
Chapter 1

CIRCULATORY BLOOD FLOW

When is a piece of matter said to be alive? When it goes on "doing something,"' moving, exchanging material with its environment.
Erwin Schrodinger

The human organism has an estimated 100 trillion cells that must go on exchanging material with the external environment to stay alive. This exchange is made possible by a circulatory system that uses a muscular pump (the heart), an exchange fluid (blood), and a network of conduits (blood vessels). Each day, the human heart pumps about 8,000 liters of blood through a vascular network that stretches more than 60,000 miles (more than twice the circumference of the Earth!) to maintain cellular exchange (1).

This chapter describes the forces responsible for the flow of blood though the human circulatory system. The first half is devoted to the determinants of cardiac output, and the second half describes the forces that influence peripheral blood flow. Most of the concepts in this chapter are old friends from the physiology classroom.

CARDIAC OUTPUT

Circulatory flow originates in the muscular contractions of the heart. Since blood is an incompressible fluid that flows through a closed hydraulic loop, the volume of blood ejected by the left side of the heart must equal the volume of blood returning to the right side of the heart (over a given time period). This conservation of mass (volume) in a closed hydraulic system is known as the *principle of continuity* (2), and it indicates that the stroke output of the heart is the principal determinant of circulatory blood flow. The forces that govern cardiac stroke output are identified in Table 1.1.

TABLE 1.1	The Forces that Determine Cardiac Stroke Output	
Force	Definition	Clinical Parameters
Preload	The load imposed on resting	End-diastolic pressure
	muscle that stretches the	
	muscle to a new length	
Contractility	The velocity of muscle	Cardiac stroke volume when
	contraction when muscle	preload and afterload are
	load is fixed	constant
Afterload	The totalload that must be	Pulmonary and systemic
	moved by a muscle when it	vascular resistances
	contracts	

Preload

If one end of a muscle fiber is suspended from a rigid strut and a weight is attached to the other free end, the added weight will stretch the muscle to a new length. The added weight in this situation represents a force called the *preload,* which is a force imposed on a resting muscle (prior to the onset of muscle contraction) that stretches the muscle to a new length. According to the length-tension relationship of muscle, an increase in the length of a resting (unstimulated) muscle will increase the force of contraction when the muscle is stimulated to contract. Therefore the preload force acts to augment the force of muscle contraction.

In the intact heart, the stretch imposed on the cardiac muscle prior to the onset of muscle contraction is a function of the volume in the ventricles at the end of diastole. Therefore the end-diastolic volume of the ventricles is the preload force of the intact heart (3).

Preload and Systolic Performance

The pressure-volume curves in Figure 1.1 show the influence of diastolic volume on the systolic performance of the heart. As the ventricle fills during diastole, there is an increase in both diastolic and systolic pressures. The increase in diastolic pressure is a reflection of the passive stretch imposed on the ventricle, while the difference between diastolic and systolic pressures is a reflection of the strength of ventricular contraction. Note that as diastolic volume increases, there is an increase in the difference between diastolic and systolic pressures, indicating that the strength of ventricular contraction is increasing. The importance of preload in augmenting cardiac contraction was discovered independently by Otto Frank (a German engineer) and Ernest Starling (a British physiologist), and their discovery is commonly referred to as the Frank-Starling *relationship of the heart* (3). This relationship can be stated as follows: In the normal heart, diastolic volume is the principal force that governs the strength of ventricular contraction (3).

Clinical Monitoring

In the clinical setting, the relationship between preload and systolic performance is monitored with *ventricular function curves* like the ones

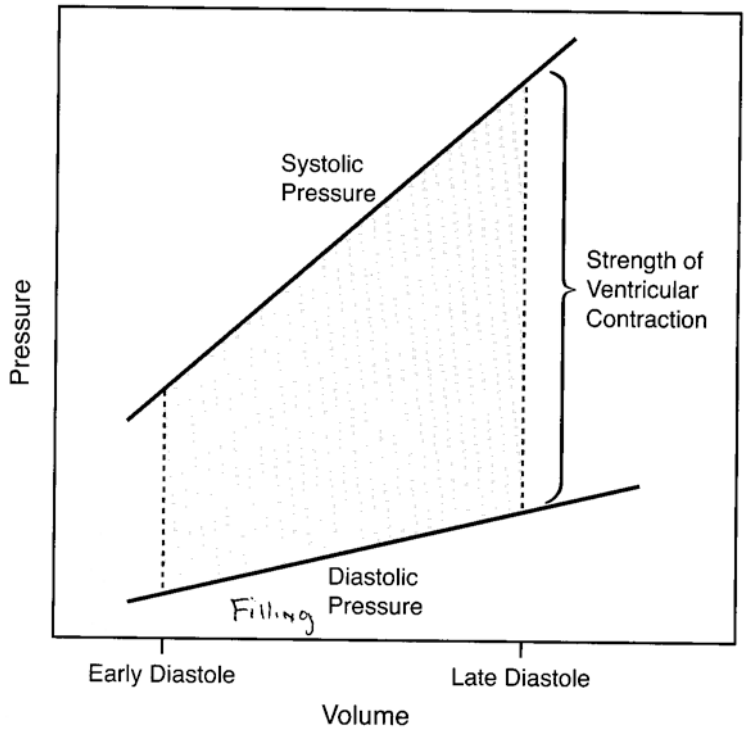


FIGURE 1.1 Pressure-volume curves showing the influence of diastolic volume on the strength of ventricular contraction.

shown in Figure 1.2. End-diastolic pressure (EDP) is used as the clinical measure of preload because end-diastolic volume is not easily measured (the measurement of EDP is described in Chapter 10). The normal ventricular function curve has a steep ascent, indicating that changes in preload have a marked influence on systolic performance in the normal heart (i.e., the Frank-Starling relationship). When myocardial contractility is reduced, there is a decrease in the slope of the curve, resulting in an increase in end-diastolic pressure and a decrease in stroke volume. This is the hemodynamic pattern seen in patients with heart failure.

Ventricular function curves are used frequently in the intensive care unit (ICU) to evaluate patients who are hemodynamically unstable. However, these curves can be misleading. The major problem is that conditions other than myocardial contractility can influence the slope of these curves. These conditions (i.e., ventricular compliance and ventricular afterload) are described next.

Preload and Ventricular Compliance

The stretch imposed on cardiac muscle is determined not only by the volume of blood in the ventricles, but also by the tendency of the ventricular wall to distend or stretch in response to ventricular filling.

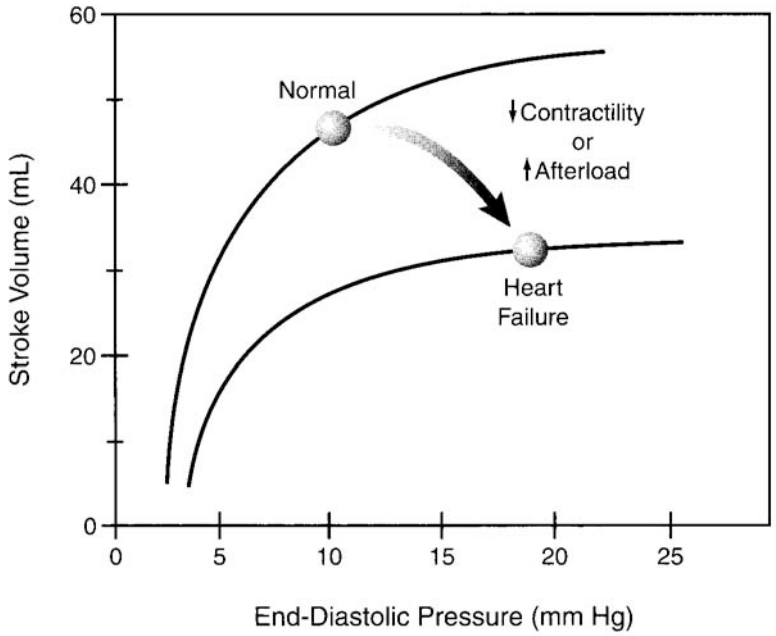


FIGURE 1.2 Ventricular function curves used to describe the relationship between preload (end-diastolic pressure) and systolic performance (stroke volume).

The distensibility of the ventricles is referred to as *compliance* and can be derived using the following relationship between changes in enddiastolic pressure (EDP) and end-diastolic volume (EDV) (5):

Compliance = deltaEDV / deltaEDP 0.1)

The pressure-volume curves in Figure 1.3 illustrate the influence of ventricular compliance on the relationship between deltaEDP and deltaEDV. As compliance decreases (i.e., as the ventricle becomes stiff), the slope of the curve decreases, resulting in a decrease in EDV at any given EDP. In this situation, the EDP will overestimate the actual preload (EDV). This illustrates how changes in ventricular compliance will influence the reliability of EDP as a reflection of preload. The following statements highlight the importance of ventricular compliance in the interpretation of the EDP measurement.

End-diastolic pressure is an accurate reflection of preload only when ventricular compliance is normal.

Changes in end-diastolic pressure accurately reflect changes in preload only when ventricular compliance is constant.

Several conditions can produce a decrease in ventricular compliance. The most common are left ventricular hypertrophy and ischemic heart

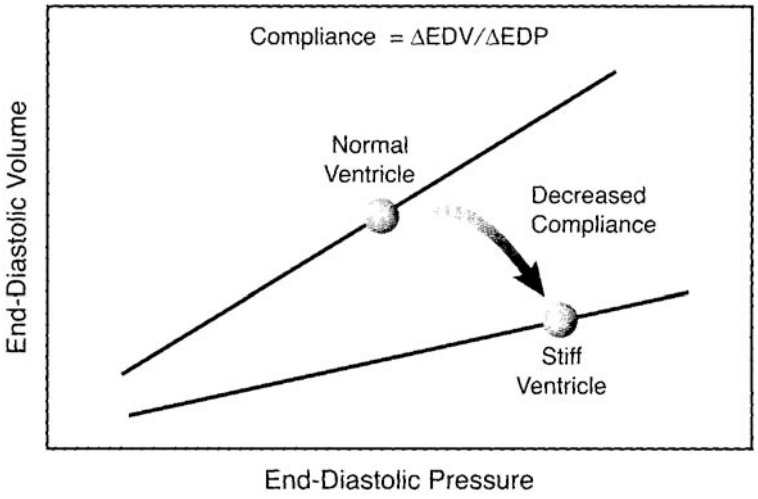


FIGURE 1.3 Diastolic pressure-volume curves in the normal and noncompliant (stiff) ventricle.

disease. Since these conditions are also commonplace in ICU patients, the reliability of the EDP measurement is a frequent concern.

Diastolic Heart Failure

As ventricular compliance begins to decrease (e.g., in the early stages of ventricular hypertrophy), the EDPrises, but the EDV remains unchanged. The increase in EDP reduces the pressure gradient for venous inflow into the heart, and this eventually leads to a decrease in EDV and a resultant decrease in cardiac output (via the Frank-Starling mechanism). This condition is depicted by the point on the lower graph in Figure 1.3, and is called *diastolic heart failure* (6). Systolic function (contractile strength) is preserved in this type of heart failure. Diastolic heart failure should be distinguished from conventional (systolic) heart failure because the management of the two conditions differs markedly. For example, since ventricular filling volumes are reduced in diastolic heart failure, diuretic therapy can be counterproductive. Unfortunately, it is not possible to distinguish between the two types of heart failure when the EDP is used as a measure of preload because the EDP is elevated in both conditions. The ventricular function curves in Figure 1.3 illustrate this problem. The point on the lower curve identifies a condition where EDP is elevated and stroke volume is reduced. This condition is often assumed to represent heart failure due to systolic dysfunction, but diastolic dysfunction would also produce the same changes. This inability to distinguish between systolic and diastolic heart failure is one of the major shortcomings of ventricular function curves. (See Chapter 14 for a more detailed discussion of systolic and diastolic heart failure.)

Afterload

When a weight is attached to one end of a contracting muscle, the force of muscle contraction must overcome the opposing force of the weight before the muscle begins to shorten. The weight in this situation represents a force called the *afterload,* which is defined as the load imposed on a muscle *after* the onset of muscle contraction. Unlike the preload force, which facilitates muscle contraction, the afterload force opposes muscle contraction (i.e., as the afterload increases, the muscle must develop more tension to move the load). In the intact heart, the afterload force is equivalent to the peak tension developed across the wall of the ventricles during systole (3).

The determinants of ventricular wall tension (afterload) were derived from observations on soap bubbles made by the Marquis de Laplace in 1820. His observations are expressed in the Law of Laplace, which states that the tension (T) in a thin-walled sphere is directly related to the chamber pressure (P) and radius (r) of the sphere: $T = Pr$. When the LaPlace relationship is applied to the heart, T represents the peak systolic transmural wall tension of the ventricle, P represents the transmural pressure across the ventricle at the end of systole, and r represents the chamber radius at the end of diastole (5).

The forces that contribute to ventricular after load can be identified using the components of the Laplace relationship, as shown in Figure 1.4. There are three major contributing forces: pleural pressure, arterial impedance, and end-diastolic volume (preload). Preload is a component of after load because it is a volume load that must be moved by the ventricle during systole.

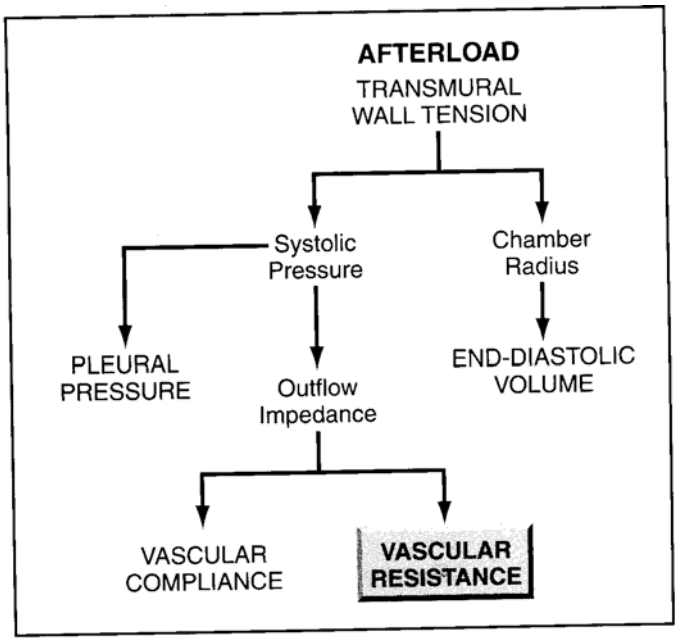


FIGURE 1.4 The forces that contribute to ventricular afterload.

Pleural Pressure

Since after load is a transmural force, it is determined in part by the pleural pressure on the outer surface of the heart. Negative pleural pressures will increase transmural pressure and increase ventricular afterload, while positive pleural pressures will have the opposite effect. Negative pressures surrounding the heart can impede ventricular emptying by opposing the inward displacement of the ventricular wall during systole (7,8). This effect is responsible for the transient decrease in systolic blood pressure (reflecting a decrease in cardiac stroke volume) that normally occurs during the inspiratory phase of spontaneous breathing. When the inspiratory drop in systolic pressure is greater than 15 mm Hg, the condition is called "pulsus paradoxus" (which is a misnomer, since the response is not paradoxical, but is an exaggeration of the normal response).

Positive pleural pressures can promote ventricular emptying by facilitating the inward movement of the ventricular wall during systole (7,9). This effect is illustrated in Figure 1.5. The tracings in this figure show the effect of positive-pressure mechanical ventilation on the arterial blood pressure. When intrathoracic pressure rises during a positive-pressure breath, there is a transient rise in systolic blood pressure (reflecting an increase in the stroke volume output of the heart). This response indicates that positive intrathoracic pressure can provide

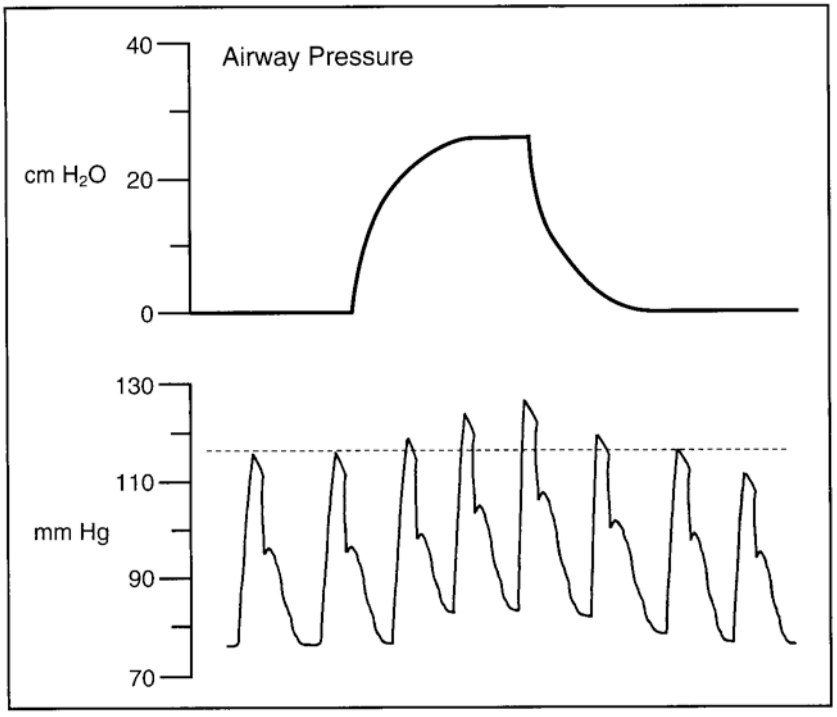


FIGURE 1.5 Respiratory variations in blood pressure during positive-pressure mechanical ventilation.

cardiac support by "unloading" the left ventricle. Although this effect is probably of minor significance, positive-pressure mechanical ventilation has been proposed as a possible therapeutic modality in patients with cardiogenic shock (O). The hemodynamic effects of mechanical ventilation are discussed in more detail in Chapter 24.

Impedance

The principal determinant of ventricular after load is a hydraulic force known as *impedance* that opposes phasic changes in pressure and flow. This force is most prominent in the large arteries close to the heart, where it acts to oppose the pulsatile output of the ventricles. Aortic impedance is the major afterload force for the left ventricle, and pulmonary artery impedance serves the same role for the right ventricle. Impedance is influenced by two other forces: (a) a force that opposes the rate of change in flow, known as *compliance,* and (b) a force that opposes steady flow, called *resistance.* Arterial compliance is expressed primarily in the large, elastic arteries, where it plays a major role in determining vascular impedance. Arterial resistance is expressed primarily in the smaller peripheral arteries, where the flow is steady and nonpulsatile. Since resistance is a force that opposes nonpulsatile flow, while impedance opposes pulsatile flow, arterial resistance may playa minor role in the impedance to ventricular emptying. Arterial resistance can, however, influence pressure and flow events in the large, proximal arteries (where impedance is prominent) because it acts as a downstream resistance for these arteries. Vascular impedance and compliance are complex, dynamic forces that are not easily measured 02,13). Vascular resistance, however, can be calculated as described next.

Vascular Resistance

The resistance (R) to flow in a hydraulic circuit is expressed by the relationship between the pressure gradient across the circuit (deltaP) and the rate of flow (Q) through the circuit:

R = deltaP /Q (1.2)

Applying this relationship to the systemic and pulmonary circulations yields the following equations for systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR):

SVR = SAP - RAP/CO (1.3)

PVR = PAP - LAP/CO 0.4)

SAP is the mean systemic arterial pressure, RAP is the mean right atrial pressure, PAP is mean pulmonary artery pressure, LAP is the mean left atrial pressure, and CO is the cardiac output. The SAP is measured with an arterial catheter (see Chapter 8), and the rest of the measurements are obtained with a pulmonary artery catheter (see Chapter 9).

Clinical Monitoring

There are no accurate measures of ventricular afterload in the clinical setting. The SVR and PVR are used as clinical measures of afterload, but they are unreliable 04,15). There are two problems with the use of vascular resistance calculations as a reflection of ventricular afterload. First, arterial resistance may contribute little to ventricular afterload because it is a force that opposes nonpulsatile flow, while afterload (impedance) is a force that opposes pulsatile flow. Second, the SVR and PVR are measures of total vascular resistance (arterial and venous), which is even less likely to contribute to ventricular afterload than arterial resistance. These limitations have led to the recommendation that PVR and SVR be abandoned as clinical measures of afterload (5).

Since afterload can influence the slope of ventricular function curves (see Figure 1.2), changes in the slope of these curves are used as indirect evidence of changes in afterload. However, other forces, such as ventricular compliance and myocardial contractility, can also influence the slope of ventricular function curves, so unless these other forces are held constant, a change in the slope of a ventricular function curve cannot be used as evidence of a change in afterload.

Contractility

The contraction of striated muscle is attributed to interactions between contractile proteins arranged in parallel rows in the sarcomere. The number of bridges formed between adjacent rows of contractile elements determines the contractile state or *contractility* of the muscle fiber. The contractile state of a muscle is reflected by the force and velocity of muscle contraction when loading conditions (i.e., preload and afterload) are held constant (3). The standard measure of contractility is the acceleration rate of ventricular pressure (dP / dt) during isovolumic contraction (the time from the onset of systole to the opening of the aortic valve, when preload and afterload are constant). This can be measured during cardiac catheterization.

Clinical Monitoring

There are no reliable measures of myocardial contractility in the clinical setting. The relationship between end-diastolic pressure and stroke volume (see Figure 1.2) is often used as a reflection of contractility; however, other conditions (i.e., ventricular compliance and afterload) can influence this relationship. There are echo cardiography techniques for evaluating contractility 05,16), but these are very specialized and not used routinely.

PERIPHERAL BLOOD FLOW

As mentioned in the introduction to this chapter, there are over 60,000 miles of blood vessels in the human body! Even if this estimate is off by 10,000 or 20,000 miles, it still points to the incomprehensible vastness of the human circulatory system. The remainder of this chapter will describe the forces that govern flow through this vast network of blood vessels.

A Note of Caution: The forces that govern peripheral blood flow are derived from observations on idealized hydraulic circuits where the flow is steady and laminar (streamlined), and the conducting tubes are rigid. These conditions bear little resemblance to the human circulatory system, where the flow is often pulsatile and turbulent, and the blood vessels are compressible and not rigid. Because of these differences, the description of blood flow that follows should be viewed as a very schematic representation of what really happens in the circulatory system.

Flow in Rigid Tubes

Steady flow (Q) through a hollow, rigid tube is proportional to the pressure gradient along the length of the tube (deltaP), and the constant of proportionality is the hydraulic resistance to flow (R):

Q = deltaP X l/R 0.5)

The resistance to flow in small tubes was described independently by a German physiologist (G. Hagen) and a French physician (j. Poisseuille). They found that resistance to flow is a function of the inner radius of the tube (r), the length of the tube (L), and the viscosity of the fluid (μ). Their observations are expressed in the following equation, known as the Hagen-Poisseuille equation (8):

Q = deltaP X (pir4/8μL) (1.6)

The final term in the equation is the reciprocal of resistance 0 /R), so resistance can be described as

R = 8μL/ pir4 (1.7)

The Hagen-Poisseuille equation is illustrated in Figure 1.6. Note that flow varies according to the fourth power of the inner radius of the tube. This means that a two-fold increase in the radius of the tube will result in a sixteen-fold increase in flow: (2r)4 = 16r. The other components of resistance (i.e., tube length and fluid viscosity) exert a much smaller influence on flow.

Since the Hagen-Poisseuille equation describes steady flow through rigid tubes, it may not accurately describe the behavior of the circulatory system (where flow is not steady and the tubes are not rigid). However, there are several useful applications of this equation. In Chapter 6, it will be used to describe flow through vascular catheters (see Figure 6.1). In Chapter 12, it will be used to describe the flow characteristics of different resuscitation fluids, and in Chapter 36, it will be used to describe the hemodynamic effects of anemia and blood transfusions.

Flow in Tubes ofVarying Diameter

As blood moves away from the heart and encounters vessels of decreasing diameter, the resistance to flow should increase and the flow should decrease. This is not possible because (according to the principle of

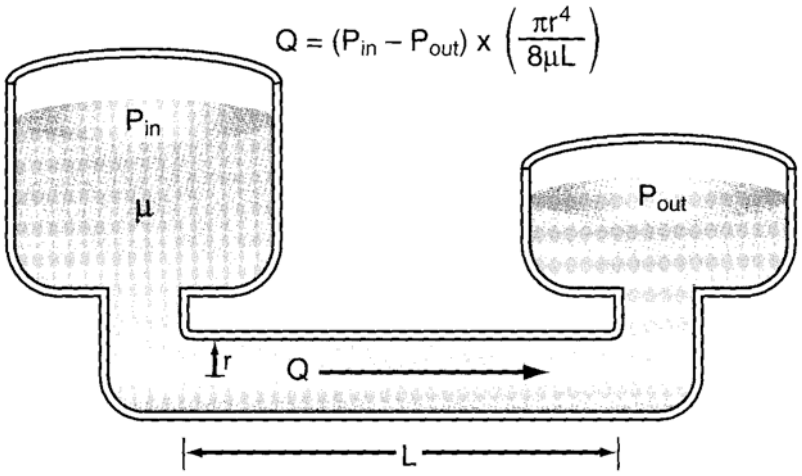


FIGURE 1.6 The forces that influence steady flow in rigid tubes. Q = flow rate, P_{in} = inlet pressure, P_{out} = outlet pressure, μ = viscosity, r = inner radius, L = length.

continuity) blood flow must be the same at all points along the circulatory system. This discrepancy can be resolved by considering the influence of tube narrowing on flow velocity. For a rigid tube of varying diameter, the velocity of flow (v) at any point along the tube is directly proportional to the bulk flow (Q), and inversely proportional to the cross-sectional area of the tube: v = Q/ A (2). Rearranging terms (and using A = pir2) yields the following:

Q = v X (pir2) 0.8)

This shows that bulk flow can remain unchanged when a tube narrows if there is an appropriate increase in the velocity of flow. This is how the nozzle on a garden hose works and is how blood flow remains constant as the blood vessels narrow.

Flow in Compressible Tubes

Flow through compressible tubes (like blood vessels) is influenced by the external pressure surrounding the tube. This is illustrated in Figure 1.7, which shows a compressible tube running through a fluid reservoir. The height of the fluid in the reservoir can be adjusted to vary the external pressure on the tube. When there is no fluid in the reservoir and the external pressure is zero, the driving force for flow through the tube will be the pressure gradient between the two ends of the tube (Pin - Pout)' When the reservoir fills and the external pressure exceeds the lowest pressure in the tube (Pext > Pout)' the tube will be compressed. In this situation, the driving force for flow is the pressure gradient between the inlet pressure and the external pressure (Pin - Pout)' Therefore when a tube is compressed by external pressure, the driving force for flow is independent of the pressure gradient along the tube (20).

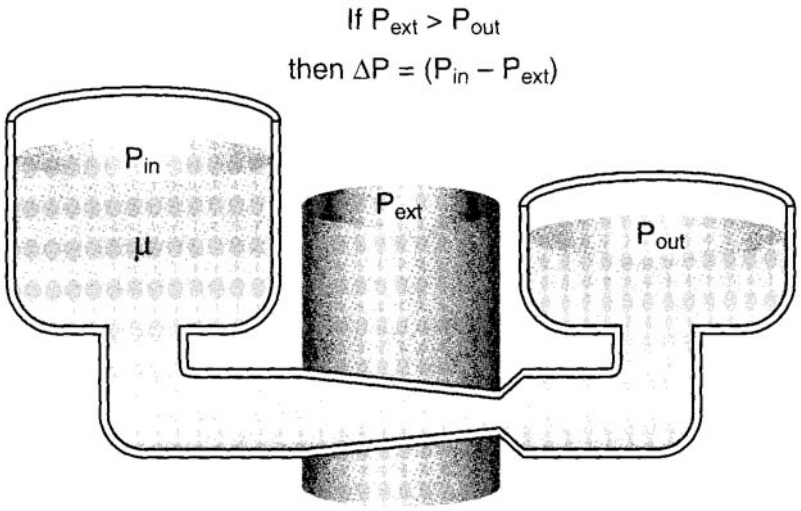


FIGURE 1.7 The influence of external pressure on flow through compressible tubes. P_{in} = inlet pressure, P_{out} = outlet pressure, P_{ext} = external pressure.

The Pulmonary Circulation

Vascular compression has been demonstrated in the cerebral, pulmonary, and systemic circulations. It can be particularly prominent in the pulmonary circulation during positive-pressure mechanical ventilation, when alveolar pressure exceeds the hydrostatic pressure in the pulmonary capillaries (20). When this occurs, the driving force for flow through the lungs is no longer the pressure gradient from the main pulmonary arteries to the left atrium (PAP - LAP), but instead is the pressure difference between the pulmonary artery pressure and the alveolar pressure (PAP - Palv). This change in driving pressure not only contributes to a reduction in pulmonary blood flow, but it also affects the pulmonary vascular resistance (PVR) calculation as follows:

Normal: PVR = PAP - LAP/CO (1.9)

When Palv > LAP: PVR = PAP - Palv /CO (1.10)

Vascular compression in the lungs is discussed again in Chapter 10 (the measurement of vascular pressures in the thorax) and in Chapter 24 (the hemodynamic effects of mechanical ventilation).

Blood Viscosity

A solid will resist being deformed (changing shape), while a fluid will deform continuously (flow) but will resist changes in the rate of deformation (i.e., changes in flow rate) (21). The resistance of a fluid to

changes in flow rate is a property known as *viscosity* (21-23). Viscosity has also been referred to as the "gooiness" of a fluid (21). When the viscosity of a fluid increases, a greater force must be applied to the fluid to initiate a change in flow rate. The influence of viscosity on flow rate is apparent to anyone who has poured molasses (high viscosity) and water (low viscosity) from a container.

Hematocrit

The viscosity of whole blood is almost entirely due to cross-linking of circulating erythrocytes by plasma fibrinogen (22,23). The principal determinant of whole blood viscosity is the concentration of circulating erythrocytes (the hematocrit). The influence of hematocrit on blood viscosity is shown in Table 1.2. Note that blood viscosity can be expressed in absolute or relative terms (relative to water). In the absence of blood cells (zero hematocrit), the viscosity of blood (plasma) is only slightly higher than that of water. This is not surprising, since plasma is 92% water. At a normal hematocrit (45%), blood viscosity is three times the viscosity of plasma. Thus plasma flows much more easily than whole blood, and anemic blood flows much more easily than normal blood. The influence of hematocrit on blood viscosity is the single most important factor that determines the hemodynamic effects of anemia and blood transfusions (see later).

Shear Thinning

The viscosity of some fluids varies inversely with a change in flow velocity (21,23). Blood is one of these fluids. (Another is ketchup, which is thick and difficult to get out of the bottle, but once it starts to flow, it thins out and flows more easily.) Since the velocity of blood flow increases as the blood vessels narrow, the viscosity of blood will also decrease as the

TABLE 1.2	Blood Viscosity as a Function of Hematocrit	
	Viscosity*	
Hematocrit	Relative	Absolute
0	1.4	
10	1.8	1.2
20	2.1	1.5
30	2.8	1.8
40	3.7	2.3
50	4.8	2.9
60	5.8	3.8
70	8.2	5.3
*Absolute viscosity expressed in centipoise (cP).		
Data from Documenta Geigy Scientific Tables. 7th ed. Basel:		
1966:557.		

blood moves into the small blood vessels in the periphery. The decrease in viscosity occurs because the velocity of plasma increases more than the velocity of erythrocytes, so the relative plasma volume increases in small blood vessels. This process is called *shear thinning* (shear is a tangential force that influences flow rate), and it facilitates flow through small vessels. It becomes evident in blood vessels with diameters less than 0.3 mm (24).

Hemodynamic Effects

The Hagen-Poisseuille equation indicates that blood flow is inversely related to blood viscosity, and further that blood flow will change in proportion to a change in viscosity (i.e., if blood viscosity is doubled, blood flow will be halved) (22). The effect of changes in blood viscosity on blood flow is shown in Figure 1.8. In this case, changes in hematocrit are used to represent changes in blood viscosity. The data in this graph is from a patient with polycythemia who was treated with a combination of phlebotomy and fluid infusion (isovolemic hemodilution) to achieve a therapeutic reduction in hematocrit and blood viscosity. The progressive decrease in hematocrit is associated with a steady rise in cardiac output, and the change in cardiac output is far greater than the change in hematocrit. The disproportionate increase in cardiac output is more than expected from the Hagen-Poisseuille equation and may be due in part

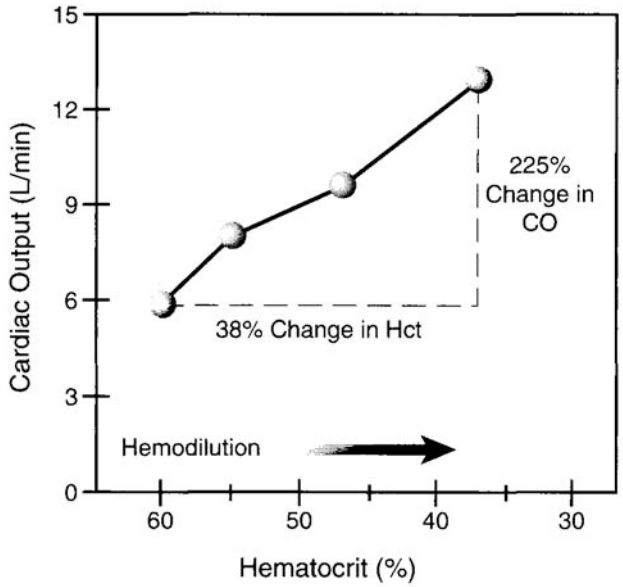


FIGURE 1.8 The influence of progressive hemodilution on cardiac output in a patient with polycythemia. CO = cardiac output. (From LeVeen HH, Ip M, Ahmed N, et al. Lowering blood viscosity to overcome vascular resistance. Surg Gynecol Obstet 1980;150:139.)

to the fact that blood viscosity varies inversely with flow rate. That is, as viscosity decreases and flow rate increases, the increase in flow rate will cause a further reduction in viscosity, which will then lead to a further increase in flow rate, and so on. This process would then magnify the influence of blood viscosity on blood flow. Whether or not this is the case, the graph in Figure 1.8 demonstrates that changes in hematocrit have a profound influence on circulatory blood flow. This topic is presented in more detail in Chapter 36.

Clinical Monitoring
Viscosity can be measured with an instrument called (what else?) a viscometer. This device has two parallel plates: one fixed and one that can move over the surface of the fixed plate. A fluid sample is placed between the two plates, and a force is applied to move the moveable plate. The force needed to move the plate is proportional to the viscosity of the fluid between the plates. Viscosity is expressed as force per area (surface area of the plates). The units of measurement are the "poise" (or dyne' sec/ cm^2) in the CGS system, and the "Pascal· second" (Pa . s) in the SI system. (A poise is one/tenth of a Pascal· second.) Viscosity is also expressed as the ratio of the test sample viscosity to the viscosity of water. This "relative viscosity" is easier to interpret.
Viscosity is rarely measured in the clinical setting. The main reason for this is the consensus view that *in vitro* viscosity measurements are unreliable because they do not take into account conditions in the circulatory system (like shear thinning) that influence viscosity (21-24). Monitoring changes in viscosity may be more useful than single measurements. For example, serial changes in blood viscosity could be used to monitor the effects of aggressive diuretic therapy (e.g., a rise in viscosity to abnormally high levels might trigger a reduction in diuretic dosage). The value of blood viscosity measurements is underappreciated at the present time.

References

Chapter 2
OXYGEN AND CARBON DIOXIDE TRANSPORT

Respiration is *thus a process* I f *combustion,* in *truth very slow, but otherwise exactly like that* if *charcoal.*
Antoine Lavoisier

The business of aerobic metabolism is the combustion of nutrient fuels to release energy. This process consumes oxygen and generates carbon dioxide. The business of the circulatory system is to deliver the oxygen and nutrient fuels to the tissues of the body, and then to remove the carbon dioxide that is generated. The dual role of the circulatory system in transporting both oxygen and carbon dioxide is referred to as the *respiratory function of blood.* The business of this chapter is to describe how this respiratory function is carried out.

OXYGEN TRANSPORT
The transport of oxygen from the lungs to metabolizing tissues can be described by using four clinical parameters: (a) the concentration of oxygen in blood, (b) the delivery rate of oxygen in arterial blood, (c) the rate of oxygen uptake from capillary blood into the tissues, and (d) the fraction of oxygen in capillary blood that is taken up into the tissues. These four *oxygen transport parameters* are shown in Table 2.1, along with the equations used to derive each parameter. Thorough knowledge of these parameters is essential for the management of critically ill patients.

02 Content in Blood
Oxygen does not dissolve readily in water (1) and, since plasma is 93% water, a specialized oxygen-binding molecule (hemoglobin) is needed to

TABLE 2.1 Oxygen and Carbon Dioxide Transport Parameters

Parameter	Symbol	Equations
Arterial 02 content	Ca02	1.34 x Hb x Sa02
Venous O2 content	*CV02*	1.34 x Hb x *SV02*
O2 Delivery	002	Q x Ca02
O2 Uptake	V02	Q x (Ca02 - *CV02)*
O2 Extraction ratio	0_2ER	V02/D02
C02 Elimination	$VC0_2$	Q x *($CvC0_2$* - $CaC0_2$)
Respiratory quotient	RQ	VC02/V02

facilitate the oxygenation of blood. The concentration of oxygen (0) in blood, also called the 02 *content,* is the summed contribution of 02 that is
bound to hemoglobin and 02that is dissolved in plasma.

Hemoglobin-Bound 02
The concentration of hemoglobin-bound 02_2 ($Hb0_2$) is determined by the
variables in Equation 2.1 (2).

$$Hb0_2 = 1.34 \times Hb \times 502 \qquad (2.1)$$

Hb is the hemoglobin concentration in blood (usually expressed in grams per deciliter, which is grams per 100 mL); 1.34 is the oxygen-binding capacity of hemoglobin (expressed in mL 02 per gram of Hb); and S02 is the ratio of oxygenated hemoglobin to total hemoglobin in blood (S02 = Hb02/total I-Ib), also called the 02*saturation of hemoglobin.* The $Hb0_2$ is expressed in the same units as the I-Ib concentration (g/ dL).
Equation 2.1 predicts that, when hemoglobin is fully saturated with 02 (i.e., when the S02 = 1), each gram of hemoglobin will bind 1.34 mL oxygen. One gram of hemoglobin normally binds 1.39 mL oxygen, but a small fraction (3% to 5%) of circulating hemoglobin is present as methemoglobin and carboxyhemoglobin and, since these forms of Hb have a reduced 02 binding capacity, the lower value of 1.34 mL/ g is considered more representative of the 02-binding capacity of the total hemoglobin pool (3).

Dissolved O2
The concentration of dissolved oxygen in plasma is determined by the solubility of oxygen in water (plasma) and the partial pressure of oxygen (P02) in blood. The solubility of 02in water is temperature-dependent (solubility increases slightly as temperature decreases). At normal body temperature (37°C), 0.03 mL of 02will dissolve in one liter of water when the P02 is 1 mm I-Ig (4). This is expressed as a *solubility coefficient* of 0.03 mL/L/mm I-Ig (or 0.003 mL/100 mL/mm Hg). The concentration of

TABLE 2.2 Normal Levels of Oxygen in Arterial and Venous Blood*

Parameter	Arterial Blood	Venous Blood
P02	90 mm Hg	40 mm Hg
O2 Saturation of Hb	0.98	0.73
Hb-bound O2	197 mL/L	147 mL/L
Dissolved O2	2.7 mL/L	1.2 mL/L
Total O2 content	200 mL/L	148 mL/L
Blood volumet	1.25 L	3.75 L
Volume of O2	250 mL	555 mL

dissolved O2 (in mL/ dL) (at normal body temperature) is then described by Equation 2.2.

$$\text{Dissolved O2} = 0.003 \times \text{P02} \qquad (2.2)$$

This equation reveals the limited solubility of oxygen in plasma. For example, if the P02 is 100 mm Hg, one liter of blood will contain only 3 mL of dissolved O2,

Arterial 02 *Content (CaO)*

The concentration of O2 in arterial blood (Ca02) can be defined by combining Equations 2.1 and 2.2, by using the 50_2 and P02 of arterial blood ($5a0_2$ and Pa02).

$$\text{Ca02} = (1.34 \times \text{I-Ib} \times 5a0_2) + (0.003 \times \text{PaO}) \qquad (2.3)$$

The normal concentrations of bound, dissolved, and total 02 in arterial blood are shown in Table 2.2. There are approximately 200 mL oxygen in each liter of arterial blood, and only 1.5% (3 mL) is dissolved in the plasma. The oxygen consumption of an average-sized adult at rest is 250 mL/min, which means that if we were forced to rely solely on the dissolved O2 in plasma, a cardiac output of 89 L/min would be necessary to sustain aerobic metabolism. This emphasizes the importance of hemoglobin in the transport of oxygen.

Venous O2 *Content (CV02)*

The concentration of O2 in venous blood (CV02) can be calculated in the same fashion as the Ca02, using the 02 saturation and P02 in venous blood (5V02 and PV02).

$$\text{CV02} = (1.34 \times \text{Hb} \times 5\text{V02}) + (0.003 \times \text{PV02}) \qquad (2.4)$$

The SV02 and PV02 are best measured in a pooled or "mixed venous" blood sample taken from the pulmonary artery (using a pulmonary artery catheter, as described in Chapter 9). As shown in Table 2.2, the normal 5V02 is 73% (0.73), the normal PV02 is 40 mm Hg, and the normal CV02 is approximately 15 mL/ dL (150 mL/L).

Simplified O2 *Content Equation*
The concentration of dissolved O2 in plasma is so small that it is usually eliminated from the O2 content equation. The O2 content of blood is then considered equivalent to the Hb-bound O2 fraction (see Equation 2.1).

O2 Content"" 1.34 X Hb X 502 (2.5)

Anemia versus Hypoxemia
Clinicians often use the arterial P02 (Pa02) as an indication of how much oxygen is in the blood. However, as indicated in Equation 2.5, the hemoglobin concentration is the principal determinant of the oxygen content of blood. The comparative influence of hemoglobin and Pa02 on the oxygen level in blood is shown in Figure 2.1. The graph in this figure shows the effect of proportional changes in hemoglobin concentration and Pa02 on the oxygen content of arterial blood. A 50% reduction in hemoglobin (from 15 to 7.5 g/ dL) is accompanied by an equivalent 50% reduction in Ca02 (from 200 to 101 mL/L), while a similar 50% reduction in the Pa02 (from 90 to 45 mm Hg) results in only an 18% decrease in Ca02 (from 200 to 163 mL/L). This graph shows that anemia has a much more profound effect on blood oxygenation than hypoxemia. It should also serve as a reminder to avoid using the Pa02 to assess arterial oxygenation. The Pa02 should be used to evaluate the efficiency of gas exchange in the lungs (see Chapter 19).

The Paucity of O2 in *Blood*
The total volume of O2 in circulating blood can be calculated as the product of the blood volume and the O2 concentration in blood. An estimate of the volume of O2 in arterial and venous blood is shown in Table 2.2. The combined volume of O2 in arterial and venous blood is a meager 805 mL. To appreciate what a limited volume this represents, consider that the whole-body 02 consumption of an average-sized adult at rest is about 250 mL/min. ThIS means that the total volume of 02 in blood is enough to sustain aerobic metabolism for only 3 to 4 minutes. Thus if a patient stops breathing, you have only a precious few minutes to begin assisted breathing maneuvers before the oxygen stores in the blood are completely exhausted.
The limited quantity of O2 in blood can also be demonstrated by considering the oxidative metabolism of glucose, which is described by the formula: C6H1206 + 6 O2 --> 6 CO2 + 6 H_20. This formula indicates that complete oxidation of one mole of glucose utilizes 6 moles of oxygen. To determine if the O2 in blood is enough to metabolize the glucose in blood, it is necessary to express the amount of glucose and oxygen in blood in

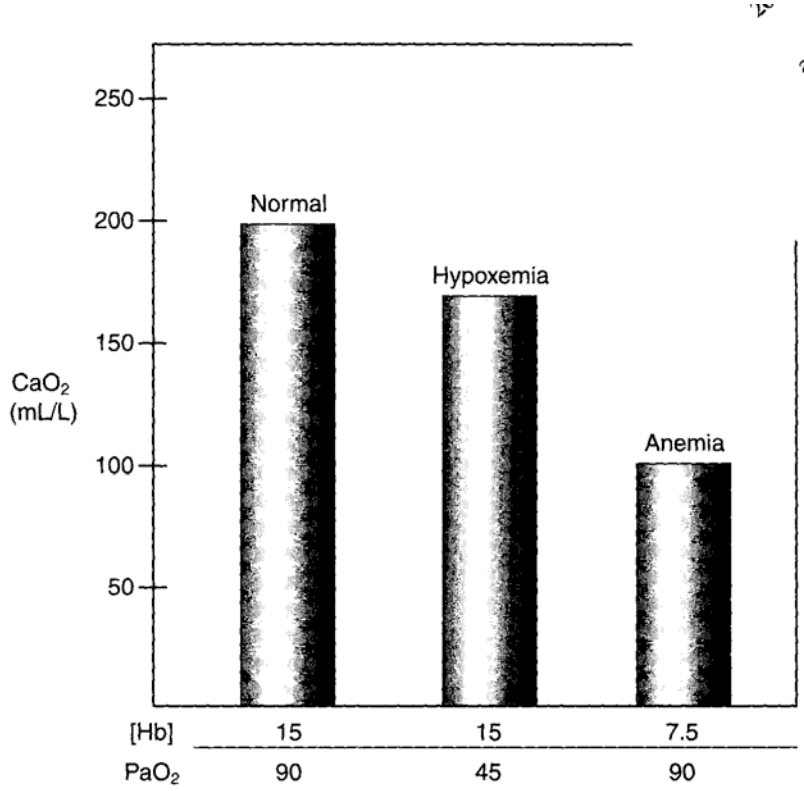


FIGURE 2.1 Graph showing the effects of equivalent (50%) reductions in hemoglobin concentration (Hb) and arterial PO_2 (PaO_2) on the oxygen concentration in arterial blood (CaO_2).

millimoles (mmol). (The values shown here are based on a blood glucose level of 90 mg/dL or 90/180 = 0.5 mmol/dL, a blood volume of 5 liters, and a total blood O2 of 805 mL or 805/22.4 = 36.3 mmol):

Total glucose in blood.	25 mmol
Total O2 in blood	36.3 mmol
O2 need of glucose metabolism.	150 mmol

This shows that the O2 in blood is only about 20% to 25% of the amount needed for the complete oxidative metabolism of the glucose in blood.

Why so *Little O2 ?*

The obvious question is why an organism that requires oxygen for survival is designed to carry on metabolism in an oxygen-limited environment? The answer may be related to the toxic potential of oxygen. Oxygen is well known for its ability to produce lethal cell injury via the production of toxic metabolites (superoxide radical, hydrogen peroxide,

and the hydroxyl radical), so limiting the oxygen concentration in the vicinity of cells may be a mechanism for protecting cells from oxygen induced cell injury. The role of oxygen-induced injury (oxidant injury) in clinical disease is a very exciting and active area of study, and the bibliography at the end of this chapter includes a textbook *(Free Radicals* in *Biology and Medicine)* that is the best single source of information on this subject.

The Abundance oj Hemoolobin

In contrast to the small volume of oxygen in blood, the total mass of circulating hemoglobin seems excessively large. If the normal serum Hb is 15 g/dL (150 g/L) and the normal blood volume is 5 liters (70 mL/kg), the total mass of circulating hemoglobin is 750 grams (0.75 kg) or 1.65 lbs. To demonstrate the enormous size of the blood hemoglobin pool, the illustration in Figure 2.2 compares the mass of hemoglobin to the normal

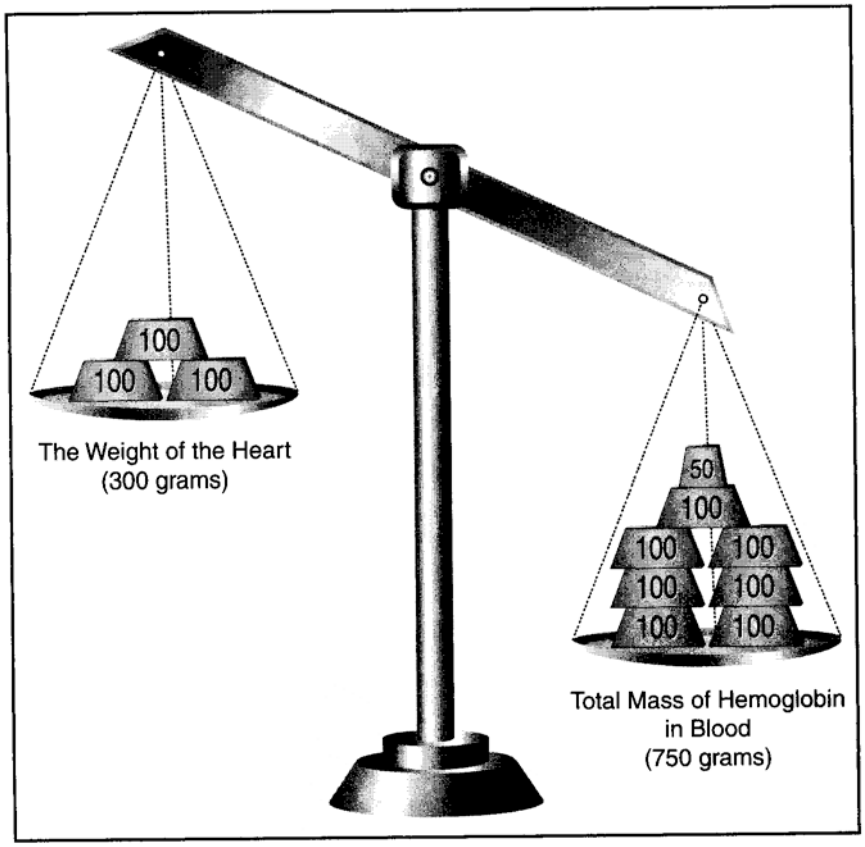


FIGURE 2.2 A balance scale demonstrating the excess weight of circulating hemoglobin when matched with the normal weight of the heart. The numbers on the small weights indicate the weight of each in grams.

weight of the heart. The heart weighs only 300 grams, so the pool of circulating hemoglobin is 2.5 times heavier than the heart! This means that every 60 seconds, the heart must move a mass that is more than twice its own weight through the circulatory system.

Is all this hemoglobin necessary? As shown later, when the extraction of oxygen from the systemic capillaries is maximal, 40% to 50% of the hemoglobin in venous blood remains fully saturated with oxygen. This means that almost half of the circulating hemoglobin is not used to support aerobic metabolism. What is the excess hemoglobin doing? Transporting carbon dioxide, as described later in the chapter.

Oxygen Delivery (D02)

The oxygen that enters the bloodstream in the lungs is carried to the vital organs by the cardiac output. The rate at which this occurs is called the *oxygen delivery* (D02). The D02 describes the volume of oxygen (in milliliters) that reaches the systemic capillaries each minute. It is equivalent to the product of the O2 content in arterial blood (Ca02) in mL/L and the cardiac output (Q) in L/min (2,5-7).

$$D02 = Q \times Ca02 \times 10 \qquad (2.6)$$

(The multiplier of 10 is used to convert the Ca02 from mL/dL to mL/L, so the D02 can be expressed in mL/min.) If the Ca02 is broken down into its components (1.34 X Hb X Sa02), Equation 2.6 can be rewritten as

$$D02 = Q \times 1.34 \times Hb \times 5a0_2 \times 10 \qquad (2.7)$$

When a pulmonary artery catheter is used to measure cardiac output (see Chapter 9), the D02 can be calculated by using Equation 2.7. The normal D02 in adults at rest is 900-1,100 mL/min, or 500-600 mL/min/m2 when adjusted for body size (see Table 2.3).

TABLE 2.3 Normal Ranges for Oxygen and Carbon Dioxide Transport Parameters

Parameter	Absolute Range	Size-Adjusted Range*
Cardiac output	5-6 L/min	2.4-4.0 L/min/m2
02 Delivery	900-1,100 mL/min	520-00 mL/min/m^2
O2 Uptake	*200-270 mL/min*	110-160 mL/min/m^2
O2 Extraction ratio	0.20-0.30	
CO2 Elimination	160-220 mL/min	*90-130 mL/min/m2*
Respiratory quotient	0.75-0.85	

'Size-adjusted values are the absolute values divided by the patient's body in square meters (m^2).

Oxygen Uptake (V02)

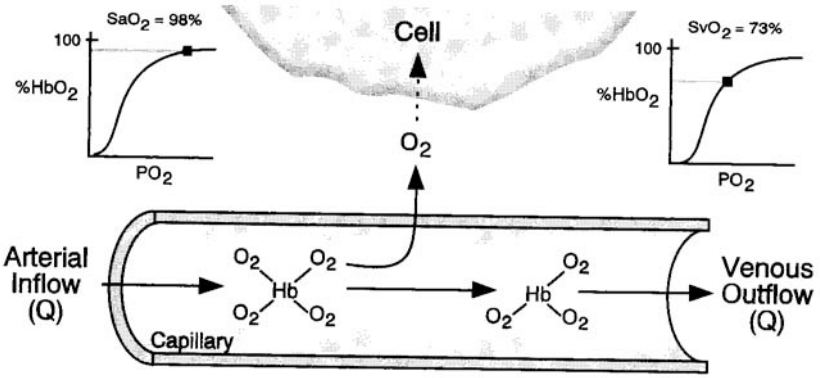
When blood reaches the systemic capillaries, oxygen dissociates from hemoglobin and moves into the tissues. The rate at which this occurs is called the *oxygen uptake* (V02). The V02 describes the volume of oxygen (in mL) that leaves the capillary blood and moves into the tissues each minute. 5ince oxygen is not stored in tissues, the V02 is also a measure of the *oxygen consumption* of the tissues. The V02 (in mL/min) can be calculated as the product of the cardiac output (Q) and the arteriovenous oxygen content difference (Ca02 - CV02).

V02 = Q X (Ca02 - CV02) X 10 (2.8)

(The multiplier of 10 is included for the same reason as explained for the D02·) This method of deriving V02 is called the *reverse Fick method* because Equation 2.8 is a variation of the Fick equation (where cardiac output is the derived variable: Q = V02/Ca02 - CV02) (8). 5ince the Ca02 and CV02 share a common term (1.34 X Hb X 10), Equation 2.8 can be restated as

V02 = Q X 13.4 X Hb X ($5a0_2$ - 5V02) (2.9)

This equation expresses V02 using variables that can be measured in clinical practice. The determinants of V02 in this equation are illustrated in Figure 2.3. The normal range for V02 in healthy adults at rest is 200-300 mL/min, or 110-160 mL/min/m^2 when adjusted for body size (see Table 2.3).



$$VO_2 = Q \times Hb \times 13.4 \times (SaO_2 - SvO_2)$$

FIGURE 2.3 A schematic representation of the factors that determine the rate of oxygen uptake (VO_2) from the microcirculation. SaO_2 and SvO_2 = Oxygen saturation of hemoglobin in arterial and venous blood, respectively; PO_2 = partial pressure of oxygen; Hb = a hemoglobin molecule.

Fick vs *Whole-BodyV02*

The V02 in the modified Fick equation is not equivalent to the wholebody V02 because it does not include the O2 consumption of the lungs (8-10). Normally, the V02 of the lungs represents less than 5% of the whole-body V02 (9), but it can make up 20% of the whole-body V02 in patients with inflammatory conditions in the lungs (which are common in ICU patients) (10). This discrepancy can be important when V02 is used as an end-point of hemodynamic management (see Chapter 11) because an underestimate of whole-body V02 could lead to overaggressive management to augment the V02. Direct measurement of the V02 (described next) is a more accurate representation of the whole-body V02.

Direct Measurement oj V02

The whole-body V02 can be measured directly by monitoring the rate of oxygen disappearance from the lungs. This can be accomplished with a specialized instrument equipped with an oxygen gas analyzer that is connected to the proximal airway (usually in intubated patients) to measure the O2 concentration in inhaled and exhaled gas. The device records and displays the V02 as the product of minute ventilation (V E) and the fractional concentration of oxygen in inhaled and exhaled gas (FI02 and FE02)·

$$V02 = VE \times (FI02 - FE02) \qquad (2.10)$$

The direct measurement of V02 is more accurate than the calculated (Fick) V02 because it is a closer approximation to the whole-body V02' **It** has several other advantages over the Fick V02, and these are described in Chapter 11. The major shortcoming of the direct V02 measurement is the lack of availability of monitoring equipment in many ICUs, and the need for trained personnel to operate the equipment.

Oxygen-Extraction Ratio (02ER)

The fraction of the oxygen delivered to the capillaries that is taken up into the tissues is an index of the efficiency of oxygen transport. This is monitored with a parameter called the *oxygen extraction ratio* (02ER), which is the ratio of O2 uptake to O2 delivery.

$$02ER = V02/D02 \qquad (2.11)$$

This ratio can be multiplied by 100 and expressed as a percentage. 5ince the V02 and D02 share common terms (Q X 1.34 X Hb X 10), Equation 2.11 can be reduced to an equation with only two measured variables:

$$02ER = (Sa02 - SV02) / Sa02 \qquad (2.12)$$

When the Sa02 is close to 1.0 (which is usually the case), the 02ER is roughly equivalent to the (Sa02 - SV02) difference: 02ER ~ Sa02 - SV02.

The 02ER is normally about 0.25 (range = 0.2-0.3), as shown in Table 2.3. This means that only 25% of the oxygen delivered to the systemic capillaries is taken up into the tissues. Although O2 extraction is normally low, it is adjustable and can be increased when oxygen delivery is impaired. The adjustability of O2 extraction is an important factor in the control of tissue oxygenation, as described next.

CONTROL OF OXYGEN UPTAKE

The oxygen transport system operates to maintain a constant flow of oxygen into the tissues (a constant V02) in the face of changes in oxygen supply (varying D02). This behavior is made possible by the ability of O2 extraction to adjust to changes in O2 delivery (11). The control system for V02 can be described by rearranging the O2 extraction equation (Equation 2.11) to make V02 the dependent variable:

V02 = D02 X 02ER

This equation shows that the V02 will remain constant if changes in O2 delivery are accompanied by equivalent and reciprocal changes in O2 extraction. However, if the O2 extraction remains fixed, changes in D02 will be accompanied by equivalent changes in V02. The ability of O2 extraction to adjust to changes in D02 therefore determines the ability to maintain a constant V02.

The D02-V02 Relationship

The normal relationship between 02 delivery and O2 uptake is shown in the graph in Figure 2.4 (11). As O2 delivery (D02) begins to decrease below normal (as indicated by the arrowhead on the graph), the 02 uptake (V02) initially remains constant, indicating that the O2 extraction (02ER) is increasing as the D02 decreases. Further decreases in D02 eventually leads to a point where the V02 begins to decrease. The transition from a constant to a varying V02 occurs when the O2 extraction increases to a maximum level of 50% to 60% (02ER = 0.5 to 0.6). Once the 02ER is maximal, further decreases in D02 will result in equivalent decreases in V02 because the O,ER is fixed and cannot increase further. When this occurs, the V02 is referred to as being *supply-dependent,* and the rate of aerobic metabolism is limited by the supply of oxygen. This condition is known as *dysoxia* (12). As aerobic metabolism (V02) begins to decrease, the oxidative production of high energy phosphates (ATP) begins to decline, resulting in impaired cell function and eventual cell death. The clinical expression of this process is *clinical shock* and progressive *multiorgan failure (13).*

The Critical D02

The D02 at which the V02 becomes supply-dependent is called the *critical oxygen delivery* (critical 00_2), It is the lowest D02 that is capable of

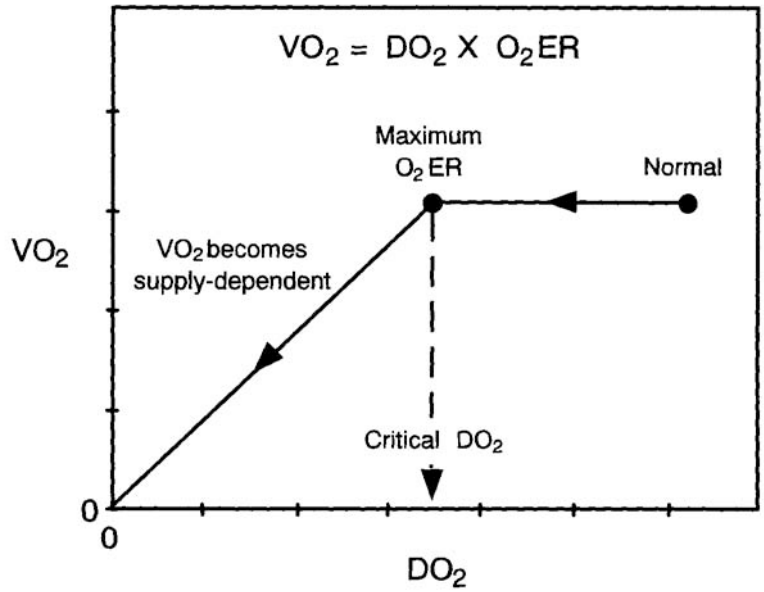


FIGURE 2.4 Graph showing the normal relationship between O_2 delivery (DO_2) and O_2 uptake (VO_2) when O_2 delivery is decreased progressively, as indicated by the *arrowheads*.

fully supporting aerobic metabolism and is identified by the bend in the D02-V02 curve (see Fig. 2.4). Despite the ability to identify the anaerobic threshold, the critical D02 has limited clinical value. First, the critical D02 has varied widely in studies of critically **ill** patients (11,13,14), and it is not possible to predict the critical D02 in any individual patient in the ICU. 5econd, the D02-V02 curve can be curvilinear (i.e., without a single transition point from constant to changing V02) (15), and in these cases, it is not possible to identify a critical D02.

The D02:V02 ratio may be a more useful parameter than the critical D02 for identifying (and avoiding) the anaerobic threshold. Maintaining a D02:V02 ratio of 4:1 or higher has been recommended as a management strategy to avoid the anaerobic threshold in critically **ill** patients (7).

CARBON DIOXIDE TRANSPORT

Carbon dioxide (C02) is the major end-product of oxidative metabolism, and because it readily hydrates to form carbonic acid, it can be a source of significant acidosis if allowed to accumulate. The importance of eliminating CO2 from the body is apparent in the behavior of the ventilatory control system, which operates to maintain a constant P02 in arterial blood ($PaC0_2$). An increase in $PaC0_2$ of 5 mm Hg can result in a twofold increase in minute ventilation. To produce an equivalent increment in ventilation, the arterial P02 must drop to 55 mm Hg (16). The tendency

for the ventilatory control system to pay attention to hypercapnia and ignore hypoxemia is intriguing because it suggests that the ventilatory system is more concerned with eliminating metabolic waste ($C0_2$) than promoting aerobic metabolism (by supplying oxygen).

The Hydration of CO2

The total body CO2 in adults is reported at 130 liters (17), which doesn't seem possible in light of the fact that the total body water of an adult averages only 40 to 45 liters. This dilemma can be explained by the tendency for CO2 to enter into a chemical reaction with water and produce carbonic acid. The hydration of CO2 and its transformation to carbonic acid is a continuous process, and this creates a perpetual gradient that drives CO2 into solution. 5ince the CO2 is continuously disappearing, the total volume of CO2 in the solution could exceed the volume of the solution. If you have ever opened a bottle of warm champagne, you have witnessed how much CO2 can be dissolved in a solution.

C02 Transport Scheme

The transport of CO2 is a complex process that is shown in Figure 2.5. The centerpiece of CO2 transport is the reaction of C02 with water. The first stage of this reaction involves the formation of carbonic acid. This is normally a slow reaction and takes about 40 seconds to complete (18). The reaction speeds up considerably in the presence of the enzyme carbonic anhydrase and takes less than 10 milliseconds (msec) to complete (18). Carbonic anhydrase is confined to the red cell and is not present in

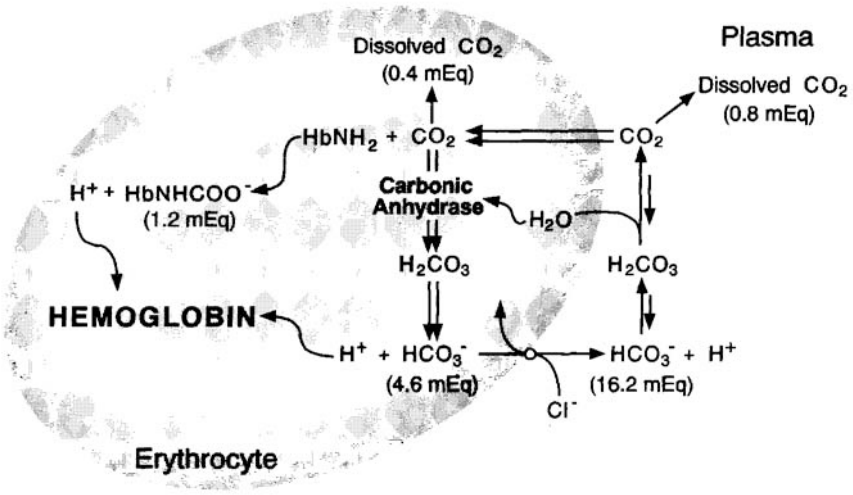


FIGURE 2.5 The chemical reactions involved in CO_2 transport. Values in parentheses indicate the amount of each component normally present in 1 L of venous blood. The *double arrows* indicate favored pathways.

plasma. Thus CO2 is rapidly hydrated only in the red blood cell, and this creates a pressure gradient that drives CO2 into the cell.
Carbonic acid dissociates instantaneously to produce hydrogen and bicarbonate ions. A large fraction of the bicarbonate generated in the red cell is pumped back into the plasma in exchange for chloride. The hydrogen ion generated in the red cell is buffered by the hemoglobin. In this way, the CO2 that enters the red cell is dismantled and the parts stored (hemoglobin) or discarded (bicarbonate) to create room for more CO2 to enter the red cell. These processes create a sink to accommodate large volumes of CO2 in the red cell.
A small fraction of CO2 in the red cell reacts with free amino groups on hemoglobin to produce carbamic acid, which dissociates to form carbamino residues (HbNHCOO) and hydrogen ions. This reaction provides another opportunity for hemoglobin to act as a buffer.

CO2 Content of Blood
The different measures of CO2 in blood are listed in Table 2.4. Like oxygen, CO2 is present in a dissolved form, and the concentration of dissolved CO2 is determined as the product of the $PC0_2$ and the solubility coefficient for CO2 in water (i.e., 0.69 mL/L/mm Hg at 37°C) (19). The dissolved CO2 content in arterial and venous blood is shown in Table 2.4 (20). Like oxygen, the dissolved CO2 is only a small fraction of the total CO2 content of blood. The total content of CO2 in blood is the summed contribution of several components, including the dissolved CO2 and bicarbonate concentrations in plasma and erythrocytes, and the carbamino CO2 content in erythrocytes. The normal values for each of these components in venous blood are shown in Figure 2.5. If these values are summed, the total CO2 content is 23 mEq/L, with 17 mEq/L in plasma and 6 mEq/L in the red cell. The preponderance of CO2 in plasma is deceiving because most of the plasma component is in the form of bicarbonate that has been expelled from the red blood cell.

TABLE 2.4 Normal Levels of C02 in Arterial and Venous Blood*

Parameter	Arterial Blood	Venous Blood
$PC0_2$	40 mm Hg	45 mm Hg
Dissolved CO2	27 mL/L	29 mL/L
Total CO2 content	490 mL/L	530 mL/L
Blood volumet	1.25 L	3.75 L
Volume of CO2	613 mL	1,988 mL

'Values shown are for a body temperature of 37"C.
tVolume estimates are based on a total blood volume (TBV) of 5 L, arterial 010.25 x TBV, and venous blood volume of 0.75 x TBV.
Abbreviations: $PC0_2$= partial pressure of CO2,

TABLE 2.5 Buffering Capacity of Blood Proteins

	Hemoglobin	Plasma Proteins
Inherent buffer capacity	0.18 mEq *Wig*	0.11 mEq *Wig*
Concentration in blood	150 giL	38.5 giL
Total buffer capacity	27.5 mEq *WIL*	4.2 mEq *WIL*

Because CO2 readily dissociates into ions (hydrogen and bicarbonate), the concentration of CO2 is often expressed in ion equivalents (mEq/L), as in Figure 2.5. Conversion to units of volume (mL/L or mL/ dL) is possible because one mole of CO2 will occupy a volume of 22.3 liters. Therefore:
CO2 (mL/L) = CO2 (mEq/L X 22.3)
Table 2.4 includes the CO2 content of blood expressed in volume units (20). Note that the total volume of CO2 in blood (about 2.6 liters) is more than 3 times the volume of O2 in blood (805 mL).

Hemoglobin As a Buffer
Figure 2.5 shows that hemoglobin plays a central role in CO2 transport by acting as a buffer for the hydrogen ions generated by the hydration of CO2 in the red blood cell. The buffering capacity of hemoglobin is shown in Table 2.5 (21). Note that the total buffering capacity of hemoglobin is six times greater than the combined buffering capacity of all the plasma proteins.
The buffering actions of hemoglobin are attributed to imidazole groups that are found on the 38 histidine residues in the molecule. These imidazole groups have a dissociation constant with a pK of 7.0, so they will act as effective buffers in the pH range from 6 to 8 (buffers are effective within one pI-I unit on either side of the pK) (20). In contrast, the carbonic acid-bicarbonate buffer system has a pK of 6.1, so this buffer system will be effective in the pH range from 5.1 to 7.1. Comparing the buffer ranges of hemoglobin and bicarbonate shows that hemoglobin is a more effective buffer than bicarbonate in the pH range encountered clinically (pI-I 7 to 8)! This aspect of hemoglobin function deserves more attention.

Why the Excess Hemoolobin?
As described earlier, the mass of hemoglobin in blood is far greater than needed to transport oxygen, and considering the role played by hemoglobin in CO2 transport, it is likely that the excess hemoglobin is needed for CO2 transport. Considering the large volume of CO2 in blood (see Table 2.4), it is easier to understand why there is so much hemoglobin in blood.

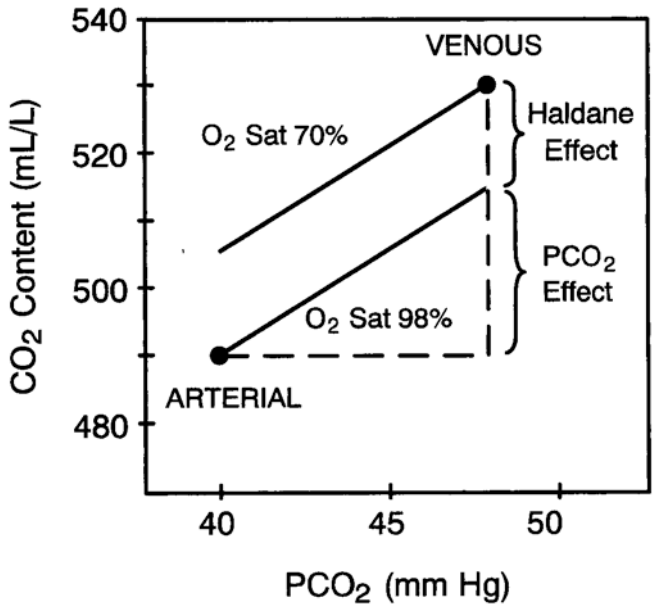


FIGURE 2.6 Carbon dioxide dissociation curves for arterial blood (O_2 Sat = 98%) and venous blood (O_2 Sat = 70%). The two points indicate the CO_2 content of arterial and venous blood. The brackets show the relative contributions of hemoglobin desaturation (Haldane effect) and metabolic CO_2 production (PCO_2 effect) to the increase in CO_2 content that occurs from arterial to venous blood. (From Forster RE II, DuBois A, Briscoe WA, et al. The lung, 3rd ed. Chicago: Yearbook Medical Publishers, 1986:238.)

The Haldane Eifect

Hemoglobin has a greater buffer capacity when it is in the desaturated form, and blood that is fully desaturated can bind an additional 60 mL/L of carbon dioxide. The increase in CO2 content that results from oxyhemoglobin desaturation is known as the *Haldane effect.* The CO2 dissociation curves in Figure 2.6 show that the Haldane effect plays an important role in the uptake of CO2 by venous blood. The two points on the graph show that the CO2 content in venous blood is 40 mL/L higher than in arterial blood. The brackets indicate that about 60% of the increased CO2 content in venous blood is due to an increase in *PC021* while 40% is due to oxyhemoglobin desaturation. Thus, the Haldane effect is responsible for almost half of the rise in CO2 content in venous blood. This is another example of the important role played by hemoglobin in CO2 transport.

CO2 Elimination (VC02)

The dissociation of CO2 that occurs during transport in venous blood is reversed when the blood reaches the lungs. The reconstituted CO2 is then eliminated through the lungs. The elimination of CO2 (VC02) can

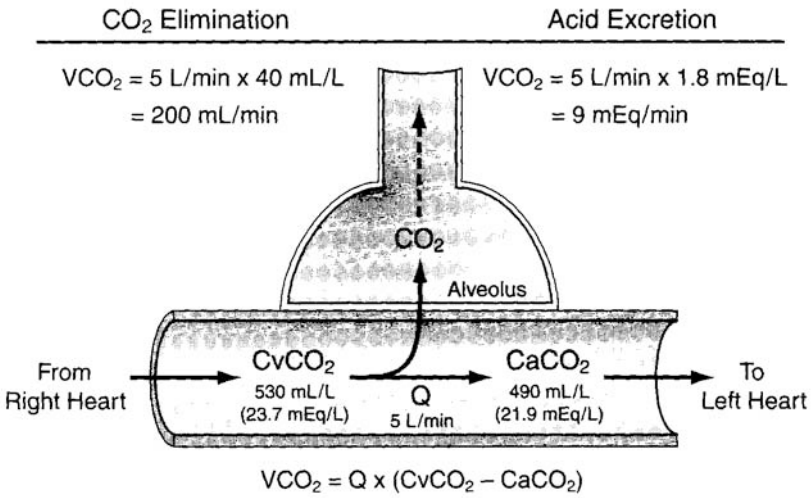


FIGURE 2.7 A schematic representation of the factors that contribute to CO_2 elimination through the lungs (VCO_2). The VCO_2 is expressed as gas flow (mL/min) and as acid excretion (mEq/min). Q = cardiac output; $CaCO_2$ = arterial CO_2 content; $CvCO_2$ = venous CO_2 content.

be described by using an equation that is similar in form to the V02 equation <Equation 2.8),

$$VC02 = Q \times (CvC0_2 - CaC0_2) \qquad (2.14)$$

$CvC0_2$ and CaC02 represent the CO2 content in venous and arterial blood, respectively (note that the arterial and venous components are reversed when compared with the V02 equation). The determination of $VC0_2$ by using the variables in Equation 2.14 is shown in Figure 2.7.

Unfortunately, there are no simple derivative equations for CO2 content in blood, so the $VC0_2$ is usually measured directly. As shown in Table 2.3, the normal $VC0_2$ in adults is 160-220 mL/min, or 90-130 mL/ min/m2 when adjusted for body size. The $VC0_2$ is normally about 80% of the V02, so the VC02/V02 ratio is normally 0.8. The VC02/ V02 ratio, which is called the *respiratory quotient* (RQ), is used to identify the predominant type of nutrient substrate (i.e., protein, fat, or carbohydrate) being metabolized. Chapter 45 contains more information on the RQ.

VC02 as Acid Excretion

Carbon dioxide is essentially an acid because of its tendency to dissociate and form carbonic acid. Thus when the CO2 content is expressed in ion equivalents (mEq/L), the $VC0_2$ (mEq/min) can be used to describe the rate of volatile acid excretion through the lungs. This is shown in

Figure 2.7. The normal rate of acid excretion via the lungs is 9 mEq/min, or 12,960 mEq in 24 hours. 5ince the kidneys excrete only 40 to 80 mEq of acid every 24 hours (20), the principal organ of acid excretion in the body is the lungs, not the kidneys.

REFERENCES