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Cardiovascular Physiology

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Case 1

You generally go for a 3-mile run in the morning, and today is no exception. Within the first minute, you feel your heart rate increase, and before long you can feel the pounding of your heart. As your run continues, you think about the blood coursing through your arteries and veins and wonder at the workings of the cardiovascular system. What caused your heart rate to increase? What makes your heart beat harder? What makes you flush by the end of the run? How is all this regulated, so that it returns to “normal” at the end of your run?

Introduction

The cardiovascular system consists of the heart and the connecting vasculature, from aorta to arterioles to capillaries to veins to vena cavae. It functions as the distributor of molecules to the billions of cells in the body. Hormones are transported to their target cells via the blood. Nutrients absorbed during digestion are delivered to cells via the circulation, and some of the waste products of cells go to the kidney for elimination, carried in the blood supply. Oxygen (O_2), essential for adenosine triphosphate (ATP) production, is carried in the blood, as is the gaseous metabolic waste product, carbon dioxide (CO_2). Transportation of all of these molecules is dependent upon the constant movement of blood within the circulatory system. This movement is achieved through the actions of a pump, our heart, and a series of non-rigid, living pipes, the vasculature.

The Anatomy of the Cardiovascular System: The Heart

The heart is a muscular organ, approximately the size of your fist, comprising four chambers: left and right atrium and left and right ventricles. It is composed of striated muscle, similar to skeletal muscle, but instead of contracting against fixed attachments to bone, as skeletal muscle does, it contracts against an incompressible fluid, blood. So the heart contracts against a hydrostatic skeleton. The walls of the atria are thin, reflecting the low pressure exerted by blood returning to the heart. The atria connect to their respective ventricles by atrioventricular (A-V) valves, which open whenever the pressure in the atrium exceeds that of the ventricle. These valves are in turn connected to the ventricular wall by papillary muscles and chordae tendineae, lengths of connective tissue that gave rise to the name “heartstrings” (**FIGURE 7.1**). These muscles contract whenever the ventricles contract, keeping the A-V valves closed during ventricular contraction. This prevents blood from returning to the atria.

The right ventricle is a thin-walled chamber, as it only needs to exert enough pressure to force blood from the ventricle to the nearby lung. The conducting vessels of the lung quickly divide into a vast capillary bed, so there is little resistance to the flow of blood. The left ventricle, however, must generate enough force to pump blood to the entire systemic circulation. To achieve this, the left ventricle is a thick-walled chamber that contracts in a spiral fashion (remember that the heart resembles a cone in shape) with sufficient force to open the semilunar valve of the aorta and pump blood throughout the body. Like skeletal muscle, cardiac muscle can hypertrophy after repeated bouts of heavy use, increasing the thickness of the ventricular wall and improving its ability to generate forceful contractions. This means your morning exercise increases your heart strength as well as your leg strength!

The heart serves as the pump of the cardiovascular system, providing the pressure head to move fluid, blood. As mentioned earlier, the heart is four-chambered, but it is best thought

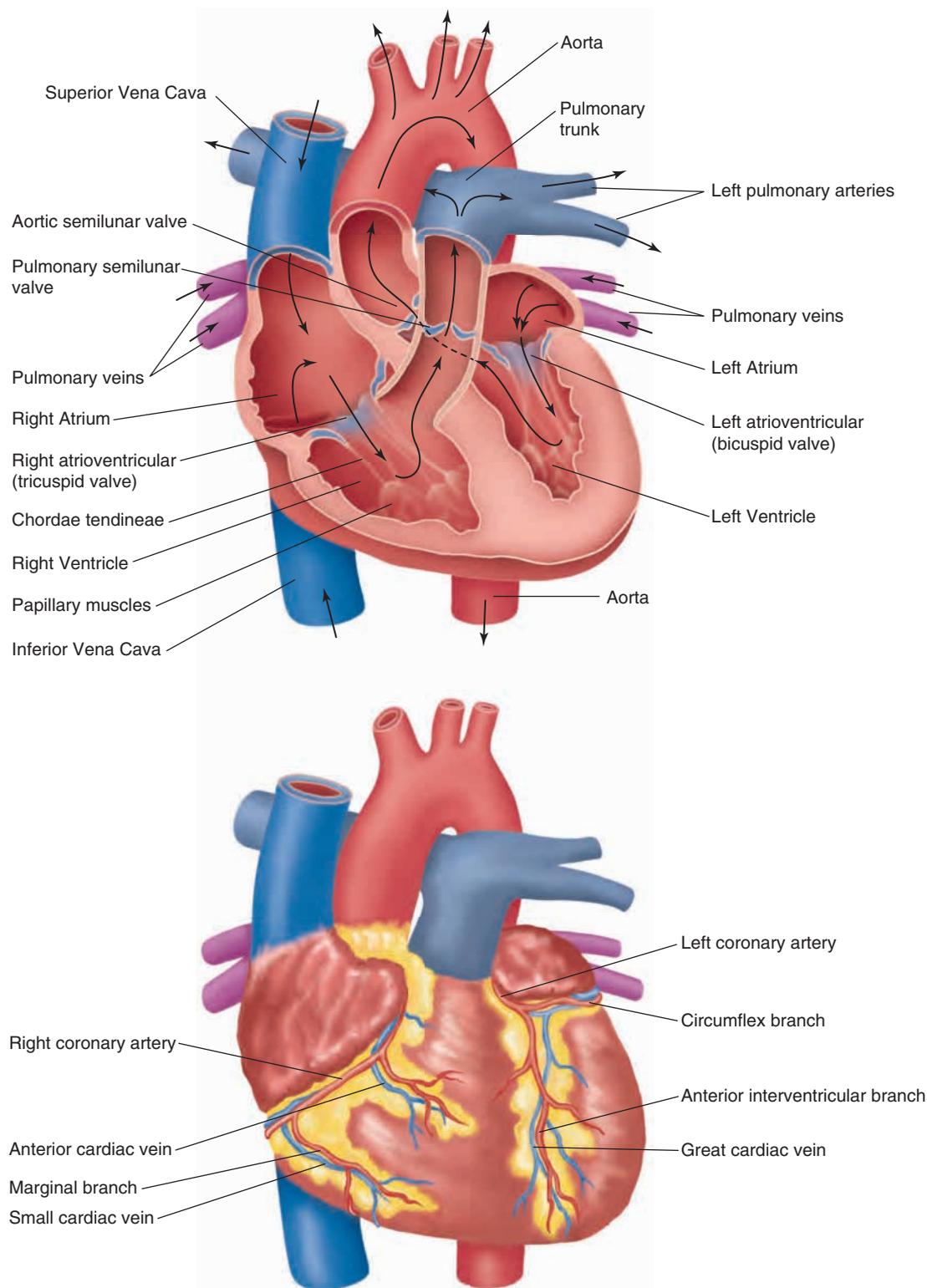


FIGURE 7.1 The structure of the heart and the path of blood flow through it.

of as two separate pumps functioning in parallel, with each atrium filling simultaneously, draining into the ventricles simultaneously and the ventricles contracting simultaneously. The right atrium receives blood from the superior and inferior vena cavae. Blood moves passively into the right ventricle following a simple pressure gradient. Contraction of the right ventricle

pumps blood into the pulmonary artery and then into the nearby pulmonary circulation of the lung. There, blood is intimately exposed to air in the alveoli, releasing CO_2 and binding O_2 . Pulmonary veins collect this oxygenated blood and return it to the left atrium through the pulmonary veins. Again, the blood moves passively, down a pressure gradient, through the A-V valve, into the left ventricle. Upon contracture, the left ventricle pumps blood through the semilunar valve into the aorta, for its transit through the vast systemic circulation. Blood will ultimately reach each cell of the body, delivering nutrients, hormones, and O_2 while picking up CO_2 , metabolic waste products, and metabolites before being returned to the right atrium via the vena cava (Figure 7.1).

Cardiac Muscle: Cellular Level of Organization

At the tissue level, cardiac muscle resembles skeletal muscle, in that it contains regular arrays of thick filaments (myosin) and thin filaments (actin and associated regulatory proteins) arranged within sarcomeres, bounded by Z disks. During contraction, cardiac muscle works on the same sliding filament mechanism described in skeletal muscle. However, there are important differences. Cardiac muscle fibers contain only one nucleus, instead of the multiple nuclei of skeletal muscle. Cardiac muscle fibers branch instead of being consistently linear. Most importantly, cardiac muscle fibers are connected to one another by intercalated disks, which contain gap junctional proteins. These proteins are most abundant on the longitudinal axis of the muscle cells and allow very low resistance conduction between two cardiac muscle cells. It is analogous to adjacent hotel rooms joined by a connecting door—transit between the two is extremely fast, becoming essentially a single room. Gap junctional proteins allow the heart muscle to function as a syncytium, that is, as though heart muscle cells were one large muscle fiber, instead of thousands of individual muscle cells (FIGURE 7.2). Simultaneous contraction is essential if coordinated force is to be

generated to pump blood out of the heart on each beat. The heart is the first organ to function in a human embryo, and it continues throughout our lives. To fuel this continual muscle work, heart cells are very rich in mitochondria, which provide the ATP required for contraction. Glycogen stores in human cardiac muscle are minimal, capable of fueling contraction for only a minute or two. The primary substrate for cardiac metabolism is fatty acids. Fatty acids do not undergo glycolysis, so there is no anaerobic component to their catabolism. This means that cardiac muscle is dependent upon O_2 for muscle contraction.

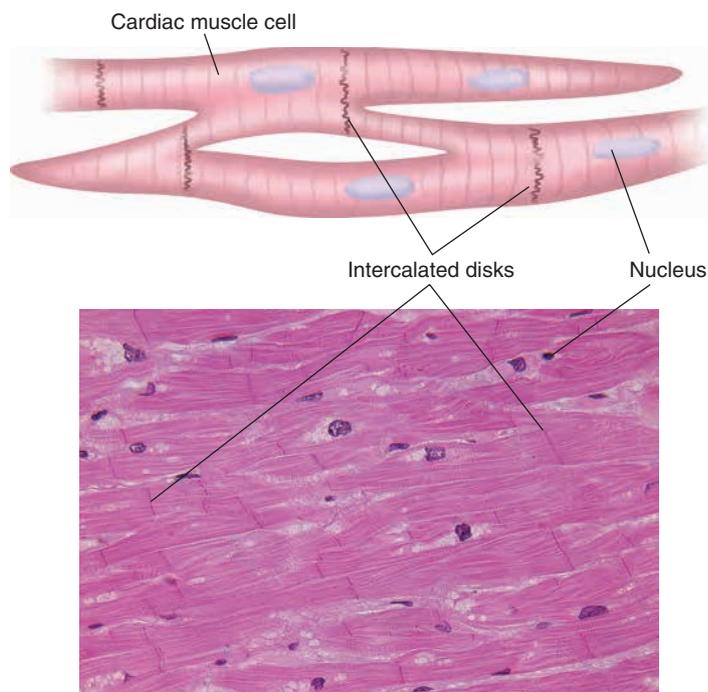


FIGURE 7.2 Gap junctions allow the heart to depolarize as a syncytium and mitochondria fuel its activity. (Photo © Donna Beer Stolz, Ph.D., Center for Biologic Imaging, University of Pittsburgh Medical School.)

Anatomy: The Vasculature

When blood leaves the left ventricle, it enters the aorta, a large, muscular vessel with a rich supply of elastic tissue. Imagine the contents of the left ventricle suddenly and forcefully entering a much smaller diameter vessel—the aorta. If the aorta were rigid, it would create an

enormous resistance to flow. However, it is elastic, which allows the aorta to expand as it fills with blood and spring back to its resting length as blood continues down the vascular tree. The elastic recoil of the aorta contributes energy to continuous flow of blood through the remainder of the blood vessels. From the aorta, the blood flows to conducting arteries, which are also fairly thick walled, and then to the arterioles. With each level of branching, a vessel divides into multiple vessels, expanding the total cross-sectional area of the arterial vessels. The walls of these vessels contain not only connective tissue but also smooth muscle, which continually alters the diameter of the vessel (**FIGURE 7.3**). You may know that the autonomic nervous system (ANS) has control over arteriole diameter; it is here that the ANS's control is exerted, constricting arterioles and reducing flow or dilating arterioles and increasing flow. The innermost layer of the blood vessels is a layer of endothelial cells that are in intimate contact with blood. Long thought to be simply a quiescent lining of the vessel, we now realize that these endothelial cells are also hormonal cells and active modulators of arteriole diameter. When the hydrostatic pressure of flow within a vessel increases, the endothelial cells experience shear stress, stress parallel to the surface of the vessel exerted by blood itself. Shear stress causes endothelial cells to release nitric oxide (NO), a gaseous signaling molecule that relaxes smooth muscle and increases vessel diameter.

Arterioles branch into thin-walled capillaries, which is where the exchange of ions, nutrients, and gases occurs. The capillaries are simply the endothelial layer surrounded only by a basement membrane. This is where our closed circulatory system comes closest to being open, and where fluid moves from capillary to interstitial space and back again. Capillaries must lie close enough to each cell in the body to perfuse that cell and provide it with the nutrition and waste removal that it needs. Remember, diffusion is a slow process, so capillary distance from a cell cannot be great.

How Does Fluid Exchange Occur within the Capillary Bed?

There are two primary forces responsible for fluid movement across the capillary: hydrostatic pressure, that is, the pressure generated by the heart, and osmotic pressure, the force generated by solutes within the blood. Hydrostatic pressure not only pushes blood through the vessels but also exerts force on the vessel walls (**FIGURE 7.4**). This pressure tends to move water out of the capillary into the interstitial space. The movement of water can occur across the plasma membrane of the endothelial cell, but it mostly travels through the perivascular spaces between endothelial cells. As water leaves the capillary bed, moving into the interstitial space, the hydrostatic pressure within the capillaries goes down, the driving gradient is reduced, and less water leaves the capillary bed.

The second force, osmotic pressure, is exerted by osmotically active particles within the blood. This can be ions and nutrients, but an important contributor to osmotic force in the blood is the protein albumin. Albumin, made in the liver, is a normal circulating protein within the blood; at the capillary, albumin is a powerful attractor of water. As blood flows through the capillary bed, hydrostatic pressure moves some water out at the arterial end of the capillary network, and albumin and other osmotically active particles draw water back into the blood at the venous end. Throughout the capillary bed, these two forces are in dynamic opposition, and together they maintain fluid balance.

There are two other forces that also contribute to vascular volume: tissue hydrostatic pressure and tissue osmotic pressure. The amount of water within the tissue will exert a hydrostatic pressure of its own, opposing the hydrostatic pressure generated by the heart, pushing blood against the capillary walls. This is one reason that more fluid leaves the capillaries at the arterial end of the capillary bed. The more fluid that leaves the vessels, the greater the tissue hydrostatic pressure will become. The second force, tissue osmotic

FIGURE 7.3 Arteries and veins differ in the amount of elastic tissue and smooth muscle each contains.

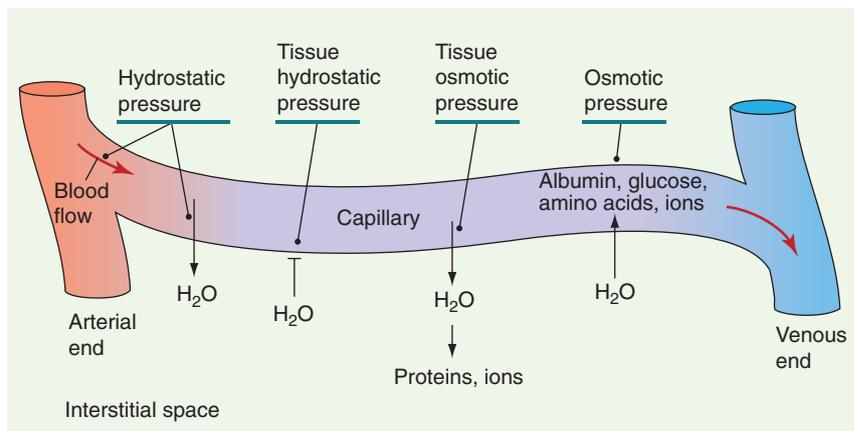
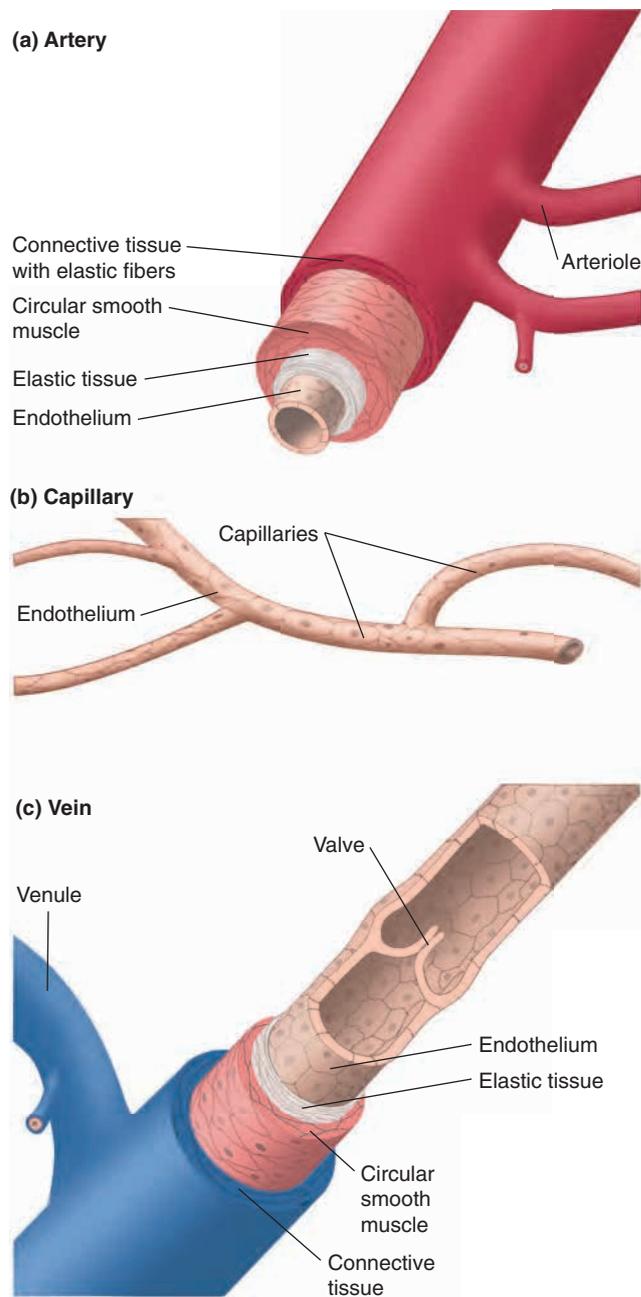


FIGURE 7.4 Movement of water into and out of capillaries is a result of four separate forces.

pressure, is exerted by proteins and ions within the interstitial space. This force tends to pull water from the vasculature into the surrounding tissue. This force is generally small, but should capillaries become leaky, allowing protein into the interstitial space, this force can become significant. This is one of the mechanisms behind tissue swelling following a bee sting, for example.

Role of the Lymphatic System in Fluid Balance

Actually, there is a small net loss of fluid from the capillaries to the interstitial fluid. This fluid moves, primarily by interstitial hydrostatic pressure, into the blind-ended lymphatic vessels. The lymphatic vessels have valves, much like the veins, and move fluid from these terminal sacs along a low-pressure, fluid-filled third vascular space back to the venous circulation (**FIGURE 7.5**). During the transit, the fluid will pass through lymph nodes, and the fluid will be monitored by the immune system. Independent of its role in the immune system, fluid recovery from tissues by the lymphatic system is essential. Malfunction of the lymphatic system—as in elephantiasis, where the lymphatic system is blocked by parasites—causes vascular fluid loss and tissue swelling.

Nutrient Exchange

Gases like O_2 and CO_2 can pass through a plasma membrane unimpeded, moving down a partial pressure gradient. Because cells use O_2 during ATP production, partial pressure of oxygen in arterial blood (PaO_2) will be higher than the tissue, and O_2 will move to the tissues from the capillary bed. Because CO_2 is produced as a cellular metabolic by-product of metabolism, CO_2 will move in the opposite direction, and, thus, the exchange of gases at the capillary bed is accomplished.

Nutrient exchange at the capillary beds can occur by diffusion. Glucose is dissolved in water in the vasculature and diffuses into the interstitial space and out again along with water. Small proteins or amino acids can also be dissolved in plasma; these also leave the capillaries by diffusion. In contrast to glucose, these nutrients rarely move back into the capillary. If they are not transported into the surrounding tissues, they are taken up by the lymphatic system and returned to the venous vasculature at the thoracic duct, near the heart (**FIGURE 7.6**).

How Does Blood Return to the Heart?

The blood leaving the capillaries goes to venules, then veins, and then great veins, and finally the inferior or superior vena cava. The venous vessels are parallel in pathway to the arteries but are dissimilar vessels. Unlike the arteries, the veins are poorly supplied with muscle but still contain elastic fibers. This makes the venous circulation a very compliant one, that is, there is a large increase in volume of the vessel for any given pressure. As a result, venous vessels serve to store blood and actually form our largest reservoir of blood. As you recall about the autonomic nervous system, sympathetic stimulation causes venoconstriction, contraction of vascular smooth muscle in the veins, which will increase the return of venous blood to the heart. However, even in the absence of sympathetic stimulation, blood is moved from the extremities to the heart by skeletal muscle, which squeezes the veins during contraction, pushing blood upward. The skeletal muscle pump plus one-way valves within the veins keep the blood moving back toward the heart (**FIGURE 7.7**). Finally, negative pressure within the thoracic cavity functions as a form of suction to bring blood back to the heart.

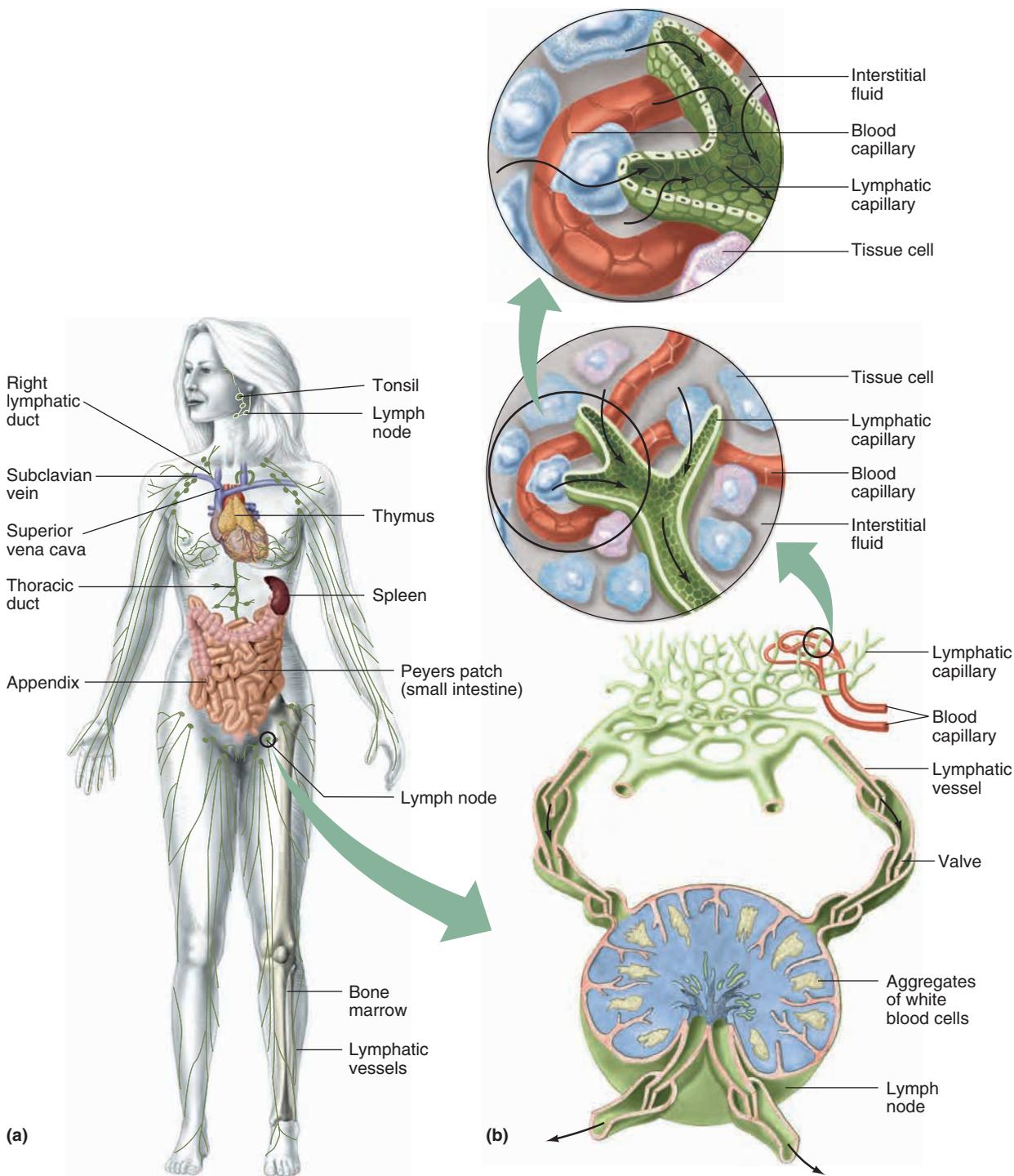


FIGURE 7.5 Lymphatic vessels (a) pick up excess fluid and move it through lymph nodes and into the venous circulation (b).

Blood: What Is Flowing Through These Vessels?

Blood is a complex fluid, containing red blood cells (erythrocytes), white blood cells (leukocytes), and plasma. Plasma is a solution in which hormones, proteins, ions, nutrients, waste products, and gases are all dissolved. In short, blood is both the supply line and the waste disposal system for the cells of your body. Selective transport at the cell membrane allows uptake of nutrients or binding of hormones to receptors, while waste products, with no available transport, stay in the blood plasma until they are either metabolized or excreted.

As we discussed above, the proteins, ions, and nutrients in blood plasma contribute to the osmotic forces that keep blood in vessels. So, in addition to serving as an avenue for communication and nutrient delivery, plasma functions to maintain itself within the blood vessels.

Erythrocytes are specialized for carrying O_2 and are essential if our cells are to be supplied with the quantity of O_2 necessary to sustain life. Erythrocytes are derived from stem cells within the bone marrow that also give rise to leukocytes: T and B lymphocytes, neutrophils, eosinophils, basophils, macrophages, megakaryocytes, and monocytes. (Although they are a component of blood, the roles of the various white blood cells will not be discussed at length here, as these functions primarily relate to the immune system.) Erythrocytes develop from a common stem cell but undergo a remarkable transformation during their maturation (**FIGURE 7.8**).

After their initial differentiation from the blood stem cell, erythrocytes contain all the normal cellular components: nucleus, mitochondria, endoplasmic reticulum (ER), ribosomes, and Golgi bodies. In addition to their traditional role in metabolism, mitochondria within developing erythrocytes transport iron from the cytoplasm into the matrix of the mitochondria and incorporate it into a porphyrin ring. The porphyrin ring is then exported out of the mitochondria into the red blood cell cytosol, where it is incorporated into a globin protein made in the cytoplasm. Four of these globin proteins unite to form one large, four-subunit protein known as hemoglobin. One red blood cell may contain as many as 300 molecules of hemoglobin formed in this way.

Once the hemoglobin molecules are created, however, the final stage of maturation for the red blood cell is exclusion of the nucleus, mitochondria, ER, and Golgi. For this reason, a mature red blood cell is small; its size allows it to move through the tiniest of capillaries, but it lacks the cellular machinery to create more hemoglobin or even to repair itself. As a result, erythrocytes have a limited life expectancy, approximately 120 days.

What can damage a red blood cell? Erythrocytes do not float quietly within the blood but are forcefully propelled through the vessels, where they are subjected to shear stress as

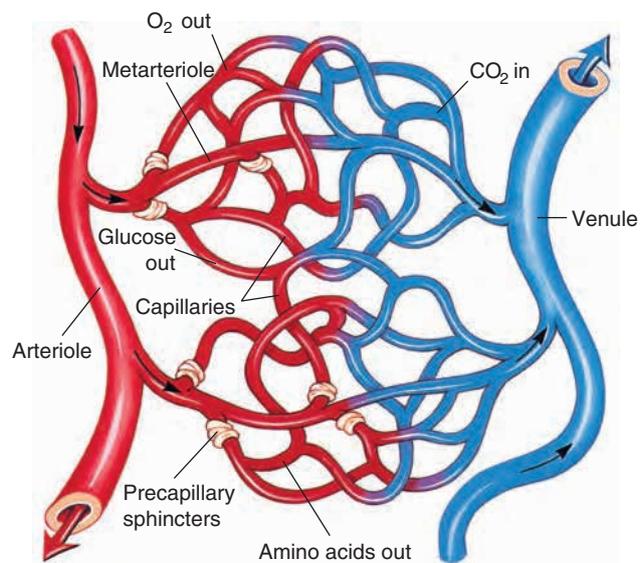


FIGURE 7.6 Gases, glucose, and amino acids all move from the capillaries into the surrounding tissue.

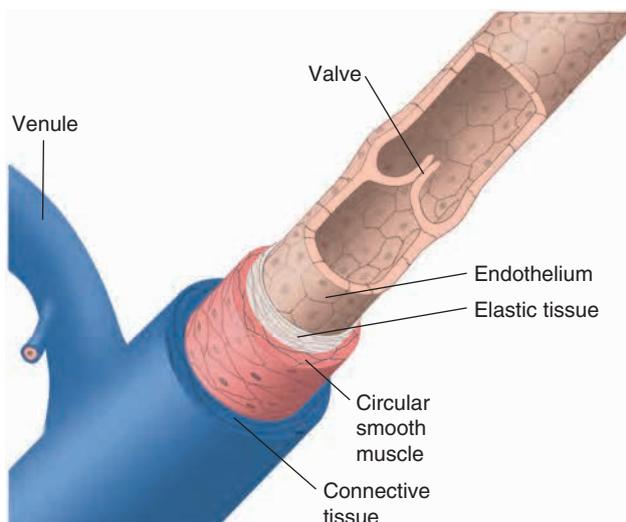


FIGURE 7.7 Veins have less smooth muscle than arteries (see Figure 7.3), making them more compliant. They also have one-way valves that move blood in one direction—toward the heart.

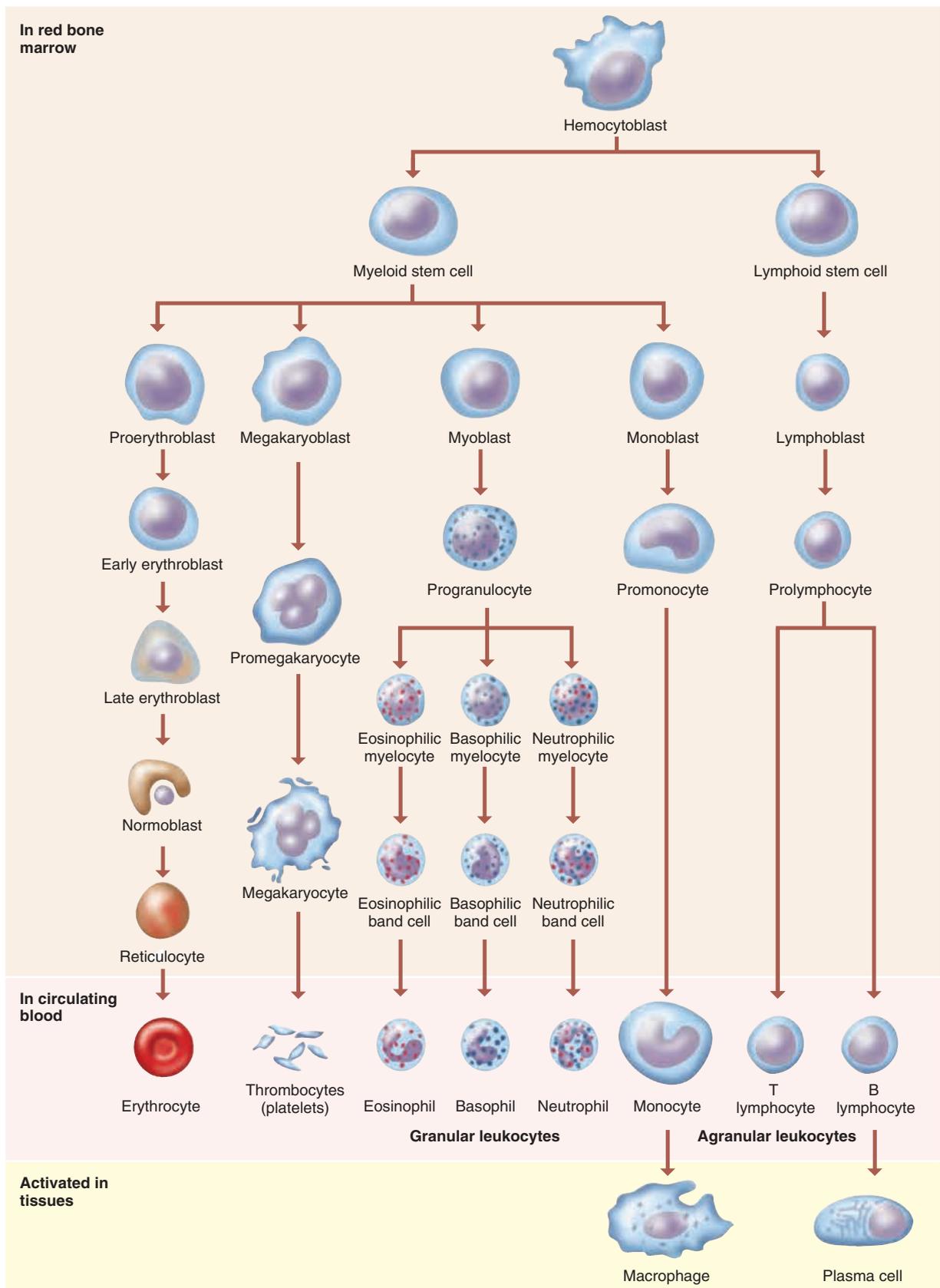


FIGURE 7.8 Red blood cells differentiate from a stem cell and mature into cells without organelles. They are specifically designed to carry hemoglobin.

they slide along vessel walls. Shear stress will eventually damage the red blood cell, causing its destruction.

Hemoglobin—A Protein with a Brain?

Hemoglobin within erythrocytes circulates in the cardiovascular system, where it binds O_2 quickly within the pulmonary capillaries and then delivers that O_2 by unbinding it just as quickly in the tissues. How can this protein bind O_2 in one location and unbind it in another? Hemoglobin is a perfect example of protein structure allowing protein function, so let's take a closer look at how hemoglobin works (**FIGURE 7.9**).

Hemoglobin consists of four protein chains, each with a porphyrin ring in its center. The porphyrin ring has a central Fe^{2+} iron, the only form that can bind O_2 . The protein chains, with the Fe^{2+} -porphyrin ring centers, function to shield the Fe^{2+} from O_2 , allowing O_2 close enough to have an affinity for the iron, but not close enough to irreversibly bind to Fe^{2+} , oxidizing it to Fe^{3+} . Each of the globins has two stable conformational states, tensed, which moves the porphyrin ring so that it has a poor attraction to O_2 and a relaxed state, where the protein changes shape enough to flatten the ring, which brings Fe^{2+} and O_2 into closer proximity, allowing O_2 binding. Movement of the globin proteins thus alters O_2 affinity for the caged Fe^{2+} ion.

What causes the structural transition between these two states? Hemoglobin has multiple allosteric binding sites, binding sites that are different from the site that binds O_2 . These binding sites influence the shape of the protein and its transition from the tensed to the relaxed state. Hemoglobin can bind H^+ ions and CO_2 , at separate sites, and each will cause the globin protein to move toward the tensed state, that is, the state where O_2 is released from the hemoglobin. Note that H^+ and CO_2 are in higher concentration at the tissues, so O_2 is released where it is needed, at the tissues. In the lungs, where H^+ and CO_2 are in lower concentration, these allosteric binding sites are emptied and hemoglobin enters a relaxed state, conducive to O_2 binding.

Mature erythrocytes have no mitochondria, so they rely exclusively on glycolysis for the production of ATP. If you recall the reactions of glycolysis, an intermediate step forms 1,3-bisphosphoglycerate. Erythrocytes contain the enzyme bisphosphoglycerate mutase,

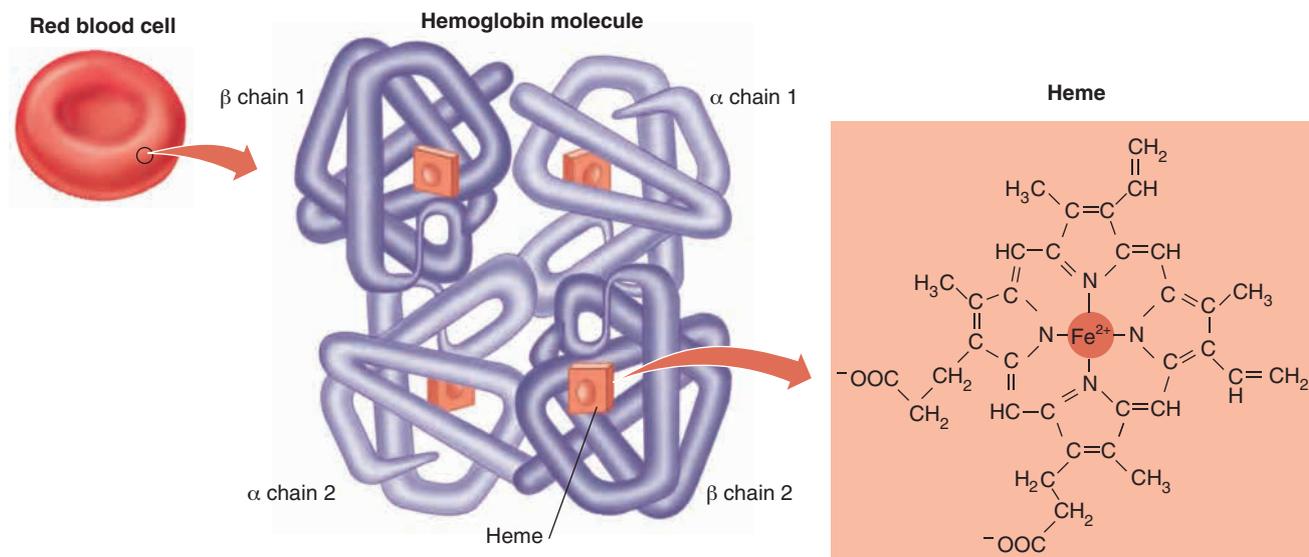
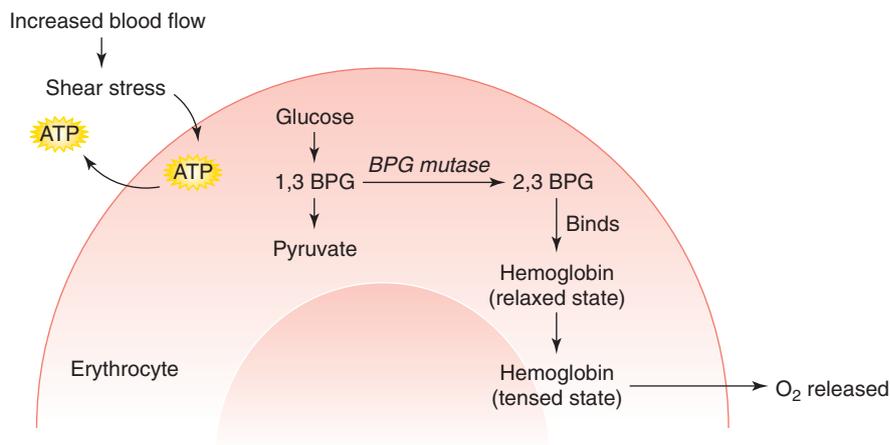


FIGURE 7.9 The structure of hemoglobin.

FIGURE 7.10 BPG is made from products of glycolysis. Once bound to hemoglobin, it reduces its affinity for O₂.



which converts 1,3-bisphosphoglycerate to 2,3-bisphosphoglycerate, or BPG. Hemoglobin within the erythrocytes possesses a binding site for BPG, which, when bound, moves hemoglobin toward the tensed state, decreasing its affinity for O₂.

When is BPG produced? Like most cells, erythrocytes have Na⁺-K⁺ ATPases and Ca²⁺ ATPases in their plasma membrane, both of which require ATP to function. In addition, erythrocytes release ATP in response to shear stress. Therefore, an increase in the rate of blood flow in the vessels will cause an increase in the rate of ATP release and production by erythrocytes. ATP production increases the number of glycolytic cycles, the potential for BPG synthesis, and binding to hemoglobin (FIGURE 7.10). Thus, increased blood flow increases O₂ release from hemoglobin, improving O₂ delivery to the tissues.

How Is Erythrocyte Synthesis Regulated?

Because of their limited lifespan, erythrocytes are continuously made. However, the rate of production is not static but is linked to blood oxygen levels. The sensor for PaO₂ lies within the kidney, in fibroblast-like cells of the interstitium of the renal cortex. The kidney receives 25% of the total output from the heart, so the cells of the kidney are in an excellent position to “sample” the composition of blood. If the fibroblast cells sense hypoxia (lowered O₂ levels), then they release the hormone erythropoietin into circulation. Erythropoietin targets stem cells within bone marrow and causes an increase in red blood cell differentiation. In this way, O₂ carrying capacity is maintained within the blood.

Isn't an increase in O₂ carrying capacity always good? As an active person, wouldn't it be beneficial to your athletic performance if you had more erythrocytes? Certainly it seems that way, but there is a downside to an increased number of red blood cells. The number of erythrocytes in blood contributes significantly to its viscosity, or stickiness. Increased viscosity increases resistance to flow. Therefore, greater blood viscosity requires more work by the heart to overcome this resistance and force blood through the vasculature. The heightened performance gained by increasing O₂ is lost via increased cardiac effort needed to move more viscous blood. So there is an ideal level of hematocrit, or red blood cell number, and that is actually the normal range of 40% to 50%.

Now that we understand the structure of the heart and vessels, the composition and characteristics of the fluid flowing through them, and some of the forces that limit flow, let's look at the pump, the heart, in more detail.

What Causes the Heart to Beat?

When we examine skeletal muscle, we see that the stimulus for contraction is the neuronal action potential from an α -motor neuron. While cardiac muscle also contracts in response to an electrical signal, it is an action potential that is spontaneously and continuously generated within the heart itself. The cellular mechanism that initiates the cardiac action potential lies in the sinoatrial node (SA node) and is elegant in its simplicity. We know that ion channel openings and closings cause action potentials. This action potential is no different in that respect. What is unique are the suite of ion channels required for the SA nodal current and their order of opening and closing.

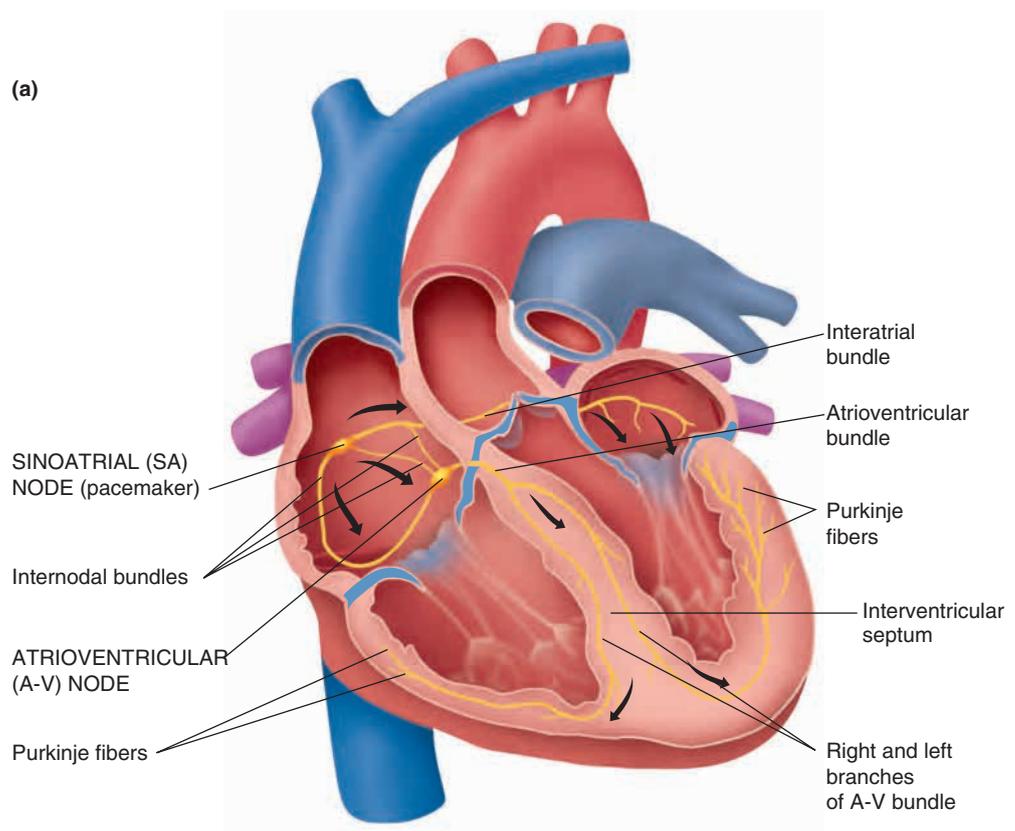
Four voltage-gated ion channels are required for the pacemaker action potential, each with overlapping voltage ranges. The first is a Na^+ channel called hyperpolarization-activated cyclic nucleotide-gated channel (HCN), which yields a current called the “funny current” (I_f)—so named because it looked “funny” (unusual) to the researchers who identified it—which opens at approximately -60 mV. This is a different Na^+ channel than the voltage-gated channel we saw in neurons or muscle. As Na^+ ions enter the cells of the SA node, the membranes are depolarized and gradually the membrane potential reaches the voltage range of a Ca^{2+} channel, called I_{CaT} , for transient calcium current. This channel opens at about -50 mV. As calcium enters the cells, the membranes depolarize further, until the long-lasting calcium channel opens at -40 mV, generating I_{CaL} . In the SA node, the final depolarization and propagation of the action potential comes from calcium channels.

As the cell depolarizes toward 0 mV, the K^+ channels open, K^+ ions leave the cells, and repolarization begins. This is the difference between the SA nodal action potential and any other: as current flowing through open voltage-gated K^+ channels repolarizes the cells, and the membrane potential returns to -60 mV, the funny channels open again, to begin another action potential. So, once begun, the SA nodal action potential is self-generating simply due to the overlapping voltage ranges of the ion channels that generate the action potential. The other consequence of this mechanism is that there is no resting membrane potential in the SA node (**FIGURE 7.11**).

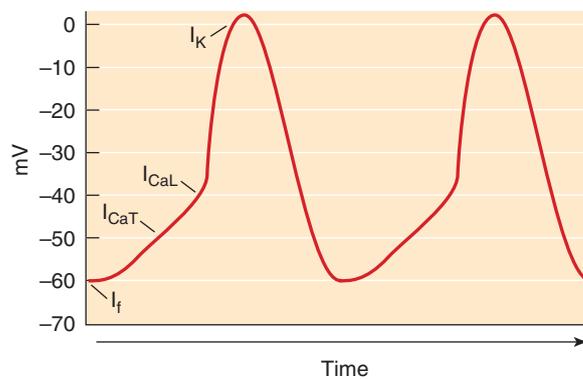
This SA nodal action potential propagates in several directions: to the Bachman’s bundle in the atria and to the internodal pathways, which lead to the A-V node. The action potential in the Bachman’s bundle causes atrial depolarization and then contraction of atrial muscle. The action potential in the internodal pathways causes depolarization at the A-V node. The ion channel distribution in the A-V node is similar to that in the SA node; however, the intrinsic speed of depolarization in the A-V node is slower, so in health, the SA node sets the pace of the heartbeat. Should the SA node fail, the spontaneous depolarizations of the A-V node will take over, but at a slower rate.

From the A-V node, the action potential travels down the bundle branch fibers in the septum of the ventricles to the Purkinje fibers, which run up the exterior cardiac wall. Finally, the action potential moves between ventricular cells, until the entire ventricle is depolarized. However, this action potential is now generated by a completely different set of ion channels. The ventricular action potential is initiated by our more familiar voltage-gated Na^+ channels, similar to the ones that initiate neuronal or skeletal muscle action potentials. Once depolarized to positive voltages, two ion channels open: the L-type (long-lasting) Ca^{2+} channel and a voltage-gated K^+ channel. Ca^{2+} ions enter the cells, depolarizing them further, while K^+ ions simultaneously exit the cells, causing repolarization. These two currents electrically negate one another, so that the ventricular action potential has a plateau and depolarization is maintained for approximately 150 milliseconds, even though the Na^+ channels have inactivated. As the L-type Ca^{2+} channels inactivate, the K^+ repolarization predominates

FIGURE 7.11 (a) The action potential in the SA node is continuous and triggers action potentials in the atria and ventricle of the heart. (b) Four ion currents generate the continuous SA nodal action potential.



(b) Ion currents of the SA node



and the ventricular action potential returns to its resting membrane potential of -90 mV (**FIGURE 7.12**). Ventricular cells will remain at this membrane potential until another action potential is triggered by the SA node.

Inactivation of Na^+ channels, a normal behavior of that channel as we have already seen in the somatic nervous system, allows for a refractory period. In cardiac tissue, the absolute refractory period, when most of the Na^+ channels are inactivated, occurs during the plateau phase. The relative refractory period occurs during the K^+ repolarization phase of the action potential (Figure 7.12). Since an action potential can be initiated during the relative refractory period, any action potential that begins inappropriately, stimulating ventricular cells during this relative refractory period, may cause a lethal ventricular arrhythmia.

What Makes the Heart Rate Increase or Decrease?

Our heart rate is not always the same, as you noticed on your run. Exercise or any physical activity will cause heart rate to increase, while relaxation slows it. We know that the autonomic nervous system can influence heart rate, through the sympathetic and parasympathetic branches. Rate change is accomplished simply by modifying the conduction of the SA nodal channels.

As you begin your run and sympathetic stimulation begins, as it always does with exercise, remember that norepinephrine is released from sympathetic nerve fibers and has the heart as its target. One specific cardiac target is the SA node. Norepinephrine, binding to β_1 at the SA node, will cause phosphorylation of ion channels, via protein kinase A. Phosphorylated ion channels increase heart rate in two ways: (1) by increasing the I_f current, causing it to reach the threshold for calcium channels faster, or (2) by increasing I_{Ca} currents, causing the cell to reach 0 mV faster. Steepening the slope of depolarization for all three currents results in a faster overall rate, that is, your heart beats faster (FIGURE 7.13). Circulating epinephrine released from the adrenal medulla will work the same way, so as your workout continues, you will experience heart rate acceleration from two separate sources: one neurotransmitter and one hormone.

At the conclusion of your run, you feel your heartbeat slowly return to normal. As you recall, the heart is dually innervated by the sympathetic and parasympathetic autonomic pathways. While the sympathetic nerves increase heart rate, as described above, the vagus nerve, from the parasympathetic system, releases acetylcholine, which slows the heart. The primary mechanism for slowing the heart comes from activation of GIRK channels. Remember that acetylcholine binds to muscarinic acetylcholine receptors at the target tissues and that the muscarinic receptors are G-protein coupled receptors. At the SA node, acetylcholine binding causes a unique signaling mechanism. The G protein uncouples from the receptor and binds to a K^+ channel, the G protein-regulated inward rectifying K^+ channel, or GIRK. As a result, the K^+ channel opens and K^+ ions flow outward, hyperpolarizing the membrane potential, moving the SA node further from depolarization. Thus, it takes longer for I_f and I_{Ca} to depolarize the pacemaker cells, the slope of depolarization becomes shallower, and the heart rate slows.

Exercise provides a graphic example of heart rate change, but there are normal variations in heart rate even when you are at rest. This is due to the dual innervation of the heart by both the sympathetic and parasympathetic nervous systems. So, even at rest, the phosphorylation reactions will increase your heart rate for a few beats, while opening of GIRK channels will slow your heart rate for a few beats. We do not notice this variation, but it can easily be seen using an electrocardiogram, or ECG.

What Is an ECG and What Information Does It Provide?

An ECG is a noninvasive measure of the sum of all electrical activity of the heart. It is not showing us an action potential, but the total electrical change generated by all the action

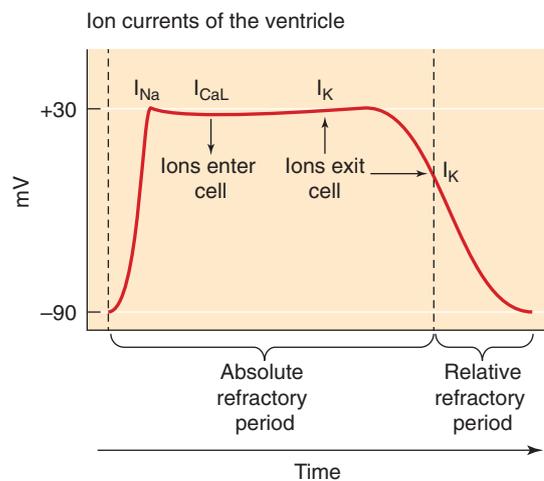
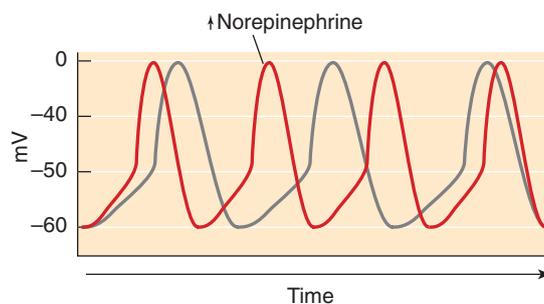
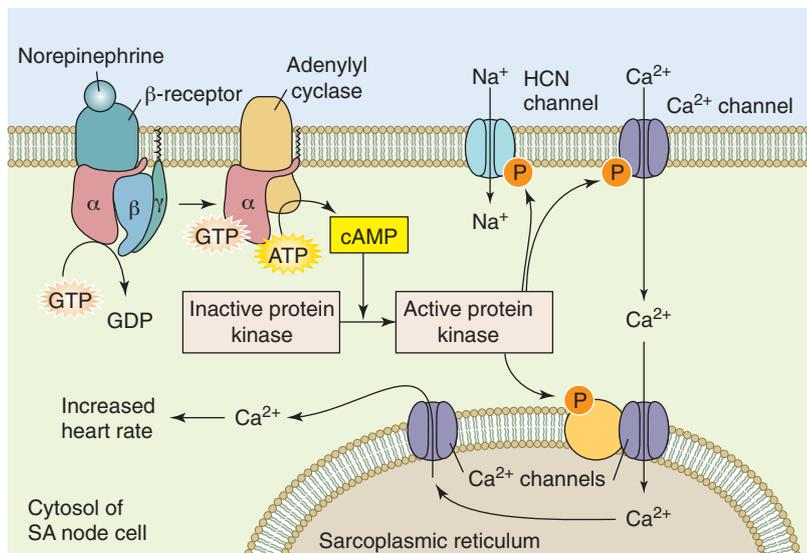


FIGURE 7.12 The action potential of the ventricle uses a different set of ion currents for depolarization. The refractory periods of the ventricular action potential can be important during dysrhythmias.

Sympathetic stimulation



Parasympathetic stimulation

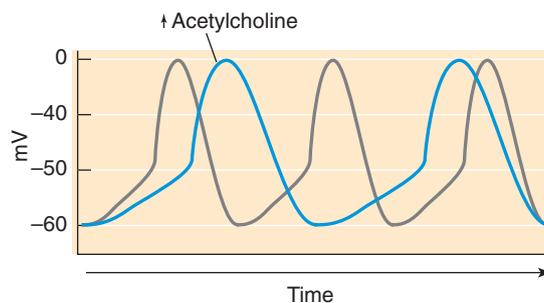
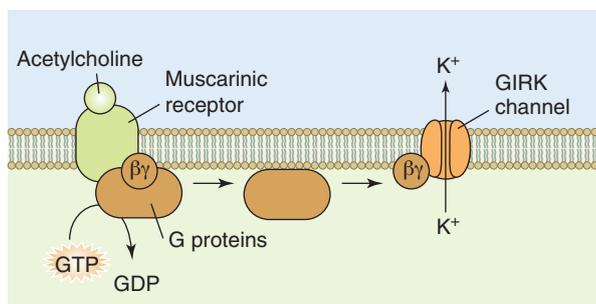


FIGURE 7.13 Sympathetic and parasympathetic nerve fibers modulate heart rate at the SA node, using adrenergic or muscarinic receptors to modify ion channel activity.

potentials that travel through the heart during a depolarization, from the SA node to the atria to the A-V node to bundle branch fibers to the ventricle and then the reverse trip of repolarization. An ECG tells us nothing about contractility or performance but can nonetheless provide an amazing amount of information. Let us first examine the tracing of lead II in a three-lead ECG, as seen in **FIGURE 7.14**.

As the pacemaker cells begin to depolarize, the ECG tracing starts up the P wave, which is completed as the electrical depolarization travels across the atria. The interval between the P and R waves is a straight line, as the impulse is slowed at the A-V node. The Q wave is the movement of the action potential through the bundle branch fibers, and the large R wave is the depolarization of the ventricle. The ST segment is relatively flat, because the entire ventricle is depolarized at this point. Finally, during the T wave, the ventricle repolarizes (Figure 7.14a). There is a resting membrane potential, before the entire complex begins again.

Each of the ECG leads provides an electrical “snapshot” of one area of the heart. Three-lead ECGs are now used only in teaching laboratories, however; clinical ECGs use 12 to 32 leads, giving the physician electrical views of the heart from every angle. If the heart has ischemic tissue or necrotic zones, these will show as electrical aberrations. But the most powerful use of ECG is in tracking cardiac rhythm and rhythm disturbances.

Consider an ECG recorded on you before and during your run. Prior to the run, your R-R interval, the duration between depolarizations of the ventricle, may have been one second apart. That would mean your heart rate was approximately 60 beats/minute. If you were to measure every R-R interval during a five-minute rest period, you would quickly notice that the R-R intervals are not always the same duration. They will actually alternate between runs of long intervals and runs of slow intervals. If you recall that heart rate is under control of both the sympathetic and parasympathetic nervous systems, you will realize that neither system is always dominant, but they trade off being “in charge,” causing this oscillation of R-R interval duration. As you begin your run, the R-R intervals would get closer together as your heart rate increased, because sympathetic stimulation becomes more consistently dominant. Thus, R-R interval can be used as a measure of instantaneous heart rate and an indicator of autonomic function.

Obviously, an ECG is invaluable for diagnosing cardiac dysrhythmias. For example, if there is A-V block, preventing the depolarization from continuing to the bundle branch fibers, a P wave may occur singly, without being followed by a QRS complex. This may happen all the time in complete block (Figure 7.14c), or only sometimes, as is first-degree block (Figure 7.14b). Ventricular dysrhythmias can also be diagnosed and are the most serious cardiac dysrhythmias since they will compromise cardiac contraction and cardiac output.

An ECG is a measure of electrical activity, but in most cases, once the cardiac tissue is depolarized, the cardiac muscle will contract. What happens during cardiac contraction, and how does it differ from skeletal muscle contraction?

Cardiac Excitation-Contraction Coupling

How does the depolarization of cardiac myocytes cause cardiac contraction? Excitation-contraction (E-C) coupling in cardiac muscle is similar to E-C coupling in skeletal muscle, but it has some unique features. Let's follow the process in detail. The ventricular action potential begins with a voltage-gated Na^+ current, which provides the depolarization. Remember that voltage-gated Na^+ channels inactivate over time, so this current ceases after several milliseconds. Voltage-gated Ca^{2+} channels open during the sodium depolarization, and, just as in skeletal muscle, the Ca^{2+} channels are located within the T-tubules, which lie very close to the sarcoplasmic reticulum (SR). In skeletal muscle, a change in SR membrane voltage caused the opening of calcium-release channels in the SR. In cardiac muscle, it is Ca^{2+} ions flowing through L-type Ca^{2+} channels of the T-tubule that trigger SR calcium release channels to open. This triggers calcium, from the extracellular fluid, is absolutely required for cardiac E-C coupling. After intracellular $[\text{Ca}^{2+}]$ rise, the binding of Ca^{2+} to troponin C, movement of tropomyosin, revealing the actin binding site, and binding of myosin heads to cause the sliding filament mode of contraction continue as in skeletal muscle. Relaxation occurs as Ca^{2+} is resequenced in the SR by the SERCA pump, an ATPase (FIGURE 7.15). Just as in skeletal muscle, myosin requires ATP for unbinding from actin, and ATP is also required for pumping Ca^{2+} up a concentration gradient, back into the SR.

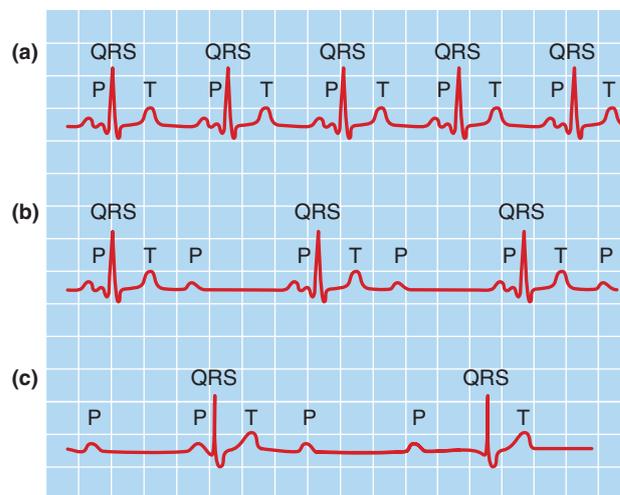
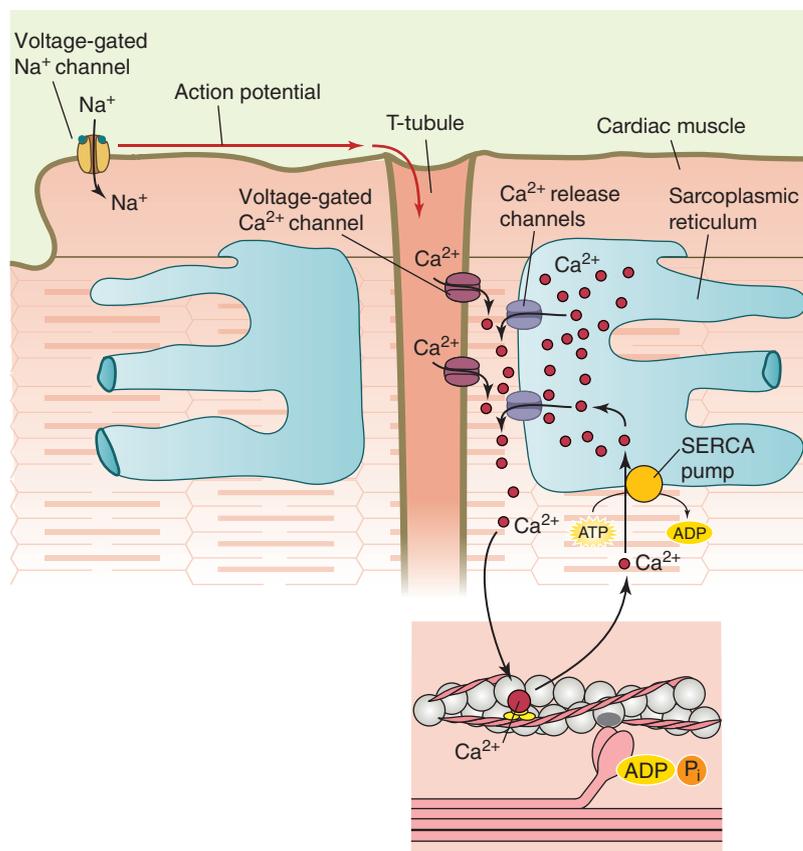


FIGURE 7.14 (a) An ECG measure the electrical activity of the heart. (b) During partial A-V block only some P waves are followed by QRS waves. (c) During complete block, P waves and QRS waves occur independently.

FIGURE 7.15 E-C coupling in cardiac muscle is dependent upon extracellular Ca^{2+} to begin release of Ca^{2+} from the sarcoplasmic reticulum.



What Makes My Heart Pound When I Run?

During your run, your heart not only depolarizes more quickly but also there is an increase in contractility, the force of contraction, which you experience as your heart pounding. The same sympathetic nerve fibers that innervate the pacemaker cells also branch off to the ventricle. Norepinephrine released from the nerve terminals will bind to β_1 receptors, phosphorylate I_{Ca} channels, and increase the amount of extracellular calcium that enters the cardiac myocytes. More trigger Ca^{2+} will increase the local Ca^{2+} concentration at the calcium release channels and stimulate their opening. The calcium release channel is part of a larger protein complex known as the ryanodine receptor. The release channel is made up of four protein tetramers that open in proportion to the amount of calcium they sense. Therefore, increased trigger Ca^{2+} is directly responsible for enhanced release of Ca^{2+} from the SR.

Sympathetic stimulation of the ventricular cells through β_1 receptors also increases the rate of the SERCA pump, by phosphorylating an associated regulatory protein, phospholamban (FIGURE 7.16). Normally, phospholamban partially inhibits the SERCA pump, but when it is phosphorylated, this inhibition is relieved. SERCA moves Ca^{2+} from the cytosol back into the SR at an accelerated rate, Ca^{2+} is removed from troponin, and cardiac myocyte relaxation can occur more quickly, a lusitropic, effect. In addition, the increased sequestering of Ca^{2+} into the SR loads it, so that more Ca^{2+} is available for release following the next release of trigger Ca^{2+} . Increased intracellular Ca^{2+} will allow greater force of contraction. At the whole organ level, phosphorylation via β_1 receptors and protein kinase A will allow the ventricle to relax and fill completely, so that when depolarization begins, the force of contraction, that is, contractility, will be greater. More blood will be forced out of the heart at each beat, and stroke volume will increase.

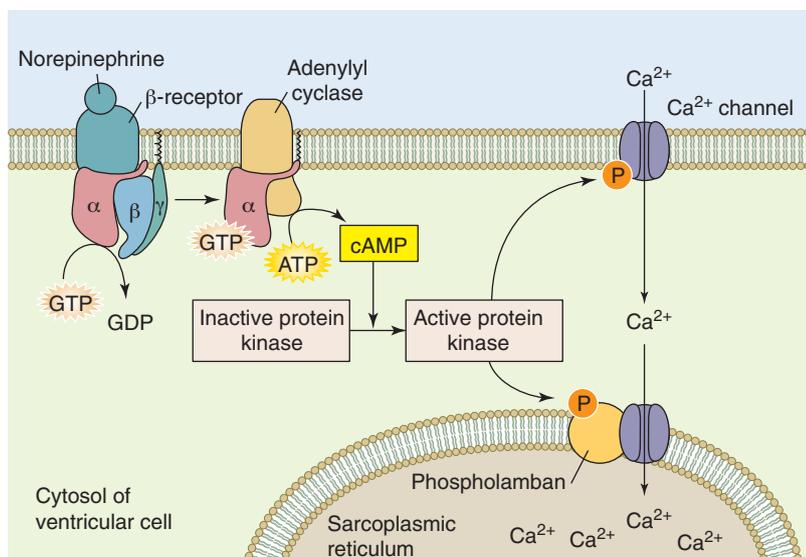


FIGURE 7.16 β-adrenergic stimulation increases contractility and stimulates the SERCA pump.

Cardiac Cycle: The Mechanics of Moving Blood Through the Heart

The heart is a living pump doing work against an incompressible fluid, blood. Forces act upon the heart, and it in turn generates forces. Let's look at the cardiac cycle in detail (**FIGURE 7.17**).

Blood returns to the heart from the superior and inferior vena cavae, emptying into the right atrium. This is a continuous process during diastole. As the right atrium fills, the pressure in the right atrium increases until it exceeds that of the right ventricle, causing the right A-V valve, the tricuspid valve, to open passively, allowing the right ventricle to fill. Simultaneously, oxygenated blood is returning to the left atrium from the lung through the pulmonary vein. As left atrial pressure increases, the left A-V valve, the mitral valve, opens, allowing the left ventricle to fill passively. All this occurs during diastole. Once the SA node depolarizes and begins an action potential, the depolarization of the atria causes atrial muscle contraction, which forces blood from the two atria into their respective ventricles. This increases the volume of blood in the two ventricles. As the depolarization travels down the bundle branch fibers, Purkinje fibers, and ventricular wall, muscle contraction of the ventricles begins. There is a period during which the ventricles contract but have not generated enough force to open the pulmonary semilunar valve, which lies between the right ventricle and the pulmonary trunk, or the aortic semilunar valve, which lies between the left ventricle and the aorta. This phase is called isovolumetric contraction, because the heart is contracting but the volume contained within the heart is not changing. The A-V valves also remain closed during isovolumetric contraction, preventing blood from returning to the atria. This occurs even though the pressure in the ventricles exceeds that of the atria.

How does this happen? The A-V valves are tethered to the ventricular wall by chordae tendineae, which connect to papillary muscles embedded in the ventricular wall. The papillary muscles contract when the ventricle depolarizes, pulling the flaps of the A-V valves closed. Thus, blood is prevented from regurgitating into the atria during ventricular contraction.

When the ventricular muscle contracts strongly enough to generate more pressure on the blood within the ventricle than exists within the arterial tree, the semilunar valves open

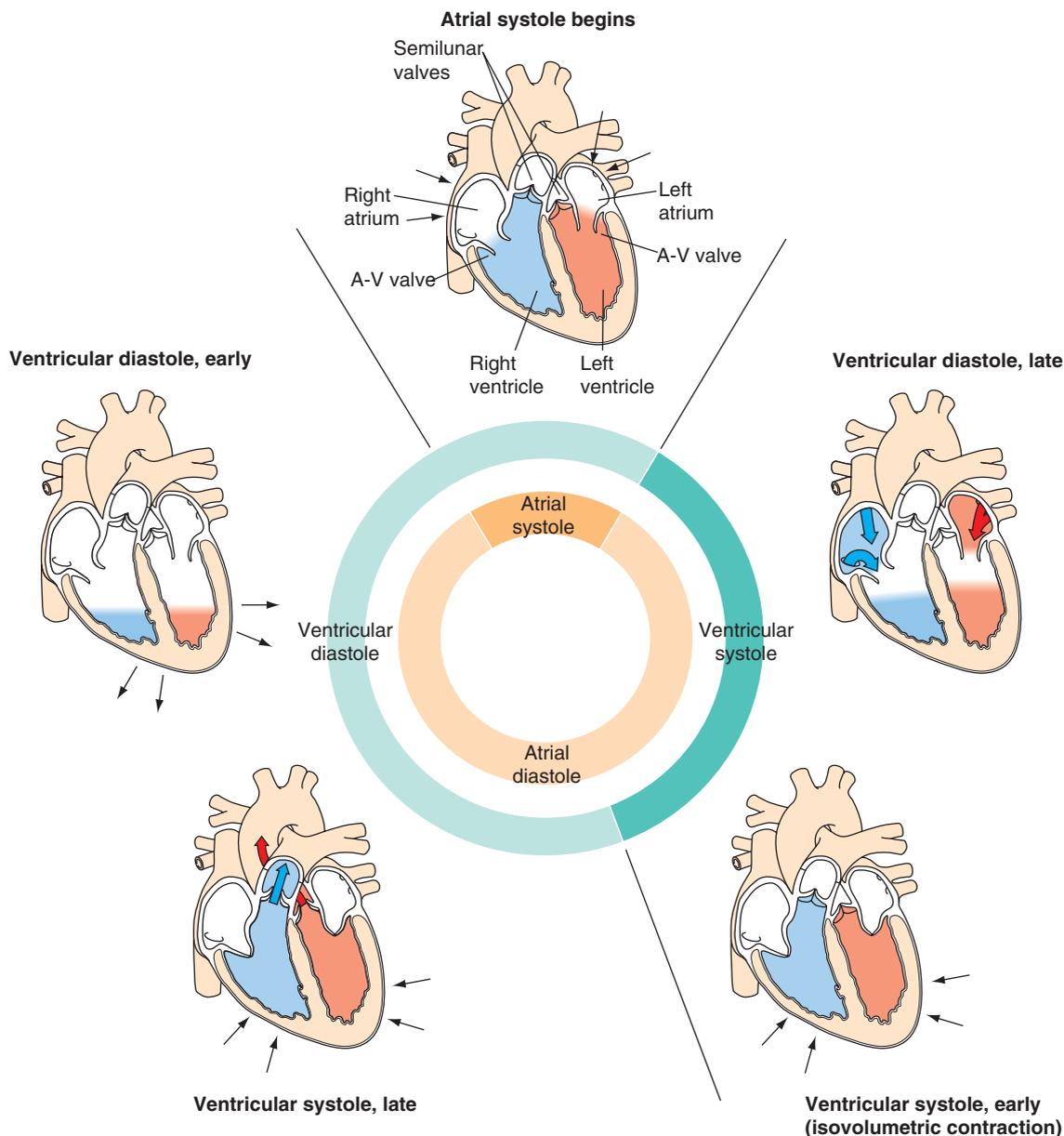


FIGURE 7.17 The cardiac cycle.

and blood is ejected from the ventricles. This is the stroke volume, or ejection volume. It also marks cardiac systole. When repolarization begins and the heart muscle relaxes, diastole and cardiac filling begin again.

What Is Cardiac Output and How Is It Regulated?

Cardiac output is defined as the volume of blood ejected from the heart per minute, but it is most easily summarized by this simple equation: $CO = HR \times SV$ —that is, cardiac output = heart rate \times stroke volume. Therefore, anything that changes heart rate or stroke volume will change cardiac output. It is actually easiest to think about the components

of heart rate and stroke volume separately, especially because in disease, each can be affected uniquely.

Heart Rate

We know that autonomic stimulation is an important controller of heart rate. On your run, sympathetic stimulation will increase your heart rate via β_1 receptors, and when you finish your workout, parasympathetic stimulation will slow heart rate via muscarinic receptors. ANS control is the primary controller of heart rate. However, there is another mechanism called the Bainbridge reflex. An increase in atrial pressure, caused by increased return of blood to the heart, causes stretch in receptors located at the junctions of the atria and the returning vessels, the superior and inferior vena cavae and the pulmonary veins. Stretch of these receptors stimulates a selective sympathetic reaction and increase in heart rate without an increase in stroke volume. So, an increase in blood returning to the heart, even momentarily, will reflexively increase heart rate.

Stroke Volume

Stroke volume is dependent upon many factors and adds complexity to the regulation of cardiac output. The absolute volume of blood in the body is an important determiner of venous return, or the amount of blood that returns to the heart during diastole. And because the heart can only pump out as much as is returned, venous return is similarly a vital component of cardiac output. Finally, the amount of time the heart is in diastole will determine the cardiac filling time, that is, the amount of time available for venous return. The longer diastole continues, the greater the amount of blood that can return to the heart and the greater the venous return. These three factors together—blood volume, venous return, and filling time—will determine cardiac preload, or the amount of blood loaded into the heart prior to systole.

It is easy to imagine the consequences of changes in preload. If you were dehydrated during your morning run and had a lower blood volume, there would be less blood returning to the right atrium and less preload. As your heart rate increases during the run, filling time is reduced, and there is less venous return and, therefore, less preload (**FIGURE 7.18**). While this sounds disastrous for the efficiency of the cardiovascular system during exercise, there are several compensatory mechanisms.

Exercise causes sympathetic stimulation, which changes vascular tone. Alpha receptors on the arterioles and veins bind norepinephrine, which will cause vasoconstriction. Venoconstriction, especially, will increase the functional blood volume returning to the heart. Remember that the veins are capacitance vessels that expand when filled. Thus, during constriction, blood is forced toward the heart, increasing venous return. There is another vascular reserve that is recruited by the sympathetic stimulation—constriction of blood vessels serving the stomach and intestines. Vasoconstriction shunts this blood away from those organs and toward skeletal muscle, where blood vessels are dilated due to β_2 receptor stimulation by epinephrine. Sympathetic stimulation will also shorten systole due to the increased rate of the SERCA pump. Shortened systole lengthens diastole and filling time, again increasing venous return. All of these effects of sympathetic activation will increase preload and, therefore, increase cardiac output.

In the early 1900s, two physiologists named Otto Frank and Ernest Starling observed that the heart pumped out what was delivered to it, or that stroke volume was dependent upon venous return. This phenomenon was not understood but was well recognized and came to be known as the Frank-Starling law of the heart. The heart contracts against an incompressible fluid, blood, which acts as a rigid component for muscle to contract

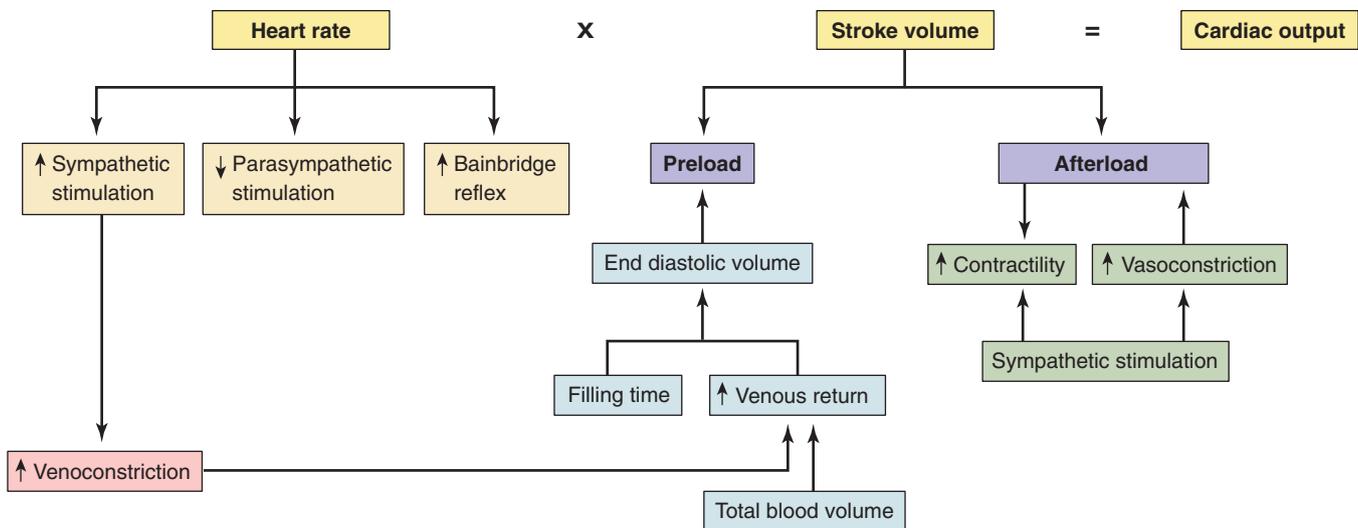


FIGURE 7.18 Factors that change heart rate or stroke volume will change cardiac output.

against. We know that the normal resting length of skeletal muscle is determined by its attachment to bone, and this normal resting length is the point at which actin and myosin are in the ideal anatomical positions for maximal binding. It is different in the heart. While you are sitting quietly, cardiac muscle is stretched minimally by the blood going through it and cross-bridge cycling is inefficient. When more blood fills the heart, as during exercise, the ventricles stretch and actin and myosin are put into improved register. More cross-bridge cycles can be formed, which improves contractility (FIGURE 7.19). This is the molecular basis of the Frank-Starling law of the heart, which links increased preload to increased contractility. Therefore, an increase in preload will cause greater contraction of the heart and more blood will be ejected at each beat, that is, a greater stroke volume.

Two final aspects of sympathetic stimulation increase stroke volume. First, phosphorylation of the L-type Ca^{2+} channels in myocytes will increase channel conductance and provide more calcium for cross-bridge cycling, thus improving contractility. Secondly, vasoconstriction of the arterioles will increase the afterload. Remember from the cardiac cycle that the ventricle must generate enough force to overcome the pressure in the vascular tree. When arterioles are constricted, this force increases, so the ventricle must generate

more muscle contraction and more force to expel blood. This increase in contractility, during healthy exercise, will increase stroke volume. When this occurs chronically, as in high blood pressure, it places an excessive burden on the heart. However, during exercise, the increase in afterload and contractility is normal and desirable.

All these adjustments to cardiac output are effective only if cardiac rhythm is maintained. If cardiac rhythm is disturbed, all of the regulatory mechanism just discussed will be compromised.

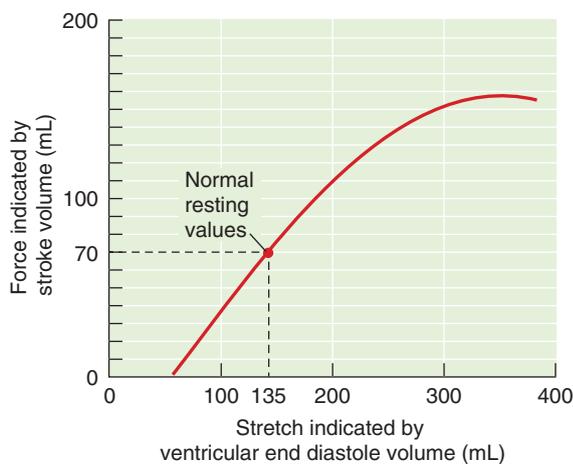


FIGURE 7.19 The Frank-Starling law of the heart reflects changes in myocardial stretch.

Metabolism, O_2 Consumption, and Cardiac Work

Cardiac myocytes are dependent upon O_2 for their metabolic needs. While other animal species maintain glycogen stores

within the heart, humans have a very limited supply, available only for minutes of cardiac work. Because the heart must continually be supplied with O_2 , there is a lavish coronary circulation within the heart; the myocytes themselves contain the O_2 storage molecule myoglobin, a single-chain protein resembling hemoglobin. Fatty acids, which are metabolized within the mitochondria in an oxygen-dependent process, are the predominant fuel of cardiac muscle. Thus, it is no surprise that mitochondria are also concentrated within cardiac tissue. If fatty acids are not available, the heart uses glucose or lactic acid as an energy source. Note that during exercise, when skeletal muscle is releasing lactic acid into the blood supply, this partially metabolized molecule can be used by the heart as long as O_2 is available. All this means that the heart is very capable of sufficient ATP production, as long as O_2 is present.

What could limit O_2 supply to the heart? Besides the obvious coronary occlusion, which would limit O_2 supply to some portions of the heart, there is another limitation to O_2 delivery. The coronary microcirculation is embedded in the myocardial wall, that is, among the cardiac myocytes themselves. This is necessary if these cells are to be supplied with O_2 . However, during systole, when the heart contracts, the muscles often produce enough force to close the capillaries, preventing blood flow and O_2 delivery. Therefore, the heart receives its nutrients primarily during diastole. The longer the period of diastole, the greater nutrient and O_2 availability there is for cardiac myocytes.

Cardiac work, like all physiological work, is measured in ATP usage. We know that cardiac output is $HR \times SV$ —but which requires less cardiac work, a faster heart rate and smaller stroke volume or a slower heart rate and a larger stroke volume? Experiments have shown that a slower heart rate and larger stroke volume require less O_2 consumption and, therefore, less cardiac work (**FIGURE 7.20**). It also allows more time for cardiac perfusion. The natural adaptation of training will increase stroke volume and lower heart rate, providing the greatest cardiac output for the least amount of cardiac work.

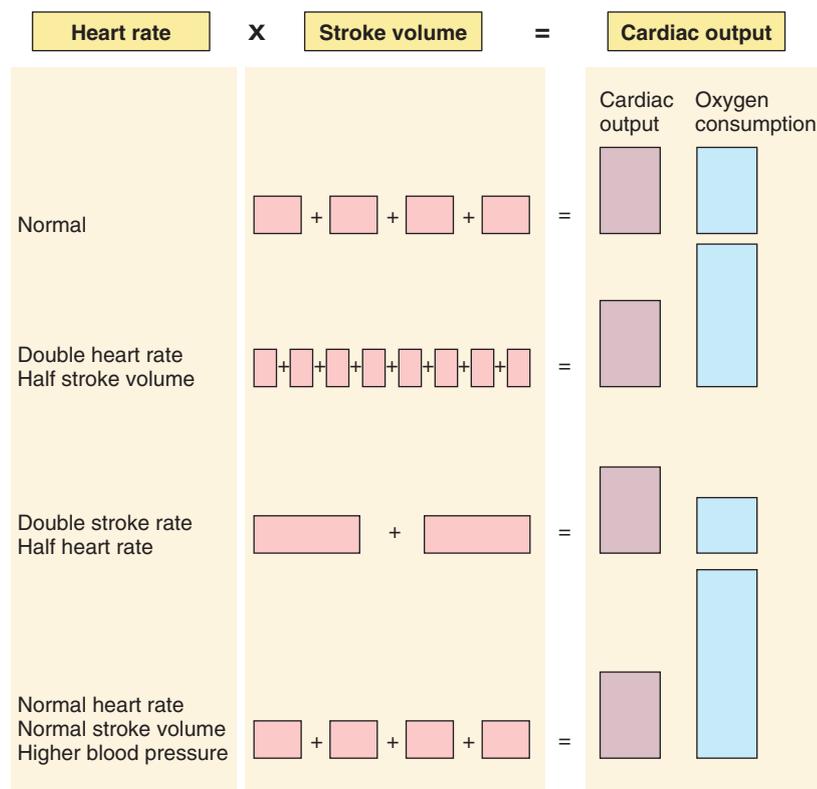


FIGURE 7.20 Cardiac output is a function of heart rate and stroke volume, an increased heart rate uses more ATP than increased stroke volume. Energetically, it is better to increase stroke volume.

Blood Vessels Carry Blood to Tissues— The End Users

If all vessels were completely dilated and fixed at that diameter, then all tissues would be maximally perfused, given a sufficient pressure head. That would mean that nonworking tissues would receive the same amount of blood flow as working tissue. This would be inefficient and wasteful of cardiac work. In fact, blood vessels continually alter their diameter, responding to tissue need and directing blood flow to working tissues.

Anatomically, a layer of smooth muscle surrounds arteries, arterioles, and, to a smaller extent, veins. Vascular smooth muscle responds to local factors that are released by the tissues themselves. For example, CO_2 , H^+ , K^+ , and adenosine (a by-product of ATP hydrolysis) can all cause vascular smooth muscle to relax and dilate, increasing the vascular diameter and increasing blood flow (FIGURE 7.21). If you think about the skeletal muscles in your legs during your run, muscle contraction is causing the production of each of these ions, gases, and molecules. Locally, the blood vessels will dilate and increase perfusion to these working muscles. This local control of blood vessel diameter is an important and efficient regulator of blood flow.

The sympathetic nervous system also regulates blood vessel diameter from its central location. Norepinephrine released from sympathetic nerve terminals will bind to α receptors on smooth muscle of vessels in the gut, causing vasoconstriction and reducing blood flow to the stomach and intestines. Blood flow to the kidneys will also be reduced because of vasoconstriction of the afferent arteriole. Constriction of veins will decrease their capacitance and increase venous return to the heart.

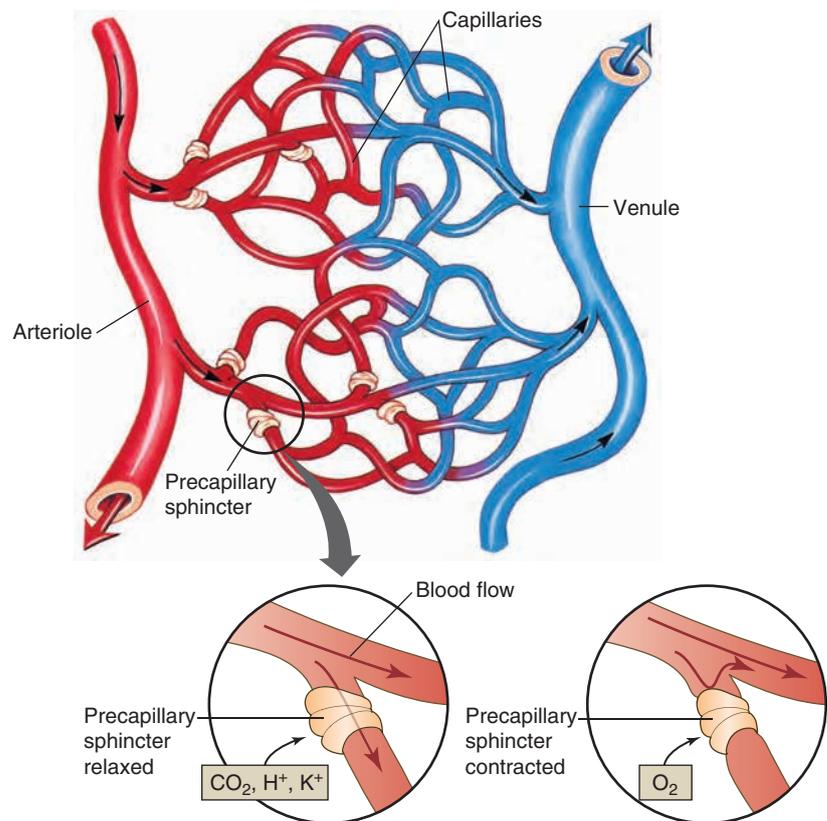


FIGURE 7.21 Metabolites produced by tissue regulate flow through local blood vessels.

Epinephrine released from the adrenal medulla will bind to β receptors on smooth muscle of blood vessels serving skeletal muscle, causing vasodilation and increased blood flow. Once again, the difference in receptor location determines the differential effects of sympathetic stimulation. Even if norepinephrine bound to a β receptor in the skeletal muscle, the effect would be vasodilation. It is the receptor not the ligand that causes the effect.

The physiological signal for nitric oxide production by vascular endothelial cells is shear stress. During exercise, the increased flow of blood through the vessels will increase shear stress and nitric oxide production. Nitric oxide will diffuse through the membranes of smooth muscle, inhibiting myosin binding and activating the SERCA pump, thus reducing $[Ca^{2+}]$. Smooth muscle contraction is inhibited and blood vessels dilate.

So, during your run, local control, that is, metabolites from working skeletal muscle, will increase vascular diameter, shear stress will dilate vessels in working muscle, and adrenergic receptors located on vascular smooth muscle will reorganize blood flow to favor maximal perfusion of skeletal muscle and increase venous return.

Blood Flow: Behavior of Fluids

There are two primary determinants of flow to the tissue: pressure head generated by the heart and resistance to flow, primarily determined by vessel radius.

A reduction of vascular diameter decreases flow to tissues downstream of these vessels because of increased resistance. Resistance to flow is proportional to vessel radius to the fourth power. Vessel diameter reduction will increase total peripheral resistance (TPR) and reduce flow. Each section of the arterial tree has parallel branching; arteries constitute one set of branches, arterioles another, and capillaries yet another. The site of greatest control of resistance is the arterioles. This occurs because arterioles do not branch as much as other portions of the arterial tree, resulting in fewer parallel arterioles, a smaller relative cross-sectional area, and, therefore, increased resistance. Also, smooth muscle in the arterioles allows for greater constriction, increasing resistance to flow and causing less blood flow.

However, TPR will increase contractility of the heart (remember, it must overcome afterload to eject blood). This will increase the pressure head and flow to areas where there is not vasoconstriction. Flow is proportional to $P_1 - P_2$, or pressure at the pressure head minus pressure at the right atrium. So, increased cardiac work will increase flow (**FIGURE 7.22**).

If Flow Is Essential to Tissues, Why Is Arterial Blood Pressure Important?

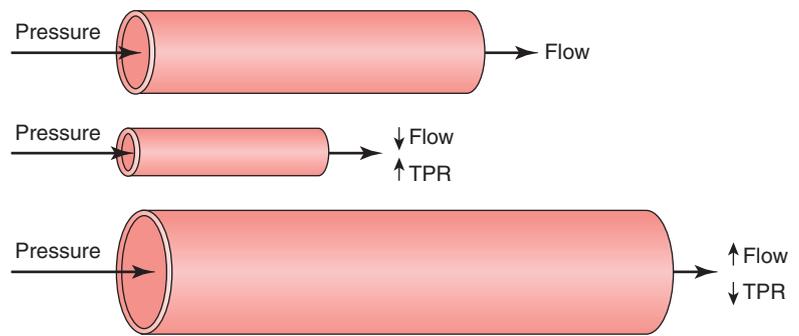
Resistance can regulate flow selectively, but flow is irretrievably compromised by a reduced pressure head. Maintaining arterial pressure allows for the greatest flexibility of control of flow, simply by altering resistance, that is, vascular diameter. Remember that increasing TPR will oblige the heart to contract more forcefully to overcome the resistance, thus increasing pressure head, so the heart and vasculature work together on this. The system is designed to maintain pressure head while selectively changing vascular diameter to move blood around to where it is needed.

What is the mean arterial pressure? Mean arterial blood pressure can be summarized by this simple equation:

$$\text{MAP} = \text{pressure during diastole } (P_2) + (\text{P during systole} - \text{P during diastole})/3$$

This quantifies the mean pressure in the arterial tree over time, compensating for the difference between systolic and diastolic pressure and the amount of time spent in each part of the cardiac cycle.

FIGURE 7.22 The pressure head generated by the heart, viscosity of the blood, and resistance of the blood vessels all contribute to flow within the cardiovascular system.



What Regulates Mean Arterial Blood Pressure?

The sympathetic nervous system can work for minutes to hours to days to regulate blood pressure, depending on stress or activity. During the course of your exercise, for example, the sympathetic nervous system increases heart rate and stroke volume, vasoconstriction of some vessels, and vasodilation of others. All this increases your exercising blood pressure slightly.

In addition to the sympathetic nervous system, we also have another short-term regulator of blood pressure—the arterial baroreceptors (**FIGURE 7.23**). These receptors are small stretch organs located in the carotid sinus and the aortic arch. They are sensitive to mechanical deformation, sending action potentials to the cardioacceleratory centers or the cardioinhibitory centers of the brain. They also connect to vasomotor centers in the brain.

What do the baroreceptors do? These receptors are functional during very short-term (seconds) changes in blood pressure, which we experience many times during the day as we make positional changes. For example, when you jumped out of bed this morning, your baroreceptors reacted. As your feet hit the floor and gravity pulled blood from your core to your feet, the baroreceptors sensed a loss of flow past the carotid sinus and the aortic arch. This caused a decrease in baroreceptor action potentials to the brain and a reflex increase in heart rate and increase in vasoconstriction. This transiently increased your blood pressure slightly but, by doing so, maintained your brain blood flow. Tonight, when you lie down again, the opposite will happen. As blood floods the core of your body, the baroreceptors will sense an increased pressure. Your heart rate will decline and your vessels will dilate, thus reducing pressure. These changes are slight, very rapid, and go unnoticed by healthy people. For those suffering malfunction of the baroreceptors, positional changes, like arising from bed, can cause lightheadedness and syncope.

Baroreceptors are important for regulating very short-term blood pressure changes. They adapt to continue to regulate changes, even in a severely hypertensive person. They have no effect on long-term blood pressure regulation.

Long-term control of blood pressure relies on changes in blood volume, using a variety of hormones you may recognize from studying the endocrine system. During your run, for example, you will lose water as sweat, as a result of your body's process of thermoregulation. Loss of water will increase your blood osmolarity, triggering the release of antidiuretic hormone (ADH) (vasopressin) from the posterior pituitary and reclamation of water at the kidney. This will preserve your blood volume and your blood pressure.

Even without a change in osmolarity, the loss of blood volume would be sensed at the kidney, releasing renin and beginning the conversion of angiotensinogen to angiotensin II.

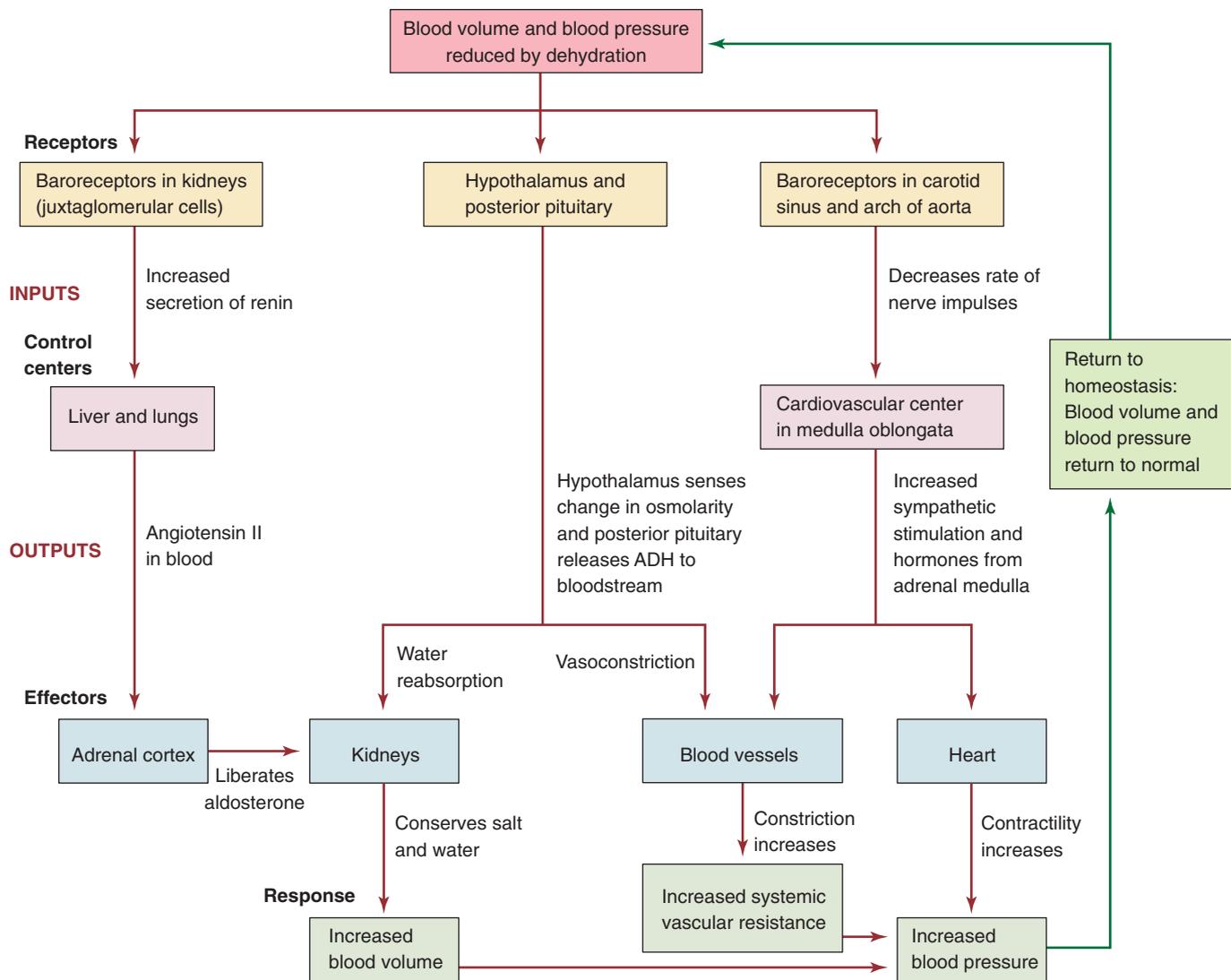


FIGURE 7.23 Short-term and long-term regulators of blood pressure.

Angiotensin II is a powerful vasoconstrictor, which will increase your blood pressure. It also stimulates the release of aldosterone and ADH, both of which work at the kidney to prevent water loss to urine and stimulate thirst centers at the brain. Once you rehydrate, levels of these hormones would go back to resting values.

Finally, if you drink too much water, ANP will increase diuresis at the kidney, bringing your total blood volume back to normal. Regulation of blood volume takes longer than sympathetic stimulation or the baroreceptor. It is minutes to hours to days in the final regulation, but it is perhaps the most important determinant of blood pressure regulation.

Summary

The sensation of a beating heart is familiar to us all. While this seems simple, the cardiovascular system, consisting of the heart, blood vessels, and blood, is not a simple system. Each

of the components interacts with one another, and the cardiovascular system is intimately tied to fluid volume control and the autonomic nervous system. All this leads to the complexity that is cardiovascular physiology.

Key Concepts

Path of blood through the heart
 Cardiac E-C coupling
 Anatomy of the vasculature
 Fluid exchange at the capillary
 Function of hemoglobin
 SA nodal action potential
 Ventricular action potential
 Autonomic regulation of heart rate and contractility
 Electrical conduction in the heart
 Phases of the cardiac cycle
 Regulation of cardiac output
 Flow of fluids
 Regulation of mean arterial pressure

Key Terms

Aorta
 Vena cava
 Hemoglobin
 Erythropoietin
 Sinoatrial node
 ECG
 Phospholamban
 Frank-Starling law
 Total peripheral resistance
 Mean arterial pressure
 Baroreceptors

Application: Pharmacology

1. Your grandfather has been prescribed an angiotensin-converting enzyme inhibitor (ACE inhibitor) for his high blood pressure. How would this drug work, and why would it be effective?
2. Your grandfather has also been prescribed a β -adrenergic antagonist, a blocker of β -receptors, to lower his heart rate and contractility. How will this affect his blood pressure? Why?
3. How might the β -blocker affect cardiac E-C coupling?

Cardiovascular Clinical Case

Type 2 Diabetes Mellitus

■ BACKGROUND

Type 2 diabetes mellitus (T2DM) not only causes metabolic dysregulation but also is a source of cardiovascular disease. Insulin resistance, hypertension, and coronary artery disease (CAD) have long been associated with diabetes, but it is now thought that insulin resistance may be a major contributor to both hypertension and CAD in patients with T2DM. The physiological mechanisms are different, so we will consider them separately.

Insulin Resistance

Under normal conditions, insulin functions as a vasodilator, increasing vascular diameter and reducing blood pressure. Several smooth muscle cellular ion pumps, including $\text{Na}^+\text{-K}^+$ ATPase and the muscular Ca^{2+} ATPase (SERCA), are insulin sensitive, presumably due to ATP availability resulting from glycolysis. Normal glucose transport into a cell allows cytoplasmic glycolysis and ATP production for use by these pumps. Thus, under normal conditions, intracellular $[\text{Na}^+]$ remains low as does intracellular $[\text{Ca}^{2+}]$.

Insulin resistance disturbs normal glucose uptake, inhibiting the $\text{Na}^+\text{-K}^+$ ATPase. Increased cellular Na^+ activates the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, which moves Na^+ out of the cell and brings Ca^{2+} into it. Raising intracellular Ca^{2+} increases the response of vascular smooth muscle to the vasoconstrictive actions of norepinephrine and angiotensin II, which also increase intracellular Ca^{2+} . At the same time, inhibition of the SERCA pump further increases Ca^{2+} concentrations in smooth muscle, facilitating contraction. Hypertension caused by constriction of arteries results from these ion concentration alterations. Because insulin is also a growth hormone, hyperinsulinemia causes proliferation of smooth muscle cells, so there is a greater mass of smooth muscle with which to constrict arteries. The increase in total peripheral resistance (TPR) is reflected as hypertension.

As TPR increases, afterload increases, requiring more cardiac work to pump blood through the systemic vasculature. A chronically increased workload causes the heart to adapt by increasing its muscle mass, also known as hypertrophy.

Hyperlipidemia

Hyperlipidemia can cause vascular problems. Remember that within the liver, where very-low-density lipoproteins (VLDLs) are made, a high triglyceride content causes the formation of VLDL particles with unusually high triglyceride concentrations. These excess triglycerides are transferred to low-density lipoprotein (LDL) in circulation, and triglyceride-rich LDL particles are formed. This species of LDL is the preferred substrate for hepatic lipase, which removes the triglyceride and converts LDL into a much smaller particle. This smaller particle is much more atherogenic, able to enter the endothelial cell wall and begin plaque formation within arteries. LDLs embedded in the vascular wall are engulfed by macrophages. In addition to the inflammatory pathways that are triggered, the macrophages, filled with lipids, transform into foam cells, which remain resident within

the vascular wall. Thus begins the deposition of arterial plaques. Small particle LDLs that remain after triglyceride removal by the liver have been shown to be the most atherogenic particles of all. Through this mechanism, T2DM becomes a serious risk factor for atherosclerosis in general and for CAD in particular.

■ THE CASE

Your aunt, a type 2 diabetic, has been given medication to lower her triglycerides and to lower her blood pressure, which is 150/90. These medications are in addition to the metformin she takes and the diet to which she is supposed to adhere. It has been a year since her diagnosis, and she hasn't lost weight or been at all successful in keeping her glucose or triglyceride levels under control. She is convinced that the high blood pressure readings are in error and is refusing to take the medication. You are worried that this condition is eroding her health. You decide to talk to her about how T2DM may be responsible for her elevated blood pressure, so she believes there is a problem and will agree to take her medication.

■ THE QUESTIONS

1. What are the intracellular events that link insulin to hypertension?
2. How would vascular plaques affect blood flow through the vessels? Would plaques increase or decrease vascular resistance? Why?
3. How will you explain the change in blood pressure and the risks that increased blood pressure and triglycerides present? Your aunt is not a scientist, so you must put this into lay terms without diluting the meaning or the seriousness of the discussion.