

The Microcirculation and the Lymphatic System

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CHAPTER OUTLINE

- THE ARTERIAL MICROVASCULATURE
 - THE CAPILLARIES
 - THE VENOUS MICROVASCULATURE
 - THE LYMPHATIC VASCULATURE
 - VASCULAR AND TISSUE EXCHANGE OF SOLUTES
- TRANSCAPILLARY FLUID EXCHANGE
 - THE REGULATION OF MICROVASCULAR PRESSURES
 - THE REGULATION OF MICROVASCULAR RESISTANCE

KEY CONCEPTS

1. Arterioles regulate vascular resistance and microvascular pressures.
2. Capillaries are the primary sites for water and solute exchange.
3. Venules collect blood from the capillaries and act as reservoirs for blood volume.
4. Lymphatic vessels collect excess water and protein molecules from the interstitial space between cells.
5. Water-soluble materials pass through tiny pores between adjacent endothelial cells.
6. Lipid-soluble molecules pass through the endothelial cells.
7. The concentration difference of solutes across the capillary wall is the energy source for capillary exchange.
8. Plasma hydrostatic and colloid osmotic pressures are the primary forces for fluid filtration and absorption across capillary walls.
9. Tissue hydrostatic and colloid osmotic pressures are minor forces for absorption and filtration of fluid across capillary walls.
10. The ratio of postcapillary to precapillary resistance is a major determinant of capillary hydrostatic pressure.
11. Myogenic arteriolar regulation is a response to increased tension or stretch of the vessel wall muscle cells.
12. By-products of metabolism cause the dilation of arterioles.
13. The axons of the sympathetic nervous system release norepinephrine, which constricts the arterioles and venules.
14. Autoregulation of blood flow allows some organs to maintain nearly constant blood flow when arterial blood pressure is changed.

The microcirculation is the part of the circulation where nutrients, water, gases, hormones, and waste products are exchanged between the blood and cells. The microcirculation minimizes diffusion distances, facilitating exchange, its most important function. Virtually every cell in the body is in close contact with a microvessel. In fact, most cells are in direct contact with at least one microvessel. As a consequence, there are tens of thousands of microvessels per gram of tissue. The lens and cornea are exceptions because their nutrients are supplied by the fluids in the eye.

A second major function of the microcirculation is to regulate vascular resistance and thereby interact with cardiac output to maintain the arterial blood pressure (see Chapter 12). Normally, all microvessels, other than capil-

laries, are partially constricted by contraction of their vascular smooth muscle cells. If all microvessels were to dilate fully because of relaxation of their smooth muscle cells, the arterial blood pressure would plummet. Cerebral blood flow in a standing individual would be inadequate, resulting in fainting, or **syncope**. Regulation of vascular resistance in the microcirculation is an important aspect of total health.

There is a constant conflict between the regulation of vascular resistance to preserve the arterial pressure and simultaneously to allow each tissue to receive sufficient blood flow to sustain its metabolism. The compromise is to preserve the mean arterial pressure by increasing arterial resistance at the expense of reduced blood flow to most organs other than the heart and brain. The organs survive this conflict by increas-

ing their extraction of oxygen and nutrients from blood in the microvessels as the blood flow is decreased.

The microvasculature is considered to begin where the smallest arteries enter the organs and to end where the smallest veins, the **venules**, exit the organs. In between are microscopic arteries, the **arterioles**, and the capillaries. Depending on an animal's size, the largest arterioles have an inner diameter of 100 to 400 μm , and the largest venules have a diameter of 200 to 800 μm . The arterioles divide into progressively smaller vessels to the extent that each section of the tissue has its own specific microvessels. The branching pattern typical of the microvasculature of different major organs and how it relates to organ function are discussed in Chapter 17.

THE ARTERIAL MICROVASCULATURE

Large arteries have a low resistance to blood flow and function primarily as conduits (see Chapter 15). As arteries approach the organ they supply, they divide into many small arteries both just outside and within the organ. In most organs, these small arteries, which are 500 to 1,000 μm in diameter, control about 30 to 40% of the total vascular resistance. These smallest of arteries, combined with the arterioles of the microcirculation, constitute the **resistance blood vessels**; together they regulate about 70 to 80% of the total vascular resistance, with the remainder of the resistance about equally divided between the capillary beds and venules. Constriction of these vessels maintains the relatively high vascular resistance in organs. Constriction results from the release of norepinephrine by the sympathetic nervous system, from the myogenic mechanism (to be discussed later), and from other chemical and physical factors.

Arterioles Regulate Resistance by the Contraction of Vascular Smooth Muscle

The vast majority of arterioles, whether large or small, are tubes of **endothelial cells** surrounded by a connective tissue **basement membrane**, a single or double layer of vascular smooth muscle cells, and a thin outer layer of connective tissue cells, nerve axons, and mast cells (Fig. 16.1). The vascular smooth muscle cells around the arterioles are 70 to 90 μm long when fully relaxed. The muscle cells are anchored to the basement membrane and to each other in a way that any change in their length changes the diameter of the vessel. Vascular smooth muscle cells wrap around the arterioles at approximately a 90° angle to the long axis of the vessel. This arrangement is efficient because the tension developed by the vascular smooth muscle cell can be almost totally directed to maintaining or changing vessel diameter against the blood pressure within the vessel.

In the majority of organs, arteriolar muscle cells operate at about half their maximal length. If the muscle cells fully relax, the diameter of the vessel can nearly double to increase blood flow dramatically (flow increases as the fourth power of the vessel radius; see Chapter 12). When the muscle cells contract, the arterioles constrict, and with intense stimulation, the arterioles can literally shut for brief periods of time. A single muscle cell will not completely encircle a

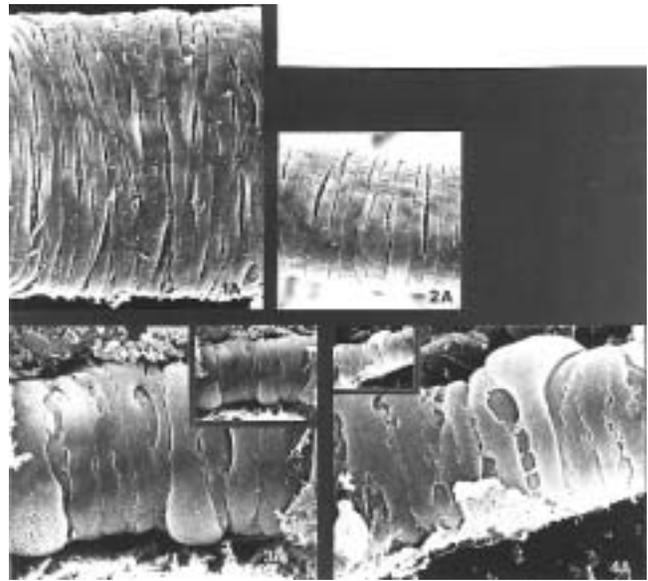


FIGURE 16.1 Scanning electron micrographs of smooth muscle cells wrapping around arterioles of various sizes. Each cell only partially passes around large-diameter (1A) and intermediate-diameter (2A) arterioles, but completely encircles the smaller arterioles (3A, 4A). 1A, 2A, and the small insets of 3A and 4A are at the same magnification. The enlarged views of 3A and 4A are at 4-times-greater magnification. (Modified from Miller BR, Overhage JM, Bohlen HC, Evan AP. Hypertrophy of arteriolar smooth muscle cells in the rat small intestine during maturation. *Microvasc Res* 1985;29:56–69.)

larger vessel, but may encircle a smaller vessel almost 2 times (see Fig. 16.1).

Vessel Wall Tension and Intravascular Pressure Interact to Determine Vessel Diameter

The smallest arteries and all arterioles are primarily responsible for regulating vascular resistance and blood flow. Vessel radius is determined by the transmural pressure gradient and wall tension, as expressed by Laplace's law (see Chapter 14). Changes in wall tension developed by arteriolar smooth muscle cells directly alter vessel radius. Most arterioles can dilate 60 to 100% from their resting diameter and can maintain a 40 to 50% constriction for long periods. Therefore, large decreases and increases in vascular resistance and blood flow are well within the capability of the microscopic blood vessels. For example, a 20-fold increase in blood flow can occur in contracting skeletal muscle during exercise, and blood flow in the same vasculature can be reduced to 20 to 30% of normal during reflex increases in sympathetic nerve activity.

THE CAPILLARIES

Exchanges Between Blood and Tissue Occur in Capillaries

Capillaries provide for most of the exchange between blood and tissue cells. The capillaries are supplied by the

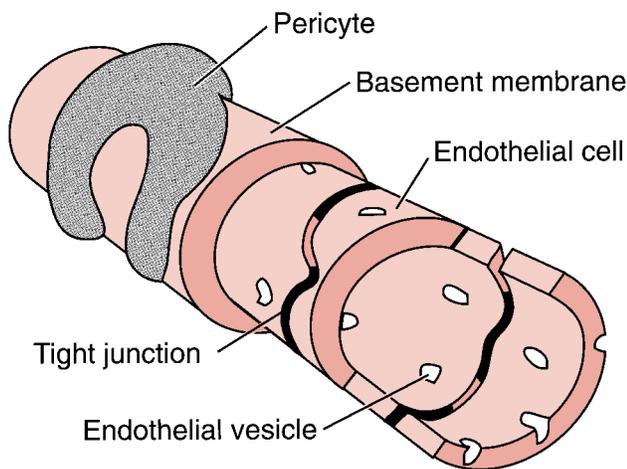


FIGURE 16.2 The various layers of a mammalian capillary. Adjacent endothelial cells are held together by tight junctions, which have occasional gaps. Water-soluble molecules pass through pores formed where tight junctions are imperfect. Vesicle formation and the diffusion of lipid-soluble molecules through endothelial cells provide other pathways for exchange.

smallest of arterioles, the **terminal arterioles**, and their outflow is collected by the smallest venules, **postcapillary venules**. A capillary is an endothelial tube surrounded by a basement membrane composed of dense connective tissue (Fig. 16.2). Capillaries in mammals do not have vascular smooth muscle cells and are unable to appreciably change their inner diameter. **Pericytes** (Rouget cells), wrapped around the outside of the basement membrane, may be a primitive form of vascular smooth muscle cell and may add structural integrity to the capillary.

Capillaries, with inner diameters of about 4 to 8 μm , are the smallest vessels of the vascular system. Although they are small in diameter and individually have a high vascular resistance, the parallel arrangement of many thousands of capillaries per mm^3 of tissue minimizes their collective resistance. For example, in skeletal muscle, the small intestine, and the brain, capillaries account for only about 15% of the total vascular resistance of each organ, even though a single capillary has a resistance higher than that of the entire organ's vasculature. The large number of capillaries arranged in hemodynamic parallel circuits allows their combined resistance to be quite low (see Chapter 15).

The capillary lumen is so small that red blood cells must fold into a shape resembling a parachute as they pass through and virtually fill the entire lumen. The small diameter of the capillary and the thin endothelial wall minimize the diffusion path for molecules from the capillary core to the tissue just outside the vessel. In fact, the diffusion path is so short that most gases and inorganic ions can pass through the capillary wall in less than 2 msec.

The Passage of Molecules Through the Capillary Wall Occurs Both Between Capillary Endothelial Cells and Through Them

The exchange function of the capillary is intimately linked to the structure of its endothelial cells and basement mem-

brane. Lipid-soluble molecules, such as oxygen and carbon dioxide, readily pass through the lipid components of endothelial cell membranes. Water-soluble molecules, however, must diffuse through water-filled pathways formed in the capillary wall between adjacent endothelial cells. These pathways, known as **pores**, are not cylindrical holes but complex passageways formed by irregular tight junctions (see Fig. 16.2).

The capillaries of the brain and spinal cord have virtually continuous tight junctions between adjacent endothelial cells; consequently, only the smallest water-soluble molecules pass through their capillary walls. In all capillaries, there are sufficient open areas in adjacent tight junctions to provide pores filled with water for diffusion of small molecules. The pores are partially filled with a matrix of small fibers of submicron dimensions. The potential importance of this **fiber matrix** is that it acts partially to sieve the molecules approaching a water-filled pore. The combination of the fiber matrix and the small spaces in the basement membrane and between endothelial cells explains why the vessel wall behaves as if only about 1% of the total surface area were available for exchange of water-soluble molecules. The majority of pores permit only molecules with a radius less than 3 to 6 nm to pass through the vessel wall. These **small pores** only allow water and inorganic ions, glucose, amino acids, and similar small, water-soluble solutes to pass; they exclude large molecules, such as serum albumin and globular proteins.

A limited number of **large pores**, or possibly defects, allow virtually any large molecule in blood plasma to pass through the capillary wall. Even though few large pores exist, there are enough that nearly all the serum albumin molecules leak out of the cardiovascular system each day.

An alternative pathway for water-soluble molecules through the capillary wall is via **endothelial vesicles** (see Fig. 16.2). Membrane-bound vesicles form on either side of the capillary wall by pinocytosis, and exocytosis occurs when the vesicle reaches the opposite side of the endothelial cell. The vesicles appear to migrate randomly between the luminal and abluminal sides of the endothelial cell. Even the largest molecules may cross the capillary wall in this way. The importance of transport by vesicles to the overall process of transcapillary exchange remains unclear. Occasionally, continuous interconnecting vesicles have been found that bridge the endothelial cell. This open channel could be a random error or a purposeful structure, but in either case, it would function as a large pore to allow the diffusion of large molecules.

THE VENOUS MICROVASCULATURE

Venules Collect Blood From Capillaries

After the blood passes through the capillaries, it enters the venules, endothelial tubes usually surrounded by a monolayer of vascular smooth muscle cells. In general, the vascular muscle cells of venules are much smaller in diameter but longer than those of arterioles. The muscle size may reflect the fact that venules operate at intravascular pressures of 10 to 16 mm Hg, compared with 30 to 70 mm Hg in arterioles, and do not need a powerful muscular wall. The smallest

venules are unique because they are more permeable than capillaries to large and small molecules. This increased permeability seems to exist because tight junctions between adjacent venular endothelial cells have more frequent and larger discontinuities or pores. It is probable that much of the exchange of large water-soluble molecules occurs as the blood passes through small venules.

The Venular Microvasculature Acts as a Blood Reservoir

In addition to their blood collection and exchange functions, the venules are an important component of the blood reservoir system in the venous circulation. At rest, approximately two thirds of the total blood volume is within the venous system, and perhaps more than half of this volume is within venules. Although the blood moves within the venous reservoir, it moves slowly, much like water in a reservoir behind a river dam. If venule radius is increased or decreased, the volume of blood in tissue can change up to 20 mL/kg of tissue; therefore, the volume of blood readily available for circulation would increase by more than 1 L in a 70-kg (154-pound) person. Such a large change in available blood volume can substantially improve the venous return of blood to the heart following depletion of blood volume caused by hemorrhage or dehydration. For example, the volume of blood typically removed from blood donors is about 500 mL, or about 10% of the total blood volume; usually no ill effects are experienced, in part because the venules and veins decrease their reservoir volume to restore the circulating blood volume.

THE LYMPHATIC VASCULATURE

Lymphatic Vessels Collect Excess Tissue Water and Plasma Proteins

Lymphatic vessels are microvessels that form an interconnected system of simple endothelial tubes within tissues. They do not carry blood, but transport fluid, serum proteins, lipids, and even foreign substances from the interstitial spaces back to the circulation. The gastrointestinal tract, the liver, and the skin have the most extensive lymphatic systems, and the central nervous system may not contain any lymph vessels. The lymphatic system typically begins as blind-ended tubes, or **lymphatic bulbs**, which drain into the meshwork of interconnected lymphatic vessels (Fig. 16.3). Although lymph collection begins in the lymphatic bulbs, lymph collection from tissue also occurs in the interconnected lymphatic vessels by the same mechanical processes.

A schematic drawing of the lymphatic system in the small intestine (Fig. 16.4) illustrates the complexity of lymphatic branching. The villus lacteals are lymphatic bulbs in individual villi of the small intestine. Note that lymph collection from the submucosal and muscle layers of this tissue must occur primarily in tubular lymphatic vessels because few, if any, lymphatic bulbs are present in these layers.

The lymphatic vessels coalesce into increasingly more developed and larger collection vessels. These larger ves-

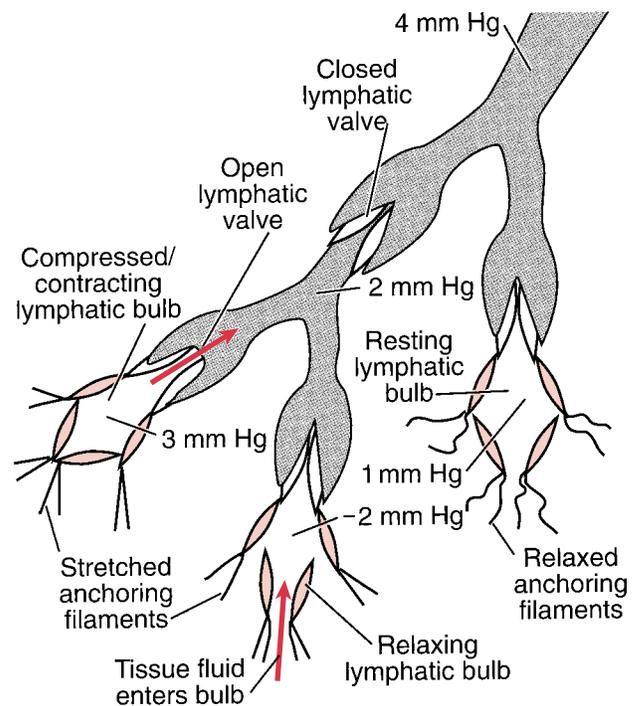


FIGURE 16.3 Lymphatic vessels: basic structure and functions. The contraction-relaxation cycle of lymphatic bulbs (bottom) is the fundamental process that removes excess water and plasma proteins from the interstitial spaces. Pressures along the lymphatics are generated by lymphatic vessel contractions and by organ movements.

sels in the tissue and the macroscopic lymphatic vessels outside the organs have contractile cells similar to vascular smooth muscle cells. In connective tissues of the mesentery and skin, even the simplest of lymphatic vessels and bulbs spontaneously contract, perhaps as a result of contractile endothelial cells. Even if the lymphatic bulb or vessel cannot contract, compression of these lymphatic structures by movements of the organ (e.g., intestinal movements or skeletal muscle contractions) changes lymphatic vessel size. Forcing lymph from the organs is important because a volume of fluid equal to the plasma volume is filtered from the blood to tissues every day. It is absolutely essential that this fluid be returned by lymph flow to the venous system.

Lymph Fluid Is Mechanically Collected Into Lymphatic Vessels From Tissue Fluid Between Cells

In all organ systems, more fluid is filtered than absorbed by the capillaries, and plasma proteins diffuse into the interstitial spaces through the large pore system. By removing the fluid, the lymphatic vessels also remove proteins. This function is essential because the protein concentration is higher in plasma than in tissue fluid and only some form of convective transport can return the protein to the plasma. The ability of lymphatic vessels to change diameter—whether initiated by the lymphatic vessel or by forces generated within a contractile organ—is important for lymph

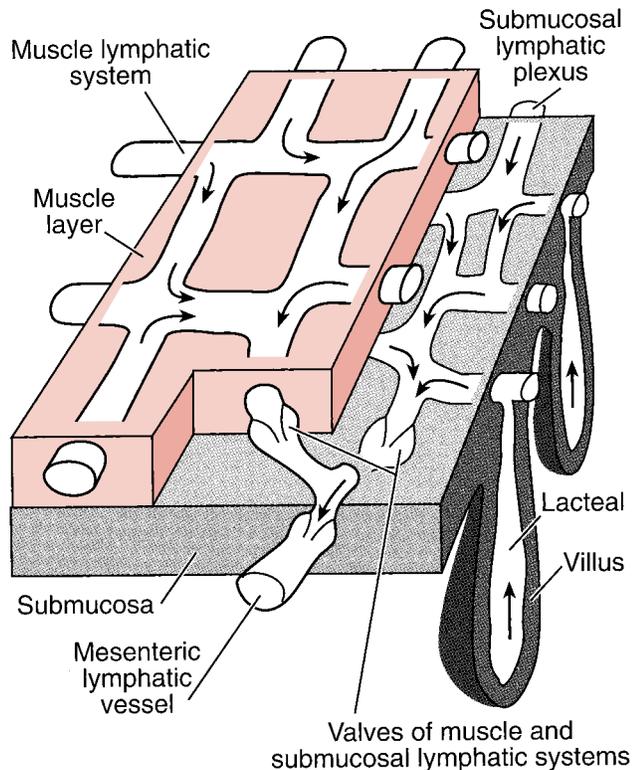


FIGURE 16.4 The arrangement of lymphatic vessels in the small intestine. The intestinal lymphatic vessels are unusual in that lymphatic valves are normally restricted to vessels about to exit the organ, whereas valves exist throughout the lymphatic system of the skin and skeletal muscles. (Modified from Unthank JL, Bohlen HG. Lymphatic pathways and role of valves in lymph propulsion from small intestine. *Am J Physiol* 1988;254:G389–G398.)

formation and protein removal. In the smallest lymphatic vessels and to some extent in the larger lymphatic vessels in a tissue, the endothelial cells are overlapped rather than fused together as in blood capillaries. The overlapped portions of the cells are attached to **anchoring filaments**, which extend into the tissue (Fig. 16.3). When stretched, anchoring filaments pull apart the free edges of the endothelial cells when the lymphatic vessels relax after a compression or contraction. The openings created in this process allow tissue fluid and molecules carried in the fluid to easily enter the lymphatic vessels.

The movement of fluid from tissue to the lymphatic vessel lumen is passive. When compressed or actively contracted lymphatic vessels are allowed to passively relax, the pressure in the lumen becomes slightly lower than in the interstitial space, and tissue fluid enters the lymphatic vessel. Once the interstitial fluid is in a lymphatic vessel, it is called **lymph**. When the lymphatic bulb or vessel again actively contracts or is compressed, the overlapped cells are mechanically sealed to hold the lymph. The pressure developed inside the lymphatic vessel forces the lymph into the next downstream segment of the lymphatic system. Because the anchoring filaments are stretched during this process, the overlapped cells can again be parted during relaxation of the lymphatic vessel.

The compression/relaxation cycle—whether controlled by lymphatic smooth muscle cells or the contractile lymphatic endothelial cells—increases in frequency and vigor when excess water is in the lymph vessels. Conversely, less fluid in the lymphatic vessels allows the vessels to become quiet and pump less fluid. This simple regulatory system ensures that the fluid status of the organ's interstitial environment is appropriate.

The active and passive compression of lymphatic bulbs and vessels also provides the force needed to propel the lymph back to the venous side of the blood circulation. To maintain directional lymph flow, microscopic lymphatic bulbs and vessels, as well as large lymphatic vessels, have one-way valves (see Fig. 16.3). These valves allow lymph to flow only from the tissue toward the progressively larger lymphatic vessels and, finally, into large veins in the chest cavity.

Lymphatic pressures are only a few mm Hg in the bulbs and smallest lymphatic vessels and as high as 10 to 20 mm Hg during contractions of larger lymphatic vessels. This progression from lower to higher lymphatic pressures is possible because, as each lymphatic segment contracts, it develops a slightly higher pressure than in the next lymphatic vessel and the lymphatic valve momentarily opens to allow lymph flow. When the activated lymphatic vessel relaxes, its pressure is again lower than that in the next vessel, and the lymphatic valve closes.

VASCULAR AND TISSUE EXCHANGE OF SOLUTES

The Large Number of Microvessels Provides a Large Vascular Surface Area for Exchange

The overall branching structure of the microvasculature is a tree-like system, with major trunks dividing into progressively smaller branches. This arrangement applies to both the arteriolar and the venular microvasculature; actually two "trees" exist—one to supply the tissue through arterioles and one to drain the tissue through venules. In general, there are four to five discrete branching steps from a small artery entering an organ to the capillary level and from the capillaries to the largest venules. These branching patterns are so consistent among like organ systems of various mammals, including humans, that they must be genetically determined.

The increasing numbers of vessels through successive branches dramatically increases the surface area of the microvasculature. The surface area is determined by the length, diameter, and number of vessels. In the small intestine, for example, the total surface area of the capillaries and smallest venules is more than 10 cm² for one cm³ of tissue. The large surface area of the capillaries and smallest venules is important because the vast majority of exchange of nutrients, wastes, and fluid occurs across these tiny vessels.

The Large Number of Microvessels Minimizes the Diffusion Distance Between Cells and Blood

The spacing of microvessels in the tissues determines the distance molecules must diffuse from the blood to the interior of tissue cells. In the example shown in Figure 16.5A, a

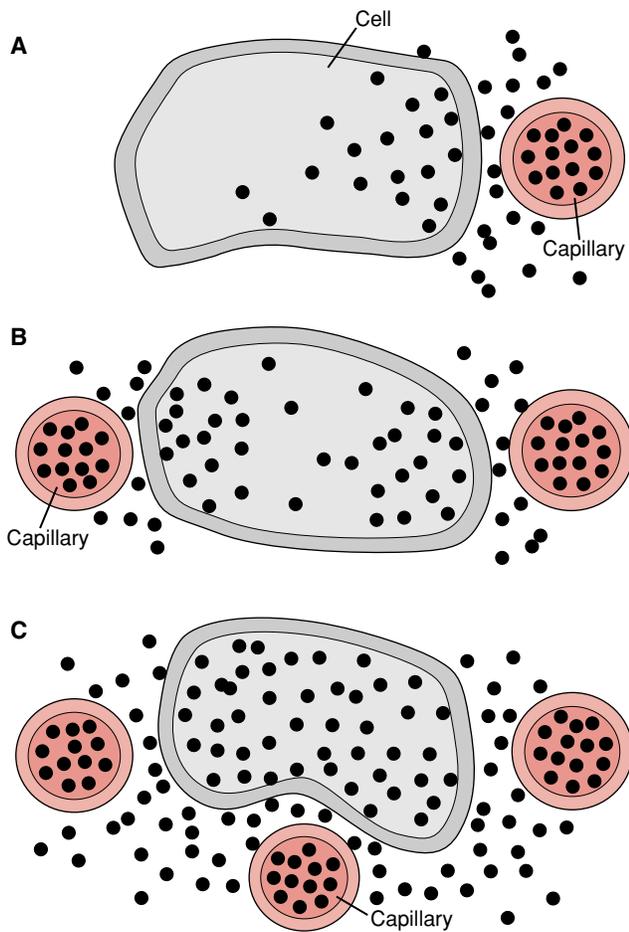


FIGURE 16.5 Effect of the number of perfused capillaries on cell concentration of bloodborne molecules (dots). A, With one capillary, the left side of the cell has a low concentration. B, The concentration can be substantially increased if a second capillary is perfused. C, The perfusion of three capillaries around the cell increases concentrations of bloodborne molecules throughout the cell.

single capillary provides all the nutrients to the cell. The concentration of bloodborne molecules across the cell interior is represented by the density of dots at various locations. Diffusion distances are important; as molecules travel farther from the capillary, their concentration decreases substantially because the volume into which diffusion proceeds increases as the square of the distance. In addition, some of the molecules may be consumed by different cellular components, which further reduces the concentration.

If there is a capillary on either side of a cell, as in Figure 16.5B, the cell has a higher internal concentration of molecules from the two capillaries. Therefore, increasing the number of microvessels reduces diffusion distances from a given point inside a cell to the nearest capillary. Doing so minimizes the dilution of molecules within the cells caused by large diffusion distances. At any given moment during resting conditions, only about 40 to 60% of the capillaries are perfused by red blood cells in most organs. The capillaries not in use do contain blood, but it is not moving. Exercise results in an increase in the number of perfused cap-

illaries, decreasing diffusion distances. The arteriolar dilation during exercise allows arterioles to supply blood flow to nearly all of the available capillaries in muscle.

Regular exercise induces the growth of new capillaries in skeletal muscle. As shown in Figure 16.5C, three capillaries contribute to the nutrition of the cell and elevate cell concentrations of molecules derived from the blood. However, decreasing the number of capillaries perfused with blood by constricting arterioles or obliterating capillaries, as in diabetes mellitus, can lengthen diffusion distances and decrease exchange.

The Interstitial Space Between Cells Is a Complex Environment of Water- and Gel-Filled Areas

As molecules diffuse from the microvessels to the cells or from the cells to the microvessels, they must pass through the **interstitial space** that forms the extracellular environment between cells. This space contains strands of collagen and elastin together with hyaluronic acid (a high-molecular-weight unbranched polysaccharide) and proteoglycans (complex polysaccharides bound to polypeptides). These large molecules are arranged in complex, water-filled coils. To some extent, the large molecules and water may cause the interstitial space to behave as alternating regions of gel-like consistency and water-filled regions. The gel-like areas may restrict the diffusion of water-soluble solutes and may exclude solutes from their water.

An implication of the gel and water properties of the interstitial space is that the effective concentration of molecules in the free interstitial water is higher than expected because the molecules are restricted to readily accessible water-filled areas. The circuitous pathway a molecule must move in the maze of the interstitial gel- and water-filled spaces slows the diffusion of water-soluble molecules. It is also possible that the relative amounts of gel and water phases can be altered in a way that diffusion in the extracellular space is changed.

The Rate of Diffusion Depends on Permeability and Concentration Differences

Diffusion is by far the most important means for moving solutes across capillary walls. The rate of diffusion of a solute between blood and tissue is given by Fick's law (see Chapter 2):

$$J_s = P (C_b - C_t) \quad (1)$$

J_s is the net movement of solute (often expressed in moles/min per 100 g tissue), P is the permeability coefficient, and C_b and C_t are, respectively, the blood and tissue concentrations of the solute.

The **permeability coefficient** is usually measured under conditions in which neither the surface area of the vasculature nor the diffusion distance is known, but the tissue mass can be determined. The permeability coefficient is directly related to the diffusion coefficient of the solute in the capillary wall and the vascular surface area available for exchange and is inversely related to the diffusion distance. The surface area and diffusion distance are determined, in part, by the number of microvessels with active blood flow. The diffusion

coefficient is relatively constant unless the capillaries are damaged because it depends on the anatomical properties of the vessel wall (e.g., the size and abundance of pores) and the chemical nature of the material that is diffusing.

The number of perfused capillaries and blood and tissue concentrations of solutes are constantly changing, and chronic changes occur as well. Therefore, the diffusion distance and surface area for exchange can be influenced by physiological events. The same is true for concentrations in the tissue and blood. In this context, microvascular exchange is dynamically altered by many physiological events. For example, about half of the capillaries of the intestinal villus are perfused when the bowel lumen is empty. During absorption of foodstuff, all of the capillaries are perfused as arterioles dilate to provide a higher blood flow to support the increased metabolic rate of villus epithelial cells.

The magnitude of the difference in blood and tissue concentrations is influenced by many simultaneous and interacting processes. It is important to remember that the diffusion rate depends on the *difference* between the high and low concentrations, not the specific concentrations. For example, if the cell consumes a particular solute, the concentration in the cell will decrease, and for a constant concentration in blood plasma, the diffusion gradient will enlarge to increase the rate of diffusion. If the cell ceases to use as much of a given solute, the concentration in the cell will increase and the rate of diffusion will decrease. Both of these examples assume that more than sufficient blood flow exists to maintain a relatively constant concentration in the microvessel.

In many cases, the above scenario may not be true. For example, as blood passes through the tissues, the tissues extract approximately one fourth to one third of the oxygen contained in arterial blood before it reaches the capillaries. The oxygen diffuses directly through the walls of the arterioles and is readily available for any cells in the vicinity. There is usually ample oxygen in the capillary blood to maintain aerobic metabolism; however, if tissue metabolism is increased and blood flow is not appropriately elevated, the tissue will exhaust the available oxygen from the blood while it is in the microvessels. The result is that, although the cells have generated conditions to increase their aerobic metabolic rate, inadequate oxygen is exchanged for this increased need. To temporarily perform their functions, the active cells resort to anaerobic glycolysis to provide cell energy. This scenario routinely occurs when skeletal muscles begin to contract and blood flow has not yet been appropriately increased to meet the increased oxygen demand.

The Extraction of Molecules From Blood Is Influenced by Vascular Permeability, Surface Area, and Blood Flow

As a result of diffusional losses and gains of molecules as blood passes through the tissues, the concentrations of various molecules in venous blood can be very different from those in arterial blood. The **extraction (E)**, or **extraction ratio**, of material from blood perfusing a tissue can be calculated from the arterial (C_a) and venous (C_v) blood concentration as:

$$E = (C_a - C_v)/C_a \quad (2)$$

If the blood loses material to the tissue, the value of E is positive and has a maximum value of 1 if all material is removed from arterial blood ($C_v = 0$). An E value of 0 ($C_a = C_v$) indicates that no loss or gain occurred. A negative E value ($C_v > C_a$) indicates that the tissue added material to the blood. The total mass of material lost or gained by the blood can be calculated as:

$$\text{Amount lost or gained} = E \times \dot{Q} \times C_a \quad (3)$$

E is extraction, \dot{Q} is blood flow, and C_a is the arterial concentration. While this equation is useful for calculating the total amount of material exchanged between tissue and blood, it does not allow a direct determination of how changes in vascular permeability and exchange surface area influence the extraction process. The extraction can be related to the permeability (P) and surface area (A) available for exchange as well as the blood flow (\dot{Q}):

$$E = 1 - e^{-PA/\dot{Q}} \quad (4)$$

The e is the base of the natural system of logarithms. This equation predicts that extraction increases when either permeability or exchange surface area increases or blood flow decreases. Extraction decreases when permeability and surface area decrease or blood flow increases. Consequently, physiologically induced changes in the number of perfused capillaries, which alters surface area, and changes in blood flow are important determinants of overall extraction and, therefore, exchange processes. The inverse effect of blood flow on extraction occurs because, if flow increases, less time is available for exchange. Conversely, a slowing of flow allows more time for exchange.

Ordinarily, the blood flow and total perfused surface area usually change in the same direction, although by different relative amounts. For example, surface area is usually able, at most, to double or be reduced by about half; however, blood flow can increase 3- to 5-fold or more in skeletal muscle, or decrease by about half in most organs, yet maintain viable tissue. The net effect is that extraction is rarely more than doubled or decreased by half relative to the resting value in most organs. This is still an important range because changes in extraction can compensate for reduced blood flow or enhance exchange when blood flow is increased.

Transcapillary Fluid Exchange

To force the blood through microvessels, the heart pumps blood into the elastic arterial system and provides the pressure needed to move the blood. This hemodynamic—**hydrostatic pressure**—while absolutely necessary, favors the pressurized filtration of water through pores because the hydrostatic pressure on the blood side of the pore is greater than on the tissue side. The capillary pressure is different in each organ, ranging from about 15 mm Hg in intestinal villus capillaries to 55 mm Hg in the kidney glomerulus. The interstitial hydrostatic pressure ranges from slightly negative to 8 to 10 mm Hg and, in most organs, is substantially less than capillary pressure.

The Osmotic Forces Developed by Plasma Proteins Oppose the Filtration of Fluid From Capillaries

The primary defense against excessive fluid filtration is the **colloid osmotic pressure**, also called plasma oncotic pressure, generated by plasma proteins. Plasma proteins are too large to pass readily through the vast majority of water-filled pores of the capillary wall. In fact, more than 90% of these large molecules are retained in the blood during its passage through the microvessels of most organs. Colloid osmotic pressure is conceptually similar to osmotic pressures for small molecules generated across selectively permeable cell membranes; both primarily depend on the number of molecules in solution. The major plasma protein that impedes filtration is serum albumin because it has the highest molar concentration of all plasma proteins. The colloid osmotic pressure of plasma proteins is typically 18 to 25 mm Hg in mammals when measured using a membrane that prevents the diffusion of all large molecules.

Colloid osmotic pressure offsets the capillary hydrostatic blood pressure to the extent that the net filtration force is only slightly positive or negative. If the capillary pressure is sufficiently low, the balance of colloid osmotic and hydrostatic pressures is negative, and tissue water is absorbed into the capillary blood. The majority of organs continuously form lymph, which indicates that capillary and venular filtration pressures generally are larger than absorption pressures. The balance of pressures is likely 1 to 2 mm Hg in most organs.

The Leakage of Plasma Proteins Into Tissues Increases the Filtration of Fluid From the Blood to the Tissues

A small amount of plasma protein enters the interstitial space; these proteins and, perhaps, native proteins of the space generate the tissue colloid osmotic pressure. This pressure of 2 to 5 mm Hg offsets part of the colloid osmotic pressure in the plasma. This is, in a sense, a filtration pressure that opposes the blood colloid osmotic pressure. As discussed earlier, the lymphatic vessels return plasma proteins in the interstitial fluid to the plasma.

Hydrostatic Pressure in Tissues Can Either Favor or Oppose Fluid Filtration From the Blood to the Tissues

The hydrostatic pressure on the tissue side of the endothelial pores is the tissue hydrostatic pressure. This pressure is determined by the water volume in the interstitial space and tissue distensibility. Tissue hydrostatic pressure can be increased by external compression, such as with support stockings, or by internal compression, such as in a muscle during contraction. The tissue hydrostatic pressure in various tissues during resting conditions is a matter of debate. Tissue pressure is probably slightly below atmospheric pressure (negative) to slightly positive (<+3 mm Hg) during normal hydration of the interstitial space and becomes positive when excess water is in the interstitial space. Tis-

sue hydrostatic pressure is a filtration force when negative and an absorption force when positive.

Support stockings are routinely prescribed for people whose feet and lower legs swell during prolonged standing. Standing causes high capillary hydrostatic pressures from gravitational effects on blood in the arterial and venous vessels and results in excessive filtration. Support stockings compress the interstitial environment to raise hydrostatic tissue pressure and compress superficial veins, which helps lower venous pressure and, thereby, capillary pressure.

If water is removed from the interstitial space, the hydrostatic pressure becomes very negative and opposes further fluid loss (Fig. 16.6). If a substantial amount of water is added to the interstitial space, the tissue hydrostatic pressure is increased. However, a margin of safety exists over a wide range of tissue fluid volumes (see Fig. 16.6), and excessive tissue hydration or dehydration is avoided. If the tissue volume exceeds a certain range, swelling or **edema** occurs. In extreme situations, the tissue swells with fluid to the point that pressure dramatically increases and strongly opposes capillary filtration. The ability of tissues to allow substantial changes in interstitial volume with only small changes in pressure indicates that the interstitial space is distensible. As a general rule, about 500 to 1,000 mL of fluid can be withdrawn from the interstitial space of the entire body to help replace water losses due to sweating, diarrhea, vomiting, or blood loss.

The Balance of Filtration and Absorption Forces Regulates the Exchange of Fluid Between the Blood and the Tissues

The role of hydrostatic and colloid osmotic pressures in determining fluid movement across capillaries was first postulated by the English physiologist Ernest Starling at the end of the nineteenth century. In the 1920s, the American physiologist Eugene Landis obtained experimental proof

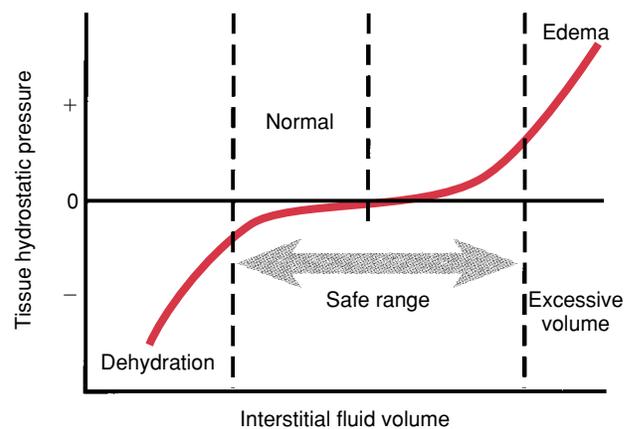


FIGURE 16.6 Variations in tissue hydrostatic pressure as interstitial fluid volume is altered. Under normal conditions, tissue pressure is slightly negative (subatmospheric), but an increase in volume can cause the pressure to be positive. If the interstitial fluid volume exceeds the “safe range,” high tissue hydrostatic pressures and edema will be present. Tissue dehydration can cause negative tissue hydrostatic pressures.

for Starling's hypothesis. The relationship is defined for a single capillary by the **Starling-Landis equation**:

$$J_V = K_h A \{(P_c - P_t) - \sigma(COP_p - COP_t)\} \quad (5)$$

J_V is the net volume of fluid moving across the capillary wall per unit of time ($\mu\text{m}^3/\text{min}$). K_h is the **hydraulic conductivity for water**, which is the fluid permeability of the capillary wall. K_h is expressed as $\mu\text{m}^3/\text{min}/(\mu\text{m}^2 \text{ of capillary surface area})$ per mm Hg pressure difference. The value of K_h increases up to 4-fold from the arterial to the venous end of a typical capillary. A is the vascular surface area, P_c is the capillary hydrostatic pressure, and P_t is the tissue hydrostatic pressure. COP_p and COP_t represent the plasma and tissue colloid osmotic pressures, respectively, and σ is the **reflection coefficient for plasma proteins**. This coefficient is included because the microvascular wall is slightly permeable to plasma proteins, preventing the full expression of the two colloid osmotic pressures. The value of σ is 1 when molecules cannot cross the membrane (i.e., they are 100% "reflected") and 0 when molecules freely cross the membrane (i.e., they are not reflected at all). Typical σ values for plasma proteins in the microvasculature exceed 0.9 in most organs other than the liver and spleen, which have capillaries that are very permeable to plasma proteins. The reflection coefficient is normally relatively constant but can be decreased dramatically by hypoxia, inflammatory processes, and tissue injury. This leads to increased fluid filtration because the effective colloid osmotic pressure is reduced when the vessel wall becomes more permeable to plasma proteins.

The capillary exchange of fluid is bidirectional because capillaries and venules may filter or absorb fluid, depending on the balance of hydrostatic and colloid osmotic pressures. It is possible that filtration occurs primarily at the arteriolar end of capillaries, where filtration forces exceed absorptive forces. It is equally likely that fluid absorption occurs in the venular end of the capillary and small venules because the friction of blood flow in the capillary has dissipated the hydrostatic blood pressure. Based on directly measured capillary hydrostatic and plasma colloid osmotic pressures, the entire length of the capillaries in skeletal muscle filters slightly all of the time, while the lower capillary pressures in the intestinal mucosa and brain primarily favor absorption along the entire capillary length. However, as each of these organs does filter fluid, some of the capillaries and, probably, the smaller arterioles are filtering fluid most of the time.

The extrapolation of fluid filtration or absorption for a single capillary to fluid exchange in a whole tissue is difficult. Within organs, there are regional variations in microvascular pressures, possible filtration and absorption of fluid in vessels other than capillaries, and physiologically and pathologically induced variations in the available surface area for capillary exchange. Therefore, for whole organs, a measurement of total fluid movement relative to the mass of the tissue is used. To take into account the various hydraulic conductivities and total surface areas of all vessels involved, the volume (mL) of fluid moved per minute for a change of 1 mm Hg in capillary pressure for each 100 g of tissue is determined. This value is called the **capillary filtration coefficient (CFC)**, although it is likely that fluid ex-

change occurs in both venules and capillaries. CFC values in tissues such as skeletal muscle and the small intestine are typically in the range of 0.025 to 0.16 mL/min per mm Hg per 100 g.

The CFC replaces the hydraulic conductivity (K_h) and capillary surface area (A) in the Starling-Landis equation for filtration across a single capillary. The CFC can change if fluid permeability, the surface area (determined by the number of perfused microvessels), or both are altered. For example, during the intestinal absorption of foodstuff, particularly lipids, both capillary fluid permeability and perfused surface area increase, dramatically increasing CFC. In contrast, the skeletal muscle vasculature increases CFC primarily because of increased perfused capillary surface area during exercise and only small increases in fluid permeability occur.

The hydrostatic and colloid osmotic pressure differences across capillary walls—the **Starling forces**—cause the movement of water and dissolved solutes into the interstitial spaces. These movements are, however, normally quite small and contribute minimally to tissue nutrition. Most solutes transferred to the tissues move across capillary walls by simple diffusion, not by bulk flow of fluid.

THE REGULATION OF MICROVASCULAR PRESSURES

The microvascular pressures, both hydrostatic and colloid osmotic, involved in transcapillary fluid exchange depend on how the microvasculature dissipates the prevailing arterial and venous pressures and on the concentration of plasma proteins. Plasma protein concentration is determined largely by the rate of protein synthesis in the liver, where most of the plasma proteins are made. Disorders that impair protein synthesis—liver diseases and malnutrition and kidney diseases in which plasma proteins are filtered into the urine and lost—result in reduced plasma protein concentration. A lowered plasma colloid osmotic pressure favors the filtration of plasma water and gradually causes significant edema. Edema formation in the abdominal cavity, known as **ascites**, can allow large quantities of fluid to collect in and grossly distend the abdominal cavity.

Capillary Pressure Is Determined by the Resistance of and Blood Pressure in Arterioles and Venules

Capillary pressure (P_c) is not constant; it is influenced by four major variables: precapillary (R_{pre}) and postcapillary (R_{post}) resistances and arterial (P_a) and venous (P_v) pressures. Precapillary and postcapillary resistances can be calculated from the pressure dissipated across the respective vascular regions divided by the total tissue blood flow (\dot{Q}), which is essentially equal for both regions:

$$R_{pre} = (P_a - P_c)/\dot{Q} \quad (6)$$

$$R_{post} = (P_c - P_v)/\dot{Q} \quad (7)$$

In the majority of organ vasculatures, the precapillary resistance is 3 to 6 times higher than the postcapillary resistance. This has a substantial effect on capillary pressure.

To demonstrate the effect of precapillary and postcapillary resistances on capillary pressure, we use the equations for the precapillary and postcapillary resistances to solve for blood flow:

$$\dot{Q} = (P_a - P_c)/R_{pre} = (P_c - P_v)/R_{post} \quad (8)$$

The two equations to the right of the flow term can be solved for capillary pressure:

$$P_c = \frac{(R_{post}/R_{pre})P_a + P_v}{1 + (R_{post}/R_{pre})} \quad (9)$$

Equation 9 indicates that the ratio of postcapillary to precapillary resistance, rather than the absolute magnitude of either resistance, determines the effect of arterial pressure (P_a) on capillary pressure. In addition, venous pressure substantially influences capillary pressure. The denominator also influences both pressure effects. At a typical postcapillary to precapillary resistance ratio of 0.16:1, the denominator will be 1.16, which allows about 80% of a change in venous pressure to be reflected back to the capillaries. The postcapillary to precapillary resistance ratio increases during the arteriolar vasodilation that accompanies increased tissue metabolism; the decreased precapillary resistance and minimal change in postcapillary resistance increase capillary pressure. Because the balance of hydrostatic and colloid osmotic pressures is usually -2 to $+2$ mm Hg, a 10- to 15-mm Hg increase in capillary pressure during maximum vasodilation can cause a profound increase in filtration. The increased filtration associated with microvascular dilation is usually associated with a large increase in lymph production, which removes excess tissue fluid.

Capillary Pressure Is Reduced When the Sympathetic Nervous System Increases Arteriolar Resistance

When sympathetic nervous system stimulation causes a substantial increase in precapillary resistance and a proportionately smaller increase in postcapillary resistance, the capillary pressure can decrease up to 15 mm Hg and, thereby, greatly increase the absorption of tissue fluid. This process is important. As mentioned earlier, fluid taken from the interstitial space can compensate for vascular volume loss during sweating, vomiting, or diarrhea. As water is lost by any of these processes, the plasma proteins are concentrated because they are not lost.

THE REGULATION OF MICROVASCULAR RESISTANCE

The vascular smooth cells around arterioles and venules respond to a wide variety of physical and chemical stimuli, altering the diameter and resistance of the microvessels. Here we consider the various physical and chemical conditions in tissues that influence the muscle cells of the microvasculature.

Myogenic Vascular Regulation Allows Arterioles to Respond to Changes in Intravascular Pressure

Vascular smooth muscle can contract rapidly when stretched and, conversely, can reduce actively developed tension when passively shortened. In fact, vascular smooth muscle may be able to contract or relax when the load on the muscle is increased or decreased, respectively, even though the initial muscle length is not substantially changed. These responses are known to persist as long as the initial stimulus is present, unless vasoconstriction reduces blood flow to the extent that tissue becomes severely hypoxic. This process, called **myogenic regulation**, is activated when microvascular pressure is increased or decreased.

The cellular mechanisms responsible for myogenic regulation are not entirely understood, but several possibilities are likely involved. The first mechanism is a calcium ion-selective channel that is opened in response to increased membrane stretch or tension. Adding calcium to the cytoplasm would activate the smooth muscle cell and result in contraction. Limiting calcium entry would allow calcium pumps to remove calcium ions from the cytoplasm and favor relaxation. The second mechanism is a nonspecific cation channel that is opened in proportion to cell membrane stretch or tension. The entry of sodium ions through open channels would depolarize the cell and lead to the opening of voltage-activated calcium channels, followed by contraction as calcium ions flood into the cell. During reduced stretch or tension, the nonspecific channels would close and allow hyperpolarization to occur.

Other mechanisms are likely involved in myogenic regulation. What is clear is that vascular smooth muscle cells depolarize as the intravascular pressure is increased and hyperpolarize as the pressure is decreased. In addition, myogenic mechanisms are extremely fast and appear to be able to adjust to most, rapid pressure changes.

Myogenic regulation has some benefits. First, and perhaps most important, blood flow can be regulated when the arterial pressure is too high or too low for appropriate tissue blood flow. Second, the myogenic response helps prevent tissue edema when venous pressure is elevated by more than about 5 to 10 mm Hg above the typical resting values. The elevation of venous pressure results in an increase in capillary and arteriolar pressures. Myogenic arteriolar constriction lowers the transmission of arterial pressure to the capillaries and small venules to minimize the risk of edema, but at the expense of a decreased blood flow. The myogenic response to elevated venous pressure may be due to venous pressures transmitted backward through the capillary bed to the arterioles and, perhaps, to some type of response initiated by venules and transmitted to arterioles, possibly through endothelial cells or local neurons.

Tissue Metabolism Influences Blood Flow

In all organs, an increase in metabolic rate is associated with increased blood flow and extraction of oxygen to meet the metabolic needs of the tissues. In addition, a reduction in oxygen within the blood is associated with dilation of the arterioles and increased blood flow, assuming neural reflexes to hypoxia are not activated. The local regulation of

the microvasculature in response to the metabolic needs of tissues involves many different types of cellular mechanisms, one of which is linked to oxygen availability.

Oxygen is not stored in appreciable amounts in tissues, and the oxygen concentration will fall to nearly zero in about one minute if blood flow is stopped in any organ. An increase in metabolic rate would decrease the tissue oxygen concentration and possibly directly signal vascular muscle to relax by limiting the production of ATP for the contraction of smooth muscle cells. Figure 16.7 shows examples of the changes in oxygen partial pressure (tension) around arterioles (periarteriolar space), in the capillary bed, and around large venules during skeletal muscle contractions. At rest, venular blood oxygen tension is usually higher than in the capillary bed, possibly because venules acquire oxygen that diffuses out of nearby arterioles. Although both periarteriolar and capillary bed tissue oxygen tensions decrease at the onset of contractions, both are restored as arteriolar dilation occurs. The oxygen tension in venular blood rapidly and dramatically decreases at the onset of skeletal muscle contractions and demonstrates little recovery despite increased blood flow. The sustained decline in venular blood oxygen tension probably reflects increased extraction of oxygen from the blood. It is apparent from Figure 16.7 that the oxygen tension of venular blood in skeletal muscle is not a trustworthy indicator of the oxygen status of the capillary bed at rest or during contractions.

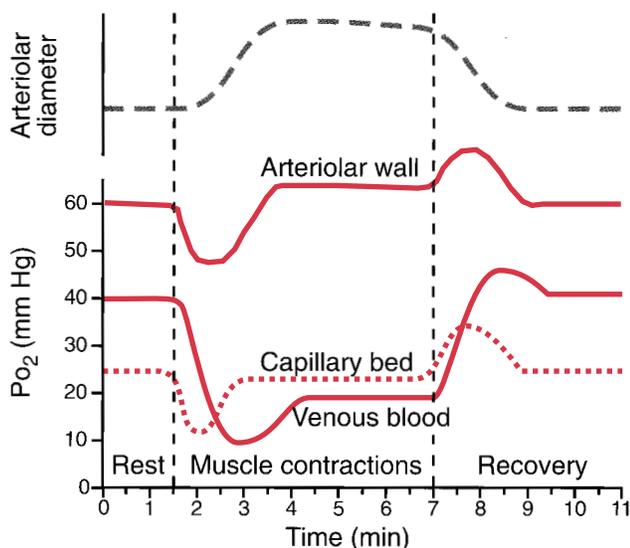


FIGURE 16.7 Arteriolar dilation and tissue oxygen tensions during skeletal muscle contractions.

The decrease in arteriolar, capillary bed, and venous oxygen tensions at the start of contractions reflects increased oxygen use, which is not replenished by increased blood flow until the arterioles dilate. As arteriolar dilation occurs, arteriolar wall and capillary bed oxygen tensions are substantially restored, but venous blood has a low oxygen tension. During recovery, oxygen tensions transiently increase above resting values because blood flow remains temporarily elevated as oxygen use is rapidly lowered to normal. (Modified from Lash JM, Bohlen HG. Perivascular and tissue PO₂ in contracting rat spinotrapezius muscle. *Am J Physiol* 1987;252:H1192–H1202.)

In contrast to venules, many arterioles have a normal-to-slightly increased periarteriolar oxygen tension during skeletal muscle contractions because the increased delivery of oxygen through elevated blood flow offsets the increased use of oxygen by tissues immediately around the arteriole. Therefore, as long as blood flow is allowed to increase substantially, it is unlikely that oxygen availability at the arteriolar wall is a major factor in the sustained vasodilation that occurs during increased metabolism.

Recent studies indicate that vascular smooth muscle cells are not particularly responsive to a broad range of oxygen tensions. Only unusually low or high oxygen tensions seem to be associated with direct changes in vascular smooth muscle force. However, either oxygen depletion from an organ's cells or an increased metabolic rate does cause the release of adenosine nucleotides, free adenosine, Krebs cycle intermediates, and, in hypoxic conditions, lactic acid. There is a large potential source of various molecules, most of which cause vasodilation at physiological concentrations, to influence the regulation of blood flow.

An increase in hydrogen ion concentration, resulting from accumulation of carbonic acid (formed from CO₂ and water) or acidic metabolites (such as lactic acid), causes vasodilation. However, usually only transient increases in venous blood and interstitial tissue acidity occur if blood flow through an organ with increased metabolism is allowed to increase appropriately.

Endothelial Cells Can Release Chemicals That Cause Relaxation or Constriction of Arterioles

An important contributor to local vascular regulation is released by endothelial cells. This substance, **endothelium-derived relaxing factor (EDRF)**, is released from all arteries, microvessels, veins, and lymphatic endothelial cells. EDRF is **nitric oxide (NO)**, which is formed by the action of **nitric oxide synthase** on the amino acid arginine. NO causes the relaxation of vascular smooth muscle by inducing an increase in cyclic guanosine monophosphate (cGMP). When cGMP is increased, the smooth muscle cell extrudes calcium ions and decreases calcium entry into the cell, inhibiting contraction and enzymatic processes that depend on calcium ions. Compounds such as acetylcholine, histamine, and adenosine nucleotides (ATP, ADP) released into the interstitial space, as well as hypertonic conditions and hypoxia cause the release of NO. Adenosine causes NO release from endothelial cells and directly relaxes vascular smooth muscle cells through adenosine receptors.

Another important mechanism to release NO is the **shear stress** generated by blood moving past the endothelial cells. Frictional forces between moving blood and the stationary endothelial cells distort the endothelial cells, opening special potassium channels and causing endothelial cell hyperpolarization. This increases calcium ion entry into the cell down the increased electrical gradient. The elevated cytosolic calcium ion concentration activates endothelial nitric oxide synthase to form more NO, and the blood vessels dilate.

This mechanism is used to coordinate various sized arterioles and small arteries. As small arterioles dilate in response to some signal from the tissue, the increased blood

flow increases the shear stress in larger arterioles and small arteries, which prompts their endothelial cells to release NO and relax the smooth muscle. As larger arterioles and small arteries control much more of the total vascular resistance than do small arterioles, the cooperation of the larger resistance vessels is vital to adjusting blood flow to the needs of the tissue. Examples of this process, called **flow-mediated vasodilation**, have been observed in cerebral, skeletal muscle, and small intestinal vasculatures. Endothelial cells of arterioles also release vasodilatory prostaglandins when blood flow and shear stress are increased. However, NO appears to be the dominant vasodilator molecule for flow-dependent regulation. Clinical Focus Box 16.1 describes the defects in endothelial cell function and NO production that are a major contribution to the pathophysiology of diabetes mellitus.

Endothelial cells also release one of the most potent vasoconstrictor agents, the 21 amino acid peptide **endothelin**. Extremely small amounts are released under natural conditions. Endothelin is the most potent biological constrictor of blood vessels yet to be found. The vasoconstriction occurs because of a cascade of events beginning with phospholipase C activation and leading to activation of protein kinase C (see Chapter 1). Two major types of endothelin receptors have been identified and others may exist. The constrictor function of endothelin is mediated by type B endothelin receptors. Type A endothelin receptors cause hyperplasia and hypertrophy of vascular muscle cells and the release of NO from endothelial cells. The precise function of endothelin in the normal vasculature is not clear; however, it is active during embryological development. In knockout mice, the absence of the endothelin A receptor results in serious cardiac defects so newborns are not viable. An absence of the type B receptor is associated with an enlarged colon, eventually leading to death. Endothelin clearly has functions other than vascular regulation.

In damaged heart tissue, such as after poor blood flow resulting in an infarct, cardiac endothelial cells increase endothelin production. The endothelin stimulates both vascular smooth muscle and cardiac muscle to contract more vigorously and induces the growth of surviving cardiac cells. However, excessive stimulation and hypertrophy of cells appears to contribute to heart failure, failure of contractility, and excessive enlargement of the heart. Part of the stimulation of endothelin production in the injured heart may be the damage per se. Also, increased formation of angiotensin II and norepinephrine during chronic heart disease stimulates endothelin production, probably at the gene expression level. Activation of protein kinase C (PKC) increases the expression of the *c-jun* proto-oncogene, which, in turn, activates the preproendothelin-1 gene. Endothelin has also been implicated as a contributor to renal vascular failure, both pulmonary hypertension and the systemic hypertension associated with insulin resistance, and the spasmodic contraction of cerebral blood vessels exposed to blood after a brain injury or stroke associated with blood loss to brain tissue.

The Sympathetic Nervous System Regulates Blood Pressure and Flow by Constricting the Microvessels

Although the microvasculature uses local control mechanisms to adjust vascular resistance based on the physical and chemical environment of the tissue and vasculature, the dominant regulatory system is the sympathetic nervous system. As Chapter 18 explains, the arterial pressure is monitored moment-to-moment by the baroreceptor system, and the brain adjusts the cardiac output and systemic vascular resistance as needed via the sympathetic and parasympathetic nervous systems. Sympathetic nerves communicate with the resistance vessels and venous system through the

CLINICAL FOCUS BOX 16.1

Diabetes Mellitus and Microvascular Function

More than 95% of persons with diabetes experience periods of elevated blood glucose concentration, or **hyperglycemia**, as a result of inadequate insulin action and the resulting decreased glucose transport into the muscle and fat tissues and increased glucose release from the liver. The most common cause of diabetes mellitus is obesity, which increases the requirement for insulin to the extent that even the high insulin concentrations provided by the pancreatic beta cells are insufficient. This overall condition is called **insulin resistance**.

Obesity independent of periods of hyperglycemia does not injure the microvasculature. However, periods of hyperglycemia over time cause reduced nitric oxide (NO) production by endothelial cells, increased reactivity of vascular smooth muscle to norepinephrine, accelerated atherosclerosis, and a reduced ability of microvessels to participate in tissue repair. The consequences are cerebrovascular accidents (stroke) and coronary artery dis-

ease as a result of endothelial cell abnormalities; loss of toes or whole legs as a result of microvascular and atherosclerotic pathology; and loss of retinal microvessels followed by a pathological overgrowth of capillaries, leading to blindness. The kidney glomerular capillaries are also damaged—this may lead to renal failure.

The mechanism of many of these abnormalities appears to stem from the fact that hyperglycemia activates protein kinase C (PKC) in endothelial cells. PKC inhibits nitric oxide synthase, so NO formation is gradually suppressed. This leads to loss of an important vasodilatory stimulus (NO) and vasoconstriction. PKC also activates phospholipase C, leading to increased diacylglycerol and arachidonic acid formation. The increased availability of arachidonic acid leads to increased prostaglandin synthesis and the generation of oxygen radicals that destroy part of the NO present. In addition, oxygen radicals damage cells of the microvasculature, and produce long-term problems caused by DNA breakage.

release of norepinephrine onto the surface of smooth muscle cells in vessel walls.

Because sympathetic nerves form an extensive meshwork of axons over the exterior of the microvessels, all vascular smooth muscle cells are likely to receive norepinephrine. Since the diffusion path is a few microns, norepinephrine rapidly reaches the vascular muscle and activates α -adrenergic receptors, and constriction begins within 2 to 5 seconds. Sympathetic nerve activation must occur quickly because rapid changes in body position or sudden exertion require immediate responses to maintain or increase arterial pressure. The sympathetic nervous system routinely overrides local regulatory mechanisms in most organs—except the heart and skeletal muscle—during exercise. But even in these, the sympathetic nervous system curtails somewhat the full increase in blood flow during submaximal contractions.

Certain Organs Control Their Blood Flow via Autoregulation and Reactive Hyperemia

If the arterial blood pressure to an organ is decreased to the extent that blood flow is compromised, the vascular resistance decreases and blood flow returns to approximately normal. If arterial pressure is elevated, flow is initially increased, but the vascular resistance increases and restores the blood flow toward normal; this is known as **autoregulation of blood flow**. Autoregulation appears to be primarily related to metabolic and myogenic control, as well as an increased release of NO if the tissue oxygen availability decreases. The cerebral and cardiac vasculatures, followed closely by the renal vasculature, are most able to autoregulate blood flow. Skeletal muscle and intestinal vasculatures exhibit less well-developed autoregulation.

A phenomenon related to autoregulation is **reactive hyperemia**. When blood flow to any organ is stopped or reduced by vascular compression for more than a few seconds, vascular resistance dramatically decreases. Absence of blood flow allows vasodilatory chemicals to accumulate as hypoxia occurs; the vessels also dilate due to decreased myogenic stimulation (low microvascular pressure). As soon as the vascular compression is removed, blood flow is dramatically increased for a few minutes. The excess blood in the part is called hyperemia; it is a reaction to the previous period of ischemia. A good example of reactive hyperemia is the redness of skin seen after a compression has been removed.

An example of autoregulation, based on data from the cerebral vasculature, is shown in Figure 16.8. Note that the arterioles continue to dilate at arterial pressures below 60 mm Hg, when blood flow begins to decrease significantly as arterial pressure is further lowered. The vessels clearly cannot dilate sufficiently to maintain blood flow at very low arterial pressures. At greater-than-normal arterial pressures, the arterioles constrict. If the mean arterial pressure is elevated appreciably above 150 to 160 mm Hg, the vessel walls cannot maintain sufficient tension to oppose passive distension by the high arterial pressure. The result is excessive blood flow and high microvascular pressures,

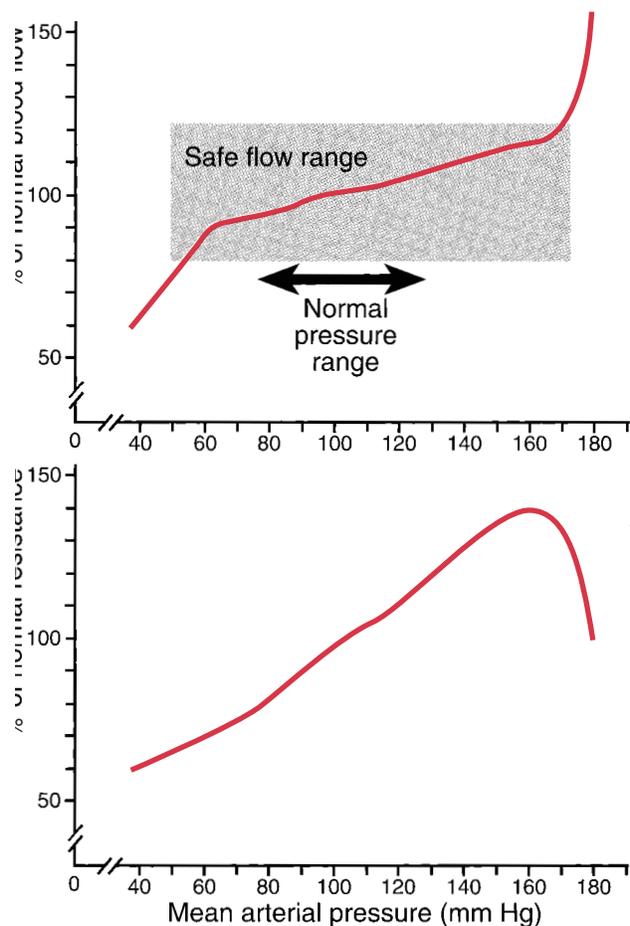


FIGURE 16.8 Autoregulation of blood flow and vascular resistance as mean arterial pressure is altered. The safe range for blood flow is about 80 to 125% of normal and usually occurs at arterial pressures of 60 to 160 mm Hg due to active adjustments of vascular resistance. At pressures above about 160 mm Hg, vascular resistance decreases because the pressure forces dilation to occur; at pressures below 60 mm Hg, the vessels are fully dilated, and resistance cannot be appreciably decreased further.

eventually leading to rupture of small vessels and excess fluid filtration into the tissue and edema.

Although the various mechanisms responsible for autoregulation are constantly interacting with the sympathetic nervous system, the actions of the sympathetic nervous system usually prevail in most organs. Only the cerebral and cardiac vasculatures exhibit impressive autoregulatory abilities because the sympathetic nervous system is incapable of causing large increases in resistance in the brain and heart. Sympathetic dominance of vascular control in the majority of organ systems is beneficial to the body as a whole. Maintenance of the arterial pressure by sustained constriction of most peripheral vascular beds and perfusion of the heart and brain at the expense of the other organs that can tolerate reduced blood flow for prolonged periods of time is lifesaving in an emergency.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

- The vessels most responsible for both controlling systemic vascular resistance and regulating blood flow to a particular organ are the
 - Small arteries
 - Arterioles
 - Capillaries
 - Venules
 - Lymphatic vessels
- The structures between adjacent capillary endothelial cells that primarily determine what size water-soluble molecules can enter the tissue are the
 - Fiber matrices at the blood side of endothelial pores
 - Molecular-sized openings within the tight junctions
 - Basement membrane structures of the capillary
 - Plasma proteins trapped in the spaces between cells
 - Rare, large defects found between adjacent endothelial cells
- The major pressures that determine filtration and absorption of fluid by capillaries are the
 - Capillary hydrostatic pressure and plasma colloid osmotic pressure
 - Plasma colloid osmotic pressure and interstitial hydrostatic pressure
 - Interstitial hydrostatic pressure and tissue colloid osmotic pressure
 - Capillary hydrostatic pressure and tissue colloid osmotic pressure
 - Plasma colloid osmotic pressure and tissue colloid osmotic pressure
- Myogenic vascular regulation is a cellular response initiated by
 - A lack of oxygen in the tissue
 - Nitric oxide release by vascular muscle cells
 - Stretch or tension on vascular muscle cells
 - Shear stress on the endothelial cells
 - An accumulation of metabolites in the tissue
- The most important function of the microcirculation is
 - The exchange of nutrients and wastes between blood and tissue
 - The filtration of water through capillaries
 - The regulation of vascular resistance
 - The autoregulation of blood flow
 - Its role as a blood reservoir
- When lipid-soluble molecules pass through a capillary wall, they primarily cross through
 - The lipid component of cell membranes
 - The water-filled spaces between cells
 - The specialized transport proteins of the cell membranes
 - The pinocytotic-exocytotic vesicles formed by endothelial cells
 - Filtration through the capillary wall
- Venules function to collect blood from the tissue and
 - Act as a substantial source of resistance to regulate blood flow
 - Serve as a reservoir for blood in the cardiovascular system
 - Are virtually impermeable to both large and small molecules
 - Are about the same diameter as arterioles
 - Exchange a large amount of oxygen with the tissue.
- The interstitial space can best be described as a
 - Water-filled space with a low plasma protein concentration
 - Viscous space with a high plasma protein concentration
 - Space with alternating gel and liquid areas with a low plasma protein concentration
 - Space primarily filled with gel-like material and a small amount of liquid
 - Major barrier to the diffusion of water and lipid-soluble molecules
- An arteriole with a damaged endothelial cell layer will not
 - Constrict when intravascular pressure is increased
 - Dilate when adenosine is applied to the vessel wall
 - Constrict in response to norepinephrine
 - Dilate in response to adenosine diphosphate (ADP) or acetylcholine
 - Dilate when blood flow is reduced
- The first step for lymphatic vessels to remove excess fluid from interstitial tissue spaces is by
 - Generating a lower intravascular than tissue hydrostatic pressure
 - Contracting and forcing lymph into larger lymphatics
 - Opening and closing one-way valves in the lymph vessels
 - Lowering the colloid osmotic pressure inside the lymph vessel
 - Closing the opening between adjacent lymphatic endothelial cells
- When the sympathetic nervous system is activated,
 - Norepinephrine is released by the vascular smooth muscle cells
 - Acetylcholine is released onto vascular smooth muscle cells
 - Norepinephrine is released from axons onto the arteriolar wall
 - The arterioles constrict because nitric oxide production is suppressed
 - The endothelial cells induce vascular smooth muscle cells to constrict
- At a constant blood flow, an increase in the number of perfused capillaries improves the exchange between blood and tissue because of
 - Greater surface area for the diffusion of molecules
 - Faster flow velocity of plasma and red blood cells in capillaries
 - Increased permeability of the microvasculature
 - Decreased concentration of chemicals in the capillary blood
 - Increased distances between the capillaries
- For an arterial blood content of 20 mL oxygen per 100 mL blood and venous blood content of 15 mL oxygen per 100 mL of blood, how much oxygen is transferred from blood to tissue if the blood flow is 200 mL/min?
 - 5 mL/min
 - 10 mL/min
 - 15 mL/min
 - 20 mL/min
 - 25 mL/min
- Assume plasma proteins have a reflection coefficient of 0.9, plasma colloid osmotic pressure is 24 mm Hg, and tissue colloid osmotic pressure is 4 mm Hg. What is the net pressure available for filtration or absorption of fluid if capillary hydrostatic pressure is 23 mm Hg and tissue hydrostatic pressure is 1 mm Hg?
 - 1 mm Hg
 - 2 mm Hg
 - 3 mm Hg
 - 4 mm Hg
 - 5 mm Hg

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