5.8 The Cardiac Function Curve

Learning Objectives

- Define the stroke volume
- Calculate the cardiac output from the stroke volume and heart rate
- List the determinants of the stroke volume
- On a PV diagram, identify: ventricular filling, isovolumetric contraction, ejection, isovolumetric relaxation
- List three components of cardiac work
- Describe the Frank–Starling Law of the Heart
- Define central venous pressure, preload, and afterload
- Draw a normal, resting cardiac function curve
- Describe what happens to stroke volume when preload is increased at constant afterload
- Describe what happens to stroke volume when afterload is increased at constant preload
- Describe Fick's method for estimating cardiac output
- Describe the indicator dilution method for estimating cardiac output
- Describe the effect of positive inotropic agents on the cardiac function curve

CARDIAC OUTPUT IS THE FLOW PRODUCED BY THE HEART

As described in Chapter 5.4, each beat of the heart ejects a volume of blood, the **stroke volume**, equal to the difference between the end-diastolic volume of the left ventricle and the end-systolic volume:

$$[5.8.1] \qquad SV = EDV - ESV$$

where SV is the **stroke volume**, EDV is the **end-diastolic volume**, and ESV is the **end-systolic volume**. The ejected volume then travels through the **systemic circulation** that perfuses all of the tissues except the lungs. The **cardiac output** is the average flow into the aorta, calculated as:

$$[5.8.2] \qquad CO = SV \times HR$$

where CO is the **cardiac output**, SV is the stroke volume, and HR is the **heart rate**, in beats per minute. The units of CO are $L\,min^{-1}$. Typical values at rest are $4–6\ L\,min^{-1}$, but this can increase as much as 5-fold during strenuous exercise. According to Eqn [5.8.2], CO can be varied by changing SV or changing HR or both.

STROKE VOLUME IS DETERMINED BY *PRELOAD, AFTERLOAD,* AND *CONTRACTILITY*

The amount of blood ejected by the heart each beat depends on the force of the heart's contraction and by how much blood is in the heart. These can be altered by two basic mechanisms: the degree of stretch of the ventricle prior to systole, and the heart's inherent ability to produce tension, or its contractility. The degree of stretch of the ventricle depends on the pressure in the veins that passively fill the heart, or the **central venous pressure**. This is also called the **preload** because it is the pressure load prior to contraction of the heart. Stretching the heart up to a point shifts the contractility up the ascending limb of the length–tension curve, and more force is generated. **The heart's contractility is its ability to produce force at any given stretch**. Sympathetic stimulation increases the heart's contractility and cardiac disease reduces it.

The heart ejects blood into the high-pressure arteries. The pressure in the arteries is called the **afterload** because the heart muscle feels this pressure after contraction has begun and intraventricular pressure rises to equal or exceed aortic pressure. If arterial pressure is raised, it takes longer for the heart to generate pressure in its isovolumetric contraction phase, and more of the contractile energy is consumed in raising the pressure as opposed to ejecting the blood. This makes subjective sense: the heart is pumping blood against the arterial pressure, much like a weight that you might lift. Increasing the arterial pressure reduces the rate of pumping blood just like increasing the weight reduces your rate of lifting it.

THE INTEGRAL OF THE PRESSURE–VOLUME LOOP IS THE PV WORK

The Wiggers diagram (Figure 5.6.11) shows the time course of pressure development and the volume of the left ventricle with time during a single cardiac cycle. At each time, we can plot the pressure in the left ventricle against its volume. The result of such a plot is the **pressure–volume loop** shown in Figure 5.8.1.

During each cycle, the pressure–volume relationship traces a counter-clockwise loop. We begin with the opening of the mitral valve (point A in Figure 5.8.1)

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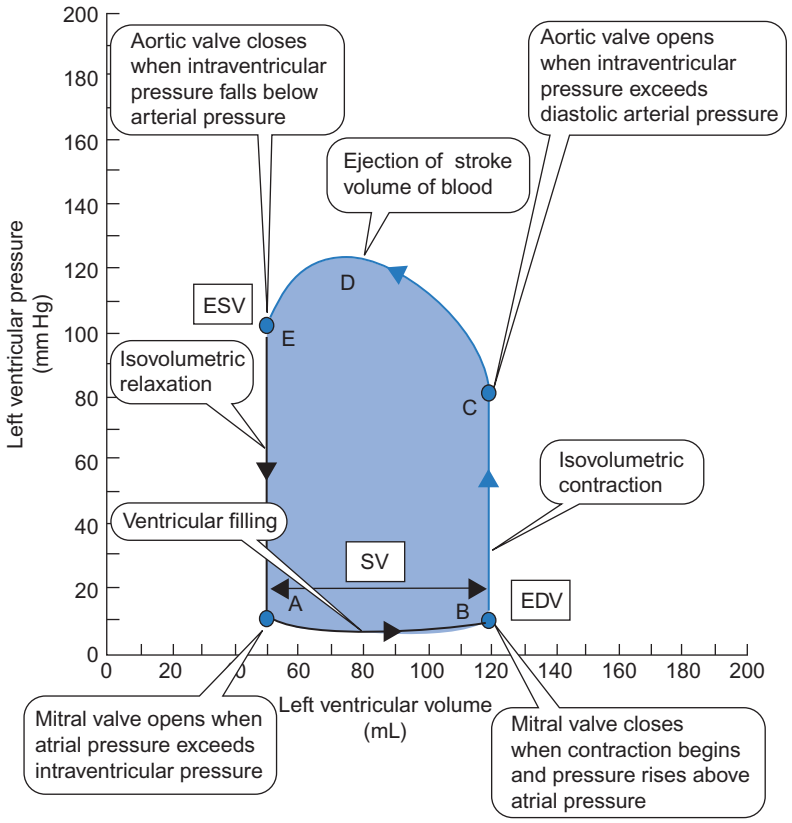

FIGURE 5.8.1 Pressure–volume loop of the cardiac cycle. Blood enters the left ventricle during diastole after the mitral valve opens (A) and continues to enter until it reaches the end-diastolic volume, about 120 mL. Isovolumetric contraction raises pressure to the level of the arterial pressure, which causes the aortic valve to open and the heart ejects about 70 mL of blood. When ventricular pressure is less than arterial pressure, the aortic valve closes (E) and the heart relaxes isovolumetrically. At this point the left ventricle contains the ESV, about 50 mL. The indicated area is the pressure–volume work done by the heart during each heart beat.

when left atrial pressure exceeds that of the left ventricle. Blood flows from the left atria into the left ventricle, and pressure in the left ventricle actually decreases because the heart is continuing its relaxation and expanding slightly faster than it is filling. At the end of diastole the heart is filled and pressure has again risen to about 7 mmHg. At this point, the **EDV** is about 120 mL. The heart begins to contract (point B in Figure 5.8.1) and enters the isovolumetric phase of contraction in which pressure develops until left ventricular pressure exceeds that in the aorta. At the point at which the aortic valve opens, arterial pressure is at its lowest point, the **diastolic pressure**. This is typically about 80 mmHg (point C in Figure 5.8.1). Once the aortic valve opens, the heart ejects blood into the aorta, causing its pressure to rise and causing passive stretch of the elastic aorta. The pressure momentarily rises and then falls again as the ejected blood travels down the arterial system and as the heart begins to relax (around point D in Figure 5.8.1). When intraventricular pressure falls below arterial pressure, the aortic valve snaps shut (point E in Figure 5.8.1) and the heart undergoes isovolumetric relaxation. The volume at this point is the **ESV**. The stroke volume is the volume of blood ejected in the heart cycle, and it corresponds to EDV − ESV = 120 mL −50 mL = 70 mL. This is a typical value for the stroke volume.

The work increment, dW, is $F \times \mathrm{d}x$, where dx is the distance increment; simultaneously multiplying and dividing by the area, we have

$$\mathrm{d}W = \frac{F}{A} A\, \mathrm{d}x = P\, \mathrm{d}V \qquad [5.8.3]$$

Thus the net pressure–volume work done *by* the heart is the integral of the pressure–volume curve minus the work done *on* the heart *by* the blood. The work done on the heart by the blood is the integral of the pressure– volume curve from points A to B in Figure 5.8.1. The net work is the area shown in Figure 5.8.1.

TOTAL WORK OF THE HEART INCLUDES PRESSURE, KINETIC, AND GRAVITATIONAL TERMS

The heart does not just raise the blood from the low end-diastolic pressure to its high systolic pressure, but it also accelerates it. The blood in the aorta has a velocity and therefore it has a kinetic energy. In addition, in the standing position, the heart lifts the blood against the force of gravity. The total work is thus given as

$$W = W_P + W_K + W_G = \frac{PV + 1/2\ \Delta V\ v^2 + \Delta \boldsymbol{g}\ h\ V}{2\ \rho\ V\ v^2 + \rho\ \boldsymbol{g}\ h\ V} \qquad [5.8.4]$$

where W_P is the pressure term, W_K is the kinetic energy term, and W_G is the gravitational energy term. V is the volume of blood, ρ is the density, $\boldsymbol{g}$ is the acceleration due to gravity, and h is the height to which the blood is raised. Ordinarily the kinetic energy is relatively small, but it can be significant in situations in which the kinetic energy is converted to pressure or *vice versa*. Each of these energy terms can be divided by the volume to derive the energy per unit volume, and are referred to as "equivalent pressures," all of which have the units of

force per unit area. The net equivalent pressure, P', is the sum of the equivalent pressures:

$$P' = P + 1/2\ \rho\ v^2 + \rho\ g\ h \quad [5.8.5]$$

The total energy difference, per unit volume, between any two points in the cardiovascular system can be expressed in terms of equivalent pressure:

$$P'_1 - P'_2 = (P_1 - P_2) + 1/2\,\rho(v_1^2 - v_2^2) + \rho g(h_1 - h_2) \quad [5.8.6]$$

STRETCH OF THE HEART DETERMINES THE STROKE VOLUME: THE FRANK–STARLING LAW OF THE HEART

In 1895, the German physiologist Otto Frank ligated the aorta of a frog heart so that the contractions of the heart were purely isovolumetric, and he then measured the pressure generated when the heart was stretched by increasing the diastolic volume. He found that **the isovolumetric pressure increased with stretch**. These experiments were extended by the English physiologist, Ernst Starling, who used a more physiological preparation of the isolated heart and lung of a dog. The heart was filled with warm oxygenated blood from a reservoir whose height controlled the **central venous pressure**, the pressure at the entrance to the right atrium. The right heart fills during diastole until the pressure in the right atrium and right ventricle is equal to this central venous pressure. Thus, the degree of distension of the right ventricle at the end of diastole is determined largely by this central venous pressure. Similarly, the pressure in the pulmonary vein determines the degree of left ventricular distension at the end of diastole. These two pressures, the central venous pressure and the pulmonary vein pressure, are called **filling pressure**. When the central venous pressure is increased, the right atrial end-diastolic pressure also increases and the right ventricle stretches. According to what Otto Frank found, this increases the force of contraction of the right ventricle, and more blood is ejected. This ejected blood flows through the lungs into the pulmonary vein and, because there is more blood filling the veins, increases the pressure in the pulmonary veins. Thus, the increased output of the right ventricle increases the pressure in the pulmonary veins, which in turn increases the end-diastolic stretch of the left ventricle. This increases the force of contraction of the left ventricle, ejecting more blood. Thus, increases in central venous pressure increases the output of both ventricles. This is the Frank–Starling Law of the Heart: **increasing right atrial pressure increases the stroke volume of both ventricles** (Figure 5.8.2).

THE VENTRICULAR FUNCTION CURVE PLOTS CARDIAC FUNCTION AGAINST RIGHT ATRIAL PRESSURE

Any curve that plots a measure of the energy of cardiac contraction (stroke volume, cardiac output) against some measure of cardiac fiber length is a ventricular function curve. Here we plot cardiac output against the right atrial pressure, as shown in Figure 5.8.3. This plot represents the **intrinsic regulation** of the heart to its inputs that occurs independently of nervous regulation of the heart. This ventricular function curve can also be regulated by the autonomic nervous system, called **extrinsic regulation**.

INCREASING PRELOAD INCREASES THE STROKE VOLUME, INCREASING AFTERLOAD DECREASES IT

The **afterload** for the heart is the arterial pressure into which the heart ejects its stroke volume. Because the heart is really two pumps in series, there are two afterload pressures. These are the pulmonary arterial pressure in the pulmonary circulation and the arterial pressure in the systemic circulation. As mentioned earlier, increasing afterload reduces the stroke volume

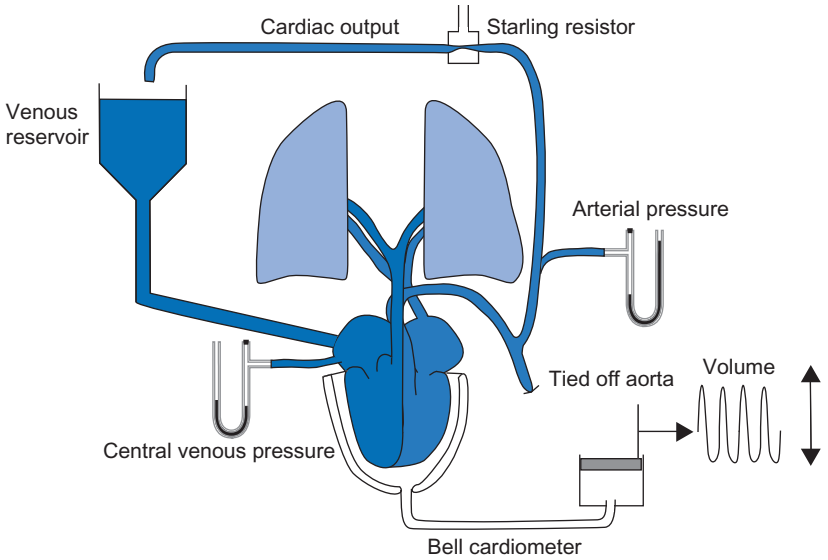

FIGURE 5.8.2 The Starling experiment. Starling perfused an isolated heart–lung preparation from dogs. The pressure of the blood returning to the right atrium was adjusted by raising or lowering the height of the venous reservoir. Both central venous pressure and arterial pressure were measured by mercury manometers. Arterial pressure were held constant by using a "Starling resistor" that mimicked the resistance of the systemic circulation, the total peripheral resistance. Heart volume was measured by using a bell cardiometer, an inverted glass bell that is attached to the atrioventricular groove by a rubber diaphragm. Ventricular volumes were recorded on a rotating drum.

because it takes longer for the heart to develop enough pressure to force open the aortic valve and more of its energy is taken to increase the pressure rather than eject the stroke volume. The PV loops that result from increased preload and increased afterload are shown in Figure 5.8.4. These PV loops are bounded by the passive and active tension curves of the heart, which are shown in Figure 5.8.4 as a function of volume, not length. When preload increases, the end-diastolic volume increases along the passive tension curve. Contraction of the heart begins its isovolumetric phase which raises the pressure to the diastolic arterial pressure. When it reaches this pressure, the aortic valve opens and the heart ejects blood into the aorta. Thus, if the afterload is kept constant while the preload increases, the stroke volume increases. If the afterload (diastolic arterial pressure) is also elevated while the preload is kept constant, it takes longer for the heart to develop pressure and it ejects blood for a consequently shorter period. Thus, the stroke volume of blood ejected at higher afterload is less and cardiac output is correspondingly less.

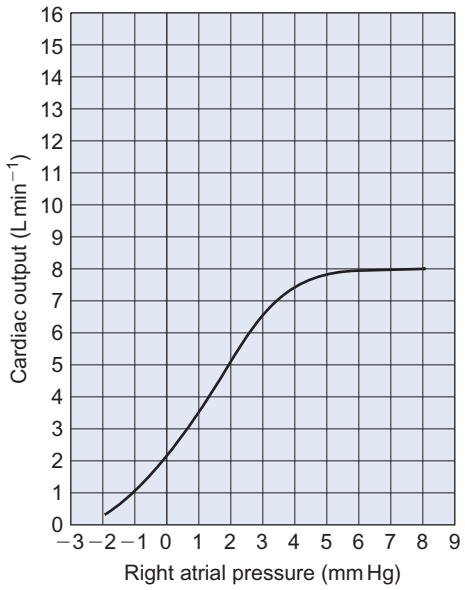

FIGURE 5.8.3 Ventricular function curve. The graph shows the cardiac output of the heart when it is pumping against a constant arterial resistance and heart rate when right atrial pressure is varied.

POSITIVE INOTROPIC AGENTS SHIFT THE CARDIAC FUNCTION CURVE UP AND TO THE LEFT

As described in Chapter 5.7, positive inotropic agents increase the force of cardiac contraction. Examples of these include the cardiac glycosides, norepinephrine that is released from sympathetic terminals, and epinephrine that is released from the adrenal gland and reaches the heart through the blood. Sympathetic stimulation increases the rate at which intraventricular pressure rises, which in turn decreases the time at which the ventricle begins ejecting blood into the aorta. Because it begins ejecting sooner, the heart empties more completely. The effect of sympathetic stimulation on left ventricular pressure is shown in Figure 5.8.5.

Alternate views of the effects of sympathetic stimulation are provided by the PV loop diagram (Figure 5.8.6) and the cardiac function curve (Figure 5.8.7). In the PV loop diagram, sympathetic stimulation increases cardiac contractility by raising the isovolumetric systolic curve and shifting it to the left. Higher pressure is developed at lower left ventricular volumes. This curve, along with the passive, diastolic curve, sets the limits of the PV loop. Increasing cardiac contractility also increases cardiac output at any given right atrial pressure, as shown in Figure 5.8.7.

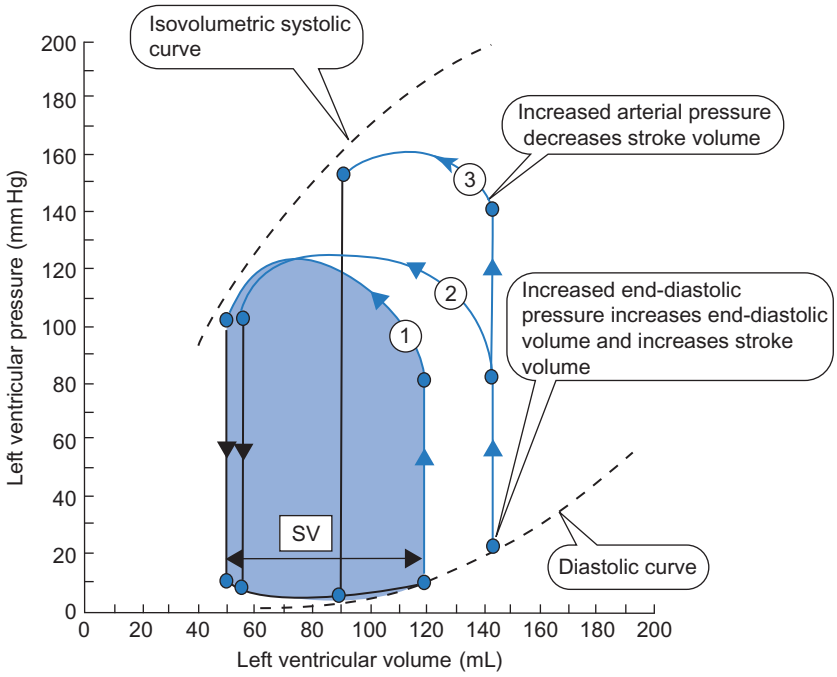

FIGURE 5.8.4 PV loops of the human ventricle. Loop 1 shows the control situation, which is identical to that shown in Figure 5.8.1. When the preload is increased while the arterial pressure is held constant (Loop 2), the end-diastolic volume increases along the passive tension curve (diastolic curve). This passive stretch of the ventricle causes an increase in stroke volume and cardiac output. Loop 3 shows the effect of increasing both the preload and the afterload. Increasing the arterial pressure reduces the stroke volume compared to the situation without increasing the afterload.

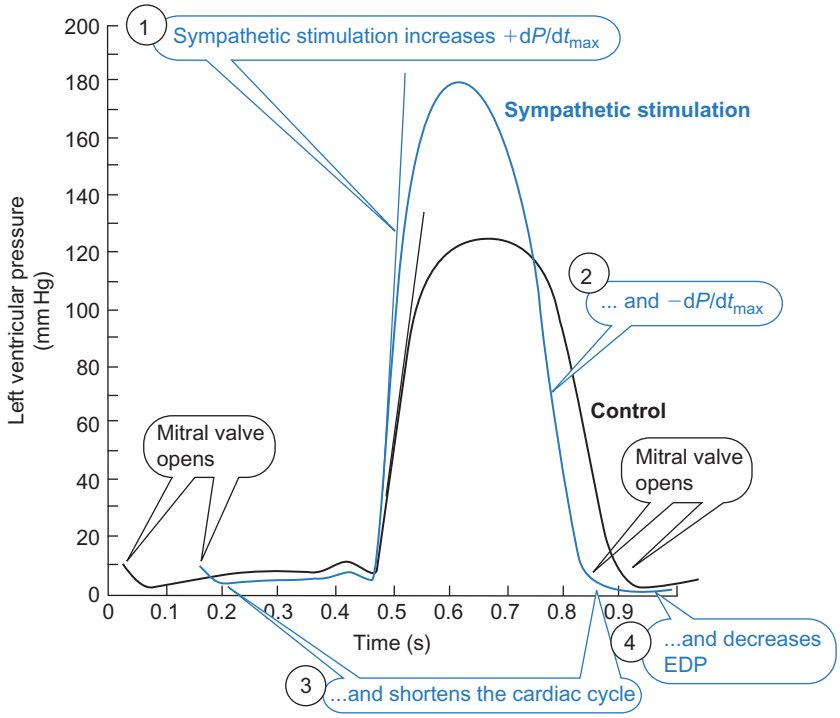

FIGURE 5.8.5 Effect of sympathetic stimulation on left ventricular pressures in the cardiac cycle. Sympathetic stimulation increases the rate of pressure rise ($+ dP/dt_{max}$) and the rate of pressure fall upon relaxation ($- dP/dt_{max}$), decreases the end-diastolic pressure (EDP) and shortens the cardiac cycle. All other things being equal, this increases cardiac output. As it turns out, this effect is limited because of the venous return—the heart cannot pump more blood than is delivered to it. Thus, sympathetic stimulation of the heart alone, by itself, only marginally increases cardiac output.

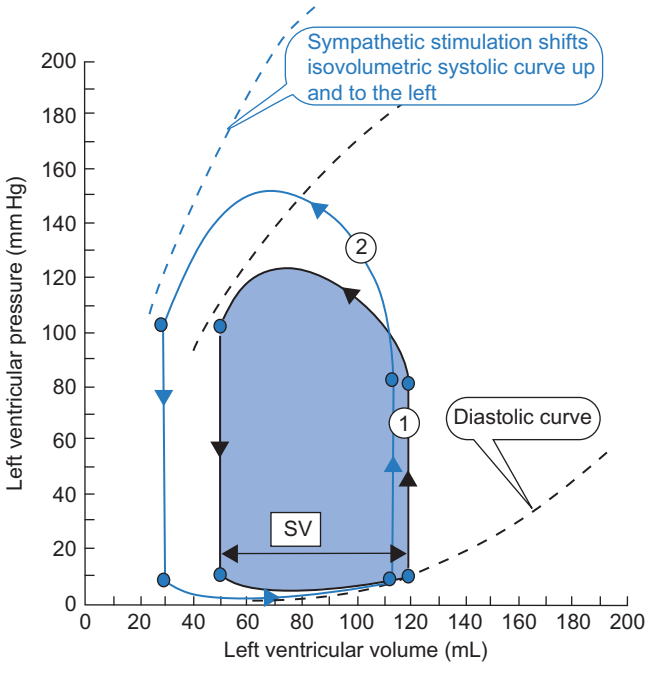

FIGURE 5.8.6 Effect of sympathetic stimulation on the PV loop of the left ventricle. Control loop (1); sympathetic stimulation (2). Sympathetic stimulation shifts the isovolumetric systolic curve up and to the left. The curve shows the effect of sympathetic stimulation on the heart alone, independent of effects on the vasculature. Thus, the diastolic and systolic pressure are shown unchanged.

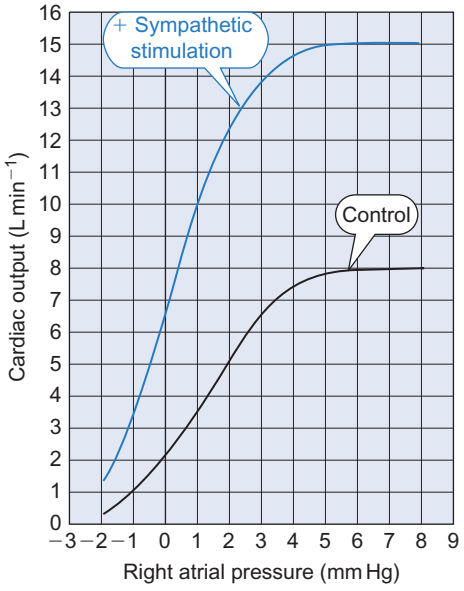

FIGURE 5.8.7 Effect of sympathetic stimulation on the cardiac function curve. Sympathetic stimulation shifts the cardiac function curve up and to the left.

FICK'S PRINCIPLE ESTIMATES CARDIAC OUTPUT FROM O_2 CONSUMPTION

In 1870, Adolf Fick pointed out that the oxygen absorbed by the lungs must be carried away by the blood that perfuses the lungs. This statement results in a simple mass balance equation:

$$[5.8.7] \qquad Q_a\ [O_2]_a + Q_{O_2} = Q_v\ [O_2]_v$$

where Q_a is the blood flow in the pulmonary arteries (in $L\,min^{-1}$), $[O_2]_a$ is the total oxygen concentration in the pulmonary arterial blood (in units such as mL O_2 per liter of blood), Q_{O_2} is the oxygen taken up by the lungs (in $mL\,O_2\,min^{-1}$), Q_v is the blood flow in the pulmonary veins, and $[O_2]_v$ is the total oxygen concentration in the pulmonary venous blood. Thus the left hand side of Eqn [5.8.7] is the oxygen input to the lungs, and the right hand side is the oxygen output. Figure 5.8.8 illustrates the situation.

EXAMPLE 5.8.1 Calculate the Cardiac Output from O_2 Consumption and A–V O_2

At rest, Q_{O_2} (oxygen consumption) is typically 250 mL O_2 min^{-1} (volumes of gas are given in volumes at STPD—standard temperature and pressure, dry: see Chapter 6.3). The arterial blood obtained from the radial, brachial, or femoral artery, $[O_2]_a$, is 19.5 mL% (volume at STPD per 100 mL of whole blood). The venous blood (obtained from the right ventricle outflow tract through a cardiac catheter inserted through the antecubital (elbow) vein had $[O_2]_v$ = 14.5 mL%. What is the cardiac output?

We can use Eqn [5.8.7] to solve for the cardiac output when we recognize that Q_a and Q_v are equal to each other and to the cardiac output. Then we have

$$Q_a([O_2]_a - [O_2]_v) = Q_{O_2}$$

$$Q_a = \frac{Q_{O_2}}{([O_2]_a - [O_2]_v)} = \frac{250 \text{ mL min}^{-1}}{(195 \text{ mL L}^{-1} - 145 \text{ mL L}^{-1})} = 5 \text{ L min}^{-1}$$

CARDIAC OUTPUT CAN BE DETERMINED BY THE *INDICATOR DILUTION METHOD*

Suppose that we inject someone with n moles of an indicator. Ideally, this indicator should be confined to the bloodstream and be relatively easy to measure. Examples include dyes that bind to plasma albumin or plasma albumin that has itself been tagged with radioactive iodine. Let the mass (or, equivalently, the number of moles) of the injected indicator be m. It becomes distributed in some volume of blood that passes through the heart and into the systemic circulation. In some time t, all of the volume of blood possessing indicator will pass each point in the circulation. If we know the volume and the time, we can calculate the cardiac output. How do we get the volume? The short answer is: by measuring the concentration of indicator over time. We assume that cardiac output, Q_a, is constant. Then in each time increment the aggregate volume of blood passing through the systemic circulation is

$$[5.8.8] \qquad dV = Q_a \; dt$$

At any time, the concentration of indicator is C_m, given as

$$[5.8.9] \qquad C_m = \frac{dm}{dV}$$

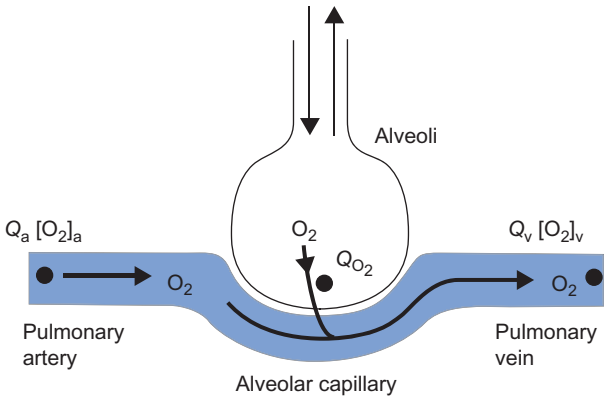

FIGURE 5.8.8 The Fick principle. The input of oxygen to the lungs from the blood is $Q_a[O_2]_a$, where Q_a is the blood flow through the pulmonary arteries, and $[O_2]_a$ is the total concentration of O_2 in this blood. This input is added to by absorption of O_2 from the alveolar air, which at steady state is the same as the rate of O_2 consumption, Q_{O_2}. This total input of O_2 is carried off by the pulmonary vein blood at the rate of $Q_v[O_2]_v$.

where dm is the amount of mass (or moles) of indicator in the volume element dV. The total mass of indicator, m, is determined by integrating Eqn [5.8.9]:

$$[5.8.10] \qquad m = \int_0^t dm = \int_0^t C_m \, dV$$

From Eqn [5.8.8] we substitute in for dV to obtain:

$$[5.8.11] \qquad m = \int_0^t Q_a \; C_m \; dt$$

$$m = Q_a \int_0^t C_m \, dt$$

And, therefore, cardiac output can be calculated as

$$[5.8.12] \qquad Q_a = \frac{m}{\int_0^t C_m dt}$$

If we know the quantity m and measure C_m with time, we can determine Q_a by dividing m by the area under the C_m versus t curve. This procedure is illustrated in Figure 5.8.9.

The plot of $C(t)$ against t is complicated. Typically, $C(t)$ rises quickly to a peak and then decays exponentially because the ventricle ejects only about two thirds of its end-diastolic volume with each heart beat. The indicator that remains in the heart at the end of systole is then diluted with fresh blood that enters the heart, and the residual indicator is then diluted a second time, and so on. The concentration of the indicator after n heart beats is given as

$$[5.8.13] \qquad C_m(n) = \left[\frac{EDV - SV}{EDV}\right]^n C_m(0)$$

Taking the logarithm of both sides, we find

$$[5.8.14] \qquad ln \; C_m(n) = n \; \ln \left[\frac{EDV - SV}{EDV}\right] + \text{In } C_m(0)$$

Because n is proportional to t through the heart rate ($n = HR \times t$), the plot of ln C_m in the decay phase of C (m) versus t is linear with t. Equation [5.8.14] can be rewritten as

$$[5.8.15] \qquad In \; C_m(n) = In \; C_m(0) + \left(HR \; ln\left[1 - \frac{SV}{EDV}\right]\right) t$$

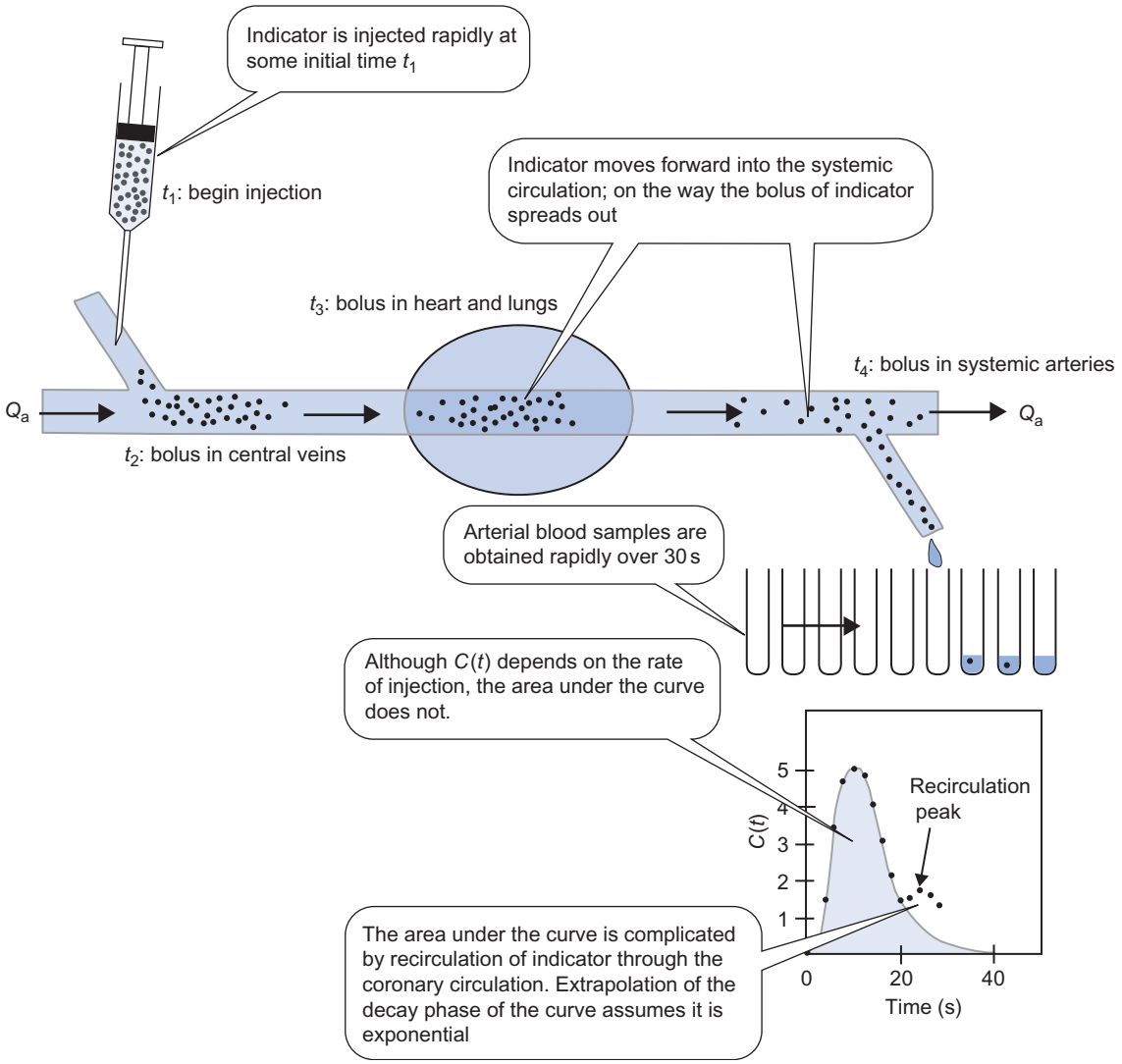

FIGURE 5.8.9 Estimation of cardiac output from the indicator dilution method. Indicator is injected into a vein and arterial concentration is measured with time. The shape of the concentration curve depends on the rate of injection, but the integral of the $C(t)$ versus t curve depends only on the amount of indicator and the cardiac output. Since the amount of indicator injected is known, the cardiac output, Q_q, can be calculated from Eqn [5.8.12]. However, the area under the curve can be overestimated if recirculation of indicator occurs. Estimation of the area can be made by extrapolating the decay curve, assuming that it decays exponentially, and integrating this extrapolated curve.

where **we identify SV/EDV as the ejection fraction**, the fraction of the end-diastolic volume that is ejected into the systemic circulation with each heart beat. Typically SV = 70 mL and EDV = 120 mL, so that the ejection fraction is typically about 0.58. Thus the slope of the decay curve ($\ln C(t)$ against t) should typically be about $70\ \text{min}^{-1} \times \ln(1 - 0.58) = -60.7\ \text{min}^{-1} = -1.01\ \text{s}^{-1}$.

This analysis is valid for the single left ventricle, but for the entire heart it is incomplete because both the right and left heart participate in this extension of the concentration profile in time. The blood entering the left heart is only gradually depleted of indicator by the right heart. If we restrict ourselves to the time before indicator can recirculate to the venous side of the circulation, our analysis does apply to the right heart. Because the blood from the right heart feeds into the left heart, the final concentration coming out of the left heart would be

$$C_m(n) = \left[\frac{\text{EDV}_l - \text{SV}_l}{\text{EDV}_l} + \frac{\text{EDV}_r - \text{SV}_r}{\text{EDV}_r}\frac{\text{SV}}{\text{EDV}_l}\right]^n C_m(0) \quad [5.8.16]$$

This equation describes the situation in which the initial concentrations in both right and left ventricles are $C_m(0)$ and the blood entering the right heart has no indicator. The subscript "l" indicates the left heart and "r" indicates the right heart. This situation would pertain exactly only if the indicator were injected over a particular time course. If we assume equal ejection fractions for right and left ventricles, the slope becomes $70\ \text{min}^{-1} \times \ln[(1 - 0.58) + (1 - 0.58) \times 70/120] = -28.6\ \text{min}^{-1} = -0.48\ \text{s}^{-1}$. Thus serial dilution by the right heart and left heart more slowly distributes indicator than either chamber alone. In practice, the injection is usually slower and subsequently the decay of indicator is also slower, with smaller slopes on the curve of $\ln C_m$ against t.

The plot of $\ln C(t)$ against t is needed because in the middle of the decay curve the concentration usually shows a recirculation hump that corresponds to indicator reentering the venous blood after completing one circuit of the circulation. Because the coronary circulation is the shortest circuit, this blood contributes first to the recirculation hump. The concentration due only to the initially injected indicator can be estimated by extrapolation of $\ln C(t)$ against t from the decay part of the curve that corresponds to indicator dilution in the heart.

THE THERMAL DILUTION METHOD

In most clinical departments, the indicator dilution method has been replaced by thermal dilution methods. In this case, a known mass of cold saline is injected rapidly into the right atrium and a thermistor placed in the distal pulmonary artery records temperature with time. The principle is the same as the indicator dilution method except that the quantity being injected is an amount of "cold", calculated as $m \times C_p \times (T_{blood} - T_{saline})$, where m is the mass of saline, C_p is its specific heat (the amount of energy necessary to raise its temperature by 1°C) and T_{blood} and T_{saline} are the temperatures of the blood and of the saline, respectively. The cardiac output in this case is calculated by dividing the amount of "cold" by the integral of the temperature–time plot.

The thermal dilution method avoids the recirculation problem because blood returning to the atrium has been warmed to tissue temperatures before it recirculates. However, heat transfer from the tissue to blood will overestimate the cardiac output by reducing the integral. Corrections can be made for this heat transfer.

SUMMARY

The function of the heart is to pump blood. A quantitative measure of this function is the cardiac output, which is the rate of blood flow out of the left ventricle. It can be determined experimentally by Fick's principle using oxygen consumption and oxygen content of mixed venous blood and arterial blood or by using indicator dilution or thermal dilution. Typical values of cardiac output at rest are about $5\,L\,min^{-1}$. The cardiac output can be calculated as the stroke volume times the heart rate.

The total work of the heart includes three terms: pressure–volume work, kinetic energy work, and gravitational work. By far the largest of these is the pressure–volume term. The pressure–volume loops of the heart are set between the passive stretch of the heart (the diastolic curve) and the isovolumetric systolic curve that the heart can develop against a closed aortic valve.

The cardiac output is determined by the preload, afterload, and cardiac contractility. The preload refers to the pressure in the large veins that feed into the atria. When preload increases, the ventricles are stretched and subsequently provide a greater force. This is the Frank–Starling Law of the Heart: increasing right atrial pressure increases the stroke volume of both ventricles. The ventricular function curve is a plot of the cardiac output against right atrial pressure.

The afterload refers to the pressure in the large arteries and derives its name from the fact that the heart does not "feel" the afterload until pressure rises enough to open the aortic valve. The afterload is the pressure

Clinical Applications: Heart Failure

Heart failure, generally called congestive heart failure, is the inability of the heart to pump enough blood to meet the needs of the body. It is a constellation of disease states generally characterized by exercise intolerance of varying degrees. In left heart failure, the left ventricle fails to pump blood out of the pulmonary circulation, leading to pulmonary congestion (edema) with attendant symptoms such as tachypnea (increased breathing frequency) and increased work of breathing. This may or may not cause right heart failure due to pulmonary hypertension. Right heart failure fails to pump blood out of the great veins, leading to systemic congestion and peripheral edema. Right and left heart failure can occur independently or together. Causes of heart failure include:

- **Coronary artery disease and heart attack.** Fat deposits in the coronary arteries build up over time, a condition called atherosclerosis, and reduce the lumen of the arteries supplying the heart muscle, leading to weak contractions due to hypoxia of the muscle. In some cases, the vessels occlude entirely, leading to death of parts of the muscle (heart attack) and complete dysfunction of part of the heart.
- **Hypertension.** This is increased pressure that can occur either in the pulmonary or systemic circulations. It increases the afterload of the heart. Chronic hypertension causes the heart to hypertrophy, or enlarge, and this requires stronger contractions to develop the same pressure, according to the Law of Laplace. Eventually the heart becomes unable to effectively pump blood.
- **Faulty valves.** Faulty valves can be due to congenital defects, or cardiac infections can lead to **stenosis** (a narrowing of the orifice through which blood exits the chamber) or leaks. Either causes an additional work load on the heart that can cause hypertrophy and eventual failure. **Aortic regurgitation**, for example, can cause left heart failure.
- **Cardiomyopathy.** This is damage to the heart muscle directly, which can be congenital or acquired through infections, alcoholism, drug abuse, or thyrotoxicosis.
- **Arrhythmias.** Tachycardia in the absence of exercise can lead to heart failure.

Treatment of heart failure generally focuses either on removal of the load on the heart or on increasing cardiac contractility. Reversible causes of heart failure need to be addressed. Front line medications include ACE (angiotensin-converting enzyme) inhibitors such as captopril, loop diuretics to inhibit salt reabsorption in the loop of Henlé (Chapter 7.5), and beta blockers. Lifestyle changes include alcohol limitation, smoking cessation, weight loss, exercise, and salt and fluid restriction.

against which the heart ejects blood. Thus, increasing the afterload increases the pressure against which the heart ejects blood. Increasing the afterload decreases the stroke volume and thereby the cardiac output.

Cardiac contractility refers to the ability of the heart to produce force at any given stretch. Positive inotropic agents increase cardiac contractility by shifting the isovolumetric systolic curve up and to the left, producing more pressure at a given ventricular volume. This increases the stroke volume at any specified preload. Positive inotropic agents also shift the ventricular function curve up and to the left, giving a greater cardiac output for any given right atrial pressure.

Cardiac output can be measured by Fick's dilution principle, the indicator dilution principle, and thermal dilution.

REVIEW QUESTIONS

1. What determines the end-diastolic volume?
2. What is the stroke volume? How do preload and afterload affect the stroke volume?
3. What is the cardiac output? How does it depend on heart rate and stroke volume?
4. Draw a pressure–volume curve for the left ventricle. Label the region of ventricular filling during diastole, the period of isovolumetric contraction, the period of ejection of blood, and the period of isovolumetric relaxation.
5. Identify components of cardiac work.
6. What is the ventricular function curve? What is meant by intrinsic regulation?
7. What effect do positive inotropic agents have on the ventricular function curve? What do these agents do to the pressure–volume curve? What do they do to stroke volume? Cardiac output?
8. Why is the output of the right heart the same as the output of the left heart?
9. How can you determine cardiac output from oxygen consumption?
10. How can you determine cardiac output from indicator or thermal dilution?