**SYSTEMIC OXYGEN SUPPLY AND DEMAND**

**Oxygen Content**

Oxygen content and oxygen delivery are important concepts in understanding and treating critical illness. Oxygen content in blood \( \text{Ca}_{\text{O}_2} \) (expressed as milliliters of oxygen per 100 mL of blood) can be defined as the oxygen bound to hemoglobin (Hb) plus the oxygen dissolved in the blood. The total content can be calculated by the following equation:

\[
\text{Ca}_{\text{O}_2} = (\text{Oxygen Bound to Hemoglobin}) + (\text{Oxygen Dissolved in Blood})
\]

or

\[
\text{Ca}_{\text{O}_2} = (1.36 \times \text{Hb} \times \text{Sa}_{\text{O}_2}) + (\text{Pa}_{\text{O}_2} \times 0.003),
\]

where 1.36 is a constant, Hb is hemoglobin (g/dL), \( \text{Sa}_{\text{O}_2} \) is the oxygen saturation, and \( \text{Pa}_{\text{O}_2} \) is the \( \text{P}_{\text{O}_2} \) obtained from an arterial blood specimen. Notice that the main determinant of oxygen content in the blood is the oxygen bound to hemoglobin. Therefore, the oxygen content can be estimated by ignoring the dissolved component in situations that entail normally functioning hemoglobin. The dissolved oxygen in the blood plays a much greater role and may contribute significantly to oxygen content.

**Oxygen Delivery and Consumption**

The oxygen in the blood must be delivered to the tissues for utilization. Oxygen delivery \( \text{Do}_{\text{O}_2} \) (expressed as mL/min) is the product of \( \text{Ca}_{\text{O}_2} \) and systemic blood flow, which is equivalent to cardiac output, except in patients with certain cardiac malformations. The equation for \( \text{Do}_{\text{O}_2} \) is

\[
\text{Do}_{\text{O}_2} = 10 \times \text{CO} \times \text{Ca}_{\text{O}_2},
\]

where \( \text{CO} \) is cardiac output (in L/min or L/min/m²) and \( \text{Ca}_{\text{O}_2} \) is the oxygen content calculated from the previous equation. The conversion factor of 10 converts the units from mL/dL to mL/min.

Under normal physiologic conditions, the delivery of oxygen exceeds oxygen consumption \( (\dot{V}_{\text{O}_2}) \) by a ratio of 5:1. Decreased oxygen transport can be tolerated because of the ability to increase extraction. When the ratio of delivery to consumption \( (\text{Do}_{\text{O}_2}/\dot{V}_{\text{O}_2}) \) falls below 2:1, oxygen supply is limited. As a result, tissue hypoxia occurs along with a change from aerobic to anaerobic metabolism, resulting in lactate production. Aerobic metabolism can also be termed supply-independent oxygen consumption, as noted in Figure 2. As oxygen delivery decreases, there is a critical point at which supply-dependent transport exists. Below this point, the tissues undergo anaerobic metabolism resulting in an “oxygen debt.” To overcome the oxygen debt, oxygen delivery must be increased by either increased blood flow or increased oxygen content.

Many factors increase oxygen consumption. Any increase in metabolic rate increases oxygen consumption. Infection, inflammation, increases in temperature, exogenous or endogenous catecholamines, and exercise are all associated with increased oxygen consumption. An increase in metabolism must result in increased oxygen delivery, extraction, or both. Otherwise, an oxygen debt will occur.

Chronic hypoxia, as occurs at high altitudes, induces changes necessary to maintain long-term oxygen delivery. For example, chronic hypoxia entails decreased muscle mass without a reduction in the number of capillaries, resulting in an increased ratio of capillaries to muscle mass. Chronic hypoxia induces increased hemoglobin dissociation production, resulting in increased oxygen-carrying capacity along with a rightward shift of the oxyhemoglobin curve (decreased affinity). Chronic hypoxia also results in increased pulmonary ventilation and increased cardiac output to maximize oxygen delivery.
Indicators of Oxygen Delivery

Fick Principle and Mixed Venous Saturations

One of the gold standards for monitoring adequacy of oxygen delivery is the Fick method. According to the Fick principle, cardiac output (CO) can be calculated as

$$\text{CO} = \frac{\dot{V}_\text{o}_2}{\text{Ca}_\text{o}_2 - \text{Cv}_\text{o}_2},$$

where $\dot{V}_\text{o}_2$ is oxygen consumption and $\text{Ca}_\text{o}_2$ and $\text{Cv}_\text{o}_2$ are the arterial and venous oxygen content, respectively. The arterial oxygen content is easily calculated by using saturations from a pulse oximeter. The venous saturation, used to calculate venous oxygen content, is best measured by sampling blood from the pulmonary artery. In most clinical situations, a catheter in the superior vena cava is used to determine the approximate pulmonary artery venous saturation. If the catheter is located in the right atrium, sampling blood preferentially from the coronary sinus must be avoided as the saturations of blood from the coronary sinus are 30% to 37%, yielding inaccurate results. No matter the source of the blood sampled, serial measurements may be obtained and used to guide therapy.

The mixed venous saturation will decrease when oxygen delivery decreases or oxygen consumption increases. Without abnormal intracardiac mixing, mixed venous saturations are about 25% less than the systemic arterial saturations, with normal values of 65% to 75%.

Lactate

A seemingly simple measurement of adequacy of oxygen delivery is the acid-base status of the patient. As hypoxia occurs, anaerobic metabolism ensues, which increases hydrogen ions, lactate, and carbon dioxide. The anion gap is the measurement of unmeasured serum cations and can provide useful information about the cause of the acidosis. If the anion gap is normal, the acidosis usually occurs because of bicarbonate loss from the kidneys or gastrointestinal tract or because of exogenous acid infusion. If the anion gap is increased, lactate is a potential cause. Serum lactate assays are clinically available and can be used to measure lactic acid levels in patients as an indicator of anaerobic metabolism. However, blood lactate concentrations can be artificially increased because of impaired clearance and may not reflect ongoing tissue hypoxia. Another cause of increased lactate is inability of cells to use available oxygen, termed tissue dysoxia. Dysoxia occurs at the mitochondrial level and is seen in the face of normal oxygen delivery, such as occurs in sepsis or multiple-organ failure.

Near-Infrared Spectroscopy

Another newer device for monitoring the adequacy of oxygen delivery and utilization is near-infrared spectroscopy. In theory, the infrared wavelength of light allows for deep tissue penetration, and the monitoring device provides a calculated venous saturation of the tissue being monitored. The use of near-infrared spectroscopy is increasing, and clinical applications and data supporting its utility continue to increase as well. Near-infrared spectroscopy monitoring provides a surrogate for tissue-specific venous oxygen
saturations, which has been shown to be useful in a number of clinical scenarios.

**Tonometry**

Tonometry is used to monitor tissue perfusion. The 2 types of tonometry most commonly used are gastric and sublingual. The principle behind tonometry involves the ability of carbon dioxide to pass freely between tissues. Placing a carbon dioxide–permeable balloon allows for measurement of carbon dioxide. As hypoperfusion occurs, carbon dioxide will increase, and when compared with carbon dioxide in the blood, it can be used to quantify the degree of hypoperfusion.

**REGIONAL CIRCULATIONS: LOCAL REGULATIONS AND MODULATION OF REGIONAL BLOOD FLOW**

**Blood Flow and Perfusion**

Blood flows from the large arteries to the arterioles to the capillaries. At the junction of the arteriole and the capillary is a band of smooth muscle called the precapillary sphincter. Capillaries are made up of endothelial cells, 1 layer thick. Blood flow through the capillaries is regulated by contraction and relaxation of the arteriolar smooth muscle and the precapillary sphincter.

**Fluid Mechanics of Blood Flow**

Velocity of blood flow can be expressed by the following equation:

\[ V = Q/A, \]

where \( V \) is velocity (cm/s), \( Q \) is blood flow, and \( A \) is the cross-sectional area. Therefore, velocity of blood flow is directly proportional to blood flow and inversely proportional to the cross-sectional area at any level of the cardiovascular system. For example, blood velocity is higher in the aorta than in the sum of the capillaries, optimizing transit time in the capillary for gas exchange. Blood flow to an organ can be expressed as

\[ Q = \frac{\Delta P}{R}, \]

where \( Q \) is blood flow, \( \Delta P \) is the change in pressure, and \( R \) is resistance. The above equation is derived from Ohm’s law \( (V = I \times R) \). The equation can be further simplified to

**Cardiac Output**

\[
\text{Cardiac Output} = \frac{\text{Mean Arterial Pressure} - \text{Right Atrial Pressure}}{\text{Total Peripheral Resistance}}
\]

In this equation, the pressure gradient drives blood flow from high pressure to low pressure. Blood flow is inversely proportional to the resistance of the blood vessels, termed total peripheral resistance. With respect to resistance, Poiseuille’s law provides factors that change resistance. The equation for resistance is

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

where \( R \) is resistance, \( \eta \) is a viscosity constant, \( l \) is the length of the vessel, and \( r \) is radius. Therefore, resistance is directly proportional to the viscosity of the fluid and the length of the vessel and is inversely proportional to the radius of the vessel. Note that if the radius of the vessel decreases by a factor of 2, the resistance increases by a factor of 16.

Resistance can be calculated depending on whether it is in series or parallel circulation. For example, parallel resistance is illustrated by the systemic circulation. Therefore, the total peripheral resistance \((R)\) is

\[
\frac{1}{R_{\text{total}}} = \frac{1}{R_{\text{artery}}} + \frac{1}{R_{\text{arterioles}}} + \frac{1}{R_{\text{capillaries}}} + \frac{1}{R_{\text{veins}}}.
\]

Conversely, series resistance is illustrated by the arrangement in any given organ, where

\[
R_{\text{total}} = R_{\text{artery}} + R_{\text{arterioles}} + R_{\text{capillaries}} + R_{\text{veins}}.
\]

The flow pattern, whether laminar or turbulent, is another variable that can affect flow dynamics. The Reynolds number predicts whether blood flow will be turbulent or laminar, and higher Reynolds numbers are consistent with turbulent flow. The Reynolds number can be increased in blood due to decreased viscosity (anemia, hemodilution) or increased blood velocity (increased cardiac output or stenosis).

Cardiac and vascular volume curves can be created to help understand the above equations and to display the complex relationships among resistance, flow, and cardiac output. These principles are well described in Chapter 1.

**Autoregulation**

Autoregulation provides a constant blood flow to an organ over a wide range of perfusion pressures. Figure 3 depicts cerebral autoregulation. However, the concept is the
same in other tissues exhibiting autoregulation. Without autoregulation, there would be a linear increase in organ blood flow as blood pressure increases. Autoregulation subsequently causes local vasoconstriction, returning organ blood flow to normal. Autoregulation is influenced by many different factors, including neural, hormonal, and hypoxic mechanisms.

**Figure 3. Autoregulation of cerebral blood flow**


Autoregulation preserves blood flow to vital organs and is generally regulated by coupling mechanisms related to local oxygen demand.

**Hormonal Control of Regional Blood Flow**

Histamine can be released locally causing arteriolar vasodilation and venous vasoconstriction, depending upon the tissue on which it is acting. The end result is increased local edema. Bradykinin can be released, causing arteriolar vasodilation and increased capillary permeability. Serotonin causes arteriolar vasoconstriction and is released in response to local injury. Another influence on blood flow is the renin–angiotensin–aldosterone system. The renin–angiotensin–aldosterone system is a slower hormonal system compared with neural control (baroreceptor) reflexes. Renin is an enzyme that catalyzes the conversion of angiotensinogen to angiotensin in the blood. Angiotensin I is biologically inactive. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme. The primary site of this conversion is the lung. Angiotensin II is physiologically active and causes release of aldosterone from the adrenal cortex, resulting in arteriolar vasoconstriction. Aldosterone also increases the reabsorption of sodium and water in the distal tubule of the kidney. This results in increased blood volume and increased blood pressure.

Other humoral agents playing a role in regional blood flow include epinephrine, norepinephrine, and antidiuretic hormone. Epinephrine and norepinephrine can act locally (by direct sympathetic stimulation) or by circulating control (when released by the adrenal medulla). Both of these hormones stimulate the heart and smooth muscle, ultimately increasing blood pressure. Epinephrine results in vasodilation by stimulation of the β receptors in the coronary arteries, resulting in increased coronary blood flow. Antidiuretic hormone is produced in the hypothalamus and released from the posterior pituitary in situations that entail an increase in plasma osmolarity or decreases in blood pressure or blood volume. Vasopressin (an exogenous form of antidiuretic hormone) causes vascular smooth muscle contraction through the V₁ receptors, resulting in decreased blood flow to the gastrointestinal tract, corona ries, and brain.

**Hypoxia, pH, and Regional Blood Flow**

Hypoxia and pH play an important role in tissue perfusion. Hypoxia causes increased pulmonary vascular resistance and decreased systemic vascular resistance. Hypoxia leads to release of lactate and hydrogen ions, which in turn causes acute vasodilation to increase oxygen delivery to the tissues. This dilation “washes out” the lactate and hydrogen ions, returning their concentrations back toward normal and thus facilitating a return to normal levels of perfusion. Alkalosis (an increase in pH) causes arteriolar vasoconstriction and decreases blood flow through the tissues. This same mechanism is clinically useful for decreasing cerebral blood volume when acute hyperventilation drives down PaCO₂, resulting in a respiratory alkalosis and decreased intracranial blood flow and therefore lowering intracranial pressure. Whereas the cerebral vasculature vasodilates under high PaCO₂, the opposite occurs in the pulmonary vascular bed; hypoventilation and higher levels of PaCO₂ lead to pulmonary vasoconstriction and a reduction in pulmonary blood flow. This phenomenon is useful in the management of single-ventricle patients with excessive pulmonary blood flow, where hypoventilation can improve the ratio of systemic to pulmonary blood flow.

**Endothelial-Derived Factors and Inflammatory Mediators**

The most important of the endothelial-derived relaxing factors is nitric oxide. Nitric oxide is a lipophilic gas that is released from endothelial cells in response to a variety of triggers. Nitric oxide is synthesized by nitric oxide
synthase from arginine and oxygen by the reduction of inorganic nitrate. After diffusing out of the cell, nitric oxide has a very short half-life, degrading in a matter of seconds. Therefore, nitric oxide’s site of action is in the local tissues. Nitric oxide activates guanylate cyclase in vascular smooth muscle cells, resulting in conversion of cyclic guanosine triphosphate (cGTP) to cyclic guanosine monophosphate (cGMP) and activation of cGMP-dependent protein kinase, which causes vascular relaxation and increases blood flow. Nitric oxide can be manipulated for clinical effect by using certain medications. For example, sildenafil inhibits the cGMP-specific phosphodiesterase-5, preventing the degradation of cGMP and therefore prolonging the action of nitric oxide.

Endothelin is a large 21-amino-acid peptide that in small quantities causes intense vasoconstriction. The substance is present in all cells, but quantities increase dramatically with vascular injury. The usual stimulus for release is injury to the endothelium, which causes intense vasoconstriction, limiting blood loss. Increased endothelin release may also contribute to vasoconstriction when the endothelium is damaged, as in hypertension. Drugs that block endothelin receptors have been used to treat pulmonary hypertension (bosentan, tezosentan).

Local regulation of vascular tone can be affected by inflammatory mediators. Platelet-activating factor is a phospholipid-derived proinflammatory mediator. Platelet-activating factor is formed by action of phospholipase A\(_2\) on phosphatidylcholine. Platelet-activating factor causes pulmonary vasoconstriction and bronchoconstriction. Eicosanoids are lipid derived, formed by the oxidation of arachidonic acid, and are important in inflammation. Eicosanoids include prostaglandins, leukotrienes, thromboxanes, and lipoxins. Prostaglandins cause vasodilation and bronchodilation, whereas thromboxanes cause vasoconstriction. Vascular response to leukotrienes appears unclear. Some studies favor vasoconstriction, whereas others show only changes in regional circulation.

**MYOCARDIAL METABOLISM AND BLOOD FLOW**

**Normal Myocardial Blood Flow and Metabolism**

Blood flow to the heart is supplied by the coronary arteries, which lie on the myocardial surface. Only the very inner portion of the endocardial surface can obtain significant nutrition directly from the blood inside the cardiac chambers. Most of the coronary blood from the left ventricle returns to the right atrium by way of the coronary sinus (approximately 75% of coronary blood flow). Most coronary venous blood flow from the right ventricle returns through small anterior cardiac veins that flow directly into the right atrium. Finally, a small amount of blood flows back into the heart through very minute Thebesian veins, which empty into all chambers of the heart.

Myocardial energy substrate under resting conditions comes from fatty acids, not carbohydrates like other cells. Up to 66% of the energy is derived from free fatty acids. Under anaerobic or ischemic conditions, cardiac muscle can undergo anaerobic glycolysis for energy. However, glycolysis consumes significant quantities of glucose, forming large amounts of lactic acid. The lactic acid and carbon dioxide production created by glucose metabolism plays a role in myocardial perfusion, which is discussed later.

**Myocardial Oxygen Demand and Blood Flow**

Myocardial workload is determined by the heart but also by the demands of the body. The left ventricle extracts most of the oxygen passing through the myocardium, as evidenced by the coronary sinus venous saturation of approximately 30%. This is different from other tissues, where increased demand can be met by increased oxygen extraction. As a result, increases in myocardial oxygen demand must be met by increased myocardial blood flow. With maximal exertion, left ventricle oxygen consumption can increase up to 4-fold.

Many factors determine the relationship between myocardial metabolic rate and blood flow. Coronary blood flow is regulated by physical forces that are related to the anatomic position within and around the dynamic myocardium, by metabolic factors that couple coronary blood flow to oxygen demand, and by neural factors.

**Physical Forces Affecting Myocardial Blood Flow**

The coronary blood flow is directly related to the difference between the aortic pressure and the right atrial pressure. As the pressure within the coronary arteries varies depending on the cardiac cycle, blood flow within the coronaries also varies. In diastole, the pressure within the coronary arteries and the aortic pressure are similar. In systole, the intramyocardial tissue pressure is determined by the magnitude of the intraventricular pressure, resulting in greater pressures in the left ventricle than the right under normal conditions. Intramyocardial tissue pressure decreases from the endocardium to the epicardium. In systole, the greater pressure in the subendocardium compared with the subepicardium can result in reversal of blood flow during the isovolumic contraction phase. In diastole, blood flows...
first to the subepicardial vessels and then to the endocardial vessels, following the tissue pressure gradient. If aortic pressure decreases or tachycardia occurs, creating less time in diastole, decreased perfusion most dramatically affects the subendocardial vessels.

**Metabolic Factors That Couple Metabolism to the Myocardium**

Coronary blood flow is tightly coupled to the ratio of oxygen supply and demand. The mechanisms for this direct coupling remain unproven. However, many substances known to participate in altering vascular tone, such as oxygen, nitric oxide, H⁺, K⁺, carbon dioxide, and prostaglandins, play a role in coronary blood flow. The coronary control of blood flow is almost completely under local control, as in other tissues such as skeletal muscle. Hypoxia is one of the most important local mediators of coronary blood flow, resulting in coronary dilation and therefore increased oxygen delivery. During hypoxia, adenosine triphosphate is degraded to adenosine monophosphate. Small portions of adenosine monophosphate are further degraded to local adenosine, which enters the heart tissue and results in decreased blood flow, although not to the same extent that occurs in the brain.

The humoral substances that play a role in regional tissue regulation (discussed previously) also play a role in myocardial metabolism and blood flow. Substances such as norepinephrine, epinephrine, angiotensin II, bradykinin, histamine, and vasopressin all affect systemic blood pressure and afterload and therefore affect coronary metabolism and blood flow. Agents that increase afterload increase myocardial workload and thus myocardial oxygen consumption.

**Myocardial Autoregulation and Coronary Vascular Resistance**

Coronary vascular resistance has 3 components: (1) a low resistance state in which vessels are maximally dilated, (2) an added resistance state in which the vessels have increased tone (autoregulatory zone), and (3) a resistance state created by physical forces that cause coronary compression whenever the ventricle contracts (discussed previously). At low flow, vessels are maximally dilated, and flow depends only on driving pressure and resistance. If heart rate is increased, maximal flow at any perfusion pressure decreases because the heart is in diastole for a shorter period of time.

**Coronary Vascular (Flow) Reserve**

At any given pressure, the difference between maximal blood flow (the ability of the coronary vessels to decrease resistance) and autoregulated blood flow can be termed the coronary vascular reserve or the coronary flow reserve (Figure 4). The coronary vascular reserve can be used to better understand myocardial ischemia in diseased states. For example, if the coronary vascular reserve is small and myocardial oxygen demand increases, ischemia results. If autoregulated flow is normal and maximal flow (dilation) is decreased, as in the diseased heart, then coronary reserve flow is also decreased (Figure 4B). This occurs

**Figure 4. Coronary flow reserve**

(A) Normal pressure-flow relations in the left coronary artery during normal autoregulated flow and during maximal vasodilation. Values are appropriate for a left ventricle weighing approximately 100 g. R1 and R2 indicate coronary flow reserve measurements at 2 different coronary perfusing pressures. (B) Effect on coronary flow reserve of a reduced maximal flow. At the same coronary perfusing pressure, flow reserve is reduced from the normal R1 to R2. (C) Effect on coronary flow reserve of an increased autoregulated flow. Flow reserve is reduced from R1 to R2. Republished with permission of Elsevier. From Pediatric Critical Care, Fuhrman B, Zimmerman J, 4th ed., 2011; permission conveyed through Copyright Clearance Center, Inc.
with tachycardia, coronary artery disease, polycythemia, an increase in left ventricular diastolic pressure, or a marked increase in contractility. Coronary flow reserve can also decrease if maximal flow is normal in the setting of increased autoregulatory flow, as occurs in anemia, increased contractility, or hypertrophy (Figure 4C). Because coronary blood flows from the subepicardium to the subendocardium, coronary ischemia is more pronounced in the subendocardium. Therefore, the coronary vascular reserve of the endocardium is much less than that of the epicardium. Finally, in a diseased heart, autoregulatory flow can be increased (increased contractility) at the same time maximal flow is decreased (increased left ventricular diastolic pressure), significantly decreasing coronary vascular reserve and predisposing to ischemia.

**Neural Factors Increasing Myocardial Blood Flow**

Despite a low concentration of parasympathetic nerve endings on the coronary arteries, acetylcholine released by the parasympathetic nerves results in coronary vasodilation. In contrast, coronary arteries are densely innervated by sympathetic nerve fibers. The \( \alpha \) receptors cause vasoconstriction, whereas \( \beta \) receptors cause vasodilation. The \( \beta \) receptors are heterogeneously distributed on the coronary arteries, as is hypothesized with \( \alpha \) receptors. As a result, it is theoretically possible for sympathetic stimulation to cause vasoconstriction or vasodilation.

**Preload, Afterload, Contractility, and Oxygen Consumption**

Myocardial work can be separated into 3 components: basal metabolism, external work (stroke work), and potential energy (internal work). Basal metabolism consumes the least amount of energy, approximately 20% of the work by the heart. External work is the work of ejecting blood against a load, calculated by the area within the pressure volume loop. Therefore, increasing stroke volume increases the area within the pressure volume loop and thus increases external work (Figure 5B). Potential energy (internal work or pressure work) is work stored at the end of systole in the elasticity of the ventricular wall (Figure 5B). An example of increasing potential energy occurs when the heart is pressure loaded, increasing the need for a high wall stress at end-diastole. The total myocardial work can be displayed graphically as the area within the ejecting pressure-volume curve plus the potential energy, which is the area in the curve to the left of the isovolumic relaxation (Figure 5B). Therefore, as the pressure-volume graph is manipulated, changes in external work, potential energy, or both can be predicted.

**Effect of Medications on Oxygen Demand and Coronary Blood Flow**

All inotropes increase myocardial oxygen demand, with the exception of the bipyridines (amrinone, milrinone), because they increase myocardial work. Norepinephrine increases coronary blood flow due to increased coronary perfusion pressure (increased systolic blood pressure) and by direct dilation of coronary arteries through \( \beta \) receptors. Nicardipine has preferential effect on smooth muscle, causing dilation and resulting in increased coronary blood flow with little or no decrease in inotropic effect. Other medications that vasodilate the coronary arteries (nitroglycerin, sodium nitroprusside) also result in increased coronary blood flow. Finally, as mentioned previously, vasopressin results in coronary vasoconstriction and decreased coronary blood flow.

**Myocardial Hypertrophy**

The interactions of blood flow and the myocardium are of particular importance in the face of ventricular hypertrophy. Coronary flow reserve is normal in a heart without significant ventricular hypertrophy. As ventricular muscle mass increases, the number of coronary vessels remains unchanged, as does vascular cross-sectional area. Ventricular hypertrophy returns wall stress to normal, but total ventricular blood flow (compared with baseline heart) is increased, thus decreasing the coronary flow reserve (Figure 4C). If the coronary flow reserve is minimal, then subendocardial ischemia can occur. Even if the heart dilates acutely, rather than undergoing hypertrophy over time, coronary flow reserve still decreases due to the increased autoregulatory flows (Figure 4C). Treatment of heart failure by decreasing preload and decreasing afterload improves coronary
flow reserve, decreases work of the heart (both internal and external), and improves oxygen availability to the subendocardium, minimizing ischemia.

**Coronary Blood Flow and the Right Ventricle**

The mechanisms of coronary blood flow are the same for the right ventricle as they are for the left, with some additions. First, oxygen demand in the right ventricle is far less than in the left due to the decreased ventricular pressure and afterload. Second, a decrease in systemic blood pressure decreases right ventricular coronary perfusion without decreasing right ventricular work. Conversely, a decrease in blood pressure decreases left ventricular coronary blood flow and left ventricular work at the same time while the work of the right ventricle remains unchanged. Third, if a normal right ventricle dilates, the increased wall stress increases oxygen consumption (increasing internal work as described previously). In situations where right ventricular systolic blood pressure is increased (pulmonary hypertension, pulmonary embolus), right ventricular myocardial oxygen demand increases and there are dramatic decreases in right ventricular coronary blood flow, predisposing the right heart to ischemia.

**Effects of Abnormal Metabolism on Myocardium**

Ischemia indicates either decreased flow to an organ, creating inability to meet its oxygen demands, or excessive utilization not matched by oxygen delivery. Hypoxia entails normal blood flow but decreased oxygen delivery. The heart is unable to work without oxygen and quickly creates an oxygen debt. Inadequate oxygen supply rapidly decreases the energy to the cardiac muscle cells. If the ischemia is local, the muscle affected stops contracting. A paradoxically bulging myocardium is associated with greater flow reductions than the a kinetic myocardium. If the ischemia is global, then the subendocardial muscles become ischemic first, because of the lower coronary flow reserve. Finally, only with severe reduction in blood flow (>90%) is function reduced completely.

Myocardial response to ischemia can be modulated by a number of processes, particularly preconditioning and reperfusion. When myocardial cells become hypoxic, there is a change from the more efficient use of fatty acids to anaerobic glycolysis. Anaerobic metabolism bypasses the mitochondrial oxidative phosphorylation pathway, resulting in an intracellular acidosis and lactate production. Ischemia occurs in the subendocardium after approximately 40 minutes and progresses to the epicardium after 3 to 4 hours. If hypoxia is brief (15 minutes) and is reversed prior to myocardial necrosis, the myocardium may develop a temporary dysfunction referred to as stunning. Stunning is a prolonged depression of the myocardial contractile mechanism. Stunning is mediated by effects of reperfusion, including injury by free radicals and other mechanisms. Stunned myocardium may eventually recover function or can progress to permanent injury. With restoration of perfusion within 2 to 3 hours, reversible injury is favored.

Myocardial preconditioning protects the myocardium from permanent injury. Preconditioning can consist of short intervals of coronary occlusion and reperfusion prior to prolonged occlusion. Preconditioning causes significantly decreased areas of infarcts after 60 to 90 minutes. The exact mechanisms of preconditioning are uncertain.

**Acid-Base Status and Cardiac Function**

Acidosis decreases myocardial function by many mechanisms. Acidosis results in increased H+ ions, which creates reversible cardiac dysfunction. This reversible dysfunction differs from lactic acidosis, which appears to induce irreversible damage to the myocardium. Acidosis also has deleterious effects on calcium metabolism within the cell and impairs myofibrillar responsiveness of the calcium that is available, decreasing maximum contractile force. Alkalosis increases the inotropic effect; however, this effect is much more modest than the effect of acidosis on the myocardium.

**Inborn Errors of Metabolism and Cardiac Function**

Inborn errors of metabolism (IEMs) can cause cardiomyopathies and therefore affect cardiac function. Most cardiomyopathies in children are idiopathic, with a definitive cause apparent in only 33%. Of the cardiomyopathies with a definitive cause, approximately 15% can be attributed to IEMs. The cardiomyopathies associated with IEMs can be grouped into categories according to the accumulated substrate or the affected organelle. Cardiomyopathies also can be grouped according to whether they are a primary or secondary feature of the overall disease. Echocardiography has indicated that more than 50% of hypertrophic cardiomyopathies caused by IEMs are caused by glycogen storage diseases, mainly Pompe disease. With dilated cardiomyopathy, oxidative phosphorylation defects and systemic carnitine deficiency account each for about 40% of cardiomyopathies. Understanding the organelle affected, the appearance by echocardiography, and adjunctive features can significantly assist in the diagnosis of cardiomyopathy due to IEM.


