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CHAPTER 18
Overview of Cardiovascular Function

KEY POINTS

1. Because normal cardiovascular function is essential for life and health, a practical understanding of cardiovascular function and dysfunction is vital to the veterinary clinician.
2. Cardiovascular dysfunctions sometimes reflect primary cardiovascular disturbances or diseases, but more often they are secondary consequences of noncardiovascular disturbances or diseases.
3. Substances transported by the cardiovascular system include nutrients, waste products, hormones, electrolytes, and water.
4. Two modes of transport are used in the cardiovascular system: bulk flow and diffusion.
5. Because diffusion is very slow, every metabolically active cell in the body must be close to a capillary carrying blood by bulk flow.
6. The pulmonary and systemic circulations are arranged in series, but the various organs within the systemic circulation are arranged in parallel.
7. Cardiac output is the volume of blood pumped each minute by one ventricle.
8. The perfusion pressure for the systemic circulation is much greater than the perfusion pressure for the pulmonary circulation.
9. Each type of blood vessel has physical properties suited to its particular function.
10. Blood is a suspension of cells in extracellular fluid (plasma).
11. The cellular component of blood includes red blood cells, white blood cells, and platelets.
12. Most of the oxygen in blood is carried in chemical combination with the protein hemoglobin within red blood cells.

Because Normal Cardiovascular Function Is Essential for Life and Health, a Practical Understanding of Cardiovascular Function and Dysfunction Is Vital to the Veterinary Clinician

Cardiovascular physiology is the study of the function of the heart, the blood vessels, and the blood. The primary function of the cardiovascular system can be summarized in one word: *transport*. The bloodstream transports numerous substances that are essential for life and health, including the oxygen and nutrients required by every cell in the body. Blood also carries carbon dioxide and other metabolic waste products away from metabolically active cells and delivers them to the lungs, kidneys, or liver, where they are excreted.

To appreciate the importance of cardiovascular transport, consider what happens if the heart stops contracting and circulation ceases: unconsciousness results within about 30 seconds, and irreversible damage to the brain and other sensitive body tissues occurs within a few minutes. However, circulation does not have to stop completely for significant dysfunction to occur. For example, the loss of as little as 10% of the normal blood volume can impair exercise performance.

In each tissue of the body, normal function depends on the delivery of adequate blood flow. The higher the rate of metabolism in a tissue, the greater is the requirement for blood flow. The condition of inadequate blood flow to any tissue is called *ischemia*. Even transient ischemia leads to *dysfunction*. Persistent ischemia leads to permanent tissue damage *(infarction)* and eventually to cell death *(necrosis)*.

Many veterinary students have difficulty understanding cardiovascular physiology. They tend to agree with William Harvey, the father of cardiovascular physiology, whose initial impression was that the motions of the heart and the blood were so complicated that they could be comprehended only by God. Harvey persisted, however, in a careful, deliberate study of cardiovascular function and in 1628 set forth the first proof that the heart propels blood through the blood vessels in a circulatory pattern. Before Harvey's time, it was thought that blood flowed out of the heart into the blood vessels and then returned to the heart by backward flow in the same vessels. In other words, blood was thought to flow in a tidal manner, in much the same way that air flows through a single set of airways: first into the lungs and then back out.

We now take for granted that the cardiovascular system is a *circulatory system,* not a tidal system. However, the circularity of the cardiovascular system is precisely what makes it difficult to understand. It has no clear beginning or ending, and disturbances in one part of the cardiovascular system end up affecting all other parts as well. In recognition of this complexity, Chapters 18 to 26 are written with the goal of identifying the most basic and important concepts of *normal cardiovascular function* and explaining them in a way that best prepares the reader to understand, diagnose, and treat *cardiovascular dysfunction* (cardiovascular disease). The remainder of this chapter reviews the general features of the cardiovascular system. Chapters 19 to 25 discuss the various elements of the cardiovascular system in detail. Chapter 26 summarizes cardiovascular function and dysfunction by describing the overall effects of heart failure, hemorrhage, and exercise.

Cardiovascular Dysfunctions Sometimes Reflect Primary Cardiovascular Disturbances or Diseases, But More Often They Are Secondary Consequences of Noncardiovascular Disturbances or Diseases

Impairment in the transport functions of the cardiovascular system is encountered frequently in veterinary medicine. Some of these cardiovascular dysfunctions are *primary,* in that the fundamental disturbance or disease process affects the cardiovascular system directly. One example of primary cardiovascular dysfunction is *hemorrhage* (loss of blood from blood vessels). Another is *myocarditis* (literally, muscle-heart-inflammation), which can be caused by a toxic chemical or by a viral or bacterial infection that inflames the heart muscle and impairs the ability of the heart to pump blood.

Cardiovascular dysfunction and disease can be either *congenital* (present at birth) or *acquired* (developing after birth). Congenital cardiovascular diseases frequently involve defective heart valves, which either cannot open fully or cannot close completely. Congenital cardiac defects are common in certain breeds of dogs and horses. Although a heart that has a congenital defect or an acquired disease may be able to pump an adequate amount of blood when the animal is at rest, it usually cannot deliver the increased blood flow required by the body during exercise. When a dysfunction in the heart impairs its ability to pump the amount of blood flow normally needed by the body, the condition is called *heart failure* (or pump failure). The patient with heart failure classically exhibits a limited ability or willingness to exercise *(exercise intolerance).*

Parasites are a common cause of acquired cardiovascular dysfunction. In dogs, for example, adult heartworms *(Dirofilaria immitis)* lodge in the right ventricle and pulmonary artery, where they impede the flow of blood. These worms also release substances into the circulation that disrupt the body's ability to control blood pressure and blood flow. In horses, bloodworms *(Strongylus vulgaris)* lodge in the mesenteric arteries and decrease the blood flow to the intestine. The resulting intestinal ischemia depresses digestive functions (motility, secretion, and absorption), and the horse exhibits signs of gastrointestinal distress *(colic).*

In many other disease states, cardiovascular complications develop even though the cardiovascular system is not the primary target of the disease. These *secondary cardiovascular dysfunctions* often become the most serious and life-threatening aspects of the disease. For example, severe burns or persistent vomiting or diarrhea leads to substantial losses of water and *electrolytes* (small, soluble ions in the body fluids; e.g., Na^+, Cl^-, K^+, Ca^{2+}) . Even if the blood volume is not depleted to dangerously low levels in these conditions, the alteration in electrolyte concentrations can lead to abnormal heart rhythms *(cardiac arrhythmias)* and ineffective pumping of blood by the heart (heart failure). The electrolyte abnormalities in such a patient can be made even worse if incorrect fluid therapy is given. Incorrect fluid therapy can also lead to an accumulation of excess fluid in the tissues of the body; this "waterlogging" of tissues is called *edema.* If the excess fluid gathers in the lung tissue, the condition is called *pulmonary edema.* Pulmonary edema is life threatening because it slows the flow of oxygen from the pulmonary air sacs *(alveoli)* into the bloodstream.

Pulmonary edema is a secondary complication in many disease states. A further example is *shock-lung syndrome,* which results when toxic substances in the body trigger an increase in the permeability of the lung blood vessels. These "leaky" vessels allow water, electrolytes, plasma proteins, and white blood cells to leave the bloodstream and accumulate in the lung tissue and airways. The resulting pulmonary edema can lead to death.

Whereas the effects of shock-lung syndrome are most serious in the pulmonary circulation, other types of shock depress the cardiovascular system in general. *Hemorrhagic shock* is a generalized cardiovascular failure caused by severe blood loss. *Cardiogenic shock* is a cardiovascular collapse caused by heart failure. *Septic shock* is caused by bacterial infections in the bloodstream *(bacteremia). Endotoxic shock* occurs when endotoxins (fragments of bacterial cell walls) enter the bloodstream; this often occurs when the epithelial lining of the intestines becomes damaged. Epithelial damage can result from bacterial infections in the intestines or from ischemia in the intestinal walls (as with bloodworms in horses). When the intestinal epithelium breaks down, endotoxins from the intestine can enter the bloodstream. These endotoxins then cause the body to produce substances that depress the pumping ability of the heart. The resulting heart failure leads to low blood flow and ischemia in all the vital body organs. Kidney (or renal) failure, respiratory failure, central nervous system (CNS) depression, and death follow.

Anesthetic overdose is another clinical problem in which the most serious and life-threatening symptoms are the secondary cardiovascular complications. Most anesthetics depress the CNS, and the resulting abnormal neural signals to the heart and the blood vessels can depress cardiac output and lower blood pressure. Some anesthetics, particularly the barbiturates, also depress the pumping ability of the heart directly.

There are many other examples of primary and secondary cardiovascular dysfunction, but those just mentioned illustrate the importance and variety of cardiovascular dysfunctions encountered in veterinary medicine. The distinction between primary and secondary cardiovascular dysfunction is sometimes unclear, but this difficulty simply emphasizes how intimately the cardiovascular system is interconnected with all the other body systems and how dependent all the other systems are on the normal functioning of the cardiovascular system.

Substances Transported by the Cardiovascular System Include Nutrients, Waste Products, Hormones, Electrolytes, and Water

The blood transports the metabolic substrates needed by every cell of the body, including oxygen, glucose, amino acids, fatty acids, and various lipids. The blood also carries away from each cell in the body various metabolic waste products, including carbon dioxide, lactic acid, the nitrogenous wastes of protein metabolism, and heat. Although the heat produced by metabolic processes within cells is not a material waste product, its transport by the cardiovascular system to the body surface is essential, because tissues deep within the body would otherwise become overheated and dysfunctional.

Blood also transports vital chemical messengers: the hormones. Hormones are synthesized and released by cells in one organ and are carried by the bloodstream to cells in other organs, where they alter organ function. For example, insulin, which is produced by cells of the pancreas, is carried by the blood to cells throughout the body, where it promotes the cellular uptake of glucose. Inadequate insulin production (as in type 1 diabetes) results in inadequate entry of glucose into cells, whereas glucose concentrations in the blood rise to very high levels. The low intracellular glucose concentration is particularly disruptive to

neural function, and the consequences can be serious (diabetic coma) or lethal. Another hormone, *adrenaline* (a mixture of *epinephrine* and *norepinephrine*), is released into the bloodstream by cells in the adrenal medulla during periods of stress. The epinephrine and norepinephrine circulate to various body organs, where they have effects that prepare a threatened animal for the "fight or flight" response. These effects include an increase in heart rate and cardiac contractility, dilation of skeletal muscle blood vessels, an increase in blood pressure, increased glycogenolysis, dilation of the pupils and airways, and piloerection (hair standing on end).

Finally, the blood transports water and essential electrolytes, including Na^+, Cl^-, K^+, Ca^{2+}, H^+, and HCO_3^-. The kidneys are the organs primarily responsible for maintaining normal water and electrolyte composition in the body. The kidneys accomplish this by altering the electrolyte concentrations in blood as it flows through the kidneys. The altered blood then circulates to all other organs in the body, where it normalizes the water and electrolyte content in the extracellular fluids of each tissue.

Two Modes of Transport Are Used in the Cardiovascular System: Bulk Flow and Diffusion

Blood moves through the heart and blood vessels by bulk flow. The most important feature of bulk flow is that it is rapid over long distances. Blood that is pumped out of the heart travels quickly through the aorta and its various branches; within 10 seconds it reaches distant parts of the body, including the head and limbs. Transport requires energy, and the source of energy for bulk flow is a hydrostatic pressure difference; unless the pressure at one end of a blood vessel is higher than the pressure at the other end, flow will not occur. The difference in pressure between two points in a blood vessel is called the *perfusion pressure difference* or, more often, simply *perfusion pressure.* Perfusion literally means "through-flow," and the perfusion pressure is the pressure difference that causes blood to flow through blood vessels. The muscular pumping action of the heart creates the perfusion pressure that constitutes the driving force for bulk blood flow through the circulation.

It is important to distinguish between perfusion pressure difference and *transmural pressure difference* (usually shortened to *transmural pressure*). Transmural means "across the wall," and transmural pressure is the difference between the blood pressure inside a blood vessel and the fluid pressure in the tissue immediately outside the vessel (transmural pressure equals inside pressure minus outside pressure). Transmural pressure is the pressure difference that would cause blood to flow out of a vessel if a hole were poked in the vessel wall. Transmural pressure is also called *distending pressure,* because it corresponds to the net outward "push" on the wall of a blood vessel. Figure 18-1 emphasizes the distinction between perfusion pressure and transmural pressure.

Diffusion is the second mode of transport in the cardiovascular system. Diffusion is the primary mechanism by which dissolved substances move across the walls of blood vessels, from the bloodstream into the interstitial fluid, or vice versa. *Interstitial fluid* is the extracellular fluid outside capillaries. It is the fluid that bathes each cell of a tissue. Most of the movement of substances between the blood and the interstitial fluid takes place across the walls of the *capillaries,* the smallest blood vessels. For a substance (e.g., oxygen) to move from the bloodstream to a tissue cell, it diffuses across the wall of a capillary and into the tissue interstitial fluid, and then diffuses from the interstitial fluid into the tissue cell.

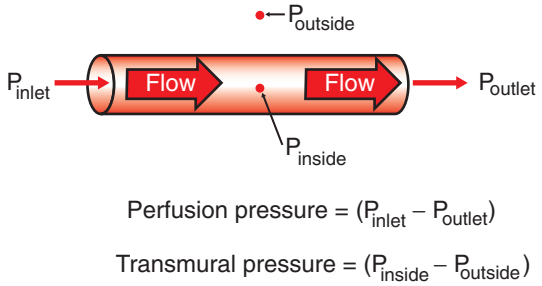

FIGURE 18-1 Fluid pressures associated with a blood vessel. P_{inlet}, P_{outlet}, and P_{inside} refer to blood pressure within the vessel. $P_{outside}$ refers to the pressure in the tissue fluid (interstitial fluid) immediately outside the blood vessel. Perfusion pressure is the pressure difference *along the length* of a blood vessel. Transmural pressure (distending pressure) is the pressure difference *across the wall* of the vessel, indicated here at the midpoint of the vessel. Perfusion pressure is the driving force for blood flow through the vessel, whereas transmural pressure is the driving force that would cause blood to flow out of the vessel if there were a hole in it.

The source of energy for diffusion is a *concentration difference.* A substance diffuses from the bloodstream, across the wall of a capillary, and into the interstitial fluid only if the concentration of the substance is higher in the blood than in the interstitial fluid (and if the capillary wall is permeable to the substance). If the concentration of a substance is higher in the interstitial fluid than in the blood, the substance will diffuse from the interstitial fluid into the capillary blood. It is important to distinguish *diffusion,* in which a substance moves passively from an area of high concentration toward an area of low concentration, from *active transport,* in which substances are forced to move in a direction opposite to their concentration gradient. In general, substances are not transported actively across the walls of capillaries. The movement of substances between the bloodstream and the interstitial fluid occurs by passive diffusion.

Because Diffusion Is Very Slow, Every Metabolically Active Cell in the Body Must Be Close to a Capillary Carrying Blood by Bulk Flow

To understand more fully how the two types of transport (bulk flow and diffusion) are used in the cardiovascular system, consider the transport of oxygen from the outside air to a neuron in the brain. With each inspiration, fresh air containing oxygen (O_2) moves by bulk flow through progressively smaller airways (trachea, bronchi, and bronchioles) and finally enters the alveolar air sacs (Figure 18-2, *A*). The thin walls separating alveoli contain a meshwork of capillaries (see Figure 18-2, *B*). Blood flowing through these *alveolar capillaries* passes extremely close (within 1 μm) to the air in the alveoli (see Figure 18-2, *C*). The blood in an alveolar capillary has just returned from the body tissues, where it gave up some of its oxygen. Therefore the concentration of oxygen in alveolar capillary blood is lower than the concentration of oxygen in alveolar air. This concentration difference causes some oxygen to diffuse from the alveolar air into the capillary blood.

A large dog has about 300 million alveoli, with a total surface area of about 130 m^2 (equal to half the surface area of a tennis court). This huge surface area is laced with pulmonary capillaries. Thus, even though only a tiny amount of oxygen diffuses into each pulmonary capillary, the aggregate uptake of oxygen into the pulmonary bloodstream is substantial (typically, 125 mL

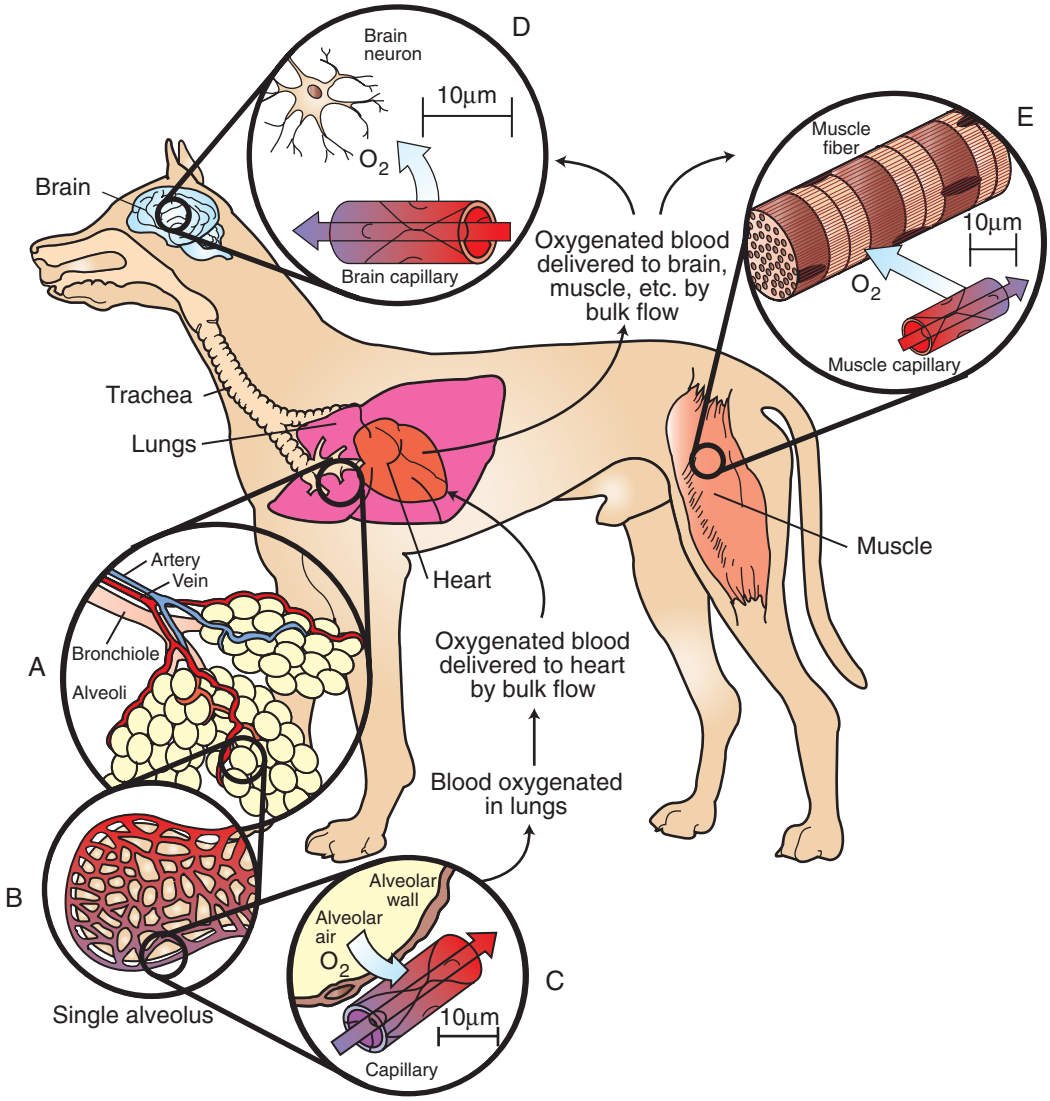

FIGURE 18-2 Oxygen (O_2) is transported from the atmosphere to cells throughout the body by a combination of bulk flow and diffusion. First, O_2 moves by bulk flow through the airways, from the atmosphere to the alveoli (tiny air sacs) of the lungs *(inset A)*. The wall of each alveolus contains a meshwork of alveolar (pulmonary) capillaries *(inset B)*. O_2 readily diffuses from the alveolar air into the blood that is flowing through the alveolar capillaries *(inset C)*. Bulk flow of blood next carries this O_2 to the heart; from there it is delivered by bulk flow into the capillaries of all the body organs (except the lungs). In the brain *(inset D)*, skeletal muscle *(inset E)*, and other tissues, O_2 moves by diffusion from the capillary blood into the interstitial fluid and then into the tissue cells, where it is utilized to support oxidative metabolism. Bulk flow is rapid; it can transport O_2 to all parts of the body within a few seconds. Diffusion is slow; it can transport O_2 efficiently only over distances less than 100 µm (note distance scales in insets C, D, and E). Oxygenated blood has a bright-red color; deoxygenated blood is darker and bluish red.

O_2/minute in a large, resting dog, increasing by a factor of 10 or more during strenuous exercise). In summary, both the large alveolar surface area and the proximity of alveolar air to the blood in alveolar capillaries promote efficient diffusion of oxygen; it takes less than 1 second for the blood in an alveolar capillary to become oxygenated.

As it leaves the lungs, each 100 mL of oxygenated blood normally carries 20 mL of oxygen. About 1.5% of this oxygen is carried in solution; the other 98.5% is bound to the protein *hemoglobin* within the *erythrocytes* (red blood cells). The oxygenated blood moves by bulk flow from the lungs to the heart. The heart pumps this oxygenated blood out into the aorta, and from there it is distributed via a complex system of branching arteries to all parts of the body (including the brain and skeletal muscles, as illustrated in Figure 18-2). Capillaries in the brain bring a bulk flow of oxygenated blood very close to each brain neuron (see Figure 18-2, *D*). Metabolic processes within the neurons consume oxygen, so the oxygen concentration inside neurons is low. The gradient of oxygen concentration between the capillary blood (high) and the neurons (low) provides the driving force for oxygen to diffuse first from the blood into the interstitial fluid and then into the neurons.

Each brain neuron must be within about 100 µm of a capillary carrying blood by bulk flow if diffusion is to deliver oxygen

rapidly enough to sustain normal metabolism in the neuron. Diffusional exchange over distances up to 100 µm typically takes only 1 to 5 seconds. If the distance involved were a few millimeters, diffusion would take minutes to occur. Diffusion of oxygen a few centimeters through body fluid would take hours. Therefore, normal life processes require that every metabolically active cell of the body be within about 100 µm of a capillary carrying blood by bulk flow. If this bulk flow is interrupted for any reason, perhaps because of a *thrombus* (blood clot) in the artery that delivers blood to a particular region of a tissue, that region of tissue becomes ischemic. As stated earlier, ischemia leads to dysfunction; persistent, severe ischemia leads to infarction and eventually to necrosis. *Cerebral infarction* causes the condition commonly known as *stroke.*

Figure 18-2, *E*, shows a capillary carrying bulk flow of blood past a skeletal muscle cell (muscle fiber). Oxygen moves by diffusion from the capillary blood into the muscle interstitial fluid and then into the muscle cell, where it is consumed in the metabolic reactions that provide energy for muscle contraction. The oxygen consumption of a skeletal muscle depends on the severity of its exercise; at a maximum, oxygen consumption may reach levels 40 times greater than the resting level. Because of its tremendous metabolic capacity, muscle tissue has an especially high density of capillaries. In fact, several capillaries are typically arrayed around each skeletal muscle fiber. This arrangement provides more surface area for diffusional exchange than would be possible with a single capillary and brings the bulk flow of blood extremely close to all parts of each skeletal muscle cell.

Heart muscle, like skeletal muscle, consumes a large amount of oxygen. Oxygenated blood is carried from the aorta to the heart muscle by a network of branching *coronary arteries.* This blood next moves by bulk flow into *coronary capillaries,* which pass close by each cardiac muscle cell. If a thrombus interrupts the bulk flow of blood in a coronary artery, the heart muscle cells supplied by that artery become ischemic. Ischemia develops even if the cardiac muscle deprived of blood flow lies within a few millimeters of the left ventricular chamber, which is filled with oxygen-rich blood. Oxygen simply cannot diffuse rapidly enough from the ventricular chamber to the ischemic cells to sustain their metabolism. Ischemic cardiac muscle loses its ability to contract forcefully; also, cardiac arrhythmias may develop. Severe myocardial ischemia causes a *myocardial infarction,* or heart attack.

Coronary artery disease and *cerebrovascular disease* are encountered more often in human medicine than in veterinary medicine. In contrast, *cardiac disease* (dysfunction of the heart muscle or valves, as distinguished from disease of the coronary arteries) is encountered more often in veterinary medicine than in human medicine. Therefore, Chapters 19 to 26 place more emphasis on cardiac physiology than on vascular physiology.

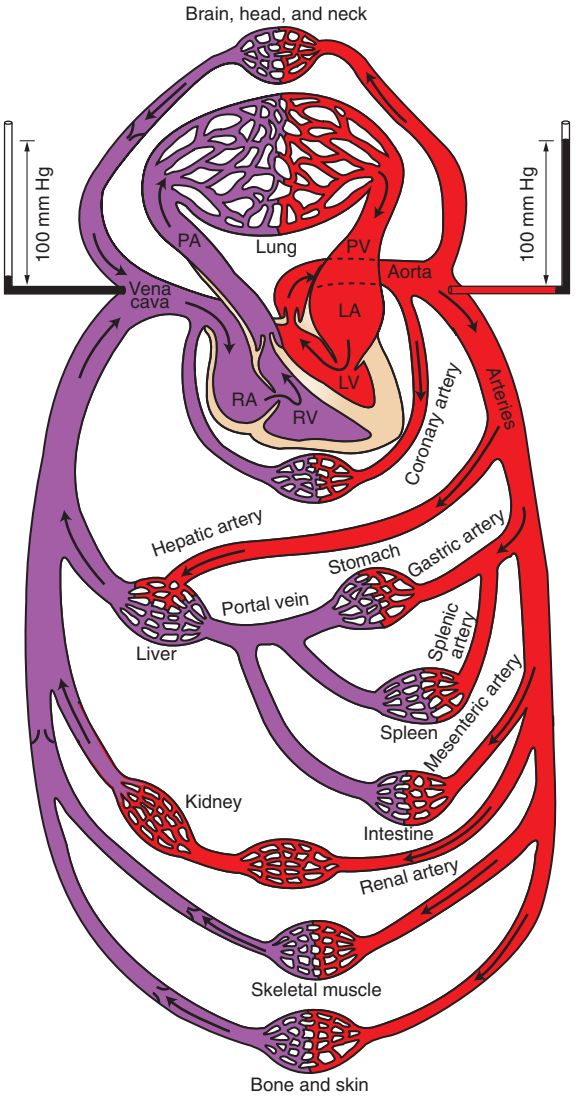

FIGURE 18-3 General layout of the cardiovascular system, showing that the systemic and pulmonary circulations are arranged in series and that the organs within the systemic circulation are arranged in parallel. *LA,* Left atrium; *LV,* left ventricle; *PA,* pulmonary artery; *PV,* pulmonary vein; *RA,* right atrium; *RV,* right ventricle. Oxygenated blood has a bright-red color; deoxygenated blood is darker and bluish red. The drawing also shows that, if an open tube containing mercury *(black)* were stuck into the aorta, the normal blood pressure within the aorta would push mercury nearly 100 mm upward into the tube, at which point the upward force of the blood pressure would be equalized by the downward force of gravity acting on the mercury. In contrast, the blood pressure in the *venae cavae* is much lower (typically about 3 mm Hg), as illustrated on the left side of the drawing. (Modified from Milnor WR: *Cardiovascular physiology,* New York, 1990, Oxford University Press.)

The Pulmonary and Systemic Circulations Are Arranged In Series, But the Various Organs Within the Systemic Circulation Are Arranged in Parallel

As shown in Figure 18-3, blood is pumped from the left ventricle into the aorta. The aorta divides and subdivides to form many arteries, which deliver fresh, oxygenated blood to each organ of the body, except the lungs. The pattern of arterial branching that delivers blood of the same composition to each organ is called *parallel.* After blood passes through the capillaries within individual organs, it enters veins. Small veins combine to form progressively larger veins, until the entire blood flow is delivered to the right atrium by way of the *venae cavae* (pleural of vena cava, includes both superior vena cava and inferior vena cava). The blood vessels between the aorta and the *venae cavae* (including the blood vessels in all organs of the body except the lungs) are collectively called the *systemic circulation.* From the right atrium, blood passes into the right ventricle, which pumps it into the pulmonary artery. The pulmonary artery branches into progressively smaller arteries, which deliver blood to each alveolar (pulmonary) capillary. Blood from pulmonary capillaries is collected in pulmonary veins and brought to the left atrium. Blood then

passes into the left ventricle, completing the circuit. The blood vessels of the lungs, including the pulmonary arteries and veins, constitute the *pulmonary circulation.* The pulmonary circulation and the heart are collectively termed the *central circulation.* The pulmonary circulation and the systemic circulation are arranged in *series;* that is, blood must pass through the pulmonary vessels between each passage through the systemic circuit.

In one pass through the systemic circulation, blood generally encounters only one capillary bed before being collected in veins and returned to the heart, although a few exceptions to this rule exist. One exception occurs in the *splanchnic circulation,* which supplies blood to the digestive organs. As shown in Figure 18-3, blood that leaves the gastric, splenic, or mesenteric capillaries enters the *portal vein.* The portal vein carries splanchnic venous blood to the liver, where the blood passes through another set of capillaries before it returns to the heart. This arrangement of two systemic capillary beds in series is called a *portal system*. The splanchnic portal system allows nutrients that have been absorbed from the gastrointestinal tract to be delivered directly to the liver. There the nutrients are transformed for storage or allowed to pass into the general circulation. The liver also receives some blood directly from the aorta through the hepatic artery.

The kidneys also contain a portal system. As shown in Figure 18-3, blood enters a kidney by way of a renal artery and passes through two sets of capillaries (called *glomerular* and *tubular*) before returning to the venous side of the systemic circulation. Large amounts of water, electrolytes, and other solutes are filtered out of the blood as it passes through the glomerular capillaries. Most of this filtered material is subsequently reabsorbed into the bloodstream as it flows through the peritubular capillaries. The remainder becomes urine. The kidneys use the *renal portal system* to adjust the amounts of water, electrolytes, and other critical solutes in the blood.

A third portal system is found in the brain and is important in the control of hormone secretion by the pituitary gland. After traversing capillaries in the hypothalamus, blood enters portal vessels that carry it to the anterior pituitary gland *(adenohypophysis)* and to another set of capillaries (see Figures 33-16 and 33-17). As blood traverses the hypothalamic capillaries, it picks up several signaling chemicals that control the release of pituitary hormones. When this blood reaches capillaries in the anterior pituitary gland, these substances diffuse out of the bloodstream and into the pituitary interstitial fluid, where they act on pituitary cells to increase or decrease their secretion of specific pituitary hormones. This system is called the *hypothalamic-hypophyseal portal system.*

To summarize, except for a few specialized portal systems, blood encounters only one capillary bed in a single pass through the systemic circulation.

Cardiac Output Is the Volume of Blood Pumped Each Minute by One Ventricle

In a resting dog, it takes about 1 minute for blood to traverse the entire circulation (from the left ventricle back to the left ventricle). Because the pulmonary and systemic circulations are in series, the volume of blood pumped by the right side of the heart each minute must equal the volume of blood pumped by the left side of the heart each minute. The volume of blood pumped per minute by either the left ventricle or the right ventricle is called *cardiac output*. Among the mammalian species typically encountered in veterinary medicine, cardiac output at rest is approximately 3 liters per minute per square meter (L/min/m^2) of body surface area. A large dog (e.g., German shepherd) typically has a body surface area a little less than 1 m^2 and a cardiac output at rest of about 2.5 L/min.

In an animal at rest, blood entering the aorta is divided so that approximately 20% of it flows through the splanchnic circulation and 20% through the kidneys. Another 20% goes to the skeletal muscles. The brain receives about 15% of the cardiac output, and the coronary arteries carry about 3% of the cardiac output. The remainder goes to skin and bone.

The Perfusion Pressure for the Systemic Circulation Is Much Greater Than the Perfusion Pressure for the Pulmonary Circulation

When the left ventricle contracts and ejects blood into the aorta, the aorta becomes distended with blood, and aortic blood pressure rises to a peak value called *systolic pressure* (typically 120 mm Hg). Between ejections, blood continues to flow out of the aorta into the downstream arteries. This outflow of blood from the aorta causes aortic pressure to decrease. The minimal value of aortic blood pressure, just before the next cardiac ejection, is called *diastolic pressure* (typically 80 mm Hg). A typical appearance of the pressure pulsations in the aorta is shown in the middle panel of Figure 22-7. The *mean aortic pressure* (average value of the pulsatile blood pressure in the aorta) is about 98 mm Hg. This means that, if an open tube containing mercury were stuck into the aorta, the blood pressure within the aorta would push mercury 98 mm upward into the tube; at which point the upward force of the blood pressure would be equalized by the downward force of gravity acting on the mercury.

The mean aortic pressure represents a potential energy for driving blood through the systemic circulation. As blood flows through the systemic blood vessels, this pressure energy is dissipated through friction. The potential energy (blood pressure) remaining by the time the blood reaches the *venae cavae* is only 3 mm Hg. Therefore the perfusion pressure for the systemic circuit is typically 98 mm Hg minus 3 mm Hg, or 95 mm Hg.

Right ventricular contractions cause pulsatile ejections of blood into the pulmonary artery. The resulting, pulsatile variations in pulmonary arterial blood pressure typically have a peak (systolic) value of 20 mm Hg and a minimum (diastolic) value of 8 mm Hg. The typical value for mean pulmonary artery blood pressure is 13 mm Hg. The blood pressure in pulmonary veins (at the point where they enter the left atrium) is typically 5 mm Hg. Under these conditions the perfusion pressure for blood flow through the lungs is 8 mm Hg (i.e., 13 mm Hg minus 5 mm Hg).

The same volume of blood (the cardiac output) flows each minute through the systemic circulation and through the lungs; however, as is evident from the typical values just given, the perfusion pressure for the systemic circuit is much greater than the perfusion pressure for the lungs. The reason for this difference in perfusion pressure is that the systemic vessels offer more friction against blood flow (i.e., have a higher *resistance*) than do the pulmonary vessels. Therefore the systemic circulation is referred to as the *high-pressure, high-resistance side of the circulation.* The pulmonary circuit is called the *low-pressure, low-resistance side.*

By convention, blood pressures are always measured with reference to atmospheric pressure. Thus an aortic pressure of 98 mm Hg means that the blood pressure in the aorta is 98 mm Hg higher than the atmospheric pressure outside the body. Also, by convention, blood pressure is measured at heart level. This is why, in human medicine, blood pressure cuffs are

typically applied over the brachial artery (in the upper arm); the brachial artery is at the same level as the heart. If blood pressure is measured in an artery or vein at a level different from heart level, an arithmetic correction should be made so that the pressure is reported as if it had been measured at heart level. This correction is necessary because gravity pulls downward on blood and therefore affects the actual pressure of blood within vessels. Gravity increases the actual blood pressure in vessels lying below heart level and decreases the actual pressure in vessels above heart level. The gravitational effect is significant in an animal the size of a dog and substantial in an animal the size of a horse. The correction factor for the effect of gravity is 1 mm Hg for each 1.36 cm above or below heart level.

Each Type of Blood Vessel Has Physical Properties Suited to Its Particular Function

In a resting animal, at any one moment, about 25% of the blood volume is in the central circulation and about 75% is in the systemic circulation (Table 18-1). Most of the blood in the systemic circulation is found in the veins. Only 20% of the systemic blood is found in the arteries, arterioles, and capillaries. Therefore, systemic veins are known as the *blood reservoirs* of the circulation. Arteries function as *high-pressure conduits* for rapid distribution of blood to the various organs. Arterioles are the "gates" of the systemic circulation; they *constrict* or *dilate* to control the blood flow to each capillary bed. Although only a small fraction of the systemic blood is found in capillaries at any one time, it is within these *exchange vessels* that the important diffusional transport takes place between the bloodstream and the interstitial fluid.

Table 18-2 compares the various types of vessels in the systemic circulation of a dog. As the aorta branches into progressively smaller vessels, the diameters of the vessels become smaller, but the number of vessels increases. One aorta supplies blood to 45,000 terminal arteries, each of which gives rise to more than 400 arterioles. Each arteriole typically branches into about 80 capillaries. The capillaries are so small in diameter that red blood cells must pass through in single file. However, because of the sheer number of capillaries, the total cross-sectional area of the capillaries is much greater than the cross-sectional area of the preceding arteries and arterioles. Because capillary blood flow is spread out over such a large cross-sectional area, the flow velocity within capillaries is low. Blood moves rapidly (about 13 cm/sec) through the aorta and large arteries. At this speed, blood is delivered from the heart to all parts of the body in less than 10 seconds. The velocity of blood flow decreases as the blood leaves arteries and enters arterioles and capillaries in each tissue. The velocity of blood flow in capillaries is so slow that blood typically takes about 1 second to travel the 0.5 mm length of a capillary. During this time, diffusional exchange takes place between the capillary blood and the interstitial fluid. Blood from the capillaries is collected by venules and veins and is carried quite rapidly back to the heart.

An understanding of the normal dynamics of blood flow provides a basis for interpretation of *capillary refill time,* which is measured during a typical clinical physical examination. The examiner locates an area of non-pigmented epithelial membrane (most commonly a non-pigmented area of the gums). Such tissue is normally pink, due to an adequate flow of well-oxygenated blood through the small vessels (arterioles, capillaries, and venules). The examiner applies firm finger pressure to the area for 1 or 2 seconds, which compresses all the small blood vessels and squeezes the blood out of them. Immediately upon release of the finger pressure, the tissue appears very pale, due to the absence of blood in the small vessels. A normal circulation will restore blood flow through the small vessels and the pink color will return within 1 to 2 seconds (the normal capillary refill time). A prolonged capillary refill time is indicative of poor perfusion of the tissue and, by inference, a sluggish circulation.

Figure 18-4 depicts the branching pattern of the systemic vessels and graphs the velocity of blood flow within the different

TABLE 18-1 Distribution of Blood Volume in the Cardiovascular System of a Normal Dog

Distribution	Percent
Between Central and Systemic Circulations	
Central circulation	25
Systemic circulation	75
TOTAL	100
Within the Various Vessels of the Systemic Circulation	
Arteries and arterioles	15
Capillaries	5
Venules and veins	80
TOTAL	100

TABLE 18-2 Geometry of Systemic Circulation of a 30-kg Resting Dog

Vessel	Number	Inside Diameter (mm)	Total Cross Sectional Area (cm^2)	Length (cm)	Velocity of Blood Flow (cm/sec)	Mean Blood Pressure (mm Hg)
Aorta	1	20.0	3.1	40.0	13.0	98
Small arteries	45,000	0.14	6.9	1.5	6.0	90
Arterioles	20,000,000	0.030	140.0	0.2	0.3	60
Capillaries	1,700,000,000	0.008	830.0	0.05	0.05	18
Venules	130,000,000	0.020	420.0	0.1	0.1	12
Small veins	73,000	0.27	42.0	1.5	1.0	6
Venae cavae	2	24.0	9.0	34.0	4.5	3

Modified from Minor WR: *Cardiovascular physiology,* New York, 1990, Oxford University Press.

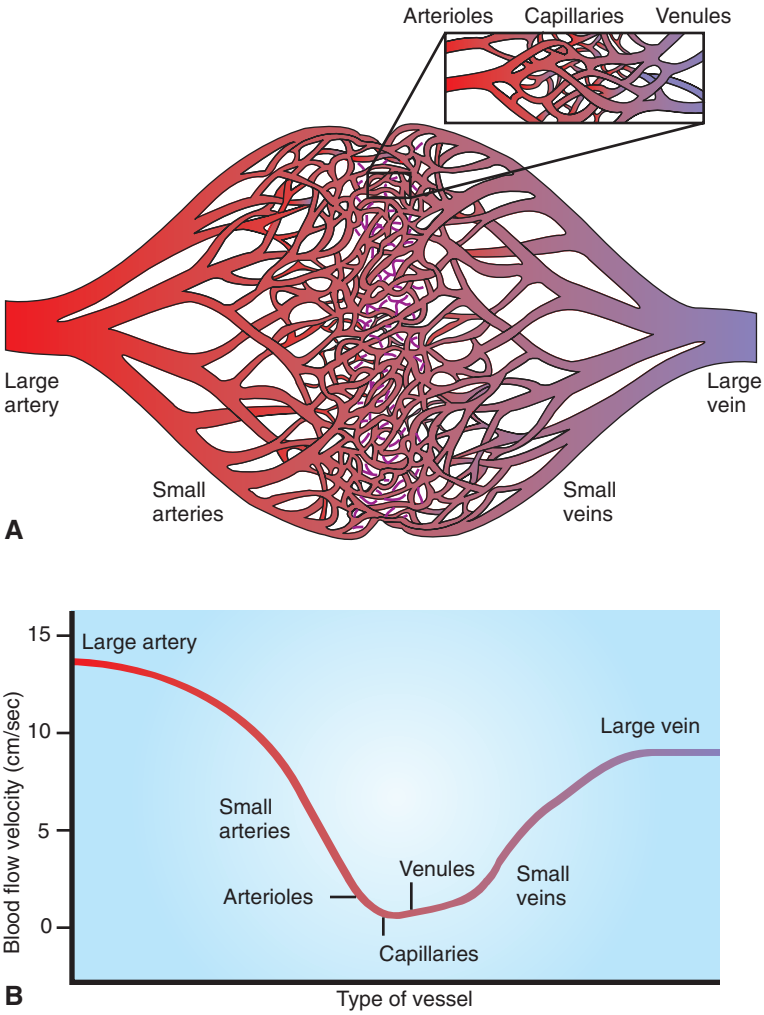

FIGURE 18-4 As the systemic arteries branch to form small arteries, arterioles, and capillaries **(A),** the total cross-sectional area of the vessels increases, so the forward velocity of blood flow decreases **(B).** As blood from the capillaries is collected into venules and veins, the total cross-sectional area is reduced, so the velocity of blood flow increases again. Therefore, blood moves quickly from the heart to the microvessels, where it stays for a few seconds before moving rapidly back to the heart.

types of vessels. This figure emphasizes the rapidity of bulk flow through large vessels and the relatively slow flow through the capillaries. Note that the *velocity* of blood flow is lowest in the capillaries; however, the same *volume* of blood necessarily flows each minute through an artery, the capillaries that it feeds, and the veins draining the capillaries.

In addition to having a large cross-sectional area (and therefore slow velocity of blood flow), capillaries have a large surface area. The total surface area of the walls of all the capillaries in the systemic circulation of a large dog is about 20 m^2, which is nearly 30 times greater than the dog's body surface area. The large surface area of capillaries helps promote efficient diffusional exchange between the capillary blood and the interstitial fluid.

Blood Is a Suspension of Cells in Extracellular Fluid (Plasma)

As shown in Figure 18-5, blood can be separated into its cellular and liquid components by centrifugation. The liquid phase of blood is lighter in weight than the cells and therefore ends up on the top of the centrifuge tube. This acellular or extracellular liquid in blood is called *plasma.* Water constitutes 93% of the plasma volume. About 5% to 7% of the plasma volume is made up of protein molecules. The presence of proteins gives plasma its typical pale-yellow color. The *plasma proteins* are synthesized in the liver and are added to the bloodstream as it passes through the liver capillaries. Globulin, albumin, and fibrinogen are the primary plasma proteins. Globulin and albumin are important in the immune responses of the body. Fibrinogen is important in the process of blood clotting. If blood is removed from the body and allowed to stand for a few moments, the soluble fibrinogen molecules polymerize to form an insoluble matrix of fibrin. This causes the blood to congeal, or *coagulate.* Coagulation can be prevented by adding an anticoagulant to the blood; the most common anticoagulants are heparin and citrate. An anticoagulant must be added in preparation for separating blood into its cellular and plasma fractions by centrifugation.

Many important substances, in addition to plasma proteins, are dissolved in plasma. Plasma contains several ions *(electrolytes)* in solution. The dominant cation is sodium (Na^+). The predominant anions are chloride (Cl^-) and bicarbonate (HCO_3^-). Other ions are present in lesser amounts, as indicated in Table 18-3. The concentration of each plasma electrolyte must be kept within narrow limits for body function to be normal, and numerous control systems accomplish this regulation. In general, the plasma electrolytes can diffuse readily across capillary walls; therefore, interstitial fluid and plasma typically have similar electrolyte concentrations.

Plasma contains small amounts of gases (O_2, CO_2, and N_2) in solution. In the lungs, O_2 enters the blood as dissolved O_2, but most of this O_2 quickly combines with hemoglobin (in the red

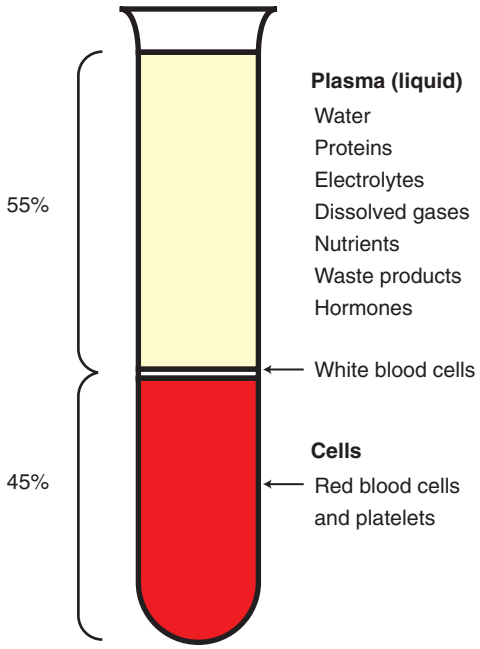

FIGURE 18-5 Anticoagulated blood can be separated into an extracellular fluid component (plasma) and a cellular component (cells) by centrifugation. Plasma is a solution of many important substances in water. The presence of proteins gives plasma its typical pale-yellow color. The cells are heavier than the plasma, and they settle to the bottom. Most of the cells are red blood cells. The white blood cells are slightly lighter in weight than the red blood cells, and they form a thin buffy coat on the top of the red cell layer. Most of the platelets end up in the buffy coat, although at slow centrifuge speeds ("soft spin"), platelets tend to remain suspended in the plasma. The fraction of cells in blood is called the hematocrit. In this example the hematocrit is 45%.

TABLE 18-3 Some Constituents of Canine Plasma (in Addition to Water, the Main Constituent)

Component	Normal Range	Units
Plasma Proteins (Carried in Colloidal Suspension)		
Globulin (total)	2.7-4.4	g/dL
Albumin	2.3-3.1	g/dL
Fibrinogen	0.15-0.30	g/dL
Electrolytes (Dissolved)		
Na^+	140-150	mmol/L
K^+	3.9-5.1	mmol/L
Ca^{2+} (ionized)	1.2-1.5	mmol/L
Mg^{2+} (ionized)	0.5-0.9	mmol/L
Cl^-	110-124	mmol/L
HCO_3^-	17-24	mmol/L
HPO_4^{2-} and $H_2PO_4^-$	1-1.4	mmol/L
H^+	38-49	nmol/L*
(H^+ expressed as pH)†	(7.31-7.42)	
Dissolved Gases (Values for Arterial Plasma)		
O_2	0.26-0.30	mL/dL
CO_2	2-2.5	mL/dL
Examples of Nutrients, Waste Products, Hormones		
Cholesterol	140-280	mg/dL
Glucose	76-120	mg/dL
Triglycerides	40-170	mg/dL
Urea nitrogen	8-28	mg/dL
Creatinine	0.5-1.7	mg/dL
Bile acids (fasting)	0-8	µmol/L
Thyroxine (T_4)	1.5-4	nmol/L*

Modified from Latimer KS, Mahaffey EA, Prasse KW: *Duncan & Prasse's veterinary laboratory medicine: clinical pathology,* ed 4, Ames, Iowa, 2003, Wiley-Blackwell.
*Note that [H^+] and [Thyroxine] are in nanomolar units; 10^3 nmol = 1 µmol, and 10^3 µmol = 1 mmol.
†pH = –log [H^+], where [H^+] is expressed in molar units; pH is dimensionless.

blood cells). As a consequence, about 98.5% of the total O_2 in blood is carried as *oxyhemoglobin* and only about 1.5% as dissolved O_2. Likewise, only a small portion of the carbon dioxide (CO_2) in blood is carried in the dissolved form. Most of the CO_2 becomes hydrated to form HCO_3^- or combines with hemoglobin or plasma proteins to form *carbamino compounds.*

Nutrient substances dissolved in plasma include glucose, amino acids, lipids, and some vitamins. Dissolved metabolic waste products (in addition to CO_2) include urea, creatinine, uric acid, and bilirubin. Plasma also contains many hormones (e.g., insulin, epinephrine, thyroxine), which are present in exceedingly tiny, but critically important amounts. Table 18-3 lists some of the normal constituents of plasma.

The Cellular Component of Blood Includes Red Blood Cells, White Blood Cells, and Platelets

Cells normally constitute 30% to 60% of the blood volume (depending on the species). The fraction of cells in blood is called the *hematocrit* (see Figure 18-5). The hematocrit is determined by adding an anticoagulant to some blood and then centrifuging it in a tube. The cells are somewhat heavier than plasma and settle to the bottom of the tube during centrifugation. Because centrifugation results in a packing of the blood cells in the bottom of the tube, the hematocrit is sometimes called the *packed cell volume.* Most of the cell component looks red because most of the blood cells are *erythrocytes* (red blood cells, RBCs). Erythrocytes acquire their red color from hemoglobin.

The *leukocytes* (white blood cells, WBCs) are slightly lighter in weight than the RBCs; in a centrifuge tube the WBCs gather in a white *buffy coat* on top of the RBCs. The buffy coat is normally very thin because there are about 1000 times more RBCs than WBCs. Leukocytes are critical in immune and allergic responses of the body. The subtypes of leukocytes include neutrophils, lymphocytes, monocytes, eosinophils, and basophils. A laboratory analysis of the total number and relative distribution of the various WBC subtypes *(differential WBC count)* provides important clues in the diagnosis of disease. Both erythrocytes and leukocytes are made in the bone marrow. They develop, by mitosis and differentiation, from a common line of progenitor cells, the *pluripotent* (uncommitted) *stem cells.*

The cellular component in a centrifuge tube also contains *platelets,* or *thrombocytes,* which are cellular fragments from their precursor cells, the *megakaryocytes.* The megakaryocytes reside in the bone marrow, and they shed bits of their cytoplasm, bounded by cell membrane, into the bloodstream. Platelets participate in *hemostasis* (the control of blood loss from injured or

severed blood vessels). In this process a clumping together of platelets *(platelet aggregation)* begins to create a physical barrier across openings in blood vessels. The platelets also release the substance *serotonin,* which causes the blood vessels to constrict, thereby reducing blood pressure and blood flow at the site of injury. Additional substances released from the platelets, along with fibrinogen and several clotting factors in the plasma, lead to the coagulation of blood and the formation of a stable, fibrin-based blood clot.

Coagulation and clotting involve complex, interconnected sequences of chemical reactions *(the coagulation cascade).* A key step in the coagulation cascade is the formation in the plasma of *thrombin,* an enzyme that catalyzes the transformation of fibrinogen to fibrin. Several laboratory tests are used to assess the status of an animal's coagulation system. Two common tests involve determination of the *prothrombin time* (PT) and the *partial thromboplastin time* (PTT).

If blood is allowed to coagulate and then is centrifuged, the fibrin and other plasma clotting factors settle to the bottom along with the RBCs, WBCs, and platelets. The liquid portion remaining above (essentially plasma without fibrinogen and other clotting factors) is called *serum.* Most of the common clinical blood chemistry analyses are performed on serum. Examples include the determination of concentrations of electrolytes and cholesterol.

If blood is treated with an anticoagulant and then allowed simply to sit in a tube (without centrifugation), the erythrocytes slowly begin to settle. For reasons that are not completely understood, the rate of their settling tends to be increased to above normal in certain disease states and decreased to below normal in others. Therefore the *erythrocyte sedimentation rate* (ESR) is a clinically useful diagnostic measurement. An important caveat is that the normal ESR varies substantially between species; for example, it is much more rapid in equine blood than in canine blood.

Blood cell counts are performed by manual or automated scanning of a very small volume (e.g., 1 µL) of anticoagulated whole blood. Table 18-4 presents a summary of normal hematologic values for the dog.

TABLE 18-4 Canine Hematology

Test	Normal Range	Units
Hematocrit	35-57	%
Blood Cell Counts		
Red blood cells	5000-7900	$\times 10^3/\mu L$
White blood cells	5-14	$\times 10^3/\mu L$
Platelets	210-620	$\times 10^3/\mu L$
Hemoglobin Measures		
Blood hemoglobin	12-19	g/dL
MCH (mean corpuscular hemoglobin)	21-26	pg
MCHC (mean corpuscular hemoglobin concentration)	32-36	g/dL

Modified from Latimer KS, Mahaffey EA, Prasse KW: *Duncan & Prasse's veterinary laboratory medicine: clinical pathology,* ed 4, Ames, 2003, Wiley-Blackwell.

Most of the Oxygen in Blood Is Carried in Chemical Combination with the Protein Hemoglobin Within Red Blood Cells

Of the 20 mL of O_2 normally carried in each 100 mL of oxygenated blood, only 1.5% (0.3 mL) is carried in dissolved form. The remaining 98.5% is carried in chemical combination with hemoglobin (in RBCs). *Oxygenated hemoglobin* (*oxyhemoglobin,* HbO_2) is bright red. When O_2 is released, HbO_2 becomes *reduced hemoglobin* (Hb), which is dark bluish red. The adequacy of oxygenation of an animal's blood can be judged somewhat by looking at the color of its nonpigmented epithelial membranes (e.g., gums, nostrils, or inside surfaces of eyelids). Well-oxygenated tissues appear pink. Poorly oxygenated tissues appear bluish *(cyanotic)* because of the prevalence of reduced Hb.

The ability of blood to carry oxygen is determined by the amount of hemoglobin in the blood and by the chemical characteristics of that Hb. For example, each deciliter (dL) of normal dog blood contains about 15 g of Hb. Each gram of Hb can combine with 1.34 mL of O_2, when fully saturated. Thus, each deciliter of fully oxygenated, normal blood carries 20 mL of O_2. Several disease states *(hemoglobinopathies)* result in the synthesis of chemically abnormal Hb, with a diminished capacity to bind O_2. Also, several common toxins, including carbon monoxide (CO) and nitrates, cause life-threatening alterations in the ability of Hb to bind O_2.

Because hemoglobin is localized inside RBCs, it is possible to derive several clinically useful relationships among the blood Hb content, RBC count, Hb content of each RBC, and hematocrit. For example, if a normal dog has 15 g of Hb in each deciliter of blood and an RBC count of 6 million cells per microliter (µL) blood, it follows that each RBC (on average) contains 25 picograms (pg) of Hb:

$$\frac{15 \text{ g of hemoglobin/dL of blood}}{6 \times 10^6 \text{ red blood cells}/\mu\text{L of blood}} = 25 \times 10^{-12} \text{ g of Hb/RBC}$$

The value calculated in this way is called the *mean corpuscular hemoglobin* (MCH).

An easier calculation, which serves the same purpose, is to determine how much hemoglobin is contained in each deciliter of packed RBCs. For example, if a dog has 15 g Hb/dL of blood and has a hematocrit of 50%, the Hb concentration in the RBC portion of the blood must be 30 g of Hb/dL of packed RBCs:

$$\frac{15 \text{ g of hemoglobin/dL of blood}}{0.5 \text{ dL of red blood cells/dL of blood}} = 30 \text{ g of Hb/dL of RBCs}$$

The value calculated in this way is called the *mean corpuscular hemoglobin concentration* (MCHC). For simplicity, the calculation is often summarized as follows:

$$\text{MCHC} = [\text{hemoglobin}]/\text{hematocrit}$$

The brackets around "hemoglobin" denote concentration.

An abnormally low value of MCH or MCHC is clinically important because it points to a deficit in hemoglobin synthesis (i.e., not enough Hb being made to load up each RBC). In contrast, an abnormally low value for Hb by itself is less informative; hemoglobin concentration in the blood could fall below normal for several reasons, including a deficit in Hb synthesis, a deficit in RBC synthesis, or a "watering down" of the blood either by addition of excess plasma fluid or by loss of RBCs.

Deviations from a normal hematocrit (Hct) can have important consequences in terms of the ability of blood to carry oxygen. Hematocrit also affects the viscosity of blood, as shown in Figure 18-6. *Viscosity* is a measure of resistance to flow. For example, honey is more viscous (more resistant to flow) than water. Plasma, by itself, is about 1.5 times more viscous than water because of the presence of plasma protein molecules (albumin, globulin, fibrinogen). The presence of cells in blood has an even greater effect on viscosity. Blood with an Hct of 40% has twice the viscosity of plasma. For Hct exceeding 50%, viscosity increases rapidly. An abnormally high hematocrit is called *polycythemia,* which literally means "many cells in the blood." The blood of a patient with polycythemia can carry more than the normal 20 mL of O_2/dL of blood (provided that the MCHC is normal), and this may be viewed as beneficial. However, the increased viscosity makes it difficult for the heart to pump the blood. Therefore, polycythemia creates a heavy workload for the heart and can lead to heart failure, particularly if the cardiac muscle is not healthy.

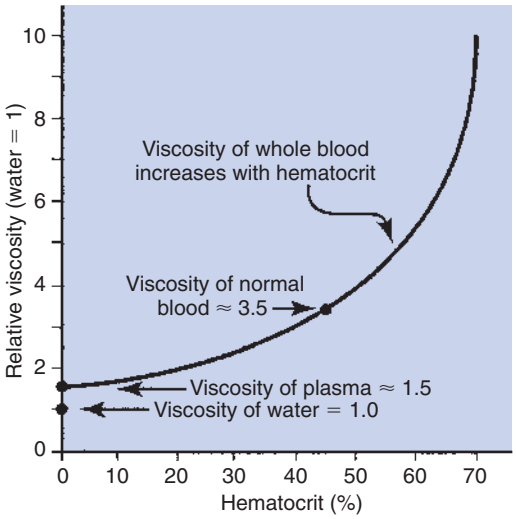

FIGURE 18-6 Plasma is more viscous than water because of the presence of plasma proteins. Blood is more viscous than plasma because of the presence of blood cells. Blood viscosity increases sharply when the fraction of cells (hematocrit) increases above 50%.

The opposite problem, in which the hematocrit is too low, is called *anemia.* Anemia literally means "no blood," but the word is used to refer to any condition in which there are abnormally few RBCs in each dL or a condition in which there is an abnormally low hemoglobin concentration in each RBC (i.e., MCH and/or MCHC is low). Each deciliter of blood of an anemic patient carries less than the normal 20 mL of O_2. Therefore, cardiac output must be increased above normal to deliver the normal amount of O_2 to the tissues each minute. The necessity to increase cardiac output also imposes an increased workload on the heart and can lead to the failure of a diseased heart. Thus, Hct within the normal range provides the blood with enough Hb to carry an adequate amount of O_2 without putting an undue workload on the heart. For additional information about the transport of O_2 and CO_2 in blood, see Chapter 48.

Figure 18-7 provides an idea of the relative sizes and shapes of the major constituents of blood. The plasma proteins are much, much larger than the ions and nutrient molecules that are dissolved in plasma. RBCs and WBCs are many, many times larger than the plasma proteins. In fact, as mentioned earlier, blood cells are so large that they can barely squeeze through a typical capillary.

CLINICAL CORRELATIONS

LETHARGIC KID GOAT

History. A 6-month-old female kid goat is presented for lethargy and difficulty breathing. Two months ago, in April, the owners bought this goat and another at a sale as pets for their children. The goats have been provided with a small amount of goat feed daily, along with access to a pasture. The owners noticed that both goats were initially very playful, but both have seemed progressively lethargic during the last month. Also, they seem to have more difficulty breathing, even at rest. No vaccinations, deworming, or other treatments have been given.

Clinical Examination. The goat is somewhat thin and is reluctant to stand. There is a swelling (likely edema fluid) under the jaw. The goat's temperature is slightly elevated. The pulse and respiratory rates are moderately increased. The mucous membranes

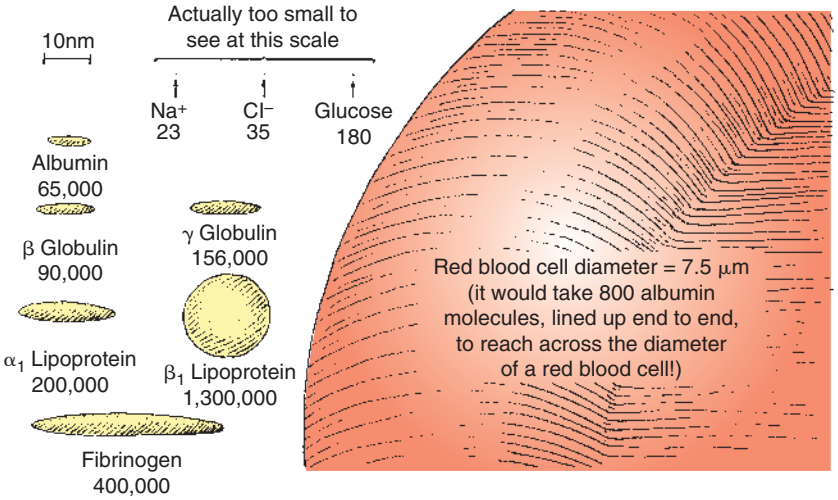

FIGURE 18-7 Relative size and shape of the major constituents of blood. The figure emphasizes two points: first, that the plasma protein molecules are huge compared with the other plasma solutes, such as glucose, Na^+, and Cl^-; and second, that the blood cells (red and white) are huge compared with plasma protein molecules. Numbers under constituents are their molecular weights (in daltons). The scale *(upper left)* indicates a length of 10 nm. In comparison, the diameter of the red blood cell is 7.5 μm, which is 750 times larger than the scale marker.

are very pale, which makes the capillary refill time difficult to assess. Respiratory sounds are increased (suggesting possible pulmonary edema). There are no other abnormal findings on physical examination.

Comment. The very pale mucous membranes suggest marked anemia. Indeed, centrifugation of a blood sample reveals that the goat's packed cell volume (Hct) is only 12%. Plasma protein concentration is also below normal, at 4.5 g/dL. Given the lack of deworming, you suspect parasitic infection associated with *Hemonchus contortus, Ostertagia,* or *Trichostrongylus.* A fecal analysis is positive for *Hemonchus* and *Ostertagia.*

Parasitism is a common problem in sheep and goats. The parasites mentioned damage the abomasum, which results in blood loss. The consequent anemia would explain the goat's lethargy, because anemia limits O_2 delivery to the organs, especially during exercise. The elevated respiratory rate and heart rate reflect the animal's attempts to compensate for low O_2 delivery to the tissues by increasing air flow into the lungs and blood flow through the circulation. Plasma protein is lost along with RBCs. This *hypoproteinemia* could account for the edema, because the proteins in plasma exert an important osmotic effect to oppose the tendency for plasma water to leak out of capillaries and into the tissue (interstitial) fluid (see Chapter 23).

Treatment. Ideally, a transfusion of whole blood would be given to help restore both RBCs and plasma proteins; the kid would then be dewormed. However, even if appropriate whole blood were available, transfusion in such an animal is risky. This goat's ability to deal with stress has been severely compromised, and even the physical restraint needed to administer a transfusion might trigger physical collapse or even death. On the other hand, without the transfusion, the animal has little chance of recovery if only treated for the parasites.

COLIC AND ENDOTOXIC SHOCK IN HORSE SECONDARY TO STRONGYLUS PARASITISM

History. A 1-year-old Standardbred filly is brought to your clinic by its new owner because the horse has been restless, rolling, kicking at its belly, and pawing the ground. The owner reports that the horse has had a poor appetite for several days and now refuses both hay and grain. The owner says he has dewormed the filly recently, but her previous deworming history is unknown.

Clinical Examination. The horse is underweight and has a dull hair coat. It is obvious that she is in pain. Physical examination reveals an abnormally high temperature (103.5° F), rapid labored breathing (40 breaths/min), and an elevated heart rate (80 beats/min). All limbs feel cool to the touch. The mucous membranes are abnormally dark, and the capillary refill time is prolonged (both these observations indicate sluggish circulation). Gastrointestinal auscultation of all four quadrants yields abnormal findings; no gastrointestinal *borborygmus* is heard on either the left or the right side, dorsally or ventrally. A rectal examination reveals several distended loops of bowel.

You perform *abdominocentesis* and withdraw some peritoneal fluid. Normally, peritoneal fluid is clear and straw colored; the fluid from this horse is darker yellow than normal and has a turbid appearance. Measurements with a refractometer indicate that the peritoneal fluid contains five times more protein than normal. Microscopic examination of the fluid reveals the presence of four times the normal number of WBCs, specifically neutrophils, and the cells contain bacteria.

Outcome. You tell the owner that the filly appears to have a badly damaged bowel and that the prognosis is poor. You inform him that surgical treatment is possible, but expensive postoperative complications are likely because infection appears to have spread into the peritoneum. After considering the options, the owner decides against surgery. You institute supportive therapy with intravenous (IV) fluids, analgesics, and antibiotics. Depending on the extent of compromise to the bowel, horses can respond to medical management. However, based on the signs that this filly is showing, including that the filly already has signs of peritonitis, the prognosis is grave.

The horse's condition deteriorates over the next 12 hours. The heart rate increases progressively to 100 beats/min. The mucous membranes show evidence of declining blood flow (darker color and longer capillary refill time). The horse begins to wheeze and becomes lethargic. Bowel sounds continue to be absent. Despite the delivery of IV fluids, there is no output of urine. With the owner's consent, you euthanize the horse.

Necropsy examination indicates that this horse had thrombi (vascular obstructions) in several major branches of her mesenteric arteries, probably secondary to a severe infestation of bloodworms *(Strongylus vulgaris).* Several areas of the intestine were necrotic. Gram-negative bacteria were cultured from both the peritoneal fluid and the blood. The lungs were edematous, and excessive fluid was found in the airways and intrapleural space.

Comment. In horses, *S. vulgaris* lodges in mesenteric arteries and decreases the blood flow to the intestine. Deworming a severely infested horse can precipitate acute intestinal ischemia, because the dead/dying worms break away from the walls of major mesenteric arteries and drift into smaller arteries, which they occlude. Also, the dying worms release substances that trigger the formation of blood clots in the arteries. Digestive processes become disrupted and may cease entirely. Intestinal ischemia and gaseous distention of the bowel cause severe pain. With persistent ischemia, segments of the bowel become permanently damaged (infarcted). Ischemic damage to the intestinal epithelium allows intestinal bacteria and bacterial products (endotoxins) to enter the peritoneum and the blood. WBCs move from the bloodstream into the peritoneal fluid, where they combat the bacteria by engulfing them (phagocytosis). However, the infection overwhelms the immune system. Bacteria and endotoxins (from gram-negative bacteria) cause the body to produce substances that depress the heart and disrupt the capillary endothelium, especially in the lungs. The resultant combination of heart failure and pulmonary edema leads to respiratory failure and subsequent renal failure. The progression of dysfunction becomes irreversible.

PRACTICE QUESTIONS

1. According to Table 18-2, how long does it take for blood to travel the length of a canine capillary?
   a. 0.05 second
   b. 0.1 second
   c. 1 second
   d. 10 seconds
   e. 20 seconds

2. The amount of blood pumped by the left ventricle in 1 minute would equal:
   a. The amount of blood that flowed through the coronary circulation (in the same minute).
   b. One half of the cardiac output.
   c. Two times the cardiac output.
   d. The amount of blood that flowed through all organs of the systemic circulation, except for coronary blood flow.
   e. The amount of blood that flowed through the lungs.

3. A transfusion of normal plasma into a normal dog would:
   a. Decrease the hematocrit of the recipient's blood.
   b. Increase the viscosity of the recipient's blood.
   c. Decrease the mean corpuscular hemoglobin concentration (MCHC) in the recipient's plasma.
   d. Increase the number of cells in the recipient's blood.
   e. Decrease the concentration of proteins in the recipient's plasma.

4. Which of the following sequences of capillary beds might a red blood cell encounter in a normal circulation?
   a. Lungs, skin, lungs, brain
   b. Spleen, liver, mesentery, lungs
   c. Coronary, kidney (glomerular), kidney (tubular), lungs
   d. Lungs, coronary, stomach, liver
   e. Brain, lungs, liver, coronary

5. The walls of most capillaries have pores or clefts in them, which are approximately 4 nm in diameter (4×10^{-9} m). According to Figure 18-7:
   a. A capillary pore is many times larger in diameter than a sodium ion.
   b. An albumin molecule is approximately 2.5 times longer than the diameter of a capillary pore.
   c. The diameter of a red blood cell is many times greater than the diameter of a capillary pore.
   d. A molecule of β globulin or γ globulin could just about squeeze through a capillary pore if it were lined up exactly right.
   e. All of the above are correct.

6. Suppose that the following conditions exist in a particular blood vessel: blood pressure (BP) inside vessel at inlet = 60 mm Hg, BP inside vessel at midpoint = 45 mm Hg, BP inside vessel at outlet = 30 mm Hg, BP outside vessel at midpoint = 5 mm Hg. Under these conditions:
   a. Perfusion pressure for blood flow through this vessel = 30 mm Hg.
   b. Perfusion pressure for blood flow through this vessel = 15 mm Hg.
   c. Distending pressure at the vessel midpoint = 45 mm Hg.
   d. Distending pressure at the vessel midpoint = 40 mm Hg.
   e. Both a and d are correct.

7. Compared with the systemic circulation, the pulmonary circulation:
   a. Carries more blood flow per minute.
   b. Has a lower perfusion pressure.
   c. Has a higher resistance to blood flow.
   d. Carries blood that has a lower hematocrit.
   e. Contains a higher blood volume.

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CHAPTER 19
Electrical Activity of the Heart

KEY POINTS

1. Contraction of cardiac muscle cells is triggered by an electrical action potential.
2. The contractile machinery in cardiac muscle is similar to that in skeletal muscle.
3. Cardiac muscle forms a functional syncytium.
4. Cardiac contractions are initiated by action potentials that arise spontaneously in specialized pacemaker cells.
5. A system of specialized cardiac muscle cells initiates and organizes each heartbeat.
6. Cardiac action potentials are extremely long.
7. Membrane calcium channels play a special role in cardiac muscle.
8. The long duration of the cardiac action potential guarantees a period of relaxation (and refilling) between heartbeats.
9. Atrial cells have shorter action potentials than ventricular cells.
10. Specialized ion channels cause cardiac pacemaker cells to depolarize to threshold and form action potentials.
11. Sympathetic and parasympathetic nerves act on cardiac pacemaker cells to increase or decrease the heart rate.
12. Cells of the atrioventricular node act as auxiliary pacemakers and protect the ventricles from beating too fast.
13. Sympathetic nerves act on all cardiac muscle cells to cause quicker, more forceful contractions.
14. Parasympathetic effects are opposite to those of sympathetic activation but are generally restricted to the sinoatrial node, atrioventricular node, and atria.
15. Dysfunction in the specialized conducting system leads to abnormalities in cardiac rhythm (arrhythmias).
16. Atrioventricular node block is a common cause of cardiac arrhythmias.
17. Cardiac tachyarrhythmias result either from abnormal action potential formation (by the sinoatrial node or ectopic pacemakers) or from abnormal action potential conduction ("reentry").
18. Common antiarrhythmic drugs affect the ion channels responsible for the cardiac action potential.

Contraction of Cardiac Muscle Cells Is Triggered by an Electrical Action Potential

The heart is a muscular pump that propels blood through the blood vessels by alternately relaxing and contracting. As the heart muscle relaxes, the atria and ventricles fill with venous blood. During cardiac contraction, some of this blood is ejected into the arteries. Cardiac contraction takes place in two stages: (1) the right and left atria begin to contract, and (2) after a delay of 50 to 150 milliseconds (msec), the right and left ventricles begin to contract. Atrial contraction helps to finish filling the ventricles with blood. The delay allows time for this "topping up" of ventricular volume. Ventricular contraction ejects blood out of the left ventricle into the aorta and out of the right ventricle into the pulmonary artery. After the atria and ventricles contract, they relax and begin to refill. The entire contractile sequence is initiated and organized by an electrical signal, an *action potential,* which propagates from muscle cell to muscle cell, through the heart.

This chapter begins with a brief description of how cardiac muscle contracts, followed by a detailed description of the action potentials that initiate and organize the heart's contractions. Several common electrical dysfunctions of the heart are then discussed.

Throughout this chapter, comparisons are made between cardiac and skeletal muscle (Table 19-1). In both cardiac and skeletal muscle, an electrical action potential in each muscle cell is necessary to trigger a contraction. The molecular mechanisms that carry out the contraction are also similar in both types of muscle. However, important differences exist between cardiac and skeletal muscle in the characteristics of the action potentials that initiate contractions.

The Contractile Machinery in Cardiac Muscle Is Similar to That in Skeletal Muscle

Cardiac muscle, like skeletal muscle, has a *striated* appearance under the light microscope (Figure 19-1). These cross-striations have the same structural basis in cardiac muscle as in skeletal muscle (see Figure 6-2). Each striated cardiac muscle cell *(muscle fiber)* is made up of a few hundred myofibrils. Each *myofibril* has a repetitive pattern of light and dark bands. The various bands within a myofibril are given letter designations (A band, I band, Z disk). The alignment of these bands in adjacent myofibrils accounts for the striated appearance of the whole muscle fiber. Each repeating unit of myofibrillar bands is called a *sarcomere.* This name, which means "little muscle," is apt because a single sarcomere constitutes the contractile subunit of the cardiac muscle. By definition, a sarcomere extends from one Z disk to the next, a distance of approximately 0.1 mm, or 100 µm.

As in skeletal muscle, each cardiac muscle sarcomere is composed of an array of thick and thin filaments. The *thin filaments* are attached to the Z disks; they interdigitate with the thick filaments. The thin filaments are composed of *actin* molecules. The

TABLE 19-1 Sequence of Events in Contraction of Skeletal Muscle and Cardiac Muscle

Skeletal Muscle	Cardiac Muscle
Action potential is generated in somatic motor neuron	*Note:* Action potentials in autonomic motor neurons are not needed to initiate heartbeats
Acetylcholine is released	*Note:* Neurotransmitters are *not* needed to make the heart beat
Nicotinic cholinergic receptors on muscle cell membrane are activated	*Note:* Activation of receptors is *not* needed—a completely isolated or denervated heart still beats
Ligand-gated Na^+ channels in muscle membrane open	Pacemaker Na^+ channels spontaneously open (and K^+ channels close) in membranes of pacemaker cells
Muscle membrane depolarizes to threshold level for formation of action potential	Pacemaker cell membranes depolarize to threshold for formation of action potential
Action potential forms in muscle cell but does not enter other cells	Action potential forms in a pacemaker cell and then propagates from cell to cell throughout the whole heart
Note: Skeletal muscle cells *do not* have slow Ca^{2+} channels	During action potential, extracellular Ca^{2+} ("trigger" Ca^{2+}) enters cell through "slow" Ca^{2+} channels
Action potential causes Ca^{2+} release from sarcoplasmic reticulum; Ca^{2+} binds to troponin	Entry of extracellular trigger Ca^{2+} causes release of more Ca^{2+} from sarcoplasmic reticulum; Ca^{2+} binds to troponin
Actin's binding sites are made available for actin-myosin cross-bridge formation	Actin's binding sites are made available for actin-myosin cross-bridge formation
Cross-bridge cycling generates contractile force between actin and myosin filaments	Cross-bridge cycling generates contractile force between actin and myosin filaments
Muscle contracts (brief "twitch"); Ca^{2+} is taken up by sarcoplasmic reticulum	Heart contracts (complete "beat" or "systole"); Ca^{2+} is taken up by sarcoplasmic reticulum or pumped back out of cell into extracellular fluid
Muscle relaxes	Heart relaxes

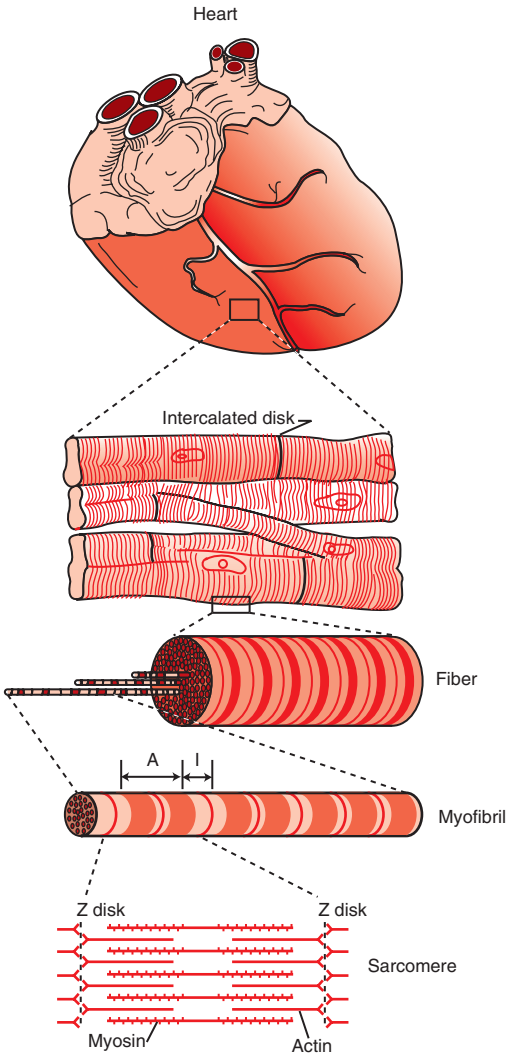

FIGURE 19-1 Under the light microscope, cardiac muscle fibers (muscle cells) are seen to be striated, similar to skeletal muscle. Electron microscopy reveals that the striations result from an orderly arrangement of actin (thin) filaments and myosin (thick) filaments into muscular subunits called sarcomeres (as shown in *bottom drawing*). Like skeletal muscle, a sarcomere is the structural and functional subunit of cardiac muscle. Unlike skeletal muscle fibers, however, cardiac muscle fibers often branch, and they link end to end with neighboring fibers at structures called intercalated disks. Unseen within the intercalated disks are nexi, or gap junctions, which are minute cytoplasmic channels that allow action potentials to propagate from cell to cell.

thick filaments are composed of *myosin* molecules. In the presence of adenosine triphosphate (ATP) and calcium ions (Ca^{2+}), myosin and actin interact in a series of steps called the *cross-bridge cycle,* which results in contraction and force generation in each sarcomere and therefore in the whole muscle cell (for details, see Figures 1-3, 1-4, 1-5, and 6-6).

Cardiac Muscle Forms a Functional Syncytium

Although the molecular basis of contraction is the same for cardiac and skeletal muscle, the two muscle types differ in regard to electrical linkages between neighboring cells, and this difference has important consequences. Individual skeletal muscle cells are electrically isolated (insulated) from one another, so action potentials cannot "jump" from one skeletal muscle cell to another. As described in Chapter 5, an action potential in a skeletal muscle cell is initiated only in response to an action potential in the somatic motor neuron that innervates the skeletal muscle cell. Each neural action potential causes release of the neurotransmitter acetylcholine, which activates nicotinic cholinergic receptors on the skeletal muscle cell, which in turn depolarizes the muscle cell to threshold for the formation of an action potential. When formed, the action potential propagates along the length of that particular muscle cell and then stops. The muscle action potential causes the cell to contract. Neighboring cells may

or may not contract at the same time, depending on whether action potentials are initiated in the neighboring cells by their motor neurons.

In contrast, cardiac muscle cells are electrically linked to one another. When an action potential is started in a single cardiac muscle cell, it propagates along the length of that cell. At specialized points of contact with neighboring cells, ionic currents created by the action potential flow into the neighboring cells and initiate action potentials in those cells, too. Because cardiac action potentials propagate from cell to cell through cardiac tissue, neighboring cardiac muscle cells all contract in synchrony, as a unit, and then they all relax. In this regard, cardiac muscle tissue behaves as if it were a single cell. Cardiac muscle is therefore said to form a *functional syncytium* (literally, "acts like same cell").

The specialized cellular structures that allow cardiac action potentials to propagate from cell to cell are evident under the light microscope (see Figure 19-1). Cardiac muscle appears as an array of fibers (individual cardiac muscle cells) that are arranged approximately in parallel but with some branching. Adjacent cells are joined together by dark-appearing structures called *intercalated disks*. Electron microscopy has revealed that within these disks are tiny open channels between neighboring cells. These *nexi,* or *gap junctions,* provide points of contact between the intracellular fluid of adjacent cells. When an action potential depolarizes the cell on one side of an intercalated disk, positive ions flow through the gap junctions and into the neighboring cell. This local, ionic current depolarizes the neighboring cell to threshold for the formation of an action potential. In effect, an action potential propagates from cell to cell through the gap junctions that are located within the intercalated disks. Skeletal muscle does not have intercalated disks or nexi (gap junctions).

Cardiac Contractions Are Initiated by Action Potentials That Arise Spontaneously in Specialized Pacemaker Cells

Because cardiac muscle tissue forms a functional syncytium, and because a cardiac action potential leads to contraction, any one cardiac muscle cell can initiate a heartbeat. In other words, if a single cardiac muscle cell depolarizes to threshold and forms an action potential, that action potential will propagate from cell to cell, throughout the heart, and cause the whole heart to contract. Most cardiac muscle cells have the property of remaining stable at a resting membrane potential; they never form action potentials by themselves. However, a few specialized cardiac muscle cells have the property of depolarizing spontaneously toward the threshold for the formation of action potentials. When any one of these specialized cells reaches threshold and forms an action potential, a heartbeat results. Cardiac cells that depolarize spontaneously toward threshold are called *pacemaker cells* because they initiate heartbeats and therefore determine the rate, or pace, of the heart.

Although all spontaneously depolarizing cells in the heart are called pacemaker cells, only one pacemaker cell, the one that reaches threshold first, actually triggers a particular heartbeat. In the normal heart, the pacemaker cells that depolarize most quickly to threshold are located in the *sinoatrial* (SA) *node*. The SA node is in the right atrial wall, at the point where the *venae cavae* enter the right atrium.

Because it has spontaneously depolarizing pacemaker cells, the heart initiates its own muscle action potentials and contractions. Motor neurons are not necessary for initiating cardiac contractions, whereas they are needed for initiating skeletal muscle contractions. Motor neurons (sympathetic and parasympathetic) do affect the heart rate, by influencing the rapidity with which the pacemaker cells depolarize to threshold, but the pacemaker cells initiate action potentials, and therefore heartbeats, even without any sympathetic or parasympathetic influences. Thus a denervated heart still beats, whereas a denervated skeletal muscle remains relaxed (in fact, paralyzed). The ability of the heart to beat without neural input enables surgically transplanted hearts to function. When a donor's heart is connected to a recipient's circulation during cardiac transplantation, no nerves are attached to the transplanted heart. The pacemaker cells in the transplanted heart initiate its action potentials and contractions. The only factor missing is control of the heart rate through cardiac sympathetic and parasympathetic nerves.

A System of Specialized Cardiac Muscle Cells Initiates and Organizes Each Heartbeat

Each normal heartbeat is initiated by an action potential that arises spontaneously in one of the pacemaker cells in the SA node (Figure 19-2). When formed, the action potential propagates rapidly, from cell to cell, across the right and left atria, causing both atria to contract. Next, the action potential propagates *slowly,* from cell to cell, through a special pathway of cardiac muscle cells that lies between the atria and the ventricles. This pathway consists of the *atrioventricular* (AV) *node* and the first part of the *AV bundle,* also called the *bundle of His*. The AV node and AV bundle provide the only route for the propagation of action potentials from the atria to the ventricles. Elsewhere, the atria and ventricles are separated by a layer of connective tissue, which can neither form nor propagate action potentials. In addition to providing the only conductive pathway between the atria and the ventricles, the AV node and the first part of the AV bundle have the special property of very slow conduction of action potentials. It takes 50 to 150 msec for an atrial action potential to travel through the AV node and the first part of the AV bundle; that is, it takes 50 to 150 msec for an atrial action potential to propagate into the ventricles. Slow conduction through the *AV junction* creates the delay between atrial and ventricular contractions.

When past the slowly conducting cells of the AV junction, the cardiac action potential enters a branching network of specialized cardiac cells that have the property of extremely rapid propagation of action potentials. The transition zone from slowly conducting to rapidly conducting cells is located within the AV bundle, which has slowly conducting cells in its first portion

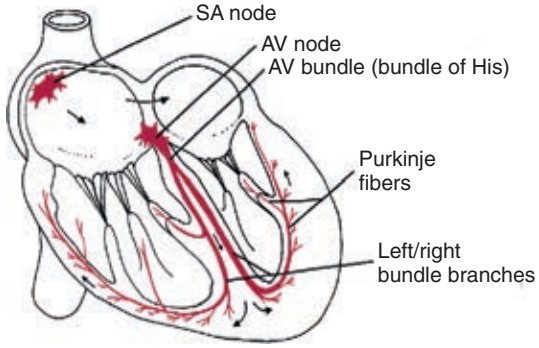

FIGURE 19-2 Specialized conduction system of the heart is responsible for the initiation and organization of cardiac contractions. The system is composed of specialized cardiac muscle fibers, not nerves. *AV,* Atrioventricular; *SA,* sinoatrial.

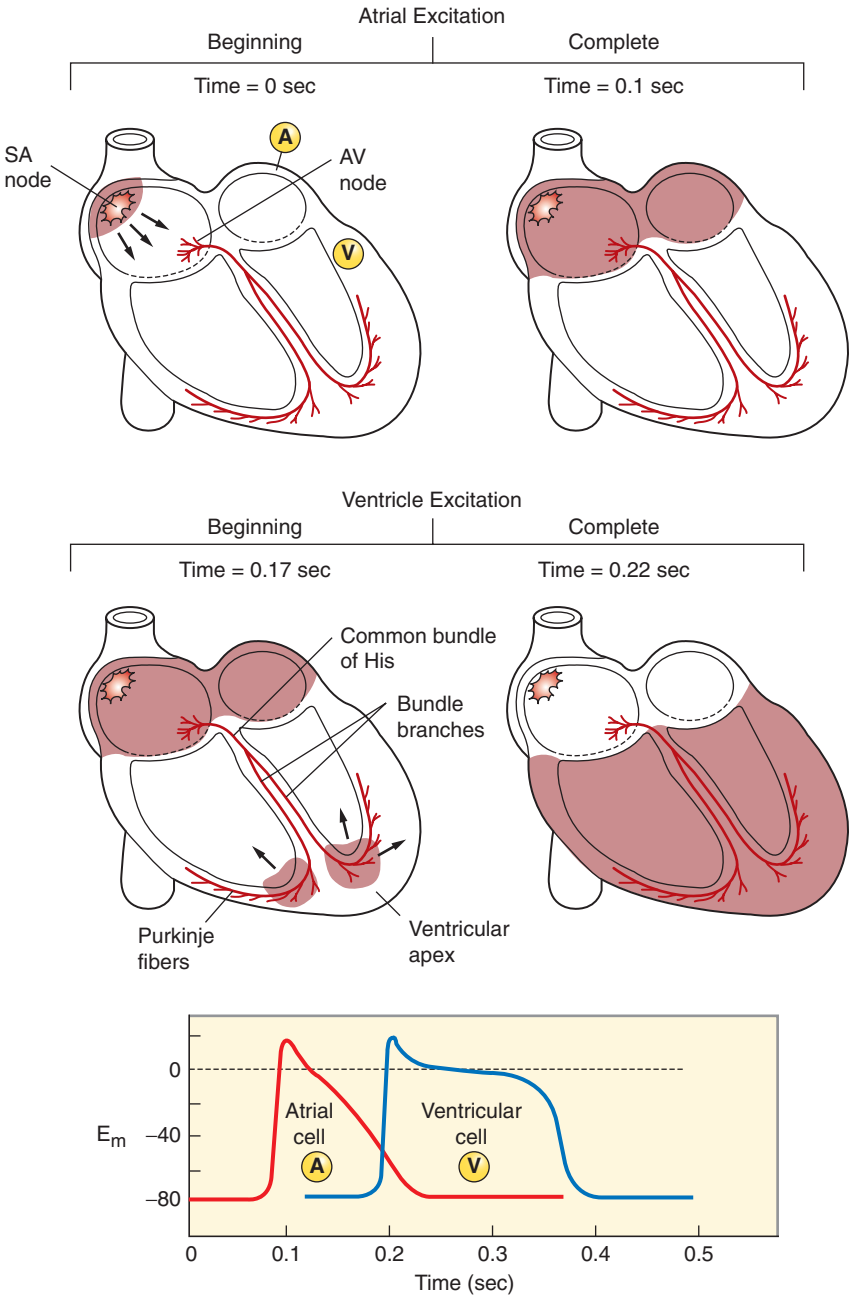

FIGURE 19-3 Heart is pictured at four instants during initiation of a normal contraction. *Shading* indicates areas of heart where an action potential is underway. *Top left* (time = 0 sec), Pacemaker cell in the sinoatrial *(SA)* node has just reached threshold, and an action potential has begun to propagate outward across the atria. *Top right* (time = 0.1 sec), Action potential has reached all parts of both atria (action potential underway in all atrial cells). *Middle left* (time = 0.17 sec), Action potential has passed through the atrioventricular *(AV)* node and down the bundle branches and has just reached the ventricular apex. *Middle right* (time = 0.22 sec), Action potential has just finished propagating outward through the walls of both ventricles (action potential is underway in all ventricular cells, but all atrial cells have finished their action potential). *Bottom,* Graph shows the timing of action potentials in a left atrial cell (at location labeled *A, top left*) and in a left ventricular cell (labeled *V, top left*). Their locations make these among the last atrial and ventricular cells to be depolarized as an action potential propagates across the atria and ventricles, respectively. E_m, Membrane potential in millivolts.

(connected to the AV node) and rapidly conducting cells beyond that. The rapidly conducting portion of the AV bundle splits to form the *left* and *right bundle branches.* At the ventricular apex, the bundle branches break up into a dispersed network of *Purkinje fibers,* which carry the action potential rapidly along the inner walls of both ventricles. The Purkinje fibers propagate action potentials into the normal ventricular muscle fibers within the inner walls *(subendocardial layers)* of both ventricles. From there, the action potentials propagate quite rapidly outward, from cell to cell, through the ventricular walls. As the action potential reaches each ventricular muscle fiber, that fiber contracts. The extremely rapid conduction of the cardiac action potential, from cell to cell, through the latter portion of the AV bundle, the bundle branches, and the Purkinje system results in a nearly synchronous contraction of all the fibers in both ventricles.

The SA and AV nodes, AV bundle, bundle branches, and Purkinje fibers are collectively called the *specialized conduction system of the heart.* This system is composed of specialized cardiac muscle cells, not nerves. The particular characteristics of the components in the specialized conduction system cause each heartbeat to follow a specific, patterned sequence. In a normal beat, both atria contract, almost simultaneously. Next, there is a brief pause (caused by slow propagation of the action potential through the AV node). The two ventricles then contract, almost simultaneously. Finally, the entire heart relaxes and refills.

Figure 19-3 reemphasizes the role of the specialized conduction system in initiating and organizing a normal cardiac contraction. In this "time lapse" illustration, atrial excitation begins at time t = 0, when one SA node cell has reached threshold and an action potential is just beginning to propagate out of the SA

node and into regular atrial tissue. Within 0.1 second, the action potential has propagated completely across the right and left atria, and a coordinated contraction of both atria is just beginning. As the action potential propagates across the atria, it also depolarizes the first cells in the AV node, beginning at time t = 0.04 second. While the atria are in a depolarized (excited) state, the action potential is propagating slowly from cell to cell through the AV node and first part of the AV bundle. After traversing this slowly conducting region, the action potential propagates rapidly through the remainder of the bundle of His and its branches. The action potential arrives at the ventricular apex at time t = 0.17 second. Note that it takes about 0.13 second [(0.17 – 0.04) second] for the action potential to travel through the AV node and bundles; that is, 0.13 second represents a typical delay between atrial depolarization and ventricular depolarization. From the ventricular apex, the Purkinje fibers propagate the action potential rapidly throughout both ventricles. Ventricular excitation (depolarization) is complete by time t = 0.22 second, and both ventricles contract. By this time the atria have repolarized to a resting state and are relaxing. After ventricular excitation and contraction, the ventricles relax, and the whole heart remains in a resting state until the next beat is originated by an SA node pacemaker cell.

Cardiac Action Potentials Are Extremely Long

Two major differences between action potentials in skeletal muscle and cardiac muscle have already been mentioned: First, action potentials propagate from cell to cell in cardiac muscle, whereas skeletal muscle cells are electrically isolated from one another. Second, the heart has pacemaker cells, which form spontaneous action potentials, whereas a skeletal muscle cell only depolarizes and forms action potentials when "commanded" to do so by its motor neuron.

A third important difference between skeletal and cardiac action potentials is their duration (Figure 19-4). The entire action potential in a skeletal muscle lasts only 1 to 2 msec. A cardiac action potential lasts about 100 times longer (100-250 msec). Prolongation of the cardiac action potential is brought about by prolonged changes in the permeability of the cardiac muscle membrane to sodium, potassium, and calcium ions (Na^+, K^+, and Ca^{2+}). Cardiac muscle cell membranes have Na^+ and K^+ channels similar to those found in skeletal muscle, but the timing of their opening and closing is different in cardiac muscle. In addition, cardiac cell membranes also have special Ca^{2+} channels that are not present in skeletal muscle. The movement of extracellular Ca^{2+} through cardiac Ca^{2+} channels has an especially important role in prolonging the cardiac action potential. The presence of Ca^{2+} channels and the important role of extracellular Ca^{2+} in the action potential is the fourth major difference between cardiac and skeletal muscle.

In addition to learning about the special significance of the membrane Ca^{2+} channels in cardiac muscle, it is useful to review the roles of K^+ and Na^+ channels in skeletal muscle and to emphasize some ways in which cardiac K^+ and Na^+ channels are similar to those in skeletal muscle. As explained in Chapter 4, many of the K^+ channels in a neuron or skeletal muscle cell membrane are open when the cell is at rest, and most of the Na^+ channels are closed. As a result, the resting cell is much more permeable to K^+ than to Na^+. As a result, there is a greater tendency for positive K^+ to exit from the cell than for positive Na^+ to enter. This imbalance is the main factor responsible for a resting membrane potential (polarization) in which the inside of the cell membrane is

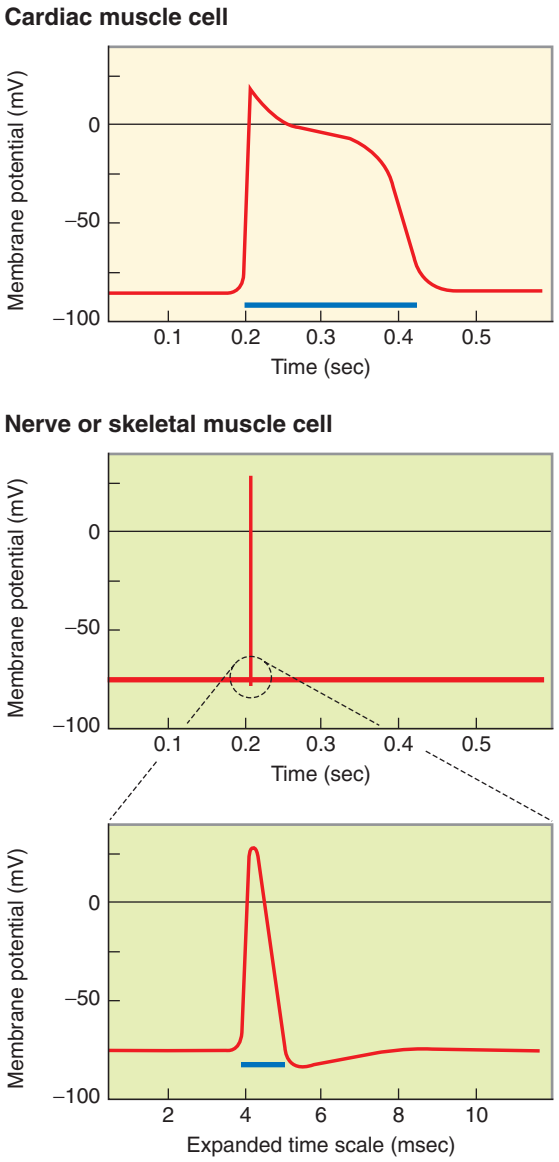

FIGURE 19-4 Action potentials in cardiac muscle cells *(top)* last 100 times longer than action potentials in nerve or skeletal muscle cells *(middle). Bottom,* The nerve or skeletal muscle action potential is shown on a greatly expanded time scale to illustrate that an action potential in a nerve or skeletal muscle cell has a different shape than a cardiac action potential, as well as a much shorter duration. The prolonged phase of depolarization in cardiac muscle cells is called the plateau of the action potential. The *dark bars* under each action potential indicate the length of the absolute refractory period.

negative in comparison with the outside. The resting membrane potential in skeletal muscle cells is typically between –70 and –80 mV (see Figure 19-4, *bottom*). An action potential is created when something *depolarizes* the cell (makes it less negative inside). Specifically, depolarization to the *threshold voltage* for opening the voltage-gated Na^+ channels allows an influx of extracellular Na^+ into the cell. This rapid entry of positive ions causes the cell membrane to become positively charged on its inside surface. This positive membrane potential persists for only a moment, however, because the Na^+ channels become *inactivated* very quickly. Na^+ entry ceases, and the cell rapidly repolarizes toward its resting membrane potential. Repolarization is also promoted

by the opening of additional K^+ channels. In fact, this opening of extra K^+ channels may cause neurons and skeletal muscle cells to become *hyperpolarized* (even more negative than normal resting membrane potential) for a few milliseconds at the end of each action potential (see Figure 19-4, *bottom*).

In a resting skeletal muscle cell, calcium ions are sequestered within the *sarcoplasmic reticulum.* The occurrence of an action potential in the skeletal muscle cell causes Ca^{2+} to be released from the sarcoplasmic reticulum into the free intracellular fluid, which is called the *cytosol.* The increase in cytosolic Ca^{2+} concentration initiates muscle contraction (see Figure 1-5). The contraction initiated by a single action potential is very brief in skeletal muscle, because the cytosolic Ca^{2+} is rapidly pumped back into the sarcoplasmic reticulum by active transport, and the muscle relaxes. Note that the Ca^{2+} responsible for initiating skeletal muscle contraction comes entirely from the intracellular storage site, the sarcoplasmic reticulum. No extracellular Ca^{2+} enters the cell during the action potential, because skeletal muscle cells do not have membrane Ca^{2+} channels. In cardiac muscle, in contrast, membrane Ca^{2+} channels and the entry of extracellular Ca^{2+} into the cells play key roles in both action potentials and contractions.

Membrane Calcium Channels Play a Special Role in Cardiac Muscle

Figure 19-5 depicts a cardiac muscle cell action potential and the sequence of changes in K^+, Na^+, and Ca^{2+} permeability that are responsible for the action potential. As the time line begins (on the left side of each graph), the cardiac cell is at a normal, negative resting membrane potential of about –80 mV. The cardiac membrane potential is negative at rest for the same reason that skeletal muscle cells have negative resting membrane potentials: many K^+ channels are open at rest, and most of the Na^+ channels are closed. As a result, membrane permeability to K^+ is much higher than membrane permeability to Na^+ (see Figure 19-5, *middle two graphs*). In resting cardiac cells, the membrane Ca^{2+} channels are closed, so Ca^{2+} permeability is very low (see Figure 19-5, *bottom*); extracellular Ca^{2+} ions are prevented from entering the cardiac cells.

As in skeletal muscle, a cardiac action potential is created when the cell is depolarized to the threshold voltage for opening the voltage-gated Na^+ channels. The rapid influx of extracellular Na^+ into the cell causes the cell membrane to become positively charged on its inside surface (*Phase 0* in Figure 19-5, *top*). The Na^+ channels inactivate very quickly, which causes the Na^+ permeability to decrease quickly; the membrane begins to repolarize *(Phase 1).* However, in cardiac muscle, repolarization is interrupted, and there is a prolonged plateau of depolarization, which lasts about 200 msec *(Phase 2).* The plateau of the cardiac action potential is brought about by two conditions that do not occur in nerves or skeletal muscle fibers: (1) some K^+ channels close, so K^+ permeability decreases; and (2) many of the Ca^{2+} channels open, so Ca^{2+} permeability increases. Because the Ca^{2+} concentration is higher in the extracellular fluid than in the intracellular fluid, Ca^{2+} flows through the open Ca^{2+} channels and into the cytosol. The combination of reducing the exit of K^+ from the cell and allowing the entrance of Ca^{2+} into the cell keeps the cell membrane in a depolarized state. After about 200 msec, the K^+ channels reopen, and the Ca^{2+} channels close; K^+ permeability increases, and Ca^{2+} permeability decreases. The combination of increasing the exit of K^+ from the cell and shutting off the entrance of Ca^{2+} into the cell causes the cell to repolarize *(Phase 3)* and eventually to return to its stable, negative resting membrane potential *(Phase 4).*

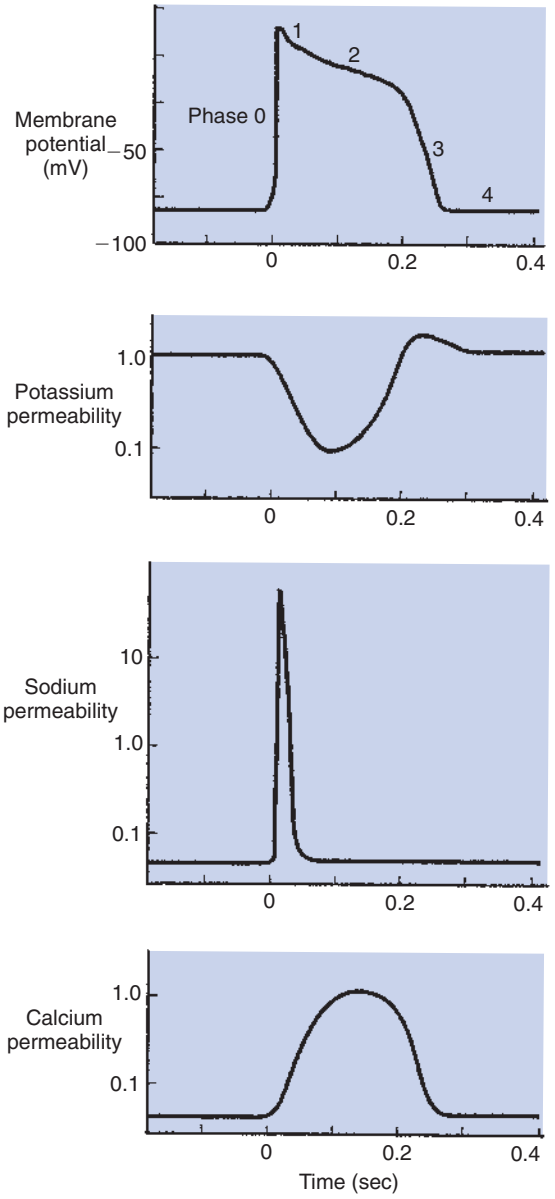

FIGURE 19-5 Membrane potential of a cardiac muscle cell *(top)* is determined by the relative permeabilities of the cell membrane to K^+ *(second from top),* Na^+ *(second from bottom),* and Ca^{2+} *(bottom).* At rest (*left side* of graphs), the cell is much more permeable to K^+ than to Na^+ or Ca^{2+}. (That is, the number of open K^+ channels greatly exceeds the number of open Na^+ or Ca^{2+} channels.) A cardiac action potential (*middle* of graphs) is produced by a characteristic sequence of permeability changes to K^+, Na^+, and Ca^{2+} (i.e., changes in the number of open K^+, Na^+, and Ca^{2+} channels). The action potential ends when the permeabilities return to their resting state (*right side* of graphs). Phases 0 to 4 are discussed in the text.

The specialized Ca^{2+} channels in cardiac muscle cell membranes are called *slow Ca^{2+} channels* (or *L-type Ca^{2+} channels*) because they take much longer to open than the Na^+ channels, and they stay open much longer. As shown in Figure 19-5, Na^+ permeability increases and then decreases (Na^+ channels open and then inactivate) within a few milliseconds. Ca^{2+} permeability, in comparison, is slow to increase (Ca^{2+} channels are slow to

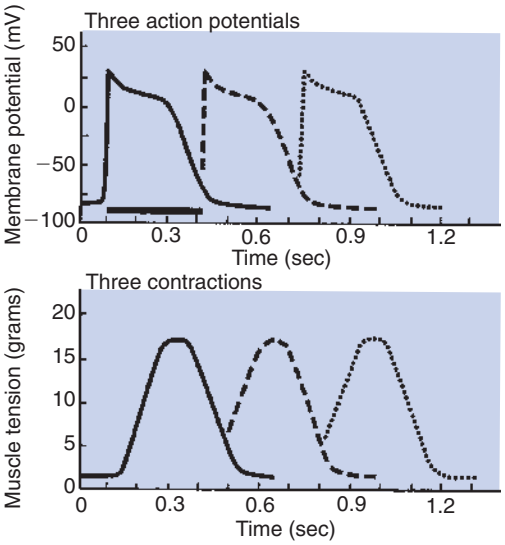

FIGURE 19-6 The first of three cardiac action potentials *(solid line, top)* causes a cardiac contraction *(solid line, bottom)*. Note that the action potential and contraction have similar durations. The *heavy horizontal bar* under the first action potential shows the duration of the absolute refractory period. The *dashed line* and *dotted line* in the top graph show the earliest possible occurrence of a second and a third action potential, each occurring right after the absolute refractory period for the preceding action potential. The *dashed line* and *dotted line* in the bottom graph depict the corresponding cardiac contractions. Because of the long refractory period, each contraction is almost over before the earliest possible next contraction can begin. This guarantees a period of cardiac relaxation between contractions.

open) and Ca^{2+} permeability remains elevated for about 200 msec (the time Ca^{2+} channels stay open). In recognition of their much quicker responses, the Na^+ channels in cardiac muscle are sometimes called *fast Na^+ channels*.

The Ca^{2+} that enters a cardiac cell during an action potential triggers the release of additional Ca^{2+} from the sarcoplasmic reticulum. This process is called *calcium-triggered calcium release* (or *calcium-induced calcium release*). In less than 0.1 second, the contraction of free Ca^{2+} in the cytosol increases about 100-fold. As in skeletal muscle, this increase in cytosolic Ca^{2+} initiates concentration. When the Ca^{2+} channels close, at the conclusion of the action potential, most of the free, cytosolic Ca^{2+} is pumped back into the sarcoplasmic reticulum or pumped back across the cell membrane into the extracellular fluid. Both these processes involve active transport, because the Ca^{2+} is being pumped against its electrochemical gradient. Once the cytosolic Ca^{2+} concentration is returned to its low, resting level, the cardiac muscle relaxes. Figure 19-6 shows the relationship between action potentials and the resulting contractions in a cardiac muscle cell.

The Long Duration of the Cardiac Action Potential Guarantees a Period of Relaxation (and Refilling) Between Heartbeats

Na^+ channels become inactivated at the peak of the cardiac action potential. Na^+ cannot pass through an inactivated channel; therefore, as long as the Na^+ channels remain inactivated, another action potential cannot occur. The inactivated state ends, and Na^+ channels become susceptible to reopening only when the cell membrane potential returns to (or nearly to) its resting level. Thus, Na^+ inactivation guarantees that the upstroke of a second action potential cannot occur until the first action potential is completed (or very nearly).

While the Na^+ channels are inactivated, the cell is *refractory* (resistant) with regard to the formation of an action potential. The time after the beginning of one action potential during which another action potential cannot be initiated is called the *absolute refractory period*. Because Na^+ inactivation lasts until the membrane potential returns to (or nearly to) its resting level, the refractory period lasts about as long as an action potential. Thus the refractory period in a cardiac muscle cell lasts 100 to 250 msec, whereas the refractory period in a nerve or skeletal muscle cell lasts only about 1 or 2 msec (see Figure 19-4).

The long refractory period in cardiac muscle guarantees a period of relaxation (and cardiac refilling) between cardiac contractions. Figure 19-6 *(top)* depicts the quickest possible succession of three action potentials in a cardiac muscle cell: the second action potential begins immediately after the conclusion of the refractory period for the first action potential. Likewise, the third action potential begins immediately after the conclusion of the refractory period for the second. The *bottom graph* in Figure 19-6 shows the pattern of muscle contraction that results from the three action potentials. Note that contractile strength reaches a peak late in the plateau phase of each action potential, and that the contractile strength decreases (the muscle begins to relax) during the repolarization phase of each action potential. As a result, the cardiac muscle cell becomes partially relaxed before the earliest possible subsequent contraction can begin; that is, each cardiac action potential produces a contraction that is distinctly separated from the preceding contraction. Because of its long refractory period, cardiac muscle cannot sustain a continuous contraction. Thus the heart has a guaranteed period of relaxation (and refilling) between heartbeats.

The pattern of changes in muscle tension depicted in the bottom of Figure 19-6 corresponds closely to the changes in the cytosolic Ca^{2+} concentration. This makes sense, considering that the increase in cytosolic Ca^{2+} concentration initiates muscle contraction, and the subsequent removal of Ca^{2+} from the cytosol permits the muscle to relax. Cytosolic Ca^{2+} concentration increases during the plateau of the action potential (because of Ca^{2+}-triggered Ca^{2+} release) and decreases back to its resting level during the repolarization phase of the action potential (as active transport pumps move Ca^{2+} back into the sarcoplasmic reticulum or out into the extracellular fluid).

In skeletal muscle cells, an action potential lasts only 1 to 2 msec. The membrane is repolarized (and the refractory period is over) even before the release of Ca^{2+} from the sarcoplasmic reticulum is finished, and many milliseconds before the released Ca^{2+} is pumped back into the sarcoplasmic reticulum. As a result, the cytosolic Ca^{2+} concentration reaches its peak level after the action potential is over, and the contractile tension resulting from the action potential also reaches its peak after the action potential is over. Because a contractile twitch lasts much longer than the refractory period in skeletal muscle, several action potentials can occur during the time of a single contractile twitch. Multiple action potentials in quick succession cause cytosolic Ca^{2+} concentration to build to a high level and stay there. The resulting contractile tension is stronger than the tension that results from a single action potential, and it is sustained for a longer time. In effect, the muscle twitches caused by successive action potentials "fuse" together. This phenomenon is called *temporal summation*. Fusion and temporal summation are the mechanisms that permit graded and prolonged tension development in skeletal muscle. In

contrast, the long refractory period in cardiac muscle cells prevents the fusion and summation of cardiac contractions. Each contraction of the heart (each heartbeat) is followed immediately by a relaxation.

Atrial Cells Have Shorter Action Potentials Than Ventricular Cells

The previous description of cardiac ion channels, action potentials, and contractions is based on properties of normal ventricular cells. Atrial cells are basically similar, except that their action potentials are shorter than action potentials in ventricular cells. Like ventricular cells, atrial cells have fast Na^+ channels that open briefly at the beginning of an action potential and then become inactivated. Likewise, atrial slow Ca^{2+} channels open during the action potential, and K^+ channels close. The differences between atrial and ventricular cells are that atrial slow Ca^{2+} channels typically stay open a shorter time than those in ventricular cells, and atrial K^+ channels stay closed for a shorter time. As a result, the plateau of an atrial cell's action potential is shorter and not as "flat" as the plateau of a ventricular cell's action potential (see Figure 19-3, *bottom*). As a consequence of having a shorter action potential, atrial cells have a shorter refractory period than ventricular cells. Therefore the atrial cells are capable of forming more action potentials per minute than ventricular cells; that is, the atria can "beat" faster than the ventricles. The implications of this difference are discussed later in this chapter.

Specialized Ion Channels Cause Cardiac Pacemaker Cells to Depolarize to Threshold and Form Action Potentials

As mentioned, the cardiac pacemaker cells of the SA node spontaneously depolarize to threshold and then form action potentials. The spontaneous depolarization is called a *pacemaker potential,* and it is the key distinguishing feature of a pacemaker cell (Figure 19-7, *top*). The action potentials of cardiac pacemaker cells typically have a rounded appearance; they lack the very rapid (phase 0) depolarization seen in ventricular and atrial cells.

The spontaneous depolarizations and rounded action potentials of pacemaker cells are consequences of the particular ion channels found in these cells. Pacemaker cells lack the usual voltage-gated fast Na^+ channels. Instead, these cells have *pacemaker Na^+ channels* (also called *funny Na^+ channels*), which close during an action potential and then begin to open again, spontaneously, once an action potential has finished. The spontaneous opening of the pacemaker Na^+ channels causes a progressive increase in the cell's Na^+ permeability (see Figure 19-7, *second from bottom*). The increase in Na^+ permeability allows Na^+ to enter the cell from the extracellular fluid, which depolarizes the cell toward threshold. Pacemaker cells also have an unusual set of K^+ channels, which participate in their spontaneous depolarization. At the end of one action potential, K^+ permeability in pacemaker cells is quite high, because most K^+ channels are open. Then some K^+ channels begin to close (see Figure 19-7, *second from top*). As K^+ permeability decreases, less K^+ leaves the cells, which makes the cells progressively less negatively charged inside. Ca^{2+} channels also make a small contribution to the pacemaker potential. Late in the pacemaker potential, just before a pacemaker cell reaches threshold, slow Ca^{2+}channels begin to open, and Ca^{2+} permeability begins to increase (see Figure 19-7, *bottom*). The resulting entry of Ca^{2+} into the cell speeds its final approach to threshold. Thus the pacemaker potential is caused by the opening of pacemaker Na^+ channels, the closing of K^+ channels, and (late in the process) the opening of Ca^{2+} channels. These

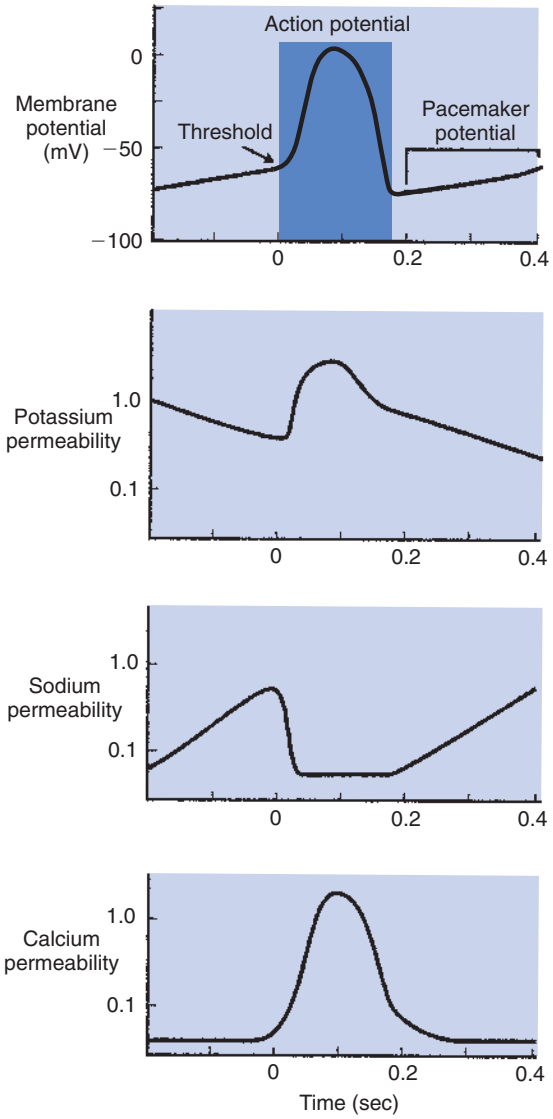

FIGURE 19-7 A cardiac pacemaker cell depolarizes spontaneously to threshold and initiates its own action potential *(top).* The spontaneous depolarization (called the *pacemaker potential*) is the result of a spontaneous, progressive decrease in K^+ permeability *(second from top)* and an increase in Na^+ permeability *(second from bottom).* An increase in Ca^{2+} permeability makes a late contribution to the depolarization toward threshold *(bottom).* When threshold level is reached, an action potential is produced. The action potential is driven primarily by a large, prolonged increase in Ca^{2+} permeability. The absence of fast Na^+ channels in pacemaker cells causes the upstroke of the pacemaker action potential to be much slower than that seen in non-pacemaker cells. (Compare with Figure 19-5.)

spontaneous changes in Na^+, K^+, and Ca^{2+} channels in pacemaker cells are in contrast to the stable status of the ion channels in normal, resting atrial or ventricular cells.

When threshold is reached in a pacemaker cell, an action potential occurs. The upstroke of the action potential is quite slow compared with the rapid (phase 0) depolarization in a normal atrial or ventricular cell, because there are no fast Na^+ channels in pacemaker cells and therefore no sudden influx of Na^+. The ion primarily responsible for the action potential in a pacemaker cell is Ca^{2+}. When threshold is reached, many of the cell's slow Ca^{2+}

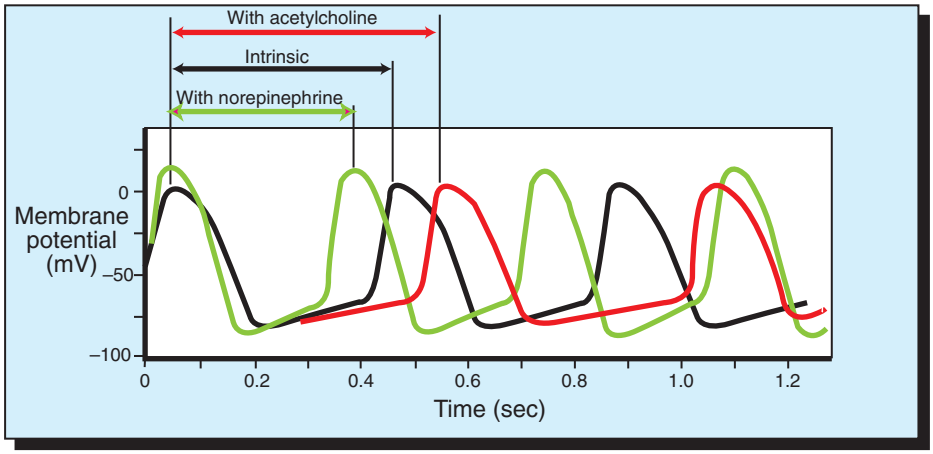

FIGURE 19-8 In the absence of neurohumoral influences, a pacemaker cell of the SA node spontaneously depolarizes to threshold and initiates a series of action potentials, three of which are shown by the *black line*. The interval between action potentials under these conditions determines the intrinsic, or spontaneous, heart rate (in this case, 0.43 sec between action potentials corresponds to a heart rate of 140 beats/min). Acetylcholine decreases the rate of depolarization and therefore lengthens the interval between action potentials (i.e., decreases heart rate). Norepinephrine increases the rate of depolarization and therefore shortens the interval between action potentials (i.e., increases heart rate).

channels open. The permeability to Ca^{2+} increases, and extracellular Ca^{2+} flows into the cell. The action potentials in pacemaker cells are often called slow action potentials, because they lack a rapid, phase 0 depolarization and because they are caused primarily by the opening of slow Ca^{2+} channels. In contrast, normal atrial or ventricular action potentials are called fast action potentials. Note, however, that all cardiac action potentials (whether "slow" or "fast") have a very long duration compared with action potentials in nerve or skeletal muscle cells.

Sympathetic and Parasympathetic Nerves Act on Cardiac Pacemaker Cells to Increase or Decrease the Heart Rate

Figure 19-8 shows how the neurotransmitters *norepinephrine* and *acetylcholine* affect the pacemaker cells of the heart. Norepinephrine exerts its effect by activating *β-adrenergic receptors* on the cell membranes of pacemaker cells. Activation of such receptors speeds up the ion channel changes that are responsible for the spontaneous depolarization of pacemaker cells. Because the pacemaker cells reach threshold more quickly in the presence of norepinephrine, there is a shorter interval between heartbeats. Therefore, heart rate is elevated above its intrinsic or spontaneous level.

Acetylcholine has the opposite effect. Acetylcholine activates *muscarinic cholinergic receptors* on the cell membranes of pacemaker cells, which slows the ion channel changes that are responsible for the pacemaker cell's spontaneous depolarization. Because the pacemaker cells take longer to reach threshold in the presence of acetylcholine, there is a longer interval between heartbeats. Therefore, heart rate is decreased below its intrinsic or spontaneous level.

Sympathetic neurons release norepinephrine at the SA node cells, and thus sympathetic nerve activity increases the heart rate. Epinephrine or norepinephrine, released from the adrenal glands and circulating in the bloodstream, has the same effect. Parasympathetic neurons release acetylcholine at the SA node cells, and thus parasympathetic activity decreases the heart rate. Figure 19-9 illustrates how sympathetic and parasympathetic neurons interact in the control of the heart rate. In the absence of

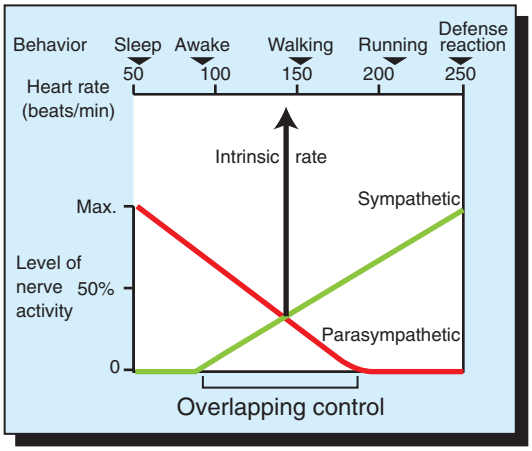

FIGURE 19-9 The upper scale shows that the heart rate of a normal, large dog ranges from 50 to 250 beats/min, depending on behavioral state. The graph illustrates that this wide range of heart rates is brought about by the interactions between sympathetic nerve activity, which speeds the heart above its intrinsic rate, and parasympathetic nerve activity, which slows the heart below its intrinsic rate. Sympathetic and parasympathetic nerves are simultaneously active over a considerable portion of the heart rate range *(overlapping control).* Note that the heart beats at its intrinsic rate (about 140 beats/min) either in the absence of any neural influence or when sympathetic and parasympathetic effects are equal and opposite.

norepinephrine and acetylcholine, the heart beats at its intrinsic rate. For a large dog, this rate is typically about 140 beats per minute (beats/min). Heart rates below the intrinsic rate are achieved by activation of parasympathetic neurons and release of acetylcholine. Accordingly, the graph in Figure 19-9 indicates that parasympathetic activity is high during awake rest (heart rate of 90 beats/min) and very high during sleep (heart rate of 55 beats/min). Heart rates above the intrinsic rate occur during exercise or emotional arousal and are achieved by activation of the sympathetic nerves to the heart and release of norepinephrine (or by

circulating epinephrine or norepinephrine). The highest possible level of sympathetic activity, and therefore the highest possible heart rate, occurs during maximal exercise or a *defense alarm reaction ("fear, fight, or flight" response).*

Through variation in the levels of sympathetic and parasympathetic *tone,* the dog's heart rate is adjusted, over a wide range, as appropriate for each behavioral situation. When both systems are partially active, the resulting heart rate represents the outcome of a "tug-of-war" between sympathetic action to increase the heart rate and parasympathetic action to decrease the heart rate. Typically, the sympathetic and parasympathetic systems are both partially active during awake states, ranging from quiet rest (heart rate about 90 beats/min) to moderate exercise (heart rate about 175 beats/min). Parasympathetic activity predominates in the lower part of this range, and sympathetic activity predominates in the higher part. When sympathetic activity and parasympathetic activity are equal, their effects cancel, and the heart rate is at its intrinsic (spontaneous) level. Simultaneous activation of sympathetic and parasympathetic neurons appears to give the nervous system tight control over the heart rate under a wide variety of behavioral conditions.

Cells of the Atrioventricular Node Act as Auxiliary Pacemakers and Protect the Ventricles from Beating Too Fast

As with SA node cells, the cells of the AV node normally exhibit pacemaker activity and slow action potentials. As shown in Figure 19-10, the AV node cells spontaneously depolarize toward threshold, but much more slowly than SA node cells. Therefore, under normal circumstances, the SA node cells reach threshold first and initiate an action potential, which then propagates from cell to cell across the atria and into the AV node. Within the AV node, this action potential encounters cells that are slowly, spontaneously depolarizing toward threshold. The arriving action potential quickly depolarizes these AV node pacemaker cells to threshold, and they form an action potential, which then propagates into the AV bundle and the ventricles. Thus, under normal conditions, each cardiac action potential is triggered by an SA node pacemaker cell, and the pacemaker activity of the AV node cells is irrelevant.

Under certain abnormal conditions, AV node pacemaker function becomes critical for survival. For example, if the SA node is damaged and does not depolarize to threshold, the AV node pacemaker cells will initiate action potentials that propagate into the ventricles, causing them to contract. If not for this *auxiliary pacemaker function of AV node cells,* the heart with a damaged SA node would not beat at all. Because the AV node pacemaker cells depolarize more slowly than normal SA node cells, the heart rate resulting from AV node pacemakers is very low, about 30 to 40 beats/min in a resting dog, compared with 80 to 90 beats/min when the SA node cells are the pacemakers. Also, action potentials initiated by the AV node pacemakers usually do not propagate "backwards" into the atria; therefore atrial contractions are absent. Nevertheless, if the SA node fails as a pacemaker, ventricular contractions are initiated by the AV node frequently enough to sustain life temporarily. Thus, AV node cells are sometimes called the heart's *emergency pacemakers.*

Another important feature of the AV node cells is that they have longer refractory periods than normal atrial cells. The long refractory period of AV node cells helps protect the ventricles from being stimulated to contract at rates that are too rapid for efficient pumping. This *protective function of the AV node* is critical to an animal's survival when atrial action potentials

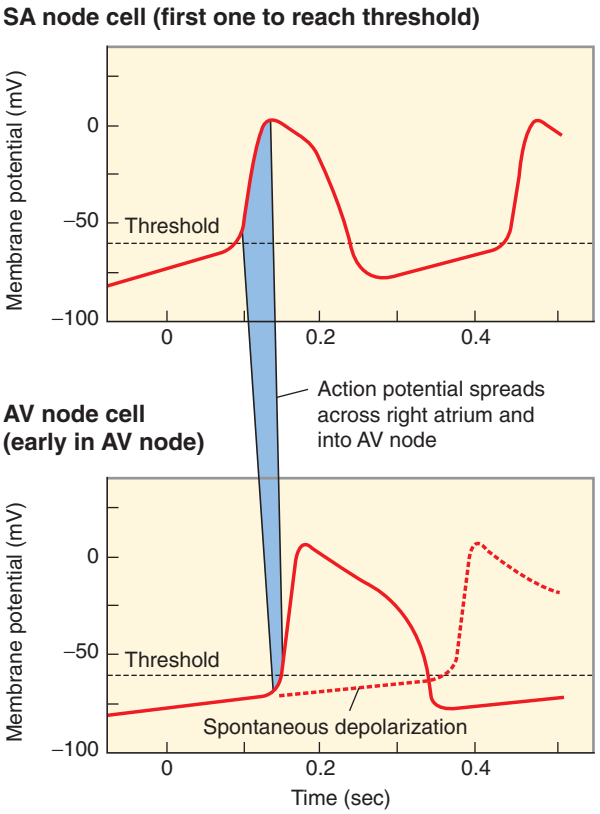

FIGURE 19-10 Both sinoatrial *(SA)* node cells and atrioventricular *(AV)* node cells exhibit pacemaker activity (spontaneous depolarization toward threshold). Normally the SA node cells depolarize more quickly and reach the threshold first *(top).* The resulting atrial action potential propagates into the AV node (as represented by *blue band*) and depolarizes the AV node cells quickly to their threshold, causing them to form an action potential *(solid line, bottom graph).* However, if the SA node pacemaker cells become nonfunctional or if atrial action potentials are not conducted into the AV node, the AV node cells eventually depolarize to threshold and initiate action potentials on their own *(dashed line, bottom graph).* In this way the AV node cells serve as an auxiliary (emergency) ventricular pacemaker.

are extremely frequent (see later discussion of atrial flutter/fibrillation). The long refractory period of the AV node cells plays an important role, even in a normal heart. When a normal action potential reaches the ventricles, it is prevented from "circling back" (and reactivating the atria) by the prolonged refractory state of the AV node cells.

Table 19-2 summarizes the four important electrical characteristics of the AV node previously discussed. Note that three of these characteristics are influenced by the nervous system. As indicated in the table, sympathetic activity increases the conduction velocity of the AV node cells, shortens their refractory period, and speeds their auxiliary pacemaker activity. Parasympathetic activation has the opposite effects. These sympathetic and parasympathetic effects are appropriate for different heart rates. For example, during exercise, when sympathetic activity is high and the SA node pacemakers are initiating heartbeats frequently, the speed of the whole process of cardiac contraction and relaxation must be increased. Thus it is appropriate that sympathetic action also increases the velocity of action potential conduction through the AV node, which shortens AV delay. In addition, sympathetic activation shortens the AV node refractory period, which allows each of the frequent atrial action potentials

TABLE 19-2 Electrical Characteristics of the Atrioventricular (AV) Node

Characteristic (Significance)	Sympathetic Effect*	Parasympathetic Effect†
Is the only conducting pathway between atria and ventricles (directs atrial action potentials into the rapidly conducting AV bundle and bundle branches)	—	—
Has a slow conduction velocity (creates AV delay)	Increases velocity (shortens AV delay)	Decreases velocity (lengthens AV delay)
Has a very long refractory period (protective effects: limits maximal rate to which atria can drive ventricles and prevents ventricular action potentials from re-exciting atria)	Shortens refractory period (appropriate for high heart rates)	Lengthens refractory period (appropriate for low heart rates)
Spontaneously depolarizes to threshold (acts as auxiliary pacemaker)	Faster depolarization (speeds auxiliary pacemaker)	Slower depolarization (slows auxiliary pacemaker)

*Through activation of β-adrenergic receptors on AV node cells.
†Through activation of muscarinic cholinergic receptors on AV node cells.

to be conducted to the ventricles. Finally, sympathetic activation enhances AV node auxiliary pacemaker activity, which provides the animal with a high enough ventricular rate to cope with some stress, even if the SA node pacemaker has failed. Conversely, when parasympathetic activation causes the SA node pacemakers to decrease the heart rate, all aspects of cardiac contraction and relaxation can proceed at a more leisurely pace. Under these conditions it is appropriate for AV node conduction velocity to be slowed and the AV node refractory period to be lengthened.

Sympathetic Nerves Act on All Cardiac Muscle Cells to Cause Quicker, More Forceful Contractions

Sympathetic neurons release norepinephrine in all regions of the heart, not only at the SA and AV nodes, and all cardiac muscle cells have β-adrenergic receptors that are activated by norepinephrine. Circulating epinephrine or norepinephrine (whether released from the adrenal medulla or administered as a drug) can also activate these same receptors. The effects of β-receptor activation on the SA and AV node cells have already been described (see Figure 19-8 and Table 19-2). In all other atrial and ventricular cells, β-receptor activation leads to taller, shorter action potentials and to stronger, quicker contractions. One reason for these effects is that activation of β receptors increases the number of L-type Ca^{2+} channels that open during the plateau (phase 2) of an action potential, which increases the amount of extracellular Ca^{2+} that enters the cell. Because Ca^{2+} entry is the primary depolarizing influence during the plateau, increased Ca^{2+} entry raises the plateau (makes the membrane potential more positive). A secondary consequence is to shorten the action potential. The action potential becomes shorter because of a complicated effect of the elevated plateau on the K^+ channels. Recall that K^+ channels close at the beginning of a cardiac action potential and then, after a time, reopen (see Figure 19-5). Reopening of the K^+ channels helps repolarize the cell to a resting state at the end of the action potential. The length of time before K^+ channels reopen depends on the membrane voltage during the plateau of the action potential. Specifically, when the membrane potential is more positive than normal during the plateau, the K^+ channels reopen sooner. This shortens the action potential and speeds repolarization. Overall, β-receptor activation makes each action potential taller and shorter. An action potential of higher amplitude propagates more quickly along each cell and from cell to cell, leading to faster conduction velocity. The shorter action potential means a shorter refractory period, which permits more heartbeats per minute.

Because β-receptor activation opens more Ca^{2+} channels and increases the entry of extracellular Ca^{2+} into cardiac muscle cells during an action potential, it also increases the strength of the resulting contraction. The entry of more extracellular "trigger" Ca^{2+} creates a greater stimulus for the release of Ca^{2+} stores from the sarcoplasmic reticulum. Therefore the cytosolic Ca^{2+} concentration increases very rapidly and reaches an exceptionally high level during the action potential, which leads to a quicker, stronger contraction. In addition, the duration of the contraction is shortened, because β-receptor activation speeds up the pumps that move cytosolic Ca^{2+} back into the sarcoplasmic reticulum and out of the cell into the extracellular fluid. Thus, even though more Ca^{2+} than normal enters the cytosol during an action potential, its removal at the end of the action potential is faster than normal. Overall, β-receptor activation makes each cardiac contraction stronger, quicker, and shorter.

In summary, sympathetic nerves act (1) on the SA node pacemaker cells to increase the heart rate, (2) on the AV node cells to increase the conduction velocity and shorten the AV delay, and (3) on all cardiac cells to shorten the refractory period and make each cardiac contraction quicker, stronger, and shorter. All these changes cause the heart to pump more blood at a higher pressure, which is an animal's normal response during exercise or emotional arousal.

Because sympathetic effects on the heart are all brought about through activation of the β-adrenergic receptors on the cardiac muscle cells, the administration of a drug that activates β receptors *(β-adrenergic agonist)* has the same effects as sympathetic activation. Epinephrine, norepinephrine, and isoproterenol are common β-adrenergic agonists. Conversely, the administration of a drug that binds to and blocks β receptors reduces all the effects of sympathetic activation. Propranolol and atenolol are common *β-adrenergic antagonists.* Examples of their use are provided later.

Parasympathetic Effects Are Opposite to Those of Sympathetic Activation But Are Generally Restricted to the Sinoatrial Node, Atrioventricular Node, and Atria

Parasympathetic nerves affect the heart by the release of acetylcholine, which activates muscarinic cholinergic receptors on cardiac muscle cells. Qualitatively, all the effects of parasympathetic activation are opposite to those of sympathetic activation,

because the effects of activating muscarinic cholinergic receptors are opposite to the effects of activating β-adrenergic receptors. Parasympathetic nerves have very powerful effects on the SA node pacemaker cells (see Figure 19-8) and on the AV node cells (see Table 19-2). In addition, parasympathetic nerves exert strong, antisympathetic influences on all the atrial cells. However, parasympathetic nerves have relatively weak effects on the ventricular muscle cells, because very few ventricular cells receive direct parasympathetic innervation. By contrast, all ventricular muscle cells receive direct sympathetic innervation. In summary, the predominant parasympathetic influences on the heart are exerted at the SA node (to decrease the rate), at the AV node (to slow conduction and lengthen the refractory period), and on all supraventricular cells (to lengthen the refractory period and make their contractions weaker and slower).

Parasympathetic neurons do exert a curious, indirect effect on ventricular muscle cells. In the ventricles, parasympathetic neurons release their acetylcholine onto sympathetic neuron terminals. This acetylcholine activates muscarinic cholinergic receptors that are located on the sympathetic neuron terminals. The effect of this activation is to inhibit the release of norepinephrine from the terminals, which weakens the effects of sympathetic activation on ventricular cells.

Parasympathetic effects on the heart can be mimicked by the administration of a *muscarinic cholinergic agonist* (e.g., acetylcholine or muscarine) and blocked by the administration of a *muscarinic cholinergic antagonist* (e.g., atropine). Some therapeutic applications are mentioned later.

Dysfunction in the Specialized Conducting System Leads to Abnormalities in Cardiac Rhythm (Arrhythmias)

Cardiac arrhythmias result either from problems with the formation of action potentials or from problems with the propagation (conduction) of action potentials. One example of a problem with action potential formation has already been mentioned: *sinus arrest,* in which the SA node completely fails to form action potentials. In a patient with sinus arrest, the auxiliary pacemaker function of the AV node keeps the ventricles beating, although at an abnormally low rate. Complete cessation of the SA node is the extreme case of the condition called *sick sinus syndrome.* In its more common and less extreme form, sick sinus syndrome is characterized by sluggish depolarization of the SA node pacemaker cells, which leads to an abnormally low intrinsic heart rate. Patients typically exhibit an abnormally low heart rate at rest *(bradycardia)* and an insufficient increase in heart rate during exercise. Specifically, in sick sinus syndrome, the intrinsic sinus rate is abnormally low.

Even though the problem in sick sinus syndrome is intrinsic to the sinus itself, one treatment strategy is to administer a cholinergic muscarinic antagonist drug (such as atropine) in order to block parasympathetic action on the heart. Table 19-3 illustrates the logic behind this treatment. In a normal, healthy large dog, the intrinsic rate of the heart is about 140 beats/min. However, resting heart rate is lower (about 90 beats/min) because parasympathetic tone slows the SA node pacemaker to a rate below its intrinsic rate. A drug that blocks parasympathetic effects on the heart would return the heart rate of a resting dog to 140 beats/min. A dog with a sick sinus has a low intrinsic heart rate, perhaps 80 beats/min. Parasympathetic tone makes the resting heart rate even lower, approximately 30 beats/min. A drug that blocks parasympathetic effects restores the heart rate to its intrinsic level, 80 beats/min. Therefore a dog with sick sinus syndrome treated with atropine has a heart rate that closely matches the rate of a normal resting dog.

TABLE 19-3 Treatment of Sick Sinus Syndrome by Blocking Parasympathetic Effects on Heart Rate with a Cholinergic Muscarinic Antagonist

Heart Rate (beats/min)	Normal Dog	Dog with Sick Sinus Syndrome
Intrinsic rate	140	80
Resting rate (with parasympathetic tone)	90	30
Resting rate after atropine	140	80

Another possible therapeutic approach is to increase the heart rate by administering a β-adrenergic agonist drug (e.g., isoproterenol). Enough isoproterenol would be given to increase the resting rate from 30 to 80 beats/min.

If drug treatment of sick sinus syndrome is ineffective, an alternative way to increase the heart rate is through the use of an *artificial cardiac pacemaker.* Such a device periodically applies an electric shock to the heart, which depolarizes cardiac muscle to threshold. Shocks applied to the atria initiate atrial action potentials. If the AV node is functioning normally, these atrial action potentials are conducted to the ventricles, and the ventricles contract. For temporary or emergency treatment, the pacemaker electrodes can be inserted intravenously (e.g., via the jugular vein) and advanced into the right atrial chamber. For long-term treatment, a battery-powered electrical stimulator can be surgically implanted under the patient's skin and attached to electrodes that are either inserted into one of the heart's chambers or attached to the outside surface of the heart.

Atrioventricular Node Block Is a Common Cause of Cardiac Arrhythmias

Whereas sick sinus syndrome exemplifies a dysfunction of action potential *formation, AV node block* is a common dysfunction of action potential *conduction.* If damage to the AV node prevents *(blocks)* conduction of atrial action potentials into the ventricles, the atria continue to beat at a rate determined by the SA node pacemaker cells. The ventricles also continue to beat, but at a much lower rate. In such a case the ventricular action potentials and contractions are being initiated by auxiliary pacemaker cells low in the AV node (i.e., below the level of the block). Because the AV node pacemaker cells depolarize more slowly than the SA node pacemaker cells, the ventricles in a resting dog with AV node block typically beat at only 30 to 40 beats/min. Furthermore, these ventricular beats are not synchronized with the atrial contractions.

Three degrees of severity of AV node block are recognized. Complete block of the AV node, in which no atrial action potentials are conducted to the ventricles, is called *third-degree AV node block.* If action potentials are conducted sporadically from the atria to the ventricles, so that the AV node transmits some atrial action potentials but not all of them, the condition is called *second-degree AV node block.* In a patient with second-degree block, some atrial contractions are followed by ventricular contractions, and others are not. Strong parasympathetic activity can

create or exaggerate second-degree AV node block because parasympathetic activity increases the refractory period of the AV node cells. For example, in quietly resting horses, parasympathetic tone is often so strong, and the AV node refractory period so long, that some atrial beats are not conducted to the ventricles. Therefore, if the pulse of a relaxed, resting horse is palpated, some "missing" ventricular contractions are likely to be noticed. During exercise the same horse does not show AV node block because parasympathetic activity has been decreased and sympathetic activity increased. Both these changes shorten the refractory period of the AV node and make it much more certain that every atrial action potential will be conducted to the ventricles.

Second-degree or third-degree AV node block often involves the electrical phenomenon known as *decremental conduction.* As mentioned, AV node cells have "slow" action potentials, characterized by a less rapid upstroke, a lower voltage amplitude, and a slower velocity of conduction than the action potentials in regular atrial or ventricular cells. All these differences make conduction of the action potential from cell to cell less reliable in the AV node than in regular atrial or ventricular tissue. When the AV node cells are in an electrically depressed state, an atrial action potential may simply die out within the AV node and not be conducted to the ventricles. This fading and eventual stoppage of a cardiac action potential in a slowly conducting region is called decremental conduction.

The mildest degree of AV node block is *first-degree block,* in which every atrial action potential is transmitted to the ventricles, but the action potential propagates even more slowly than normal through the AV node. Therefore, in first-degree block, the delay between atrial contraction and ventricular contraction is abnormally long. Because the AV node conduction velocity can be slowed by parasympathetic activity and sped by sympathetic activity, the behavioral state of the patient characteristically influences the severity of first-degree block.

AV node block can be caused by cardiac trauma, toxins, viral or bacterial infections, ischemia, congenital heart defects, or cardiac fibrosis. AV node block is sometimes caused by inadvertent damage of AV node tissue during a surgical repair of a ventricular septal defect.

AV node block must be treated if the resulting ventricular rate is too low to maintain adequate blood flow to the body. In such a patient, administration of a muscarinic cholinergic antagonist (e.g., atropine) may reduce the AV node refractory period and decremental conduction sufficiently to overcome the blocked state. The same effect might be achieved with a drug that mimics the effect of sympathetic nerves by activating β-adrenergic receptors (e.g., isoproterenol) (see Table 19-2). If drug treatment fails to correct AV node block, an artificial pacemaker is needed. In the case of AV node block, the pacemaker needs to be applied to the ventricles; pacing the atria would not be beneficial because atrial action potentials are not being reliably conducted to the ventricles.

Cardiac Tachyarrhythmias Result Either from Abnormal Action Potential Formation (by the Sinoatrial Node or Ectopic Pacemakers) or from Abnormal Action Potential Conduction ("Reentry")

Tachyarrhythmias are arrhythmias in which the atrial rate or the ventricular rate (or both) is abnormally high. An occasional extra atrial or ventricular beat is called a *premature contraction* (or *precontraction).* Occasional precontractions are common both in animals and in humans and usually have no clinical significance. If the precontractions become frequent or continuous, the condition is called *tachycardia,* which means "rapid heart." Tachycardia is a heart rate that is more rapid than is appropriate for the behavioral circumstances (e.g., 160 beats/min in a resting dog). Tachycardia is a clinically significant sign.

Tachyarrhythmias result from abnormal pacemaker activity. The pacemaker initiating the rapid or "extra" beats can be the SA node itself. Alternatively, a region of abnormal cardiac muscle outside the SA node can act as a pacemaker by spontaneously depolarizing to threshold before the regular SA node pacemaker does. Any such region is called an *ectopic pacemaker.* Common causes of ectopic pacemaker activity include cardiac infection or trauma, reaction to a drug or toxin, electrolyte imbalances, myocardial ischemia, and myocardial infarction.

The tachyarrhythmias are named for the site of the pacemaker at which they originate. Hence, if tachycardia appears to be caused by abnormally rapid depolarizations of SA node pacemaker cells, the condition is called *sinus tachycardia.* If tachycardia originates from an ectopic pacemaker within the atria, it is called *atrial tachycardia.* Atrial tachycardia is common in some canine breeds, including boxers and wolfhounds. *Junctional tachycardia* originates from ectopic pacemakers within the AV node or first part of the AV bundle. *Supraventricular tachycardia* is a collective term that encompasses sinus tachycardia, atrial tachycardia, and junctional tachycardia. If the ectopic pacemaker causing tachycardia is within the ventricles, the condition is called *ventricular tachycardia.* In this situation the ventricles beat at a rapid rate, as dictated by the ectopic ventricular pacemaker. In occasional patients, some of the action potentials initiated by an ectopic ventricular pacemaker may be conducted backward through the AV node and may cause atrial precontractions. Usually, however, the AV node does not conduct action potentials backward; the atria continue to beat at the rate dictated by the normal SA node pacemaker. In either case, ventricular contractions are not preceded in the normal way by atrial contractions. The major dysfunction associated with ventricular tachycardia is that the ventricles do not relax long enough between contractions for adequate filling, and this problem is exacerbated by the absence of appropriately timed atrial contractions.

An extremely rapid atrial tachycardia is called *atrial flutter.* Atrial flutter does not lead to ventricular flutter because of the long refractory period of the AV node cells; the AV node conducts some, but not all, of the frequent atrial depolarizations to the ventricles. This is an example of the AV node protecting the ventricles from beating at too rapid a rate. If atrial contractions become so rapid that they lose synchrony, the condition is called *atrial fibrillation.* Atrial fibrillation is characterized by the continuous, random passage of action potentials through the atria. Fibrillating atria appear to quiver; there is no effective, coordinated contraction, and no blood is pumped. Atrial fibrillation is common in horses and in certain breeds of dogs, including Doberman pinschers. Atrial fibrillation usually does not lead to ventricular fibrillation because of the protective effect of the AV node. The ventricles continue to contract with a synchronized, effective pumping stroke, in response to some, but not all atrial action potentials, at a rate that is limited by the refractory period of the AV node.

Synchronous ventricular contractions are essential for life. If the synchrony of ventricular contractions is disrupted and the ventricles begin to fibrillate, ventricular pumping stops. In *ventricular fibrillation ("V-fib"),* each tiny region of the ventricular wall contracts and relaxes at random, in response to action

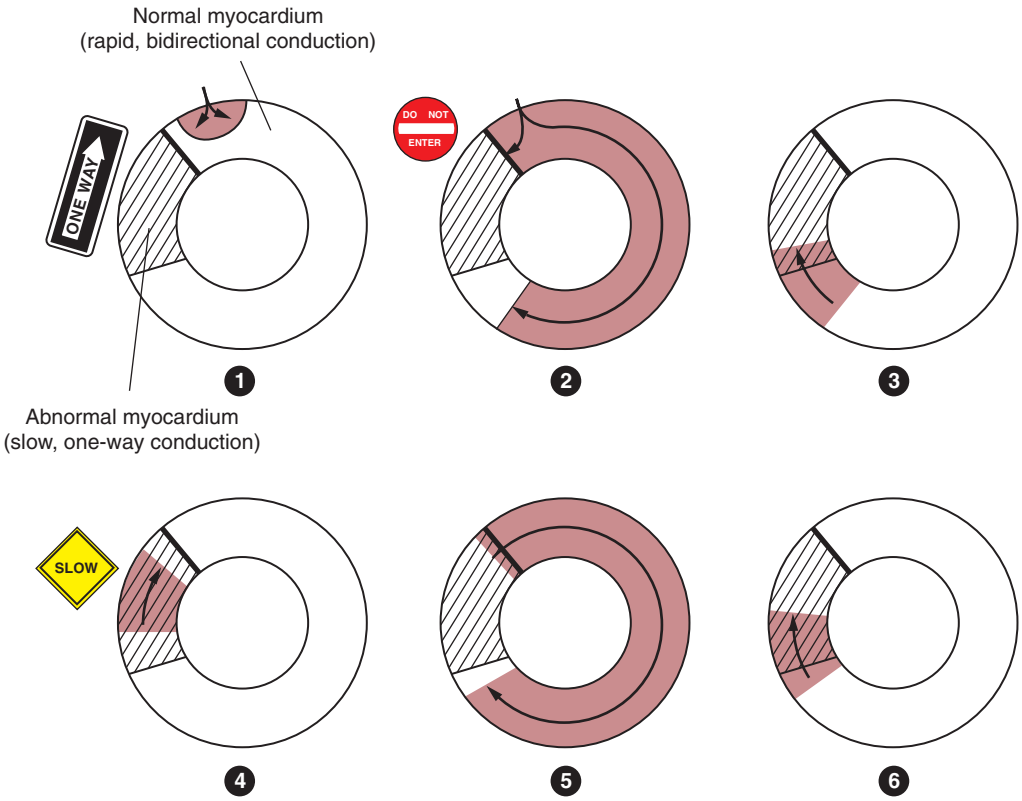

FIGURE 19-11 Cross section of a cardiac chamber (atrium or ventricle) is pictured at six different instants to illustrate how reentrant arrhythmias occur. A region of abnormal myocardium (cross-hatched area) conducts action potentials slowly and only in one direction (clockwise in this example). *Colored shading* indicates areas of heart where an action potential is underway. *1,* Normal action potential has just entered this ring of tissue, and only the *shaded area* is depolarized. *2,* Action potential propagates rapidly in both directions through the normal cardiac tissue but cannot propagate into the abnormal myocardium in a counterclockwise direction. *3,* The clockwise-going action potential can enter the abnormal region. *4,* While the action potential propagates slowly, in a clockwise direction through the abnormal region, the normal cardiac tissue repolarizes to a resting state (indicated by *lack of shading*). *5,* Action potential emerges from the abnormal region into normal cardiac tissue and propagates through the normal tissue for a second time. Meanwhile, the abnormal tissue repolarizes to a resting state. *6,* Action potential begins to move slowly through the abnormal region for a second time. States 4, 5, and 6 repeat themselves. Thus, the abnormal region functions as an ectopic pacemaker.

potentials that propagate randomly and continuously throughout the ventricles. The condition of ventricular fibrillation is synonymous with *sudden cardiac death.*

In most cases, ventricular fibrillation can be reversed only by electrical *defibrillation*. In this process a strong electrical current is passed briefly through the heart muscle. This current depolarizes all the cardiac cells simultaneously and holds them in a depolarized state for several milliseconds. It is hoped that when the current is turned off, all the cardiac muscle cells will simultaneously repolarize to a resting membrane potential, so that the normal pacemaker of the heart will again have a chance to initiate beats in an organized and synchronized manner. Sometimes it works; however, if the cardiac problems that caused ventricular fibrillation to develop in the first place are still present, fibrillation is likely to recur. Usually, defibrillation is performed by placing stimulating electrodes *(paddles)* on either side of the thorax. Therefore the stimulating current passes through, and depolarizes, the skeletal muscles of the thorax as well as the cardiac muscle of the heart. The resulting, involuntary contraction of the skeletal muscles causes the patient to "jump" at the moment of defibrillation.

Ectopic pacemaker activity typically arises when a region of ischemic or damaged cardiac muscle develops the abnormal, twin properties of slow conduction of action potentials and an ability to conduct action potentials in only one direction. Figure 19-11 illustrates how a region of slow, one-way conduction in the wall of one cardiac chamber can function as an ectopic pacemaker. The process begins with a normally originating action potential arriving at the region of slow, one-way conduction. The action potential can only enter the abnormal region from one side. If the one-way conduction through the abnormal muscle is so slow that all the normal, surrounding muscle is past its refractory period by the time the action potential emerges from the abnormal region, the emerging action potential can trigger another action potential in the normal muscle. If this second action potential then propagates around the cardiac chamber and back into the abnormal region, a self-perpetuating cycle can develop. The action potential again propagates slowly through the abnormal region, and again it emerges from the abnormal region after the normal muscle is past its refractory period. The result is a sequence of *reentrant* action potentials, each one initiating a contraction (an "extra" beat) as it propagates through the normal

cardiac muscle. The reentrant pathway does not necessarily have to be all the way around the circumference of a cardiac chamber. A damaged, ischemic, or infarcted area of cardiac muscle can form the nonconducting center around which reentrant action potentials can travel. The passage of an action potential around and around a nonconducting center is called a *circus movement.* For the circus movement of the action potential to be self-regenerating, however, a portion of the circular, conducting pathway must have the twin properties of slow and one-way conduction. In effect, an area of slow, one-way conduction within a circular conducting pathway (and around a nonconducting center) functions as an ectopic pacemaker. Reentry of cardiac action potentials can lead to occasional precontractions, continuous tachycardia, or even fibrillation. In any of these cases, the resulting tachyarrhythmia is called a *reentrant arrhythmia.*

Common Antiarrhythmic Drugs Affect the Ion Channels Responsible for the Cardiac Action Potential

Whereas ventricular fibrillation is generally lethal without electrical defibrillation, other tachycardias can often be treated successfully with *antiarrhythmic drugs.* Because tachyarrhythmias result from extra cardiac action potentials, effective antiarrhythmic drugs must work by counteracting either the formation or the propagation of the extra action potentials.

Local anesthetics (e.g., quinidine, lidocaine, procaine) constitute one category of antiarrhythmic drugs. They act by binding to some of the voltage-gated Na^+ channels (fast Na^+ channels) in cardiac muscle cells and preventing them from opening. This counteracts membrane depolarization and action potential formation. In essence, blocking some of the Na^+ channels raises the threshold for action potential formation. This tends to "quiet" ectopic pacemakers and to stifle reentrant arrhythmias. Na^+ channel blockers such as lidocaine or procaine (Novocain) are called *local anesthetics* because, when applied to sensory neurons, they prevent the propagation of neural action potentials that would signal pain to the brain. The cardiac, antiarrhythmic effect of local anesthetics is not the result of their blockage of pain pathways.

A second category of antiarrhythmic drugs is the *calcium channel blockers.* Examples include verapamil, diltiazem, and nifedipine. These drugs bind to L-type (slow) Ca^{2+} channels and prevent them from opening, which decreases the entry of Ca^{2+} into cardiac muscle cells during an action potential. Because Ca^{2+} entry is the primary depolarizing influence during the plateau (phase 2) of the cardiac action potential, one major effect of a Ca^{2+} channel blocker is to lower the plateau (make the membrane potential less positive). A secondary consequence is to lengthen the action potential. The action potential is longer because of a complicated effect of the height of the plateau on K^+ channels, as discussed earlier in connection with sympathetic effects on cardiac action potentials. Drugs that lengthen the cardiac action potential also lengthen the refractory period, which makes it less likely that early extra action potentials will be formed in ectopic pacemakers or that they will propagate even if they are formed.

The calcium channel blockers have especially strong effects on the cells of the SA and AV nodes. As mentioned, Ca^{2+} entry through slow Ca^{2+} channels is the main event in the slow action potentials of these cells. Not surprisingly, therefore, the amplitude of slow action potentials is greatly reduced by Ca^{2+} channel blockers; these action potentials are also lengthened. The consequent increase in refractory period decreases the likelihood that early extra action potentials will form or propagate in SA or AV node cells. The increased refractory period in the AV node is especially effective in protecting the ventricles from rapid rates in cases of persistent atrial flutter or fibrillation. Many of the extra atrial action potentials simply *die out* (through decremental conduction) in the AV node.

By reducing the entry of extracellular Ca^{2+} into cardiac muscle cells during an action potential, Ca^{2+} channel blockers not only suppress tachyarrhythmias, but also decrease the strength of cardiac contractions. Less entry of extracellular "trigger" Ca^{2+} means a less powerful stimulus for the release of stored Ca^{2+} from the sarcoplasmic reticulum. Therefore the cytosolic Ca^{2+} concentration does not increase as much as normal during the action potential, so there is a less forceful contraction. Some clinical situations in which it is desirable to decrease cardiac contractility are discussed in Chapter 21.

The *cardiac glycosides* (e.g., digitalis) constitute a third category of antiarrhythmic drugs. Cardiac glycosides act by inhibiting the Na^+,K^+ pump in cell membranes. As mentioned in Chapters 1 and 4, the Na^+,K^+ pump is an antiport carrier that uses energy from ATP to transport Na^+ out of cells and K^+ into cells. The pump also indirectly supplies energy to a Na^+,Ca^{2+} antiporter that helps to transport Ca^{2+} back out of cardiac cells after it enters during an action potential. Inhibition of the Na^+,K^+ pump with a cardiac glycoside has several important effects on cardiac function. The effects are listed here without much explanation because the mechanisms are quite complex. First, cardiac muscle cells do not repolarize fully at the end of an action potential; the resting membrane potential is not as negative as normal. As a consequence, some Na^+ channels remain inactivated, which makes the cells somewhat refractory with regard to the formation of subsequent action potentials. This tends to quiet ectopic pacemakers. Second, effects on the central nervous system lead to an increase in parasympathetic tone. This slows the heart rate, quiets atrial ectopic pacemakers, slows conduction through the AV node, and increases the refractory period of AV node cells. The overall effect is to suppress ectopic atrial action potentials or cause extra atrial action potentials to die out in the AV node and not to be conducted to the ventricles. A third effect of cardiac glycosides is to allow more Ca^{2+} than normal to accumulate inside cardiac cells, resulting in stronger cardiac contractions. In summary, the cardiac glycosides are antiarrhythmic and increase cardiac contractility.

Beta-adrenergic antagonists (e.g., propranolol) constitute a fourth class of antiarrhythmic drug. Beta (β) blockers, as they are called, bind to some of the β-adrenergic receptors on cardiac cells and prevent their activation by norepinephrine from sympathetic nerves or by epinephrine and norepinephrine from the adrenal medulla. Sympathetic activation tends to promote tachyarrhythmias by increasing heart rate, shortening refractory period, and speeding conduction of action potentials, especially through the AV node. Beta blockers reduce these effects and therefore reduce the likelihood that extra action potentials will form or propagate. An additional effect of β blockers is to reverse sympathetic-induced increases in cardiac contractility.

In summary, of the four categories of drugs used to treat tachyarrhythmias, three also have pronounced effects on cardiac contractility. The calcium channel blockers and β blockers decrease cardiac contractility, whereas cardiac glycosides increase contractility. Local anesthetics have little effect on contractility. This variety of effects allows a clinician to select the type of antiarrhythmic drug that is best matched to each patient's cardiac contractile state.

Electrical dysfunction of the heart has been discussed in considerable detail to illustrate how specific abnormalities in the specialized cardiac conduction system can result in specific and serious arrhythmias. Electrical dysfunction of the heart is encountered often in clinical practice, and its consequences are often serious or even lethal. Because electrical dysfunction is so important, Chapter 20 is devoted to an explanation of the electrocardiogram, which is the most commonly used tool for evaluating electrical dysfunction of the heart.

CLINICAL CORRELATIONS

THIRD-DEGREE ATRIOVENTRICULAR BLOCK

History. A 5-year-old male English bulldog has fainted several times during the past 3 weeks. On each occasion he collapses, is apparently unconscious for a few seconds, and then slowly recovers. These episodes occur most often during exertion. In general, he tends to be less active than normal, but he has no other obvious signs of illness.

Clinical Examination. The dog is moderately obese. There are no obvious neurological deficits. His mucous membranes appear normal; they are pink, and the capillary refill time is normal (1.5 seconds). Auscultation of the chest reveals a slow, regular heart rate of 45 beats/min. The femoral pulse rate is also 45 beats/min and strong. Thoracic radiography reveals a mildly enlarged heart, but the radiographs are otherwise within normal limits.

The electrocardiogram (ECG) reveals a disparity between the atrial rate (atrial depolarizations occurring regularly, 140 times/min) and the ventricular rate (ventricular depolarizations occurring regularly, 45 times/min). There is no consistent time interval between the atrial and ventricular depolarizations.

Comment. As will be discussed in Chapter 20, atrial and ventricular depolarizations produce characteristic voltage fluctuations at the body surface, which are detected by the ECG. The ECG of this dog shows a complete dissociation between atrial and ventricular depolarizations, which provides definitive diagnostic evidence of complete (third-degree) AV node block. The dog's atria are depolarizing 140 times/min in response to action potentials being initiated in the normal manner by pacemaker cells of the SA node. However, the atrial action potentials are not being conducted through the AV node. Ventricular action potentials are being initiated, at the slow rate of 45 times/min, by auxiliary pacemaker cells located below the blocked region of the AV node.

The low ventricular rate in this dog allows a longer-than-normal time for ventricular filling between beats. Therefore the volume of blood ejected with each beat (the stroke volume) is greater than normal. The increased stroke volume causes the femoral pulse to be very strong.

In a normal dog, sympathetic and parasympathetic nerves acting on the SA node pacemaker cells adjust the heart rate so that cardiac output is matched to the metabolic requirements of the body. In a dog with complete AV block, the ventricles do not respond to these autonomically mediated changes in SA node pacemaker rate. Typically, the rate of ventricular contractions is low at rest and does not increase much during exercise. Therefore, cardiac output does not increase enough during exertion to meet the increased metabolic needs of exercising skeletal muscle. As a consequence, arterial blood pressure decreases. The decreased arterial pressure during attempted exercise causes brain blood flow to fall below the level needed to sustain consciousness. The dog faints.

Treatment. Drug therapy for AV node block involves either blocking the effects of parasympathetic nerves on the AV node (with a muscarinic cholinergic antagonist drug such as atropine) or mimicking the effects of sympathetic activation (with cautious use of a β-adrenergic agonist such as isoproterenol or dopamine). The rationale for these treatments is based on the following physiology: AV node block occurs because atrial action potentials die out in the AV node (decremental conduction). Parasympathetic activation increases the tendency for decremental conduction because parasympathetic nerves act on AV node cells to increase their refractory period and to decrease the velocity with which action potentials spread from cell to cell. Therefore, blocking parasympathetic effects is occasionally effective in reversing AV node block. In contrast, sympathetic activation decreases the tendency for decremental conduction by decreasing the refractory period of AV node cells and increasing their conduction velocity. A sympathomimetic drug (one that mimics sympathetic effects by activating β-adrenergic receptors) has the same effect, and therefore may unblock the AV node. Even if administration of a sympathomimetic drug does not reverse the AV node block, it usually increases the rate of the auxiliary (emergency) pacemaker cells in the AV node or bundle, which are initiating the ventricular contractions. The increased ventricular rate improves cardiac output.

Many cases of third-degree AV block cannot be managed effectively with drugs, so an artificial ventricular pacemaker must be installed. The procedure is straightforward; pacemaker electrodes can be inserted into the right ventricle through a systemic vein (e.g., external jugular) with only sedation and local anesthesia. The electrode wires are attached to a battery-powered pacemaker unit that is then implanted under the skin.

PRACTICE QUESTIONS

1. An increase in heart rate could result from:
   a. An increase in sympathetic nerve activity to the heart.
   b. An abnormally rapid decrease in permeability of SA node cells to K^+ during diastole.
   c. An abnormally rapid increase in permeability of SA node cells to Na^+ during diastole.
   d. A decrease in parasympathetic nerve activity to the heart.
   e. All the above.

2. In which of the following arrhythmias will there be more atrial beats per minute than ventricular beats?
   a. Complete (third-degree) AV block
   b. Frequent premature ventricular contractions
   c. Sick sinus syndrome (sinus bradycardia)
   d. First-degree AV block
   e. Ventricular tachycardia

3. The normal pathway followed by a cardiac action potential is to begin in the SA node and then propagate:
   a. Across the atria in the bundle of His.
   b. Through the connective tissue layers that separate the atria and ventricles.
   c. Across the atria and to the AV node.
   d. From the left atrium to the right atrium.
   e. From the left atrium to the left ventricle and from the right atrium to the right ventricle.

4. Which statement is *true*?
   a. The refractory period of cardiac muscle cells is much shorter than their mechanical contraction.
   b. The cardiac action potential propagates from one cardiac cell to another through nexi, or gap junctions.
   c. Purkinje fibers are special nerves that spread the cardiac action potential rapidly through the ventricles.
   d. Ventricular muscle cells characteristically depolarize spontaneously to threshold.
   e. The permeability of ventricular muscle cells to Ca^{2+} is lower during the plateau of an action potential than it is at rest.

5. Which of the following types of drugs would be the best choice to treat a patient with both supraventricular tachycardia and inadequate cardiac contractility?
   a. Local anesthetic (fast Na^+ channel blocker)
   b. Muscarinic cholinergic antagonist
   c. Beta-adrenergic agonist
   d. Cardiac glycoside (inhibits Na^+,K^+ pump)
   e. Calcium channel blocker

6. During which phase of a normal ventricular action potential is it most likely that fast Na^+ channels are in an inactivated state, slow Ca^{2+} channels are open, and most K^+ channels are closed?
   a. Phase 0 (rapid depolarization)
   b. Phase 1 (partial repolarization)
   c. Phase 2 (plateau)
   d. Phase 3 (repolarization)
   e. Phase 4 (rest)

7. Which of the following is *true* for *both* cardiac muscle and skeletal muscle?
   a. The muscle forms a functional syncytium.
   b. An action potential in the muscle cell membrane is required to initiate contraction.
   c. Pacemaker cells spontaneously depolarize to threshold and initiate action potentials.
   d. Frequent action potentials in motor neurons can cause a sustained *(tetanic)* muscle contraction.
   e. Extracellular Ca^{2+} that enters the muscle cell during an action potential triggers the release of additional Ca^{2+} from the sarcoplasmic reticulum.

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CHAPTER 20
The Electrocardiogram

KEY POINTS

1. An electrocardiogram is simply a graph, made by a voltmeter that is equipped to plot voltage as a function of time.
2. Atrial depolarization, ventricular depolarization, and ventricular repolarization cause characteristic voltage deflections in the electrocardiogram.
3. The electrocardiogram reveals the timing of electrical events in the heart.
4. Six standardized electrocardiographic leads are used in veterinary medicine.
5. Abnormal voltages in the electrocardiogram are indicative of cardiac structural or electrical abnormalities.
6. Electrical dysfunctions in the heart cause abnormal patterns of electrocardiogram waves.
7. In large animals there is considerable variability in the polarity and size of the electrocardiogram waves.

An Electrocardiogram Is Simply a Graph, Made By a Voltmeter That Is Equipped to Plot Voltage as a Function of Time

The *electrocardiogram* (ECG) is the most frequently used clinical tool for diagnosing electrical dysfunctions of the heart. In its most common application, two or more metal electrodes are applied to the skin surface, and the voltages recorded by the electrodes are displayed on a video screen or drawn on a paper strip. The physics of how the heart produces voltages that are detectable at the body surface is extraordinarily complex. However, it is not difficult to develop an intuitive model of how electrocardiography works; this intuitive model is adequate for most clinical applications.

An intuitive understanding of the ECG begins with the concept of an *electrical dipole* in a *conductive medium* (Figure 20-1). A dipole is a pair of electrical charges (a positive charge and a negative charge) separated by a distance. A common flashlight battery is a good example of a dipole. A battery has an excess of positive charges at one end (the "+" end) and an excess of negative charges at its other end (the "–" end), and the two ends are separated by a distance. If this dipole is placed in a conductive medium (e.g., a bowl containing a solution of sodium chloride in water), ionic currents will flow through the solution. Positive ions (Na^+) in the solution flow toward the negative end of the dipole, and negative ions (Cl^-) flow toward the positive end. The flow of ions creates voltage differences within the salt solution. These voltage differences can be detected by placing the electrodes of a simple voltmeter at the perimeter of the salt solution. In Figure 20-1 an electrode placed at point A is closer (more exposed) to the positive end of the dipole, and an electrode at point B is closer (more exposed) to the negative end of the dipole. Therefore the voltage at point A will be positive in comparison with the voltage at point B. The voltmeter would detect a positive voltage difference between point A and point B. Using *V* as an abbreviation for *voltage,* we would summarize this condition by saying, "$V_{A–B}$ is positive." Points C and D are equally near (equally exposed to) the positive and negative ends of the dipole, so no voltage difference would exist between electrodes placed at points C and D. We would say, "$V_{C–D}$ is zero."

In Figure 20-2 the battery in the NaCl solution has been replaced with an elongated strip of cardiac muscle. Again, a voltmeter is set up to detect any voltage differences that are created at point A compared with point B, and at point C compared with point D. The voltage differences (A–B and C–D) are plotted for five different conditions. In *condition 1,* all the cells in the strip of cardiac muscle are at a resting membrane potential; each cell is charged negatively on its inside and positively on its outside. Because cardiac cells are electrically interconnected by gap junctions, the strip of cardiac muscle behaves electrically as if it were one large cell (a functional syncytium). From the outside, the strip of cells looks like one large cell that is symmetrically charged positively around its perimeter. Therefore, no dipole exists. There would be no voltage difference between point A and point B (i.e., $V_{A–B}$ would be zero). There would also be no voltage difference between point C and point D (i.e., $V_{C–D}$ would also be zero).

In *condition 2,* a pacemaker cell at the left end of the muscle strip has depolarized to threshold level and formed an action potential. The action potential is propagating from cell to cell, through the muscle strip, from left to right. In other words, the cells at the left end of the strip are depolarized and are at the plateau of their action potential, whereas the cells at the right end of the strip are still at a resting membrane potential. Under this condition, the outside of each depolarized cell is charged negatively, whereas the outside of each resting cell is still charged positively. The strip of muscle has created an electrical dipole, positive at its right end and negative at its left end. Therefore a positive voltage would exist at point A compared with point B. Note, however, that the voltage at point C compared with point D would still be zero, because neither of these points is closer to the positive end of the dipole. The graphs in Figure 20-2 summarize condition 2 by showing that $V_{A–B}$ is positive at this time, and $V_{C–D}$ is zero.

In co*ndition 3,* the entire muscle strip is depolarized; that is, all the cells are at the plateau of their action potential, with a

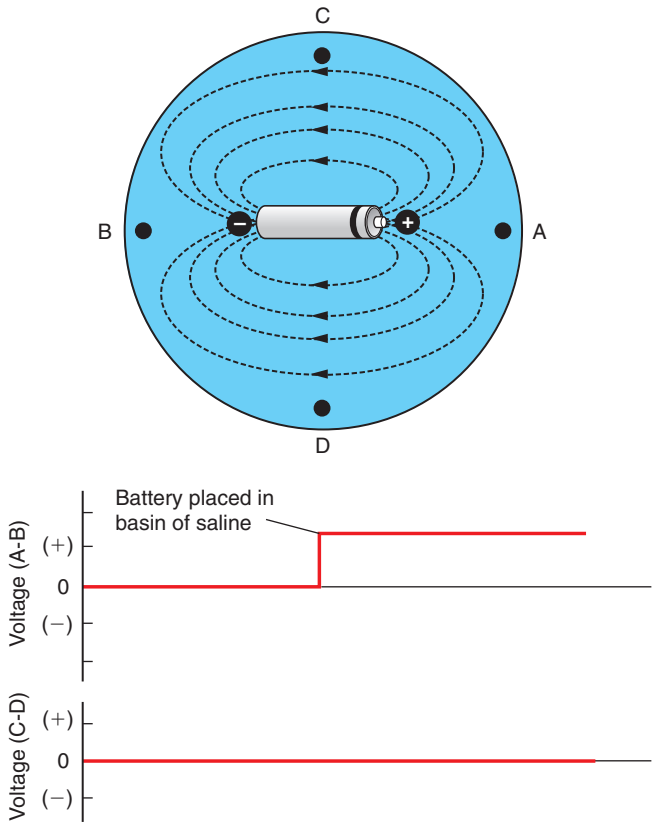


FIGURE 20-1 If an electric dipole (battery) is placed into a conductive medium (e.g., solution of NaCl in water), the charge difference between the two ends of the dipole (battery) will cause positive ions (Na^+) to flow within the solution, as indicated by the *dashed lines* and *arrows*. Negative ions (Cl^-) will flow in the opposite direction. These ionic currents will create voltage differences within the solution. A simple voltmeter can be used to detect these voltage differences, as shown in the lower graphs. In this example the ionic currents would create a positive voltage at point A compared with point B, because point A is "exposed to more positive" than is point B (i.e., voltage A–B is positive). No voltage difference would exist between point C and point D, because these two points are "equally exposed to positive" (i.e., voltage C–D is zero).

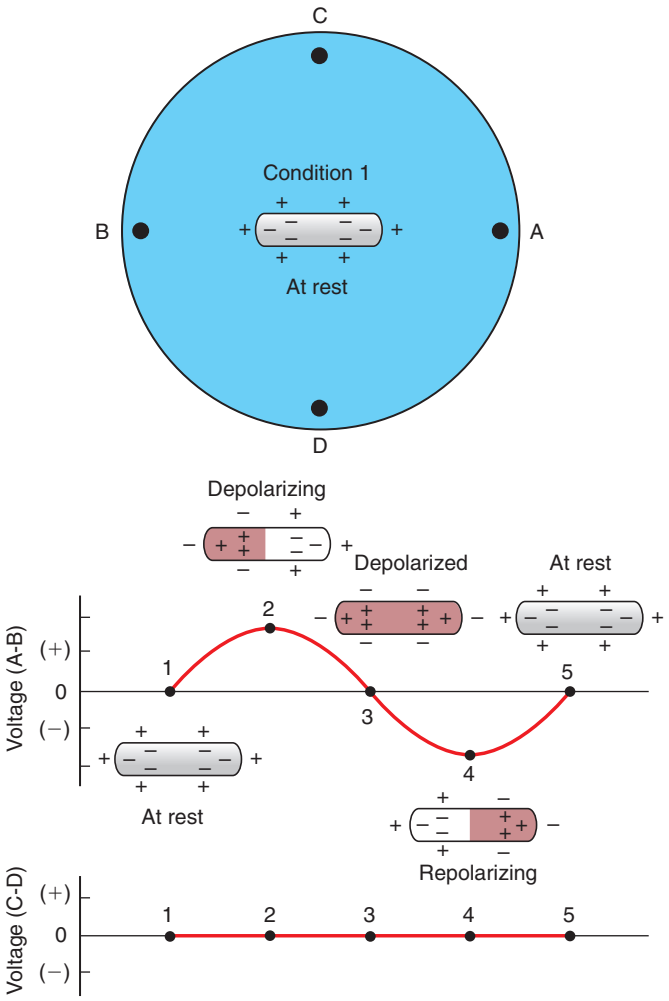


FIGURE 20-2 Strip of cardiac muscle cells in sodium chloride solution produces voltage differences between point A and point B during a phase of spreading depolarization or spreading repolarization, but not when all the cells are in a uniform state of polarization (i.e., not when all the cells are at rest or when all the cells are depolarized). No voltage difference is created between point C and point D. See text for a complete description.

uniform negative charge outside of each cell. Therefore, no voltage differences exist around the perimeter of the muscle strip. No dipole exists, so the recorded voltages (A–B and C–D) are both zero.

In *condition 4,* the muscle strip is repolarizing; cells at the left end have returned to a resting state, whereas cells at the right end are still at the plateau of their action potential. Under this condition, the outside of the muscle strip is charged negatively at its right end and positively at its left end. A dipole exists, with the voltage at point A being negative compared with point B. That is, $V_{A–B}$ is negative. The dipole does not create a voltage difference between C and D, so $V_{C–D}$ is still zero.

In *condition 5,* all the cells in the muscle strip have returned to a resting state (same as condition 1). Again, $V_{A–B}$ is zero and $V_{C–D}$ is zero.

Note that if the depolarization (in condition 2) had been spreading from right to left in the muscle strip (instead of from left to right), the voltage at point A compared with point B ($V_{A–B}$) would have been negative during depolarization. Likewise, if the repolarization (in condition 4) had been spreading from right to left in the muscle strip, $V_{A–B}$ would have been positive during repolarization. Table 20-1 summarizes these relationships.

TABLE 20-1 Sign (Polarity) of Voltages Created at Point A Compared with Point B ($V_{A–B}$)*

	Depolarization	Repolarization
Approaching A	+	–
Going away from A	–	+

*When a strip of muscle within a conductive medium is depolarizing or repolarizing. The arrangement of muscle and electrodes is depicted in Figure 20-2.

Figure 20-3 takes the intuitive model of the ECG one step further by picturing the entire heart (rather than a strip of cardiac muscle) in the bowl of saline. The graphs below the drawing show the voltage differences that would be detected by electrodes at the perimeter of the basin during atrial depolarization.

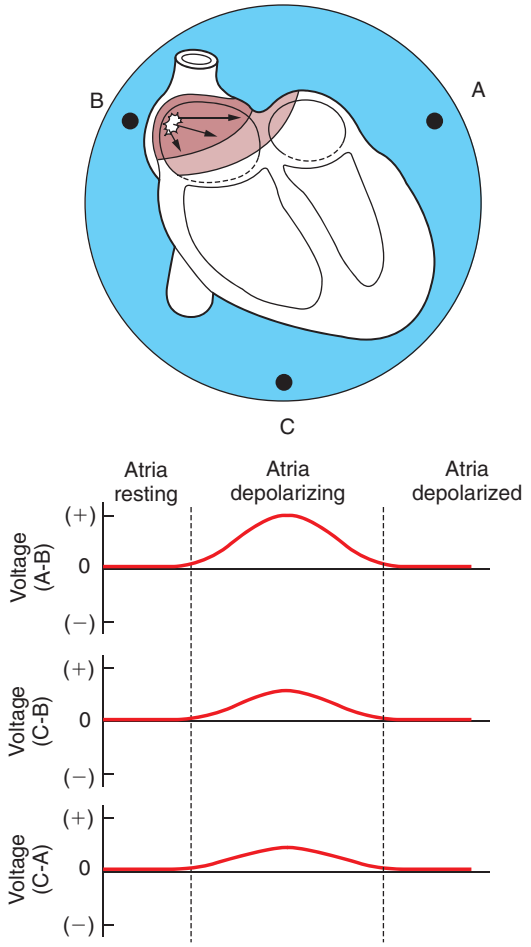


FIGURE 20-3 A resting heart, placed in sodium chloride solution, would not create voltage differences among electrodes A, B, and C. However, during depolarization of the atria, a positive voltage would be created at point A compared with point B. Atrial depolarization would also create positive voltages at point C compared with point B and at point C compared with point A. See text for a complete description.

The plots start at a time between cardiac contractions, when all the cells in the heart are at a resting membrane potential. Every cardiac cell is charged negatively on the inside of its membrane and positively on the outside. Therefore, all around the entire heart, viewed as one large cell, the charge would be positive, and no voltage differences would exist between any of the electrodes.

When the cells in the sinoatrial (SA) node depolarize to threshold level, they initiate an action potential that propagates from cell to cell outward from the SA node. As indicated by the arrows in the top diagram of Figure 20-3, the action potential propagates (spreads) simultaneously downward in the right atrium and leftward (across the right atrium and into the left atrium). At the moment depicted in Figure 20-3 *(top)*, the right atrial cells near the SA node are at the plateau of their action potential (i.e., negatively charged on their outside), whereas the cells in the left atrium and the cells in the inferior part of the right atrium are still at rest (i.e., positively charged on their outside). Therefore the depolarizing atria create an electrical dipole with its positive end angled downward and toward the left atrium. This dipole of atrial depolarization creates a voltage that is positive at point A compared with point B. Similarly, a voltage is created at point C that is positive compared with point B. Atrial depolarization also creates a positive voltage at point C compared to point A, although the reason for this is admittedly not evident from the two-dimensional view of the atria depicted in Figure 20-3. The voltage differences created during atrial depolarization are summarized by the graphs in Figure 20-3. The graphs also show that, once the atria are completely depolarized (with every atrial cell at the plateau of its action potential), the voltage differences between all points return to zero.

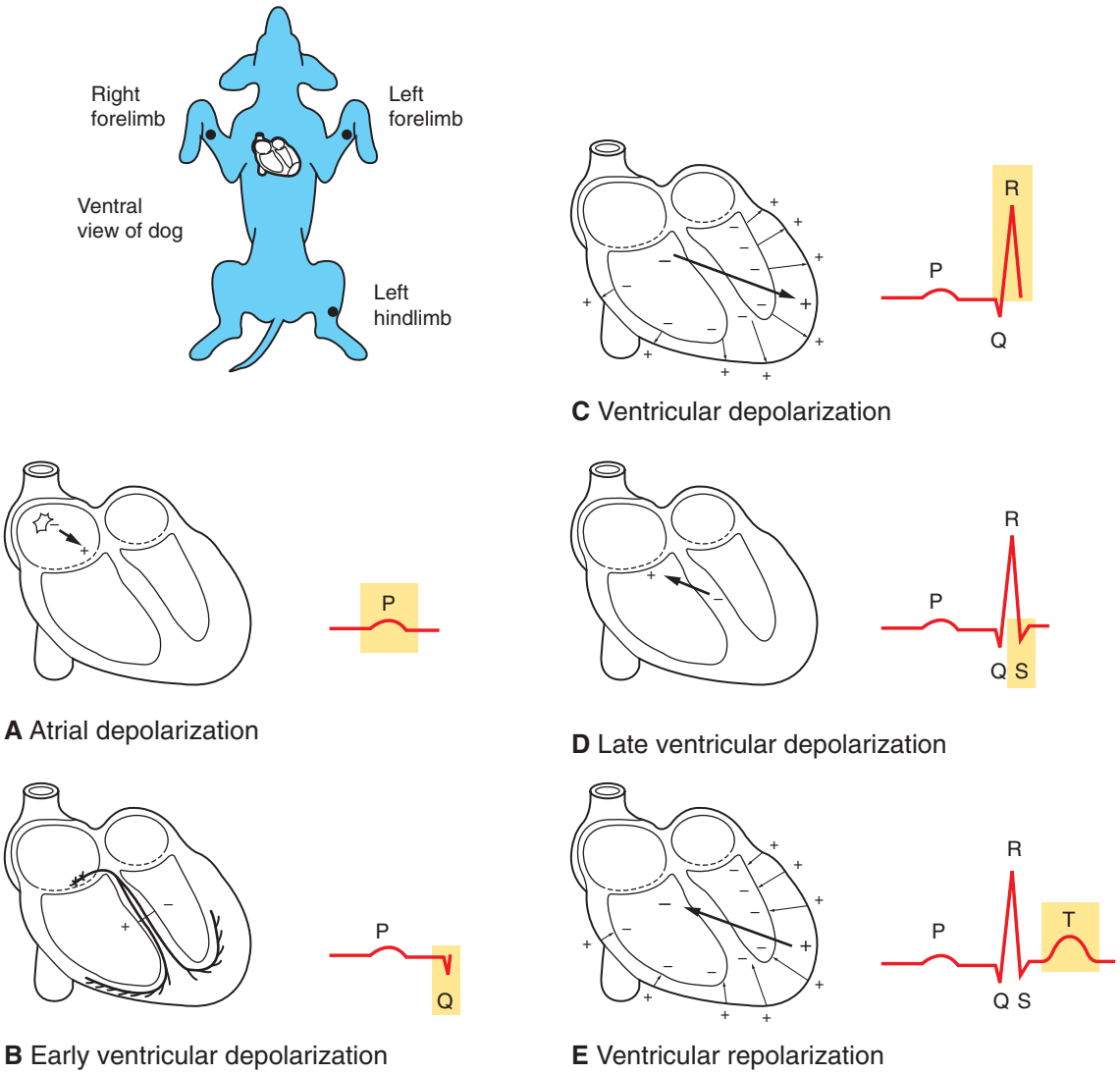
Atrial Depolarization, Ventricular Depolarization, and Ventricular Repolarization Cause Characteristic Voltage Deflections in the Electrocardiogram

In Figure 20-4 the heart is pictured in its normal position in the thorax of a dog. The extracellular fluids of the body contain NaCl (and other salts) in solution, so the body can be imagined as a substitute for the bowl of saline shown in the previous figures. The positions of the left forelimb, right forelimb, and left hind limb in Figure 20-4 correspond with points A, B, and C in Figure 20-3. Figure 20-4, *A*, shows that, while atrial depolarization is in progress at the beginning of a heartbeat, there would be a positive voltage in the left forelimb compared with the right forelimb. This is simply a repetition of the idea illustrated in Figure 20-3, the left forelimb being equivalent to point A and the right forelimb equivalent to point B.

The deflection in the ECG trace during atrial depolarization is called the *P wave*. At the end of atrial depolarization (i.e., at the end of the P wave), the ECG voltage returns to zero. At this moment during a normal cardiac cycle, the action potential is propagating slowly, from cell to cell, through the atrioventricular (AV) node and the first part of the AV bundle. However, these tissues are so small that their depolarization generally does not create a voltage difference that is detectable at the body surface.

The next voltage differences that are detectable at the body surface are those associated with the depolarization of the ventricles. The first part of ventricular depolarization usually involves a depolarization that spreads from left to right (i.e., dog's left to dog's right) across the interventricular septum, as shown in Figure 20-4, *B*. This first phase of ventricular depolarization usually causes a small voltage difference *(Q wave)* between the left forelimb and the right forelimb, with the left forelimb being slightly negative compared with the right.

The next event in ventricular depolarization usually causes a large, positive voltage *(R wave)* at the left forelimb compared with the right, as depicted in Figure 20-4, *C*. To understand why this R wave is large and positive, recall that during ventricular depolarization, the left and right bundle branches conduct the spreading action potential to the ventricular apex. From there, Purkinje fibers carry the action potential rapidly up the inside walls of both ventricles. From there, the depolarization spreads from cell to cell, outward through the walls of both ventricles, as pictured by the small arrows in Figure 20-4, *C*. This outward-spreading action potential creates dipoles in each region of the ventricular wall. Therefore, each small arrow in Figure 20-4, *C*, can be considered a dipole, with its positive end pointing toward the outside wall of the ventricle (because the inside surfaces of each ventricle depolarize before the outside surface). The net electrical effect of depolarizations spreading outward through the walls of both ventricles is a large electrical dipole pointed diagonally downward (caudad) and toward the dog's left. This *net dipole* is depicted by the bold arrow in Figure 20-4, *C*. The net dipole points toward the left for two reasons. First, the cardiac axis is tilted toward the left (i.e.,



A Atrial depolarization

B Early ventricular depolarization

C Ventricular depolarization

D Late ventricular depolarization

E Ventricular repolarization

FIGURE 20-4 As a normal cardiac action potential is conducted through the atria and ventricles, a characteristic sequence of voltage differences is created between the left forelimb (analogous to point A in Figure 20-3) and the right forelimb (analogous to point B in Figure 20-3). See text for a complete description.

the normal orientation of the heart is with the ventricular apex angled toward the left wall of the thorax). Second, the left ventricle is much more massive than the right ventricle, so the dipoles created by depolarizations spreading outward in the massive wall of the left ventricle dominate electrically over the dipoles created by depolarizations spreading outward in the thinner wall of the right ventricle. The net result is a large, positive voltage (R wave) at the left forelimb compared with the right. The R wave is the predominant feature of a normal ECG. Abnormalities in the magnitude or polarity of the R wave have great diagnostic significance, as explained later.

As the depolarizations finish spreading outward through the walls of both ventricles, the voltage in the left forelimb compared with the right forelimb returns to zero and then often becomes slightly negative for a few milliseconds (as pictured in Figure 20-4, *D*). The physical basis of this small, negative S wave is obscure. After the S wave, the voltage in the left forelimb compared with the right forelimb returns to zero and stays there for a time, because all the cells throughout both ventricles are uniformly at the plateau of their action potential; no dipole exists.

Altogether, the process of *ventricular depolarization* produces a pattern of voltages in the ECG called the *QRS wave* (or *QRS complex*). The important feature to understand about the QRS complex is why its predominant component, the R wave, is normally large and positive.

Figure 20-4, *E*, shows that repolarization of the ventricular muscle causes a voltage deflection in the ECG called the *T wave*. Whereas the wave of *depolarization* spreads outward through the walls of both ventricles, the pattern of *repolarization* is not as predictable. Figure 20-4, *E*, illustrates one common pattern, in which the repolarization spreads inward through the walls of both ventricles; that is, the outside surface of the ventricles was the last ventricular tissue to depolarize but the first to repolarize. The inward-going repolarization creates dipoles, as depicted by the small arrows in Figure 20-4, *E*, with their negative end pointed toward the inside surface of both ventricles. The net dipole during this repolarization has its negative end pointed upward (craniad) and toward the dog's right, as depicted by the bold arrow in Figure 20-4, *E*. This net dipole creates a positive voltage in the left forelimb compared with the right forelimb

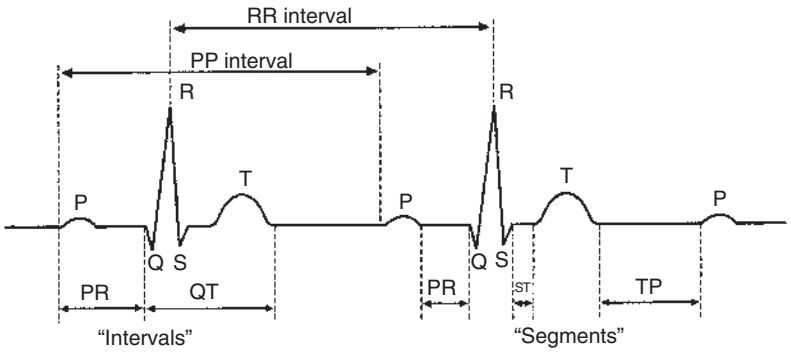


FIGURE 20-5 The time between various waves of the electrocardiogram corresponds to the timing of specific electrical events in the heart. See text for a complete description. The equations show how the atrial rate and the ventricular rate can be calculated from the P-P and R-R intervals, respectively. Of course, in a normally functioning heart, atrial rate = ventricular rate = heart rate.

$$\text{Atrial rate (per minute)} = \frac{60{,}000 \text{ ms/min}}{\text{P-P Interval (in ms)}}$$

$$\text{Ventricular rate (per minute)} = \frac{60{,}000 \text{ ms/min}}{\text{R-R Interval (in ms)}}$$

(T wave). The net dipole in Figure 20-4, *E*, points toward the dog's right, simply because the left ventricular wall is so much more massive than the right ventricular wall. That is, the repolarization proceeding from outside to inside in the massive walls of the left ventricle creates larger voltages (stronger dipoles) than the repolarization proceeding from outside to inside in the thinner walls of the right ventricle.

In many normal dogs ventricular repolarization proceeds in the same direction as the depolarization (from inside the ventricles to outside). This pattern of repolarization creates a negative voltage in the left forelimb compared with the right forelimb; that is, the T wave is negative. Whether positive or negative, T waves are caused by repolarization of the ventricles.

To summarize, the P wave is caused by atrial depolarization, the QRS complex by ventricular depolarization, and the T wave by ventricular repolarization. The pattern of ventricular repolarization varies from dog to dog, so the T wave may be positive or negative. Atrial repolarization does not cause an identifiable wave in the normal ECG, because atrial repolarization does not proceed in an orderly enough pattern or direction to create a significant net electrical dipole.

The Electrocardiogram Reveals the Timing of Electrical Events in the Heart

Because the predominant waves in an ECG correspond to specific electrical events in the heart, the time between these waves can be measured to determine the timing of events in the heart. Figure 20-5 indicates the conventions used to define the important *intervals* and *segments* in the ECG. The *PR interval* corresponds to the time between the start of atrial depolarization (start of P wave) and the start of ventricular depolarization (start of QRS complex). The PR interval is typically about 0.13 second in a large, resting dog. During this time the cardiac action potential is conducted slowly through the AV node. The duration of the QRS complex corresponds to the time it takes for the ventricles to depolarize, once the cardiac action potential emerges from the AV node and AV bundle. Typically this is less than 0.1 second. The *QT interval* (beginning of Q wave to end of T wave) corresponds to the time from the beginning of ventricular depolarization to the end of ventricular repolarization. This approximates the duration of an action potential in ventricular tissue. Typically the QT interval is about 0.2 second. The time between successive P waves *(PP interval)* corresponds to the time between atrial depolarizations (and thus atrial contractions). The PP interval can be used to calculate the number of atrial contractions per minute (the atrial rate), as illustrated in Figure 20-5. Likewise, the time between successive R waves *(RR interval)* corresponds to the time between ventricular depolarizations (and thus ventricular contractions), so the RR interval can be used to calculate the ventricular rate. Of course, in a normal heart, the atrial rate equals the ventricular rate.

Six Standardized Electrocardiographic Leads Are Used in Veterinary Medicine

Figure 20-6 shows actual ECG records obtained from a normal dog. To obtain these recordings, electrodes were placed on the left forelimb, right forelimb, and left hind limb. Electrodes on these limbs are usually envisioned as forming a triangle around the heart (just as electrodes at points A, B, and C form a triangle around the heart in Figure 20-3). The various ECG tracings in Figure 20-6 were obtained by interconnecting these electrodes in standardized combinations prescribed by Willem Einthoven, inventor of the ECG. As shown in Figure 20-6, *B*, the voltage in the left forelimb compared with the right forelimb is called *lead I*. Note that lead I corresponds to the voltage measurements discussed with Figure 20-4. The same pattern of distinct P, R, and T waves is evident in the lead I tracing in Figure 20-6, as seen in Figure 20-4 (although the T wave happens to be negative in Figure 20-6).

In accordance with Einthoven's convention, the connections for the three standard limb leads are depicted in Figure 20-6 in the form of a triangle *(Einthoven's triangle)*. The triangle indicates that to make a lead I ECG, the voltage is recorded in the left forelimb (labeled the + *electrode*) compared with the right forelimb (called the − *electrode*). Similarly, the diagram indicates that *lead II* is the voltage measured in the left hind limb compared with the right forelimb, and *lead III* is defined as the voltage in the left hind limb compared with the left forelimb. It is important to remember that the + and − signs on Einthoven's triangle are simply notations about how to hook up the electrodes. They indicate, for example, that lead I is obtained by measuring the voltage in the left forelimb compared with the right forelimb (not vice versa). The + and − signs on the triangle do not necessarily correspond to the orientation of the dipoles created in the heart.

As illustrated in Figure 20-6, *A*, the major ECG events (P, R, and T waves) are normally evident whether one is looking at tracings from leads I, II, or III. These *standard limb leads* simply provide different angles for viewing the electrical dipoles created

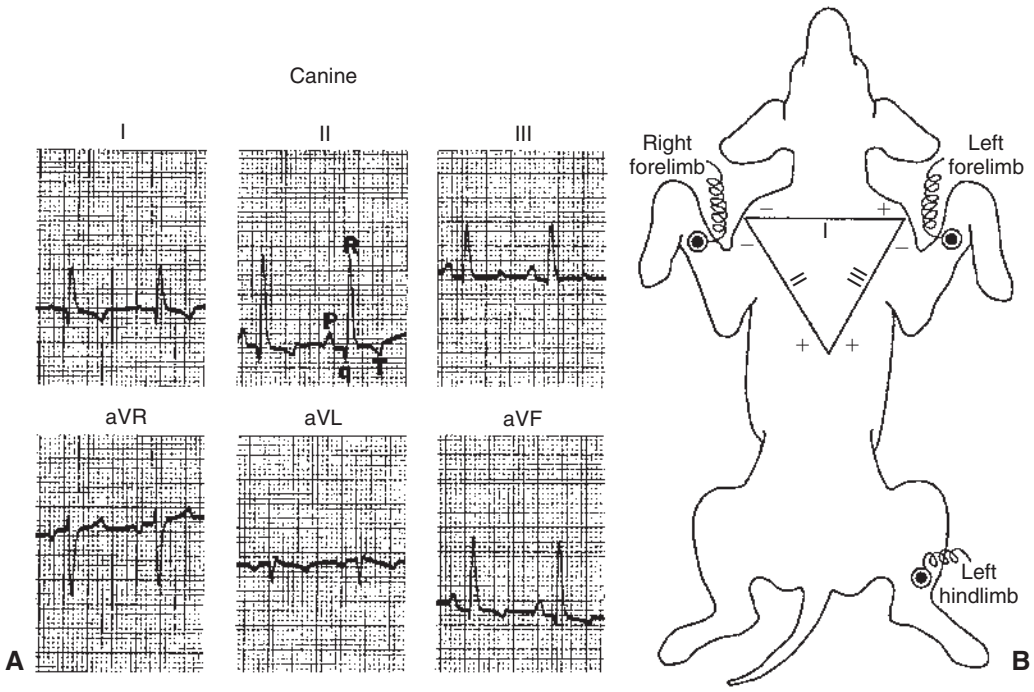


FIGURE 20-6 **A,** Six-lead electrocardiogram (ECG) from a normal dog. P, Q, R, and T waves (visible in all six leads) are labeled in lead II. There are no distinct S waves in these ECG recordings, and the T waves happen to be negative in leads I, II, aVL, and aVF. These are not abnormal signs. **B,** Einthoven's triangle (superimposed on ventral view of dog) depicts the standard conventions for interconnecting the three limb electrodes to obtain lead I, lead II, and lead III ECGs. See text for additional explanation. (*A,* From Tilley LP: *Essentials of canine and feline electrocardiography: interpretation and treatment,* ed 2, Philadelphia, 1985, Lea & Febiger.)

by the heart muscle as it depolarizes and repolarizes. Three additional electrical views are provided by the *augmented unipolar limb leads* (aV_R, aV_L, and aV_F). Lead aV_R measures the voltage from the right forelimb electrode compared with the average voltage from the other two limb electrodes. Similarly, aV_L and aV_F measure the voltages from the left forelimb and left hind limb electrodes compared with the average voltage from the other two electrodes.

Leads I, II, and III are used routinely in veterinary electrocardiography. Recordings from the augmented unipolar limb leads (aV_L, aV_R, and aV_F) are often included as well. Special additional leads are sometimes recorded by placing ECG electrodes at standardized sites on the thorax. These *precordial (chest) leads* are used more often in human medicine than in veterinary medicine. They are helpful in evaluation of very specific cardiac electrical dysfunctions.

The standardized vertical calibration on an ECG is that two major divisions equal 1 millivolt (mV). Two standard chart speeds are used: 25 millimeters per second (mm/sec), whereby five major divisions on the horizontal axis (time) equal 1 second; or 50 mm/sec, whereby 10 major divisions on the horizontal axis equal 1 second. Using the faster chart speed (50 mm/sec) helps to spread out the ECG events in an animal with a rapid heart rate (e.g., a cat). Chart speed is a convention derived from older, analog, paper-readout (strip chart) ECG machines. Although ECG is now more commonly captured and stored digitally, the chart speed convention is still used to set the resolution of the digital display. Furthermore, many of these digital units can produce a permanent paper printout of their data that looks just like the older strip chart.

Abnormal Voltages in the Electrocardiogram Are Indicative of Cardiac Structural or Electrical Abnormalities

The ECG in Figure 20-7 was obtained from a dog with right ventricular hypertrophy. Note that the sequence of waves in the ECG appears to be normal; that is, each heartbeat begins with an upward-going P wave, which is followed by a QRS complex and a T wave (which happens to be positive in this dog). The atrial and ventricular rates are equal, at about 100 beats per minute (beats/min). An abnormality is evident, however, because the predominant polarity of the QRS complex recorded from lead I is negative. As mentioned, the QRS complex is caused by ventricular depolarization, and its dominant feature is normally a large, positive R wave. The R wave is normally positive as recorded from lead I, because the cardiac axis is normally angled to the left side of the thorax and because the left ventricular wall is much more massive than the right ventricular wall. Both these features have the effect of making the predominant direction of ventricular depolarization right-to-left (as shown in Figure 20-4, *C*). Therefore, reversal of this polarity suggests that the cardiac axis has shifted to the right, that the mass of the right ventricle has dramatically increased, or both. The abnormally high voltages of the QRS complex recorded from leads II and III are indicative of ventricular hypertrophy. The pronounced negative components in the QRS complexes recorded from leads II and III suggest that during part of ventricular depolarization, the predominant direction of depolarization is away from the left hind limb. This is consistent with a cardiac axis shifted to the right and a massive right ventricle. Substantial right ventricular hypertrophy is a common consequence of cardiac defects that increase the pressure that must be generated within the right ventricle during its

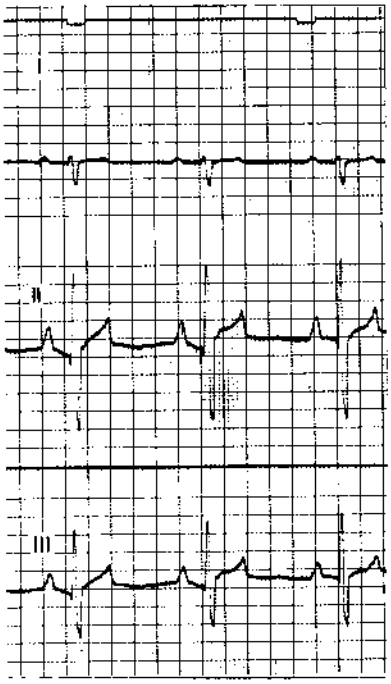
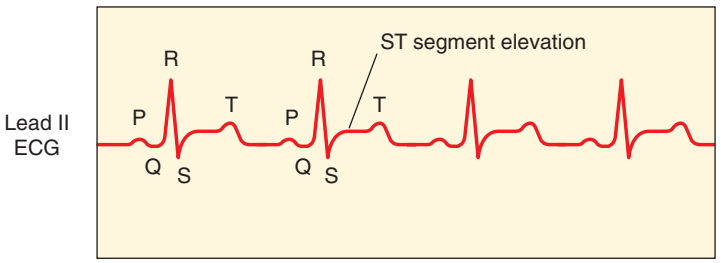


FIGURE 20-7 ECG from a dog with right ventricular hypertrophy. The chart speed is 50 mm/second; therefore, 10 major grid divisions on the horizontal axis equal 1 second. One-second timing marks are visible as small, downward deflections at the very top. Both the PP and the RR intervals are 0.6 second, so both atrial and ventricular rates are 100 per minute. The salient abnormalities are (1) predominantly negative QRS complexes recorded from lead I and (2) large-amplitude, bidirectional QRS complexes recorded from leads II and III. (From Ettinger SJ: *Textbook of veterinary internal medicine,* ed 3, Philadelphia, 1989, Saunders.)

contractions. Examples include pulmonic stenosis, patent ductus arteriosus, and ventricular septal defect (see Chapter 21).

Sometimes, ECG voltages are abnormally low. One common cause of low-voltage ECG waves is an accumulation of fluid in the pericardium. This condition is called *cardiac tamponade*. In a sense the pericardial fluid creates a short circuit for the ionic currents that would ordinarily flow outward toward the body surface. Therefore, voltages smaller than normal are created at the body surface.

An upward or downward shift of the ST segment, compared with the rest of the ECG, is often indicative of an area of ischemic or infarcted ventricular muscle. Typically, ischemic or infarcted ventricular muscle cells cannot maintain a normal, negative resting membrane potential; these cells are always more or less depolarized. Therefore, in between ventricular contractions, when normal ventricular cells are at a normal resting membrane potential, a voltage difference exists between the normal and ischemic (or infarcted) ventricular cells. This voltage difference creates an electrical dipole between normal, resting ventricular muscle and ischemic (or infarcted) ventricular muscle. Figure 20-8 *(bottom left)* shows the orientation of this dipole for the case of an ischemic area in the inferior (caudal) part of the ventricles. The dipole creates a negative voltage in lead II during ventricular rest (i.e., during the TP segment). When an action potential enters this ventricle, the normal ventricular tissue becomes depolarized, and a QRS complex is observed. The ischemic area cannot form action potentials; it simply remains depolarized. As a result, during the ST segment, the entire ventricle, normal and ischemic, is depolarized (Figure 20-8, *bottom right*). During the ST segment, there is no voltage difference (no dipole) between the injured area and the normal area. With no dipole present, the ECG voltage during the ST segment is close to a true zero level. However, the



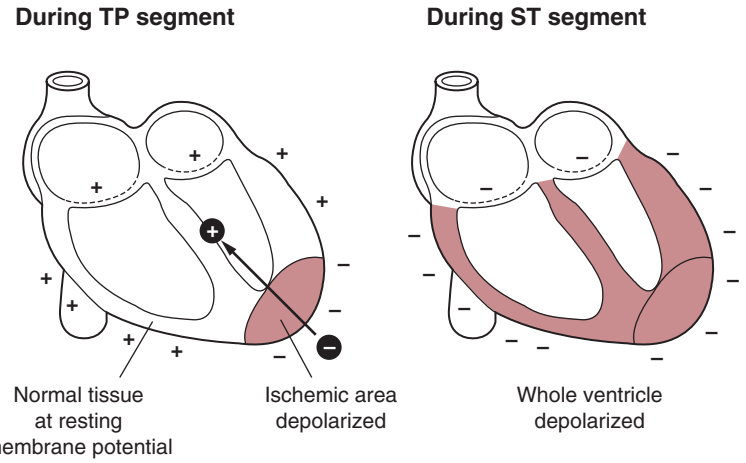


FIGURE 20-8 Voltage recorded during the ST segment is elevated compared with the baseline (TP segment) in this lead II ECG from a dog with an inferior (caudal) ventricular infarction. The drawings show why an ischemic or infarcted area of ventricle creates a net electrical dipole in the resting ventricle (during TP segment) but not in the depolarized ventricle (during ST segment).

ST segment is elevated in relation to the more negative voltage during the TP segment (ventricular rest). Thus, *ST segment elevation* (which is actually "TP segment depression") is indicative of an ischemic or infarcted area in the inferior (caudal) part of the ventricle. Ischemia or infarction in the anterior (cranial) ventricular area would cause *ST segment depression.*

Making a diagnosis solely on the basis of abnormal ECG voltage is risky. Theoretically, if the structural and electrical properties of a particular heart are known in detail, the appearance of the ECG can be predicted with certainty. However, the reverse situation is not strictly true. Several different cardiac defects may result in similar voltage abnormalities. Thus a voltage abnormality in an ECG cannot be ascribed with certainty to a particular cardiac defect. However, in conjunction with other clinical data (e.g., thoracic radiographs), ECG abnormalities are often strongly indicative of specific structural or electrical abnormalities in the heart.

Electrical Dysfunctions in the Heart Cause Abnormal Patterns of Electrocardiogram Waves

Figure 20-9 is an ECG from a dog with *premature ventricular contractions* (PVCs). This lead I strip begins with five normal beats (each QRS complex is preceded by a P wave and followed by a T wave). The P waves are evenly spaced, with a PP interval of 0.5 second (so heart rate is 120 beats/min). After five normal beats, a large-voltage complex of abnormal shape occurs without a preceding P wave. This is indicative of a premature ventricular depolarization (atrial depolarization could not produce such large voltage deflections). The predominant voltage in the abnormal complex is positive in lead I, indicating that the premature ventricular depolarization propagated predominantly in a right-to-left direction. The abnormal shape and long duration of the complex indicate that the premature depolarization did not spread across the ventricles by way of the rapidly conducting bundle branches and Purkinje fibers. In other words, the ectopic site that originated the premature depolarization was not within the AV bundle or bundle branches. Instead, the ventricular depolarization must have spread through more slowly conducting pathways. The abnormally large T wave associated with the premature beat further emphasizes this premature action potential spread across the ventricles with abnormal direction and speed.

If a premature ventricular depolarization originates from an ectopic pacemaker within the AV bundle or bundle branches, the pattern of ventricular depolarization and the pattern of ventricular repolarization would be normal; that is, the QRS complex and the T wave of the premature beat would look like the normal QRS and T waves. The QRS-T sequence would simply occur earlier than expected and would not be preceded by a P wave. Sometimes, premature contractions are initiated by ectopic pacemakers in the atria (*premature atrial contractions,* PACs). If an early atrial depolarization is conducted to the ventricles (i.e., if the AV node is not still refractory from the preceding atrial depolarization), the resulting ventricular depolarization and repolarization would follow normal ventricular pathways. Therefore, the ECG would show an earlier-than-expected P wave, followed by QRS-T sequence of normal size and shape.

Figure 20-10 shows additional examples of cardiac electrical dysfunctions, recorded from resting dogs. In the ECG in Figure 20-10, *A,* the R waves are evenly spaced and indicate a ventricular rate of 235 beats/min. This is fast for a resting dog. However, the pattern of ECG waves appears to be normal; each QRS complex is preceded by a clear, positive P wave and is followed by a positive T wave (which overlaps the next P wave). The most likely diagnosis is *sinus tachycardia* (rapid heart rate initiated by SA node pacemakers). Figure 20-10, *B,* shows the opposite extreme. The pattern of ECG waves is normal, but the heart rate is only 55 beats/min. The diagnosis is *sinus bradycardia* (the SA node is the pacemaker, but its rate is abnormally slow).

The ECG provides an easy way to diagnose AV node block. The ECG in Figure 20-11, *A,* looks normal, except that there is an abnormally long PR interval, which is indicative of abnormally slow conduction of the action potential through the AV node and AV bundle, and thus *first-degree AV node block.* In Figure 20-11, *B,* the P wave spacing indicates an atrial rate of 123 beats/min. Four of the P waves are followed by tall (but faintly visible) QRS complexes and large, negative T waves, but the other seven P waves are not followed by QRS-T sequences. Apparently some, but not all, atrial depolarizations are conducted through the AV node, which indicates a condition of *second-degree AV block.* The condition is not life threatening unless there are so many missed ventricular beats that cardiac output falls to dangerously low levels.

Figure 20-11, *C,* shows *third-degree (complete) AV node block* (and, incidentally, ST segment depression). Two large QRS complexes are visible, each followed by a negative T wave. The RR interval is about 2.9 seconds, indicating that the ventricular rate is only 21 beats/min. The QRS complexes are not immediately preceded by P waves. Small, evenly spaced, positive P waves are present, indicating a constant atrial rate of 142 beats/min, but

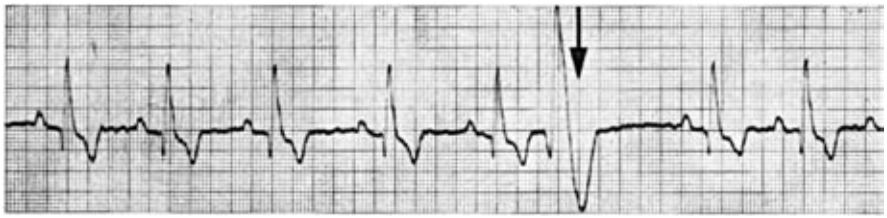


FIGURE 20-9 Lead I ECG of a dog showing five normal beats (normal P-QRS-T pattern) followed by one premature ventricular beat. A sixth P wave would be expected at the time marked by the *arrow.* This P wave is obscured by the large voltages associated with the premature ventricular beat. Also, the refractory period associated with the premature beat prevented the sixth normal ventricular beat from occurring; this creates a long pause (called the *compensatory pause*) between the premature beat and the next regular beat. In this and the remaining ECG examples, chart speed is 50 mm/sec (10 major grid divisions equal 1 second). (From Ettinger SJ: *Textbook of veterinary internal medicine*, ed 3, Philadelphia, 1989, Saunders.)

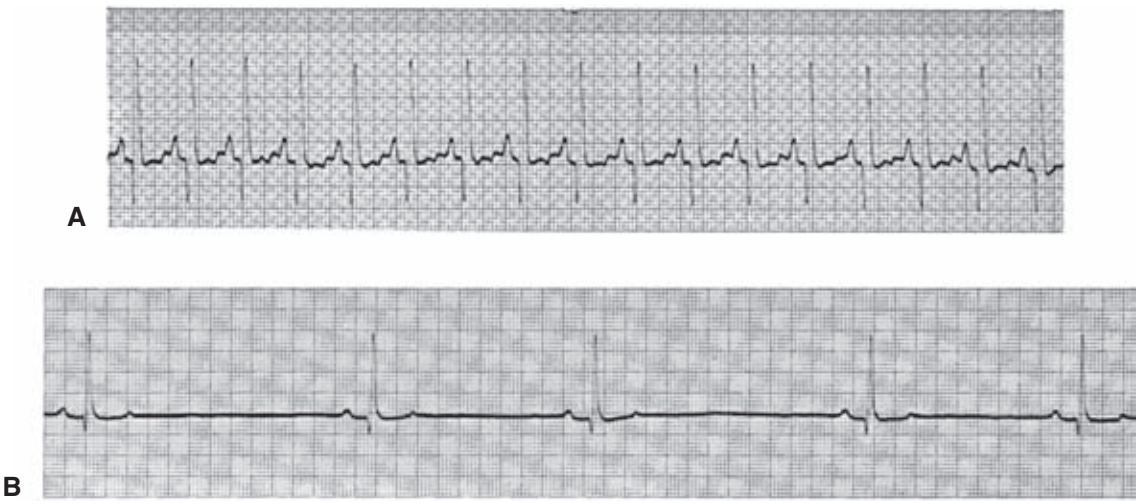


FIGURE 20-10 Sinus tachycardia **(A)** and sinus bradycardia **(B)** are evident in these otherwise-normal ECGs from two resting dogs. Chart speed is 50 mm/sec. (From Ettinger SJ: *Textbook of veterinary internal medicine,* ed 3, Philadelphia, 1989, Saunders.)

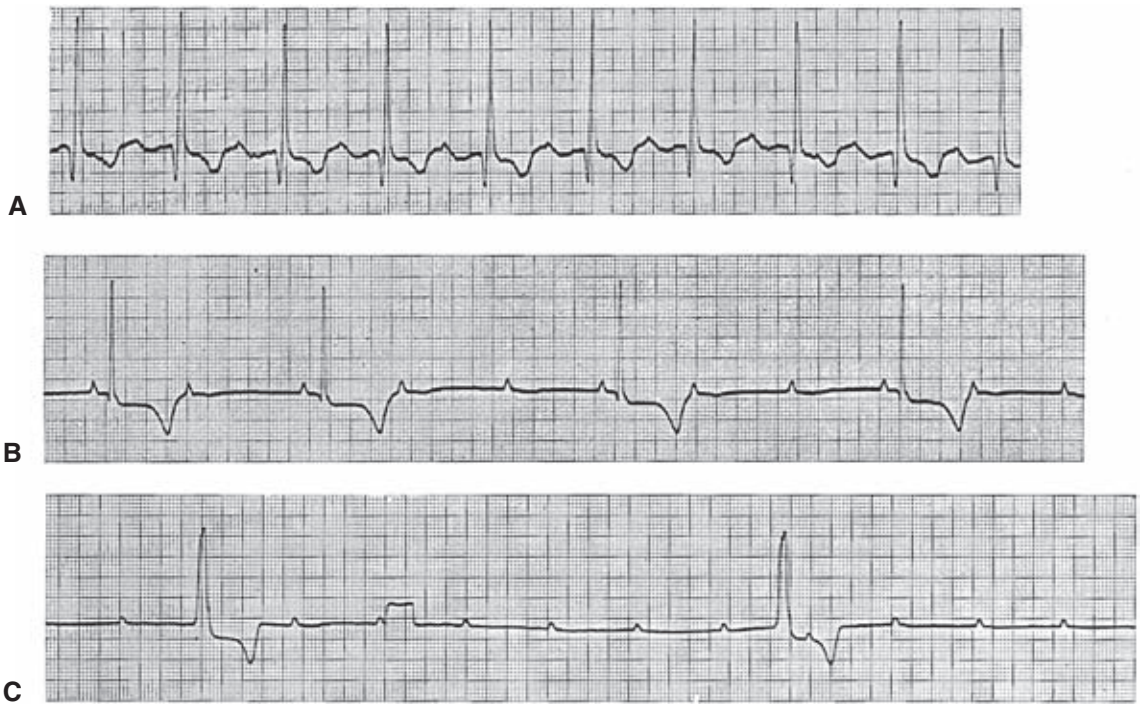


FIGURE 20-11 **A,** Example of first-degree AV node block (abnormally slow AV conduction). Each QRS complex is preceded by a positive P wave and followed by a negative T wave, which is normal. However, the PR interval is 0.2 second (normal for a dog is less than 0.14 second). **B,** Example of second-degree AV node block (sporadic AV conduction). The small, positive deflections are P waves. The broad, negative deflections are T waves, which follow the tall (but faintly visible) QRS complexes. Where P waves are followed by QRS-T complexes, the PR interval is normal. However, only every second or third P wave is followed by a QRS-T complex; that is, there are two or three atrial beats for every ventricular beat. **C,** Example of third-degree (complete) AV node block. Regularly spaced P waves are evident (although two of them are obscured by the two large QRS-T complexes). The QRS-T complexes are not immediately preceded by P waves. ST segment depression is also evident, but this is irrelevant to the diagnosis of AV block. The rectangular deflection one third of the way through the record is a voltage calibration signal (1 mV). Chart speed is 50 mm/sec. (From Ettinger SJ: *Textbook of veterinary internal medicine,* ed 3, Philadelphia, 1989, Saunders.)

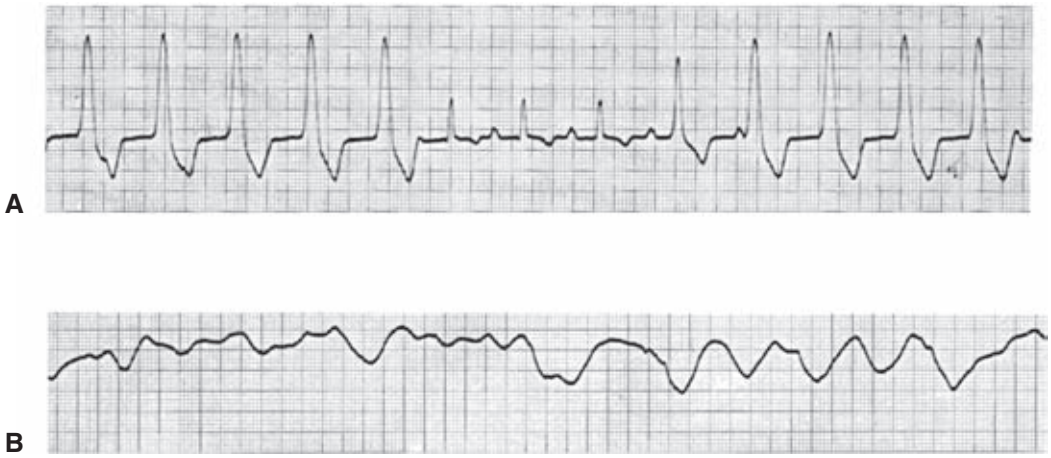


FIGURE 20-12 **A,** Example of ventricular tachycardia, which reverts briefly to a sinus rhythm. The ventricular rate is about 165 beats/min. This pattern would be typical for a dog with an ectopic ventricular pacemaker functioning at almost the same rate as the SA node pacemaker; some ventricular beats would be initiated by the ectopic pacemaker, and others would be initiated in the normal way through the AV node. **B,** Example of ventricular fibrillation. The random voltage fluctuations generated by the fibrillating ventricles would obscure any P waves that might be present, so it is not possible to determine whether the atria are beating normally or are also fibrillating. Chart speed is 50 mm/sec. (From Ettinger SJ: *Textbook of veterinary internal medicine,* ed 3, Philadelphia, 1989, Saunders.)

there is no synchronization between the P waves and the QRS complexes. Atrial action potentials are apparently being blocked at the AV node. The ventricles are beating slowly in response to an auxiliary pacemaker in the AV node or in the bundle of His.

Figure 20-12, *A*, shows an ECG record of a dog that is drifting in and out of ventricular tachycardia. The first five waves are abnormally shaped ventricular complexes, indicative of an ectopic ventricular pacemaker located outside the normal ventricular conduction system. No P waves are evident. Then there are three normal-appearing P-QRS-T sequences, which suggests that a normal rhythm is being established. However, the ectopic ventricular pacemaker usurps control again, and ventricular tachycardia returns.

Ventricular tachycardia degenerates frequently into ventricular fibrillation. The ECG in Figure 20-12, *B,* indicates ventricular fibrillation. The record shows fairly large, irregular voltage fluctuations with no discernible pattern. The atria may or may not be fibrillating; regularly occurring P waves may be present but obscured by the random electrical activity in the ventricles. However, ventricular fibrillation stops the heart from pumping blood, regardless of whether the atria continue to contract in a synchronized manner.

Atrial fibrillation, as with ventricular fibrillation, typically produces random voltage dipoles. However, because the atrial muscle mass is relatively small, the ECG voltages generated by atrial fibrillation are always much smaller than those seen in Figure 20-12, *B.* An ECG from an animal with atrial fibrillation would typically show normally shaped QRS-T sequences against a background of low-amplitude voltage fluctuations created by the fibrillating atria. In such a case the AV node is bombarded with very frequent action potentials from the fibrillating atria. Some of these action potentials are conducted to the ventricles, and others are blocked (because of the long refractory period of the AV node). Thus, in the case of atrial fibrillation, the QRS-T sequences would typically have normal shape but irregular spacing in time.

In Large Animals There Is Considerable Variability in the Polarity and Size of the Electrocardiogram Waves

The appearance of the normal ECG waves varies more, from animal to animal, among horses and cattle than among dogs and cats. For example, healthy cattle are likely to have QRS complexes (in any particular ECG lead) that are rather different in magnitude, duration, and shape, between individuals. This variability arises from the less consistent pathways followed by cardiac depolarizations in the atria and ventricles of large animals as compared to small animals. As a consequence, the ECG is less useful for diagnosing cardiac structural abnormalities (e.g., ventricular hypertrophy) in large animals than in small animals. Nevertheless, there is consistency in the basic sequence of electrical events in the hearts of normal animals, whether large or small. Each normal heartbeat begins with a depolarization of the SA node, and the consequent sequence of events (depolarization of the atria, depolarization of the ventricles, and repolarization of the ventricles) produces waves of voltage that are evident on an ECG. Therefore, the ECG is very useful in large animals for detecting and characterizing cardiac arrhythmias. Standardizing the placement of electrodes for particular ECG leads is usually not necessary for this purpose. Any ECG lead or electrode placement that yields clearly discernable P waves, QRS complexes, and T waves will suffice.

Sophisticated techniques are widely used in the analysis of ECGs both in human medicine and in many veterinary clinics. The purpose in this chapter is to introduce only enough complexity to establish a conceptual model for thinking about the ECG and to illustrate the usefulness of that model in the clinical diagnosis of cardiac electrical dysfunctions.

CLINICAL CORRELATIONS

DILATIVE CARDIOMYOPATHY WITH PAROXYSMAL ATRIAL TACHYCARDIA

History. An owner brings his 5-year-old male Saint Bernard to you because of a distended abdomen, weakness, coughing, and difficulty breathing. The owner believes these signs developed gradually over several weeks; however, before the last few weeks, there were occasional episodes when the dog suddenly seemed weak and very listless. The episodes lasted from a few minutes to about an hour.

Clinical Examination. Palpation reveals that the dog has muscle wasting and marked ascites (fluid in the abdominal cavity). The jugular veins are distended. The arterial pulse is rapid and irregular; there are frequent pulse deficits ("missing" beats). Thoracic radiography reveals an enlarged heart and an accumulation of fluid near the lung hilus.

You record the dog's ECG for several minutes. You note that P waves usually occur at a rate of 160 to 170 per minute and that each P wave is followed by a QRS-T complex. However, the ECG also shows frequent episodes when there are 210 to 230 P waves per minute. During these episodes, most P waves are followed by QRS-T complexes, but others are not. As a result, the QRS-T complexes occur irregularly, with about 180 per minute.

Echocardiography reveals severe dilation of all four cardiac chambers, particularly the atria. Even though the ventricles are enlarged, the ventricular walls are thinner than normal, a condition called *eccentric hypertrophy.* Ventricular contractions are weak.

Comment. The ECG indicates that this dog has atrial tachycardia. The information presented does not establish whether the atrial pacemaker is located in the SA node or somewhere else in the atria. It is likely that one atrial pacemaker area is initiating depolarizations at a rate of 160 to 170 per minute and that another atrial area intermittently preempts the first pacemaker by initiating depolarizations at the more rapid rate of 210 to 230 per minute. When the atrial rate is 160 to 170 per minute, the AV node conducts every atrial action potential to the ventricles, so that the ventricles also contract 160 to 170 times/min. However, when the atrial rate is 210 to 230 per minute, some of the atrial action potentials arrive at the AV node when the nodal cells are still refractory from the preceding action potential. These atrial action potentials are not conducted into the ventricles, which is why there are only about 180 ventricular contractions per minute. This is a case in which a second-degree AV node block, created by the relatively long refractory period of AV node cells, is beneficial, because it prevents the ventricles from beating too rapidly. The problem, when an arrhythmia triggers very frequent ventricular contractions, is that the time available between contractions becomes too short for adequate ventricular refilling. As ventricular rate increases, the volume of blood pumped with each beat (stroke volume) decreases, and so does cardiac output. At ventricular rates above 180 per minute, cardiac output could fall to such a low level that the dog would collapse.

This dog's primary problem is probably a chronic, progressive weakening of his heart muscle *(cardiomyopathy).* All the clinical signs, including atrial tachycardia, can be attributed to a primary cardiomyopathy. Dilative cardiomyopathy is common in giant-breed dogs, especially males, and often (as in this case) there is no discernible cause.

Even though the cause of the cardiomyopathy could not be determined from the evidence available in this case, the sequence of dysfunctions that resulted from the cardiomyopathy can be inferred with near-certainty. Ventricular weakness caused heart failure; the cardiac output fell below normal, especially during exercise. The dog's body attempted to compensate for the heart failure by increasing blood volume, which increased both venous and atrial pressures far above normal. The elevated atrial pressure had the beneficial effect of "supercharging" the ventricles with an extra volume of blood before each contraction, which partially returned the volume of blood pumped by a ventricle with each heart beat *(stroke volume)* toward normal. However, the excessive volume and pressure of blood in the veins caused pulmonary edema (which led to coughing and difficulty breathing) and systemic edema (which led to fluid in the abdomen). Also, distention of the atria made the atrial cells more excitable electrically, which resulted in the formation of ectopic pacemakers and the onset of atrial tachycardia. The tachycardia limited the ventricular refilling time, causing further compromise in cardiac output. A vicious cycle began in which decreased cardiac output caused further venous congestion and atrial distention, which aggravated the arrhythmia, and so forth. The atrial tachycardia will likely progress to atrial fibrillation. The prognosis is poor without treatment.

This case of heart failure provides a good preview for the next several chapters, which deal in detail with the physiological mechanisms of cardiac and vascular control in both normal and heart failure states.

Treatment. A diuretic drug (e.g., furosemide) is administered to promote an increase in urine formation. The goal is to reduce the blood volume and venous and atrial pressures, thereby reducing the signs resulting from congestion and edema. Sometimes the paroxysmal atrial tachycardia resolves after diuretic-induced reductions in atrial size. If it does not, antiarrhythmic drugs (e.g., quinidine or lidocaine, and/or a cardiac glycoside such as digitalis) can be used to try to reduce the electrical excitability of atrial tissue.

PRACTICE QUESTIONS

1. In which of the following arrhythmias will the ECG characteristically show the same number of P waves and QRS complexes?
   a. Complete (third-degree) AV block
   b. First-degree AV block
   c. Ventricular tachycardia
   d. Atrial flutter
   e. All the above

2. The time required for the conduction of the cardiac action potential through the AV node would be approximately equal to the:
   a. RR interval.
   b. PR interval.
   c. ST interval.
   d. PP interval.
   e. QT interval.

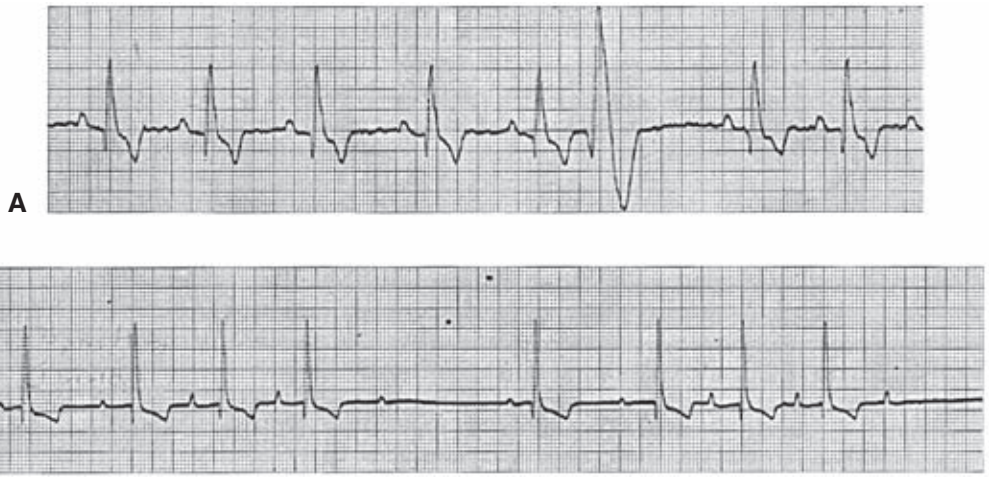


FIGURE 20-13 Lead I ECG recordings from two dogs. **A** is the basis for Practice Question 4. **B** is the basis for Practice Question 5. Chart speed is 50 mm/sec. (From Ettinger SJ: *Textbook of veterinary internal medicine*, ed 3, Philadelphia, 1989, Saunders.)

3. The T wave in a normal ECG is:
   a. Always negative.
   b. Always positive if the R wave is positive.
   c. Also known as the *pacemaker potential.*
   d. Caused by the delay between atrial and ventricular depolarization.
   e. Caused by ventricular repolarization.

4. The ECG in Figure 20-13, *A*, indicates:
   a. Sinus arrhythmia.
   b. Right ventricular hypertrophy.
   c. ST segment elevation.
   d. Premature ventricular contraction.
   e. Atrial fibrillation.

5. The ECG in Figure 20-13, *B*, indicates
   a. Second-degree AV block.
   b. Third-degree AV block.
   c. Sinus bradycardia.
   d. Ventricular tachycardia.
   e. ST segment elevation.

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CHAPTER 21
The Heart as a Pump

KEY POINTS

1. Each heartbeat consists of ventricular systole and ventricular diastole.
2. Cardiac output equals heart rate multiplied by stroke volume.
3. Increases in end-diastolic ventricular volume cause increases in stroke volume.
4. End-diastolic ventricular volume is determined by ventricular preload, ventricular compliance, and diastolic filling time.
5. Increases in ventricular contractility cause decreases in ventricular end-systolic volume.
6. Increasing the heart rate does not increase cardiac output substantially unless stroke volume is maintained.
7. Murmurs are abnormal heart sounds caused by turbulent flow through cardiac defects.
8. Some cardiac defects increase the heart's workload, which causes cardiac hypertrophy.
9. The pathophysiological consequences of cardiac defects are direct results of the abnormal pressures, volumes, and workloads created in the cardiac chambers.

Each Heartbeat Consists of Ventricular Systole and Ventricular Diastole

The heart is actually two pumps (two ventricles) that work together, side by side. Each ventricular pump works in a cycle, first relaxing and filling with blood and then contracting and ejecting some blood. In each *cardiac cycle* (heartbeat) the left ventricle takes in a volume of blood from the pulmonary veins and left atrium, then ejects it into the aorta. The right ventricle takes in a similar volume of blood from the systemic veins and right atrium, then ejects it into the pulmonary artery.

Figure 21-1 shows the events of a single cardiac cycle. A normal electrocardiogram (ECG) tracing is presented at the top of the figure. Atrial contraction is initiated by atrial depolarization, which is indicated by the P wave. Ventricular contraction is initiated by ventricular depolarization, which is indicated by the QRS complex. The period of ventricular contraction is called *ventricular systole*. Blood is ejected from the ventricles during ventricular systole. Each systole is followed by *ventricular diastole,* during which the ventricles relax and refill with blood before the next ventricular systole. Note that ventricular diastole corresponds to the period between a T wave and the subsequent QRS complex, when ventricular cells are at resting membrane potential.

The ventricles do not empty completely during systole. As shown in the graph of ventricular volume (see Figure 21-1, *second from top*), each ventricle of a large dog contains about 60 mL of blood at the end of diastole. This is called *end-diastolic volume*. During systole, about 30 mL of this blood is ejected from each ventricle, but 30 mL remains. This is called *end-systolic volume*. The volume of blood ejected from one ventricle in one beat is called *stroke volume*, expressed as follows:

$$\text{Stroke volume} = \text{end-diastolic volume} - \text{end-systolic volume}$$

The fraction of end-diastolic volume that is ejected during ventricular systole is called the *ejection fraction*, as follows:

$$\text{Ejection fraction} = \frac{\text{Stroke volume}}{\text{End-diastolic volume}}$$

In the example depicted in Figure 21-1, ejection fraction is 50%. Values between 50% and 65% are typical for resting dogs.

As shown in Figure 21-1, left ventricular pressure is low at the beginning of ventricular systole, but the powerful contraction of the ventricular muscle causes the ventricular pressure to increase rapidly. The increase in left ventricular pressure causes a momentary backflow of blood from the left ventricle to the left atrium, which closes the *left atrioventricular (AV) valve* (the *mitral valve*). Blood is not immediately ejected from the left ventricle into the aorta at the beginning of systole, because the *aortic valve* remains closed until the left ventricular pressure exceeds the aortic pressure. Therefore, ventricular volume remains unchanged during this first phase of systole, which is aptly named *isovolumetric contraction.*

When left ventricular pressure does rise above aortic pressure, the aortic valve is pushed open, and there is a *rapid ejection* of blood into the aorta. Rapid ejection is followed by a phase of *reduced ejection* of blood as both ventricular pressure and aortic pressure pass their peak *(systolic)* values and begin to decrease. (During the period of reduced ejection, the ventricular pressure actually falls below the aortic pressure, but ejection continues for a few moments, because the blood flowing out of the ventricle is carried along by the momentum imparted to it during rapid ejection.) As the ventricular pressure continues to decrease, ejection comes to an end. A momentary backflow of blood from the aorta into the left ventricle closes the aortic valve. The closure of the aortic valve demarcates the end of ventricular systole and the beginning of ventricular diastole.

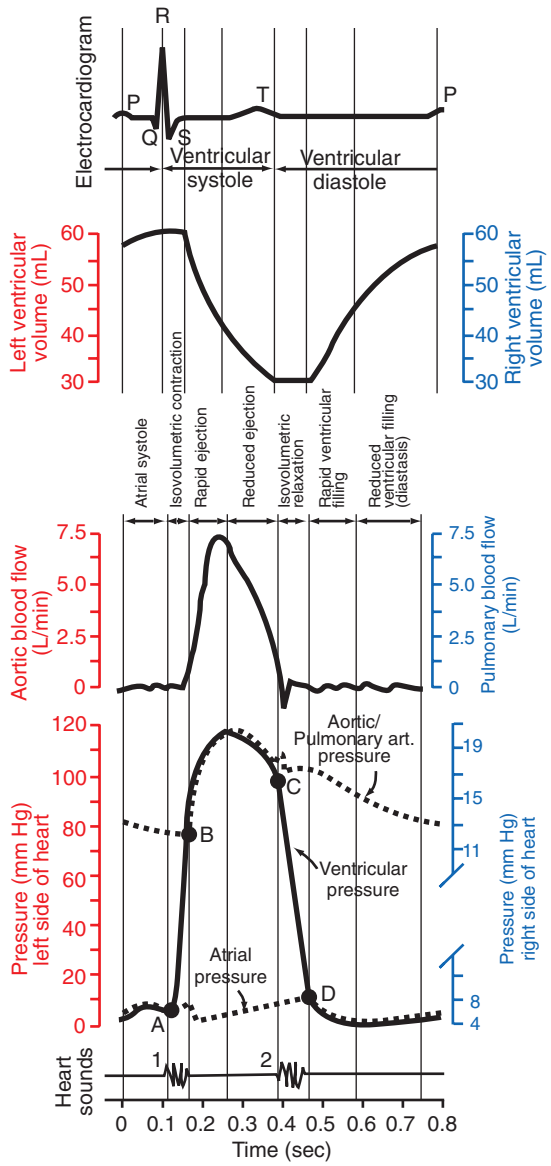

FIGURE 21-1 Events and terminology associated with one cardiac cycle (heartbeat) in a normal dog. Vertical scales on the left side of the graphs *(red)* are for the left side of the heart. Vertical scales on the right side of the graphs *(blue)* are for the right side of the heart. In the graph of *ventricular pressure,* point *A* indicates closure of the mitral and tricuspid valves (the atrioventricular valves); point *B* indicates opening of the aortic and pulmonic valves; point *C* indicates closure of the aortic and pulmonic valves; and point *D* indicates opening of the mitral and tricuspid valves. See text for details.

During the first phase of ventricular diastole, the ventricular muscle relaxes, and left ventricular pressure declines from a value near aortic pressure to a value near left atrial pressure. However, no filling of the ventricle can occur because the mitral valve remains closed until left ventricular pressure drops below left atrial pressure. This first phase of ventricular diastole is called *isovolumetric relaxation* because there is neither filling nor emptying of the ventricle.

When left ventricular pressure does fall below left atrial pressure, the mitral valve is pushed open, as blood begins to flow from the atrium into the ventricle. First, there is a period of *rapid ventricular filling,* which is followed by a phase of *reduced ventricular filling (diastasis).* Diastasis persists until the sinoatrial node cells initiate an atrial action potential and atrial contraction *(atrial systole).* In a resting dog, as depicted in Figure 21-1, ventricular volume is nearly at its end-diastolic level even before atrial systole. Typically, 80% to 90% of ventricular filling occurs before atrial systole. Atrial systole simply "tops up" the almost-full ventricles. An important clinical consequence of this fact is that the ventricles in a resting animal can pump a nearly normal stroke volume even in the absence of properly timed atrial contractions (e.g., during atrial fibrillation). During exercise, however, atrial contractions make a relatively greater contribution to ventricular filling because the rapid heart rate in exercise leaves a shorter time for diastolic filling. Therefore, animals with atrial fibrillation typically exhibit exercise intolerance. Ventricular filling also becomes more dependent on atrial systole in patients with certain valve defects, such as narrowing of the mitral valve *(mitral stenosis).*

At the end of atrial systole, the atria begin to relax. The left atrial pressure drops slightly. Then, as the ventricles begin to contract, there is a momentary backflow of blood from the left ventricle to the left atrium. The backflow closes the mitral valve, which marks the end of ventricular diastole and the beginning of another left ventricular systole.

By definition, the cardiac cycle is divided into ventricular systole and ventricular diastole. Closure of the mitral valve marks the beginning of ventricular systole. Closure of the aortic valve marks the beginning of ventricular diastole. Note that atrial systole takes place during ventricular diastole.

The preceding six paragraphs discussed pressure changes in the left atrium, left ventricle, and aorta. However, all the events of the cardiac cycle also take place on the right side of the heart. Therefore, all the statements made about the left side of the heart also hold true for the right side of the heart; simply substitute "pulmonary artery" for "aorta," "pulmonic valve" for "aortic valve," and "tricuspid valve" for "mitral valve." As indicated in Figure 21-1, the ventricular volumes are similar for the left and right sides, and so are the blood flow rates. The pressures, however, differ greatly on the two sides. Systolic (peak) pressure in the right ventricle and pulmonary artery is only about 20 mm Hg, whereas systolic pressure on the left side of the heart reaches 120 mm Hg. This explains why there are different scales on the pressure axes in Figure 21-1 for the left and right sides of the heart.

The timing of the two major heart sounds is also shown in Figure 21-1 *(bottom).* The *first heart sound* (S1) is associated with the closure of the AV valves (the mitral and tricuspid valves). The actual closure of the valves does not make this sound; the valve leaflets are so light and thin that their closing would be almost silent. However, there is a momentary backflow of blood from the ventricles to the atria at the beginning of ventricular systole. When this backflow of blood is brought to a sudden stop against the closing valves, brief vibrations are created in the blood and in the cardiac walls. These vibrations create the heart sound.

The *second heart sound* (S2) is associated with closure of the aortic valve on the left side of the heart and the pulmonic valve on the right side of the heart. It is usually briefer, sharper, and higher pitched than the first heart sound. Again, what makes the sound is not the valve leaflets closing, but rather the reverberation produced when the momentary backflow of blood into the ventricles is brought to a sudden stop by closure of the valves. The closures of the aortic and pulmonic valves are normally simultaneous. Under certain circumstances, however, the two valves close at slightly different times, and the second heart sound is

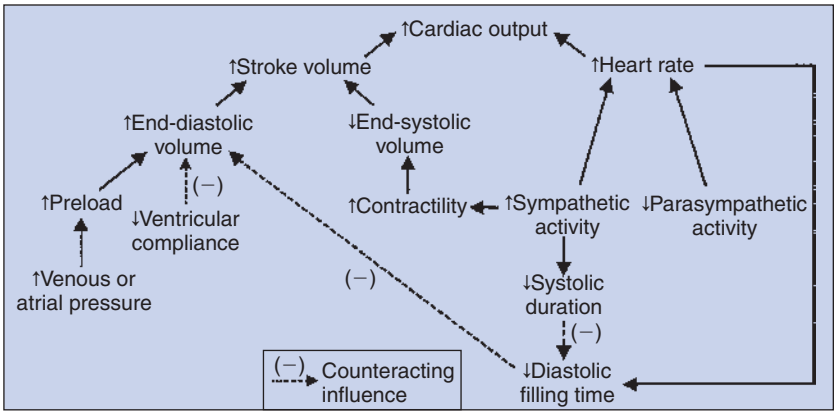

FIGURE 21-2 Summary of the control of cardiac output. The relationships shown here are described in detail in the text.

heard as two distinct sounds in quick succession; this condition is called a *split second heart sound.*

The AV valves close at the beginning of ventricular systole, and the aortic and pulmonic valves close at the end of ventricular systole. Therefore, ventricular systole is sometimes defined as the part of the cardiac cycle between the first heart sound and the second heart sound.

Two additional heart sounds can commonly be heard in large animals (and occasionally in dogs). The rush of blood into the ventricles during the rapid filling phase of early diastole can create sufficient turbulence and enough vibration of the ventricular walls to be heard as a *third heart sound* (S3). A *fourth heart sound* (S4), if audible, occurs right at the end of diastole, during atrial systole.

Cardiac Output Equals Heart Rate Multiplied by Stroke Volume

All the events diagrammed in Figure 21-1 occur during each heartbeat, and each heartbeat results in the ejection of one stroke volume of blood into the pulmonary artery and aorta. The number of heartbeats per minute is called the *heart rate*. Therefore, *cardiac output* (the total volume of blood pumped by each ventricle in 1 minute) is expressed as follows:

$$\text{Cardiac output} = \text{Stroke volume} \times \text{Heart rate}$$

This relationship emphasizes that cardiac output can be increased only if stroke volume increases, heart rate increases, or both increase. Therefore, to understand how the body controls cardiac output, you must understand how the body controls stroke volume and heart rate. Figure 21-2 summarizes the factors that affect stroke volume and heart rate. These factors are described in detail in the following three sections.

Increases in End-Diastolic Ventricular Volume Cause Increases in Stroke Volume

Stroke volume equals end-diastolic volume minus end-systolic volume. Therefore, as shown in Figure 21-2, stroke volume can be increased only by increasing end-diastolic volume (i.e., filling the ventricles fuller during diastole) or by decreasing end-systolic volume (i.e., emptying the ventricles more completely during systole), or both.

The effect of increasing end-diastolic ventricular volume (EDV) on stroke volume is plotted in Figure 21-3, *A*. The detailed physiological mechanisms underlying this relationship are complex. Basically, however, greater ventricular filling during diastole places the ventricular muscle fibers in a more favorable geometry for the ejection of blood during the next systole. Also, stretching the ventricular muscle fibers during diastole causes a greater amount of calcium (Ca^{2+}) to be released from the sarcoplasmic reticulum during the subsequent systolic contraction, and this enhances the force of contraction. Resting conditions in a normal animal are somewhere around the middle of this *ventricular function curve.* Therefore, increases or decreases from normal ventricular end-diastolic volume result in approximately proportional increases or decreases in stroke volume.

End-Diastolic Ventricular Volume Is Determined By Ventricular Preload, Ventricular Compliance, and Diastolic Filling Time

Ventricular preload is the pressure within a ventricle during diastolic filling. Because ventricular pressure changes throughout filling (see Figure 21-1), the value of ventricular pressure at the end of diastole is usually accepted as a singular measure of preload. Normal values of preload *(end-diastolic ventricular pressure)* are about 5 mm Hg for the left ventricle and 3 mm Hg for the right ventricle. In a normal heart, ventricular pressure at the end of diastole is essentially equal to atrial pressure because the AV valves are open widely during late diastole. Also, because there are no valves between the veins and the atria, the atrial pressure is almost identical to the pressure within the nearby veins. Thus, pulmonary venous pressure, left atrial pressure, and left ventricular end-diastolic pressure are all essentially equivalent measures of left ventricular preload. Similarly, right ventricular end-diastolic pressure, right atrial pressure, and vena caval pressure are all essentially equivalent measures of right ventricular preload. In the clinic, right ventricular preload is measured by introducing a catheter into a peripheral vein (e.g., the jugular vein) and advancing it into the cranial vena cava (precava) or right atrium. Such a catheter is called a *central venous catheter,* and the pressure measured at its tip is called *central venous pressure.* Left ventricular preload is more difficult to measure clinically because there is no easy way to place a catheter tip into the left atrium or pulmonary veins.

Figure 21-3, *B,* shows that increases in preload are associated with increases in end-diastolic ventricular volume. The graph depicts a left ventricle that has a natural volume of 30 mL in a relaxed, nonpressurized state (i.e., when the preload equals 0 mm Hg). Increases in preload distend and fill the ventricle. A preload of 5 mm Hg brings about the normal left ventricular end-diastolic volume of 60 mL. However, ventricular tissue reaches its elastic

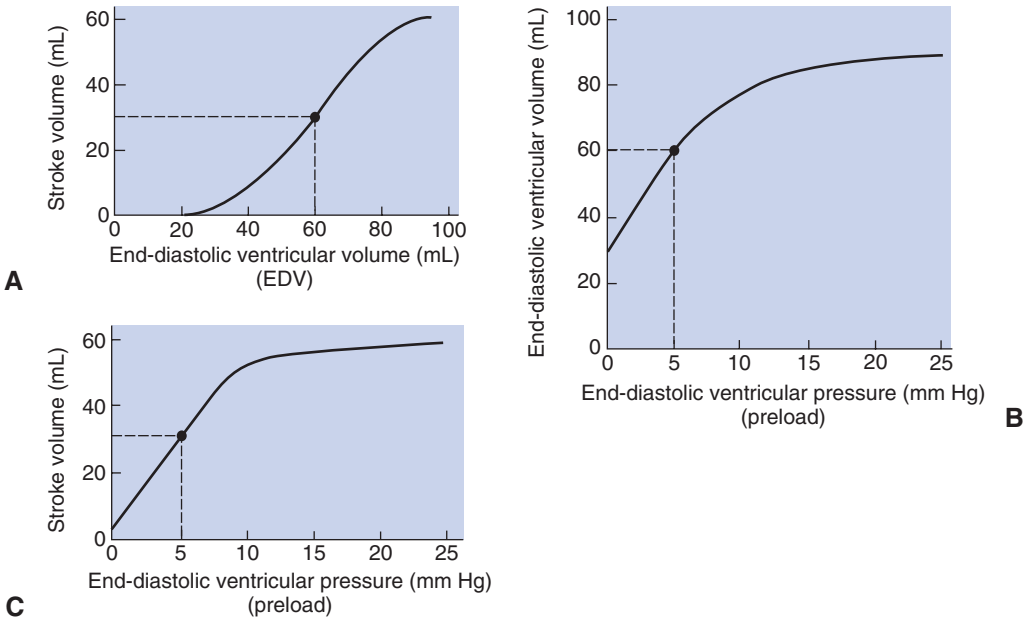

FIGURE 21-3 **A,** Increase in end-diastolic ventricular volume causes increased stroke volume. **B,** Increase in end-diastolic ventricular pressure (preload) causes increased end-diastolic ventricular volume. **C,** Combines the relationships of *A* and *B* to show that an increase in ventricular preload causes increased stroke volume. An upper limit is reached in each relationship (*A* to *C*) primarily because, at high levels of end-diastolic ventricular volume, the ventricular walls become stretched to their elastic limit. The numerical data are for the left ventricle of a large dog. The *points* and *dashed lines* indicate normal values for the resting state.

limit when the ventricular volume approaches 90 mL. Further increases in the preload do not cause much additional ventricular filling.

Increases in ventricular preload cause increases in end-diastolic volume (see Figure 21-3, *B*), and increases in end-diastolic volume cause increases in stroke volume (see Figure 21-3, *A*). Therefore, it follows that increases in preload cause increases in stroke volume (see Figure 21-3, *C*). Each of these relationships reaches an upper limit. Several factors are involved, but the main one (already mentioned) is that the ventricular walls become stretched to their elastic limit at high levels of end-diastolic ventricular volume. In a resting dog the normal values of ventricular preload, end-diastolic volume, and stroke volume are about midway between their minimum and maximum values (see Figure 21-3). Therefore a decrease below normal in preload will cause a decrease in both end-diastolic ventricular volume and stroke volume. This happens, for example, in response to hemorrhage (see Chapter 26).

The relationships among ventricular preload, end-diastolic volume, and stroke volume were first studied in detail by Ernest Henry Starling. The observation that changes in preload cause corresponding changes in end-diastolic ventricular volume and stroke volume is called *Starling's law of the heart.* The Starling mechanism is critical for moment-to-moment adjustments of stroke volume. For example, if the right ventricle begins, for any reason, to pump an increased stroke volume, the resulting additional pulmonary blood flow causes an increase in the pulmonary venous pressure, which increases left atrial pressure, which in turn increases left ventricular preload, which increases the filling of the left ventricle during diastole. The resulting increase in left ventricular end-diastolic volume leads to a greater stroke volume from the left ventricle. Thus an increase in right ventricular stroke volume quickly results in a corresponding increase in left ventricular stroke volume. The reverse is also true.

The sequence just described has a potential for developing into a vicious circle, with runaway increases in stroke volume. Other control mechanisms prevent this from happening, as discussed in Chapter 25. The point here is that the Starling mechanism keeps the stroke volumes of the left and right ventricles balanced. If this equality were not maintained (and one ventricle pumped more blood than the other for several minutes), a large part of the body's blood volume would accumulate either in the lungs or in the systemic circulation.

An alternate name for Starling's law of the heart is *heterometric autoregulation.* This name implies self-control *(autoregulation)* of stroke volume as a result of different *(hetero)* initial volumes *(metric);* that is, *heterometric* refers to different end-diastolic volumes.

End-diastolic ventricular volume is determined not only by preload but also by *ventricular compliance.* Compliance is a measure of the ease with which the ventricular walls stretch to accommodate incoming blood during diastole. A compliant ventricle is one that yields easily to preload pressure and readily fills with blood during diastole. Compliance is more rigorously defined as follows:

$$\text{Compliance} = \text{Change in volume} \div \text{Change in pressure}$$

Ventricular compliance therefore corresponds to the slope of a ventricular volume versus pressure curve, such as the one shown in Figure 21-3, *B.* This figure illustrates that a normal ventricle is quite compliant over the range of ventricular volumes up to and including the normal end-diastolic ventricular volume. Within this range, small changes in preload result in substantial changes in end-diastolic ventricular volume. At preloads higher than

about 10 mm Hg, however, the ventricle becomes less compliant (stiffer). Inelastic connective tissue in the ventricular walls prevents increases in ventricular volume above about 90 mL.

Myocardial ischemia, certain cardiac diseases, or mere advancing age can cause the ventricular walls to become stiff and noncompliant even at normal preloads. Figure 21-4 shows a comparison of volume versus pressure curves for a normal ventricle and for a noncompliant ventricle. In the noncompliant ventricle, there is a smaller increase in ventricular volume for any given increase in ventricular preload. As a consequence, a larger-than-normal preload is needed to obtain a normal end-diastolic ventricular volume and a normal stroke volume. An elevated preload necessitates elevated atrial and venous pressure, which leads to edema (detailed in Chapters 23 and 26). Thus, stiffening of the left ventricle leads to elevated pressure in pulmonary veins and pulmonary edema; stiffening of the right ventricle leads to elevated pressure in the systemic veins and systemic edema.

In addition to preload and compliance, the third factor that affects ventricular end-diastolic volume is the length of time available for ventricular filling during diastole. Heart rate is the main determinant of *diastolic filling time*. At a normal resting heart rate, there is ample time for ventricular filling during diastole; in fact, ventricular filling is almost complete even before atrial systole occurs. As heart rate increases, however, diastolic duration decreases. At heart rates greater than about 160 beats/min, the shortness of diastolic filling time precludes achievement of normal end-diastolic ventricular volume. This limitation on ventricular filling would dramatically reduce stroke volume when heart rate is high if not for an additional, compensating influence brought about by the sympathetic nervous system, as discussed later.

Figure 21-2 *(left side)* provides a useful summary of the preceding discussion. End-diastolic ventricular volume is determined by ventricular preload, ventricular compliance, and diastolic filling time. An elevated preload increases ventricular filling. Decreased ventricular compliance or decreased diastolic filling time can limit ventricular filling.

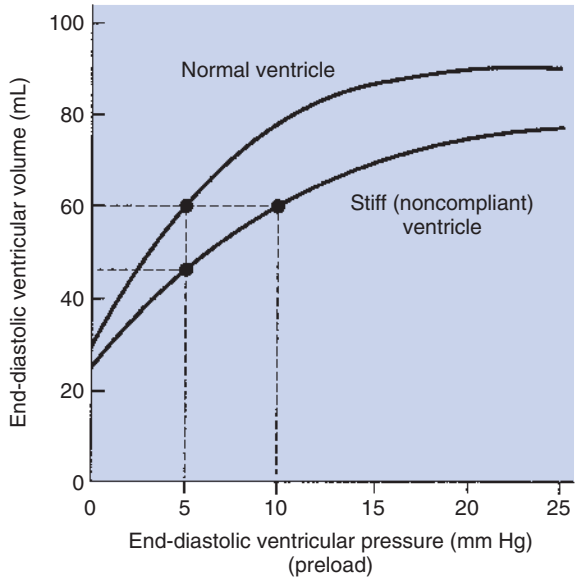

FIGURE 21-4 Stiff, noncompliant ventricle requires a higher filling pressure (higher preload) to reach a normal degree of filling (normal end-diastolic ventricular volume).

Increases in Ventricular Contractility Cause Decreases in Ventricular End-Systolic Volume

Contractility refers to the pumping ability of a ventricle. With increased contractility, there is a more complete emptying of the ventricle during systole and therefore a decreased end-systolic volume (see Figure 21-2, *middle*). An increase in contractility brings about an increase in stroke volume without requiring an increase in end-diastolic volume. Figure 21-5 shows graphically that increased contractility brings about an increased stroke volume for any given end-diastolic volume.

Sympathetic nerve activity increases ventricular contractility through the action of the neurotransmitter norepinephrine, which activates β-adrenergic receptors on ventricular muscle cells. As discussed in Chapter 19, activation of β-adrenergic receptors leads to an increased influx of extracellular Ca^{2+} into cardiac cells during an action potential (and to several other effects); the overall result is that cardiac contractions are stronger, quicker to develop, and shorter. Epinephrine and norepinephrine released from the adrenal medulla and circulating in the blood can likewise activate β-adrenergic receptors and increase contractility, as can β-adrenergic agonist drugs (e.g., epinephrine, isoproterenol). The cardiac glycosides (e.g., digitalis) are another class of drugs that increases cardiac contractility, again by increasing the cytosolic Ca^{2+} concentration during an action potential.

If cardiac contractility becomes depressed, there is less-than-normal ventricular emptying during systole. End-systolic volume increases, and stroke volume decreases, as shown in Figure 21-5. A decrease in sympathetic activity causes a decrease in cardiac contractility, as do β-adrenergic antagonist drugs, which block the β-adrenergic receptors on cardiac muscle cells. Propranolol and atenolol are the β-adrenergic antagonists used most often to decrease cardiac contractility. As with β-adrenergic antagonists, calcium channel–blocking drugs also decrease cardiac contractility by making less Ca^{2+} available for the activation of

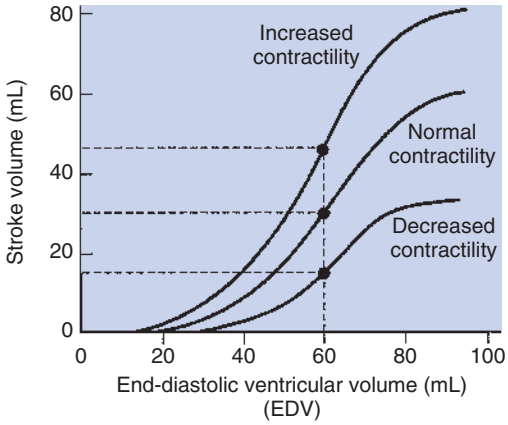

FIGURE 21-5 Increase in cardiac contractility is identifiable graphically as a leftward and upward shift of the ventricular function curve. Increase in contractility means that there will be a larger stroke volume for any given end-diastolic volume. Conversely, decrease in contractility (rightward and downward shift) means that there will be a smaller stroke volume for any given end-diastolic volume. With normal contractility and a normal end-diastolic volume of 60 mL, the end-systolic volume is 30 mL, and so the stroke volume is 30 mL *(middle dot)*. Increased contractility (with no change in end-diastolic volume) results in decreased end-systolic volume. For example, if end-systolic volume is reduced to 15 mL, the stroke volume increases to 45 mL *(upper dot)*.

the contractile proteins. Barbiturates, opioids, and some general anesthetics depress cardiac contractility as well; this must be kept in mind, particularly when administering such drugs to a patient who may already have compromised cardiac function. A decrease in cardiac contractility causes a decrease in stroke volume and therefore cardiac output. Consequently, the patient's blood pressure may fall to dangerously low levels.

A decreased cardiac contractility is the hallmark of the general clinical condition called *heart failure (myocardial failure).* Although there are many forms of heart failure, they share one characteristic: a decrease in pumping ability of one or both ventricles. Heart failure can result from coronary artery disease, myocardial ischemia, myocardial infarction, myocarditis, toxins, or electrolyte imbalances.

Although ventricular contractility is usually the predominant factor affecting ventricular end-systolic volume, the effect of arterial blood pressure must also be considered. A substantial increase in arterial blood pressure impairs ventricular ejection because the left ventricular pressure during systole must exceed aortic pressure before ejection of blood from the ventricle can occur. Arterial pressure is called the *cardiac afterload;* this is the pressure against which the ventricle must pump in order to eject blood. The higher the afterload, the more difficult it is for the ventricle to eject blood. If arterial pressure is excessively high, ventricular ejection is impaired, end-systolic volume increases, and stroke volume decreases. This effect is minor for a normal heart and within the normal range of arterial pressure. However, high afterload can significantly limit stroke volume for a heart that is in failure.

Increasing the Heart Rate Does Not Increase Cardiac Output Substantially Unless Stroke Volume Is Maintained

Because cardiac output is equal to stroke volume multiplied by heart rate, cardiac output might be expected to be proportional to heart rate; that is, doubling the heart rate would be expected to double cardiac output (Figure 21-6, *dashed line*). However, if the heart rate is experimentally increased above its normal level with an electrical pacemaker, cardiac output increases somewhat, but not in proportion to the increase in heart rate. The reason, as mentioned earlier, is that increasing heart rate reduces diastolic filling time. The resulting reduction in end-diastolic volume reduces stroke volume, so cardiac output does not increase in proportion to heart rate (see Figure 21-6, *lower solid line*). In fact, at heart rates greater than about 160 beats/min, stroke volume decreases so much that cardiac output actually declines with further increases in heart rate. This problem was encountered when early versions of artificial cardiac pacemakers malfunctioned in ways that caused high ventricular rates. Decreases in stroke volume at high heart rates are also encountered in certain cardiac arrhythmias. In *paroxysmal atrial tachycardia,* for example, a rapid heart rate is originated by an ectopic atrial pacemaker. The tachycardia occurs typically in bursts or paroxysms. The high heart rate limits diastolic filling so much that cardiac output falls below normal. This causes the blood pressure to fall so low that the patient becomes lethargic and may even faint.

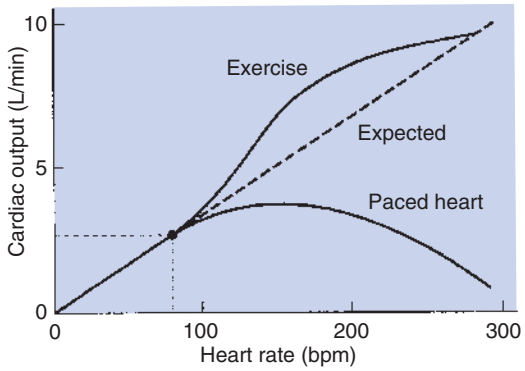

FIGURE 21-6 Point indicates normal, resting values of heart rate (80 beats/min) and cardiac output (2.4 L/min) for a dog. *Dashed line* shows the expected increase in cardiac output in proportion to increases in heart rate (assuming stroke volume remains constant). However, if the heart is paced to higher and higher rates, the observed increase in cardiac output is less than expected because stroke volume decreases *(lower solid line).* In contrast, when a dog increases its own heart rate through sympathetic activation (e.g., during exercise), cardiac output increases even more than expected because stroke volume increases *(upper solid line).*

Although cardiac pacing does not cause a large increase in cardiac output, increases in heart rate in the course of normal daily activities are accompanied by substantial increases in cardiac output. An example is the increase in cardiac output that normally accompanies exercise. As shown in Figure 21-6 *(upper solid line),* the actual increase in cardiac output during progressively more intense exercise is even greater than would be expected on the basis of the associated increase in heart rate. The reason that cardiac output increases so much during exercise is that stroke volume also increases. During exercise, increases in heart rate are brought about by increases in sympathetic activity. This sympathetic activation also increases cardiac contractility, so the ventricles empty more completely with each beat. In addition, sympathetic activation shortens the duration of systole, which helps to preserve diastolic filling time. In summary, under sympathetic action, the heart not only contracts more frequently (increased rate) and more forcefully (increased contractility), but also contracts and relaxes more quickly (helping to preserve diastolic filling time).

Figure 21-7 illustrates how the shortening of systole helps to preserve diastolic filling time. When heart rate is 60 beats/min, each beat takes 1 second. This 1 second must include one systole and one diastole. Typically, systole lasts about ⅓ second, which leaves ⅔ second (plenty of time) for diastolic filling. If heart rate is increased to 120 beats/min, each beat lasts only ½ second. If systole remains at ⅓ second, there is only ⅙ second left for diastolic filling (not enough time). However, if the increase in heart rate occurs because of an increase in sympathetic activity, systole becomes shorter, which restores part of the lost diastolic filling time. Diastole is shorter under these conditions than at rest, but it is longer than it would have been if systole were not shortened. Thus, sympathetic activation is said to help preserve the diastolic filling time. Overall, sympathetic activation (especially when coupled with a decrease in parasympathetic activity) can dramatically increase cardiac output (Table 21-1).

It is useful at this point to review the control of cardiac output, as summarized in Figure 21-2. Cardiac output is determined by stroke volume and heart rate. Stroke volume is determined by end-diastolic volume and end-systolic volume. End-diastolic volume depends on preload, ventricular compliance, and diastolic filling time. End-systolic volume depends on contractility and, to a lesser extent, on arterial pressure or afterload (not shown in Figure 21-2). Sympathetic activation increases contractility. Heart failure decreases contractility, as do several drugs often used in veterinary practice. Increased heart rate acts directly to increase cardiac output, but it also decreases diastolic filling time,

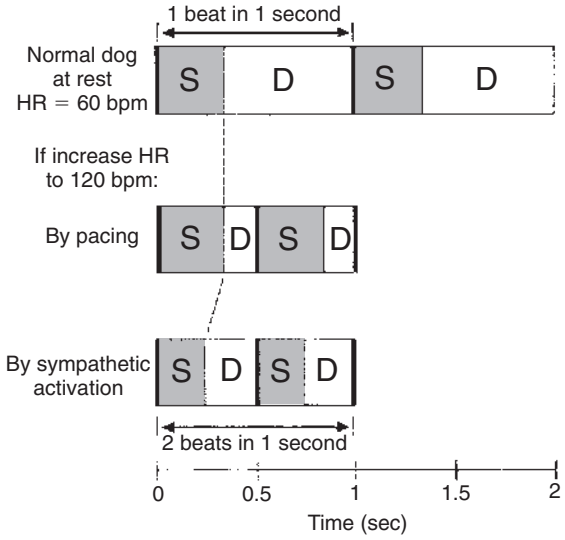

FIGURE 21-7 How shortening of systole (by sympathetic activation) helps to preserve diastolic filling time. *Top,* In this example, a large dog is resting very quietly with a heart rate *(HR)* of 60 beats per minute *(bpm).* Systole *(S)* takes about one-third second, leaving two thirds of each beat for diastole *(D)* and filling. *Middle,* If HR is increased to 120 bpm by an artificial pacemaker, the duration of systole is unchanged, so diastolic duration (filling time) is greatly reduced. *Bottom,* If the same increase in heart rate is brought about by sympathetic activation, systole becomes shorter, which restores part of the lost diastolic filling time.

TABLE 21-1 Typical Cardiac Changes During Vigorous Exercise in a Large Dog

Measurement	Rest	Exercise
Ventricular end-diastolic volume (mL)	60	55
Ventricular end-systolic volume (mL)	30	15
Stroke volume (mL)	30	40
Ejection fraction (%)	50	73
Heart rate (beats/min)	80	240
Cardiac output (L/min)	2.4	9.6

which compromises the increased cardiac output. Heart rate is increased by sympathetic activation and parasympathetic withdrawal. Sympathetic activation also shortens systolic duration, which helps to preserve diastolic filling time. The aggregate effects of sympathetic activation on the heart are made evident by comparing cardiac function in a normal dog during rest and vigorous exercise (see Table 21-1).

Murmurs Are Abnormal Heart Sounds Caused By Turbulent Flow Through Cardiac Defects

Cardiac murmurs are abnormal heart sounds, and they often indicate the presence of cardiac abnormalities. Some murmurs are exaggerations of normal heart sounds; others are additional ("extra") heart sounds. Murmurs are caused by turbulent flow through cardiac defects. The underlying physical principle is that *laminar* or *smooth flow* of blood through the heart or blood vessels is quiet, whereas *turbulent flow* is noisy. An analogy is that a river does not make any sound as it flows smoothly through a broad, relatively flat channel. If the same river enters a channel that is restricted or drops steeply, a rapid or cataract forms. The flow becomes turbulent, and the turbulent flow makes noise.

TABLE 21-2 Cardiac Valve Defects and Resulting Murmurs

	Nature of Defect	
Site of Defect	Incompetence or Insufficiency (Allows Regurgitation)	Stenosis (Narrow Valve Opening, Creates Restriction)
Atrioventricular valves	Systolic murmur	Diastolic murmur
Aortic or pulmonic valves	Diastolic murmur	Systolic murmur

The flow of blood through the heart and blood vessels is normally smooth, and therefore quiet, during the majority of the cardiac cycle. A moment of turbulent flow normally occurs at the beginning of ventricular contraction, on closure of the AV valves. A second moment of turbulent flow occurs at the end of ventricular systole, when the aortic and pulmonic valves close. The momentary turbulence and vibration associated with valve closure create the first and second heart sounds (S1 and S2) as discussed previously and as illustrated in Figure 21-1. On occasion (particularly in large animals), normal third and fourth heart sounds are faintly audible with the stethoscope, during rapid ventricular filling (S3) or during atrial systole (S4). In comparison, clinically important murmurs are louder and usually persist through a greater portion of the cardiac cycle. Sometimes, murmurs are even louder than the normal first and second heart sounds.

Table 21-2 lists cardiac valve defects that cause additional instances of turbulent flow and therefore murmurs. The table also indicates the timing of the murmurs in relation to the cardiac cycle. *Systolic murmurs* occur during ventricular systole; *diastolic murmurs* occur during ventricular diastole. *Continuous murmurs* occur throughout both systole and diastole. The timing of each murmur is easy to understand if two basic principles are kept in mind: murmurs are caused by turbulent blood flow, and blood flows in response to pressure differences. In other words, turbulent (noisy) flow through a cardiac defect occurs only if there is a substantial pressure difference from one side of the defect to the other.

Figure 21-8 indicates how these principles can be used to account for systolic murmurs. The numbers in the figure indicate the maximum pressures that normally exist in each cardiac chamber during ventricular systole. Note, for example, that the pressure in the left ventricle is normally much higher than the pressure in the left atrium during ventricular systole. The mitral valve is normally closed during ventricular systole, so no blood flows backward from the ventricle to the left atrium. If the mitral valve fails to close completely during ventricular systole, the large pressure difference between the left ventricle and the left atrium causes a rapid, backward flow of blood through the partially closed valve. This turbulent backflow creates a systolic murmur. A mitral valve that fails to close completely is said to be *insufficient* or *incompetent.* The backflow across the valve is called

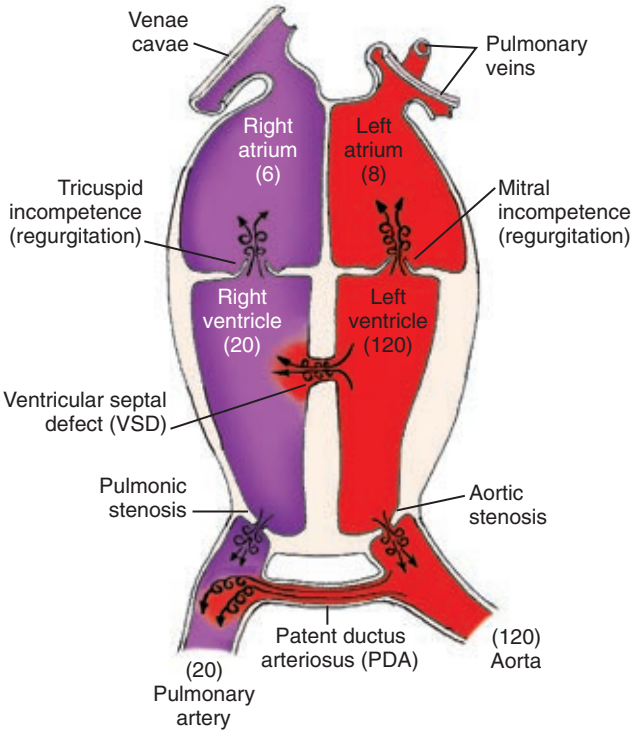

FIGURE 21-8 Schematic view of the heart showing cardiac defects that cause systolic murmurs. The *numbers in parentheses* indicate normal maximum pressures (mm Hg) during ventricular systole. The *swirled arrows* indicate the sites of turbulent (noisy) flow. See text for details.

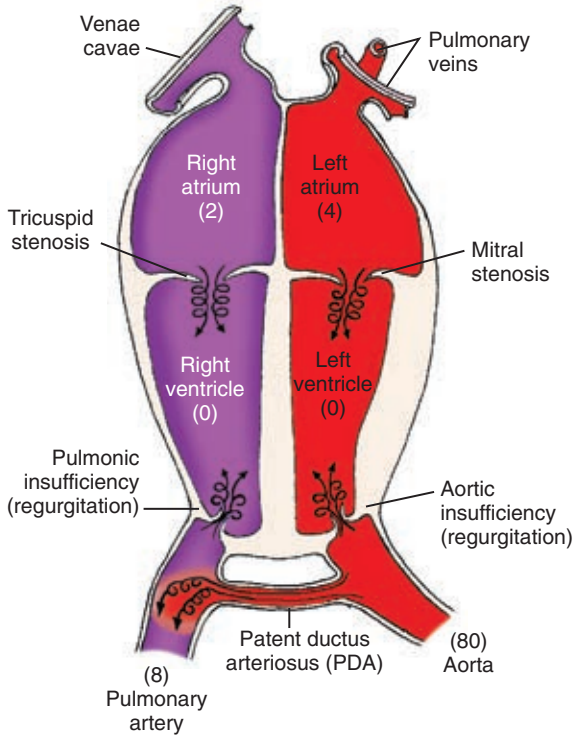

FIGURE 21-9 Cardiac defects that cause diastolic murmurs. The *numbers in parentheses* indicate normal minimum pressures (mm Hg) during ventricular diastole. The *swirled arrows* indicate the sites of turbulent (noisy) flow. See text for details.

regurgitation. Mitral regurgitation is present in about 8% of dogs over 5 years of age.

A *ventricular septal defect* (VSD) is a hole or cleft in the interventricular septum. Blood flows through a VSD from the left ventricle to the right ventricle during ventricular systole because systolic pressure is much higher in the left ventricle than in the right ventricle. Typically, the flow of blood through a VSD is turbulent, and a systolic murmur is created.

Systolic turbulence is also created if the aortic valve does not open widely enough. Blood ejected from the ventricle accelerates to a high velocity as it squeezes through the restricted aortic opening, and turbulence occurs. A valve that fails to open widely enough is called *stenotic;* the defect of *aortic stenosis* produces a systolic murmur. Likewise, *pulmonic stenosis* causes a systolic murmur. Aortic and pulmonic stenosis are common congenital defects in dogs.

A *patent ductus arteriosus* (PDA) is persistence after birth of the opening between the aorta and the pulmonary artery (see Chapter 51). A PDA produces a murmur during systole because the pressure in the aorta is much higher than the pressure in the pulmonary artery. Blood flows from the aorta into the pulmonary artery, and turbulence occurs. The murmur of a PDA is not restricted to systole, however, because the aortic pressure remains higher than the pulmonary artery pressure throughout diastole as well. Therefore the murmur of PDA is heard in both systole and diastole and is thus a *continuous murmur.* It is also called a *machinery murmur* because it characteristically sounds like the rumble of machinery. PDA is common in young dogs, especially females.

The site on the thorax from which a particular murmur can be heard *(auscultated)* best is often indicative of the particular location and type of defect that causes the murmur. For example, the murmur of PDA is characteristically heard best over the left heart base. Occasionally, the turbulence caused by a cardiac defect will be so extreme as to cause a palpable thoracic vibration *(thrill).*

Animals sometimes have open pathways for blood flow between peripheral arteries and peripheral veins. These openings are called *arteriovenous fistulae.* Arteriovenous fistulae carry flow (and create turbulence) during both systole and diastole and therefore create continuous murmurs. The murmur of an arteriovenous fistula is most audible at the body surface close to the point of the fistula.

The numerical values in Figure 21-9 correspond to the minimum pressures that normally exist in the various cardiac chambers during ventricular diastole. These pressures form the basis for understanding why certain cardiac defects chacteristically produce diastolic murmurs. For example, a normal mitral valve opens widely during ventricular diastole, which creates a low-resistance pathway for blood to flow from the left atrium into the left ventricle. However, if the mitral valve fails to open widely *(mitral stenosis),* ventricular filling must occur through a stenotic (narrow) valve. This creates turbulent flow and a diastolic murmur. Mitral stenosis is a common murmur among humans who have developed calcification of the mitral valve as a result of rheumatic heart disease.

During diastole the normal aortic valve is closed, and no blood flows backward from the aorta into the left ventricle. If the aortic valve does not close tightly, blood flows backward (regurgitates) from the aorta to the left ventricle during diastole. Therefore, *aortic regurgitation* produces a diastolic murmur. The defect is called *aortic incompetence* or *aortic insufficiency.* Aortic regurgitation is common in horses but not in dogs.

Diastolic murmurs can also be produced by defects on the right side of the heart. Pulmonic regurgitation produces a diastolic murmur, but it is relatively rare. Tricuspid stenosis is uncommon, at least as a congenital defect. However, a heavy infestation of heartworms in the right side of the heart can create a stenosis at the tricuspid valve and a diastolic murmur.

Cardiac murmurs themselves are not harmful. They are clinically important, however, because the defects that cause the murmurs also have pathophysiological consequences. Cardiac defects typically lead to one or more of these consequences: (1) abnormally high or low blood flow to a region of the body, (2) abnormally high or low blood pressure in a region of the body, and (3) *cardiac hypertrophy* (enlargement of cardiac muscle).

It is not difficult to understand why cardiac defects lead to abnormal blood flows or abnormal blood pressures. For example, in the presence of a ventricular septal defect, the right ventricle receives blood from both the right atrium and the left ventricle, which leads to an abnormally high blood flow through the pulmonary circulation. In the presence of aortic stenosis, the left ventricle must generate an abnormally high systolic pressure to eject blood through the narrow valve opening. In the presence of mitral stenosis, blood dams up (and excessive pressure builds up) in the left atrium and pulmonary veins. It is more difficult to understand why some cardiac defects lead to cardiac hypertrophy. The underlying principle is that some cardiac defects increase the workload of one or both ventricles, and an increase in the workload of cardiac muscle leads to hypertrophy. Developing this concept more fully requires an understanding of cardiac energetics, as described next.

Some Cardiac Defects Increase the Heart's Workload, Which Causes Cardiac Hypertrophy

Cardiac defects often compromise the heart's ability to supply the systemic organs with the blood flow they need to support their metabolism. Compensating for such a *pump failure* frequently requires one or both ventricles to pump more blood than normal or to pump blood at a higher pressure than normal. These adaptations increase the workload of the heart. A persistent increase in cardiac workload leads, over several weeks, to cardiac hypertrophy. A ventricle that must pump more blood volume than normal will develop some hypertrophy, whereas a ventricle that must pump blood at a higher pressure than normal develops a huge hypertrophy. This observation is the basis for the clinical aphorism, "Pressure work is harder for the heart [i.e., causes more hypertrophy] than volume work." To understand the physiological reason of this difference, we must delve into cardiac muscle energetics. To get started, it is useful to consider the analogous case of skeletal muscle hypertrophy in response to increased workload (physical conditioning).

A skeletal muscle does work by exerting a force while shortening. The useful mechanical work *(external work)* done by a skeletal muscle is equal to the force developed by the contracting muscle, multiplied by the distance moved during one contraction, multiplied by the number of contractions (that is, work equals force multiplied by distance). Therefore, the external work done by a skeletal muscle can be increased by increasing the forcefulness of contraction, the distance moved, or the number of contractions. In weight lifting conditioning the emphasis is on performing a few very forceful contractions of skeletal muscle. In contrast, conditioning that involves repetitive, low-force contractions of skeletal muscle (e.g., running, swimming) emphasizes primarily the distance and duration components of skeletal muscle work. Both "weight work" and "distance work" lead to skeletal muscle hypertrophy. However, a common observation is that weight work causes substantially more hypertrophy than does distance work. The basis for this difference is that weight work involves the generation of huge amounts of *internal work (wasted work),* which appears as heat. This large expenditure of energy on internal work greatly increases the *total work* (external work plus internal work) being done during weight lifting as compared to distance running. It is the increase in total work of muscle, not just the external work, that is the primary stimulus for hypertrophy.

The heart does work by pumping blood. The useful mechanical work (external work) done by any pump is equal to the pressure generated by the pump, multiplied by the volume of fluid that is pumped in one pump stroke, multiplied by the number of pump strokes. Therefore the external work done by the left ventricle in 1 minute is equal to the pressure generated, multiplied by the stroke volume, multiplied by the heart rate. The pressure generated by the left ventricle can be approximated by the average (mean) pressure in the aorta, as follows:

$$\textit{Minute work of left ventricle} = \text{Mean aortic pressure} \times \text{Stroke volume} \times \text{Heart rate}$$

The external work done by the ventricle in one cardiac cycle is called the *stroke work,* as follows:

$$\textit{Stroke work of left ventricle} = \text{Mean aortic pressure} \times \text{Stroke volume}$$

(The work of the right ventricle can be calculated in a similar way, but using mean pulmonary artery pressure.)

In accordance with the analogy to skeletal muscle conditioning, the average aortic pressure is analogous to the force developed by the contracting skeletal muscle; the stroke volume is analogous to the distance moved during one contraction; and the heart rate is analogous to the number of contractions. Obviously, the external work done by the left ventricle could be increased by increasing the pressure that the left ventricle generates, by increasing the stroke volume, or by increasing the heart rate. For example, a 50% increase in ventricular work can result from a 50% increase in the left ventricular pressure, a 50% increase in the left ventricular stroke volume, or a 50% increase in the heart rate. Any of these changes results, over a period of weeks, in left ventricular hypertrophy. However, an increase in the ventricular pressure causes a much more pronounced hypertrophy than does an increase in the stroke volume or heart rate. The basis for this difference is that increasing the pressure involves the generation of much more *internal work (wasted work),* which appears as heat. This large expenditure of energy on internal work greatly increases the *total work* (external work plus internal work) being done by cardiac muscle. It is the total work of the cardiac muscle, not just the external work, that is the primary stimulus for hypertrophy.

Under normal resting conditions, about 85% of the metabolic energy consumed by the heart appears as heat, and only 15% appears as external work. A physicist would say that the heart has a "thermodynamic efficiency" of about 15%. However, the "cardiac efficiency" depends on the type of work being done by the ventricles. The heart becomes less efficient when the external work is increased by increasing the pressure. Conversely, the heart becomes more efficient when the external work is increased by an increase in the volume of blood pumped.

The dominant role of pressure in determining total ventricular energy consumption is evident from a comparison of the work

done by the left and right ventricles. The stroke volume and heart rate are equivalent for the left and right ventricles, but the pressure generated is about five times higher in the left ventricle than in the right (mean aortic pressure is about five times higher than mean pulmonary artery pressure). Therefore the external work done by the left ventricle is approximately five times greater than the external work done by the right ventricle. However, the total metabolic energy consumption of the left ventricle is much more than five times greater than the energy consumption of the right ventricle, because the extra external work performed by the left ventricle is in the form of greater pressure. Consequently, the internal (wasted) work of the left ventricle is hugely greater than the internal (wasted) work of the right ventricle. Therefore, almost all the energy consumed by the heart is consumed by the left ventricle; almost all the coronary blood flow is delivered to the left ventricular muscle, and almost all the oxygen consumed by the heart is consumed by the left ventricle. Because of the high amount of pressure work done by the left ventricle compared with the right ventricle, the left ventricle develops much heavier and thicker muscle walls than the right ventricle.

A clinical observation from human medicine provides a further illustration of how an increase in the ventricular pressure work leads to ventricular hypertrophy. About 20% of adult humans have hypertension. In most of these patients, cardiac output is normal. Their arterial blood pressure is elevated because of an increased resistance to blood flow in the systemic arterioles. An elevated left ventricular pressure is required to force the cardiac output through these constricted systemic arterioles. The increased pressure work done by the left ventricle in hypertensive patients results in a striking left ventricular hypertrophy.

Up to a point, ventricular hypertrophy is an appropriate and beneficial adaptation to an increased workload imposed on the ventricular muscle. However, excessive hypertrophy is deleterious for three reasons. First, enlargement of the ventricular muscle restricts the opening of the aortic valve (or pulmonic valve, in the case of right ventricular hypertrophy). A vicious cycle develops. Ventricular hypertrophy leads to aortic or pulmonic stenosis, which necessitates that the ventricle generate an even greater systolic pressure to eject blood, which leads to more ventricular hypertrophy, and so on. A second complication of excessive hypertrophy is that the coronary circulation may be unable to provide enough blood flow to meet the increased metabolic demand of the massive ventricular muscle, particularly during exercise. Inadequate coronary blood flow is especially likely if the coronary vessels have become constricted because of coronary artery disease (atherosclerosis). As a result, patients with ventricular hypertrophy and coronary artery disease are at high risk for cardiac ischemia, myocardial infarction, ventricular arrhythmias, and sudden death during periods of exercise. This explains why the all-too-common combination of hypertension and coronary artery disease is such a serious problem in human medicine. Fortunately, coronary artery disease is rare in most animals. The third complication of cardiac hypertrophy is that the cellular growth factors that mediate the hypertrophy also predispose the cardiac muscle to apoptosis.

The Pathophysiological Consequences of Cardiac Defects Are Direct Results of the Abnormal Pressures, Volumes, and Workloads Created in the Cardiac Chambers

Figure 21-10 summarizes the consequences associated with some common cardiac defects. First, consider *mitral regurgitation.* With each contraction of the left ventricle, a normal volume of blood is ejected into the aorta, and an additional volume of blood is ejected backward (through the regurgitant valve) into the left atrium. As a result, there is an increase in the volume work performed by the left ventricle. Therefore, mild to moderate left ventricular hypertrophy develops. Also, in a heart with mitral regurgitation, the left atrium becomes distended, and left atrial pressure increases, as does pulmonary venous pressure. Elevated pressure in the pulmonary blood vessels forces water and electrolytes out of the bloodstream and into the pulmonary interstitial spaces, causing *pulmonary edema.* When left atrial pressures exceed about 20 mm Hg, pulmonary edema becomes so severe that the lungs' ability to transfer oxygen into the bloodstream is substantially reduced. The result is respiratory distress.

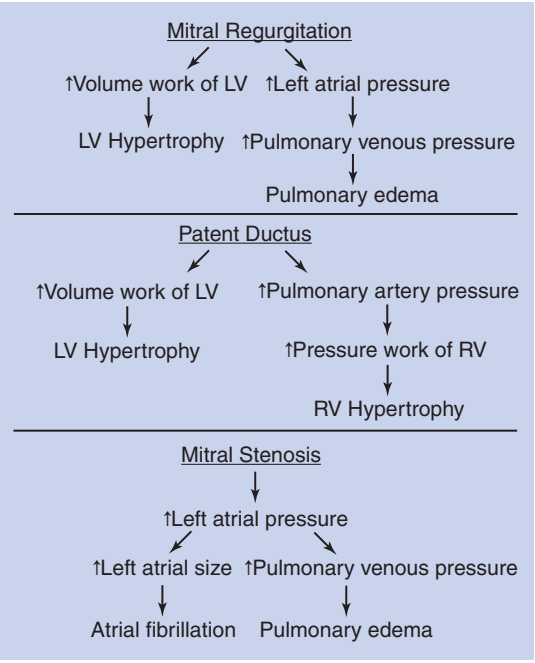

FIGURE 21-10 Pathophysiological consequences of several common cardiac defects. *LV,* Left ventricle; *RV,* right ventricle.

The consequences of mitral regurgitation are usually more noticeable during exercise than during rest. One reason is that despite the regurgitation, the left ventricle can usually adapt enough through hypertrophy and an increase in heart rate to maintain a normal cardiac output into the aorta (and therefore into the systemic circulation) at rest. Also, despite some pulmonary edema, the oxygenation of the blood is sufficient to meet the animal's needs during rest. During exercise, however, the output of the left ventricle into the systemic circulation must increase several-fold to supply adequate blood to exercising skeletal muscle. Also, the delivery of oxygen into the blood must increase several-fold. Despite the hypertrophy, the left ventricle may not be able to deliver adequate blood flow to the systemic circulation during exercise if mitral regurgitation is serious. Also, pulmonary edema may prevent delivery of enough oxygen into the blood to support the metabolism of the exercising animal.

Consider next the abnormalities associated with *aortic stenosis* (not shown in Figure 21-10). To eject a normal volume of blood with each beat through a stenotic aortic valve, the left ventricle must develop an abnormally high systolic pressure. This increases the pressure work of the left ventricle, which leads to a marked left ventricular hypertrophy. The hypertrophy has the desirable

effect of increasing the contractility of the left ventricular muscle so that it can generate the increased pressure required to maintain normal cardiac output. As hypertrophy progresses, however, the ventricular muscle begins to impinge on the aortic outflow pathway, which further hampers the ability of the ventricle to eject blood. In a sense, the hypertrophic ventricular muscle "gets in its own way" or becomes muscle bound. The resulting limitation in aortic outflow is much more likely to be a problem during exercise than at rest. A patient with aortic stenosis may be able to function normally at rest but characteristically exhibits exercise intolerance.

Patent ductus arteriosus (PDA) is a defect that typically results in both left and right ventricular hypertrophy (Figure 21-10). In a typical patient with a PDA, the left ventricle pumps a near-normal volume of blood per minute to the systemic circulation and pumps two to three times that volume of blood per minute through the PDA. As a result, the volume work done by the left ventricle greatly exceeds normal amounts, which leads to left ventricular hypertrophy. The blood flowing through the PDA enters the pulmonary artery, and thus pulmonary arterial pressure exceeds normal levels. This in turn increases the pressure work that must be done by the right ventricle. The right ventricle receives a near-normal volume of blood back from the systemic circulation each minute, and the right ventricle must generate an elevated systolic pressure to eject this blood into the high-pressure pulmonary artery. The increased pressure work for the right ventricle is a powerful stimulus for hypertrophy, and pronounced right ventricular hypertrophy develops.

As a patient with PDA grows, exercise intolerance becomes evident. Despite hypertrophy, the left ventricle cannot supply both the increased blood flow needed by growing, exercising skeletal muscles, and also the blood that flows through the PDA. In patients with PDA the pulmonary artery and the pulmonary blood vessels must carry not only the blood that is pumped by the right ventricle (as in a normal animal), but also the blood that is pumped through the PDA. In a severe case, pulmonary blood flow can be more than four times greater than normal. The resulting increases in pulmonary vascular pressure can lead to pulmonary edema. Surgical repair of a PDA in a young animal leads to a rapid reversal of all these cardiovascular and pulmonary abnormalities.

An understanding of the preceding examples should make it easy to predict the pathological consequences of a *ventricular septal defect.* These consequences include increased volume work of the left ventricle, moderate left ventricular hypertrophy, increased volume and pressure work of the right ventricle, pronounced right ventricular hypertrophy, increased blood flow through the lungs, possible pulmonary edema, and probable exercise intolerance. It should also be clear why pulmonic stenosis leads to increased pressure work for the right ventricle and pronounced right ventricular hypertrophy (see Clinical Correlations).

Figure 21-10 also summarizes the pathological consequences associated with the diastolic murmur of *mitral stenosis.* The left atrial pressure must exceed normal levels to force a normal volume of blood through the stenotic mitral valve and into the left ventricle during each ventricular diastole. The elevated left atrial pressure distends the left atrium. There may be some hypertrophy of the atrial muscle. The atrium continues to function, however, mainly as a reservoir to collect and hold blood during ventricular systole, rather than as a pumping chamber to force blood into the ventricle during its diastole. One problem is that atrial action potentials tend to become discoordinated in a distended atrium, and atrial fibrillation is a common consequence. Also, the increase in the left atrial pressure causes blood to back up and accumulate in the pulmonary blood vessels, so pulmonary edema is likely. It might seem that the backup of blood in the pulmonary vessels would eventually also increase the pressure in the pulmonary artery and thereby increase the pressure work of the right ventricle. In other words, mitral stenosis might be predicted to lead to right ventricular hypertrophy. This prediction is logical, but in practice, animals with greatly elevated left atrial pressures usually die from the effects of pulmonary edema before right ventricular pressures have had a chance to become high enough to induce right ventricular hypertrophy. Therefore, mitral stenosis does not generally lead to hypertrophy of either ventricle.

The defect of *aortic regurgitation* leads to left ventricular hypertrophy. With each systole, the left ventricle must eject an abnormally large volume of blood into the aorta. Of this, a normal volume of blood goes on into the systemic circuit; the rest is simply regurgitated back from the aorta into the left ventricle during diastole. Thus the volume work of the left ventricle is increased to above-normal levels, and left ventricular pressures may rise as well. Both these factors stimulate left ventricular hypertrophy. In severe cases of aortic regurgitation, diastolic ventricular pressure becomes elevated (because during diastole the left ventricle receives blood from both the left atrium and the aorta). This leads to increases in left atrial pressure, and pulmonary edema may develop.

Consideration of the abnormalities associated with cardiac defects is important for two reasons. First, these defects and their consequences are often encountered in veterinary medicine. Second, this discussion illustrates how the clinical signs and consequences of disease states can be understood and predicted in a rational way, on the basis of an understanding of basic principles of cardiac physiology.

CLINICAL CORRELATIONS

PULMONIC STENOSIS

History. A 6-month-old female schnauzer is referred to your clinic because of a heart murmur that was detected during a routine health care visit. The puppy is fairly active but is slightly smaller than her female littermates. She also tires more quickly than her littermates when they play together.

Clinical Examination. All physical parameters are normal except for a systolic heart murmur that can be heard best over the left third to fourth intercostal space. Femoral pulses are normal, and the jugular veins are not distended. Electrocardiography reveals that the dog is in normal sinus rhythm with a heart rate of 118 beats/min. The PR interval is normal. However, the major QRS deflection is negative in leads I and aV_F. Also, deep S waves are noted in leads II and III, and the QRS complexes are slightly prolonged as a result of the wide S waves. Thoracic radiographs show right ventricular enlargement; the right border of the cardiac silhouette is more rounded, and closer to the right thoracic wall, than normal.

A catheter is inserted into the jugular vein, and the following pressures are measured as the catheter is advanced through the right side of the heart and into the pulmonary artery: central venous pressure (mean right atrial pressure), 8 mm Hg (normal, 3 mm Hg); right ventricular systolic pressure, 122 mm Hg (normal, 20 mm Hg); and pulmonary artery systolic pressure, 16 mm Hg (normal, 20 mm Hg).

The jugular catheter is withdrawn until the catheter tip is in the right ventricle. Additional radiographs are then taken while a radiopaque dye is injected through the catheter. These radiographs reveal that the right ventricular outflow tract is narrowed just below the pulmonic valve and that the pulmonic valve does not open widely during ventricular systole.

Comment. The young age of this dog and the absence of other signs of illness suggest that the murmur results from a congenital cardiac abnormality. Murmurs are graded on a scale of I through VI, with VI being the most severe. This dog's murmur is graded IV. A systolic murmur can result from aortic or pulmonic stenosis, mitral or tricuspid regurgitation, or a ventricular septal defect (see Figure 21-8). On the basis of the location from which this murmur can be heard best, aortic or pulmonic stenosis is the most likely cause. All the additional clinical evidence supports a diagnosis of pulmonic stenosis.

The electrocardiogram indicates that the sinoatrial node is acting as the pacemaker and that the AV node is conducting each atrial action potential into the ventricles. However, the abnormalities observed in the polarities and shapes of the QRS complex are indicative of right ventricular hypertrophy, and the radiographs corroborate this finding. Pulmonic stenosis leads to right ventricular hypertrophy, because the right ventricle must generate much higher pressures than normal during systole in order to eject blood through the narrow outflow tract.

Normally, the pulmonic valve opens widely during systole, and the ventricular systolic pressure closely matches the pulmonary artery systolic pressure. In this dog, there is a difference of 106 mm Hg between right ventricular systolic pressure and the systolic pressure in the pulmonary artery just beyond the pulmonic valve. This difference indicates a severe pulmonic obstruction. The degree of obstruction can be visualized on the radiographs taken during dye injection.

Right ventricular hypertrophy is one of two adaptive responses that help this dog maintain a near-normal right ventricular stroke volume, despite the pulmonic stenosis. The other adaptive response is that the mean right atrial pressure is higher than normal (8 vs. 3 mm Hg). The right atrial pressure is elevated because blood backs up or accumulates in areas upstream from the stenosis (i.e., in the right ventricle, right atrium, and systemic veins). The elevated atrial pressure is adaptive because it increases the right ventricular preload, which increases the end-diastolic volume, which (according to Starling's law of the heart) helps keep the right ventricular stroke volume at a normal level, despite the stenosis. The right atrial pressure is not quite high enough in this dog to cause systemic edema or abdominal ascites (see Chapter 23). However, both these signs are sometimes seen in dogs with severe pulmonic stenosis because excessively elevated right atrial pressure leads to marked increases in blood pressure (hydrostatic pressure) within the systemic capillaries.

The combined effects of right ventricular hypertrophy and elevated right ventricular preload allow this dog's heart to pump a near-normal stroke volume during rest. However, the pulmonic obstruction limits the increase in the stroke volume that can occur during exercise. The resulting limitation in cardiac output accounts for this dog's lack of stamina during exercise. Over a prolonged period, such a limitation in cardiac output will likely stunt growth.

Treatment. Theoretically, the best treatment for pulmonic stenosis is to remove the obstruction surgically. A valve dilator can be used, or an artificial conduit can be installed across the stenotic valve. Although seriously affected dogs require such interventional treatment, dogs with mild to moderate pulmonic stenosis can lead sedentary lives without any treatment.

Some evidence indicates that the adverse effects of pulmonic stenosis can be minimized by the administration of β-adrenergic antagonists (e.g., propranolol) or calcium channel blockers (e.g., verapamil). Although the mechanism and efficacy of these drugs remain unclear, there is speculation that these drugs are beneficial because they limit ventricular contractility, which limits the work of the heart. Because an increase in cardiac work is the stimulus for hypertrophy, a drug that limits the increase in work also limits the hypertrophy. Although moderate hypertrophy can be adaptive (as explained earlier), excessive hypertrophy is detrimental for two reasons. First, the enlarged ventricular muscle can crowd the pulmonic outflow tract, worsening the stenosis. Second, the coronary circulation may be unable to deliver the increased amounts of blood flow required by the massive ventricular muscle.

OLDER HORSE WITH EXERCISE INTOLERANCE

History. A 22-year-old Thoroughbred mare is presented for exercise intolerance. The owner uses her for trail riding and some low-level eventing. The mare has had some mild arthritis during her career, but in the last 2 to 3 months she seems reluctant to work, takes longer to recover after rides, and seems lethargic. Vaccinations and deworming are current.

Clinical Examination. The mare appears to be slightly underweight. She is responsive but quiet (more quiet than normal, according to the owner). Her temperature is normal; pulse and respiration are slightly increased. Her mucous membranes are darker pink than normal (suggesting reduced blood flow), but capillary refill time is not abnormally long. She has a grade IV systolic murmur on the left side, most consistent with mitral regurgitation. Her lungs are normal on auscultation. No other abnormal findings are noted on physical examination. The mare is lunged for several minutes and reauscultated. No additional abnormalities are detected, except the mare's heart rate and respiratory rate seem to take longer than normal to return to their resting levels. A blood sample is taken for analysis.

Comment. Results of the complete blood count (CBC) and serum chemistry are within normal limits. Echocardiography reveals mitral regurgitation associated with fibrotic thickening of the mitral valve. The *chordae tendineae* are intact. There is some dilation (eccentric hypertrophy) of the left ventricle, but not of the left atrium.

Mitral valve thickening and insufficiency often develop with age, and mitral regurgitation is likely limiting this mare's left ventricular performance. The resulting tendency for inefficient pumping of blood into the systemic circulation can account for the decreased perfusion of the mucous membranes at rest and for the exercise intolerance and listlessness noticed by the owner. With each systolic contraction, the left ventricle is pumping blood both forward, into the aorta, and backward, through the leaky mitral valve and into the left atrium. The mild left ventricular hypertrophy and dilation are likely adaptive responses to this increased volume work. Animals with more severe mitral regurgitation also have left atrial dilation, associated with a much poorer prognosis than if there is no dilation or only left ventricular dilation.

Treatment. No medical treatment is indicated at this time. However, the owner needs to decrease the work by the mare. The mare should have only light, non-stressful activity. A follow-up examination is recommended in 3 to 6 months to assess the rate of progression of the mitral valve disease. If marked progression is noted at that time, the mare should be retired.

PRACTICE QUESTIONS

1. In the normal cardiac cycle:
   a. Ventricular systole and ventricular ejection begin at the same time.
   b. The second heart sound coincides with the beginning of isovolumetric relaxation.
   c. The highest left ventricular pressure is reached just as the aortic valve closes.
   d. Aortic pressure is highest at the beginning of ventricular systole.
   e. Atrial systole occurs during rapid ventricular ejection.

2. Figure 21-11 shows a plot of the changes in pressure and volume that occur in the left ventricle during one cardiac cycle. Which of the following is *true?*
   a. Point D marks the beginning of isovolumetric relaxation.
   b. Point B marks the closure of the aortic valve.
   c. Point C marks the opening of the mitral valve.
   d. Point A marks the beginning of isovolumetric contraction.
   e. Point D marks the beginning of ventricular systole.

3. Which statement is *true* for a normal heart?
   a. Sympathetic activation causes end-systolic ventricular volume to increase.
   b. An increase in ventricular preload causes end-diastolic ventricular volume to decrease.
   c. An increase in ventricular contractility causes systolic duration to increase.
   d. An increase in ventricular contractility causes the external work of the heart to decrease.
   e. Pacing the heart at a high rate causes stroke volume to decrease.

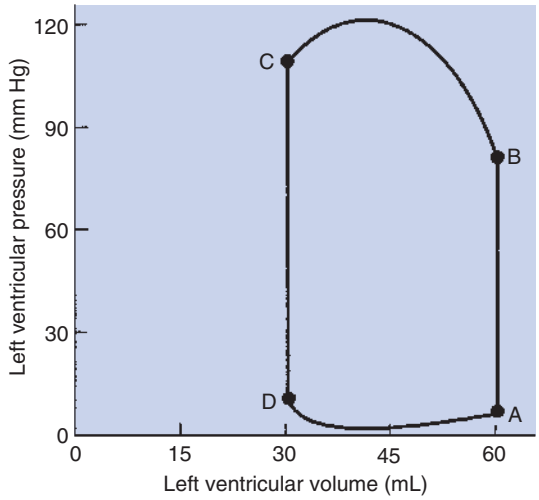

FIGURE 21-11 Closed loop depicts the changes in left ventricular pressure and volume that occur during one cardiac cycle. Practice Question 2 is based on this graph. The first step in understanding the figure is to determine whether the normal sequence of events proceeds clockwise or counterclockwise around the loop. To make this distinction, recall that the ventricles fill when ventricular pressure is low and they empty when ventricular pressure is high. Next, identify the phases of the cardiac cycle that correspond with each limb of the loop. Finally, determine what happens to the mitral and aortic valves at each corner of the loop. *Hint: A, B, C,* and *D* in this figure match the similarly labeled points in Figure 21-1 (on the graph of *ventricular pressure*).

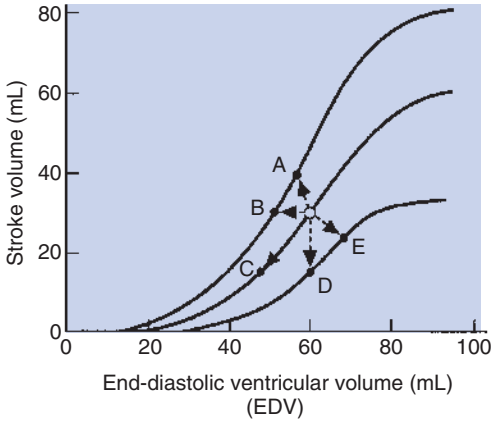

FIGURE 21-12 Practice Question 4 is based on this graph of three ventricular function curves.

4. Starting at the open circle in Figure 21-12, which point would be reached after the contractility decreased and the preload increased?
   a. Point A
   b. Point B
   c. Point C
   d. Point D
   e. Point E

5. You examine a 7-year-old poodle and find evidence of a systolic murmur (no diastolic murmur), pulmonary edema (indicated by rapid, noisy respiration and cough), left ventricular hypertrophy (no right ventricular hypertrophy), and exercise intolerance. The most likely explanation for the symptoms is:
   a. Mitral regurgitation.
   b. Mitral stenosis.
   c. Aortic regurgitation.
   d. Pulmonic stenosis.
   e. Ventricular septal defect.

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CHAPTER 22
The Systemic and Pulmonary Circulations

KEY POINTS

1. Blood pressure represents a potential energy that propels blood through the circulation.
2. Vascular resistance is defined as perfusion pressure divided by flow.
3. The net resistance of the systemic circulation is called the *total peripheral resistance*.
4. Arterial pressure is determined by the cardiac output and the total peripheral resistance.
5. Blood flow to each organ is determined by perfusion pressure and by the organ's vascular resistance.
6. The pulmonary circulation offers much less resistance to blood flow than does the systemic circulation.
7. Arterial pressures are measured in terms of systolic, diastolic, and mean levels.
8. Pulse pressure increases when the stroke volume increases, heart rate decreases, aortic compliance decreases, or total peripheral resistance increases.

Blood Pressure Represents a Potential Energy That Propels Blood Through the Circulation

The *systemic circulation* has the aorta as its inlet point and the *venae cavae* as its outlet. The remainder of the circulation (i.e., right heart, pulmonary circuit, and left heart) is, by definition, the *central circulation.* Blood enters the central circulation from the *venae cavae* and leaves the central circulation through the aorta.

Figure 22-1 shows the normal pressure profile in the systemic circulation. This figure portrays the pressures that would be measured if a miniature pressure gauge were inserted into the various vessels that blood passes through in its journey through the systemic circulation. The blood pressure is highest in the aorta (typically, mean aortic pressure is 98 mm Hg) and lowest in the *venae cavae* (typically, 3 mm Hg). The difference between these pressures (i.e., 95 mm Hg) constitutes the driving force for the movement of blood, by bulk flow, through the systemic circulation. As discussed in Chapter 18, such a pressure difference between the inlet and outlet of a tube (or system of tubes) is called *perfusion pressure difference* (or more commonly, just *perfusion pressure*).

Aortic blood pressure can be thought of as the potential energy available to move blood; the decrease in pressure in the sequential segments of the systemic circuit represents the amount of this potential energy that is "used up" in moving blood through each segment. Pressure energy is used up through *friction,* which is generated as the molecules and cells of blood rub against each other and against the walls of the blood vessels. The energy used up through friction is converted to heat, although the actual increase in the temperature of the blood and blood vessels as a result of friction is very small.

The amount of the blood pressure energy used up in each of the sequential segments of the systemic circulation depends on the amount of friction or resistance that the blood encounters. The aorta and large arteries offer very little resistance to blood flow (very little friction), so the blood pressure decreases only a little in these vessels (from 98 to about 95 mm Hg). The greatest pressure decrease (greatest loss of pressure energy through friction) occurs as blood flows through arterioles; that is, the resistance to blood flow is greater in the arterioles than in any other segment of the systemic circulation. The capillaries and the venules offer a substantial resistance to blood flow, but the resistance (and therefore the pressure decrease) is not as great in these vessels as it is in the arterioles. The large veins and the *venae cavae* are low-resistance vessels, so little pressure energy is expended in driving the blood flow through these vessels.

The pumping of blood by the heart maintains the pressure difference between the aorta and the *venae cavae.* If the heart stops, blood continues to flow for a few moments from the aorta toward the *venae cavae.* As this blood leaves the aorta, the aortic walls become less distended, and the blood pressure inside the aorta decreases. As extra blood accumulates in the *venae cavae,* they become more distended than before, and the blood pressure inside the *venae cavae* increases. Soon, there is no pressure difference between the aorta and the *venae cavae.* Blood flow in the systemic circuit ceases, and the pressure everywhere in the systemic circulation is the same. It has been demonstrated experimentally that this eventual pressure is about 7 mm Hg. This pressure, in a static circulation, is called the *mean circulatory filling pressure.* The mean circulatory filling pressure is greater than zero (i.e., above atmospheric pressure), because there is a "fullness" to the circulation; that is, even if the heart stops, blood still distends the vessels that contain it. The vessel walls, being elastic, recoil ("push back") against this distention, which accounts for the persistence of pressure in the circulation even if the heart stops. If a transfusion of blood is administered to an animal with the heart stopped, the vessels become more distended, and the mean circulating filling pressure rises above 7 mm Hg. Conversely, if blood is removed from an animal with the heart stopped, the pressure everywhere falls to a level below 7 mm Hg.

Consider what happens if the heart is restarted in an animal after the pressure has equalized everywhere at 7 mm Hg. With

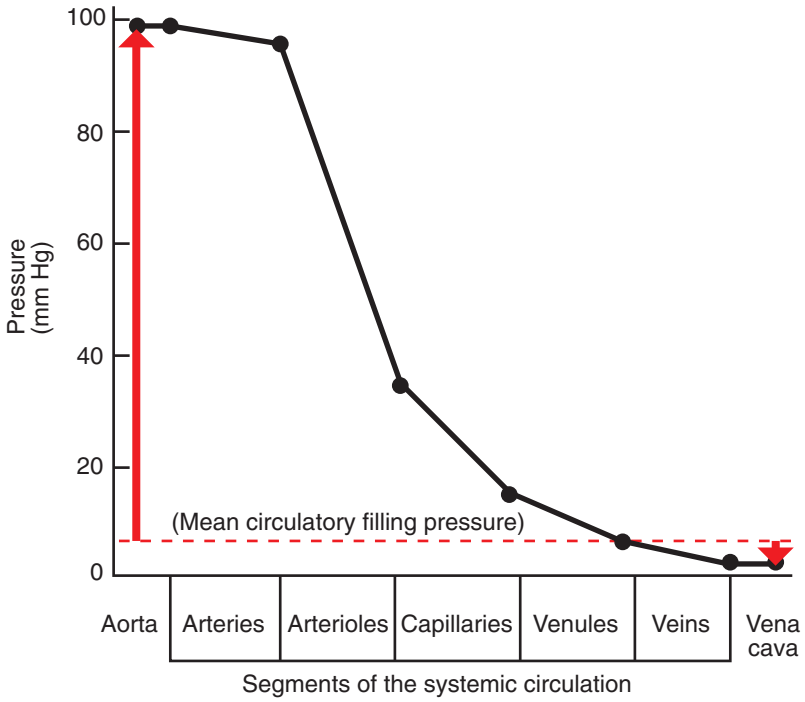


FIGURE 22-1 Graph of the blood pressures (hydrostatic pressures) that typically exist in the systemic circulation of a dog at rest *(solid black line).* The blood pressure in the aorta and arteries is actually pulsatile, increasing with each cardiac ejection and falling between ejections. The values plotted here are the average (mean) values of those pulsatile pressures. Mean circulatory filling pressure *(dashed red line)* is the pressure that would persist throughout the systemic circulation if the heart were stopped. *Red arrows* show the contrasting directions and magnitudes of the pressure changes that would occur in the aorta and *venae cavae* if a stopped heart were restarted and cardiac output returned to normal (see text for details). All pressures are measured at heart level, with reference to atmospheric pressure (taken as zero).

each heartbeat, the heart takes some blood out of the *venae cavae* and this volume of blood is transferred (via the pulmonary circulation) into the aorta. The volume of blood in the *venae cavae* decreases, so the *venae cavae* become less distended and vena caval pressure drops below 7 mm Hg. The volume of blood in the aorta increases, so the aorta becomes more distended and aortic pressure rises above 7 mm Hg. As illustrated in Figure 22-1, the vena caval pressure drops about 4 mm Hg (from 7 to 3 mm Hg), and the aortic pressure rises about 91 mm Hg (from 7 to 98 mm Hg). It is important to understand why the pressure decreases only a little in the *venae cavae* but increases so much in the aorta, even though the volume of blood removed from the *venae cavae* with each heartbeat is the same as the volume of blood added to the aorta. The reason is that the veins are much more compliant (distensible) than the arteries; one can add or remove blood from veins without changing the venous pressure very much, whereas the addition or removal of blood from arteries changes the arterial pressure a great deal.

A compliant vessel readily distends when pressure or volume is added. It yields to pressure. By definition, *compliance* is the change in the volume within a vessel or a chamber divided by the associated change in distending (transmural) pressure, as follows:

$$\text{Compliance} = \frac{\Delta\text{Volume}}{\Delta\text{Transmural pressure}}$$

Compliance corresponds to the slope of a volume-versus-pressure graph. As illustrated in Figure 22-2, veins are about 20 times more compliant than arteries (over the range of pressures typically encountered in the circulation). Therefore, veins can accept or give up a large volume of blood without incurring much of a change in pressure. Veins readily expand or contract to accommodate the changes in blood volume that occur with fluid intake (e.g., drinking) or fluid loss (e.g., sweating). Veins thus function as the major blood *volume reservoirs* of the body. In contrast, arteries function as *pressure reservoirs,* providing the temporary storage site for the surge of pressure energy that is created with each cardiac ejection. Arteries are tough vessels, with low compliance. Therefore, arteries can accommodate a large increase in pressure during a cardiac ejection and then sustain the pressure high enough between cardiac ejections to provide a continuous flow of blood through the systemic circulation.

Vascular Resistance Is Defined as Perfusion Pressure Divided by Flow

Everyday experience tells us that it is easier to force fluid through a large tube than through a small tube. For example, it is easier to drink a milk shake through a large-diameter straw than through a small-diameter straw. For a given driving force (perfusion pressure difference), the flow is higher in the large tube because it offers less resistance to flow (less friction) than the small tube. The precise definition of resistance is:

$$\text{Resistance} = \frac{\Delta\text{Pressure}}{\text{Flow}}$$

Where *Δ Pressure* is *perfusion pressure difference*, or simply *perfusion pressure* (i.e., the pressure at the tube inlet minus the pressure at its outlet). Figure 22-3 presents these concepts in pictorial and

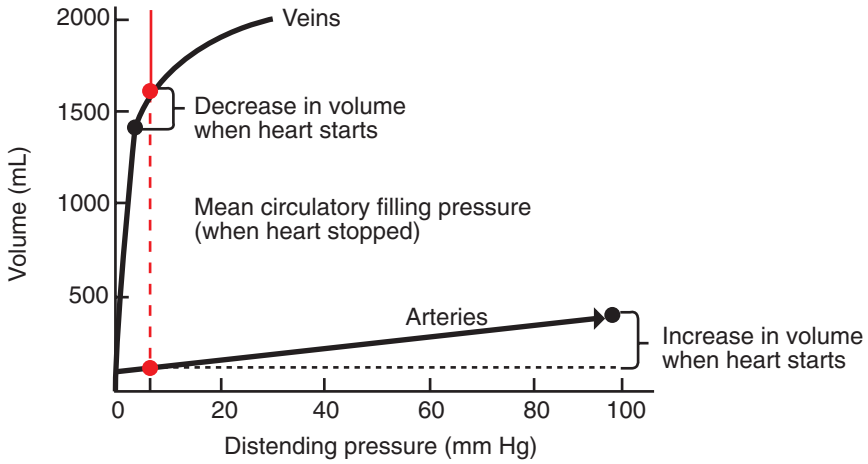
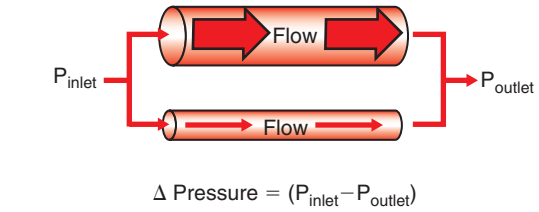


FIGURE 22-2 Typical relationships between volume (of blood) and distending pressure for veins and arteries. Veins are more compliant (easier to distend) than arteries, so they hold a greater volume of blood for a given distending pressure. This concept is illustrated for a distending pressure of 7 mm Hg *(vertical dashed red line),* which is a normal value for the mean circulatory filling pressure (the pressure that would exist in the circulation if the heart were stopped, as shown in Figure 22-1). For a distending pressure of 7 mm Hg, the veins contain about 1600 mL of blood and the arteries only 125 mL *(red circles).* When the heart is restarted, the venous volume decreases, and the arterial volume increases *(black circles).* Because the veins are much more compliant than the arteries, the venous pressure changes very little (decreases from 7 to 3 mm Hg), whereas the arterial pressure changes greatly (increases from 7 to 98 mm Hg).



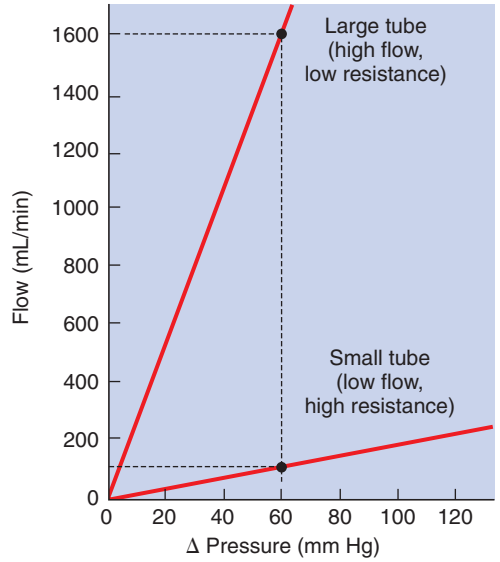


FIGURE 22-3 Relationship between fluid flow and perfusion pressure *(Δ Pressure)* for two tubes. The perfusion pressure is the pressure at the inlet (P_{inlet}) of the tube minus the pressure at the outlet (P_{outlet}). In this example, the larger tube has twice the radius of the smaller tube. For a given perfusion pressure, the flow through the larger tube is 16 times greater than the flow through the smaller tube. That is, the resistance of the larger tube is one-sixteenth the resistance of the smaller tube.

graphic form. The dashed lines in this figure indicate that a perfusion pressure of 60 mm Hg causes a flow of 1600 milliliters per minute (mL/min) through the large tube. Thus the resistance of the large tube is 37.5 mm Hg/liter per minute (L/min). The same perfusion pressure (60 mm Hg) causes a flow of only 100 mL/min through the small tube. The resistance of the small tube is therefore 600 mm Hg/L/min. The resistance of the small tube is 16 times greater than the resistance of the large tube.

In the late 1800s the French physician J.L.M. Poiseuille demonstrated the dominant effect of radius on the resistance of a tube. He showed the following:

$$\text{Resistance of a tube} \cong \frac{8\eta l}{\pi r^4}$$

Where l is the length of the tube, r is the radius, η is the viscosity of the fluid flowing through the tube, and π has its usual meaning.

This equation *(Poiseuille's law)* emphasizes that radius *(r)* is the dominant factor influencing the resistance of a tube; resistance varies inversely with the fourth power of radius. Doubling the radius of a tube decreases its resistance by a factor of 16 (2^4). This explains why using a larger diameter straw makes it so much easier to drink a milk shake. Resistance is also influenced by the length *(l)* of the tube; it is harder to force fluid through a long tube than through a short tube of the same radius. The final determinant of resistance is the viscosity *(η)* of the fluid. The higher the viscosity of the fluid, the higher is the resistance to its flow through a tube. For example, honey is more viscous than water, so a tube offers a higher resistance to the flow of honey than to the flow of water.

As already described, the arterioles are the segment of the systemic circulation with the highest resistance to blood flow (see Figure 22-1). It may seem paradoxical that the arterioles are the site of highest resistance when the capillaries are smaller vessels. After all, Poiseuille's law and Figure 22-3 emphasize that a smaller tube has a much higher resistance than a larger tube. The resolution of this paradox is presented in Figure 22-4. It is true that each

capillary has a smaller radius and therefore a greater resistance than each arteriole. However, each arteriole in the body distributes blood to many capillaries, and the *net resistance* of all those capillaries is less than the resistance of the single arteriole that delivers blood to them. It is only because each arteriole delivers blood to so many capillaries that the net resistance of the capillaries is less than the resistance of the arteriole.

Arterioles are the site not only of the highest resistance in the circulation, but also of adjustable resistance. Variation in arteriolar resistance is the main factor that determines how much blood flows through each organ in the body; an increase in arteriolar resistance in an organ decreases the blood flow through that organ, and vice versa. Arterioles change their resistance, moment to moment, by changing their radius. (The length of an arteriole does not change, at least not over the short term.) The walls of arterioles are relatively thick and muscular. Contraction of the arteriolar smooth muscle decreases the radius of arterioles, and this *vasoconstriction* substantially increases resistance to blood flow. Relaxation of the smooth muscle allows the radius of the vessels to increase, and this *vasodilation* substantially reduces the resistance to blood flow.

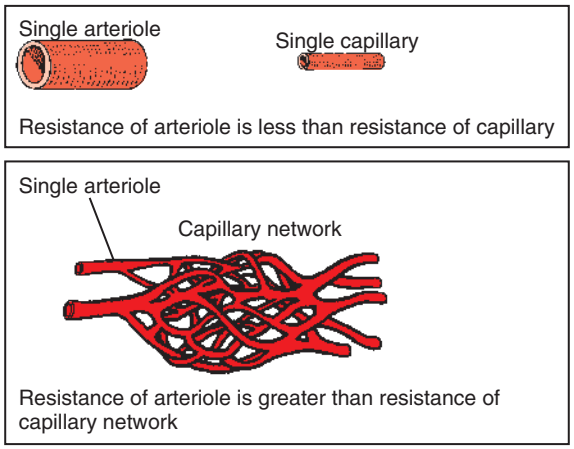


FIGURE 22-4 The resistance of a single arteriole is less than the resistance of a single capillary, because arterioles are larger in diameter. However, each arteriole supplies blood to a whole network of capillaries, and the resistance of an arteriole is greater than the resistance of the capillary network that it supplies with blood.

Figure 22-5 illustrates that a small change in the radius of arterioles in an organ brings about a large change in resistance and therefore in blood flow. In this example the arterial pressure is 93 mm Hg and the venous pressure is 3 mm Hg, so the perfusion pressure is 90 mm Hg. The brain blood flow is initially observed to be 90 mL/min. Based on the mathematical definition of resistance, the resistance of the brain blood vessels is 1000 mm Hg/L/min. Most of this resistance is provided by the brain arterioles. Next, consider the consequence of a slight vasodilation, such that the radius of the arterioles increases by 19% (e.g., from a radius of 1.00 to a radius of 1.19). Recall from Poiseuille's law that the resistance varies inversely as the fourth power of the radius. Because 1.19^4 equals 2.00, a 19% increase in radius cuts the resistance in half. Decreasing the brain's resistance by half (to 500 mm Hg/L/min) would double the brain blood flow (to 180 mL/min).

The Net Resistance of the Systemic Circulation Is Called the Total Peripheral Resistance

As with any other resistance, *systemic vascular resistance* (SVR), also called *total peripheral resistance* (TPR), is defined as a pressure difference (perfusion pressure) divided by a flow. In a calculation of the resistance of the systemic circulation, the perfusion pressure is the pressure in the aorta minus the pressure in the *venae cavae*. The flow is the total amount of blood that flows through the systemic circuit, which is equal to the cardiac output:

$$\text{TPR} = \frac{(\text{Mean aortic pressure} - \text{Mean vena caval pressure})}{\text{Cardiac output}}$$

For a typical dog at rest, the mean aortic pressure is 98 mm Hg, the mean vena caval pressure is 3 mm Hg, and the cardiac output is 2.5 L/min. Under these conditions, TPR is 38 mm Hg/L/min, which means that it takes a driving pressure of 38 mm Hg to force 1 L/min of blood through the systemic circuit.

Because the pressure in the *venae cavae* is usually close to zero, it is sometimes ignored in the calculation of TPR. The resultant simplified equation states that TPR is approximately equal to mean aortic pressure divided by the cardiac output. Usually, this equation is rearranged to form the statement that the mean aortic blood pressure (Pa) is approximately equal to the cardiac output (CO) multiplied by TPR:

$$\text{Pa} \cong \text{CO} \times \text{TPR}$$

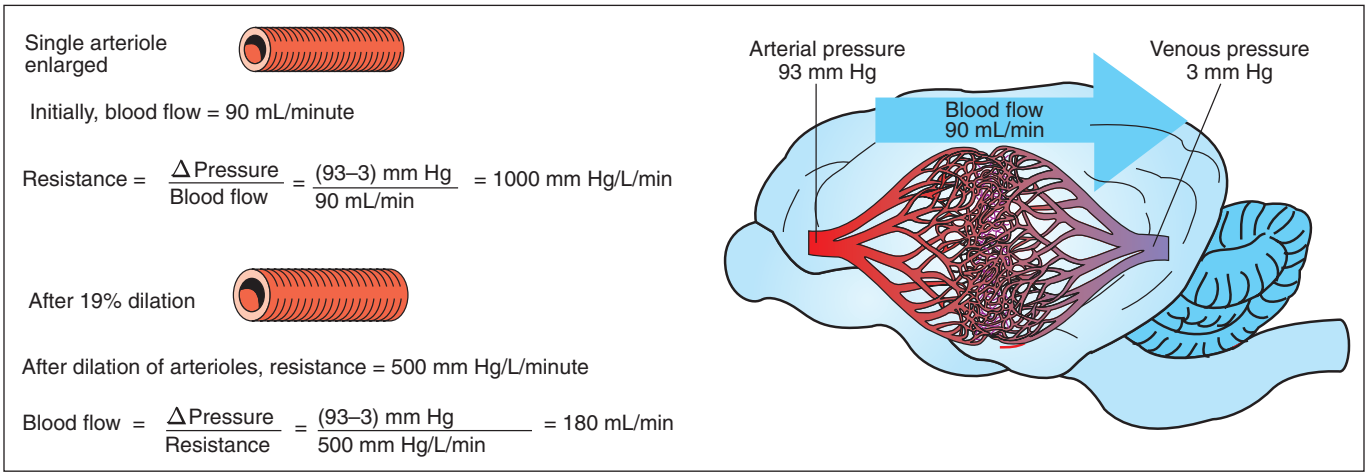


FIGURE 22-5 Example illustrating that a small arteriolar dilation (vasodilation) would substantially increase blood flow to an organ (brain, in this case).

This equation expresses one of the central concepts in cardiovascular physiology, namely that mean aortic blood pressure is determined by two, and only two, factors. Thus, if the aortic pressure is increased, it must be because the cardiac output increased, the TPR increased, or both. There are no other possibilities.

Arterial Pressure Is Determined by the Cardiac Output and the Total Peripheral Resistance

Three examples illustrate the application of the concept that the mean aortic blood pressure is determined by cardiac output and TPR. First, in the most common form of human essential hypertension, the cardiac output is normal. The blood pressure is elevated because of excessively constricted systemic arterioles, which increases TPR above normal. What remains unclear about human essential hypertension is why the arterioles are constricted. High blood pressure is a serious health problem in human medicine, because patients with uncontrolled hypertension often develop cardiac hypertrophy, and they are at high risk for cardiac arrhythmias, myocardial infarction, renal failure, and stroke. Naturally occurring hypertension is rare in veterinary species, although several techniques have been developed to induce hypertension in laboratory animals for research purposes.

Severe hemorrhage or dehydration is another condition in which the arterial pressure becomes abnormal, and it provides several distinct contrasts to chronic hypertension. For example, hemorrhage and dehydration are often encountered in veterinary medicine. Also, the arterial pressure is reduced in these conditions, not elevated. The cause of the decreased pressure is a decreased cardiac output. Hemorrhage or dehydration characteristically reduces the cardiac preload, which reduces the stroke volume and cardiac output. TPR is actually increased above normal because the body constricts the arterioles in the kidneys, splanchnic circulation, and resting skeletal muscle. Vasoconstriction in these organs minimizes the fall in arterial pressure and diverts the available cardiac output to the organs that are most critical for moment-to-moment survival, which include the brain, exercising skeletal muscle, and the heart (i.e., coronary circulation).

The response to vigorous exercise provides a third application of the concept that the mean aortic blood pressure is determined by the cardiac output and TPR. As in hemorrhage, exercise causes the cardiac output and TPR to change in opposite directions. In exercise, however, the cardiac output is elevated, and TPR is decreased. TPR decreases because the arterioles in the exercising skeletal muscle dilate, which increases skeletal muscle blood flow. During vigorous exercise, TPR decreases to about one-fourth of its resting value. The cardiac output increases about fourfold. The result is that the aortic pressure is negligibly changed. Figure 22-6 depicts the cardiovascular adjustments to vigorous exercise.

Blood Flow to Each Organ Is Determined by Perfusion Pressure and by the Organ's Vascular Resistance

If the equation that defines resistance is solved for flow, the result is:

$$\text{Flow} = \frac{\Delta\text{Pressure}}{\text{Resistance}}$$

As applied to the blood flow through any organ, this equation points out that the blood flow is determined by perfusion pressure (mean arterial pressure minus mean venous pressure) and by the resistance of the organ's blood vessels. There are no other factors. All the organs of the systemic circulation receive arterial blood flow via branches of the aorta, so all are exposed to essentially the same arterial pressure. Similarly, the venous blood from all the organs of the systemic circulation is collected into the *venae cavae,* so under normal circumstances, mean venous pressure is the same for all organs. Since all the systemic organs are exposed to nearly the same perfusion pressure, the differences in blood flow to the various organs result solely from their different vascular resistances. As explained earlier, the vascular resistance of an organ is determined primarily by the diameter of its arterioles. Thus, arteriolar vasodilation and vasoconstriction are the primary mechanisms that increase or decrease the blood flow in one organ relative to another organ.

Figure 22-6 illustrates how changes in the vascular resistance of various organs alter the distribution of cardiac output among the organs. In a typical dog at rest, the arteriolar resistances are similar in the splanchnic, renal, and skeletal vascular beds. Therefore, each of these beds receives about the same blood flow (indicated in Figure 22-6 by arrows of equal width). During exercise, skeletal muscle arterioles dilate greatly, almost doubling in diameter, which decreases their resistance to blood flow by a factor of almost 16. Therefore the skeletal muscle blood flow increases almost sixteenfold (from 0.5 to 7.8 L/min). Also during exercise, coronary arterioles dilate, so the coronary blood flow increases. Brain arterioles remain the same, so the brain blood flow is unchanged. By contrast, the arterioles in the splanchnic and renal circulations constrict slightly during exercise, which causes splanchnic and renal resistance to increase by about 20%. Therefore the splanchnic and renal blood flows decrease by about 20% (from 0.5 to 0.4 L/min).

This discussion of blood flow during exercise describes the responses of a normal dog with a healthy heart. Such a dog can readily increase its cardiac output enough to meet the increased blood flow needs of the skeletal and cardiac muscle. As a consequence, the arterial pressure (and hence the perfusion pressure) is very similar during rest and exercise. By contrast, a dog with heart failure cannot increase its cardiac output much above its resting level. Therefore the arterial pressure (and perfusion pressure) declines during exercise, and none of the organs receives the blood flow that it requires. This is why animals with heart failure exhibit weakness, fatigue, and exercise intolerance. (Additional complications of heart failure are discussed in Chapter 26.) The point for now is that the equation that relates blood flow, perfusion pressure, and vascular resistance is fundamental and inescapable; this relationship is profoundly important to an understanding of cardiovascular function and dysfunction.

The Pulmonary Circulation Offers Much Less Resistance to Blood Flow Than Does the Systemic Circulation

As with any other resistance, pulmonary resistance is calculated as a pressure difference (perfusion pressure) divided by a flow. The perfusion pressure that forces blood through the pulmonary circuit is the pressure in the pulmonary artery minus the pressure in the pulmonary veins. The flow that traverses the pulmonary circuit is equal to the cardiac output. Therefore:

$$\begin{matrix}\text{Pulmonary}\\ \text{vascular}\\ \text{resistance}\end{matrix} = \frac{\begin{matrix}(\text{Mean pulmonary artery pressure}\\ -\ \text{Mean pulmonary venous pressure})\end{matrix}}{\text{Cardiac output}}$$

For a typical dog at rest, the mean pulmonary arterial pressure is 13 mm Hg, the mean pulmonary venous pressure is 5 mm Hg,

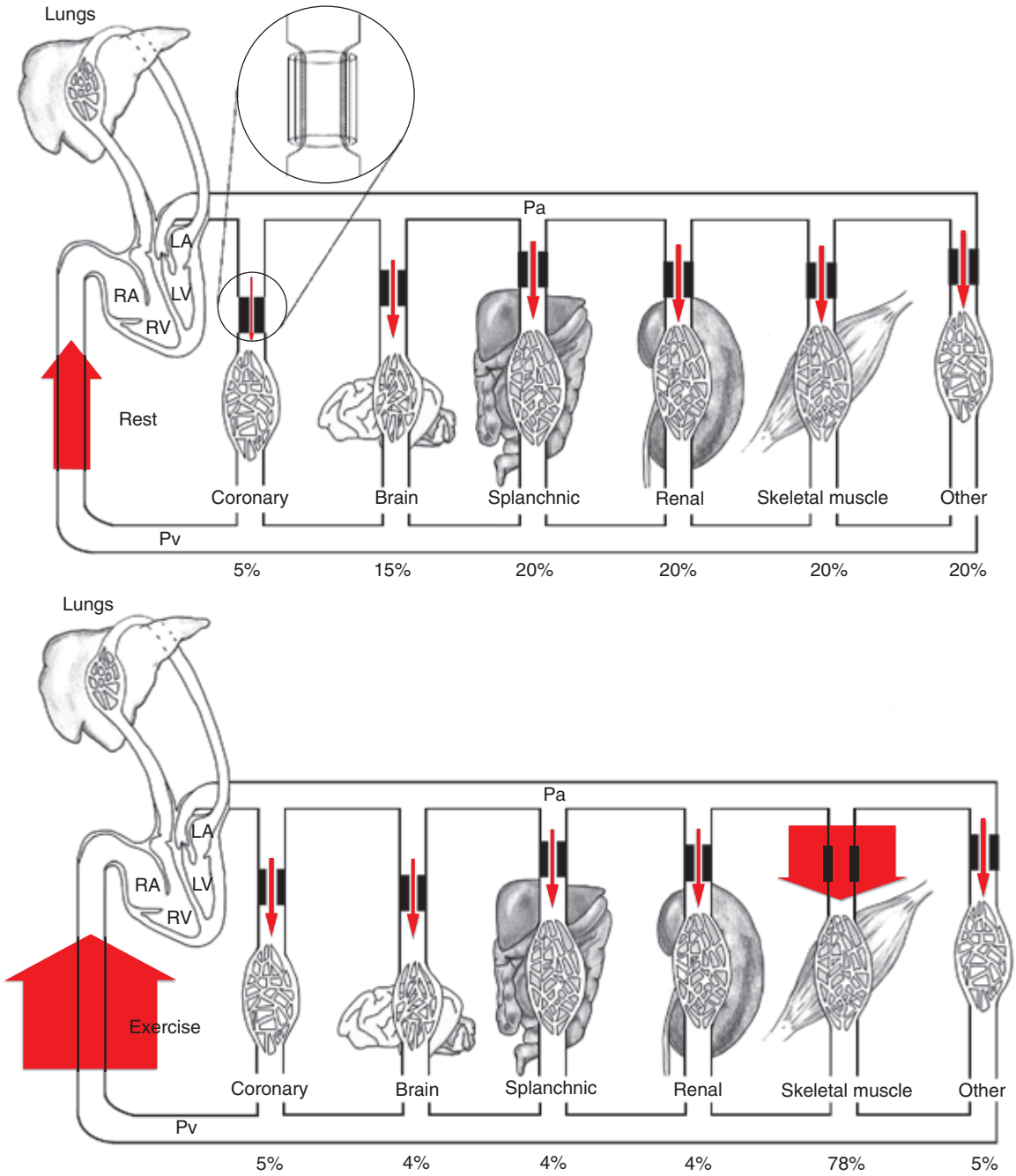


FIGURE 22-6 Cardiac output and its distribution compared during rest *(top)* and vigorous exercise *(bottom)* in a typical large dog. The width of the *red arrows* denotes the amount of blood flow. The flow of blood into the right side of the heart (which is equal to the cardiac output) is represented by the *very wide arrows* on the left. The cardiac output is 2.5 L/min at rest and increases to 10.0 L/min during exercise (fourfold increase). The entire cardiac output passes through the lungs and then is pumped by the left ventricle *(LV)* into the systemic arterial system *(horizontal tube across top).* The systemic arteries deliver blood to each of the systemic vascular beds, which are grouped here into *Coronary, Brain, Splanchnic, Renal, Skeletal muscle,* and *Other.* In each systemic organ, blood must pass through high-resistance arterioles *(heavy bars)* before reaching the capillaries. The arterioles act as adjustable cuffs or constrictors (see magnified view, *top*). The proportion of the total cardiac output that passes through each organ is indicated by a percentage at the bottom. Because each organ is exposed to the same arterial pressure *(Pa)* and venous pressure *(Pv),* the proportion of cardiac output that each organ receives is determined by its resistance. Resistance is determined primarily by the arteriolar diameter, which is indicated by the size of the opening between the heavy bars. During vigorous exercise, skeletal muscle arterioles dilate maximally, and the blood flow to the exercising muscles increases sixteenfold (from 0.5 L/min at rest to 7.8 L/min). Coronary arterioles also dilate, and the coronary blood flow increases about fourfold, which meets the increased demand by the heart muscle for oxygen. Vasoconstriction causes a small decrease in blood flow to the splanchnic and renal circulations. Blood flow to the brain is basically unchanged, although the percentage of total cardiac output received by the brain decreases. *RV,* Right ventricle; *LA,* left atrium; *RA,* right atrium.

and the cardiac output is 2.5 L/min. Thus, pulmonary resistance is 3.2 mm Hg/L/min. Note that this is only about $\frac{1}{12}$ the resistance of the systemic circulation.

The entire cardiac output passes through the lungs, so a fourfold increase in cardiac output during exercise also necessitates a fourfold increase in pulmonary blood flow. Pulmonary blood vessels are quite compliant, and they readily distend to accept the increase in blood flow. Because even a small increase in vessel radius greatly decreases resistance (in accordance with Poiseuille's law, as mentioned earlier), the resistance of the pulmonary blood vessels drops greatly during exercise. The decreased pulmonary resistance during exercise is advantageous because it allows the pulmonary flow to increase greatly without necessitating a large increase in the pulmonary arterial pressure.

Chapters 46 and 47 present additional details about the characteristics of pulmonary blood flow, including an explanation of the mechanisms that adjust the vascular resistance in various regions of the lungs so that the amount of blood that flows through each region of the lungs is appropriately matched to the amount of fresh air that is being delivered to the alveoli in that region *(ventilation-perfusion matching)*.

Arterial Pressures Are Measured in Terms of Systolic, Diastolic, and Mean Levels

The pressures in the pulmonary artery and aorta are not constant but rather are *pulsatile,* as shown in Figure 21-1 and repeated in Figure 22-7. With each cardiac ejection, the pulmonary artery and aorta become distended with blood, which causes the pressures within these vessels to increase to peak values, called *systolic pressures.* Between cardiac ejections (i.e., during ventricular diastole), blood continues to flow out of the pulmonary artery and aorta into the pulmonary and systemic circulations, respectively. As the volume of blood in these large arteries decreases, the arteries become less distended, so arterial pressure decreases. Pressure continues to decrease until the next cardiac ejection begins. The minimal pressure reached before each new ejection is called the *diastolic pressure.* Figure 22-7 illustrates typical values for systolic and diastolic pressures.

The amplitude of the pressure pulsations in an artery is called the *pulse pressure*, specifically:

$$\text{Aortic pulse pressure} = (\text{Aortic systolic pressure} - \text{Aortic diastolic pressure})$$

and

$$\text{Pulmonary artery pulse pressure} = (\text{Pulmonary artery systolic pressure} - \text{Pulmonary artery diastolic pressure})$$

Typical values for pulse pressure are given in Figure 22-7. Note how much lower the systolic, diastolic, and pulse pressures are in the pulmonary artery than in the aorta. These differences illustrate why the pulmonary circulation is called the *low-pressure circulation,* whereas the systemic circulation is called the *high-pressure circulation.*

It is important to distinguish among systolic pressure, diastolic pressure, and pulse pressure; and to distinguish all of them from *mean pressure*. Mean aortic pressure is the average pressure in the aorta over the course of one or more complete cardiac cycles. Likewise, mean pulmonary artery pressure is the average pressure in that vessel. Obviously, the mean pressure in an artery is somewhere between the systolic (maximal) and diastolic (minimal) pressure levels. However, because the pressure waveforms in arteries are not symmetric, the mean pressure is generally not exactly midway between the systolic and diastolic pressures.

A popular approximation is that mean pressure is about one third of the way up from diastolic toward systolic pressure; that is:

$$\text{Mean arterial pressure} \cong \text{Diastolic pressure} + \tfrac{1}{3}\,\text{Pulse pressure}$$

Figure 22-7 reveals that this is *not* a valid approximation for the determination of mean pressure in the aorta. However, the approximation is a good one for pressures measured in the femoral artery or in most other major arteries distal to the aorta. The reason that the rule applies in the distal arteries but not in the aorta is that the waveform of the arterial pressure pulsations changes as the pulses move away from the heart. The pressure pulses become narrower and more sharply peaked. This pronounced asymmetry of the pressure pulses causes the mean level in distal arteries to be closer to the diastolic pressure than to the systolic pressure (see Figure 22-7).

For complex reasons, the pulse pressure typically *increases* as blood flows from the aorta into the distal arteries. However, the mean pressure necessarily *decreases* in accordance with the principle of the conservation of energy. As stated earlier, mean arterial pressure is a measure of the potential energy in the bloodstream, and this potential energy is used up (converted into heat by friction) as blood flows from the aorta through the systemic circulation. The aorta and large arteries offer only a small resistance to blood flow; mean arterial pressure decreases only 1 to 3 mm Hg between the aorta and the femoral artery (see Figure 22-7). Most of the resistance to blood flow is found in the arterioles and capillaries. Therefore the largest decrements in *mean pressure* occur in these segments of the systemic circulation (see Figure 22-1).

An important point to remember is that mean aortic pressure (not systolic, diastolic, or pulse pressure) must be used when calculating total peripheral resistance as:

$$\text{Total peripheral resistance} = \frac{(\text{Mean aortic pressure} - \text{Mean vena caval pressure})}{\text{Cardiac output}}$$

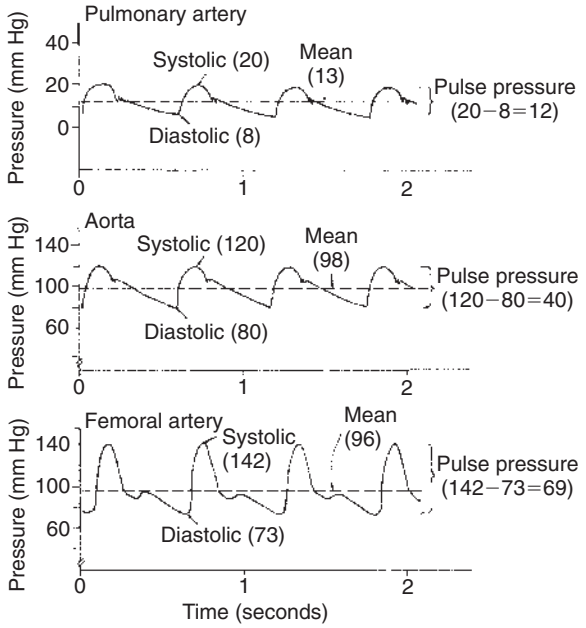


FIGURE 22-7 Blood pressure in the large arteries is pulsatile. The pressure patterns typical of the pulmonary artery, aorta, and femoral artery of the dog are shown.

Likewise, mean pulmonary artery pressure (not systolic, diastolic, or pulse pressure) must be used when calculating pulmonary vascular resistance as:

$$\text{Pulmonary vascular resistance} = \frac{\text{(Mean pulmonary arterial pressure} - \text{Mean pulmonary vein pressure)}}{\text{Cardiac output}}$$

Unfortunately, the only way to measure a mean vascular pressure is by inserting a needle or catheter into the vessel of interest. The first direct measurement of mean arterial blood pressure was carried out by Stephen Hales, an English clergyman. In about 1730, Hales inserted a tube (catheter) into the femoral artery of a conscious horse and found that blood rose in the tube to a height of more than 8 feet. An 8-foot column of blood represents a pressure of more than 180 mm Hg, almost twice the mean arterial pressure expected in a normal resting animal. The high pressure undoubtedly reflected the physical and emotional distress of the horse, which was restrained upside down during the episode. In the present day, arterial catheterization (with anesthetic agents to reduce pain) is routine in human medicine (e.g., in cardiac catheterization laboratories) and is becoming more common in veterinary medicine. However, the lesson that physical or emotional distress can dramatically increase blood pressure is as relevant today as it was in Hales' time.

In human medicine, systolic and diastolic arterial pressures can be measured quite accurately with a blood pressure cuff and stethoscope. Mean arterial pressure can then be approximated using the equation given earlier. Blood pressure cuffs are less frequently used on veterinary species, but the pulse is often palpated by placing the fingertips over a major artery, such as the femoral artery. Palpation of an artery allows the clinician to sense the pulse pressure on the basis of the magnitude of the pulsations felt in the artery. A low pulse pressure is referred to as a *thready,* or weak, pulse. A high pulse pressure may be called a *bounding,* or strong, pulse.

Pulse Pressure Increases When the Stroke Volume Increases, Heart Rate Decreases, Aortic Compliance Decreases, or Total Peripheral Resistance Increases

Because the arterial pulse is so frequently palpated in patients, it is important for the veterinary clinician to understand the factors that typically influence pulse pressure. First, an increase in stroke volume tends to increase pulse pressure. Because cardiac ejections create the arterial pulsations in the first place, it is not surprising that larger ejections create larger pulsations. Figure 22-8, *A,* depicts this effect and shows that an increase in stroke volume also increases mean arterial pressure. Mean pressure increases because an increased stroke volume increases cardiac output.

A second factor that tends to increase pulse pressure is a decrease in heart rate. Between cardiac ejections, aortic pressure decreases as blood continues to run out of the aorta and through the systemic circulation. Aortic pressure falls to a minimal (diastolic) level before being boosted again by the next cardiac ejection. When heart rate decreases, there is a longer time between ejections and therefore a longer time for blood to run out of the aorta and into the systemic circulation. The blood pressure in the aorta falls to a lower level before the next cardiac ejection, and pulse pressure is increased (Figure 22-8, *B*). A decrease in heart rate results in a decrease in cardiac output, so a decrease in heart rate decreases the mean arterial pressure (Figure 22-8, *B*).

Figure 22-8, *C,* shows the effect of a simultaneous increase in stroke volume and decrease in heart rate. In this example, cardiac output, which is stroke volume multiplied by heart rate, remains unchanged. Therefore, mean arterial pressure remains unchanged. However, pulse pressure is greatly increased as a result of the combined effects of an increase in stroke volume and a decrease in heart rate. Aerobic conditioning in humans, and in some animals, leads to increased stroke volume and decreased heart rate at rest. Therefore, in a well-trained athlete at rest, mean arterial pressure is typically normal, but pulse pressure is greater than normal. Palpation of the arteries of an athlete at rest reveals a strong, slow pulse.

A decrease in arterial compliance (stiffening of the arteries) is a third factor that tends to increase pulse pressure (see Figure 22-8, *D*). With each ventricular systole, the heart ejects blood into the aorta and large arteries, which distends these vessels. If these vessels become stiff, a greater increase in pressure is required to distend them. Arterial stiffening also decreases diastolic arterial pressure. This effect is more difficult to grasp intuitively but should not be surprising. Just as aortic pressure rises to higher-than-normal systolic levels when the heart ejects blood into a stiff aorta, so does aortic pressure fall to lower-than-normal diastolic levels when blood runs out of the stiff aorta between cardiac ejections. The higher systolic pressure and lower diastolic pressure are simply two direct consequences of the same phenomenon: decreased arterial compliance. The major arteries tend to become stiffer as a result of the normal aging process, which accounts for the increase in pulse pressure that is typical in older humans and some animals.

In general, cardiac output is not affected by arterial stiffening. A healthy ventricle is able to generate the higher systolic pressures needed to eject blood into a stiff arterial system, although ventricular hypertrophy is sometimes triggered. Moreover, arterial stiffening generally has very little effect on TPR because the arterioles remain normal. The arteries, although stiff, retain their large diameters, and therefore arterial resistance remains low. *Mean* arterial pressure, the product of cardiac output and TPR, is therefore generally unchanged by arterial stiffening.

Arteriolar vasoconstriction is a fourth factor that typically increases pulse pressure (Figure 22-8, *E*). In actuality, vasoconstriction does not affect pulse pressure directly but acts through a stiffening of the arteries. Vasoconstriction increases TPR, which causes blood to back up or accumulate in the large arteries. As the arteries become more distended, arterial pressure increases. Distention forces the arteries toward their elastic limit, so they also become stiffer than arteries under normal pressurization (Figure 22-9). This stiffening of the arteries causes pulse pressure to increase, for the reasons already explained. Moreover, because TPR is elevated, mean arterial pressure also increases.

Many human patients develop both stiffening of arteries (as a consequence of aging) and essential hypertension (caused by increased TPR). This combination produces dramatic increases in pulse pressure. As illustrated in Figure 22-8, *F,* an older person with severe hypertension might have a pulse pressure of 110 mm Hg (200 mm Hg systolic minus 90 mm Hg diastolic). Arterial hypertension and arterial stiffening both are less common in veterinary species.

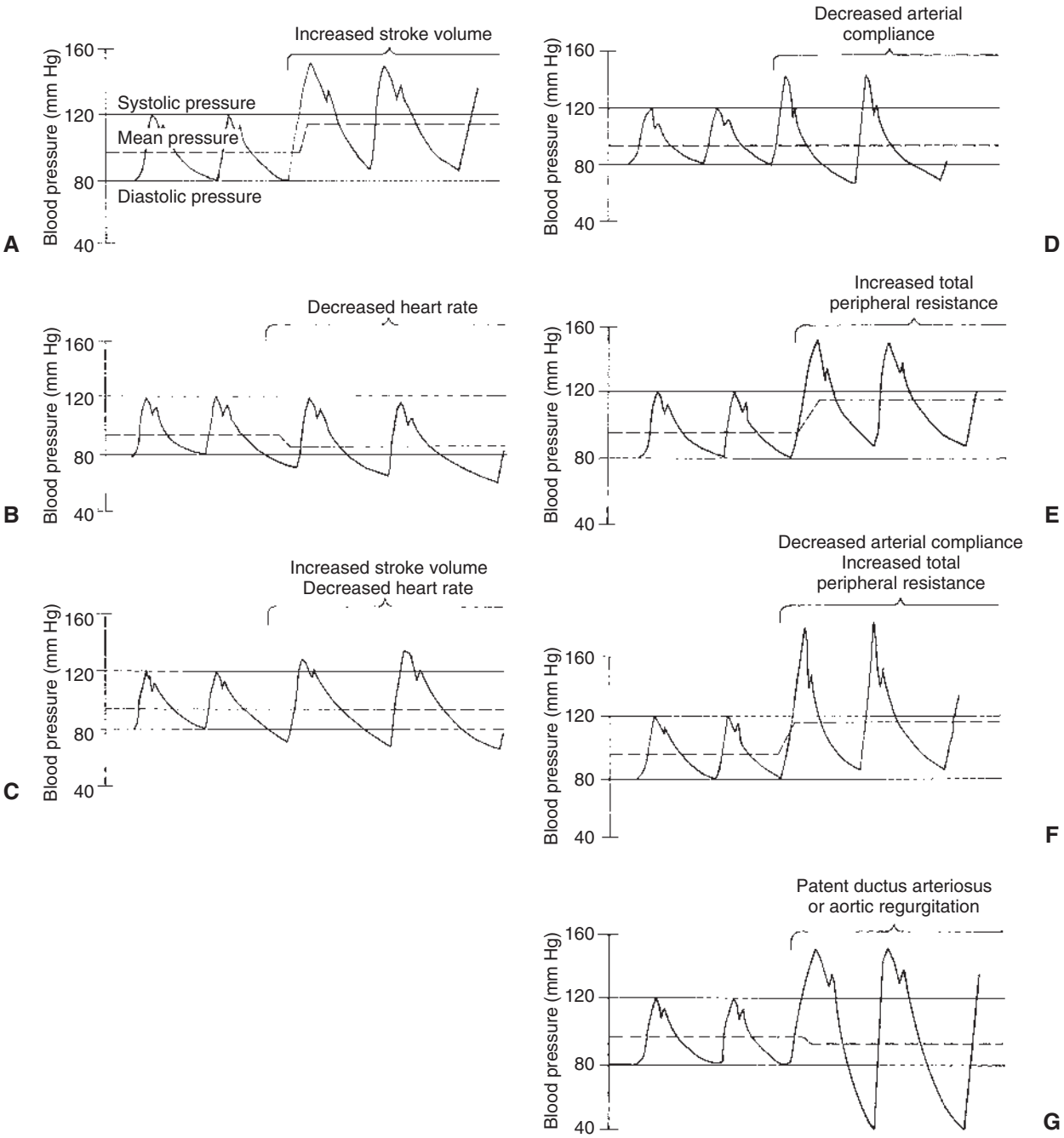


FIGURE 22-8 Various conditions that increase arterial pulse pressure are compared with regard to their effects on systolic pressure, diastolic pressure, and mean pressure (see text).

In summary, pulse pressure tends to be increased by increased stroke volume, decreased heart rate, decreased arterial compliance, or vasoconstriction.

Some of the cardiac defects that produce murmurs also cause characteristic changes in pulse pressure. For example, a patient with patent ductus arteriosus has a large left ventricular stroke volume, which elevates aortic systolic pressure. Aortic diastolic pressure is much lower than normal because, between cardiac ejections, blood runs out of the aorta by two pathways: into the systemic circuit and through the open ductus. Pulse pressure is dramatically increased (Figure 22-8, *G*). Aortic regurgitation causes a similar, characteristic increase in pulse pressure. During diastole, blood leaves the aorta through two pathways: forward into the systemic circuit and backward (through the incompetent valve) into the left ventricle. Stroke volume is elevated because, with each systole, the left ventricle ejects both the blood that has returned to it through the normal pathway and also the regurgitant blood.

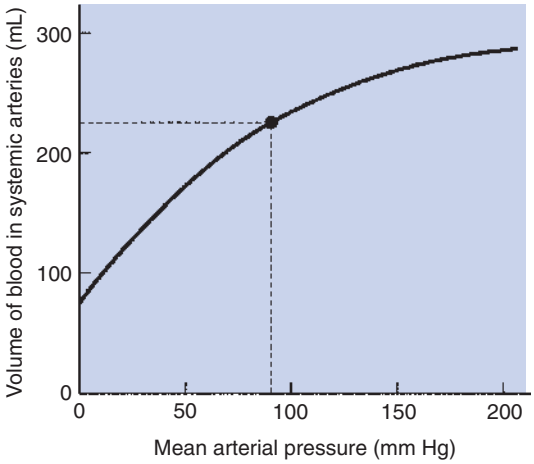


FIGURE 22-9 This volume-pressure graph shows that normal systemic arteries become stiffer (less compliant) when mean arterial pressure increases above its normal value *(dot).* (Recall that compliance is equal to the slope of a volume-pressure curve.)

CLINICAL CORRELATIONS

CANINE HEARTWORM DISEASE WITH PULMONARY EMBOLISM

History. You examine a 6-year-old male beagle that has been a hunting companion of his owner for several years. The owner reports that the dog tires more easily than usual and has developed a cough that is worse during exercise. You treated this dog for a laceration when he was 3 years old, and your records indicate that the dog was otherwise in excellent health at that time. The owner acknowledges that the dog has not been given any immunizations or heartworm prophylactic medication for the past 2 years.

Clinical Examination. On physical examination of the dog, you notice the cough reported by the owner and an apparent, modest accumulation of fluid in the abdominal cavity *(ascites).* You also auscultate a systolic murmur that is loudest over the left third and fourth intercostal spaces. The chest radiograph and electrocardiogram show evidence of right ventricular enlargement. In addition, the pulmonary vessels are more prominent than normal on the radiograph and are tortuous (twisted). You suspect canine heartworm disease. You obtain a blood sample, some of which you submit for an enzyme-linked immunosorbent assay (ELISA) to test for heartworm antigen. Additionally, you use a pipette to apply a sample of the buffy coat (from the centrifuge tube) onto a glass slide for microscopic examination. You see microfilaria of the type shed by adult canine heartworms *(Dirofilaria immitis),* and the ELISA is positive for the presence of *D. immitis* antigen. You diagnose canine heartworm parasitism.

Comment. Mosquitoes transfer the microfilaria from the bloodstream of an infected dog to the bloodstream of a noninfected dog. The microfilaria develop into adult worms, which grow to a length of 10 to 20 cm while clinging to the walls of the pulmonary artery and its major branches. Heartworm infestation typically causes pulmonary arterial vessels to become enlarged and tortuous. In heavily infested dogs, adult worms also reside in the right ventricle and right ventricular outflow tract, where they cause pulmonic stenosis. The resulting turbulence during right ventricular ejection accounts for the murmur heard in this dog. The pulmonic stenosis and the increased pulmonary resistance created by the worms also lead to right ventricular hypertrophy, exercise intolerance, and ascites (review the Clinical Correlation on pulmonic stenosis in Chapter 21 for an explanation of why these complications develop). An additional problem is that the adult worms release vasoactive substances into the circulation, which disrupt some of the normal mechanisms that adjust arteriolar diameter, control blood flow, and regulate arterial pressure. Heavily infested dogs become very ill.

Treatment. You advise the owner that the dog should be treated with an arsenic-containing medication that kills adult worms over several days. You also warn the owner that the treatment of severely infested dogs is risky. Dead adult worms break away from the right ventricle and pulmonary artery and lodge in smaller pulmonary vessels. These vascular occlusions *(pulmonary emboli)* restrict pulmonary blood flow and reduce cardiac output. Therefore, it is necessary to keep the dog in a quiet, unstressed state for 8 to 10 days after beginning treatment. In addition to restricting pulmonary blood flow, the emboli are likely to cause inflammation and blood clots in the lungs. Pulmonary edema is expected. Pulmonary blood vessels may break down, allowing blood to enter the airways of the lungs. Respiratory failure is possible. Anti-inflammatory drugs are sometimes administered to reduce these complications.

With the owner's consent, you keep the dog at your clinic for 2 days (to allow him to become accustomed to the surroundings) and then begin treatment. During the next week, the dog becomes even more lethargic than before and begins to cough up blood. The dog has a low-grade fever (102°-103° F), and his ascites becomes worse. However, his systolic murmur begins to fade. After 1 week, all the clinical signs have greatly improved. The dog is sent home for a prolonged period of recuperation. The long-term prognosis is good.

DUMMY FOAL: HYPOXEMIC ISCHEMIC ENCEPHALOPATHY

History. A 14-year-old Thoroughbred mare is presented for *dystocia* (difficult birth). The foal (a filly) was pulled with some difficulty. The filly was slow to stand and did not nurse voluntarily for several hours. The mare was *stripped* (milked) of colostrum, which was fed to the foal by nasogastric tube.

Clinical Examination. The foal has a slightly low temperature and increased pulse and respiratory rates. The mucous membranes are tacky to the touch (dehydrated) and dark pink in color (indicating poor perfusion and/or poor oxygenation). Capillary refill time is prolonged (consistent with poor perfusion). The foal has a marked murmur similar to that heard with a patent *ductus arteriosus.* Peripheral pulses are decreased (weak), and distal extremities are cool. Gastrointestinal motility is decreased. The foal appears mature physically, but she is acting dysmature when she attempts to stand, nurse, or lie down. Blood studies reveal that the foal is not septic, but she is hypoxemic, has evidence of poor kidney function, and is acidotic.

Comment. *Hypoxemic ischemic encephalopathy* (HIE) occurs when a foal receives decreased oxygen for some time. This can occur before, during, or after foaling. With a dystocia, after the water breaks and while the foal is being pulled, the oxygen supply to the foal is decreased. The foal must rely on anaerobic metabolism during the period of low oxygen, which results in acidosis.

Decreased oxygen also causes pulmonary blood vessels to constrict (*hypoxic pulmonary vasoconstriction,* discussed further in Chapter 46). The resulting increase in pulmonary vascular resistance causes blood to back up or accumulate in the pulmonary artery, right ventricle, and right atrium, and this increases the pressure in these chambers. If pressures in the right side of the heart exceed those in the left side, blood flow persists (from right to left) through the foramen ovale. (When a normal foal begins to breathe, pressures in the right side fall below those in the left side of the heart, so the foramen ovale closes.) The blood that flows through the foramen ovale in this foal reaches the aorta without passing through the lungs, and therefore without being oxygenated at all *(right-to-left shunt).*

Treatment. The foal needs oxygen to reverse the hypoxic pulmonary vasoconstriction and the consequent high pressure in the right heart, persistent flow through the foamen ovale, and hypoxemia. Supplemental oxygen can be provided by *nasal insufflation* (tube placed in nasal cavity for delivery of oxygen). Additionally, the foal will be given drugs, such as dopamine, to increase cardiac contractility, cardiac output, and blood pressure. This treatment, in addition to intravenous fluids, will likely improve blood flow to the vital organs, including the brain and kidneys. Improved respiratory and renal function will reverse the acidosis. Foals with HIE often develop other complications, which need to be addressed as they arise.

PRACTICE QUESTIONS

1. Which of the following is a correct comparison between segments of the systemic circulation?
   a. The aorta and large arteries have a higher compliance than the veins.
   b. The aorta and large arteries have a higher resistance to blood flow than the capillaries.
   c. The veins have a higher resistance to blood flow than the capillaries.
   d. The arterioles have a higher resistance to blood flow than the capillaries.
   e. If the heart is stopped, the pressure in the veins will become higher than the pressure in the aorta and large arteries.

2. If aortic compliance decreases while heart rate, cardiac output, and total peripheral resistance (TPR) remain unchanged:
   a. Pulse pressure will be unchanged.
   b. Pulse pressure will increase.
   c. Pulse pressure will decrease.
   d. One cannot know the effect on pulse pressure because stroke volume may have changed.
   e. One cannot know the effect on pulse pressure because mean aortic pressure may have changed.

3. Which of the following would cause mean aortic pressure to *increase*?
   a. Stroke volume increases from 30 to 40 mL, and heart rate decreases from 100 to 60 beats/min.
   b. Arterial compliance decreases.
   c. Cardiac output decreases.
   d. Arterioles throughout the body dilate.
   e. TPR increases.

4. The following measurements are made on a dog: heart rate, 80 beats/min; stroke volume, 30 mL; mean aortic pressure, 96 mm Hg; mean pulmonary artery pressure, 30 mm Hg; left atrial pressure, 5 mm Hg; and right atrial pressure, 12 mm Hg. The TPR of this dog (taking into account both arterial and atrial pressures) is exactly:
   a. 10.42 mm Hg/L/min
   b. 12.50 mm Hg/L/min
   c. 35.00 mm Hg/L/min
   d. 37.92 mm Hg/L/min
   e. 40.00 mm Hg/L/min

5. Which of the following would cause the largest *decrease* in coronary blood flow?
   a. Coronary arterioles constrict to half their normal diameter.
   b. Coronary arteries develop atherosclerosis, and lipid plaques plug up half their normal cross-sectional area.
   c. Mean aortic pressure decreases to half its normal level.
   d. The resistance to coronary blood flow doubles.
   e. The resistance to coronary blood flow decreases to ¼ its normal value.

6. A change from breathing normal air (21% O_2) to breathing a gas mixture with only 10% O_2 would cause pulmonary blood vessels to _____ and pulmonary vascular resistance to _____.
   a. Constrict; increase
   b. Constrict; decrease
   c. Dilate; increase
   d. Dilate; decrease
   e. Remain unchanged; remain unchanged

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CHAPTER 23
Capillaries and Fluid Exchange

KEY POINTS

1. Capillaries, the smallest blood vessels, are the sites for the exchange of water and solutes between the bloodstream and the interstitial fluid.
2. Lipid-soluble substances diffuse readily through capillary walls, whereas lipid-insoluble substances must pass through capillary pores.
3. Fick's law of diffusion is a simple mathematical accounting of the physical factors that affect the rate of diffusion.
4. Water moves across capillary walls both by diffusion (osmosis) and by bulk flow.
5. The Starling equation quantifies the interaction of oncotic and hydrostatic forces acting on water.
6. Several common physiological changes alter the normal balance of Starling forces and increase the filtration of water out of capillaries.
7. Edema is a clinically noticeable excess of interstitial fluid.

Capillaries, the Smallest Blood Vessels, Are the Sites for the Exchange of Water and Solutes Between the Bloodstream and the Interstitial Fluid

Because of their small size, the capillaries are sometimes called the *microcirculation.* They are also called the *exchange vessels,* because the exchange of water and solutes between the bloodstream and the interstitial fluid takes place across the walls of the capillaries. Each type of blood vessel in the body is structurally suited for its primary function, and the walls of the capillaries are especially well adapted for their exchange function.

Figure 23-1 shows the contrasting features of the walls of the various types of blood vessels in the systemic circulation. The distinguishing feature of the walls of the aorta and large arteries is the presence of a large amount of elastic material along with smooth muscle. These vessels are called the *elastic vessels;* elasticity is necessary because the aorta and large arteries must distend with each pulsatile ejection of blood from the heart. The arterial walls are also strong and quite stiff (low compliance). There is no contradiction in saying that the arteries are elastic and have low compliance. *Elasticity* denotes distensibility and an ability to return to the original shape after the distending force or pressure is removed. *Compliance* is a measure of how much force or pressure is required to achieve distention. The arteries are elastic, but a high pressure (systolic pressure) is required to distend them.

Small arteries, and particularly arterioles, have relatively thick walls with less elastic tissue and a predominance of smooth muscle, so they are called the *muscular vessels.* Contraction and relaxation of the smooth muscle enables these vessels to constrict or dilate, which varies their resistance to blood flow. The muscular vessels vary the total peripheral resistance and direct blood flow toward or away from particular organs or particular regions within an organ.

Capillaries are the smallest vessels, being about 8 μm in diameter and about 0.5 mm long. Capillaries are so small that red blood cells (7.5 μm in diameter) must squeeze through in single file. Capillary walls consist of a single layer of endothelial cells. The small diameter of the capillaries and the thinness of their walls facilitate the exchange of water and solutes between the blood within capillaries and the interstitial fluid immediately outside the capillaries.

Venules and veins are larger than capillaries, and they have thicker walls. Venules and veins have both elastic tissue and smooth muscle in their walls. However, the walls of veins are not as thick or as muscular as the walls of arteries or arterioles. The primary role of veins is to serve as *reservoir vessels.* Veins are very compliant, and many veins in the body are normally in a state of partial collapse. Therefore, veins can accommodate substantial changes in blood volume without much change in venous pressure.

Capillaries form a network (see Figure 18-4). In most tissues the capillary network is so dense that each cell of the tissue is within 100 μm of a capillary. However, not all the capillaries of a tissue carry blood at all times. In most tissues the arterioles alternate between constriction and dilation, so blood flow is periodically reduced or even stopped in most capillaries. Also, in some tissues (e.g., intestinal circulation), tiny cuffs of smooth muscle encircle capillaries at the points where they branch off from arterioles. Contraction of these *precapillary sphincters* can reduce or stop the flow of blood in individual capillaries. When the metabolic rate of a tissue increases (and therefore its need for blood flow increases), the arterioles and precapillary sphincters still constrict periodically, but they spend more time in the dilated (relaxed) state. This increases the fraction of capillaries in which blood is flowing at any one time. At maximal metabolic rate (e.g., maximal exercise in a skeletal muscle), blood flows through all the capillaries all the time. Sending blood flow to all the capillaries not only increases the total blood flow through a tissue but also minimizes the distance between each cell of the tissue and the nearest capillary carrying blood by bulk flow. Both these effects speed up diffusional exchange between the capillary blood and the tissue cells.

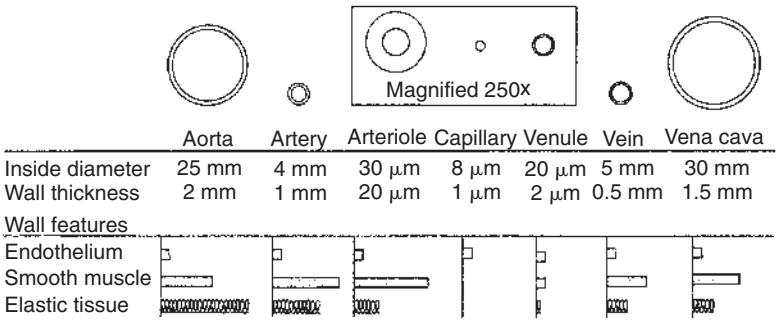

FIGURE 23-1 Each type of blood vessel in the systemic circulation is specifically suited to its particular function by its size, wall thickness, and wall composition. In this drawing, each type of vessel is shown in cross section. The drawings are to scale (note that the arteriole, capillary, and venule are magnified 250 times to make them visible). Also shown are the relative proportions of the three most important types of tissue found in blood vessel walls.

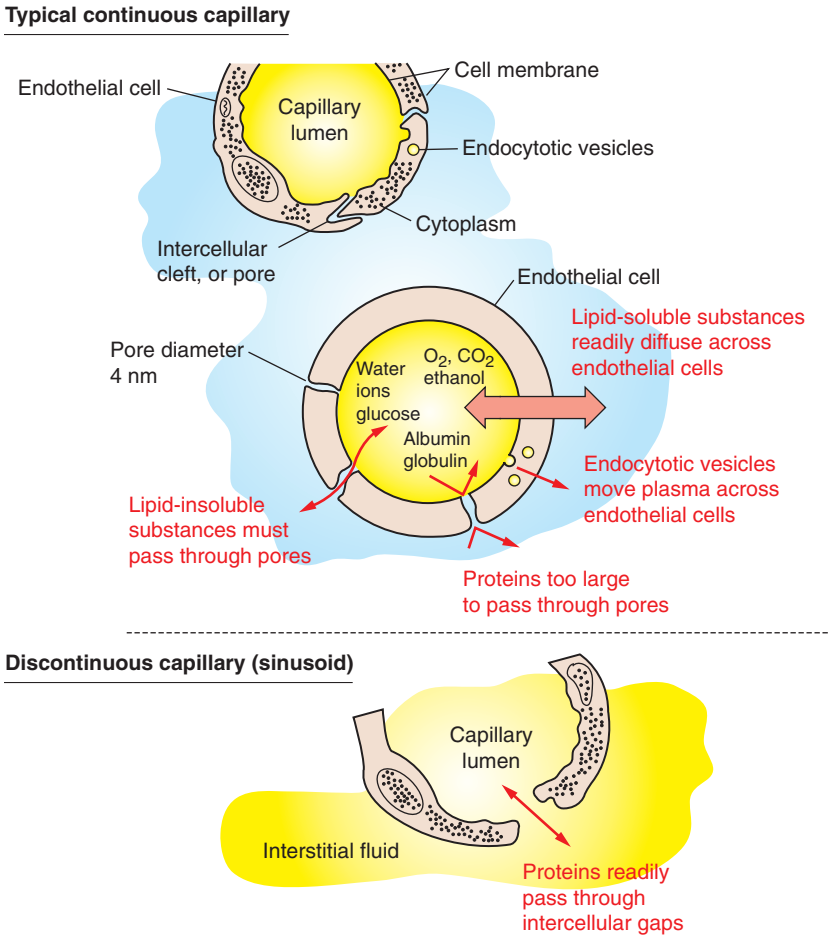

FIGURE 23-2 Capillaries in cross section. Typical continuous capillaries have small clefts, or pores, between endothelial cells *(top).* Water and small, lipid-insoluble solutes move between the capillary plasma *(yellow)* and the interstitial fluid *(blue)* through these pores *(center).* Plasma protein molecules are too large to pass through the pores. However, plasma proteins, along with other plasma constituents, are taken into endocytotic vesicles, which can deliver their contents into the interstitial fluid via exocytosis, although this is a relatively slow process. In contrast, lipid-soluble substances can diffuse directly, and very quickly, through the capillary endothelial cells. The size of the clefts between endothelial cells varies greatly from tissue to tissue, with the smallest being in brain capillaries and the largest being in the discontinuous capillaries, or sinusoids, such as those in the liver *(bottom).*

Lipid-Soluble Substances Diffuse Readily Through Capillary Walls, Whereas Lipid-Insoluble Substances Must Pass Through Capillary Pores

The rate of diffusional exchange between capillary blood and the surrounding interstitial fluid depends both on the properties of the substances being exchanged and on the features of the capillary wall. Small, lipid-soluble substances (e.g., dissolved oxygen and carbon dioxide, fatty acids, ethanol, and some hormones) readily dissolve in the cell membranes of the endothelial cells that form the capillary walls. Such lipid-soluble substances can diffuse very rapidly through the endothelial cells from blood to interstitial fluid, or vice-versa. In contrast, lipid-insoluble substances (e.g., ions, glucose, and amino acids) do not dissolve in cell membranes and so cannot diffuse through the endothelial cells. Instead, such substances must pass through the *pores*, or *clefts,* that exist between the endothelial cells (Figure 23-2). These pores create tiny, water-filled channels between the capillary blood and the interstitial fluid. The diffusional movement of lipid-insoluble substances across capillary walls is much slower than the movement of lipid-soluble substances, because the lipid-insoluble substances are restricted to passage through the capillary pores, which constitute only about 1% of the total wall surface area of a typical capillary.

The capillaries in most tissues are called *continuous capillaries* because the endothelial cells form a continuous tube, except for the tiny, water-filled pores between the endothelial cells. In typical continuous capillaries, the diameter of the pores is about 4 nm, which is large enough to permit the passage of water and of all

the small solutes in plasma and interstitial fluid. The plasma protein molecules, however, are a little too large to pass through pores of this size. Blood cells, of course, are far too large to pass through such small openings (see Figure 18-7).

The main route for the delivery of plasma proteins into the interstitial fluid is through the three-step process of *transcytosis.* The first step is *pinocytosis* (a form of *endocytosis*), which involves the invagination of the capillary endothelial cell membrane to form an intracellular vesicle that contains plasma, including plasma proteins (see Figure 23-2). Second, some of these vesicles cross the capillary endothelial cell from the side facing the bloodstream to the side facing the interstitial fluid. In the third step, these vesicles fuse with the membrane of the endothelial cell on the interstitial fluid side; the vesicles discharge their contents into the interstitial space. This third step is called *exocytosis.* The delivery of plasma constituents into the interstitial fluid by transcytosis is extremely slow, compared with the diffusion of lipid-soluble substances through endothelial cells, or the passage of small, lipid-insoluble substances through capillary pores.

The size of the capillary pores, or clefts, varies from tissue to tissue. Two extremes are found in the brain and the liver. In brain capillaries, the junctions between adjacent endothelial cells are so tight that only water and small ions (e.g., Na^+ and Cl^-) can pass through them; not even glucose or amino acid molecules can pass through these tiny pores. Yet brain neurons require glucose to carry out their normal metabolism. Glucose is moved across the brain capillary endothelial cells by means of specialized protein carrier molecules that are embedded in the cell membranes of the endothelial cells. The energy to drive this *facilitated diffusion* comes from the glucose concentration difference between the blood and the brain interstitial fluid. The tight junctions between endothelial cells in brain capillaries create a barrier between the bloodstream and the brain tissue that is called the *blood-brain barrier* (also discussed in Chapter 15). One function of the blood-brain barrier is to protect brain neurons from exposure to toxic substances that may be in the blood.

In the liver, the clefts between capillary endothelial cells are so large that these vessels are called *discontinuous capillaries* (or *sinusoids*). Even plasma proteins such as albumin and globulin can readily pass through these large clefts, which typically exceed 100 nm in width (see Figure 23-2, *bottom*). Large gaps between endothelial cells are an appropriate feature for capillaries in the liver because the plasma proteins are produced by liver cells *(hepatocytes).* The large gaps between endothelial cells permit the newly synthesized protein molecules to enter the bloodstream. The large gaps are also appropriate for the role of the liver in detoxification. Some toxins become bound to plasma proteins in the bloodstream, and then are removed from the blood by the liver and chemically changed into less toxic substances. Discontinuous (sinusoidal) capillaries are also found in the spleen and bone marrow.

Fenestrated capillaries ("capillaries with windows") present an additional variation on capillary pores. Fenestrae are holes or perforations through (not between) endothelial cells. Fenestrae are typically 50 to 80 nm in diameter, which is larger than the intercellular clefts of typical continuous capillaries but smaller than the clefts of discontinuous capillaries. Very fine diaphragms span most fenestrae, but these diaphragms do not prevent the passage of either lipid-soluble or lipid-insoluble substances. Fenestrae may be formed when endocytotic and exocytotic vesicles line up and merge, thus creating a temporary water-filled channel through an endothelial cell. Fenestrated capillaries are characteristically found in places where large amounts of fluid and solutes must pass into or out of capillaries (e.g., gastrointestinal tract, endocrine glands, kidneys).

Fick's Law of Diffusion Is a Simple Mathematical Accounting of the Physical Factors That Affect the Rate of Diffusion

Most of the factors that affect the rate of diffusional exchange between capillary blood and interstitial fluid have been mentioned. These factors include the distance involved, the size of the capillary pores (or fenestrae, when present), and the properties of the diffusing substance (i.e., lipid-soluble vs. lipid insoluble). The German physiologist Adolph Fick incorporated all these factors into an equation: *Fick's law of diffusion.* Figure 23-3 shows how Fick's law applies to the diffusional exchange between capillary fluid and interstitial fluid. The rate of diffusion of any substance (S) depends, first, on the *concentration difference,* that is, the difference between the concentration of the substance in capillary fluid and its concentration in interstitial fluid. Diffusion is driven by this concentration difference, and diffusion always proceeds

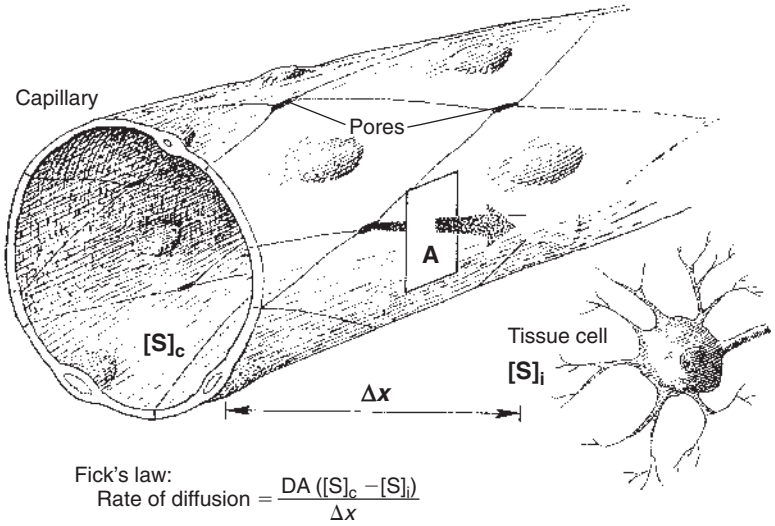

FIGURE 23-3 According to Fick's law, the four factors that affect the rate of diffusion of a particular substance *S* from the capillary plasma to the interstitial fluid next to a tissue cell are $[S]_c - [S]_i$, the concentration difference between the capillary plasma and interstitial fluid; *A*, area available for diffusion; Δx, distance involved; and *D*, diffusion coefficient for the substance.

from the area of higher concentration toward the area of lower concentration. Next, the rate of diffusion is determined by the *area available for diffusion,* the term *A* in the equation. For lipid-soluble substances, this area is equivalent to the total surface area of the capillaries. For lipid-insoluble substances, this area is much smaller, being equal to the area of the pores (or clefts) between capillary endothelial cells (plus the area of fenestrae, when present).

The term Δx in the equation represents the *distance* over which diffusion must occur. Functionally, Δx equals the distance from a tissue cell to the nearest capillary that is carrying blood by bulk flow (see Figure 23-3). The greater the distance from the tissue cells to the capillaries, the slower is the rate of diffusional exchange of substances between that cell and the capillary blood; therefore, Δx appears in the denominator in the equation.

The term *D* in the equation is a *diffusion coefficient.* The value of *D* increases with temperature because diffusion depends on the random (Brownian) motion of particles in solution, and the velocity of Brownian motion increases with temperature. *D* also depends on the molecular weight of the diffusing substance and on its solubility. For example, *D* for carbon dioxide is about 20 times greater than *D* for oxygen. As a result, carbon dioxide diffuses much more rapidly than does oxygen for a given concentration difference, area, and diffusion distance. This difference is inconsequential under normal physiological conditions. In certain disease states, however, the area available for diffusion decreases, and the diffusion distance increases. Under these conditions, the delivery of oxygen to the metabolizing cells of a tissue generally becomes critically impaired before the removal of carbon dioxide from the cells becomes inadequate.

Several of the factors that affect the rate of diffusion are physiologically adjustable. For example, in skeletal muscle at rest, the arterioles cycle between open and closed, and even when open, their diameter is small. Consequently, at any one moment, blood flows through only about one-fourth of the skeletal muscle capillaries. Blood sits still in the remainder of them. Nevertheless, this low and "part-time" blood flow through capillaries is adequate to deliver oxygen and nutrients to the resting skeletal muscle cells and to remove the small amounts of carbon dioxide and other waste products being produced by those cells. In contrast, during exercise, the metabolic rate of the skeletal muscle cells increases several-fold, as does their need for blood flow. During exercise, skeletal muscle arterioles dilate. Increasingly more of them remain open on a "full-time" basis as the level of exercise increases. Consequently, blood flow through the capillaries increases and becomes more continuous.

These changes act in three ways to speed the delivery of oxygen and metabolic substrates to the exercising muscle cells and to facilitate the removal of carbon dioxide and other metabolic waste products. First, when more capillaries carry blood, the area available for diffusion (*A* in Fick's diffusion equation) is increased. Second, because more capillaries carry blood, the distance between each exercising skeletal muscle cell and the nearest open capillary (Δx in the diffusion equation) is decreased. Third, the driving force for diffusion of oxygen (the oxygen concentration difference between the capillary blood and the interstitial fluid) is increased. The concentration difference is increased because (1) the greater blood flow brings more freshly oxygenated blood into the capillaries, and (2) the rapid utilization of oxygen by the exercising skeletal muscle cells decreases the concentration of oxygen within these cells and therefore within the surrounding interstitial fluid.

The same factors that increase the rate of oxygen diffusion during exercise also increase the rate of delivery of glucose and other nutrients. Furthermore, the same factors act to increase the rate at which carbon dioxide and other metabolic products are removed from the tissue cells and into the bloodstream. In the case of carbon dioxide and other metabolic products, the concentration is highest in the cells and lowest in the capillary plasma, so diffusional movement is from the cells toward the bloodstream.

Water Moves Across Capillary Walls Both by Diffusion (Osmosis) and by Bulk Flow

The exchange of water between the capillary plasma and the interstitial fluid merits special consideration for two reasons. First, the forces that govern water movement are more complicated than the simple diffusive forces that affect solute movement. Second, a particular imbalance in these forces causes an excessive amount of water to accumulate in the interstitial space, which leads to the important clinical sign, *edema.*

As the preceding discussion emphasized, solutes such as oxygen, carbon dioxide, glucose, electrolytes, and fatty acids move between the capillary plasma and the interstitial fluid by diffusion. Water also moves by diffusion; the diffusional movement of water is called *osmosis.* The physical prerequisites for osmosis are (1) the presence of a *semipermeable membrane* (a membrane that is permeable to water but not to specific solutes), and (2) a difference in the total concentration of the *impermeable solutes* on the two sides of the membrane.

The capillary wall constitutes a semipermeable membrane. Water can readily pass through capillary pores; however, the pores in continuous capillaries are too small to permit the passage of plasma proteins. As a consequence, the concentration of plasma proteins is normally much higher in the capillary plasma than in the interstitial fluid. Protein concentration is typically 7 grams per deciliter (g/dL) within the capillary plasma but only 0.2 g/dL in the interstitial fluid. These dissimilar protein concentrations create an osmotic imbalance. As a consequence, water molecules tend to move by osmosis from the interstitial fluid into the capillary blood plasma. (Remember that water moves by osmosis toward the side of the semi-permeable membrane with the higher concentration of impermeable solute.)

The tendency for water to move by diffusion is quantified as *osmotic pressure* (see Chapter 1). The normal osmotic pressure created by the proteins in the plasma is 25 mm Hg; that is, the osmotic effect of the plasma proteins is equivalent to a pressure of 25 mm Hg driving water into the capillaries. The osmotic pressure created by the plasma proteins is also called *plasma oncotic pressure* or *colloid osmotic pressure*. (The term *colloid* is used because the plasma proteins are not in a true solution but rather in a colloidal suspension.)

The plasma proteins in the interstitial fluid also exert an osmotic effect. However, because the concentration of plasma proteins in interstitial fluid is normally quite low, the oncotic pressure created in the interstitial fluid by these proteins is normally only about 1 mm Hg. The imbalance of oncotic pressures (higher in the capillary fluid than in the interstitial fluid) creates a net driving force for the diffusion (osmotic movement) of water from the interstitial fluid into the capillaries.

The movement of water into a capillary is called *reabsorption.* The movement of water in the opposite direction, from the capillary plasma into the interstitial fluid, is called *filtration.* The

oncotic pressure difference normally favors reabsorption. Oncotic pressure difference is calculated by subtracting the oncotic pressure of interstitial fluid from the oncotic pressure of capillary blood (e.g., 25 mm Hg − 1 mm Hg = 24 mm Hg).

In addition to being affected by diffusional (osmotic) forces, water responds to hydrostatic pressure differences across the capillary wall. Hydrostatic pressure differences cause water to move by bulk flow; in this case the bulk flow occurs through the capillary pores. The hydrostatic pressure within the capillaries (capillary blood pressure) is higher at the arteriolar end of capillaries than at the venous end (see Figure 22-1). However, a representative average capillary hydrostatic pressure would be about 18 mm Hg. In contrast, interstitial fluid hydrostatic pressure is normally about −7 mm Hg. The negative sign simply means that interstitial fluid pressure is *less,* (although only slightly less) than atmospheric pressure. The negative interstitial fluid pressure (−7 mm Hg) together with the positive capillary hydrostatic pressure (18 mm Hg) creates a hydrostatic pressure difference of 25 mm Hg across the wall of a typical capillary. This hydrostatic pressure difference tends to force water out of the capillaries and into the interstitial spaces; that is, the *hydrostatic pressure difference* favors filtration.

In most capillaries of the systemic circulation, the hydrostatic pressure difference (which favors filtration) almost balances the oncotic pressure difference (which favors reabsorption). However, the balance is rarely perfect. Usually, the hydrostatic pressure difference slightly exceeds the oncotic pressure difference, so there is a small, net filtration of water out of the capillaries. This water would simply accumulate in the interstitial spaces and cause swelling there if not for the lymph vessels, which collect excess interstitial fluid and return it to the bloodstream through the subclavian veins (Figure 23-4).

Capillary hydrostatic pressure and interstitial fluid hydrostatic pressure are, by convention, always measured relative to atmospheric pressure. Thus, to say that interstitial pressure is normally "negative" does not imply that a vacuum exists in the interstitium but only that the interstitial pressure is slightly below atmospheric pressure. If all the interstitial spaces of the body had a hydrostatic pressure higher than atmospheric pressure, all parts of the body would bulge outward. The subatmospheric interstitial fluid pressure probably accounts for the fact that the skin normally stays snug against the underlying tissue and that some body surfaces normally have a concave shape (e.g., axillary space, orbits of the eyes).

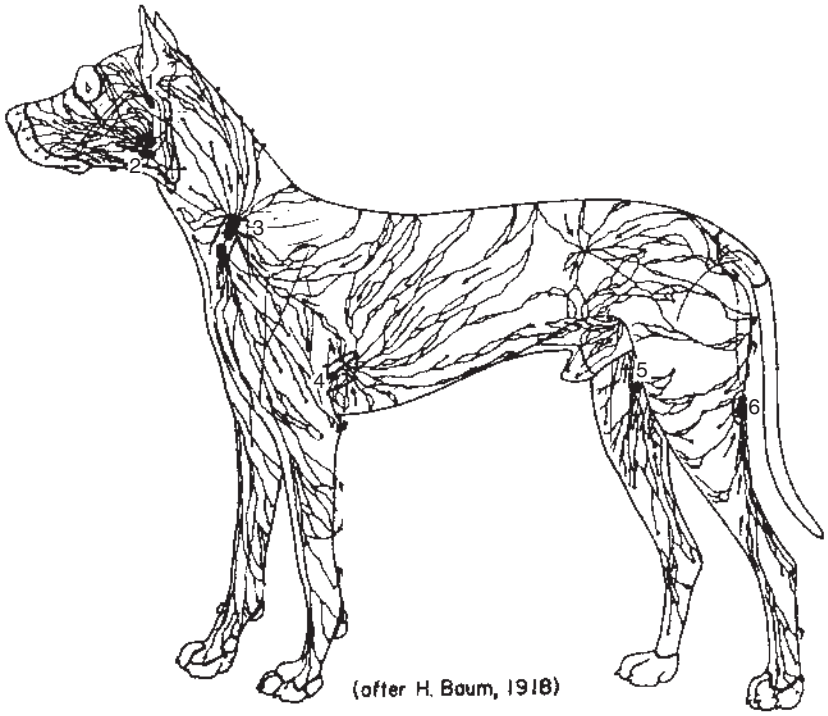

FIGURE 23-4 Anatomical **(A)** and schematic **(B)** overviews of the lymphatic system. The lymphatic vessels collect excess interstitial fluid from tissues throughout the body (including the lungs) and carry it to the subclavian veins, where the lymph reenters the bloodstream. Lymph moves through lymph vessels via bulk flow. The driving force for this flow is interstitial fluid hydrostatic pressure minus subclavian vein pressure. Lymph flow is also promoted by the massaging action exerted on lymph vessels by contraction and relaxation of skeletal muscles and (in the lungs) by the pressure variations accompanying inspiration and expiration. The lymph vessels contain one-way valves, which prevent the backflow of lymph. Thus, massaging actions propel lymph in one direction only: toward the subclavian vein. In addition, some lymph vessels have smooth muscle in their walls, and the alternating contraction and relaxation of this smooth muscle also propels lymph flow toward the subclavian veins. The *numbers* in **A** identify the major lymph nodes. The *magnified inset* in **B** depicts the typical, net filtration of fluid out of a blood capillary and into the interstitial space. This excess interstitial fluid is collected and carried away by the lymph capillaries. Three red blood cells are depicted in the blood capillary. Plasma is indicated in *yellow,* interstitial fluid and lymph in *blue.* (**A** from Getty R: *Sisson and Grossman's the anatomy of the domestic animal,* vol 2, Philadelphia, 1975, Saunders.)

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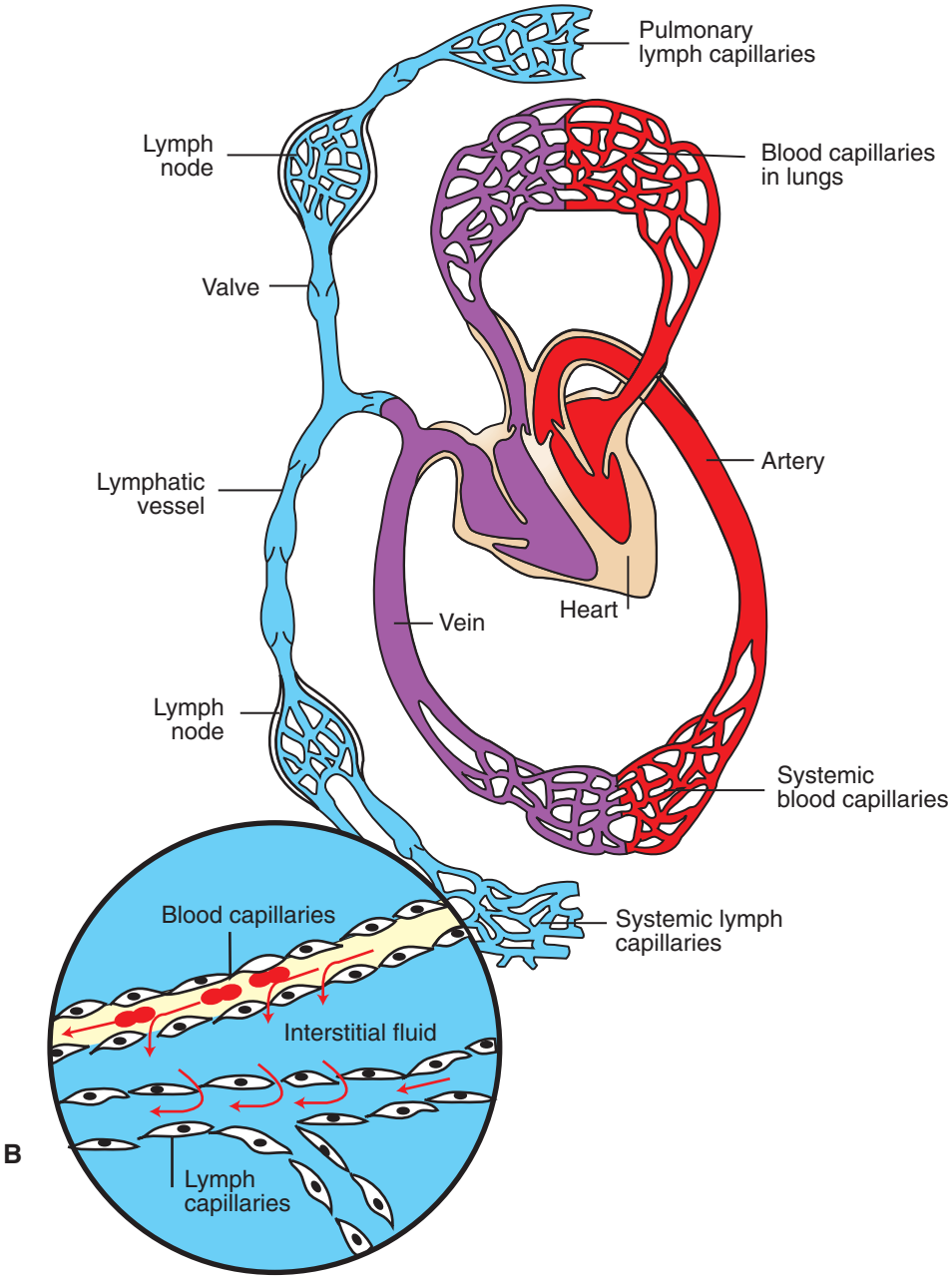

FIGURE 23-4, cont'd.

The Starling Equation Quantifies the Interaction of Oncotic and Hydrostatic Forces Acting on Water

The following equation expresses mathematically the interaction between osmotic pressures and hydrostatic pressures in determination of the net force (net pressure) acting on water:

$$\text{Net pressure} = (P_c - P_i) - (\pi_c - \pi_i)$$

Where P_c is capillary hydrostatic pressure, P_i is interstitial fluid hydrostatic pressure, π_c is capillary plasma oncotic pressure, and π_i is interstitial fluid oncotic pressure. Nominal values for these pressures in systemic tissues are as follows:

$P_c = 18$ mm Hg
$P_i = -7$ mm Hg
$\pi_c = 25$ mm Hg
$\pi_i = 1$ mm Hg

The solution of this equation, with nominal values inserted for each term, is:

$$\begin{aligned}\text{Net pressure} &= (18 \text{ mm Hg} - -7 \text{ mm Hg}) \\ &\quad - (25 \text{ mm Hg} - 1 \text{ mm Hg}) \\ &= +1 \text{ mm Hg}\end{aligned}$$

A positive net pressure favors filtration (a negative net pressure would indicate that reabsorption is favored). The small magnitude of the net pressure (1 mm Hg) indicates that the hydrostatic and osmotic forces that affect water are almost in balance (i.e., there is only a slight tendency for filtration). The quantitative analysis of how oncotic and hydrostatic pressures affect water movement across capillary walls was first derived by Ernest Henry Starling (the same scientist for whom Starling's law of the heart is named). Therefore the oncotic and hydrostatic pressures

that act on water are often called *Starling forces*. Furthermore, the tendency for the net oncotic effect to be closely balanced by the net hydrostatic effect is often referred to as the *balance of Starling forces*. Starling realized that the actual rate of water movement across capillary walls is affected both by the magnitude of the imbalance between hydrostatic and oncotic forces and by the permeability of the capillary wall to water. These ideas are expressed in the following equation, which indicates that the movement of water is equal to the permeability of the capillary wall (given as the filtration coefficient K_f) multiplied by the net difference between the hydrostatic and oncotic pressures:

$$\text{Transcapillary water flux} = K_f[(P_c - P_i) - (\pi_c - \pi_i)]$$

Examination of this equation reveals that the tendency for the filtration of water out of capillaries can be enhanced by (1) increasing the hydrostatic pressure difference between capillary blood and interstitial fluid, (2) decreasing the osmotic tendency for water to be reabsorbed, or (3) increasing the permeability of the capillary to water (i.e., increasing the filtration coefficient).

Several Common Physiological Changes Alter the Normal Balance of Starling Forces and Increase the Filtration of Water Out of Capillaries

An increase in capillary hydrostatic pressure (P_c) favors a greater filtration of water. Capillary hydrostatic pressure can be increased by an increase in arterial blood pressure or by a decrease in arteriolar resistance. An increase in arterial pressure causes more pressure to be transmitted down through the arterioles and into the capillaries. Likewise, a decrease in arteriolar resistance (e.g., a dilation of the arterioles) allows a greater portion of the arterial pressure to be transmitted into the capillaries. Capillary hydrostatic pressure can also be increased by a "backing up" (or "damming up") of venous blood. For example, an increase in central venous pressure causes blood to accumulate in the systemic capillaries and raises capillary pressure. An obstruction to venous outflow (e.g., too tight a dressing on a limb) also causes blood to back up in the capillaries of the limb, which increases capillary hydrostatic pressure.

The primary determinant of interstitial fluid hydrostatic pressure is the volume of fluid present in the interstitial space. An accumulation of interstitial fluid increases interstitial hydrostatic pressure. Removal of interstitial fluid decreases the pressure. As stated earlier, interstitial fluid hydrostatic pressure is usually slightly subatmospheric (e.g., −7 mm Hg). When interstitial fluid hydrostatic pressure rises above atmospheric pressure, the accumulation of interstitial fluid becomes clinically noticeable as a swelling, or *edema*.

The net oncotic pressure depends on the concentrations of proteins in the capillary plasma and in the interstitial fluid. The normal protein concentration in plasma is 7 g/dL, which results in a plasma oncotic pressure of 25 mm Hg. Any alteration in the concentration of proteins in the capillary plasma alters the plasma oncotic pressure.

Similarly, changes in the interstitial protein concentration alter interstitial fluid oncotic pressure. In most organs of the systemic circulation protein molecules do not readily pass through the capillary pores or clefts. As already described, the main route for the delivery of plasma proteins into the interstitial fluid is through the three-step process of *transcytosis*. An increase in the rate of vesicle formation and discharge increases the delivery of plasma proteins into the interstitial space and therefore increases interstitial fluid oncotic pressure. In addition, abnormal circumstances (e.g., tissue inflammation) can cause the capillary pores to open wide enough that plasma proteins can pass through.

Plasma proteins are removed from the interstitial space through lymph flow. The smallest lymphatic vessels *(lymphatic capillaries)* are structured much like blood capillaries. One difference is that the clefts between the endothelial cells of lymphatic capillaries are large enough to readily accommodate the passage of plasma protein molecules. Therefore, when excess interstitial fluid flows into lymph capillaries, any plasma proteins that are present in the interstitial fluid are also carried into the lymph capillaries. The lymphatic fluid, containing these plasma proteins, flows to the thorax, where the fluid reenters the bloodstream at the subclavian veins (see Figure 23-4).

The role of lymphatic flow in counteracting the accumulation of excessive interstitial fluid is especially important in the lungs. Lung capillaries are more permeable to plasma proteins than are most capillaries in the systemic circulation. As a result, the oncotic pressure of interstitial fluid in the lungs is normally rather high (nominally 18 mm Hg). Capillary hydrostatic pressure in the lungs is generally about 12 mm Hg. (This value is lower than the capillary hydrostatic pressure in systemic capillaries because pulmonary arterial pressure is so much lower than systemic arterial pressure.) Interstitial hydrostatic pressure in the lungs is generally about −4 mm Hg (the same as intrapleural pressure). Summation of these Starling forces for lung capillaries yields the following:

$$\begin{aligned}\text{Net pressure} &= (P_c - P_i) - (\pi_c - \pi_i)\\ &= (12\text{ mm Hg} - -4\text{ mm Hg})\\ &\quad - (25\text{ mm Hg} - 18\text{ mm Hg})\\ &= +9\text{ mm Hg}\end{aligned}$$

A net pressure of +9 mm Hg indicates that there is a substantial driving force for filtration of fluid out of the capillaries and into the lung interstitial spaces. The lung interstitial spaces would fill rapidly with water, and pulmonary edema would develop, were it not for the well-developed system of lymph vessels in the lungs. These vessels continuously remove interstitial fluid and prevent its excessive accumulation.

Edema Is a Clinically Noticeable Excess of Interstitial Fluid

Edema is a common clinical problem. Edema results either from excessive filtration of fluid out of capillaries or from depressed lymphatic function. One common cause is increased venous pressure. Increased venous pressure can result from the application of a too-tight dressing on the extremity of an animal. The resulting constriction of the veins impedes the outflow of venous blood from the limb. Blood backs up in the limb veins, which increases venous pressure. Blood then backs up in the capillaries and increases capillary hydrostatic pressure. As shown in Figure 23-5, the increase in capillary hydrostatic pressure leads to excessive filtration of capillary fluid into the interstitial space. When this accumulation of fluids becomes clinically noticeable, the patient is said to exhibit edema.

Other causes of increased venous pressure are severe pulmonic stenosis (see Clinical Correlation for Chapter 21) and severe heartworm disease (see Clinical Correlation for Chapter 22). In these conditions, an excessive volume of blood accumulates in the right atrium and systemic veins. The resulting increase in venous pressure causes blood to back up in the systemic

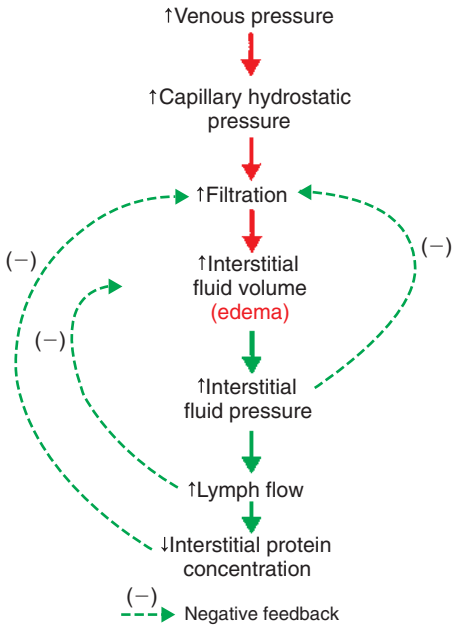

FIGURE 23-5 Increase in venous pressure leads to increase in interstitial fluid volume (edema). The *dashed lines (negative feedback)* indicate the counteracting effects of the three safety factors against edema. First, an increase in interstitial fluid hydrostatic pressure reduces the rate of filtration back toward normal. Second, an increase in lymph flow reduces interstitial fluid volume back toward normal. Third, a decrease in interstitial fluid protein concentration reduces the rate of filtration back toward normal.

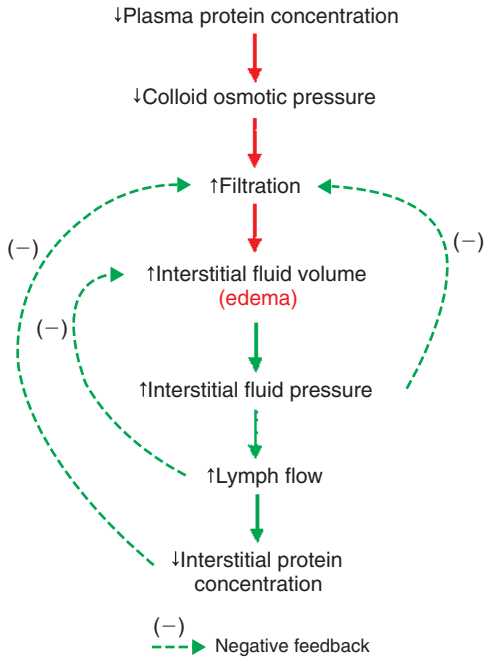

FIGURE 23-6 Decrease in plasma protein concentration leads to edema, but the degree of edema is limited by the same three safety factors as shown in Figure 23-5.

capillaries and this increases capillary hydrostatic pressure and leads to edema, as shown in Figure 23-5.

Whatever the cause of an increase in venous pressure, three factors *(safety factors)* limit the degree of the resulting edema. All three safety factors depend on an increased interstitial fluid volume leading to an increase in interstitial fluid hydrostatic pressure. The first safety factor is that the increased interstitial fluid pressure acts directly to oppose or limit filtration. Interstitial fluid pressure does not need to rise above capillary hydrostatic pressure to limit edema. Any increase in interstitial fluid pressure (e.g., from a normal value of −7 to +2 mm Hg) helps to change the net balance of the Starling forces in the direction of reducing excessive filtration.

The second safety factor against edema is that increased interstitial fluid pressure promotes lymph flow. Lymph flow removes edema fluid from the tissue and therefore helps to limit the degree of edema.

The third safety factor is an indirect consequence of increased lymph flow. Recall that interstitial fluid normally contains a small amount of plasma protein, usually the result of transcytosis. This protein exerts a small but significant oncotic pressure that favors filtration. Under the circumstance of increased capillary hydrostatic pressure, the increased capillary filtration delivers fluid into the interstitial space that is relatively free of proteins. Meanwhile, the elevated lymph flow carries away not only interstitial fluid but also the proteins that were originally present in the interstitial fluid. Therefore, the combination of increased filtration and increased lymph flow leads to a reduction in the interstitial protein concentration. The resulting decrease in interstitial fluid oncotic pressure helps reduce the excess filtration back toward normal.

To summarize, an increase in venous pressure leads to an increase in capillary hydrostatic pressure, which increases filtration. Edema develops. Three safety factors then come into play to reduce filtration back toward normal and to limit the degree of edema. A steady-state degree of edema is eventually reached, in which interstitial fluid is removed by lymph vessels as fast as it is filtered.

The *systemic edema* that results from an increase in systemic venous pressure is often most noticeable in the dependent regions of the body, such as the lower extremities in human patients or the abdominal organs in humans or animals. When edema develops in the abdominal organs, excess interstitial fluid tends to ooze out of the edematous tissues and accumulate in the peritoneal space. Excessive fluid in the peritoneum is called *ascites.*

Marked systemic edema and ascites is common in patients with right ventricular heart failure. By contrast, failure of the left ventricle leads to *pulmonary edema.* Ineffective pumping by the left ventricle results in increased blood volume and increased pressure in the left atrium and pulmonary veins. This elevated pressure extends back into the pulmonary capillaries, which increases capillary filtration in the lung tissue. In severe cases of pulmonary edema, some of the excess interstitial fluid oozes into the alveoli and bronchial airways. Such a patient typically coughs up a frothy fluid. Excess edema fluid may also ooze into the intrapleural space, which is called *pleural effusion.* The consequences of heart failure are discussed more fully in Chapter 26.

A decreased plasma protein concentration *(hypoproteinemia)* is another common cause of edema (Figure 23-6). One cause of hypoproteinemia is a decrease in the rate of plasma protein production by the liver. This occurs in malnutrition and leads to the clinical syndrome of *kwashiorkor.* Victims of kwashiorkor typically look emaciated, except that the abdomen is grossly distended by edema and ascites. Another cause of abnormally low plasma protein concentration is an increase in the rate of loss of

plasma proteins from the body. Protein loss occurs in kidney disease. For example, in *nephrotic syndrome,* the kidney glomerular capillaries become permeable to plasma proteins. Plasma proteins leave the bloodstream and enter the urinary tubules (nephrons) of the kidney. A chronic loss of proteins in the urine reduces the plasma protein concentration. Therefore the presence of substantial amounts of plasma protein in the urine is an alarming clinical sign.

Severe burns also cause the loss of plasma proteins from the body. The capillaries of burned skin become very permeable to both fluid and proteins. Substantial amounts of plasma can leave the body through these damaged capillaries. The presence of plasma proteins in the fluid weeping from a burn site accounts for the typical yellow color of that fluid. If the water and electrolytes lost through burns are replaced through drinking or an intravenous administration of fluids, and if the plasma proteins are not also replaced, the plasma protein concentration in the blood decreases.

Whether it results from decreased production or increased loss, hypoproteinemia leads to a decrease in plasma colloid osmotic pressure. This alters the balance of the Starling forces in a direction that favors excessive filtration of fluid from the capillaries (see Figure 23-6). Interstitial fluid accumulates and edema is noticed. However, the same three safety factors that limit edema in the case of increased venous pressure (see Figure 23-5) also operate in the case of decreased plasma protein concentration. The degree of edema is limited by (1) an increased interstitial fluid pressure, (2) an increased lymph flow, and (3) a decreased interstitial protein concentration.

Another cause of edema is lymphatic obstruction. Clinically, this situation is called *lymphedema.* The passage of lymph through lymph nodes can be impaired by inflammation of the nodal tissue or cancerous tumors growing within the nodes. Also, in certain parasitic diseases, microfilariae lodge in the lymph nodes and obstruct lymph flow. Filarial parasites cause the pronounced edema seen in cases of *elephantiasis.* Lymphedema also occurs as a secondary consequence of surgical procedures that damage lymph nodes. A common example of this in human medicine is the edema of the arm that follows radical mastectomy. The removal of axillary lymph nodes during radical mastectomy creates scar tissue that impairs lymphatic drainage from the arm.

Figure 23-7 traces the causes of edema after lymphatic obstruction and shows why lymphedema is clinically so troublesome. Lymphatic obstruction decreases lymph flow. Interstitial fluid accumulates in the tissues, instead of being removed by the lymph, and edema results. The accumulation of edema fluid raises interstitial fluid pressure, which acts as a safety factor by reducing capillary filtration. However, the second and third safety factors discussed earlier are absent in the case of lymphedema because these factors depend on an increase in lymph flow. In lymphedema a decreased lymph flow is the causative problem, so there cannot be an increased lymph flow (second safety factor) to compensate for the edema. Moreover, when lymph flow is impaired, plasma proteins accumulate in the interstitial fluid instead of being carried away by the lymph. Therefore the third safety factor that protects against edema (decreased interstitial fluid oncotic pressure) is also compromised in lymphedema.

Another cause of edema is physical injury or an allergic reaction to antigen challenges. Physical trauma, such as a scratch or a cut on the skin, results in a localized bump or swelling. A similar swelling is observed when the skin reacts to an irritating agent or antigen challenge (e.g., response to an insect bite). An allergic swelling can also occur in bronchial tissue during an asthmatic reaction. The edema of asthma can be life threatening because it limits airflow to the lungs. As shown in Figure 23-8, an injury or antigen challenge leads to the release of the chemical *histamine* from mast cells in the affected tissue. Histamine has two effects that cause edema. First, histamine increases the permeability of capillaries to proteins. As proteins leave the bloodstream and

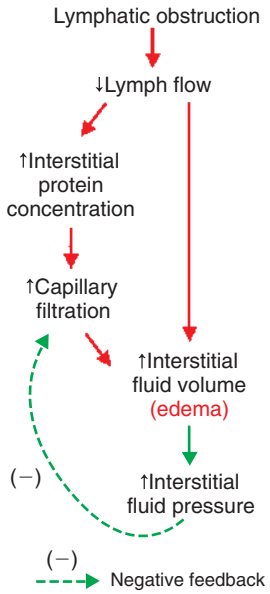

FIGURE 23-7 Lymphatic obstruction leads to edema. Lymphedema is clinically troublesome because only one of the normal three safety factors is operative to limit the degree of edema.

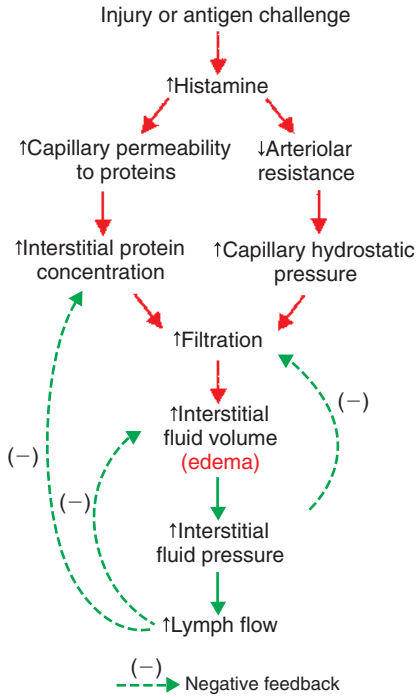

FIGURE 23-8 Histamine mediates the changes that lead to edema in response to a physical injury or an antigen challenge. The normal three safety factors against edema are intact and help to limit the degree of edema. Treatment with an antihistamine (a drug that blocks histamine receptors on arterioles and capillaries) also helps to reduce edema in these cases.

accumulate in the interstitial space of the damaged tissue, they increase the interstitial fluid oncotic pressure, which promotes filtration of fluid. Second, histamine relaxes arteriolar smooth muscle. The arterioles dilate, and the resulting decrease in arteriolar resistance allows more of the arterial blood pressure to impinge on the capillaries. This leads to an increase in the capillary hydrostatic pressure, which promotes filtration. Although histamine promotes excess filtration and edema through two mechanisms, all three safety factors that protect against edema are intact and act to limit the degree of edema.

Other situations also cause edema, but the examples discussed here cover some of the most common causes of clinical edema. These examples also reinforce an understanding of the interplay of the osmotic (oncotic) and hydrostatic forces that act on water to govern its filtration out of capillaries or its reabsorption into capillaries.

CLINICAL CORRELATIONS

ACUTE PROTEIN-LOSING ENTEROPATHY IN A HORSE

History. You are called to a home a few miles from your clinic by parents who are concerned about their daughter's 4-year-old Quarter Horse mare. They report that the horse is listless and has had diarrhea for 2 days.

Clinical Examination. You arrive at the client's home to find that the horse is stabled in a small barn with poor ventilation and no access to pasture. Low-quality grass hay is stacked in the barn. On physical examination, you find the horse to be somewhat emaciated, with dry mucous membranes, a foul-smelling diarrhea, and an elevated heart rate (tachycardia). When you pinch a section of the horse's skin, it falls back to the normal position slowly, which indicates dehydration. The horse's temperature is within a normal range.

You take a blood sample and then begin an intravenous administration of polyionic fluid (lactated Ringer's solution). You tell the clients that you will return later. Analysis of the blood sample indicates a hematocrit of 55% (normal range for the horse, 35% to 45%) and a plasma protein concentration of 4.5 g/dL (normal range, 5.9 to 7.8 g/dL). You become concerned that the administration of fluids, without replacement of plasma proteins, will exacerbate the horse's hypoproteinemia, so you arrange to obtain plasma from a donor horse. You return with the plasma and find that the sick horse is still listless. Edema is now evident along the horse's ventral abdomen and in the limbs.

Comment. *Acute enteropathy* (intestinal disorder) often causes diarrhea. The loss of water and solutes leads to dehydration; blood volume and interstitial fluid volume are both reduced. The hematocrit (fraction of cells in blood) is typically elevated because fluid is being removed from the bloodstream but blood cells are not. In some forms of enteropathy (called *protein-losing enteropathy*) the capillaries in the intestine become leaky to plasma proteins. Albumin, in particular, moves from the bloodstream into the intestinal lumen and is eliminated in the feces.

This horse has a severe shortage of plasma proteins. The shortage of plasma proteins probably resulted from a combination of poor nutrition (which depresses the production of plasma proteins by the liver) and protein-losing enteropathy. The deficit of plasma proteins in this horse is even more severe than might be suspected on the basis of the plasma protein concentration of 4.5 g/dL, because this value is the net result of two opposing processes. The loss of protein in the diarrhea lowered the plasma protein concentration, but the loss of water (dehydration) decreased plasma volume and therefore increased the concentration of the remaining proteins in the plasma.

The development of edema in this horse was predictable. The administration of intravenous fluids added water and electrolytes to the circulating blood volume, but this reduced the concentration of the plasma proteins remaining in the bloodstream. As a result, plasma oncotic pressure decreased even further, and this led to excess filtration of water out of capillaries and into the interstitial space. The result was edema, especially in the dependent regions of the body (ventral abdomen and legs). Restoration of a normal plasma protein concentration would reverse the edema.

Treatment. Bacterial or parasitic infections are a common cause of protein-losing enteropathy. If this horse had a fever, an infectious cause would be more likely. Acute enteropathy without fever (as in this case) is often self-limiting. Therefore the aim of treatment should be to remedy the dehydration, the electrolyte loss, and the plasma protein deficit. Intravenous administration of plasma, in addition to polyionic fluids, is usually effective. In some cases, antibiotics are also indicated, because enteropathy involves inflammation of the intestinal wall, which can allow transmural migration of bacteria (and toxic bacterial products) from the gastrointestinal tract into the peritoneum. Important steps for long-term health in this horse would include better nutrition, regular deworming, and improved stable management.

PRACTICE QUESTIONS

1. Which of the following will *not* cause pulmonary edema?
   a. An increase in pulmonary capillary permeability to protein
   b. A blockage of pulmonary lymph vessels
   c. An increase in left atrial pressure
   d. A constriction of pulmonary arterioles
   e. Left-sided heart failure

2. A patient with a form of protein-losing kidney disease has a plasma colloid osmotic pressure of 10 mm Hg. The patient has edema but is not getting any worse. Blood pressure and heart rate are normal. Which of the following is probably preventing further edema?
   a. Increased interstitial fluid hydrostatic pressure
   b. Increased capillary hydrostatic pressure
   c. Decreased lymph flow
   d. Increased plasma sodium ion concentration
   e. Increased interstitial fluid oncotic pressure

3. The following parameters were measured in the microcirculation of a skeletal muscle during a period of vigorous exercise:
   P_c (capillary hydrostatic pressure) = 34 mm Hg
   P_i (interstitial fluid hydrostatic pressure) = 10 mm Hg
   π_c (capillary plasma oncotic pressure) = 24 mm Hg
   π_i (interstitial fluid oncotic pressure) = 3 mm Hg
   Which of the following is *true*?
   a. These conditions would favor filtration.
   b. These conditions would favor reabsorption.
   c. These conditions would favor neither filtration nor reabsorption.
   d. It is not clear what these conditions favor because the concentration of plasma protein is not specified.

4. The rate of diffusion of glucose molecules from capillary blood to interstitial fluid is most directly affected by the:
   a. Voltage difference between capillary blood and interstitial fluid.
   b. Interstitial fluid hydrostatic pressure.
   c. Size and number of capillary pores.
   d. Amount of oxygen in the blood.
   e. Hematocrit.

5. During a 30-minute hemorrhage, a horse loses a substantial volume of blood. The horse's mean arterial pressure decreases from 90 to 75 mm Hg, and the heart rate increases from 40 to 90 beats/min. The skin becomes cold and the mucous membranes become pale, suggesting marked vasoconstriction. Because hemorrhage involves the loss of whole blood (both plasma and cells), you might expect that, soon after such a hemorrhage, the horse's remaining blood would still have a normal composition. However, you take a blood sample and discover that the hematocrit is abnormally low (only 28%). Which of the following would *most likely* account for the decrease in hematocrit observed after the hemorrhage?
   a. Arteriolar constriction has caused capillary hydrostatic pressure to increase above normal.
   b. Low capillary hydrostatic pressure has caused interstitial fluid to be reabsorbed into the bloodstream.
   c. Many blood cells have been filtered out of capillaries and into the interstitial fluid.
   d. Excess capillary filtration has caused interstitial fluid pressure to increase above normal.
   e. Excess capillary filtration has caused capillary colloid osmotic pressure to increase above normal.

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CHAPTER 24
Local Control of Blood Flow

KEY POINTS

1. Vascular resistance is affected by intrinsic and extrinsic control mechanisms.
2. Metabolic control of blood flow is a local mechanism that matches the blood flow of a tissue to its metabolic rate.
3. Autoregulation is a relative constancy of blood flow in an organ despite changes in perfusion pressure.
4. Many chemical signals act locally (as paracrines) to exert important control on vascular resistance.
5. Regardless of the status of arterioles, mechanical compression can reduce blood flow to a tissue.

Vascular Resistance Is Affected by Intrinsic and Extrinsic Control Mechanisms

As described in Chapter 22, the blood flow through any organ or tissue is determined by the perfusion pressure (arterial pressure minus venous pressure) and by the resistance of the blood vessels of the organ (and by no other factors), as follows:

$$\text{Blood flow} = \text{Perfusion pressure} \div \text{Vascular resistance}$$

Normally, all the organs of the systemic circulation are exposed to the same perfusion pressure. Therefore, differences in blood flow to the various organs result from their different vascular resistances. The vascular resistance of an organ is determined mainly by the diameter of its arterioles. Thus, arteriolar vasodilation and vasoconstriction are the mechanisms that increase or decrease the blood flow in one organ relative to another organ.

In general, the factors that affect arteriolar resistance can be divided into intrinsic and extrinsic factors. *Extrinsic control* involves mechanisms that act from outside an organ or tissue, through nerves or hormones, to alter arteriolar resistance. *Intrinsic control* is exerted by local mechanisms within an organ or tissue. For example, as described in Chapter 23, histamine is released from mast cells of a tissue in response to injury or during an allergic reaction. Histamine acts locally on the arteriolar smooth muscle to relax it. Dilation of the arterioles decreases arteriolar resistance and therefore increases blood flow to the tissue. Histamine is an example of a *paracrine:* a substance released from one type of cell that acts on another cell type in the vicinity. Paracrine signaling molecules move by diffusion, which is why paracrine signaling is only effective over very short distances. A second example of intrinsic control is the arteriolar dilation and increased blood flow during exercise in skeletal muscle. This example illustrates the general phenomenon of *metabolic control* of blood flow: tissues tend to increase their blood flow whenever their metabolic rate increases.

Although the arterioles in all tissues are affected by both intrinsic and extrinsic mechanisms, intrinsic mechanisms predominate over extrinsic mechanisms in the control of arterioles in the brain, heart (i.e., coronary circulation), and working skeletal muscle. By contrast, extrinsic mechanisms predominate over intrinsic mechanisms in the control of blood flow to the kidneys, splanchnic organs, and resting skeletal muscle. Skin is an example of an organ in which both intrinsic and extrinsic control mechanisms have strong influences. In general, local (intrinsic) control dominates extrinsic control in the *critical organs:* those that must have sufficient blood flow to meet their metabolic needs on a second-by-second basis for an animal to survive. Extrinsic control dominates intrinsic control in organs that can withstand temporary reductions in blood flow (and metabolism) to make extra blood available for the critical organs.

Metabolic Control of Blood Flow Is a Local Mechanism That Matches the Blood Flow of a Tissue to Its Metabolic Rate

Metabolic control of blood flow is the most important local control mechanism. For example, metabolic control accounts for the huge increase in blood flow through a skeletal muscle as it goes from rest to maximal exercise. The functional significance of metabolic control of blood flow is that it matches the blood flow in a tissue to the metabolic rate of the tissue. An increase in tissue blood flow in response to increased metabolic rate is called *active hyperemia* (*hyper* means "elevated," *emia* refers to blood, and *active* implies an increased metabolic rate).

Metabolic control of blood flow works by means of chemical changes within the tissue. When the metabolic rate of a tissue increases, its consumption of oxygen increases, and there is an increased rate of production of metabolic products, including carbon dioxide, adenosine, and lactic acid. Also, some potassium ions (K^+) escape from rapidly metabolizing cells, and these ions accumulate in the interstitial fluid. Therefore, as the metabolism of a tissue increases, the interstitial concentration of oxygen decreases, and the interstitial concentrations of metabolic products and K^+ increase. All these changes have the same effect on arteriolar smooth muscle: they relax it (Table 24-1). The arterioles dilate, vascular resistance decreases, and more blood flows through the tissue.

TABLE 24-1 Chemical Signals Important in Local Control of Systemic Arterioles*

Chemical Signal	Source	Effect
Signals Related to Metabolism		
Oxygen	Delivered by arterial blood; consumed in aerobic metabolism	Vasoconstriction. (Rapid metabolism depletes O_2, which causes vasodilation.)
Carbon dioxide	Produced by aerobic metabolism	Vasodilation
Potassium ions (K^+)	Released from rapidly metabolizing cells	Vasodilation
Adenosine	Released from rapidly metabolizing cells	Vasodilation
Metabolic acids (e.g., lactic acid)	Produced by anaerobic metabolism	Vasodilation
Other Local Chemical Signals (Paracrines)		
Endothelin-1 (ET1)	Endothelial cells	Vasoconstriction
Nitric oxide (NO)	Endothelial cells and some parasympathetic nerve endings	Vasodilation
Thromboxane A_2 (TXA_2)	Platelets	Vasoconstriction (also increases platelet aggregation)
Prostacyclin (PGI_2)	Endothelial cells	Vasodilation (also decreases platelet aggregation)
Histamine	Mast cells	Vasodilation (also increases capillary permeability)
Bradykinin	Globulins in blood or tissue fluid	Vasodilation (also increases capillary permeability)

*Some of these chemical signals have different effects on pulmonary blood vessels than on systemic vessels. A high level of oxygen, for example, causes dilation of pulmonary vessels, whereas the effect in systemic vessels is vasoconstriction. See Chapter 46 for more details.

Low levels of oxygen and high concentrations of metabolic products and K^+ also cause relaxation of the precapillary sphincters (in the tissues that have them), and this opens more of the capillaries in the tissue to blood flow. As explained in Chapter 23, the opening of more capillaries decreases the diffusion distance between fresh, oxygenated blood and the metabolizing cells of the tissue. Opening more capillaries also increases the total capillary surface area for diffusional exchange. The net result of the increased blood flow, the decreased diffusion distance, and the increased total capillary surface area is a more rapid delivery of oxygen and other metabolic substrates to the tissue cells and a more rapid removal of metabolic waste products from the tissue.

Metabolic control of blood flow involves negative feedback. The accumulation of metabolic products and the lack of oxygen initiate vasodilation, which increases blood flow. The increased blood flow removes the accumulating metabolic products and delivers additional oxygen. A new balance is reached when the increased blood flow closely matches the increased metabolic needs of the tissue. Figure 24-1 summarizes the major features of metabolic control of blood flow.

Reactive hyperemia is a temporary increase above normal in the flow of blood to a tissue after a period when blood flow was restricted. In this case the increased flow (hyperemia) is a response (reaction) to a period of inadequate blood flow. Mechanical compression of blood vessels is one cause of inadequate blood flow, and release of that mechanical compression elicits reactive hyperemia. This can be easily demonstrated in any accessible nonpigmented epithelial tissue. For example, press a finger against nonpigmented skin hard enough to occlude the blood flow. Maintain the pressure for about 1 minute, and then release. After release of the pressure, the previously compressed skin will appear

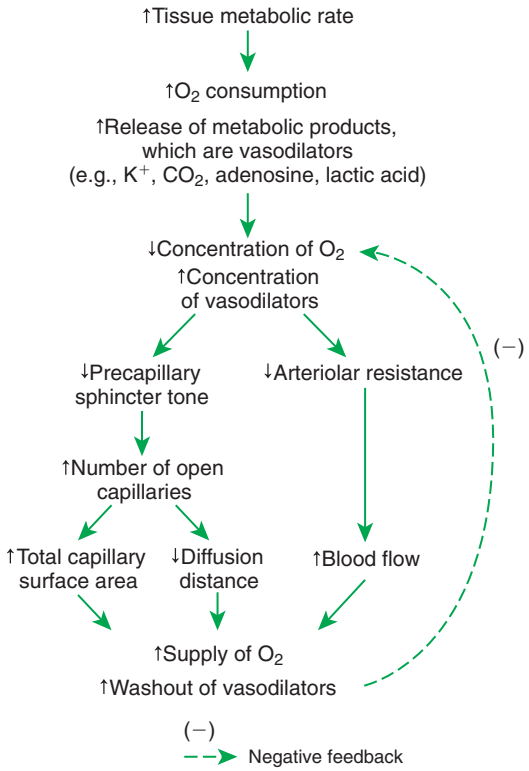

FIGURE 24-1 Metabolic control of blood flow is a local (intrinsic) mechanism that acts within a tissue to match the blood flow to the tissue with the metabolic activity of the tissue. As a tissue becomes more active metabolically, the metabolic control mechanism increases blood flow and thereby regulates the concentration of oxygen and metabolic products in the tissue.

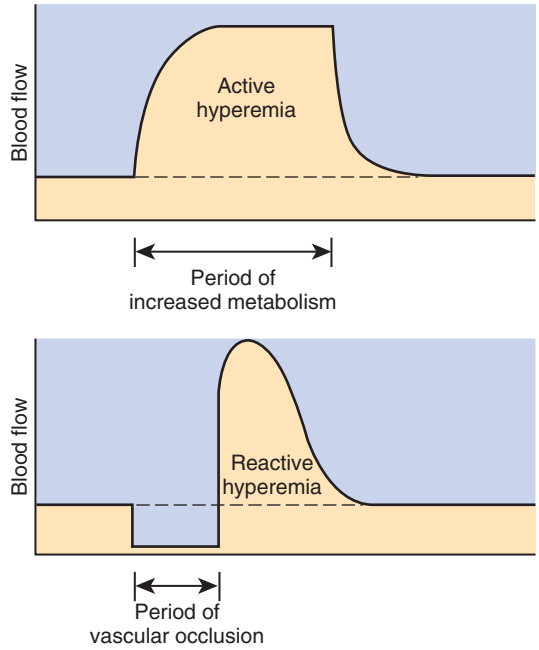

FIGURE 24-2 Both active hyperemia and reactive hyperemia involve increases above normal in blood flow. Both phenomena are brought about by the mechanisms for the local, metabolic control of blood flow.

darker (redder) for a short time, because blood flow will become greater than normal after the compression is released.

The same metabolic control mechanisms that account for active hyperemia also explain reactive hyperemia. During the period when mechanical compression restricts blood flow, metabolism continues in the compressed tissue; metabolic products accumulate, and the local concentration of oxygen decreases. These metabolic effects cause dilation of the arterioles and a decrease in arteriolar resistance. When the mechanical obstruction to flow is removed, blood flow increases above normal until the "oxygen debt" is repaid and the excess metabolic products have been removed from the compressed tissue. Figure 24-2 compares active and reactive hyperemia.

Autoregulation Is a Relative Constancy of Blood Flow in an Organ Despite Changes in Perfusion Pressure

Metabolic control mechanisms also participate in the phenomenon known as *blood flow autoregulation.* Autoregulation is evident in denervated organs and organs in which local control of blood flow is predominant over neural and humoral control (e.g., in coronary circulation, brain, and working skeletal muscle).

Figure 24-3 summarizes an experiment that demonstrates autoregulation in the brain. Initially, the perfusion pressure (arterial pressure minus venous pressure) in this animal is 100 mm Hg, and the blood flow to the brain is 100 milliliters per minute (mL/min) (point *A*). When perfusion pressure is increased suddenly to 140 mm Hg, brain blood flow rises initially to 140 mL/min but returns toward its initial level over the next 20 to 30 seconds. Eventually, blood flow reaches a stable level of about 110 mL/min (point *B*). Conversely, if the perfusion pressure is decreased suddenly from 100 to 60 mm Hg, blood flow in the brain decreases initially to 60 mL/min but returns toward its initial level over the next 20 to 30 seconds (see *dashed lines* in the top and middle graphs of Figure 24-3). Eventually, blood flow reaches a stable level of about 90 mL/min (point *C*). These stable responses are

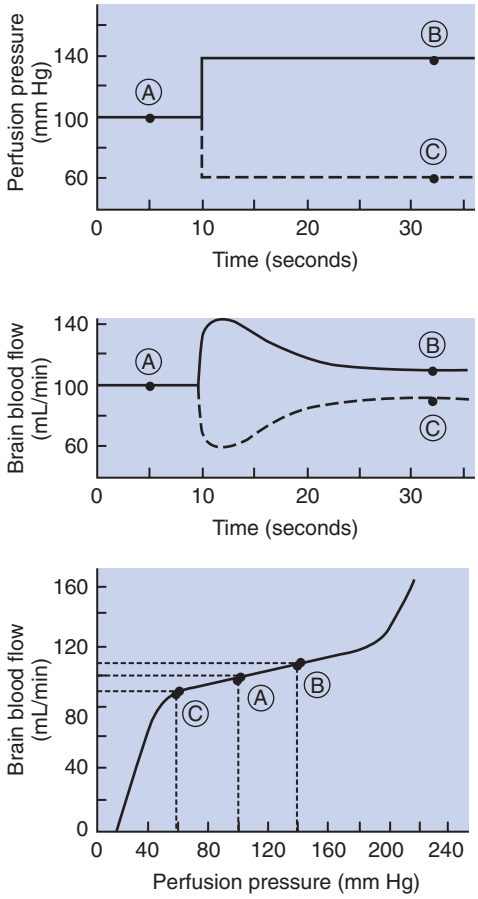

FIGURE 24-3 The experiment summarized here demonstrates autoregulation of blood flow in the brain. Perfusion pressure was artificially set to various levels *(top),* and the resulting changes in brain blood flow were measured *(middle).* The steady-state values of blood flow were then plotted against perfusion pressure *(bottom).* Points *A, B,* and *C* are discussed in the text.

plotted in the bottom graph. The remainder of the bottom graph is obtained in a similar way; that is, perfusion pressure is set artificially to various levels, ranging from 40 to 220 mm Hg, and the resulting steady-state levels of blood flow are plotted.

Over a considerable range of perfusion pressure (about 60 to 190 mm Hg), relatively little change occurs in steady-state blood flow to the brain; that is, brain blood flow is autoregulated. The range of perfusion pressures over which flow remains relatively constant is called the *autoregulatory range.* Autoregulation fails at very high and very low perfusion pressures. Extremely high pressures result in marked increases in blood flow, and extremely low pressures result in marked decreases in blood flow. Nevertheless, over a considerable range of perfusion pressure, autoregulation keeps blood flow in the brain relatively constant.

Figure 24-4 shows how the metabolic control mechanisms previously described can account for the phenomenon of autoregulation. If the metabolic rate of an organ does not change but perfusion pressure is increased above normal, the increased pressure forces additional blood flow through the organ. The additional blood flow accelerates the removal of metabolic products from the interstitial fluid and increases the rate of oxygen delivery to the interstitial fluid. Therefore the concentration of vasodilating metabolic products in the interstitial fluid decreases,

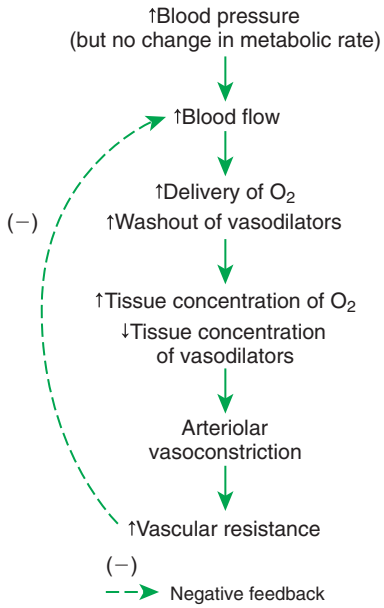

FIGURE 24-4 The same metabolic mechanism that is responsible for active hyperemia and reactive hyperemia can also account for autoregulation, in which blood flow to an organ stays relatively constant despite changes in perfusion pressure.

and the concentration of oxygen in the interstitial fluid increases. These changes cause the arterioles of the tissue to constrict, which increases the resistance to blood flow above normal. The consequence is that blood flow decreases back toward its initial level, despite the continuation of the elevated perfusion pressure.

To summarize, metabolic control mechanisms bring about active hyperemia (the increase in blood flow in an organ in response to an increased metabolic rate, in the absence of any blood pressure change). The same metabolic mechanisms can also account for reactive hyperemia (the increase in blood flow above normal in an organ after a period of flow restriction). In addition, the same metabolic mechanisms can account for autoregulation (the relative constancy of blood flow in an organ when there has been no change in metabolic rate but blood pressure has either increased or decreased). Other mechanisms also contribute to autoregulation, and the reader may encounter discussions of these under the terms *myogenic hypothesis* and *tissue pressure hypothesis*. However, metabolic control plays a major role in autoregulation of blood flow in the critical tissues of a body (brain, coronary vessels, and exercising skeletal muscle).

Many Chemical Signals Act Locally (as Paracrines) to Exert Important Control on Vascular Resistance

As already described, metabolic control of blood flow is mediated by chemical changes that occur when tissue metabolism increases. In addition to the signaling molecules that mediate metabolic control of blood flow, there are many other chemicals that act locally, within a tissue, to affect vascular resistance and therefore blood flow. Some of these locally acting *(paracrine)* chemical signals are listed in Table 24-1.

Endothelin-1 (ET1) is released from endothelial cells in response to a variety of mechanical or chemical stimuli, especially those that traumatize the endothelium. Endothelin-1 causes vascular smooth muscle to contract, which results in vasoconstriction and a decrease in blood flow. *Nitric oxide* (NO), another signaling molecule released from endothelial cells, has the opposite effect. NO relaxes vascular smooth muscle, which results in vasodilation. One stimulus for NO release is an increase in blood flow velocity past the endothelium. The NO acts locally to dilate vessels, especially small arteries, which allows them to accommodate an increased blood flow without such high flow velocities. In some tissues, most notably the erectile tissues of the external genital organs (penis and clitoris), parasympathetic nerve endings release NO and the neurotransmitter acetylcholine. The acetylcholine stimulates endothelial cells to release additional NO. The NO from the nerve endings, augmented by the NO from the endothelial cells, dilates local blood vessels, which causes engorgement of the tissues with blood, and therefore erection.

Thromboxane A_2 (TXA_2) and *prostacyclin* (PGI_2) act antagonistically in the control of vascular smooth muscle and also in the control of platelet aggregation. Thus the relative balance between TXA_2 and PGI_2 is more important than the absolute level of either chemical alone. Under normal conditions the balance ensures adequate blood flow to tissues and prevents platelet aggregation. If blood vessels become traumatized or rupture, the balance shifts in favor of TXA_2. The resulting vasoconstriction and platelet aggregation are critical in minimizing blood loss. In some pathological states, imbalances develop between TXA_2 and PGI_2. Depending on the direction of the imbalance, the result is either excessive vasoconstriction and blood coagulation or excessive vasodilation and bleeding.

Histamine, which is released from mast cells, is another locally acting vasodilator. The role of histamine in the vascular responses to tissue injury or antigen challenge is described in Chapter 23 (see Figure 23-8). *Bradykinin* is another signaling chemical that causes vasodilation. Bradykinin is a small polypeptide that is split away by the proteolytic enzyme *kallikrein* from globulin proteins that are present in plasma or tissue fluid. Bradykinin may also be formed in sweat glands when they are activated by acetylcholine that is released from sympathetic nerve endings. The resulting vasodilation of skin blood vessels, together with the evaporation of sweat, promotes heat loss from the skin. Both histamine and bradykinin exert their vasodilating effects, at least in part, by stimulating the formation of NO.

Regardless of the Status of Arterioles, Mechanical Compression Can Reduce Blood Flow to a Tissue

Mechanical compression can reduce blood flow in a tissue by literally squeezing down on all its blood vessels. The example of compressing skin blood vessels for a minute and then releasing the compression has been mentioned as a way to trigger a readily visible reactive hyperemia. Long-term mechanical pressure on the skin must be avoided, however, because a prolonged period of subnormal blood flow (ischemia) leads to irreversible tissue damage (infarction) and cell death (necrosis). Pressure sores are an unfortunate and common example of this sequence. Three other specific instances of mechanical compression are also described because of their clinical importance.

Figure 24-5 illustrates the effect of mechanical compression on blood flow through the coronary vessels. The top tracing shows the changes in arterial (aortic) blood pressure during one complete cardiac cycle and the beginning of a second one. The periods of ventricular systole and ventricular diastole are labeled at the bottom of the figure. One would expect that blood flow through the coronary circulation would be highest during ventricular systole (when the aortic pressure is highest) and that flow would be lowest during diastole (when the aortic pressure is lowest). However, the tracings of left coronary blood flow indicate that

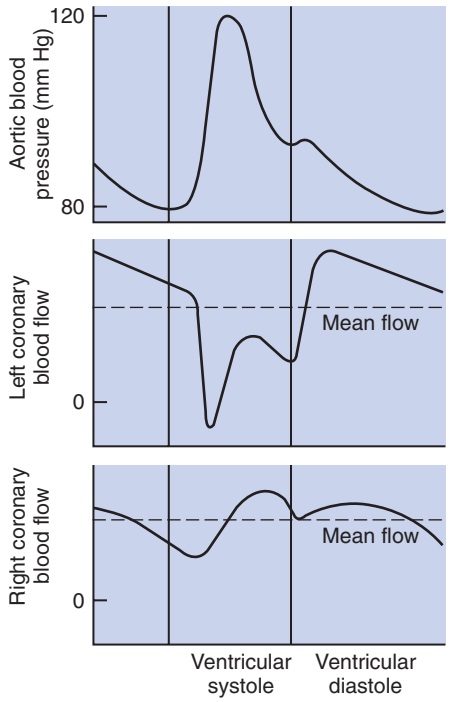

FIGURE 24-5 Coronary blood flow to the left ventricular muscle is greatly reduced during ventricular systole because the left ventricular muscle contracts so forcefully that it compresses the left ventricular blood vessels. Coronary blood flow to the right ventricular muscle is less affected by mechanical compression because the contractions of the right ventricle are less forceful that those of the left ventricle.

blood flow through the left ventricular wall is actually depressed during systole and much higher during diastole. Flow even reverses (blood flows backward, *toward* the aorta) momentarily near the beginning of systole. The fact that left coronary blood flow is much lower during systole, even though the perfusion pressure is higher, implies that the resistance of the coronary vessels must be substantially higher during systole than during diastole.

Left coronary resistance is high during systole because the contracting left ventricular muscle squeezes down on the coronary blood vessels. The coronary vessels are not constricted in this way during diastole because the ventricular muscle is relaxed. Therefore, coronary vascular resistance decreases dramatically (and blood flow increases) during diastole. The bottom tracing in Figure 24-5 indicates that mechanical compression has relatively little influence on blood flow through the right ventricular wall. That is, the magnitude of right coronary blood flow closely follows the changes in arterial pressure (being highest during systole and lowest during diastole). Right coronary flow is not restricted by mechanical compression during systole because the right ventricle contracts with much less force than the left ventricle. The right ventricle simply does not develop sufficient compressive force to constrict its own blood vessels.

Most of the blood that is needed to support left ventricular metabolism must be delivered during ventricular diastole, when the vessels are not compressed. This fact has great clinical significance. In a resting animal with a low heart rate, there is adequate time during diastole for the coronary vessels to supply the amount of blood needed by the ventricular tissue. During exercise, heart rate and cardiac contractility both increase, which greatly increases the metabolic rate of the ventricular muscle cells. To support the increased metabolic rate, the ventricular tissue needs much more blood flow than at rest. However, the duration of diastole is reduced during exercise, so there is less time available for delivery of this increased flow. Nevertheless, normal, healthy coronary vessels have a sufficiently low resistance (during diastole) to supply the needed blood flow, even during maximal exercise. The situation is different, however, in animals with coronary artery disease. In animals whose coronary vessels are narrowed because of atherosclerosis, blood flow cannot increase enough to supply the needs of the vigorously working ventricular muscles. This is why ventricular ischemia develops during exercise in patients with coronary artery disease. Ischemic areas of the ventricle fail to contract normally. Ischemia can also cause arrhythmias or even ventricular fibrillation (sudden death). Coronary artery disease is more common in humans than in veterinary species, so this scenario is more likely to occur in the veterinarian than in the veterinarian's patients.

Mechanical compression caused by muscle contraction can also restrict blood flow through skeletal muscles. The blood vessels within skeletal muscles become compressed during strenuous, sustained contractions of the muscle. The compression reduces blood flow through the muscle, which can create ischemia. Ischemic muscles cannot contract with normal vigor. Ischemia also activates sensory nerve endings in the muscle, which causes pain. Activation of these muscle ischemia receptors also triggers a reflex increase in arterial pressure. The high arterial pressure is advantageous because it helps to force blood flow through the skeletal muscle blood vessels, despite the compressive effects of the muscle contraction. The high arterial pressure of ischemic exercise is risky for patients with coronary artery disease, however, because high arterial pressure imposes a tremendous increase in workload on the heart. This is why patients with coronary artery disease are cautioned against types of exercise that involve strenuous, sustained muscle contractions, such as weightlifting.

Mechanical compression has important effects on the pulmonary circulation. Pulmonary vessels are more compliant than their counterparts in the systemic circulation. Greater compliance makes the pulmonary vessels more distensible, but also makes them more susceptible to narrowing under the influence of mechanical compression. Moreover, because pulmonary arterial pressure is much lower than systemic arterial pressure, there is less intravascular pressure in a pulmonary vessel to oppose any external force acting to compress the vessel. Most pulmonary vessels travel within the tissues that comprise the walls of the airways, including the very thin walls of alveoli. Figure 24-6 shows how an abnormal elevation in airway pressure can compress pulmonary blood vessels. This could happen during surgery if a patient has a tracheal tube inserted into its airway and if the tracheal tube is attached to a source of elevated pressure. The elevated pressure could be generated by a mechanical respirator that is not adjusted properly or by an anesthetist when he or she squeezes the bag that is attached to the tracheal tube. In either case, the pressures generated in the tracheal tube are transmitted through the airways and into the alveoli. An increase in airway pressure exerts a compressing force on the pulmonary blood vessels.

Alveolar pressures exceeding 10 to 15 mm Hg compress pulmonary blood vessels sufficiently to raise the resistance to blood flow through the lungs. As a result, blood ejected by the right ventricle dams up in the pulmonary arteries. This causes pulmonary arterial pressure to increase. An elevated pulmonary arterial pressure helps force blood through the compressed vessels.

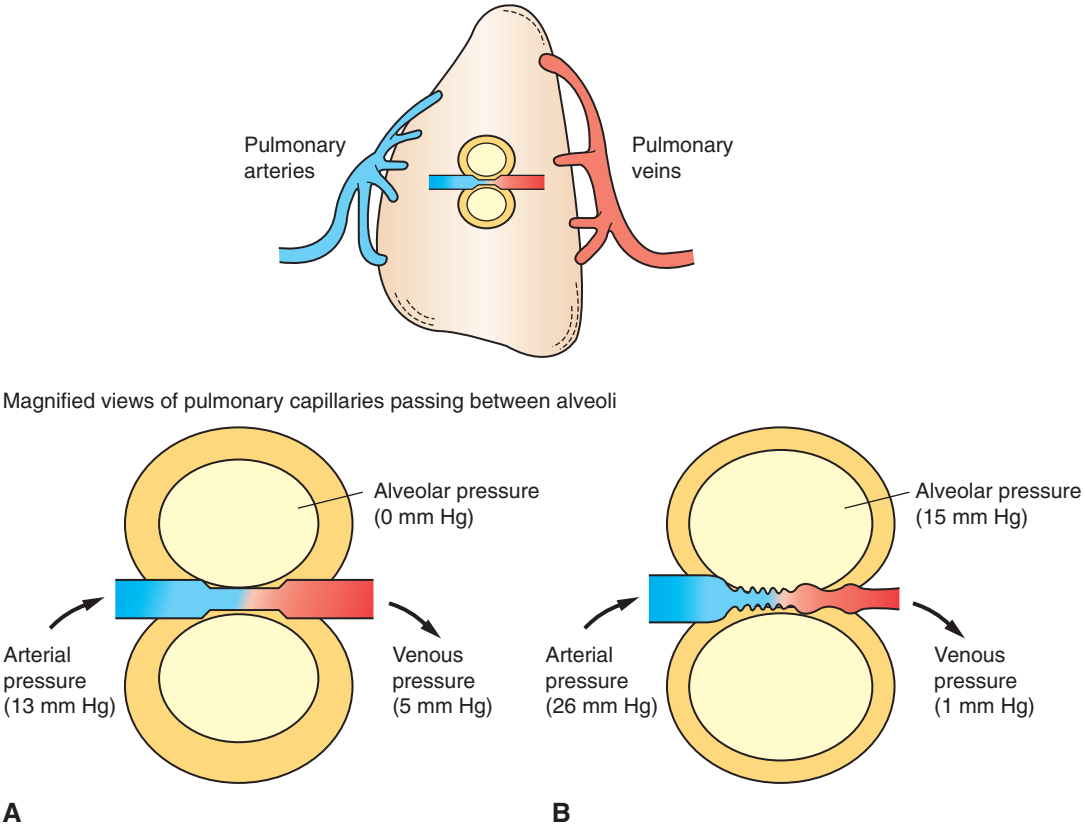

FIGURE 24-6 Pulmonary blood vessels are susceptible to mechanical compression, which can be created by abnormally high pressure within the airways. **A**, Under normal conditions pulmonary arterial pressure is about 13 mm Hg and the venous pressure is about 5 mm Hg. The pressure within the pulmonary capillary depicted here would be intermediate between these two values. The pressure just outside the capillary (in the alveolar air space) is even lower; alveolar pressures typically vary between –1 mm Hg (during inspiration) and +1 mm Hg (during expiration). Because the pressure inside pulmonary vessels is greater than the pressure outside, the vessels are not compressed. **B**, If alveolar pressure increases to 15 mm Hg or higher, the pulmonary vessels become compressed. The resulting increase in pulmonary vascular resistance causes pulmonary blood flow to decrease, pulmonary arterial pressure to increase, and pulmonary venous pressure to decrease.

However, the increased pulmonary artery pressure also imposes an increased workload on the right ventricle. If the pressure in the airways is not excessively high, the right ventricle can generate a big enough increase in pulmonary arterial pressure to restore pulmonary blood flow almost to normal. However, with extremely high airway pressures, the right ventricle may be unable to raise pulmonary arterial pressure high enough to sustain flow. Under these conditions, pulmonary blood flow falls substantially below normal. Because the left heart can only pump as much blood as it receives via the pulmonary circulation, left ventricular output also decreases. The consequences can be fatal. The veterinary clinician must be mindful of the risks of high airway pressures whenever a patient is intubated and attached to a mechanical respiratory device.

CLINICAL CORRELATIONS

PATENT DUCTUS ARTERIOSUS

History. A 3-month-old female Welsh corgi is brought to your clinic by its owner, who has noticed a "rumbling noise" in the dog's chest. The dog is smaller than her littermates and less playful. The dog coughs occasionally, but the cough does not produce fluid.

Clinical Examination. The dog appears to be in good health except for the occasional cough. The mucous membranes are pink, and the capillary refill time is normal (1.5 seconds). However, when you place your hand on the anterior left chest, you feel an abnormal vibration *(thrill)* with each heartbeat. With a stethoscope, you can auscultate a cardiac murmur that is loudest during systole but continues throughout both systole and diastole *(continuous murmur).* The murmur is heard most loudly at the ventral third intercostal space on the left side. Expiratory sounds are slightly louder than normal. The heart rate is 152 beats/min, which you consider to be above normal for a dog of this size and age. While you are listening to the heart with the stethoscope, you palpate the femoral pulses, which are synchronized with the heart rate and very strong.

The electrocardiogram indicates that the dog has sinus tachycardia; the atrial and ventricular rates are both 152 beats/min. The R waves are abnormally large in leads II and III (2.5 and 3.5 mV, respectively). The QRS complex in lead I shows a large negative deflection followed immediately by a slightly larger positive deflection.

Thoracic radiographs show a generalized enlargement of the heart. The initial portion of the pulmonary artery is also

substantially larger than normal, and the pulmonary blood vessels appear generally to be more prominent than normal.

An echocardiogram confirms the presence of a *patent ductus arteriosus.*

Comment. A murmur in a young, otherwise-healthy dog is most likely the result of a congenital cardiac abnormality. A continuous murmur can occur only if a defect causes turbulent flow throughout both systole and diastole. Because flow can occur only when there is a pressure gradient, the defect in this dog must be in a location where there is a substantial pressure gradient throughout the cardiac cycle. No single intracardiac defect meets this criterion; that is, a stenotic or regurgitant valve produces either a systolic murmur or a diastolic murmur, but not both. A valve that is both stenotic and regurgitant produces two murmurs: one in systole and one in diastole. In such a case, however, there are brief moments during the cardiac cycle when no pressure gradient exists across the valve, so there are moments of silence between the systolic murmur and the diastolic murmur. (Admittedly, if the heart rate is high, these moments of silence are very brief, and the two murmurs can be mistaken for a continuous murmur, particularly in the case of combined aortic stenosis and regurgitation.)

The most common cardiac defect that causes turbulent flow throughout both systole and diastole is a *patent ductus arteriosus* (PDA). This vessel is normal in the fetus but should close shortly after birth. The flow through a PDA is continuous because aortic pressure is higher than pulmonary artery pressure throughout the cardiac cycle. The resulting murmur is usually heard best in the left third intercostal space. All the other clinical signs in this dog are consistent with the diagnosis of PDA. The prominence of the pulmonary vessels on the radiographs indicates that pressure and flow are abnormally high in the pulmonary artery and its branches. In a dog with a PDA the pulmonary artery receives blood flow from both the right ventricle and the aorta, which increases both pulmonary arterial pressure and pulmonary flow.

The radiographs and electrocardiograms indicate that this dog has both right and left ventricular hypertrophy. The large R waves in leads II and III indicate left ventricular hypertrophy, and the large negative deflection during the QRS complex in lead I suggests that the right ventricle is hypertrophic as well. The left ventricle becomes hypertrophic in a dog with PDA because it is called on to pump three to five times the normal cardiac output. (It pumps a near-normal volume of blood to the organs of the systemic circulation and two to four times that much through the PDA.) The flow through the PDA is large because the PDA offers little resistance to flow. The demand on the left ventricle to pump so much blood (increased volume work) leads to left ventricular hypertrophy. The volume of blood pumped by the right ventricle is almost normal; it only needs to pump the blood that returns through the venae cavae from the systemic organs. However, the right ventricle must develop higher systolic pressures than normal to eject this blood into the pulmonary artery because pulmonary artery pressure is higher than normal, as explained earlier. This increase in pressure work leads to right ventricular hypertrophy.

Because the PDA carries so much blood away from the aorta, dogs with PDA tend to have an abnormally low aortic pressure. Diastolic pressure is particularly reduced because of the rapid outflow of blood from the aorta during ventricular diastole. Therefore, PDA is typically associated with low mean aortic pressure but elevated pulse pressure (review Figure 22-8, *G*).

Two mechanisms work together to keep blood flow to the systemic organs almost normal despite the fact that a large fraction of cardiac output is "lost" through the PDA. First, reflex mechanisms (discussed in Chapter 25) increase sympathetic activity to the heart, which increases heart rate and contractility above normal. These sympathetic effects keep left ventricular output (and aortic pressure) sufficiently high to supply blood to the systemic organs, despite the PDA. Second, metabolic control mechanisms cause the systemic organs to vasodilate, which keeps their blood flow almost normal despite the subnormal aortic pressure.

The compensatory mechanisms just described allow most dogs with a PDA to maintain a nearly normal blood flow to the systemic organs at rest. Several months may pass before the dog's owner notices limitations in the dog's activity or growth. Eventually, however, the heart cannot increase its output sufficiently to supply the systemic blood flow needed by the muscles during exercise, so as time passes, a puppy with a PDA becomes less playful and energetic than its normal littermates. Also, if the heart is unable to supply the blood flow needed by metabolically active tissues, the owner may notice some stunting of growth. In any case, a dog with a widely open ductus has a poor long-term prognosis, unless treated.

Treatment. You show the dog's owner a diagram of the fetal circulation and explain that the *ductus arteriosus* normally closes and seals itself within 1 to 6 weeks after birth, but that the *ductus* fails to close spontaneously in about 1 of every 700 newborns (the condition is four times more common in female pups than in male pups). Treatment involves closure of the *ductus,* either by ligation during open-chest surgery or by insertion of a specially designed plug during a cardiac catheterization procedure. Most dogs treated before age 6 months go on to lead completely normal lives. However, you inform the owner that PDA is hereditary and that this puppy should probably not be used for breeding.

The owner elects to have the dog treated surgically, and the surgery is successful. The murmur and cough disappear immediately. Within 1 week the dog is noticeably more energetic. At age 6 months, the dog has "grown into" her enlarged heart, and all physical findings are within normal limits.

ENDOTOXEMIA IN A FOAL

History. A 3-day-old Tennessee Walking Horse filly presents with progressive signs of lethargy, diarrhea, decreased eating, and weakness. The owners report that the filly appeared to be normal at birth, and shortly thereafter, she nursed briefly. Her condition did not cause them great concern until about a day ago.

Clinical Examination. The filly is markedly dehydrated. Although the environment is not cold, the filly has subnormal rectal temperature, suggesting that she can no longer thermoregulate. She has increased heart rate and respiratory rate. Her mucous membranes are dark red and exhibit prolonged capillary refill time, and her distal extremities feel cool. These signs indicate poor perfusion, low blood pressure, and hypoxia. She has hypermotile gut sounds and diarrhea. She only supports herself voluntarily for short periods of time. You suspect that the foal has an infection and is likely septic (bacteria and endotoxins in the blood). You submit a venous blood sample for immunoglobulin status (IgG), complete blood count (CBC) and biochemical profile, and culture. You also collect an arterial blood sample for measurement of blood gases.

Comment. This foal likely has acquired an infection from either ingestion or inhalation of contaminated liquid. Foals are frequently infected with gram-negative bacteria, and if they have not received adequate protection from antibodies in colostrum, the bacteria proliferate and release endotoxins. Circulating in the bloodstream, the bacteria and endotoxins stimulate the production of a large number of chemical mediators that cause inflammation, increased capillary permeability, intravascular coagulation, cardiac depression, poor perfusion, and hypoxia. These chemical mediators include host proinflammatory intercellular signaling molecules (i.e., cytokines and chemokines), procoagulants, adhesion molecules, enzymes, and acute phase proteins (plasma concentrations change in association with inflammatory states). An additional complication is hypoproteinemia, resulting both from impaired intestinal absorption of nutrients and from loss of protein in the diarrhea.

Treatment. The bacterial infection must be treated aggressively with appropriate antibiotics. Additional treatments would include nutritional support, oxygen, and intravenous fluid therapy. The fluid therapy would include a combination of plasma (to counteract hypoproteinemia) and electrolytes (to correct dehydration). Glucose (dextrose in water) can also be given intravenously to prevent hypoglycemia. The foal must be monitored closely so that she does not become overhydrated, as she will then develop edema due to hypoproteinemia. Pulmonary edema would further jeopardize the oxygenation of blood and the delivery of adequate oxygen to the tissues. Additional drug treatments may be needed to enhance cardiac function and support blood pressure. In cases such as this one, foals are encouraged to nurse, or else are provided with milk, provided they do not develop ileus (a type of intestinal obstruction). Alternatively, parenteral (non-oral, often intravenous) nutrition can be provided. Anti-inflammatory medications can be helpful; however, they must be used with caution, as they can cause renal (kidney) failure or gastric and colonic ulcers. Prognosis is guarded in these cases because of the severity of disease and the lasting damage that it can cause in multiple organ systems (also including lungs and joints).

PRACTICE QUESTIONS

1. The increase in coronary blood flow during exercise is:
   a. Called Starling's law of the heart.
   b. Caused by activation of parasympathetic nerves to the heart.
   c. Caused by compression of the coronary blood vessels during systole.
   d. Closely matched to the metabolic requirements of the heart.
   e. Called reactive hyperemia.

2. A dog with an arterial blood pressure of 120/80 mm Hg has a cerebral blood flow of 100 mL/min. When blood pressure is increased to 130/100 mm Hg, the cerebral blood flow increases to 105 mL/min. This is an example of:
   a. Active hyperemia.
   b. Autoregulation.
   c. Reactive hyperemia.
   d. The blood-brain barrier.
   e. Hypoxic vasoconstriction.

3. Local, metabolic control of blood flow through skeletal muscle:
   a. Characteristically dominates over neurohumoral control.
   b. Characteristically is subservient to neurohumoral control.
   c. Can either dominate or be subservient to neurohumoral control, depending on whether the muscle is exercising or resting.
   d. Depends primarily on changes in the resistance of the veins within the muscle.
   e. Depends on the release of histamine from mast cells within the skeletal muscle.

4. In response to an increase in perfusion pressure, the arterioles of an autoregulating organ _____, and the vascular resistance of the organ _____.
   a. constrict; increases
   b. constrict; decreases
   c. dilate; increases
   d. dilate; decreases

5. When a young dog with a PDA attempts vigorous exercise:
   a. Arterioles in the exercising skeletal muscle constrict.
   b. Oxygen concentration in the skeletal muscle interstitial fluid decreases.
   c. Left ventricular output decreases.
   d. Right ventricular output decreases.
   e. Mean arterial pressure increases to very high levels.

6. Which of the following characteristically acts as a paracrine to cause vasoconstriction in systemic arterioles?
   a. Carbon dioxide
   b. Nitric oxide
   c. Prostacyclin (PGI_2)
   d. Endothelin-1 (ET1)
   e. Bradykinin

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CHAPTER 25
Neural and Hormonal Control of Blood Pressure and Blood Volume

KEY POINTS

1. Neurohumoral mechanisms regulate blood pressure and blood volume to ensure adequate blood flow for all body organs.
2. The autonomic nervous system affects the cardiovascular system through the release of epinephrine, norepinephrine, and acetylcholine.
3. The arterial baroreceptor reflex regulates arterial blood pressure.
4. The atrial volume receptor reflex regulates blood volume and helps to stabilize blood pressure.
5. The cardiovascular state of conscious subjects is determined by an ongoing and ever-changing mixture of reflex effects and psychogenic responses.

Neurohumoral Mechanisms Regulate Blood Pressure and Blood Volume to Ensure Adequate Blood Flow for All Body Organs

The influences of the nervous system and hormones on the cardiovascular system are referred to collectively as the *neurohumoral mechanisms* of cardiovascular control. The neurohumoral mechanisms are also called *extrinsic control mechanisms* because they act on organs from the outside. As described in Chapter 24, the mechanisms of cardiovascular control that act locally, within individual tissues, are referred to as *intrinsic control mechanisms.* The local, or intrinsic, mechanisms predominate over extrinsic mechanisms in the control of blood flow to the "critical" organs, which include the heart (i.e., coronary circulation), brain, and working (exercising) skeletal muscle. In contrast, neurohumoral, or extrinsic, control mechanisms predominate over the intrinsic mechanisms in the control of blood flow to the "noncritical" organs, which include the kidneys, the splanchnic organs, and resting skeletal muscle. The noncritical organs are those that can withstand temporary reductions in blood flow (and metabolism) to make extra blood flow available for the critical organs, whose optimal function on a moment-to-moment basis may be necessary for survival (e.g., in a life-threatening situation involving "fight or flight").

Neurohumoral mechanisms also control the heart rate and cardiac contractility. This allows cardiac output to be adjusted to provide adequate blood flow for all the systemic organs, or at least for the critical organs. An important distinction is that cardiac muscle is under neurohumoral control, whereas the coronary blood vessels are primarily under local control. When neurohumoral mechanisms increase the heart rate and cardiac contractility, the cardiac metabolic rate also increases. The increased metabolic rate acts via local metabolic control mechanisms to dilate coronary arterioles, which increases coronary blood flow.

To appreciate the importance of neurohumoral control mechanisms, consider what would happen in their absence. For example, what would occur during exercise if all the body organs relied on local control mechanisms to adjust their blood flow? At the onset of exercise, metabolic control mechanisms would cause vasodilation in the exercising skeletal muscles. Vascular resistance would decrease in the exercising muscles, and the blood flow through the muscles would increase. However, decreasing the vascular resistance in skeletal muscles would lower the total peripheral resistance (TPR). As a consequence, arterial blood pressure would decrease. This would decrease the perfusion pressure for all the systemic organs, and blood flow would therefore decrease below normal levels in the brain, kidneys, splanchnic organs, and so forth. The decreased blood flow in these organs would trigger autoregulatory responses, and these organs would vasodilate. However, the vasodilation would lower the TPR even further, which would reduce arterial pressure even more. This in turn would limit the increase in skeletal muscle blood flow. The end result would be some increase in blood flow in the exercising muscle and decreased blood flow elsewhere, but none of the organs (including skeletal muscle) would be receiving sufficient blood flow to meet their metabolic needs. Arterial pressure would be dangerously low, and the animal would exhibit profound exercise intolerance.

Neurohumoral control mechanisms allow an animal to avoid these complications. First, cardiac output is increased sufficiently to meet the increased need for blood flow in the exercising muscle (and in the coronary circulation) while keeping all the other organs supplied with a normal blood flow. If cardiac output cannot be increased sufficiently to meet all these needs, the control mechanisms take the additional step of temporarily reducing blood flow in the noncritical organs and making this extra flow available to the critical organs.

How do the neurohumoral control systems "know" when cardiac output is sufficiently high to meet the needs of all the organs and when to initiate vasoconstriction in the noncritical organs? An indirect strategy is used: cardiac output is increased enough to keep arterial pressure at a normal level. As long as arterial pressure is maintained at the normal level, local metabolic control mechanisms can successfully match blood flow to

metabolic need in each individual organ. If cardiac output cannot be sufficiently increased to keep arterial pressure from falling, neurohumoral mechanisms initiate vasoconstriction in the noncritical organs. Thus, neurohumoral control mechanisms will deprive noncritical organs of an ideal level of blood flow if the critical organs are in need of more blood flow than can be supplied by the heart.

There are many important neurohumoral control mechanisms, but four are emphasized in the following presentation. The first two of these are *cardiovascular reflexes.* The *arterial baroreceptor reflex* works to regulate arterial pressure through the continual adjustment of cardiac output and vascular resistance (in the noncritical organs). The *atrial volume receptor reflex* works in conjunction with the arterial baroreceptor reflex to regulate arterial pressure and to adjust cardiac preload. The other two neurohumoral mechanisms described in this chapter are the *defense-alarm reaction* (the "fight or flight response") and *vasovagal syncope* (the "playing dead" reaction). These responses exemplify *psychogenic influences* on the cardiovascular system.

The Autonomic Nervous System Affects the Cardiovascular System Through the Release of Epinephrine, Norepinephrine, and Acetylcholine

The autonomic nervous system is the "neuro" arm of neurohumoral control. Sympathetic and parasympathetic neurons influence the cardiovascular system through the release of the neurotransmitters norepinephrine and acetylcholine. In addition, sympathetic nerves affect the cardiovascular system by stimulating the release of epinephrine and norepinephrine from the adrenal medulla. The adrenal secretions enter the bloodstream as hormones and circulate throughout the body. Chapter 13 contains additional, basic information about the autonomic nervous system.

Whether acting as neurotransmitters or as hormones, epinephrine, norepinephrine, and acetylcholine exert their cardiovascular effects by activating receptor proteins located in the membranes of cardiac muscle cells or of the smooth muscle cells (or in some cases the endothelial cells) in the walls of blood vessels. The receptors activated by epinephrine and norepinephrine are called *adrenergic receptors* (named after the *adrenal gland*). There are two major types: *α-adrenergic receptors* and *β-adrenergic receptors*. The α-adrenergic receptors are subdivided into α_1 and α_2. There are three subtypes of β-receptors: β_1, β_2, and β_3, with the first two of these being important in cardiovascular control.

Acetylcholine activates *cholinergic receptors.* There are two major types: *muscarinic cholinergic receptors* and *nicotinic cholinergic receptors.* The main cardiovascular effects of acetylcholine are mediated through muscarinic cholinergic receptors located on cardiac, smooth muscle, or endothelial cells. Of five subtypes of muscarinic receptors, the M_2 and M_3 receptor subtypes have the greatest cardiovascular importance.

Table 25-1 summarizes the main cardiovascular consequences of the activation of adrenergic and cholinergic receptors. α-Adrenergic receptors (both α_1 and α_2) are located in the cell membranes of the smooth muscle cells of the arterioles in all organs and in the smooth muscle cells of the abdominal veins. These adrenergic receptors are innervated by postganglionic sympathetic neurons, which release the neurotransmitter norepinephrine. Circulating epinephrine or norepinephrine can also activate the adrenergic receptors. Activation of these α-adrenergic receptors leads to constriction of the arterioles or the veins.

Arteriolar vasoconstriction increases the resistance and decreases the blood flow through an organ. If one or more major body organs are vasoconstricted, the *total peripheral resistance* (TPR) increases. TPR (along with cardiac output) determines arterial blood pressure, so widespread α-adrenergic vasoconstriction in the body leads to an increase in arterial blood pressure. The increase in arterial pressure increases the driving force for blood flow in all organs of the systemic circulation. In effect, the sympathetic nervous system can vasoconstrict some organs and thereby direct more blood flow to other, non-vasoconstricted organs.

The major role of veins is to act as reservoirs for blood. *Venoconstriction* displaces venous blood toward the central circulation, which increases central venous pressure, right ventricular preload, and (by the Starling mechanism) stroke volume. Venoconstriction in the abdominal organs is particularly effective in increasing central venous pressure. Venoconstriction causes a relatively small increase in the resistance to blood flow through an organ because the veins, whether dilated or constricted, offer much less resistance to blood flow than do the arterioles.

Sympathetic control of the heart is exerted through the β_1-adrenergic receptors, which are found on every cardiac muscle cell. These beta receptors are activated by norepinephrine or epinephrine. Chapters 19 and 21 discuss the effects of activation of the cardiac β-adrenergic receptors. In brief, pacemaker rate increases, cell-to-cell conduction velocity increases, and refractory period decreases. In addition, contractility is increased, so the cardiac contractions are quicker and stronger. The overall effect is increased heart rate and increased stroke volume.

β_2-Adrenergic receptors are found on the arterioles, particularly in the coronary circulation and in skeletal muscles. The activation of arteriolar β_2-adrenergic receptors causes relaxation of the vascular smooth muscle and dilation of the arterioles. However, these β_2-adrenergic receptors are not innervated by the sympathetic nervous system, so they are not activated directly by sympathetic nerves. Instead, they respond to circulating epinephrine and norepinephrine (released from the adrenal medulla). The adrenal medulla releases epinephrine and norepinephrine in situations that involve trauma, fear, or anxiety. Dilation of arterioles in the coronary circulation and in skeletal muscles is appropriate in such "fear, fight, or flight" response situations because the dilation results in an anticipatory increase in blood flow to the heart and skeletal muscle. Appropriately for its role in emergency situations, β_2-adrenergic vasodilation can overpower α-adrenergic vasoconstriction in the coronary circulation and in skeletal muscles.

Parasympathetic effects on the heart are mediated via the neurotransmitter acetylcholine, which activates cholinergic muscarinic receptors of the M_2 type. Cardiac muscle cells of the sinoatrial and atrioventricular nodes are densely innervated by postganglionic parasympathetic neurons. Atrial cells also receive strong parasympathetic innervation. In these parts of the heart, activation of cardiac M_2 receptors has effects basically opposite to those of the activation of β_1-adrenergic receptors. Parasympathetic activation powerfully slows the cardiac pacemakers, decreases cell-to-cell conduction velocity, and increases refractory period. Curiously, ventricular muscle cells receive very little direct parasympathetic innervation. Therefore, parasympathetic activation has only a minor, direct effect on ventricular contractility. However, parasympathetic neurons do exert an interesting, indirect effect on ventricular muscle cells. Most parasympathetic neurons in the ventricles release their acetylcholine onto sympathetic

TABLE 25-1 Receptors Involved in Autonomic Control of the Cardiovascular System

Receptor Type	Location	Usual Activator	Effect of Activation	Function
		α Adrenergic		
α_1 and α_2	Arterioles (all organs)	Norepinephrine from sympathetic neurons, or circulating epinephrine and norepinephrine	Vasoconstriction	Decreases blood flow to organs; increases total peripheral resistance **(major effect)**
	Veins (abdominal organs)	Norepinephrine from sympathetic neurons, or circulating epinephrine and norepinephrine	Venoconstriction	Displaces venous blood toward heart
		β Adrenergic		
β_1	Heart (all cardiac muscle cells)	Norepinephrine from sympathetic neurons, or circulating epinephrine and norepinephrine	Increased pacemaker rate; faster speed of conduction; decreased refractory period; quicker, stronger contractions	Increases heart rate, stroke volume, and cardiac output **(major effects)**
β_2	Arterioles (coronary and skeletal muscle)	Circulating epinephrine and norepinephrine [β_2 receptors not innervated]	Vasodilation	Increases coronary blood flow; increases skeletal muscle blood flow
		Muscarinic Cholinergic		
M_2	Heart (all cardiac muscle cells, but sparse direct innervation of ventricular muscle cells)	Acetylcholine from parasympathetic neurons	Opposite of β_1	Decreases heart rate and cardiac output **(major effect)**
	Sympathetic nerve endings at ventricular muscle cells	Acetylcholine from parasympathetic neurons	Inhibition of norepinephrine release from sympathetic neurons	Decreases magnitude of sympathetic effects on ventricular muscle cells
M_3	Arterioles (coronary)	Acetylcholine from parasympathetic neurons	Vasodilation (mediated via nitric oxide)	Increases coronary blood flow (minor effect)
	Arterioles (genitals)	Acetylcholine from parasympathetic neurons	Vasodilation (mediated via nitric oxide)	Causes engorgement and erection
	Arterioles (skeletal muscle)	Acetylcholine from specialized sympathetic neurons	Vasodilation (mediated via nitric oxide)	Increases muscle blood flow (in anticipation of exercise)
	Arterioles (most other organs)	[Receptors not innervated; normal activator unknown]	Vasodilation (mediated via nitric oxide)	Function unknown

neuron terminals, rather than directly onto ventricular muscle cells. This acetylcholine activates muscarinic cholinergic receptors on the sympathetic neuron terminals, which inhibits the release of norepinephrine from the terminals and thus weakens the effects of sympathetic activity on ventricular cells. By decreasing heart rate and by opposing sympathetic effects on ventricular contractility, parasympathetic activation can profoundly decrease cardiac output.

Cholinergic muscarinic receptors of the M_3 type are found on the endothelial cells and also on the smooth muscle cells of most arteries and arterioles. Activation of M_3 receptors on smooth muscle cells causes them to contract. However, this *vasoconstrictor* effect is usually overridden by a *vasodilatory* effect of activating the M_3 receptors on the vascular endothelial cells. In this strange arrangement, activation of M_3 receptors on endothelial cells causes the synthesis of *nitric oxide,* which then diffuses out of the endothelial cells and into the nearby smooth muscle cells, where it causes vasodilation. The vasodilatory effect of stimulating the M_3 receptors on endothelial cells is stronger than the vasoconstrictor effect of stimulating the M_3 receptors on smooth muscle cells.

The M_3 receptors on vascular endothelial cells are innervated in three organs. Parasympathetic neurons innervate vascular M_3 receptors in the coronary circulation, where the effect of parasympathetic activation is vasodilation. This vasodilatory effect is minor, however, and the function of this innervation is unclear. In the blood vessels of the external genital organs, parasympathetic neurons release both acetylcholine and nitric oxide. The acetylcholine activates M_3 receptors on the endothelial cells to stimulate the release of additional nitric oxide from endothelial cells. The nitric oxide relaxes vascular smooth muscle, which causes vasodilation, engorgement of the organs with blood, and

therefore erection. The third tissue in which vascular M_3 receptors are innervated is skeletal muscle. In some species (e.g., cats and dogs) but not in others (e.g., primates), the M_3 receptors of skeletal muscle blood vessels are innervated by special postganglionic sympathetic neurons that release acetylcholine as a neurotransmitter (rather than the usual, norepinephrine). These *sympathetic cholinergic neurons* appear to be activated specifically in anticipation of muscular exercise and during the "fear, fight, or flight" (defense-alarm) reaction. The resulting vasodilation increases blood flow through the skeletal muscle just before and during the initiation of exercise. Although primates do not have sympathetic cholinergic vasodilatory nerves, they can bring about an anticipatory vasodilation of skeletal muscle arterioles through activation of β_1-adrenergic receptors by circulating epinephrine and norepinephrine, as mentioned earlier.

To summarize, arteries and arterioles throughout the body have M_3 adrenergic receptors, and these blood vessels dilate when exposed to acetylcholine (with nitric oxide serving as the mediator). But acetylcholine-releasing autonomic neurons only innervate the blood vessels in the heart, the external genitalia, and (in some species) skeletal muscle. The functional significance of the M_3 receptors on arteries and arterioles in other organs is unclear because no neurons (either sympathetic or parasympathetic) appear to innervate them, and neither acetylcholine nor any other muscarinic receptor agonist normally circulates in the bloodstream.

Of all the autonomic influences on the cardiovascular system just mentioned, three stand out as most important. The first is α_1- and α_2-adrenergic vasoconstriction in the arterioles of all body organs, which is brought about by the sympathetic nervous system. The second is β_1-adrenergic excitation of cardiac muscle, which is brought about by the sympathetic nervous system and results in an increased heart rate and stroke volume. The third is the decrease in heart rate brought about by parasympathetic activation of cardiac M_2 receptors.

The Arterial Baroreceptor Reflex Regulates Arterial Blood Pressure

Arterial blood pressure is monitored by pressure-sensitive nerve endings known as *baroreceptors*. The baroreceptors send afferent impulses to the central nervous system (CNS), which reflexively alters cardiac output and vascular resistance (in noncritical organs) to keep blood pressure at a set point. The reflex is called the *arterial baroreceptor reflex*.

The arterial baroreceptors are specialized nerve endings that are embedded in the walls of the carotid arteries and aortic arch (Figure 25-1). The baroreceptors are concentrated at the origin of each internal carotid artery in enlarged parts of the arteries called the *carotid sinuses*. Similar nerve endings are found in the wall of the aortic arch, especially at the origin of its major branches. These nerve endings are sensitive to stretch *(distention)* of the arterial wall. In effect, they sense arterial pressure because blood pressure is the natural force that distends these arteries. Therefore, these nerve endings are called *baroreceptors* (literally, "pressure sensors") even though the actual physical factor being sensed is not pressure but rather stretch.

With every systolic ejection from the heart, blood distends the aorta and arteries, including the carotid sinuses, which causes the baroreceptors to initiate neural impulses (action potentials). Figure 25-2 illustrates that the frequency of these action potentials is proportional to the arterial blood pressure. The tracing on

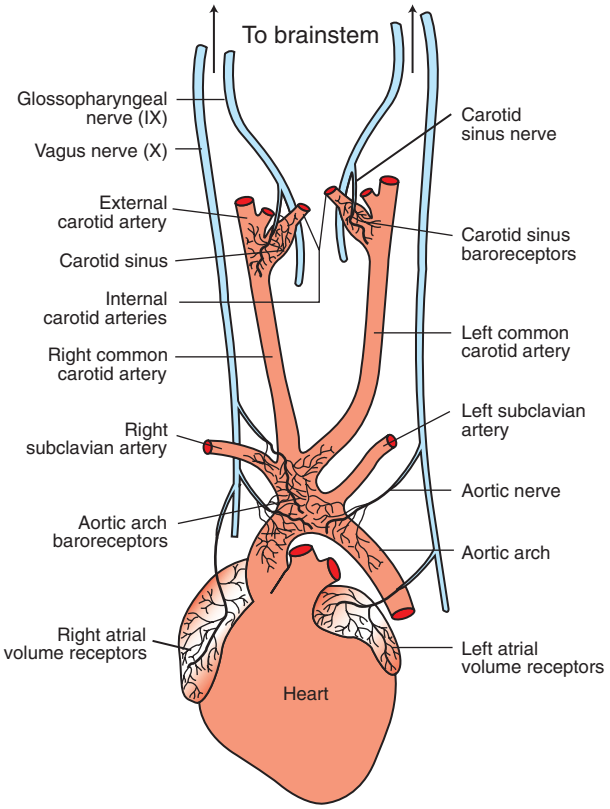

FIGURE 25-1 Arterial baroreceptors are located in the walls of the carotid sinuses and in the walls of the aortic arch and its major branches. The atrial volume receptors are located in the walls of the right and left atria. See text for a description of the neural pathways followed by the baroreceptor and volume receptor afferents.

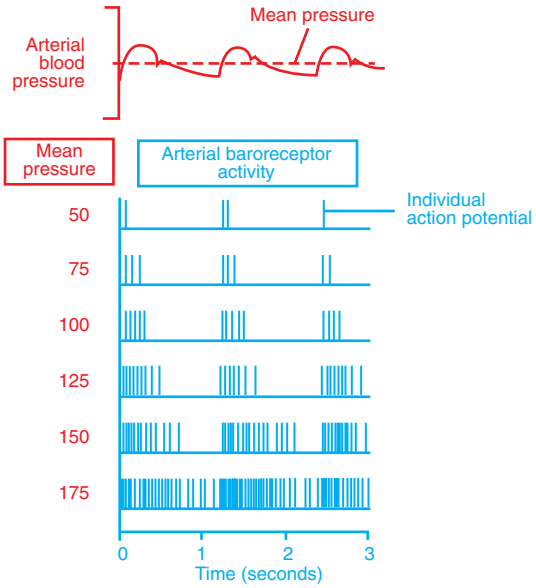

FIGURE 25-2 Each arterial pressure pulse causes action potentials to be generated in baroreceptor afferent neurons. The number of action potentials generated per heartbeat increases dramatically with increases in mean arterial pressure.

the top shows the pulsatile arterial pressure on three successive heartbeats. The mean level of arterial pressure is indicated by the dashed line. The tracings below depict the typical patterns of action potentials that would be seen in a baroreceptor afferent neuron for various levels of *mean arterial pressure* (MAP). When MAP is lower than normal (e.g., 50 mm Hg), there are only one or two action potentials with each heartbeat. These action potentials occur during the rapid upstroke of the pressure wave, because the baroreceptors are sensitive to the rate of change of pressure as well as to mean pressure. When MAP is at a higher level (e.g., 75 mm Hg), more action potentials are formed during each heartbeat, but the action potentials still tend to occur during the rapid pressure increase at the beginning of the cardiac ejection. The higher the MAP, the more action potentials are formed in each heartbeat. Thus the arterial baroreceptors signal increases in pressure by increasing their action potential frequency. Because the baroreceptors are active when arterial pressure is normal (MAP near 100 mm Hg), they can also signal a decrease in arterial pressure by decreasing their action potential frequency.

The afferent neurons from the aortic arch baroreceptors join the vagus nerves (see Figure 25-1). In some species the aortic baroreceptor afferents form a distinct bundle within the vagal nerve sheath, called the *aortic depressor nerve*. The stretch receptors in the carotid sinuses have their afferents in the carotid sinus nerves (Hering's nerves), which join the glossopharyngeal (ninth cranial) nerve. By way of these afferent neurons, the brain receives beat-by-beat information about the level of arterial blood pressure.

Figure 25-3 summarizes the reflex consequences of a decrease in blood pressure, which decreases afferent baroreceptor activity. The brain responds to a decrease in the afferent activity from the baroreceptors by increasing sympathetic activity. In the heart, sympathetic activation results in increased stroke volume and heart rate, which increases cardiac output. The increase in cardiac output helps to restore blood pressure toward normal. The sympathetically driven increase in heart rate is augmented by a simultaneous reduction in parasympathetic activity to the sinoatrial node. Thus the baroreceptor reflex uses reciprocal changes in sympathetic and parasympathetic activity to control heart rate. Sympathetic activity is also increased to the arterioles of all organs, but the consequent vasoconstriction is most pronounced in the noncritical organs (kidney, splanchnic organs, and resting skeletal muscle) because these are the organs in which neurohumoral control of arterioles predominates over local (metabolic) control. Vasoconstriction in the noncritical organs increases the resistance to blood flow through these organs and therefore increases total peripheral resistance (TPR). The increase in TPR helps to restore arterial blood pressure back toward its normal level. The fact that resistance increased in the noncritical organs has the effect of preserving adequate blood flow in the critical organs.

To understand fully the function of the baroreceptor reflex, it is important to recognize that the reflex does not *reverse* disturbances that alter blood pressure but only *minimizes* them. Also, it is important to distinguish between cause and effect when thinking about the baroreflex. What *causes* blood pressure to decrease *below normal* is a decrease *below normal* in cardiac output, TPR, or both. *There is no other way to lower blood pressure.* If TPR falls below normal and causes blood pressure to decrease below normal, the *compensatory response* of the baroreceptor reflex is (1) to increase cardiac output above normal through increased sympathetic (and decreased parasympathetic) activation of the heart and (2) to minimize the decrease in TPR by initiating a sympathetic vasoconstriction in the noncritical organs. After compensation by the baroreceptor reflex, cardiac output is above normal. TPR is still *below* normal, but not as far below normal as in the uncompensated state. Blood pressure is still below normal, but not as far below normal as in the uncompensated state. Similarly, if the initiating disturbance is that cardiac output falls below normal, the compensatory response of the baroreceptor reflex is to increase TPR *above* normal and to restore cardiac output *toward* normal. Blood pressure is still below normal, but not as far below normal as in the uncompensated state.

All the reflex responses just described for a decrease in arterial blood pressure occur in reverse in response to an increase in arterial blood pressure above its normal level. Thus the *baroreflex* acts to counteract and minimize both decreases and increases in blood pressure.

The baroreflex responds quickly, initiating compensations for disturbances in blood pressure within 1 second. The reflex is also very powerful. For example, a hemorrhage that would decrease blood pressure by 40 to 50 mm Hg if there were no baroreflex decreases blood pressure by only 10 to 15 mm Hg in an animal with intact baroreflexes. The baroreflex also acts to maintain blood pressure close to normal during changes in posture or activity. In a dog without baroreflexes, changes in posture are accompanied by large, uncontrolled variations in blood pressure,

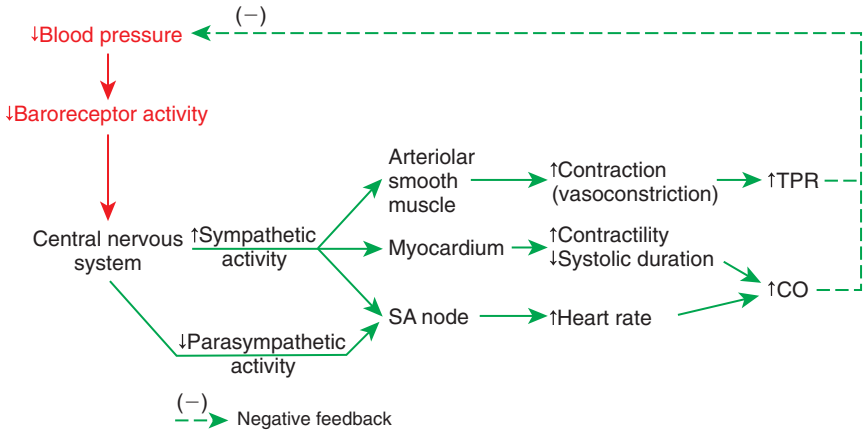

FIGURE 25-3 The arterial baroreceptor reflex responds to decreases in blood pressure *(top left)* by increasing cardiac output *(CO)*, total peripheral resistance *(TPR)*, or both *(far right)*. These reflex effects offset the initial fall in blood pressure *(dashed line)*. *SA*, Sinoatrial.

as shown in Figure 25-4. By minimizing fluctuations in blood pressure, the baroreflex helps ensure an adequate driving force for blood flow to the critical organs.

Although the baroreceptor reflex is essential for the moment-to-moment stability of blood pressure, it does not appear to be the major mechanism responsible for setting the long-term level of arterial blood pressure, because baroreceptors slowly adapt or *reset* to the prevailing level of arterial pressure. In other words, the baroreceptors come to accept whatever the prevailing blood pressure is as if it were the normal pressure. For example, in an animal or a human who has been hypertensive for a few days or weeks, the baroreflex functions to regulate blood pressure at the elevated level rather than to restore blood pressure toward its normal level. Also, the baroreflex can become reset in a downward direction during a period of sustained hypotension. For example, in chronic heart failure, in which arterial pressure may be below normal for days or weeks, the baroreflex appears to regulate blood pressure at a depressed level rather than to push it back toward its normal level.

In summary, the baroreflex responds quickly and powerfully to counteract sudden changes in blood pressure, but it has little influence on the long-term level of blood pressure over days or weeks.

The Atrial Volume Receptor Reflex Regulates Blood Volume and Helps to Stabilize Blood Pressure

The *atrial volume receptor reflex* is initiated by specialized sensory nerve endings that are located primarily in the walls of the left and right atria (see Figure 25-1). These nerve endings are activated by stretch, but they are called *volume receptors* because the volume of blood in each atrium determines how much the atrial wall is stretched. For example, a decrease in the total blood volume of an animal (e.g., hemorrhage) results in a decrease in the amount of blood in the major veins and in the atria. When atrial volume decreases, atrial pressure decreases, as does the stretch on the atrial walls. This decreases the frequency of action potentials generated in atrial stretch receptors. Conversely, increases in blood volume result in increased atrial stretch and an increased frequency of action potentials generated by the atrial stretch receptors. Therefore, these atrial stretch receptors are sensitive detectors of atrial blood volume and, indirectly, of total blood volume. Additional stretch-sensitive nerve endings, which act in concert with the atrial volume receptors, are located in the walls of the pulmonary veins.

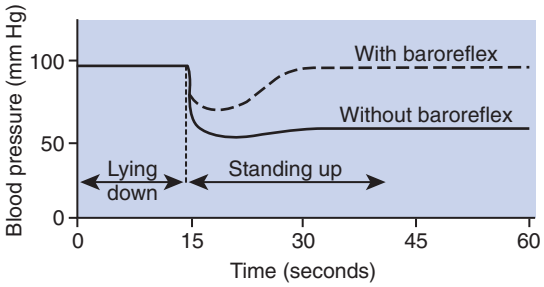

FIGURE 25-4 The baroreflex is essential for normal, moment-to-moment stability of blood pressure. Dogs in which baroreflexes are eliminated exhibit much larger swings in blood pressure in response to postural changes than do dogs with intact baroreflexes.

Figure 25-5 summarizes the reflex consequences of a decrease in blood volume, which decreases atrial volume receptor activity. The CNS responds reflexively to the decrease in afferent activity from the atrial volume receptors by increasing sympathetic efferent activity to the heart and systemic arterioles and decreasing parasympathetic efferent activity to the heart. In this respect, the atrial volume receptor reflex and the baroreceptor reflex exert synergistic effects; that is, a decrease in blood volume leads (via the atrial volume receptor reflex) to the same responses that are triggered by the baroreflex in response to a decrease in arterial blood pressure. In both cases the reflex responses include an increase in cardiac contractility, a decrease in systolic duration, and an increase in heart rate as well as arteriolar vasoconstriction in the noncritical organs. By initiating these responses, the atrial volume receptor reflex helps to combat the decrease in arterial blood pressure that would otherwise result from a decreased blood volume. In this regard, the atrial volume receptor reflex augments the effectiveness of the baroreceptor reflex as a regulator of blood pressure.

The atrial volume receptor reflex acts in three additional ways to help restore lost blood volume (see Figure 25-5). First, the reflex acts through the hypothalamus to increase the sensation of thirst. If water is available, the animal drinks. This provides the fluid necessary to increase blood volume back toward normal. Second, the atrial volume receptor reflex acts through the hypothalamus and pituitary gland to increase the release of *antidiuretic hormone* (ADH, also known as *arginine vasopressin*). ADH is synthesized in hypothalamic neurons, which transport it to the

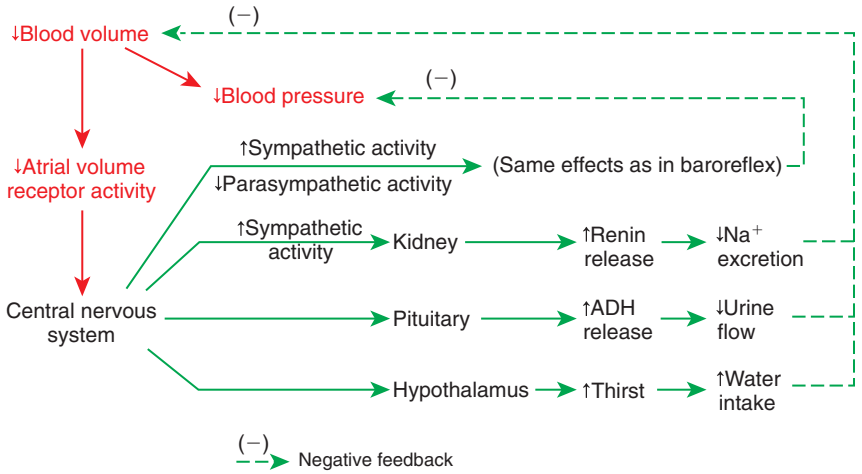

FIGURE 25-5 The atrial volume receptor reflex responds to a decrease in blood volume by decreasing sodium and water loss in the urine and by increasing oral water intake. The reflex also helps support blood pressure by increasing cardiac output and total peripheral resistance (similar to baroreflex). *ADH,* Antidiuretic hormone.

posterior pituitary gland. From there, ADH is released into the bloodstream (see Chapter 33). ADH acts on the kidneys to decrease urine production. The third way in which the atrial volume receptor reflex helps to restore lost blood volume is to stimulate the release of the hormone *renin* from the kidneys. Renin acts to increase the production of the hormone *angiotensin II,* which acts to increase production of the hormone *aldosterone,* which acts to decrease the amount of sodium excreted by the kidneys; that is, activation of the *renin-angiotensin-aldosterone system* causes the body to conserve available sodium.

The combination of decreased sodium excretion (by the actions of renin) and decreased urine flow (by the actions of ADH) results in the conservation of body fluid. The conservation of body fluid, combined with an increased water intake, eventually restores blood volume back toward normal.

Although not diagrammed in Figure 25-3, the arterial baroreceptor reflex also responds to decreases in arterial pressure by increasing thirst, ADH release, and renin release. An increase in arterial pressure above normal initiates the opposite effects. Thus the arterial baroreceptor reflex and the atrial volume receptor reflex are synergistic partners in the interrelated tasks of regulating arterial pressure and blood volume.

The Cardiovascular State of Conscious Subjects Is Determined by an Ongoing and Ever-Changing Mixture of Reflex Effects and Psychogenic Responses

The baroreceptor reflex and the atrial volume receptor reflex are only two of several important cardiovascular reflexes. They are primarily responsible for the regulation of blood pressure and blood volume, and they illustrate several properties common to all cardiovascular reflexes. First, these reflexes originate from changes detected by peripheral sensory receptors. Second, the reflexes occur at a subconscious level, through neural pathways that primarily involve cardiovascular centers in the brainstem and midbrain. Consequently, cardiovascular reflexes persist in unconscious and anesthetized subjects, although the strength and character of the reflexes are altered by anesthesia. Finally, the reflexes use sympathetic and parasympathetic neurons as well as hormonal and behavioral responses to bring about cardiovascular changes.

In conscious subjects, neurohumoral control of the cardiovascular system involves both cardiovascular reflexes and psychogenic effects. Psychogenic responses originate from conscious perceptions or emotional reactions. They are eliminated by unconsciousness or general anesthesia. They involve neural pathways of the midbrain and forebrain, including the limbic system and cerebral cortex. Psychogenic responses are often triggered by sensory stimuli. For example, the sights, sounds, and smells of a veterinary clinic may trigger perceptions and emotions that cause increases in heart rate and blood pressure in both animal patients and their human companions. Psychogenic responses can also occur without any obvious sensory triggers. For example, anxiety about a future event can increase heart rate and blood pressure, at least in humans. Cardiovascular reflexes and psychogenic reactions use the same sympathetic and parasympathetic neurons and some of the same hormonal responses to bring about cardiovascular changes.

Two important psychogenic responses are the defense-alarm reaction and vasovagal syncope (the "playing dead" reaction). The *defense-alarm reaction* ("fear, fight, or flight" response) is an emotional and behavioral response to a threatening situation, physical injury, or trauma. The cardiovascular component of this reaction involves increased sympathetic activity and decreased parasympathetic activity. Typically, the sympathetic activation is sufficiently strong to cause the release of epinephrine and norepinephrine from the adrenal medulla. The cardiovascular responses during a defense-alarm reaction therefore include an increased heart rate, increased stroke volume, vasoconstriction in noncritical organs (kidneys, splanchnic organs, resting skeletal muscle), vasoconstriction in skin, vasodilation in coronary vessels and in working skeletal muscle, and increased blood pressure. The cardiovascular responses during the defense reaction are enhanced by other circulating hormones, including ADH and angiotensin II. The resulting elevated blood pressure helps to ensure adequate blood flow for the critical organs (exercising skeletal muscles, heart, and brain).

During a defense-alarm reaction, the baroreceptor reflex is reset by the CNS so that it regulates blood pressure at an elevated level rather than acting to oppose the increased pressure. This is analogous to resetting the cruise control on a car so that it regulates speed at an elevated level rather than acting to oppose an increased speed. Thus it is more accurate to say that the baroreceptor reflex regulates blood pressure at a variable set point (set by the CNS) than to say that the baroreflex regulates arterial pressure at any single "normal" pressure.

It is important to recognize that the defense-alarm reaction is simply the extreme form of a continuum of states of emotional arousal. Sleep is at the opposite end of this cardiovascular and emotional continuum. In quiet rest or sleep, sympathetic activity is minimal and parasympathetic activity is maximal. During a full-blown defense-alarm reaction, sympathetic activity is maximal and parasympathetic activity is minimal. Between these extremes lie all the levels of emotional arousal experienced by animals and humans, from moment to moment, during ordinary and extraordinary daily activities. Cardiovascular variables, such as heart rate and blood pressure, are sensitive to these changes in emotional state (Figure 25-6). For example, a large dog may normally have a heart rate of 70 beats/min while resting at home; but it would be entirely normal for the same dog to have a heart rate of 120 beats/min while "resting" in a clinic, if the dog is apprehensive in that setting. Another important point for the clinician to remember is that emotional responses are subjective. Situations that severely agitate one animal may cause only a mild alerting response in another animal. The clinician must evaluate heart rate, blood pressure, and other cardiovascular signs with respect to the particular patient's emotional state.

Vasovagal syncope is another psychogenic response that may be encountered in veterinary practice. This response is also called "playing dead" or "playing possum" (i.e., behaving like an opossum). In response to certain threatening or emotional situations, some humans and animals experience a psychogenic decrease in blood pressure and may faint. In many ways, this

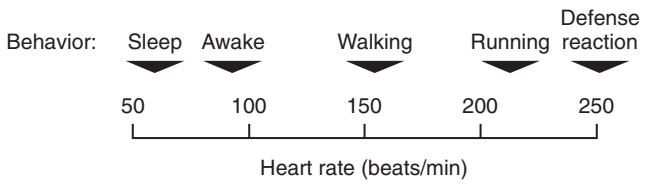

FIGURE 25-6 The defense-alarm reaction is simply the extreme on a continuum of emotional and physical arousal. Cardiovascular variables (e.g., heart rate, plotted here for a typical large dog) respond sensitively to every change along this arousal scale.

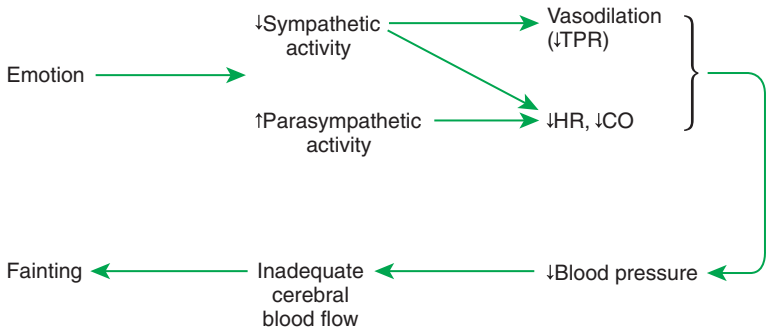

FIGURE 25-7 Vasovagal syncope ("playing dead" reaction) is an emotional response that involves decreases in sympathetic activity and increases in parasympathetic activity. *CO,* Cardiac output; *HR,* heart rate; *TPR,* total peripheral resistance.

response is the opposite of the defense-alarm reaction. As shown in Figure 25-7, vasovagal syncope involves a decrease in sympathetic activity and an increase in parasympathetic activity. These neural changes bring about a vasodilation in the noncritical organs, with a consequent decrease in TPR. Heart rate and cardiac output also decrease, so there is a large drop in arterial blood pressure. The expected compensatory reflex responses do not take place because emotional state appears to override the baroreceptor reflex in this case. If blood pressure falls so low that there is inadequate cerebral blood flow, the patient faints. The term *vasovagal syncope* denotes *vaso*dilation, *vagal* (parasympathetic) activation, and *syncope* (fainting). It is not clear why some animals respond to a threatening situation with a defense-alarm reaction, whereas others exhibit vasovagal syncope.

CLINICAL CORRELATIONS

INTRAOPERATIVE HEMORRHAGE

History. Four hours after abdominal surgery for a splenic sarcoma, a 30-kg, 9-year-old male Labrador retriever is observed to be severely lethargic and recumbent. An abnormally large amount of blood had been lost during the surgical removal of the spleen because the dog had a hereditary blood-clotting defect (von Willebrand's disease).

Clinical Examination. The dog's gums are pale, and his capillary refilling time is abnormally prolonged (3 sec). His extremities are cool to the touch. The femoral pulse is rapid and weak. An electrocardiogram indicates sinus tachycardia at a rate of 185 beats/min. The hematocrit (packed cell volume) is 38%, and the plasma protein concentration is 5.6 g/dL; both values are below normal. A jugular catheter is inserted, and central venous pressure is measured and found to be –1 mm Hg (normal, 0 to +3 mm Hg). Despite the intravenous administration of 600 mL of lactated Ringer's solution during surgery, the dog has not produced any urine. About 100 mL of blood-tinged fluid is removed from the abdomen by *abdominocentesis.*

Comment. This case illustrates the clinical signs that are typical of hemorrhage. Most of the blood in a dog is in the systemic veins, so most of the blood missing after hemorrhage is missing from the veins. The result is an abnormally low central venous pressure, as observed in this dog. The decreased central venous pressure causes a decreased ventricular preload and a decreased ventricular end-diastolic volume. This leads to decreases in stroke volume (Starling's law of the heart), cardiac output, and arterial blood pressure. Inadequate cardiac output and blood pressure lead to behavioral depression.

Neurohumoral compensation for the hemorrhage is initiated by the atrial volume receptor reflex and the arterial baroreceptor reflex. Heart rate is increased by the combination of increased sympathetic activation and decreased parasympathetic activation. The combination of high heart rate and low stroke volume accounts for the rapid but weak (low pulse pressure) femoral pulse. Sympathetic activity also causes vasoconstriction in the mucous membranes, resting skeletal muscle, splanchnic organs, and kidneys (noncritical organs and tissues). The reduced blood flow in these tissues accounts for the pale gums, the slow refilling of capillaries, the cool limbs, and the lack of urine production by the kidneys. Urine formation by the kidneys is also being depressed by the combined hormonal effects of ADH and the renin-angiotensin-aldosterone system.

Hemorrhage does not directly reduce either the hematocrit or the plasma protein concentration, because whole blood is being lost. However, two factors caused the hematocrit and plasma protein concentration to decrease in this dog. First, the fluid administered intravenously during surgery (lactated Ringer's solution) contained neither red blood cells nor plasma proteins, so the cells and proteins remaining in the bloodstream were diluted by the addition of the fluid. Second, the hemorrhage reduced not only venous and arterial pressures but also capillary hydrostatic pressure, which changed the balance of hydrostatic and oncotic forces (Starling forces) across the capillary walls in favor of reabsorption. The interstitial fluid that was reabsorbed into the bloodstream contained no red blood cells and almost no plasma proteins. This caused a further dilution of the cells and proteins in the blood.

Treatment. Therapy for this dog involves measures to stop ongoing blood loss and to restore the lost blood volume. In this dog the hemorrhage is predominantly seepage from small intra-abdominal vessels as a result of the coagulation defect. Transfusions of fresh blood or plasma, or concentrated preparations of clotting proteins, would promote clotting and limit subsequent hemorrhage. After measures are taken to promote clotting, additional crystalloid solutions (e.g., lactated Ringer's solution) can be infused into this dog because the hematocrit and plasma protein concentration are not dangerously low. If crystalloid solutions are administered, the hematocrit and plasma protein concentration should be monitored closely to avoid the hypoxia that results from too much dilution of the red blood cells, or the edema that results from too much dilution of the plasma proteins. Renal function should be monitored closely because the combination of hypoxia and reflex vasoconstriction can lead to ischemic damage of kidney tissue, resulting in renal failure.

PRACTICE QUESTIONS

1. Vasovagal syncope:
   a. Involves decreased blood pressure and heart rate.
   b. Involves increased sympathetic activity.
   c. Involves decreased cardiac parasympathetic activity.
   d. Prepares an animal for "fight or flight."
   e. Involves constriction of splanchnic arterioles.

2. The dilation of arterioles that occurs during steady-state exercise in active skeletal muscles could be eliminated by:
   a. Pharmacological blockade of action potentials in all autonomic nerves innervating the muscles.
   b. Complete surgical removal of sympathetic innervation of the skeletal muscles.
   c. Administration of a muscarinic cholinergic blocking agent.
   d. Administration of a β-adrenergic blocking agent.
   e. None of the above.

3. A drug is injected intravenously into a dog and causes a transient increase in mean arterial pressure and a transient decrease in heart rate. The baroreceptor nerves are cut; the drug is reinjected and now causes a greater increase in blood pressure but no change in heart rate. These results are most consistent with the primary action of the drug being to:
   a. Activate the muscarinic cholinergic (M_3) receptors of arterioles.
   b. Activate the α-adrenergic receptors of arterioles.
   c. Activate β_1-adrenergic receptors of the pacemaker cells of the SA node.
   d. Increase the synthesis of nitric oxide in arterioles.
   e. Decrease the activity of arterial baroreceptors.

4. A dog has had a hemorrhage. The heart rate is increased above normal, and the skin is cold. The mucous membranes are pale. In this situation (compared with normal):
   a. The baroreceptor nerves are firing at a higher rate.
   b. The sympathetic nerves to the heart are firing at a decreased rate.
   c. The sympathetic nerves to the blood vessels of the skin and mucous membranes are firing at an increased rate.
   d. The parasympathetic fibers to the blood vessels are firing at an increased rate.
   e. The release of renin by the kidney is decreased.

5. Blood (250 mL) is taken from a vein of a dog. Mean arterial pressure does not decrease measurably. Nevertheless, it is likely that:
   a. Stimulation of atrial stretch receptors has decreased.
   b. Stroke volume has increased.
   c. Stimulation of aortic arch baroreceptors has increased.
   d. Total peripheral resistance has decreased.
   e. Secretion of ADH by the pituitary has decreased.

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CHAPTER 26
Integrated Cardiovascular Responses

KEY POINTS

1. Both Starling's mechanism and the arterial baroreflex help compensate for heart failure.
2. Serious complications secondary to heart failure include exercise intolerance, edema, salt and water retention, kidney failure, uremia, septic shock, and decompensation.
3. The immediate cardiovascular effects of hemorrhage are minimized by compensations initiated by the atrial volume receptor reflex and the arterial baroreceptor reflex.
4. The blood volume lost in hemorrhage is restored through a combination of capillary fluid shifts and hormonal and behavioral responses.
5. In large animals, the transition from a recumbent to a standing posture elicits the same cardiovascular responses as hemorrhage.
6. The initiation of exercise involves an interplay of local and neural changes that increases cardiac output and delivers increased flow to exercising muscle.

Chapters 18 to 25 describe the various elements of cardiovascular function and control. An understanding of these individual elements is not sufficient, however, to provide a basis for the diagnosis and treatment of cardiovascular dysfunction. The veterinary clinician must understand the *interaction* of these elements in both normal and abnormal situations. Therefore this chapter discusses three fundamentally important, *integrated* cardiovascular responses: (1) the response to heart failure, (2) the response to hemorrhage, and (3) the response to exercise. In addition to elucidating important, integrated responses, this discussion provides a review and summary of key concepts of cardiovascular physiology.

Both Starling's Mechanism and the Arterial Baroreflex Help Compensate for Heart Failure

There are many types and causes of *heart failure.* Some clinicians use the term very broadly to refer to any condition in which a problem in the heart limits its ability to deliver a normal cardiac output to the body tissues. Such conditions would include various valve defects, arrhythmias, and even heartworm infestation. A more restrictive definition, and one favored by physiologists, is that *heart failure* is any condition in which a depressed *cardiac contractility* limits the ability of the heart to deliver a normal cardiac output. The broader definition of heart failure encompasses virtually any problem with the heart as a pump; a common synonym is *pump failure.* The more restrictive definition, as used in this chapter, equates heart failure with *myocardial failure,* a depressed contractility of the heart muscle itself.

A depressed cardiac contractility can result from coronary artery disease, cardiac hypoxia, myocarditis, toxins, drug effects, or electrolyte imbalances. If the decrease in contractility affects both sides of the heart, the condition is called *bilateral heart failure.* In other circumstances, failure may be restricted primarily to either the left ventricle or the right ventricle and thus is called *left-sided heart failure* or *right-sided heart failure.*

Ventricular function curves provide a helpful way to envision the consequences of heart failure and the compensations for heart failure. In Figure 26-1 the curve labeled *Normal* indicates the relationship between stroke volume and preload for a normal ventricle (for a review, see Figure 21-3, *C*). The curve labeled *Initially severe failure* shows that a ventricle in failure has a depressed contractility (i.e., a smaller stroke volume for any given preload). If a normal heart suddenly goes into severe failure, stroke volume changes from its normal value (shown by point 1) to the low value (shown by point *2*). For purposes of illustration, imagine that these curves define the function of the left ventricle and that the left ventricle is the one that fails. A decrease in left ventricular stroke volume causes a decrease in left ventricular output, which results in a decrease in mean arterial blood pressure. If there is inadequate compensation for this fall in blood pressure, severe exercise intolerance is certain, inadequate perfusion of the critical organs is likely, and death is a strong possibility. However, several mechanisms react rapidly, within seconds to minutes, to compensate for heart failure and to minimize its adverse effects.

One compensation for heart failure is *Starling's mechanism.* If the left ventricle suddenly decreases its stroke volume, the right ventricle (at least for a few heartbeats) maintains a higher stroke volume than the failing left ventricle. The excess blood pumped by the right ventricle has to "go somewhere," and most of the excess accumulates in the pulmonary veins and left atrium. In effect, blood backs up or dams up behind (i.e., upstream of) the left ventricle. The resulting increase in left atrial pressure creates an increase in left ventricular preload, which leads to an increase in left ventricular end-diastolic volume and, by Starling's mechanism, an increase in stroke volume. This improvement in stroke volume is depicted in Figure 26-1 as a transition from point *2* to point 3. The sequence of events, whereby an increase in preload helps offset the initial fall in stroke volume, is also diagrammed in Figure 26-2 *(top left loop)*. Note that the compensation by Starling's mechanism does not return stroke volume to its normal value because contractility remains severely depressed; however, without this compensation severe heart failure would be fatal.

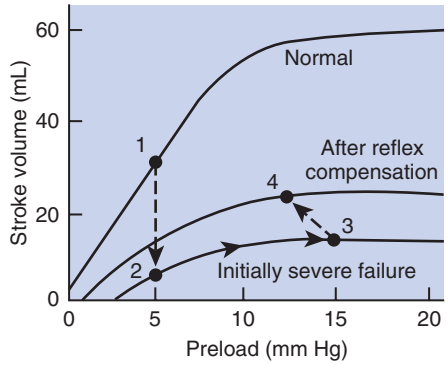

FIGURE 26-1 Ventricular function curves depicting the consequences and compensations for heart failure in terms of changes in preload (end-diastolic ventricular pressure) and stroke volume. See text for details.

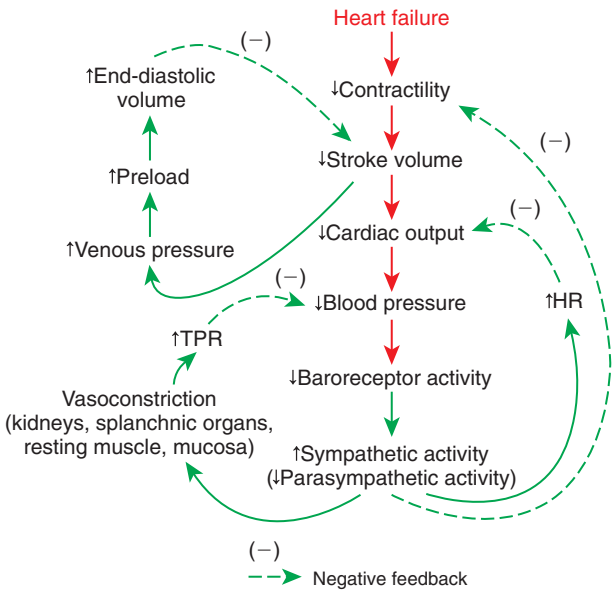

FIGURE 26-2 Consequences *(red arrows)* and compensations *(green arrows)* for heart failure. The changes described here include those presented graphically in Figure 26-1. See text for details. *HR,* Heart rate; *TPR,* total peripheral resistance.

The arterial baroreflex is another mechanism that reacts rapidly to compensate for heart failure. Even after compensation by Starling's mechanism, left ventricular output remains below normal, as does arterial blood pressure. Therefore, baroreceptor activity is below normal. The central nervous system (CNS) responds reflexively by increasing sympathetic efferent activity to the heart and blood vessels and by decreasing parasympathetic activity to the heart.

The sympathetic effect on the heart increases ventricular contractility. Contractility is not restored to normal but is brought to a higher level than existed in the absence of reflex compensation. Graphically, the effect of the baroreflex is to move the failing ventricle to a function curve that is intermediate between the *Normal* curve and the curve of *Initially severe failure* (see point 4 in Figure 26-1). Note that the increase in contractility also brings stroke volume back toward (but not reaching) its normal level.

The reflexive increase in sympathetic activity raises heart rate above normal and decreases systolic duration; these changes also help to restore cardiac output and arterial pressure toward normal despite the persistently depressed stroke volume. Finally, sympathetic activation causes vasoconstriction, particularly in the noncritical organs, which increases total peripheral resistance (TPR) above normal. This also helps to return arterial pressure toward its normal level.

The net effect of the compensations by way of Starling's mechanism and the baroreflex is that arterial blood pressure can be maintained near its normal level, at least when the animal is at rest, despite a severe ventricular failure. Figure 26-2 summarizes these reflex effects. Note that after compensation by Starling's mechanism and the baroreflex, contractility, stroke volume, cardiac output, and blood pressure remain at least somewhat below normal. By contrast, preload, sympathetic activity, heart rate, and TPR are above normal.

Serious Complications Secondary to Heart Failure Include Exercise Intolerance, Edema, Salt and Water Retention, Kidney Failure, Uremia, Septic Shock, and Decompensation

Even though Starling's mechanism and the baroreflex can compensate to a remarkable degree for severe heart failure, important secondary complications often develop. These complications make heart failure a serious clinical problem, even in cases where compensatory mechanisms can maintain cardiac output and arterial pressure at near-normal levels when the animal is at rest.

Heart failure causes *exercise intolerance.* In a normal animal the ability of the heart to increase cardiac output during exercise depends on sympathetically mediated increases in stroke volume and heart rate. In a patient with heart failure, however, sympathetic activation is being harnessed to restore cardiac output toward normal in the resting state. Therefore the patient has a limited ability to invoke an effective, further increase in sympathetic activity. The failing heart cannot provide the increased cardiac output required to meet the blood flow requirements of exercising skeletal muscle. In the absence of an adequate increase in cardiac output, metabolic vasodilation in the exercising muscle results in a large decrease in arterial pressure and inadequate blood flow to all organs, including the exercising muscle. The patient exhibits lethargy and weakness; even mild exercise leads quickly to exhaustion.

Edema is another serious complication secondary to heart failure. As noted, blood dams up in the atrium and veins behind a failing ventricle. In the case of left ventricular failure, left atrial pressure increases, as does pressure in the pulmonary veins and pulmonary capillaries. The increase in pulmonary capillary hydrostatic pressure leads to an increase in the filtration of capillary fluid into the interstitial spaces of the lungs. *Pulmonary edema* develops. The excess of interstitial fluid slows the transfer of oxygen from the lung alveoli into the lung capillaries and can result in inadequate oxygenation of the blood *(hypoxemia).* In extreme cases, interstitial fluid leaks into the intrapleural space *(pleural effusion)* or into the alveolar air spaces, which causes a further reduction in lung function. The resulting hypoxia in critical organs can be fatal. In a patient with right ventricular failure the increase in venous pressure occurs in the systemic circulation. Therefore the resulting edema occurs in the systemic organs, particularly in dependent extremities and in the abdomen. The cause-and-effect sequence by which heart failure leads to edema is summarized in Figure 26-3 *(top left).*

Whether the edema is in the lungs or in the systemic circulation, its degree is limited by the three safety factors previously

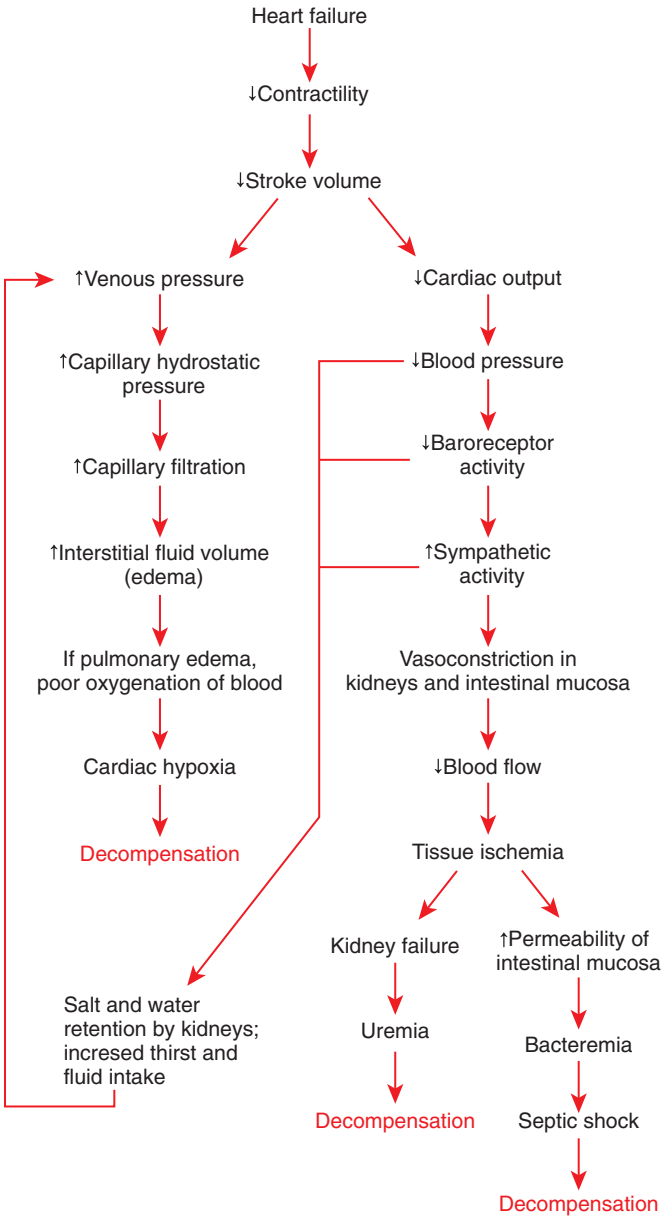

FIGURE 26-3 Heart failure leads to exercise intolerance. Additional, life-threatening complications secondary to heart failure are diagrammed here, including edema, salt and water retention and increased fluid intake, kidney failure, uremia, and septic shock. Vicious cycles develop in which the effects of heart failure make the heart failure worse *(decompensation)*. See text for details.

discussed (see Figure 23-5). These safety factors would probably keep the edema of heart failure well controlled were it not for an additional factor that exaggerates the elevation of venous pressure in heart failure. As long as arterial pressure remains subnormal in a patient with heart failure, the baroreceptor reflex and some mechanisms involving the kidneys work to raise blood volume above normal. These volume-increasing mechanisms include increased thirst (which raises fluid intake), increased release of antidiuretic hormone (ADH) from the pituitary (which decreases the amount of fluid lost in the urine), and activation of the renin-angiotensin-aldosterone system (which decreases sodium loss in the urine). These effects of the baroreflex were mentioned briefly in Chapter 25; the mechanisms involving the kidneys are described in more detail in Chapters 41 and 43.

The point for now is that the patient with severe heart failure experiences a substantial and persistent increase in blood volume. The excess blood accumulates particularly in the veins upstream from the failing ventricle, which exaggerates the increases in venous pressure and capillary filtration. The normal safety factors against may be overwhelmed. This is why one of the main goals in the clinical treatment of heart failure is to counteract the buildup of excessive blood volume and interstitial fluid volume. *Diuretic drugs* are the main therapies used for this purpose (see Chapter 43).

Severe, persistent heart failure leads to several additional adverse effects. The baroreceptor reflex responds to an abnormally low arterial pressure in heart failure by initiating arteriolar vasoconstriction, primarily in the kidneys, splanchnic organs, and resting skeletal muscle (the noncritical organs). In severe heart failure the skin and mucous membranes are also vasoconstricted. Vasoconstriction in these organs helps compensate for heart failure by permitting the available cardiac output to be routed to the critical organs (brain, heart, and working skeletal muscle). However, persistent vasoconstriction leads to the additional complications of kidney failure, uremia, and septic shock.

Vasoconstricted kidneys cannot form urine in a normal manner and therefore do not rid the body of the excess volume of blood and interstitial fluid that accumulates in heart failure. Persistent vasoconstriction damages kidney tissue and leads to a buildup of nitrogenous and acidic waste products in the body. The condition is called *uremia,* which literally means "urine in the blood." To make matters worse, after a prolonged period of intense vasoconstriction, damage to the kidney tissue becomes irreversible. At this stage, uremia, acidosis, and salt and water retention may persist even if clinical treatment is temporarily successful in returning cardiac output and blood pressure close to normal. For this reason, *renal failure* often is the terminal event in chronic heart failure.

Intense and prolonged vasoconstriction in the splanchnic circulation can also have lethal consequences. The mucosa of the gastrointestinal tract is particularly susceptible to ischemic damage. Normally, the intestinal mucosa creates a barrier between the contents of the intestinal lumen and the bloodstream. Ischemic damage to the intestinal mucosa allows bacteria and bacterial toxins to pass into the bloodstream or the peritoneum. The resulting bacteremia or peritonitis can cause septic shock and death. The causes and consequences of renal and splanchnic ischemia are summarized in Figure 26-3 *(bottom right)*.

Cardiac decompensation is an additional (and frequently terminal) complication secondary to heart failure. The basic concept of decompensation is that when heart failure reaches a certain degree of severity, the body's attempted compensations for heart failure end up making the heart failure worse. Vicious decompensatory cycles develop and can lead to death within a few hours unless there is vigorous medical intervention.

The specific mechanisms of the *decompensatory cycles* are very complex, but three examples illustrate the concept. As previously explained, in the case of left ventricular failure, the damming up of blood in the left atrium is compensatory because it increases left ventricular preload, which helps boost stroke volume back toward normal. However, the increased left ventricular preload leads to the secondary complication of pulmonary edema. If severe, pulmonary edema interferes with the oxygenation of blood. One tissue that depends critically on an

adequate supply of oxygen is cardiac muscle; hypoxia depresses the contractility of cardiac muscle. Thus a vicious cycle can develop: severely depressed ventricular contractility → severe pulmonary edema → inadequate oxygenation of blood → hypoxia of the left ventricular muscle → further depression of ventricular contractility.

For a second example of a vicious decompensatory cycle, consider again the effects of the baroreflex on the kidneys. Renal vasoconstriction is compensatory for heart failure in that it helps increase TPR, which helps raise arterial pressure back toward normal, which helps keep perfusion pressure high enough to deliver adequate blood flow to the critical organs. However, as already mentioned, intense and prolonged renal vasoconstriction leads to kidney failure and an accumulation of acidic and nitrogenous waste products in the blood (uremia). Uremia depresses cardiac contractility. Thus, another vicious cycle can develop: severe ventricular failure → intense and prolonged renal vasoconstriction → damage to kidney tissues → uremia → metabolic waste products accumulate in cardiac muscle → further depression of ventricular contractility.

A third vicious decompensatory cycle results from the fact that septic shock depresses cardiac contractility. The cycle is: severe ventricular failure → intense and prolonged splanchnic vasoconstriction → ischemic damage to intestinal mucosa → bacteria and endotoxins pass through the damaged mucosa, from intestines into bloodstream → bacteremia causes further depression of ventricular contractility.

Other decompensatory cycles develop in cases of severe, prolonged heart failure, but these three examples (which are illustrated in Figure 26-3) show why decompensation is such a serious development.

Careful clinical diagnosis and prompt treatment of heart failure are imperative, even if compensatory mechanisms have maintained blood pressure near its normal level when the patient is at rest. In evaluating the severity of heart failure and the extent of compensation, it is clinically useful to group the signs of heart failure into two categories. The first category is referred to as *backward heart failure*. The signs of backward heart failure include the changes in the circulation *upstream* from the failing ventricle: increased atrial pressure, increased venous pressure, excessive capillary filtration, edema, and the functional changes secondary to edema (e.g., respiratory failure). The category *forward heart failure* refers to the consequences of heart failure *downstream* from the failing ventricle: decreased cardiac output, decreased arterial blood pressure, and the consequences of excessive vasoconstriction in the systemic organs, especially the kidneys and intestines.

The Immediate Cardiovascular Effects of Hemorrhage Are Minimized by Compensations Initiated by the Atrial Volume Receptor Reflex and the Arterial Baroreceptor Reflex

Figures 26-4 and 26-5 summarize the cardiovascular responses to hemorrhage. The curve labeled *Normal* in Figure 26-4 shows that the maintenance of a normal stroke volume depends on the maintenance of a normal level of ventricular preload. When hemorrhage occurs, blood is lost from the whole cardiovascular system, but particularly from the veins, which are the blood reservoirs of the body. Hemorrhage therefore decreases venous volume, venous pressure, atrial pressure, ventricular preload, and ventricular end-diastolic ventricular volume. In the absence of any compensation, ventricular stroke volume decreases from point 1 in Figure 26-4 to point 2.

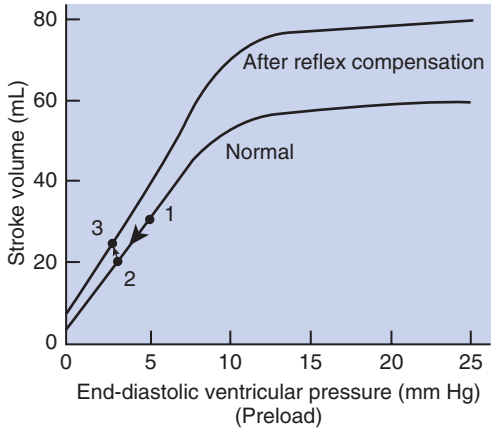

FIGURE 26-4 Direct effect of hemorrhage is to decrease ventricular preload, which decreases stroke volume (transition from *point 1,* which is normal, to *point 2*). A reflex increase in sympathetic activity increases ventricular contractility above normal *(upper curve),* which restores stroke volume *toward normal* (transition from *point 2* to *point 3*).

Note that no specification was made in the preceding paragraph about whether the itemized sequence of events was affecting the right heart or the left heart. The distinction is irrelevant because the right and left hearts are part of a series circuit. Therefore, the volumes of blood pumped by the right and left ventricles must always come into balance within a few beats. Specifically, if hemorrhage lowers right ventricular preload (and therefore right ventricular output), the consequence will be decreased venous return to the left heart, which will decrease left ventricular preload (and therefore left ventricular output).

Figure 26-4 shows that the normal ventricular function curve is rather steep to the left of point 1 (the normal operating point). Therefore a 40% hemorrhage results in approximately 40% reductions in venous pressure, atrial pressure, ventricular preload, and stroke volume. In the absence of compensations, cardiac output and mean arterial pressure (MAP) would also decrease by 40%. MAP would then be inadequate to sustain normal function in the critical organs, and the animal would die. With intact compensatory mechanisms, however, a normal animal can withstand a 40% hemorrhage without death and have only about a 10% decrease in MAP.

The immediate compensations for hemorrhage are initiated by the arterial baroreflex and atrial volume receptor reflex. Hemorrhage decreases MAP, which decreases the activity of arterial baroreceptors. The baroreflex response is to increase sympathetic activity and to decrease parasympathetic activity. The increased sympathetic activity acts on the heart to increase cardiac contractility. This helps restore stroke volume back toward normal, despite a persistent, subnormal preload and end-diastolic volume. The effect of this sympathetic compensation is diagrammed in Figure 26-4 as point 3. Although stroke volume is returned toward normal, it remains low; after compensation for a 40% hemorrhage, the stroke volume may remain 25% below normal.

Additional compensations help restore MAP closer to normal despite the persistence of low stroke volume. First, heart rate increases above normal, which brings cardiac output back to within about 20% of its normal level. In addition, sympathetic vasoconstriction in the noncritical organs raises TPR above

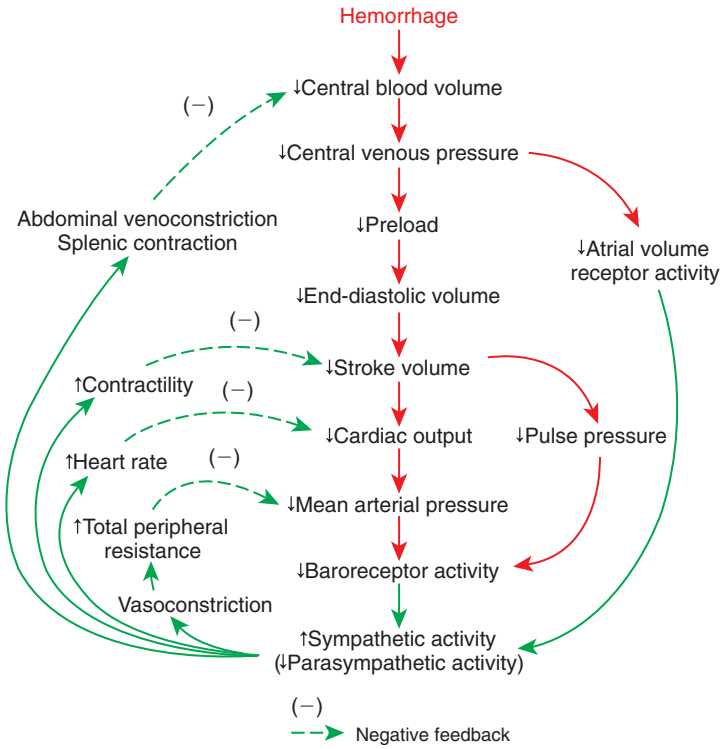

FIGURE 26-5 Summary of the consequences of hemorrhage *(red arrows)* and the rapid compensations initiated by the arterial baroreflex and atrial volume receptor reflex *(green arrows)*. The changes described here include those portrayed graphically in Figure 26-4.

normal, resulting in a MAP that remains within approximately 10% of its normal level, despite a persistent 20% drop in cardiac output. Review the compensations described thus far by locating them on Figure 26-5.

You may wonder why baroreflex compensatory actions continue if MAP is returned most of the way toward normal. Compensatory baroreflex responses are sustained because baroreceptors are responsive to changes in pulse pressure as well as to changes in MAP, and pulse pressure remains low. There are two reasons for the subnormal pulse pressure: (1) the persistent decrease in stroke volume and (2) the increase in heart rate above normal. Thus, even if MAP is returned substantially toward normal after compensation for a hemorrhage, baroreceptor activity (action potential frequency) remains below normal.

The atrial volume receptor reflex also contributes to the sustained increase in sympathetic activity after hemorrhage. Hemorrhage leads to a persistent decrease in central venous pressure and atrial pressure. Therefore the activity of the atrial volume receptors is decreased below normal. The CNS responds to this decreased afferent activity from atrial volume receptors by elevating sympathetic efferent activity and by decreasing cardiac parasympathetic efferent activity. Thus, as illustrated in Figure 26-5, the atrial volume receptor reflex and the arterial baroreflex work synergistically to compensate for hemorrhage.

In severe hemorrhage the reflex increases in sympathetic activity affect not only the heart and resistance vessels but also the veins. The abdominal veins in particular are constricted when sympathetic activation is intense. Sympathetic venoconstriction displaces blood from the abdominal veins and moves it toward the central circulation, which helps to restore the low central venous pressure, atrial pressure, and preload back toward normal (see Figure 26-5, *left side*). Sympathetic activation also constricts the blood vessels within the spleen and the muscular capsule around the spleen. Some of the blood that is sequestered in the spleen is expelled into the abdominal veins, and then it moves toward the heart. In species that have large spleens (e.g., dog and horse), splenic contraction can mobilize a volume of blood equal to 10% of the total blood volume. An additional, adaptive feature of the blood sequestered in the spleen is that it has a higher-than-normal hematocrit. The mobilization of these sequestered red blood cells helps to offset the fall in hematocrit that is a normal consequence of interstitial fluid reabsorption after hemorrhage (as described next).

The arterial baroreceptor reflex and the atrial volume receptor reflex act within a few seconds to restore blood pressure toward its normal level after a hemorrhage. Other compensations come into play in the minutes and hours after hemorrhage to restore the lost fluid volume.

The Blood Volume Lost in Hemorrhage Is Restored Through a Combination of Capillary Fluid Shifts and Hormonal and Behavioral Responses

Hemorrhage causes both venous and arterial pressures to fall below normal, so capillary hydrostatic pressure also falls below normal throughout the body. This alters the balance of hydrostatic and oncotic pressures acting on water in a direction that favors reabsorption of interstitial fluid back into the capillaries (Figure 26-6). The volume of interstitial fluid that can be reabsorbed by this process in 1 hour is approximately 10% of the volume lost in the hemorrhage. However, the rate of reabsorption of interstitial fluid becomes limited after 3 to 4 hours. As interstitial fluid is reabsorbed, there is a decrease in interstitial fluid hydrostatic pressure (it becomes even more negative than normal), and this opposes further reabsorption. Also, as interstitial fluid is reabsorbed, the interstitial fluid protein concentration increases because proteins in the interstitial fluid are not reabsorbed. The

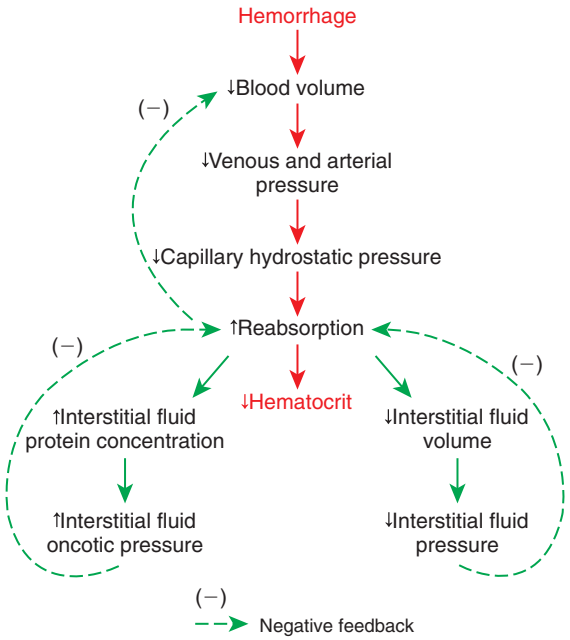

FIGURE 26-6 During the first 3 to 4 hours after a hemorrhage, interstitial fluid is reabsorbed into the bloodstream, which helps compensate for the lost blood volume. A complication is that the hematocrit decreases. Reabsorption is limited by decreases in interstitial fluid hydrostatic pressure and by increases in interstitial fluid oncotic pressure.

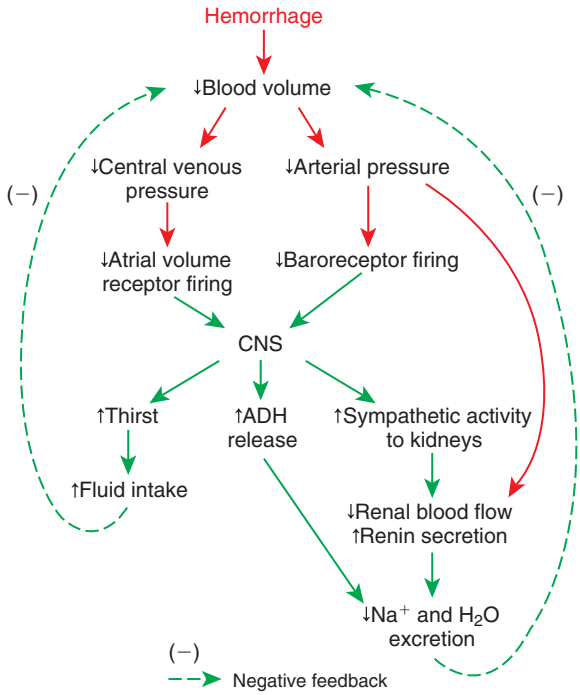

FIGURE 26-7 Behavioral and hormonal responses after hemorrhage include increased fluid intake and decreased salt and water loss in the urine, which lead to the eventual restoration of the blood volume lost in the hemorrhage. *ADH,* Antidiuretic hormone; *CNS,* central nervous system.

resulting increase in interstitial fluid oncotic pressure also opposes further reabsorption. Despite these limits, the reabsorption of interstitial fluid is an important compensation for hemorrhage in the first few hours.

The interstitial fluid that is reabsorbed into the bloodstream after a hemorrhage contains neither plasma proteins nor blood cells. Therefore the proteins and cells remaining in the bloodstream after the hemorrhage become diluted as interstitial fluid is reabsorbed. As a consequence the concentration of plasma proteins in blood decreases, and so does the hematocrit. This is why a decreasing hematocrit over a few hours in an otherwise normal patient is presumptive evidence that a hemorrhage has occurred recently or is continuing to occur. In the absence of an obvious hemorrhage, such a patient should be examined for evidence of internal bleeding.

Figure 26-7 illustrates how the atrial volume receptor reflex and the arterial baroreceptor reflex participate in the eventual, complete restoration of blood volume after a hemorrhage. As mentioned, hemorrhage leads to a decrease in the activity of both atrial volume receptors and arterial baroreceptors. One reflexive response to the decreased receptor activity is activation of sympathetic nerves, and some of the effects of the sympathetic activation have already been described (see Figure 26-5). Sympathetic activity (coupled with a decrease in arterial pressure) also acts on the kidneys to increase their release of the hormone renin. As mentioned in Chapter 25, renin works through the renin-angiotensin-aldosterone system to decrease sodium excretion by the kidneys. Decreased activity of the baroreceptors and atrial volume receptors also triggers increased ADH secretion from the pituitary gland. ADH circulates to the kidneys, where it reduces urine formation. Through the combined actions of renal vasoconstriction, the renin-angiotensin-aldosterone system, and ADH, sodium excretion and water excretion are both decreased. Note that these actions *conserve* the available body fluid volume after hemorrhage, but they do not *restore* it to normal. The actual restoration of body fluid volume after hemorrhage requires increased fluid intake. The baroreceptor reflex and the atrial volume receptor reflex act through the hypothalamus to increase the sensation of thirst. If water is available, fluid intake increases until the lost body fluid volume is restored to normal. This may take 1 to 2 days.

The final compensations for hemorrhage involve the restoration of the lost plasma proteins and blood cells. The plasma proteins are synthesized by the liver, and the blood cells are produced by the bone marrow. The time required may be several days for the plasma proteins and a few weeks for the blood cells.

The preceding discussion focused on the effects of severe hemorrhage. All the same compensations occur to a lesser degree after mild hemorrhage. For example, when a human donates blood, about 10% of the blood volume (0.5 L) is removed. All the compensations just described are evident after this 10% hemorrhage.

In Large Animals, the Transition from a Recumbent to a Standing Posture Elicits the Same Cardiovascular Responses as Hemorrhage

You can understand the reason for this if you consider the effect of gravity on blood contained within blood vessels of the body. In a standing subject, gravity increases the distending pressure in the dependent vessels (those below heart level), particularly in the leg vessels. The gravitational effect does not cause much accumulation of blood in the arteries and arterioles because these

vessels are not easily distensible (i.e., they have low compliance). However, the gravitational effect causes a significant distention of the dependent veins because of their much greater compliance. The extra blood that pools in the dependent veins is blood that would otherwise have returned to the central circulation. Therefore, in an upright subject, there is a decrease in central blood volume and central venous pressure, just as there would be after hemorrhage. In a normal human the assumption of an upright posture is equivalent to a 10% hemorrhage, and it triggers all the compensatory responses already described for hemorrhage. In small animals the gravitational effect of standing is negligible. In some large animals, such as horses and cattle, the volume of blood that pools in the leg veins is minimized by the relatively small size of veins in the extremities.

The Initiation of Exercise Involves an Interplay of Local and Neural Changes That Increases Cardiac Output and Delivers Increased Flow to Exercising Muscle

As discussed in Chapter 24, local metabolic control mechanisms dilate skeletal muscle arterioles during exercise. As reviewed in Figure 26-8 (*top*), metabolic products accumulate in exercising muscle, and the local oxygen concentration decreases. The metabolic products and hypoxia both cause dilation of the arterioles within the exercising muscle. This vasodilation is a local response, not dependent on nerves or hormones. The result is an increased blood flow to the exercising muscle *(active hyperemia)*. The increased blood flow delivers more oxygen and removes some of the accumulated metabolic vasodilating products. In this way, muscle blood flow is matched to metabolic rate.

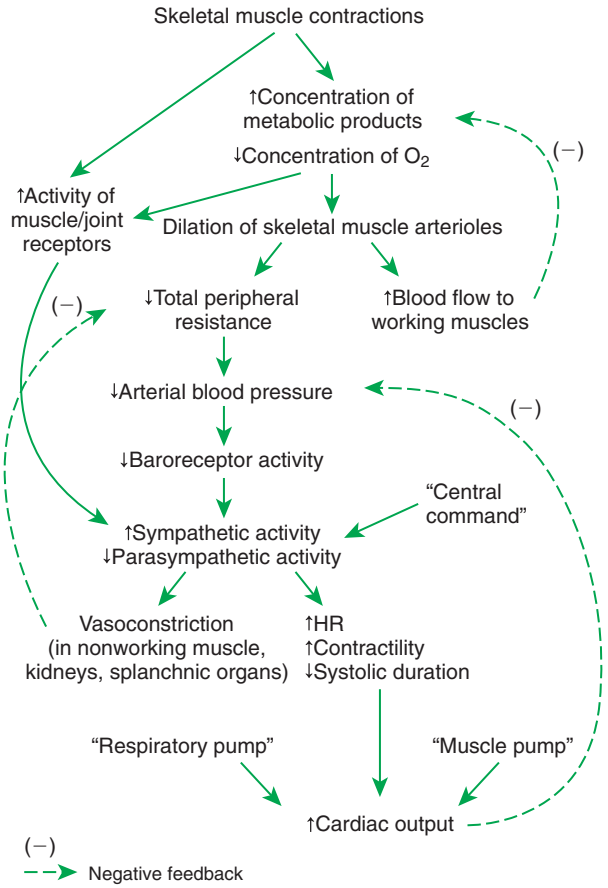

FIGURE 26-8 Cardiovascular responses to exercise involve a complex interplay of local metabolic control mechanisms with central command, reflexes, and the blood-pumping effects of muscle contraction and respiration. The overall result is increased blood flow in exercising muscle, decreased blood flow in the noncritical organs, decreased total peripheral resistance, increased cardiac output, and (normally) maintenance of arterial blood pressure near its normal level. *HR,* Heart rate.

Metabolic control of blood flow in exercising muscle can succeed only if arterial blood pressure is maintained at a level sufficient to provide the needed additional blood flow. This necessitates a substantial increase in cardiac output and, in extreme exercise, vasoconstriction in the noncritical organs (which makes more blood flow available for the exercising muscle and other critical organs). These adjustments are brought about by three neural mechanisms: central command, the exercise reflex, and the arterial baroreflex.

Central command is a psychogenic effect. In preparation for exercise (and continuing during exercise) the CNS increases sympathetic activity to the heart and blood vessels and decreases parasympathetic activity to the heart. The sympathetic and parasympathetic changes are graded, depending on the intensity of the exercise. In effect, central command represents a "guess" by the brain as to the levels of sympathetic and parasympathetic activity that will be needed during the exercise to match cardiac output to the needs of the systemic organs.

The *exercise reflex* is the second mechanism that helps set the level of sympathetic and parasympathetic activity during exercise. The exercise reflex is initiated by specialized nerve endings within muscles and joints. An increase in muscular work and in the movement of the body joints activates these muscle and joint receptors. The resulting increased afferent neural activity initiates a reflex increase in sympathetic (and decrease in parasympathetic) efferent drive. Although the mechanism for excitation of the muscle and joint receptors is not completely understood, it is clear that the activation of these receptors is necessary to keep blood pressure from falling during exercise.

The *arterial baroreceptor reflex* is the third major controller of sympathetic and parasympathetic activity during exercise. The baroreflex serves to fine-tune autonomic drive to the heart and arterioles to keep arterial pressure at its set point. If central command and the exercise reflex do not raise sympathetic activity to a sufficiently high level during a particular bout of exercise, arterial pressure falls below normal. The arterial baroreceptors detect this low pressure, and the baroreflex responds by increasing sympathetic activity. Conversely, if central command and the exercise reflex raise sympathetic activity too high for the level of exercise, arterial pressure rises above normal. The response of the baroreflex is to decrease sympathetic activity.

In effect, central command and the exercise reflex initiate the autonomic adjustments for exercise, and the arterial baroreflex performs the fine-tuning to keep arterial pressure near its set point (see Figure 26-8).

Two additional, nonneural mechanisms also help to increase the cardiac output during exercise. The first of these is the *muscle pump* (Figure 26-9). When skeletal muscles contract, they tend to squeeze the blood vessels contained within them. One consequence of this is the tendency for a muscle to restrict its blood flow during a sustained contraction (see Chapter 24). If the contractions are rhythmical, however, each contraction causes blood to be expelled out of the muscle veins and thus toward the central circulation. Minimal backflow of blood occurs from the central circulation into the veins during muscular relaxation because the

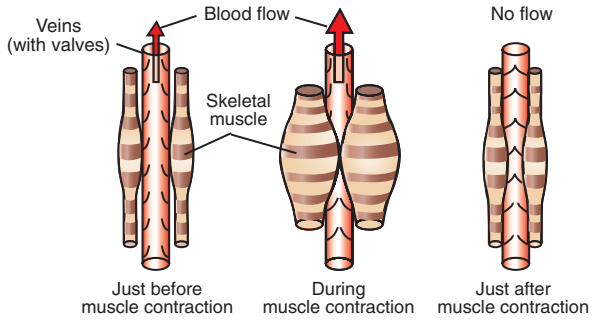

FIGURE 26-9 During dynamic exercise, the rhythmical contractions of the skeletal muscles squeeze venous blood back toward the central circulation. This so-called muscle pump helps increase central venous pressure in an exercising animal.

veins have one-way valves within them. Thus, by massaging the veins, exercising muscles exert a pumping action that displaces venous blood toward the central circulation and increases central venous pressure. The consequence is an increase in ventricular preload above the level that would otherwise exist.

The second nonneural mechanism that helps to increase cardiac output during exercise is the *respiratory pump*. Vigorous exercise involves an increase in the rate and the depth of respiration. During each inspiration, a subatmospheric pressure is generated within the intrapleural space. This negative pressure distends the airways of the lungs and expands them. It also increases the distending pressure on the central veins and the heart. Distention of the central veins and heart helps promote the flow of blood from the abdominal veins into the central veins and heart. In addition, the diaphragm muscle moves caudally during inspiration and compresses the abdominal organs. The resulting increase in intraabdominal pressure "squeezes" blood out of the abdominal veins and toward the central veins. Overall, the respiratory pumping action helps to increase venous return, central venous volume, and ventricular preload during exercise.

Cardiac output in well-conditioned humans and many animal species can increase to six times its resting level during vigorous exercise, as a result of the combined effects of sympathetic and parasympathetic responses, the muscle pump, and the respiratory pump. Note, however, that the success of the mechanisms that increase cardiac output during exercise depends on the heart's ability to respond normally both to increased sympathetic drive and to increases in preload. As mentioned earlier, during heart failure the autonomic mechanisms available to increase cardiac contractility and heart rate are invoked simply to maintain a normal cardiac output at rest. Therefore the autonomic nervous system in a patient with heart failure has a limited ability to bring about further increases in cardiac output during the initiation of exercise. For this reason, patients with heart failure typically exhibit exercise intolerance.

Maximal exercise ability in normal humans and animals appears to be limited by cardiac output. That is, the respiratory system can oxygenate as much blood as the heart can deliver to the lungs, and skeletal muscle can take up and metabolize as much oxygen as the heart can deliver to it. When cardiac output has reached a maximal level, however, oxygen transport from the lungs to the skeletal muscle also is maximized. This sets the upper limit to the level of exercise that can be sustained.

CLINICAL CORRELATIONS

EXERCISE INTOLERANCE SECONDARY TO CONGESTIVE HEART FAILURE

History. An 8-year-old female Great Dane has been diagnosed previously with idiopathic dilative cardiomyopathy. Severe, generalized cardiac enlargement was evident on thoracic radiographs. The dog has been losing weight and is unable to complete daily walks with her owners.

Clinical Examination. Femoral pulses are weak but regular at 140 beats/min. The mucous membranes are pale, and the capillary refill time is prolonged. Heart sounds are muffled, and a murmur is heard on the left side over the atrioventricular valve. Respiratory rate is greater than normal (45 breaths/min). Auscultation reveals increased bronchovesicular (respiratory) sounds. The abdomen is distended, and the abdominal organs are difficult to palpate. The electrocardiogram shows sinus tachycardia with broad, high-voltage QRS complexes. Thoracic radiography reveals a greatly enlarged heart and moderate pulmonary edema. Echocardiography reveals dilation of all four cardiac chambers. Ejection fraction is below normal, and there is mitral regurgitation.

Additional diagnostic tests are conducted to help assess the degree of complications secondary to the heart failure. The percentage saturation of hemoglobin in arterial blood is 78% (normal, 95% to 100%), the difference in oxygen content between arterial and venous blood is 8.5 mL of O_2 per deciliter of blood (normal, 4 to 6 mL), the serum creatinine concentration is 3 mg/dL (normal, <1 mg/dL), urine specific gravity is 1.036 (high normal), and central venous pressure is 14 mm Hg (normal, 0 to 3 mm Hg).

When persuaded to exercise, the dog appears to become tired after walking less than 1 minute. Her legs begin to tremble, and then she collapses. Her pulse rate is 180 beats/min, and her mucous membranes are dark and cyanotic (blue).

Comment. Chronic heart failure secondary to cardiomyopathy is common in large dogs older than 4 years of age. Often the cardiomyopathy is idiopathic (of unknown cause). The case presented here is fairly typical of advanced heart failure. All the clinical findings are either direct consequences of the heart failure or consequences of attempts by the body to compensate for the heart failure (see Figures 26-1, 26-2, and 26-3). In brief, ventricular failure (decreased contractility) leads to decreased stroke volume, cardiac output, and blood pressure.

Compensations for the heart failure involve reflex decreases in parasympathetic activity, increases in sympathetic activity, and increases in the release of ADH and renin. Heart rate is increased, which helps raise cardiac output back toward normal. Pulse pressure, judged by palpation of the femoral pulse, is reduced (because heart rate is high and stroke volume is low). There is decreased blood supply to the mucosa, splanchnic organs, kidneys, and resting skeletal muscle because of vasoconstriction. This helps support arterial pressure and reserves the available cardiac output for the heart and brain. The vasoconstriction is evident in the pale color and slow refilling of the mucous membranes. Renal vasoconstriction reduces the rate of urine formation. Urinary loss of salt and water is further reduced by the actions of ADH and the renin-angiotensin-aldosterone system. The urine that does form has a high solute concentration (high specific gravity). Metabolic products (e.g., creatinine) that are normally eliminated by the kidneys accumulate in the blood. The resulting uremia, if severe, can

further depress cardiac function and initiate the vicious cycle of decompensation.

Salt and water retention increases blood volume above normal. Most of the excess blood volume is in the veins, so venous and atrial pressures are above normal. The elevated atrial pressure (preload) increases ventricular end-diastolic volume above normal, which helps the failing heart to pump a larger stroke volume than it otherwise would. However, the excessive volume and pressure of blood in the veins also cause systemic edema (distended abdomen caused by ascites) and pulmonary edema (visible on the radiograph). Pulmonary edema impairs the ability of the lungs to oxygenate blood. Therefore the hemoglobin saturation and the oxygen content of arterial blood are both below normal in this dog. The tissues of the body respond to the low rate of oxygen delivery by unloading as much oxygen as they can from the blood as it flows through the tissue. This makes the arteriovenous difference in oxygen content greater than normal. The general inadequacy of cardiovascular transport leads to poor gastrointestinal function and metabolic stresses on the tissues of the dog, and weight loss occurs.

Despite many compensatory mechanisms, this dog is unable to deliver a normal amount of well-oxygenated blood to the body tissues, even at rest. When the dog tries to exercise, cardiac output increases very little. Therefore, when exercise-induced vasodilation occurs in the exercising muscles and total peripheral resistance decreases, blood pressure falls dramatically. There is a further decrease in blood flow in the tissues of the systemic circulation that were already vasoconstricted (e.g., mucous membranes), and these tissues become hypoxic and cyanotic. Inadequate blood flow in the exercising skeletal muscles leads to hypoxia and acidosis, and the dog collapses.

Treatment. The ideal treatment strategy for this dog is to improve the contractile performance of the myocardium. Theoretically, β-adrenergic agonists or cardiac glycosides could be administered to increase cardiac contractility. However, currently available drugs are either ineffective or only mildly effective in dogs with severe, chronic heart failure. One reason is that dogs in heart failure have already engaged adrenergic drive to the heart through activation of their sympathetic nervous systems. Therefore, treatment emphasizes symptomatic therapy, with the goals of controlling pulmonary congestion and improving cardiac output. Diuretics or venodilators reduce venous pressures and are usually effective in controlling signs of congestion (venous distention and edema). Such drugs must be used cautiously, however, because they create the risk of lowering preload and therefore exacerbating the low cardiac output. Arteriolar vasodilators can augment the output of a failing heart by reducing the afterload (arterial pressure) against which the heart must eject blood. An appropriate initial treatment for this dog includes a diuretic (furosemide) and a cardiac glycoside (digitalis). If digitalis fails to improve cardiac contractility in this advanced case of cardiomyopathy, an arteriolar vasodilator (hydralazine) or a mixed vasodilator-venodilator (enalapril) can be added to the furosemide regimen.

Despite therapy, the prognosis for a dog with such severe, chronic heart failure is poor.

COW WITH "HARDWARE DISEASE"

History. A 4-year-old, pregnant Holstein cow is presented for lethargy, poor appetite, and edema. She is due to calve in 2 months. The producer noticed that over the last few weeks the cow has seemed progressively more lethargic and reluctant to move. He observed swelling below her jaw and in her brisket. She has lost 75 to 125 pounds.

Clinical Examination. The cow appears depressed. She is dehydrated. Her mucous membranes are dark (indicating poor perfusion), and capillary refill time is prolonged. She has marked brisket and submandibular edema. Her jugular veins are prominent. She grunts when she moves. Her temperature, pulse, and respiratory rates are all increased. Her heart sounds are muffled (as if heard through fluid), and she has a murmur ("washing machine" murmur). She has increased bronchovesicular (respiratory) sounds dorsally, but the sounds are muffled ventrally. Peripheral pulses are weak. Rumen contractions are decreased (one every 1 to 3 minutes). Feces are scant. Blood is submitted for a complete blood count and chemistry profile. Results indicate that the white blood cell count is low and serum creatinine concentration is increased. Fibrinogen, globulins, and total protein are all increased. Calcium and potassium levels are low.

An electrocardiogram reveals decreased amplitude of QRS complexes and ST segment elevation. Echocardiography reveals excessive fluid and gas in the pericardial space. Fibrin tags are also present. The right atrium and right ventricle appear to collapse during diastole, which is consistent with *cardiac tamponade* (excessive pericardial fluid pushing in on the heart). The left ventricle also contracts less forcefully and less completely than normal during systole (*decreased left ventricular free wall motion*).

With guidance from the echocardiogram, a sample of pericardial fluid is obtained. The fluid is reddish in color (rather than clear) and has a distinct, bad odor. Laboratory analysis reveals elevated protein concentration and an elevated count of white blood cells (primarily neutrophils) in the pericardial fluid. Culture reveals that both aerobic and anaerobic bacteria are present.

Comment. This cow has traumatic reticuloperitonitis with pericarditis. *Traumatic reticuloperitonitis* (TRP), or "hardware disease," is common in cattle. Cattle are indiscriminate eaters, and they accidentally swallow sharp metal objects that get mixed into their feed. Metal objects settle in the reticulum of the rumen. Contractions of the reticulum may push sharp objects through the wall of the reticulum and into the peritoneum. Bacteria follow and cause peritonitis. Subsequently, the sharp object may penetrate the diaphragm, which is located just cranial to the reticulum, and may then move on to penetrate the pericardium. The consequence is pericarditis (inflammation of the pericardium). Sequelae include formation of scar tissue (seen as fibrin tags), pericardial bacterial infection, and accumulation of inflammatory fluid in the pericardium. The pericardial fluid presses on the cardiac chambers, restricting their filling during diastole, and this causes pump failure.

Evidence of congestive pump failure in this cow includes poor perfusion (weak pulses, dark mucous membranes, and prolonged capillary refill time), cardiac abnormalities (subnormal right atrial and ventricular filling, decreased left ventricular motion), elevated heart rate, distended jugular veins, edema, and lethargy.

Treatment. Prognosis is poor in this case because of the combination of pericardial infection and congestive pump failure. The producer could try to treat the infection, in hopes of delivering a live calf. Because the cow is already in pump failure with very limited cardiac output, however, it is likely that the calf is not receiving sufficient blood flow and oxygen. The calf could die in utero and could be aborted by the cow.

PRACTICE QUESTIONS

1. During experimental trials on a new artificial aortic valve, a dog is anesthetized and placed on cardiac bypass for 1 hour (i.e., a heart-lung machine is substituted for the dog's own heart and lungs). After successful installation of the artificial valve, the dog is taken off bypass, and the normal circulation is restored. Ten minutes later, the dog's central venous pressure is 20 mm Hg, mean arterial pressure is 90 mm Hg, and heart rate is 130 beats/min. The cardiac output is not measured, but the surgeon suspects that it is too low and therefore the patient's tissues are not being adequately supplied with blood. Which of the following measures would be most likely to improve the delivery of blood to the patient's tissues?
   a. Transfusion with 500 mL of whole blood
   b. Administration of isoproterenol (selective β-adrenergic agonist)
   c. Increasing the heart rate by electrical pacing
   d. Administration of norepinephrine (nonselective α/β-adrenergic agonist)
   e. Administration of a β-adrenergic antagonist, such as propranolol

2. One of the nerves leading to a dog's heart is stimulated for 1 minute while left atrial pressure, heart rate, and left ventricular output are measured (Figure 26-10). During this stimulation:
   a. Venous return to the left atrium transiently exceeds left ventricular output.
   b. The increase in left ventricular output at the beginning of stimulation can be explained by Starling's law of the heart.
   c. Stroke volume is lower after 15 seconds of stimulation than before stimulation.
   d. The effects of the nerve stimulation are similar to those caused by sympathetic activation of the heart.
   e. The progressive decline in left ventricular output during the stimulation is probably caused by a progressive increase in ventricular end-diastolic volume.

3. One hour after a severe hemorrhage, a dog's arterial pulse pressure, mean pressure, and hematocrit are all below normal. Which of the following statements is *true*?
   a. The diminished pulse pressure reflects decreased aortic compliance.
   b. The diminished mean pressure probably results from decreased total peripheral resistance (TPR).
   c. The diminished hematocrit probably results from reabsorption of interstitial fluid into the bloodstream.
   d. Under these conditions, the action potential frequency of the arterial baroreceptors is greater than normal.
   e. Under these conditions, sympathetic activity is probably less than normal.

4. When a sheep is held in a vertical, head-up position, arterial pressure decreases because:
   a. The baroreceptor reflex causes an increase in TPR.
   b. Valves in the leg veins promote the return of blood to the heart.
   c. The respiratory pump promotes movement of abdominal venous blood into the thorax.
   d. Central blood volume is increased.
   e. Right atrial pressure is decreased.

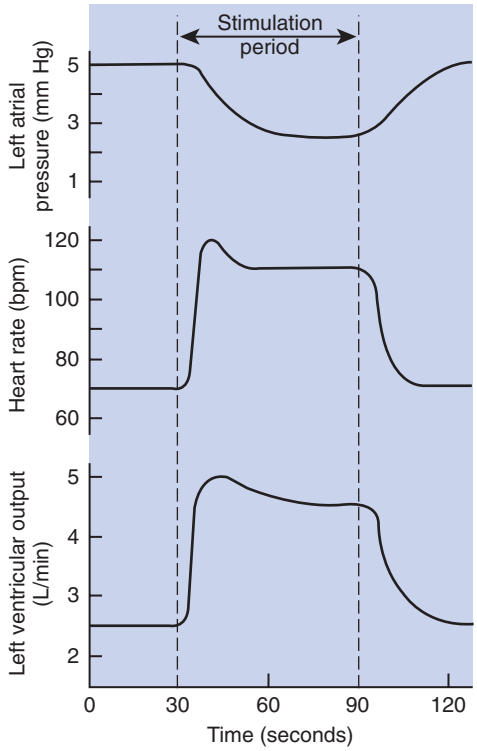

FIGURE 26-10 Cardiovascular data for Practice Question 2.

5. During exercise in a normal animal:
   a. TPR is decreased.
   b. Cardiac output is increased.
   c. Stroke volume is increased.
   d. Blood pressure is nearly normal.
   e. All the above are true.

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