_2O) \times FI_{O_2}$$
$$= (760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 1.0$$
$$= 713 \text{ mm Hg}$$

$$PA_{O_2} = PI_{O_2} - \frac{PA_{CO_2}}{R}$$
$$= 713 \text{ mm Hg} - \frac{36 \text{ mm Hg}}{0.8}$$
$$= 668 \text{ mm Hg}$$

   From this calculation, we know that when Mr. Neiswander breathed 100% O_2, his alveolar P_{O_2} (PA_{O_2}) was expected to be 668 mm Hg. Assuming that his systemic arterial blood was equilibrated with alveolar gas, the measured Pa_{O_2} of 660 mm Hg makes perfect sense.

7. The **A–a gradient** is the difference in P_{O_2} between alveolar gas ("A") and arterial blood ("a"). In other words, the A–a gradient tells us whether equilibration of O_2 between alveolar gas and pulmonary capillary blood has occurred. If the A–a gradient is zero or close to zero, then perfect (or nearly perfect) equilibration of O_2 occurred, as is normally the case. Increases in the A–a gradient indicate a lack of equilibration, as with a ventilation–perfusion ($\dot{V}/\dot{Q}$) defect (e.g., obstructive lung disease),

when a diffusion defect is present (e.g., fibrosis), or with a right-to-left cardiac shunt (i.e., a portion of the cardiac output bypasses the lungs and is not oxygenated).

Mr. Neiswander's $P_{A_{O_2}}$ was calculated from the alveolar gas equation (see Question 6), and his Pa_{O_2} was measured in arterial blood. His A–a gradient is the difference between the two values:

$$\begin{aligned} \text{A–a gradient} &= P_{A_{O_2}} - Pa_{O_2} \\ &= 668 \text{ mm Hg} - 660 \text{ mm Hg} \\ &= 8 \text{ mm Hg} \end{aligned}$$

This small difference between the P_{O_2} of alveolar gas and the P_{O_2} of arterial blood implies that pulmonary capillary blood equilibrated almost perfectly with alveolar gas. In other words, CO poisoning caused *no problems* with $\dot{V}/\dot{Q}$ matching or O_2 diffusion.

Key topics

- A–a gradient
- Alveolar gas equation
- Carbon monoxide (CO) poisoning
- Diffusion of O_2
- Left shift of the O_2-hemoglobin dissociation curve
- O_2-hemoglobin dissociation curve
- Right-to-left cardiac shunts
- Ventilation–perfusion ($\dot{V}/\dot{Q}$) ratio

4

Renal and Acid–Base Physiology

Case 25

Essential Calculations in Renal Physiology

Case

This case will guide you through some of the basic equations and calculations in renal physiology. Use the data provided in Table 4–1 to answer the questions.

▼ **Table 4–1.** Renal Physiology Values for Case 25

$\dot{V}$ (urine flow rate)	1 ml/min
P_{inulin} (plasma concentration of inulin)	100 mg/ml
U_{inulin} (urine concentration of inulin)	12 g/ml
RA_{PAH} (renal artery concentration of PAH)	1.2 mg/ml
RV_{PAH} (renal vein concentration of PAH)	0.1 mg/ml
U_{PAH} (urine concentration of PAH)	650 mg/ml
P_A (plasma concentration of A)	10 mg/ml
U_A (urine concentration of A)	2 g/ml
P_B (plasma concentration of B)	10 mg/ml
U_B (urine concentration of B)	10 mg/ml
Hematocrit	0.45

PAH, para-aminohippuric acid. *A,* Substance A; *B,* Substance B

QUESTIONS

1. What is the value for the glomerular filtration rate (GFR)?

2. What is the value for the "true" renal *plasma* flow? What is the value for the "true" renal *blood* flow? What is the value for the "effective" renal plasma flow? Why is effective renal plasma flow different from true renal plasma flow?

3. What is the value for the filtration fraction, and what is the meaning of this value?

4. Assuming that Substance A is freely filtered (i.e., not bound to plasma proteins), what is the filtered load of Substance A? Is Substance A reabsorbed or secreted? What is the rate of reabsorption or secretion?

5. What is the fractional excretion of Substance A?

6. What is the clearance of Substance A? Is this value for clearance consistent with the conclusion you reached in Question 4 about whether Substance A is reabsorbed or secreted?

7. Substance B is 30% bound to plasma proteins. Is Substance B reabsorbed or secreted? What is the rate of reabsorption or secretion?

ANSWERS AND EXPLANATIONS

1. GFR is measured by the clearance of a glomerular marker. A **glomerular marker** is a substance that is freely filtered across the glomerular capillaries and is neither reabsorbed nor secreted by the renal tubules. The ideal glomerular marker is **inulin.** Thus, the clearance of inulin is the GFR.

   The generic equation for **clearance** of any substance, X, is:

$$\mathbf{C_x = \frac{U_x \times \dot{V}}{P_x}}$$

   where

   C_x = clearance (ml/min)

   U_x = urine concentration of substance X (e.g., mg/ml)

   P_x = plasma concentration of substance X (e.g., mg/ml)

   $\dot{V}$ = urine flow rate (ml/min)

   The **GFR**, or the clearance of inulin, is expressed as:

$$\mathbf{GFR = \frac{U_{inulin} \times \dot{V}}{P_{inulin}}}$$

   where

   GFR = glomerular filtration rate (ml/min)

   U_{inulin} = urine concentration of inulin (e.g., mg/ml)

   P_{inulin} = plasma concentration of inulin (e.g., mg/ml)

   $\dot{V}$ = urine flow rate (ml/min)

   In this case, the value for GFR (clearance of inulin) is:

$$GFR = \frac{U_{inulin} \times \dot{V}}{P_{inulin}}$$

$$= \frac{12 \text{ g/ml} \times 1 \text{ ml/min}}{100 \text{ mg/ml}}$$

$$= \frac{12{,}000 \text{ mg/ml} \times 1 \text{ ml/min}}{100 \text{ mg/ml}}$$

$$= 120 \text{ ml/min}$$

2. Renal plasma flow is measured with an organic acid called ***para*-aminohippuric acid (PAH).** The properties of PAH are very different from those of inulin. PAH is both filtered across the glomerular capillaries *and* secreted by the renal tubules, whereas inulin is only filtered. The equation for measuring "true" renal plasma flow with PAH is based on the Fick principle of conservation of mass. The Fick principle states that the amount of PAH entering the kidney through the renal artery equals the amount of PAH leaving the kidney through the renal vein and the ureter. Therefore, the equation for **"true" renal plasma flow** is as follows:

$$\mathbf{RPF = \frac{U_{PAH} \times \dot{V}}{RA_{PAH} - RV_{PAH}}}$$

where

RPF = renal plasma flow (ml/min)

U_{PAH} = urine concentration of PAH (e.g., mg/ml)

RA_{PAH} = renal artery concentration of PAH (e.g., mg/ml)

RV_{PAH} = renal vein concentration of PAH (e.g., mg/ml)

$\dot{V}$ = urine flow rate (ml/min)

Thus, in this case, the "true" renal plasma flow is:

$$RPF = \frac{650 \text{ mg/ml} \times 1 \text{ ml/min}}{1.2 \text{ mg/ml} - 0.1 \text{ mg/ml}}$$

$$RPF = \frac{650 \text{ mg/min}}{1.1 \text{ mg/ml}}$$

$$= 591 \text{ ml/min}$$

Renal blood flow is calculated from the measured renal plasma flow and the hematocrit, as follows:

$$\mathbf{RBF = \frac{RPF}{1 - Hct}}$$

where

RBF = renal blood flow (ml/min)

RPF = renal plasma flow (ml/min)

Hct = hematocrit (no units)

In words, RBF is RPF divided by one minus the hematocrit. **Hematocrit** is the fractional blood volume occupied by red blood cells. Thus, one minus the hematocrit is the fractional blood volume occupied by plasma. In this case, RBF is:

$$RBF = \frac{591 \text{ ml/min}}{1 - 0.45}$$

$$= 1075 \text{ ml/min}$$

Looking at the equation for "true" renal plasma flow, you can appreciate that this measurement would be difficult to make in human beings—blood from the renal artery and renal vein would have to be sampled directly! The measurement can be simplified, however, by applying two reasonable assumptions. (1) The concentration of PAH in the renal vein is zero, or nearly zero, because all of the PAH that enters the kidney is excreted in the urine through a combination of filtration and secretion processes. (2) The concentration of PAH in the renal artery equals the concentration of PAH in any systemic vein (other than the renal vein). This second assumption is based on the fact that no organ, other than the kidney, extracts PAH. With these two assumptions (i.e., renal vein PAH is zero and renal artery PAH is the same as sys-

temic venous plasma PAH), we have a much simplified version of the equation, which is now called "effective" renal plasma flow. Note that **"effective" renal plasma flow** is also the **clearance of PAH,** as follows:

$$\textbf{Effective RPF} = \frac{\mathbf{U_{PAH}} \times \dot{\mathbf{V}}}{\mathbf{P_{PAH}}}$$
$$= C_{PAH}$$

For this case, effective RPF is:

$$\text{Effective RPF} = \frac{650 \text{ mg/ml} \times 1 \text{ ml/min}}{1.2 \text{ mg/ml}}$$
$$= 542 \text{ ml/min}$$

Effective RPF (542 ml/min) is less than true RPF (591 ml/min). Thus, the effective RPF underestimates the true RPF by approximately 10% [(591 − 542)/591 = 0.11, or 11%]. This underestimation occurs because the renal vein concentration of PAH is *not exactly* zero (as we had assumed), it is *nearly* zero. Approximately 10% of the RPF serves renal tissue that is not involved in the filtration and secretion of PAH (e.g., renal adipose tissue). The PAH in that portion of the RPF appears in renal venous blood, not in the urine.

Naturally, you are wondering, "When should I calculate true RPF and when should I calculate effective RPF?" Although there are no hard and fast rules among examiners, it is safe to assume that if you are given values for renal artery and renal vein PAH, you will use them to calculate true RPF. If you are given only the systemic venous plasma concentration of PAH, then you will calculate effective RPF.

3. Filtration fraction is the fraction of the renal plasma flow that is filtered across the glomerular capillaries. In other words, **filtration fraction** is GFR divided by RPF:

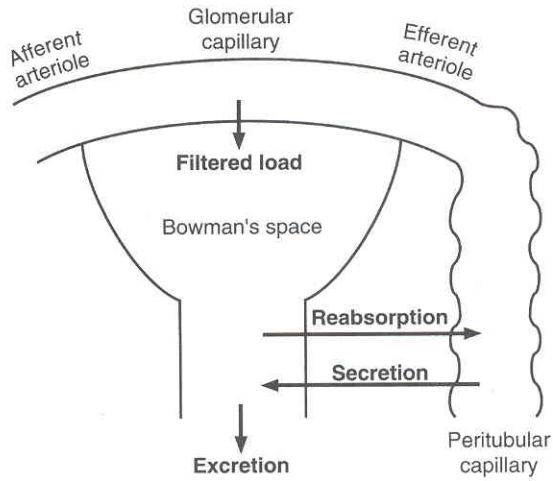
$$\textbf{Filtration fraction} = \frac{\mathbf{GFR}}{\mathbf{RPF}}$$

In this case:

$$\text{Filtration fraction} = \frac{120 \text{ ml/min}}{591 \text{ ml/min}}$$
$$= 0.20$$

This value for filtration fraction (0.20, or 20%) is typical for normal kidneys. It means that approximately 20% of the renal plasma flow entering the kidneys through the renal arteries is filtered across the glomerular capillaries. The remaining 80% of the renal plasma flow leaves the glomerular capillaries through the efferent arterioles and becomes the peritubular capillary blood flow.

4. These questions concern the calculation of filtered load, excretion rate, and reabsorption or secretion rate of Substance A (Figure 4–1).



▲ **Figure 4–1.** Processes of filtration, reabsorption, secretion, and excretion in the nephron. (Reprinted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 163.)

An interstitial-type fluid is filtered from glomerular capillary blood into Bowman's space (the first part of the proximal convoluted tubule). The amount of a substance filtered per unit time is called the **filtered load.** This glomerular filtrate is subsequently modified by reabsorption and secretion processes in the epithelial cells that line the nephron. With **reabsorption,** a substance that was previously filtered is transported *from* the lumen of the nephron into the peritubular capillary blood. Many substances are reabsorbed, including Na^+, Cl^-, HCO_3^-, amino acids, and water. With **secretion,** a substance is transported from peritubular capillary blood *into* the lumen of the nephron. A few substances are secreted, including K^+, H^+, and organic acids and bases. **Excretion** is the amount of a substance that is excreted per unit time; it is the sum, or net result, of the three processes of filtration, reabsorption, and secretion.

We can determine whether net reabsorption or net secretion of a substance has occurred by comparing its excretion rate with its filtered load. If the excretion rate is *less than* the filtered load, the substance was reabsorbed. If the excretion rate is *greater than* the filtered load, the substance was secreted. Thus, it is necessary to know how to calculate filtered load and excretion rate. With this information, we can then calculate reabsorption or secretion rate intuitively.

The filtered load of any substance, X, is the product of GFR and the plasma concentration of X, as follows:

$$\textbf{Filtered load} = \textbf{GFR} \times \textbf{P}_x$$

where

Filtered load = amount of X filtered per minute (e.g., mg/min)

GFR = glomerular filtration rate (ml/min)

P_x = plasma concentration of X (e.g., mg/ml)

The excretion rate of any substance, X, is the product of urine flow rate and the urine concentration of X:

Excretion rate = $\dot{V} \times U_x$

where

Excretion rate = amount of X excreted per minute (e.g., mg/min)
$\dot{V}$ = urine flow rate (ml/min)
U_x = urine concentration of X (e.g., mg/ml)

Now we are ready to calculate the values for filtered load and excretion rate of Substance A, and to determine whether Substance A is reabsorbed or secreted. The GFR was previously calculated from the clearance of inulin as 120 ml/min.

Filtered load of A = GFR $\times$ P_A
= 120 ml/min $\times$ 10 mg/ml
= 1200 mg/min

Excretion rate of A = $\dot{V} \times U_A$
= 1 ml/min $\times$ 2 g/ml
= 1 ml/min $\times$ 2000 mg/ml
= 2000 mg/min

The filtered load of Substance A is 1200 mg/min, and the excretion rate of Substance A is 2000 mg/min. How can there be more of Substance A excreted in the urine than was originally filtered? Substance A must have been *secreted* from the peritubular capillary blood into the tubular fluid (urine). Intuitively, we can determine that the net rate of secretion of Substance A is 800 mg/min (the difference between the excretion rate and the filtered load).

5. The **fractional excretion** of a substance is the fraction (or percent) of the filtered load that is excreted in the urine. Therefore, fractional excretion is excretion rate ($U_x \times \dot{V}$) divided by filtered load (GFR $\times$ P_x), as follows:

$$\textbf{Fractional excretion} = \frac{U_x \times \dot{V}}{GFR \times P_x}$$

where

Fractional excretion = fraction of the filtered load excreted in the urine
U_x = urine concentration of X (e.g., mg/ml)
P_x = plasma concentration of X (e.g., mg/ml)
$\dot{V}$ = urine flow rate (ml/min)
GFR = glomerular filtration rate (ml/min)

For Substance A, fractional excretion is:

$$\text{Fractional excretion} = \frac{\text{Excretion rate}}{\text{Filtered load}}$$

$$= \frac{U_A \times \dot{V}}{GFR \times P_A}$$

$$= \frac{2 \text{ g/ml} \times 1 \text{ ml/min}}{120 \text{ ml/min} \times 10 \text{ mg/ml}}$$

$$= \frac{2000 \text{ mg/min}}{1200 \text{ mg/min}}$$

$$= 1.67, \text{ or } 167\%$$

You may question how this number is possible. Can we actually excrete 167% of the amount that was originally filtered? Yes, if secretion adds a large amount of Substance A to the urine, over and above the amount that was originally filtered.

6. The concept of clearance and the clearance equation were discussed in Question 1. The renal clearance of Substance A is calculated with the clearance equation:

$$C_A = \frac{U_A \times \dot{V}}{P_A}$$

$$= \frac{2 \text{ g/ml} \times 1 \text{ ml/min}}{10 \text{ mg/ml}}$$

$$= \frac{2000 \text{ mg/ml} \times 1 \text{ ml/min}}{10 \text{ mg/ml}}$$

$$= 200 \text{ ml/min}$$

The question asked whether this calculated value of clearance is consistent with the conclusion reached in Questions 4 and 5. (The conclusion from Questions 4 and 5 was that Substance A is secreted by the renal tubule.) To answer this question, compare the clearance of Substance A (200 ml/min) with the clearance of inulin (120 ml/min). Inulin is a pure glomerular marker that is filtered, but neither reabsorbed or secreted. The clearance of Substance A is higher than the clearance of inulin because Substance A is both filtered and secreted, whereas inulin is only filtered. Thus, comparing the clearance of Substance A with the clearance of inulin gives the same qualitative answer as the calculations in Questions 4 and 5- Substance A is secreted.

7. The approach to this question is the same as that used in Question 4, except that Substance B is 30% bound to plasma proteins. Because plasma proteins are not filtered, 30% of Substance B in plasma cannot be filtered across the glomerular capillaries; only 70% of Substance B in plasma is filterable. This correction is applied in the calculation of filtered load.

$$\text{Filtered load of B} = GFR \times P_B \times \% \text{ filterable}$$

$$= 120 \text{ ml/min} \times 10 \text{ mg/ml} \times 0.7$$

$$= 840 \text{ mg/min}$$

$$\text{Excretion rate of B} = \dot{V} \times U_B$$
$$= 1 \text{ ml/min} \times 10 \text{ mg/ml}$$
$$= 10 \text{ mg/min}$$

Because the excretion rate of Substance B (10 mg/min) is much less than the filtered load (840 mg/min), Substance B must have been reabsorbed. The rate of reabsorption, calculated intuitively from the difference between filtered load and excretion rate, is 830 mg/min.

Key topics

- Clearance
- Effective renal plasma flow
- Excretion rate
- Filtered load
- Filtration fraction
- Fractional excretion
- Glomerular filtration rate (GFR)
- Hematocrit
- Reabsorption
- Renal blood flow
- Renal plasma flow
- Secretion

Case 26

Essential Calculations in Acid–Base Physiology

Case

This case will guide you through essential calculations in acid–base physiology. Use the values provided in Table 4–2 to answer the questions.

▼ **Table 4–2.** Constants for Case 26

pK of HCO_3^-/CO_2	6.1
$[CO_2]$	$P_{CO_2} \times 0.03$

QUESTIONS

1. If the H^+ concentration of a blood sample is 40×10^{-9} Eq/L, what is the pH of the blood?

2. A weak acid, HA, dissociates in solution into H^+ and the conjugate base, A^-. If the pK of this weak acid is 4.5, will the concentration of HA or A^- be higher at a pH of 7.4? How much higher will it be?

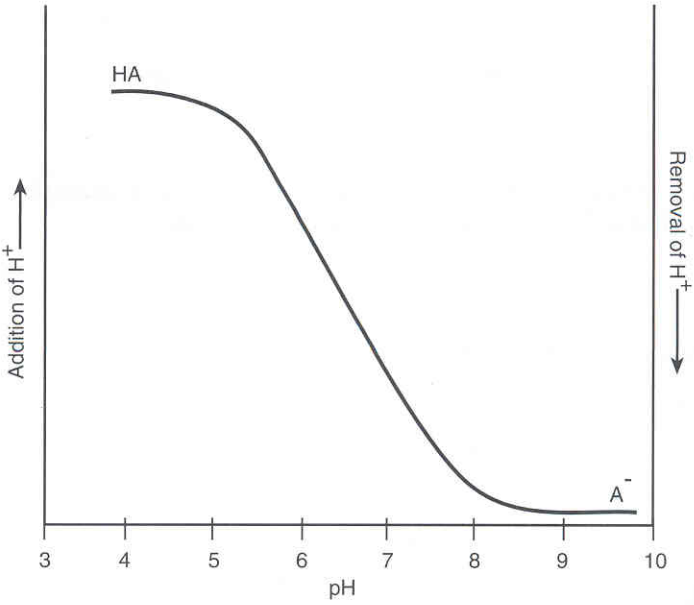
3. For the three sets of information shown in Table 4–3, calculate the missing values.

▼ **Table 4–3.** Acid–Base Values for Case 26

	pH	HCO_3^-	P_{CO_2}
A		14 mEq/L	36 mm Hg
B	7.6		48 mm Hg
C	7.2	26 mEq/L	

4. A man with chronic obstructive pulmonary disease is hypoventilating. The hypoventilation caused him to retain CO_2 and to increase his arterial P_{CO_2} to 70 mm Hg (much higher than the normal value of 40 mm Hg). If his arterial HCO_3^- concentration is normal (24 mEq/L), what is his arterial pH? Is this value compatible with life? What value of arterial HCO_3^- would make his arterial pH 7.4?

5. Figure 4–2 shows a titration curve for a hypothetical buffer, a weak acid.



▲ **Figure 4–2.** Titration curve for a weak acid. *HA,* weak acid; A^-, conjugate base.

What is the approximate pK of this buffer? At a pH of 7.4, which is the predominant form of the buffer, HA or A^-? If H^+ was added to a solution containing this buffer, would the greatest change in pH occur between pH 8 and 9, between pH 6 and 7, or between pH 5 and 6?

ANSWERS AND EXPLANATIONS

1. The pH of a solution is $-\log_{10}$ of the H^+ concentration:

$$\mathbf{pH = -\log_{10}\,[H^+]}$$

Thus, the pH of a blood sample with an H^+ concentration of 40×10^{-9} Eq/L is:

$$\begin{aligned}
\text{pH} &= -\log_{10} 40 \times 10^{-9}\ \text{Eq/L} \\
&= -\log_{10} 4 \times 10^{-8}\ \text{Eq/L} \\
&= -\log_{10} (4) + -\log_{10} (10^{-8}) \\
&= -0.6 + (-)(-8) \\
&= -0.6 + 8 \\
&= 7.4
\end{aligned}$$

In performing this basic calculation, you were reminded that: (1) a logarithmic term is more than a "button on my calculator"; (2) a blood pH of 7.4 (the normal value) corresponds to an H^+ concentration of 40×10^{-9} Eq/L; and (3) the H^+ concentration of blood is *very low*!

2. The **Henderson-Hasselbalch equation** is used to calculate the pH of a buffered solution when the concentrations of the weak acid (HA) and the conjugate base (A^-) are known. Or, it can be used to calculate the relative concentrations of HA and A^- if the pH is known.

$$\mathbf{pH = pK + \log \frac{A^-}{HA}}$$

where

pH = $-\log_{10}\,[H^+]$

pK = $-\log_{10}$ of the equilibrium constant

A^- = concentration of the conjugate base, the proton acceptor

HA = concentration of the weak acid, the proton donor

For this question, you were given the pK of a buffer (4.5) and the pH of a solution containing this buffer (7.4), and you were asked to calculate the relative concentrations of A^- and HA.

$$\text{pH} = \text{pK} + \log \frac{A^-}{HA}$$

$$7.4 = 4.5 + \log \frac{A^-}{HA}$$

$$2.9 = \log \frac{A^-}{HA}$$

Taking the antilog of both sides of the equation:

$794 = A^-/HA$

Thus, at pH 7.4, for a weak acid with a pK of 4.5, much more of the A^- form than the HA form is present (794 times more).

3. These questions concern calculations with the HCO_3^-/CO_2 buffer pair, which has a pK of 6.1. For this buffer, HCO_3^- is the conjugate base (A^-) and CO_2 is the weak acid (HA). The Henderson-Hasselbalch equation, as applied to the HCO_3^-/CO_2 buffer, is written as follows:

$$pH = 6.1 + \log \frac{HCO_3^-}{CO_2}$$

Although values for CO_2 are usually reported as P_{CO_2}, for this calculation we need to know the CO_2 *concentration*. The CO_2 concentration is calculated as $P_{CO_2} \times 0.03$. (The conversion factor, 0.03, converts P_{CO_2} in mm Hg to CO_2 concentration in mmol/L.)

$$\mathbf{pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2} \times 0.03}}$$

where

pH = $-\log_{10}$ of $[H^+]$

6.1 = pK of the HCO_3^-/CO_2 buffer

HCO_3^- = HCO_3^- concentration (mmol/L or mEq/L)

P_{CO_2} = partial pressure of CO_2 (mm Hg)

0.03 = factor that converts P_{CO_2} to CO_2 concentration in blood (mmol/L/mm Hg)

A. $$pH = 6.1 + \log \frac{14}{36 \times 0.03}$$
$$= 6.1 + \log 12.96$$
$$= 6.1 + 1.11$$
$$= 7.21$$

B. $$7.6 = 6.1 + \log \frac{HCO_3^-}{48 \times 0.03}$$

$$7.6 = 6.1 + \log \frac{HCO_3^-}{1.44}$$

$$1.5 = \log \frac{HCO_3^-}{1.44}$$

Taking the antilog of both sides:

$$31.62 = \frac{HCO_3^-}{1.44}$$

HCO_3^- = 45.5 mEq/L

C. $7.2 = 6.1 + \log \dfrac{26}{P_{CO_2} \times 0.03}$

$1.10 = \log \dfrac{26}{P_{CO_2} \times 0.03}$

Taking the antilog of both sides:

$12.6 = \dfrac{26}{P_{CO_2} \times 0.03}$

$P_{CO_2} \times 0.03 = \dfrac{26}{12.6}$

$P_{CO_2} \times 0.03 = 2.06$

$P_{CO_2} = 69$ mm Hg

4. For this question, we were given a P_{CO_2} of 70 mm Hg and an HCO_3^- concentration of 24 mEq/L. We apply the Henderson-Hasselbalch equation to calculate the pH.

$$pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2} \times 0.03}$$

$$= 6.1 + \log \frac{24}{70 \times 0.03}$$

$$= 6.1 + \log 11.4$$

$$= 6.1 + 1.06$$

$$= 7.16$$

The lowest arterial pH that is compatible with life is 6.8. Technically, this calculated pH of 7.16 is compatible with life, but it represents severe acidemia (acidic pH of the blood). To make the person's pH normal (7.4), his blood HCO_3^- concentration would have to be:

$$7.4 = 6.1 + \log \frac{HCO_3^-}{70 \times 0.03}$$

$$= 6.1 + \log \frac{HCO_3^-}{2.1}$$

$$1.3 = \log \frac{HCO_3^-}{2.1}$$

Taking the antilog of both sides:

$$19.95 = \frac{HCO_3^-}{2.1}$$

$HCO_3^- = 41.9$ mEq/L

This calculation is not just an algebraic exercise; it illustrates the concept of "compensation," which is applied in several cases in this chapter. In acid–base balance,

compensation refers to processes that help correct the pH toward normal. This exercise with the Henderson-Hasselbalch equation shows how a normal pH can be achieved in a person with an abnormally high P_{CO_2}. (A normal pH can be achieved if the HCO_3^- concentration is increased proportionately as much as the P_{CO_2} is increased.) Note, however, that in real-life situations, compensatory mechanisms may restore the pH nearly (but never perfectly) to 7.4.

5. Titration curves are useful visual aids for understanding buffering and the Henderson-Hasselbalch equation. The **pK of the buffer** shown in Figure 4–2 is the pH at which the concentrations of the HA and the A^- forms are equal (i.e., pH = 6.5). This pH coincides with the midpoint of the linear range of the titration curve, where addition or removal of H^+ causes the smallest change in pH of the solution. To determine which form of the buffer predominates at pH 7.4, locate pH 7.4 on the x-axis; visually, you can see that the predominant form at this pH is A^-. If H^+ were added to a solution containing this buffer, the greatest change in pH (of the stated choices) would occur between pH 8 and 9.

Key topics

- Buffers
- Conjugate base
- HCO_3^-/CO_2 buffer
- Henderson-Hasselbalch equation
- pH
- pK
- Titration curve
- Weak acid

Case 27

Glucosuria: Diabetes Mellitus

Case

David Mandel was diagnosed with type I (insulin-dependent) diabetes mellitus when he was 12 years old, right after he started middle school. David was an excellent student, particularly in math and science, and had many friends, most of whom he had known since nursery school. Then, at a sleepover party, the unimaginable happened: David wet his sleeping bag! He might not have told his parents if he had not been worried about other symptoms he was experiencing. He was constantly thirsty (drinking a total of 3–4 quarts of liquids daily) and was urinating every 30–40 minutes. (The night of the accident, he had already been to the bathroom four times.) Furthermore, despite a voracious appetite, he seemed to be losing weight. David's parents panicked: they had heard that these were classic symptoms of diabetes mellitus. A urine dipstick test was positive for glucose, and David was immediately seen by his pediatrician. Table 4–4 shows the findings on physical examination and the results of laboratory tests.

▼ **Table 4–4.** David's Physical Examination Findings and Laboratory Values

Height	5 feet, 3 inches
Weight	100 lb (115 lb at his annual checkup 2 months earlier)
Blood pressure	90/55 (lying) 75/45 (standing)
Fasting plasma glucose	320 mg/dl (normal, 70–110 mg/dl)
Plasma Na^+	143 mEq/L (normal, 140 mEq/L)
Urine glucose	4+ (normal, none)
Urine ketones	2+ (normal, none)
Urine Na^+	Increased

In addition, David had decreased skin turgor, sunken eyes, and a dry mouth.

All of the physical findings and laboratory results were consistent with type I diabetes mellitus. David's pancreatic beta cells had stopped secreting insulin (perhaps secondary to autoimmune destruction after a viral infection). His insulin deficiency caused hyperglycemia (an increase in blood glucose concentration) through two effects: (1) increased hepatic gluconeogenesis and (2) inhibition of glucose uptake and utilization by his cells. Insulin deficiency also increased lipolysis and hepatic ketogenesis. The resulting ketoacids (acetoacetic acid and β-OH butyric acid) were excreted in David's urine (urinary ketones).

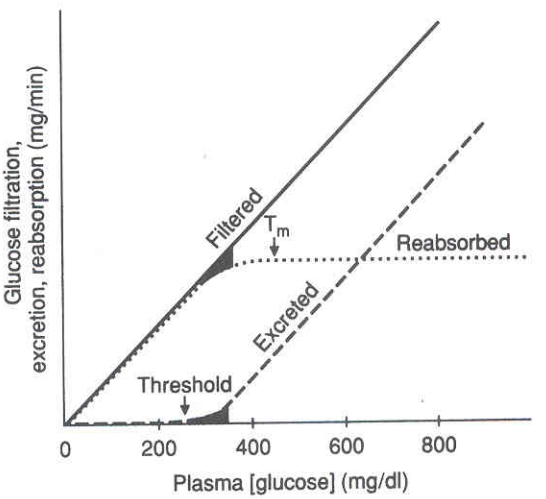
David immediately started taking injectable insulin and learned how to monitor his blood glucose level. In high school, he excelled academically and served as captain of the wrestling team and as class president. Based on his extraordinary record, he won a full scholarship to the state university, where he is currently a premedical student and is planning a career in pediatric endocrinology.

QUESTIONS

1. How is glucose normally handled in the nephron? (Discuss filtration, reabsorption, and excretion of glucose.) What transporters are involved in the reabsorption process?

2. At the time of the diagnosis, David's blood sugar level was significantly elevated (320 mg/dl). Use Figure 4–3, which shows a glucose titration curve, to explain why David was excreting glucose in his urine (glucosuria).

   Does the fact that David was excreting glucose in his urine indicate a defect in his renal threshold for glucose, in his transport maximum (T_m) for glucose, or in neither?



▲ **Figure 4–3.** Glucose titration curve. Glucose filtration, excretion, and reabsorption are shown as a function of plasma glucose concentration. Shaded areas indicate the "splay." T_m, transport maximum. (Reprinted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 164.)

3. David's glucosuria abated after he started receiving insulin injections. Why?

4. Why was David polyuric (increased urine production)? Why was his urinary Na^+ excretion elevated?

5. Plasma osmolarity (mOsm/L) can be estimated from the plasma Na^+ concentration (in mEq/L), the plasma glucose (in mg/dl), and the blood urea nitrogen (BUN, in mg/dl), as follows:

$$\text{Plasma osmolarity} \cong 2 \times \text{plasma } [Na^+] + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}$$

   Why does this formula give a reasonable estimate of plasma osmolarity? Use the formula to estimate David's plasma osmolarity (assuming that his BUN is normal

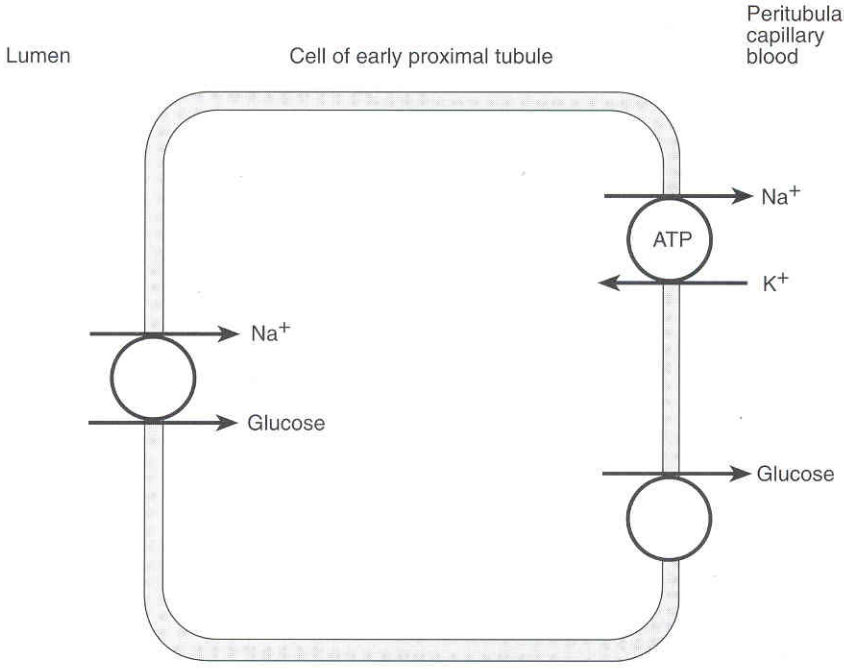
at 10 mg/dl). Is David's plasma osmolarity normal, increased, or decreased compared with normal?

6. Why was David constantly thirsty?

7. Why was David's blood pressure lower than normal? Why did his blood pressure decrease further when he stood up?

ANSWERS AND EXPLANATIONS

1. The nephron handles glucose by a combination of **filtration** and **reabsorption,** as follows. Glucose is freely filtered across the glomerular capillaries. The filtered glucose is subsequently reabsorbed by epithelial cells that line the early renal proximal tubule (Figure 4–4). The luminal membrane of these early proximal tubule cells contains an **Na^+-glucose cotransporter** that brings both Na^+ and glucose from the lumen of the nephron into the cell. The cotransporter is energized by the Na^+ gradient across the cell membrane (**secondary active transport**). Once glucose is inside the cell, it is transported across the basolateral membranes into the blood by **facilitated diffusion.** At a normal blood glucose concentration (and normal filtered load of glucose), all of the filtered glucose is reabsorbed, and none is excreted in the urine.



▲ **Figure 4–4.** Mechanism of glucose reabsorption in the early proximal tubule.

2. The **glucose titration curve** (see Figure 4–3) shows the relationship between plasma glucose concentration and rate of glucose reabsorption. Filtered load and excretion rate of glucose are shown on the same graph for comparison. By interpreting these three curves simultaneously, we can understand why David was "spilling" (excreting) glucose in his urine. The filtered load of glucose is the product of GFR and plasma glucose concentration. Therefore, as the plasma glucose concentration increases, the filtered load increases in a linear fashion. In contrast, the curves for reabsorption and excretion are not linear. (1) When the plasma glucose concentration is less than 200 mg/dl, all of the filtered glucose is reabsorbed because the Na^+-glucose cotransporters are not yet saturated. In this range, reabsorption equals filtered load, and no glucose is "left over" to be excreted in the urine. (2) When the plasma glucose concentration is between 200 and 250 mg/dl, the reabsorption curve starts to "bend." At this point, the cotransporters are nearing saturation, and some

of the filtered glucose escapes reabsorption and is excreted. The plasma glucose concentration at which glucose is first excreted in the urine (approximately 200 mg/dl) is called the **threshold,** or renal threshold. (3) At a plasma glucose concentration of 350 mg/dl, the cotransporters are fully saturated and the reabsorption rate levels off at its maximal value (**transport maximum,** or $\mathbf{T_m}$). Now the curve for excretion increases steeply, paralleling that for filtered load.

You may be puzzled as to why *any* glucose is excreted in the urine before the transporters are completely saturated. Stated differently: Why does threshold occur at a lower plasma glucose concentration than does T_m (called **splay**)? Splay has two explanations. (1) All nephrons don't have the same T_m (i.e., there is nephron heterogeneity). Nephrons that have a lower T_m excrete glucose in the urine before nephrons that have a higher T_m. (Of course, the final urine is a mixture from all nephrons.) Therefore, glucose is excreted in the urine before the average T_m of all of the nephrons is reached. (2) The affinity of the Na^+-glucose cotransporter is low. Thus, approaching T_m, if a glucose molecule becomes detached from the carrier, it will likely be excreted in the urine, even though a few binding sites are available on the transporters.

In healthy persons, the fasting plasma glucose concentration of 70–110 mg/dl is below the threshold for glucose excretion. In other words, healthy fasting persons excrete *no* glucose in their urine because the plasma glucose concentration is low enough for all of the filtered glucose to be reabsorbed.

Because of his insulin deficiency, David's fasting plasma glucose value was elevated (320 mg/dl); this value is well above the threshold for glucose excretion. His Na^+-glucose cotransporters were nearing saturation, and any filtered glucose that escaped reabsorption was excreted in the urine (**glucosuria**).

Now we can answer the question of whether David was "spilling" glucose in his urine because of a defect in his renal threshold (increased splay) *or* a defect in his T_m. The answer is: neither! David was spilling glucose in his urine simply because he was hyperglycemic. His elevated plasma glucose level resulted in an increased filtered load that exceeded the reabsorptive capacity of his Na^+-glucose cotransporters.

3. After treatment, David was no longer glucosuric because insulin decreased his plasma glucose concentration, and he was no longer hyperglycemic. With his plasma glucose level in the normal range, he could reabsorb all of the filtered glucose, and no glucose was left behind to be excreted in his urine.

4. David was polyuric (had increased urine production) because un-reabsorbed glucose acts as an **osmotic diuretic.** The presence of un-reabsorbed glucose in the tubular fluid draws Na^+ and water osmotically from peritubular blood into the lumen. This back-flux of Na^+ and water (primarily in the proximal tubule) leads to increased excretion of Na^+ and water (diuresis and polyuria).

5. **Osmolarity** is the total concentration of solute particles in a solution (i.e., mOsm/L). The expression shown in the question can be used to estimate plasma osmolarity from plasma Na^+, glucose, and BUN because these are the major solutes (osmoles) of extracellular fluid and plasma. Multiplying the Na^+ concentration by two reflects the fact that Na^+ is balanced by an equal concentration of anions. (In plasma, these anions are Cl^- and HCO_3^-.) The glucose concentration (in mg/dl) is

converted to mOsm/L when it is divided by 18. BUN (in mg/dl) is converted to mOsm/L when it is divided by 2.8.

David's estimated **plasma osmolarity (P_{osm})** is:

$$P_{osm} = 2 \times [Na^+] + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}$$

$$= 2 \times 143 + \frac{320}{18} + \frac{10}{2.8}$$

$$= 286 + 17.8 + 3.6$$

$$= 307 \text{ mOsm/L}$$

The normal value for plasma osmolarity is 290 mOsm/L. At 307 mOsm/L, David's osmolarity was significantly elevated.

6. There are two likely reasons why David was constantly **thirsty.** (1) His plasma osmolarity, as calculated in the previous question, was elevated at 307 mOsm/L (normal, 290 mOsm/L). The reason for this elevation was hyperglycemia; the increased concentration of glucose in plasma caused an increase in the total solute concentration. The increased plasma osmolarity stimulated thirst and drinking behavior through **osmoreceptors** in the hypothalamus. (2) As discussed for Question 4, the presence of un-reabsorbed glucose in the urine produced an osmotic diuresis, with increased Na^+ and water excretion. Increased Na^+ excretion led to decreased Na^+ content in the extracellular fluid (ECF) and decreased ECF volume (**volume contraction**). ECF volume contraction activates the renin-angiotensin II-aldosterone system. The increased levels of **angiotensin II** stimulate thirst.

7. David's **arterial blood pressure** was lower than that of a normal 12-year-old boy because osmotic diuresis caused **ECF volume contraction.** Decreases in ECF volume are associated with decreases in blood volume and blood pressure. Recall from cardiovascular physiology that decreases in blood volume lead to decreased venous return and decreased cardiac output, which decreases arterial pressure. Other signs of ECF volume contraction were his decreased tissue turgor and his dry mouth, which signify decreased interstitial fluid volume (a component of ECF).

   David's blood pressure decreased further when he stood up (**orthostatic hypotension**) because blood pooled in his lower extremities; venous return and cardiac output were further compromised, resulting in further lowering of arterial pressure.

Key topics

- Diabetes mellitus type I
- Glucose titration curve
- Glucosuria
- Hyperglycemia
- Hypotension
- Orthostatic hypotension
- Osmoreceptors
- Plasma osmolarity
- Polydipsia
- Polyuria
- Reabsorption
- Splay
- Threshold
- Transport maximum (T_m)
- Volume contraction (extracellular fluid volume contraction)

Case 28

Hyperaldosteronism: Conn's Syndrome

Case

Seymour Simon is a 54-year-old college physics professor who maintains a healthy lifestyle. He exercises regularly, doesn't smoke or drink alcohol, and keeps his weight in the normal range. Recently, however, he experienced generalized muscle weakness and headaches that "just won't quit." He attributed the headaches to the stress of preparing his grant renewal. Over-the-counter pain medication did not help. Professor Simon's wife was very concerned and made an appointment for him to see his primary care physician.

On physical examination, he appeared healthy. However, his blood pressure was significantly elevated at 180/100, both in the lying (supine) and the standing positions. His physician ordered laboratory tests on his blood and urine that yielded the information shown in Table 4–5.

▼ **Table 4–5.** Professor Simon's Laboratory Values

Arterial blood	
pH	7.50 (normal, 7.4)
PCO_2	48 mm Hg (normal, 40 mm Hg)
Venous blood	
Na^+	142 mEq/L (normal, 140 mEq/L)
K^+	2.0 mEq/L (normal, 4.5 mEq/L)
Total CO_2 (HCO_3^-)	36 mEq/L (normal, 24 mEq/L)
Cl^-	98 mEq/L (normal, 105 mEq/L)
Creatinine	1.1 mg/dl (normal, 1.2 mg/dl)
Urine	
Na^+ excretion	200 mEq/24 hr (normal)
K^+ excretion	1350 mEq/24 hr (elevated)
Creatinine excretion	1980 mg/24 hr
24-hr urinary catecholamines	Normal

QUESTIONS

1. Professor Simon's arterial blood pressure was elevated in both the supine and the standing positions. Consider the factors that regulate arterial pressure, and suggest several potential causes for his hypertension. What specific etiology is ruled out by the normal value for 24-hour urinary catecholamine excretion?

2. The physician suspected that Professor Simon's hypertension was caused by an abnormality in the renin-angiotensin II-aldosterone system. He ordered additional tests, including a plasma renin activity, a serum aldosterone, and a serum cortisol, which yielded the information shown in Table 4–6.

▼ **Table 4–6.** Professor Simon's Additional Laboratory Values

Plasma renin activity	Decreased
Serum aldosterone	Increased
Serum cortisol	Normal

Using your knowledge of the renin-angiotensin II-aldosterone system, suggest a pathophysiologic explanation for Professor Simon's hypertension that is consistent with these findings.

3. The physician suspected that Professor Simon had primary hyperaldosteronism (Conn's syndrome), which means that the *primary* problem was that his adrenal gland was secreting too much aldosterone. How does an increased aldosterone level cause increased arterial pressure?

4. What effect would you expect primary hyperaldosteronism to have on urinary Na^+ excretion? In light of your prediction, explain the observation that Professor Simon's urinary Na^+ excretion was normal.

5. What explanation can you give for Professor Simon's hypokalemia? If the physician had given him an injection of KCl, would the injection have corrected his hypokalemia?

6. Explain Professor Simon's muscle weakness based on his severe hypokalemia. (Hint: Think about the resting membrane potential of skeletal muscle.)

7. What acid–base abnormality did Professor Simon have? What was its etiology? What is the appropriate compensation for this disorder? Did appropriate compensation occur?

8. What was Professor Simon's glomerular filtration rate?

9. What was his fractional Na^+ excretion?

10. A computed tomographic scan confirmed the presence of a single adenoma on the left adrenal gland. Professor Simon was referred to a surgeon, who wanted to schedule surgery immediately to remove the adenoma. Professor Simon requested a 2-week delay so that he could meet his grant deadline. The surgeon reluctantly agreed on the condition that Professor Simon take a specific diuretic in the meantime. What diuretic did the physician prescribe, and what are its actions? Which abnormalities would be corrected by the diuretic?

ANSWERS AND EXPLANATIONS

1. To answer this question about the etiology of hypertension, recall from cardiovascular physiology the determinants of **arterial pressure (P_a).** The equation for P_a is a variation on the pressure, flow, resistance relationship, as follows:

P_a = cardiac output × TPR

In words, arterial pressure depends on the volume ejected from the ventricle per unit time (cardiac output) and the resistance of the arterioles (total peripheral resistance, or TPR). Thus, arterial pressure will increase if there is an increase in cardiac output, an increase in TPR, or an increase in both.

Cardiac output is the product of stroke volume and heart rate. Thus, cardiac output increases if there is an increase in either stroke volume or heart rate. An increase in stroke volume is produced by an increase in contractility (e.g., by catecholamines) or by an increase in preload or end-diastolic volume (e.g., by increases in extracellular fluid volume). An increase in heart rate is produced by catecholamines. An increase in **TPR** is produced by substances that cause vasoconstriction of arterioles (e.g., norepinephrine, angiotensin II, thromboxane, antidiuretic hormone) and by atherosclerotic disease. Thus, hypertension can be caused by an increase in cardiac output (secondary to increased contractility, heart rate, or preload) or an increase in TPR.

One of the potential causes of Professor Simon's hypertension (i.e., increased circulating catecholamines from an adrenal medullary tumor, or **pheochromocytoma**) was ruled out by the normal value for 24-hour urinary catecholamine excretion.

2. This question asked you to explain how the findings of an increased aldosterone level, a decreased renin level, and a normal level of cortisol could explain Professor Simon's hypertension.

Figure 2–10 (see Chapter 2) shows the **renin-angiotensin II-aldosterone system.** This figure shows how aldosterone secretion is increased secondary to a decrease in arterial pressure (e.g., caused by hemorrhage, diarrhea, or vomiting). Decreased arterial pressure leads to decreased renal perfusion pressure, which increases renin secretion. Renin, an enzyme, catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin-converting enzyme then catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates the secretion of aldosterone by the adrenal cortex. Clearly, Professor Simon's elevated aldosterone level *could not* have been caused by decreased blood pressure as shown in Figure 2–10; his blood pressure was *increased.*

Another possibility, also based on the renin-angiotensin II-aldosterone system, is renal artery stenosis (narrowing of the renal artery). Renal artery stenosis leads to decreased renal perfusion pressure, which increases renin secretion, increases aldosterone secretion, and causes hypertension (so-called renovascular hypertension). In that scenario, both renin levels and aldosterone levels are increased, a picture that is also inconsistent with Professor Simon's results: his renin levels were decreased, not increased.

Finally, Professor Simon's aldosterone levels could be increased if his adrenal cortex autonomously secreted too much aldosterone (**primary hyperaldosteronism**). In that case, high levels of aldosterone would lead to increases in Na^+ reabsorption, extracellular fluid (ECF) and blood volume, and blood pressure. The increased blood pressure would then cause *increased* renal perfusion pressure, which would inhibit renin secretion. This picture is entirely consistent with Professor Simon's increased aldosterone level and decreased plasma renin activity.

The normal level of cortisol suggests that an adrenal cortical tumor was selectively secreting aldosterone. If the entire adrenal cortex was oversecreting hormones (e.g., Cushing's disease), then cortisol levels would be elevated as well (see Figure 6–6 in Chapter 6).

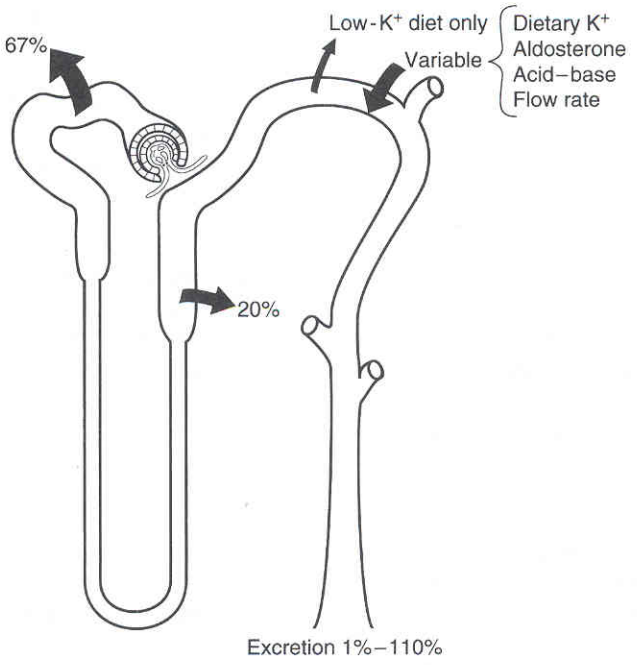
3. **Primary hyperaldosteronism (Conn's syndrome)** is associated with increased circulating levels of aldosterone, which increases Na^+ reabsorption in the late distal tubule and collecting ducts. Since the amount of Na^+ in the ECF determines the ECF volume, increased Na^+ reabsorption produces an increase in ECF volume and blood volume. Increased blood volume produces an increase in venous return and, through the Frank-Starling mechanism, an increase in cardiac output. As discussed in Question 1, increased cardiac output leads to an increase in arterial pressure.

4. In the initial phase of primary hyperaldosteronism, because aldosterone increases renal Na^+ reabsorption, we expect urinary Na^+ excretion to be decreased. However, as a consequence of the Na^+-retaining action of aldosterone, both the Na^+ content and the volume of ECF are increased (ECF volume expansion). **ECF volume expansion** then *inhibits* Na^+ reabsorption in the proximal tubule. In this later phase (when Professor Simon's urinary Na^+ excretion was measured), urinary Na^+ excretion increases toward normal, although ECF volume remains high.

   This so-called "escape" from aldosterone (or **mineralocorticoid escape**) is a safety mechanism that limits the extent to which hyperaldosteronism can cause ECF volume expansion. Three physiologic mechanisms underlie mineralocorticoid escape, and all of them lead to an increase in Na^+ excretion. (1) ECF volume expansion inhibits renal sympathetic nerve activity. This **decreased sympathetic nerve activity** inhibits Na^+ reabsorption in the proximal tubule. (2) ECF volume expansion causes dilution of the peritubular capillary protein concentration. The resulting decrease in peritubular capillary oncotic pressure causes a decrease in Na^+ reabsorption in the proximal tubule (by decreasing the **Starling forces** that drive reabsorption). (3) ECF volume expansion stimulates the secretion of **atrial natriuretic peptide (ANP,** or atrialpeptin). ANP simultaneously causes dilation of renal afferent arterioles and constriction of renal efferent arterioles. The combined effect on the two sets of arterioles is to increase the glomerular filtration rate (GFR). As the GFR increases, more Na^+ is filtered; the more Na^+ that is filtered, the more Na^+ that is excreted. ANP may also directly inhibit Na^+ reabsorption in the collecting ducts.

5. Professor Simon's **hypokalemia** was another consequence of his primary hyperaldosteronism. In addition to increasing Na^+ reabsorption, aldosterone stimulates K^+ secretion by the principal cells of the late distal tubule and collecting ducts. Increased K^+ secretion leads to excessive urinary K^+ loss, **negative K^+ balance,** and hypokalemia. If Professor Simon's physician had given him an injection of KCl, it

would *not* have effectively corrected his hypokalemia. Because of his high aldosterone level, the injected K^+ would simply have been excreted in the urine (Figure 4–5).



▲ **Figure 4–5.** K^+ handling along the nephron. *Arrows* indicate reabsorption or secretion of K^+. *Numbers* indicate the percentage of the filtered load of K^+ that is reabsorbed, secreted, or excreted. (Reprinted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 171.)

6. Hypokalemia was responsible for Professor Simon's generalized **skeletal muscle weakness.** Remember that, at rest, excitable cells (e.g., nerve, skeletal muscle) are very permeable to K^+. In fact, the resting membrane potential is close to the K^+ equilibrium potential, as described by the Nernst equation. (Intracellular K^+ concentration is high, and extracellular K^+ concentration is low; K^+ diffuses down this concentration gradient, creating an inside-negative membrane potential.) When the extracellular K^+ concentration is lower than normal (i.e., hypokalemia), as in Professor Simon's case, the resting membrane potential becomes even more negative (hyperpolarized). When the resting potential is hyperpolarized, it is further from threshold and it is more difficult to fire action potentials in the muscle (see Case 4).

7. The alkaline arterial pH of 7.50 and the elevated HCO_3^- concentration of 36 mEq/L are consistent with **metabolic alkalosis.** The elevated P_{CO_2} of 48 mm Hg is the result of hypoventilation, which is the respiratory compensation for metabolic alkalosis. Decreased ventilation caused CO_2 retention, which decreased (compensated) the pH toward normal.

We can apply the **Henderson-Hasselbalch** equation to the HCO_3^-/CO_2 buffer pair to demonstrate why hypoventilation is a compensation for metabolic alkalosis:

$$pH = pK + \log \frac{HCO_3^-}{P_{CO_2}}$$

In metabolic alkalosis, the primary disturbance is an increase in HCO_3^- concentration. By itself, this change would profoundly increase blood pH. However, the respiratory compensation (hypoventilation) elevates P_{CO_2}, which tends to normalize the ratio of HCO_3^- to CO_2 and decrease the pH toward normal. Respiratory compensation never corrects the pH perfectly and, as you can see, Professor Simon's pH was still alkaline (7.5).

The "renal rules" shown in the Appendix provide a method for determining whether the degree of respiratory compensation for metabolic alkalosis is appropriate. According to the rules, in simple metabolic alkalosis, P_{CO_2} should increase by 0.7 mm Hg for every 1 mEq/L increase in HCO_3^-. Therefore, in Professor Simon's case:

$$\begin{aligned}
\text{Increase in } HCO_3^- \text{ (above normal value of 24 mEq/L)} &= +12 \text{ mEq/L} \\
\text{Predicted increase in } P_{CO_2} &= 0.7 \times 12 \text{ mEq/L} \\
&= +8.4 \text{ mm Hg} \\
\text{Predicted } P_{CO_2} &= 40 \text{ mm Hg} + 8.4 \text{ mm Hg} \\
&= 48.4 \text{ mm Hg}
\end{aligned}$$

Based on this renal rules calculation, the *predicted* P_{CO_2} is 48.4 mm Hg, which is virtually identical to Professor Simon's *actual* P_{CO_2} of 48 mm Hg. Thus, he had simple metabolic alkalosis with appropriate respiratory compensation.

The etiology of Professor Simon's metabolic alkalosis was hyperaldosteronism. Recall that, in addition to its actions to increase Na^+ reabsorption and K^+ secretion, aldosterone stimulates H^+ secretion by the α-intercalated cells of the late distal tubule and collecting ducts. This H^+ secretion is linked to the synthesis and reabsorption of new HCO_3^-, which elevates the blood HCO_3^- concentration and produces metabolic alkalosis.

8. **GFR** is calculated from the inulin clearance or the **creatinine clearance.** Because creatinine is an endogenous substance and inulin is not, the creatinine clearance is often preferred.

$$\begin{aligned}
GFR &= C_{creatinine} \\
&= \frac{U_{creatinine} \times \dot{V}}{P_{creatinine}}
\end{aligned}$$

The plasma creatinine concentration is provided in the laboratory data, although the urine creatinine concentration and urine flow rate are not provided. Are we stuck? Not at all. To perform the calculation, you must realize that the numerator of the clearance equation, $U \times \dot{V}$, is equal to excretion rate. The 24-hour excretion rate of creatinine is provided in the laboratory data. Thus, the calculation is as follows:

$$\begin{aligned}
GFR &= C_{creatinine} \\
&= \frac{U_{creatinine} \times \dot{V}}{P_{creatinine}} \\
&= \frac{\text{Creatinine excretion rate}}{P_{creatinine}} \\
&= \frac{1980 \text{ mg/24 hr}}{1.1 \text{ mg/dl}} \\
&= \frac{1980 \text{ mg/24 hr}}{11 \text{ mg/L}} \\
&= 180 \text{ L/24 hr, or } 180 \text{ L/day}
\end{aligned}$$

9. In words, **fractional Na^+ excretion** is the fraction of the filtered load of Na^+ that is excreted in urine. It is calculated as follows:

$$\begin{aligned}
\text{Fractional } Na^+ \text{ excretion} &= \frac{Na^+ \text{ excretion}}{\text{Filtered load of } Na^+} \\
&= \frac{Na^+ \text{ excretion}}{GFR \times P_{Na}} \\
&= \frac{200 \text{ mEq/24 hr}}{180 \text{ L/24 hr} \times 142 \text{ mEq/L}} \\
&= \frac{200 \text{ mEq/24 hr}}{25{,}560 \text{ mEq/24 hr}} \\
&= 0.0078, \text{ or } 0.78\%
\end{aligned}$$

10. While Professor Simon awaited surgery for removal of the aldosterone-secreting tumor, he was treated with **spironolactone,** an aldosterone antagonist. Spironolactone blocks the actions of aldosterone by preventing aldosterone from entering the nucleus of its target cells in the late distal tubule and collecting ducts. (Normally, aldosterone enters the nucleus and directs the synthesis of messenger ribonucleic acids that encode specific transport proteins.) Thus, spironolactone inhibits all of the actions of aldosterone: Na^+ reabsorption, K^+ secretion, and H^+ secretion. The drug was expected to decrease Professor Simon's ECF volume and arterial pressure and to correct his hypokalemia and metabolic alkalosis.

Key topics

- Aldosterone
- Angiotensin II
- Arterial blood pressure (P_a)
- Atrial natriuretic peptide, or atrialpeptin (ANP)
- Cardiac output
- Conn's syndrome
- Cortisol
- Creatinine clearance
- Equilibrium potential
- Fractional excretion
- Frank-Starling mechanism
- Glomerular filtration rate (GFR)
- Henderson-Hasselbalch equation
- Hyperaldosteronism
- Hyperpolarization
- Hypokalemia
- α-Intercalated cells
- K^+ balance
- Metabolic alkalosis
- Mineralocorticoid escape (escape from aldosterone)
- Na^+ excretion
- Nernst equation
- Pheochromocytoma
- Plasma renin activity
- Principal cells
- Renal artery stenosis
- Renin
- Renin-angiotensin II-aldosterone system
- Renovascular hypertension
- Respiratory compensation
- Resting membrane potential
- Spironolactone
- Starling forces
- Total peripheral resistance (TPR)

Case 29

Central Diabetes Insipidus

Case

Lisa Kim is a 19-year-old prenursing student who works part-time in a pediatrician's office. Recently, Lisa's life seemed to revolve around being close to a bathroom and a drinking fountain. Lisa was urinating every hour (polyuria) and drinking more than 5 L of water daily (polydipsia). She always carried a water bottle with her and drank almost constantly. Lisa's employer, a physician, was concerned, and wondered whether Lisa had either a psychiatric disorder involving compulsive water drinking (primary polydipsia) or diabetes insipidus. He convinced Lisa to make an appointment with her personal physician.

The findings on physical examination were normal. Lisa's blood pressure was 105/70, her heart rate was 85 beats/min, and her visual fields were normal. Blood and urine samples were obtained for evaluation (Table 4–7).

▼ **Table 4–7.** Lisa's Laboratory Values

	Plasma	Urine
Na^+	147 mEq/L (normal, 140 mEq/L)	
Osmolarity	301 mOsm/L (normal, 290 mOsm/L)	70 mOsm/L
Glucose (fasting)	90 mg/dl (normal, 70–100 mg/dl)	Negative

Because of these initial laboratory findings, Lisa's physician performed a 2-hour water deprivation test. At the end of the test, Lisa's urine osmolarity remained at 70 mOsm/L and her plasma osmolarity increased to 325 mOsm/L. Lisa was then injected subcutaneously with dDAVP (an analogue of arginine vasopressin). After the injection, Lisa's urine osmolarity increased to 500 mOsm/L and her plasma osmolarity decreased to 290 mOsm/L.

Based on the test results and her response to vasopressin [also called antidiuretic hormone (ADH)], Lisa was diagnosed with central diabetes insipidus. Because she had no history of head injury and subsequent magnetic resonance imaging scans ruled out a brain tumor, Lisa's physician concluded that Lisa had developed a form of central diabetes insipidus in which there are circulating antibodies to ADH-secreting neurons.

Lisa started treatment with dDAVP nasal spray. She describes the spray as "amazing." As long as Lisa uses the nasal spray, her urine output is normal, and she is no longer constantly thirsty.

QUESTIONS

1. What is the normal value for urine osmolarity? Describe the mechanisms that regulate the urine osmolarity.

2. The initial measurements on Lisa's blood and urine (see Table 4–7) suggested that the cause of her polyuria was *not* primary polydipsia. Why not? What additional information, provided by the water deprivation test, confirmed that she did not have primary polydipsia?

3. What important potential diagnosis, associated with polyuria and polydipsia, was ruled out by the absence of glucose in the urine?

4. After the initial blood and urine tests were performed, Lisa's physician suspected that Lisa had *either* central *or* nephrogenic diabetes insipidus. Explain how each of these diagnoses could be consistent with her measured values for plasma and urine osmolarity.

5. How did the physician confirm that Lisa had central (rather than nephrogenic) diabetes insipidus?

6. Although it was not measured, the serum ADH level could also have distinguished between central and nephrogenic diabetes insipidus. How?

7. When Lisa's physician administered the "test" dose of dDAVP, he was surprised that Lisa's urine osmolarity increased to only 500 mOsm/L. He thought that her urine osmolarity would be higher. Then he recalled that her response is typical when exogenous vasopressin is first administered to a person with central diabetes insipidus. Why did he initially think that her urine osmolarity would be higher than 500 mOsm/L? Why wasn't it higher?

8. Why was dDAVP effective in treating Lisa's central diabetes insipidus?

9. The physician explained to Lisa that she is at risk for developing hyposmolarity while she is taking dDAVP. Why? How can she avoid becoming hyposmolar?

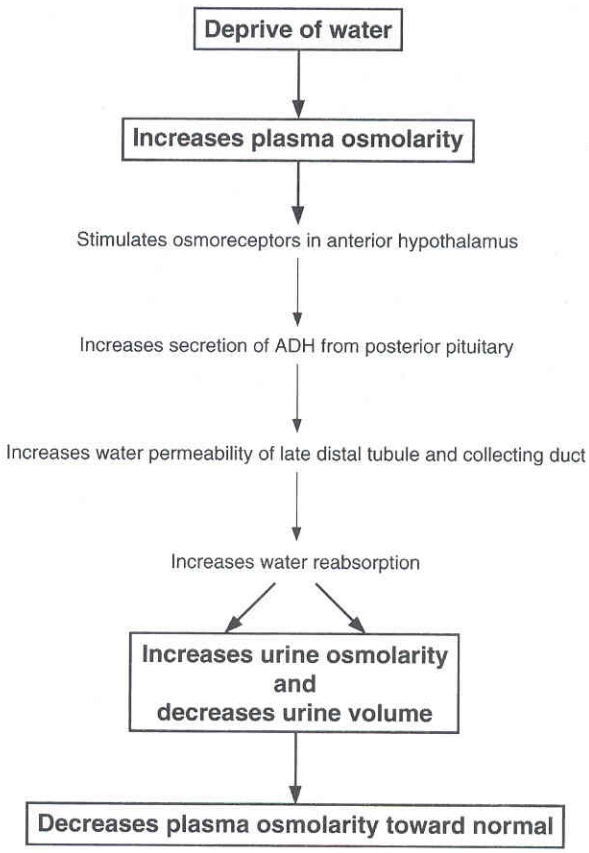
10. If Lisa had nephrogenic diabetes insipidus, how would her treatment been different?

ANSWERS AND EXPLANATIONS

1. Urine osmolarity has no single "normal" value. It can be as low as 50 mOsm/L, as high as 1200 mOsm/L, or any value in between. Normal urine osmolarity depends on the person's plasma osmolarity and water status. For example, in a person who is dehydrated, the kidneys should concentrate the urine; in this case, "normal" urine osmolarity is higher than plasma osmolarity [i.e., > 300 mOsm/L (hyperosmotic)]. In a person who is drinking water, the kidneys should dilute the urine; in this case, "normal" urine osmolarity is lower than plasma osmolarity [i.e., < 300 mOsm/L (hyposmotic)].

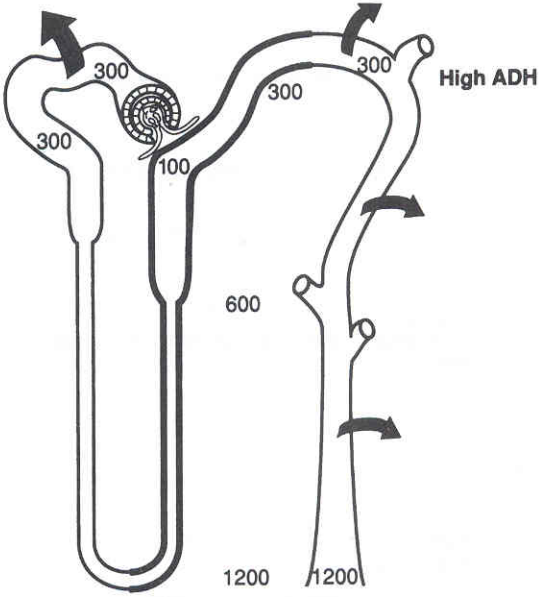
   The question about regulation of urine osmolarity is really asking how plasma osmolarity is maintained constant at a value of 290 mOsm/L. Constant plasma osmolarity is possible because the amount of water reabsorbed by the collecting ducts varies according to the body's need, as follows.

   In a person who is **dehydrated,** plasma osmolarity increases. As a result, osmoreceptors in the anterior hypothalamus are stimulated, triggering the release of ADH from the posterior pituitary. ADH circulates to the kidneys and increases the water permeability of the **principal cells** of the late distal tubule and collecting ducts. As a result, water is reabsorbed into the bloodstream and the urine is rendered hyperosmotic. The water that is reabsorbed helps to restore plasma osmolarity back to normal (Figure 4–6).



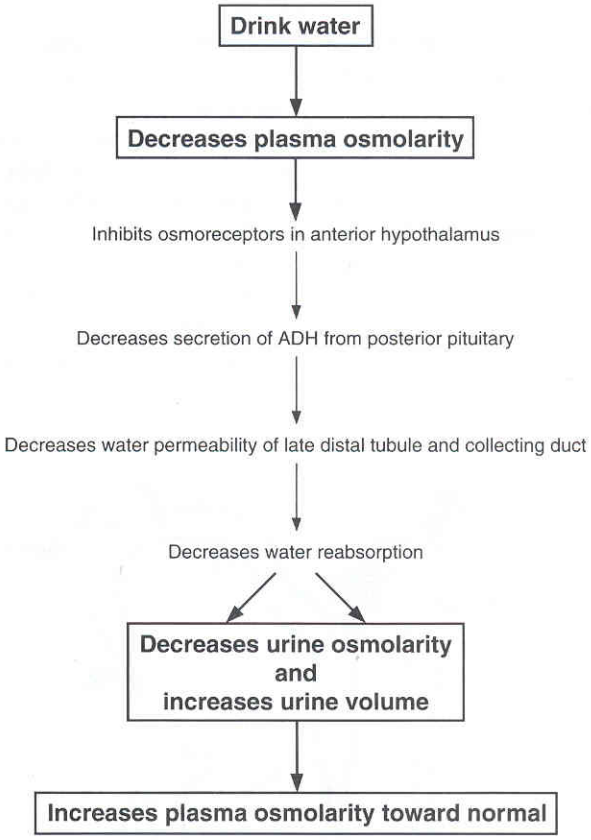
▲ **Figure 4–6.** Responses to water deprivation. *ADH,* antidiuretic hormone. (Reprinted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 176.)

The diagram of a nephron in Figure 4–7 shows how the urine becomes hyperosmotic in a person who is dehydrated. The **proximal tubule** reabsorbs solute and water isosmotically. Two later segments of the nephron are impermeable to water: the **thick ascending limb** and the **early distal tubule** (diluting segments). These segments reabsorb solute, but do not reabsorb water; the water that is "left behind" in the tubular fluid (free water, or solute-free water) dilutes the tubular fluid with respect to the plasma. In the presence of **ADH,** this free water is reabsorbed by the **late distal tubule** and **collecting ducts** until the tubular fluid equilibrates osmotically with the surrounding interstitial fluid. In the collecting ducts, which pass through the medulla and papilla of the kidney, the tubular fluid equilibrates with the **corticopapillary osmotic gradient.** The osmolarity of the final urine becomes equal to the osmolarity at the tip of the papilla (1200 mOsm/L).



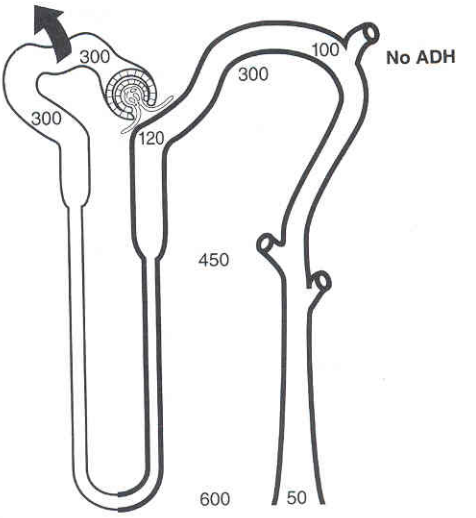
▲ **Figure 4–7.** Mechanisms for producing hyperosmotic (concentrated) urine in the presence of antidiuretic hormone (*ADH*). *Numbers* indicate osmolarity. *Heavy arrows* indicate water reabsorption. The *thick outline* shows the water-impermeable segments of the nephron. (Adapted with permission from Valtin H: *Renal Function,* 2nd ed. Boston, Little, Brown, 1983, p 162.)

In a person who is **drinking water,** plasma osmolarity decreases, inhibiting osmoreceptors in the anterior hypothalamus and inhibiting the release of ADH from the posterior pituitary. When circulating levels of ADH are low, the principal cells of the late distal tubule and collecting ducts are impermeable to water. Instead of water being reabsorbed by these segments of the nephron, it is excreted and the urine becomes hyposmotic. The water that was ingested is excreted in the urine and, as a result, plasma osmolarity returns to normal (Figure 4–8).



▲ **Figure 4–8.** Responses to water intake. *ADH,* antidiuretic hormone. (Reprinted with permission from Costanzo LS: *BRS Physiology,* 2nd ed. Baltimore, Williams & Wilkins, 1998, p 177.)

The diagram of a nephron in Figure 4–9 shows how the urine becomes hyposmotic in a person who is drinking water. The thick ascending limb and early distal tubule dilute the tubular fluid by reabsorbing solute and leaving free water behind in the tubular fluid, as discussed earlier. When ADH is suppressed or is absent, this free water cannot be reabsorbed by the late distal tubule and collecting ducts; as a result, the urine remains dilute, or hyposmotic, with an osmolarity as low as 50 mOsm/L.



▲ **Figure 4–9.** Mechanisms for producing hyposmotic (dilute) urine in the absence of antidiuretic hormone (*ADH*). *Numbers* indicate osmolarity. The *heavy arrow* indicates water reabsorption. The *thick outline* shows the water-impermeable segments of the nephron. (Adapted with permission from Valtin H: *Renal Function,* 2nd ed. Boston, Little, Brown, 1983, p 162.)

2. Lisa's initial plasma and urine values suggested that she did *not* have primary excessive polydipsia. Although her hyposmotic urine (70 mOsm/L) was consistent with excessive water drinking, her plasma osmolarity (301 mOsm/L) was not. If Lisa's *primary* problem was drinking too much water, her plasma osmolarity would have been lower than the normal value of 290 mOsm/L (leading to inhibition of ADH secretion and subsequent water diuresis).

   This conclusion is also supported by the results of the **water deprivation test.** If Lisa had primary polydipsia, her urine would have become hyperosmotic when drinking water was withheld (because ADH would no longer have been suppressed by excessive water intake). Instead, despite 2 hours of water deprivation, Lisa's urine remained hyposmotic (70 mOsm/L). Continued loss of free water in the urine (without replacement by drinking water) caused her plasma osmolarity to rise even further (325 mOsm/L).

3. Untreated **diabetes mellitus** is associated with polyuria and polydipsia. The polyuria occurs as a result of osmotic diuresis that is caused by un-reabsorbed glucose (see Case 27). Because no glucose was detected in Lisa's urine, it can be concluded that she was not undergoing a glucose-based osmotic diuresis.

4. In **central diabetes insipidus** (secondary to head injury, a hypothalamic or pituitary tumor, or idiopathic causes), ADH secretion from the posterior pituitary is deficient. In the absence of ADH, the principal cells of the late distal tubule and collecting ducts are impermeable to water. As a result, free water is not reabsorbed in these segments and the urine is rendered hyposmotic. Because excess free water is excreted, the plasma osmolarity increases.

   In **nephrogenic diabetes insipidus** (secondary to lithium toxicity or hypercalcemia), ADH is secreted normally by the posterior pituitary. However, the renal

principal cells do not respond to the hormone because of a defect in cell signaling (a defect in the ADH receptor, the G protein, or the adenylyl cyclase). Because the principal cells are "resistant" to ADH, free water is not reabsorbed in the late distal tubule and collecting ducts, and the urine is rendered hyposmotic. Excess free water is excreted, and the plasma osmolarity increases.

Thus, both forms of diabetes insipidus (central and nephrogenic) are associated with hyposmotic urine and hyperosmotic plasma. The central form is caused by ADH deficiency; the nephrogenic form is caused by ADH resistance.

5. The physician gave Lisa a test dose of **dDAVP,** an analogue of vasopressin (ADH). Lisa's kidneys responded to dDAVP and started to produce hyperosmotic urine with an osmolarity of 500 mOsm/L. Because her kidneys responded to ADH, the physician concluded that Lisa had *central* diabetes insipidus. If she had *nephrogenic* diabetes insipidus, exogenous ADH could not have elicited an increase in urine osmolarity.

6. Another way to distinguish central from nephrogenic diabetes insipidus is to measure the serum ADH level. In the central form, by definition, ADH levels are low. In the nephrogenic form, ADH levels are even higher than in a healthy person because plasma hyperosmolarity stimulates ADH secretion from the person's own (normal) posterior pituitary.

7. The physician initially thought that Lisa's urine would become maximally concentrated, or maximally hyperosmotic (1200 mOsm/L), when she received the test dose of dDAVP. He knew that exogenous ADH should increase the water permeability of the collecting ducts, and that water would be reabsorbed until her urine osmolarity was equal to the osmolarity at the tip of the papilla (which he presumed was 1200 mOsm/L). Why was Lisa's urine osmolarity only 500 mOsm/L, not 1200 mOsm/L? Was ADH ineffective?

Actually, ADH was quite effective, but Lisa's **corticopapillary gradient** was not as large as that of a healthy person. A lesser known consequence of ADH deficiency is that it decreases the corticopapillary gradient. Normally, ADH stimulates two processes that create and maintain the gradient: (1) **countercurrent multiplication** (a function of the loops of Henle) and (2) **urea recycling** (a function of the inner medullary collecting ducts). During prolonged ADH deficiency, both countercurrent multiplication and urea recycling are reduced. Consequently, the size of the corticopapillary osmotic gradient is reduced. Continuous treatment with dDAVP would eventually restore Lisa's corticopapillary osmotic gradient; at that point, she would be able to produce maximally concentrated urine.

8. Lisa was treated with dDAVP, a vasopressin (ADH) analogue that acts just like the endogenous ADH that Lisa was lacking. Thus, exogenous dDAVP increased the water permeability of the principal cells of the late distal tubule and collecting ducts. As a result, water was reabsorbed from these segments, her urine became hyperosmotic, and her urine flow rate decreased. As this water was reabsorbed into the bloodstream, plasma osmolarity was reduced to normal. As discussed in the previous question, we would also expect dDAVP to eventually restore Lisa's corticopapillary osmotic gradient, by stimulating countercurrent multiplication and urea recycling.

9. The physician warned Lisa that she could become hyposmolar (have decreased plasma osmolarity) while taking dDAVP because the treatment exposes the kidneys

to a constant high level of ADH. With dDAVP treatment, her urine would always be hyperosmotic, regardless of how much water she was drinking. In healthy persons, ADH is secreted from the posterior pituitary only when it is needed (during water deprivation). To avoid becoming hyposmolar, Lisa must not drink too much water, thus obviating the need to make hyposmotic urine.

10. The underlying problem in **nephrogenic diabetes insipidus** is resistance to ADH. The kidneys do not respond to exogenous dDAVP, just as they do not respond to endogenous ADH. In some cases, the underlying cause of nephrogenic diabetes insipidus can be treated (e.g., stopping Li^+ therapy, correcting hypercalcemia). In other cases, the treatment is **thiazide diuretics.** The rationale for using thiazide diuretics is to prevent dilution of urine in the early distal tubule. Recall that in the early distal tubule, NaCl is normally reabsorbed without water, leaving free water behind in the tubular fluid. In nephrogenic diabetes insipidus, ADH cannot promote water reabsorption in the collecting ducts, and this free water is excreted in the urine. Thiazide diuretics inhibit NaCl reabsorption in the early distal tubule, causing more NaCl to be excreted and making the urine less dilute. Thiazide diuretics also decrease glomerular filtration rate; as less water is filtered, less free water is excreted.

Key topics

- Antidiuretic hormone (ADH)
- Central diabetes insipidus
- Corticopapillary osmotic gradient
- Countercurrent multiplication
- Diabetes mellitus
- Diluting segments
- Early distal tubule
- Free water, or solute-free water
- Nephrogenic diabetes insipidus
- Osmotic diuresis
- Polydipsia
- Polyuria
- Response to dehydration
- Response to water drinking
- Thiazide diuretics
- Thick ascending limb of the loop of Henle
- Urea recycling
- Urine osmolarity
- Vasopressin

Case 30

Syndrome of Inappropriate Antidiuretic Hormone

Case

Krishna Sharma is a 68-year-old mechanical engineer who retired 1 year ago, when he was diagnosed with oat cell carcinoma of the lung. Always an active person, he has tried to stay busy at home with consulting work, but the disease has sapped his energy. After dinner one evening, his wife noticed that he seemed confused and lethargic. While he was sitting in his recliner watching television, he had a grand mal seizure. His wife called the paramedics, who took him to the emergency department of the local hospital. In the emergency department, the information shown in Table 4–8 was obtained.

▼ **Table 4–8.** Mr. Sharma's Laboratory Values

Plasma Na^+	112 mEq/L (normal, 140 mEq/L)
Plasma osmolarity	230 mOsm/L (normal, 290 mOsm/L)
Urine osmolarity	950 mOsm/L

Mr. Sharma's blood pressure was normal, both supine (lying) and upright. He was treated immediately with an infusion of hypertonic (3%) NaCl. He was released from the hospital a few days later, with strict instructions to limit his water intake.

QUESTIONS

1. Oat cell carcinomas of the lung may secrete antidiuretic hormone (ADH). Unlike ADH secretion from the posterior pituitary, ectopic hormone secretion from the cancer cells is not feedback-regulated. As a result, blood levels of ADH can become extraordinarily high. What is the major effect of these high levels of ADH on the kidney? In light of this effect, explain Mr. Sharma's urine osmolarity.

2. Why was Mr. Sharma's plasma Na^+ concentration so low? Why was his plasma osmolarity so low?

3. Mr. Sharma's disease is called syndrome of inappropriate ADH (SIADH). What is "inappropriate" about SIADH?

4. Why did Mr. Sharma have a grand mal seizure?

5. Was Mr. Sharma's total body water increased, decreased, or normal? Why was his blood pressure normal?

6. Hypertonic NaCl is 3% NaCl, which corresponds to an NaCl concentration of 517 mEq/L. How did infusion of hypertonic NaCl help to correct Mr. Sharma's low plasma Na^+ concentration?

7. Why was it so important that Mr. Sharma restrict his water intake when he went home? What would happen if he did not limit his water intake?

8. If Mr. Sharma found water restriction too difficult, his physician planned to treat him with demeclocycline, an ADH antagonist. How would this drug have helped him?

ANSWERS AND EXPLANATIONS

1. The major action of ADH is to increase the **water permeability** of the **principal cells** of the late distal tubule and collecting ducts. As a result, the tubular fluid equilibrates osmotically with the interstitial fluid surrounding the nephron. Because the collecting ducts pass through the corticopapillary osmotic gradient of the medulla and papilla, the tubular fluid becomes hyperosmotic (see Figure 4–7). In the presence of high levels of ADH, the final urine osmolarity is equilibrated with the osmolarity at the tip of the papilla, which can be as high as 1200 mOsm/L.

   A urine osmolarity of 950 mOsm/L indicates that Mr. Sharma was, most definitely, concentrating his urine. To concentrate his urine, he needed both a corticopapillary osmotic gradient (for the urine to equilibrate with) and ADH (to increase water permeability and permit that osmotic equilibration). You may wonder why his urine osmolarity was only 950 mOsm/L (rather than 1200 mOsm/L, as shown in the ideal nephron in Figure 4–7). In all likelihood, at the time of measurement, the osmolarity at the tip of his renal papilla happened to be 950 mOsm/L. In the presence of high ADH, his collecting ducts equilibrated with *that* osmolarity.

2. It is tempting to say that Mr. Sharma's plasma Na^+ concentration was low (**hyponatremia**) because he lost Na^+ from his body. However, loss of Na^+ is not the only possible reason for a low plasma Na^+ concentration. Remember, the question is about Na^+ *concentration,* which is the amount of Na^+ divided by the volume. Thus, plasma Na^+ concentration can be decreased if the amount of Na^+ in plasma is decreased *or* if the amount of water in plasma is increased. In fact, *decreased plasma Na^+ concentration is almost always the result of water excess, not Na^+ loss.*

   In Mr. Sharma's case, SIADH, with its high circulating levels of ADH, caused increased water reabsorption by the collecting ducts. This excess water was retained in the body and diluted the plasma Na^+ concentration. Mr. Sharma's plasma osmolarity was low for the same reason that his plasma Na^+ concentration was low: reabsorption of too much water by the collecting ducts led to dilution of solutes in the plasma.

3. The "inappropriate" aspect of SIADH refers to an inappropriately high ADH level and high water reabsorption when there is already too much water in the body. (Evidence of too much water in the body is provided by the low plasma Na^+ concentration and osmolarity.) For example, Mr. Sharma's very low plasma osmolarity (230 mOsm/L) should have completely inhibited ADH secretion by his posterior pituitary. No doubt, it did! However, Mr. Sharma's lung cancer cells secreted their own ADH autonomously, without any feedback control or regulation. This autonomous secretion by the cancer cells was not inhibited by his low plasma osmolarity and was *inappropriate for his plasma osmolarity.*

4. Mr. Sharma had a seizure because of swelling of his brain cells. As discussed earlier, high levels of ADH stimulated water reabsorption by his kidneys. This excess water diluted his extracellular osmolarity, as reflected in his decreased plasma osmolarity. As a result, extracellular osmolarity became transiently lower than intracellular osmolarity. Extracellular osmolarity was lower only *transiently,* however, because water shifted from extracellular fluid (ECF) to intracellular fluid (ICF) to reestablish osmotic equilibrium. This shift of water caused swelling of all cells. Because the brain is contained in a fixed structure (the skull), swelling of brain cells caused a seizure.

5. Mr. Sharma's total body water was *increased.* High levels of ADH caused increased water reabsorption and net addition of water to the body. This additional water distributed between ECF and ICF in the usual proportions (i.e., one-third to the ECF and two-thirds to the ICF).

   One of the puzzling features of SIADH (and one exhibited by Mr. Sharma) is that this addition of water to the body does not usually cause an increase in blood pressure. (One might expect increased ECF volume to be associated with increased blood volume and increased blood pressure.) In SIADH, blood pressure usually does not increase for two reasons. (1) Most (two-thirds) of the excess water retained in the body goes to the ICF rather than to the ECF; thus, ECF volume, blood volume, and blood pressure are not affected as much as you might initially think. (2) The initial increase in ECF volume activates atrial volume receptors that stimulate secretion of atrial natriuretic peptide (ANP). ANP causes increased Na^+ excretion, which decreases the Na^+ content and volume of the ECF toward normal. In essence, there is an "escape" from the effects of high ADH on ECF volume.

6. Hypertonic NaCl has an Na^+ concentration of 517 mEq/L. Mr. Sharma's ECF (which includes plasma) had an Na^+ concentration of 112 mEq/L. Thus, the infused solution, with its much higher Na^+ concentration, increased Mr. Sharma's plasma Na^+ concentration and osmolarity.

7. The primary treatment for chronic SIADH is water restriction. Mr. Sharma's cancer cells are likely to continue their unrelenting secretion of ADH, which will continue to "force" his urine to be concentrated. If Mr. Sharma restricts his water intake, then hyperosmotic urine is "appropriate." However, if he drinks large quantities of water, his kidneys will not be able to make appropriately dilute urine (because of his permanently high ADH state) and he will become hyponatremic and hyposmolar again.

8. **Demeclocycline,** an ADH antagonist, would be expected to block the action of ADH on the collecting ducts and inhibit ADH-stimulated water reabsorption. Therefore, it is possible that Mr. Sharma would not have to restrict his water intake while taking this drug.

Key topics

- Antidiuretic hormone (ADH)
- Atrial natriuretic peptide, or atrialpeptin (ANP)
- Corticopapillary osmotic gradient
- Demeclocycline
- Hyperosmotic urine
- Hyponatremia
- Hyposmolarity
- Principal cells
- Syndrome of inappropriate ADH (SIADH)

Case 31

Metabolic Acidosis: Diabetic Ketoacidosis

Case

David Mandel, who was diagnosed with type I diabetes mellitus when he was 12 years old (see Case 27), is now a third-year medical student. David's diabetes remained in control throughout middle and high school, college, and the first 2 years of medical school. However, when David started his surgery clerkship, his regular schedule of meals and insulin injections was completely disrupted. One morning, after a very late night in trauma surgery, David completely forgot to take his insulin! At 5 A.M., before rounds, he drank orange juice and ate two doughnuts. At 7 A.M., he drank more juice because he was very thirsty. He mentioned to the student next to him that he felt "strange" and that his heart was racing. At 9 A.M., he excused himself from the operating room because he thought he was going to faint. Later that morning, he was found unconscious in the call room. He was transferred immediately to the emergency department, where the information shown in Table 4–9 was obtained.

▼ **Table 4–9.** David's Physical Examination and Laboratory Values

Blood pressure	90/40
Pulse rate	130/min
Respirations	32/min, deep and rapid
Plasma concentration	
Glucose	560 mg/dl
Na^+	132 mEq/L (normal, 140 mEq/L)
K^+	5.8 mEq/L (normal, 4.5 mEq/L)
Cl^-	96 mEq/L (normal, 105 mEq/L)
HCO_3^-	8 mEq/L (normal, 24 mEq/L)
Ketones	++ (normal, none)
Arterial blood	
P_{O_2}	112 mm Hg (normal, 100 mm Hg)
P_{CO_2}	20 mm Hg (normal, 40 mm Hg)
pH	7.22 (normal, 7.4)

Based on the information shown in Table 4–9, it was determined that David was in diabetic ketoacidosis. He was given an intravenous infusion of saline and insulin. Later, after his blood glucose had decreased to 175 mg/dl and his plasma K^+ had decreased to 4 mEq/L, glucose and K^+ were added to the infusion. David stayed in the hospital overnight. By the next morning, his blood glucose, electrolytes, and blood gas values were normal.

QUESTIONS

1. What acid–base disorder did David have? What was its etiology?

2. Did David's lungs provide the expected degree of "respiratory compensation"?

3. Why was his breathing rate so rapid and deep? What is this type of breathing called?

4. How did David's failure to take insulin cause his acid–base disorder?

5. What was David's serum anion gap, and what is its significance?

6. Why was David so thirsty at 7 A.M.?

7. Why was his pulse rate increased?

8. What factors contributed to David's elevated plasma K^+ concentration (hyperkalemia)? Was his K^+ balance positive, negative, or normal?

9. How did the initial treatment with insulin and saline help to correct David's fluid and electrolyte disturbances?

10. Why were glucose and K^+ added to the infusion after his plasma glucose and K^+ levels were corrected to normal?

ANSWERS AND EXPLANATIONS

1. David's pH, HCO_3^-, and P_{CO_2} values are consistent with metabolic acidosis: decreased pH, decreased HCO_3^-, and decreased P_{CO_2} (Table 4–10).

▼ Table 4–10. Summary of Acid–Base Disorders

Disorder	$CO_2 + H_2O \leftrightarrow$	H^+	Respiratory + HCO_3^-	Renal Compensation	Compensation
Metabolic acidosis	↓ (respiratory compensation)	↑	**↓**	Hyperventilation	
Metabolic alkalosis	↑ (respiratory compensation)	↓	**↑**	Hypoventilation	
Respiratory acidosis	**↑**	↑	↑		↑ H^+ excretion ↑ HCO_3^- reabsorption
Respiratory alkalosis	**↓**	↓	↓		↓ H^+excretion ↓ HCO_3^- reabsorption

Heavy arrows indicate *primary* disturbance. (Reprinted with permission from Costanzo LS: *BRS Physiology*, 2nd ed. Baltimore, Williams & Wilkins, 1998, p 187.)

David had **metabolic acidosis** [diabetic ketoacidosis (DKA)] secondary to overproduction of the ketoacids β-OH-butyric acid and acetoacetic acid. Metabolic acidosis is usually caused by an increase in the amount of fixed acid in the body, as a result of either ingestion or overproduction of acid. The excess fixed acid is buffered by extracellular HCO_3^- and, as a result, the HCO_3^- concentration in blood decreases. This decrease in blood HCO_3^- concentration causes the pH of the blood to decrease (**acidemia**), as described by the **Henderson-Hasselbalch equation** (see Case 26):

$$pH = 6.1 + \log \frac{HCO_3^-}{P_{CO_2}}$$

The acidemia then causes an increase in breathing rate, or **hyperventilation,** by stimulating **central chemoreceptors.** As a result, arterial P_{CO_2} decreases. This decrease in arterial P_{CO_2} is the **respiratory compensation** for metabolic acidosis. Essentially, the lungs are attempting to decrease the denominator (CO_2) of the Henderson-Hasselbalch equation as much as the numerator (HCO_3^-) is decreased, which tends to normalize the ratio of HCO_3^- to CO_2 and to normalize the pH.

2. The expected degree of **respiratory compensation** can be calculated from the **"renal rules."** These rules predict the appropriate compensatory responses for simple acid–base disorders (see Appendix). For example, in simple metabolic acidosis, the renal rules can determine whether the lungs are hyperventilating to the extent expected for a given decrease in HCO_3^- concentration. David's HCO_3^- concentration is decreased to 8 mEq/L (normal, 24 mEq/L). The rules can be used to predict the expected decrease in P_{CO_2} for this decrease in HCO_3^-. If David's actual P_{CO_2} is the same as the predicted P_{CO_2}, the respiratory compensation is considered to be appropriate, and no other acid–base abnormality is present. If David's actual P_{CO_2} is

different from the predicted value, then another acid–base disorder is present (in addition to the metabolic acidosis).

The renal rules shown in the Appendix tell us that in simple metabolic acidosis, the expected change in P_{CO_2} (from the normal value of 40 mm Hg) is 1.3 times the change in HCO_3^- concentration (from the normal value of 24 mEq/L). Thus, in David's case:

$$\text{Decrease in } HCO_3^- \text{ (from normal)} = 24 \text{ mEq/L} - 8 \text{ mEq/L}$$
$$= 16 \text{ mEq/L}$$
$$\text{Predicted decrease in } P_{CO_2} \text{ (from normal)} = 1.3 \times 16 \text{ mEq/L}$$
$$= 20.8 \text{ mm Hg}$$
$$\text{Predicted } P_{CO_2} = 40 \text{ mm Hg} - 20.8 \text{ mm Hg}$$
$$= 19.2 \text{ mm Hg}$$

The predicted P_{CO_2} is 19.2 mm Hg. David's actual P_{CO_2} was 20 mm Hg. Thus, his degree of respiratory compensation was both appropriate and expected for a person with an HCO_3^- concentration of 8 mEq/L; no additional acid–base disorders were present.

3. David's rapid, deep breathing is the respiratory compensation for his metabolic acidosis. This hyperventilation, typically seen in diabetic ketoacidosis, is called **Kussmaul respiration.**

4. David has type I diabetes mellitus. The beta cells of his endocrine pancreas do not secrete enough insulin, which is absolutely required for storage of ingested nutrients (see below). Even since David developed type I diabetes mellitus in middle school, he has depended on injections of exogenous insulin to store the nutrients he ingests. When David forgot to take his insulin in the morning and then ate a high-carbohydrate meal (orange juice and doughnuts), he was in trouble!

   If you have not yet studied endocrine physiology, briefly, the major **actions of insulin** are coordinated for **storage of nutrients.** They include uptake of glucose into cells and increased synthesis of glycogen, protein, and fat. Therefore, **insulin deficiency** has the following effects: (1) decreased glucose uptake into cells, resulting in **hyperglycemia;** (2) increased protein catabolism, resulting in increased blood levels of amino acids, which serve as gluconeogenic substrates; (3) increased lipolysis, resulting in increased blood levels of free fatty acids; and (4) increased hepatic **ketogenesis** from the fatty acid substrates. The resulting ketoacids are the fixed acids **β-OH-butyric acid** and **acetoacetic acid.** Overproduction of these fixed acids causes **diabetic ketoacidosis** (discussed in Question 1).

5. The serum anion gap is "about" electroneutrality, which is an absolute requirement for every body fluid compartment (e.g., serum). That is, in every compartment, the concentration of cations must be exactly balanced by an equal concentration of anions. In the serum compartment, we usually measure Na^+ (a cation) and Cl^- and HCO_3^- (anions). When the concentration of Na^+ is compared with the sum of the concentrations of Cl^- and HCO_3^-, there is a "gap." This gap, the **anion gap,** is comprised of unmeasured anions and includes plasma albumin, phosphate, sulfate, citrate, and lactate (Figure 4–10).