CHAPTER 17

Special Circulations

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CHAPTER OUTLINE

KEY CONCEPTS

1. The ability of the heart to pump blood depends almost exclusively on oxygen supplied by the coronary microcirculation.
2. Brain blood flow increases when the neurons are active and require additional oxygen.
3. The regulation of intestinal blood flow during nutrient absorption depends on the elevated sodium chloride concentration in the tissue and the release of nitric oxide (NO).
4. The liver receives the portal venous blood from the gastrointestinal organs as its main blood supply, supplemented by hepatic arterial blood.
5. Skeletal muscle tissue receives minimal blood flow at rest because of its limited oxygen requirements, but flow and oxygen use can increase up to or beyond 20-fold during intense muscle activity.
6. The skin has a low oxygen requirement, but the high blood flow during warm temperatures or exercise supplies a large amount of heat for dissipation to the external environment.
7. The fetus obtains nutrients and oxygen from the mother's blood supply, using the combined maternal and fetal placental circulations.
8. The heart chambers have radically different roles in pumping blood in the fetus and adult.

This chapter discusses the anatomical and physiological properties of the vasculatures in the heart, brain, small intestine, liver, skeletal muscle, and skin. Table 17.1 presents data on blood flow and oxygen use by these different organs and tissues. The features of each vasculature, which are related to the specific functions and specialized needs of each organ or tissue, are described. The vascular anatomy and physiology of the fetus and placenta and the circulatory changes that occur at birth are also presented. The pulmonary and renal circulations are discussed in Chapters 20 and 23.

CORONARY CIRCULATION

The Work Done by the Heart Determines Its Oxygen Use and Blood Flow Requirements

The coronary circulation provides blood flow to the heart. During resting conditions, the heart muscle consumes about as much oxygen as does an equal mass of skeletal muscle during vigorous exercise (see Table 17.1). Coronary blood flow can normally increase about 4- to 5-fold, to provide more of the heart's oxygen needs, during heavy exercise. This increment in blood flow constitutes the **coronary blood flow reserve**. The ability to increase the blood flow to provide additional oxygen is imperative. Heart tissue extracts almost the maximum amount of oxygen from blood during resting conditions. Because the heart's ability to use anaerobic glycolysis to provide energy is limited, the only practical way to increase energy production is to increase blood flow and oxygen delivery. The production of lactic acid by the heart is an ominous sign of grossly inadequate oxygenation.

Cardiac Blood Flow Decreases During Systole and Increases During Diastole

Blood flow through the left ventricle decreases to a minimum when the muscle contracts because the small blood vessels

TABLE 17.1 Blood Flow and Oxygen Consumption of the Major Systemic Organs Estimated for a 70-kg Adult Man

Organ	Mass(kg)	Flow (mL/100g per min)	Total Flow (mL/min)	Oxygen Use (mL/100g per min)	Total Oxygen Use (mL/min)
Hear					
Rest	0.4–0.5	60–80	250	7.0–9.0	25–40
Exercise		200–300	1,000–1,200	25.0–40.0	65–85
Brain	1.4	50–60	750	4.0–5.0	50–60
Small intestine					
Rest	3	30–40	1,500	1.5–2.0	50–60
Absorption		45–70	2,200–2,600	2.5–3.5	80–110
Liver					
Total	1.8–2.0	100–300	1,400–1,500	13.0–14.0	180–200
Portal		70–90	1,100	5.0–7.0	
Hepatic Artery		30–40	350	5.0–7.0	
Muscle					
Rest	28	2–6	750–1,000	0.2–0.4	60
Exercise		40–100	15,000–20,000	8.0–15.0	2,400–?
Skin					
Rest	2.0–2.5	1–3	200–500	0.1–0.2	2–4
Exercise		5–15	1,000–2,500		

are compressed. Blood flow in the left coronary artery during cardiac systole is only 10 to 30% of that during diastole, when the heart musculature is relaxed and most of the blood flow occurs. The compression effect of systole on blood flow is minimal in the right ventricle, probably as a result of the lower pressures developed by a smaller muscle mass (Fig. 17.1). Changes in blood flow during the cardiac cycle in healthy people have no obvious deleterious effects even during maximal exercise; however, in people with compromised coronary arteries, an increased heart rate decreases the time spent in diastole, impairing coronary blood flow.

The heart musculature is perfused from the epicardial (outside) surface to the endocardial (inside) surface. Microvascular pressures are dissipated by blood flow friction as the vessels pass through the heart tissue. Therefore, the mechanical compression of systole has more effect on the blood flow through the endocardial layers where compressive forces are higher and microvascular pressures are lower. This problem occurs particularly in heart diseases of all types, and most kinds of tissue impairment affect the subendocardial layers.

Coronary Vascular Resistance Is Primarily Regulated by Responses to Heart Metabolism

Animal studies indicate that about 75% of total coronary vascular resistance occurs in vessels with inner diameters of less than about 200 μm. This observation is supported by clinical measurements in humans that show little arterial pressure dissipation in normal coronary arteries prior to their smaller branches entering the heart muscle tissue. The majority of the coronary resistance vessels—the small arteries and arterioles—are surrounded by cardiac muscle cells and are exposed to chemicals released by cardiac cells into the interstitial space. Many of these chemicals cause dilation of the coronary arterioles. For example, adenosine, derived from the breakdown of adenosine triphosphate (ATP) in cardiac cells, is a potent vasodilator, and its release increases whenever cardiac metabolism is increased or blood flow to the heart is experimentally or pathologically decreased. Blockade of the vasodilator actions of adenosine with theophylline, however, does not prevent coronary vasodilation when cardiac work is increased, blood flow is suppressed, or the arterial blood is depleted of oxygen. Therefore, while adenosine is likely an important contributor to cardiac vascular regulation, there are obviously other potent regulatory agents. Vasodilatory prostaglandins, H^+, CO_2, NO, and decreased availability of oxygen, as well as myogenic mechanisms, are capable of contributing to coronary vascular regulation. No single mechanism adequately explains the dilation of coronary arterioles and small arteries when the metabolic rate of the heart is increased, or when pathological or experimental means are used to restrict blood flow. However, the release of NO from endothelial cells—in response to blood flow-mediated dilation (see Chapter 16) and in response to ATP, adenosine diphosphate (ADP), tissue acidosis, and decreased oxygen availability—appears to be one of the most important mechanisms to produce vasodilation.

Coronary arteries and arterioles are innervated by the sympathetic nervous system and can be constricted by norepinephrine, whether released from nerves or carried in the arterial blood. The constrictor mechanism appears to be more important in equalizing blood flow through the layers of the heart than in reducing blood flow to the heart muscle in general. The coronary arteries and larger arterioles predominately have α_1 receptors, which induce vascular constriction when activated by norepinephrine. Smaller arterioles predominately have β receptors, which cause vasodilation in response to epinephrine released by the adrenal medulla during sympathetic activity. In addition, epinephrine increases the metabolic rate of the heart via β_1

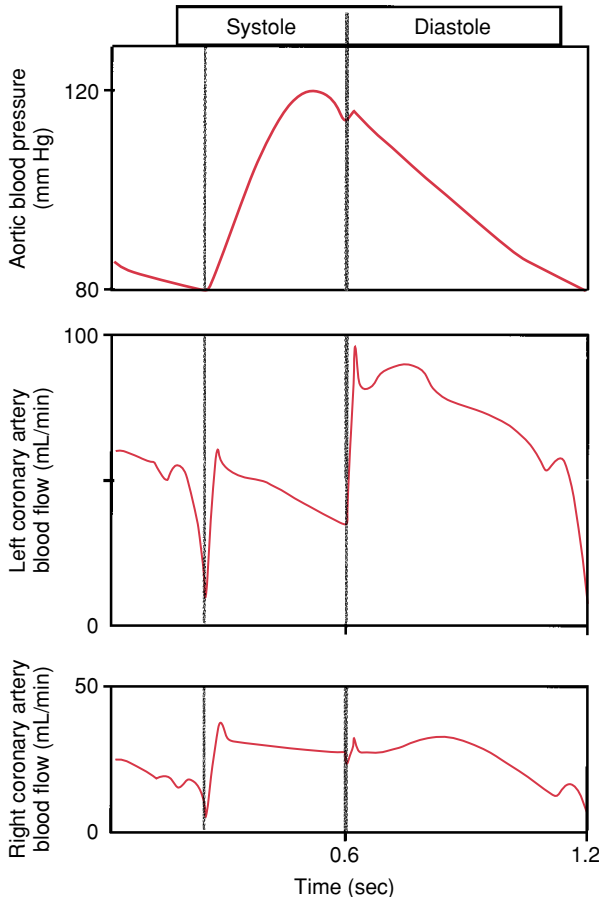

FIGURE 17.1 Aortic blood pressure and left and right coronary blood flows during the cardiac cycle. Note that left coronary artery blood flow decreases dramatically during the isovolumetric phase of systole, prior to opening of the aortic valve. Left coronary artery blood flow remains lower during systole than during diastole because of compression of the coronary blood vessels in the contracting myocardium. The left ventricle receives most of its arterial blood inflow during diastole. Right coronary artery blood flow tends to be sustained during both systole and diastole because lower intraventricular pressures are developed by the contracting right ventricle, resulting in less compression of coronary blood vessels. (Adapted from Gregg DE, Khouri EM, Rayford CR. Systemic and coronary energetics in the resting unanesthetized dog. Circ Res 1965;16:102–113; and Lowensohn HS, et al. Phasic right coronary artery blood flow in conscious dogs with normal and elevated right ventricular pressures. Circ Res 1976;39:760–766.)

receptors. This, in turn, leads to dilatory stimuli that potentially could overcome vasoconstriction.

The overall concept evolving from both human and animal studies is that the sympathetic nervous system suppresses the decrease in coronary vascular resistance during exercise despite the metabolic effects of epinephrine mentioned. The partial constriction of large coronary arterioles and most arteries by norepinephrine appears to limit the retrograde flow of blood during ventricular systole and, in doing so, prevents part of the decreased flow in the deep layers of the heart wall. In effect, the body trades a small decrease in flow, relative to what would exist without sympathetic effects on resistance vessels, for improved perfusion of the tissue at risk in the deeper layers of the heart.

Coronary Vascular Disease Limits Cardiac Blood Flow and Cardiac Work

Pathology of the coronary vasculature is the direct cause of death in about one third of the population in developed societies. Prior to death, most of these people have impaired cardiac function as a result of coronary artery disease, leading to heart failure with decreased quality of life. Progressive occlusion of coronary arteries by atherosclerotic plaques and acute occlusion as a result of the formation of blood clots in damaged coronary arteries are life-threatening because the metabolic needs of the cardiac muscle can no longer be met by the blood flow. Because the plaque or clot partially occludes the vessel lumen, vascular resistance is increased, and blood flow would decrease if smaller coronary vessels did not dilate to restore a relatively normal blood flow at rest. In doing so, the reserve for dilation of these vessels is compromised. While this usually has no effect at rest, when cardiac metabolism is increased, the decreased ability to increase blood flow can limit cardiac performance. In many cases, inadequate blood flow is first noticed as chest pain—known as **angina pectoris**—originating from the heart, and a feeling of shortness of breath during exercise or work. The vascular occlusion can cause conditions ranging from impaired contractile ability of the cardiac muscle, which limits cardiac output and tolerance to everyday work and exercise, to death of the muscle tissue, a **cardiac infarct**.

If the coronary occlusion is not severe, medication can be used to cause coronary vasodilation or decreased cardiac work, or both. If the arterial pressure is higher than normal, various approaches are used to lower the blood pressure, decreasing the heart's workload and oxygen needs. In addition to pharmacological treatment, mild to moderate exercise, depending on the status of the coronary disease, is often advised. Aerobic exercise stimulates the development of collateral vessels in the heart, improves the overall performance of the cardiovascular system, and increases the efficiency of the body during work and daily activities. This latter effect lowers the cardiac output needed for a given task, thereby decreasing the heart's metabolic energy requirement.

Significant changes in lifestyle—including strictly limiting dietary fat (especially saturated fat), strenuous and prolonged daily exercise, and reduced mental stress—have been shown to greatly slow and even slightly reverse coronary atherosclerosis. The goal is to lower blood levels of low-density lipoproteins (LDLs), which are known to accelerate the formation of cholesterol-containing arterial plaques. The LDL concentration should typically be lowered below 120 mg/dL, but some cardiologists favor lowering levels below 100 mg/dL. For most people, reductions in LDL below 120 mg/dL are not attainable with diet and exercise. In those persons, drugs, known as **statins**, which block the formation of cholesterol in the liver, appear to be highly effective in decreasing the risk and severity of coronary artery disease. Simultaneous

treatment with an aerobic exercise program and large amounts of niacin, to increase high-density lipoproteins (HDLs), may help the body remove cholesterol for processing in the liver. (See Clinical Focus Box 17.1).

Collateral Vessels Interconnect Sections of the Cardiac Microvasculature

One of the likely contributing factors to compensate for slowly developing coronary vascular disease is the enlargement of **collateral blood vessels** between the left and right coronary arterial systems or among parts of each system. In the healthy heart of a sedentary person, collateral arterial vessels are rare, but arteriolar collaterals (internal diameter, <100 μm) do occur in small numbers. The expansion of existing collateral vessels and the limited formation of new collaterals provide a partial bypass for blood flow to areas of muscle whose primary supply vessels are impaired. Subendocardial arteriolar collaterals usually enlarge more than epicardial collaterals. In part, the greater collateral enlargement in the endocardium compared to the epicardium may be due to the lower pressure and blood flow in reaching the endocardial vessels.

The exact mechanism responsible for the development of collateral vessels is unknown. However, periods of inadequate blood flow to the heart muscle caused by experimental flow reduction do stimulate collateral enlargement in healthy animals. It is assumed that in humans with coronary vascular disease who develop functional collateral vessels, the mechanism is related to occasional or even sustained periods of inadequate blood flow. Whether or not routine exercise aids in the development of collaterals in healthy humans is debatable; the benefits of exercise may be by other mechanisms, such as enlargement of the primary perfusion vessels and the reduction of atherosclerosis. However, there is no doubt that frequent and relatively intense aerobic exercise is beneficial to cardiac vascular function.

CEREBRAL CIRCULATION

The ultimate organ of life is the brain. Even the determination of death often depends upon whether or not the brain is viable. The most common cause of brain injury is some form of impaired brain blood flow. Such problems can develop as a result of accidents to arteries in the neck or brain, occlusion of vessels secondary to atherosclerotic processes, and, surprisingly frequently, **aneurysms** that occur as a result of vessel wall tearing. Fortunately, treatment of these problems is constantly improving.

Brain Blood Flow Is Virtually Constant Despite Changes in Arterial Blood Pressure

The cerebral circulation shares many of the physiological characteristics of the coronary circulation. The heart and brain have a high metabolic rate (see Table 17.1), extract a large amount of oxygen from blood, and have a limited ability to use anaerobic glycolysis for metabolism. Their vessels have a limited ability to constrict in response to sympathetic nerve stimulation. As described in Chapter 16, the brain and coronary vasculatures have an excellent ability to *autoregulate* blood flow at arterial pressures from about 50 to 60 mm Hg to about 150 to 160 mm Hg. The vasculature of the brainstem exhibits the most precise autoregulation, with good but less precise regulation of blood flow in the cerebral cortex. This regional variation in autoregulatory ability has clinical implications because the region of the brain most likely to suffer at low arterial pressure is the cortex, where consciousness will be lost long before the automatic cardiovascular and ventilatory regulatory functions of the brainstem are compromised.

A variety of mechanisms are responsible for cerebral vascular autoregulation. The identification of a specific chemical that causes cerebral autoregulation has not been possible. For example, when blood flow is normal, regardless of the arterial blood pressure, little extra adenosine, K^+, H^+, or other

CLINICAL FOCUS BOX 17.1

Coronary Vascular Disease

Approximately 45% of the adult population in the United States will, at some time during their lifetimes, require medical or surgical intervention because of atherosclerosis of the coronary arteries. The typical circumstance is rupture of the endothelial layer over an atherosclerotic plaque, followed by a clot that occludes or nearly occludes a coronary artery. About 10% of these incidents result in death before the patient reaches the hospital. For those who reach a coronary care facility, about 70% will be alive 1 year later, and about 50% will be alive in 5 years. If the patient does not have a risk of bleeding, the clot can be dissolved by administering tissue plasminogen activator or streptokinase. If the blood flow is quickly restored within a few hours, the damage to the heart muscle can be minimal. In some cases, advancing a catheter into the blocked artery to expand the vessel and remove the clot is the best approach. In a few cases, emergency replacement of the blocked artery is required; this is a much more invasive surgery and often requires several months of recovery.

Despite, the multiple treatments available to deal with existing coronary artery blockage, the ideal treatment is to avoid the problem. Excessive intake of cholesterol-rich food, sedentary lifestyles that tend to raise low-density lipoproteins (LDL) and lower high-density lipoproteins (HDL), and obesity leading to insulin resistance are key problems leading to accelerated coronary heart disease. Two of the three can be addressed with a lowered cholesterol and calorie-restricted diet to promote loss of body fat. Aerobic exercise of any type for approximately 30 minutes, 3 days a week, has consistently been shown to lower LDL and raise HDL, as well as aid in body fat loss. Pharmacological blockade of cholesterol synthesis in the liver with the statin family of compounds is effective to both prevent second heart attacks and lower the risk of a first heart attack. These drugs are so effective that in the near future, most persons older than age 50 may be advised to follow a dietary and exercise plan complemented with statin therapy.

vasodilator metabolites are released, and brain tissue P_{O2} remains relatively constant. However, increasing concentrations of any of these chemicals causes vasodilation and increased blood flow. The brain vasculature does exhibit myogenic vascular responses and may use this mechanism as a major contributor to autoregulation. Animal studies indicate that both the cerebral arteries and cerebral arterioles are involved in cerebral vascular autoregulation and other types of vascular responses. In fact, the arteries can change their resistance almost proportionately to the arterioles during autoregulation. This may occur in part because cerebral arteries exhibit myogenic vascular responses and because they are partially to fully embedded in the brain tissues and would likely be influenced by the same vasoactive chemicals in the interstitial space as affect the arterioles.

Brain Microvessels Are Sensitive to CO_2 and H^+

The cerebral vasculature dilates in response to increased CO_2 and H^+ and constricts if either substance is decreased. Both of these substances are formed when cerebral metabolism is increased by nerve action potentials, such as during normal brain activation. In addition, interstitial K^+ is elevated when a large number of action potentials are fired. The cause of dilation in response to both K^+ and CO_2 involves the formation of nitric oxide (NO). However, the mechanism is not necessarily the typical endothelial formation of NO. The source of NO appears to be from nitric oxide synthase in neurons, as well as endothelial cells. The H^+ formed by the interaction of carbon dioxide and water or from acids formed by metabolism does not appear to cause dilation through a NO-dependent mechanism, but additional data are needed on this topic.

Reactions of cerebral blood flow to chemicals released by increased brain activity, such as CO_2, H^+, and K^+, are part of the overall process of matching the brain's metabolic needs to the blood supply of nutrients and oxygen. The 10 to 30% increase in blood flow in brain areas excited by peripheral nerve stimulation, mental activity, or visual activity may be related to these three substances released from active nerve cells. The cerebral vasculature also dilates when the oxygen content of arterial blood is reduced, but the vasodilatory effect of elevated CO_2 is much more powerful.

Cerebral Blood Flow Is Insensitive to Hormones and Sympathetic Nerve Activity

Circulating vasoconstrictor and vasodilator hormones and the release of norepinephrine by sympathetic nerve terminals on cerebral blood vessels do not play much of a role in moment-to-moment regulation of cerebral blood flow. The blood-brain barrier effectively prevents constrictor and dilator agents in blood plasma from reaching the vascular smooth muscle. Though the cerebral arteries and arterioles are fully innervated by sympathetic nerves, stimulation of these nerves produces only mild vasoconstriction in the majority of cerebral vessels. If, however, sympathetic activity to the cerebral vasculature is permanently interrupted, the cerebral vasculature has a decreased ability to autoregulate blood flow at high arterial pressures, and the integrity of the blood-brain barrier is more easily disrupted. Therefore, some aspect of sympathetic nerve activity other than the routine regulation of vascular resistance is important for the maintenance of normal cerebral vascular function. This may occur because of a trophic factor that promotes the health of endothelial and smooth muscle cells in the cerebral microvessels.

The Cerebral Vasculature Adapts to Chronic High Blood Pressure

In conditions of chronic hypertension, cerebral vascular resistance increases, thereby allowing cerebral blood flow and, presumably, capillary pressures to be normal. The adaptation of cerebral vessels to sustained hypertension lets them maintain vasoconstriction at arterial pressures that would overcome the contractile ability of a normal vasculature (Fig. 17.2).

The mechanisms that enable the cerebral vasculature to adjust the autoregulatory range upward appear to be hypertrophy of the vascular smooth muscle and a mechanical constraint to vasodilation, as a result of more muscle tissue,

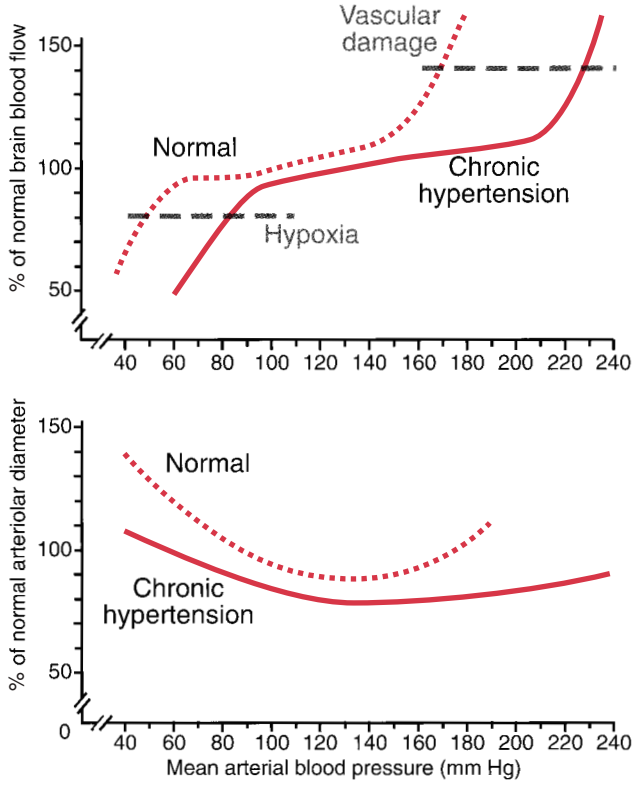

FIGURE 17.2 **Chronic hypertension.** This condition is associated with a rightward shift in the arterial pressure range over which autoregulation of cerebral blood flow occurs (upper panel) because, for any given arterial pressure, resistance vessels of the brain have smaller-than-normal diameters (lower panel). As a consequence, people with hypertension can tolerate high arterial pressures that would cause vascular damage in healthy people. However, they risk reduced blood flow and brain hypoxia at low arterial pressures that are easily tolerated by healthy people.

or more connective tissue, or both. The drawback to such adaptation is partial loss of the ability to dilate and regulate blood flow at low arterial pressures. This loss occurs because the passive structural properties of the resistance vessels restrict the vessel diameter at subnormal pressures and, in doing so, increase resistance. In fact, the lower pressure limit of constant blood flow (autoregulation) can be almost as high as the normal mean arterial pressure (see Fig. 17.2). This can be problematic if the arterial blood pressure is rapidly lowered to normal in a person whose vasculature has adapted to hypertension. The person may faint from inadequate brain blood flow, even though the arterial pressure is in the normal range. Fortunately, a gradual reduction in arterial pressure over weeks or months returns autoregulation to a more normal pressure range.

Cerebral Edema Impairs Blood Flow to the Brain

The brain is encased in a rigid bony case, the cranium. As such, should the brain begin to swell, the intracranial pressure will dramatically increase. There are many causes of **cerebral edema**—an excessive accumulation of fluid in the brain substance—including infection, tumors, trauma to the head that causes massive arteriolar dilation, and bleeding into the brain tissue after a stroke or trauma. In each case, the following approximate scenario occurs. As the intracranial pressure increases, the venules and veins are partially collapsed because their intravascular pressure is low. As these outflow vessels collapse, their resistance increases and capillary pressure rises (see Chapter 16). The increased capillary pressure favors increased filtration of fluid into the brain to further raise the intracranial pressure. The end result is a positive feedback system in which intracranial pressure will become so high as to begin to compress small arterioles and decrease blood flow.

Excessive intracranial pressure is a major clinical problem. Hypertonic mannitol can be given to promote water loss from swollen brain cells. Sometimes opening of the skull and drainage of cerebrospinal fluid or hemorrhaged blood, if any, may be necessary. Hemorrhaged blood is particularly a problem because clotted blood contains denatured hemoglobin that destroys nitric oxide. This in turn leads to inappropriate vasoconstriction of the arterioles in the area of the hemorrhage.

If blood flow to the pons and medulla of the brain is decreased, tissue hypoxia will activate the sympathetic nervous system control centers. This response—called **Cushing's reflex**—raises the arterial blood pressure, often dramatically. This can be viewed as an attempt to raise cerebral blood flow. While blood flow may improve, microvascular pressures are elevated, which worsens cerebral edema.

SMALL INTESTINE CIRCULATION

The small intestine completes the digestion of food and then absorbs the nutrients to sustain the remainder of the body. At rest, the intestine receives about 20% of the cardiac output and uses about 20% of the body's oxygen consumption. Both of these numbers nearly double after a large meal. Unless the blood flow can increase, food digestion and absorption simply do not occur. For example, if intense exercise is required in the midst of digesting a meal, blood flow through the small intestine can be reduced to half of normal by the sympathetic nervous system with no ill effects, other than delayed food absorption. Once the stress imposed on the body is over, intestinal blood flow again increases and the process of digesting and absorbing food resumes.

The Three Regions of the Intestinal Wall Are Supplied From a Common Set of Large Arterioles

Small arteries and veins penetrate the muscular wall of the bowel and form a microvascular distribution system in the submucosa (Fig. 17.3). The muscle layers receive small arterioles from the **submucosal vascular plexus**; other small arterioles continue into individual vessels of the deep submucosa around glands and to the villi of the mucosa. Small arteries and larger arterioles preceding the separate muscle and submucosal-mucosal vasculatures control about 70% of the intestinal vascular resistance. The small arterioles of the muscle, submucosal, and mucosal layers can partially adjust blood flow to meet the needs of small areas of tissue.

Compared with other major organ vasculatures, the circulation of the small intestine has a poorly developed autoregulatory response to locally decreased arterial pressure, and as a result, blood flow usually declines because resistance does not adequately decrease. However, elevation of venous pressure outside the intestine causes sustained myogenic constriction; in this regard, the intestinal circulation equals or exceeds similar regulation in other organ systems. Intestinal motility has little effect on the overall intestinal blood flow, probably because the increases in metabolic rate are so small. In contrast, the intestinal blood flow increases in approximate proportion to the elevated metabolic rate during food absorption.

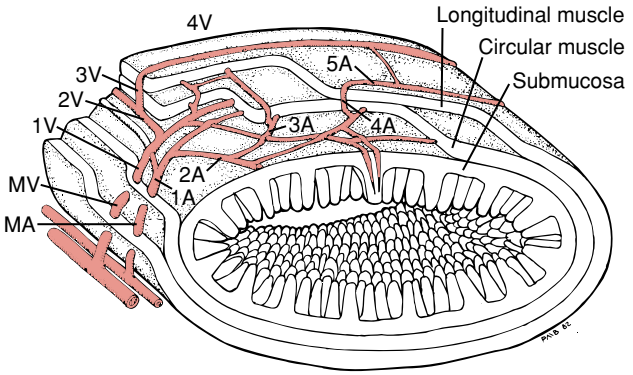

FIGURE 17.3 **The vasculature of the small intestine.** The intestinal vasculature is unusual because three very different tissues—the muscle layers, submucosa, and mucosal layer—are served by branches from a common vasculature located in the submucosa. Most of the intestinal vascular resistance is regulated by small arteries and arterioles preceding the separate muscle and submucosal and mucosal vasculatures. MA, muscular arteriole; 1A to 5A, successive branches of the arterioles; 1V to 4V, successive branches of the venules; MV, muscular venule. (Modified from Connors B. Quantification of the architectural changes observed in intestinal arterioles from diabetic rats. Ph.D. Dissertation, Indiana University, 1993.)

The Microvasculature of Intestinal Villi Has a High Blood Flow and Unusual Exchange Properties

The intestinal mucosa receives about 60 to 70% of the total intestinal blood flow. Blood flows of 70 to 100 mL/min per 100 g in this specialized tissue are probable and much higher than the average blood flow for the total intestinal wall (see Table 17.1). This blood flow can exceed the resting blood flow in the heart and brain.

The mucosa is composed of individual projections of tissue called **villi.** The interstitial space of the villi is mildly hyperosmotic (~400 mOsm/kg H_2O) at rest as a result of NaCl. During food absorption, the interstitial osmolality increases to 600 to 800 mOsm/kg H_2O near the villus tip, compared with 400 mOsm/kg H_2O near the villus base. The primary cause of high osmolalities in the villi appears to be greater absorption than removal of NaCl and nutrient molecules. There is also a possible countercurrent exchange process in which materials absorbed into the capillary blood diffuse from the venules into the incoming blood in the arterioles.

Food Absorption Requires a High Blood Flow to Support the Metabolism of the Mucosal Epithelium

Lipid absorption causes a greater increase in intestinal blood flow, a condition known as **absorptive hyperemia,** and oxygen consumption than either carbohydrate or amino acid absorption. During absorption of all three classes of nutrients, the mucosa releases adenosine and CO_2 and oxygen is depleted. The hyperosmotic lymph and venous blood that leave the villus to enter the submucosal tissues around the major resistance vessels are also major contributors to absorptive hyperemia. By an unknown mechanism, hyperosmolality resulting from NaCl induces endothelial cells to release NO and dilate the major resistance arterioles in the submucosa. Hyperosmolality resulting from large organic molecules that do not enter endothelial cells does not cause appreciable increases in NO formation, producing much less of an increase in blood flow than equivalent hyperosmolality resulting from NaCl. These observations suggest that NaCl entering the endothelial cells is essential to induce NO formation.

The active absorption of amino acids and carbohydrates and the metabolic processing of lipids into chylomicrons by mucosal epithelial cells place a major burden on the microvasculature of the small intestine. There is an extensive network of capillaries just below the villus epithelial cells that contacts these cells. The villus capillaries are unusual in that portions of the cytoplasm are missing, so that the two opposing surfaces of the endothelial cell membranes appear to be fused. These areas of fusion, or **closed fenestrae,** are thought to facilitate the uptake of absorbed materials by capillaries. In addition, intestinal capillaries have a higher filtration coefficient than other major organ systems, which probably enhances the uptake of water absorbed by the villi (see Chapter 16). However, large molecules, such as plasma proteins, do not easily cross the fenestrated areas because the reflection coefficient for the intestinal vasculature is greater than 0.9, about the same as in skeletal muscle and the heart.

Low Capillary Pressures in Intestinal Villi Aid in Water Absorption

Although the mucosal layer of the small intestine has a high blood flow both at rest and during food absorption, the capillary blood pressure is usually 13 to 18 mm Hg and seldom higher than 20 mm Hg during food absorption. Therefore, plasma colloid osmotic pressure is higher than capillary blood pressure, favoring the absorption of water brought into the villi. During lipid absorption, the plasma protein reflection coefficient for the overall intestinal vasculature is decreased from a normal value of more than 0.9 to about 0.7. It is assumed that most of the decrease in reflection coefficient occurs in the mucosal capillaries. This lowers the ability of plasma proteins to counteract capillary filtration, with the net result that fluid is added to the interstitial space. Eventually, this fluid must be removed. Not surprisingly, the highest rates of intestinal lymph formation normally occur during fat absorption.

Sympathetic Nerve Activity Can Greatly Decrease Intestinal Blood Flow and Venous Volume

The intestinal vasculature is richly innervated by sympathetic nerve fibers. Major reductions in gastrointestinal blood flow and venous volume occur whenever sympathetic nerve activity is increased, such as during strenuous exercise or periods of pathologically low arterial blood pressure. Venoconstriction in the intestine during hemorrhage helps to mobilize blood and compensates for the blood loss. Gastrointestinal blood flow is about 25% of the cardiac output at rest; a reduction in this blood flow, by heightened sympathetic activity, allows more vital functions to be supported with the available cardiac output. However, gastrointestinal blood flow can be so drastically decreased by a combination of low arterial blood pressure (**hypotension**) and sympathetically mediated vasoconstriction that mucosal tissue damage can result.

HEPATIC CIRCULATION

The hepatic circulation perfuses one of the largest organs in the body, the liver. The liver is primarily an organ that maintains the organic chemical composition of the blood plasma. For example, all plasma proteins are produced by the liver, and the liver adds glucose from stored glycogen to the blood. The liver also removes damaged blood cells and bacteria and detoxifies many man-made or natural organic chemicals that have entered the body.

The Hepatic Circulation Is Perfused by Venous Blood From Gastrointestinal Organs and a Separate Arterial Supply

The human liver has a large blood flow, about 1.5 L/min or 25% of the resting cardiac output. It is perfused by both arterial blood through the **hepatic artery** and venous blood that has passed through the stomach, small intestine, pancreas, spleen, and portions of the large intestine.

The venous blood arrives via the **hepatic portal vein** and accounts for about 67 to 80% of the total liver blood flow (see Table 17.1). The remaining 20 to 33% of the total flow is through the hepatic artery. The majority of blood flow to the liver is determined by the flow through the stomach and small intestine.

About half of the oxygen used by the liver is derived from venous blood, even though the splanchnic organs have removed one third to one half of the available oxygen. The hepatic arterial circulation provides additional oxygen. The liver tissue efficiently extracts oxygen from the blood. The liver has a high metabolic rate and is a large organ; consequently, it has the largest oxygen consumption of all organs in a resting person. The metabolic functions of the liver are discussed in Chapter 28.

The Liver Acinus Is a Complex Microvascular Unit With Mixed Arteriolar and Venular Blood Flow

The liver vasculature is arranged into subunits that allow the arterial and portal blood to mix and provide nutrition for the liver cells. Each subunit, called an **acinus,** is about 300 to 350 μm long and wide. In humans, usually three acini occur together. The core of each acinus is supplied by a single **terminal portal venule**; **sinusoidal capillaries** originate from this venule (Fig. 17.4). The endothelial cells of the capillaries have fenestrated regions with discrete openings that facilitate exchange between the plasma and interstitial spaces. The capillaries do not have a basement membrane, which partially contributes to their high permeability.

The **terminal hepatic arteriole** to each acinus is paired with the terminal portal venule at the acinus core, and blood from the arteriole and blood from the venule jointly perfuse the capillaries. The intermixing of the arterial and portal blood tends to be intermittent because the vascular smooth muscle of the small arteriole alternately constricts and relaxes. This prevents arteriolar pressure from causing a sustained reversed flow in the sinusoidal capillaries, where pressures are 7 to 10 mm Hg. The best evidence is that hepatic artery and portal venous blood first mix at the level of the capillaries in each acinus. The sinusoidal capillaries are drained by the **terminal hepatic venules** at the outer margins of each acinus; usually at least two hepatic venules drain each acinus.

The Regulation of Hepatic Arterial and Portal Venous Blood Flows Requires an Interactive Control System

The regulation of portal venous and hepatic arterial blood flows is an interactive process: Hepatic arterial flow increases and decreases reciprocally with the portal venous blood flow. This mechanism, known as the **hepatic arterial buffer response,** can compensate or buffer about 25% of the decrease or increase in portal blood flow. Exactly how this is accomplished is still under investigation, but vasodilatory metabolite accumulation, possibly adenosine, during decreased portal flow, as well as increased metabolite removal during elevated portal flow, are thought to influence the resistance of the hepatic arterioles.

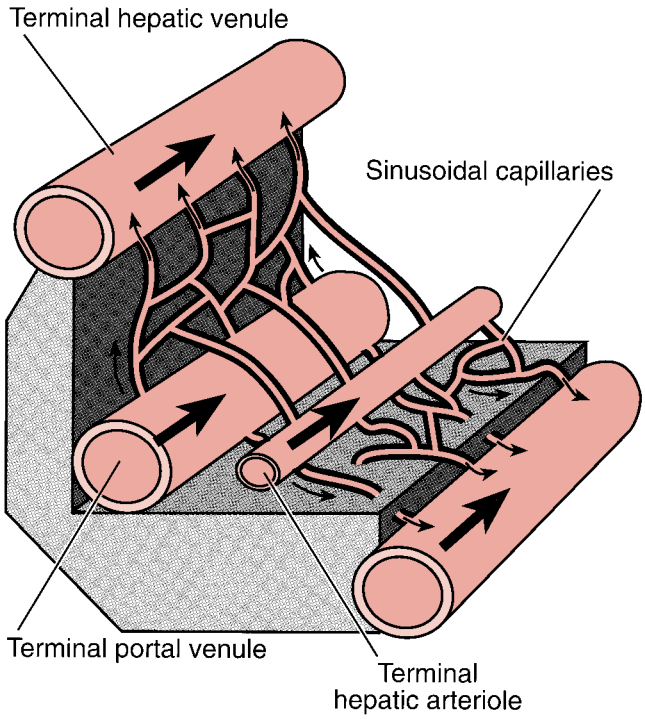

FIGURE 17.4 **Liver acinus microvascular anatomy.** A single liver acinus, the basic subunit of liver structure, is supplied by a terminal portal venule and a terminal hepatic arteriole. The mixture of portal venous and arterial blood occurs in the sinusoidal capillaries formed from the terminal portal venule. Usually two terminal hepatic venules drain the sinusoidal capillaries at the external margins of each acinus.

One might suspect that during digestion, when gastrointestinal blood flow and, therefore, portal venous blood flow are increased, the gastrointestinal hormones in portal venous blood would influence hepatic vascular resistance. However, at concentrations in portal venous blood equivalent to those during digestion, none of the major hormones appears to influence hepatic blood flow. Therefore, the increased hepatic blood flow during digestion would appear to be determined primarily by vascular responses of the gastrointestinal vasculatures.

The vascular resistances of the hepatic arterial and portal venous vasculatures are increased during sympathetic nerve activation, and the buffer mechanism is suppressed. When the sympathetic nervous system is activated, about half the blood volume of the liver can be expelled into the general circulation. Because up to 15% of the total blood volume is in the liver, constriction of the hepatic vasculature can significantly increase the circulating blood volume during times of cardiovascular stress.

SKELETAL MUSCLE CIRCULATION

The circulation of skeletal muscle involves the largest mass of tissue in the body: 30 to 40% of an adult's body weight. At rest, the skeletal muscle vasculature accounts for about 25% of systemic vascular resistance, even though individual muscles receive a low blood flow of about 2 to 6 mL/min

per 100 g. The dominant mechanism controlling skeletal muscle resistance at rest is the sympathetic nervous system. Resting skeletal muscle has remarkably low oxygen consumption per 100 g of tissue, but its large mass makes its metabolic rate a major contributor to the total oxygen consumption in a resting person.

Skeletal Muscle Blood Flow and Metabolism Can Vary Over a Large Range

Skeletal muscle blood flow can increase 10- to 20-fold or more during the maximal vasodilation associated with high-performance aerobic exercise. Comparable increases in metabolic rate occur. Under such circumstances, total muscle blood flow may be equal to three or more times the resting cardiac output; obviously, cardiac output must increase during exercise to maintain the normal to increased arterial pressure (see Chapter 30).

With severe hemorrhage, which activates baroreceptor-induced reflexes, skeletal muscle vascular resistance can easily double as a result of increased sympathetic nerve activity, reducing blood flow. Skeletal muscle cells can survive long periods with minimal oxygen supply; consequently, low blood flow is not a problem. The increased vascular resistance helps preserve arterial blood pressure when cardiac output is compromised. In addition, contraction of the skeletal muscle venules and veins forces blood in these vessels to enter the general circulation and helps restore a depleted blood volume. In effect, the skeletal muscle vasculature can either place major demands on the cardiopulmonary system during exercise or perform as if expendable during a cardiovascular crisis, enabling absolutely essential tissues to be perfused with the available cardiac output.

The Regulation of Muscle Blood Flow Depends on Many Mechanisms to Provide Oxygen for Muscular Contractions

As discussed in Chapter 16, many potential local regulatory mechanisms adjust blood flow to the metabolic needs of the tissues. In fast-twitch muscles, which primarily depend on anaerobic metabolism, the accumulation of hydrogen ions from lactic acid is potentially a major contributor to the vasodilation that occurs. In slow-twitch skeletal muscles, which can easily increase oxidative metabolic requirements by more than 10 to 20 times during heavy exercise, it is not hard to imagine that whatever causes metabolically linked vasodilation is in ample supply at high metabolic rates.

During rhythmic muscle contractions, the blood flow during the relaxation phase can be high, and it is unlikely that the muscle becomes significantly hypoxic during submaximal aerobic exercise. Studies in humans and animals indicate that lactic acid formation, an indication of hypoxia and anaerobic metabolism, is present only during the first several minutes of submaximal exercise. Once the vasodilation and increased blood flow associated with exercise are established, after 1 to 2 minutes, the microvasculature is probably capable of maintaining ample oxygen for most workloads, perhaps up to 75 to 80% of maximum performance because remarkably little additional lactic acid accumulates in the blood. While the tissue oxygen content likely decreases as exercise intensity increases, the reduction does not compromise the high aerobic metabolic rate except with the most demanding forms of exercise. The changes in oxygen tensions before, during, and after a period of muscle contractions in an animal model were illustrated in Figure 16.7.

To ensure the best possible supply of nutrients, particularly oxygen, even mild exercise causes sufficient vasodilation to perfuse virtually all of the capillaries, rather than just 25 to 50% of them, as occurs at rest. However, near-maximum or maximum exercise exhausts the ability of the microvasculature to meet tissue oxygen needs and hypoxic conditions rapidly develop, limiting the performance of the muscles. The burning sensation and muscle fatigue during maximum exercise or at any time muscle blood flow is inadequate to provide adequate oxygen is partially a consequence of hypoxia. This type of burning sensation is particularly evident when a muscle must hold a weight in a steady position. In this situation, the contraction of the muscle compresses the microvessels, stopping the blood flow and, with it, the availability of oxygen.

The vasodilation associated with exercise is dependent upon NO. However, exactly which chemicals released or consumed by skeletal muscle induce the increased release of NO from endothelial cells is unknown. In addition, skeletal muscle cells can make NO and, although not yet tested, may produce a substantial fraction of the NO that causes the dilation of the arterioles. If endothelial production of NO is curtailed by the inhibition of endothelial nitric oxide synthase, the increased muscle blood flow during contractions is strongly suppressed. However, there is concern that the resting vasoconstriction caused by suppressed NO formation diminishes the ability of the vasculature to dilate in response a variety of mechanisms. Flow-mediated vasodilation, for example, appears to be used to dilate smaller arteries and larger arterioles to maximize the increase in blood flow initiated by the dilation of smaller arterioles in contact with active skeletal muscle cells. Studies in animals indicate these vessels make a major contribution to vascular regulation in skeletal muscle and must be participants in any significant increase in blood flow.

DERMAL CIRCULATION

The Skin Has a Microvascular Anatomy to Support Tissue Metabolism and Heat Dissipation

The structure of the skin vasculature differs according to location in the body. In all areas, an arcade of arterioles exists at the boundary of the dermis and the subcutaneous tissue over fatty tissues and skeletal muscles (Fig. 17.5). From this arteriolar arcade, arterioles ascend through the dermis into the superficial layers of the dermis, adjacent to the epidermal layers. These arterioles form a second network in the superficial dermal tissue and perfuse the extensive capillary loops that extend upward into the dermal papillae just beneath the epidermis.

The dermal vasculature also provides the vessels that surround hair follicles, sebaceous glands, and sweat glands.

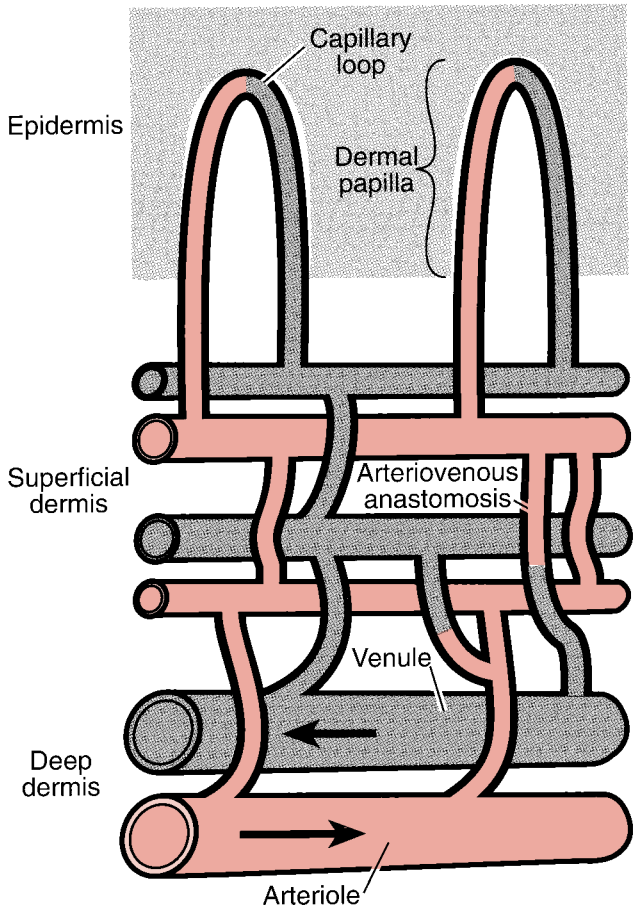

FIGURE 17.5 **The vasculature of the skin.** The skin vasculature is composed of a network of large arterioles and venules in the deep dermis, which send branches to the superficial network of smaller arterioles and venules. Arteriovenous anastomoses allow direct flow from arterioles to venules and greatly increase blood flow when dilated. The capillary loops into the dermal papillae beneath the epidermis are supplied and drained by microvessels of the superficial dermal vasculature.

Sweat glands derive virtually all sweat water from blood plasma and are surrounded by a dense capillary network in the deeper layers of the dermis. As explained in Chapter 29, neural regulation of the sweating mechanism not only causes the formation of sweat but also substantially increases skin blood flow. All the capillaries from the superficial skin layers are drained by venules, which form a venous plexus in the superficial dermis and eventually drain into many large venules and small veins beneath the dermis.

The vascular pattern just described is modified in the tissues of the hand, feet, ears, nose, and some areas of the face in that direct vascular connections between arterioles and venules, known as **arteriovenous anastomoses,** occur primarily in the superficial dermal tissues (see Fig. 17.5). By contrast, relatively few arteriovenous anastomoses exist in the major portion of human skin over the limbs and torso. If a great amount of heat must be dissipated, dilation of the arteriovenous anastomoses allows substantially increased skin blood flow to warm the skin, thereby increasing heat loss to the environment. This allows vasculatures of the hands and feet and, to a lesser extent, the face, neck, and ears to lose heat efficiently in a warm environment.

Skin Blood Flow Is Important in Body Temperature Regulation

The skin is a large organ, representing 10 to 15% of total body mass. The primary functions of the skin are protection of the body from the external environment and dissipation or conservation of heat during body temperature regulation.

The skin has one of the lowest metabolic rates in the body and requires relatively little blood flow for purely nutritive functions. Consequently, despite its large mass, its resting metabolism does not place a major flow demand on the cardiovascular system. However, in warm climates, body temperature regulation requires that warm blood from the body core be carried to the external surface, where heat transfer to the environment can occur. Therefore, at typical indoor temperatures and during warm weather, skin blood flow is usually far in excess of the need for tissue nutrition. The reddish color of the skin during exercise in a warm environment reflects the large blood flow and dilation of skin arterioles and venules (see Table 17.1).

The increase in the skin's blood flow probably occurs through two main mechanisms. First, an increase in body core temperature causes a reflex increase in the activity of sympathetic cholinergic nerves, which release acetylcholine. Acetylcholine release near sweat glands leads to the breakdown of a plasma protein (kininogen) to form bradykinin, a potent dilator of skin blood vessels, which increases the release of NO as a major component of the dilatory mechanism. Second, simply increasing skin temperature will cause the blood vessels to dilate. This can result from heat applied to the skin from the external environment, heat from underlying active skeletal muscle, or increased blood temperature as it enters the skin.

Total skin blood flows of 5 to 8 L/min have been estimated in humans during vigorous exercise in a hot environment. During mild to moderate exercise in a warm environment, skin blood flow can equal or exceed blood flow to the skeletal muscles. Exercise tolerance can, therefore, be lower in a warm environment because the vascular resistance of the skin and muscle is too low to maintain an appropriate arterial blood pressure, even at maximum cardiac output. One of the adaptations to exercise is an ability to increase blood flow in skin and dissipate more heat. In addition, aerobically trained humans are capable of higher sweat production rates; this increases heat loss and induces greater vasodilation of the skin arterioles.

The vast majority of humans live in cool to cold regions, where body heat conservation is imperative. The sensation of cool or cold skin, or a lowered body core temperature, elicits a reflex increase in sympathetic nerve activity, which causes vasoconstriction of blood vessels in the skin. Heat loss is minimized because the skin becomes a poorly perfused insulator, rather than a heat dissipator. As long as the skin temperature is higher than about 10 to 13°C (50 to 55°F), the neurally induced vasoconstriction is sustained. However, at lower tissue temperatures, the vascular smooth muscle cells progressively lose their contractile ability, and the vessels

passively dilate to various extents. The reddish color of the hands, face, and ears on a cold day demonstrates increased blood flow and vasodilation as a result of low temperatures. To some extent, this cold-mediated vasodilation is useful because it lessens the chance of cold injury to exposed skin. However, if this process included most of the body surface, such as occurs when the body is submerged in cold water or inadequate clothing is worn, heat loss would be rapid and hypothermia would result. (Chapter 29 discusses skin blood flow and temperature regulation.)

FETAL AND PLACENTAL CIRCULATIONS

The Placenta Has Maternal and Fetal Circulations That Allow Exchange Between the Mother and Fetus

The development of a human fetus depends on nutrient, gas, water, and waste exchange in the maternal and fetal portions of the placenta. The human **fetal placenta** is supplied by two **umbilical arteries**, which branch from the internal iliac arteries, and is drained by a single **umbilical vein** (Fig. 17.6). The umbilical vein of the fetus returns oxygen and nutrients from the mother's body to the fetal cardiovascular system, and the umbilical arteries bring in blood laden with carbon dioxide and waste products to be transferred to the mother's blood. Although many liters of oxygen and carbon dioxide, together with hundreds of grams of nutrients and wastes, are exchanged between the mother and fetus each day, the exchange of red blood cells or white blood cells is a rare event. This large chemical exchange without cellular exchange is possible because the fetal and maternal blood are kept completely separate, or nearly so.

The fundamental anatomical and physiological structure for exchange is the **placental villus**. As the umbilical arteries enter the fetal placenta, they divide into many branches that penetrate the placenta toward the maternal system. These small arteries divide in a pattern similar to a fir tree, the placental villi being the small branches. The fetal capillaries bring in the fetal blood from the umbilical arteries

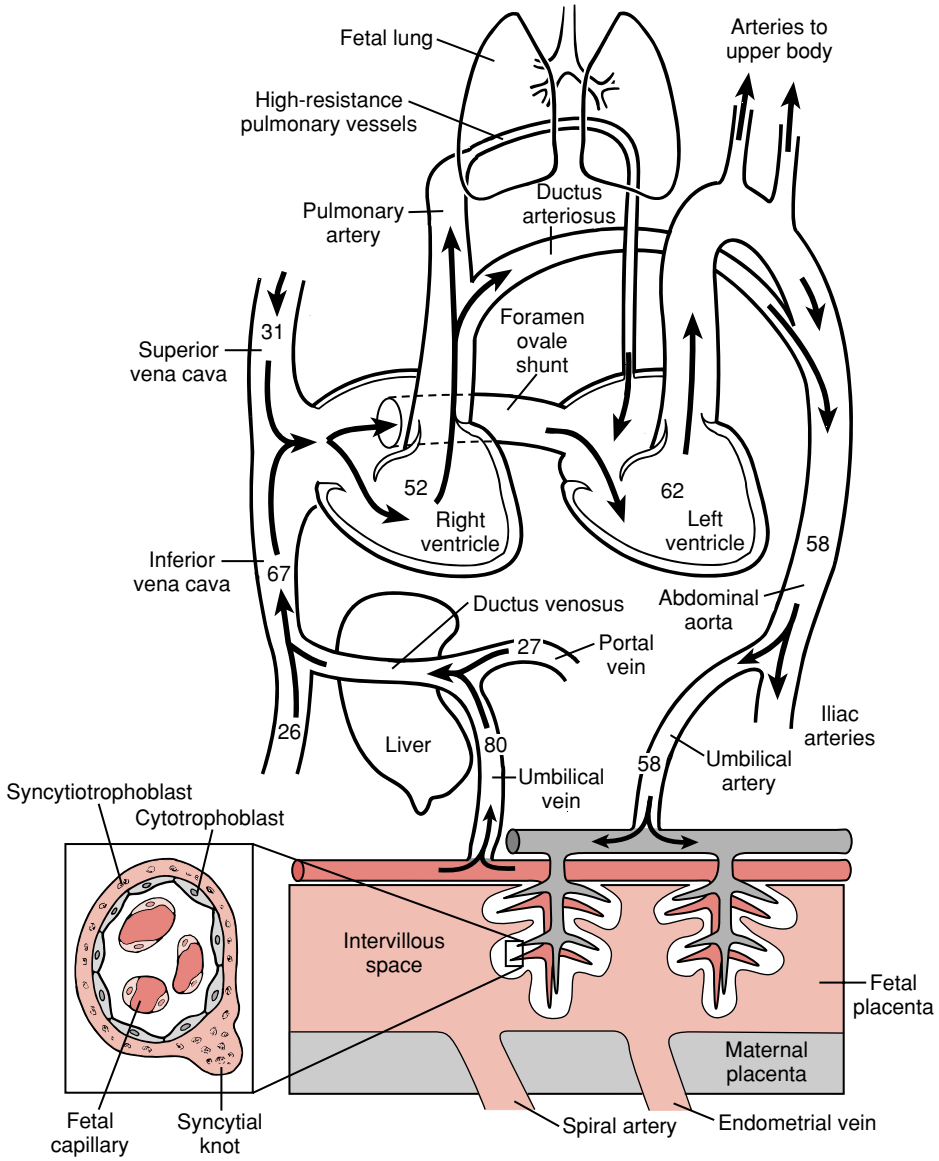

FIGURE 17.6 The fetal and placental circulations. Schematic representation of the left and right sides of the fetal heart are separated to emphasize the right-to-left shunt of blood through the open foramen ovale in the atrial septum and the right-to-left shunt through the ductus arteriosus. Arrows indicate the direction of blood flow. The numbers represent the percentage of saturation of blood hemoglobin with oxygen in the fetal circulation. Closure of the ductus venosus, foramen ovale, ductus arteriosus, and placental vessels at birth and the dilation of the pulmonary vasculature establish the adult circulation pattern. The insert is a cross-sectional view of a fetal placental villus, one of the branches of the tree-like fetal vascular system in the placenta. The fetal capillaries provide incoming blood, and the sinusoidal capillaries act as the venous drainage. The villus is completely surrounded by the maternal blood, and the exchange of nutrients and wastes occurs across the fetal syncytiotrophoblast.

and then blood leaves through sinusoidal capillaries to the umbilical venous system. Exchange occurs in the fetal capillaries and probably to some extent in the sinusoidal capillaries. The mother's vascular system forms a reservoir around the tree-like structure such that her blood envelops the placental villi.

As shown in Figure 17.6, the outermost layer of the placental villus is the **syncytiotrophoblast**, where exchange by passive diffusion, facilitated diffusion, and active transport between fetus and mother occurs through fully differentiated epithelial cells. The underlying **cytotrophoblast** is composed of less differentiated cells, which can form additional syncytiotrophoblast cells as required. As cells of the syncytiotrophoblast die, they form **syncytial knots**, and eventually these break off into the mother's blood system surrounding the fetal placental villi.

The placental vasculature of both the fetus and the mother adapt to the size of the fetus, as well as to the oxygen available within the maternal blood. For example, a minimal placental vascular anatomy will provide for a small fetus, but as the fetus develops and grows, a complex tree of placental vessels is essential to provide the surface area needed for the fetal-maternal exchange of gases, nutrients, and wastes. If the mother moves to a higher altitude where less oxygen is available, the complexity of the placental vascular tree increases, compensating with additional areas for exchange. If this type of adaptation does not take place, the fetus may be underdeveloped or die from a lack of oxygen.

During fetal development, the fetal tissues invade and cause partial degeneration of the maternal endometrial lining of the uterus. The result, after about 10 to 16 weeks gestation, is an **intervillous space** between fetal placental villi that is filled with maternal blood. Instead of microvessels, there is a cavernous blood-filled space. The intervillous space is supplied by 100 to 200 **spiral arteries** of the maternal endometrium and is drained by the **endometrial veins.** During gestation, the spiral arteries enlarge in diameter and simultaneously lose their vascular smooth muscle layer—it is the arteries preceding them that actually regulate blood flow through the placenta. At the end of gestation, the total maternal blood flow to the intervillous space is approximately 600 to 1,000 mL/min, which represents about 15 to 25% of the resting cardiac output. In comparison, the fetal placenta has a blood flow of about 600 mL/min, which represents about 50% of the fetal cardiac output.

The exchange of materials across the syncytiotrophoblast layer follows the typical pattern for all cells. Gases, primarily oxygen and carbon dioxide, and nutrient lipids move by simple diffusion from the site of highest concentration to the site of lowest concentration. Small ions are moved predominately by active transport processes. Glucose is passively transferred by the GLUT 1 transport protein, and amino acids require primarily facilitated diffusion through specific carrier proteins in the cell membranes, such as the system A transporter protein.

Large-molecular-weight peptides and proteins and many large, charged, water-soluble molecules used in pharmacological treatments do not readily cross the placenta. Part of the transfer of large molecules probably occurs between the cells of the syncytiotrophoblast layer and by pinocytosis and exocytosis. Lipid-soluble molecules diffuse through the lipid bilayer of cell membranes. For example, lipid-soluble anesthetic agents in the mother's blood do enter and depress the fetus. As a consequence, anesthesia during pregnancy is somewhat risky for the fetus.

The Placental Vasculature Permits Efficient Exchanges of O_2 and CO_2

Special fetal adaptations are required for gas exchange, particularly oxygen, because of the limitations of passive exchange across the placenta. The P_{O2} of maternal arterial blood is about 80 to 100 mm Hg and about 20 to 25 mm Hg in the incoming blood in the umbilical artery. This difference in oxygen tension provides a large driving force for exchange; the result is an increase in the fetal blood P_{O2} to 30 to 35 mm Hg in the umbilical vein. Fortunately, **fetal hemoglobin** carries more oxygen at a low P_{O2} than adult hemoglobin carries at a P_{O2} 2 to 3 times higher. In addition, the concentration of hemoglobin in fetal blood is about 20% higher than in adult blood. The net result is that the fetus has sufficient oxygen to support its metabolism and growth but does so at low oxygen tensions, using the unique properties of fetal hemoglobin. After birth, when much more efficient oxygen exchange occurs in the lung, the newborn gradually replaces the red cells containing fetal hemoglobin with red cells containing adult hemoglobin.

The Absence of Lung Ventilation Requires a Unique Circulation Through the Fetal Heart and Body

After the umbilical vein leaves the fetal placenta, it passes through the abdominal wall at the future site of the umbilicus (navel). The umbilical vein enters the liver's portal venous circulation, although the bulk of the oxygenated venous blood passes directly through the liver in the **ductus venosus** (see Fig. 17.6). The low-oxygen-content venous blood from the lower body and the high-oxygen-content placental venous blood mix in the inferior vena cava. The oxygen content of the blood returning from the lower body is about twice that of venous blood returning from the upper body in the superior vena cava. The two streams of blood from the superior and inferior vena cavae do not completely mix as they enter the right atrium. The net result is that oxygen-rich blood from the inferior vena cava passes through the open **foramen ovale** in the atrial septum to the left atrium, while the upper-body blood generally enters the right ventricle as in the adult. The preferential passage of oxygenated venous blood into the left atrium and the minimal amount of venous blood returning from the lungs to the left atrium allow blood in the left ventricle to have an oxygen content about 20% higher than that in the right ventricle. This relatively high-oxygen-content blood supplies the coronary vasculature, the head, and the brain.

The right ventricle actually pumps at least twice as much blood as the left ventricle during fetal life. In fact, the infant at birth has a relatively much more muscular right ventricular wall than the adult. Perfusion of the collapsed lungs of the fetus is minimal because the pulmonary vasculature has

a high resistance. The elevated pulmonary resistance occurs because the lungs are not inflated and probably because the pulmonary vasculature has the unusual characteristic of vasoconstriction at low oxygen tensions. The right ventricle pumps blood into the systemic arterial circulation via a shunt—the **ductus arteriosus**—between the pulmonary artery and aorta (see Fig. 17.6). For ductus arteriosus blood to enter the initial part of the descending aorta, the right ventricle must develop a higher pressure than the left ventricle—the exact opposite of circumstances in the adult. The blood in the descending aorta has less oxygen content than that in the left ventricle and ascending aorta because of the mixture of less well-oxygenated blood from the right ventricle. This difference is crucial because about two thirds of this blood must be used to perfuse the placenta and pick up additional oxygen. In this situation, a lack of oxygen content is useful.

The Transition From Fetal to Neonatal Life Involves a Complex Sequence of Cardiovascular Events

After the newborn is delivered and the initial ventilatory movements cause the lungs to expand with air, pulmonary vascular resistance decreases substantially, as does pulmonary arterial pressure. At this point, the right ventricle can perfuse the lungs, and the circulation pattern in the newborn switches to that of an adult. In time, the reduced workload on the right ventricle causes its hypertrophy to subside.

The highly perfused, ventilated lungs allow a large amount of oxygen-rich blood to enter the left atrium. The increased oxygen tension in the aortic blood may provide the signal for closure of the ductus arteriosus, although suppression of vasodilator prostaglandins cannot be discounted. In any event, the ductus arteriosus constricts to virtual closure and over time becomes anatomically fused. Simultaneously, the increased oxygen to the peripheral tissues causes constriction in most body organs, and the sympathetic nervous system also stimulates the peripheral arterioles to constrict. The net result is that the left ventricle now pumps against a higher resistance. The combination of greater resistance and higher blood flow raises the arterial pressure and, in doing so, increases the mechanical load on the left ventricle. Over time, the left ventricle hypertrophies.

During all the processes just described, the open foramen ovale must be sealed to prevent blood flow from the left to right atrium. Left atrial pressure increases from the returning blood from the lungs and exceeds right atrial pressure. This pressure difference passively pushes the tissue flap on the left side of the foramen ovale against the open atrial septum. In time, the tissues of the atrial septum fuse; however, an anatomic passage that is probably only passively sealed can be documented in some adults. The ductus venosus in the liver is open for several days after birth but gradually closes and is obliterated within 2 to 3 months.

After the fetus begins breathing, the fetal placental vessels and umbilical vessels undergo progressive vasoconstriction to force placental blood into the fetal body, minimizing the possibility of fetal hemorrhage through the placental vessels. Vasoconstriction is related to increased oxygen availability and less of a signal for vasodilator chemicals and prostaglandins in the fetal tissue.

The final event of gestation is separation of the fetal and maternal placenta as a unit from the lining of the uterus. The separation process begins almost immediately after the fetus is expelled, but external delivery of the placenta can require up to 30 minutes. The separation occurs along the **decidua spongiosa,** a maternal structure, and requires that blood flow in the mother's spiral arteries be stopped. The cause of the placental separation may be mechanical, as the uterus surface area is greatly reduced by removal of the fetus and folds away from the uterine lining. Normally about 500 to 600 mL of maternal blood are lost in the process of placental separation. However, as maternal blood volume increases 1,000 to 1,500 mL during gestation, this blood loss is not of significant concern.

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.

1. Which of the following would be an expected response by the coronary vasculature?
   (A) Increased blood flow when the heart workload is increased
   (B) Increased vascular resistance when the arterial blood pressure is increased
   (C) Decreased blood flow when mean arterial pressure is reduced from 90 to 60 mm Hg by hemorrhage
   (D) Decreased blood flow when blood oxygen content is reduced
   (E) Increased vascular resistance during aerobic exercise
2. The intestinal blood flow during food digestion primarily increases because of
   (A) Decreased sympathetic nervous system activity on intestinal arterioles
   (B) Myogenic vasodilation associated with reduced arterial pressure after meals
   (C) Tissue hypertonicity and the release of nitric oxide onto the arterioles
   (D) Blood flow-mediated dilation by the major arteries of the abdominal cavity
   (E) Increased parasympathetic nervous system activity associated with food absorption
3. Incoming arterial and portal venous blood mix in the liver
   (A) As the hepatic artery and portal vein first enter the tissue
   (B) In large arterioles and portal venules
   (C) In the liver acinus capillaries
   (D) In the terminal hepatic venules
   (E) In the outflow venules of the liver
4. As arterial pressure is raised and lowered during the course of a day, blood flow through the brain would be expected to
   (A) Change in the same direction as the arterial blood pressure because of the limited autoregulatory ability of the cerebral vessels
   (B) Change in a direction opposite the change in mean arterial pressure

(continued)

(C) Remain about constant because cerebral vascular resistance changes in the same direction as arterial pressure
(D) Fluctuate widely, as both arterial pressure and brain neural activity status change
(E) Remain about constant because the cerebral vascular resistance changes in the opposite direction to the arterial pressure

5. Which of the following special circulations has the widest range of blood flows as part of its contributions to both the regulation of systemic vascular resistance and the modification of resistance to suit the organ's metabolic needs?
(A) Coronary
(B) Cerebral
(C) Small intestine
(D) Skeletal muscle
(E) Dermal

6. Which of the following sequences is a possible anatomic path for a red blood cell passing through a fetus and back to the placenta? (Some intervening structures are not included.)
(A) Umbilical vein, right ventricle, ductus arteriosus, pulmonary artery
(B) Ductus venosus, foramen ovale, right ventricle, ascending aorta
(C) Spiral artery, umbilical vein, left ventricle, umbilical artery
(D) Right ventricle, ductus arteriosus, descending aorta, umbilical artery
(E) Left ventricle, ductus arteriosus, pulmonary artery, left atrium

7. How does chronic hypertension affect the range of arterial pressure over which the cerebral circulation can maintain relatively constant blood flow?
(A) Very little change occurs
(B) The vasculature primarily adapts to higher arterial pressure
(C) The vasculature primarily loses regulation at low arterial pressure
(D) The entire range of regulation shifts to higher pressures
(E) The entire range of regulation shifts to lower pressures

8. Why is the oxygen content of blood sent to the upper body during fetal life higher than that sent to the lower body?
(A) Blood oxygenated in the fetal lungs enters the left ventricle
(B) Oxygenated blood passes through the foramen ovale to the left ventricle
(C) The upper body is perfused by the ductus arteriosus blood flow
(D) The heart takes less of the oxygen from the blood in the left ventricle
(E) The right ventricular stroke volume is greater than that of the left ventricle

SUGGESTED READING

Bohlen HG. Integration of intestinal structure, function and microvascular regulation. Microcirculation 1998;5:27–37.
Bohlen HG, Maass-Moreno R, Rothe CF. Hepatic venular pressures of rats, dogs, and rabbits. Am J Physiol 1991;261:G539–G547.
Delp MD, Laughlin MH. Regulation of skeletal muscle perfusion during exercise. Acta Physiol Scand 1998;162:411–419.
Fiegl EO. Neural control of coronary blood flow. J Vasc Res 1998;35:85-92.
Johnson JM. Physical training and the control of skin blood flow. Med Sci Sports Exerc 1998;30:382–386.
Golding EM, Robertson CS, Bryan RM. The consequences of traumatic brain injury on cerebral blood flow and autoregulation: A review. Clin Exp Hypertens 1999;21:229–332.