

THIRD EDITION

CARDIOVASCULAR HEMODYNAMICS FOR THE CLINICIAN

EDITED BY GEORGE A. STOUFFER

✓ 2025 Edition



WILEY

Cardiovascular Hemodynamics for the Clinician

 **2025** Edition

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THIRD EDITION

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PART I

Basics of hemodynamics

 **2025** Edition

CHAPTER 1

Introduction to basic hemodynamic principles

James E. Faber and George A. Stouffer

[This is a revision of a chapter written for the first two editions of this book by James E. Faber and George A. Stouffer]

Hemodynamics is concerned with the mechanical and physiologic properties controlling blood pressure and flow through the body. Although a full discussion of hemodynamic principles is beyond the scope of this book, we present an overview of ten basic principles that are helpful in understanding hemodynamics.

Energy in the bloodstream exists in three interchangeable forms: pressure arising from cardiac output and vascular elasticity, “hydrostatic” pressure from gravitational forces, and kinetic energy of blood flow

Energy of a fluid in a straight tube exists in three interchangeable forms: perpendicular pressure (force exerted on the walls of the tube perpendicular to flow; a form of potential energy), kinetic energy of the flowing fluid, and pressure due to gravitational forces. Perpendicular pressure is transferred to the blood and vessel wall by cardiac pump function and vascular elasticity and is a function of cardiac output and vascular resistance.

Total energy (TE) = potential energy + kinetic energy

TE = (perpendicular pressure + gravitational pressure) + kinetic energy

$$TE = (P_{\text{Per}} + P_{\text{grav}}) + \frac{1}{2} \rho V^2$$

where V is velocity and ρ is density of blood (approximately 1060 kg/m^3)

$$TE = P_{\text{Per}} + (\rho \times h \times g) + \frac{1}{2} \rho V^2$$

where g is the gravitational constant and h is the height of fluid above the point of interest.

Since pressure is the force applied per unit area of a surface, blood pressure is the summation of three components: lateral pressure, gravitational forces, and kinetic energy (also known as the impact pressure or the pressure required to cause flow to stop). Lateral pressure on the blood vessel, due to cardiac output, is the most important contributor to blood pressure. In blood vessels or in the heart, the transmural pressure (i.e., pressure across the vessel wall or ventricular chamber wall) is equal to the intravascular pressure minus the pressure outside the vessel. The intravascular pressure is responsible for transmural pressure (i.e., vessel distention) and for longitudinal transport of blood through the vessels.

Kinetic energy is greatest in the ascending aorta where velocity is highest, but even there it contributes less than 5 mm Hg of equivalent pressure. Gravitational forces are important in a standing person. Arterial pressure in the foot will exceed thoracic aortic pressure due to gravitational pull on a column of blood. Likewise, arterial pressure in the head will be less than thoracic aortic pressure. Similarly, gravitational forces are important in the venous system, since blood will pool in the legs when an individual is standing. Decreased ventricular filling pressure results in lower cardiac output and explains why a person will feel lightheaded if rising abruptly from a sitting or supine position. In contrast, gravity has a negligible effect on arterial or venous pressure when a person is lying flat. Gravitational pressure equals the height of a column of blood $\times$ the gravitational constant $\times$ the fluid density. To calculate hydrostatic pressure at the bedside (in mm Hg), measure the distance in millimeters between the points of interest, for example, heart and foot, and divide by 13 (mercury is 13 times denser than water).

Blood flow is a function of pressure gradient and resistance

One of the properties of a fluid is that it will flow from a region of higher pressure (e.g., the left ventricle) toward a region of lower pressure (e.g., the right atrium; Figure 1.1). In clinical practice, the patient is assumed to be supine (negating the gravitational component of pressure) and at rest. As already mentioned, the contribution of kinetic energy to blood pressure is negligible at normal cardiac outputs and thus blood flow is estimated using the pressure gradient and resistance.

The primary parameter used in clinical medicine to describe blood flow through the systemic circulation is cardiac output, which is the total volume of blood pumped by the left ventricle per unit of time (generally expressed in liters per minute (L/min)). To compare cardiac output among individuals of different sizes, the cardiac index (cardiac output divided by body surface area) is used. Normalization of cardiac output for body surface area is important, as it enables proper interpretation of data independent of the patient's size (e.g., cardiac output will obviously differ widely between a 260-pound man and a 100-pound woman).

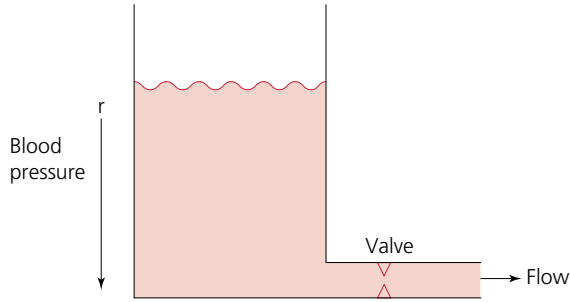


Figure 1.1 A simple hydraulic system demonstrating fluid flow from a high-pressure reservoir to a low-pressure reservoir. Note that the volume of flow can be affected by a focal resistance (i.e., the valve).

Indexing to body surface area is also used for other measurements such as aortic valve area.

Cardiac output and index are generally measured using the Fick equation or via thermodilution techniques, which are discussed in Chapter 6.

The relationship between blood flow, resistance, and pressure can be determined using a modification of Ohm's law for the flow of electrons in an electrical circuit:

$$\text{Flow}(Q) = \frac{\text{pressure gradient}(\Delta P)}{\text{resistance}(R)}$$

where ΔP is the difference in pressure between proximal and distal points in the system and R is the hydraulic resistance to blood flow between the proximal and distal points.

A useful clinical equation based on Ohm's law is:

$$\begin{aligned} &\text{Mean arterial pressure(MAP)} - \text{central venous pressure(CVP)} \\ &= \text{cardiac output(CO)} \times \text{systemic vascular resistance(SVR)} \end{aligned}$$

Using this equation, we can calculate systemic vascular resistance by knowing cardiac output, CVP, and arterial pressure. MAP is the average arterial pressure over time and is generally estimated using the following formula:

$$\text{MAP} = \left(\frac{1}{3} \times \text{aortic systolic pressure} \right) + \left(\frac{2}{3} \times \text{aortic diastolic pressure} \right).$$

This formula was developed for a heart rate of 60 beats per minute (bpm; at this heart rate, diastole is twice as long as systole) and becomes progressively more inaccurate as heart rate increases. In a patient in shock (i.e., low blood pressure and impaired tissue perfusion), measurement of CO and calculation of SVR can help identify the etiology (e.g., septic shock with high CO + low SVR or cardiogenic shock with low CO + high SVR).

In the mammalian circulation, resistance is greatest at the level of the arterioles. While the radius of a typical capillary (e.g., 2.5 μm) is smaller than the radius of the smallest arterioles (e.g., 4 μm), the number of capillaries greatly exceeds the number of arterioles, and thus the effective area is much larger. Also of importance is that arteriolar resistance can be regulated (capillaries have no smooth muscle and thus resistance cannot be regulated at that level; however, pericyte cells can constrict capillaries in certain specialized structures like the kidney's glomerulus). This enables rapid changes in vascular resistance to maintain blood pressure (e.g. in hypovolemic shock) and also enables regulation of blood flow to various organs (i.e., autoregulation). A general principle to remember is that reduction of arteriolar resistance in a tissue decreases SVR, resulting in increased cardiac output while simultaneously decreasing pressure proximal to the arterioles and increasing pressure distal to the arterioles.

Resistance to flow can be estimated using Poiseuille's law

Energy (and pressure) is lost as flowing blood encounters resistance to flow. Resistance to blood flow is a function of viscosity, vessel radius, and vessel length in a vessel without any focal obstruction (resistance to blood flow also occurs from focal obstruction such as seen with atherosclerotic disease of arteries). The relationship is known as Poiseuille's law (sometimes referred to as the Poiseuille–Hagen law) and is described by the following equation:

$$\text{Resistance} = \frac{8 \times \text{viscosity} \times \text{length}}{\pi \times \text{radius}^4}$$

or, since flow = difference in pressure/resistance:

$$\text{Blood flow} = \frac{\pi \times \text{radius}^4 \times \text{difference in pressure}}{8 \times \text{viscosity} \times \text{length}}$$

Since radius is raised to the fourth power, its importance in determining resistance is paramount. A 20% increase in radius leads to a doubling in flow if all other variables are constant. Or, as another example, resistance is 16 times greater in a coronary artery with a diameter of 2 mm (e.g., a distal obtuse marginal) than in a coronary artery with a diameter of 4 mm (e.g., the proximal left anterior descending).

Viscosity is also important in determining resistance (commonly abbreviated as η , commonly expressed as Pascal-seconds (Pa·s) (also known as Poiseuille units; it is the International System of Units unit for viscosity) or dynes per second per square centimeter (also known as poise units). It is difficult to measure directly and thus is commonly reported as relative to water. The viscosity of plasma is 1.7 $\times$ viscosity of water and the viscosity of blood is 3–4 $\times$ viscosity of water, the difference being due to red blood cells and thus hematocrit.

It is important to note that Poiseuille's law only provides an approximation of resistance when used in blood vessels. The four important assumptions underlying the derivation of this equation are: (1) the viscosity of the fluid is unchanging over time or space; (2) the tube is rigid and cylindrical; (3) length of the tube greatly exceeds diameter; and (4) flow is steady, nonpulsatile, and nonturbulent. Many of these assumptions are violated when this equation is applied to blood flow in the body. Poiseuille's law is important, however, as it indicates the variables that are the important determinants of resistance to flow.

Reynold's number can be used to determine whether flow is laminar or turbulent

Flow in blood vessels, as in any hydraulic system, is usually smooth and orderly because the fluid separates into an infinite number of concentric layers, with the highest velocity in the center and the lowest next to the vessel wall. When a fluid (such as blood) flows past a solid surface (such as the vascular wall), a thin layer develops adjacent to the surface where frictional forces retard the motion of the fluid (Figure 1.2). There is a gradient of frictional resistance (and thus velocity) between fluid in contact with the solid surface and fluid in the center of the stream. If the fluid elements travel along well-ordered, nonintersecting layers, this is termed laminar flow. The flow resistance in laminar flow is due entirely to viscous resistance of the fluid and the interactions between the fluid and the stationary wall. In laminar flow, the average velocity of a fluid is one-half of the maximum velocity observed in the center of the stream.

In contrast, turbulent flow occurs when fluid elements from adjacent layers become mixed. Turbulent flow is chaotic and less efficient because of energy losses (these losses are termed inertial resistance). In turbulent flow, the relationship between pressure difference and flow is no longer linear, since the amount of resistance in the tube increases with flow. Thus, larger pressure differences are

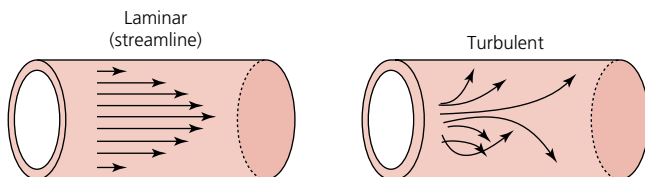


Figure 1.2 Schematic of laminar flow. Flow in straight, nonbranching tubes is usually smooth and orderly because the fluid separates into an infinite number of concentric layers with different velocities. When a fluid (such as blood) flows past a stationary surface (such as the vascular wall), a thin layer develops adjacent to the surface where frictional forces tend to retard the motion of the fluid. There is a gradient of frictional resistance (and thus velocity) between fluid in contact with the solid surface and fluid in the center of the stream. If the fluid particles travel along well-ordered, nonintersecting layers, this is termed laminar flow.

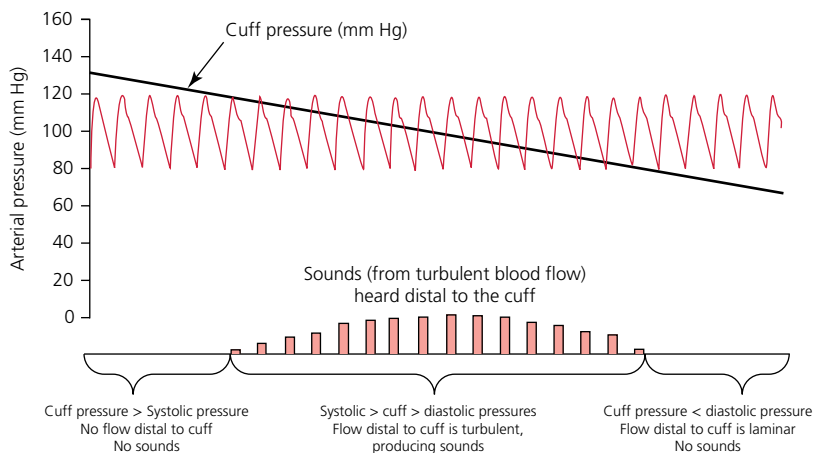


Figure 1.3 Schematic illustrating the use of transient transition from laminar to turbulent flow in measuring blood pressure.

required to maintain flow. Turbulence (with an associated loss of energy) and narrowed radius are two of the primary causes of the drop in pressure that occurs distal to severe stenosis.

Turbulence is important for several reasons, one of which is that it creates noise (e.g., in a pipe when flow velocity is high), which is the cause of some cardiac murmurs and the Korotkoff sounds (used when measuring blood pressure; Figure 1.3). Another is that turbulence alters the relationship between flow and perfusion pressure, as already mentioned. Because of increased energy losses associated with turbulence, the relationship between perfusion pressure and blood flow is no longer linear (as described by the Poiseuille relationship) but rather, greater pressure is required to maintain adequate flow (Figure 1.4).

The transition from laminar to turbulent flow can be predicted by calculating Reynold's number, which is the ratio of inertial forces ($V\eta$) to viscous forces (ρ/L):

$$R = \frac{\text{diameter} \times \text{velocity} \times \text{density}}{\text{viscosity}}$$

where viscosity (η) of blood at 37°C is 0.0035 Pa·s (pascal-seconds; 3.5 centipoise), density (ρ) of blood is approximately 1060 kg/m³, velocity (V) of blood is in m/s, and the diameter of the tube is in meters. The Reynold's number is dimensionless.

In a given hydraulic system, a critical Reynold's number exists below which flow is laminar. At Reynold's numbers near this critical number, a transitional zone exists where flow is neither completely laminar nor turbulent. Higher Reynold's numbers are associated with turbulent flow. In a long, straight, non-branching pipe with nonpulsatile flow, flow is generally laminar if $R < 2000$ and turbulent if $R > 2000$. It is important to note that the Reynold's number depends on the exact flow configuration and must be determined experimentally.

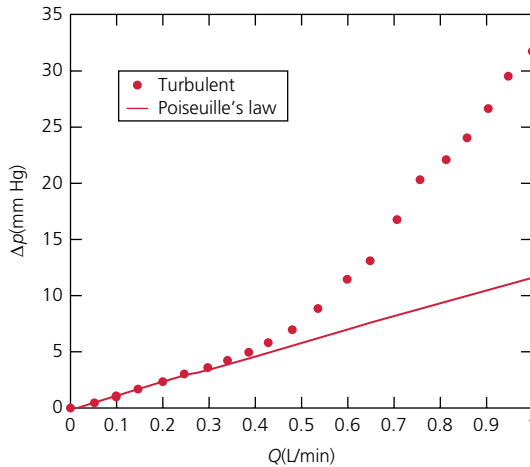


Figure 1.4 Transition from laminar to turbulent flow. Note that the pressure gradient required to increase flow increases markedly when flow transitions from laminar to turbulent.

In the aorta, transition from laminar to turbulent flow generally occurs at Reynold's number between 2000 and 2500. In atherosclerotic arteries and/or at branch points, the critical Reynold's number is much lower and there can be turbulence even at normal physiologic flow velocities. In severe stenoses, turbulence can be initiated at Reynold's numbers an order of magnitude less than in the theoretical straight pipe.

The Reynold's equation is important for demonstrating variables important in determining whether flow is laminar or turbulent. As a simple approximation from this equation, we see that laminar flow is difficult to maintain in conditions of high velocity (e.g., stenotic artery) and large diameter. Vessel diameter is doubly important, for it is not only a direct variable in the equation but also influences velocity. Because of the continuity equation (see Principle 9), we know that velocity increases as diameter decreases. Thus, effects of blood vessel diameter on Reynold's number are magnified. Because both velocity and diameter decrease in the microcirculation, the flow there tends to be laminar.

Force developed by the ventricles is a function of preload or stretch—the Frank–Starling law

The three most important factors in the regulation of ventricular function (and thus cardiac output) are preload, afterload, and contractility. Preload for the ventricles is defined as amount of passive tension or stretch exerted on the ventricular walls (i.e., intraventricular pressure) just prior to the initiation of systole. This “load” applied to the ventricular wall determines end-diastolic sarcomere length and thus the force of contraction. The Frank–Starling law states that the passive

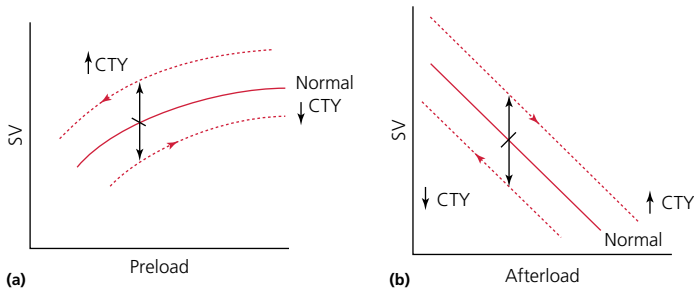


Figure 1.5 Frank–Starling principle. In panel (a), note that stroke volume (SV) increases as preload increases on any given line of contractility (CTY). Panel (b) demonstrates that stroke volume increases as afterload decreases.

length to which the myocardial cells are stretched at the end of diastole is a determinant of the active tension they develop when stimulated to contract. The Frank–Starling law is an intrinsic property of myocytes; that is, it is not dependent on nerve signals or hormones. The general principle is that increased preload causes increased force of contraction, which increases stroke volume and thus cardiac output (Figure 1.5). The Frank–Starling law (or mechanism) helps the heart match cardiac output to venous return.

The Frank–Starling law was derived from independent work by two investigators. In the 1890s, Otto Frank measured pressure developed by the isolated beating frog ventricle against an occluded aorta under varying preloading conditions. He found that as end-diastolic volume increased, ventricular systolic pressure and the maximum rate of pressure development ($dP/dT_{\max}$) increased. Approximately, 20 years later, Ernst Starling found similar results using a heart–lung preparation in an anesthetized dog in which he controlled heart rate, venous pressure, venous return, arterial pressure, and arterial resistance.

For any given heart, there is not just a single Frank–Starling curve. Rather, there is a family of curves, each of which is determined by the afterload and inotropic state (i.e., contractility) of the heart. While changes in venous return cause a ventricle to move along a single Frank–Starling curve, changes in contractility and afterload cause the heart to shift to a different Frank–Starling curve.

Wall tension is a function of pressure and radius divided by wall thickness—the Laplace relationship

Laplace’s law describes the relationship between the transmural pressure difference and the tension, radius, and thickness of the vessel wall or ventricular chamber (Figure 1.6). A good approximation of wall tension in a vessel or chamber according to Laplace is:

$$\text{Wall tension} = \frac{\text{pressure} \times \text{radius}}{\text{wall thickness}}$$

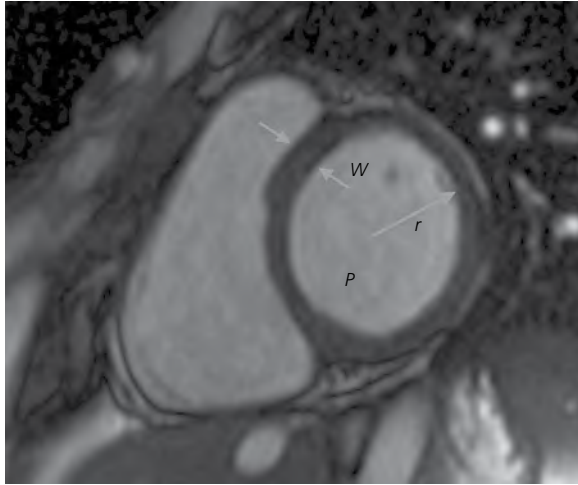


Figure 1.6 Magnetic resonance imaging (MRI) of a right ventricle and a left ventricle. The left ventricle is labeled to demonstrate Laplace's law: $t = (P \times r)/W$, where P is pressure; r is radius; W is wall thickness; and t is wall tension.

The pressure inside a blood vessel or ventricle exerts a distending force (tension) on the walls that is proportional to the magnitude of the pressure and radius. Thus, wall tension in the aorta is high. In chronic hypertension, aortic wall thickness increases as an adaptation to normalize wall tension. Similarly, LV hypertrophy develops in response to chronic elevations in ventricular pressure and/or dilatation, again as an adaptation.

There are several important implications of this relationship. One is that larger arteries must have stronger walls since an artery of twice the radius must be able to withstand twice the wall tension at a given blood pressure. Similarly, the increased wall tension is thought to contribute to the development of aneurysms (and possibly to predict aneurysm rupture) in larger arteries. Another implication is that as the radius of the LV increases (e.g., in dilated cardiomyopathy), increased active wall tension must be developed during systole by the myocytes in order to create the same ventricular pressures for ejection. Thus, a dilated ventricle uses more adenosine triphosphate (ATP) and oxygen to generate the same stroke volume.

The normal venous system is a low-pressure, large-volume reservoir of blood which enables rapid increases in cardiac output

Approximately 60–80% of blood in the normal individual is in the venous system (with 8–10% being within the heart, 15–20% in arteries, and 5% in capillaries). There is a large capacitance in the normal venous system, and large veins are not

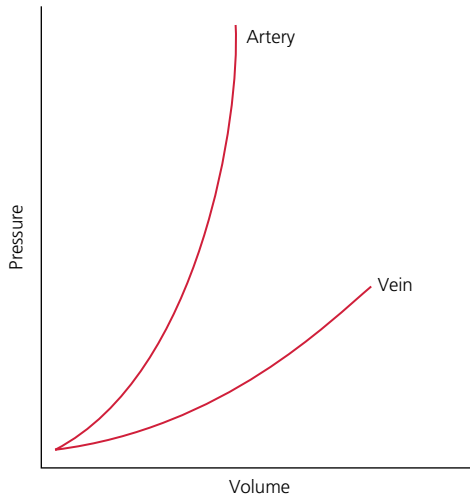


Figure 1.7 Pressure–volume relationship for arteries and veins.

fully filled but instead partially collapsed (elliptical). Thus, the venous system can absorb a large amount of volume with minimal increase in pressure. Once veins become fully distended, however, the pressure–volume relationship changes significantly (Figure 1.7). Veins have limited elasticity once they are fully distended, and at this point, pressure increases rapidly with increased volume.

Since the cardiovascular system is a closed loop, venous return and cardiac output are closely coupled, and increased venous return to the heart is one of the primary mechanisms by which preload and thus cardiac output is increased rapidly. For example, venous return (and cardiac output) can be rapidly augmented by increased sympathetic tone, which causes the smooth muscle in veins to contract. Similarly, skeletal muscular contractions during exercise reduce venous capacitance in the muscle beds by rhythmically compressing the veins and can markedly increase venous return.

The pressure and velocity of a fluid in a closed system are related

Daniel Bernoulli was a physician and mathematician who lived in the eighteenth century. He had wide-ranging scientific interests and won the Grand Prize of the Paris Academy 10 times for advances in fields ranging from astronomy to physics. One of his insights was that the energy of an ideal fluid (a hypothetical concept referring to a fluid that is not subject to viscous or frictional energy losses) in a straight tube can exist in three interchangeable forms: perpendicular pressure (force exerted on the walls of the tube perpendicular to flow; a form of potential

energy), kinetic energy of the flowing fluid, and pressure due to gravitational forces (as we saw in Principle 1). Bernoulli derived the formula (now known as the Bernoulli equation) that relates the pressure, velocity, and height (i.e., gravitational forces) in the steady motion of an ideal fluid. The usual form is $TE = P_{\text{Per}} + (\rho \times h \times g) + 1/2 \rho V^2$, where TE is the total energy, V the blood velocity, P_{Per} the perpendicular pressure, ρ the blood density, g the gravitational constant, and h the height above an arbitrary reference level. It is based on the law of conservation of energy and states that the sum of potential and kinetic energy is the same at every point throughout a rigid tube.

The Bernoulli equation provides the theoretical foundation for the use of pulse wave and continuous wave Doppler to estimate pressures. While the actual derivation is more complex, for practical use in Doppler echocardiography, the Bernoulli equation is simplified to $P_1 - P_2 = 4V^2$, where P is pressure and V is velocity (labeled the modified Bernoulli equation). Because of the relationship between velocity and pressure, Doppler-determined blood velocity can be used to estimate pressures within the heart and vasculature (e.g., estimating pulmonary artery systolic pressures at the time of echocardiography by measuring the velocity of tricuspid regurgitation).

Derivation of the modified Bernoulli equation

Ignoring gravitational forces, the Bernoulli equation predicts that the relationship between pressures at two points (P_1 and P_2) within a system with a flowing fluid would be:

$$P_1 + \frac{1}{2} \rho V^2 = P_2$$

Or, stated another way, the difference in pressure between the two points would be:

$$P_2 - P_1 = \frac{1}{2} \rho V^2$$

Inserting units and blood density ($\rho = 1050 \text{ kg/m}^3$):

$$\Delta P (\text{kg/ms}^2) = 1/2 (1050 \text{ kg/m}^3) V^2 (\text{m}^2/\text{s}^2)$$

Since $1 \text{ mm Hg} = 133.3 \text{ Pa} = 133.3 \text{ kg/m}^2$

$$\Delta P \times 133.3 = \frac{1}{2} (1050) V^2$$

and thus we arrive at the formula we recognize:

$$\Delta P (\text{mmHg}) = 3.938 V^2$$

commonly abbreviated to:

$$\Delta P (\text{mmHg}) = 4V^2$$

The velocity of blood increases and pressure decreases as the cross-sectional area of the blood vessel decreases

An important hemodynamic concept is the continuity equation, which is derived from the law of conservation of mass. This equation is based on the principle that flow at any given point in a closed hydraulic system will be equal to flow at any other point. Thus, since flow is constant, velocity is inversely proportional to the cross-sectional area (Figure 1.8):

$$Q = A_1V_1 = A_2V_2 = A_3V_3$$

where A is area and V is velocity at any given point within the system. An implication of this equation is that velocity increases as the cross-sectional area decreases (e.g., at the site of an arterial stenosis). Similarly, blood velocity decreases as it flows from the aorta into the capillary system (which, for the purpose of this discussion, can be thought of as “one very large vessel” in series with the aorta and vena cava), but then increases again as it coalesces from venules to veins to the vena cava. An average velocity of blood at any given point within the major divisions of the circulation (i.e., aorta, arteries, arterioles, capillaries, venules, veins, vena cava) can be estimated, knowing the volume of blood and the aggregate cross-sectional area of the blood vessels in a given division.

The continuity equation is used in the echocardiography laboratory to estimate aortic valve area. The cross-sectional area of the LV outflow tract is measured along with blood velocity at that point (using pulse wave Doppler) and then volumetric blood flow in the outflow tract is calculated. Using the continuity equation, the cross-sectional area of the valve can be calculated by dividing volumetric blood flow by the measured velocity at the valve.

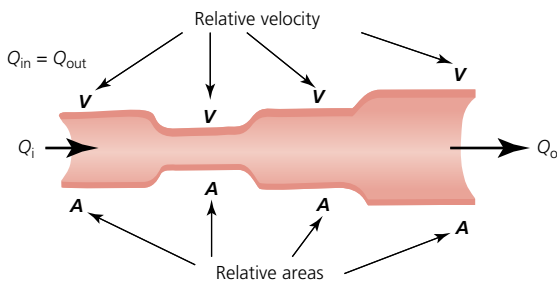


Figure 1.8 Relationship between blood velocity and cross-sectional area of blood vessels. Because of the law of conservation of mass, flow within any given major division of the circulatory system in a closed hydraulic system will be equal to flow within any other major division. Thus, velocity in a major division is inversely proportional to the aggregate vessel cross-sectional area in that division.

Resistance increases when blood vessels are connected in series and decreases when blood vessels are connected in parallel

Poiseuille's equation estimates resistance to flow in a single vessel. The human cardiovascular system, however, includes complex circuitry with distinct blood vessels in series (connected one after another) and in parallel (arising from the dichotomous divisions of larger vessels into smaller branches). Blood ejected from the heart moves from aorta → large arteries → small arteries → arterioles → capillaries → venous system → heart. While the aorta is a single vessel, the rest of the circulatory system involves multiple vessels connected in parallel (e.g., the carotid arteries, renal arteries, and other major branches from the aorta form a parallel circuit).

For blood vessels connected in series, the total resistance of the system is equal to the sum of resistance in each vessel (Figure 1.9):

$$R_{\text{total}} = R_1 + R_2 + R_3$$

Thus, for blood vessels connected in series, the resistance of the system is always greater than resistance in any one vessel. Thus, for three vessels in series, each with resistance R , the total resistance of the system is $3R$.

For blood vessels connected in parallel, resistance is equal to the sum of the reciprocal of the resistance in each vessel:

$$\frac{1}{R_{\text{total}}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}$$

Thus, for blood vessels connected in parallel, resistance of the system is always less than resistance in any vessel. For three vessels in parallel, each with resistance R , the total resistance of the system is $R/3$.

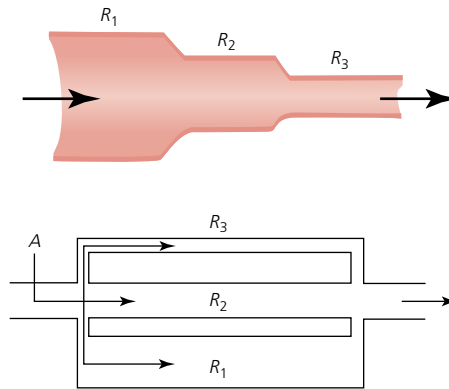


Figure 1.9 Circuits (or blood vessels) in series and in parallel.

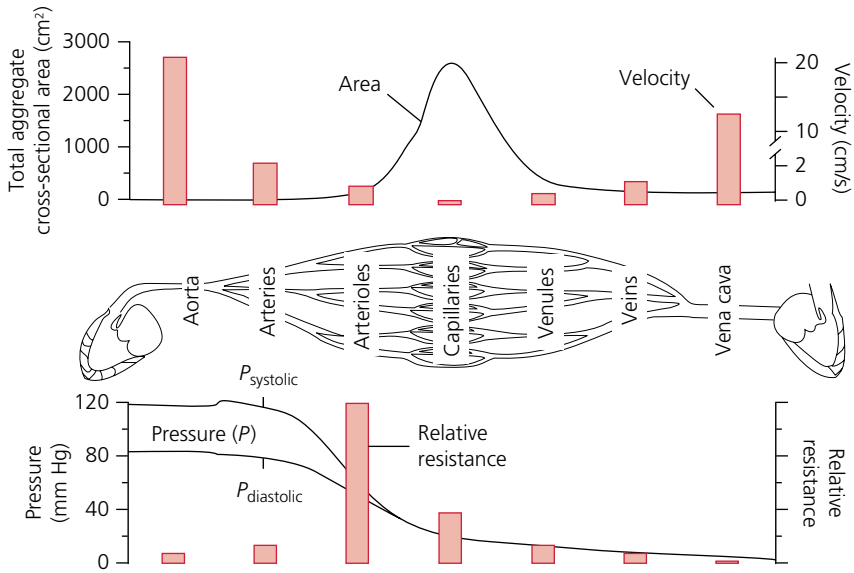


Figure 1.10 Pressure, velocity, and flow in various parts of the circulation.

An important principle is that more than 60% of the resistance to flow occurs within the arterioles. The diameter of the arterial system progressively decreases from aorta → arteriole. Energy losses (pressure drop) are minimized in the larger arteries, despite decreases in diameter, by having many arteries in parallel. The large pressure loss in arterioles is due to a dramatic decrease in diameter (Figure 1.10) without a correspondingly large enough increase in the number of arterioles in parallel. It goes without saying that the energy loss in arterioles serves many important functions, such as lowering pressure and velocity in capillaries to allow optimal transit time for red blood cells for diffusion of oxygen (O_2) and carbon dioxide (CO_2).

Since the greatest resistance occurs within the arterioles, systemic vascular resistance is very sensitive to changes in arteriolar diameter from constriction and dilation. Assuming constant cardiac output (keep in mind that cardiac output is a dynamic process and may increase or decrease by mechanisms other than changes in vascular resistance), agents that dilate arterioles in a tissue bed will not only decrease blood pressure (i.e., pressure proximal to the arterioles) but also increase pressures in the capillary bed. Similarly, vasoconstrictors increase blood pressure but reduce pressure within capillaries. In real life, cardiac output does not remain constant. The use of vasopressors to maintain blood pressure will increase vascular resistance but at a potential cost of decreased cardiac output (e.g., in the patient with cardiogenic shock) and/or organ failure due to increased vascular resistance (e.g., worsening renal function in patients on vasopressors).

CHAPTER 2

The nuts and bolts of right heart catheterization and PA catheter placement

Vickie Strang and George A. Stouffer

The pulmonary artery catheter

The pulmonary artery (PA) catheter (also known as the Swan–Ganz catheter or right heart catheter) was developed in the 1960s by Dr. Harold Swan, Dr. William Ganz, and colleagues [1]. The typical PA catheter is 100–110 cm long and has either 3 or 4 lumens (one lumen is used to inflate the balloon and thus there is one less port than the number of lumens). There is a proximal port approximately 30 cm from the tip that generally lies in the right atrium (RA) and can be used to transduce pressure or as an infusion port. The distal port is at the tip of the catheter and is used to measure PA pressure and pulmonary capillary wedge pressure (PCWP). Near the tip is a balloon that can be inflated and a thermistor to measure temperature (Figure 2.1).

A PA catheter can provide a large amount of hemodynamic information including:

Directly measured

- Central venous pressure (CVP)
- Mixed venous oxygen saturation
- Cardiac output (CO)
- RA pressure
- Right ventricular (RV) systolic pressure
- RV diastolic pressure
- PA systolic pressure (PASP)
- PA diastolic pressure (PADP)
- PCWP

Calculated

- Cardiac index (CI) = CO divided by body surface area (BSA)
- Cardiac power index = $\frac{\text{MAP} - \text{CVP}}{451} \times \text{CI}$

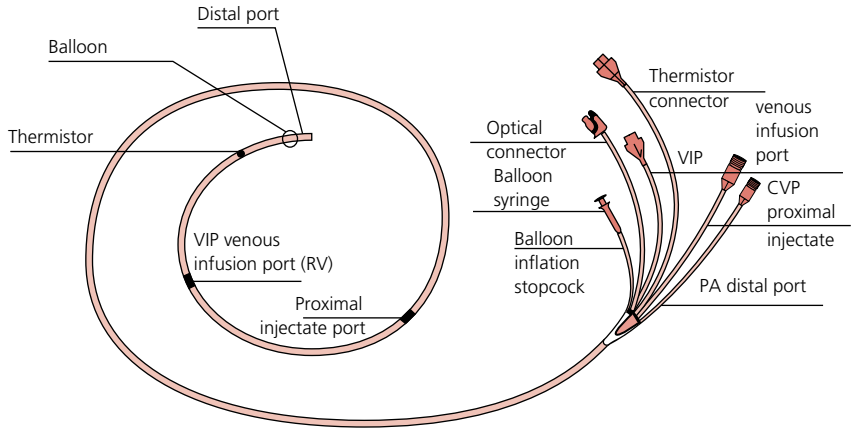


Figure 2.1 Schematic of PA catheter.

- Stroke volume = $\frac{CO}{\text{heart rate}} \times 1000$
- Stroke volume index (SVi) = SV divided by BSA
- Systemic vascular resistance = $80 \times \frac{MAP - CVP}{CO}$
- Systemic to pulmonary pressure ratio = $\frac{MAP}{MPAP}$
- Pulmonary vascular resistance = $80 \times \frac{MPAP - PCWP}{CO}$
- Pulmonary artery pulsatility index = $\frac{PASP - PADP}{CVP}$
- LV stroke work index = $SVi \times (MAP - PCWP) \times 0.0136$
- RV stroke work index = $SVi \times (MPAP - CVP) \times 0.0136$
- RV function index = $\frac{PASP}{CI}$

where MAP = mean arterial pressure and MPAP = mean PA pressure (= $1/3$ PASP + $2/3$ PADP).

The PA catheter provides information about ventricular preload (e.g., RA pressure is a reflection of right ventricular [RV] preload and PCWP is a reflection of left ventricular [LV] preload), afterload (systemic vascular resistance and pulmonary vascular resistance), and CO. The PA catheter can be helpful in various clinical scenarios, including valvular heart disease, congestive heart failure, cardiomyopathy, pericardial tamponade, shock, renal failure, pulmonary edema, pulmonary hypertension, or cardiac structural abnormalities.

PA catheters are used primarily in three different settings: in the cardiac catheterization laboratory, in intensive care units (ICUs), and in the operating room. Despite the tremendous theoretical benefits that could accrue from having the information obtainable from PA catheters, these catheters have never been shown in a large

randomized controlled trial to improve patient outcomes in either the operating room or ICU (potential benefit has never been studied in the cardiac catheterization laboratory). In numerous studies examining various groups such as patients with heart failure, patients undergoing high-risk noncardiac surgery, patients undergoing cardiac surgery and patients with acute respiratory distress syndrome (ARDS), PA catheters have in general had no beneficial effects on survival with increased rates of complications (Table 2.1) [8, 10–12]. These studies have been criticized for several reasons, including improper patient selection (e.g., including low-risk patients who

Table 2.1 Sample of trials that have examined the effect of PA catheter use on mortality.

	Study population	N	Type of study	Outcomes
SUPPORT [2]	Medical and surgical ICU patients	5735	Prospective cohort study	Increased mortality with PAC: odds ratio, 1.24; 95% confidence interval, 1.03–1.49
Sandham <i>et al.</i> [3]	High-risk surgical patients	1994	Randomized controlled trial	No difference in mortality
Richard <i>et al.</i> [4]	Septic shock and/or ARDS	676	Randomized controlled trial	No difference in mortality
ESCAPE [5]	Heart failure	433	Randomized controlled trial	No difference in mortality; in-hospital adverse events were more common among patients in the PAC group
PAC-Man [6]	Intensive care unit patients	1041	Randomized controlled trial	No difference in mortality
Fluid and Catheter Treatment Trial (FACTT) [7]	Acute lung injury	1000	Randomized controlled trial with explicit management protocol	No difference in mortality, ICU days or time on ventilator
Brown <i>et al.</i> [8]	Cardiac surgery patients	11820	Retrospective study of the STS database with propensity matching	Compared with central venous pressure monitoring, PAC use was not associated with differences in operative mortality, stroke, sepsis or new renal failure. ICU length of stay was longer and there were more transfusions in the PAC group.
Kadosh <i>et al.</i> [9]	Cardiogenic shock patients	2583	Retrospective analysis of Critical Care Cardiology Trials Network database	PAC use was associated with higher survival in cardiac patients with shock presenting to CICUs

would not be expected to benefit), study design (e.g., expecting a monitoring tool to affect outcomes without specified treatment protocols), and not controlling for operator experience in either insertion of the catheter or interpretation of data. Currently, there is no clear consensus on whether PA catheters are beneficial or harmful, with articulate proponents on both sides [12, 13]. An area that is currently under active investigation is the use of PA catheters in cardiogenic shock, with a special emphasis on patients receiving mechanical circulatory support.

Despite these data, PA catheters remain in widespread use presumably because they provide benefit to individual patients, but the studies sound a note of caution against indiscriminate use of these catheters. This has been reflected in national data on usage of PACs, which has declined significantly from the heydays of last century. The use of PAC among medical admissions decreased by 65% between 1993 and 2004 [14] and by 68% between 1999 and 2013 [15].

The effectiveness of a PA catheter depends on accurate assessment of the information provided. Waveform analysis is crucial for proper interpretation of data from a PA catheter and is discussed in detail in Chapters 3, 4, and 5. CO is discussed in Chapter 6. In this chapter, we will concentrate on the following topics:

- Brief review of physiology relevant to right heart and PA catheterization
- Vascular access
- Right heart catheterization and placement of a PA catheter
- Ensuring that accurate data are obtained from a PA catheter
- Cardiac output
- Calculating vascular resistance
- SvO₂ monitoring
- Complications of PA catheters

Brief review of physiology relevant to right heart and pulmonary artery catheterization

Let us begin by looking at one mechanical cardiac cycle. While the ventricles are in systole, the atria are filling, as blood flows continually from the venous system, with the inferior and superior vena cava emptying into the RA and the pulmonary veins emptying into the left atrium (LA). Meanwhile, the tricuspid valve and the mitral valve remain closed as long as the pressure in the ventricles exceeds the pressure in the atria.

Blood flow in the heart occurs due to pressure gradients. As ventricular pressure decreases during isovolumetric ventricular relaxation (Figure 2.2a), it reaches a point where atrial pressure is higher than ventricular pressure and the mitral and tricuspid valves open due to hydrostatic pressure. The ventricles now rapidly fill (rapid ventricular filling; Figure 2.2b). This rapid filling characterizes the first phase of diastole. During the second phase of diastole, the pressures in the atria and the ventricles are the same. During this time, only a small amount of blood normally flows into the ventricles (slow ventricular filling). This is primarily blood

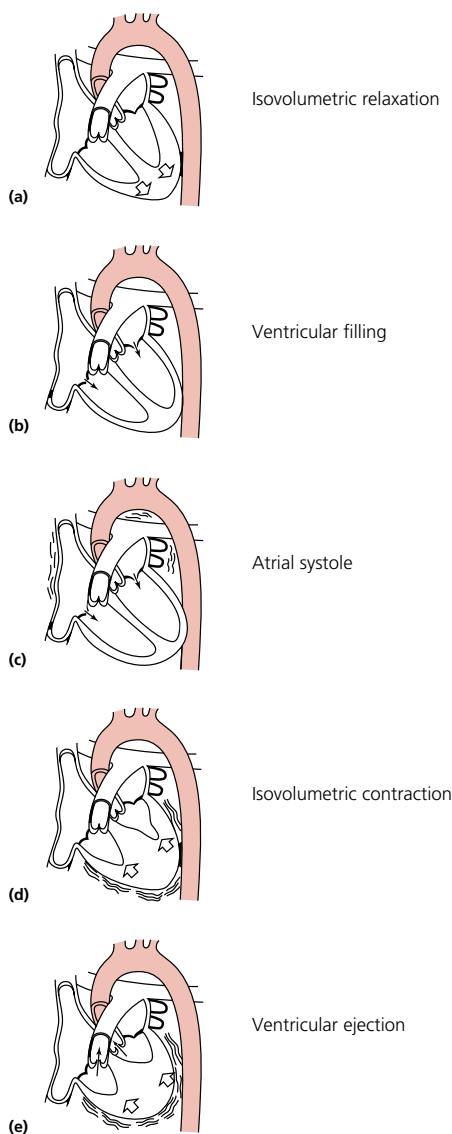


Figure 2.2 Schematic of blood flow in the heart. Phases represented include isovolumetric ventricular relaxation (a), rapid ventricular filling (b), atrial contraction (c), isovolumetric contraction (d), and ventricular ejection (e).

returning to the atria from the great veins or pulmonic veins, which then passes into the ventricle. Near the end of diastole, the atria contract (atrial systole), which generates an increase in pressure in the atrium and enhances blood flow into the ventricles (Figure 2.2c).

Systole begins when electrical activation of the ventricles (QRS complex) leads to mechanical activation of the ventricles. Very shortly after onset of ventricular contraction, the pressure in the ventricle increases to the point where it exceeds atrial pressure and the mitral and tricuspid valves close (all four valves are now closed). As the ventricles continue to contract (isovolumetric contraction; Figure 2.2d), right and left ventricular pressures increase until RV pressure exceeds PA pressure and LV pressure exceeds aortic pressure. At these points, the pulmonic and aortic valves open and ejection occurs (ventricular ejection; Figure 2.2e). At the end of systole, isovolumetric ventricular relaxation begins and ventricular pressures fall.

A point to remember is that as heart rate increases, myocardial oxygen consumption increases while supply decreases. This is because time in diastole decreases and time in systole increases as heart rate increases; while most coronary artery filling occurs during diastole, oxygen consumption of the heart is maximal during systole. About 70–90% of blood flow in the left coronary artery and one-half of blood flow in the right coronary artery occur during diastole. During systole, intramural arteries and capillaries are compressed by the contracting heart muscle, which limits blood flow.

Vascular access

A PA catheter can be inserted via any vein that has uninterrupted access to the RA. The most commonly used insertion sites include subclavian veins, internal jugular veins, brachial veins and femoral veins. The site is generally chosen based on patient preference and operator experience. All things being equal, the right internal jugular vein provides the shortest and straightest path to the heart. The use of ultrasound increases success rates for venous access and decreases complications. Complications associated with venous access include bleeding, hematoma, arterial puncture, infection, pneumothorax, and hemothorax (Table 2.2). Advantages and disadvantages of various access sites are listed in Table 2.3.

Right heart catheterization and placement of a PA catheter

A PA catheter can be positioned using either fluoroscopy or pressure monitoring. Fluoroscopy is preferred for femoral artery insertion and/or if there is significant hardware in the right heart (e.g., biventricular pacer). If continuous pressure monitoring is used, transduce the distal tip while advancing the catheter. CVP is initially obtained. As the catheter is being “floated” into the heart, it first enters the RA and then goes into the RV. Atrial waveforms consist of an A wave, a V wave, a C wave, and X and Y descents (Figure 2.3a). The A wave in the RA waveform coincides with atrial contraction and occurs simultaneously with the PR

Table 2.2 Complications of PA catheters.

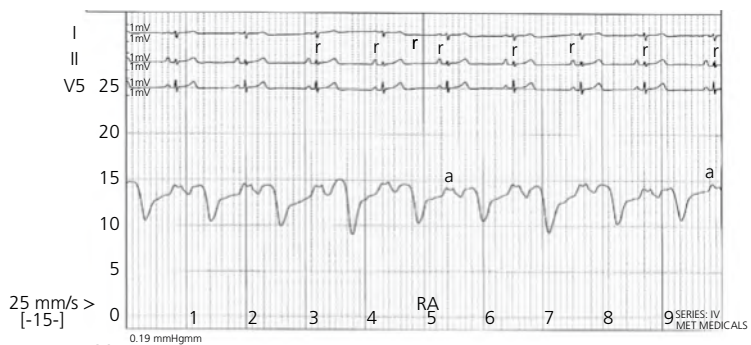
Complications associated with vascular access	Complications associated with PA catheter insertion or removal	Complications associated with indwelling PA catheters	Problems causing inaccurate data interpretation
Hematoma	Arrhythmias	Damage to tricuspid or pulmonic valve	Improper calibration Improper leveling of transducer
Bleeding	Damage to tricuspid or pulmonic valve	Infection	Air in tubing Interpretation without using ECG
Arterial puncture	Infection	Thromboembolic	Effects of respiration not noted
Pneumothorax	Pulmonary infarction Right bundle branch block	Pulmonary infarction	Inaccurate computation constant used to determine cardiac output
Hemothorax	Pulmonary artery rupture	Pulmonary artery rupture	Use of improper pressure scale

Table 2.3 Advantages and disadvantages of venous access sites.

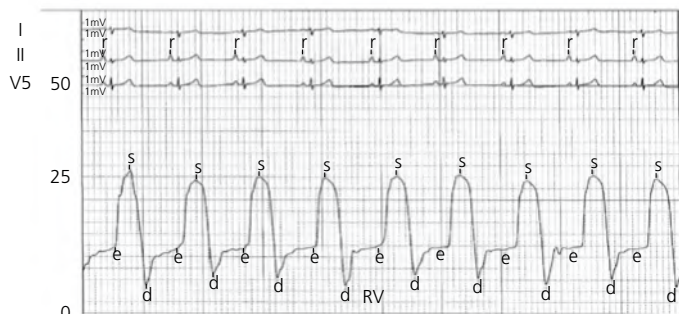
Site	Advantages	Disadvantages
Subclavian vein	Patient mobility; sterility	Risk of pneumothorax (especially in patients with COPD or on positive pressure ventilation); noncompressible site
Internal jugular vein	Compressible site; patient mobility; easily accessible	Inadvertent puncture of carotid; catheter can be dislodged from pulmonary capillary wedge position with neck movement; risk of pneumothorax
Femoral vein	Compressible site; easily accessible	Patient must remain in bed; infection risk
Brachial vein	Right heart catheterization can be done at the same time as left heart catheterization via radial artery	Brachial vein is smaller than subclavian, internal jugular, or femoral vein. Inadvertent cannulation of cephalic vein can make right heart catheterization more difficult

interval on the electrocardiogram (ECG), whereas the peak of the V wave in the RA waveform can be found near or at the end of the T wave. A further discussion of interpretation of atrial waveforms can be found in Chapter 5.

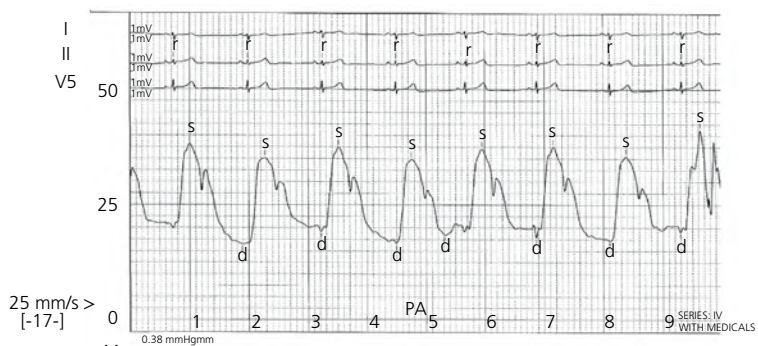
Entry of the catheter into the RV can be identified by the appearance of ventricular systole on the pressure tracing (Figure 2.3b). There will be a rapid upstroke reflective of ventricular contraction and a rapid decline reflective of ventricular



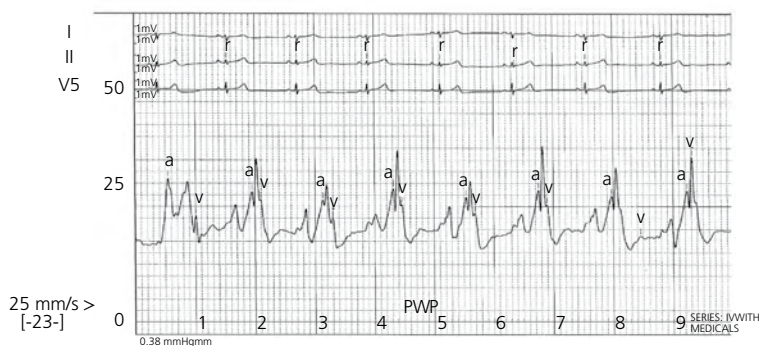
(a)



(b)



(c)



(d)

Figure 2.3 Pressure tracings encountered during the insertion of a PA catheter including RA (a), RV (b), PA (c) and PCWP (d).

relaxation. Diastole will be similar to atrial tracing. A further discussion of interpretation of ventricular waveforms can be found in Chapter 3. Normal RV systolic pressure is approximately 25 mm Hg, with diastolic pressures ranging from 0 to 8 mm Hg. The only time you should see an RV tracing is when the PA catheter is being inserted or removed. An RV pressure tracing from the distal port of the catheter appearing on the monitor at any other time is an indication that the catheter is no longer correctly placed. With the tip of the catheter in the RV, the risk of ventricular tachycardia is markedly increased.

As the catheter is advanced, it will leave the RV and enter the PA (Figure 2.3c). Remember that RV and PA systolic pressures are the same in the absence of pulmonic valve dysfunction (both should coincide with the T wave on the ECG). Thus passage into the PA will be evident from diastolic pressures. If an RV waveform is still present approximately 20 cm after the initial RV pattern appears, the catheter may be coiling in the RV.

PCWP can be obtained by inflating the balloon on the catheter and advancing the catheter until it “wedges” (Figure 2.3d). When the balloon is “wedged,” blood flow is stopped in that portion of the PA. Pressure equalizes in a nonflowing segment and, since there are no valves between the pulmonary arteries and pulmonary veins or between the pulmonary veins and the LA, pressure at the tip of the balloon is reflective of LA pressure. In general, PCWP is assumed based on the pressure tracing and the lack of balloon movement on fluoroscopy. A study of 111 patients undergoing right heart catheterization found that despite apparent confirmation of PCWP occlusion by fluoroscopy and typical hemodynamic waveform appearance, an occlusive PCWP SaO_2 ($\text{SaO}_2 > 90\%$ or within 5% of systemic arterial saturation), was obtained on the first attempt only 50% of the time. With up to two additional attempts, an occlusive PCWP SaO_2 was obtained in 91%. In patients in whom additional attempts were necessary to obtain an occlusive PCWP SaO_2 , 64% had a lower final PCWP compared with the initial PCWP by an average of 5 ± 1 mm Hg [16].

The A and V waves of the PCWP tracing will be delayed relative to RA tracing and ECG, with the A wave starting in or at the end of the QRS complex, and the V wave starting later in the T–P interval. This is because LA pressure is reflected back to the PA catheter via the pulmonary veins and through a static column of blood. PCWP is an important measurement since it is an estimate of LV diastolic pressure and thus LV preload.

Tempe *et al.* [17] measured the distance to various chambers in 300 adult patients who had PA catheters placed via the right internal jugular vein. The right ventricle was reached at 25 ± 3 cm, the PA at 36 ± 4 cm, and the wedge position at 43 ± 6 cm. The length of catheter required was directly related to the height of the patient and was greater in patients with valvular heart disease. In general, when using the left IJ vein, you need to add 5 cm to each of these measurements.

Most commonly, indwelling PA catheters rest in the PA (Figure 2.4), continuously giving a readout of PA systolic and PA diastolic pressure. Mean RA pressure

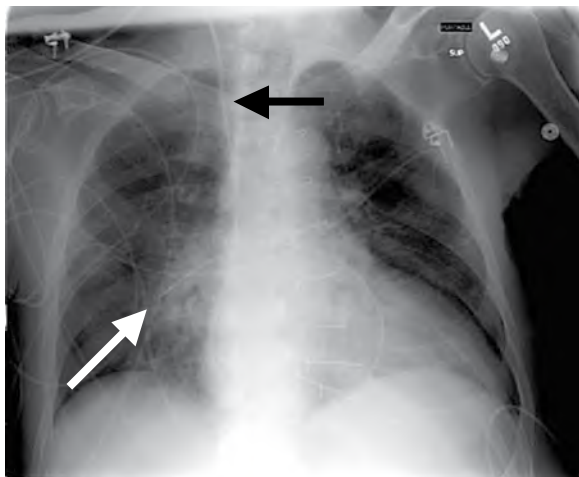


Figure 2.4 Chest X-ray showing placement of a PA catheter. The catheter was inserted via the right internal jugular vein. It passes through the superior vena cava (black arrow), RA, and RV. The tip rests in the right PA (white arrow).

can be obtained if the CVP port is transduced (but will often appear damped because the lumen is small).

Always deflate the balloon before withdrawing the PA catheter.

Ensuring that accurate data is obtained from a PA catheter

Remember the old saying: “Trash in equals trash out.” The integrity of the data obtained from a PA catheter is dependent on the accuracy of the system. A few simple rules to start with:

- The PA catheter needs to be “zeroed” at the level of the RA.
- Minimize the length of pressure tubing, the number of stopcocks, and the number of connections. Avoid narrow tubing, as the smaller the diameter of the tubing, the more pressure damping that occurs.
- Eliminate any air bubbles in the pressure line.
- The proper pressure scale needs to be used.
- Pressure tracings need to be interpreted in conjunction with an ECG tracing.
- The effects of respiration have to be identified.

It is essential that the PA catheter be properly “zeroed” at the level of the RA, which in the supine patient is assumed to be in the fourth intercostal space at the midaxillary line. Once the transducer is properly positioned, opening the stopcock to ambient air and pressing “zeroing” on the monitor, establishes atmospheric pressure at that location as the zero-reference point. In other words, proper

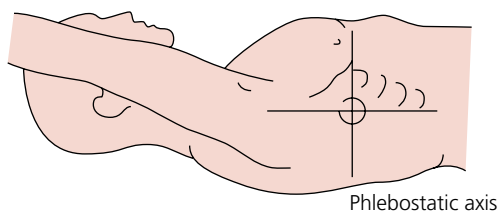


Figure 2.5 Phlebostatic axis.

“zeroing” removes the effect of gravity on pressures. To locate the level of the RA, two imaginary lines are drawn (Figure 2.5) and the place where they intersect is called the phlebostatic axis. To locate the phlebostatic axis, locate the fourth intercostal space on the edge of the sternum, draw an imaginary line along the fourth intercostal space laterally on the chest wall, and draw a second line from the axilla downward, midway between the anterior and posterior chest wall (i.e., the midaxillary line). The transducer does not need to be located at the phlebostatic axis but does need to be at the midaxillary line.

For every centimeter that the transducer is not correctly levelled, pressures will change by 0.75 mm Hg. If the transducer is too high, pressures will be falsely low. Alternatively, if the transducer is too low, pressures will be falsely high.

Pressure is transmitted from the catheter to the transducer via tubing filled with fluid, usually saline. Small changes in pressure in the PA are transmitted through the tubing and cause deflection of the transducer membrane, which converts these changes into electrical signals. Anything that hampers transmission of these small pressure changes to the membrane will distort pressure measurements and cause pressure “damping.” Thus, it is important to use semirigid, non-compliant tubing, to minimize the length of tubing, and to make sure that there is no air in the pressure tubing. Causes of pressure damping include long or compliant tubing, multiple stopcocks, transducer malfunction, loose connections, and partial occlusion of the port (e.g., with thrombus).

It is important that the proper scale be used when interpreting the pressure tracings. For example, when measuring LV pressure a scale of 0–200 mm Hg is useful. However, if this scale is used when examining RA pressure tracings, much of the information is lost about the “A” and “V” waves and “X” and “Y” descents that would be apparent if a scale of 0–25 mm Hg was used.

Proper analysis of waveforms

Multiple studies have shown that errors in waveform analysis and interpretation are common. For example, a study of 496 physicians found that only 53% were able to correctly identify the PCWP from a clear tracing [18]. Even in physicians who were considered high users of PA catheters (> 6 patients/month), only 72%

could correctly identify PCWP. There are multiple other examples—a study of 345 anesthesiologists reported that only 61% correctly identified PCWP from a clear tracing whereas 28% identified an incorrect value and 11% were uncertain [19]. In a study of 216 intensive care nurses, only 58% were able to correctly identify PCWP from a clear tracing [20]. Examples of normal waveforms, waveform inaccuracies and pressure tracings in various cardiac disease states are shown in Figure 2.6.

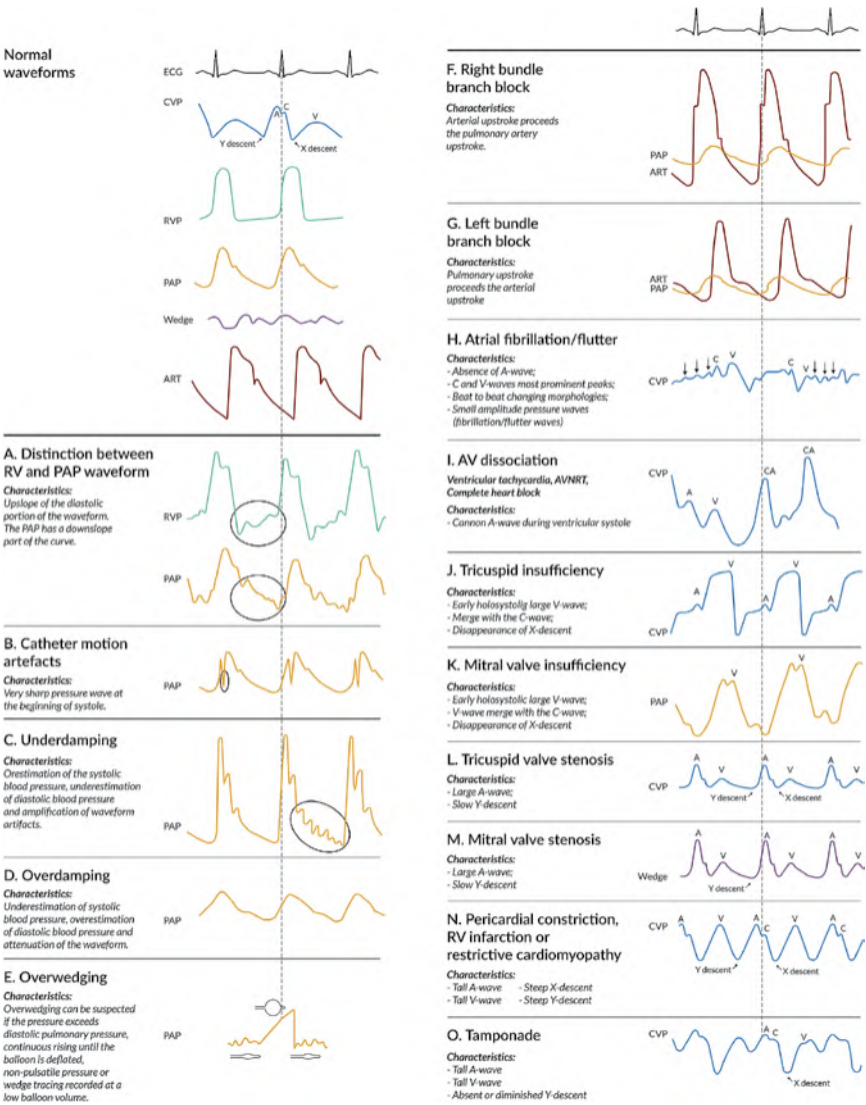


Figure 2.6 Pulmonary artery catheter waveforms. Source: [21] / Springer Nature / CC BY 4.0.

It is important that pressure tracings be interpreted in conjunction with an ECG recording. The most accurate method of obtaining hemodynamic data is to use a dual channel strip recorder, which will allow analysis of the waveform and ECG together.

When interpreting atrial pressure waveforms, emphasis should be placed on mean pressures or pressures obtained at end-expiration. In many ICUs, all waveforms are read at end-expiration because this is when intrapleural pressures are negligible, which means that the waveforms are an accurate reflection of cardiac pressures.

In a spontaneously breathing patient, intrathoracic and thus intracardiac pressures will decline during inspiration and rise during expiration (Figure 2.7). During inspiration, the diaphragm pulls downward, creating a negative pleural pressure during inspiration, while during expiration, the diaphragm relaxes and the elastic recoil of the lungs, chest wall, and abdominal structures compress the lung.

In patients who are mechanically ventilated, end-expiration is still used to record pressures. The difference is that pressures increase with inspiration and decrease with expiration. If the patient is not breathing over the ventilator, then interpretation is straightforward. If the patient is ventilated and also breathing spontaneously, then waveform interpretation becomes more difficult, as inspiration can be associated with decreases in pressure (spontaneous respiration) and increases in pressure (ventilator). The spontaneous breath with pressure support will result in an initial decrease in pressure, which can be used to locate end-expiration (just prior to the inspiratory effort marked by the dip in pressure). In patients receiving intermittent mandatory ventilation, identifying end-expiration can be a challenge. There are newer ventilators that show graphic respiratory waveforms that provide a means for accurately identifying end-expiration.

In the ICU, manual interpretation of waveforms using a printed copy is necessary to ensure that pressures are interpreted at end-expiration unless a monitor is available that displays the ECG, respiratory recording, and PA pressure waveforms on a single screen.

Cardiac output

A brief overview of CO is presented here. For a more detailed discussion, see Chapter 6.

There are two primary methods used to calculate CO when utilizing a PA catheter: thermodilution and assumed Fick. The thermodilution method requires that a substance that is cooler than blood (usually saline) be injected through the CVP port of the PA catheter. This injection should be smooth and take less than 4 seconds. The temperature in the PA is measured and the change over time, as the

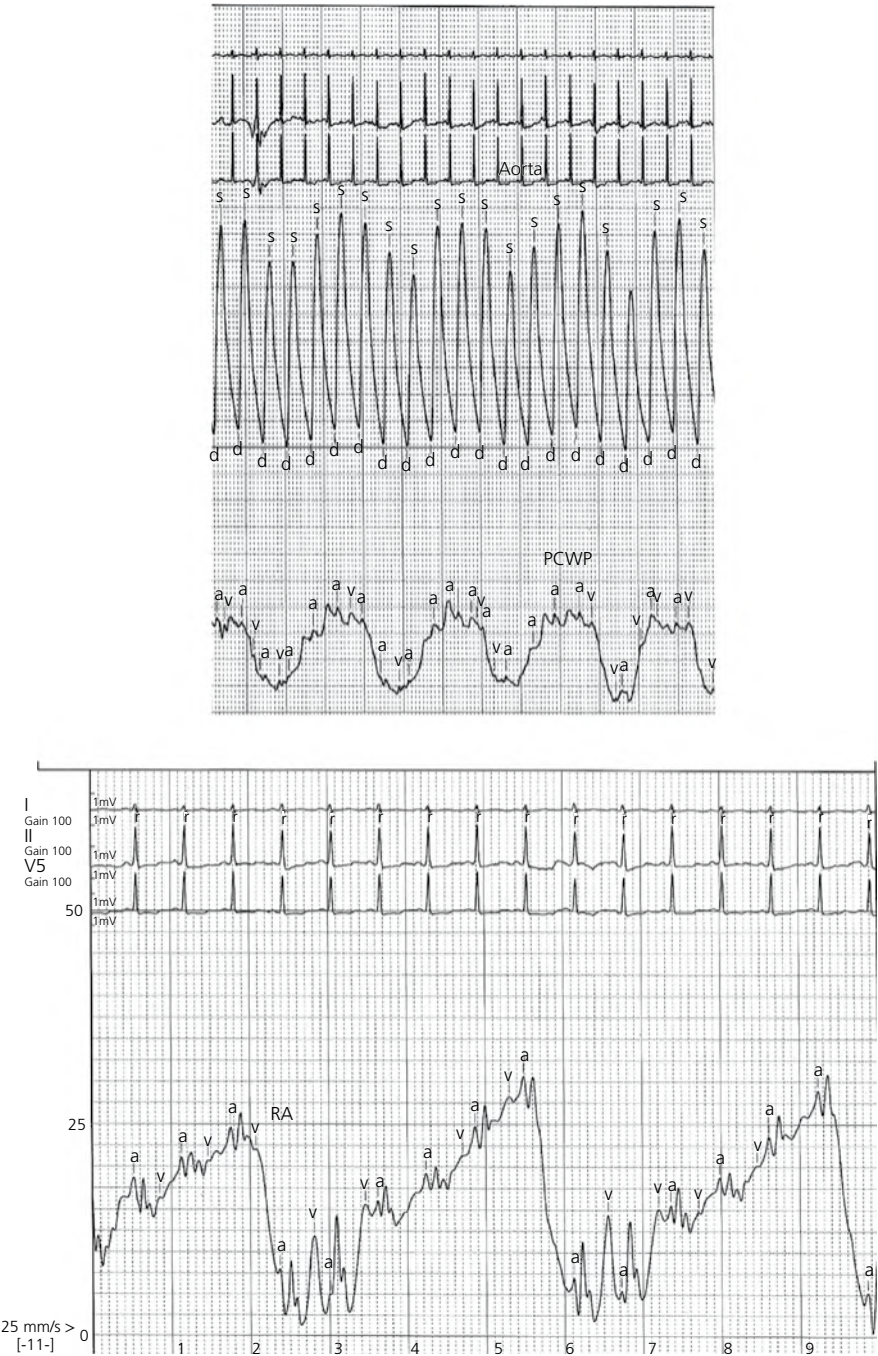


Figure 2.7 Effect of respiratory variation on RA and PCWP pressures.

cooler injectate passes through the PA, is used to calculate CO. The computer in the CO machine uses the following formula:

$$CO = \frac{CC \times (Tb - Ti)}{\text{area under the curve}}$$

where CC is the computation constant, Tb the blood temperature, and Ti the injectate temperature.

A computation constant needs to be entered to provide the CO computer with information on the amount and temperature of the injectate. Each PA catheter comes with an insert describing computation constants to be used under various conditions.

If you enter a computation constant that calls for 10 cc and you inject 9 cc, the measured CO will be incorrect. Most of the time room-temperature saline is used as the injectate. If a different temperature injectate is used (e.g., iced saline), the computation constant must be changed.

The other method used to estimate CO was first described by Adolph Fick in 1870. He postulated that the total uptake or release of a substance by an organ is the product of the blood flow through that organ and the arteriovenous difference of the substance. To directly measure oxygen consumption requires a Water's hood for the nonventilated patient or a metabolic cart for the ventilated patient. This is cumbersome and rarely used in daily practice. Instead, oxygen consumption is "assumed" (methods used to arrive at oxygen consumption are described in detail in Chapter 6).

The arterial-venous (A - V) O₂ gradient in the body is determined by comparing arterial oxygen saturation (measured directly or obtained via a pulse oximeter) with "mixed venous" oxygen saturation. Blood is considered "mixed venous" when it has circulated through the right side of the heart, to the PA. This mixing includes blood from the inferior and superior vena cava and the heart itself.

The formula used to estimate CO using the assumed Fick approach is:

$$O_2 \text{ consumption} = CO(A - VO_2 \text{ difference})$$

or

$$CO = \frac{O_2 \text{ consumption}}{A - VO_2 \text{ difference}}$$

$$CO = \frac{130 \times BSA}{1.36 \times Hgb \times 10 \times (SaO_2 - SvO_2)}$$

where BSA = body surface area; 130 mL/min = standard oxygen consumption; 1.36 = a gram of hemoglobin (Hgb) holds 1.36 mm of oxygen; Hgb = reported as grams per deciliter; 10 = to convert deciliters to liters you need to multiply the Hgb by this; SaO₂ = either from an ABG or from the pulse oximeter; SvO₂ = either from an oximetric PA catheter or by during oxygen saturation on a blood sample drawn from the PA port.

An example of calculating cardiac output using the assumed Fick method

The "assumed oxygen consumption" is 130 mL/min

If BSA = 1.7; Hg = 12, $\text{SaO}_2 = 0.98$, and $\text{SvO}_2 = 0.55$

$$\text{CO} = \frac{130 \times 1.7}{1.36 \times 12 \times 10 \times (0.98 - 0.55)} = \frac{221}{70.1} = 3.16 \text{ L/min}$$

The cardiac index (CI) enables comparison of CO between patients of different sizes. It is calculated by dividing CO by BSA. The normal CI is 2.5–4 L/min.

Calculating systemic vascular resistance and pulmonary vascular resistance

Vascular resistance is an indicator of ventricular afterload. Systemic vascular resistance (SVR) can be calculated using the following formula:

$$\text{SVR} = \frac{\text{MAP} - \text{CVP}}{\text{CO}} \times 80$$

Normal SVR is 800–1200 dynes / sec / cm^5 .

An example of calculating SVR

If MAP = 93 mm Hg, CVP = 3 mm Hg and CO = 5 L/min:

$$\text{SVR} = \frac{(93 - 3) \times 80}{5} = 1440 \text{ dynes / sec / cm}^5$$

The CI enables comparison of CO between patients of different sizes. It is calculated by dividing CO by body surface area. The normal CI is 2.5–4 L/min.

Pulmonary vascular resistance (PVR) is an estimate of RV afterload. Normal PVR is in the range of 40–150 dynes/sec/ cm^5 . PVR can be calculated using the following formula:

$$\text{PVR} = \frac{\text{Mean PAP} - \text{PCWP}}{\text{CO}} \times 80$$

Mean PA pressure (PAP) is calculated similarly to mean arterial pressure:

$$\text{Mean PAP} = \frac{\text{PA systolic pressure} + (2 \times \text{PA diastolic pressure})}{3}$$

An example of calculating PVR

If PAS = 30 mm Hg, PAD = 15 mm Hg, PWP = 10 mm Hg, and CO = 5 L/min:

$$\text{PVR} = \frac{20 - 10}{5} \times 80 = 2 \times 80 = 160 \text{ dynes / sec/ cm}^5$$

Occasionally, PVR will be reported in Wood units (named after Paul Wood, a British cardiologist). It is the same formula as earlier, but the conversion factor of 80 is not used. To calculate PVR in Wood units, do the same calculation as earlier but do not multiply by 80 (i.e., $\text{PVR} = 160 \text{ dynes/sec/cm}^5 = 2 \text{ Wood units}$).

PVR is an important parameter in patients being evaluated for a heart transplant. If PVR is elevated, the right heart in the transplanted heart will not be able to generate enough pressure to maintain CO. In general, survival in transplanted patients is better if $\text{PVR} < 3 \text{ Wood units}$.

SvO₂ monitoring

A full discussion of mixed venous oxygen saturation monitoring (SvO₂) is beyond the scope of this chapter; however, we will cover some of the basic concepts.

The body maintains a balance between the oxygen delivered and the oxygen consumed. The supply side consists of CO, oxygenation, and hemoglobin. The demand side is basal energy consumption plus anything that increases oxygen use, for example, pain, shivering, infection, agitation, or any number of disease processes. Oxygen use is decreased by various factors, including anesthesia, hypothyroidism, paralyzing agents, sleep, and pain medication. SvO₂ is a function of oxygen delivered minus oxygen consumed. For example, assume that 1000 mL/O₂/min of oxygenated blood is delivered to the tissues. Next, assume that the tissues use or consume 250 mL/O₂/min. This would leave 750 mL/O₂/min to return to the lungs through the venous system. A total of $1000 - 250 = 750 \text{ mL}$ or 75% of the oxygenated blood is returned to the lungs. This 75% is the venous oxygen reserve.

If a healthy individual's oxygen consumption increases, the body will increase CO and respiratory rate to ensure that demand is met and blood is kept fully oxygenated. In a critically ill patient, the situation is different and some patients are incapable of meeting even resting oxygen demands. When supply fails to meet demand despite maximal extraction of oxygen from the blood, anaerobic metabolism and lactic acidosis may occur.

SvO₂ can be measured continuously if the patient has an oximetric PA catheter in place. The oximetric catheter has fiberoptic technology that enables measurement of oxygen saturation of hemoglobin within the PA. Alternatively, if the patient does not have an SvO₂ catheter in place, oxygen saturation in PA blood

can be measured via an oximeter by obtaining intermittent blood samples from the PA via the catheter. There are several uses of continuous oximetry, including measuring tissue oxygen consumption, obtaining real-time estimation of CO, and monitoring responses to medications.

Important points about SvO₂ monitoring:

- Mixed oxygen saturation monitoring and arterial saturation monitoring may allow identification of an imbalance of oxygen supply and demand.
- CO is the largest determinant of oxygen supply.
- Normal SvO₂ is 60–80%.
- Oximetric catheters allow continuous monitoring of SvO₂.
- If the patient does not have an oximetric catheter in place, intermittent PA blood samples can be used to determine SvO₂. The disadvantage of this method is that you only know what the SvO₂ is at that specific time.
- SvO₂ may be high in sepsis because of impaired oxygen extraction. In this case, tissues are generally hypoxic despite high SvO₂. Some practitioners are using ScvO₂ (central venous oxygen saturation monitoring) in patients with sepsis. The concept is the same. However, the blood sample is taken from distal port of a triple lumen that has been placed in the right subclavian vein. Therefore, this saturation measurement does not include venous return from the heart.

Complications of pulmonary artery catheterization

There are several risks associated with PA catheter insertion that are independent of vascular access (Table 2.2). These include arrhythmias, transient right bundle branch block (RBBB) infection, pulmonary infarction, PA rupture, myocardial perforation, damage to the pulmonic or tricuspid valves, thromboembolic complications, air embolism, and knotting of the catheter.

Arrhythmias primarily occur during passage through the RV and are increased in patients with acute ischemia, hypocalcemia, hypokalemia, hypomagnesemia, hypoxemia, acidosis, shock, or digitalis toxicity. Atrial arrhythmias can also be precipitated by PA catheter placement.

RBBB can occur during passage of the catheter through the tricuspid valve. The right bundle is a fairly discrete and superficial structure in the septal wall and thus subject to trauma during the catheter advancement. RBBB is usually transient and does not cause any problems unless the patient has a preexisting left bundle branch block (LBBB), in which case complete heart block develops. In patients with LBBB, it is prudent to have a transcutaneous pacemaker readily available. In one series of 82 patients with LBBB, two episodes of complete heart block occurred. Both of these episodes occurred in patients with recent-onset LBBB and both occurred one day after the catheter had been inserted [5].

PA catheters have been associated with an increase in the risk of pulmonary embolus. In a randomized trial of PA catheters in 1994 high-risk surgical

patients, there was a higher rate of pulmonary embolism in the catheter group than in the standard care group (8 events versus 0 events, $P = 0.004$) [3]. One clue to the appearance of thrombus on the tip of a PA catheter can be pressure damping.

PA catheters have also been associated with valve damage and endocarditis. A study of autopsies from 55 patients who had undergone PA catheterization found that 53% had right-sided endocardial lesions. These included 22% with subendocardial hemorrhage, 20% with thrombus, 4% with hemorrhage and thrombus, and 7% with infective endocarditis. The pulmonic valve was the most common site of lesions (56%) followed by tricuspid valve (15%), RA (15%), right ventricle (10%), and PA (5%) [22].

There are two complications that can occur with wedging of the PA catheter: PA ischemia and/or infarction and PA rupture. As the PA catheter wedges, it blocks blood flow in a branch of the PA and therefore can cause ischemia and/or infarction if the balloon is left inflated too long. Alternatively, the catheter can migrate into a small branch and occlude flow without balloon inflation (called "spontaneous wedge"). During the first few hours that the PA catheter is in place, it warms up and can migrate further into the distal lung vasculature.

The most feared complication of PA catheters is PA rupture. The presentation can be dramatic, with sudden onset of hemoptysis followed by cardiovascular collapse. It generally occurs when the balloon is inflated in a small nondistensible branch, but can also be caused by the tip of the catheter perforating the artery. Risk factors for PA rupture include pulmonary hypertension, age, female gender, anticoagulation, and frequent wedging. This complication is fatal approximately 50% of the time.

To avoid complications from wedging the PA catheter, inflate the balloon slowly with continuous waveform monitoring. If a PCWP tracing is obtained, stop inflating the balloon. If the PA catheter wedges with 0.5 cc of air or less, then it probably needs to be repositioned. A few other important points: try never to wedge longer than 2 respiratory cycles; never inflate the balloon with more than 1.5 cc of air; continuously monitor waveforms to ensure that the PA catheter does not spontaneously wedge; and never flush the catheter in a wedged position. When a PA catheter overwedges, the waveform usually goes straight up or down. If you see this waveform you should immediately let the air out of the balloon and obtain a chest X-ray to determine the location of the tip of the catheter.

If PA diastolic pressure and PCWP are closely related (a widely used rule of thumb is if they are within 6 mm Hg), there is no need to obtain wedge pressures repeatedly. PA diastolic pressure can be used to make clinical decisions.

One of the most common sources of errors when using PA catheters is inaccurate interpretation of data. Multiple studies have demonstrated inconsistent, incomplete, and improper data interpretation. It is important to obtain a complete understanding of how best to analyze the data obtained at the time of PA catheter placement in order to use the PA catheter optimally.

Case studies

- 1 You are working in surgical ICU caring for a 75-year-old male who was in a motor vehicle accident 36 hours ago. Despite adequate fluid resuscitation with a CVP reading of 10 mm Hg, he remains hypotensive, acidotic, and has a base balance of -3 . Vital signs: HR 120 bpm, BP 90/40 mm Hg with MAP 56 mm Hg, urine output = 15 mL/hour. Ventilator settings are as follows: SIMV/PRVC, $\text{FiO}_2 = 70\%$, TV 450 mL, Rate 14, PS 10 cm H_2O , PEEP 5 cm H_2O . He is not breathing over the ventilator.

The decision is made to place a PA catheter to evaluate his cardiac status. His PA catheter numbers are CVP = 10 mm Hg, PA pressures = 40/20 mm Hg, PCWP = 16 mm Hg, CO/CI = 3.5/1.8 L/min.

- (a) What is his stroke volume (SV)?
 - (b) What is his SVR?
 - (c) Based on the PA numbers, would you change your therapy?
 - (d) On his pressure waveforms, how will you identify end-expiration?
- 2 You are working in the medical ICU when a 69-year-old female is admitted with the diagnosis of severe dyspnea. There is no documented history of heart disease. Vital signs: HR = 130 bpm, BP = 80/30 mm Hg with MAP = 46 mm Hg, urine output = 10 mL/hour, Temp 35°C orally, lactate = 4 mg/dL. Ventilator settings = SIMV/PRVC, $\text{FiO}_2 = 100\%$, TV 400 mL, Rate 22, PS 10 cm H_2O , PEEP 10 cm H_2O . Initially she had a CVP of 2 mm Hg and an ScvO_2 of 65%. Despite an increase in CVP to 10 mm Hg after fluid resuscitation and the addition of two vasopressors, her blood pressure does not improve. Her chest X-ray shows diffuse pulmonary edema. To answer the question of whether the pulmonary edema is cardiogenic or noncardiogenic, a PA catheter is inserted and the following information obtained: CVP = 10 mm Hg, PA pressure = 25/15 mm Hg, PCWP = 12 mm Hg, $\text{SvO}_2 = 60\%$, and CO = 8 L/min with CI = 3.5 L/min.
- (a) Based on the information available, is the primary etiology of the pulmonary edema cardiogenic or noncardiogenic?

- 3 You are working in the coronary care unit (CCU) when a 62-year-old female is admitted with the diagnosis of cardiogenic shock. The patient became extremely fatigued 48 hours ago, but only recently came to the emergency room (ER) when she became very short of breath. The ECG shows Q waves in leads I, aVL, and V1–V6, consistent with a large anterolateral MI. Her vital signs are as follows: HR 120 bpm, BP 86/40 mm Hg with MAP 55 mm Hg, RR 32 times per minute. Pulse oximetry is reading 85% on room air. Temp = 36.5°C .

A PA catheter is inserted to assist with her treatment and the following information is obtained: CVP = 15 mm Hg, PA pressure = 45/30 mm Hg, PCWP = 26 mm Hg, and CO = 3 L/min with CI = 1.7 L/min.

- (a) What is her SV?
 - (b) What is her SVR?
 - (c) Based on the PA numbers, would you change your therapy?
 - (d) Would you use beta blockers to decrease the heart rate at this time?
- 4 You are working in the cardiac catheterization laboratory and a 33-year-old male is referred for evaluation for a potential orthotopic heart transplant. He was well until 18 months ago when he developed severe LV dysfunction of unclear etiology but thought to be a sequela of a viral syndrome. He has had a steady downward course during the past 3 months, during which his symptoms have progressed to Class III (i.e., he cannot walk across a room without having to stop to catch his breath). Ventriculography confirms

severe LV dysfunction. Coronary angiography is normal. A right heart catheterization is performed and the following information obtained: RA pressure = 20 mm Hg, PA pressure = 78/41 (mean of 58 mm Hg), PCWP = 38 mm Hg, and CO = 4.6 L/min.

(a) What is the PVR?

(b) What would you do next?

Nitroprusside infusion was begun and titrated until systemic systolic blood pressure was approximately 80 mm Hg. The following information was obtained from the PA catheter: PA pressure = 65/30 (mean of 46 mm Hg), PCWP = 24 mm Hg, and CO = 7.9 L/min.

(a) What is the PVR now?

(b) Is the patient a candidate for heart transplantation?

Case study answers

1 (a) $SV = \frac{CO}{HR} = 3500 \text{ mL/min} / 120 \text{ bpm} = 29 \text{ mL}$.

The patient's stroke volume is 29 mL.

(b) $SVR = \frac{(MAP - CVP) \times 80}{CO} = \frac{(56 - 10) \times 80}{3.5} = 1051 \text{ dynes/sec/cm}^5$.

(c) LV Preload is reflected by PCWP = 16 mm Hg with an afterload (SVR) of 1051 dynes/sec/cm⁵. CO is low despite reasonable preload, suggesting LV dysfunction (possibly due to a cardiac contusion suffered at the time of the accident). An echocardiogram would be useful. Giving intravenous (IV) fluids to increase PCWP might increase CO (at the risk of worsening oxygenation) and/or an inotrope such as dobutamine might be used to increase contractility.

(d) The patient is receiving positive pressure ventilation and thus inspiration is characterized by an increase in pressure on RA and PCWP waveforms. End-expiration will be just prior to the ventilator-stimulated increase. If the patient has any spontaneous respirations, remember to ignore the initial inspiratory dip in pressure—end-expiration will be just prior to this brief drop in pressure.

2 (a) A PCWP less than 18 mm Hg favors pulmonary edema of noncardiac origin rather than of cardiogenic origin. According to Schwarz and Albert [7], "acute lung injury (ALI) and ARDS (ALI/ARDS) are defined as follows: (1) an illness having an acute onset, (2) an arterial oxygen tension/inspired oxygen fraction ≤ 200 mm Hg (or ≤ 300 mm Hg for ALI), (3) the presence of bilateral infiltrates on frontal chest radiographs, and (4) a pulmonary artery occlusion pressure ≤ 18 mm Hg if measured, or no clinical evidence of left atrial hypertension when not measured." According to the Berlin Modification of the American-European Consensus Conference [9], ARDS can be divided into three categories of severity based on degree of hypoxemia: mild

(200 mm Hg < PaO₂/FIO₂ ≤ 300 mm Hg), moderate (100 mm Hg < PaO₂/FIO₂ ≤ 200 mm Hg), and severe (PaO₂/FIO₂ ≤ 100 mm Hg).

3 (a) $SV = \frac{CO}{HR} = 3000 \text{ mL/min} / 120 \text{ bpm} = 25 \text{ mL}.$

(b) $SVR = \frac{(MAP - CVP) \times 80}{CO} = \frac{(55 - 15) \times 80}{3} = 1067 \text{ dynes/sec/cm}^5.$

(c) Her preload is high (CVP = 15 mm Hg and PCWP = 26 mm Hg), her afterload is within the normal range, and her CO is low. These numbers confirm the diagnosis of cardiogenic shock. Treatments might include pharmacologic diuresis to decrease preload and thus improve LV function according to the Frank-Starling curve. An IABP could be inserted to augment coronary artery perfusion, increase MAP, and decrease afterload. Some practitioners might also use dobutamine to improve LV contractility.

(d) No, as the heart rate is necessary to maintain blood pressure. The heart rate has increased in order to enhance CO in the setting of a decreased stroke volume.

4 (a) $PVR = \frac{(\text{Mean PAP} - \text{PCWP})}{CO} = \frac{(58 - 38)}{4.6} = 4.4 \text{ Wood units}.$

(b) In severe LV dysfunction, total PVR includes both a “fixed” component and a “dynamic” component, which is dependent on LA pressure. Following a heart transplant, LA pressure is less and the dynamic component of PVR is greatly reduced or eliminated. The fixed component of PVR persists, however, and the new RV must be able to maintain CO against this resistance. In determining which patients are at risk for acute RV failure following heart transplantation, it is essential to quantify the fixed component of PVR. This can be done by measuring PA pressures, PCWP, and CO during infusion of a vasodilator (e.g., prostacyclin, adenosine, or nitroprusside).

(c) The PVR is now $\frac{(46 - 24)}{7.9} = 2.8 \text{ Wood units}.$

(d) This level of PVR would not exclude the patient from receiving a heart transplant in most centers.

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CHAPTER 3

Normal hemodynamics

Revised and updated by George A. Stouffer

[This is a revision of a chapter written for the first two editions of this book by Alison Keenon, Eron D. Crouch, James E. Faber, and George A. Stouffer]

Cardiac cycle

The cardiac cycle is a series of events related to cardiac contraction, which results in changes in cardiac pressure and blood flow. Mechanical events of the cardiac cycle, as they occur in series, are as follows: right atrium (RA) contracts, left atrium (LA) contracts, left ventricle (LV) begins contraction, mitral valve closes, right ventricle (RV) begins contraction, tricuspid valve closes, pulmonary valve opens, aortic valve opens, aortic valve closes, pulmonary valve closes, tricuspid valve opens, mitral valve opens. The events of the cardiac cycle superimposed on cardiac pressure tracings and an electrocardiogram (ECG) tracing, often called the Wiggers diagram after Dr. Carl Wiggers, who first arranged data in this useful manner, is helpful in illustrating the relationship and timing of events in the cardiac cycle to hemodynamic phenomena (a stylized version of a Wiggers diagram is shown in Figure 3.1).

The cardiac cycle is often divided into systole (ventricular contraction) and diastole (ventricular filling; Figure 3.2). Systole can be further divided into three stages: isovolumetric contraction, rapid ejection, and reduced ejection (Figure 3.3). The isovolumic phase of LV contraction is that time in which ventricular pressure is increasing but is not sufficient to open the aortic valve (Figure 3.1). This phase ends when the aortic valve opens and blood is ejected (ejection phase). On LV pressure tracing, the onset of ventricular contraction coincides with the R wave on the ECG and is indicated by the earliest rise in pressure after atrial contraction. During ventricular systole, the atrial pressure initially declines. This is thought to be due to stretch of the atria as the base of the heart descends. Following this brief period, atrial pressure progressively increases during the rest of ventricular systole as blood flow into the atria increases.

Diastole is the period during the cardiac cycle between aortic valve closure and mitral valve closure. A common mistake is to think of diastole as less important

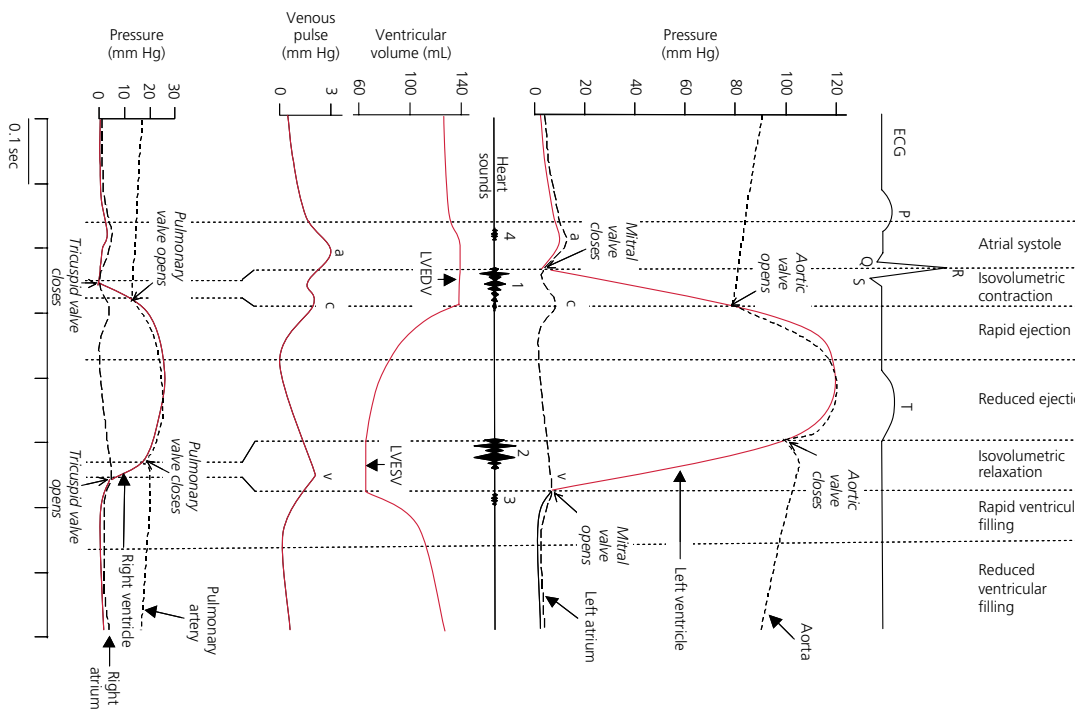


Figure 3.1 Wiggers diagram.

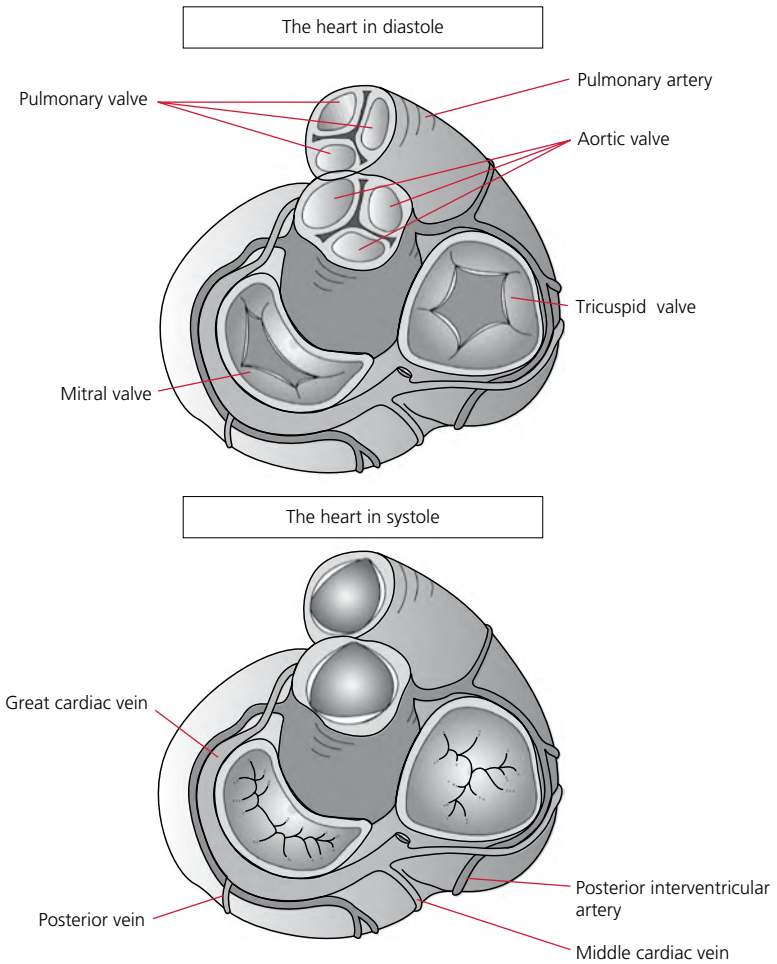


Figure 3.2 Cardiac structures during systole and diastole.

than systole, or more inaccurately as merely the absence of systole. Our appreciation of diastole has increased over the years as we have realized the importance of diastolic dysfunction in patients with heart failure with preserved ejection fraction (HFpEF). Diastole is commonly divided into four components: isovolumetric relaxation, rapid filling (RF) phase, slow filling (SF) phase, and atrial systole (Figure 3.3). Isovolumic relaxation is the period between the closing of the semilunar valve and the opening of the atrioventricular (AV; = mitral and tricuspid) valve. It is very brief and dependent on the relaxation properties of the ventricle. Analysis of this phase is useful experimentally but has limited application clinically.

The RF period occurs immediately upon opening of the AV valve. In normal individuals, this phase accounts for the majority of ventricular filling. This phase

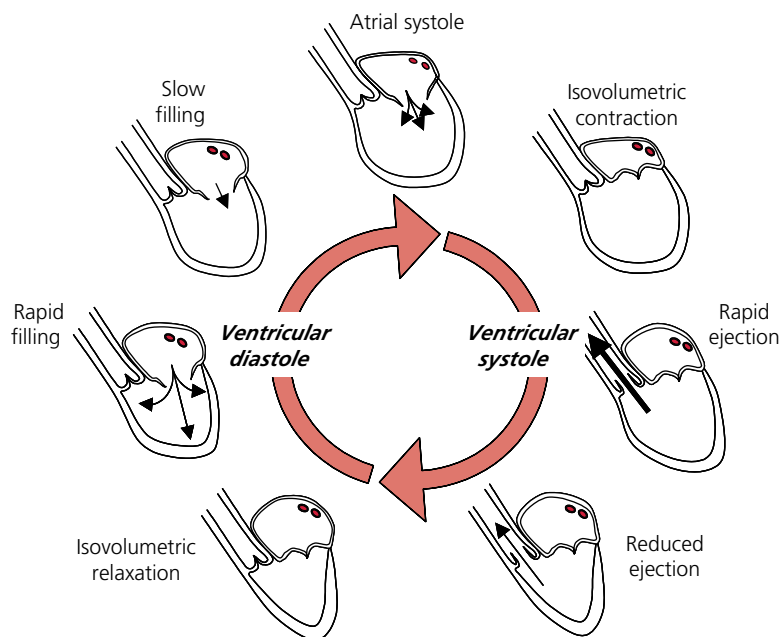


Figure 3.3 Mechanical events of the cardiac cycle.

is characterized by the Y descent on atrial pressure tracings and by a rapid fall (because the ventricle is still relaxing) and then an equally rapid rise in ventricular pressure (as the ventricle fills). As the rate of ventricular filling declines, the SF phase is entered, followed by diastasis (a period when ventricular filling ceases). During the SF period in a normal heart, the atrial and ventricular pressures are similar and continued filling of the RVs and LVs is dependent on blood returning from the peripheral circulation and the lungs, respectively. The SF phase lasts longer than the RF phase in the normal heart. In patients with noncompliant ventricles, true diastasis may not occur. Rather, in the setting of elevated atrial pressure, passive blood flow from the atrium to the ventricle continues throughout diastole, with the rate of flow and increase in ventricular pressure dependent on the compliance of the diseased ventricle.

Atrial systole is the last phase of diastole. It occurs soon after the beginning of the P wave on the ECG and is concurrent with the A wave on the atrial pressure tracing. In the normal heart at rest, atrial systole contributes relatively little blood to the already-filled ventricle. In the diseased heart, or in the normal heart during exercise, the contribution of atrial systole assumes a larger importance. In clinical practice, it is common to see patients with hypertrophied ventricles who do well until they develop atrial fibrillation which precipitates heart failure due to the rapid heart rate and the loss of atrial contraction.

Cardiac chambers

Right atrium

Normal RA pressure is 2–8 mm Hg (Table 3.1) and is determined by central venous pressure (CVP), RA compliance, tricuspid valve function, and RV compliance (Figure 3.4). CVP, and thus RA pressure, is primarily influenced by blood volume, body position, reflex changes in venous tone, skeletal muscle contraction, and the respiratory cycle.

An examination of the RA pressure waveform in a patient in normal sinus rhythm reveals two major positive deflections, the A and V waves, and two negative deflections, the X and Y descents (Figure 3.5). The A wave results from RA contraction and occurs immediately following the P wave on a surface ECG, with the peak of the A wave on the pressure tracing following the peak of the P wave on the ECG by approximately 60–80ms. Following RA contraction, the pressure declines, and this is manifested as the X descent. The X descent is caused by atrial relaxation as well as downward motion of the atrioventricular junction during early ventricular systole. A third minor positive deflection, the C wave, may be seen in some settings between the A and V waves. The C wave, when present, will interrupt the X descent, and is caused by tricuspid valve closure. It marks the onset of RV systole and will be seen as a minor positive deflection immediately

Table 3.1 Normal hemodynamic values.

Pressure measurement	Normal value (mm Hg)	Temporal relationship of ECG to mechanical events
Right atrium (RA)		Onset of P wave to RA contraction is ~60–80 ms
Mean pressure	2–8	
Right ventricle (RV)		Onset of Q wave to RV contraction is ~65 ms
Peak-systolic pressure	17–32	
End-diastolic pressure	2–8	
Pulmonary artery		Onset of Q wave to RV ejection is ~80 ms
Mean pressure	9–19	
Peak-systolic pressure	17–32	
End-diastolic pressure	4–13	
Left atrium (PCWP)		Onset of P wave to LA contraction is ~85 ms.
Mean pressure	2–12	Onset of P wave on ECG to A wave on PCWP tracing will vary and may be >200ms
Left ventricle (LV)		Onset of Q wave to LV contraction is ~52 ms
Peak-systolic pressure	90–140	
End-diastolic pressure	5–12	
Aorta		Onset of Q wave to LV ejection is ~115 ms
Mean pressure	70–105	

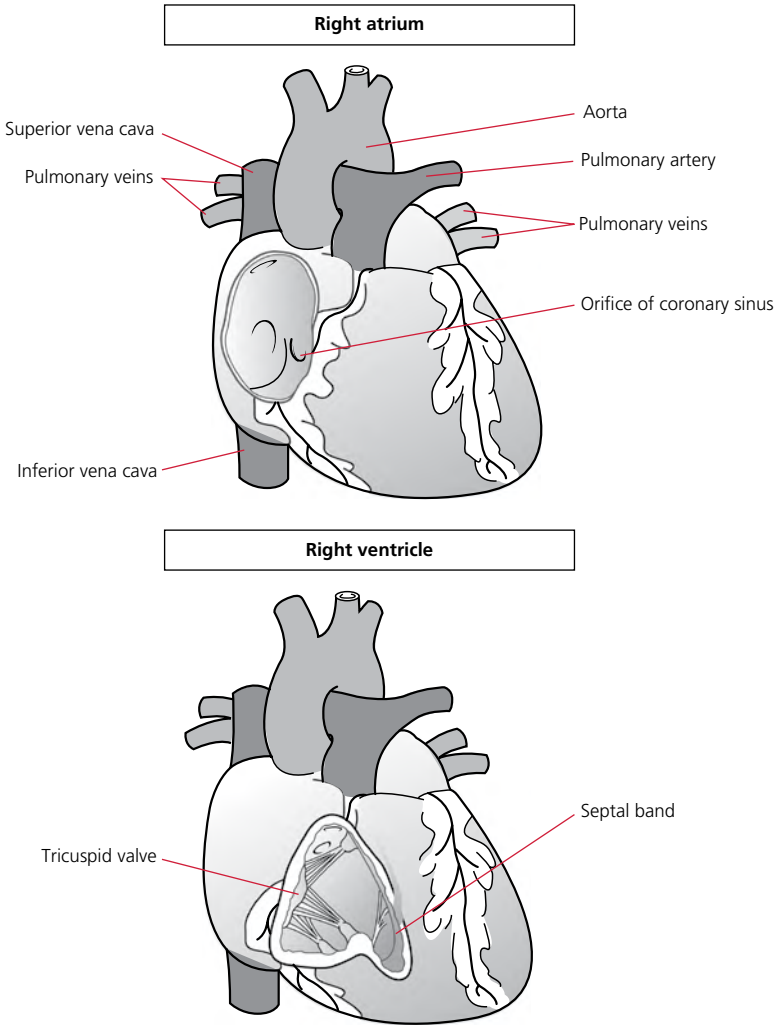


Figure 3.4 Schematic of RA and RV.

following the QRS complex, that follows the A wave by a duration equal to the PR interval. After the peak of the C wave, the X descent continues (and is then called X prime; X') as atrial relaxation occurs and the pressure declines. The V wave is seen following the nadir of the X descent and represents venous filling of the RA while the tricuspid valve is closed. The peak of the V wave occurs at the end of ventricular systole, just prior to tricuspid valve opening. V waves generally occur simultaneously with the T wave on a surface ECG. The Y descent follows the V wave and denotes the onset of RV diastole. This descent reflects the rapid fall of

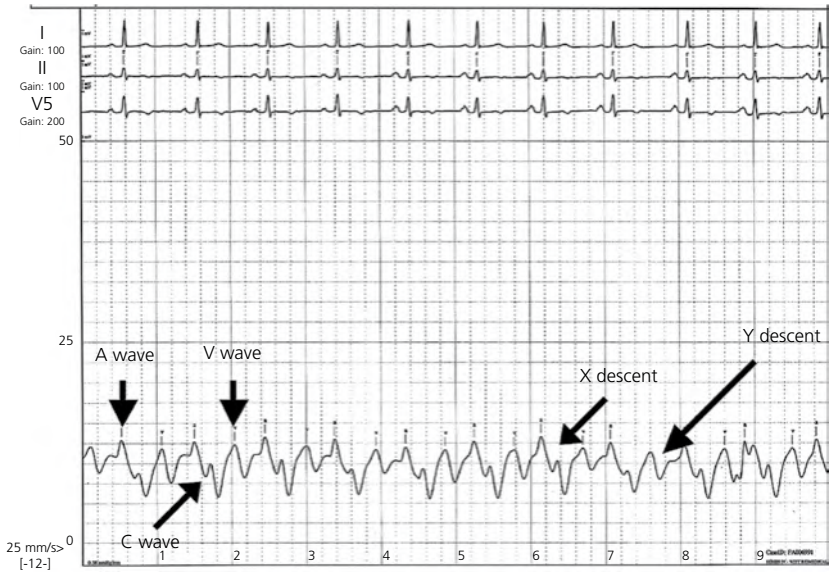


Figure 3.5 Right atrial pressure waveform.

RA pressure in conjunction with the exit of blood from the RA into the RV when the tricuspid valve opens (see Chapter 5 for a further discussion of atrial waveforms).

Right ventricle

Normal RV pressures are 2–8 mm Hg at the end of diastole and 17–32 mm Hg during systole. The pressure in the RV rises rapidly during systole, and when it exceeds the pressure in the RA, the tricuspid valve closes. Pressure rises further as contraction continues in the closed chamber, and when the pressure exceeds that in the pulmonary artery, the pulmonary valve will open. The waveform reflecting RV systole has a rapid upstroke and will occur with or immediately following the QRS complex (Figure 3.6). The peak of this waveform is the RV systolic pressure. As systole ends and ventricular relaxation occurs, pressure in the RV will rapidly fall to baseline, marking the onset of ventricular diastole. The pulmonary valve will close when the pressure in the RV falls below pressure in the pulmonary artery. When the pressure falls below that in the RA, the tricuspid valve will open.

RV diastole can be divided into three phases (Figure 3.7). The first phase comes with the opening of the tricuspid valve, and accounts for early filling of the ventricle, approximately 60–75% of total filling in the normal heart (RF phase). The second phase is the SF period and accounts for 15–25% of RV filling. In some patients, this phase will include a period of diastasis in which ventricular filling slows or ceases. Finally, the third phase occurs with RA systole and accounts for 10–25% of total filling. At this point, the tricuspid valve is open, creating

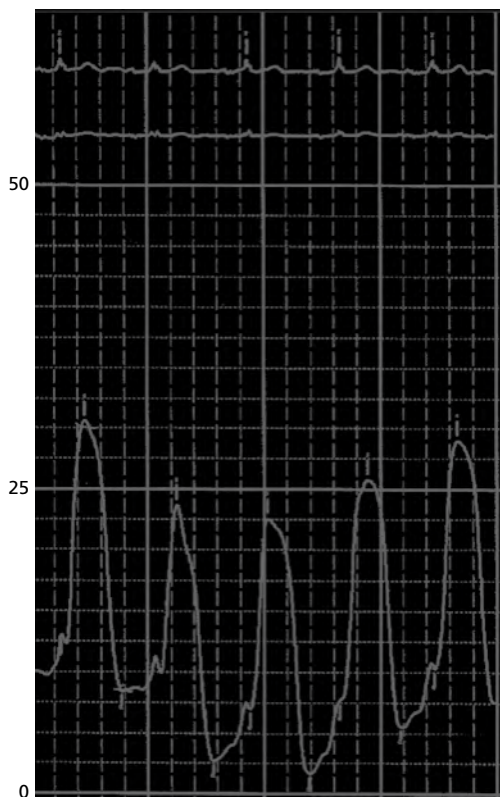


Figure 3.6 Right ventricular pressure tracing.

essentially one right-sided chamber. So, it follows that this waveform is simultaneous with and identical in morphology and amplitude to the A wave on the RA pressure tracing. The pressure at the end of this waveform represents RV end-diastolic pressure (EDP).

Left atrial pressure (or its surrogate – pulmonary capillary wedge pressure)

Normal LA pressure ranges from 2 to 12 mm Hg, and is typically measured indirectly, via a balloon-tipped catheter placed in a distal branch of the pulmonary artery. Inflation of the balloon obstructs blood flow in that branch and allows pressure to equilibrate along the column of blood, thus giving an estimate of LA pressure. This pressure is called the pulmonary capillary wedge pressure (PCWP), or simply wedge pressure. LA mechanical events are transmitted retrograde through this column of blood in a wedge pressure tracing. Thus, the deflections on the wedge pressure waveform are often damped and delayed relative to events in

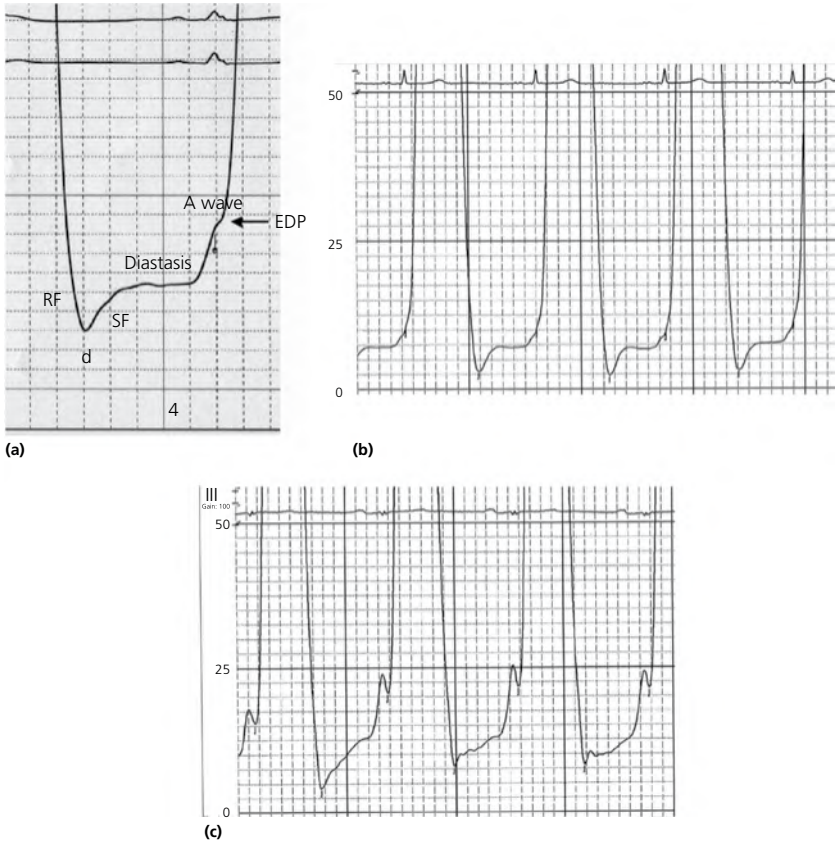


Figure 3.7 Ventricular diastole. The ventricular diastolic pressure waveform can be divided into three phases (a): the early or rapid filling (RF) phase occurs with the opening of the tricuspid valve. The slow filling (SF) phase follows and extends until the onset of right atrial systole (A wave). The pressure following the A wave just prior to ventricular contraction is the right ventricular end-diastolic pressure (RVEDP). Left ventricular diastolic pressure is shown in a normal heart (b) and in a stiff, non-compliant ventricle (c). Note the elevated LVEDP, prominent A wave, and rapid rise in LV diastolic pressures with atrial contraction.

the LA (and on the ECG). The LA (or PCWP) pressure wave, like an RA pressure wave, consists of positive A, C, and V waves, and negative X and Y descents.

Left ventricle

Normal LV pressure is from 90 to 140 mm Hg during systole and 5–12 mm Hg during diastole. While the pressures in the LV are much higher than in the RV, the pressure waveform components are similar. LV systole leads to a rapid increase in pressure. The mitral valve closes when the pressure exceeds that in the LA (Figure 3.8). The pressure rises with continued contraction, and when it exceeds

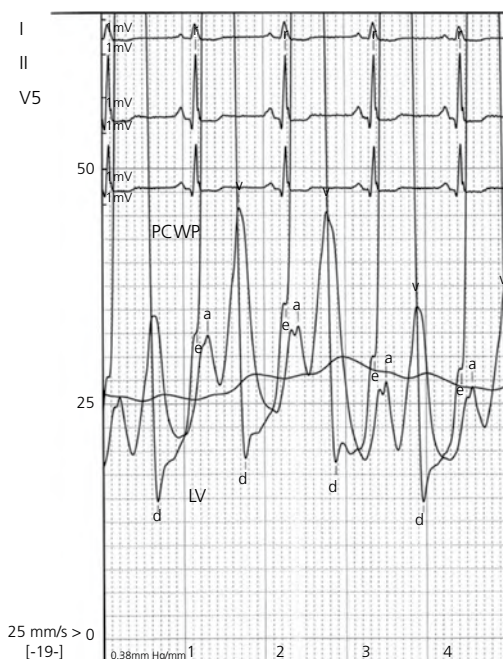


Figure 3.8 Simultaneous LV and PCWP tracings. The pressure tracing was taken from a 57-year-old male with severe ischemic cardiomyopathy. Note the large V wave and prominent A wave in the PCWP tracing. The PCWP tracing is slightly delayed relative to the LV tracing (e.g. the “A” wave in the PCWP tracing occurs slightly after the “A” wave in the LV tracing).

the pressure in the aorta, the aortic valve opens, and ventricular ejection begins. LV pressure then continues to rise through the rapid ejection phase of systole, and peaks during the T wave of a surface ECG. Pressure in the LV then begins to decline through the reduced ejection phase of systole. When the pressure in the LV falls below that in the aorta, the aortic valve closes, and LV pressure continues to decline due to isovolumetric ventricular relaxation. When the pressure drops below that of the LA, the mitral valve opens, and the LA empties into the LV. The mitral valve opening marks the onset of ventricular diastole. LV diastole, like RV diastole, consists of three phases.

Pulmonary artery

Normal pulmonary artery pressures range from 17 to 32 mm Hg during systole and from 4 to 13 mm Hg during diastole. The pulmonary artery waveform reflects the pressure seen during systole as blood is ejected from the RV into the pulmonary artery. Because of the pulmonic valve is open at this point, this waveform will be similar to the right ventricular systolic waveform. The pressure in the pulmonary artery and the RV declines as systole comes to an end. When the pressure in the RV falls below that in the pulmonary artery, the pulmonic valve closes,

marked by a dicrotic notch on the downslope of the pulmonary artery pressure waveform. The dicrotic notch marks the end of ventricular ejection. The decline in pressure in the pulmonary artery continues gradually after closure of the pulmonary valve as blood flows through the pulmonary arteries and veins into the LA. Note that the peak of the pulmonary artery waveform occurs concurrent with the T wave on a surface ECG.

Aorta

The shape of the pressure waveform generated in the aorta is similar to that generated in the pulmonary artery, with pressures significantly higher in the aorta. The upstroke of the aortic pressure waveform denotes the onset of left ventricular ejection and occurs once the pressure in the LV has exceeded the pressure in the aorta and the aortic valve has opened (Figure 3.1). In the absence of aortic valve or perivalvular pathology, the aortic systolic pressure will be equal to the left ventricular systolic pressure. Aortic and left ventricular pressures decline with reduced ejection and contraction, and when the ventricular pressure drops below that of the aorta, the aortic valve closes. This is sometimes apparent in the pressure waveform as a dicrotic notch in the downslope of the aortic pressure tracing.

The definition of hypertension has changed over time as the deleterious effects of even minor increases in blood pressure have been realized. The classification of normal blood pressure and hypertension is described in Chapter 5.

Left ventricular function

Myocardial contractile dysfunction is an important cause of morbidity and mortality, and LV systolic function is an important determinant of survival in patients with cardiomyopathy and/or coronary artery disease. Despite its tremendous importance, clinical measurement of LV function is limited by the inability to assess myocyte performance directly. Instead, various surrogates such as ejection fraction are used. In interpreting these tests, it is important to remember that LV function is a dynamic process that varies not only with contractility but also with preload and afterload.

Measurement of left ventricular preload

Preload for the ventricles is defined as the amount of passive tension or stretch exerted on the ventricular walls (i.e., intraventricular pressure) just prior to the initiation of systole. This load determines end-diastolic sarcomere length and thus the force of contraction. The Frank–Starling law states that the passive length to which the myocardial cells are stretched at the end of diastole determines the active tension they develop when stimulated to contract. The Frank–Starling law is an intrinsic property of myocytes and is not dependent on extrinsic factors such as the autonomic nervous system or circulating hormones. The general principle

is that increased preload causes increased force of contraction, which increases stroke volume and thus cardiac output.

In a given patient, elevated filling pressures do not differentiate primary diastolic dysfunction from primary systolic dysfunction but do give an indication of the preload required to obtain a specific cardiac output.

Left ventricular preload as measured by LVEDP is a common tool used clinically in assessment of LV performance. The LVEDP immediately precedes isometric ventricular contraction (Figure 3.6). This point, also known as the “Z” point, is located on the downslope of the LV “A” wave at the crossing over of LA and LV pressures and is coincident with the R wave on the surface ECG. Since the mitral valve is open during atrial contraction, the A wave is represented in the LV pressure tracing coincident with the A wave in the atrial tracing. Identification of the true LVEDP can at times be difficult, especially when using fluid-filled catheters.

LVEDP is influenced by ventricular compliance and intravascular volume status. LVEDP is normally <12 mm Hg, but may be elevated when the LV experiences volume (e.g., mitral regurgitation or aortic regurgitation) or pressure (e.g., hypertension or aortic stenosis) overload. Impairment of myocardial contractility also alters the diastolic pressure–volume relationship and shifts the EDP point upward (Figure 3.9).

Inspection of the waveform in diastole provides information about LV diastolic function that can supplement LVEDP. A struggling ventricle will be marked by elevated pressures throughout diastole while myocardial relaxation abnormalities are suggested by the continuing decline of pressure during early diastole, with the pressure nadir occurring midway through the diastolic period. Alternatively, a stiff, poorly compliant ventricle is suggested by an abnormally tall A wave, resulting in a marked elevation of LVEDP, although the diastolic pressure prior to atrial contraction can be normal (Figure 3.10). Rapid changes in diastolic pressures can be observed in various conditions such as with pericardiocentesis (Figure 3.11).

Pressure–volume loops

A useful method of displaying the relationship between ventricular volume and pressure during the cardiac cycle is the pressure–volume loop (Figure 3.12). Stroke volume (change in volume) and stroke work (stroke volume $\times$ mean arterial pressure [MAP] or alternatively the area inscribed by the P–V loop) can be calculated using PV loops. Different pressure–volume loops are obtained following changes in preload, afterload, or contractility (Figure 3.13) and in different disease states (Figure 3.14).

Ventricular performance can be depicted by plotting LVEDP versus stroke volume or cardiac output (Figure 3.15). This curvilinear relationship is commonly called the LV function curve. Ventricular function curves are shifted upward by inotropes and downward by interventions impairing inotropic activity. Afterload may also significantly influence the elevation or decline of the ventricular function curve.

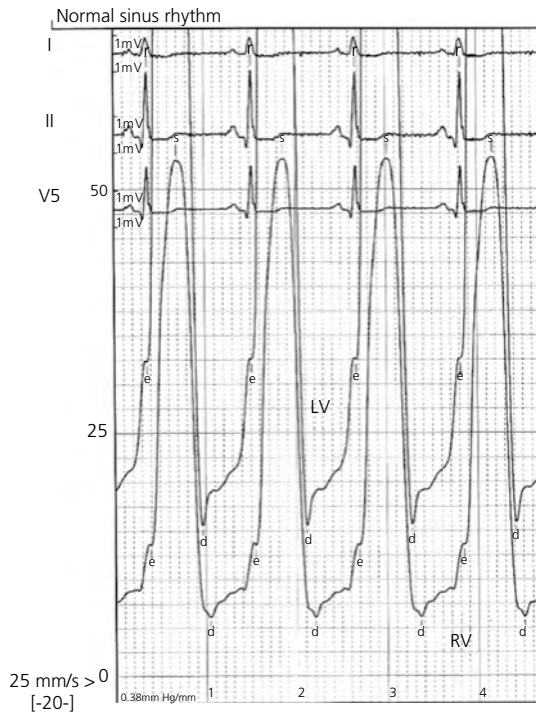


Figure 3.9 Abnormal EDP. Simultaneous RV and LV pressures from the 57-year-old male with severe ischemic cardiomyopathy depicted in Figure 3.8. Note that both LVEDP and RVEDP are elevated with a relatively rapid increase in ventricular diastolic pressures with atrial contraction, demonstrating that both RV and LV are poorly compliant. EDP is defined as the ventricular pressure after the a wave and just before the abrupt rise in systolic pressure that occurs with ventricular contraction.

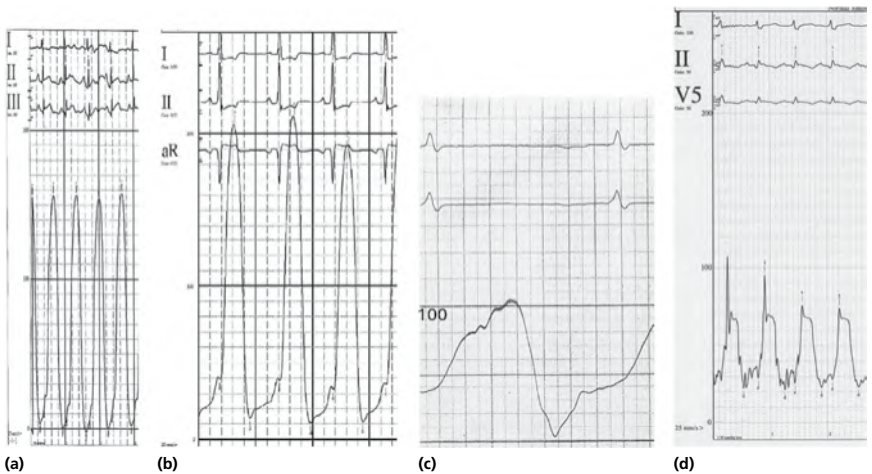


Figure 3.10 Examples of different left ventricular waveforms. LV tracings taken from a patient with (a) normal heart, (b) severe aortic stenosis with rapid rise in pressure at the end of diastole, (c) severe aortic insufficiency (AI) with a rapid rise in pressure in early diastole and (d) cardiogenic shock with low systolic pressure and markedly elevated diastolic pressure. All pressures are recorded on a 200-mm Hg scale but sweep speed differs.

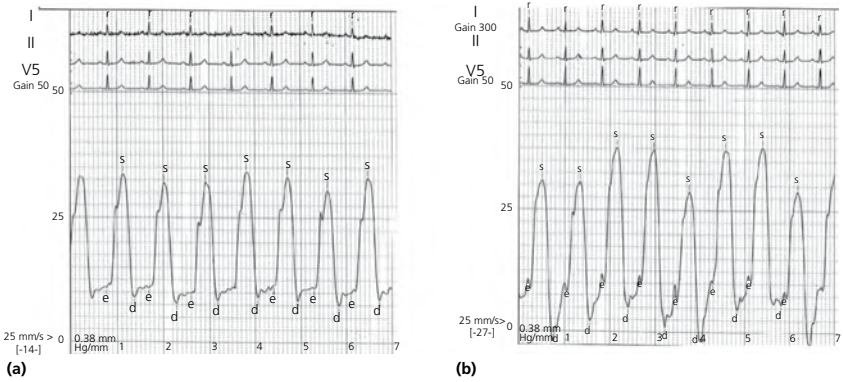


Figure 3.11 Impact of pericardiocentesis on right ventricular diastolic pressures in a patient with cardiac tamponade. Tracings were taken before (a) and after (b) pericardiocentesis.

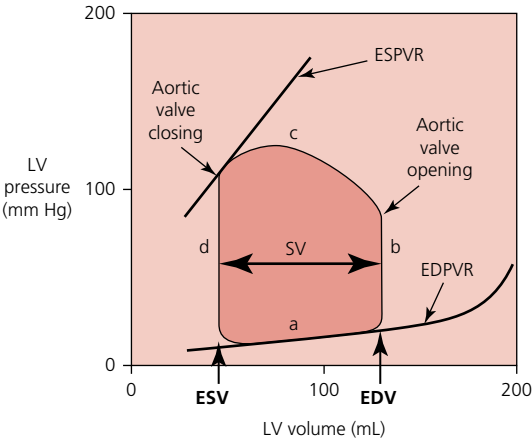
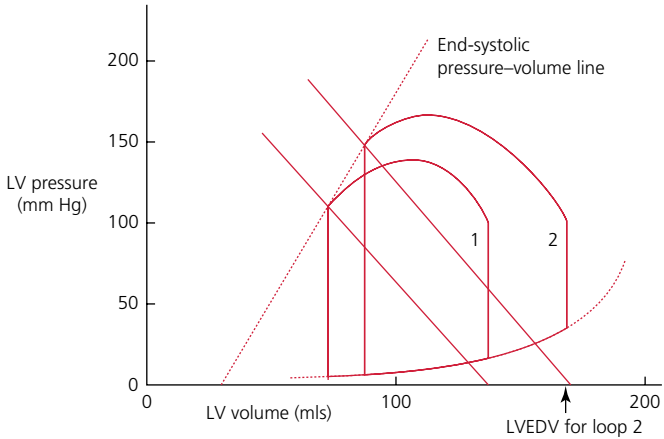


Figure 3.12 Schematic of pressure–volume loop in a normal heart. Following mitral valve opening, ventricular filling occurs with only a small increase in pressure despite a large increase in volume (a). The first segment of systole is isovolumic contraction (b). When the aortic valve opens, ejection begins and LV volume falls as LV pressure continues to rise (c). After closure of the aortic valve, isovolumic relaxation occurs (d). This point marks the end-systolic pressure–volume point on the curve. [EDPVR = end-diastolic pressure–volume relationship; ESPVR = end-systolic pressure–volume relationship.]

Indices of contractility

A completely satisfactory clinical index of contractility that is independent of preload and afterload has not been defined. The maximal rate of myocyte fiber shortening in the isolated heart correlates well with contractility and is little affected by preload or afterload, but is obviously of no use clinically. In the intact

Effect of increased preload on LV pressure–volume loop



Loop 2 has an increased preload (increased LVEDV) as compared to loop 1.

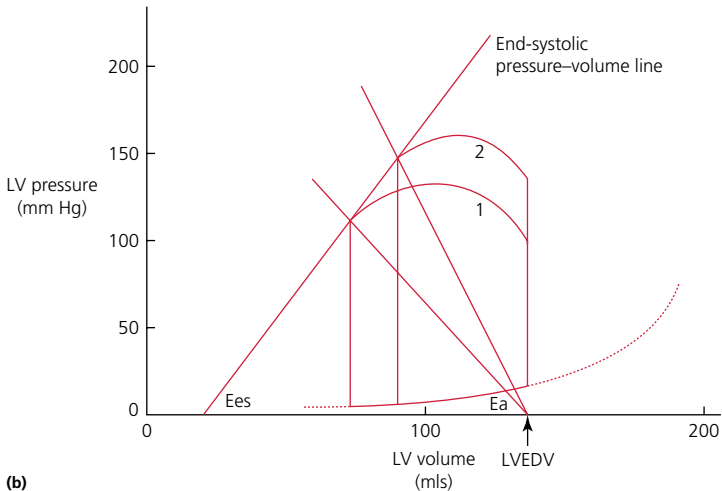
Note: Loop 2 has a larger stroke volume than loop 1.

The afterload and contractility have remained constant. The afterload lines for the two loops are parallel so they have the same afterload. Both end-systolic points are on the same contractility line so the two loops have the same contractility.

(See discussion of contractility and afterload lines later in the chapter.)

(a)

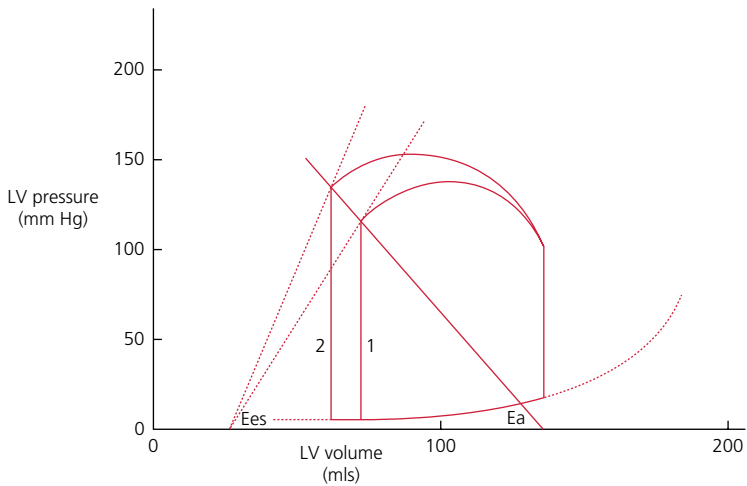
Effect of increased afterload on LV pressure–volume loop



(b)

Figure 3.13 Effect of changes in preload (a), afterload (b), and contractility (c) on pressure–volume relationship.

Effect of increased contractility on LV pressure–volume loop



Note the increased stroke volume for loop 2 (which has the increased contractility).

- The increased slope of the end-systolic pressure–volume line is an index of the increased contractility.
- The end-systolic points of both loops lie on the same 'afterload line' so their afterload is the same for the two loops.
- The LVEDV is the same for the loops so the preload is the same.

(c)

Figure 3.13 (Continued)

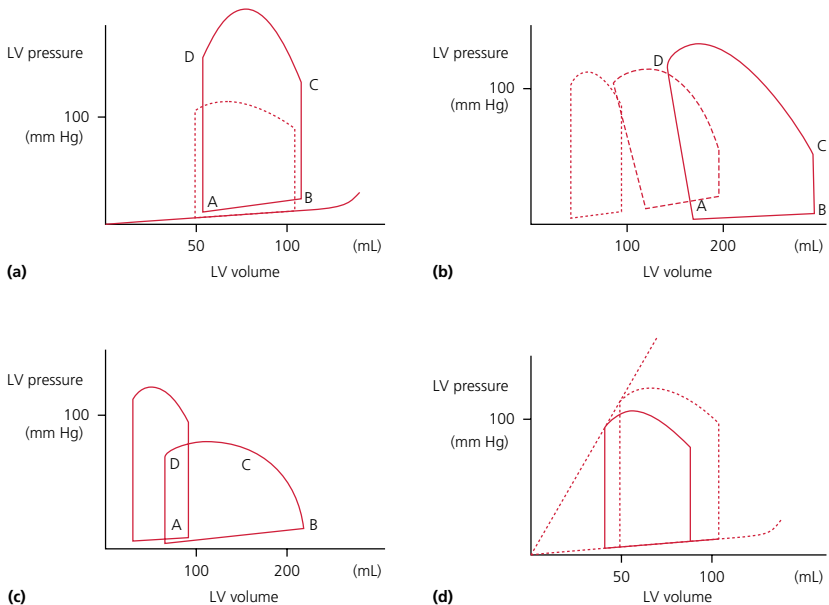


Figure 3.14 Schematics of pressure–volume loops in various disease states. (a) Aortic stenosis is characterized by a marked increase in afterload, minimal increase in preload, and increased contractility (dotted line is normal ventricle). (b) Aortic insufficiency (AI) is characterized by a marked increase in preload, with a smaller increase in afterload and decreased contractility. Acute AI manifests as increased preload with minimal change in afterload or contractility (dotted line, normal ventricle; dashed line, acute AI; full line, chronic AI). (c) Chronic mitral regurgitation is associated with a marked increase in preload, decreased afterload, and decreased contractility. (d) Mitral stenosis is primarily characterized by decreased preload.

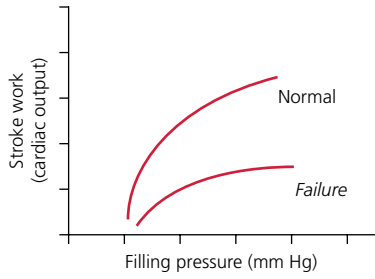


Figure 3.15 Ventricular function curve. Schematic of the relationship between filling pressure and cardiac output (or stroke volume) in a normal and in a failing LV.

heart, contractility is best measured by the pressure–volume point as the aortic valve closes. Another index of contractility is $dp/dt_{\max}$, which is the derivative of the maximal rate of ventricular pressure rise during the isovolumetric period. A complete discussion of indices of contraction is beyond the scope of this chapter.

Respiratory variation

The act of breathing influences hemodynamic measurements (Figure 3.16). Even in healthy patients, intravascular pressure in the thoracic aorta and vena cava (and thus preload and afterload) may be significantly altered by normal respiration. During normal, spontaneous respiration, intrathoracic pressure may drop from -3 to -4 mm Hg at end-expiration to -7 to -8 mm Hg during end-inspiration. With regard to cardiac chambers, this decreases transmural pressure in the normally compliant LA, resulting in an underestimation of wedge pressure. Conversely, during mechanical ventilation, intrathoracic pressure may increase to >10 mm Hg during end-inspiration. PCWP measurement is also particularly vulnerable to elevations in intrathoracic pressure, because elevated intrathoracic pressure blocks retrograde transmission of left atrial pressure events to the catheter tip, resulting in a significant underestimation of wedge pressure. In both cases, since end-expiration more closely resembles atmospheric pressure, intra-cardiac pressures should be recorded at end-expiration (Figure 3.17).

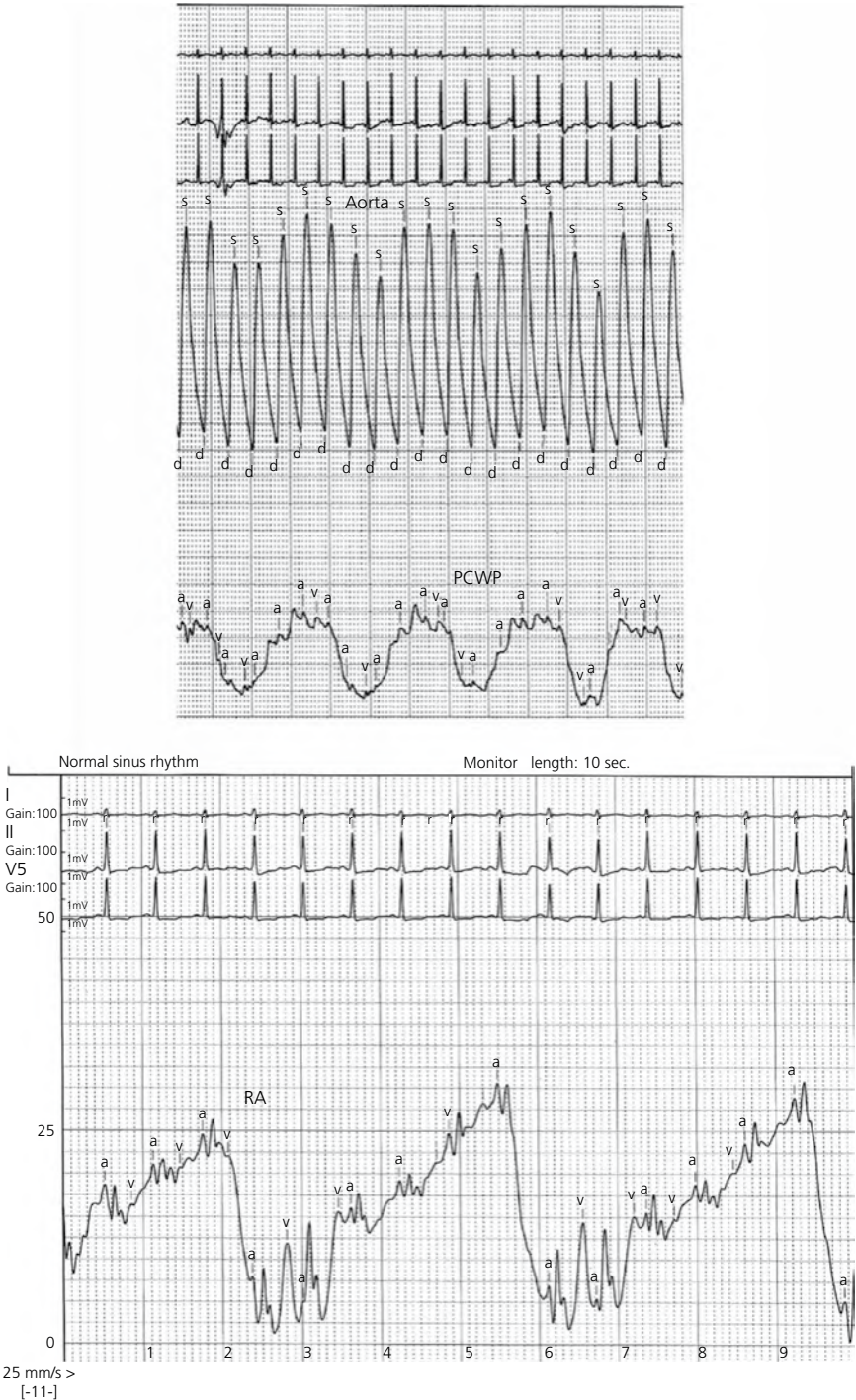


Figure 3.16 Respiratory variation. Aortic, PCWP, and RA pressure in a patient with large respiratory variation.

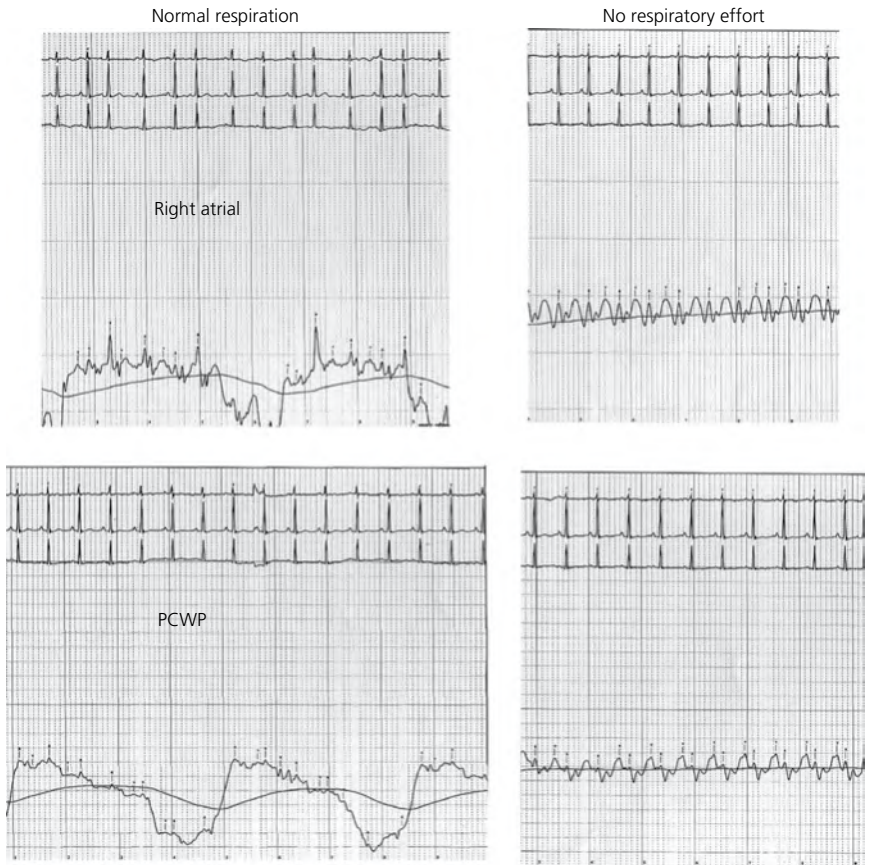


Figure 3.17 Comparison of spontaneous respiration (left-sided tracings) and end-expiratory breath-hold (right-sided tracings) on RA and PCW pressures (all pressures recorded on a 25-mm Hg scale).

CHAPTER 4

Arterial pressure

George A. Stouffer

Arterial blood pressure is one of the most fundamental measurements in hemodynamics. Because of the need to quantify pressure levels, emphasis is placed on mean, systolic, or diastolic values (see Table 4.1 and Figure 4.1). These values, while tremendously useful, do not provide complete information to characterize the composite pressure wave, either within the aorta or as it undergoes significant changes during propagation within the arterial system.

The aortic pressure wave is not just determined by left ventricular mechanics but rather results from hydraulic interactions between blood ejected from the contracting left ventricle (LV) and the systemic arterial system. The central aortic pressure wave is composed of a forward-traveling wave generated by left ventricular ejection followed by a backward-traveling wave reflected from the periphery. Ejection of blood into the aorta generates a pressure wave that is propagated to other arteries throughout the body at a given velocity (termed pulse wave velocity, PWV). At any discontinuity of the vascular wall, but mainly at the arteriolar branching points, the wave is reflected and comes back toward the heart at the same PWV. One way to think about reflected waves is to note that they would be absent if the aorta were an open tube rather than part of a closed system.

Pressure wave reflection in the arterial system serves two beneficial purposes. When normally timed, the reflected wave returns to the central aorta in diastole and therefore enhances diastolic perfusion pressure in the coronary circulation. Partial wave reflection also returns a portion of the pulsatile energy content of the waveform to the central aorta where it is dissipated by viscous damping. Thus, wave reflection limits transmission of pulsatile energy into the periphery where it might, under certain conditions, damage the microcirculation.

The velocity at which the outgoing and reflected waves travel is dependent on the properties (especially elasticity) of the arteries along which they propagate. PWV increases with stiffness and is defined by the Moens–Korteweg equation, $PWV = (Eh/2\rho R)$, where E is Young's modulus of the arterial wall (a measurement

Table 4.1 Definition of terms used to describe blood pressure.

Term	Definition
Systolic blood pressure	Maximum pressure (peak of arterial pressure wave)
Diastolic blood pressure	Minimum pressure (trough of arterial pressure wave)
Pulse pressure	Difference between systolic and diastolic pressure
Mean arterial pressure	Average pressure during the cardiac cycle

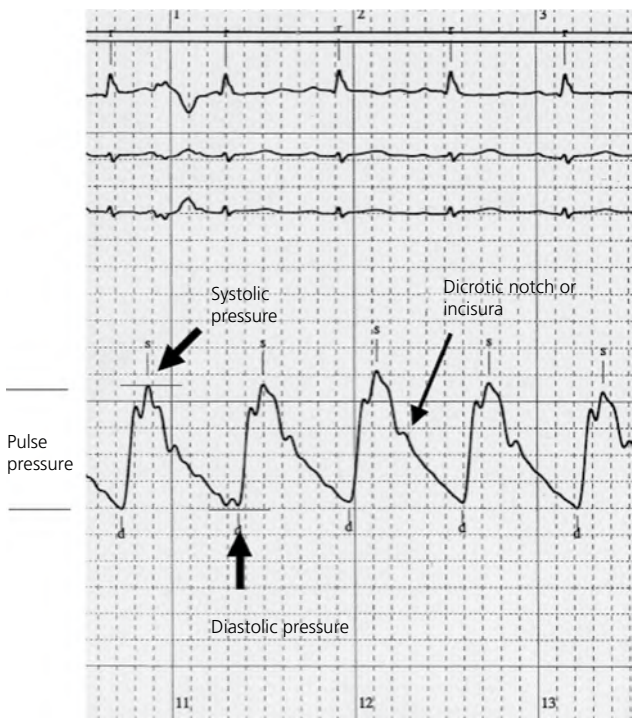


Figure 4.1 Aortic pressure recorded with a 6F fluid-filled catheter.

of elasticity), h is wall thickness, R is arterial radius at the end of diastole, and ρ is blood density. An important, although simplified, concept is that the longitudinal velocity of pressure waves traveling in distensible tubes is slowed by the extent that the vessel expands with each pulsation. In the normal arterial system, there is a steep gradient of increasing arterial stiffness moving outward from the heart. In a young adult, PWV is only 4–6 m/s in the highly compliant proximal aorta and increases to 8–10 m/s in the stiffer peripheral muscular arteries.

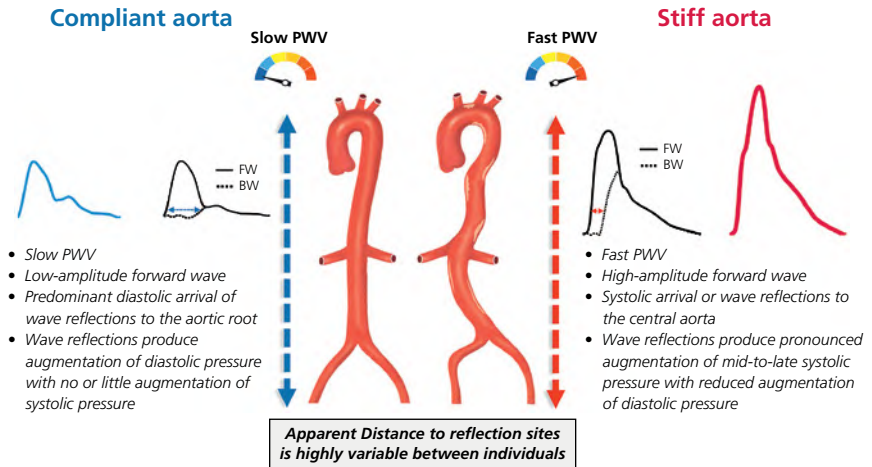


Figure 4.2 Consequences of increased aortic stiffness on the central pressure waveform.

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Disturbed reflection can cause the reflected waves to occur earlier, arriving in the central arteries during systole and not during diastole. Thus, as aortic elasticity declines, transmission velocity of both forward and reflected waves increases, which causes the reflected wave to arrive at the central aorta earlier in the cardiac cycle and therefore augment pressure in late systole (Figure 4.2). This in turn contributes to an increase in systolic blood pressure and pulse pressure and a decrease in diastolic blood pressure [1]. These changes increase left ventricular afterload and decrease coronary perfusion pressure.

The concept of PWV was originally described early in the twentieth century, but recent advances in noninvasive technologies have increased the interest in using PWV as a marker of vascular disease. There are many different ways to measure PWV, but the concept is similar in each. The time delay between arterial pulse wave arrival at a proximal artery (e.g., carotid) and a more distal artery (e.g., the femoral) is measured noninvasively. The distance travelled by the pulse wave is estimated (unless aortic imaging is available to enable direct measurement) and PWV is then calculated as distance/time (m/s). Measurement of PWV has been shown to correlate with aortic stiffness and, more importantly, to be predictive of clinical events [2]. Not surprisingly, PWV is increased in individuals with hypertension, diabetes mellitus (DM), tobacco use, atherosclerosis, and chronic kidney disease (CKD).

The augmentation Index (AIx) is the proportion of central PP that results from arterial wave reflection and is a commonly used measure of arterial stiffness (Figure 4.3). AIx is a function of the timing of the arrival of the reflected wave at the proximal aorta (determined mostly by large artery PWV) and the magnitude of the reflected waves. The magnitude of reflected waves is determined by the

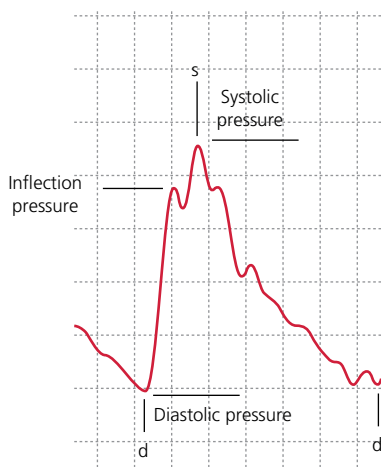


Figure 4.3 Augmentation index—the augmentation index (AIx) is given by $AIx = \pm \frac{P_s - P_i}{P_s - P_d}$ with P_s , P_d , and P_i indicating systolic, diastolic, and inflection pressure, respectively.

diameter and elasticity of small arteries and arterioles and is thus influenced by vasoactive drugs. AIx is positively correlated with age and blood pressure, and inversely correlated with height and heart rate.

A simplified relationship to remember is:

stiffer arteries $\rightarrow$ increased PWV $\rightarrow$ earlier arrival of reflected waves $\rightarrow$ augmentation of systolic rather than diastolic pressure $\rightarrow$ increased pulse pressure.

Aortic pressure

Aortic pressure is the primary determinant of the afterload against which the LV must pump blood. Given constant preload and contractility, an increase in afterload will reduce cardiac output. The primary determinants of afterload are mean arterial pressure (MAP), aortic compliance (distensibility), and aortic valve resistance (the normal aortic valve presents minimal resistance to flow). Thus, hypertension, calcified arteries, and aortic stenosis all represent conditions of increased afterload.

The MAP is the average pressure during the cardiac cycle. Calculation of the true MAP requires integration of the arterial pressure over time. In clinical medicine, a useful approximation of MAP when the heart rate is 60bpm can be obtained using the following formula:

$$MAP = 1/3 SBP + 2/3 DBP = DBP + 1/3 \text{ pulse pressure}$$

where DBP is the diastolic blood pressure. This formula is only applicable at lower heart rates because the relative amount of time spent in systole increases at higher heart rates.

The major determinant of systolic pressure is stroke volume. Lesser influences include diastolic pressure and aortic compliance. The major determinant of diastolic pressure is systemic vascular resistance (in turn, primarily determined by arteriolar resistance). Lesser determinants include systolic pressure, aortic compliance, and heart rate. The normal aorta is distensible, and the diameter can increase up to 15% during LV systole. During diastole, this stored potential energy is released as the aorta recoils, thus helping to maintain diastolic blood pressure (sometimes called the diastolic pump). With age, compliance of the aorta decreases as elastin and collagen change in both amount and properties. Diastolic pressure, largely determined by peripheral arterial resistance, increases until middle age and then tends to fall. In contrast, systolic pressure and pulse pressure, influenced more by the stiffness of large arteries and peripheral pulse wave reflection, increase continuously with age.

Pressure waveform

A pressure waveform generated in the aorta has a characteristic waveform (Figure 4.1). When pressure in the LV exceeds aortic pressure, the aortic valve opens and blood flows rapidly from the LV into the aorta. The steep upstroke (or anacrotic limb) coincides with opening of the aortic valve and reflects the stroke volume ejected by the LV into the aorta (Figure 4.4). The rounded part at the top of the waveform (or anacrotic shoulder) reflects continued flow from the LV to the aorta but at a reduced rate. The downslope of the pressure tracing (or dicrotic limb) is divided by the dicrotic notch (or incisura), which represents closure of the aortic valve. The location of the dicrotic notch varies according to the timing of aortic closure in the cardiac cycle and will be delayed in patients with hypovolemia (Figure 4.5).

Aortic and LV systolic pressures decline during the “reduced ejection” phase, which coincides with LV repolarization. When the ventricular pressure drops below that of the aorta, the aortic valve closes. This is represented in the pressure waveform as a dicrotic notch in the downslope of the aortic pressure tracing. This marks the end of LV ejection. Diastolic pressure declines gradually as blood flows from the aorta into the peripheral vessels.

The contour of the aortic pressure tracing can provide clues to various disease states (Table 4.2 and Figure 4.6): for example, aortic pressure that rises rapidly, dips, and then rises again (*pulsus bisferiens*) in hypertrophic obstructive cardiomyopathy or rises slowly (*pulsus parvus et tardus*) in aortic stenosis (Figure 4.7).

Effects of respiration on aortic pressure

Changes in thoracic pressure with respiration will influence blood pressure. During normal, spontaneous respiration, intrathoracic pressure decreases during inspiration, which in turn causes a decrease in pericardial and right atrial

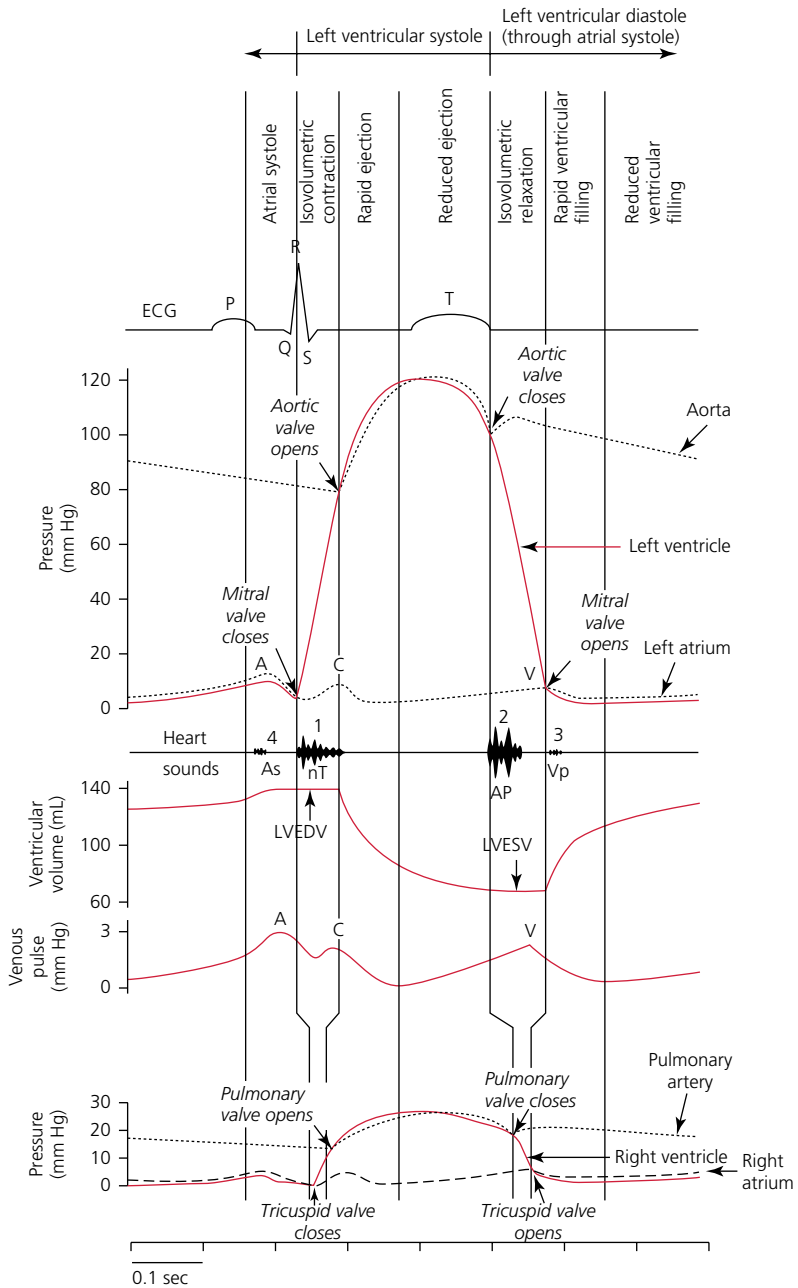


Figure 4.4 Wiggers diagram. [LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume.]

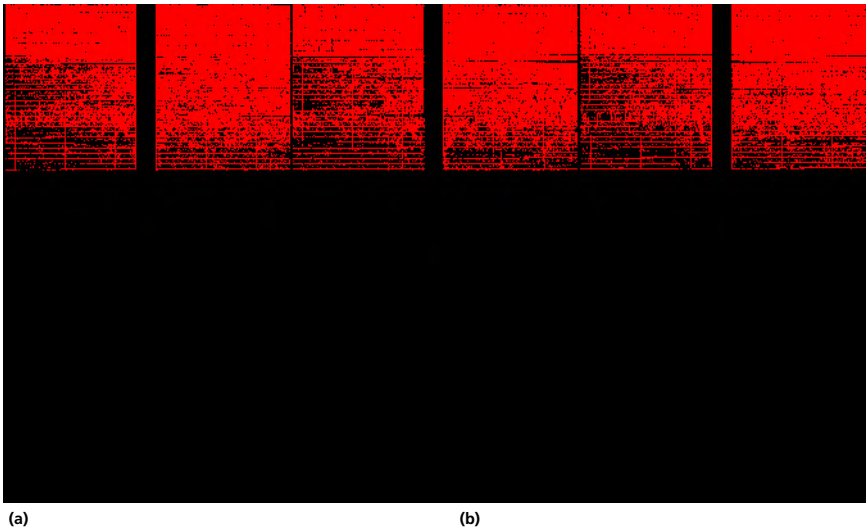


Figure 4.5 Aortic pressure in a hypovolemic patient. Aortic pressure tracings taken in a patient before (a) and after (b) an intravenous (IV) fluid bolus. The aortic waveform has a characteristic shape when left ventricular filling pressures are low. Aortic pressures are low, pulse pressure decreases, the dicrotic limb is steeper, and the dicrotic notch is delayed. The diastolic phase of the aortic pressure tracing gives an indication of peripheral runoff and may also be abnormal. In severe dehydration, there is a sudden descent in aortic pressure and then an almost flat diastolic phase.

Table 4.2 Disease states associated with various pulse characteristics.

Label	Characteristics	Disease states
Bounding	Large pulse pressure	Aortic insufficiency, hyperkinetic states (e.g., fever, thyrotoxicosis, anemia), AV fistula
Pulsus parvus et tardus	Slow and weak pulse	Aortic stenosis
Pulsus bisferiens	Two systolic peaks prior to dicrotic notch	Hypertrophic obstructive cardiomyopathy; more rarely in aortic insufficiency
Pulsus alternans	Alternating strong and weak pulses	Severe LV dysfunction
Pulsus paradoxus	Excessive decrease (>10 mm Hg) in systolic pressure with inspiration	Cardiac tamponade; less frequently it can be observed with acute aortic regurgitation (i.e., acute aortic dissection), elevated LVEDP, atrial septal defect, pulmonary hypertension, or right ventricular hypertrophy, hypovolemia
Dicrotic pulse	Two systolic peaks with one occurring after dicrotic notch	Low cardiac output + low peripheral resistance; rare in patients >45 years old

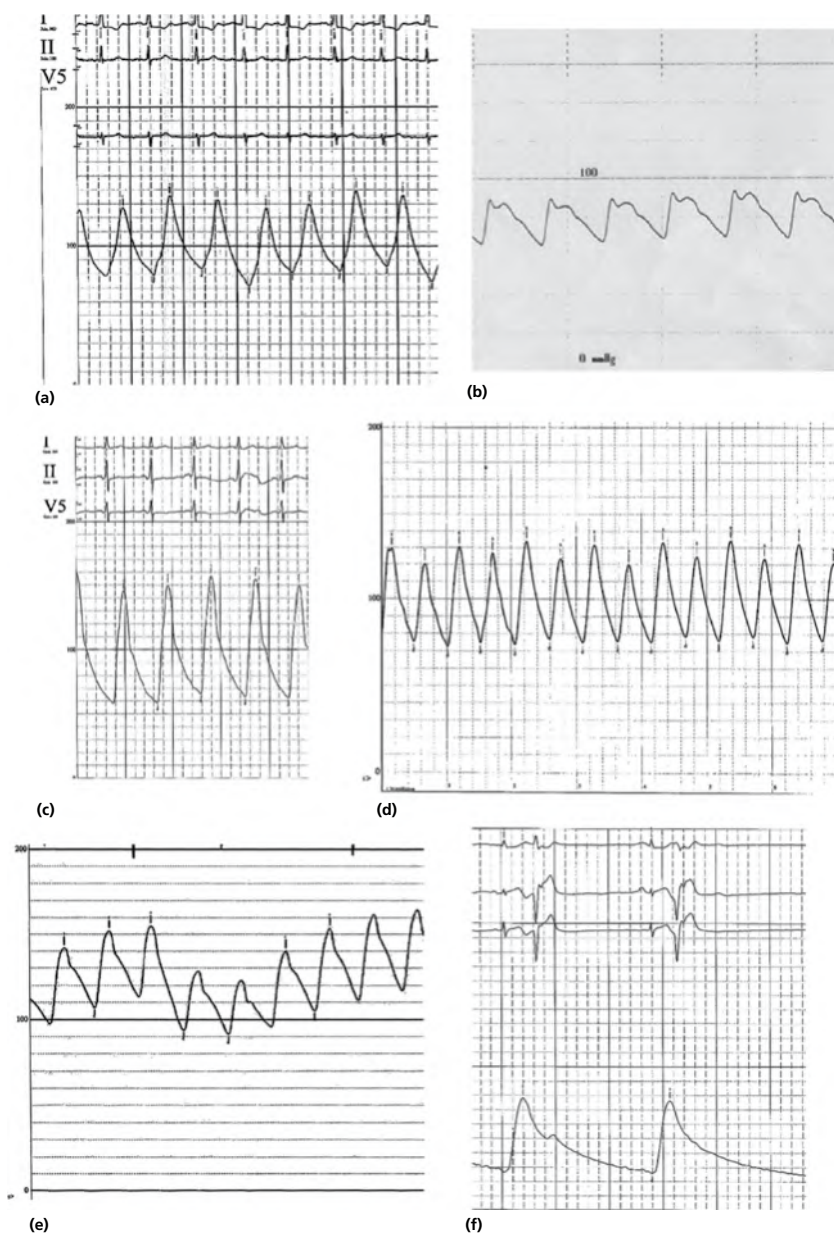
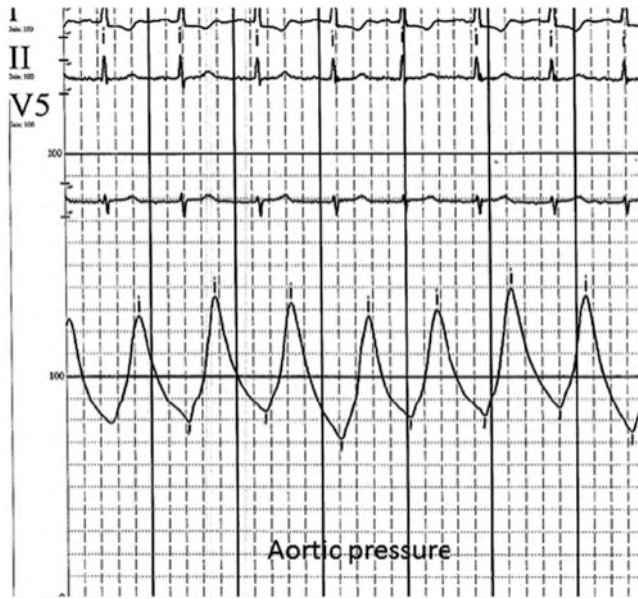
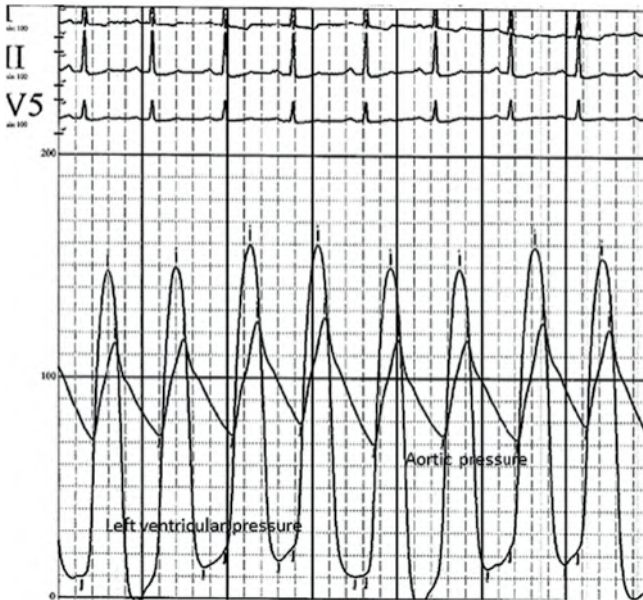


Figure 4.6 Arterial pressure tracings in various pathologic conditions. (a) Aortic stenosis is characterized by slow upstroke. (b) Bisferiens pulse, a name derived from Latin *bis* (= two) + *feriere* (= to beat), is characterized by an initial rapid rise in aortic pressure (spike), followed by a slight drop in pressure (dip), and then a secondary peak (dome), and is most commonly associated with hypertrophic obstructive cardiomyopathy. (c) Severe aortic regurgitation is characterized by a wide pulse pressure. (d) Pulsus alternans with beat-to-beat variability in systolic pressure is found in a patient with cardiomyopathy. (e) Exaggerated decrease in systolic pressure with inspiration defines pulsus paradoxus. (f) Bradycardia with hypotension and ineffective generation of systolic blood pressure during PVCs is apparent in a patient with inferior myocardial infarction.



(a)



(b)

Figure 4.7 Aortic pressure in patients with aortic stenosis. Aortic pressure tracings taken in a 60-year-old male with aortic valve area of 0.4 cm^2 (a) and in a 58-year-old male with aortic valve area of 1.1 cm^2 (b). Note the delayed upstroke in the aortic pressure tracing during ventricular systole, especially in relation to the rise in left ventricular pressure (b).

pressures. This results in augmented systemic venous return to right-sided chambers and decreased venous return to left-sided chambers. It is thus normal to have a slight decrease in systolic blood pressure (approximately 5 mm Hg) with inspiration (Figure 4.8). Pulsus paradoxus is an exaggerated decrease in systolic pressure with inspiration and has been variously defined as a drop of >12 mm Hg, a drop of ≥ 10 mm Hg, or a drop of $\geq 9\%$ during normal inspiration.

Not surprisingly, positive pressure ventilation causes an inversion in the normal relationship between respiration and blood pressure. Blood pressure will increase during inspiration (as thoracic pressure increases).

Peripheral amplification

Peripheral amplification is said to occur when systolic blood pressure is higher in peripheral arteries (e.g., femoral or brachial) than in the aorta (mean pressures will be the same). It is primarily observed in young individuals and is caused by the reflected pressure waves returning to the aorta during diastole (and to the peripheral arteries in late systole), making pulse pressure higher in peripheral than in central arteries (Figure 4.9).

Noninvasive measurement of blood pressure

Intra-aortic pressures are measured directly in the intensive care unit, operating room, and cardiac catheterization laboratory. Most clinical decisions are, however, based on noninvasive measurement of blood pressure. This introduces two potential problems: inaccuracies associated with noninvasive measurement of arterial pressure; and inaccuracies associated with the use of the brachial artery, rather than the aorta, as the site of measurement. Despite these limitations, there is a large amount of information on the association of noninvasively determined brachial blood pressure with morbidity and mortality including a study of more than 1,000,000 patients [3].

Determination of blood pressure by sphygmomanometer utilizes sounds that are thought to originate from a combination of turbulent flow and arterial wall oscillations. As the blood pressure cuff is deflated from a supraphysiologic pressure, flow through the brachial artery will begin once the systolic pressure is reached. Turbulent flow (and arterial oscillation) ceases once cuff pressure falls below diastolic pressure.

In 1905, at a conference at the Imperial Medical Academy, Dr. Nicolai Korotkoff announced a new way to measure blood pressure. Since that time, the sounds heard by a stethoscope placed over the brachial artery during blood pressure cuff deflation have been called Korotkoff sounds and can be divided into five phases. Phase 1 occurs when the cuff pressure equals the systolic pressure and is characterized by a sharp tapping sound. As cuff pressure is lowered, phase 2 occurs,

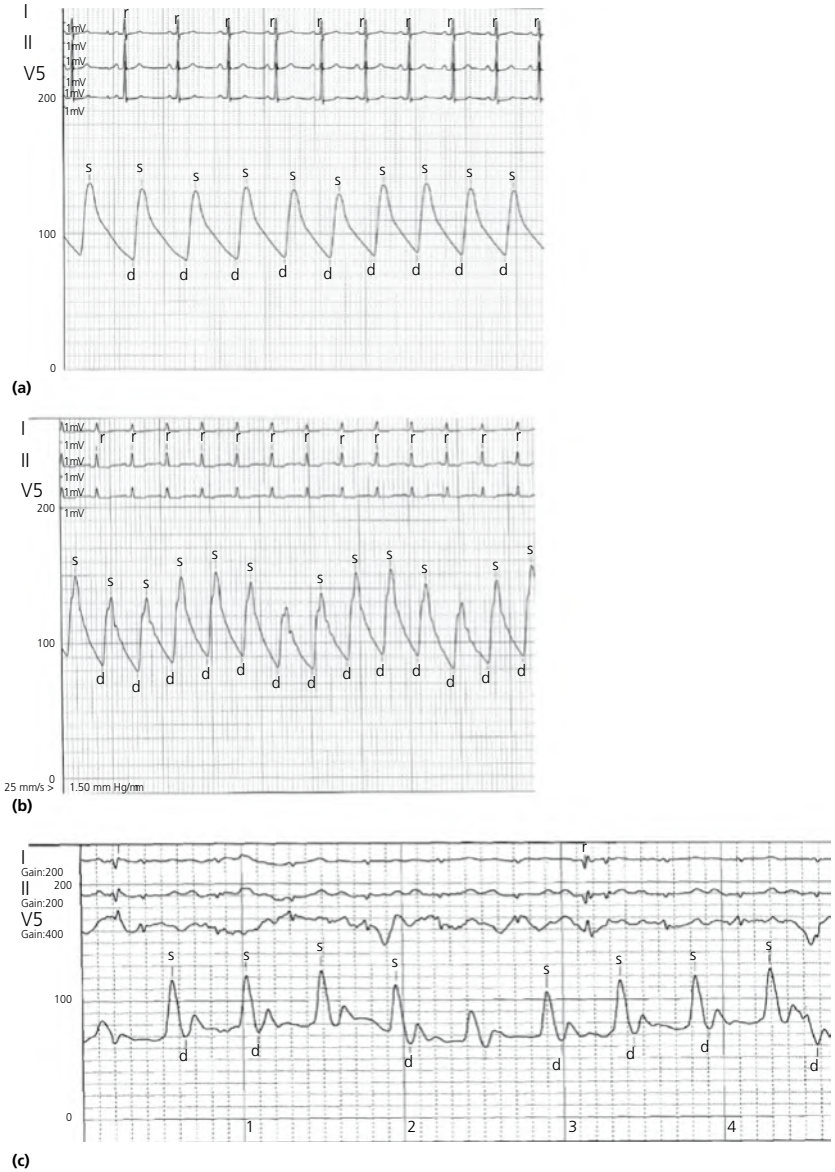


Figure 4.8 Effect of respiration on aortic pressure. The tracing in (a) is from a healthy 43-year-old female. Note the slight decrease (<10 mm Hg) in systolic pressure with respiration. The tracing in (b) is from a patient with pleural effusions. Note that the systolic pressure declines by 18–22 mm Hg with respiration. The tracing in (c) is taken from a patient in cardiac tamponade. Systolic pressure decreases by approximately 30 mm Hg with inspiration. Note also that the waveform is very abnormal with a steep diastolic limb, narrow ejection phase, and flat diastolic phase. These findings are consistent with decreased stroke volume and vasoconstriction.

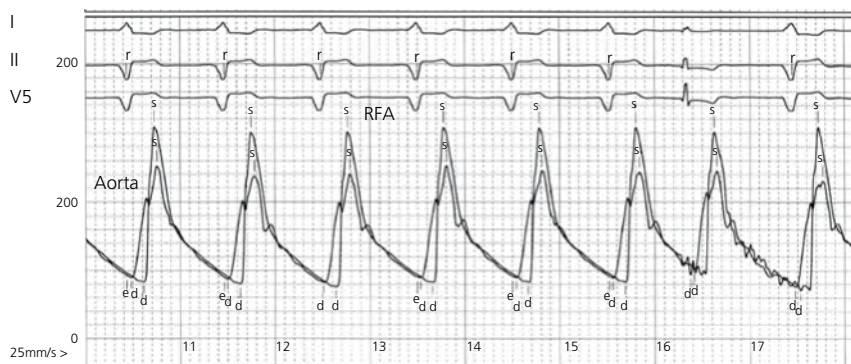


Figure 4.9 Peripheral amplification. Simultaneous aortic and right femoral artery pressures in a 49-year-old male with aortic insufficiency. Note that the systolic pressure is higher and the rapid increase phase narrower in the RFA.

which is characterized by softer and longer sounds. Phase 3 is defined by a resumption of crisp tapping sounds, similar to those heard in phase 1. Phase 4 begins when there is an abrupt muffling of sound as turbulent flow decreases. Finally, phase 5 is when turbulent flow ceases and thus no sound is heard. There is agreement that the onset of phase 1 corresponds to systolic and that the disappearance of sounds (phase 5) corresponds to diastolic pressure. Although some investigators have advocated using phase 4 to define diastole, general practice now is to use phase 4 only in situations in which sounds are audible even after complete deflation of the cuff, such as in pregnancy, arteriovenous fistulas, and aortic insufficiency. No clinical significance has been attached to phases 2 and 3. It is important to note that using Korotkoff sounds to measure blood pressure tends to underestimate intra-arterial systolic pressure and overestimate intra-arterial diastolic pressure [4].

Oscillometric blood pressure devices

Automated oscillometric devices are commonly used to measure brachial artery blood pressure. These devices work by measuring the amplitude of pressure changes as the cuff is deflated. In general, oscillometric devices measure MAP and then calculate systolic SBP and DBP based on a proprietary algorithm that, for each manufacturer, is the same for all patients irrespective of age, height, sex, vascular disease, or other clinical variables. Oscillometric MAP correlates well with central aortic MAP, but the assumption that a common algorithm can be used to determine SBP and DBP for all patients may not be correct. Studies have shown that the accuracy of oscillometric pressure is dependent on height, gender, and age [5, 6].

Fun fact: The ascending aortic pressure waveform in a kangaroo has a very large secondary wave that begins in late systole or early diastole and continues throughout most of diastole. The peak of this secondary wave is often greater than peak systolic pressure (similar to the aortic pressure waveform obtained in a patient with an intra-aortic balloon pump). The accentuated secondary wave in the kangaroo results from intense wave reflections in the large muscular lower body, which dominate the small wave reflections from the diminutive upper body (*Circulation Research* 1986;**59**:247–255).

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CHAPTER 5

The atrial waveform

David P. McLaughlin and George A. Stouffer

[This is a revision of a chapter written by David P. McLaughlin and George A. Stouffer]

A fundamental understanding of the atrial waveform is important for anyone applying hemodynamics to patient care. Data regarding volume status, valvular pathology, and ventricular compliance are contained within the tracings when examined carefully. The right atrial (RA) waveform is typically measured directly with a fluid-filled pressure catheter. The left atrial waveform can be measured directly by transeptal atrial puncture or more commonly indirectly via a balloon-tipped pulmonary artery catheter. In most cases, the pulmonary capillary wedge pressure (PCWP) accurately reflects mean left atrial (LA) pressure; however, the pressure wave deflections are delayed and damped on a PCWP tracing compared to LA pressures [1]. Similarly, the timing of the atrial waves and descents in reference to the electrocardiogram (ECG) will occur later in the PCWP tracing than the RA tracing because of the delay in transmission of pressures from the left atrium through the pulmonary vein, capillaries, and pulmonary artery to the tip of the catheter.

Components of the atrial wave

In patients who are in sinus rhythm, the atrial waveform is composed of two positive and two negative deflections (Figure 5.1). The A wave is caused by atrial contraction and usually occurs 60–80 ms after the onset of the P wave on the ECG. The A wave is delayed to about 200 ms after the onset of the P wave when measured using PCWP, due to the time delay in transmission of the reflected wave. The A wave is absent in atrial fibrillation (because of the lack of atrial contraction) and is exaggerated in patients with a noncompliant ventricle or in the presence of tricuspid or mitral stenosis.

The decay of the A wave is the X descent, which is due to the decrease in atrial pressure as a consequence of atrial relaxation (Figure 5.1). In the RA, the

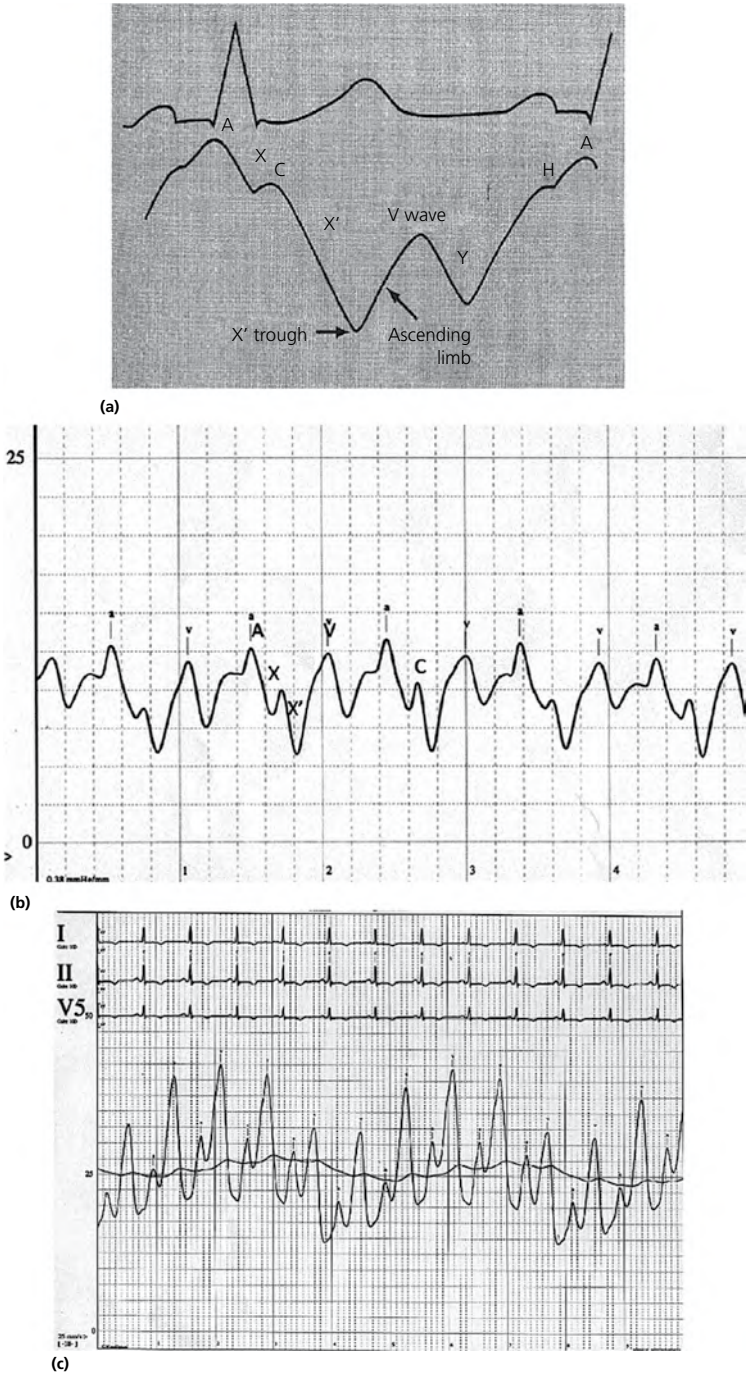


Figure 5.1 Atrial pressure waveforms. Schematic (a) and actual tracing (b) of RA pressure showing A and V waves and X and Y descents. Panel (c) is a PCWP tracing showing V wave > A wave. Source: Adapted from [2].

X descent can be interrupted by a small positive deflection, with the C wave resulting from closure of the tricuspid valve during isovolumetric contraction of the ventricle. The C wave is more commonly seen in RA compared to PCWP tracings and is prominent in patients with prolonged PR intervals. Additional X descent after the C wave is referred to as the X' descent. The nadir of the X descent is influenced by atrial relaxation, annular descent, and atrial volume.

The second positive deflection in the atrial pressure tracing is the V wave, which represents rapid atrial filling during ventricular systole while the atrioventricular valve is closed. The peak of the V wave usually corresponds to the T wave on the ECG. The decay of the V wave is referred to as the Y descent (Figure 5.1). The Y descent corresponds to rapid ventricular filling in early diastole as the atrioventricular valve opens. The nadir of the Y descent is influenced by ventricular compliance and stiffness.

The waveforms are dependent on heart rate. Tachycardia reduces the duration of diastole and can abbreviate the Y descent, thus causing the V and A waves to merge. Bradycardia causes the waves to become more distinct and can elicit an H wave, a mid- to late-diastolic plateau that follows the Y descent and precedes the A wave.

The mean LA pressure is higher than the mean RA pressure in the normal heart. The A wave is usually higher than the V wave in the RA; in the LA, either the V wave is greater than the A wave or the A and V waves are nearly equal. Also in the normal heart, mean atrial pressure falls with inspiration. The opposite effect, in which the mean RA pressure does not decrease with inspiration, is seen in constrictive pericarditis and occasionally other conditions and is referred to as Kussmaul's sign.

It is important to remember that atrial pressure tracings represent pressure (and provide some indirect information on atrial volume) but not flow. Venous return to the RA is dependent on the pressure gradient between the venous system and the RA. Consequently, venous return to the RA is maximal during periods of low pressure (X and Y descents).

Abnormalities in atrial pressures

Elevations in RA pressure are often a clue to cardiovascular pathology. Increased mean RA pressure is seen in valvular heart disease, constrictive pericarditis, restrictive cardiomyopathy, cardiac tamponade, fluid overload (e.g., renal failure), pulmonary hypertension, left to right shunts, pulmonary embolus, RV infarction, LV systolic or diastolic failure, and congenital heart disease. It is important to note that mean RA pressures may appear normal in patients with heart disease who are dehydrated.

The A wave is accentuated in patients with noncompliant ventricles and therefore can be increased in patients with ventricular ischemia, infarction, or hypertrophy from pressure or volume overload. A prominent RA A wave can

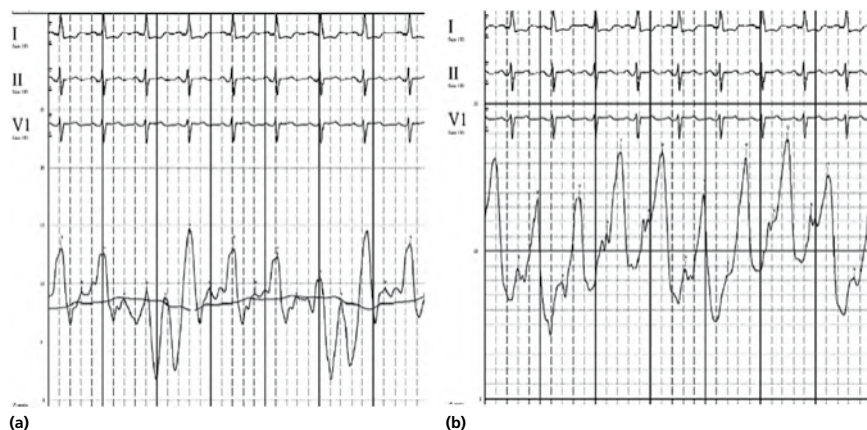


Figure 5.2 Examples of prominent A waves in RA tracing (a) and prominent V waves in PCWP tracing (b) in a 62-year-old female with severe mitral regurgitation and left ventricular systolic dysfunction.

occur in tricuspid regurgitation (TR), pulmonic regurgitation, or stenosis as well as pulmonary embolus or cor pulmonale from any cause (Figure 5.2a and Tables 5.1 and 5.2). Intermittent cannon A waves can be seen in complete heart block or ventricular tachycardia as the atria are contracting intermittently against a closed AV valve (Figure 5.2b). In patients with atrial flutter or atrial tachycardia, A waves may be present at an accelerated rate. Small A waves are rare in RA tracings but common in LA tracings (Figure 5.2c).

Abnormalities in the X descent are seen with severe TR or mitral regurgitation (MR) when the X descent and C wave can be interrupted by a prominent V wave.

The V wave reflects atrial pressures during ventricular systole and thus can be useful as a clue to the presence of AV valve regurgitation. In the RA a prominent V wave can be seen in patients with TR and the RA pressure tracing can take on a ventricularized character when TR is severe (Figure 5.3) [3]. Ventricularization of the RA pressure tracing is a specific but not sensitive finding in severe TR (see Chapter 13). In a study of 60 patients who had right ventriculography, Lingamneni *et al.* found that ventricularization of the RA pressure contour was present in only 40% of patients with severe TR [4]. Cha *et al.*, in their study of 59 patients with severe TR diagnosed on right ventriculography and/or at the time of surgery, found that a ventricularization pattern was present in 31%, and that prominent V waves (not further defined in the paper) and steep Y descents were present in an additional 37% of the patients [5]. In contrast, Pitts *et al.* reported that neither prominent RA V waves nor elevated mean RA pressures reliably predicted the presence of moderate or severe TR (as determined by echocardiography), but that the absence of RA V waves and elevated mean RA pressures were relatively specific for excluding significant TR [6]. For the purposes of their study, a “prominent”

Table 5.1 Conditions associated with abnormal right atrial pressure tracings.

	Prominent	Blunted
A wave	A–V dissociation (e.g., complete heart block or ventricular tachycardia) Decreased ventricular compliance Tricuspid regurgitation or stenosis Pulmonary stenosis or regurgitation	Atrial arrhythmia
X descent	Tamponade RV ischemia (without RA involvement) Atrial septal defect	Atrial arrhythmia RA ischemia Tricuspid regurgitation
V wave	Tricuspid regurgitation RV failure	Tamponade Constrictive pericarditis Hypovolemia
Y descent	Constrictive pericarditis Restrictive cardiomyopathy Tricuspid regurgitation	Tamponade RV ischemia Tricuspid stenosis

right-sided V wave was defined as (1) V wave >15 mm Hg, (2) a difference between V wave and mean RA pressure >5 mm Hg, or (3) a ratio of V wave to mean RA pressure >1.5.

Commonly, however, the left-sided V wave receives the most attention and that is what we will focus on in this section (examples are shown in Figure 5.4). The PA systolic pressure waveform and left atrial V wave are generated at the same time (assuming that the ventricles contract at the same time). However, the V wave in the PCWP tracing will be seen later because of the delay in transmission of left atrial pressure to the catheter tip. Moore *et al.*, in their study of 13 patients with large V waves, found that the onset of the V wave was approximately 110 ms after the onset of the pulmonary arterial upstroke [7].

The V wave in the PCWP (or LA) tracing is dependent on the pressure–volume relationship of the LA and left atrial compliance as well as the volume of blood entering the atrium. A large V wave indicates a rapid rise in LA pressure during ventricular systole and can occur in setting of a noncompliant left atrium and normal flow (e.g., atrial ischemia or stiff LA syndrome) or a normally compliant left atrium with large flow (e.g., acute mitral regurgitation). Conversely, if the left atrium has a large capacitance, then a prominent V wave may be absent even in the presence of severe mitral regurgitation.

In the LA or PCWP tracing, a prominent V wave suggests mitral regurgitation, but is neither sensitive nor specific. Some investigators have advocated using a

Table 5.2 Right atrial pressure tracing findings in various conditions.

	V wave	Y descent	A wave	X descent	RA mean pressure	Misc.
Normal	Atrial filling following ventricular contraction	Rapid ventricular filling phase	Atrial contraction		0–5	RA: A > V LV: V > A normal delay in pressure transmission from LA to pulmonary cap: 140–200ms
Constriction		Prominent		Preserved	Elevated	Tracings can have M or W form; Kussmaul's sign
Tamponade		Small/absent		Preserved	Elevated	
Effusive constrictive		Prominent			Persistent elevation after pericardiocentesis	RA pressure remains elevated despite complete drainage (pericardial pressure = 0)
Restriction		Prominent		Preserved	Elevated	RA tracings can have M or W form
RV infarct		Impaired			Elevated	RA intact: increased A wave and steep X descent RA infarct: decreased A wave and impaired X and Y descents
Severe TR	Prominent			Blunted	Elevated	RA tracing may have the appearance of an RV tracing (ventricularization)

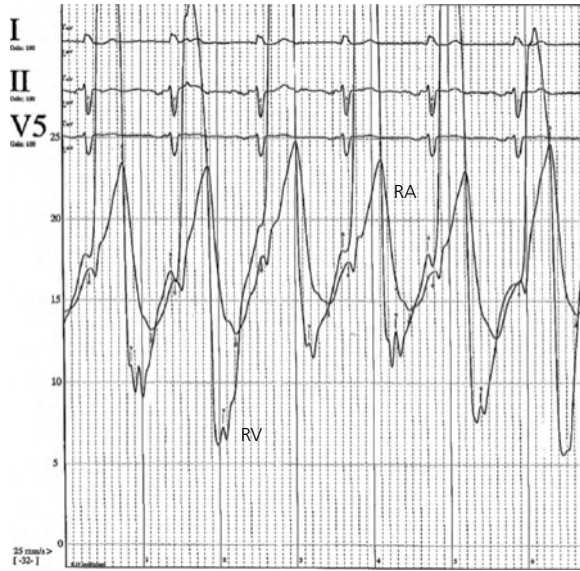


Figure 5.3 Pressure tracing from a patient with severe tricuspid regurgitation. Simultaneous RA and RV pressures are recorded in a 60-year-old male with severe TR. Note the ventricularization of the atrial pressure.

grading system where a V wave that is twice the mean wedge pressure is suggestive of severe MR and a V wave maximum of three times mean wedge pressure is diagnostic of severe MR, but this has not been widely validated (Table 5.3). Although not typical, a prominent V wave can occasionally be observed in patients with mitral stenosis if the LA is relatively noncompliant, with limited ability to accept expanded filling volumes.

In patients with severe MR and a large V wave, mean PCWP can overestimate LV end-diastolic pressure (LVEDP). In a study by Haskell and French [8], mean PCWP pressure overestimated LVEDP by approximately 30% (in this study, a large V wave was defined as being greater than the A wave by more than 10 mm Hg). A better estimate of LVEDP was obtained by using the trough of the X descent.

The Y descent or decay in the V wave occurs during the opening of the AV valve and represents rapid emptying of the atria into the ventricle (which results in a drop in pressure). It is a marker of passive ventricular filling and thus anything that prevents or enhances early diastolic filling affects the character of the Y descent. Conditions with high ventricular pressures during early diastole tend to be associated with blunted Y descents (e.g., tamponade or mitral stenosis). Y descents are usually blunted in cardiac tamponade but can become more prominent during inspiration; the Y descent becomes more apparent following pericardiocentesis. Conditions with low ventricular pressures during early diastole and prominent passive filling of the ventricle (e.g., constrictive pericarditis) tend to

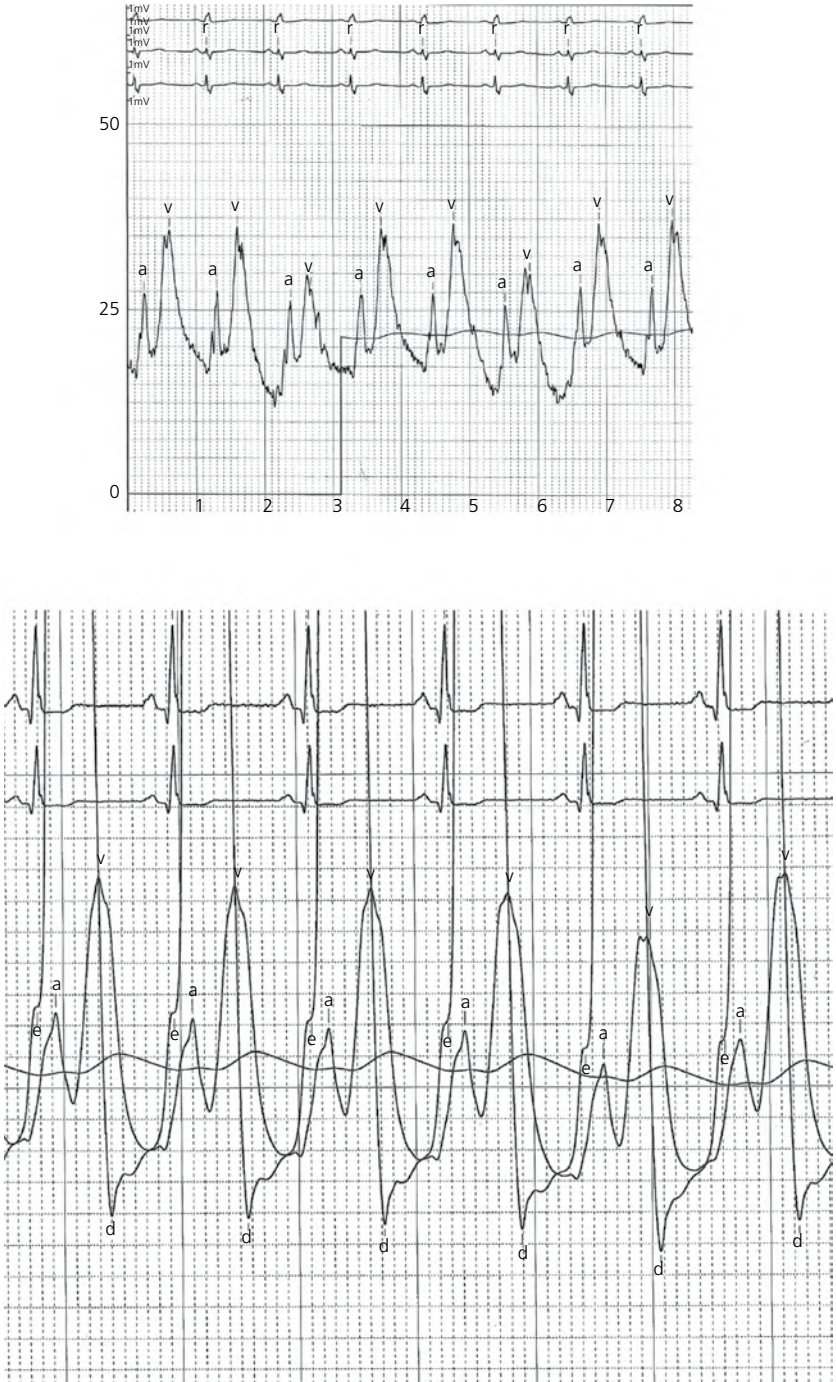


Figure 5.4 Examples of prominent V waves.

Table 5.3 Important points about V waves.

The V wave on PCWP tracing corresponds to (1) T wave on ECG and (2) descent of pressure tracing on LV recording

V wave $>2\times$ mean PCWP is suggestive of severe MR

V wave $>3\times$ mean PCWP is diagnostic of severe MR

Absence of significant V waves does not exclude significant MR

When large V waves are present, trough of Y descent is better predictor of LVEDP than is mean PCWP [8]

V waves are affected by arterial systolic blood pressure (i.e., ventricular afterload)

have large Y descents. Various examples of Y descents are shown: mitral stenosis can cause attenuation or flattening of the terminal Y descent (Figure 5.5); venous pressures are elevated and Y descents are prominent in constrictive pericarditis (Figure 5.6); both X and Y descents are blunted in a case of right ventricular infarction (Figure 5.7); and Y descents are blunted, especially during expiration, in a case of cardiac tamponade (Figure 5.8). The Y descent can vary with the position of the patient in the rare instance of large atrial myxoma.

Physical examination

Physical examination of jugular venous pulse (JVP) provides valuable information to clinicians, as the JVP is a manometer of pressure in the right atrium. To determine JVP, sit the patient at 45° and turn his or her head slightly away from you. Use the internal jugular vein (not external jugular vein) medial to the clavicular head of sternocleidomastoid and measure JVP in centimeters above the sternal notch (vertical not diagonal distance). The venous pulse can usually be analyzed more readily using the right internal jugular vein, as the right innominate and jugular veins extend in an almost straight line from the superior vena cava. Sir Thomas Lewis in 1930 proposed a simple bedside method for measuring central venous pressure. He found that the catheter-measured CVP was equal to 5 cm plus the vertical distance of the JVP from the sternal angle and that this measurement was independent of the individual's position (e.g., supine, semiupright, or upright). Remember that CVP in cm of blood must be divided by 1.34 to get pressure in mm Hg. Also note that the distance between the sternal angle and the midportion of the RA, which Lewis estimated at 5 cm, varies considerably between individuals and is affected by age and anterior–posterior diameter of the chest [9].

JVP can be used to assess right heart filling pressures and the waveform can provide information suggestive of specific diagnoses. Raised JVP with normal waveform is suggestive of right heart failure and/or fluid overload. The lack of pulsations in a patient with elevated JVP would be suggestive of SVC obstruction.

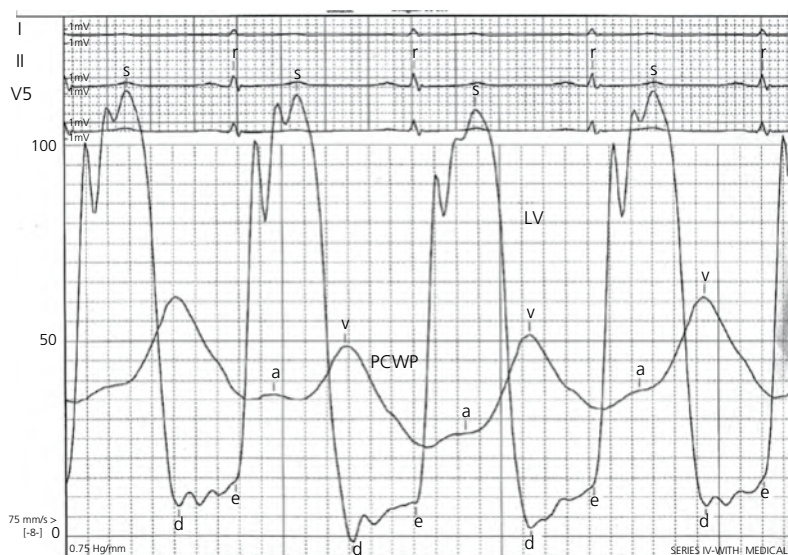


Figure 5.5 Example of simultaneous PCWP and left ventricular pressure tracings in a patient with mitral stenosis and mitral regurgitation. Note the persistent pressure gradient between the chambers throughout diastole. Note also that the PCWP pressure is delayed relative to LV pressure, and that accurate determination of diastolic pressure gradient and mitral valve area requires shifting the PCWP tracing to the left. The V wave on the PCWP tracing should coincide with the downstroke (isovolumetric relaxation) of the LV tracing.

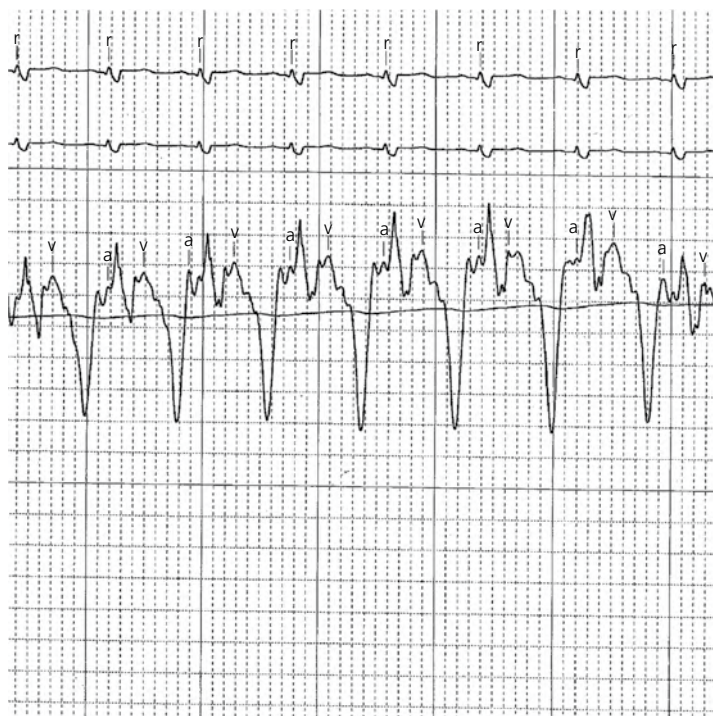


Figure 5.6 RA tracing in a patient with constrictive pericarditis. Constrictive pericarditis and restrictive cardiomyopathy are two hemodynamic states that cause significant abnormalities of the atrial wave with prominent Y descents. There are typically high atrial pressures and prominent early diastolic filling waves.

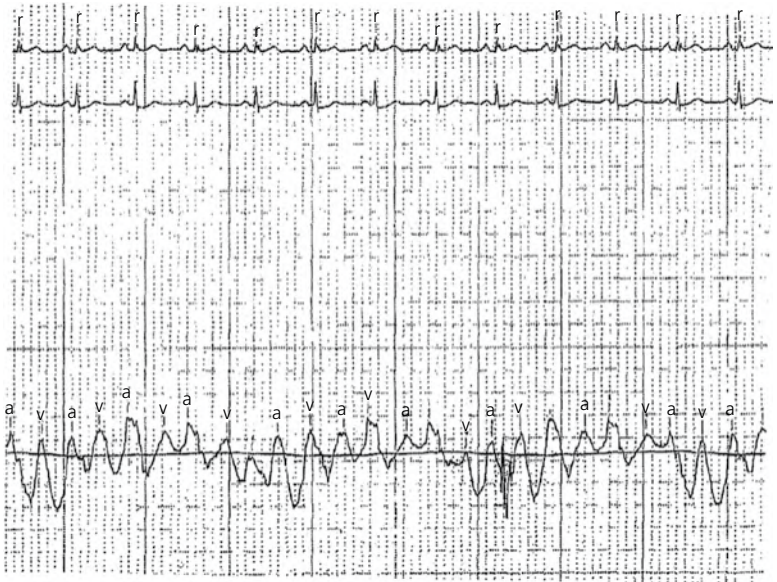


Figure 5.7 RA tracing in a patient with right ventricular myocardial infarction. RV infarction can occasionally cause a pattern of pseudoconstriction with a prominent X and Y descent. This occurs due to acute distention of the volume-overloaded RV in a constrained pericardial space.

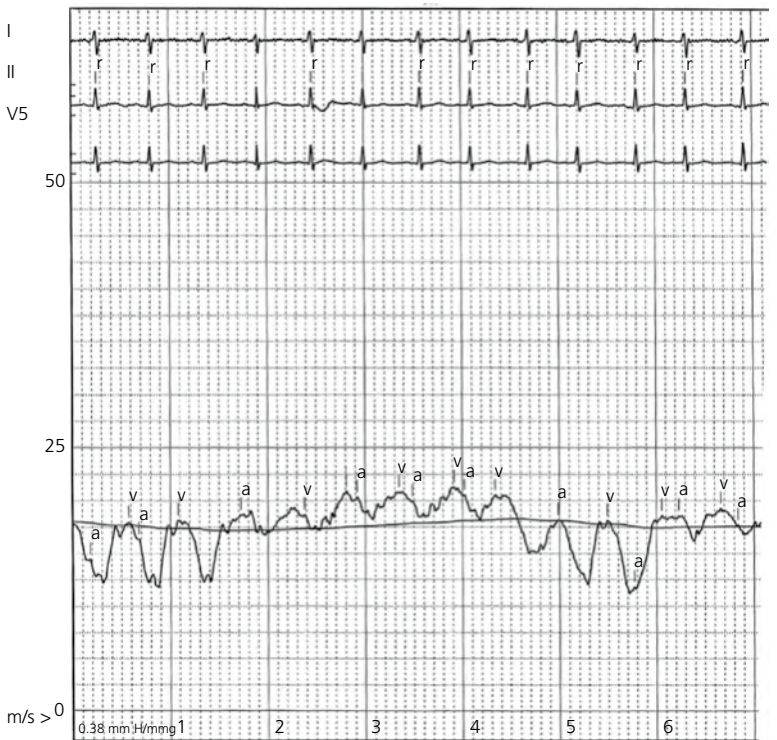


Figure 5.8 RA tracing in a patient with pericardial tamponade. Tamponade results in pandiastolic restriction of ventricular filling, as pericardial pressure exceeds RA pressure throughout diastole. This results in blunting of both the X and Y descents, which often return following successful pericardial drainage.

Various abnormalities of the A wave, V wave, X descent, or Y descent suggest diseases outlined in Tables 5.2 and 5.3. An increase in JVP with inspiration (Kussmaul's sign) is suggestive of constrictive pericarditis.

Measuring LV preload – mean LA (or mean PCWP) vs LVEDP

LA pressures (and PCW pressures) and LVEDP pressures are commonly used to estimate LV preload, but it is important to realize that they provide different, although complementary, information. Mean LA (PCW) pressures integrate atrial pressure during both systole and diastole and are a better reflection of effects of left heart pressures on the pulmonary circulation. In contrast, LVEDP measures the pressure in the LV just prior to the onset of ventricular systole. It provides a measurement of LV distending pressure and thus LV compliance but is measured at only a single point in diastole and does not reflect LA compensatory mechanisms.

As stated in a recent review, “the LVEDP is a surrogate measure of LV preload and LV diastolic operating compliance. In contrast, the mean PCWP is a better reflection of the cumulative hemodynamic impact of ventriculoatrial coupling and its operating compliance on the pulmonary circulation. Thus, when trying to calculate pulmonary arteriolar resistance or evaluate the cause of dyspnea that occurs on exertion, clinicians should use the mean PCWP instead of the LVEDP” [10].

Important points

- The atrial waveform is composed of the positive atrial (A) and ventricular (V) waves and the X and Y descents.
- The A wave is prominent with abnormalities of RV and LV compliance (e.g., hypertrophy, ischemia).
- The V wave is accentuated in cases of atrioventricular valve regurgitation (RA V wave in TR, LA V wave in MR).
- The X and Y descents are diminished or absent in pericardial tamponade.
- The X and Y descents are accentuated in constriction and restrictive myocardial disease.

Historical anecdote

Karel Wenckebach described the arrhythmia that bears his name (also known as Mobitz type 1 AV block) in a paper titled “On the analysis of irregular pulses” that was published in 1899, before the advent of clinical electrocardiography. He described the arrhythmia based on a careful examination of the arterial pulse and the A wave in the jugular venous waveform in a “forty-year-old lady . . . with a pulse that was small, soft and intermittent after 3 to 6 contractions” who had consulted him (more details can be found in *Ann Intern Med* 1999;**130**:58–63 or *Tex Heart Inst J* 1999;**26**:8–11).

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CHAPTER 6

Cardiac output

George A. Stouffer

[This chapter is revised and modified from a chapter written for the first and second editions by Robert V. Kelly, Chadwick Huggins and George A. Stouffer]

A key component of evaluating the hemodynamic status of a patient is the measurement of cardiac output. Cardiac output is the amount of blood moved per unit of time from the venous system (i.e., the vena cava) to the arterial system (i.e., aorta). It is a dynamic process and tightly regulated so that the blood flow through the heart equals the perfusion needs of the body.

Cardiac output is primarily regulated by preload, afterload, heart rate, and myocardial contractility. Many factors have rapid effects on cardiac output, including metabolic demands, posture, volume status, adrenergic state, and respiratory rate. Cardiac output decreases with age [1] and increases with exercise. For example, cardiac output can increase up to sixfold with exercise in trained athletes; oxygen extraction also increases with exercise and thus oxygen delivery to tissues can increase twelvefold to eighteenfold.

Cardiac index is the cardiac output divided by the body surface area. A cardiac index <1 L/min/m² is generally incompatible with life.

Measurement of cardiac output enables the determination of systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) using the following formulas:

$$\text{SVR}(\text{in dynes/cm}^5) = \frac{(\text{mean arterial pressure} - \text{right atrial pressure}) \times 80}{\text{cardiac output}}$$

where SVR = systemic vascular resistance. Normal SVR = 700–1600 dynes s/cm⁵

$$\text{PVR}(\text{in dynes} - \text{sec/cm}^5) = \frac{(\text{mean PA pressure} - \text{PCWP}) \times 80}{\text{cardiac output}}$$

where PA = pulmonary artery, PCWP = pulmonary capillary wedge pressure, and PVR = pulmonary vascular resistance. Pressures are in mm Hg and cardiac output

in liters/min. Normal PVR was traditionally thought to be 20–130 dynes s/cm⁵ or 1–3 Wood units [Wood units = (PA mean – PCWP mean)/cardiac output)] but newer guidelines define normal PVR as <160 dynes sec/cm⁵ or <2 Wood units [2].

Invasive assessment of cardiac output

Cardiac output is equal to the heart rate × ventricular stroke volume (in the absence of valvular regurgitation). Measurement of the heart rate is easily attainable, but an accurate measurement of stroke volume is more challenging. Because of the difficulty in measuring left ventricular stroke volume, several methods have been developed that estimate blood flow through the right heart.

In the cardiac catheterization laboratory or the intensive care unit, cardiac output is primarily measured using either the Fick method or the indicator dilution method (e.g., thermodilution). Each of these techniques has advantages and pitfalls that are discussed in detail in this chapter (see Table 6.1).

Table 6.1 Comparison of Fick and thermodilution methods of determining cardiac output.

	Fick	Thermodilution
Underlying principle	Fick principle (conservation of mass): the uptake or release of a substance by an organ is the product of blood flow to the organ × difference in the concentration of the substance between blood entering and blood leaving the organ	Conservation of energy: that is, there is no loss of cold injectate between the site of injection and detection Other underlying assumptions are that mixing of the indicator and blood is complete and that the temperature change elicited by injection of saline can be discriminated accurately from the fluctuations in baseline temperature in the pulmonary artery
Sources of error	• Determination of oxygen saturations • Assumption of steady state • Assumed oxygen consumption values	• Warming of injectate during transit through catheter • Irregular heart rates • Tricuspid regurgitation • Temperature of blood in PA varies with respiratory and cardiac cycles
Advantages	More accurate than TD in low output states, tricuspid regurgitation, and irregular heart rates	More accurate than Fick in high output states
Variation under ideal conditions	~10% when measuring oxygen consumption. Using the assumed Fick method introduces additional variation and inaccuracies.	5–20%

The Fick method is the most accurate way to measure oxygen consumption in low-output states. This is because the difference between arterial and mixed venous oxygen saturation is larger in these states, making measurement errors less significant. The Fick method is also preferred for patients with irregular heart rhythms such as atrial fibrillation or ventricular bigeminy and in patients with severe tricuspid regurgitation.

Fick method

In 1870, Adolph Fick described the first method to estimate cardiac output in humans. He postulated that oxygen uptake in the lungs is entirely transferred to the blood and therefore that cardiac output can be calculated knowing the oxygen consumption of the body and the difference in oxygen content between arterial and mixed venous blood. Cardiac output can be calculated using the Fick method knowing the oxygen saturation of arterial and mixed venous blood, the hemoglobin concentration, and the oxygen consumption based on this equation:

$$\text{Cardiac output} = \frac{\text{oxygen consumption}}{(\text{arterial} - \text{venous})\text{O}_2 \times \text{hemoglobin concentration} \times 1.36 \times 10}$$

The constant 1.36 is expressed in mL O₂/g hemoglobin.

Direct measurement of oxygen consumption is cumbersome and time-consuming and requires a tight-fitting gas exchange system. An alternative approach, although less accurate, is to estimate the oxygen consumption based on the patient's body surface area (the "assumed Fick" method). The assumed Fick method is used frequently, and thus it is important to realize its limitations.

A major source of error is the Inherent variability in oxygen consumption, thus leading to inaccuracies when "assumed" values are used. The initial evaluation of the assumed Fick method was performed in young healthy adults. Subsequently, Krovetz and Goldbloom [3], LaFarge and Miettinen [4], and Bergstra *et al.* [5] derived empiric formulas to estimate VO₂, while others advocate assuming oxygen consumption of 125 mL/min/m² in adults with or without a correction for age. In a study of 108 patients (mean age 49 years) undergoing cardiac catheterization, Dehmer *et al.* found the mean oxygen consumption to be 126 mL/min/m², but with a large standard deviation of 26 mL/min/m² [6]. Oxygen consumption was not affected by age or sex, but varied with level of sedation. In a study of 80 patients, Kendrick *et al.* compared assumed (calculated using five different estimation methods) and directly measured values of oxygen consumption and found significant discrepancies, with over half the estimated values differing by more than 10% from directly measured amount and 35% differing by more than 25% [7]. Similarly, Wolf *et al.* directly measured oxygen consumption in 57 nonsedated patients (mean age 52 years) undergoing evaluation in a metabolic laboratory and found the mean to be 126.5 mL/min/m², but with large variation

(71–176 mL/min/m²) [8]. Comparison with assumed values calculated using the LaFarge and Miettinen equation showed that there were large, unpredictable errors when assumed values were used.

The assumed value of oxygen consumption is generally the largest error in using the assumed Fick method; however, other sources of error exist including measurement of oxygen saturation (see Chapter 7 on intracardiac shunts for a more complete discussion of potential errors) and the assumption of steady state. Even under the best conditions, the error associated with measuring cardiac output using the assumed Fick method is generally 10–15%. Under less stringent conditions, this variation can rise significantly.

Supplemental oxygen use during measurement of the cardiac output should be avoided. If oxygen is required, maintaining a steady state is imperative to obtaining the most accurate measurement.

Assumed oxygen consumption formulas (BSA = m² for all formulas)

Krovetz and Goldbloom [3] – $\text{O}_2/\text{BSA (mL/min)/m}^2 = (1.39 \times \text{height[cm]} + 0.84 \times \text{weight[kg]} - 35.6)/\text{BSA}$

LaFarge and Miettinen [4] – $\text{VO}_2/\text{BSA (mL/min)/m}^2 = (138.1 - 17.04 \times \text{Ln}(\text{age}) + 0.378 \times \text{HR})/\text{BSA}$ for female subjects and $\text{VO}_2/\text{BSA} = (138.1 - 11.49 \times \text{Ln}(\text{age}) + 0.378 \times \text{HR})/\text{BSA}$ for male subjects, where age is in years (and Ln = natural logarithm) and HR is heart rate (beats per minutes).

Bergstra *et al.* [5] – $\text{VO}_2(\text{mL/min}) = (157 - 3 \times \text{BSA} + 100 \times \text{Sex} - 10.5 \times \text{Ln Age} + 4.8)$, where Sex = 0 for female and 1 for male and Age is in years.

Thermodilution method

The indicator dilution method was first used in 1897. In its simplest form, it involves injection (via either bolus or continuous infusion) of an indicator substance into the circulation and then measurement of this substance at a point in the circulation downstream of the injection. The amount of indicator that is measured downstream, per unit time after injection, will be a function of cardiac output. The substance must be nontoxic, capable of mixing completely with blood, not taken up from the bloodstream, and capable of being accurately measured. Numerous indicators have been studied over the years, including indocyanine green, but currently room temperature saline is the substance most commonly used.

The thermodilution method involves injecting cold or room temperature saline into the right atrium and then measuring the temperature of blood in the pulmonary artery. The typical technique involves placement of a right heart catheter with multiple ports into the pulmonary artery. Several injections (usually at least 3) of 10 mm of cold saline is injected into the right atrium and temperature changes are measured in the pulmonary artery. The cardiac output values with each injection are averaged. Accurate measurement requires that a

“mixing chamber” be present between the injection site and the measurement site. Thus, the proximal port should lie in the right atrium and the distal tip of the catheter should be beyond the pulmonary valve.

Injection of saline into the right atrium will cause a small, transient decrease in pulmonary artery temperature and a thermodilution curve is generated by plotting the temperature of the pulmonary artery versus time. The curve generally has a smooth upslope and a gentler decline (Figure 6.1). The area under the thermodilution curve is inversely related to the cardiac output and can be used to calculate the cardiac output. The calculation of the area under the curve and calculation of cardiac output are performed by a computer, but an estimate of the validity of the measurement can be obtained by checking the waveform of the thermodilution curve.

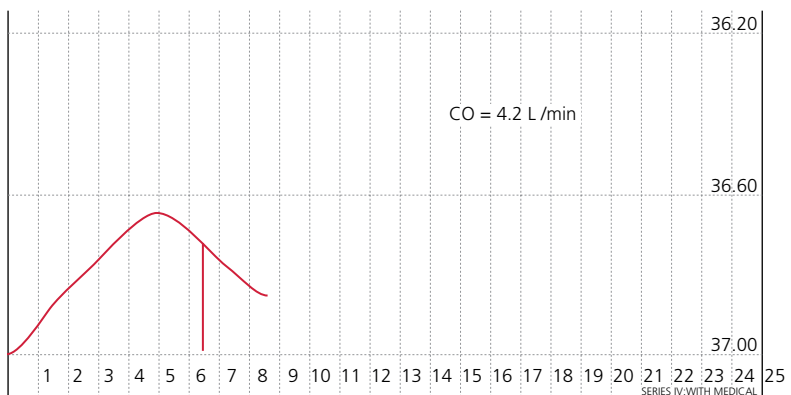
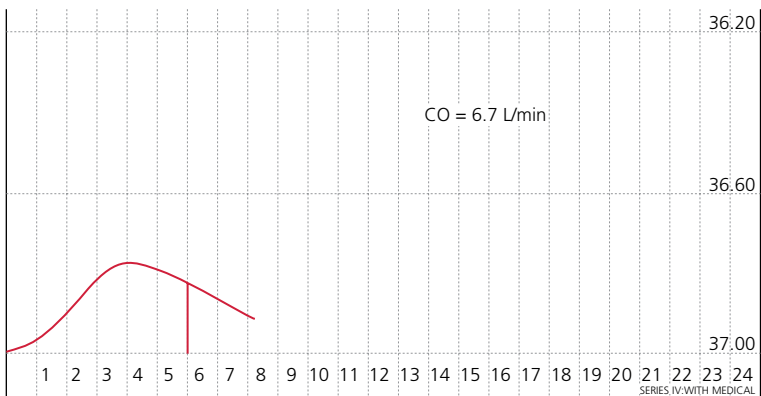


Figure 6.1 Thermodilution curves. Pulmonary artery temperature versus time is plotted in patients with thermodilution cardiac outputs of 6.7 L/min and 4.2 L/min. Note that the temperature curve is inverted so a rise in the graph is indicative of a fall in PA temperature.

Significant tricuspid regurgitation is generally considered a contraindication to the use of thermodilution for measurement of cardiac output. An early study by Konishi *et al.* [9] did not find a significant difference in cardiac outputs measured using thermodilution or Fick in the presence of tricuspid regurgitation. Later studies, however, found that a high degree of tricuspid regurgitation was associated with underestimation of cardiac output by the thermodilution technique. Cigarroa *et al.* in their study of 30 patients (mean age 50 years) found excellent agreement between thermal dilution cardiac output and Fick or indocyanine green dye cardiac output in patients without tricuspid regurgitation, but results of thermodilution were consistently lower (by approximately 20%) than those obtained by the Fick or indocyanine green dye methods in the 17 patients with tricuspid regurgitation (see Table 6.1) [10].

Of note is that mechanical ventilation can have an effect on cardiac output measurement with the thermodilution technique by causing or worsening tricuspid regurgitation. In a small study, Artucio *et al.* found that the use of positive end-expiratory pressure (PEEP) caused tricuspid regurgitation to develop or worsen in six out of seven patients studied [11]. Balik *et al.*, in their study of 27 ventilated patients undergoing cardiac surgery, found that thermodilution underestimated cardiac output (using transesophageal echocardiographic cardiac output as the gold standard) and that inaccuracies increased proportionally to the amount of tricuspid regurgitation [12].

For the sake of simplicity, room-temperature saline is often used, but this can lead to less accurate measurements. Berthelsen *et al.* reported a significant rise in variation and a loss of precision with the use of 20°C saline versus the use of 0°C saline [13]. They also noted, however, that if room-temperature saline was injected through a right heart catheter that had both proximal and distal thermistors, the variation was within an acceptable range. If ice-cold saline is used, careful attention must be paid to not allowing the saline to warm prior to injection. Iced injectate in a plastic syringe warms by 1°C for every 28 seconds at room temperature. The rate of warming increases if the injectate is held in a gloved hand.

Potential sources of error in using thermodilution to measure cardiac output include “catheter warming” and temperature variation in the pulmonary artery. Catheter warming refers to the increase in temperature of the injectate as it passes through the catheter. Commercially available systems include an empiric constant that corrects for this warming. Variations in the temperature of blood in the pulmonary artery are generally minimal, except in cases of deep inspiration or positive pressure ventilation. In some cases, the variation in the temperature of the blood is enough to affect cardiac output determination. An additional limitation to thermodilution is the inaccuracy associated with determining accurate cardiac output with irregular heart rates or rhythms.

Thermodilution is most accurate when used in high output states, as the errors introduced by injectate warming are proportionally smaller. As cardiac output declines, the accuracy of thermodilution cardiac output declines (in contrast to the Fick method, in which accuracy increases with decreasing cardiac output).

Van Grondelle *et al.* compared 57 cardiac output measurements by the thermodilution and direct Fick methods in 26 patients and found that thermodilution values were higher in all 16 cases in which Fick outputs were less than 3.5 L/min. In 10 cases where Fick values were less than or equal to 2.5 L/min, thermodilution and Fick measurements differed by an average of 35% [14]. They postulated that thermodilution is less accurate at low cardiac outputs because of warming of the injectate during conditions of low flow. Under ideal conditions, thermodilution can determine cardiac output within an error range of 5–20%. Age may also increase the discrepancy between cardiac output measurements. In a study of 213 right heart catheterizations, the average difference between thermodilution and assumed Fick cardiac outputs ($\pm$ SD) was -0.39 ± 2.03 L/min ($P = 0.006$) with 43% of patients having >20% difference between thermodilution and Fick. The difference between the two methods was not affected by pulmonary hypertension but in a multivariable analysis, the difference increased with age ($P = 0.001$) [15].

Echocardiographic assessment of cardiac output

Echocardiography can be used to assess cardiac output and stroke volume via Doppler-derived, two-dimensional (2D), and three-dimensional (3D) methods. The underlying principle of the Doppler-derived method is that the volume of flow can be determined by multiplying the velocity of flow by the area through which the blood is flowing. Thus, cardiac output can be calculated as the product of the heart rate, aortic velocity time integral (VTI), and the area of the left ventricular outflow tract (LVOT) (Figure 6.2). This equation assumes that the area is constant and unchanging, and the LVOT is frequently used because it is the least dynamic. Because blood flow is pulsatile, a simple velocity cannot be used. Instead, a VTI must be derived from Doppler measurements of flow.

Cardiac output = heart rate $\times$ stroke volume

Where stroke volume = LVOT Area $\times$ LVOT VTI

And where LVOT area = $(1/2 \times \text{diameter})^2 \times \pi$

This technique is very useful and can provide an accurate measurement of cardiac output, but as with all techniques, it too has pitfalls. The measurement of the VTI using Doppler requires diligence. One must measure with pulse wave Doppler at the precise location where the LVOT diameter will be measured. Additionally, the pulse wave Doppler must be parallel to the flow. Any variance greater than 20° off the direction of flow will significantly change the calculated result. Another source of potential area is the measurement of the diameter of the LVOT. The area of the outflow tract is calculated by squaring the diameter and multiplying by 0.785. Even very small errors in the measurement of the LVOT diameter will result in large variations in the area because the diameter is squared in this calculation.

3D echocardiography is being used more commonly to assess CO and is recommended by the most recent echocardiographic guidelines [16]. 3D imaging

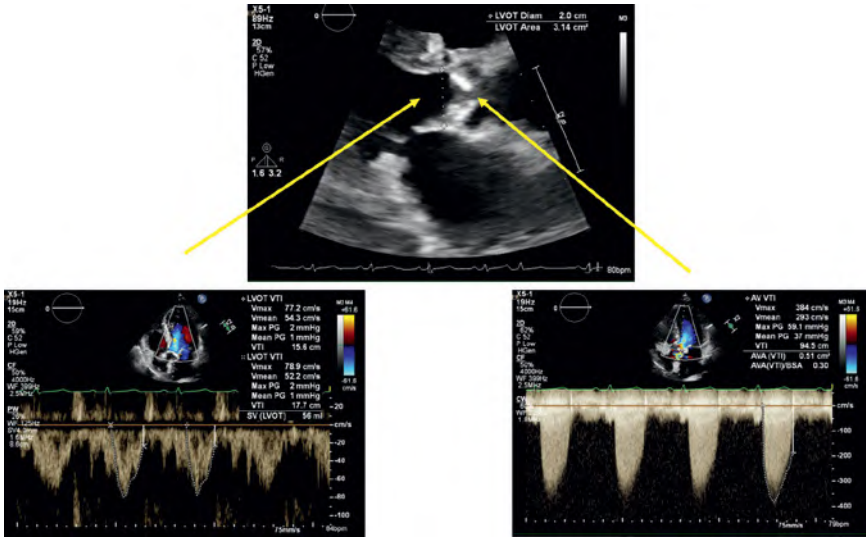


Figure 6.2 Estimation of stroke volume using left ventricular output track diameter and velocity time integral. By comparison, the VTI through a stenotic aortic valve is shown on the right.

overcomes several limitations of 2D imaging including that it is not affected by foreshortening and does not rely on geometric assumptions regarding LV shape.

Cardiac output measurement in intensive care units

One of the primary goals for patients in shock is to increase tissue perfusion. Clinical surrogates, such as blood pressure, pulse rate, central venous pressure, and arterial oxygen saturation have not consistently proven useful in guiding use of therapies to maximize cardiac output. In the absence of a measurement of cardiac output, volume resuscitation is often the first approach to treating shock. However, studies have shown that tissue perfusion does not increase in response to volume resuscitation in a significant number of hemodynamically unstable patients. In nonresponsive patients, volume resuscitation does not improve stroke volume and carries some risk of harm. Therefore, there is a large interest in developing methods to measure cardiac output continuously and accurately in critically ill patients. This would enable accurate fluid administration and optimal use of inotropic agents and vasopressors to maximize tissue perfusion [17].

Traditionally, continuous cardiac output monitoring has been accomplished using a pulmonary artery catheter. Because of the well-known limitations of PA catheters and the lack of evidence that they improve outcomes in critically ill patients, several new technologies have been developed to measure cardiac

output continuously. An invasive method that is useful only in ventilated patients involves using an esophageal Doppler probe to measure velocity and diameter continuously in the descending aorta. Newer noninvasive methods include pulse contour analysis, bioimpedance systems, CO₂ partial rebreathing technique, and various noninvasive devices employing Doppler technology.

The concept of pulse contour analysis is based on the relationship between stroke volume, blood pressure, arterial compliance, and SVR. Stroke volume, and thus cardiac output, can be calculated from the arterial pressure waveform if arterial compliance and SVR are known. Bioimpedance systems measure the resistance to flow of electric current through the thorax. This resistance is referred to as impedance (Zo), which in the thorax includes impedance due to tissues that do not change over time (such as lung, muscle, bone, and fat) and impedance due to the amount of blood in the thorax. Thus Zo varies in proportion to the amount of fluid in the thorax and the instantaneous rate of the change of Zo is related to instantaneous blood flow in the aorta. The limitations of bioimpedance systems are many and include being sensitive to the placement of the electrodes on the body, variations in body size, and other physical factors such as temperature and humidity that have an impact on electric conductivity. Newer technologies have been developed, including bioreactance, which is used to measure the phase shift in voltage across the thorax. Pulsatile ejection of blood leads to instantaneous changes in the phase of Zo; phase shifts in Zo can thus be used as a surrogate for aortic flow. The CO₂ partial rebreathing technique uses the modified Fick equation to estimate pulmonary capillary blood flow (a surrogate for cardiac output that assumes the absence of any shunting) based on a comparison of end-tidal carbon dioxide partial pressure obtained during a period of no rebreathing with that obtained during a subsequent period of rebreathing.

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CHAPTER 7

Detection, localization, and quantification of intracardiac shunts

Frederick M. Costello and George A. Stouffer

In normal human circulation, blood passes from the venous system through the right heart, into the pulmonary circulation, then into the left heart, and finally into the systemic circulation in a continuous, unidirectional manner. In certain conditions, however, oxygenated blood is shunted from the left heart directly to the right heart, as in the case of atrial septal defects (ASD; Figure 7.1) or ventricular septal defects (VSD; Figure 7.2), or from the aorta to the pulmonary artery (PA) as in the case of a patent ductus arteriosus (PDA). More rarely, unoxygenated blood can be shunted from the right heart to the left heart (e.g., Eisenmenger's syndrome). Intracardiac shunts can be either congenital (Figures 7.1 and 7.2) or acquired (e.g., a VSD as a complication of myocardial infarction).

Intracardiac shunting of blood results when there is an opening between the right and left heart chambers and a pressure difference to drive flow between the connected chambers. Because pressures (both systolic and diastolic) on the left side of the heart are generally higher than on the right side, most shunts are predominantly left to right, although right to left and bidirectional shunts are seen. Of note is that arterial-to-venous shunts can exist outside of the heart (e.g., intrapulmonary, intrahepatic, arterial-venous malformations) and affect oxygen saturations. We will not address these shunts in this chapter but rather concentrate on intracardiac shunts.

Detection of an intracardiac shunt

The presence of a shunt can be determined either invasively or noninvasively (e.g., radionuclide studies, magnetic resonance imaging [MRI], or Doppler echocardiography). In current practice, many shunts are suspected based on physical exam or electrocardiogram (ECG), diagnosed at echocardiography and then quantified using right heart catheterization.

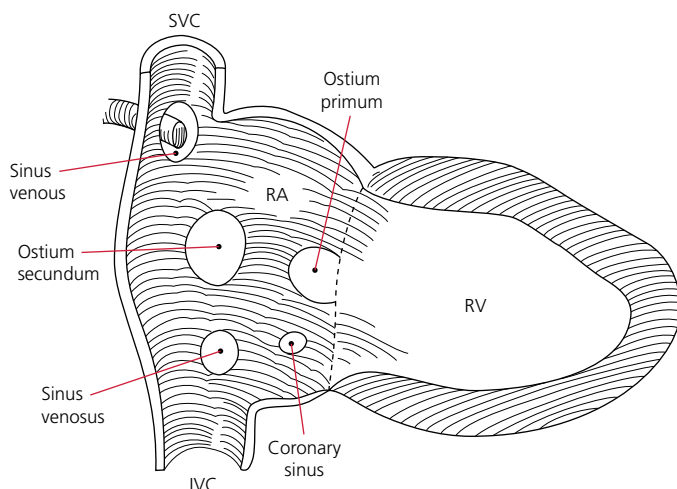


Figure 7.1 Schematic showing the location of various types of atrial septal defects.

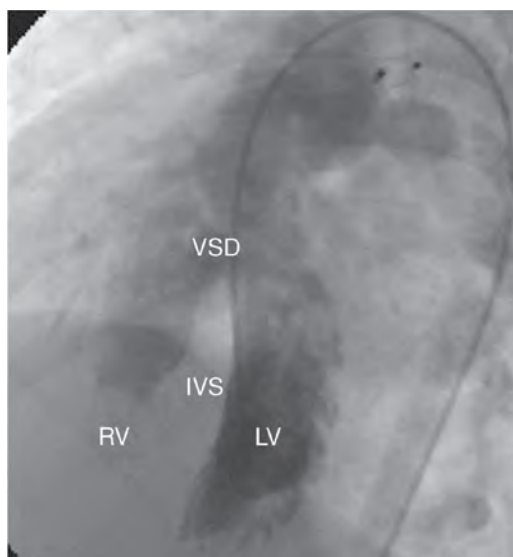


Figure 7.2 Left ventriculogram in an LAO cranial projection showing efflux of dye from the left ventricle into the right ventricle via a VSD. [IVS = intraventricular septum; LV = left ventricle; RV = right ventricle; VSD = ventricular septal defect.]

There are several methods by which an intracardiac shunt can be detected, localized, and quantified in the catheterization laboratory. The indicator dilution method is of historical interest but is rarely used outside of research studies. It involves injecting a substance, such as indocyanine green, into the venous systems or a right heart chamber and then monitoring its appearance in the systemic

circulation. Dye curve measurements are very accurate, but are slow and require specialized equipment that is rarely available in modern catheterization laboratories. Contrast angiography, in which contrast dye is injected into the higher pressure chamber of a suspected shunt (e.g., left ventricle), is occasionally used to identify a VSD or PDA. It has limited ability to diagnose ASD and is a poor tool for quantifying the size of a shunt.

Oximetry, or measurement of the oxygen saturations in various locations in the venous system and the right heart ("oxygen saturation run"), is the most frequently used invasive technique due to its simplicity and reliance on readily available equipment.

Oxygen saturation run

The oxygen saturation run is performed as a catheter is passed through the venous system, right heart, and pulmonary circulation. The samples need to be acquired with the patient breathing room air or a gas mixture containing no more than a maximum of 30% oxygen [1]. Saturation data may be inaccurate in patients breathing more than 30% oxygen, since a significant amount of oxygen may be present in dissolved form in the pulmonary venous sample. Dissolved oxygen is not factored into calculations when saturations are used and thus pulmonary flow will be overestimated and the amount of shunt exaggerated.

The oxygen saturation run includes obtaining saturations from the superior vena cava (SVC), inferior vena cava (IVC), right atrium (RA), right ventricle (RV), PA, and arterial circulation. Pulmonary capillary wedge and/or left atrial samples are also sometimes obtained. Samples can be obtained as the right heart catheter is advanced, although many clinicians choose to place the catheter in the PA first and then obtain samples as the catheter is withdrawn. This latter technique can improve the speed of obtaining samples, which can become an issue if there is difficulty advancing the catheter into the PA.

Blood samples should be taken from the locations listed in Table 7.1 and oxygen saturations determined. IVC saturation varies depending on where the sample is obtained, and the sampling site should be at the level of the diaphragm to ensure that hepatic venous blood is taken into account. An arterial blood sample should be collected at the same time as the venous samples are being obtained.

Multiple samples may have to be taken in various chambers to ensure accuracy; however, it is important to note that variability in oxygen saturation (in the absence of shunt) decreases as blood flows through the heart. Oxygen content varies by approximately 2 mL O₂/100 mL blood in the RA, 1 mL O₂/100 mL blood in the RV, and 0.5 mL O₂/100 mL blood in the PA [2]. These values were determined by direct measurement of oxygen content in the days prior to the development of oximetry. Oxygen content can be approximated by the following formula:

$$\begin{aligned} \text{Oxygen content (mLO}_2\text{/100 mL of blood)} \\ = \text{hemoglobin (g/dL)} \times 1.36 \text{ (mLO}_2\text{/g of Hg)} \times \text{percent saturation} \end{aligned}$$

Table 7.1 Sites from which oxygen saturation should be measured when quantifying intracardiac shunts.

Superior vena cava just above the junction with the right atrium
Inferior vena cava just below the diaphragm
Low right atrium
Mid-right atrium
High right atrium
Right ventricle
Left, right, and/or main pulmonary artery
Pulmonary capillary wedge (or left atrium)
Arterial and/or Left ventricle

In a patient with a hemoglobin of 15 mg/dL, a difference in saturation of 5% is approximately equal to a difference in oxygen content of 1 mL O₂/100 mL of blood.

The goal of the oxygen saturation run is to measure differences in oxygen saturation in various chambers of the heart. There are several practical factors that must be kept in mind to ensure accurate results:

- The oxygen saturation method assumes that the body is in a steady state during the collection of samples. To ensure that the results are as accurate as possible, the samples must be collected as close in time as good technique permits. For this reason, many physicians perform a retrograde oxygen saturation run in which they begin with the catheter in the PA.
- Blood samples should not be withdrawn into the syringe too rapidly. Matta *et al.* found that rapid aspiration increased oxygen saturation [3].
- Complete mixing of blood is assumed in all chambers.
- There has to be adequate flushing of the catheter between samples.

Limitations of using oximetry to detect and quantify intracardiac shunts

Using the saturation “step-up” method to detect and quantify intracardiac shunts has some limitations that should be noted. First, because of the inherent variability in determining oxygen saturations, the oximetry method of quantifying shunts loses accuracy when determining small shunts or in the presence of high cardiac output (which decreases arterial-venous O₂ differences).

Second, the magnitude of the step-up varies with the oxygen-carrying capacity of blood and the cardiac output. Saturation step-ups are increased if hemoglobin concentration is low or cardiac output is low. As Shepherd *et al.* [4] note, a 5% step-up occurs with a shunt flow of 3400 mL/min when systemic blood flow is

7.5 L/min, a shunt flow of 1300 mL/min when systemic blood flow is 5 L/min, and a shunt flow of only 285 mL/min if systemic blood flow is 2.5 L/min.

Third, the relationship between the magnitude of step-up and the shunt flow is nonlinear and, with increasing left-to-right shunting, a given change in shunt flow produces less of a change in the saturation step-up. In contrast, quantification of shunt size using the ratio of pulmonary blood flow versus the systemic blood flow (termed the Q_p/Q_s , where Q_p is the pulmonary blood flow and Q_s is the systemic flow), is not affected by hemoglobin concentration and the relationship between Q_p/Q_s and shunt flow is linear. Q_p/Q_s is sensitive to cardiac output and some investigators advocate using exercise in patients with low cardiac output to improve accuracy.

Diagnosis of intracardiac shunts at right heart catheterization

Patients are often referred for cardiac catheterization to confirm and quantify a shunt that has been detected by physical exam and/or imaging. Occasionally, however, a patient will have a shunt that is unsuspected prior to right heart catheterization. These patients can be identified by routinely measuring oxygen saturation in the PA and the RA. Hillis *et al.* found that the difference (mean $\pm$ SD) between RA and PA saturations in 980 patients without intracardiac shunts was $2.3\% \pm 1.7\%$. In this same population, the difference (mean $\pm$ SD) between SVC and RA saturations was $3.9\% \pm 2.4\%$. Using threshold values of 8.7% between SVC and RA and 5.7% between RA and PA as “cut-offs” (mean + 2 SD) to identify patients with intracardiac shunts had excellent sensitivity and specificity [5]. Similarly, differences in oxygen saturation of 8% between SVC and PA and 5% between RV and PA can be used to detect intracardiac shunts.

Quantifying a left-to-right shunt

Quantifying a left-to-right shunt is generally done in two ways. The ratio of pulmonary blood flow to the systemic blood flow Q_p/Q_s can be calculated. Alternatively, the actual flow of the shunt can be calculated. This is the difference between the pulmonary blood flow and the systemic blood flow (these two are equal in a normal heart).

The pulmonary (Q_p) and systemic (Q_s) blood flows are calculated using the Fick method of estimating cardiac output (Table 7.2). The only difference between the pulmonary flow equation and the systemic flow equation is in the arterial and venous saturations used.

$$CO = \frac{VO_2}{[10 \times (SaO_2 - SvO_2) \times Hg \times 1.36]}$$

Table 7.2 Important formulas in quantifying shunts.

$$Q_p = \frac{\text{Oxygen consumption (mL / min)}}{\text{Oxygen content in pulmonary veins} - \text{oxygen content in pulmonary artery (mL / L)}}$$

$$Q_s = \frac{\text{Oxygen consumption (mL / min)}}{\text{Oxygen content in systemic artery} - \text{oxygen content in mixed venous sample}}$$

Simplified formula for calculating Q_p/Q_s in patients with left-to-right shunts.

$$\frac{Q_p}{Q_s} = \frac{(\text{arterialsat} - \text{mixed venous sat})}{(\text{pulm veinsat} - \text{pulm artery sat})}$$

- Pulmonary vein samples are rarely obtained. Instead, pulmonary capillary wedge samples or left atrial samples can be used. Alternatively, arterial saturation (in the absence of right-to-left shunt) can be substituted or an assumed value of 98% may be used
- Left ventricular may be substituted for arterial saturation, provided that there is no right-to-left shunt
- For PDA, use RV sample to determined mixed venous O_2
- For VSD, use RA sample to determined mixed venous O_2
- For ASD, calculate using mixed venous $O_2 = 3(\text{SVC}) + \text{IVC}/4$ (see Table 7.3 for a more complete discussion of calculating mixed venous O_2 from SVC and IVC samples)

For right-to-left and bidirectional shunts:

1. Calculate whole body oxygen extraction ratio (OER) = oxygen consumption (either measured or estimated in mLO_2/min)/hemoglobin (g/dL) $\times 1.36$ ($\text{mL O}_2/\text{g}$)
2. Calculate Q_p , Q_s , and Q_{EP} (the amount of oxygenated blood delivered to the body) using the following equations:

$$Q_p \text{ (L/min)} = \text{OER} / (\text{pulm venous sat} - \text{PA sat})$$

$$Q_s \text{ (L/min)} = \text{OER} / (\text{arterial sat} - \text{mixed venous sat})$$

$$Q_{EP} \text{ (L/min)} = \text{OER} / (\text{pulm venous sat} - \text{mixed venous sat})$$

3. Calculate the right-to-left and left-to-right shunts using these equations

$$\text{Right} - \text{to} - \text{left shunt} = Q_s - Q_{EP}$$

$$\text{Left} - \text{to} - \text{right shunt} = Q_p - Q_{EP}$$

where:

CO = cardiac output (L/min)

VO_2 = oxygen consumption at rest (liters/min), e.g., $125 \text{ mL O}_2/\text{min}/\text{m}^2 \times \text{body surface area in m}^2$ [BSA]

SvO_2 = mixed venous oxygen saturation

SaO_2 = arterial oxygen saturation

Hg = hemoglobin (g/dl)

The Q_p and Q_s equations are:

$$Q_p = \frac{\text{oxygen consumption}}{(\text{PVO}_2 - \text{PA O}_2) \times \text{hemoglobin concentration} \times 1.36 \times 10}$$

where PVO_2 is the pulmonary venous oxygen saturation and PAO_2 is the pulmonary artery oxygen saturation

$$Q_s = \frac{\text{oxygen consumption}}{(\text{SAO}_2 - \text{MVO}_2) \times \text{hemoglobin concentration} \times 1.36 \times 10}$$

where SAO_2 is the systemic arterial oxygen saturation and MVO_2 is the mixed venous oxygen saturation.

These equations can be simplified to calculate Q_p/Q_s . The simplified equation is the difference of the systemic arterial oxygen saturation minus the mixed venous oxygen saturation divided by the pulmonary venous oxygen concentration minus the pulmonary arterial oxygen concentration. This equation is:

$$\frac{Q_p}{Q_s} = \frac{(\text{SAO}_2 - \text{MVO}_2)}{(\text{PVO}_2 - \text{PAO}_2)}$$

Since pulmonary veins are rarely entered during cardiac catheterization, a pulmonary catheter wedge sample or left atrial sample (if the left atrium is entered via an ASD) can be used in its place. Alternatively, arterial saturation (in the absence of a right-to-left shunt) can be substituted, or an assumed value of 98% may be used.

There are four factors that will help us understand this simplified equation. The first is that the difference in the arterial–venous oxygen saturations is systemic over pulmonary, despite the fact that the ratio is Q_p/Q_s . This is somewhat counter-intuitive, but a quick reference to the earlier flow equations will reveal the reason for this (i.e., cardiac output is inversely related to the difference in saturations).

The second factor is that the difference between the arterial and venous oxygen saturations in the Q_p equation is $PVO_2 - PAO_2$. This is because the difference is between oxygenated and unoxygenated blood. The anatomical pulmonary arteries carry unoxygenated blood and the pulmonary veins carry oxygenated blood, thus (oxygenated – unoxygenated) is equal to $(PVO_2 - PAO_2)$.

The third factor is the mixed venous oxygen saturation (MVO_2) in the Q_s equation. Different values should be used depending on where the shunt is located. The MVO_2 should be from the chamber preceding the shunt, thus if there is a VSD the average of samples from the RA should be used. If there is an ASD, the MVO_2 is calculated from the superior vena cava (SVC) and the IVC. While theoretically coronary sinus blood flow contributes to mixed venous blood along with blood from IVC and SVC, the contribution is so small as to be safely ignored. The equation most frequently used is $(3 \times \text{SVC} + \text{IVC})/4$. This is the most common, but certainly not the only calculation proposed as an appropriate estimate of the MVO_2 . At least six different calculations have been suggested as ways to estimate MVO_2 (see Table 7.3).

Lastly, this equation can be used to calculate the ratio of pulmonary blood flow to the systemic blood flow, but should not be confused as a measure of the actual shunt blood flow. Shunt flow can be determined by calculating Q_p and Q_s ; the shunt flow is the difference between the pulmonary and systemic flow, $Q_p - Q_s$. This can be useful in assessing the significance of the shunt.

Table 7.3 Determination of mixed venous oxygen saturation.

In the absence of an intracardiac shunt, the pulmonary artery provides a site of mixed venous blood. If there is a VSD, RA blood can be assumed to be mixed venous. In the presence of an ASD, mixed venous saturation needs to be estimated. In these cases, the formula most commonly used to determine mixed venous oxygen saturation is $MV = (3 \times SVC + IVC)/4$ (where MV = mixed venous, SVC = superior vena cava, and IVC = inferior vena cava). Formulas that have been advocated for estimating mixed venous oxygen saturation include:

First author	Year	Formula
Flamm	1969	$MV = (3 \times SVC + IVC)/4$
Iskandrian	1976	$MV = (2 \times SVC + IVC)/3$
Swann	1954	$MV = (SVC + 2 \times IVC)/3$
Barratt-Boyd	1957	$MV = (SVC + IVC)/2$
Miller	1974	$MV = IVC$
Goldman	1968	$MV = SVC$

Shunt management

Once a shunt has been detected, management varies depending on the severity and patient symptoms. Q_p/Q_s can be a very useful tool in making decisions about the need for repair of a shunt. The following numbers are generalizations about left-to-right shunts:

- A Q_p/Q_s of 1–1.5: observation is generally recommended.
- A Q_p/Q_s ratio of 1.5–2.0: significant enough that closure (either surgically or percutaneously) should be considered if the risk of the procedure is low.
- A Q_p/Q_s ratio of greater than 2: closure (either surgically or percutaneously) should be undertaken unless there are specific contraindications.

These recommendations are not absolutes and the entire clinical scenario should be considered along with these findings. Shunt flows can change over time. For example, left-to-right shunts via an ASD can increase with age as left atrial pressures rise in response to decreased left ventricular compliance. Alternatively, left-to-right shunts via an ASD can decrease in response to pulmonary hypertension.

Right-to-left shunting

Right-to-left shunting is unusual except in the case of Eisenmenger’s syndrome. In right-to-left shunting, the effective pulmonary flow is reduced by the amount of the shunt (flow through the pulmonary valve+flow through the shunt = flow through the

aortic valve). The amount of blood shunted as a percentage of cardiac output can be calculated using the Q_p/Q_s equation. In this case, the value will be less than 1. Other calculations that are useful in quantifying right-to-left shunts are shown in Table 7.2.

Sample case

The patient is a 50-year-old woman with hypertension and a known ASD. The ASD was detected 10 years ago and cardiac catheterization demonstrated a Q_p/Q_s ratio of 1.4:1. The ASD was not closed and the patient was lost to follow-up. She now returns with complaints of exertional dyspnea and paroxysmal atrial fibrillation and is referred for repeat cardiac catheterization to quantify the shunt. The following oxygen saturations were obtained:

SVC 69%
IVC 64%
RV 82%
PA 84%
FA 98%

Using the equations discussed in this chapter, we can determine the Q_p/Q_s ratio for this patient. The equations and calculations are shown here. Because the shunt is at the level of the atrium, the MVO_2 is calculated from the SVC and IVC saturations:

$$MVO_2 = \frac{[(3 \times \text{SVC}) + (1 \times \text{IVC})]}{4}$$

$$MVO_2 = \frac{[(3 \times 69) + (1 \times 64)]}{4}$$

$$MVO_2 = \frac{(207 + 64)}{4}$$

$$MVO_2 = \frac{271}{4}$$

$$MVO_2 = 67.75$$

With the MVO_2 calculated, the other variables are obtained directly from the collected oxygen saturations:

$$\frac{Q_p}{Q_s} = \frac{(\text{SAO}_2 - \text{MVO}_2)}{(\text{PVO}_2 - \text{PAO}_2)}$$

$$\frac{Q_p}{Q_s} = \frac{(98 - 68)}{(98 - 84)}$$

$$\frac{Q_p}{Q_s} = \frac{(30)}{(14)}$$

$$\frac{Q_p}{Q_s} = 2.2$$

This case illustrates an ASD with a significant left-to-right shunt developing over the course of many years. The magnitude of left-to-right shunting is determined primarily by the relative compliance of the two ventricles. Because of this individual's hypertension and the aging process, her left ventricular compliance decreased over time, resulting in increased left-to-right shunting.

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PART II

Valvular heart disease

 **2025** Edition

CHAPTER 8

Aortic stenosis

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[Revised for the 3rd edition by George A. Stouffer]

The basic function of the aortic valve is to separate the aorta from the left ventricle cavity during diastole. At peak left ventricular (LV) ejection the aortic valve opens briskly to an average area of 4 cm². In rare conditions, there can be obstruction of forward flow that can occur either at the subvalvular level (e.g., subaortic membrane or hypertrophic obstructive cardiomyopathy) or supra-ventricular (e.g., Noonan's syndrome). However, the overwhelming majority of cases are due to valvular stenosis. Pathologic thickening and fusion of the aortic valve leaflets results in restricted leaflet mobility and a decrease in the effective aortic valve area, leading to aortic valve stenosis (in this chapter, we will use the abbreviation AS to refer to aortic valvular stenosis).

The etiology of aortic valve disease in developed countries has changed dramatically in the last few decades. With the aging of the population and concurrent decrease in rheumatic fever, degenerative calcific AS is now by far the most common cause of AS and AS is the most common nonrheumatic valvular heart disease, affecting 2–5% of adults over 65 years [1]. There is evidence that AS has similar histological findings to atherosclerosis with lipid infiltration and inflammation, but statin drugs have been largely ineffective in slowing the progression of AS in clinical studies. A congenitally malformed (bicuspid) aortic valve is one of the most common congenital cardiac defects and is currently the second most common underlying lesion in AS.

As aortic valve disease progresses and the valve orifice narrows, resistance to blood flow increases. In order to maintain stroke volume, the velocity of blood exiting the LV increases and a pressure gradient develops from the LV to the aorta (Figure 8.1). This leads to elevations in LV systolic pressure and this “pressure overload” of the LV leads in turn to compensatory concentric LV hypertrophy. This adaptation allows the LV to generate the necessary pressure to maintain cardiac output but can lead to diastolic LV dysfunction, impaired coronary perfusion, and eventually LV systolic dysfunction.

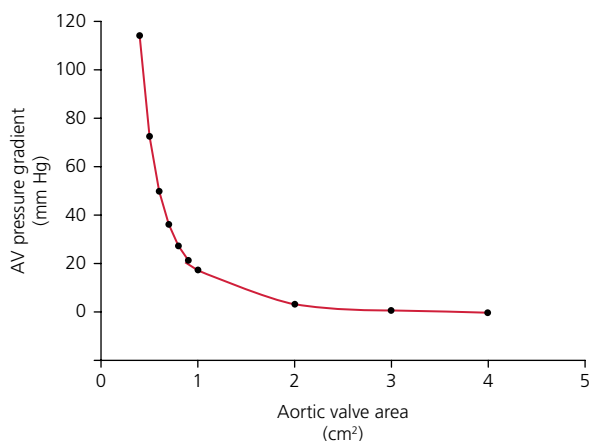


Figure 8.1 AV pressure gradient versus aortic valve area in a hypothetical patient with cardiac output = 5 L/min, HR = 80 bpm, and systolic ejection period (SEP) = 0.33 sec.

Progressive increase in the pressure gradient across the aortic valve and cardiac (mal)adaptation explain the stages of hemodynamic findings that patients go through as progresses. In mild AS, intracardiac pressures and cardiac output will appear normal. As the valve becomes more stenotic, the patient may have normal hemodynamic findings at rest but may be unable to increase cardiac output during exercise. Progressive narrowing of the valve leads to decreased stroke volume and cardiac output, even at rest. In moderate to severe AS, patients will develop elevated left atrial pressures in response to increases in LV end-diastolic pressure. In a minority of patients, LV systolic failure also occurs, which may lead to further elevation in intracardiac pressures.

It is important to remember that the pressure gradient across the aortic valve increases exponentially (not linearly) with decreasing aortic valve area. Thus, in patients with severe AS, small changes in aortic valve area can lead to large changes in hemodynamics (Figure 8.1). A meta-analysis of 24 studies that included 5450 patients with AS found an annualized progression of the mean gradient of +4.1 mm Hg, aortic valve area of -0.08 cm^2 , peak velocity of 0.2 m/s and peak gradient of 7.9 mm Hg. Increasing baseline severity of AS was predictive of higher rates of progression for mean gradient and peak velocity [2].

Adaptive mechanisms of the LV and circulation allow most patients to remain asymptomatic until marked narrowing of the aortic valve orifice occurs. The prognosis of patients with asymptomatic severe AS is good, with a low risk of sudden death rate [3, 4]. The onset of symptoms, however, heralds a marked change in the natural history of AS, with poor outcomes unless the patient undergoes aortic valve replacement. The classic clinical presentation of severe AS is typically an insidious onset of any of the triad of effort angina, exertional syncope, or dyspnea [5]. The average survival in untreated patients with severe AS is classically

thought to be 2, 3, or 5 years after the onset of heart failure, syncope, or chest pain, respectively. Importantly, many patients report being asymptomatic, although careful questioning reveals that they have gradually decreased their level of activity and would, in fact, be symptomatic at their previous level of exertion. Extensive questioning, often involving a family member, is imperative. Occasionally, careful exercise treadmill testing can be useful in the nominally “asymptomatic” patient.

Physical examination

The physical examination of patients with AS can often be helpful in predicting which patients have hemodynamically severe disease. A low-volume, late-onset arterial pulse, referred to as *parvus et tardus*, is often present in severe AS. This finding can be appreciated on palpation of the carotid upstroke. It may not be manifest in the elderly owing to a noncompliant vasculature. Other physical findings include a systolic murmur that is crescendo–decrescendo in intensity. The duration will vary with the severity of disease, but the murmur always begins after S1 and ends prior to S2. The timing of the loudest portion of the murmur correlates with the severity of AS, with late-peaking murmurs being more common in critical AS. The murmur is generally heard best in the right second intercostal space and can radiate to the carotid arteries. A diminished aortic component of the second heart sound is not uncommon and the second heart sound can also split paradoxically in severe AS (delayed aortic component with narrowing of the splitting with inspiration). Elderly patients with heavily calcified valves may develop systolic murmurs that radiate prominently to the apex (Gallavardin’s phenomenon). Physical exam findings that are suggestive of severe AS include diminished carotid pulses, late-peaking systolic murmur, and absent aortic component of the second heart sound; however, it is important to realize that even in experienced hands the physical exam can be unreliable in terms of quantifying AS severity (see Table 8.1).

Table 8.1 Findings during physical examination of severe AS.

-
- Parvus et tardus pulse (low amplitude, delayed upstroke)
 - Sustained LV impulse
 - Late-peaking systolic murmur (although murmur can be absent)
 - Diminished or absent aortic component of the second heart sound
 - Paradoxical splitting of the second heart sound
 - Prominent fourth heart sound
 - Gallavardin’s phenomenon (radiation of murmur to the apex in the elderly)
-

Echocardiographic hemodynamics

Echocardiographic evaluation of aortic valve disease has greatly facilitated the management of these patients [6–8]. Two-dimensional (2D) echo provides important information about valve morphology (Figure 8.2) and LV function as well as important prognostic ancillary findings, such as degree of LV hypertrophy, presence of mitral regurgitation, and pulmonary artery pressures.

Flow through a stenotic AV is well approximated by flow through a convergent orifice (e.g., a nozzle), which causes acceleration of blood velocity as it passes from the LV outflow tract (LVOT) through the stenotic valve. The point of maximum velocity is termed the vena contracta (VC) of the jet and the area of the flow jet at the VC is known as the effective orifice area (EOA). Doppler evaluation enables the noninvasive measurement of blood flow velocity with estimation of aortic valve gradient and valve area. The LV–aortic pressure gradient is estimated by measuring blood flow velocity across the aortic valve and then using the Bernoulli equation to determine pressure gradient.

The primary hemodynamic parameters measured by echocardiography in patients with AS are (1) maximum systolic velocity across the aortic valve measured using continuous-wave Doppler; (2) mean aortic valve pressure gradient; and (3) aortic valve area as determined by continuity equation.

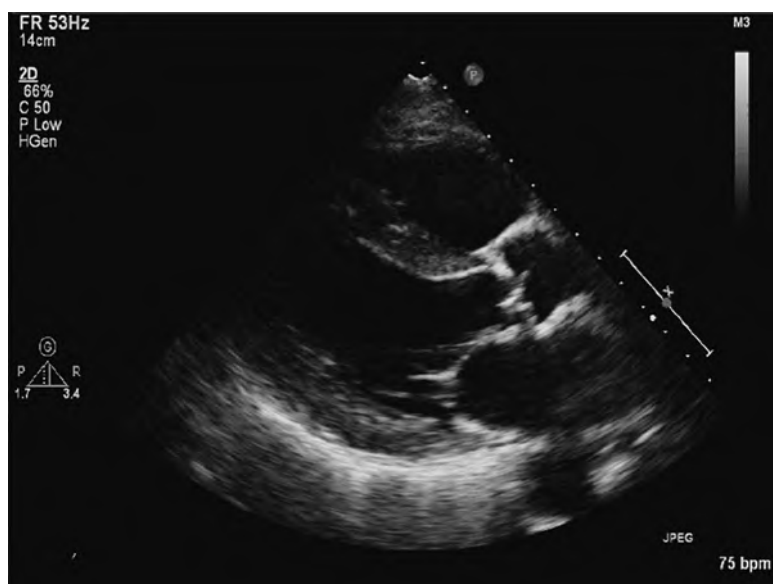


Figure 8.2 2D echocardiographic still frame in the parasternal long axis in a 73-year-old male with severe AS. Note the calcified aortic valve and left ventricular (LV) hypertrophy.

Maximum systolic velocity should be measured using multiple views, a time scale on the x-axis of 100 mm/s, and a gray scale that allows visual separation of noise from the true velocity signal. In severe AS, the continuous-wave Doppler curve is generally more rounded, reflecting a high gradient throughout systole. A few additional caveats: (1) it is essential to measure velocity parallel to blood flow, as significant deviation results in velocity underestimation (underestimation is 5% or less if the intercept angle is within 15° of parallel); (2) avoid recording the continuous-wave Doppler signal of an eccentric mitral regurgitation jet; and (3) be careful of interpreting maximum velocity in the setting of irregular rhythms.

Mean transaortic pressure gradient is the average difference in pressure between the LV and aorta during systole. Peak velocity and mean gradient provide independent information regarding AS severity, with the relationship depending on the shape of the velocity curve. The mean gradient is calculated by averaging the instantaneous gradients over the ejection period followed by calculation of pressure from velocity using a simplification of the Bernoulli equation:

$$\Delta P = 4v^2$$

The mean transaortic gradient is easily measured with current echocardiography technology, but it is important to remember that the assumptions in the simplified Bernoulli equation include that (1) viscous losses and local acceleration effects are negligible; (2) there is an approximation for the constant that relates to the mass density of blood; and (3) the velocity in the proximal portion of the LVOT can be ignored, a reasonable assumption only when the proximal velocity is <1.5 m/s and the aortic velocity is ≥ 3.0 m/s. Also the effects of pressure recovery, the conversion of kinetic energy into potential energy with a corresponding increase in pressure distal to a stenosis, are ignored, but these are generally small unless aortic diameter is <3 cm.

Maximum velocity and mean pressure gradients across a stenotic aortic valve are both flow-dependent. In contrast, aortic valve area is independent of the conditions in which it is measured (at least in theory). When using echocardiography, aortic valve area is calculated based on the continuity equation, which was derived based on the assumption that the stroke volume flowing through the LVOT and the stenotic aortic valve are the same (Figure 8.3). Because volume flow rate at any point in the LVOT is equal to the cross-sectional area times velocity over the systolic ejection period (SEP) (the velocity time interval of the systolic velocity curve), the equation can be solved for aortic valve area:

$$AVA = \frac{CSA_{LVOT} \times VTI_{LVOT}}{VTI_{AV}}$$

$$\text{and } CSA_{LVOT} = \pi \left(\frac{D}{2} \right)^2$$

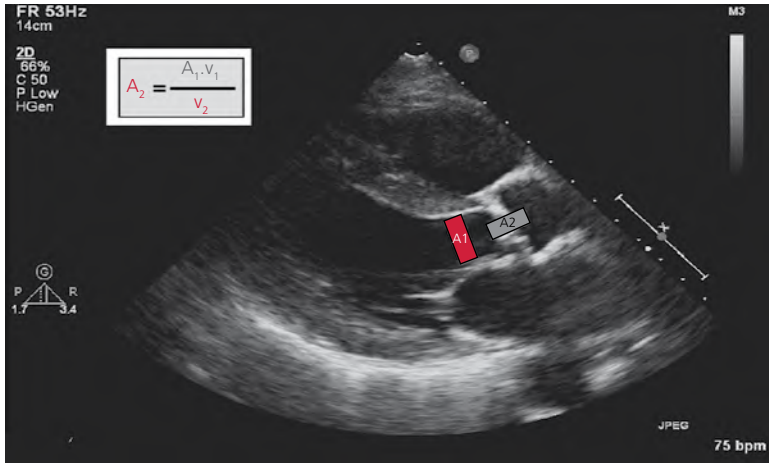


Figure 8.3 The image from Figure 8.2 is used to show the underlying assumption for the continuity equation: the amount of blood flowing through area 1 = the amount of blood flowing through area 2.

where

CSA = cross-sectional area

D = diameter

VTI = velocity time integral.

In practice, determination of aortic valve area by the continuity equation requires measurement of velocity across the aortic valve by continuous-wave Doppler, LVOT diameter, and LVOT velocity by pulse-wave Doppler. There are several important caveats to keep in mind: (1) LVOT diameter and velocity measurements should be made at the same distance from the aortic valve; (2) the LVOT becomes progressively more elliptical (the equation assumes that the LVOT is circular) near the valve in many patients; and (3) this method assumes laminar flow in the LVOT, which may not be valid if there is dynamic subaortic obstruction, a subaortic membrane, or significant aortic regurgitation (AR). Despite these limitations, continuity equation valve area calculations have been well validated [6–8].

A simplified continuity equation can be used, although there tends to be more variability when using maximum velocities rather than velocity time integral (VTI). The simplified equation assumes that the shape of the velocity curve in the LVOT and aorta are similar, so that the ratio of LVOT VTI to aortic valve VTI is identical to the ratio of the LVOT maximum velocity to aortic valve maximum velocity:

$$AVA = \frac{CSA_{LVOT} \times V_{LVOT}}{V_{AV}}$$

Dimensionless index (DI) is another commonly used echocardiographic measurement of severity of AS. **DI** is the ratio of the VTI of the LVOT to the VTI in the aortic valve (as above, measurement of velocity across the aortic valve is

generally by continuous-wave Doppler and measurement of LVOT velocity is by pulse-wave Doppler).

$$\text{Dimensionless index (DI)} = \frac{\text{VTI in the LVOT}}{\text{VTI at the aortic valve}}$$

DI represents the size of the valvular orifice as a proportion of the LVOT cross-sectional area and does not require a measurement of LVOT cross-sectional area, which is a source of error in the estimation of AVA. In general, the relationship between DI and AS severity is as follows:

	DI
Mild aortic stenosis	>0.5
Moderate aortic stenosis	0.25–0.50
Severe aortic stenosis	<0.25

Other hemodynamic measurements of AS such as energy-loss index, AV resistance, valvuloarterial impedance, and LV stroke loss are less commonly used.

Determination of severity of AS by echocardiography

Echocardiography grading of AS severity is based on maximum velocity, mean gradient, and valve area. General guidelines for determining mild, moderate, and severe AS set forth by the American College of Cardiology/American Heart Association (ACC/AHA) are listed in Table 8.2.

Table 8.2 Quantification of AS severity based on echocardiographic measurements as delineated in the AHA/ACC guidelines.

	Mild	Moderate	Severe
Aortic jet velocity (m/s)	2.6–2.9	3.0–4.0	>4.0
Mean gradient (mm Hg)	<20	20–40	>40
AVA (cm ²)	>1.5	1.0–1.5	<1.0
Indexed AVA (cm ² /m ²)	>0.85	0.60–0.85	<0.6

Comparison between invasive and echocardiographic measurements of hemodynamics

It is common for different aortic valve pressure gradients to be reported by the echocardiographic laboratory and the cardiac catheterization laboratory in the same patient (Figure 8.4) [9]. This has led to the common misconception that AV gradients vary depending on whether echocardiography or left heart catheterization is used and that there is a poor correlation between hemodynamics found in the catheterization laboratory and in the echocardiographic laboratory. This misconception is based on comparing apples to oranges. In the catheterization laboratory, gradients are commonly expressed as “peak to peak” (the difference between the maximum LV systolic pressure and the maximum aortic systolic pressure), whereas the echocardiographic laboratory reports peak instantaneous gradients (Figure 8.4). Maximum LV and aortic pressure do not occur at the same time and thus peak-to-peak gradient measured during cardiac catheterization is a nonphysiologic measurement that does not have any echo correlate.

Another common misconception is that peak-to-peak pressure defines the maximum pressure difference; this is not the case, as the peak-to-peak difference is always less than the maximum instantaneous pressure difference. The Doppler-derived mean gradient obtained from the VTI correlates well with cardiac catheterization mean gradients. Likewise, the peak Doppler-derived gradient by echo correlates well with the peak instantaneous transvalvular gradient at cardiac catheterization (although this is rarely calculated or reported).

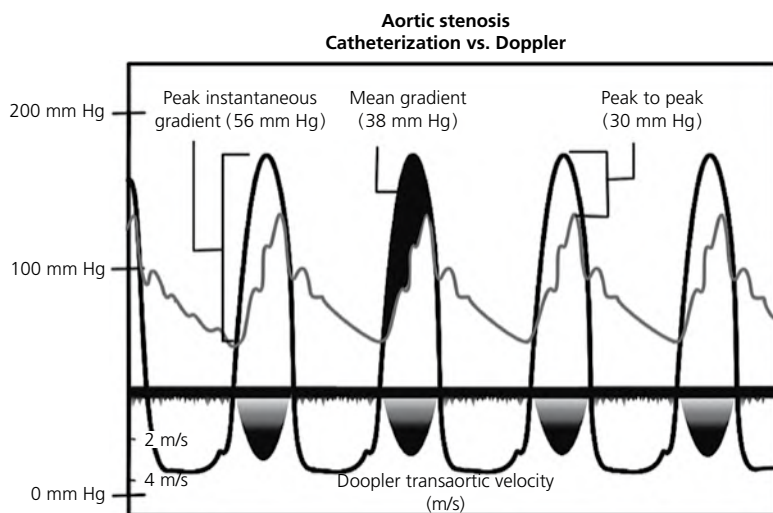


Figure 8.4 Comparison of invasive and echocardiographically derived hemodynamics in a hypothetical patient with AS. Source: Courtesy of Jatin Joshi.

Invasive hemodynamics

Hemodynamic findings associated with AS include fixed LVOT obstruction at the aortic valve and diastolic dysfunction. In contrast to a dynamic LVOT obstruction (e.g., hypertrophic obstructive cardiomyopathy), the aortic valve gradient will increase with preload enhancement and thus pulse pressure will increase after a PVC (negative Brockenbrough sign). Over time, the left ventricle in patients with AS hypertrophies in response to the pressure overload. Increased wall thickness causes the left ventricle to become stiffer and less compliant and thus higher end-diastolic pressures are required to maintain LV filling. This, in turn, leads to higher left atrial pressures and elevated pulmonary capillary wedge pressures. PA pressures are normal or only mildly elevated early in the disease and increase as LV failure (both systolic and diastolic) worsens.

In the catheterization laboratory, the calculation of aortic valve area is traditionally performed using the Gorlin formula. This formula was initially derived in the early 1950s in patients with mitral stenosis [10]. Although the Gorlin formula is seemingly straightforward, there are a number of potential pitfalls and meticulous detail is necessary to obtain an accurate estimation of aortic valve area.

The Gorlin formula requires measurement of cardiac output, heart rate, SEP, and *mean* transvalvular gradient. The transvalvular gradient requires simultaneous LV and aortic pressure measurement (Figure 8.5). The cardiac output can be obtained either by the thermodilution method or the Fick method (in many cases both are used). The SEP extends from when the aortic valve opens (i.e., intraventricular pressure rises above aortic pressure) and ends with aortic valve closure.

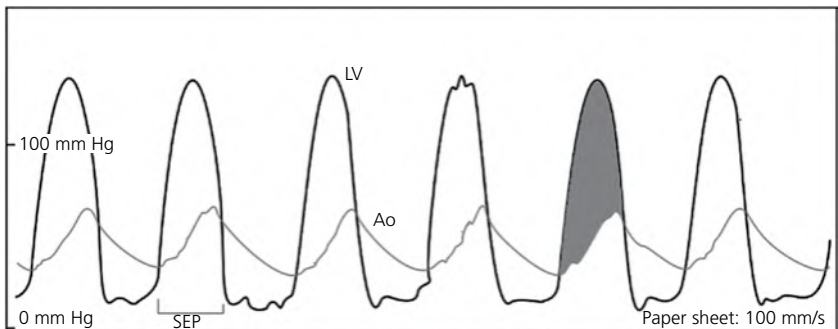


Figure 8.5 Simultaneous LV–aortic pressure tracings with SEP and systolic transvalvular gradient (shaded area) indicated.

Gorlin formula for estimating aortic valve area

$$AVA(\text{cm}^2) = \frac{CO / (SEP)(HR)}{44.3 \times \sqrt{\text{mean pressure gradient}}}$$

CO = cardiac output (mL/min); HR = heart rate; SEP = systolic ejection period (s/beat);
44.3 = constant.

Clinical pearl

Aortic valve area can be estimated in patients with severe AS by dividing the cardiac output by the square root of the peak-to-peak systolic pressure gradient measured in the catheterization laboratory. This is the so-called Hakki formula [11, 12]:

$$AVA(\text{cm}^2) = \frac{CO(\text{L/min})}{\sqrt{\text{peak LV systolic pressure} - \text{peak aortic systole pressure}}}$$

Common pitfalls

There are many common pitfalls in the estimation of aortic valve area in the catheterization laboratory:

- Peripheral amplification (physiological phenomenon that is characterized by widening of pulse pressure in peripheral arteries compared to central aorta due to reflection of pressure waves)
- Aortoiliac stenosis if femoral artery pressure is being compared to left ventricular pressure
- Aortic regurgitation
- Low-gradient AS (see below)
- Poor-fidelity LV tracing

It is best to use simultaneous LV and ascending aortic pressures when determining the invasive hemodynamics of AS. If femoral artery pressure is used as a surrogate for central aortic pressure, obtaining the true LV–aortic gradient can be challenging in patients with peripheral amplification or with peripheral vascular disease. Peripheral amplification refers to the increase in peak systolic pressure and pulse pressure in peripheral arteries as compared to the central aorta (Figure 8.6; see also Chapter 4). It is important to account for peripheral amplification because determination of AV gradient by comparing femoral artery and LV pressure will underestimate transvalvular gradient compared to a simultaneous recording of LV and aortic pressure.

In contrast, the presence of iliac artery disease causing decreased femoral artery pressures will result in overestimation of the severity of AS if a comparison is made between femoral artery and LV pressure (Figure 8.7). It is essential to

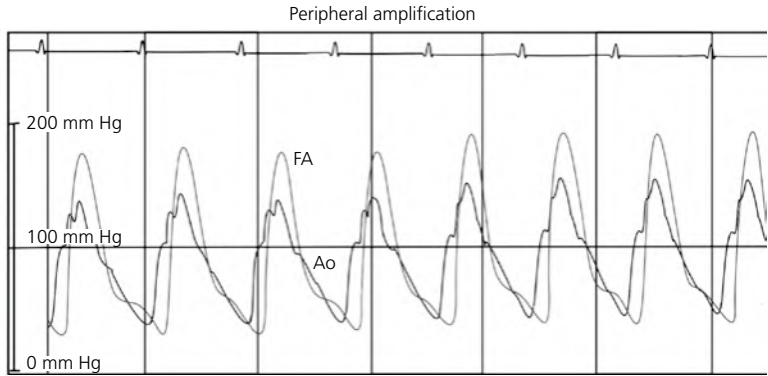


Figure 8.6 Simultaneous measurement of aortic and femoral artery pressure demonstrating peripheral amplification.

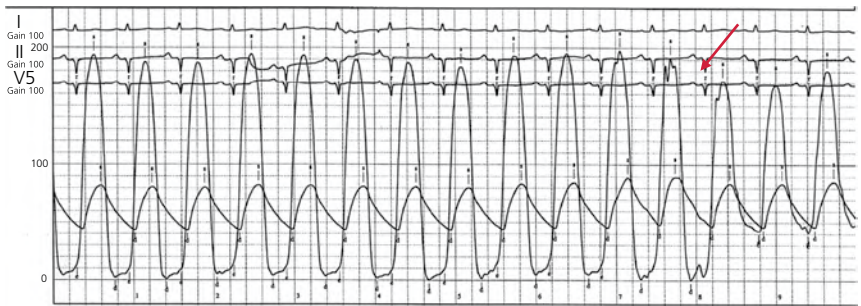


Figure 8.7 Simultaneous recording of LV and right femoral artery pressure followed by a pullback of LV catheter to aorta. The patient is a 65-year-old male with mild AS by echo. Note that there is a significant pressure gradient between LV and right femoral artery, but that most of the gradient persists even after the LV catheter is pulled back into the aorta (there is a ~20 mm Hg gradient between LV and aorta consistent with mild AS; shown by the arrow). This demonstrates that the pressure gradient is primarily due to an obstruction between the ascending aorta and right femoral artery. In this case, the patient had an 80% right common iliac artery stenosis.

measure femoral artery and central aortic pressure simultaneously to confirm that there is no significant peripheral obstruction if femoral artery pressure is used to determine the severity of aortic valve disease. Potential pitfalls in utilizing femoral artery pressure to measure aortic valve gradient can be remedied by using either a pressure wire or a double-lumen pigtail, thus allowing simultaneous measurement of LV and central aortic valve pressure. Another approach is to use a long sheath that enables comparison of LV and distal aortic pressure.

Careful attention to detail and examination of the fidelity of the LV waveform are imperative. It is not uncommon to find LV–aortic tracings in which the side holes of the pigtail catheter are in the aorta; this will lead to underestimation of the true valve gradient and overestimation of the valve area. Another potential

source of error is shown in Figure 8.8. In this case, a pigtail catheter is “pulled back” from the LV to the aorta. A comparison of systolic pressures indicates a 40 mm Hg difference between the last beat in the LV and the first in the aorta (Figure 8.8). More careful examination, however, revealed that the heart rate had slowed. Within five beats, the aortic systolic pressure was the same as that observed in the LV. In general, catheter pullback across the aortic valve is a suboptimal way to measure aortic valve gradients.

Another potential mistake is illustrated in Figure 8.9. There appears to be a 40–50 mm Hg gradient between LV and femoral artery and on catheter pullback

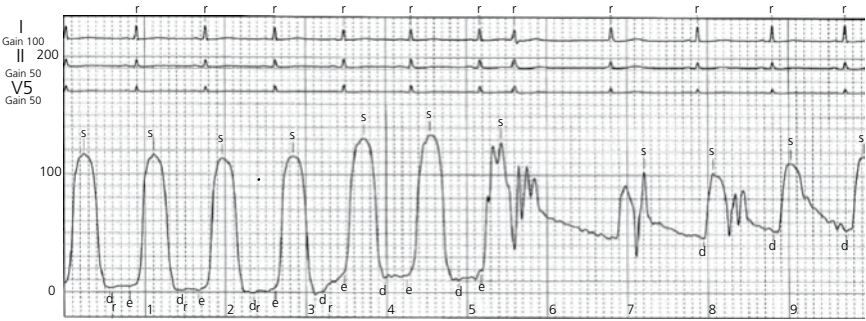


Figure 8.8 Pullback of pigtail catheter from LV to aorta.



Figure 8.9 Pullback of pigtail catheter from LV to aorta while simultaneously measuring pigtail and femoral artery pressure.

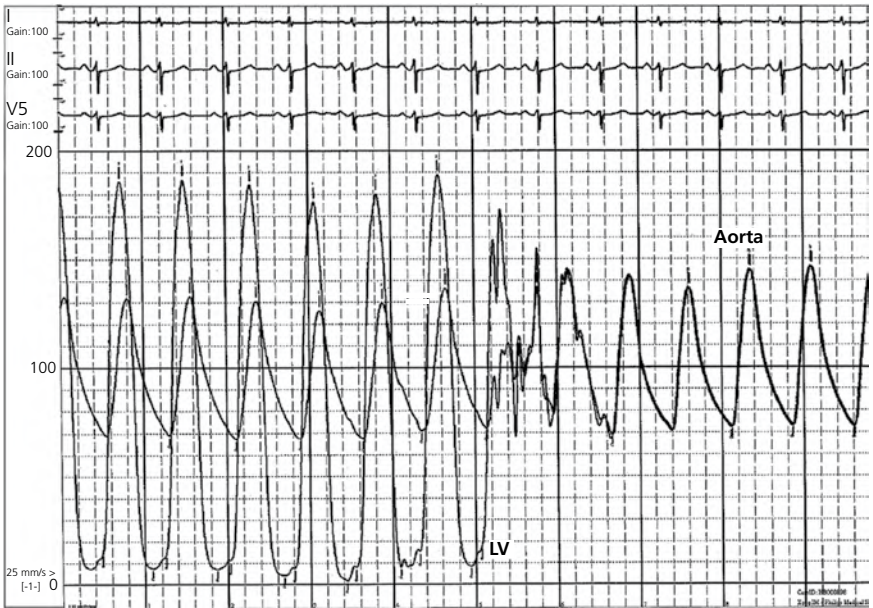


Figure 8.10 Carrabello's sign. Pullback of pigtail catheter from LV to aorta while simultaneously measuring aortic pressure in a 63-year-old male with severe AS (aortic valve area of 0.5 cm^2). Note the small rise in aortic pressure when the catheter is removed from the LV.

the gradient resolves. Closer inspection, however, revealed that the femoral artery pressure increased following pullback and now corresponded with LV systolic pressure. The cause of the pressure gradient in this patient was an obstruction in the femoral artery sheath that was dislodged with manipulation of the catheter. Of note is that while aortic pressure can increase following removal of a catheter from the left ventricle in severe AS (Carrabello's sign; discussed in what follows and shown in Figure 8.10), it is never this dramatic and aortic systolic pressure will always be less than LV systolic pressure.

The challenge of low-gradient AS

One-third of patients with severe AS have a calculated AVA $<1.0 \text{ cm}^2$ but with a mean gradient $<40 \text{ mmHg}$ and maximum velocity $<4 \text{ m/s}$ [13–15]. While low-gradient AS is often seen in patients with LV dysfunction (defined as low-flow low-gradient AS), low gradient can also be seen in patients with LV ejection fraction $\geq 50\%$ (defined as paradoxical low-flow, low-gradient AS). Low gradient is due to decreased cardiac output which depresses the transvalvular gradient as the gradient is flow-dependent. In both classical and paradoxical low-flow, low-gradient AS, it can be difficult to differentiate a true-severe from a pseudo-severe

stenosis. This is an important diagnostic dilemma because in true low-flow, low-gradient AS, aortic valve replacement will decrease afterload resulting in an improvement in cardiac output and LV ejection fraction. A discussion of aortic valve replacement in low-gradient AS can be found in chapter 9.

Classical low-flow, low-gradient AS

This entity is found in about 5–10% of the patients with severe AS and it is characterized by a reduced LVEF (<50%) and a discordance between the aortic valve area (AVA<1 cm² and/or <0.6 cm²/m²) and the mean gradient (<40 mm Hg). In patients with low cardiac output and a small pressure gradient across the aortic valve, calculation of aortic valve area with the Gorlin formula can be problematic. The fundamental question in these patients is whether true severe AS coexists with secondary LV systolic dysfunction, or alternatively, whether the low gradient is due to a low cardiac output from the cardiomyopathy and the valve stenosis is minimal. Differentiating these two entities is critical, as the former may respond favorably to aortic valve replacement whereas the latter does not.

Increasing cardiac output pharmacologically (typically with dobutamine or nitroprusside), either in the catheterization laboratory or during echocardiography, can be helpful in this regard (Figure 8.11). Patients with true severe AS who will likely improve with aortic valve replacement manifest contractile reserve

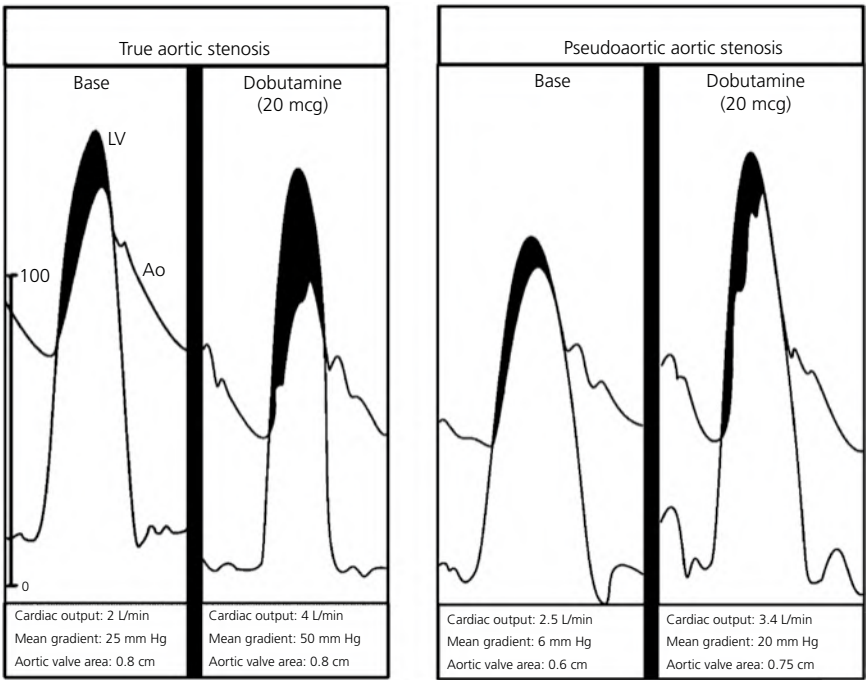


Figure 8.11 Effects of dobutamine infusion in patients with and without valvular aortic stenosis.

(25% increase in stroke volume) and/or show an increase in their transvalvular gradient and cardiac output with no change or a decrease in the calculated aortic valve area. In contrast, patients with pseudo AS will not have contractile reserve, will not significantly increase their LV–aortic pressure gradient, and will often have an increase in calculated aortic valve area with dobutamine. These latter patients typically have myocardial disease as their primary lesion and “incidental” AS. They do not respond favorably to aortic valve replacement.

Paradoxical low-flow, low-gradient AS

This entity is found in 10–25% of patients with AS and is defined as a LVEF $\geq 50\%$, LV stroke volume index (SVI) $< 35 \text{ mL/m}^2$, AVA $\leq 1 \text{ cm}^2$ and $\leq 0.6 \text{ cm}^2/\text{m}^2$, and mean gradient $< 40 \text{ mm Hg}$. In these patients, the LV is generally small with pronounced LV concentric remodeling and diastolic dysfunction. Other factors may also contribute to the reduced stroke volume including atrial fibrillation, mitral regurgitation, and/or other valvular heart disease. As in patients with classical low-flow, low-gradient AS, dobutamine stress echocardiography may be useful to differentiate true- versus pseudo-severe stenosis. A study of 41 patients with severe, symptomatic AS using pressure-volume loops found that paradoxical low-flow, low-gradient AS was characterized by small LV volumes, decreased cardiac index, decreased systolic contractility and lower stroke work, than high-gradient AS. They further found that the hemodynamics of paradoxical low-flow, low-gradient AS was primarily explained by two mechanisms: (1) a small, stiff left ventricle with reduced contractility, and (2) increased afterload due to increased arterial stiffness, similar to findings observed in patients with heart failure with preserved ejection fraction [16]. Thus, many patients with paradoxical low-flow, low-gradient AS can be regarded as having two independent resistors in series, one at the valve level and one due to increased arterial resistance. Lowering the systemic blood pressure in these patients is very important as it can result in a dramatic reduction in LV filling pressures, independent of the AS [17].

A study of 11 patients with paradoxical low-flow, low-gradient AS who underwent transcatheter aortic valve replacement, found that these patients had more severe symptoms, a greater prevalence of hypertension, lower total systemic arterial compliance, and higher effective arterial elastance than a control group of 29 patients with high-gradient AS. Following TAVR, low-flow, low-gradient patients had a greater increase in SVI with an inverse linear relationship observed between baseline SVI and change in SVI with TAVR [18].

The challenge of estimating aortic valve area in patients with AS and significant AR

Another major challenge is accurate calculation of aortic valve area in patients with concurrent AR. The problem lies in the numerator of the Gorlin equation; namely the accurate determination of flow across the aortic valve. Commonly

used ways to estimate cardiac output such as Fick and thermodilution measure effective and right-sided cardiac output, respectively, and thus will underestimate the flow across the aortic valve (flow across the aortic valve = cardiac output + regurgitant volume) and overestimate the severity of AS.

Case study

A 70-year-old man with 3 months of progressive chest pain presents with loss of consciousness while ascending a hill. Examination reveals a blood pressure of 136/80 mm Hg and a delayed carotid upstroke. The second heart sound is split paradoxically. There is a late-peaking systolic murmur heard best at the right upper sternal border radiating to the carotids. A technically difficult 2D echo demonstrates a calcified trileaflet aortic valve with decreased leaflet mobility, normal left ventricular function, and severe LV hypertrophy. Doppler evaluation demonstrated an aortic velocity of 4 m/s corresponding to a peak instantaneous gradient of 64 mm Hg and a mean gradient of 50 mm Hg.

Invasive hemodynamics are shown in Figure 8.12. Note the large mean transvalvular gradient of 110 mm Hg and slow upstroke of the aortic tracing. A cardiac output of 4.2 L/min, with a systolic ejection period of 0.33 s/beat at a heart rate of 70 bpm, yields the following in the Gorlin equation:

$$AVA = \frac{(4200 \text{ mL/min}) / (70 \text{ beats/min})(0.33 \text{ s/beat})}{44.3\sqrt{110}}$$

$$AVA = 0.4 \text{ cm}^2$$

This patient went on to aortic valve replacement and recovered fully.

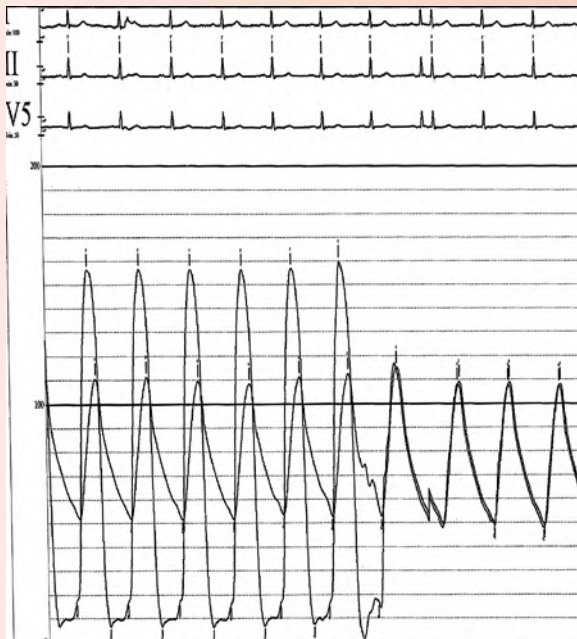


Figure 8.12 LV to aortic pullback of a pigtail catheter with simultaneous measurement of femoral artery pressure. Source: Courtesy of Cardioville.com.

Carabello's sign

In patients with AS, Carrabello's sign is defined as a rise in peak aortic systolic pressure by greater than 5 mm Hg when a catheter is removed from the left ventricle (Figure 8.10). This phenomenon occurs in the setting of a highly stenosed valve because the additional occlusive effect of the catheter across the valve is enough to further decrease aortic pressure. Carrabello and colleagues found this sign in 15 of 20 patients with $AVA < 0.6 \text{ cm}^2$ and in none of 22 patients with $AVA > 0.7 \text{ cm}^2$ [8].

Subaortic membrane

Obstruction within the LVOT below the aortic valve can be either fixed or dynamic. Dynamic subvalvular stenosis is primarily due to hypertrophic cardiomyopathy (reviewed in Chapter 15). Fixed obstruction can be due to a thin membrane that is attached to the ventricular septum or completely encircles the LVOT (Figure 8.13). Rarely, subvalvular AS is due to a thick fibromuscular ridge, diffuse obstruction, abnormal attachment of the mitral valve, or accessory endocardial cushion tissue. Clinically significant AS is rare in adults and is often found in patients with prior history of resection while in infancy or childhood.



Figure 8.13 Subaortic membrane in a 31-year-old female with hypertension and tobacco abuse who was diagnosed with a possible subaortic membrane at the age of 2. She presented with exertional dyspnea and several episodes of near syncope. She had class III symptoms with dyspnea when walking across a room. This tracing is recorded as an endhole catheter is slowly pulled back from the apex of the LV to the aorta (with simultaneous continuous monitoring of aortic pressure). Note that there is a portion of the tracing when the systolic pressure decreases but there is still a ventricular waveform as the catheter is pulled back across the membrane. In the next portion of the tracing, the catheter is still in the LV but there is minimal systolic gradient between LV and aorta; this is the portion of the left ventricle between the membrane and the aortic valve.

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CHAPTER 9

Hemodynamics of transcatheter and surgical aortic valve replacement

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Cassandra J. Ramm

Aortic valve replacement (AVR) is the only definitive therapy for the treatment of severe aortic valve stenosis (AS). As the proportion of the US population over the age of 65 years expands, the prevalence of degenerative calcific AS is growing rapidly. The 2020 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines list AVR as a class I therapy for the treatment of severe symptomatic AS [1]. Indeed, AVR in patients with progressive symptoms, such as heart failure, angina, syncope, or left ventricular dysfunction, can not only dramatically improve a patient's quality of life, but is also a life-saving procedure. Contemporary data demonstrate the ineffectiveness of medical treatment of severe symptomatic AS with an average life expectancy of approximately one year for patients with heart failure due to severe AS in the absence of valve replacement [2].

For decades, the only option for AVR was open-heart surgery, usually through a median sternotomy incision requiring cardiopulmonary bypass. Unfortunately, many of the patients with severe AS are older and frail, with multiple comorbidities that make them high or even prohibitive risk for surgical AVR (SAVR). Thankfully, over the last two decades, a new therapeutic option, minimally invasive transcatheter AVR (TAVR), has emerged as a viable alternative for these patients. Data from large randomized controlled trials comparing TAVR to SAVR demonstrated 1-year mortality rates with TAVR that are comparable to, or even lower than, those seen with SAVR [3–6]. The uptake of TAVR as a treatment option for severe AS has been brisk and this therapy is now approved by the Food and Drug Administration in the United States for use in patients across the surgical risk spectrum, including low risk, intermediate risk, and high surgical risk patients in addition to those considered inoperable.

Selection of appropriate patients

A successful outcome with TAVR starts with appropriate patient selection. The TAVR devices currently approved for use in the United States are designed to treat calcific AS and are less well suited to treating other forms of aortic valve disease. In particular, pure aortic valve insufficiency, heavily calcified and dysmorphic bicuspid aortic valves, and disrupted aortic valves from ascending aortic aneurysms or dissections are best treated surgically, albeit with some exceptions.

In general, patients who are candidates for AVR are those who have symptoms attributable to AS and meet the criteria for severe AS, defined as having an aortic valve area (AVA) of $<1.0\text{ cm}^2$ and either a mean aortic valve gradient above 40 mm Hg or jet velocity across the aortic valve of at least 4.0 m/s. The severity of AS can be determined by measuring simultaneous left ventricular and aortic pressure or by echocardiography, which uses Doppler ultrasound to determine jet velocity across the stenotic valve as well as mean and peak aortic valve gradients. Further details on the hemodynamic assessment of AS are provided in Chapter 8.

Low-flow–low-gradient aortic stenosis

An increasingly recognized form of AS is low-flow–low-gradient (LFLG) severe AS. Classical low-flow–low-gradient severe aortic valve stenosis is characterized by a depressed left ventricular ejection fraction (LVEF), an AVA $<1.0\text{ cm}^2$, and a mean aortic gradient $<40\text{ mm Hg}$. Because the transvalvular aortic pressure gradient, as estimated by echocardiography, is dependent upon the square of the measured velocity across the valve, a low flow state (e.g., as seen in systolic heart failure) can significantly diminish the pressure gradient despite the presence of severe AS. These patients often have a dilated left ventricle secondary to the aortic valve pathology and they represent approximately 5–10% of the total patients evaluated with severe AS [7].

Pseudo-severe AS is a condition where there is minimal aortic valve disease in the setting of severe cardiomyopathy. Echocardiographic assessment reveals poor aortic valve leaflet mobility, which is primarily due to the myocardial disease and low flow rather than inherent calcific aortic pathology. The decrease in aortic valve excursion is a function of the overall depressed cardiac state and is not due to AS.

Patients presenting with pseudo-severe AS can be differentiated from LFLG severe AS by performing a dobutamine challenge during either echocardiography or cardiac catheterization. This is important, because patients with LFLG severe AS will generally benefit from AVR, whereas patients with pseudo-severe AS will not. For those with truly severe AS, a dobutamine challenge will result in an increase in cardiac index and an increase in mean gradient across the aortic valve, with little to no change in the AVA. A dobutamine challenge in a patient with pseudo-severe AS will result in an increase in cardiac index and AVA with relatively no change in the transvalvular mean gradient.

A dobutamine challenge is also useful in order to assess contractility and/or flow reserve. This is defined as an increase in stroke volume (SV) by at least 20% from baseline. Contractile reserve has important prognostic implications since its absence portends a poor prognosis regardless of valve replacement. However, this should not be used as a reason to withhold valve replacement therapy since patients with no LV contractile reserve who undergo AVR still have a better survival rate compared to those managed medically, despite a higher perioperative risk.

Alternatively, the dimensionless index (a ratio of left ventricular outflow track velocity time integral (VTI) to aortic valve VTI) can be used to help determine the severity of AS in a low flow state because this ratio is independent of flow. A ratio of <0.25 is consistent with severe aortic valve stenosis.

More recently, a “paradoxical” LFLG severe AS entity has been described, whereby patients have an AVA $<1.0\text{ cm}^2$ and a low transvalvular aortic gradient ($<40\text{ mm Hg}$), but normal LVEF. These patients are analogous to patients with heart failure with preserved ejection fraction, who have persistent symptoms despite a preserved LVEF, and are characterized by a small, restrictive LV cavity along with impaired diastolic filling. The small restrictive LV cavity leads to a low flow state, despite a preserved ejection fraction, and thus a mean gradient under 40 mmHg . The criteria proposed to define this condition are a cardiac index $<3.0\text{ L/min/m}^2$ or a SV index $<35\text{ mL/m}^2$. Currently, the most widely used measurement is the SV index since it is readily obtained by echocardiogram by taking SV in mL divided by the body surface area (BSA) in m^2 . This condition is often seen in elderly women with small body size [8]. It is estimated that up to 10–25% of patients undergoing evaluation for severe AS may fall into this category [9].

Further details on low-gradient AS are provided in Chapter 8.

Using hemodynamics to avoid pitfalls during TAVR

TAVR requires a multidisciplinary heart team approach to achieve optimal outcomes. Invasive hemodynamics are an essential component of periprocedural patient monitoring as they help identify potential complications that may occur.

In the early stages of the TAVR procedure, a pigtail catheter is inserted into the left ventricle across the stenotic aortic valve. Simultaneous LV and aortic pressures are measured to confirm the severity of the aortic stenosis, but other hemodynamic parameters should also be assessed and noted (Figure 9.1). Left ventricular end-diastolic pressure (LVEDP) and aortic diastolic blood pressure (DBP) should be recorded. Often, these patients have stiffened calcified peripheral vessels and low DBP is not an unusual finding. Noting this at the start of the procedure is helpful because a significant reduction in DBP following valve deployment can be a sign of severe aortic valve insufficiency and/or paravalvular leak. An elevated LVEDP is also a common finding given the longstanding pressure overload of the ventricle from the stenotic aortic valve.

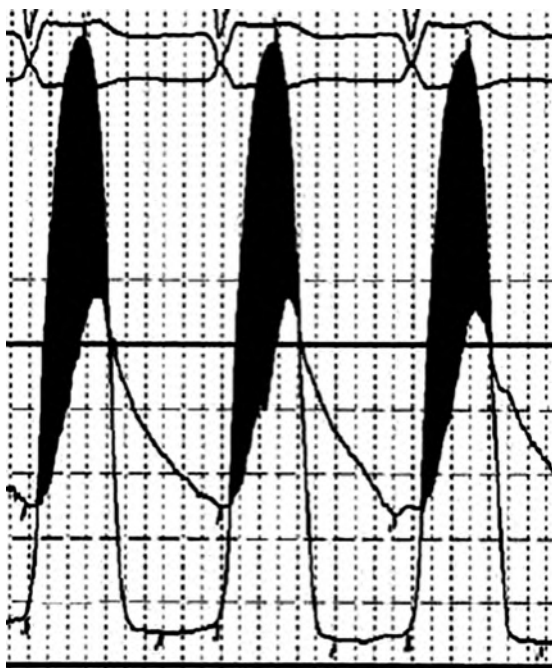


Figure 9.1 Simultaneous left ventricular and aortic pressure tracing showing severe aortic valve stenosis. The high transvalvular pressure gradient and delayed aortic pressure upstroke confirm the diagnosis. It is important during a TAVR procedure to note the starting left ventricular end-diastolic pressure (LVEDP) and starting aortic diastolic pressure (DP).

Hypotension during a TAVR procedure can be due to many causes. In severe AS, placing a catheter across the aortic valve can result in a drop in aortic systolic blood pressure (a drop in aortic systolic blood pressure (SBP) after a catheter is placed in the left ventricle is known as Carrabello's sign and is due to the occlusive effect of the catheter in very severe AS) [10]. This can be remedied by balloon aortic valvuloplasty followed by TAVR. Less commonly, hypotension may be an ominous sign of a serious complication. Hypotension may indicate ventricular perforation with cardiac tamponade, severe mitral valve regurgitation due to catheter or wire entanglement into the mitral valve cords and leaflets, or serious vascular injury, usually at the site of vascular access. A pulmonary artery catheter and transesophageal echo, if available, can help quickly differentiate among these potential complications. Severe mitral regurgitation (discussed in Chapter 12) generally results in a large V wave on wedge tracing, while cardiac tamponade (discussed in Chapter 19) is associated with elevated central venous pressure and equalization of diastolic pressures in the cardiac chambers. Vascular trauma and hemorrhagic shock usually manifest with a low central venous pressure (Table 9.1).

During balloon aortic valvuloplasty or deployment of a balloon expandable TAVR valve, rapid ventricular pacing is performed to transiently diminish cardiac output and drop the forward flow across the left ventricular outflow tract.

Typically, this requires rapid VVI pacing at 160–200bpm to decrease the peak systolic aortic pressure to <50mm Hg. Although self-expanding transcatheter valves may be deployed at lower pacing rates of 90–100bpm, the concept of diminishing cardiac output remains paramount. Once this drop in pressure is achieved, valve implantation can occur without fear of the TAVR valve being ejected out of the aortic valve annulus due to LV systolic contraction (Figure 9.2).

Table 9.1 Differentiating between causes of hypotension during TAVR.

Potential intraprocedural causes of hypotension	Pulmonary artery catheter findings
Severe mitral regurgitation	Large V wave on PCWP
Cardiac tamponade	Elevated CVP and equalization of RV and LV diastolic pressures
Vascular trauma/hemorrhagic shock	Low CVP, tachycardia

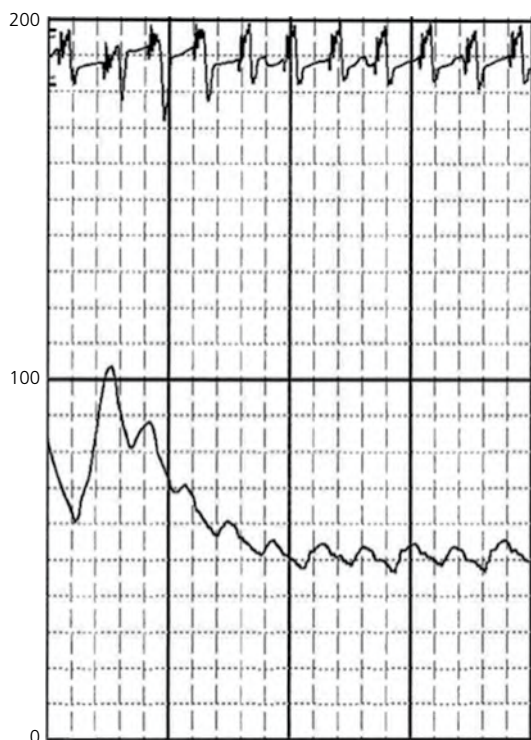


Figure 9.2 Aortic pressure tracing during rapid ventricular pacing. The aortic systolic pressure should decrease below 50mm Hg before inflating the aortic valvuloplasty balloon or deploying the transcatheter aortic valve.



Figure 9.3 Hemodynamics after successful TAVR deployment on the same patient from Figure 9.1. There is no residual aortic stenosis and good separation between the aortic DP and LVEDP.

Hemodynamic markers of successful valve deployment are minimal residual pressure gradient across the aortic valve and good separation of the aortic DP and LVEDP (Figure 9.3).

Assessing aortic insufficiency

After deployment of the transcatheter aortic valve, assessment for paravalvular leak and aortic valve insufficiency is essential. Several studies have now demonstrated worse long-term outcomes with moderate or severe aortic insufficiency (AI) compared to mild or less AI [11, 12]. A low diastolic aortic pressure with a wide pulse pressure may be the first indication of severe aortic valve insufficiency. Low DBPs are not unusual in the TAVR population, especially while under anesthesia. However, a newly low DBP, particularly in the presence of a high systolic pressure,

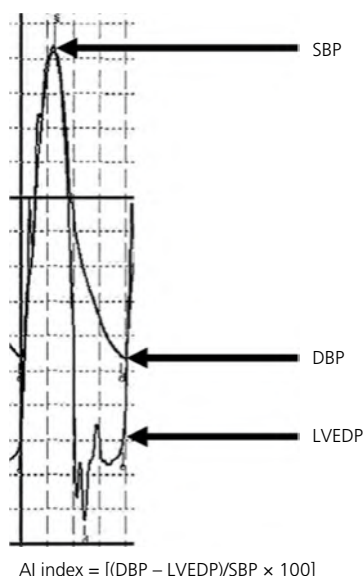


Figure 9.4 Simultaneous aortic and left ventricular pressure tracing indicating significant aortic insufficiency (AI). There is a wide pulse pressure (aortic systolic blood pressure [SBP] – aortic diastolic blood pressure [DBP]), low aortic DBP, high LVEDP, and low AI index (~18).

may be due to hemodynamically significant AI. Additionally, an abrupt rise in left ventricular diastolic pressures may be an indication of severe AI (Figure 9.4).

An AI index can be calculated from simultaneous LV and aortic pressure measurements and has been correlated with both the severity of AI and long-term mortality. The AI index is calculated using the aortic DBP minus the LVEDP and dividing that by the peak SBP and multiplying by 100 (Figure 9.4). In one study, an AI index of <25 was associated with increased 1-year mortality (46%) as compared to those with an AI index ≥25 (16.7%) [11].

$$\text{AI index} = \frac{\text{DBP} - \text{LVEDP}}{\text{SBP}} \times 100$$

Expected residual gradients after surgical valve replacement

After both TAVR and SAVR, some degree of residual transvalvular gradient is expected. With SAVR, it is important to note the reference ranges of the estimated orifice area of the prosthesis to be implanted (Table 9.2) [13]. Residual pressure gradients tend to be higher after SAVR than TAVR since most surgical valves have an integrated sewing cuff or region where the valve is implanted into the annulus after debridement. These sewing rings decrease the overall residual orifice area at

Table 9.2 Normal reference values of effective orifice area (EOA) for aortic valve prostheses.

	Prosthetic valve size, mm					
	19	21	23	25	27	29
Aortic stented bioprosthesis						
Mosaic	1.1 ± 0.2	1.2 ± 0.3	1.4 ± 0.3	1.7 ± 0.4	1.8 ± 0.4	2.0 ± 0.4
Hancock II	...	1.2 ± 0.1	1.3 ± 0.2	1.5 ± 0.2	1.6 ± 0.2	1.6 ± 0.2
Carpentier–Edwards Perimount	1.1 ± 0.3	1.3 ± 0.4	1.50 ± 0.4	1.80 ± 0.4	2.1 ± 0.4	2.2 ± 0.4
Carpentier–Edwards Magna*	1.3 ± 0.3	1.7 ± 0.3	2.1 ± 0.4	2.3 ± 0.5	...	...
Biocor (Epic)*	...	1.3 ± 0.3	1.6 ± 0.3	1.8 ± 0.4	...	...
Mitroflow*	1.1 ± 0.1	1.3 ± 0.1	1.5 ± 0.2	1.8 ± 0.2	...	...
Aortic stentless bioprosthesis						
Medtronic Freestyle	1.2 ± 0.2	1.4 ± 0.2	1.5 ± 0.3	2.0 ± 0.4	2.3 ± 0.5	...
St Jude Medical Toronto SPV	...	1.3 ± 0.3	1.5 ± 0.5	1.7 ± 0.8	2.1 ± 0.7	2.7 ± 1.0
Aortic mechanical prostheses						
Medtronic-Hall	1.2 ± 0.2	1.3 ± 0.2	...	...	...	...
Medtronic Advantage*	...	1.7 ± 0.2	2.2 ± 0.3	2.8 ± 0.6	3.3 ± 0.7	3.9 ± 0.7
St Jude Medical Standard	1.0 ± 0.2	1.4 ± 0.2	1.5 ± 0.5	2.1 ± 0.4	2.7 ± 0.6	3.2 ± 0.3
St Jude Medical Regent	1.6 ± 0.4	2.0 ± 0.7	2.2 ± 0.9	2.5 ± 0.9	3.6 ± 1.3	4.4 ± 0.6
MCRI On-X	1.5 ± 0.2	1.7 ± 0.4	2.0 ± 0.6	2.4 ± 0.8	3.2 ± 0.6	3.2 ± 0.6
Carbomedics Standard	1.0 ± 0.4	1.5 ± 0.3	1.7 ± 0.3	2.0 ± 0.4	2.5 ± 0.4	2.6 ± 0.4

Note: EOA is expressed as mean values (cm²) available in the literature.
* These results are based on a limited number of patients and thus should be interpreted with caution.
Source: Adapted from Pibarot 2009 [12].

the level of the annulus. Selection of a valve size that is too small for the annulus can lead to the phenomenon of patient–prosthetic mismatch (PPM). This occurs when gradients are higher than expected for that prosthesis. PPM is associated with lower survival and worse hemodynamic function.

With TAVR, the risk of PPM is decreased as the valve has no sewing cuff. Additionally, valve sizing is performed prior to the procedure based on CT and echocardiographic data, which decreases the risk of undersizing the valve prosthesis. The data on post-procedure TAVR is striking, with low gradients and high effective orifice area (EOA), and residual gradients usually in the 5–12 mm Hg range and EOA in the 1.8–2.0 cm² range. Contemporary data out to 5 years and longer show stable hemodynamics of transcatheter valves [12, 14]. It is important to note that the transcatheter valve can deploy in an asymmetric shape due to the

calcium burden at the annulus, thereby affecting the final EOA and gradient. However, the performance of these valves is impressive, with consistently high EOA and low gradients with little to no PPM.

Long-term follow-up after valve replacement

Currently, there are no specific guidelines on the long-term follow-up for patients after TAVR. Much of the follow-up is extrapolated from surgical practice. Most surgical valves are evaluated intraoperatively with transesophageal echocardiogram (TEE). Usually, a transthoracic echocardiogram (TTE) is obtained prior to discharge and then at 3–6 months. After noting no surgical complications, this surveillance may be extended to echocardiographic evaluations at 1–3-year intervals. With transcatheter valves, close surveillance is important as the rate of perivalvular leak is higher than with surgical valves and the true lifespan of the transcatheter valves is still unknown, due to the limited experience with this technology (although data from randomized trials show good durability of TAVR valve function now out to more than 5 years) [10, 13]. Cardiac catheterization with crossing of the valve for measurement of pressure gradients should be reserved only for interrogating a failing valve or when echocardiography is unable to adequately diagnose a suspected valvular issue.

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CHAPTER 10

Mitral stenosis

George A. Stouffer

[This chapter is revised and modified from a chapter written for the first and second editions by Robert V. Kelly, Chadwick Huggins, and George A. Stouffer]

The cross-sectional area of the mitral valve is 4–6 cm² in healthy adults. Mitral stenosis (MS) occurs when this area decreases, resulting in increased resistance to flow from the left atrium (LA) to the left ventricle (LV), which in turn results in increased LA pressure. The increased LA pressure is transmitted to the pulmonary circulation, resulting in elevated right heart pressures and, in some cases, elevated pulmonary vascular resistance (Figure 10.1). As a generalization, transmittal valve pressure gradients usually begin to appear when valve area is <2 cm² and symptoms are present when valve area is <1.5 cm².

The vast majority of cases of MS are rheumatic in origin. Isolated MS occurs in 40% of all adults presenting with rheumatic heart disease and women with MS outnumber men by more than 2:1. Rheumatic mitral valve changes including thickening of the mitral valve leaflets, calcification, and commissural fusion, which occurs over the course of decades. Other rare causes of MS include systemic lupus erythematosus, rheumatoid arthritis, carcinoid, mucopolysaccharidosis, mitral annular calcification, and congenital valve deformity [1].

There are some rare conditions that cause increased LA pressure that can mimic MS. Examples include LA myxoma, pulmonary vein obstruction, and cor triatriatum (a thin membrane across the LA that obstructs pulmonary venous inflow).

MS is a progressive disorder with symptoms worsening as the mitral valve area decreases. Initially, symptoms occur only with exertion, emotional stress, or pregnancy and consist primarily of dyspnea. Symptoms can progress over time and in severe cases eventually include dyspnea at rest, orthopnea, and paroxysmal nocturnal dyspnea. More rarely, there may be angina, palpitations, recumbent cough, and/or hemoptysis. Symptoms can occur more acutely if the patient becomes pregnant, develops a systemic illness, or goes into atrial fibrillation.

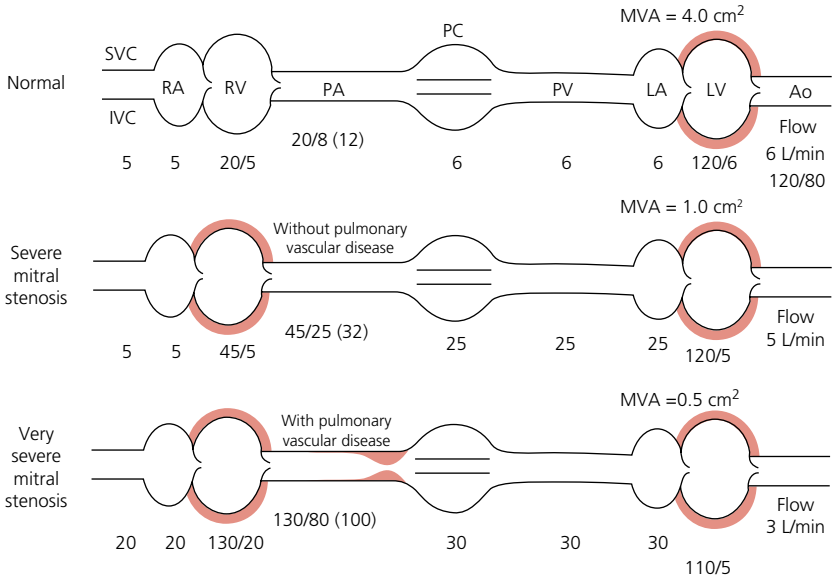


Figure 10.1 Hemodynamic changes of mitral stenosis. [LA = left atrium; LV = left ventricle; PA = pulmonary artery; PV = pulmonary veins; RA = right atrium; RV = right ventricle.]

Patients with MS generally pass through four separate hemodynamic stages (Figure 10.2):

- 1 Normal hemodynamics
- 2 Normal filling pressures at rest but increased filling pressures with normal cardiac output during exercise
- 3 Increased filling pressures at rest and inability to increase cardiac output with exercise
- 4 Markedly increased filling pressures at rest

In addition to increasing resistance to flow, MS also increases transvalvular blood velocity and the ratio of turbulent to laminar flow across the mitral valve. For example, LV inflow velocity across the normal valve is approximately 1 m/s but can reach 3 m/s in severe MS. The effects of accelerated velocity of blood are not completely understood.

Cardiac hemodynamics in patients with MS

The classic hemodynamic findings associated with MS include elevated LA pressure and a gradient between the LA and LV that persists throughout diastole (Table 10.1). There are several other findings that are discussed below in relation to the cardiac chamber involved.

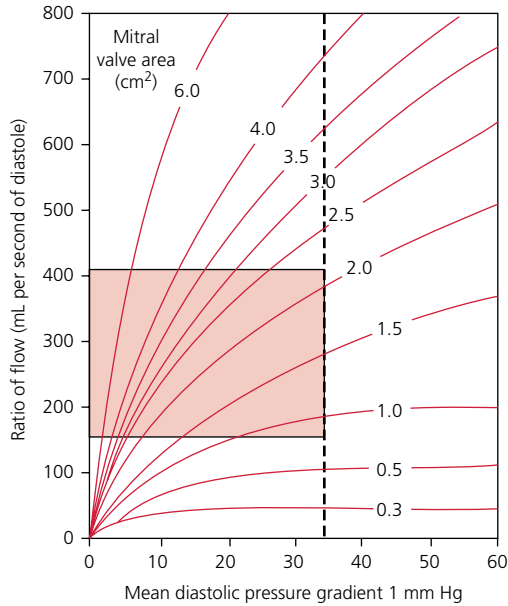


Figure 10.2 Hemodynamic effects of different degrees of mitral stenosis (calculations performed assuming $HR \times DFP = 32$).

Table 10.1 Findings of cardiac catheterization.

- Increased LA pressure
- Increased right heart pressures with exercise and/or at rest
- Prominent A wave on LA or PCWP tracing
- Decreased slope of Y descent on LA or PCWP tracing
- Gradient between LA and LV persists throughout diastole

Left atrium

- LA pressure is increased and there is a gradient between LA and LV during diastole (Figure 10.3).
- Chronic LA hypertension causes LA dilation over time in patients with MS. LA dilation is accelerated in patients with atrial fibrillation.
- Passive LV filling is slowed, accounting for a prominent A wave and decreased slope of the Y descent on pulmonary capillary wedge pressure (PCWP) tracing (Figure 10.4) or LA pressure tracing.
- Atrial contraction becomes more important for ventricular filling as MS progresses. Because of this, atrial arrhythmias are poorly tolerated. Somewhat paradoxically, however, the contribution of active atrial contraction to transvalvular flow can decrease as the severity of MS increases. Meisner *et al.* in a study

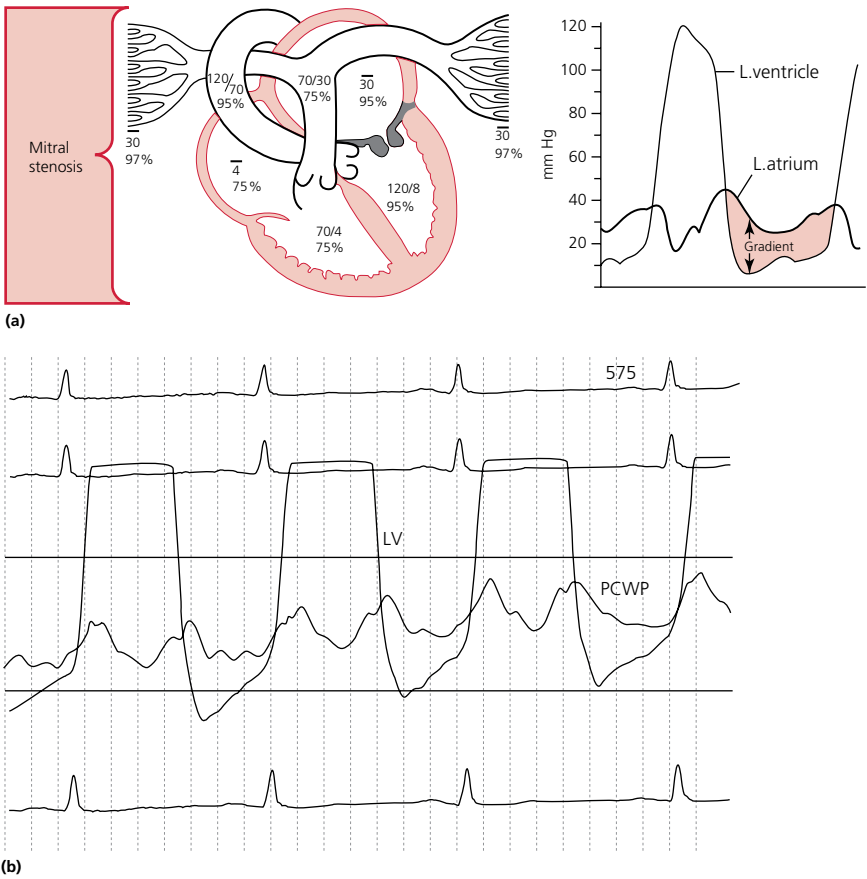


Figure 10.3 Transvalvular pressure gradient in a patient with MS. Schematic (a) and actual recordings (b) of simultaneous LV and PCWP pressures in a patient with MS. Note that in (b), the PCWP is delayed relative to LV and should be phase shifted prior to performing any calculations.

of 30 patients with MS found that atrial contraction accounted for $29 \pm 5\%$ of filling volume in mild MS and only $9 \pm 5\%$ in severe MS. Computer modelling suggested that increased heart rate, rather than loss of atrial contraction, was the primary mechanism responsible for decompensation of patients with severe MS who develop atrial fibrillation [2].

Pulmonary artery

In mild to moderate MS, pulmonary artery pressures may be normal or slightly elevated at rest but significantly increase with exercise. In severe MS, pulmonary artery pressure will be elevated at rest. Pulmonary hypertension in severe MS can be caused by both elevated LA pressures and increased pulmonary vascular



Figure 10.4 LA pressure tracing from a patient with severe MS. Note the prominent A wave and decreased Y descent.

resistance due to pulmonary arteriolar constriction and obliterative changes in the pulmonary vascular bed. It has been speculated that the increased resistance in the pulmonary vasculature protects the patient from developing pulmonary edema in the setting of chronically elevated LA pressures.

Evidence for a reversible component of pulmonary vascular resistance was shown in a study of 18 women with MS and pulmonary hypertension. Inhaled nitric oxide reduced pulmonary artery systolic pressure by approximately 15% and pulmonary vascular resistance by 30% without having any effect on LV end-diastolic pressure (LVEDP), LA pressure, cardiac output, or systemic vascular resistance [3]. Following mitral valve surgery or percutaneous balloon mitral valvuloplasty (PBMV), pulmonary artery pressures decrease immediately due to decreased LA pressure. Over time, pulmonary artery pressures continue to decrease as pulmonary vascular resistance decreases. This was demonstrated in a study of 21 patients with severe MS and pulmonary hypertension undergoing PBMV. Mean PCWP decreased from 27 ± 5 (pre-procedure) to 15 ± 4 mm Hg (immediately post-procedure) and then remained constant at a mean follow-up

of 1 year. Mean mitral valve gradient decreased from 18 ± 4 to 6 ± 2 mm Hg and then remained constant. Pulmonary artery systolic pressure decreased from 65 ± 13 to 50 ± 13 mm Hg to 38 ± 9 mm Hg and pulmonary vascular resistance decreased from 5.8 ± 1.9 to 5.0 ± 2.8 to 2.7 ± 1.2 Wood units (461 ± 149 to 401 ± 227 to 212 ± 99 dynes/sec/cm⁵) [4].

Left ventricle

In most patients with MS, the LVEDP is normal but it is reduced in about 15% of cases. In the presence of heart failure or mitral regurgitation (MR), LVEDP can be elevated. Since flow across the mitral valve in MS is directly proportional to transvalvular pressure gradient, as LVEDP increases, LA pressure must also increase to maintain the transvalvular pressure gradient. LV systolic dysfunction is seen in 25–33% of patients with MS.

Some generalizations about LV pressure and function in MS:

- 1 Filling is impaired and determined by the degree of MS.
- 2 Passive LV filling is slowed, accounting for the delayed rise in LV diastolic pressure.
- 3 LV systolic function is normal in most patients with MS.
- 4 LV diastolic function may be abnormal which will directly influence LA pressure.

Right ventricle

Right ventricular systolic pressures rise in line with the increases in pulmonary artery systolic pressures.

Cardiac output

- 1 The flow across the mitral valve during diastole can be approximated by flow = pressure gradient/resistance. As resistance increases (i.e., as MS becomes more severe), the transvalvular pressure gradient must increase to maintain flow. In most cases of MS, the primary mechanism to increase transvalvular gradient is via increased LA pressures. In mild to moderate MS, cardiac output is normal at rest but increases in LV stroke volume (e.g., with exercise) are associated with further increases in LA pressures. This is why LA and pulmonary artery pressures can increase markedly with exercise. In severe MS, cardiac output can be decreased under basal conditions despite elevated LA pressures.
- 2 The length of the diastolic filling period is important in determining transvalvular flow. Tachycardia impairs LV filling, further increasing LA pressure, and LV filling can be worsened by atrial fibrillation and rapid ventricular response.
- 3 The flow across the mitral valve = cardiac output + amount of MR. Thus, as MR increases, flow across the mitral valve during diastole must increase to maintain cardiac output.
- 4 Low-flow/low-gradient MS has been defined in patients with severe MS with mean transmitral gradient <10 mm Hg and stroke volume index ≤ 35 mL/m² by

echocardiography. In a study of 101 patients, patients with low-flow/low-gradient MS had higher arterial afterload, a greater prevalence of atrial fibrillation, more subvalvular thickening, decreased left ventricular compliance and less symptomatic improvement with PBMV compared with those with high-gradient MS [5].

Quantification of severity of MS

The severity of obstruction in MS can be quantified using mitral valve area, mitral valve resistance, or mitral valve gradient. Mitral valve area remains the standard used in most laboratories because it includes the three major hemodynamic variables: transvalvular pressure gradient, cardiac output, and diastolic filling period. Traditionally, mitral valve area $<1\text{ cm}^2$ was considered severe MS, a valve area of $1\text{--}1.5\text{ cm}^2$ was moderate stenosis, and a valve area $1.5\text{--}2\text{ cm}^2$ was mild stenosis. In the most recent guidelines, mitral valve area of $\leq 1.5\text{ cm}^2$ is considered severe MS [6].

Mitral valve resistance is a useful research tool, although its clinical use lags behind mitral valve area. It is a measurement of the opposition to blood flow of the stenotic mitral valve and is computed by dividing pressure gradient by transvalvular flow. Mitral valve resistance has been advocated as being more accurate in patients with low cardiac output and low-pressure gradients.

The degree of MS can also be defined by the gradient across the mitral valve. By convention, a mean gradient $>10\text{ mm Hg}$ at rest is severe MS, a mean gradient of $5\text{--}10\text{ mm Hg}$ at rest is moderate stenosis, and a mean gradient $<5\text{ mm Hg}$ at rest is mild MS. Transvalvular gradient will increase in direct proportion to flow across the valve and thus conditions that increase cardiac output (e.g., anemia, hyperthyroidism, anxiety, exercise, MR) will result in increased gradients.

Some patients may report significant exertional symptoms but have only a mild to moderate resting mitral valve gradient. In these patients, measuring hemodynamic response to exercise can be very helpful. With exercise, blood flow across the mitral valve increases and this can dramatically change the gradient resulting in increased LA and pulmonary artery pressures. If the mitral valve pressure gradient increases with exercise and symptoms develop, the patient's symptoms can be attributed to mitral valve disease (Figure 10.5).

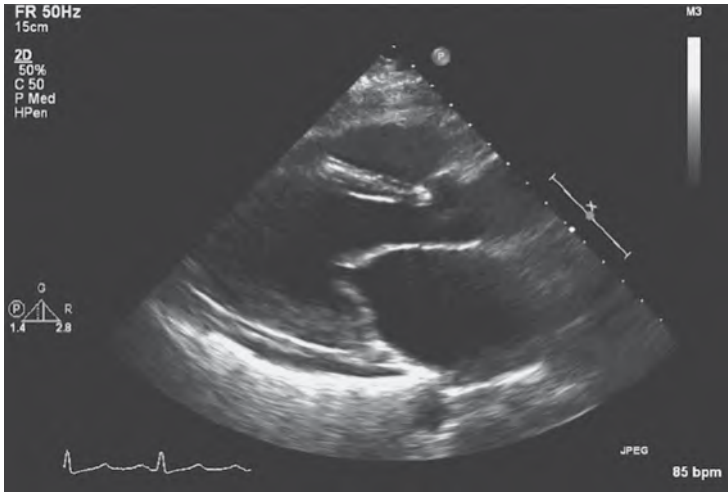
Assessing mitral stenosis in the echocardiography laboratory

Transthoracic echocardiography is essential for diagnosing MS and provides an accurate and noninvasive measurement of mitral valve area. In the parasternal long-axis view, the rheumatic mitral valve has a "hockey stick" deformity (Figure 10.6). Evaluation of MS severity relies on accurate echocardiographic

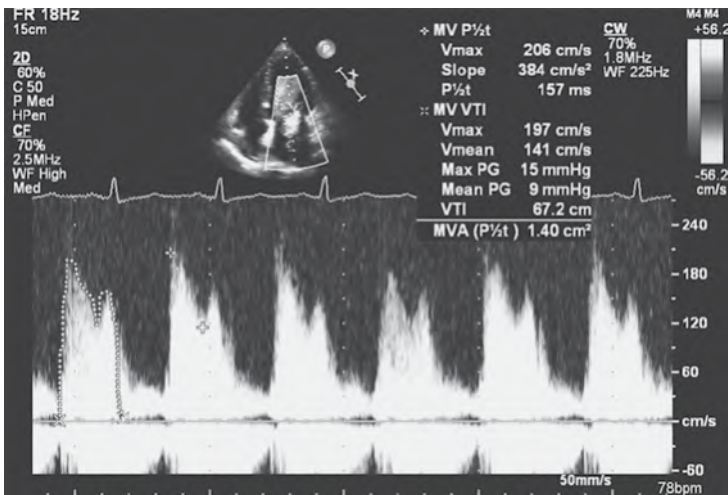


Figure 10.5 Exercise hemodynamics in a patient with MS. Transvalvular pressure gradient (simultaneous recording of LV and PCWP pressure tracings) at rest (a) and with exercise (b). Note the marked rise in PCWP with exercise.

assessment of the mitral valve area. Several methods can be used, often in combination. In the short-axis view (2D or 3D), the mitral valve area can be measured by planimetry. In practice, the mitral valve area is commonly estimated using the pressure half-time (PHT) method and/or the continuity equation.



(a)



(b)

Figure 10.6 Echocardiographic findings in a patient with mitral stenosis. A 57-year-old female presented with worsening dyspnea on exertion. She was receiving home oxygen and carried a diagnosis of severe chronic obstructive pulmonary disease before the diagnosis of MS was made. Two-dimensional echocardiography showed limited excursion of the mitral valve (a) and continuous-wave Doppler estimated a mean gradient of 9 mm Hg across the mitral valve (b).

Use of planimetry is the “gold-standard” method but the assessment must be precise with accurate determination of the tips of the leaflets in a well-oriented plane. Two-dimensional echocardiography assessment of mitral valve area can be problematic in patients with extensively distorted and/or thickened mitral valves,

especially after commissurotomy, and in these situations, new imaging technologies, such as 3D-echocardiography, MRI or computed tomography are useful.

The mean mitral valve gradient may be determined by Doppler examination in which an estimation of the diastolic pressure gradient is derived from the transmitral velocity flow curve using the simplified Bernoulli equation: $DP = 4v^2$ [6]. The Doppler gradient is usually assessed using the apical window, as that view is best for parallel alignment of the ultrasound beam and mitral inflow. For measuring maximal velocities, continuous-wave Doppler is preferred over pulse-wave Doppler. Maximal and mean mitral gradients are calculated based on the Doppler diastolic mitral flow waveforms. Mean gradient is very useful information but is influenced by factors other than mitral valve area, such as cardiac output, heart rate, MR, LA compliance, and LV diastolic function.

Pressure half-time

PHT ($T_{1/2}$) is a commonly used echocardiographic method to estimate mitral valve area. PHT is the time interval between the maximum early diastolic gradient and the point at which the gradient is half this maximum value (i.e. the time interval in milliseconds between the maximum velocity and the point where the velocity is half the maximum). The decline of the velocity of transmitral flow during diastole is inversely proportional to valve area and MVA can be calculated using the empiric formula:

$$MVA = 220 / T_{1/2}$$

The accuracy of the PHT method is influenced by abnormal LA or LV compliance, tachycardia, atrial fibrillation, and/or moderate to severe aortic regurgitation. The effect of aortic regurgitation on PHT is due to a rapid rise in left ventricular diastolic pressure and with a corresponding reduction in transmitral pressure gradient. PHT is likely to overestimate mitral valve area in cases of MS with moderate to severe aortic regurgitation. There is also a rapid rise in left ventricular diastolic pressures in patients with noncompliant LVs due to hypertension, ischemic heart disease or cardiomyopathy, and PHT might overestimate mitral valve area in MS. In clinical practice, a correlation between planimetry and PHT depends on the patient population with one study reporting discrepancies $\geq 0.3 \text{ cm}^2$ in 20% of patients [7].

Continuity equation

The continuity equation is based upon the fluid dynamic principle that, in any steady-state process, the rate at which mass leaves a system is equal to the rate at which mass enters a system. In practice, this means that mitral valve area can be calculated by assuming that the diastolic flow across the mitral valve is the same as the systolic flow that passes through the left ventricular outflow tract (LVOT).

gradients are measured. For best results, the fastest paper recording speed (generally 100 mm/s) and a 0–50 mm Hg scale are used. The gradient across the mitral valve should be measured using an average of five cardiac cycles in patients with normal sinus rhythm and at least ten cardiac cycles in patients with atrial fibrillation.

Calculating mitral valve area

The Gorlin formula is the standard for mitral valve area calculation (see text box). It was derived by the Gorlins (father and son) based on Torricelli's law for flow across a round orifice [8]. An empiric constant was added (initially 0.7 and later changed to 0.85) to account for the difference between calculated and actual mitral valve areas.

Gorlin formula for calculating mitral valve area

$$\text{MVA} = \frac{(\text{CO} / \text{DFP} \times \text{HR})}{(44.3 \times 0.85 \times \text{square root of mean gradient})}$$

where:

MVA = mitral valve area (cm²)

CO = cardiac output (cm³/min)

HR = heart rate (bpm)

Mean gradient = average diastolic gradient across mitral valve (mm Hg)

DFP = diastolic filling period (secs/beat) [measured between initiation of diastole (PCWP/LV crossover) and end of diastole (peak of R wave on ECG)]

44.3 × 0.85 = 37.7 is an empiric constant.

Potential sources of error in quantifying the severity of MS by using the Gorlin formula in the cardiac catheterization laboratory

1 Use of PCWP. To avoid a transseptal puncture, PCWP is commonly used in place of LA pressure. In this scenario, it is essential to ensure that an accurate wedge tracing is obtained. An oxygen saturation >95% helps ensure that the tracing is not a damped pulmonary artery tracing. Potential sources of error when using PCWP tracing include:

- Using damped PA tracing instead of PCWP.
- Inability to obtain PCWP in patients with severe pulmonary hypertension.
- Delay in transmittal of LA pressure to proximal PA, leading to alignment mismatch in PCWP/LV pressure tracing (in general, the PCWP is 40–120 ms delayed compared to LA pressure).
- PCWP does not approximate LA pressure in patients with veno-occlusive disease or cor triatriatum.

Lange *et al.* compared PCWPs and LA pressures in 10 patients with MS. PCWP was measured using a Goodale–Lubin catheter and confirmed by oximetry. The mean and phasic LA pressure and PCWP were similar. Use of the PCWP with adjustment for time delay resulted in similar values for transvalvular pressure gradient and mitral valve area compared to use of LA pressure. In contrast, when PCWP was used without adjustment for time delay, the transvalvular pressure gradient and mitral valve area were significantly different from the values obtained with use of LA pressure [9].

More recently, Nagy *et al.* studied the correlation between PCWP (measured with a 6 F catheter) and LA pressure in 117 patients with pure MS. Exclusion criteria included significant aortic disease, more than mild (grade >1) MR, associated ischemic heart disease, systemic hypertension, or diabetes mellitus [10]. The average age was 32 ± 9 years, 67% were females, and the average mitral valve area was 0.9 cm^2 . The authors found a very strong correlation between PCWP and LA pressure measurements (correlation coefficient = 0.97, mean bias $\pm$ CI, 0.3 ± -3.7 to 4.2 mm Hg). A statistical analysis showed that the two measurements demonstrated consistent correlation, independent of the value of PCWP. Multiple regression analysis found no association between the accuracy of PCWP and heart rate, left ventricular ejection fraction, cardiac output, right ventricular systolic pressure, systemic vascular resistance, or pulmonary vascular resistance.

- 2 Measurement of cardiac output. See Chapter 6 for a discussion of the limitations of measuring cardiac output.
- 3 Atrial fibrillation. The Gorlin formula was developed based on the patient being in sinus rhythm. It is commonly used in patients with atrial fibrillation, but mean transvalvular gradient will vary with differing diastolic filling periods, and thus it is important to average at least 10 consecutive heartbeats.
- 4 Poor calibration of equipment.
- 5 Mitral regurgitation. This will increase flow across the mitral valve and can lead to an overestimation of the severity of MS if systemic cardiac output is used in the Gorlin equation. In patients with MR, blood flow across the mitral valve equals systemic cardiac output + regurgitant flow. Since the pressure gradient is dependent on flow across the valve, use of systemic cardiac output in patients with significant MR underestimates flow and thus overestimates the severity of stenosis.

Hemodynamic effects on the physical examination in MS

On physical examination, patients with severe MS may have “mitral facies” as a result of low cardiac output and systemic vasoconstriction. The amplitude of the arterial pulse will be small. Jugular venous pressures will be elevated and have a prominent A wave. In atrial fibrillation, this is absent and a CV wave

predominates. Palpation of the apex may reveal a presystolic wave and a diastolic thrill may be felt in the left lateral position. An RV heave in the left parasternal area and a loud P2 in the left second intercostal space suggest pulmonary hypertension.

On auscultation, there is classically a loud S1, an opening snap (OS), and a diastolic rumble. The first heart sound may be lessened with a more calcified mitral valve. In addition, there may be a tricuspid regurgitation murmur, pulmonary regurgitation murmur (Graham Steel murmur), and an S4. An S3 may occur if MR or aortic regurgitation are present. In MS, the low-pitched rumbling diastolic murmur is best heard at the apex with the bell of the stethoscope and the patient in the left lateral position. It may radiate if loud. The intensity and duration of the diastolic rumble increase as the gradient across the mitral valve increases. The murmur persists as long as the mitral valve gradient is more than 3 mm Hg. If a diastolic rumble is not heard, perform maneuvers to increase the patient's heart rate. The increased heart rate decreases the diastolic filling period and therefore causes the LA pressure to increase. Despite maneuvers, some patients with severe MS will not have an audible diastolic rumble due to body habitus.

The duration between A2 and the OS is indicative of the severity of MS. As the LA pressure increases, the A2–OS interval decreases. In mild MS, the A2–OS interval is >100–110 ms. In severe MS, the A2–OS interval is <60–70 ms.

In acute mitral valvulitis due to acute rheumatic fever, the Carey Coombs murmur can be heard. This is a soft early diastolic murmur that varies from day to day. It is also higher pitched than the classic MS murmur.

Hemodynamics of mitral valve surgery and percutaneous balloon mitral valvuloplasty (PBMV) for rheumatic MS

There are currently two primary treatment options for rheumatic MS: surgery and PBMV. In PBMV, a transeptal sheath is placed in the LA via a femoral vein. A balloon is placed in the mitral valve and inflated, resulting in fracture of the commissures. A Class I indication for PBMV is: symptomatic patients (New York Heart Association [NYHA] class II, III, or IV) with severe rheumatic MS (valve area $\leq 1.5 \text{ cm}^2$) and valve morphology favorable for PBMV in the absence of left atrial thrombus or moderate to severe MR. A class 2A recommendation for PBMV is in asymptomatic patients with severe rheumatic MS and valve morphology that is favorable for percutaneous mitral balloon valvotomy who have pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg) in the absence of left atrial thrombus or moderate to severe MR [6].

The Wilkins score is an echocardiographic grading system, based on 2D imaging of the valve and the subvalvular apparatus, that is used in decision making for mitral valve surgery versus PBMV. There are four categories: leaflet thickening, leaflet calcification, leaflet mobility, and subvalvular fusion. A score of 1–4 is

assigned to each category, with 1 being least involvement and 4 being severe involvement. In general, a score ≤ 8 suggests a pliable, noncalcified valve in which PBMV may be technically possible. Newer scores have also been developed but a full discussion of echocardiographic scoring prior to PBMV is beyond the scope of this book.

Among the surgical options are closed commissurotomy, open commissurotomy, and mitral valve replacement. Closed commissurotomy was developed prior to cardiopulmonary bypass. It involves a lateral thoracotomy and a splitting of the commissures with either a finger or a dilator. The success is limited by the amount of calcification present. An open commissurotomy utilizes cardiopulmonary bypass. The surgeon has direct visualization of the valve and is able to incise the commissures and perform subvalvular repair if needed. Mitral valve replacement is a third option. This option is often necessary in patients with heavily calcified valves.

Both PBMV and mitral valve surgery significantly improve mitral valve area, decrease transmitral pressure gradient, reduce pulmonary artery pressure, and increase cardiac output. In a multicenter registry of 290 patients undergoing PBMV, mitral valve area increased from 1.0 to 1.7 cm², mean LA pressure decreased from 24 to 19 mm Hg, transvalvular pressure gradient decreased from 13.4 to 6.1 mm Hg, mean pulmonary artery pressure decreased from 34 to 29 mm Hg, and cardiac output increased from 4.1 to 4.4 L/min immediately post-procedure [11].

Transcatheter mitral valve replacement for bioprosthetic valve MS

Transcatheter implantation of a bioprosthetic valve in the mitral position can be used to treat patients with a failing surgically implanted bioprosthetic valve or ring if they have suitable anatomy. In a study from the Valve-in-Valve International Data Registry, 27% of 1079 patients enrolled between 2006 and 2020 were treated for MS [12]. Post-implantation of a transcatheter valve, mean gradient across the mitral valve post-procedure was 5.7 ± 2.8 mmHg with significant residual MS (defined as immediate post-procedure mean gradient ≥ 10 mmHg) occurring in 8.2% of the valve in valve and 12.0% of the valve in ring patients. The rates of significant residual MS were higher in patients with baseline stenosis and smaller true internal diameter.

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CHAPTER 11

Aortic regurgitation

George A. Stouffer

The aortic valve separates the left ventricle (LV) from the aorta. In normal hearts, it is pliable, opens widely, and presents minimal resistance to flow. The normal aortic valve is a trileaflet structure that is composed of three equal-sized bowl-shaped tissues that are referred to as cusps (left coronary cusp, right coronary cusp, and noncoronary cusp). The aortic valve serves an essential hemodynamic function in isolating the LV from the arterial circulation and can fail in two ways. The valve can fail to open properly during systole, which thus inhibits ejection of blood from the LV (aortic stenosis). Alternatively, the valve can fail by becoming incompetent, thus enabling backflow into the ventricle during diastole (aortic regurgitation, AR) [1].

AR can be caused by abnormalities of the aortic leaflets and/or aortic root dilation [2, 3]. Disease states that can impair the leaflets include rheumatic heart disease, congenital heart disease (e.g. bicuspid aortic valve), infective endocarditis, connective tissue or inflammatory diseases, trauma, antiphospholipid syndrome, trauma, and/or as a result of subaortic stenosis. Aortic root dilation can result from a diverse set of pathologies including Marfan syndrome, aortoannular ectasia, Ehlers-Danlos syndrome, osteogenesis imperfecta, aortic dissection, syphilitic aortitis, or various connective tissue diseases. A bicuspid aortic valve and ankylosing spondylitis can be associated with both impaired leaflet function and aortic root dilation. Hypertension rarely causes aortic root dilation that results in significant AR.

The hemodynamic changes associated with AR depend on the time-course of the valve dysfunction. If AR develops rapidly (i.e., acute or subacute AR), the LV is unable to handle the pressure and volume overload, causing a rapid increase in LV pressures during diastole, markedly elevated pressures at end diastole, and premature closure of the mitral valve. Systemic diastolic pressures may be low, but generally there is a minimal increase in pulse pressure; in very severe cases of

acute AR, cardiac output may fall, leading to hypotension. Left ventricular function can be further impaired by decreased coronary blood flow resulting from the combination of decreased aortic diastolic pressure and elevated left ventricular diastolic pressure.

Chronic severe AR imposes a combined volume and pressure overload on the LV. Stroke volume increases to maintain effective forward flow. This causes dilation of the LV, leading in some patients to the development of a massively dilated LV termed *cor bovinum* (the largest LVs are seen in patients with chronic AR). The body's adaptation to chronic AR results, at least in part, in the classic physical examination findings of a widened pulse pressure and low aortic diastolic pressure. If and when the regurgitant flow overwhelms the adaptive mechanisms, this leads to decompensated chronic AR with signs and symptoms of heart failure.

Before the development of aortic valve replacement, severe AR had an ominous prognosis. The availability of surgical treatment has greatly reduced the mortality of this disease (there are now also percutaneous options available for AR). The important question in treating patients with this disease is the timing of aortic valve replacement. An understanding of the hemodynamic changes associated with chronic AR can provide important information on cardiac adaptation to the regurgitant flow and the severity of AR. The latter is particularly important in patients whose AR appears moderate by angiography or echocardiography but who have symptoms and/or a decreased ejection fraction.

Hemodynamic changes of chronic aortic regurgitation

Hemodynamic changes associated with chronic AR result from aorta to left ventricular blood flow during diastole, compensatory responses of the LV to increased diastolic filling, and adaptations by the cardiovascular system to maintain systemic blood flow. In mild AR, increased ejection fraction and/or heart rate result in an increased cardiac output across the aortic valve, thus maintaining systemic blood flow. As the severity of AR increases, increases in left ventricular stroke volume are necessary to maintain cardiac output and thus the LV begins to remodel and dilate. This remodeling allows the maintenance of relatively normal filling pressures as left ventricular volumes increase. Left ventricular dilation progresses as the severity of AR worsens and patients with severe chronic AR, if untreated, often develop the largest end-diastolic volumes associated with any heart disease (*cor bovinum*). Left ventricular end-diastolic pressure (LVEDP) will increase if the progression of the valve incompetence exceeds the rate of left ventricular remodeling (e.g., acute AR), if the limits of left ventricular remodeling are reached, or if systemic vascular resistance increases to such a degree as to increase regurgitant flow above the ability of the LV to adapt.

Aortic pressures

The two most common blood pressure manifestations associated with chronic AR are a wide systemic pulse pressure and a low aortic diastolic pressure. The wide pulse pressure results from an increased stroke volume (which is needed to deliver enough blood to the aorta to maintain systemic blood flow despite large regurgitant fractions) and decreased peripheral vascular resistance. The low diastolic aortic pressure results from a relatively low resistance to aortic diastolic flow: as the competence of the aortic valve decreases, resistance to flow from aorta to LV decreases, regurgitation increases, and aortic diastolic blood pressure drops. A widened and elevated systemic arterial pressure without a dicrotic notch is sometimes observed.

There are other, more subtle changes in arterial pressure that are associated with AR. Peripheral arterial systolic pressures are generally higher than aortic pressures because of amplification due to summation of pressure wave reflections. In AR, because of the accelerated velocity of ventricular ejection, peripheral amplification is more profound than normal. This phenomenon may also lead to the appearance of a bisferiens systolic aortic pressure waveform, in which the first peak is due to ventricular emptying and the second peak is due to wave reflections propagated back from the peripheral arterial circulation.

Diastolic blood pressure and heart rate were independently associated with mortality in a study of 820 patients (age 59 ± 17 years; 82% men) followed for 5.5 ± 3.5 years with chronic AR. Age, symptoms, left ventricular ejection fraction (LVEF), LV end-systolic diameter-index (LVESDi), diastolic blood pressure and heart rate were univariable predictors of all-cause mortality (all $p \leq 0.002$). When adjusted for demographics, comorbidities, and surgical triggers (symptoms, LVEF, and LVESDi), diastolic blood pressure and heart rate were independently associated with all-cause mortality [4].

Left ventricular pressures

The LV hemodynamic findings associated with chronic AR depend on the extent of ventricular remodeling. In mild to moderate AR, filling from the aorta enables the LV to increase stroke volume by increasing LV end-diastolic volume (i.e., Starling's law). As the AR becomes more severe, the LV dilates in order to handle increased volumes with minimal changes in ventricular diastolic pressure. Thus, patients with longstanding, severe AR may have very large hearts with normal diastolic pressure. In some patients with AR and dilated LVs, myocardial function begins to decline for reasons that are poorly understood. The development of LV dysfunction leads to increased LV diastolic pressures and eventually to development of pulmonary congestion and symptoms of dyspnea.

Hemodynamic findings in aortic regurgitation

Aorta

- Wide pulse pressure
- Low diastolic pressure
- Increased peripheral amplification of systolic pressure

Left ventricle

- Increased LV end-diastolic pressure (LVEDP); in severe AR, LVEDP and aortic diastolic pressure will be equal
- Early closure of the mitral valve during diastole

Hemodynamic changes detected by physical exam

There are several physical findings associated with chronic AR. In the absence of left ventricular failure, patients generally have a wide pulse pressure (the aortic diastolic pressure is usually less than one-half of the systolic pressure). This wide pulse pressure produces a variety of physical findings that are described in the text box. A low diastolic pressure is observed with Korotkoff sounds occasionally persisting to zero. On auscultation, there is a diastolic murmur that usually increases during maneuvers that increase peripheral resistance (e.g., handgrip, squatting). If the AR is heard best along the left sternal border, the etiology may be either valvular or from aortic root pathology, while AR heard best along the right sternal border is typically due to aortic dilation (Harvey's sign). The duration and intensity of the murmur correlate poorly with severity of AR. More subtle diastolic murmurs may be better appreciated with the patient sitting up and leaning forward. A systolic murmur (usually due to increased and/or turbulent flow across the aortic valve) may be present. A₂ may be soft or absent and a blowing, high-pitched diastolic murmur may be heard along the sternal border.

A mid- to late-diastolic apical rumble that resembles the murmur of mitral stenosis may be heard in patients with AR (Austin Flint murmur). This murmur was initially thought to reflect rapid antegrade flow across a structurally normal mitral valve that is partially closed in response to rapid increases in LV diastolic pressures. More recent studies have suggested that the murmur is present in patients in whom the AR jet is directed at the anterior mitral valve leaflet. Shuddering of the MV causes vibrations and shock waves that distort the AR jet, leading to the murmur. Mitral stenosis may coexist in patients with AR (particularly in patients with rheumatic disease); the presence of a loud S₁ and/or an opening snap are clues that the mitral valve is abnormal. Exercise, amyl nitrite inhalation, or any maneuver that decreases peripheral resistance intensifies the murmur of mitral stenosis while diminishing the murmur of AR and the Austin Flint murmur. Handgrip and other maneuvers that increase peripheral resistance will have the opposite effect.

In patients with chronic AR, cardiac palpation generally reveals that the apical impulse is hyperdynamic, diffuse, and displaced laterally and inferiorly. In patients

with left ventricular systolic dysfunction, the precordial impulse may be less prominent and there may be findings of left-sided heart failure (e.g., pulmonary rales, S3).

Physical exam findings of chronic aortic regurgitation

- Wide pulse pressure
- Low diastolic pressure
- Blowing, high-pitched diastolic murmur $\pm$ a systolic murmur
- A2 may be soft or absent
- Austin Flint murmur, a mid- to late-diastolic apical rumble that resembles the murmur of mitral stenosis
- Apical impulse is hyperdynamic, diffuse, and displaced laterally and inferiorly

Classic physical examination findings described in patients with severe chronic AR

- de Musset's sign: head bobbing with systolic pulse
- Muller's sign: uvula bobbing with systolic pulse
- Corrigan's pulse: booming pulse with quick collapse
- Quincke's pulse: capillary pulsations seen in digits
- Traube's sign: pistol shot sounds heard over femoral artery during systole
- Duroziez's sign: systolic murmur heard over femoral artery with proximal compression and diastolic murmur heard with distal compression
- Hill's sign: defined as popliteal systolic pressure exceeding brachial pressure by 30 mm Hg.
- Of note is that two studies, with a relatively small number of patients, found that Hill's sign was due to inaccurate noninvasive measurement of pressures in the thigh. Intra-arterial pressure recordings found minimal differences between arm and leg systolic pressures

Source: Adapted from [5].

Hemodynamic changes detected by echocardiography

Echocardiography (transthoracic or transesophageal) enables visualization of the valve and identification of congenital abnormalities, rheumatic changes, vegetations, thickening, and/or calcification [6]. Echocardiography also provides information about the size of the LV and aortic root and LV systolic function. Severity of AR may be estimated based on measurement of velocity of regurgitant flow between aorta and LV during diastole by continuous-wave Doppler. The rate of decay of the velocity of flow between aorta and LV during diastole (i.e., pressure half-time) gives an estimate of the gradient between the aorta and LV. A rapid decay indicates equalization of left ventricular and aortic pressures and suggests severe AR. The amount of regurgitant flow can be estimated by several techniques, but a discussion of the relative advantages and disadvantages of these methods is outside the scope of this chapter [7]. Other parameters that can indirectly indicate the hemodynamic severity of AR include (a) measurement of the velocity of

tricuspid regurgitation that enables an estimate of pulmonary artery pressures, which in turn may be related to elevated left atrial pressures; and (b) M-mode echocardiography of the mitral valve, which can demonstrate “flutter” of the valve from AR and/or premature closing of the mitral valve during diastole.

The regurgitant fraction tends to decrease in patients with AR as they exercise because (a) the increase in heart rate shortens diastole and (b) peripheral vascular resistance decreases. As the patient exercises more vigorously, further increases in cardiac output are dependent on increased ejection fraction. Thus, some investigators advocate the use of exercise echocardiography in patients with moderate AR. The inability to augment ejection fraction during exercise may be an indication for earlier valve replacement surgery.

Acute aortic regurgitation

Acute AR generally results from endocarditis, aortic dissection, trauma, or failure of a prosthetic valve. The clinical presentation is usually dramatic, with hypotension and pulmonary edema (Table 11.1). LV diastolic pressures increase markedly as the LV is suddenly exposed to regurgitant flow from the aorta. In acute AR, the LV does not have time to dilate in response to the regurgitant flow and thus markedly increased diastolic pressures are found.

In acute AR, the “classic” hemodynamic changes associated with chronic AR, for example, wide pulse pressure or low diastolic pressure, are often absent. There are, however, several characteristic hemodynamic changes that can be observed in these patients:

- Left ventricular and aortic pressures may equalize during diastole. There can be a very pronounced rate of increase (slope) of the LV pressure during diastole

Table 11.1 Hemodynamic differences between chronic severe AR and acute severe AR.

	Acute severe AR	Chronic severe AR
Typical clinical presentation	Acute onset of pulmonary edema	Progressive dyspnea
Aortic systolic pressure	Normal or decreased	Increased
Aortic diastolic pressure	Normal or decreased	Decreased
Aortic pulse pressure	Normal	Increased
Cardiac output	Decreased	Normal
LVEDP	Markedly elevated	Normal until late in the disease process
LV size	Normal	Enlarged
Stroke volume	Normal or mildly increased	Markedly increased

due to rapid filling from the aorta. This is due to the large volume of blood entering a normal, relatively noncompliant chamber.

- Rapid filling from the aorta can lead to premature closure of the mitral valve. In a heart with a competent aortic valve, LV pressure does not exceed left atrial pressure during diastole and the mitral valve remains open until the LV begins to contract. In acute AR, however, filling of the ventricle from the aorta during diastole leads to a rapid increase in LV pressure. If LV pressure exceeds left atrial pressure, the mitral valve will close before the end of diastole. Premature closure of the mitral valve protects the left atrium and pulmonary circulation from elevated diastolic pressures but reduces flow of blood from the left atrium to the LV.
- Decreased systemic flow leads to activation of compensatory mechanisms that cause left atrial pressure to rise (with corresponding increases in pulmonary capillary wedge pressure) and development of pulmonary edema.
- Myocardial ischemia can occur because of inadequate coronary perfusion (even in the absence of coronary artery disease). This occurs as coronary perfusion pressures decrease due to low aortic diastolic pressures and elevated LV diastolic pressures (Figure 11.1).
- Increased LVEDP.

Pharmacologic treatment of AR

The preferred treatment of patients with severe AR is valve replacement, but there are patients with less severe disease who will be treated medically. Pharmacologic treatment is based on the principle that the amount of regurgitation is a function of valve incompetence, length of diastole, and peripheral arterial resistance. Thus, in patients with AR, drugs that decrease peripheral resistance (e.g., nifedipine, angiotensin-converting enzyme inhibitors) are beneficial, whereas drugs that lengthen diastole (e.g., beta-blockers or rate-slowing calcium channel blockers) are deleterious.

Hemodynamic tracings of a patient with severe AR

These are shown in Figure 11.2 and a further example is given in the case study.



Figure 11.1 Coronary ischemia in a patient with acute on chronic AR. A 31-year-old male with a history of ankylosing spondylitis presented with a one-week history of progressive dyspnea, low-grade fevers (100.5°F), cough, nausea, and diarrhea. He reported a rapid decline in exercise tolerance over the week and experienced dyspnea when walking only 10–20 feet. After admission, he developed severe chest pain and an ECG showed anterior ST elevation that was not present on an ECG taken on admission (a). His blood pressure as determined by sphygmomanometry was 90/30 mm Hg. Emergent cardiac catheterization showed no evidence of coronary artery disease but severe AR with equalization of aortic and left ventricular end-diastolic pressures (b).

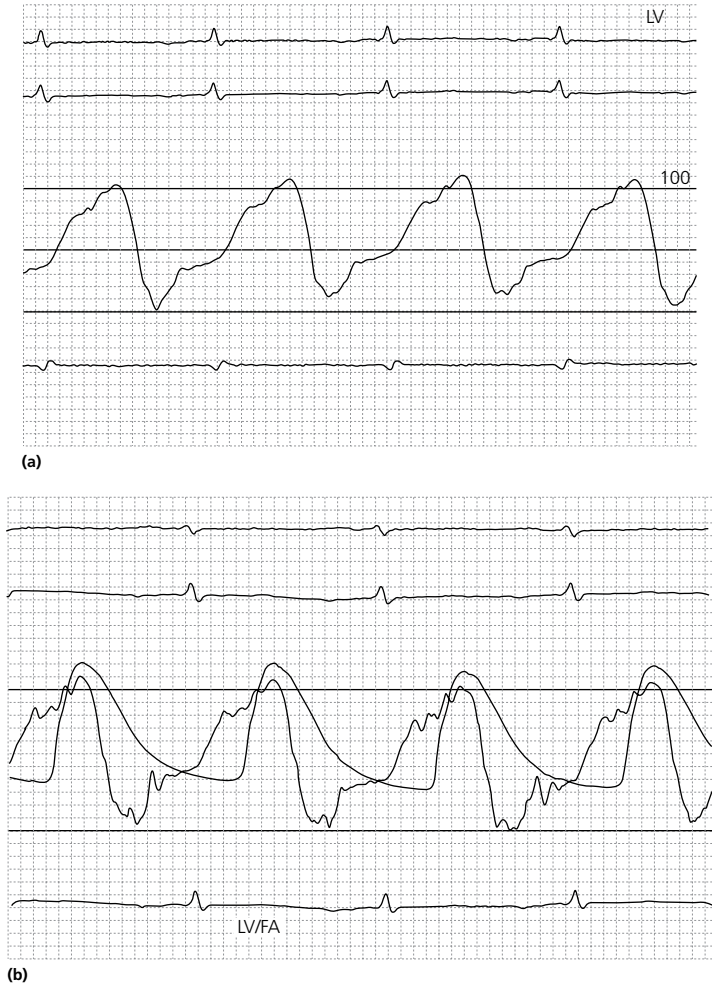


Figure 11.2 Left ventricular tracings alone (a), with femoral artery pressure (b), and with PCWP (c) in a patient with severe chronic AR (all tracings are on a 200 mm Hg scale).

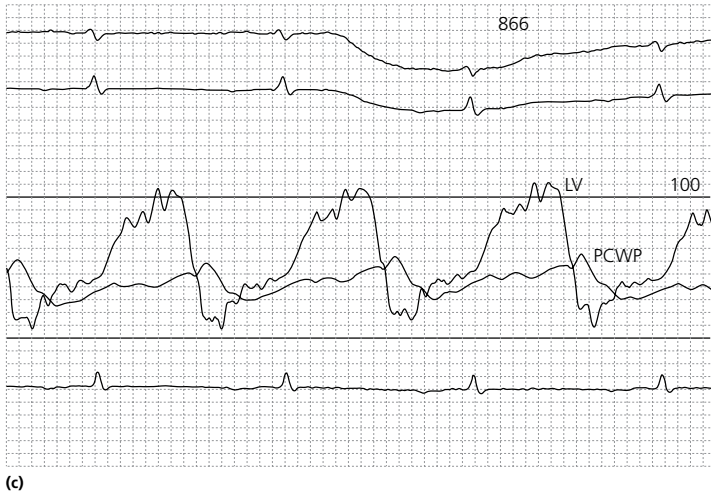


Figure 11.2 (Continued)

Case study

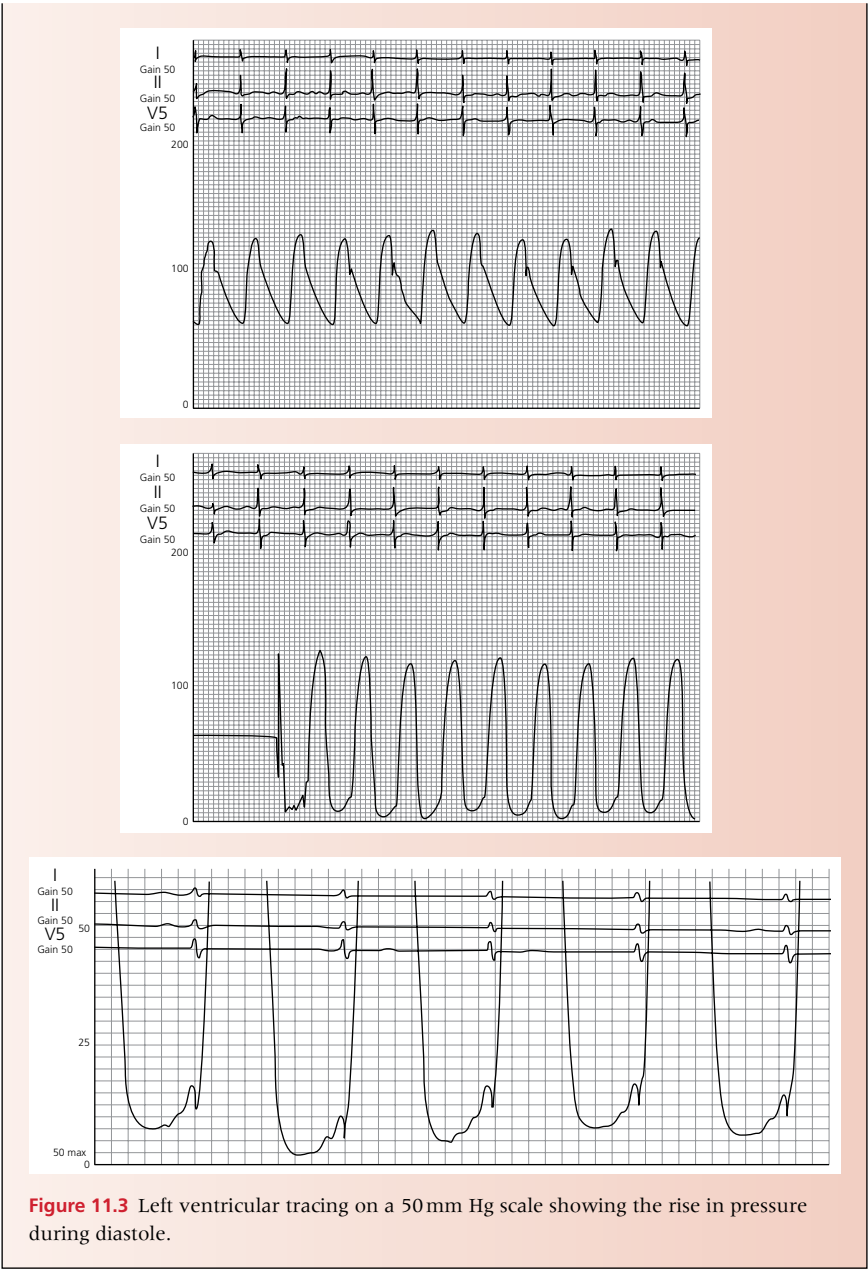
A 65-year-old male with chronic severe aortic regurgitation was referred for cardiac catheterization prior to valve replacement. He had carried the diagnosis of severe AR for several years and was being treated with enalapril. Annual echocardiograms confirmed the presence of AR but showed no chamber dilation. He had been asymptomatic for years but recently developed dyspnea on exertion.

The hemodynamic tracings are shown in Figure 11.3.

Note that the pulse pressure is 60 mm Hg with an aortic diastolic pressure of 62 mm Hg. A clear dicrotic notch is present on the aortic tracing. While the LV diastolic pressure rises more rapidly than normal, the LVEDP is only 15 mm Hg.

The hemodynamics are not consistent with severe AR. This was confirmed by aortic angiography that revealed 2+ AR. In the absence of elevated filling pressures and with normal LV size, there is no evidence that this patient will improve with valve replacement. Looked at a different way, valve replacement will probably not result in a favorable change in hemodynamics (in AR, this usually involves a decrease in LVEDP and an increase in aortic diastolic pressure).

A severe lesion was found in the right coronary artery that was treated by placement of an intracoronary stent. Following the procedure, the patient's symptoms resolved.



Angiographic classification of severity of aortic regurgitation (based on the amount of contrast dye entering the left ventricle during an aortogram)

- 1+ some dye enters ventricle but clears with every systole
- 2+ the ventricle becomes completely opacified after several heartbeats and remains opacified throughout the cardiac cycle
- 3+ the ventricle becomes as dark as the aorta after several heartbeats
- 4+ the ventricle becomes darker than the aorta after several heartbeats

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CHAPTER 12

Mitral regurgitation

Akhil Reddy and Matt Cavender

[Portions of this chapter were adapted from Mitral Regurgitation by RV Kelly, MG Cohen and GA Stouffer in the second edition of this book]

Anatomy

The mitral valve is a complex structure that separates the left atrium (LA) and the left ventricle (LV). The mitral valve apparatus is comprised of two leaflets (anterior and posterior), a fibrous mitral annulus, chordae tendinae, two papillary muscles, and the ventricular wall (Figure 12.1) [1]. The anterior leaflet of the mitral valve is semicircular in shape and has a free edge without indentations. This leaflet is larger and thicker than the posterior leaflet. Each leaflet can be subdivided into three, roughly equal in size, segments (A1/P1 [lateral], A2/P2 [middle], and A3/P3 [medial]) [2–4].

The mitral valve annulus is a complex, three-dimensional, fibrous structure that serves as the anchor for the valve leaflets. The fibrous tissue of the mitral valve annulus is continuous with the fibrous skeleton of the aortic annulus and aorta. As the LV contracts during systole, the pressure in the LV increases resulting in closure of the mitral valve. The contraction of the LV also reduces the area of annulus.

The subvalvular apparatus of the mitral valve includes two papillary muscles that give off multiple chordae tendinae that connect the papillary muscles with the leaflets of the mitral valve. The anterolateral papillary muscle provides chordae to the anterolateral half of both anterior and posterior leaflets. The posteromedial papillary muscle provides chordae to the posteromedial aspect of both leaflets. The posterior papillary muscle is supplied solely by the posterior descending artery, whereas the anterolateral papillary muscle has a dual blood supply from both the left anterior descending coronary artery and the left circumflex artery. As a result of its singular blood supply, the posterior papillary muscle is a risk of rupture in the setting of a large inferior myocardial infarction (MI). Disruption of any of the components of the mitral valve apparatus can result in dysfunction of the valve.

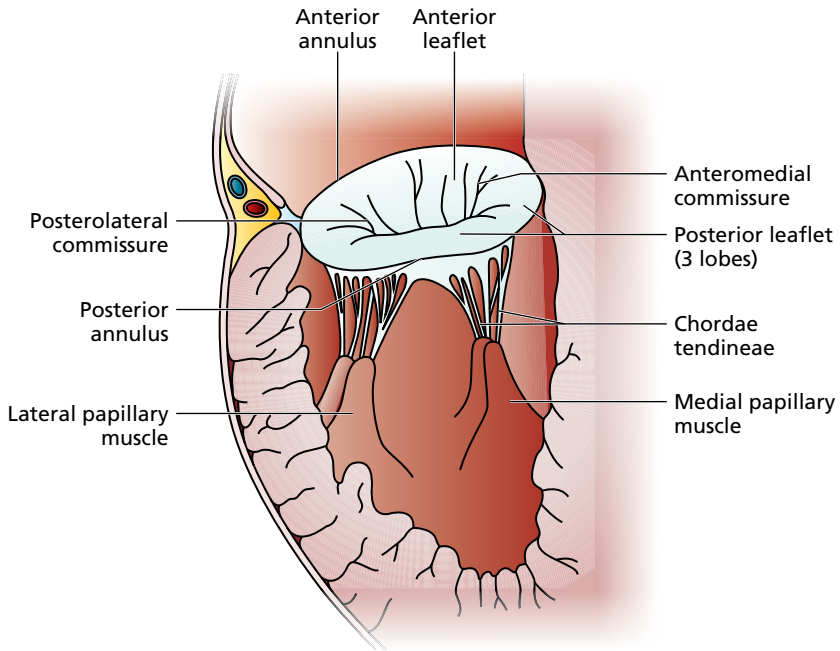


Figure 12.1 Anatomy of the mitral valve apparatus. Source: Adapted from Otto [1].

Pathology

Primary mitral regurgitation (MR) is caused by structural abnormalities of the mitral valve and/or the mitral valve apparatus. Etiologies of primary MR include myxomatous/prolapsed mitral valve leaflets, ruptured papillary muscles, and torn chordae tendineae. In contrast, *secondary MR* is due to non-valvular etiologies including dysfunction of the LA or LV. Dilation of these structures can cause dilatation of the mitral valve annulus and leaflet restriction, which results in the lack of coaptation of the mitral leaflets. Mitral annular calcification (MAC) typically results in mitral stenosis but can also cause regurgitation by immobilizing the mitral leaflets and preventing the leaflets from closing. MAC is associated with hypertension, diabetes, aortic stenosis, Marfan's syndrome, Hurler's syndrome, and chronic renal failure. Carpentier has provided an alternative classification scheme that discriminates based on the motion of the mitral valve leaflets and is useful in planning surgical intervention (Figure 12.2).

Patients with MR can remain asymptomatic for prolonged periods of time before developing symptoms (e.g. dyspnea, volume overload, lower extremity edema, paroxysmal nocturnal dyspnea, and/or atrial fibrillation). The natural history of chronic MR is variable and depends on a variety of factors including the

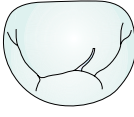
Type	Leaflet motion		Etiologies
I	Normal leaflet motion		Endocarditis causing perforation Annular dilation due to left atrial enlargement
II	Excessive excursion of one or both mitral valve leaflets into the left atrium during systole		Degenerative mitral valve disease (e.g. Marfan syndrome) Mitral valve prolapse (e.g. fibroelastic deficiency, Barlow's disease) Ehlers-Danlos syndrome Trauma
IIIa	Restricted leaflet motion in systole and diastole (e.g. commissural fusion, leaflet thickening, chordal fusion)		Rheumatic disease Radiation Carcinoid Systemic lupus erythematosus Antiphospholipid syndrome
IIIb	Restricted leaflet motion in systole		Cardiomyopathies Ischemic MR post myocardial infarction

Figure 12.2 Carpentier classification of etiologies of mitral regurgitation [4].

acuity of the regurgitation, the volume of regurgitation, LV function, and the underlying cause of MR. The development of symptoms in patients with chronic MR is an indication of mitral valve intervention.

Acute MR

Acute MR is a relatively rare but potentially life-threatening condition that is generally associated with abrupt onset of dyspnea, heart failure, and shock. In contrast to chronic MR, patients with acute, severe MR have sudden onset of pulmonary edema and can even develop cardiogenic shock. Characteristic hemodynamic changes include increased LV preload, compromised forward stroke volume, decreased LV end-systolic diameter, and increased ejection fraction. Causes of acute MR include ruptured papillary muscles (e.g., during acute MI), ruptured chordae (e.g., from myxomatous disease, infective endocarditis, chest trauma, acute rheumatic fever, spontaneous/idiopathic), or iatrogenic trauma to

leaflets or chordae tendinae secondary to catheter-based procedures that involve the LV. Acute MR following an MI is more commonly seen following an inferior MI due to occlusion of the right coronary artery since the posteromedial papillary muscle has a singular blood supply and occlusion can result in papillary muscle ischemia leading to rupture.

Acute MR is characterized hemodynamically by regurgitation in the absence of any compensatory dilation of a relatively noncompliant LA or LV. The lack of time for compensatory mechanisms to develop results in an abrupt rise in LA pressure, which is generally accompanied by large V waves on pulmonary capillary wedge pressure (PCWP) tracing (Figure 12.3a) and appearance of large V waves in the PA tracing resulting in a “camelback” PA tracing, in which V waves are reflected through a compliant pulmonary vasculature (Figure 12.3b). There is also a rapid Y descent as the distended LA quickly empties. These hemodynamic factors can result in adverse changes including significant pulmonary edema/symptoms.

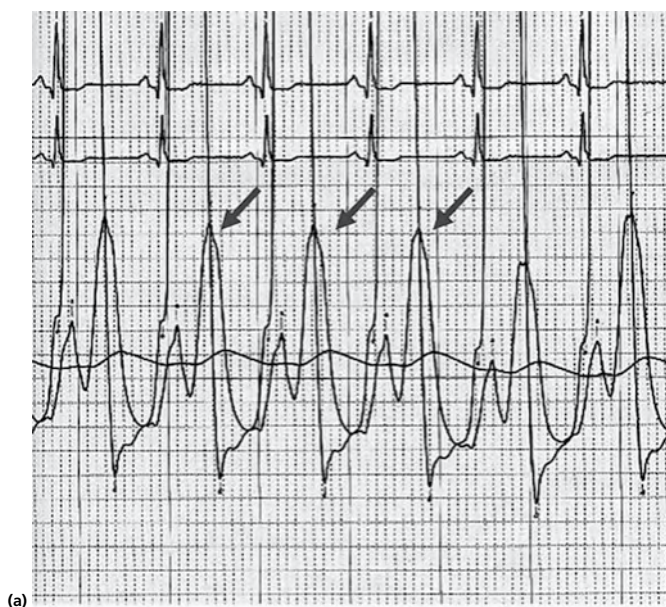


Figure 12.3 Simultaneous LV and PCWP tracing (a) and pulmonary artery tracing (b) in a patient with severe MR. The PCWP tracing shows a large V wave (arrow). The giant V wave results from regurgitation of blood into a relatively small and noncompliant LA. The electrocardiogram (ECG) illustrates the timing of the PCW V wave with the peak of the V wave occurring after ventricular repolarization, as manifested by the T wave of the ECG. The pulmonary artery tracing illustrates the bifid appearance characteristic of a reflected V wave (arrow). [LV = left ventricle; PCWP = pulmonary capillary wedge pressure].

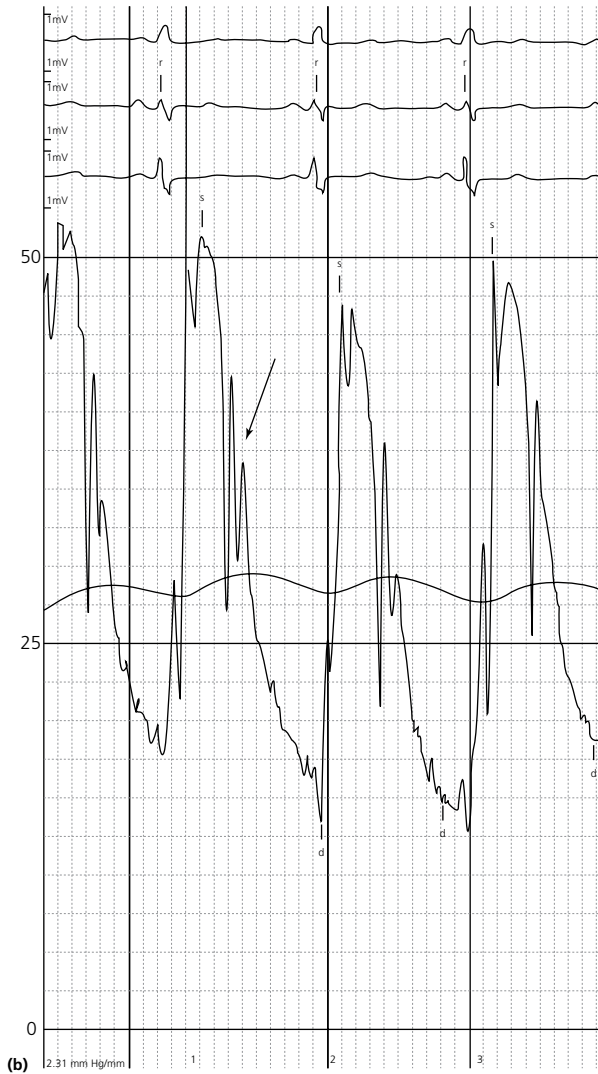


Figure 12.3 (Continued)

Hemodynamic principles in patients with chronic MR

1 The amount of MR is dynamic and will be influenced by the following:

- Size of regurgitant orifice—there is a direct relationship between the size of the regurgitant orifice and the regurgitant volume. In secondary MR, the cross-sectional area of the annulus may be influenced by LV size. LV dilation will result in an increase in the annulus size and the regurgitant orifice, whereas a decrease in LV size (e.g., by reducing volume, inotropic medications, or afterload reducing agents) will cause a reduction in the regurgitant orifice.

- Left atrial compliance—the LA dilates over time in patients with chronic MR so that large regurgitant volumes can be accommodated with minimal increases in pressure.
 - Pressure difference between LV and LA during systole
 - Duration of systole
 - Afterload—systolic blood flow from the LV goes in two directions: into a high-pressure, high-capacitance system (the aorta) and a low-pressure, low-capacitance system (the LA) (Figure 12.4). Thus, the amount of regurgitant flow is influenced by the ratio of resistance to flow across the aortic valve to resistance to flow across the mitral valve. Increases in aortic afterload (e.g., blood pressure, aortic stenosis, etc.) will increase the amount of MR. Because of blood flow into the LA, the effective afterload seen by the LV is reduced regardless of the aortic afterload.
- 2 In the setting of MR, there is no true isovolumetric contraction phase on the LV pressure–volume loop since regurgitant flow across the mitral valve occurs before the aortic valve opens.
 - 3 Left ventricular end-diastolic volume (LVEDV) increases to maintain stroke volume and compensate for the regurgitant volume. Increased diastolic volumes result in increased contractility (Starling's law). In MR, there is increased stroke volume and stroke work, although effective forward stroke volume may be normal or reduced.
 - 4 The compliance of the LA and pulmonary veins is an important determinant of the severity of MR symptoms. In patients with a normal-sized LA and severe MR, marked elevation in LA pressure occurs, with a prominent V wave on the

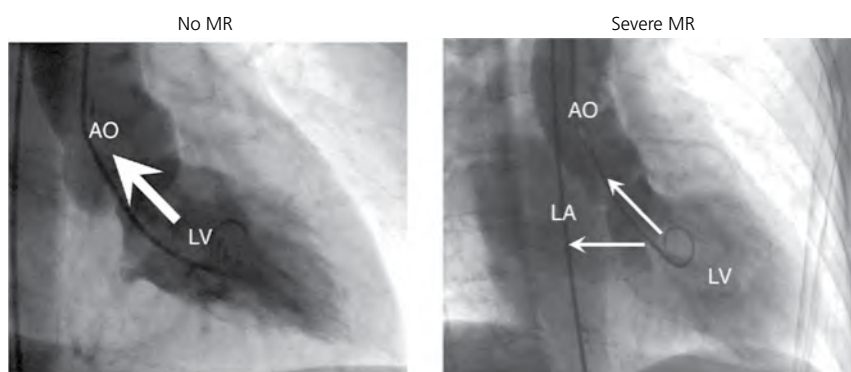


Figure 12.4 Left ventriculography in patients with and without mitral regurgitation. Still frames from left ventriculogram showing no mitral regurgitation on the left and severe mitral regurgitation on the right. In both cases, dye has been injected into the left ventricle. Note that the left atrium is opacified on the left but not on the right indicative of mitral regurgitation. The arrow represents blood flow. With a competent mitral valve, all of the blood ejected by the left ventricle goes into the aorta. In patients with mitral regurgitation, a portion of left ventricular stroke volume goes into the left atrium. [LA = left atrium and Ao = aorta; LV = left ventricle].

PCWP tracing and pulmonary congestion. In patients with acute MR, the LA initially operates on the steep portion of the Frank–Starling curve, with a marked rise in pressure for a small increase in volume. In chronic MR, the LA dilates over time and can accommodate large regurgitant volumes. This usually occurs over a 6–12-month period. Increased LA compliance is a feature of longstanding MR (i.e., increased LA size with minimal increases in LA pressure). In this situation, longstanding MR shifts the LA Starling curve to the right, minimizing the increases in LA pressures in response to large volume increases.

- 5 LV loading conditions in MR with preserved ejection fraction because LV preload is increased while LV afterload is normal or reduced. In patients with chronic MR, LV systolic contractility can become progressively impaired, with clinical indexes of LV function (e.g., ejection fraction and fractional shortening) remaining normal. This is why a fall in ejection fraction in patients with severe MR is an ominous finding and why ejection fraction may worsen after mitral valve surgery (as opposed to aortic regurgitation, in which ejection fraction may improve after valve replacement because afterload is decreased).
- 6 Symptoms commonly occur initially with exercise in patients with MR. There is controversy about whether exertional dyspnea in patients with chronic MR is due to increases in pulmonary artery pressure or to inability to increase cardiac output.

Compensatory mechanisms in chronic MR

Chronic MR results in compensatory changes to the LV that have effects on cardiac hemodynamics. Chronic MR results in dilation of the LA and LV. The LV adapts to substantial regurgitant volumes according to Laplace's law (wall tension = radius $\times$ intraventricular pressure). MR results in the ventricle being in a volume overload state. As the LVEDV increases, cardiac output is preserved. However, these changes increase wall tension. In chronic MR, LVEDV and LV mass increase in proportion to the degree of LV dilatation. The degree of hypertrophy correlates with the amount of chamber dilation so that the ratio of LV mass to end-diastolic volume remains in the normal range (in contrast to the situation in patients with LV pressure overload). At the same time, there is a greater volume at a given pressure, resulting in a shift in the pressure–volume relationship (Figure 12.5). In most patients, LV compensation is maintained for a prolonged period; however, if untreated, LV failure will ultimately occur. This results in an increase in preload and LV end-systolic volume (LVESV), and a decrease in LVEF and stroke volume. The transition from a compensated state to a decompensated state in chronic MR occurs when LV systolic function begins to decline, LVEDV increases, and filling pressures rise. Thus, chronic decompensated MR results in both systolic and diastolic dysfunction.

LVESV is an important pre-operative prognostic marker of morbidity following mitral valve surgery including mortality, post-operative heart failure, and

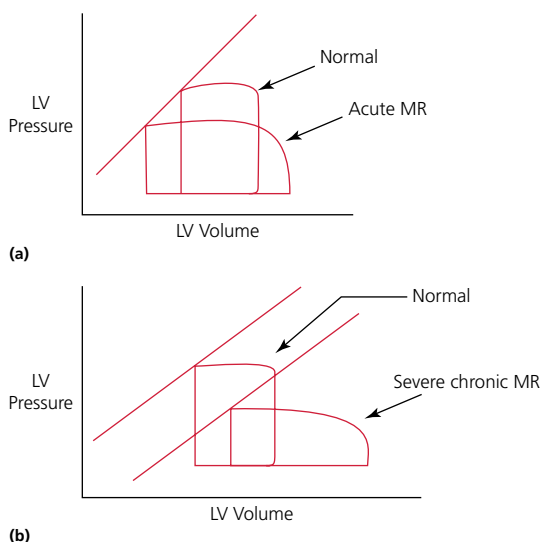


Figure 12.5 Relationship between left ventricular pressure and left ventricular volume in patients with acute MR (a) or chronic MR (b).

post-operative LV systolic function. An LV end-systolic diameter >45 mm is generally used as an indication for surgery, although in cases in which the mitral valve can be repaired, a lower cutoff value has been advocated.

Cardiac catheterization and MR hemodynamics

The primary findings of catheterization in chronic MR include:

- Increased LA (or PCWP), pulmonary artery, right ventricular, and right atrial pressures.
- In severe MR, effective cardiac output is usually depressed while stroke volume (i.e., the combination of forward and regurgitant flow) is usually increased. Functional capacity during exercise depends primarily on cardiac output and not the regurgitant volume.
- V waves may or may not be present in the PCWP tracing (Figure 12.3a). They occur during ventricular systole and coincide with the T wave on the ECG and descent of pressure (isovolumetric relaxation) on the LV tracing. The V wave represents the rise in LA pressure during ventricular contraction and the height of the V wave is determined by the volume of blood entering the LA, LA compliance, and LA size. Because the size of the V wave is influenced by factors other than regurgitant flow, large V waves are neither sensitive nor specific for MR, nor does the absence of a significant V wave rule out significant MR (for a more detailed discussion of V waves, see Chapter 5).

- There may be a “camelback” appearance to the PA waveform. This tracing is characterized by a bifid appearance in which the systolic peak is followed by a second peak, which is a reflected V wave (Figure 12.3b).
- In MR, the A wave is generally not affected. In cases of pure MR, the Y descent in the PCWP is rapid (pseudo constriction pattern) as the distended LA empties rapidly during early diastole. However, in patients with mixed mitral valve disease, the Y descent is gradual. A brief early diastolic pressure gradient between LA and LV may occur in patients with isolated severe MR because of increased blood flow across a normal-size mitral orifice early in diastole.
- The pressure gradient across a stenotic mitral valve is a function of resistance and flow ($P = R \times F$). In patients with mild mitral stenosis and severe MR, the diastolic gradient across the mitral valve can simulate severe mitral stenosis resulting in pseudo-mitral stenosis. This occurs because the excessive flow across the valve is equal to cardiac output + regurgitant volume. Thus, in severe MR, flow across the mitral valve may exceed $2 \times$ cardiac output resulting in an increase in the transmitral gradient that is independent of orifice size.

Physical examination

The pulse is sharp in severe chronic MR and the pulse volume is usually normal. The apical impulse is brisk and hyperdynamic. It is often displaced to the left and can be associated with a prominent LV-filling thrill. On auscultation, the first heart sound is diminished in severe MR. A wide splitting of S2 is common. It results from the shortening of the LV ejection and an earlier aortic valve closure because of reduced resistance to LV outflow. If severe pulmonary hypertension develops, P2 can be louder than A2.

The MR murmur is classically described as a ‘blowing’ holosystolic murmur. In severe MR, it commences immediately after a soft S1. It may extend beyond A2 because of the persisting pressure difference between the LV and LA after aortic closure. The murmur is typically loudest at the apex and radiates to the axilla. However, the murmur can also be heard at the left lower sternal border if there is posterior leaflet prolapse, which results in MR that is more anteriorly directed. The murmur of MR is usually accentuated by isometric exercise in which afterload is increased resulting in an increase in regurgitant volume. In papillary dysfunction, the MR murmur may occur later in systole, with preservation of a normal S1 because the initial closure of the mitral valve is unaffected. A third heart sound (but not a fourth heart sound) is typical of chronic MR. In MR caused by mitral valve prolapse and myxomatous degeneration of the valve, the murmur may not be holosystolic but rather tend to be more early or mid-systolic and have a more musical quality.

In acute severe MR, patients may not have a prominent murmur due to rapid equalization of the pressure difference between the LV and LA (since the LA volume has not yet increased due to the acuity of the murmur). The murmur, if

present, may be short. The murmur of acute MR is lower in pitch and softer than the murmur of chronic MR. S3 and S4 are common, but there may not be a hyperdynamic apical impulse if the ventricle is normal in size.

Assessment of MR severity

Transthoracic echocardiogram (TTE) provides significant information regarding valvular and ventricular anatomy and hemodynamics. The volume and diameter of cardiac chambers (particularly the LA and LV) can be assessed. The mitral valve, valve apparatus, chordae, and papillary muscles are also well visualized [5].

Transesophageal echocardiogram (TEE) can provide additional information on the severity of MR and the etiology of regurgitation. In most cases, TEE is not necessary to diagnose MR or evaluate the severity of MR; but it is very helpful if the TTE is suboptimal and/or additional information is needed to plan for either percutaneous or surgical mitral interventions.

Severity of MR can be defined by several different echocardiographic parameters (Table 12.1) [6]. The intensity of the Doppler signal across the mitral valve provides a qualitative measure of MR severity. A dense MR signal indicates a more severe MR than a faint MR signal. There are a variety of quantitative measures that can assess MR severity. The ratio of the regurgitant flow to the forward flow, regurgitant jet area, length of the regurgitant jet, ratio of regurgitant jet to LA area, and effective regurgitant orifice (ERO) can all be used to assess the severity of MR. Color flow area of the regurgitant jet on a Doppler is not the optimal technique to quantify the severity of MR since regurgitant

Table 12.1 Echocardiographic assessment of mitral regurgitation.

	I (mild)	II	III	IV (severe)
Vena contracta (mm)	<3	3–4.9	6–6.9	≥7
EROA (cm ²)	<0.2	0.2–0.29	0.3–0.39	≥0.4
PISA	Small			Large
PV flow				Systolic reversal
MR jet (% of LA)	<15	15–30	35–50	≥50
RF (%)	<30	30–39	40–49	≥50
LA size	Normal	Normal	Mildly increased	Moderately or severely increased
LV size	Normal	Normal	Mildly increased	Moderately or severely increased

EROA = effective regurgitant orifice area; LA = left atrium; LV = left ventricle; MR = mitral regurgitation; PISA = proximal isovelocity surface area.

volume varies depending on loading conditions of the heart. For example, patients with similar volumes of MR can have smaller regurgitant jet areas in the setting of an enlarged LA when compared to patients with LA pressures or sizes that are normal.

The vena contracta is defined as the jet width at the level of the valve and can often be identified as the narrowest portion of the regurgitant jet which occurs at the regurgitant orifice. Measurement of the vena contracta can help quantify MR severity. A vena contracta size of <3 mm is indicative of mild MR, a size of 3–7 mm is indicative of moderate MR, and a size of >7 mm is indicative of severe MR. The PISA (proximal isovelocity surface area) method is used for quantification of the severity when there is a single or dominant regurgitant orifice. This calculation allows for the measurement of the ERO area (EROA) and regurgitant volume. An EROA >40 mm or regurgitant volume of >60 mL is consistent with severe MR.

Pulsed Doppler evaluation of the pulmonary venous flow can also provide important data in the assessment of MR severity. In a normal hemodynamic state, the flow through the pulmonary vein results in a positive systolic wave followed by a smaller diastolic wave. With increasing severity of the MR, there is a decrease in S wave velocity. In severe MR, S wave is reversed providing a specific measure of severe MR (Figure 12.6). It should be noted that pulmonary vein assessment is not helpful in patients with atrial fibrillation due to the blunted effect of flow from arrhythmia.

In patients undergoing cardiac catheterization, a left ventriculogram obtained at 30° right anterior oblique can be helpful in assessing severity of MR (Figure 12.4 and Table 12.2).

Important points

- 1 MR is dynamic and is dependent on multiple factors including:
 - Size of regurgitant orifice
 - Left atrial compliance
 - Mean pressure difference between LV and LA
 - Duration of systole
 - Afterload (i.e., blood pressure)
- 2 Acute MR is generally associated with abrupt onset of heart failure, normal-size LV, hyperdynamic LV, and a murmur that is short, soft, and potentially even absent.
- 3 Chronic MR is associated with reduced LV afterload. This is why a fall in ejection fraction is ominous and why ejection fraction does not improve after valve replacement.
- 4 To maintain stroke volume in the setting of MR, the LVEDV will increase.
- 5 Pronounced V waves on PCWP tracing are suggestive of MR, but are neither sensitive nor specific.

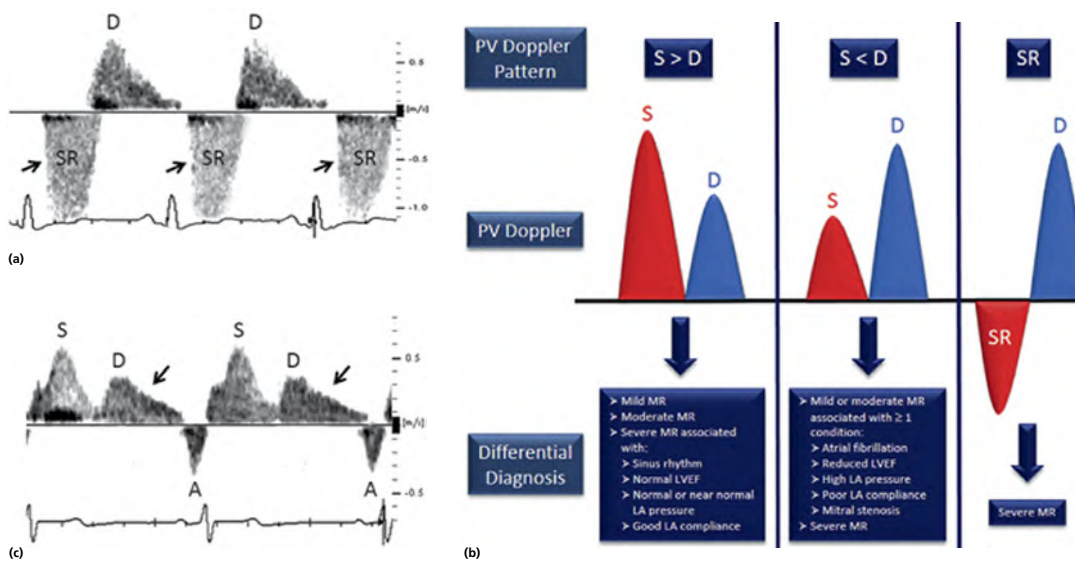


Figure 12.6 Pulmonary vein interrogation during echocardiography in mitral valve disease. (a) Severe MR in a 55-year-old man with ischemic heart disease. The PV Doppler profile demonstrates characteristic systolic reversal of flow (arrows), occurring in the last two-thirds of systole and replacing the forward S wave. (b) Various pulmonary venous flow patterns associated with MR. (c) Severe mitral stenosis in a 44-year-old woman with rheumatic heart disease. There is prolongation of the D-wave pressure halftime at 160ms (arrows), which is comparable with the transmitral E-wave pressure halftime of 165 ms, reflecting the obstruction to flow across the MV. [MR = mitral regurgitation; PCW = pulmonary capillary wedge; PV = pulmonary vein]. Source: Reproduced with permission from Fadel *et al.* [7]/Elsevier.

Table 12.2 Assessment of mitral regurgitation on LV angiography.

-
- 1** Contrast enters LA but clears with each beat and never fills the entire LA.
 - 2** Faint filling of the entire LA but the opacification of the LA remains less than that of the LV.
 - 3** Complete opacification of LA with opacification of the LA equal to that of the LV.
 - 4** Complete and dense filling of the LA with the initial beat and opacification of the LA becoming darker than LV; evidence of contrast in the pulmonary veins.
-

Hemodynamics of mitral regurgitation

Acute

- Elevated PCWP and pulmonary artery pressure
- Prominent V wave
- Pseudo constriction (rapid dilation of left atria, right ventricle, and right atria can simulate hemodynamic findings of constrictive pericarditis)
- Hyperdynamic left ventricular function with increased ejection fraction
- Normal left ventricular dimensions
- May have hypotension and shock

Chronic compensated

- Normal or mildly elevated right heart pressures
- Less prominent V wave
- Mild-to-moderate left ventricular dilation
- Normal ejection fraction

Chronic decompensated

- Elevated left atrial/PCWP, pulmonary artery, and right heart pressures
- Marked left ventricular dilation
- Decreased ejection fraction

Treatment of mitral regurgitation

Current guidelines support a multifaceted approach to the treatment of patients with MR [8]. Medical therapy cannot modify the underlying pathology of primary MR, although medications that reduce afterload can temporarily reduce the volume of MR. In contrast, patients with secondary MR can have significant improvements in this form of MR. Patients should be treated with maximally tolerated, guideline-based therapy including therapies that target the renin-angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers with/without neprilysin inhibitors, mineralocorticoid receptor antagonists, and SGLT2 inhibitors). All patients with atrial fibrillation should receive chronic anticoagulation, and appropriate measures should be taken to control the ventricular response rate and/or restore sinus rhythm.

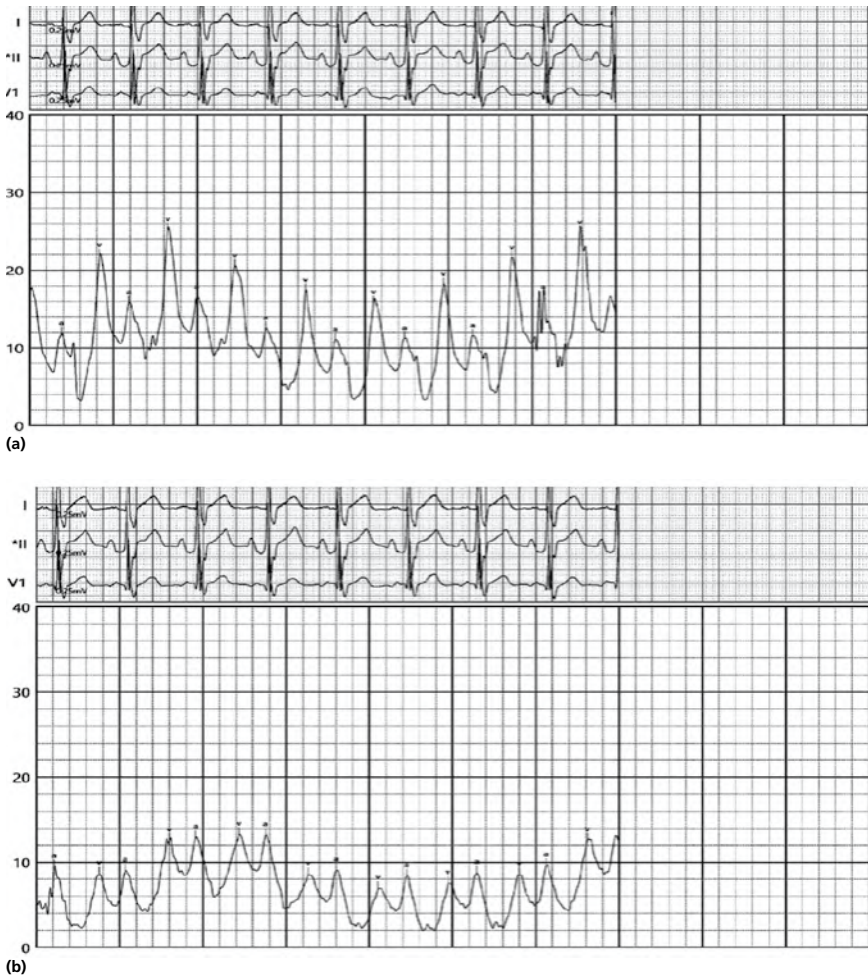


Figure 12.7 Left atrial pressure with large V waves in a patient with severe MR prior to transcatheter edge-to-edge mitral valve repair (TEER) (a). Panel (b) shows left atrial pressure post-TEER with a reduction in V waves.

Surgical treatment with mitral valve repair or replacement is warranted in patients with severe, primary MR if there is evidence of symptoms, LV changes (either dilation or decrement in LV function), or atrial fibrillation. Patients with heart failure who have NYHA III/IV symptoms despite maximally tolerated medical therapy and have severe, secondary MR should be considered for transcatheter edge-to-edge repair (TEER). TEER is a catheter-based procedure that is performed through a transseptal approach. A clasp-like device approximates the anterior and posterior mitral leaflets, reducing and, in some cases, eliminating the MR (Figure 12.7). The reduction in MR is associated with favorable LV remodeling and amelioration of symptoms, both immediately and up to 4 years, with clinical results equivalent to those achieved via surgery [9, 10].

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CHAPTER 13

The tricuspid valve

Tamari Papidze and Matt Cavender

[Some of the text and figures were taken from *The Tricuspid Valve* by David A. Tate and George A. Stouffer in the first and second editions of this book]

The tricuspid valve separates the right atrium (RA) from the right ventricle (RV). This valve has a larger orifice size (7–9 cm²) than the other cardiac valves [1]. The tricuspid valve is typically made up of three leaflets (septal, anterior, posterior). These leaflets differ in size, with the anterior leaflet usually being the largest. The posterior leaflet is the most likely to have variable anatomy and can have multiple segments. The septal leaflet inserts into the interventricular septum. The anatomy of the tricuspid valve leaflets is more variable than that of the other valves. There can be significant variation of the components of the valve with some tricuspid valves having four functioning leaflets rather than three [2]. The tricuspid valve leaflets are thin and translucent, which is adequate since there are relatively lower pressures and hemodynamic stresses typically seen on the right side of the heart (Figure 13.1).

The remainder of tricuspid valve apparatus is somewhat comparable to the mitral valve. Components include papillary muscles, which attach to the ventricular wall (typically 2 with the anterior papillary muscle supporting the anterior and posterior leaflets and the posterior papillary muscle attaching to the septal and posterior leaflets), chordae tendinae that attach the valve leaflets to the papillary muscles, and an annulus which serves as the anchor point for the valve leaflets. Unlike some of the other cardiac valves, the tricuspid annulus does not have significant fibrous tissue and, in some cases, is actually made up of endocardium [3]. Structural tricuspid valvular abnormalities do occur; however, issues with the tricuspid valve are far more commonly seen in patients with morphologically normal valves subjected to abnormal hemodynamic stresses. Morphologic changes in the RV or RA that affect the geometry of the valve can cause a lack of coaptation of the valve leaflets.

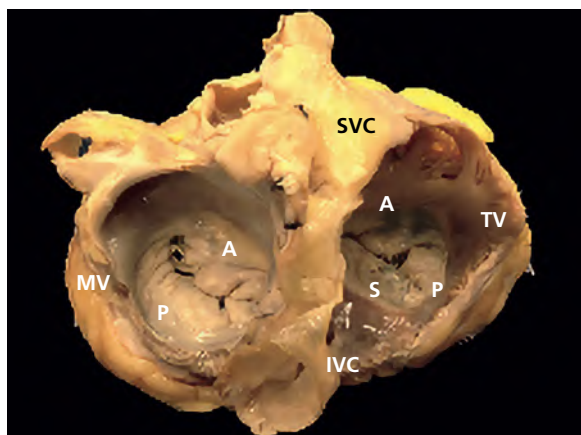


Figure 13.1 Anatomy of the tricuspid valve. [IVC = inferior vena cava; LV = left ventricle; MV = mitral valve; P = posterior leaflet; PV = pulmonic valve; S = septal leaflet; SVC = superior vena cava; TV = tricuspid valve]. Source: Dahou *et al.* [2]/with permission of Elsevier.

Tricuspid regurgitation

Pathophysiology

Tricuspid regurgitation due to primary structural valvular abnormalities is rare. Structural abnormalities can be seen with rheumatic heart disease, myxomatous disease (prolapse), infective endocarditis, marantic endocarditis, carcinoid heart disease, anorectic drugs, trauma, Marfan's syndrome, or Ebstein's anomaly. Transvenous pacemaker leads can impinge on the septal leaflet preventing the coaptation of the leaflets resulting in iatrogenic tricuspid regurgitation. Other less common etiologies of iatrogenic tricuspid regurgitation included torn papillary muscle related to pacemaker lead extraction or right ventricular biopsies in heart transplant recipients (Figure 13.2).

Secondary functional tricuspid regurgitation is the most common etiology of tricuspid regurgitation seen in adults. Etiologies of secondary tricuspid regurgitation include left-sided cardiac disease (e.g. left ventricular systolic or diastolic dysfunction, mitral regurgitation, mitral stenosis, pulmonary valve stenosis), pulmonary hypertension (e.g. primary/secondary pulmonary hypertension, cor pulmonale secondary to pulmonary embolism, left to right shunts), and/or RV dysfunction (e.g. prior RV myocardial infarction). In addition, secondary tricuspid regurgitation can be idiopathic and caused by dilatation of the tricuspid annulus resulting in functional tricuspid regurgitation despite anatomically normal leaflets and chords. These etiologies share common morphological abnormalities that may occur simultaneously including: (1) tethering or tenting of the tricuspid leaflets, (2) displacement of the papillary muscles, (3) RV dysfunction, and (4) dilation of the annulus and/or RA [2].

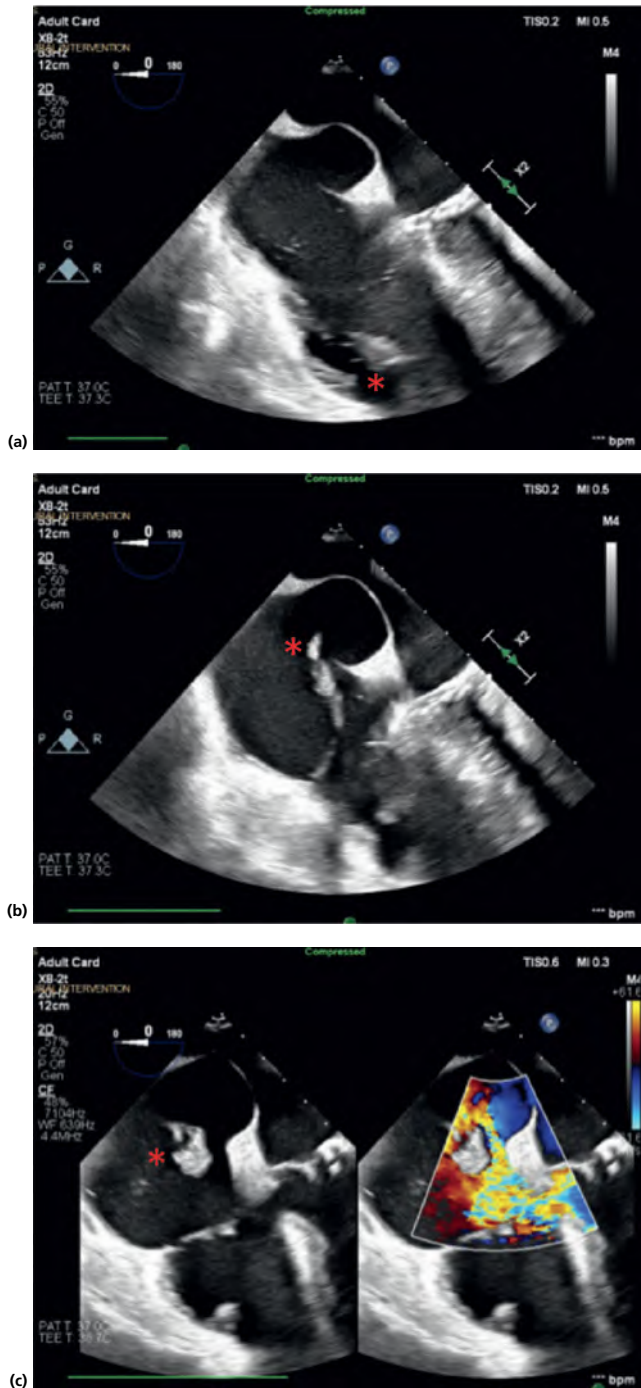


Figure 13.2 Ruptured anterior papillary muscle (*) seen during (a) diastole and (b) systole that is resulting in (c) severe mitral regurgitation.

Tricuspid regurgitation is common and frequently of little clinical significance if the severity is moderate or less. As tricuspid regurgitation becomes more severe, the signs and symptoms of elevated systemic venous pressure become evident and include congestive findings on physical exams such as pedal edema, ascites, and hepatic enlargement. Cardiac output can be diminished in patients with severe tricuspid regurgitation resulting in fatigue and decreased exertional tolerance.

Physical exam findings in patients with severe tricuspid regurgitation include jugular venous distention. This elevation is reflective of increased right atrial pressure. A distinct and prominent CV wave reflecting systolic regurgitant flow into the RA is frequently noted. The typical murmur is holosystolic and located at the left or right mid-sternal edge or at the subxiphoid area. In patients with torrential tricuspid regurgitation, the murmur can be soft or even absent which is reflective of the equalization of pressures between the RA and right ventricle. Augmentation of the murmur with inspiration helps distinguish tricuspid from mitral regurgitation.

Hemodynamic changes detected by echocardiography

Two-dimensional (2D) and Doppler echocardiography are the foundational elements for evaluating tricuspid regurgitation [4]. The 2D echocardiography provides insight into the structure of the valvular apparatus and the mechanism/etiology of regurgitation. Right atrial and ventricular sizes and volumes provide insight into the duration and severity of tricuspid regurgitation.

The Doppler components of the echocardiogram provide important hemodynamic data and other information necessary to determine the severity of tricuspid regurgitation. Color flow and pulse-wave examination reveal the presence, direction, and magnitude of the regurgitant jet. A vena contracta width of 0.7 cm or more and systolic flow reversal in the hepatic veins are seen with severe tricuspid regurgitation (Figure 13.3). Finally, continuous-wave Doppler and the modified Bernoulli equation can be used to estimate the RV and pulmonary artery systolic pressures where $RV \text{ systolic pressure} = \text{the gradient between the RV and the RA during systole (approximated by multiplying the square of the velocity across the tricuspid valve by four)} + \text{estimated RA pressure (based on the inferior vena cava [IVC] size and changes with inspiration)}$. In the absence of pulmonic stenosis, RV systolic pressure is equal to the pulmonary systolic pressure. The RV systolic pressure, in and of itself, is not helpful in determining the severity of the tricuspid regurgitation.

Hemodynamic changes evident at catheterization

Invasive hemodynamic findings associated with tricuspid regurgitation are most evident in the RA pressure tracing (Figure 13.4). The normal RA waveform consists of an A wave associated with atrial contraction, a C wave associated with ventricular contraction, and a V wave associated with rising atrial pressure just prior to opening of the tricuspid valve. With volumetrically important tricuspid regurgitation, there is a large systolic wave in the RA tracing, reflecting retrograde

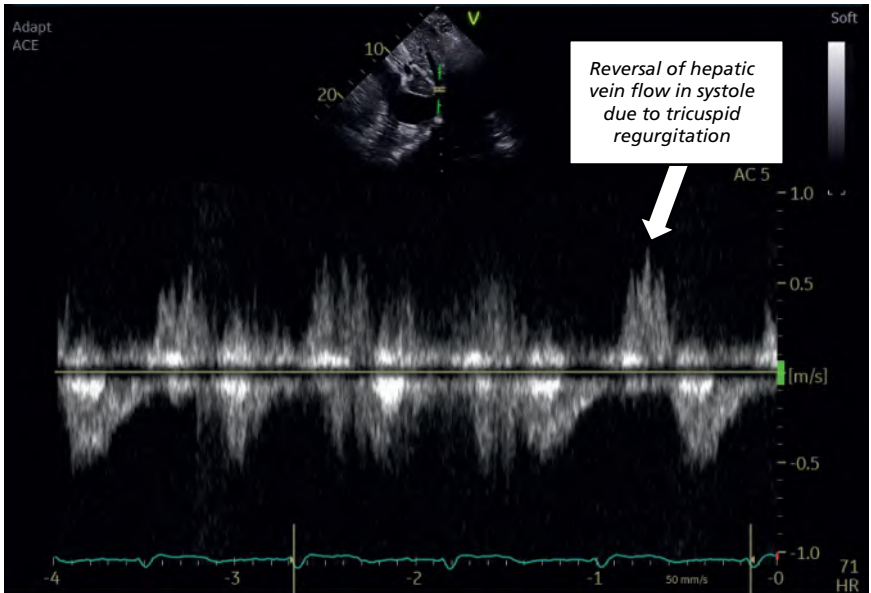


Figure 13.3 Doppler interrogation of hepatic vein flow showing systolic flow reversal consistent with severe tricuspid regurgitation.

ejection of blood and consequent transmission of pressure from the RV to the RA. This waveform is variously termed an S wave or a CV wave, as it occurs during systole and subsumes the normally independent C and V waves. This CV wave corresponds to the reversal of hepatic vein systolic flow seen with echocardiography discussed in the prior section. The magnitude of the systolic wave is determined by both the severity of the regurgitation and the compliance of the RA [5].

With severe tricuspid regurgitation, the systolic wave in the RA becomes so prominent that the tracing resembles the right ventricular tracing. Indeed, in very severe tricuspid regurgitation, the RA and RV pressure tracings are virtually identical, reflecting the fact that in the absence of a competent tricuspid valve, the RA and RV become, functionally, a single chamber (Figure 13.5). While this may be most evident with a dual lumen catheter in the RA and RV, the catheter across the tricuspid valve can itself cause tricuspid regurgitation. Careful performance and observation of RV to RA “pullback” pressures, paired with Doppler and echocardiographic analysis, can provide compelling evidence for severe tricuspid regurgitation. A ventriculogram (typically at 30° right anterior oblique) can help assess the severity of tricuspid regurgitation; however, it is rarely necessary. Moreover, the catheter across the tricuspid valve and the ectopy associated with right ventricular contrast injection often introduce artifacts. With current echocardiographic and Doppler techniques, angiography is of little additional utility.

Catheterization data do not allow definitive distinction between structural and functional tricuspid regurgitation. However, severe tricuspid regurgitation

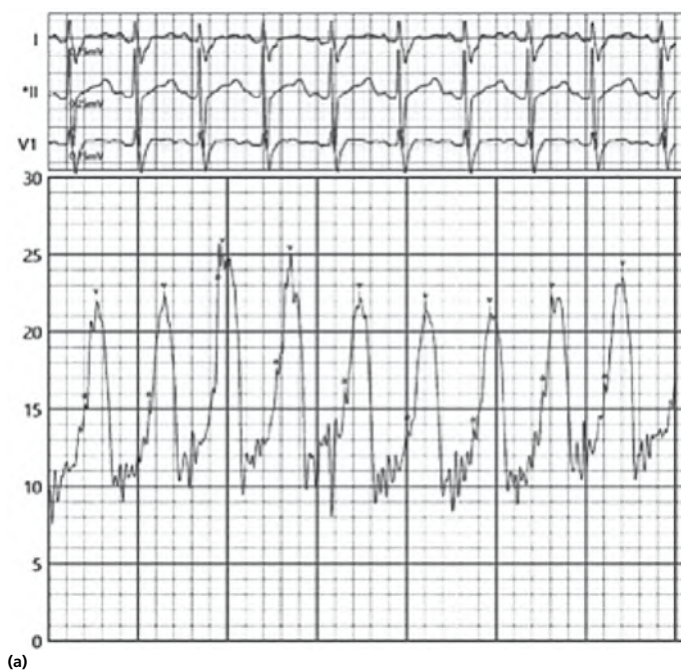


Figure 13.4 RA pressure in a patient with severe tricuspid regurgitation before (a) tricuspid valve replacement and after (b) tricuspid valve replacement.

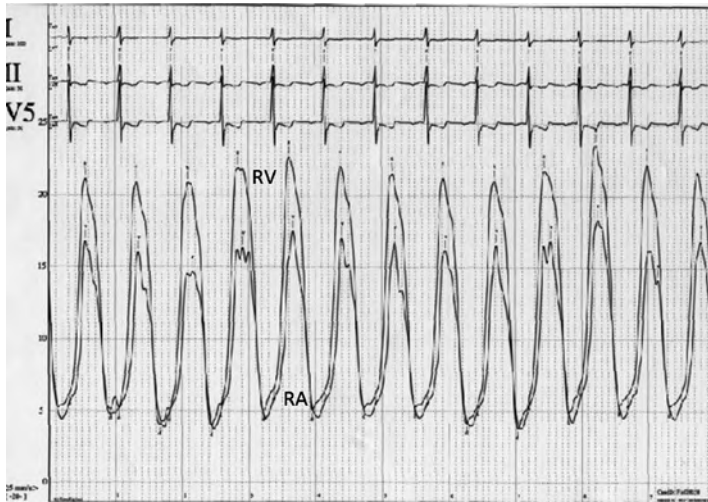


Figure 13.5 Simultaneous RA and RV pressures from a 67-year-old male who had undergone heart transplantation 9 years previously. Source: Rao *et al.* [5]. Reproduced with permission of John Wiley and Sons.

associated with relatively low RV and PA systolic pressures (less than 40 mm Hg) is more likely to be at least partially due to organic valvular disease. On the other hand, tricuspid regurgitation associated with very high RV systolic pressures is much more likely to be functional.

Treatment

In the case of functional tricuspid regurgitation, the mainstay of therapy is treatment of the underlying condition. This may be medical therapy in the setting of left ventricular failure, or procedural in the setting of mitral stenosis. Loop diuretics and aldosterone antagonists may be useful for fluid management. Indications for tricuspid valve repair or replacement have historically been based on surgical treatments and include patients who are refractory to medical therapy and are appropriate surgical patients or who are undergoing cardiac surgery for a separate indication (e.g., mitral or aortic valve disease). With a surgical approach, tricuspid valve repair with an annuloplasty ring is preferred to tricuspid valve replacement. If valve replacement is necessary, bioprostheses are favored because the low-pressure state of the right heart can predispose a mechanical tricuspid valve to thrombosis.

Clinical trials have now shown that percutaneous transcatheter edge-to-edge repair and tricuspid valve replacement are effective treatments for tricuspid regurgitation [6, 7]. With the advent of transcatheter therapies that allow for either edge-to-edge repair or tricuspid valve replacement, the indications for interventions are changing. Trials evaluating these therapies have included patients with tricuspid regurgitation despite optimal medical therapy. The inclusion and

exclusion criteria had some differences between the trials and more research is needed to better understand which patients do and do not benefit from transcatheter therapies. In addition, it remains unclear whether edge-to-edge repair or replacement is preferable and whether certain situations benefit from one therapy over another.

Tricuspid stenosis

Pathophysiology

Acquired native tricuspid stenosis is uncommon. Most cases are due to rheumatic heart disease, carcinoid heart disease, or stenosis of a prosthetic valve initially placed for tricuspid regurgitation. When rheumatic tricuspid stenosis is present, it is generally associated with mitral stenosis, which accounts for most of the presenting signs and symptoms. The signs and symptoms of tricuspid stenosis may be mimicked by tumors (myxoma or metastasis) or vegetations that obstruct RV inflow. Patients with prior bioprosthetic tricuspid valve replacement can develop tricuspid stenosis due to valve leaflet thrombosis or valve degeneration.

Hemodynamic changes detected by physical exam

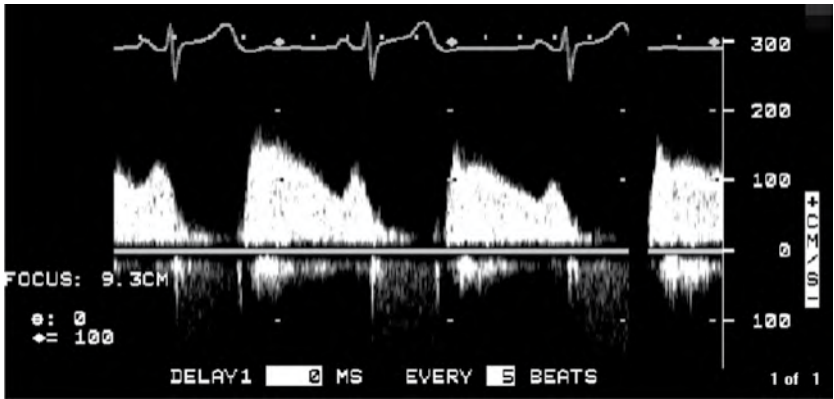
The signs and symptoms of tricuspid stenosis are primarily due to increased systemic venous pressure. Peripheral edema, ascites, hepatic enlargement, and right upper quadrant discomfort may develop with chronic tricuspid stenosis or regurgitation. Decreased cardiac output may cause pronounced fatigue. Jugular venous pressure is increased and, if the patient is in sinus rhythm, there is a prominent A wave in the RA tracing due to impaired RV filling during atrial systole. Atrial fibrillation is common and related to increased RA pressure. Though clinically subtle, the finding of a blunted or absent Y descent supports the diagnosis. The murmur of tricuspid stenosis is a low-pitched diastolic murmur at the lower left sternal edge, in the fourth intercostal space, although this is often difficult to appreciate. Accentuation of the murmur during inspiration may help identify a component of tricuspid stenosis, even if there is concurrent mitral stenosis.

Hemodynamic changes detected by echocardiography

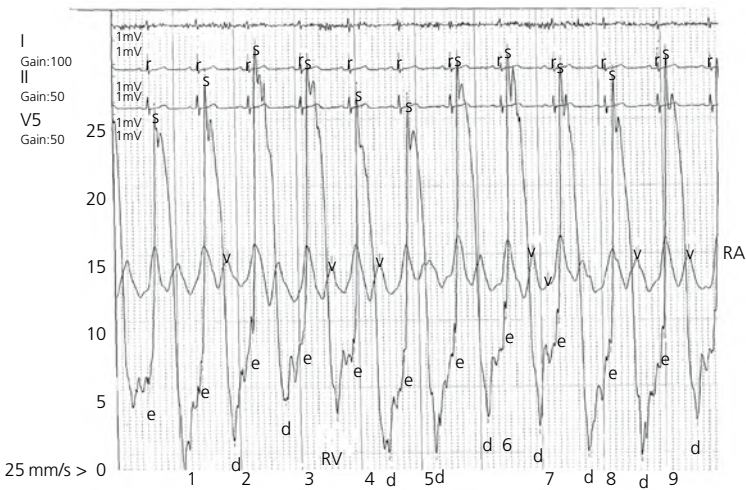
Echocardiography typically reveals thickened tricuspid leaflets, decreased mobility, scarred chordae, and sometimes doming of the leaflets if they remain pliable. Carcinoid heart disease is associated with a distinctive morphology of a thickened tricuspid valve that is narrowed and fixed in the open position resulting in both stenosis and regurgitation. The pandiastolic gradient of tricuspid stenosis is reflected in the slowly falling velocity of the turbulent flow on Doppler assessment (as measured by the pressure half-time). Doppler evaluation also allows estimation of the diastolic pressure gradient by the modified Bernoulli equation [8].

Hemodynamic changes evident at catheterization

With modern echocardiographic and Doppler techniques, cardiac catheterization is generally not necessary for the diagnosis of tricuspid stenosis [9] (Figure 13.6). When the diagnosis is in doubt, however, careful invasive determination of the transvalvular gradient is necessary. This can be done by assessing simultaneous RA and RV pressures with a dual-lumen catheter. If the cardiac output is low, tricuspid gradients are often low and may not be adequately evaluated with a



(a)



(b)

Figure 13.6 Doppler echocardiography and invasive hemodynamics in a patient with severe tricuspid stenosis. Doppler recording across the tricuspid valve (a) and simultaneous RA and RV pressures (b) were recorded in a patient with severe tricuspid stenosis. Panel (c) highlights the transvalvular gradient during diastole. Hemodynamic tracings showed a pandiastolic gradient between the RA and RV. The mean RA pressure was 13 mm Hg, the RV end-diastolic pressure was 8 mm Hg, the mean gradient was 7.3 mm Hg, and the calculated valve area was 1 cm².

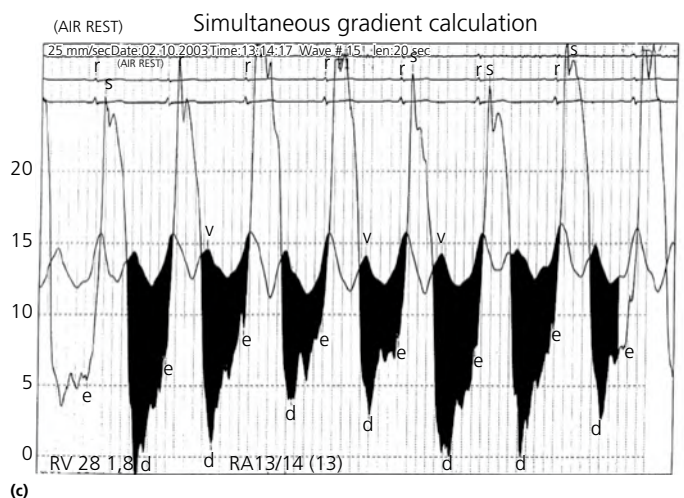


Figure 13.6 (Continued)

catheter pullback. The gradients are generally small, in the range of 4–8 mm Hg and a gradient of >5 mm Hg is typically considered to be severe. The Gorlin equation used for calculating the aortic valve area can be used to also calculate the tricuspid valve area. Clinically significant tricuspid stenosis is usually associated with a valve area of 1.5 cm² or less.

Treatment

Treatment of tricuspid stenosis includes diuretics and beta blockers to allow for prolonged diastolic filling. Refractory patients can undergo tricuspid valve replacement, but in most cases, the concomitant mitral valve disease primarily determines the indication and timing of surgery. A surgical approach may also be indicated for debulking obstructive tumors or myxoma. Patients with bioprosthetic tricuspid valve stenosis can be treated with percutaneous valve-in-valve tricuspid valve replacement.

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CHAPTER 14

Hemodynamic findings in pulmonic valve disease

Cynthia Zhou, Anand Shah and George A. Stouffer

[Revised by George A. Stouffer]

The pulmonic valve is a tricuspid semilunar valve, which divides the right ventricle (RV) from the main pulmonary artery (PA). Pulmonary stenosis (PS) is rare and usually diagnosed at birth or in childhood. It accounts for approximately 8% of all congenital heart defects and can be part of genetic syndromes such as Noonan, Alagille, or Williams syndromes [1]. It is commonly due to isolated valvular obstruction but may also be due to either subvalvular or supra-valvular obstruction. PS is typically diagnosed in childhood, but some patients with milder forms of PS present as adults and PS can also be acquired (e.g. rheumatic heart disease or carcinoid syndrome). The clinical presentation of PS varies from critical stenosis to asymptomatic mild stenosis without the need for therapy.

Severe pulmonary regurgitation (PR) most commonly occurs as a sequelae of treatment of PS or Tetralogy of Fallot, with fewer cases of primary pulmonic valvular regurgitation [2]. The amount of PR is influenced by valvular integrity, RV size, and RV diastolic pressures. In chronic severe PR, the RV remodels to accommodate the regurgitant flow and RV stroke volume increases to maintain effective forward blood flow. Hemodynamic changes include widened PA pulse pressure and low PA diastolic pressures. As the amount of regurgitation increases, RV end-diastolic pressure becomes elevated and systemic cardiac output is reduced, especially with exercise. “Ventricularization” of the PA pressure tracing, in which the contour of the PA pressure is similar to the contour of the RV pressure, is a specific but not sensitive finding in severe PR.

Pulmonic valve stenosis

The stenotic area in PS can be either valvular, subvalvular, or supra-valvular (Figure 14.1) [3–5]. PS is often seen in conjunction with other congenital heart abnormalities. Most adults with mild to moderate PS are asymptomatic

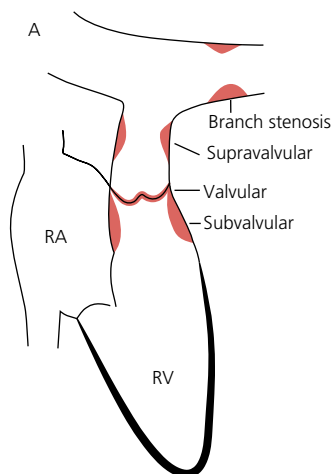


Figure 14.1 Schematic showing various locations of stenotic areas in patients with PS.

and it will be discovered when a murmur is found during routine physical examination. Patients with more severe PS may experience exertional dyspnea and fatigue.

Mild, moderate, and severe PS as determined by echocardiography are defined as peak pressure gradients of <36 mm Hg, $36\text{--}64$ mm Hg, and >64 mm Hg, respectively [6]. Long-term outcomes of patients with PS are dependent on pressure gradient across the valve, with patients with invasively measured peak-to-peak gradient of ≤ 25 mm Hg having normal survival and no progression of their stenosis in 25 years of follow-up, and patients with a gradient between 25 and 49 mm Hg having a 20% chance of needing an intervention [7].

Valvular pulmonary stenosis

In valvular PS, the pulmonary valve is generally shaped like a dome and has a narrow central opening. Alternatively, the valve may be dysplastic with myxomatous thickened leaflets, which is seen in Noonan syndrome. There can be a stenotic bicuspid or unicuspid pulmonary valve in Tetralogy of Fallot. Valvular PS can also be associated with other congenital heart defects such as atrial septal defect (ASD), Ebstein's anomaly, double outlet RV, and transposition of the great arteries.

Subvalvular pulmonary stenosis

Subvalvular PS can be infundibular or subinfundibular. Primary infundibular PS is generally seen as part of Tetralogy of Fallot, while secondary infundibular hypertrophy may occur in valvular PS and result in dynamic RVOT obstruction. Subinfundibular PS is very rare and referred to as double chambered RV (DCRV).

Supravalvular pulmonary stenosis

Supravalvular PS can occur as a result of congenital rubella syndrome or can be found in association with other congenital abnormalities, such as in Williams–Beuren, Noonan, Allagile, DiGeorge, and Leopard syndromes. The stenosis can be found in the common pulmonary trunk, the bifurcation, or the pulmonary branches (Figure 14.1).

Noninvasive imaging

The clinical standard to diagnose PS and quantify its severity is transthoracic 2D echocardiography with Doppler imaging. The valve morphology can be assessed and peak and mean gradients can be measured by Doppler imaging [8]. Computed tomography (CT) scanning can be used to image the anatomy of the right ventricular outflow tract (RVOT) and the pulmonary arterial tree but lacks the ability to analyze function. Cardiac magnetic resonance (CMR) is beneficial for analyzing the anatomy of the RVOT, the PA, and its branches. The exact location of the stenosis can be identified, which enables a distinction between valvular, subvalvular, and supravalvular stenosis. CMR is considered the gold standard for assessment and quantification of right ventricular volume, mass, and function.

Cardiac catheterization and invasive hemodynamics

Right heart catheterization has been the traditional way of measuring the severity of PS and is still used prior to treatment, but has largely been supplanted by echocardiography for establishing the diagnosis of PS. Pressure gradients can be measured directly (Figures 14.2 and 14.3) and angiography provides information on the anatomy (Figure 14.4). Cardiac catheterization also provides the opportunity for treatment via balloon valvuloplasty.

Hemodynamic findings associated with PS include fixed outflow tract obstruction (Figures 14.2a and 14.3a) and diastolic dysfunction (Figures 14.2b and 14.3b). Over time, the RV will hypertrophy in patients with PS in response to the pressure overload. Increased wall thickness causes the RV to become stiffer and less compliant and higher end-diastolic pressures are required to maintain RV filling. This, in turn, leads to higher RA pressures (Figures 14.2b and 14.3b), which will further increase if RV systolic function starts to fail.

Unlike mitral and aortic stenosis in which severity is estimated by calculated valve area, this is rarely used in PS. Rather, severity and need for treatment are generally determined based on peak-to-peak gradient across the pulmonic valve (Table 14.1). The success of treatment is also determined by measuring pressure gradients, with treatment considered a success when the invasively measured transvalvular gradient is <30 mm Hg.

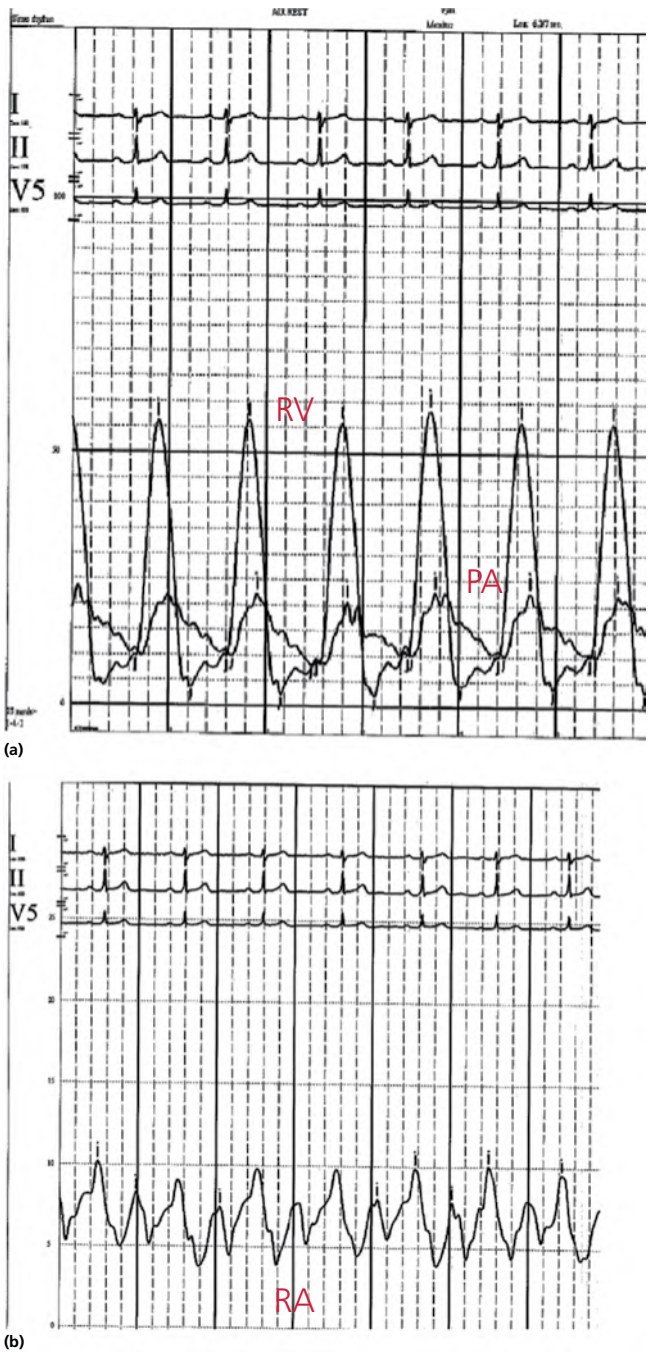


Figure 14.2 Simultaneous RV and PA tracings (a) and RA tracing (b) in a 28-year-old female with moderate PS.

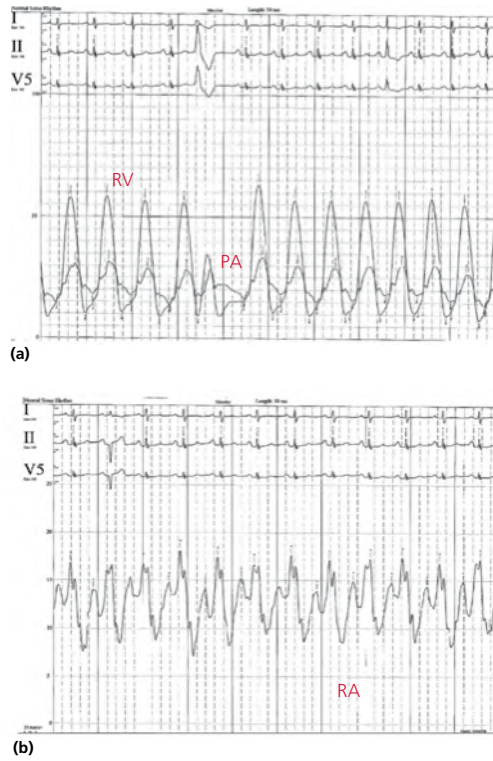


Figure 14.3 Simultaneous RV and PA tracings (a) and RA tracing (b) in a 42-year-old female with moderate PS.

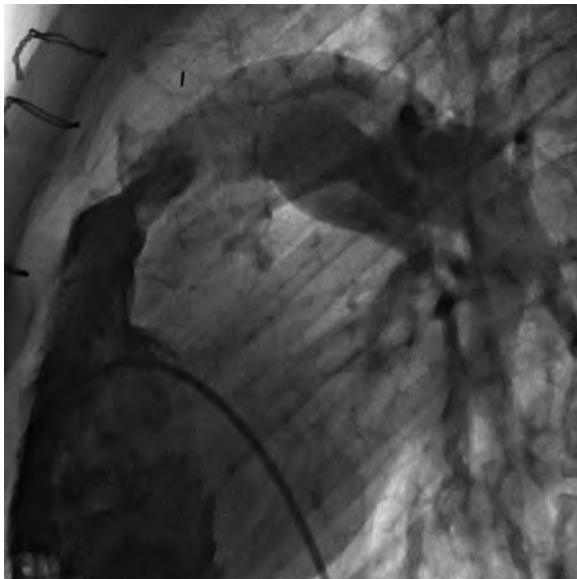


Figure 14.4 Right ventriculogram in a patient with PS. Note the post-stenotic dilation.

Table 14.1 Severity grading of pulmonary stenosis [6].

	Mild	Moderate	Severe
Peak Doppler velocity (m/s)	<3	3–4	>4
Peak Doppler gradient (mm Hg)	<36	36–64	>64
Mean Doppler gradient (mm Hg)			>40

Source: Adapted from [6].

Treatment of PS

The preferred treatment is balloon pulmonary valvuloplasty (BPV), as long-term outcomes are generally good with persistent reductions in pressure gradients. Analysis of multiple studies showed that 8–10% of patients have restenosis at <2-year follow-up, where restenosis is defined as an invasive gradient >50 mm Hg. Most studies of BPV were performed in children with only a few studies in adults. A sample of four studies that evaluated BPV in adults showed a drop in transpulmonic valve gradient from 53.2±24.8mm Hg to 15.5±11.5mm Hg (*n* = 19), from 121.9±53.2mm Hg to 30.1±11.9mm Hg (*n* = 41), from 107±29mm Hg to 37±25mm Hg (*n* = 40) and from 91±46mm Hg to 38±32mm Hg (*n* = 53) [9–12].

Class 1 indications for BPV in the 2018 AHA/ACC guideline for the management of adults with congenital heart disease are moderate or severe valvular PS and otherwise unexplained symptoms of HF, cyanosis from interatrial right-to-left communication, and/or exercise intolerance. A class IIa recommendation is BPV in asymptomatic adults with severe valvular PS [6].

Pulmonic regurgitation

Although many adults have modest amounts of pulmonic valve regurgitation on echocardiography, severe PR is rarely seen [3]. The most common cause of severe PR is sequelae of treatment of a congenital disorder involving stenosis of the pulmonic valve and/or RVOT, most frequently in Tetralogy of Fallot or PS. Treatment of PS with either surgical valvotomy or balloon valvuloplasty can eventually result in significant PR due to dilation of the annulus and/or damage to the pulmonic valve leaflets. Severe PR in the absence of prior treatment of RVOT obstruction or PS is rare and usually due to (1) a dilated pulmonary annulus, which can be congenital or acquired (e.g., pulmonary hypertension, Marfan’s syndrome, idiopathic PA dilation, or connective tissue disorders); (2) congenitally abnormal pulmonic valve (e.g., absent valves, absent leaflets, bicuspid valve, malformed tricuspid valve, or quadricuspid valve); or (3) acquired abnormalities of the pulmonic valve (e.g., infective endocarditis, carcinoid, syphilis, rheumatic heart disease, rheumatoid arthritis, or trauma from PA catheters).

Hemodynamic changes in chronic PR

Hemodynamic changes associated with chronic PR result from PA to RV blood flow during diastole and compensatory responses of the RV to increased diastolic filling. In mild PR, increased RV stroke volume and/or heart rate leads to an increase in RV output across the pulmonic valve, thus maintaining systemic cardiac output. As the severity of PR increases, the RV begins to remodel and dilate. This remodeling allows the maintenance of RV output with relatively normal filling pressures. In patients with severe PR, chronic volume overload can result in increased RV end-diastolic volume and increased RV diastolic pressures. If the degree of regurgitation exceeds the ability of the RV to remodel, this can result in increased RV systolic volume, RV systolic dysfunction, and impaired systemic cardiac output.

Common hemodynamic manifestations of severe PR are shown in Table 14.2. PA pressure manifestations associated with chronic PR are a wide pulse pressure and a low diastolic pressure (similar to aortic pressures in aortic valve regurgitation). Other hemodynamic changes result from an increased RV stroke volume coupled with low afterload (due to regurgitant flow across the pulmonic valve and decreased pulmonary vascular resistance). These include:

- A rapid diastolic collapse that leads to early equilibration of the PA and RV diastolic pressures (Figures 14.5 and 14.6)
- RV and PA pressures that may equalize during diastole (“ventricularization” of PA pressure; Figure 14.6)
- A rate of increase (slope) of RV diastolic pressures that is elevated due to rapid filling from the PA (Figure 14.7)
- Premature closure of the tricuspid valve due to rapid filling of the RV from the PA (Figure 14.7)

In chronic severe PR, RV stiffness can play an important role in the hemodynamic response since increased stiffness will raise RV diastolic pressure and therefore decrease the pressure gradient for PR. In a series of repaired tetralogy patients, RV stiffness was seen to prevent dilation despite the increased preload associated with chronic PR. The clinical benefit of this was demonstrated by better exercise tolerance [13].

A few additional factors influence the hemodynamics in patients with severe PR. Increased airway or intrathoracic pressure can increase the resistance in the

Table 14.2 Hemodynamic findings in severe PR.

-
- Wide pulmonary artery pulse pressure
 - Low pulmonary artery diastolic pressure
 - A rapid diastolic collapse that leads to early equilibration of the PA and RV diastolic pressures
 - RV and PA pressures that may equalize during diastole (“ventricularization” of PA pressure)
 - A rate of increase (slope) of RV diastolic pressures that is elevated due to rapid filling from the PA
 - Premature closure of the tricuspid valve due to rapid filling of the RV from the PA
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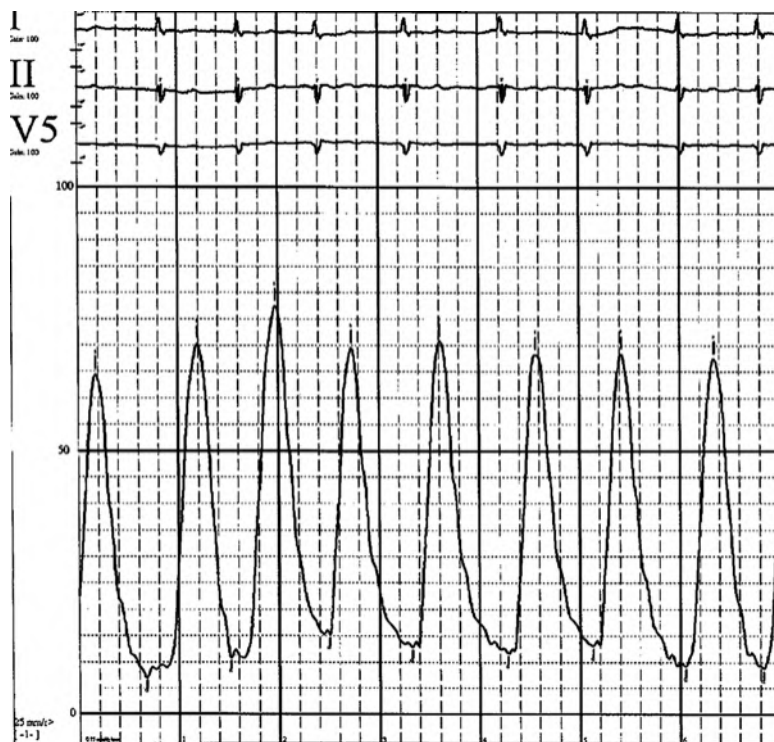


Figure 14.5 PA tracing in a female with severe PR. Note the wide pulse pressure and low pulmonary artery diastolic pressure.

pulmonary microvasculature, increasing RV afterload and therefore the amount of PR. For example, small incremental changes in airway pressures in mechanically ventilated patients can influence the degree of PR. Chronic PR can be associated with branch PS, which can mimic findings of PS and result in a gradient between RV and PA systolic pressures. RA contraction can contribute to forward flow in patients with severe PR and RV systolic failure, leading to late diastolic forward flow in the PA. Last, PR is exacerbated by conditions that lead to elevated arteriolar resistance to PA outflow, such as bronchopulmonary disease, left ventricular dysfunction, or pulmonary vascular disease [2].

Right ventricular function in chronic PR

The ability of the RV to maintain system cardiac output in the presence of significant PR is facilitated by the relatively low resistance of the pulmonary microvasculature. However, over time, the increased volume results in increased diastolic pressures and RV remodeling, with hemodynamic findings depending on the degree of regurgitation and extent of RV remodeling. In mild to moderate PR,



Figure 14.6 Simultaneous RV and PA tracings in a 75-year-old female with severe PR.

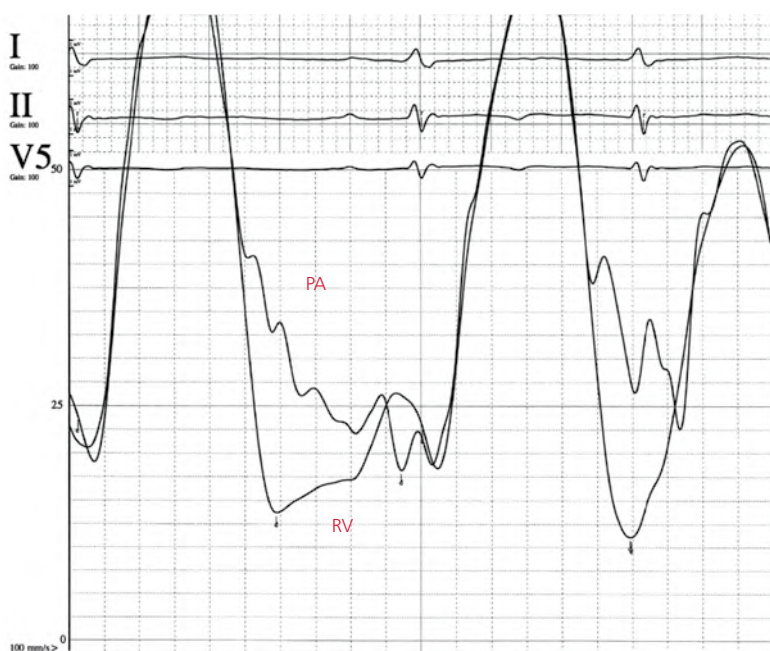


Figure 14.7 Simultaneous RV and PA tracings in a 69-year-old female with severe PR.

filling from the PA enables the RV to increase stroke volume by increasing RV end-diastolic volume (i.e., Starling's Law). As PR becomes more severe, the RV dilates in order to handle increased volumes with minimal changes in RV diastolic pressures. In some patients with PR and dilated RVs, RV myocardial contractile function declines. The development of RV dysfunction leads to further increases in RV diastolic pressures and eventually to development of fluid overload, signs of right heart failure, and decreased cardiac output. With progressive RV and tricuspid annular dilation, tricuspid regurgitation ensues, which in turn can lead to further RV and RA dilation.

The remodeling process can be reversed in some patients with repaired tetralogy of Fallot and PR by valve replacement [14]. In one study of 170 patients with severe chronic PR, there were significant reductions in RV volumes and improvement in RV systolic function following pulmonary valve replacement. Changes in RV function tended to be irreversible when RV end-diastolic volume index exceeded 163 mL/m² or end-systolic volume index exceeded 80 mL/m² [15].

Hemodynamic changes detected by noninvasive imaging in chronic PR

Echocardiography enables visualization of the pulmonic valve and identification of congenital abnormalities, vegetations, thickening, and/or calcification [8]. The rate of decay of the velocity of flow between PA and RV during diastole (i.e., pressure half-time) gives an estimate of the gradient between PA and RV. A rapid decay indicates equalization of RV and PA pressures and suggests severe PR. Other echocardiographic measurements of the hemodynamic effects of PR include RV size, RV systolic function, evidence of elevated RA pressures, amount of tricuspid regurgitation, and estimation of PA systolic pressure by measurement of the velocity of tricuspid regurgitation.

Cardiovascular magnetic resonance (CMR) imaging provides a quantitative assessment of RV volume and systolic function, valvular insufficiency, and regurgitant volume and fraction. CMR is unique in that it directly quantifies valvular regurgitation in mL/min rather than providing an estimate based on a surrogate measure. In patients who cannot have a CMR, CT scanning can be used to measure RV volume and systolic function. Rarely, the severity of PR is assessed angiographically by injecting a large volume of contrast into the proximal PA and observing retrograde filling of the RV. The severity is estimated using the four-point scale utilized to measure regurgitant flow across other cardiac valves.

Natural history of chronic PR

In general, even severe PR is well tolerated for many years, with symptoms developing only when RV failure occurs. One study examining severe PR found that 6% of patients developed symptoms within 20 years and that 29% developed symptoms by 40 years [16]. Late complications of severe PR include RV dilation,

RV dysfunction, secondary tricuspid regurgitation, development of atrial or ventricular arrhythmias, and/or deteriorating exercise capacity. Percutaneous pulmonary valve implantation has been associated with hemodynamic improvement in patients with severe PR following Tetralogy of Fallot repair [17].

Pregnancy

Early in pregnancy, stroke volume increases, heart rate increases 15–20%, and left ventricular end-diastolic volume increases; the total effect is a 30–50% increase in cardiac output by the end of the first trimester, with peak cardiac output occurring between the second and third trimesters [18, 19]. Additionally, vascular resistance decreases by 30–50% by the end of the second trimester, and then rises toward the end of the third trimester. Significant hemodynamic changes occur during delivery, including catecholamine-induced increases in heart rate, stroke volume, and cardiac output. Arterial blood pressure increases during each contraction by up to 15–20 mm Hg.

Pregnancy is well tolerated in women with mild to moderate PS, but the increased cardiac output of pregnancy can lead to right-sided heart failure in severe PS. Uncorrected severe PS has been linked to an increased risk of pre-term birth and fetal mortality of 4.8%. Severe PR has been associated with a progressive RV dilatation that may persist after pregnancy. In one study, severe PR was found to be an independent predictor of maternal complications, particularly in patients with impaired right ventricular function [20].

Ideally, intervention should take place in severe PS or severe PR prior to pregnancy.

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PART III

Cardiomyopathies

 **2025** Edition

CHAPTER 15

Hypertrophic cardiomyopathy

Jayadeep S. Varanasi and George A. Stouffer

Hypertrophic cardiomyopathy (HCM) is the name given to a heterogeneous family of disorders characterized by genetic defects involving myocyte sarcomeric proteins [1]. More than 1400 mutations in >12 genes encoding proteins have been described, with the most common defect being a mutation in the gene that encodes beta-myosin heavy chain, but defects in other genes encoding for sarcomeric proteins including troponin T, troponin I, myosin light chains, alpha tropomyosin, and myosin-binding protein C have been implicated in causing HCM [2]. Inheritance is usually autosomal dominant with variable penetrance. Classically, HCM was defined by excessive septal hypertrophy (usually the width of the septum on echocardiography exceeding 1.5 cm) with or without the presence of outflow tract obstruction, and even today most studies of HCM use echocardiographic, rather than genetic, criteria to determine eligibility.

Various microscopic features of HCM distinguish it from other diseases that cause left ventricular hypertrophy (LVH). The principal aspect of HCM is myocyte disarray in which cells lose their normal parallel arrangement. Individual myocytes often show variability in size and may form circular patterns around areas of fibrous tissue. Myocyte disarray can be seen in other illnesses; however, it tends to affect less of the left ventricle when caused by hypertension or aortic stenosis. In HCM, intramyocardial arteries are often obliterated, creating small areas of fibrosis within the ventricular wall, especially within the interventricular septum.

On gross examination in patients with HCM, there is increased myocardial mass with a normal or small left ventricular chamber size. The disease usually affects the left ventricle more than the right ventricle, with the interventricular septum and anterolateral free wall being the most common segments involved. The hypertrophy is often asymmetric, with differing wall thicknesses noted in contiguous segments. Left atrial enlargement is common because of both

impaired ventricular relaxation and mitral regurgitation. Along with fibrosis in the ventricular wall, a fibrotic plaque is sometimes seen on the interventricular septum and is thought to be the result of repetitive contact between the anterior mitral leaflet and the septum. “Burned-out” HCM, in which there is LV wall thinning, chamber enlargement, and systolic dysfunction resembling dilated cardiomyopathy, develops in 5–10% of patients.

Several anatomic variants of HCM have been described. The most well-known phenotype from a hemodynamic standpoint is hypertrophic obstructive cardiomyopathy (HOCM; also known as idiopathic hypertrophic subaortic stenosis). It was formally described as a distinct clinical entity in 1958 and consists of a narrowing of the left ventricular outflow tract (LVOT) with ventricular contraction causing a dynamic pressure gradient (Figure 15.1). This anatomic pattern occurs in 25–50% of cases of HCM and will be the type of HCM that we concentrate on in this chapter. Other anatomic forms of HCM that have been described include apical HCM, concentric hypertrophy, localized hypertrophy (e.g., posterior portion of septum, posterobasal free wall of the LV, or at the mid-ventricular level), and HCM of the elderly, characterized by severe concentric LVH, a small LV cavity, and hypertension [3, 4]. The vast majority of intraventricular pressure gradients are localized to the LVOT, although mid-cavity obstruction has also been reported. Note that in the rest of this chapter, HCM will refer to all types of hypertrophic cardiomyopathy, while HOCM will refer only to hypertrophic cardiomyopathy in which there is a pressure gradient in the left ventricle at rest or with provocation.

The most feared complication of HCM is sudden cardiac death. HCM is one of the most common causes of sudden death in individuals between the ages of 12 and 35 and is also a common cause of death in young athletes. Not all patients with HCM are symptomatic, but in those who are, dyspnea, angina, and palpitations are common.

Physical exam

Signs of LVH, such as an S4 and laterally displaced precordial impulse, may be present. Most patients with intraventricular gradients have a double or triple apical impulse. Atrial contraction may be noted as a presystolic apical impulse, as well as a prominent A wave in the jugular venous pulsation. The carotid pulse may display a “spike and dome” configuration. In patients with an LVOT obstruction, there is a harsh mid-systolic murmur that commences well after the first heart sound and becomes louder with maneuvers that decrease LV size and filling pressures (e.g., standing from squatting, Valsalva, or dehydration). The murmur often decreases with handgrip exercise. A murmur of mitral regurgitation may be present as well.

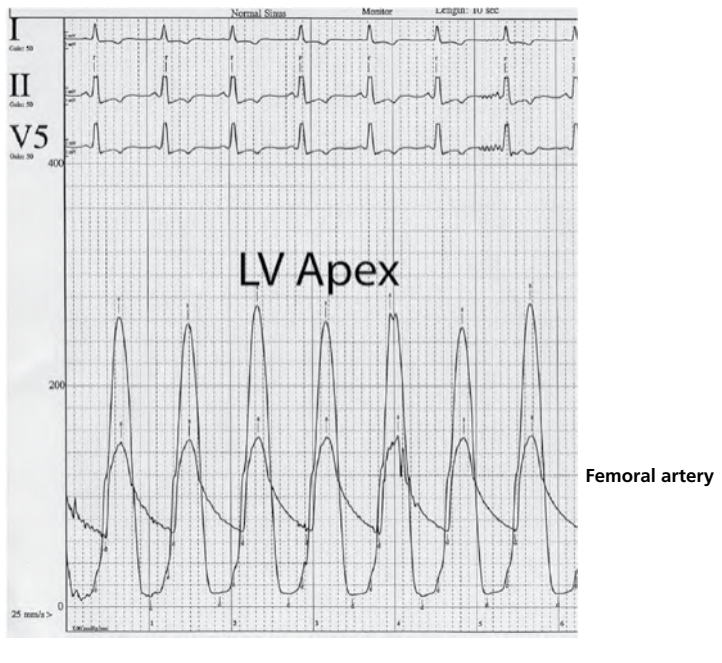
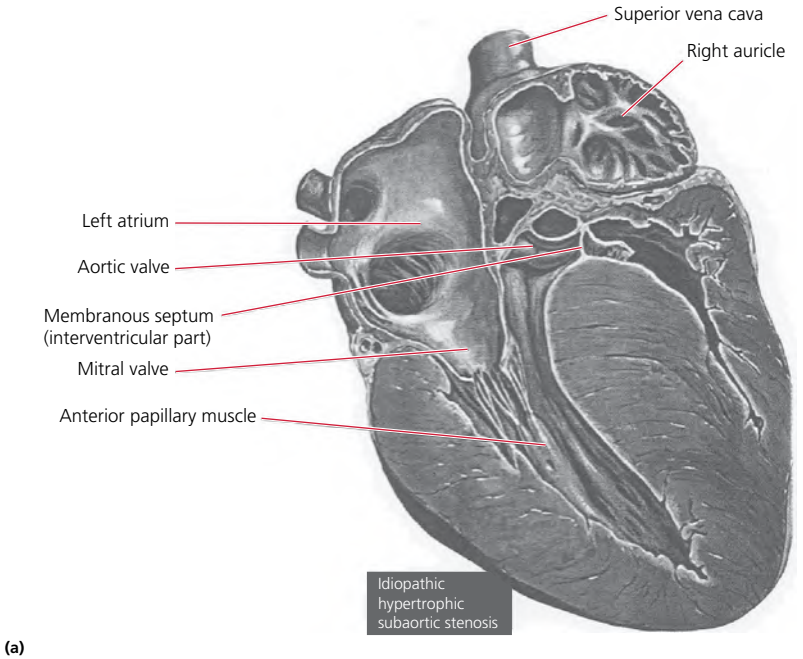


Figure 15.1 Eccentric hypertrophy and LV outflow tract gradient in HOCM. HOCM is characterized by asymmetric septal hypertrophy (a) which causes an obstruction to LV outflow and a pressure drop in the LV outflow tract (b).

Hemodynamics

The hemodynamic manifestations of HOCM are primarily caused by four factors: (1) diastolic dysfunction, (2) LVOT obstruction, (3) mitral regurgitation, and (4) abnormal coronary flow reserve (Table 15.1). We will discuss the causative factors separately, realizing that in a given patient, there will be significant interactions between these factors.

Diastolic dysfunction is present, to some degree, in almost all patients with HCM. Diastolic dysfunction progresses as the ventricle hypertrophies and becomes less compliant. Higher pressures are required to fill the ventricle, leading to increased left atrial, pulmonary artery (PA), right ventricular (RV), and right atrial (RA) pressures. Progressive diastolic dysfunction results in clinical manifestations of congestive heart failure in some patients with HOCM.

Outflow tract obstruction in patients with HOCM is “dynamic,” which means that the resistance to flow changes depending on filling pressures, afterload (e.g., aortic pressure), and force of contractility. LVOT obstruction changes in severity depending on the force of systolic contraction and the dimensions of the LV (in contrast to aortic stenosis, which is a fixed obstruction since it is valvular and not muscular). Thus, patients with HOCM may not have any obstruction while at rest but may develop significant pressure gradients during any activity that increases the force of cardiac contraction (e.g., exercise, emotional stress) or at times when their LV is smaller because of incomplete filling (e.g., dehydration). This obstruction can cause pressure gradients of greater than 100 mm Hg and is thought to be one etiology of exercise-induced syncope in these patients (another potential etiology is arrhythmias).

LVOT gradients can be provoked in the cardiac catheterization laboratory and echocardiography laboratory using methods that decrease filling pressures and stroke volume (e.g., Valsalva maneuver or nitroglycerin) or methods that increase the force of contraction (post-PVC or isoproterenol infusion). Dobutamine should be avoided as it can cause subaortic pressure gradients in normal hearts due to

Table 15.1 Hemodynamic findings in HOCM.

Spike and dome configuration of arterial pulse	On aortic pressure tracing, there is a rapid rise during systole, which is followed by a mild drop in pressure and then a secondary peak
Systolic intraventricular pressure gradient	Simultaneous intraventricular and aortic pressure tracings will show a difference in maximum systolic pressure at rest and/or with provocation
Diastolic dysfunction	LV end-diastolic pressure will be elevated, the rapid phase of LV filling will be prolonged, and atrial contribution to LV filling will be accentuated
Brockenbrough sign	Aortic pulse pressure fails to widen during a post-extrasystolic beat

catecholamine stimulant effects. Current guidelines note that effort-related symptoms due to LVOT obstruction generally require resting or provoked gradient >50 mm Hg. They emphasize that since LVOT gradients are dynamic, they can be missed on resting echocardiography in up to 50% of patients with obstructive physiology [5].

Mitral regurgitation is thought to be caused by systolic anterior motion (SAM) of the mitral valve during mid-systole, which interferes with normal valve closure. Mitral regurgitation is usually mild but can become significant, especially in association with large subaortic pressure gradients. The magnitude of pressure gradients measured at cardiac catheterization correlates well with Doppler velocities on echo and with the duration of SAM. Prolonged mitral valve septal coaptation ($>30\%$ of systole) is invariably associated with high LVOT gradients and mild to severe mitral regurgitation. Although the role of SAM in producing the gradient is controversial, there is a close relationship between the degree of SAM and the size of the LVOT gradient in patients with subaortic obstruction (as opposed to mid-cavity obstruction) [6].

Coronary flow reserve, the ratio of the maximal to the resting coronary blood flow and thus an index of the ability to increase coronary flow under physiologic stress, is abnormal in most patients with HOCM [7]. A study of 20 patients with HCM found higher resting coronary blood flow and lower coronary resistance in comparison to 28 controls. Most patients with HCM achieved maximum coronary vasodilation and flow at modest increases in heart rate. Higher heart rates resulted in myocardial ischemia, elevation in LV end-diastolic pressure (LVEDP), and a decline in coronary flow [8]. The same group of investigators, in a subsequent study of 50 patients with HCM, found that patients with LVOT obstruction at rest had higher coronary flow and regional myocardial oxygen consumption at rest and with pacing compared to patients with HCM but without obstruction. In patients with obstruction, transmural coronary flow reserve was exhausted at a heart rate of 130 bpm. Interestingly, in patients without obstruction, myocardial ischemia occurred at a lower coronary flow than in patients with obstruction [9]. A more recent study found that several mechanisms contributed to decreased coronary flow reserve in HCM patients including a large backward compression wave during systole and a smaller backward expansion wave with control subjects. These coronary flow abnormalities occurred due to effects resulting from compression and deformation of the intramural blood vessels and impaired ventricular relaxation [10].

Findings at cardiac catheterization

Cardiac catheterization is usually not needed to confirm the diagnosis, but occasionally patients with HCM will undergo catheterization for evaluation of chest pain or congestive heart failure.

Left atrium or pulmonary capillary wedge pressure

Pulmonary capillary wedge pressure (PCWP) is generally elevated in patients with HCM, even more so when there is significant mitral regurgitation. The A wave may be accentuated due to a stiff ventricle and the V wave can be increased, either from mitral regurgitation or reduced LA compliance. RV systolic and PA pressures are generally only mildly elevated, and cardiac output is preserved until LV failure occurs.

As an example of filling pressures in patients with HCM, a study of 20 patients with HCM (9 with significant outflow tract gradients) compared to 28 controls found higher LVEDP (16 ± 6 versus 11 ± 3 mm Hg) and mean PCWP (13 ± 5 versus 7 ± 3 mm Hg) [8].

LV pressure

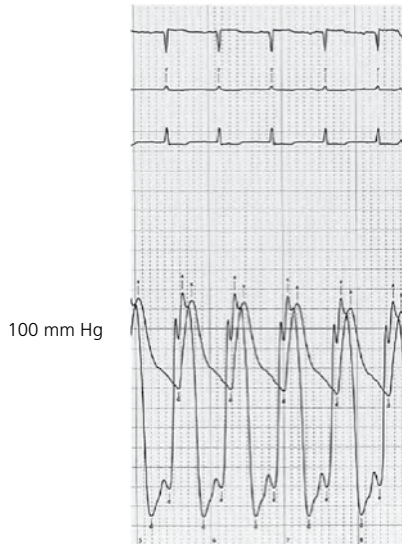
LVEDP is generally elevated, but there are no pathognomonic findings for HCM in the LV pressure tracing. The rapid filling phase of LV may be significantly prolonged and a prominent atrial contraction wave may be present (Figure 15.2). The upstroke of the LV pressure tracing may have a notch that corresponds with the anterior leaflet of the mitral valve coming into contact with the septum because of SAM.

Aortic pressure

A variable finding in HOCM is that the dynamic nature of the outflow tract obstruction causes a “spike and dome” configuration of the aortic or peripheral pulse (Figure 15.3). This is known as a bisferiens pulse, a name derived from Latin *bis* (= two) + *feriere* (= to beat). The bisferiens pulse is characterized by an initial rapid rise in aortic pressure (spike), followed by a slight drop in pressure (dip), and then a secondary peak (dome), and is most prominent in central aortic pressure but can also be transmitted to the carotids. It is enhanced by maneuvers that increase intra-ventricular pressure gradients (e.g., following a PVC or by the Valsalva maneuver), and in patients with obstruction only during provocation, a normal-appearing pressure tracing will often be replaced by the spike and dome during provocative maneuvers. A bisferiens pulse should not be confused with a dicotic pulse, a pulse with an exaggerated dicotic wave. A bisferiens pulse is most commonly associated with HOCM, but can also be seen in severe aortic regurgitation.

Outflow tract gradient

A gradient can be demonstrated by comparing pressure in the LV apex (using an end-hole catheter) to aortic pressure or by a slow pullback of the catheter through the LV (Figure 15.4). In the cardiac catheterization laboratory, dynamic outflow tract



(a)



(b)

Figure 15.2 LV tracings in a patient with HOCM. In panel (a), pressures are obtained at baseline. Note the elevated LVEDP, prominent A wave in LV tracing, and lack of an outflow tract gradient. Panel (b) was obtained after inhalation of amyl nitrate. LVEDP is increased and an A wave is prominent. Aortic pressure is decreased compared to basal conditions and a small outflow tract gradient is present.

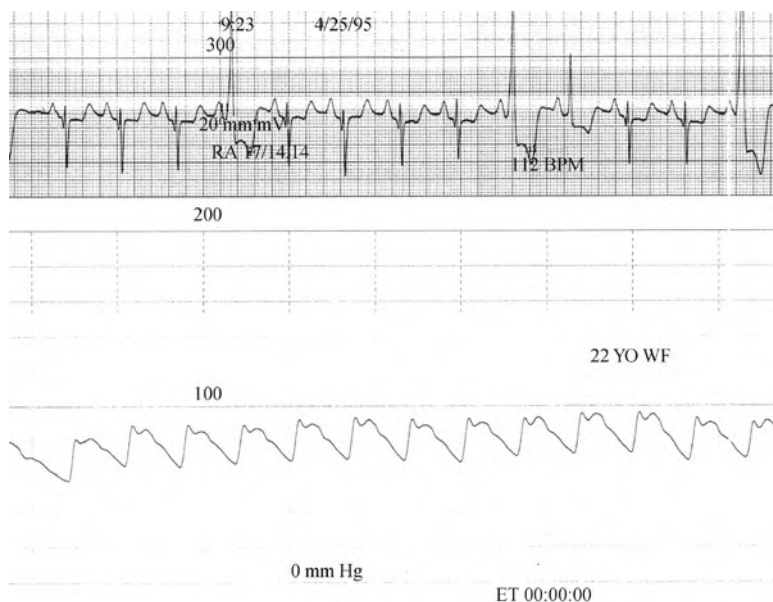


Figure 15.3 Aortic pressure in a patient with HOCM demonstrating a “spike and dome” configuration.

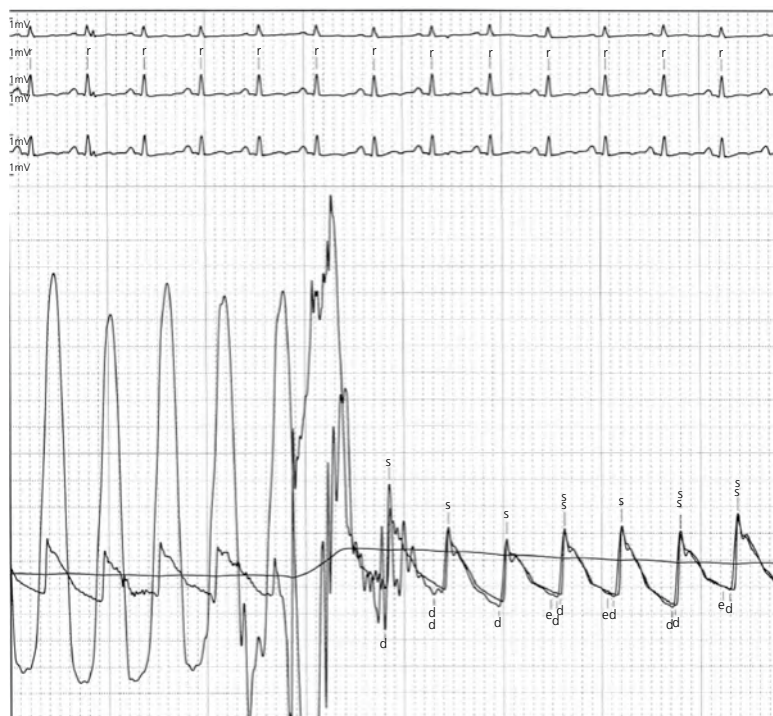


Figure 15.4 LV to aortic pullback using a dual lumen end-hole catheter during amyl nitrate administration in a patient with HOCM. Aortic pressure is measured continuously through the second lumen.

obstruction can be provoked by a variety of maneuvers, including methods that decrease preload and/or afterload (e.g., Valsalva maneuver, administration of amyl nitrate or nitroglycerin; Figure 15.5) or methods that increase the force of contraction (e.g., isoproterenol infusion or PVC; Figure 15.6). LV outflow obstruction can be reduced or eliminated by maneuvers that increase chamber size (e.g., hydration).

The Brockenbrough–Braunwald–Morrow sign was originally described in 1961. This sign is present if the aortic pulse pressure falls in the first normal beat post-PVC in HOCM (Figure 15.7). While originally thought to be specific for HOCM, it has since been described in some cases of aortic stenosis.

RV intraventricular gradient is common in infants and children with HOCM but is rarely seen in adults. Maron reported that RV obstruction was observed in 60% of infants with HOCM and that RV outflow tract obstruction was frequently greater than LV outflow tract obstruction [11].

Echocardiography

Since the initial development of ultrasonic evaluation of the heart, echocardiography has been the gold standard for diagnosing HOCM. The cardinal echocardiographic features of HOCM are LVH, an intraventricular pressure gradient, and SAM of the mitral valve. There is considerable variability in the degree and pattern of hypertrophy and in some patients, there is variation in the extent of LVH from region to region. The finding of a thickened septum that is at least 1.3–1.5 times the thickness of the posterior wall when measured in diastole just prior to atrial systole has been a commonly used criterion for the diagnosis of asymmetric septal hypertrophy.

An intraventricular pressure gradient as measured by continuous-wave Doppler interrogation in the aortic outflow tract is present in some patients. Provocative maneuvers (e.g., inhalation of amyl nitrate, Valsalva maneuver) can be performed in the echocardiography laboratory. Some investigators have criticized these maneuvers as being nonphysiologic and advocated using echocardiography in conjunction with treadmill or bicycle exercise testing to determine provokable gradients.

Clinically, it may be helpful to classify patients with HCM into one of three groups based on the peak instantaneous gradient as assessed with continuous-wave Doppler: (1) resting obstruction—gradient under basal (resting) conditions equal to or greater than 30 mm Hg (2.7 m/s by Doppler); (2) provokable obstruction—gradient < 30 mm Hg under basal conditions and $\geq$ 30 mm Hg with provocation; and (3) nonobstructive—gradient < 30 mm Hg at rest and with provocation. A resting outflow tract gradient of $\geq$ 30 mm Hg (measured by continuous-wave Doppler) is an independent determinant of symptoms of progressive heart failure and death.

Other common echocardiographic findings in HCM include normal systolic function, diastolic dysfunction with reduced LV compliance, a mitral valve E/A ratio less than 1.0 (usually < 0.8), and an enlarged left atrium [3].

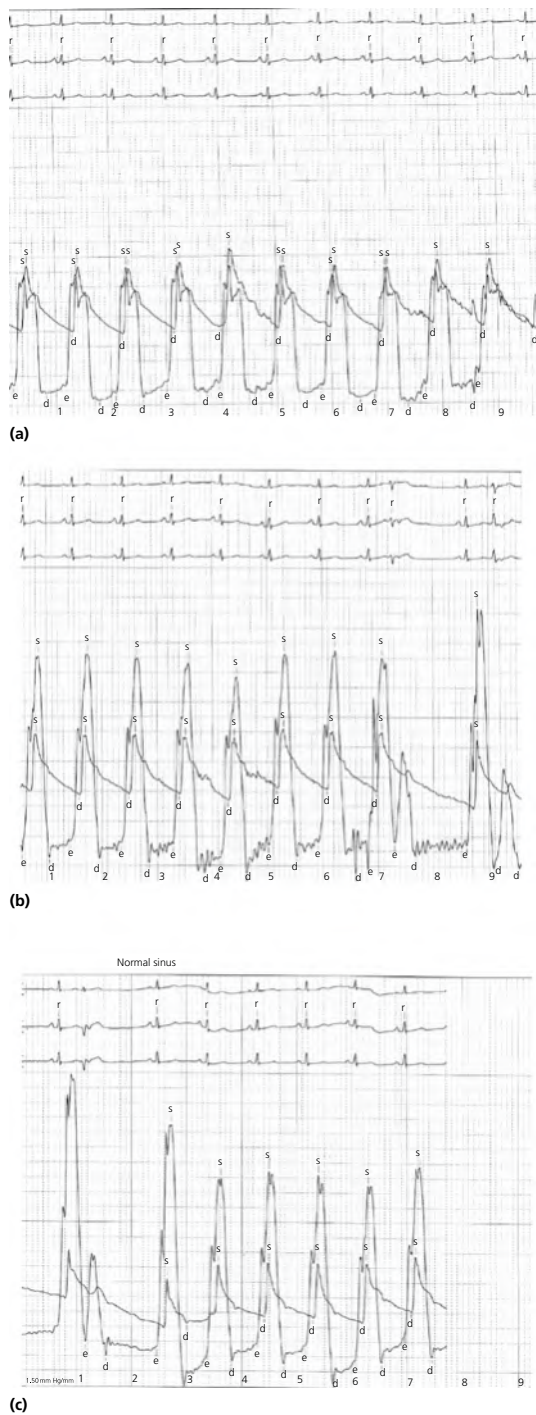


Figure 15.5 Demonstration of a provokable gradient with inhalation of amyl nitrate. There is no LVOT gradient under basal conditions (a). Following inhalation of amyl nitrate, aortic pressure falls, and a gradient is apparent (b). Over time, aortic pressure continues to fall and the gradient increases (c). All tracings are recorded on a 200 mm Hg scale.



Figure 15.6 Demonstration of a provokable gradient with PVCs during administration of amyl nitrate.

Effect of various treatment modalities on hemodynamics

Septal reduction for refractory symptoms

Invasive treatments are reserved for patients who have severe refractory symptoms (class III or IV) despite medical treatment and intraventricular gradients of ≥ 30 mm Hg. The classic Morrow myectomy is performed through an aortotomy and involves resection of a relatively small amount of tissue from the proximal septum. Surgical resection of the hypertrophied septum has an initial success rate of 90% in decreasing symptoms and LV outflow obstruction. In a study of 64 patients who underwent transaortic myectomy, there was a sustained improvement in symptoms and a decrease in LVOT resting gradient from 73.2 ± 14.8 mm Hg to 13.6 ± 2.7 mm Hg at an average follow-up of 4.6 years (4 months to 12 years) [12]. A review of 11 studies of myectomy performed at experienced centers found that pre-surgery LVOT gradients of 50–90 mm Hg were reduced to 1–14 mm after surgery [13].

Alcohol septal ablation has been developed as a treatment for LV outflow obstruction due to septal hypertrophy. In this procedure, alcohol is injected into a septal branch of the left anterior descending artery, causing localized infarction of the septum. Alcohol septal ablation appears to elicit a sustained reduction in outflow tract gradient. In a study of 50 patients, septal ablation (mean creatine kinase value 413 ± 193 U/L) reduced LVOT gradients from 80 ± 33 to 18 ± 17 mm Hg after 4–6 months and to 17 ± 15 mm Hg after 12–18 months [14].



Figure 15.7 Brockenbrough–Braunwald–Morrow sign. Pulse pressure falls in the first normal beat post-PVC (arrows) in HOCM.

Alabdjalbar et al. studied 156 patients who underwent alcohol septal ablation [15]. A resting LVOT gradient of >30 mm Hg was present in 67% and a resting LVOT gradient of >50 mm Hg was present in 56%. The average septal thickness was 19.2 ± 3.7 mm. Alcohol septal ablation resulted in reductions in various hemodynamic parameters including mean LA pressures; LV systolic and diastolic pressures; aortic systolic and diastolic pressures; pulse pressure; and LVOT gradient. Interestingly, there was no effect on LV end diastolic pressure although $p = 0.06$. They found that percentage changes in pulse pressure and LVOT gradient were predictive of survival.

There is considerable controversy about proper patient selection for alcohol septal ablation and surgical myectomy. Current guidelines emphasize several important points: (1) both ASA and myectomy are effective at reducing LVOT gradient; (2) myectomy produces more complete gradient relief, particularly in patients <65 years of age and/or with a septal thickness >18 mm; (3) residual gradients are more common after alcohol septal ablation [5].

Cardiac myosin inhibitors

Cardiac myosin inhibitors are a new class of medications that inhibit actin-myosin interaction, thus decreasing cardiac contractility and reducing LVOT obstruction. Mavacamten is currently the only US Food and Drug Administration–approved agent and has been shown to improve LVOT gradients, symptoms, and functional capacity in 30–60% of patients with obstructive HCM. The EXPLORER-HCM study enrolled patients with HOCM defined by maximal LV wall thickness of ≥ 15 mm or ≥ 13 mm if familial HCM); peak LVOT gradient at least 50 mm Hg at rest, after Valsalva maneuver or exercise; left ventricular ejection fraction $\geq 55\%$; and NYHA class II–III symptoms and found that patients on mavacamten had greater reductions in post-exercise LVOT gradient compared to the placebo control group (-36 mm Hg with 95% CI of -43 to -28) [16]. Mavacamten also improved measures of left ventricular diastolic function and SAM [17].

The Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM (SEQUOIA-HCM) trial was a randomized controlled trial that enrolled 282 patients with symptomatic obstructive HCM with a mean resting LVOT gradient of 55 mm Hg. Patients randomized to receive aficamten, a cardiac myosin inhibitor, had greater reductions in Valsalva-induced LVOT gradient at 12 weeks compared to the placebo control group (-48 mm Hg with 95% CI of -55 to -42) [18].

Dual-chamber pacemaker

Dual-chamber pacing has largely been abandoned as a treatment option in HOCM because data from randomized, double-blind, crossover trials failed to show any benefit. RV pacing causes the interventricular septum to move paradoxically, and in theory, this should increase LVOT dimensions and thus reduce LVOT blood velocities, which results in less SAM of the mitral valve and less mitral regurgitation. While initially proposed in 1975, interest in AV sequential pacing for HCM was revived by a study of DDD devices in 84 patients with obstructive HCM and severe symptoms refractory to medical therapy [19]. Symptoms were abolished in 33.3% of the patients, reduced in 56%, and unchanged in 8%. At a mean follow-up of 2.3 ± 0.8 years, only four patients had to undergo a surgical procedure. In this study, there was significant improvement in NYHA class, in exercise capacity, and in resting LVOT gradient.

Subsequent studies produced less enthusiastic results and dual-chamber pacing is rarely utilized as a treatment for HOCM. In a multicenter, randomized, double-blind, crossover study of permanent DDD pacing in 48 patients with

drug-refractory HOCM, Maron *et al.* found an average reduction of outflow gradient of 40%, but no change in exercise capacity, peak oxygen consumption, or LV wall thickness in the overall group [20].

Case study

A 75-year-old male with a history of atrial fibrillation reported increasing dyspnea on exertion and lower-extremity edema. A nuclear stress test was suggestive of ischemia and he was referred for cardiac catheterization. Simultaneous measurement of LV apex and femoral artery pressures revealed no gradient under basal conditions. Initiation of a PVC elicited a Brockenbrough sign (Figure 15.8a) and Valsalva maneuver precipitated a marked, transient increase in LVOT gradient (Figures 15.8b, 15.8c). These findings are consistent with HOCM.

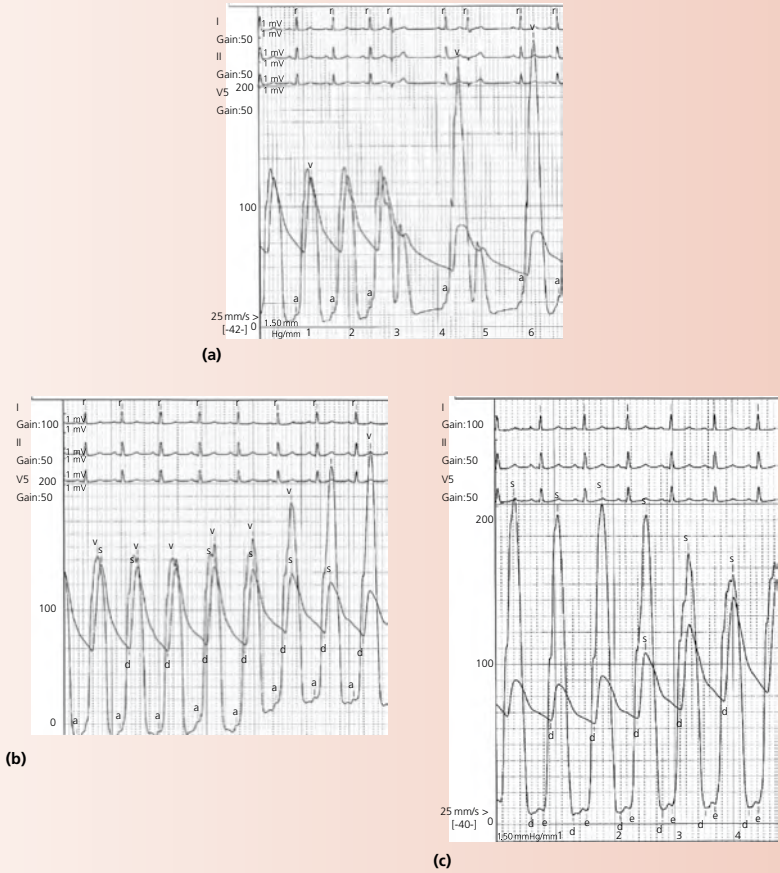


Figure 15.8 Illustrative case—simultaneous IV apex and femoral artery pressures demonstrating a Brockenbrough sign (a) and precipitation of an intraventricular gradient during Valsalva maneuver, onset in (b) and offset in (c).

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CHAPTER 16

Chronic heart failure

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Heart failure (HF) is a complex clinical syndrome caused by failure of the heart to meet the physiological demands of the body, with symptoms due to a structural or functional impairment of ventricular filling or ejection of blood causing elevated intracardiac filling pressures and/or decreased effective cardiac output (CO). The most common classification of HF is based on left ventricular ejection fraction (LVEF), as determined by some form of cardiac imaging (most commonly an echocardiogram). Current guidelines label HF with reduced ejection fraction (HFrEF) as those with $LVEF \leq 40\%$, HF with preserved EF (HFpEF) as $LVEF > 50\%$, and HF with mildly reduced EF as LVEF between 41% and 49%. These separate definitions are important given notable differences in both underlying etiologies and treatment approaches. The etiologies of HF are highly heterogeneous (Table 16.1).

The pressure-volume (P-V) loop best illustrates the hemodynamic differences between HFrEF and HFpEF (Figure 16.1). Since patients with HFrEF have reduced myocardial contractility, the left ventricle dilates to accommodate a higher preload necessary to maintain an effective CO. In regard to hemodynamic variables, patients with HFrEF have higher left ventricular end-diastolic volume (LVEDV) and pressure (LVEDP), as well as lower stroke volume, pulse pressure, and effective CO, which then translate to higher left ventricular end-systolic volume (LVESV) and pressure (LVESP). As the degree of systolic dysfunction worsens, the P-V loop shifts further to the right. Likewise, in the presence of significant mitral regurgitation, the forward stroke volume and effective CO are further reduced due to the absence of isovolumetric contraction.

In contrast to HFrEF, the underlying pathophysiology of HFpEF is complex but results in a final pathway of abnormal myocardial relaxation, or lusitropy, with increased myocardial stiffening leading to higher filling pressures, especially with exertion, given the same incremental changes in volume (Figure 16.1). Thus, a much lower LVEDV is needed to overcome aortic pressure, resulting in reductions

Table 16.1 Common etiologies of heart failure.

Coronary artery disease (ischemic cardiomyopathy)
Hypertension
Primary valvular disease
Rhythm-related (e.g., tachycardia-mediated, PVCs, RV pacing)
Chemotherapy and cardiotoxic medications (e.g., anthracyclines, tyrosine kinase inhibitors, immunomodulators)
Rheumatologic or autoimmune (e.g., systemic lupus erythematosus, connective tissue disease)
Toxin-related/Substance abuse (e.g., alcohol, cocaine, methamphetamine)
Familial cardiomyopathy and genetic heart disease
Stress-induced cardiomyopathy (Takotsubo)
Congenital heart disease
Infectious (e.g., HIV, Chagas disease, coxsackie, COVID-19)
Infiltrative disease (e.g., amyloidosis, sarcoidosis, hemochromatosis)
Myocarditis (e.g., giant cell, lymphocytic, eosinophilic)
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Peripartum cardiomyopathy
Nutritional deficiencies (e.g., selenium, copper, thiamine)
Metabolic (e.g., thyroid disease)
High-output states (e.g., arteriovenous fistula, hyperthyroidism)
Idiopathic

in stroke volume, effective CO, and LVESV. LVEF, defined as the ratio of stroke volume to LVEDV, is preserved in HFpEF where both the numerator and denominator are reduced.

History, physical examination, cardiac biomarkers, chest radiography, and cardiac imaging are central to the medical management of acute decompensated HF. In some cases, it may be difficult to accurately estimate the true hemodynamic status of the chronic HF patient using these tools alone. Physical examination findings of HF can be absent in as many as 40% of patients with elevated pulmonary capillary wedge pressure (PCWP) [1, 2]. Additionally, chest radiography often does not show pulmonary congestion in advanced HF patients due to increased pulmonary lymphatic drainage [3]. In light of this, judicious utilization of right heart catheterization (RHC) can be helpful in certain clinical scenarios.

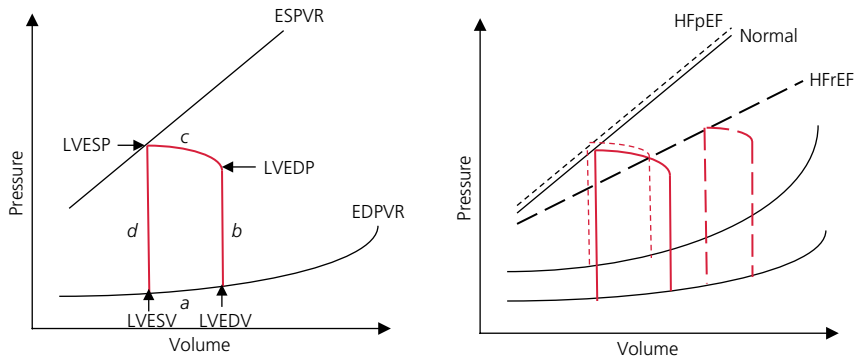


Figure 16.1 Left ventricular pressure-volume loops. The left panel reflects the normal left ventricular pressure-volume loop demonstrating pressure and volume changes during the cardiac cycle: (a) the left ventricle fills during diastole, followed by (b) isovolumetric contraction at end-diastole, which ends when the aortic valve opens (at the highest LVEDV and LVEDP), followed by (c) left ventricular ejection (systole), followed by (d) isovolumetric relaxation (beginning with the aortic valve closing). The slope of the end-systolic pressure-volume relationship (ESPVR) provides an index of contractility. The end-diastolic pressure-volume relationship (EDPVR) represents the passive filling (compliance) of the LV, and the slope of this curve represents ventricular stiffness (the reciprocal of ventricular compliance). Stroke volume is $LVEDV - LVESV$. The right panel reflects pressure-volume loops for normal (solid line), HFpEF (thin dash line), and HFrEF (bold dash line).

It should be noted that *routine* pulmonary artery catheter (PAC) use has never been shown to improve mortality or long-term clinical outcomes in patients with HF [4–11]. In the randomized, multicenter Evaluation Study of Congestive HF and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, the addition of routine PAC to clinical assessment, compared to clinical assessment alone, did not improve clinical outcomes in patients with severe symptomatic and recurrent HFrEF [11]. Even though use of PAC failed to demonstrate improved mortality or time out of the hospital at 6 months, with higher adverse events reported in the PAC group (mostly PAC-associated infections), clinical status significantly and continuously improved in both groups, with a trend suggesting greater clinical improvement in the PAC group at 1 month. More recent studies have evaluated PAC use in cardiogenic shock (CS) populations with results demonstrating favorable clinical outcomes [12–14]. Thus, PAC use can be helpful for optimizing hemodynamic management in certain patients presenting with severe HF when clinically indicated. Table 16.2 lists common indications for RHC.

The hemodynamic findings of HFrEF and HFpEF are often similar in terms of elevated intracardiac filling pressures, but decreased effective CO in HFpEF is usually seen only in advanced disease, whereas it is generally seen earlier in HFrEF. Typically, patients with chronic HF have higher baseline intracardiac pressures than those with acute HF, because those with chronic HF require higher filling pressures to maintain optimal CO (as illustrated by the Frank-Starling relationship, Figure 16.2).

Table 16.2 Indications for right heart catheterization in patients with heart failure.

- Heart failure (HF) management: Determination of true hemodynamic/intravascular status when non-invasive clinical evaluation is insufficient
- Cardiogenic shock (CS): Diagnosis and assessment, including titration of inotropes and need for mechanical circulatory support
- Pulmonary hypertension (PH): Gold standard for diagnosis and subtyping, including vasodilator provocation
- Advanced HF: Evaluation for candidacy, including assessing for precapillary PH before transplant, and assessing risk of right HF after left ventricular assist device (LVAD) implantation
- Heart transplant: Utilized concurrently with endomyocardial biopsy to evaluate for allograft rejection
- LVAD management: Optimizing perfusion and filling pressures with speed adjustments, assessing precapillary PH, and diagnosing LVAD complications
- Pericardial disease: Differentiating constrictive from restrictive pericardial process (together with left heart catheterization)
- Valvular disease: Determination of severity when discrepancies exist between clinical and other diagnostic assessments

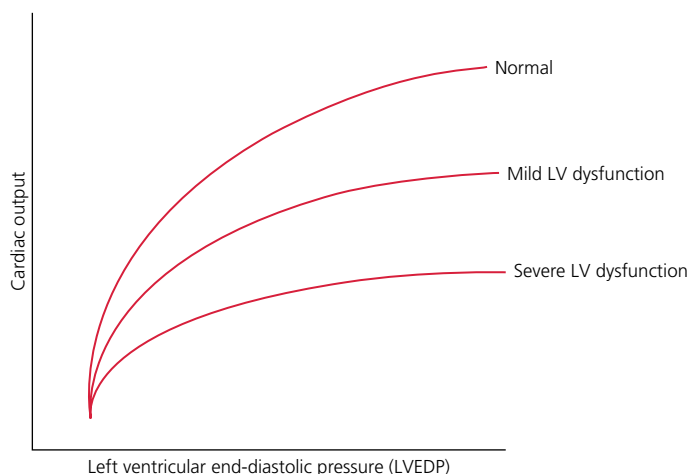


Figure 16.2 Frank-Starling curve of cardiac output as a function of left ventricular end-diastolic pressure (LVEDP). Idealized Frank-Starling curves with varying degrees of left ventricular (LV) contractile dysfunction. In the normal heart, an increase in preload results in a steep increase in cardiac output. With LV systolic dysfunction, the curves are displaced down and rightward, such that higher filling pressures are needed to maintain the same amount of cardiac output. With advanced LV diastolic dysfunction, cardiac output can also be decreased, especially with exertion, due to limited stroke volume reserve despite adequate filling pressures.

Thus, functional parameters of higher ventricular filling pressures and higher ventricular volumes are observed in patients with chronic HF_rEF compared to patients with normal cardiac function. Specific conditions such as restrictive cardiomyopathy (Chapter 17), constrictive pericarditis (Chapter 18), and hypertrophic cardiomyopathy (Chapter 15) will be discussed elsewhere in this book. Table 16.3 summarizes the directly measured intracardiac pressures and the derived parameters used to manage patients with HF.

Directly measured intracardiac pressures

The best measurement of LV preload is left atrial pressure (LAP). In practice, direct LAP is difficult to obtain and thus two surrogate measurements are commonly used (Figure 16.3): LVEDP and PCWP.

Left ventricular end-diastolic pressure (normal 4–12 mm Hg)

Since LVEDP is measured at the end of diastole, the major contribution is from atrial contraction for patients in sinus rhythm. While it is noteworthy that the end-diastolic P-V relationship (EDPVR) is curvilinear (Figure 16.1), but the more severe the degree of systolic and diastolic dysfunction, the less likely this generalization is to hold. In HF_rEF, where the left ventricular chamber size is dilated, increased LVEDV is needed to produce a proportionate increase in LVEDP, which, in turn, is needed to optimize CO. In contrast, the abnormal left ventricular relaxation or ventricular stiffness in HF_pEF creates a stiff and poorly compliant LV. Thus, a relatively small change in LVEDV leads to a significant elevation in LVEDP, especially with exertion. Direct measurement of LVEDP is achieved by placing a catheter into the left ventricle via arterial access (Figure 16.3).

Pulmonary capillary wedge pressure (normal 4–12 mm Hg)

The PCWP profile is different in acute and chronic HF patients. For example, in a patient with an acute myocardial injury due to sudden complete occlusion of the proximal left anterior descending artery with resultant myocardial dysfunction, a sudden rise in PCWP to 17–20 mm Hg could be sufficient to cause acute pulmonary edema. In contrast, a patient with chronic HF often needs a mean PCWP of 17–20 mm Hg to optimize CO, as explained by the Frank-Starling mechanism (Figure 16.2).

The PCWP waveform in HF patients is often characterized by prominent V waves (Figure 16.4). This augmented V wave morphology can be due to large regurgitant volume from significant functional mitral regurgitation causing sharp increases in atrial pressure. However, large V waves can also be observed in a noncompliant and/or congested LA with abrupt increases in pressures along the usual compliance curve. With prominent V waves, the calculated mean PCWP will be higher and not accurately reflect LVEDP, as the increased pressure in the

Table 16.3 Summary of intracardiac measurements commonly used in patients with chronic heart failure. [mPCWP = mean pulmonary capillary wedge pressure; WU = Wood units.]

	Formula	Normal Range
Direct measurements		
Right atrial pressure (RAP)		0–6 mm Hg (mean)
Right ventricular systolic pressure (RVSP)		15–25 mm Hg
Right ventricular diastolic pressure (RVDP)		1–7 mm Hg (end diastole)
Pulmonary artery systolic pressure (PASP)		15–25 mm Hg
Pulmonary artery diastolic pressure (PADP)		8–15 mm Hg
Mean pulmonary artery pressure (mPAP)	$\frac{[PASP + (2 \times PADP)]}{3}$ or $\frac{[PASP - PADP]}{3} + PADP$	10–20 mm Hg
Pulmonary capillary wedge pressure (PCWP)		4–12 mm Hg (mean)
Calculated measurements		
Cardiac output (CO, per indirect Fick)	$\frac{VO_2}{[10 \times (SaO_2 - SvO_2) \times Hgb \times 1.36]}$	4.0–8.0 L/min
Cardiac index (CI)	CO/BSA	2.5–4.0 L/min/m ²
Cardiac power output (CPO)	(MAP × CO)/451	>0.6 W
Cardiac power index (CPI)	CPO/BSA	>0.4 W/m ²
Aortic pulsatility index (API)	(SBP – DBP)/mPCWP	>3.0
Transpulmonary gradient (TPG)	mPAP – mPCWP	<13 mm Hg
Diastolic pulmonary gradient (DPG)	PADP – mPCWP	<7 mm Hg
Pulmonary vascular resistance (PVR)	(mPAP – mPCWP)/CO	<3 WU
Pulmonary artery pulsatility index (PAPI)	(PASP – PADP)/RAP	>2.0
Right ventricular stroke work index (RVSWI)	$\frac{(mPAP - RAP) \times (CI/HR) \times 13.6}{13.6}$	8–12 g·m/m ²
RAP:PCWP	RAP/mPCWP	<0.6
Systemic vascular resistance (SVR)	$80 \times \frac{(MAP - RAP)}{CO}$	800–1200 dynes·sec/cm ⁵

Source: Adapted from references [43–45].

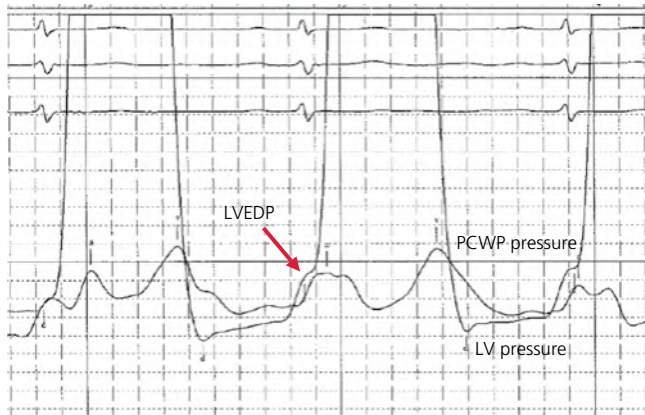


Figure 16.3 Simultaneous left ventricular end-diastolic (LVEDP) and pulmonary capillary wedge (PCWP) pressures in a 59-year-old female.

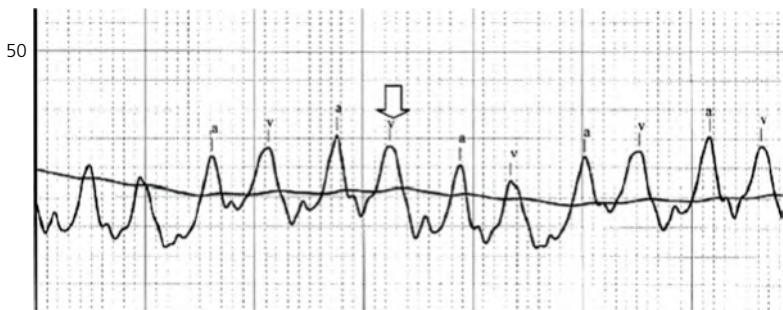


Figure 16.4 Pulmonary capillary wedge pressure (PCWP) tracing in a patient with dilated cardiomyopathy and severe mitral regurgitation. The mean PCWP is elevated at approximately 25 mm Hg and prominent V waves are also noted (arrow).

V waves is transmitted to the pulmonary vessels and contributes to elevated pulmonary artery pressures; in these cases, the mean PCWP should be reported as associated with large V waves.

Pulmonary artery pressure (normal 15–25/8–15 mm Hg)

In the most recent guidelines, pulmonary hypertension (PH) was defined as a mean pulmonary artery pressure (mPAP) >20 mm Hg, which is lower than the previous ESC/ERS guidelines of 2015 [15, 16]. World Health Organization Group 2 PH, or PH due to left heart disease (PH-LHD), is classified when the PCWP is >15 mm Hg. PH-LHD is by far the most common cause of PH and involves a wide spectrum of different clinical diagnoses. Up to 60% of patients with HF_rEF and up to 70% of HF_pEF may present with PH [17]. PH carries a poor prognosis for patients with chronic HF and is further discussed in Chapter 30.

In the absence of significant pulmonary vasculature remodeling, the PA diastolic pressure should correlate well with the PCWP. It is important to mention that the mPAP is used to calculate the transpulmonary gradient, pulmonary vascular resistance, right ventricular stroke work index (RVSWI), and pulmonary artery pulsatility index (PAPI), all of which are important parameters in deciding eligibility for heart transplantation or durable left ventricular assist device (LVAD) implantation.

Right ventricular pressures (normal 15–25/1–7 mm Hg)

RV systolic pressure (RVSP) should correlate with the PA systolic pressure, in the absence of pulmonary stenosis, and RV diastolic pressure should correlate with the mean right atrial pressure (RAP) in the absence of significant tricuspid valve disease. An elevated RVSP usually indicates preserved RV myocardial contractility. One needs to consider RV failure if the RVSP is low in the setting of elevated RAP (>15 mm Hg) and depressed cardiac index (CI) (<2.2 mL/min/m²) [16].

Right atrial pressure (normal 0–6 mm Hg)

Examination of the jugular venous pulse and sonographic assessment of the jugular vein and inferior vena cava are noninvasive estimates of RAP. Typically, the mean PCWP is greater than the mean RAP in chronic HF and in normal hearts. Tricuspid regurgitation can raise the mean RAP above the mean PCWP and show a prominent V wave on the RA waveform. In patients with predominantly right-sided HF characterized by a distended or noncompliant RV, the mean RAP can dominate the RA waveform with a prominent V wave and a steep Y descent, which represents a rapid decline in pressure as blood rushes to fill the RV in early diastole. Steep Y descents have prognostic value given their association with negative clinical outcomes in HFpEF and after LVAD implantation [18, 19].

Derived parameters from measured intracardiac pressures

Mixed venous oxygen saturation (normal 70–75%)

The mixed venous oxygen saturation (SvO₂) is a marker of tissue perfusion and decreases when oxygen delivery falls or tissue oxygen demand increases. It is directly measured in a venous blood sample obtained from the pulmonary artery. SvO₂ in patients with HF is usually decreased, often less than 60%, and may be as low as 30% or less in severely decompensated patients. Measurement of SvO₂ is useful when monitoring progression of disease in HF patients and is a critical component of the Fick equation for derivation of CO (Chapter 6). SvO₂ is directly related to CO, hemoglobin, and arterial oxygen saturation; and inversely related to metabolic oxygen consumption. Mixed venous oxygen saturation can be derived from the Fick equation as follows:

$$SvO_2 = SaO_2 - \left[\frac{VO_2}{(Hg \times 1.36 \times 10 \times CO)} \right]$$

where:

SvO_2 = mixed venous oxygen saturation

SaO_2 = arterial oxygen saturation

VO_2 = oxygen consumption at rest (e.g., $125 \text{ mL O}_2/\text{min}/\text{m}^2 \times \text{body surface area in m}^2$ [BSA])

Hg = hemoglobin (g/dL)

CO = cardiac output (L/min)

Cardiac output and cardiac index

CO and CI in HFrEF and advanced HFpEF are low. In de novo acute HF, a $CI < 2.2 \text{ L}/\text{min}/\text{m}^2$ characterizes cardiogenic shock (CS). However, patients with chronic HF adapt to a low CI by increasing oxygen extraction in tissues, which results in a decrease in SvO_2 . As such, chronic HFrEF patient may have CI as low as $1.0\text{--}1.5 \text{ L}/\text{min}/\text{m}^2$ without demonstrating clinical signs of shock. A detailed overview of CS is discussed in Chapter 21. CO is estimated during RHC from either the thermodilution (TD) method or by the Fick principle, as discussed in Chapter 6. Each method for estimating CO has strengths and limitations depending on certain conditions. The Fick method is based on a calculation of oxygen consumption (VO_2) divided by the arteriovenous oxygen difference ($SaO_2 - SvO_2$). The most commonly used Fick estimate of CO is by the indirect Fick method, with an assumed VO_2 for any given patient. In contrast, measurement of CO by the direct Fick method requires specialized equipment to directly measure patient oxygen consumption (VO_2) during the RHC. However, estimating CO at rest by the indirect Fick method utilizes directly measured SvO_2 , hemoglobin, and arterial saturation, as well as an assumed resting VO_2 (typically $125 \text{ mL O}_2/\text{min}/\text{m}^2 \times \text{BSA}$, which is derived from mostly nonobese subjects without significant cardiopulmonary disease). This assumption may lead to inaccurate assessments of CO when using the indirect Fick method, since the assumed VO_2 will defer from patient to patient (likely lower in a patient with decompensated or advanced HF) [20]. As such, the indirect Fick-derived CO should never be the sole estimate of CO during exercise RHC, with TD and direct Fick methods as preferred measurements. Estimating CO by the indirect Fick method can be done using the following equation:

$$CO = \frac{VO_2}{10 \times (SaO_2 - SvO_2) \times Hg \times 1.36}$$

Estimating CO by the TD method involves injecting a fixed volume of saline at room temperature into the proximal port of the PAC. Following saline injection, CO is estimated by the relative change in blood temperature over time by a thermal sensor at the distal port of the PAC. A final estimate of CO is then averaged from three or more consistent values. Notably, the TD-derived CO is a measurement of RV CO and is assumed to reflect left ventricular CO. Limitations of this measured CO are therefore related to interrupted flow from the right atrium to the pulmonary artery (e.g., right-sided valvular disease and intracardiac shunts).

The TD method should not be used to estimate CO in the presence of an intracardiac shunt; instead, the indirect Fick method using the Flamm formula to calculate an SvO₂ from superior and inferior vena cavae oxygen saturations can be utilized (see chapter 7 for a more detailed discussion of calculating mixed venous saturation):

$$\text{SvO}_2 = \frac{[(3 \times \text{SVC}) + \text{IVC}]}{4}$$

While CO is often important for medical decision making, understanding the potential limitations and observing the trend of each derived type of CO during PAC-guided therapy remains vital for optimal clinical management.

Transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR)

The transpulmonary gradient is the difference between the mean PAP and mean PCWP (TPG = mPAP – mPCWP). PVR (in Wood units) is the TPG (in mm Hg) divided by CO (in L/min):

$$\text{PVR} = \frac{\text{TPG}}{\text{CO}} = \frac{(\text{mPAP} - \text{mPCWP})}{\text{CO}}$$

A TPG that exceeds 15 mm Hg or a PVR > 3 Woods units suggests pulmonary vascular remodeling secondary to longstanding pulmonary venous hypertension. A PVR > 5 Woods units is an absolute contraindication to heart transplantation, as it increases the risk for right HF of the cardiac allograft. Implantation of an LVAD can decrease the TPG and PVR, but persistent elevation is concerning for the development or progression of post-LVAD RV dysfunction [21].

Left ventricular function (cardiac power, aortic pulsatility index)

Cardiac power output (CPO) is a measure of left ventricular function that is directly proportional to stroke work (i.e., the effective work done by the LV represented by the area within the PV loop) [22, 23]. CPO, represented in Watts (W), is calculated as the product of CO and mean arterial pressure (MAP) divided by a reference standard of 451 [24]. Cardiac power index (CPI) is CPO indexed to BSA (W/m²). A calculated CPO < 0.6 W and CPI < 0.4 W/m² has been associated with increased mortality in patients with cardiogenic shock due to an acute myocardial infarction, which results in a sudden decrease in stroke work [25–27]. However, this association is less prognostic in patients with chronic advanced HF resulting in CS [28–31]. This discrepancy is likely due to the relatively preserved stroke work and stroke volume in a patient with HF-related CS at the expense of increased filling pressures and reduced systemic blood pressure.

Alternatively, the aortic pulsatility index (API) is calculated as the systemic pulse pressure (diastolic blood pressure subtracted from the systolic blood pressure) divided by the mean PCWP. A reduced API of < 1.45 has been associated with adverse outcomes in HF patients with and without CS [29, 30].

$$\text{CPO} = \text{SW} \times \text{HR} = \frac{(\text{CO} \times \text{MAP})}{451}$$

$$\text{CPI} = \frac{\text{CPO}}{\text{BSA}}$$

$$\text{API} = \frac{(\text{SBP} - \text{DBP})}{\text{PCWP}}$$

Right ventricular function (RV stroke work index, pulmonary artery pulsatility index)

RV function is important to assess in patients with HF and CS. The presence of RV dysfunction has notable clinical implications and is associated with worse clinical outcomes [31]. RVSWI, PAPI, and RA/PCWP ratio are important hemodynamic surrogates of RV function and are all calculated based on direct measurements from a PAC [31].

$$\text{RVSWI} = (\text{mPAP} - \text{RAP}) \times \text{SVI} \times 13.6 = (\text{mPAP} - \text{RAP}) \times \left(\frac{\text{CI}}{\text{HR}} \right) \times 13.6$$

$$\text{PAPI} = \frac{(\text{PASP} - \text{PADP})}{\text{RAP}}$$

RVSWI accounts for the beat-to-beat work of the RV. A reduced RVSWI is associated with adverse outcomes in advanced HF and has also been predictive of post-operative RV failure following LVAD implantation [31–33].

PAPI is calculated as the pulmonary artery pulse pressure (difference between the systolic and diastolic pulmonary artery pressures) divided by the RAP. This parameter has been evaluated in several clinical scenarios including inferior myocardial infarction and advanced HF. A reduced PAPI of <2 is typically associated with clinically meaningful RV failure and is prognostic for adverse outcomes including mortality and advanced mechanical support needs [31, 33].

The ratio of RAP to PCWP can be increased in RV dysfunction with a disproportionate rise in RAP as compared to PCWP [34, 35]. An elevated RAP:PCWP ratio (>0.8) has been associated with adverse outcomes in patients with CS despite underlying etiology of either HF or acute myocardial infarction [31]. Similar findings of an increased RAP:PCWP ratio have also been noted in patients with decompensated HF and associated with mortality following LVAD implantation [32, 35].

Systemic vascular resistance

Systemic vascular resistance (SVR), also known as peripheral vascular resistance, is the resistance in the systemic circulatory system that is related to systemic arterial blood pressure, blood flow, and cardiac function. Similar to PVR, its components and calculation are based on the principle of Ohm's Law, where differences in pressure through vessel compliance or resistance govern blood flow. Specifically,

SVR is calculated as the difference between the MAP and the mean central venous pressure (CVP or RAP) divided by cardiac output.

$$\text{SVR} = \frac{(\text{MAP} - \text{CVP})}{\text{CO}}$$

SVR increases with vasoconstriction and decreases with vasodilation. In chronic HF, vasodilators (including guideline-directed medical therapy) should be used to reduce SVR (thus myocardial afterload) to normal range, in order to optimize cardiac output and function.

Additional hemodynamic considerations

Pulsus alternans

Pulsus alternans may also be seen on the aortic pressure tracing, noted by the beat-to-beat variation in the peak systolic pressure amplitude (Figure 16.5). While the precise mechanism of pulsus alternans is not known, it is a sign of severe left ventricular dysfunction. Proposed mechanisms include changes in preload and contractility leading to alterations in stroke volume [36, 37]. Post-ectopic potentiation and increased preload may play a role in the initiation of pulsus alternans. Pulsus alternans is more common during tachycardia and occurs more frequently with inotropic therapy. It should be noted that the absence of pulsus alternans does not exclude severe left ventricular dysfunction. In one study, only 19.1% of patients with moderate to severe left ventricular dysfunction (mean LVEF 35%) had pulsus alternans at rest [37].

Ambulatory monitoring of pulmonary artery pressures (CardioMEMS)

The goal of ambulatory monitoring of PA pressures is to assess fluid status in HF patients remotely and intervene before clinical symptoms emerge to the point of requiring hospital admission for decompensation. The CardioMEMS system was approved by the Food and Drug Administration (FDA) in 2014 and consists of a battery-free capacitive pressure sensor permanently implanted in the pulmonary artery and a transmission station that acquires and processes signals from the implantable device transmitting PA pressure measurements to a remote database that is monitored by the treating physician (Figure 16.6). The CardioMEMS device was evaluated in the prospective, multicentered, randomized, single-blinded CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III HF Patients) trial. In this study of 550 NYHA class III HF patients with any LVEF and at least one hospitalization in the prior year, there was a significant 28% reduction in HF-related hospitalizations at 6 months with a number needed to treat 8 [38]. These findings were further supported in a pre-COVID-19 impact analysis of the GUIDE-HF trial, which evaluated

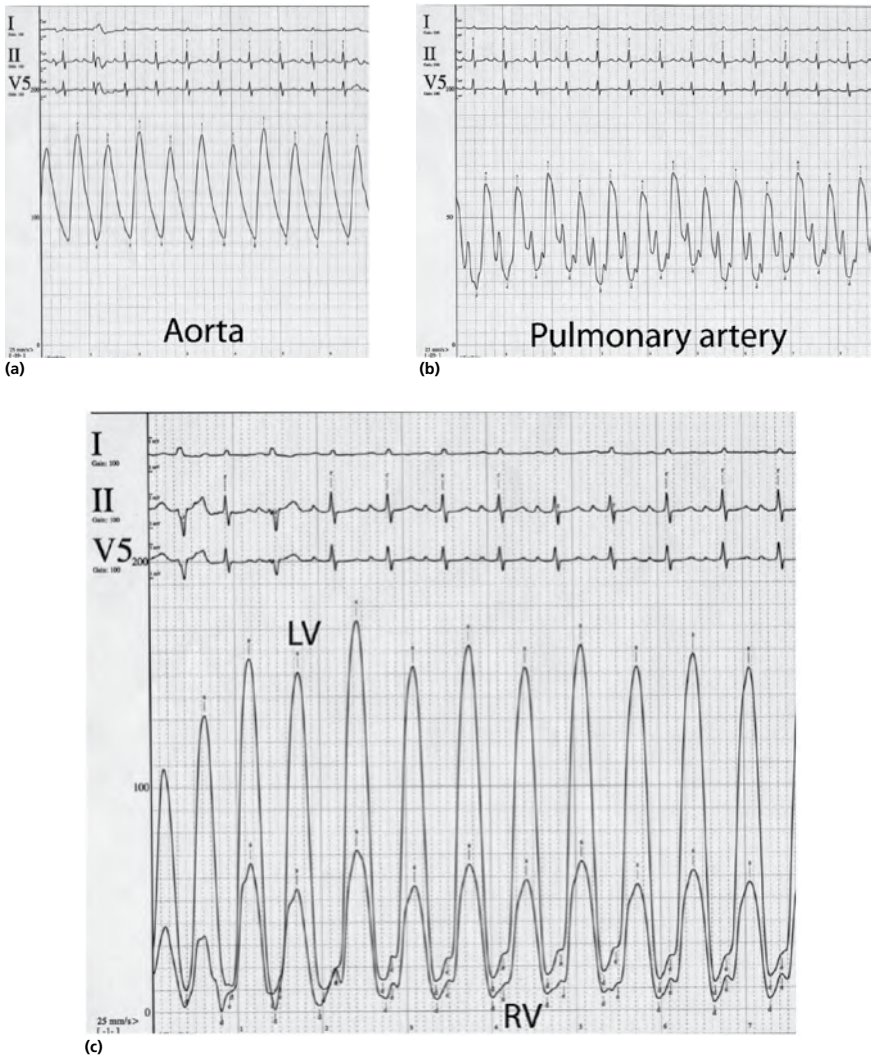


Figure 16.5 Pulsus alternans—beat-to-beat variation in systolic pressure in aortic (a), pulmonary artery (b), and left and right ventricular (c) pressure tracings in a 62-year-old female with biventricular failure. Source: Cardiology Research and Practice 2009 / John Wiley & Sons / CC-BY-4.0.

the CardioMEMS system in an expanded HF population to include NYHA class II–IV [39].

The CardioMEMS system is the only FDA-approved implantable hemodynamic monitoring device that measures intracardiac pressures. The now obsolete Chronicle device, which continuously measured RV systolic and diastolic

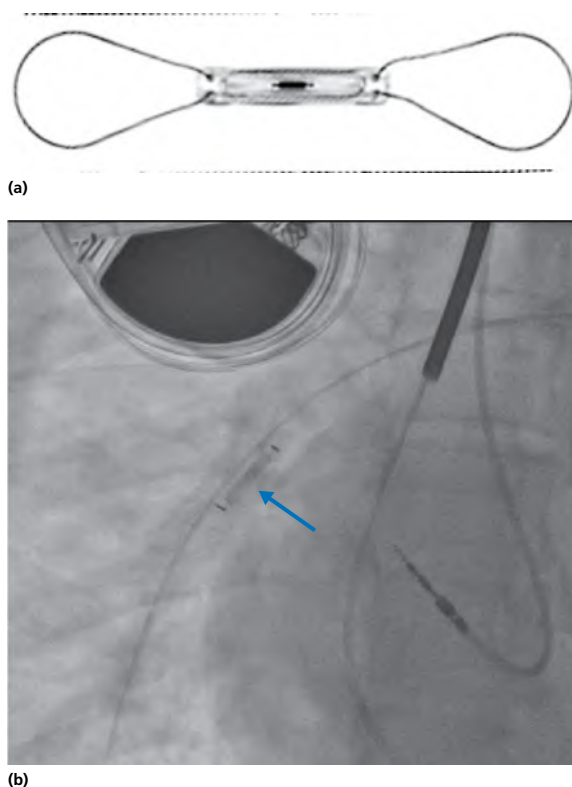


Figure 16.6 The CardioMEMS HF system pulmonary pressure monitoring device prior to (a) and after implantation (arrow) in a branch of the right pulmonary artery (b). Source: a) Reproduced with permission of Abbott, © 2024.

pressure (RVSP, RVDV) and estimates pulmonary artery diastolic pressure (ePAD), was never FDA-approved despite initial promising results [40]. Other electrophysiology-based implantable cardiac devices (namely implantable cardioverter-defibrillators and cardiac resynchronization therapy devices) can be used to indirectly monitor fluid status (e.g., measuring thoracic impedance and other proprietary sensor-based parameters). While useful, these measurements are derived from sensor-based algorithms and are at best indirect measurements of fluid status. Newer technologies of direct hemodynamic measurements are currently under investigation, such as the Cordella system (an implant in the right pulmonary artery), the V-LAP sensor (an implant across the interatrial septum to directly measure LAP), and the FIRE1 device (an inferior vena cava implant) [41]. A more recent pooled meta-analysis of ambulatory implantable hemodynamic monitoring systems in HFrEF demonstrated a reduction in HF hospitalizations within the first year of implantation followed by a mortality benefit after 1 year [42].

Important points: hemodynamics in chronic heart failure

- Patients with chronic HF typically have higher baseline intracardiac filling pressures
- Mixed venous oxygen saturation (SvO₂) is a useful surrogate measurement for assessing cardiac output
- Both indirect Fick and thermodilution (TD) methods for estimating cardiac output (CO) have important limitations
- Several hemodynamic surrogates of left and RV dysfunction are associated with adverse outcomes
- Pulmonary vascular remodeling can increase the risk of RV failure and have important implications in advanced HF
- Invasive hemodynamic monitoring with a pulmonary artery catheter (PAC) can be useful in the assessment and management of select HF patients

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CHAPTER 17

Restrictive cardiomyopathy

David P. McLaughlin and George A. Stouffer

Restrictive cardiomyopathy is a disease of the myocardium characterized by impaired relaxation and diastolic dysfunction of either or both ventricles. Causes of restrictive cardiomyopathy can be classified as infiltrative, storage disease, noninfiltrative, and endomyocardial and include amyloidosis, hemochromocytosis, metabolic storage diseases, hypereosinophilic syndrome, metastatic malignancies, sarcoid, carcinoid, idiopathic, endomyocardial fibrosis, and mediastinal radiation [1].

The disease tends to be progressive and as the ventricles become less distensible, diastolic filling and cardiac output are impaired and filling pressures increase. A reduction in systolic function may also occur as the disease progresses. Initial symptoms are usually low output-type complaints (e.g., exertional dyspnea or exercise intolerance) because of inability to augment stroke volume. As right atrial (RA) pressure increases, symptoms of systemic venous congestion may predominate. Further increases in RA and pulmonary capillary wedge (PCW) pressures will be accompanied by symptoms of orthopnea and paroxysmal nocturnal dyspnea.

The clinical presentation of restrictive cardiomyopathy can be similar to constrictive pericarditis and differentiation of these processes can be difficult. Additionally, some disease processes (e.g., amyloid) can involve both myocardium and pericardium, leading to a mixed hemodynamic profile.

Hemodynamic principles

The hemodynamic findings of restrictive cardiomyopathy and constrictive pericarditis are similar. Chapter 18 contains a more detailed description of the findings in constrictive pericarditis.

1 Diastolic filling is impaired and determined by the degree of restriction.

- Pressures during diastole are elevated and similar in all cardiac chambers. Right and left ventricular diastolic pressures are elevated and equal in early diastole, but generally end-diastolic pressures differ by more than 5 mm Hg;

in contrast to constrictive pericarditis, where left ventricular end-diastolic pressure (LVEDP) and right ventricular end-diastolic pressure (RVEDP) will be similar.

- The difference between LVEDP and RVEDP is accentuated by exercise.
 - Stroke volume is decreased and cardiac output will fall in the absence of tachycardia.
 - Severe pulmonary hypertension is more common than constrictive pericarditis. RV and pulmonary systolic pressures may exceed 50 mm Hg.
 - Pulsus paradoxus is not found in restrictive cardiomyopathy because of a stiff, noncompliant septum.
- 2 Almost all ventricular filling occurs in early diastole.
- Exaggerated Y descent in atrial tracings (Figure 17.1).
 - Usual respiratory variation of atrial pressures is reduced, but the Y descent may become deeper during inspiration.
 - RA tracing may have a classic M or W configuration.
 - Dip and plateau configuration in RV and LV tracings.

Differentiating restrictive cardiomyopathy from constrictive pericarditis

The hemodynamic effects of restrictive cardiomyopathy are similar to those of constrictive pericarditis, and it is generally difficult to make a correct diagnosis based on hemodynamics alone. Having said that, however, there are certain hemodynamic criteria that favor restrictive cardiomyopathy including:

- Equalization of left and right ventricular filling pressures, but with a difference of more than 5 mm Hg between LVEDP and RVEDP. Note that the studies from which the 5 mm Hg cutoff was determined were generally performed with high-fidelity manometric catheters.
- RVEDP does not exceed one-third of the level of the right ventricular systolic pressure.
- RV systolic pressure may be greater than 50 mm Hg.
- Concordance, defined as an inspiratory decrease in both RV and LV systolic pressures during normal respiration (Figure 17.1). This is in contrast to discordance, which is an increase in RV systolic pressure simultaneous with a decrease in LV systolic pressure (seen in constrictive pericarditis). The difference in ventricular interdependence is due to the effects of respiration on ventricular filling. It is imperative to record RV and LV simultaneously on a 100–200 mm Hg scale (depending on systolic pressure) on slow sweep speed and to assess over several respiratory cycles.

A review of 82 cases of constrictive pericarditis and 37 cases of restrictive cardiomyopathy found that the predictive accuracy of a difference between RVEDP and LVEDP >5 mm Hg was 85%, the predictive accuracy of RV systolic pressure >50 mm Hg was 70%, and the predictive accuracy of a ratio of RVEDP to RV

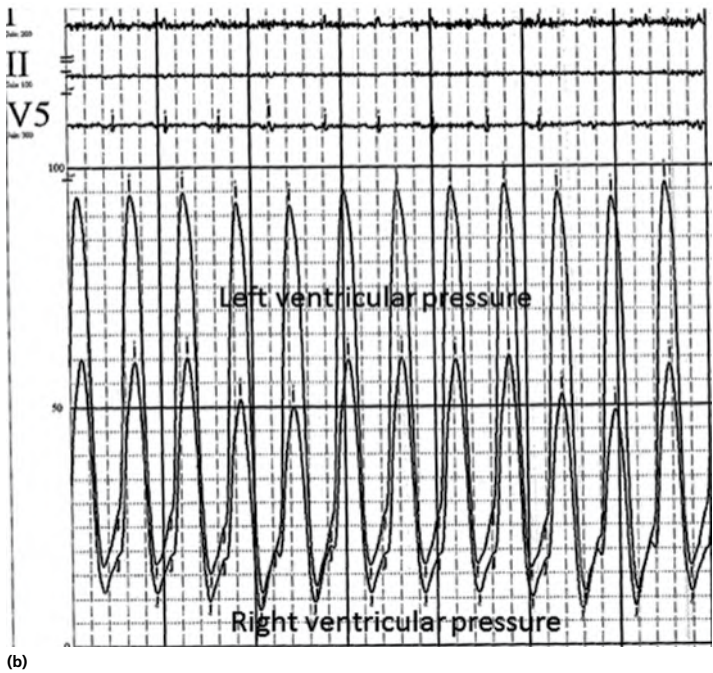
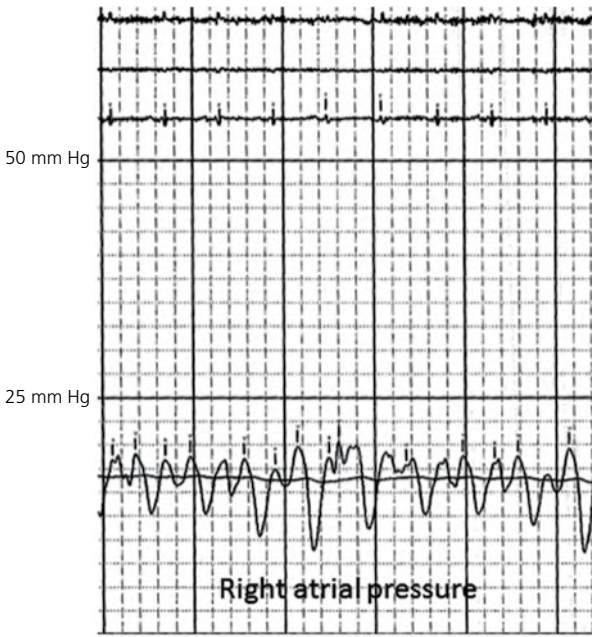


Figure 17.1 Pressure tracings from a patient with cardiac amyloidosis. Note the elevated RA pressures with an exaggerated Y descent (a). Simultaneous RV and LV pressures show equalization during diastole (most notable during expiration) and concordance in which RV and LV systolic pressures both decrease with inspiration (b).

systolic pressure of less than 0.33 was 76%. If all three criteria were present, the probability of having classified the patient correctly was greater than 90%. However, one-fourth of patients could not be classified by hemodynamic criteria [2].

Jain et al proposed using aortic and pulmonic ejection time measurements to differentiate restrictive pericarditis from constrictive pericarditis as they are functional surrogates for respiratory changes in RV and LV stroke volumes [3].

A more detailed description of hemodynamic findings that can be used to differentiate restrictive cardiomyopathy from constrictive pericarditis can be found in Chapter 18.

Echocardiography

The ventricles are usually normal in size. LV hypertrophy is frequently present (of note is that decreased R wave amplitude on ECG coupled with LV hypertrophy on echo is frequently a clue to restrictive cardiomyopathies). Mitral inflow velocity in restrictive cardiomyopathy is typically one of a prominent E wave, decreased A wave, an increased ratio of early diastolic filling to atrial filling (>2), decreased deceleration time (<150 ms), and a decreased isovolumic relaxation time (<70 ms). Cardiac valves may be involved in restrictive cardiomyopathy, leading to regurgitation.

Significant respiratory variation of mitral, tricuspid, pulmonary, and hepatic flows occurs only with constriction and not in restrictive cardiomyopathy however the magnitude of variation is dependent upon the volume status of the patient and their inspiratory effort. Respiratory variation in mitral valve inflow is less in restrictive cardiomyopathy compared to constrictive pericarditis [4]. An echocardiographic study of 30 patients (19 with constrictive pericarditis and 11 with restrictive cardiomyopathy) found that significant respiratory variation in the ventricular inflow peak velocity $\geq 10\%$ predicted constrictive pericarditis with a sensitivity and specificity of 84% and 91%, respectively [5]. Remember that mitral valve inflow velocity is dependent on preload and that marked elevation in LA pressure may mask respiratory variation [6]. Reducing preload (e.g., by head-up tilting) may accentuate respiratory variation in inflow velocity.

Doppler findings in constrictive pericarditis and restrictive cardiomyopathy

- RV and LV inflow show prominent E wave due to rapid early diastolic filling
- Short deceleration time of E wave as filling abruptly stops
- Small A wave as little filling occurs in late diastole following atrial contraction

Case study

A 49-year-old female with pulmonary sarcoidosis reported increasing dyspnea associated with chest tightness. Echocardiogram showed normal LV chamber size, wall thickness, and function. Initial hemodynamic evaluation in the cardiac catheterization laboratory showed a mean RA pressure of 8 mm Hg. The waveform had a "W" configuration with accentuation of the Y descent during inspiration (Figure 17.2a). RA and LV pressures during diastole were

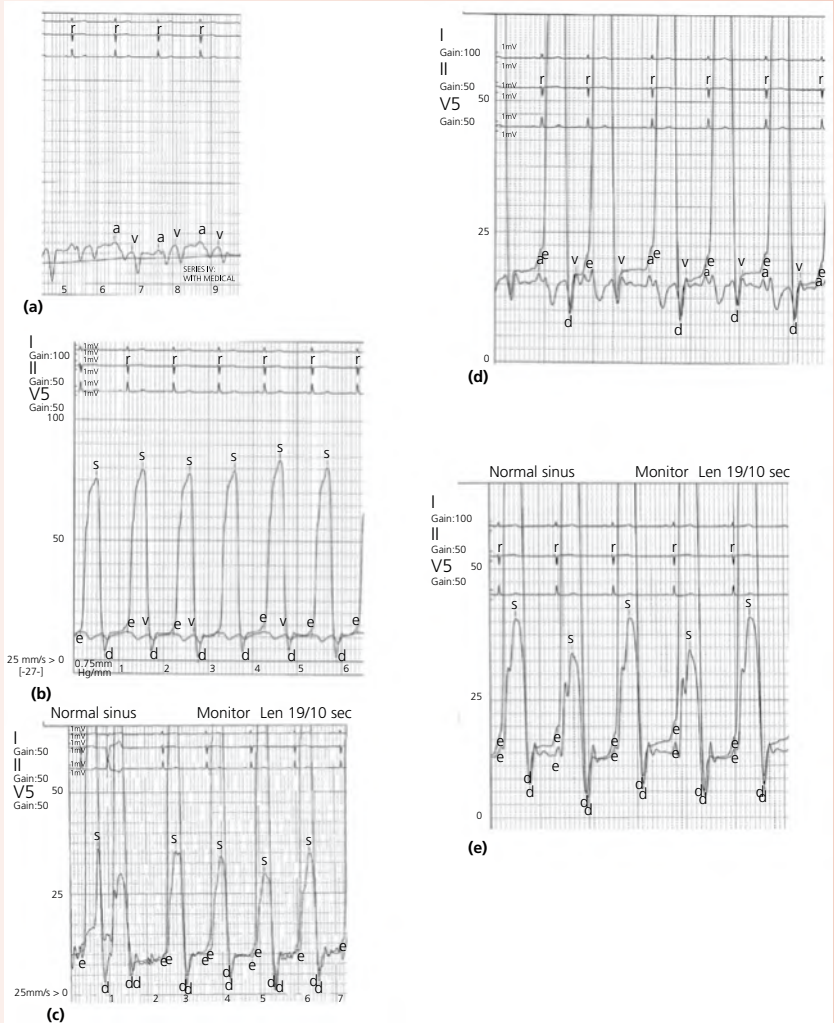


Figure 17.2 Pressure tracings from a patient with cardiac sarcoidosis. Pressure tracings at baseline include RA (a), simultaneous RA and LV (b), and simultaneous RV and LV (c). Pressures were again obtained after 500 ml infusion of saline including simultaneous RA and LV (d) and simultaneous RV and LV (e).

similar (Figure 17.2b). The RV pressure tracing showed a “dip and plateau” configuration and RV diastolic pressures approximated LV diastolic pressures (Figure 17.2c). Following rapid infusion of 500 mL of saline, RA, RVEDP, and LVEDP increased markedly. RA, RV, and LV pressures were similar during diastole, but some separation of RA and LV at the end of diastole (Figure 17.2d) and RVEDP from LVEDP (Figure 17.2e) was evident. These findings are consistent with restrictive cardiomyopathy from sarcoid.

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PART IV

Pericardial disease

 **2025** Edition

CHAPTER 18

Constrictive pericarditis

David P. McLaughlin and George A. Stouffer

The pericardium is a two-layered sac that encircles the heart. The visceral pericardium is a mesothelial monolayer that is adherent to the epicardium, which is reflected back on itself at the level of the great vessels. The cardiac chambers are covered by the pericardium, with the exception of the left atrium and pulmonary veins, which are mostly outside of the pericardium. The parietal layer is a tough, fibrous outer layer. In the potential space that exists between these two layers, there is normally 5–50 mL of serous fluid. The normal pericardium serves three primary functions: fixing the heart within the mediastinum, limiting the spread of adjacent infections, and limiting acute cardiac distention during sudden increases in intracardiac volumes.

Constrictive pericarditis is a condition characterized by a dense, fibrous thickening of the pericardium that adheres to and encases the myocardium, resulting in impaired diastolic ventricular filling. The general paradigm is that constrictive pericarditis occurs over a period of years, due either to an acute insult (e.g., an infection) that elicits a chronic fibrosing reaction or to an ongoing insult that stimulates a persistent reaction (e.g., renal failure). In the past the most common etiology was tuberculosis, but currently, idiopathic pericardial constriction is the most frequent offender.

Clinically, constrictive pericarditis is generally a chronic disease with symptom progression over a period of years. The clinical presentation is that of right-sided heart failure and may resemble restrictive cardiomyopathy, cirrhosis, or cor pulmonale, among other conditions. Occasionally patients will go for years without the correct diagnosis being made. Recently, the advent of newer diagnostic technologies and a change in the predominant etiologies of constriction have led to increasing recognition of subacute presentations occurring over a period of months [1].

Pericardial constriction occurring after acute pericarditis of any cause is rare but can occur early or later after the insult. This often resolves and the possible

transient nature must be carefully considered when planning treatment. A study of 500 patients with acute pericarditis found that the risk of developing chronic constrictive pericarditis was low, but varied depending on the etiology. The incidence rate of constrictive pericarditis per 1000 person-years was 0.8 cases for idiopathic/viral pericarditis, 4.4 cases for connective tissue disease/pericardial injury syndrome, 6.3 cases for neoplastic pericarditis, 31.7 cases for tuberculous pericarditis, and 52.7 cases for bacterial pericarditis [2]. Constrictive physiology can occur in the weeks following cardiac surgery or following an episode of acute pericarditis. Constriction following radiation therapy for malignancy can be a difficult diagnostic dilemma, as it can coexist with radiation-induced restrictive myocardial disease. In patients with permanent constrictive pericarditis, the presentation is usually years after the initial insult.

Hemodynamics of constrictive pericarditis

Elevation and equalization of diastolic pressures are the hallmarks of constriction (Table 18.1). Right atrial (RA), left atrial (LA), right ventricular (RV), and left ventricular (LV) diastolic pressures are elevated and nearly identical. In contrast to the normal heart, where pressures in the right-sided and left-sided cardiac chambers are independent (i.e., unrelated) during diastole, in constrictive pericarditis, the stiff pericardium limits expansion of the cardiac chambers. The chambers can fill beyond a certain limited point only by compressing other chambers and thus the diastolic pressures equalize. The ventricular waveform has a characteristic square root sign due to the rapid rise in early diastolic pressure during passive filling after which filling is impaired due to the constraining effects upon chamber expansion of the rigid pericardium (Figure 18.1).

Hemodynamic principles

- 1 Diastolic filling is impaired and determined by degree of constriction.
 - Pressures during diastole are elevated and equal in all cardiac chambers. RV and LV end-diastolic pressures (RVEDP and LVEDP) are elevated and within 5 mm Hg of each other.

Table 18.1 Hemodynamic findings in constrictive pericarditis.

• Almost all ventricular filling occurs in early to mid-diastole • Elevation of atrial pressures • Equalization of early and mid-diastolic pressures (e.g., RV and LV or RA and LV) • Increase in RA pressure during inspiration (Kussmaul's sign) • Exaggerated X and Y descents • Intrathoracic pressure is not transmitted to the cardiac chambers • Ventricular systolic discordance—defined as inspiratory augmentation of RV systolic pressure simultaneous with a decrease in LV systolic pressure. Occurs due to the effects of respiration on ventricular filling

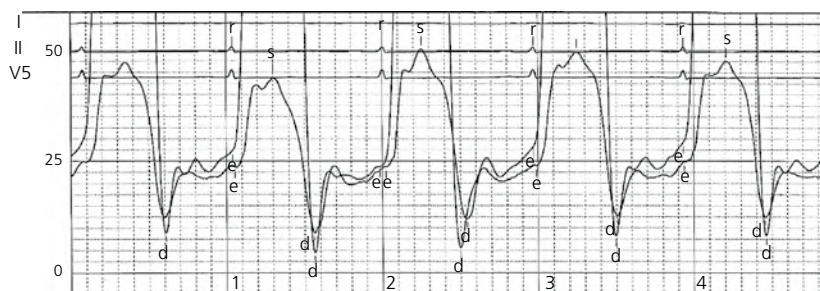


Figure 18.1 Ventricular pressure tracings in constrictive pericarditis. Simultaneous LV and RV tracings in a patient with constrictive pericarditis. Note the “dip and plateau” configuration and the near equalization during mid and late diastole. Operative findings in this patient included a dense, adherent pericardium. CVP dropped by approximately 15 mm Hg in the operating room with removal of the pericardium from the anterior RV and the RA.

- Stroke volume is decreased. Cardiac output will fall in the absence of tachycardia.
 - Hypovolemia may mask constriction because diastolic filling pressures do not appear elevated (especially in patients who are over-diuresed). A fluid challenge may help in establishing the diagnosis.
 - Severe pulmonary hypertension is rare. Usually, RV and pulmonary artery (PA) systolic pressures are <50 mm Hg.
- 2 Almost all ventricular filling occurs in early diastole (Figure 18.2).
 - Exaggerated Y descent.
 - RA tracing may have a classic M or W configuration (Figure 18.3).
 - Dip and plateau configuration in RV and LV tracings.
 - 3 In severe constrictive pericarditis, intrathoracic pressure is not communicated to the intrapericardial space (Figure 18.4).
 - Central venous pressure (CVP) and RA pressure do not decrease, and may actually increase, with inspiration. Classically this is described as Kussmaul's sign, which is defined as a reversal of the normal pattern of decreasing jugular venous pressure (JVP) during inspiration [3]. Venous flow to RA does not accelerate with inspiration.
 - Pulsus paradoxus is minimal or absent in rigid constrictive pericarditis because ventricular filling is not affected by intrathoracic pressure. In some cases, the pericardium retains some elasticity as it thickens and pulsus paradoxus may be present.
 - Interdependence of ventricular filling—on inspiration, intrathoracic pressure and pulmonary venous pressure decrease, but LA pressure does not. A reduced pulmonary vein to LA pressure gradient results in decreased flow into the LA and LV. Decreased LV filling during diastole allows for increased RV filling, which leads to an increase in flow across the tricuspid valve. Thus, on inspiration, RV systolic pressure increases while LV systolic pressure decreases. On expiration, increased LV filling occurs at the expense of RV filling and the opposite effect occurs on mitral valve and tricuspid valve flow.

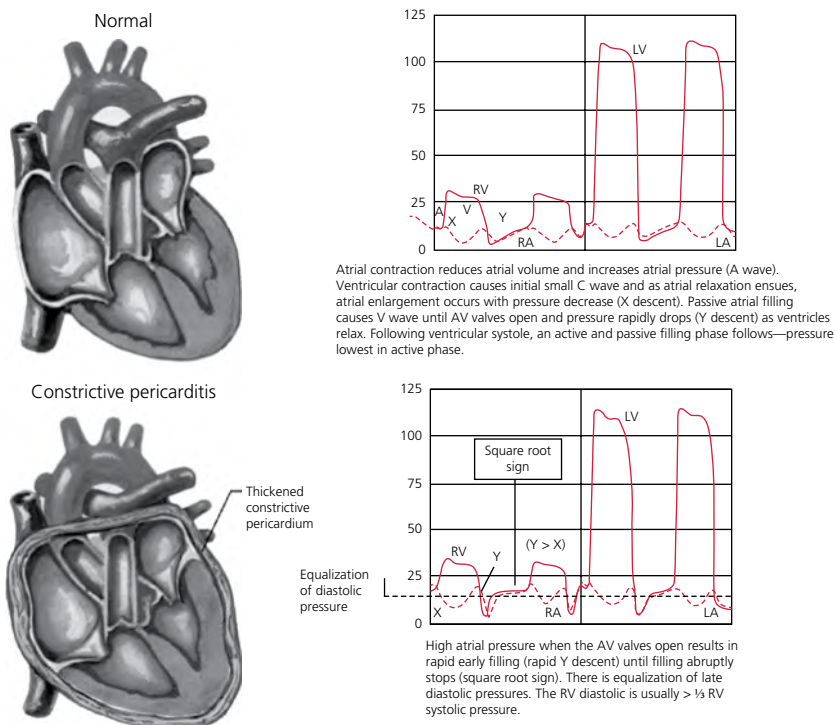
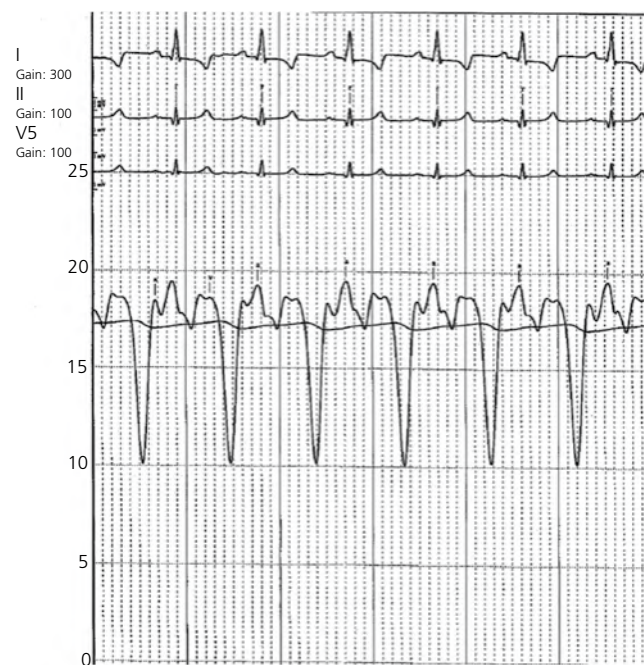


Figure 18.2 Comparison of intracardiac pressures in the normal heart and in constrictive pericarditis.

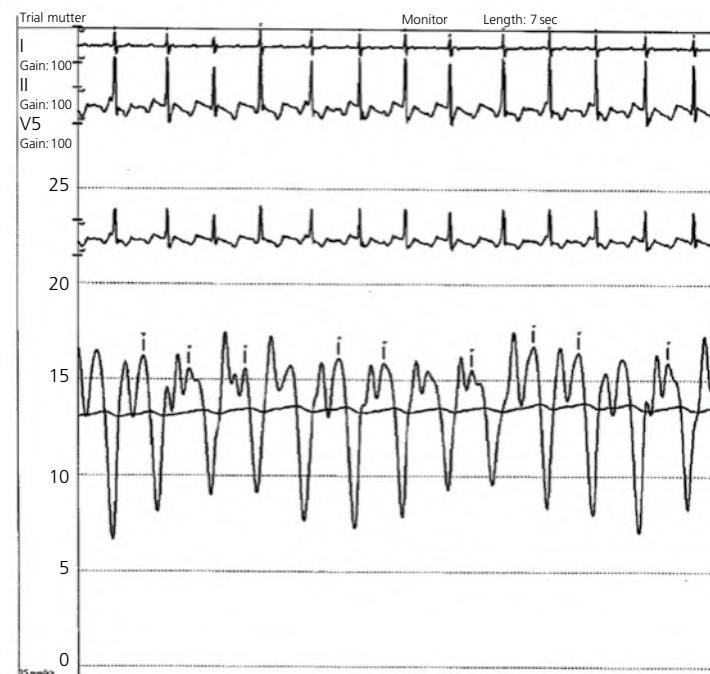
4 Constrictive physiology can be mimicked by restrictive cardiomyopathy and acute or subacute volume overload of the heart (pseudo-constriction). Pseudo-constriction occurs when LV or RV volume overload happens rapidly, such that the pericardium does not have time to expand to accommodate the increased size. It is defined as constrictive-appearing physiology in the absence of pericardial pathology, and as such, is a diagnosis of exclusion. The following list gives the most common causes of pseudo-constrictive physiology.

- Acute RV volume overload (e.g., pulmonary embolus)
- Large RV infarcts
- Acute severe mitral regurgitation
- Acute severe tricuspid regurgitation
- Acute severe aortic regurgitation
- Aneurysms

Severe bradycardia does not cause compressive physiology per se but can result in a square root appearance in ventricular tracings in patients with heart rates < 50 bpm.



(a)



(b)

Figure 18.3 RA tracings from two patients with constrictive pericarditis. Note the elevated RA pressure, prominent Y descent, and lack of respiratory variation (both patients were breathing normally during these recordings).

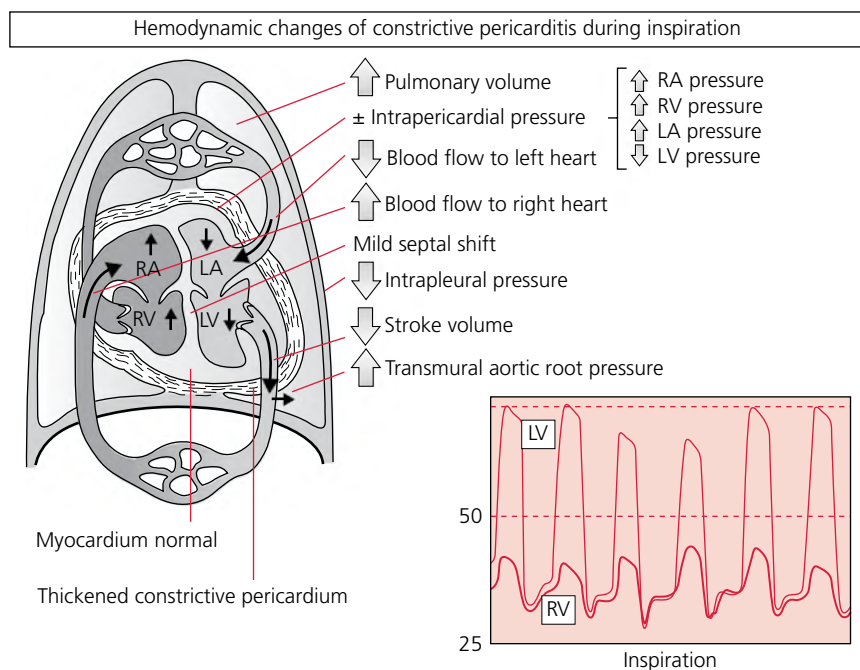


Figure 18.4 Effect of respiration on blood flow in mild constrictive pericarditis. Note the discordance in the ventricular pressure tracings.

The differentiation of constrictive pericarditis from restrictive cardiomyopathy or pseudo-constriction due to volume overload based solely on hemodynamics is difficult and will be discussed in more detail later in this chapter.

Physical exam

The most obvious findings are related to elevated right heart pressures and include elevated JVP, hepatomegaly, ascites, and peripheral edema. The general physical examination in patients with constrictive pericarditis is not unlike that for those with right heart failure of any cause. There are, however, a few fairly specific physical findings that are important to recognize.

Careful examination of JVP will invariably reveal elevation. Normally, inspiration leads to a fall in JVP, as the negative thoracic pressure generated in the thorax is transmitted to the right-sided cardiac chambers. Kussmaul described a paradoxical rise in JVP with inspiration in patients with pericardial constriction that is rare in restrictive myocardial disease. Occasionally, prominent X and Y descents can be seen on examination of the neck veins. Friedreich's sign, the sudden

collapse of previously distended neck veins during early diastole, is found in patients with constrictive pericarditis. A high-pitched early diastolic sound or pericardial knock occurring before a typical S3 is often heard.

Pericardial imaging techniques

A chest X-ray has some value in chronic pericardial constriction, as calcification of the pericardium can be seen in up to 25% of cases. Pericardial thickening can be seen on echocardiography but must be distinguished from gain artifacts or harmonics. Pericardial effusion is occasionally present and typically small. CT scanning and cardiac MRI are now the gold standard of cardiac imaging modalities used in diagnosing pericardial thickening. A pericardial thickness of >3 mm is suggestive of pericardial constriction, but it is important to note that pericardial thickening on imaging is absent in up to 20% of cases. Similarly, not all patients with thickened pericardium will have constrictive pericarditis, although a thickness of >6 mm adds considerable specificity to the diagnosis.

Findings at cardiac catheterization

- 1 Diastolic pressures are elevated. This is an important finding as equalization of diastolic pressures can be observed in the normal heart when filling pressures are low and paradoxically constrictive pericarditis can be masked with hypovolemia. Thus, it is essential that IV fluids be given in sufficient quantities to increase diastolic pressures in patients with low filling pressures if the diagnosis of constrictive pericarditis is being considered.
- 2 Prominent Y descent on RA tracing. X descent is usually preserved.
- 3 RV and LV diastolic pressures are elevated and similar (Figure 18.5). In a study of 15 patients with surgically proven constrictive pericarditis, LVEDP minus RVEDP (determined using high-fidelity manometric catheters) at endexpiration was 4 ± 4 mm Hg [4]. While a comparison of LVEDP and RVEDP is a time-honored way to evaluate for constrictive pericarditis, a comparison of mean pressures in the RA and the LA (or PCWP) may be more useful, as such recordings are less subject to artifacts.
- 4 LV and RA diastolic pressures are similar.
- 5 Characteristic dip and plateau configuration to LV and RV pressure tracings.
- 6 RA pressure does not decrease with inspiration (i.e., Kussmaul's sign). The Y descent may become more prominent with inspiration in patients with some remaining elasticity in their pericardium.
- 7 Ventricular systolic discordance is thought by some to be the most specific hemodynamic sign of constrictive pericarditis. This is defined as inspiratory augmentation of RV systolic pressure simultaneous with a decrease in LV systolic pressure and occurs due to the effects of respiration on ventricular filling

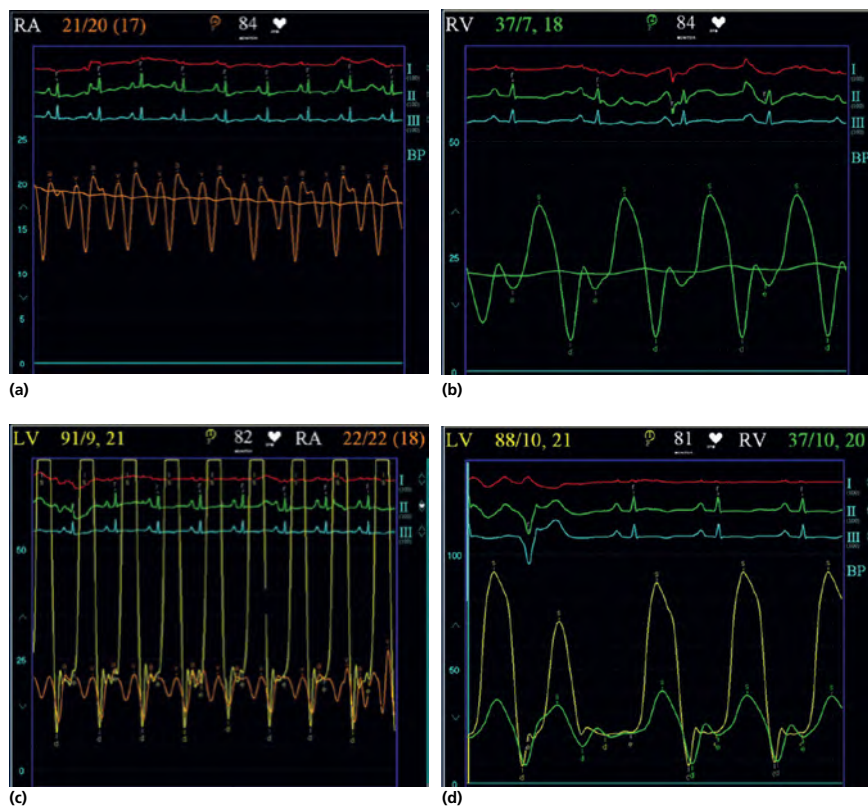


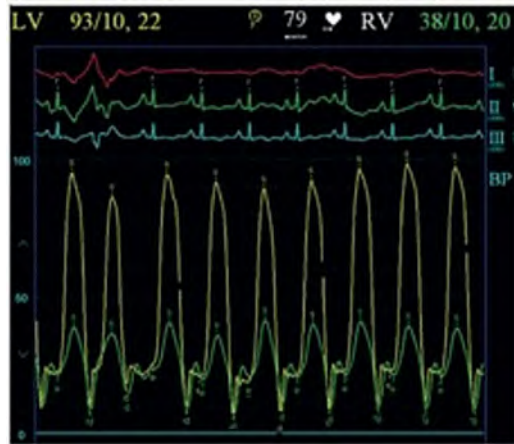
Figure 18.5 Equalization of right heart and LV diastolic pressures in a 50-year-old male who presented with progressive worsening of shortness of breath and severe lower extremity edema two years after an episode of acute pericarditis. His echo and chest CT were suggestive of constrictive pericarditis. Panels (a) and (b) are pressures in the RA and RV, respectively, while panels (c) and (d) are simultaneous pressures in the RA/LV and RV/LV, respectively.

(Figure 18.6). Inspiration augments right heart filling at the expense of left heart filling. This is reflected as a drop in LV systolic pressure on particular cycles when the RV is rising. It is imperative to record RV and LV simultaneously on a 200 mm Hg scale at a slow sweep speed and to assess several respiratory cycles.

- 8 The RVEDP is usually greater than one-third of the RV systolic pressure. In a study of 15 patients with surgically proven constrictive pericarditis, the ratio of RVEDP to RVSP was 0.57 ± 0.14 [4].
- 9 PA diastolic pressure (and occasionally PCWP) can be less than LVEDP during inspiration. The PA, but not the LA, is subject to intrathoracic pressure changes in patients with constrictive pericarditis and thus will fall with inspiration.
- 10 A study of 10 patients with surgically proven constrictive pericarditis and 10 patients without constrictive pericarditis found that there was a significantly greater



(a)



(b)

Figure 18.6 Examples of concordance and discordance. Ventricular systolic discordance which is common in constrictive pericarditis is defined as inspiratory augmentation of RV systolic pressure simultaneous with a decrease in LV systolic pressure and occurs due to the effects of respiration on ventricular filling. Source: Courtesy of CardioVillage.com.

decrease in PA ejection times and a nonstatistically significant greater increase in aortic ejection time during expiration vs inspiration in patients with constrictive pericarditis. Ejection times were manually measured (in milliseconds) from systolic upstroke to diastolic notch with a sweep speed of 100mm/s. Measurements were taken at peak inspiration and expiration in patients breathing spontaneously [5].

Sensitivity and specificity of various hemodynamic findings in constrictive pericarditis

A study from the Mayo Clinic of 15 patients with constrictive pericarditis and 7 patients with restrictive cardiomyopathy provides some useful information [4]. Note, however, that this study was performed with high-fidelity manometric catheters. The small, soft fluid-filled catheters that are commonly used in cardiac catheterization laboratories can distort waveforms to a significant extent.

- Sensitivity and specificity of an LVEDP–RVEDP ≤ 5 mm Hg for the diagnosis of constrictive pericarditis were 60% and 71%, respectively.
- Sensitivity and specificity of an RVEDP/RV systolic pressure $>1/3$ for the diagnosis of constrictive pericarditis were 93% and 57%, respectively.
- Ventricular concordance/discordance was 100% sensitive and specific.
- Respiratory change in RA pressure <3 mm Hg was 93% sensitive and 48% specific.
- Another study found that Kussmaul's sign was neither sensitive nor specific for constrictive pericarditis. In a study of 135 patients, Kussmaul's sign was present in only 21% of patients with surgically proven constrictive pericarditis [1]. Kussmaul's sign may also occur in right-sided heart failure, RV infarction, and tricuspid stenosis.

Findings on echocardiography

The two-dimensional and Doppler echocardiographic features of constriction include a thickened pericardium, abnormal ventricular septal motion, flattening of the LV posterior wall during diastole, respiratory variation in ventricular size, dilated inferior vena cava (IVC), impaired diastolic filling, and dissociation of intracardiac and intrathoracic pressures [6, 7]. In constrictive pericarditis, there is a decrease in the mitral inflow velocity of greater than 25% with respiration. Also with respiration, variation in ventricular filling can sometimes be seen. During inspiration, a decrease in LV filling makes more room for RV filling, as the interventricular septum moves to the left and hepatic diastolic flow velocities increase during inspiration. During expiration, LV filling increases, which decreases right heart filling and therefore hepatic diastolic forward flow velocity is decreased. In constriction, diastolic forward flow is usually greater than systolic forward flow. Additionally, hepatic diastolic flow reversal is increased, as the inflow across the tricuspid valve is interrupted by the pericardium and movement of the septum toward the right ventricle with expiration. Plethora of the IVC is common and failure of the IVC to decrease in diameter by 50% during the respiratory cycle is the echo equivalent of Kussmaul's sign. M-mode imaging can demonstrate an early diastolic notch of the interventricular septum corresponding to rapid cessation of filling, the pericardial knock, and the onset of the plateau phase of the ventricular diastolic waveform.

Table 18.2 Sensitivity and specificity of echo findings in differentiating constrictive pericarditis and restrictive cardiomyopathy.

Echo parameter	Sensitivity	Specificity
Ventricular septal shift	93	69
Change in mitral <i>E</i> velocity $\geq 14.6\%$	84	73
Medial <i>e'</i> velocity ≥ 9 cm/s	83	81
Medial <i>e'</i> /lateral <i>e'</i> ≥ 0.91	75	85
Hepatic vein ratio in expiration ≥ 0.79	76	88

The Mayo Clinic has developed echo criteria for the diagnosis of constrictive pericarditis that includes five echo parameters. The sensitivity and specificity in Table 18.2 are from a study of 130 patients with surgically confirmed constrictive pericarditis from 2008–2010 compared to 36 patients with restrictive cardiomyopathy or severe tricuspid regurgitation [7]. Of the five echocardiographic criteria studied, the three most important for the diagnosis of constrictive pericarditis seem to be the presence of respiration-related ventricular septal shift, preserved or increased medial mitral annular *e'* velocity, and prominent hepatic vein expiratory diastolic flow reversals.

Differentiation of constrictive pericarditis and restrictive cardiomyopathy

Constrictive pericarditis and restrictive cardiomyopathy are very different diseases sharing a similar hemodynamic profile. Both have as the primary hemodynamic abnormality altered mid to late diastolic filling of the ventricles, leading to a syndrome of congestive heart failure. Often heart failure is insidious in onset and predominantly right-sided. These syndromes may mimic many other disease entities and it is common for both conditions to go undiagnosed for years.

In the case of constrictive pericarditis, the impediment to filling is caused by the thickened unyielding pericardium. In restrictive cardiomyopathy, the abnormality is a result of a poorly compliant myocardium that limits the ability of the ventricles to expand and accept the filling volume of the atria. Rarely, there is overlap and both entities can coexist (e.g., radiation-induced myopericardial disease). The possibility of constriction or restriction should be entertained in any patient presenting with heart failure and normal systolic function (although systolic function will decline as restrictive cardiomyopathy progresses), particularly when other causes of this entity are not present.

Table 18.3 Hemodynamic findings in constrictive pericarditis and restrictive cardiomyopathy.

	Constrictive Pericarditis	Restrictive cardiomyopathy
LV systolic function	Usually normal	May be reduced
PA systolic pressure	Usually <50 mm Hg	May be >50 mm Hg
RV/LV systolic pressure	Discordant	Concordant
RVEDP/LVEDP separation	<5 mm Hg	>5 mm Hg
RVEDP/RV systolic pressure	>1/3	<1/3
Kussmaul's sign	Present	Absent

Table 18.4 Effects of respiration on hemodynamic findings in restrictive cardiomyopathy, constrictive pericarditis, and cardiac tamponade.

	Restrictive cardiomyopathy	Constrictive pericarditis	Cardiac tamponade
Intrathoracic pressure	Transmitted to intracardiac chambers and pulmonary venous circulation	Not transmitted to intracardiac chambers but to pulmonary venous circulation	Right-sided chambers have increased filling during inspiration, whereas left-sided chambers have increased filling during expiration. The inferior vena cava shows little or no change in respiration
RA pressure	Decreases with inspiration	Increases or does not change with inspiration (Kussmaul's sign)	Decreases with inspiration
Mitral inflow on echocardiography	No significant change in mitral <i>E</i> wave, deceleration time, or isovolumic relaxation time (IVRT) with phases of respiration	Marked respiratory variation in biventricular inflow. Decrease of >25% in mitral <i>E</i> wave velocity and prolonged IVRT on inspiration	Mitral valve <i>E</i> wave velocity decreases and IVRT increases by more than 30% on inspiration compared with expiration. Tricuspid valve <i>E</i> wave velocity increases with respiration
LV systolic pressure	Decreases with inspiration	Decreases with inspiration	Exaggerated decrease in LV systolic pressure with inspiration (pulsus paradoxus)
RV systolic pressure	Decreases with inspiration	Increases with inspiration	Increases with inspiration
Ventricular interdependence	Concordant	Discordant	

Hemodynamic factors that are helpful in differentiating constrictive pericarditis from restrictive cardiomyopathy are listed in Table 18.3, and some generalities regarding the effects of respiration on hemodynamic findings in restrictive cardiomyopathy, constrictive pericarditis, and cardiac tamponade are shown in Table 18.4. A meta-analysis of the Mayo echocardiographic findings from 17 case-control studies including 889 patients are shown in Table 18.5 [8].

Although the differentiation of these two entities can be quite challenging to the clinician, a thorough understanding of both the similarities and differences is imperative to arrive at the correct diagnosis. Experience teaches that it is rare to arrive at a firm diagnosis of either restrictive cardiomyopathy or constrictive pericarditis based on hemodynamics alone.

Table 18.5 Echocardiographic findings useful in differentiating constrictive pericarditis from restrictive cardiomyopathy.

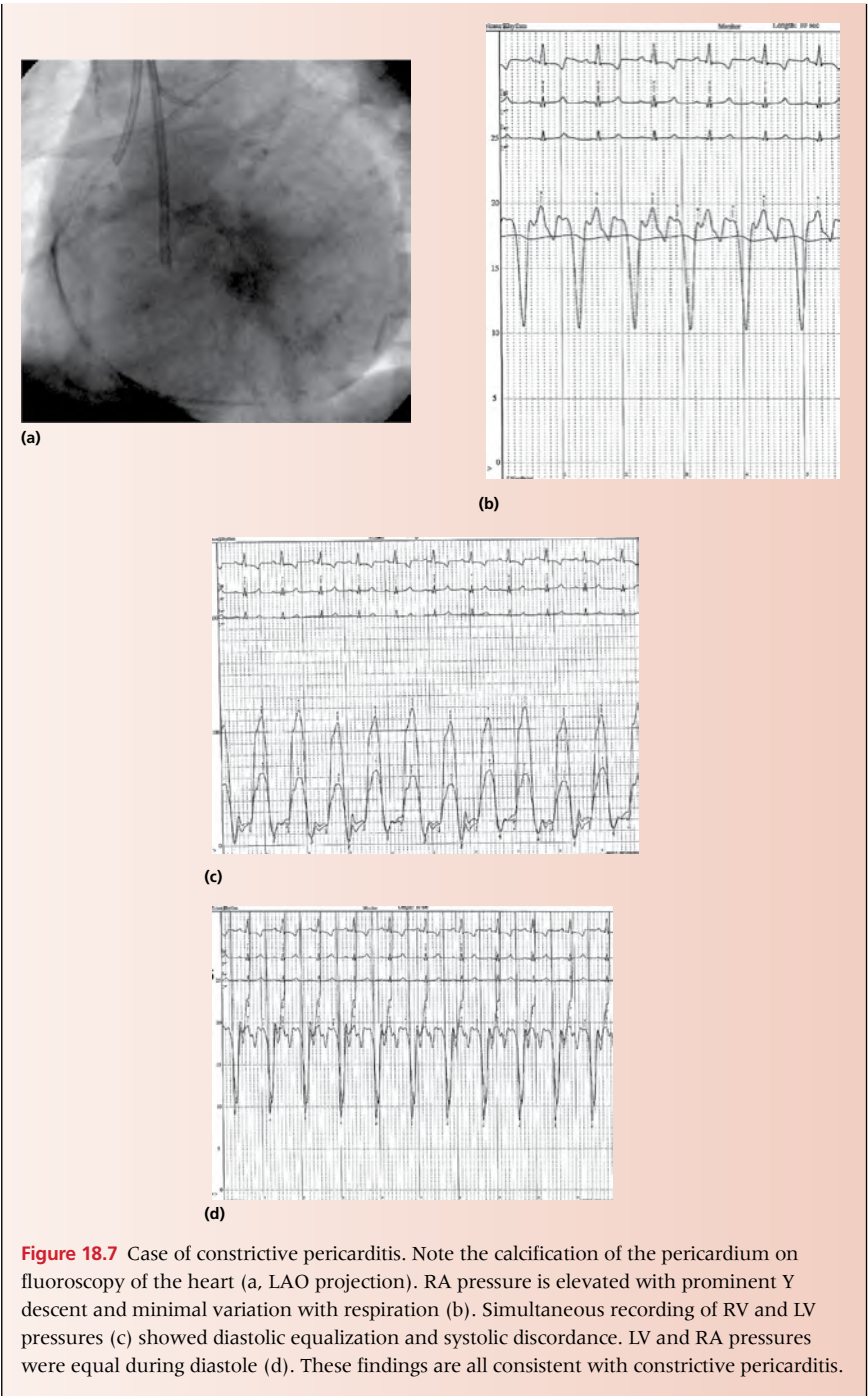
Echo parameter	Sensitivity	Specificity
Ventricular septal shift	82% (60–94%)	78% (65–87%)
Respiratory variation in mitral inflow $\geq 14.6\%$	71% (51–85%)	82% (66–91%)
Septal e' velocity $\geq 8\text{ cm/s}$	83% (80–87%)	90% (83–95%)
Septal e' velocity/lateral e' velocity ≥ 0.88	74% (64–82%)	81% (70–88%)
Hepatic vein ratio in expiration ≥ 0.79	73% (65–81%)	71% (19–96%)

Note: Data are pooled sensitivity and specificity (95% CI) derived from a meta-analysis of 17 case-control studies that included 889 patients.

Source: Adapted from [8].

Case study

A 54-year-old male with end-stage renal failure was admitted to the hospital with signs and symptoms of right heart failure. He had been admitted 10 times during the previous 2-year period. Past medical history was remarkable for an episode of uremic pericarditis 8 years previously requiring pericardiocentesis. The pericardium was calcified on fluoroscopy (Figure 18.7a). Hemodynamics revealed elevated RA pressure with prominent Y descent and minimal variation with respiration (Figure 18.7b). Simultaneous recording of RV and LV pressures (Figure 18.7c) showed end-diastolic equalization and systolic discordance. LV and RA pressures were equal during diastole (Figure 18.7d). These findings are all consistent with constrictive pericarditis.



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CHAPTER 19

Cardiac tamponade

Siva B. Mohan and George A. Stouffer

The pericardium is a fibroserous sac consisting of two parts: (1) a strong external layer composed of tough fibrous tissue, called the fibrous pericardium; and (2) an internal double-layered sac (visceral and parietal pericardium) composed of a transparent membrane called the serous pericardium. The parietal pericardium is fused to the internal surface of the fibrous pericardium. The visceral pericardium is reflected onto the heart, where it forms the epicardium, the external layer of the heart wall. The potential space between the parietal and visceral layers of the serous pericardium is called the pericardial cavity. It normally contains a thin film of serous fluid that enables the heart to move and beat in a frictionless environment. The pericardium stabilizes the heart within the thoracic cavity by virtue of its ligamentous attachments and also prevents extreme dilatation in the setting of a sudden rise of intracardiac volume.

The normal pericardial space contains 15–40 mL of pericardial fluid. A myriad of conditions produce pathologic accumulation of fluid in the pericardial cavity. Fluid that accumulates in the pericardial space can be serous, sero-sanguineous, hemorrhagic, chylous, or a combination of the above. Once a critical threshold of pericardial fluid is reached, the pericardial pressure rises in a nonlinear fashion, resulting in hemodynamic compromise or cardiac tamponade (Figure 19.1).

Hemodynamic pathophysiology

The primary hemodynamic pathophysiologic process in the development of tamponade is increased pericardial pressure that impairs diastolic filling [1–3]. Normal pericardial pressure is zero; any increase can have hemodynamic consequences. One way of looking at tamponade is that the effusion competes with the cardiac chambers to occupy the limited volume within the pericardium. Another way to think of tamponade is as a rubber band around the cardiac chambers, exerting a

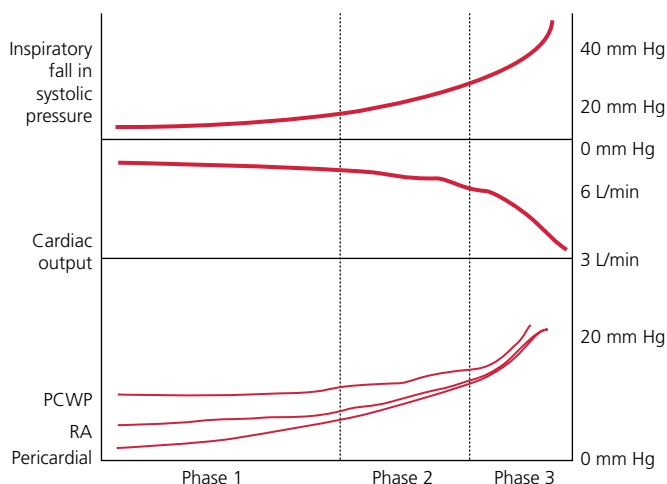


Figure 19.1 Schematic of the phases of cardiac tamponade. Source: Courtesy of Cardioville.com.

constrictive force and preventing adequate expansion. Resultant elevations in intracardiac diastolic pressures impair systemic and pulmonary venous return, leading to venous congestion and reduced cardiac output (Figure 19.2). As pericardial pressures increase, a variety of compensatory mechanisms are elicited, including sympathetic nervous system activation, which leads to tachycardia, increased ejection fraction, peripheral vasoconstriction, and sodium and fluid retention.

The pericardium is a relatively noncompliant structure and thus the relationship between pericardial pressure and volume is nonlinear. Pericardial pressure rises exponentially as pericardial fluid volume increases after a certain threshold is reached. Factors that influence the development of hemodynamic compromise in the setting of pericardial effusion include the rate at which the fluid accumulates, the amount of pericardial fluid, the compliance of the pericardium, the size of the pericardial space, and ventricular compliance. The pericardium expands only minimally in the acute setting, but can greatly increase in size over prolonged periods of time. Thus, patients with a slowly developing effusion may be asymptomatic even with a large-volume effusion. In contrast, if the rate of accumulation is rapid, even a small volume of effusion may trigger hemodynamic compromise (e.g., in the setting of cardiac trauma). The inherent compliance of the pericardium also plays a role in determining the hemodynamic significance of an effusion. Several disease processes may render the pericardium more stiff or noncompliant, allowing for a smaller effusion to cause cardiac tamponade. Left and right ventricular (RV) hypertrophy renders the heart most resistant to elevated pericardial pressures.

The hemodynamic effects of increased pericardial pressure occur on a spectrum and cardiac tamponade can be divided into three phases [4, 5]. As pericardial fluid accumulates, pericardial pressure rises. Increasing pericardial pressure leads to increasing right atrial (RA) pressure. At this point, clinical signs of tamponade

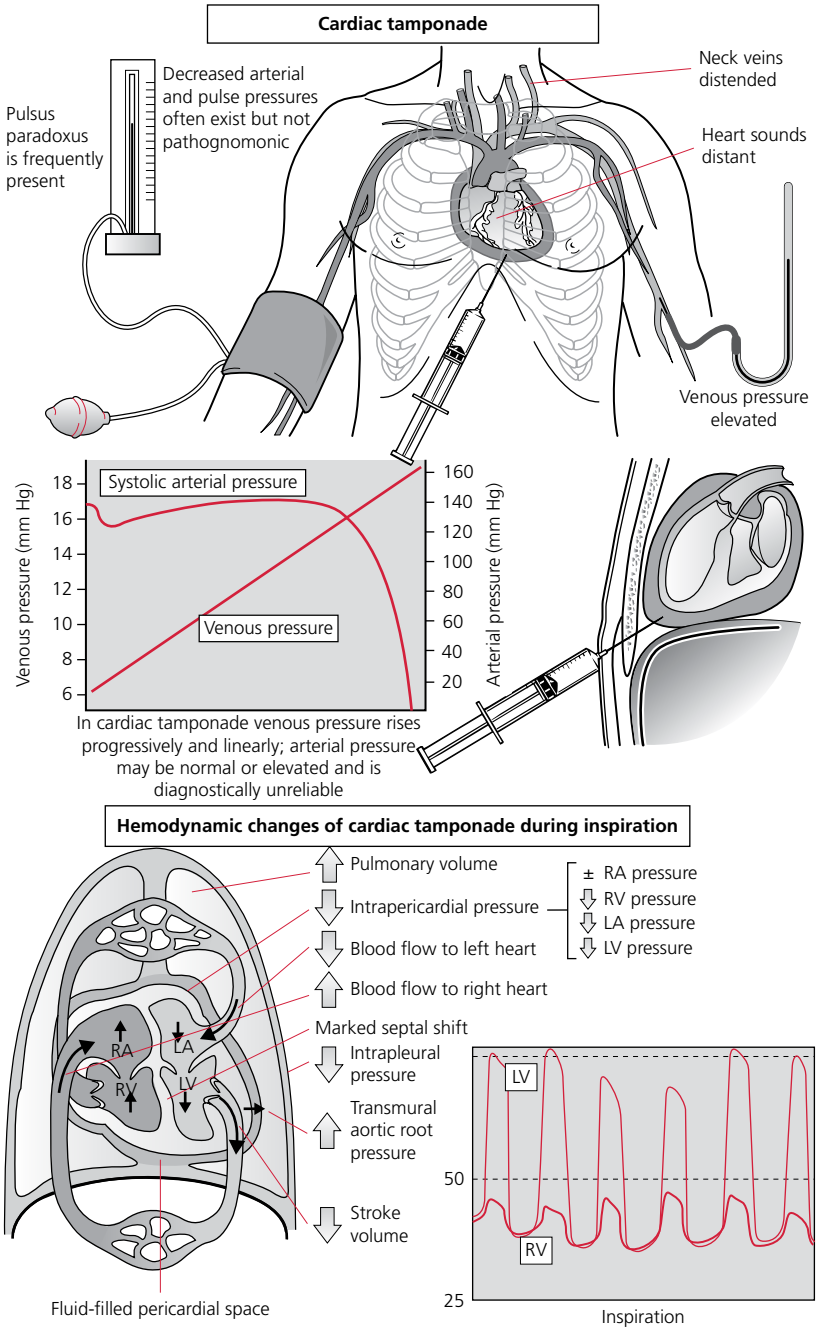


Figure 19.2 Cardiac tamponade.

may be absent as the right heart, including RV stroke volume, but not the left heart is compromised (phase 1). As pericardial fluid continues to accumulate and pericardial pressure rises, left atrial (LA) and thus pulmonary capillary wedge pressure (PCWP) begins to rise and external compression of both left and right ventricles during diastole is present (phase 2). End-diastolic pressures (EDP) throughout the cardiac chambers are elevated and within 5 mm Hg of each other, including RA, RVEDP, pulmonary artery, PCWP, and LVEDP. At this stage, classic signs and symptoms of cardiac tamponade are usually seen. In this phase, compensatory tachycardia maintains cardiac output in the presence of diminished stroke volume. Eventually, if pericardial pressures continue to rise and approximate RA and RV diastolic pressures, cardiac output falls, and cardiac tamponade progresses to shock with impaired tissue perfusion (phase 3).

Hemodynamic findings of cardiac tamponade

(below and Table 19.1)

- 1 Elevated pericardial pressure (Figure 19.2).
- 2 Elevated and near equalization of end-diastolic pressures (RA, RVEDP, pulmonary artery, LA, PCWP, and LVEDP). Since cardiac chamber filling pressures intracardiac chamber pressure minus pericardial pressure, intracardiac pressures must increase as pericardial pressure increases to maintain a pressure gradient between the atria and ventricles (remember that blood flow through the heart is determined by pressure gradients).
- 3 Elevated RA pressures with a prominent X descent and blunted Y descent. In the setting of a hemodynamically significant pericardial effusion, diastolic filling is impaired and affected by pericardial pressure. A unique feature of cardiac tamponade is the continuous compression of the heart throughout the cardiac cycle. This limits the fall in ventricular pressure during early diastole and thus causes a decrease in the normal atrium to ventricular pressure gradient in early diastole. This, in turn, restricts the amount of early diastolic filling of the ventricles and blunts the Y descent seen in the atrial pressure tracings (Figure 19.3).
- 4 In patients with tamponade, a relatively larger amount of atrial filling occurs following ventricular contraction, since as blood is ejected to the great vessels

Table 19.1 Findings on catheterization.

Elevated diastolic pressures and equalization of end-diastolic pressures
X descent is preserved, but Y descent is small or absent on RA pressure tracing
Pericardial pressure is elevated
RV pressure does not fall in early diastole (i.e., there is no dip and plateau configuration)
Pulsus paradoxus

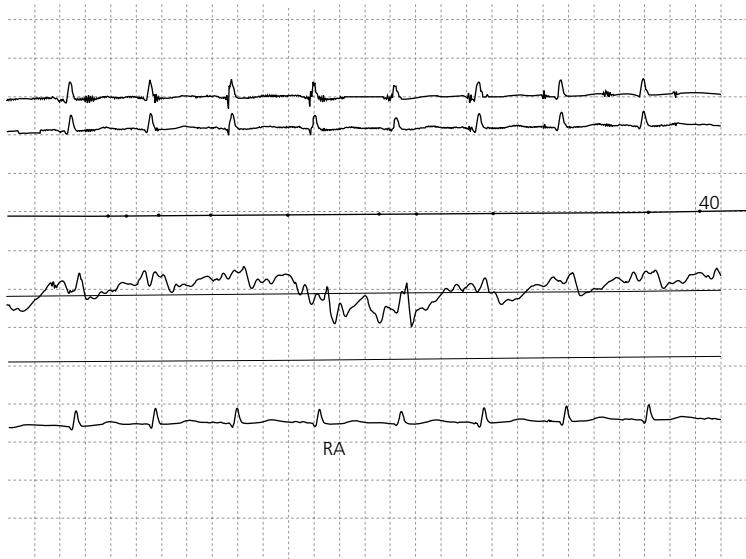


Figure 19.3 RA pressure tracing in a patient with tamponade. Note the increased RA pressures, preserved respiratory variation, and blunted Y descent.

during ventricular systole, ventricular volume transiently falls, enabling atrial expansion and filling. RA pressure drops immediately following ventricular contraction as atrial volume increases; this large swing in RA pressure gradient in the setting of cardiac tamponade elicits an exaggerated RA X descent. The X descent may be exaggerated during inspiration since a decrease in pericardial pressure leads to augmentation of blood flow to the RV during inspiration (Figure 19.2). Conversely, the Y descent corresponds to passive ventricular filling and is blunted.

Following removal of pericardial fluid with a resulting reduction in pericardial pressure, the Y descent in the RA tracing will become more apparent (Figure 19.4).

- 5 RV pressure tracing lacks the “dip and plateau” of constrictive pericarditis. Unlike constrictive pericarditis, cardiac tamponade is not characterized by rapid ventricular filling in early diastole, nor does RV pressure fall below pericardial pressure in early diastole. Therefore, there is no “dip and plateau” configuration in the RV tracing. RV hypertrophy is one exception to the rule. Because of the thickness of the RV-free wall, early passive diastolic filling may still occur, and therein the Y descent is preserved.
- 6 Pulsus paradoxus is an exaggerated decrease in arterial systolic pressure during inspiration. This occurs because of compromised LV diastolic filling during inspiration and is due to a chain of events: (1) pericardial and RA pressures decrease due to negative intrathoracic pressure; (2) this results in augmented systemic venous return to right-sided chambers and a marked increase in RV volume; (3) this results in an increase in RV filling during inspiration that, in the setting of cardiac tamponade, compromises LV filling. Note that it is normal

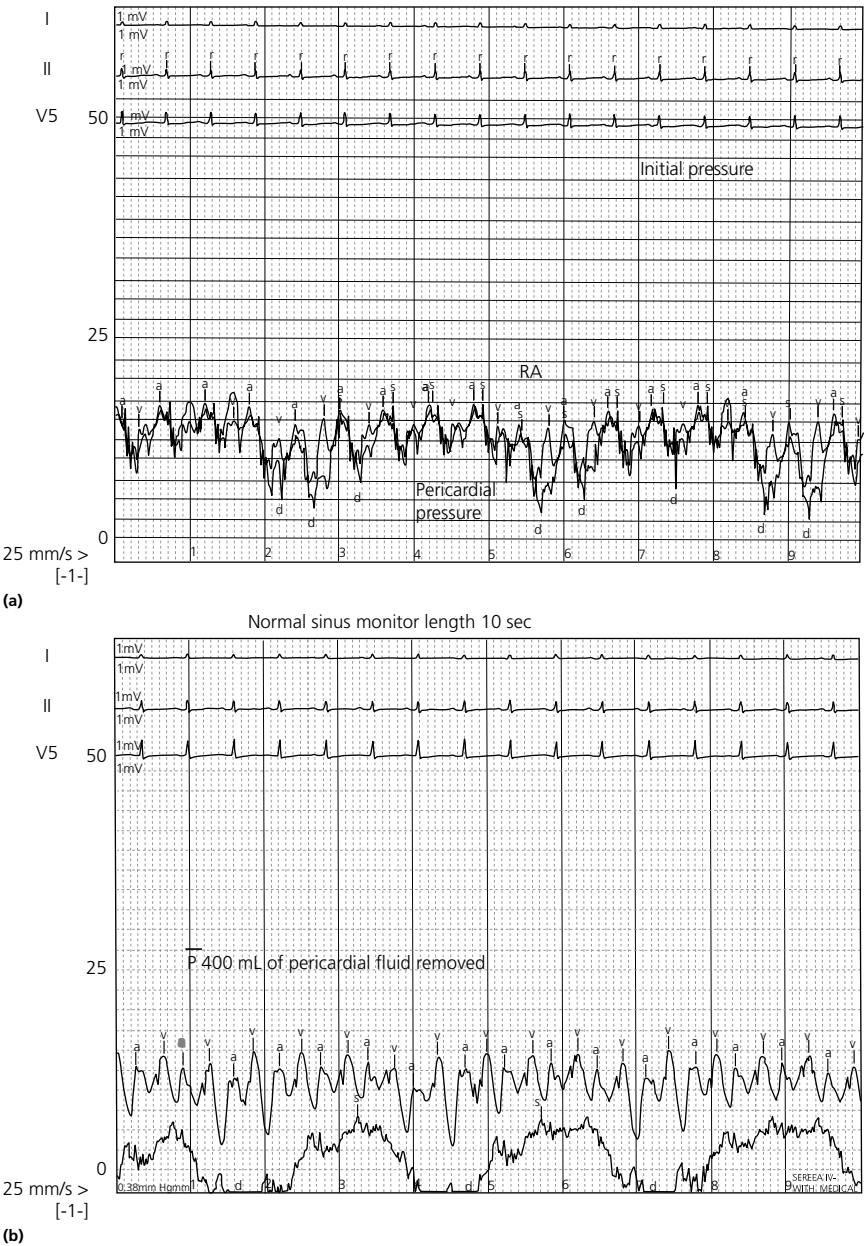


Figure 19.4 Simultaneous right atrial and pericardial pressure tracings in a patient with tamponade before (a) and after (b) the removal of 400 mL of pericardial fluid.



Figure 19.5 Aortic pressure tracing in a patient with tamponade showing pulsus paradoxus. Source: Courtesy of CardioVillage.com.

to have a drop in systolic blood pressure with inspiration and that pulsus paradoxus is defined by the magnitude of the decrease (an “exaggerated” drop). Pulsus paradoxus is variously defined as a drop of >12 mm Hg, a drop of ≥ 10 mm Hg, or a drop of $\geq 9\%$ during normal inspiration (Figure 19.5). Note that pulsus paradoxus is neither a sensitive nor specific finding. It may not be present in patients with tamponade and can occur in other conditions such as

- acute aortic regurgitation (i.e., acute aortic dissection)
 - elevated LVEDP
 - atrial septal defect
 - pulmonary hypertension
 - right ventricular hypertrophy
 - chronic obstructive pulmonary disease
 - extreme volume depletion
- 7** Respiratory variation in atrial pressures. Negative thoracic pressure is transmitted to the fluid-filled pericardial space, unlike the situation in constrictive pericarditis, and influences atrial pressures.
 - 8** Inspiratory traction. As described by Boltwood *et al.*, this is the diastolic equalization of PCWP and RA pressures, predominantly during inspiration [6]. It is due to inspiratory traction of the taut pericardium by the diaphragm.
 - 9** Stroke volume and cardiac output are decreased. Cardiac output will fall in absence of tachycardia.

Several scenarios can mask the clinical diagnosis of tamponade. In the setting of hypovolemia and suspected tamponade, the typical hemodynamic findings may be masked. Low-pressure effusions equilibrate only with right-sided diastolic pressures and at first only during inspiration. A fluid bolus may elicit classic findings. Severe left ventricular dysfunction may also mask tamponade. In this setting, LV diastolic pressures are higher than RV diastolic pressures and the diagnosis of cardiac tamponade should be dependent on demonstrating elevated pericardial pressures equal to RA pressures. Regional cardiac tamponade can occur when some, but not all, cardiac chambers are compressed by loculated effusions. Typical hemodynamic abnormalities may be found only in the compressed chambers or zones. In some cases, a loculated effusion may produce classic tamponade, presumably by “stretching” the pericardium.

Tremendous efforts are expended in determining whether a patient is “in tamponade” and, thus, qualifies for emergent therapy. It is important to note that increased pericardial pressure is a clinical spectrum rather than an all-or-none phenomenon. The important questions are “What is the approximate pericardial pressure?” and “What effect is the pericardial fluid having on cardiac output, arterial blood pressure, and intracardiac pressures?” The determination of the need for pericardiocentesis must weigh the risk of the procedure versus these questions and other important considerations, including the rate of accumulation and the potential diagnostic value of obtaining pericardial fluid. The European Society of Cardiology Working Group on Myocardial and Pericardial Diseases has proposed a stepwise scoring system to be used in patients with suspect tamponade. A score ≥ 6 warrants immediate pericardiocentesis in the absence of contraindications [7].

Physical exam findings

The physical examination can provide clues to cardiac tamponade. Sinus tachycardia and hypotension with narrow pulse pressure are hallmarks. The clinician needs to remember that blood pressure may remain normal or even elevated until cardiovascular collapse is imminent.

Pulsus paradoxus, as already described, is an “exaggerated” drop in systolic blood pressure during normal inspiration (not forced inspiration). This is a common finding in moderate to severe tamponade. To measure pulsus paradoxus, the sphygmomanometer should be inflated to suprasystolic pressure, deflating until Korotkoff sounds are initially heard in expiration only. Then, the cuff should be deflated until Korotkoff sounds are heard throughout the respiratory cycle. The difference between these two pressures is the “paradox” (normal pulsus paradox is <10 – 12 mm Hg). This finding is neither specific nor sensitive and may be seen in other conditions, including constrictive pericarditis, severe obstructive pulmonary disease, restrictive cardiomyopathy, pulmonary embolus, obesity, and RV infarction (Figure 19.6).

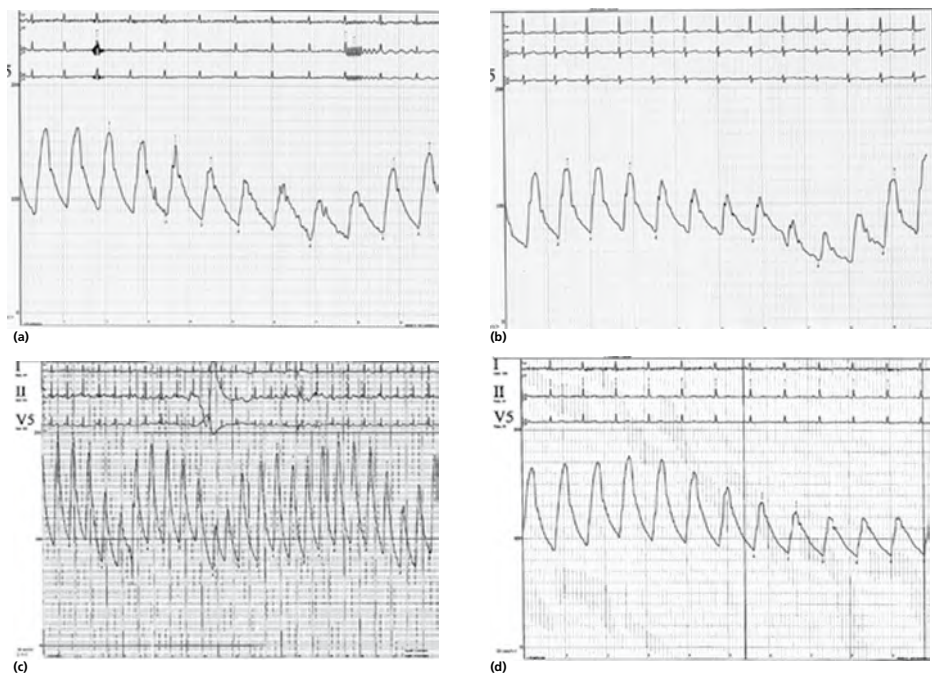


Figure 19.6 Aortic pressure tracings from four patients with pulsus paradoxus. Only the patient in (d) had tamponade. Note that the recording in (c) was made at a speed slower than normal to show several respiratory cycles.

Jugular venous distension is usually present with a preserved X descent. In tamponade, venous waves in the neck are not outward pulsations, but rather X descents are apparent as a collapse from a high standing pressure level. The Y descent is typically not seen.

Kussmaul's sign, which was originally described as an increase in the jugular venous pressure with inspiration but is now commonly used to describe the lack of a decrease in jugular venous pressure (JVP) with inspiration, is not classically seen in tamponade without a component of constrictive disease (i.e., effusive-constrictive disease) [8].

Beck's Triad, described in 1935, is a cluster of findings in cardiac tamponade characterized by hypotension, muffled heart sounds, and jugular venous distension.

A pericardial friction rub may be heard in the setting of pericarditis.

Hemodynamics of cardiac tamponade as measured with echocardiography

The echocardiogram is a useful tool in the diagnosis of cardiac tamponade; however, it is important to note that cardiac tamponade is a clinical diagnosis. The echocardiogram is a relatively quick, noninvasive test, which may aid the clinician in delineating the size, morphology, hemodynamic impact, and location of the effusion. Important findings on echocardiography include the following:

- The presence of an effusion is the only sensitive sign in tamponade. The absolute size of the effusion is not as useful in predicting tamponade, with the caveat that larger effusions confer a greater risk of tamponade.
- RV diastolic collapse occurring in early diastole is believed to occur only with higher pericardial pressures. However, the lack of RV diastolic collapse does not indicate a nonhemodynamically significant effusion.
- RA collapse occurring in late diastole or early systole is a relatively early sign of increased pericardial pressure.
- Small chamber sizes.
- Inferior vena cava plethora with attenuated respiratory variation.
- Significant changes in inflow across both mitral and tricuspid valves during inspiration. Doppler transmitral flow velocity paradoxus, a reciprocal respiratory variation in transvalvular right- and left-sided flow velocities, has been thought to be a sensitive sign of tamponade. Normally, there is no substantial variation in early diastolic filling velocities throughout the respiratory cycle. With cardiac tamponade, there are exaggerated increases in right-sided flow velocities and exaggerated decreases in left-sided flow velocities during inspiration (Figure 19.7). A substantial decrease in Doppler transmitral flow velocity with inspiration (>25%) may serve as an indicator of flow velocity paradoxus and tamponade physiology.

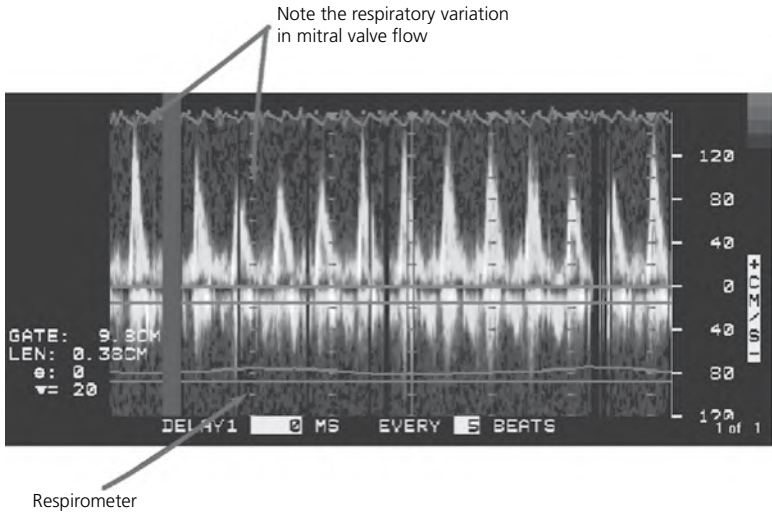


Figure 19.7 Doppler recording of LV inflow with a superimposed respirometer in a patient with tamponade. Note the decrease in mitral valve flow during inspiration.

- Abnormal septal motion. On inspiration, the ventricular septum moves toward the left heart, whereas the septum moves toward the right heart on expiration. The filling of the different ventricles is dependent on the position in the respiratory cycle; an echocardiographic demonstration of pulsus paradoxus.

Pericardiocentesis in patients with pulmonary hypertension

Special care has to be taken when performing pericardiocentesis in patients with pulmonary hypertension as pericardial drainage in these patients is associated with significant morbidity and mortality [9–11]. The physiology of pericardial compression is different in these patients due to elevated right heart pressures from pulmonary hypertension. In the setting of chronically elevated filling pressures, the right heart can tolerate higher pericardial pressures than the normal heart and thus classic findings of pulsus paradoxus or RA or RV inversion might be absent.

Management of pericardial effusions in patients with pulmonary hypertension remains challenging. Numerous case reports and small series have documented hemodynamic collapse after rapid removal of pericardial fluid, potentially due to sudden decreases in RA and thus RV filling pressures and/or acute RV dilatation compromising LV filling. Several studies have advocated hemodynamically guided removal of pericardial fluid over several days [9, 12].

Case Study

A 42-year-old female with metastatic lung cancer presented with fatigue and dyspnea on minimal exertion. She was found to have a large pericardial effusion with tamponade physiology on echocardiography (Figure 19.8). On examination, she had muffled heart sounds, JVP at 16 cm, and a blood pressure of 92/68 mm Hg with a heart rate of 112 bpm. Her pulsus paradoxus was 15–18 mm Hg. She was referred for right heart catheterization and pericardiocentesis. The initial RA waveform showed exaggerated X descent with blunted Y descent (Figure 19.9a). The RV waveform showed elevated RV diastolic pressures with minimal change from early diastole to late diastole (Figure 19.9b). Pericardial pressure was elevated and equalized with RA pressure during inspiration (Figure 19.9c). Pericardiocentesis was performed and 600 mL of fluid was removed. The final pericardial pressure was 0 mm Hg. Following pericardiocentesis, Y descents were apparent on RA tracing and evidence of early diastolic filling was also apparent on RV tracing.

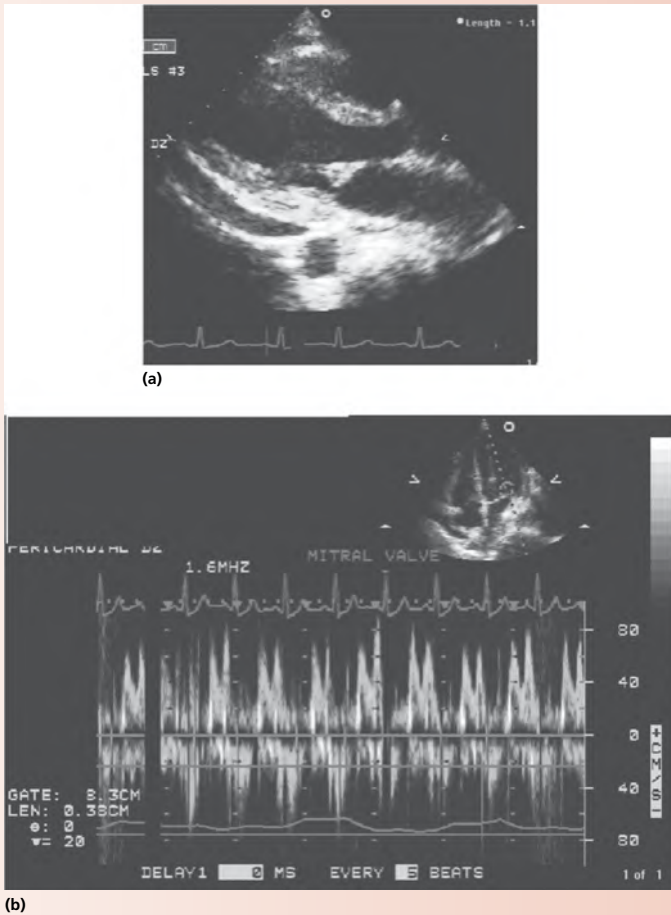


Figure 19.8 Echocardiographic findings from the patient described in the case study. Panel (a) is a still 2D frame from the parasternal long axis showing a 1.1 cm pericardial effusion. Panel (b) is a Doppler image with the probe at the level of the mitral valve.

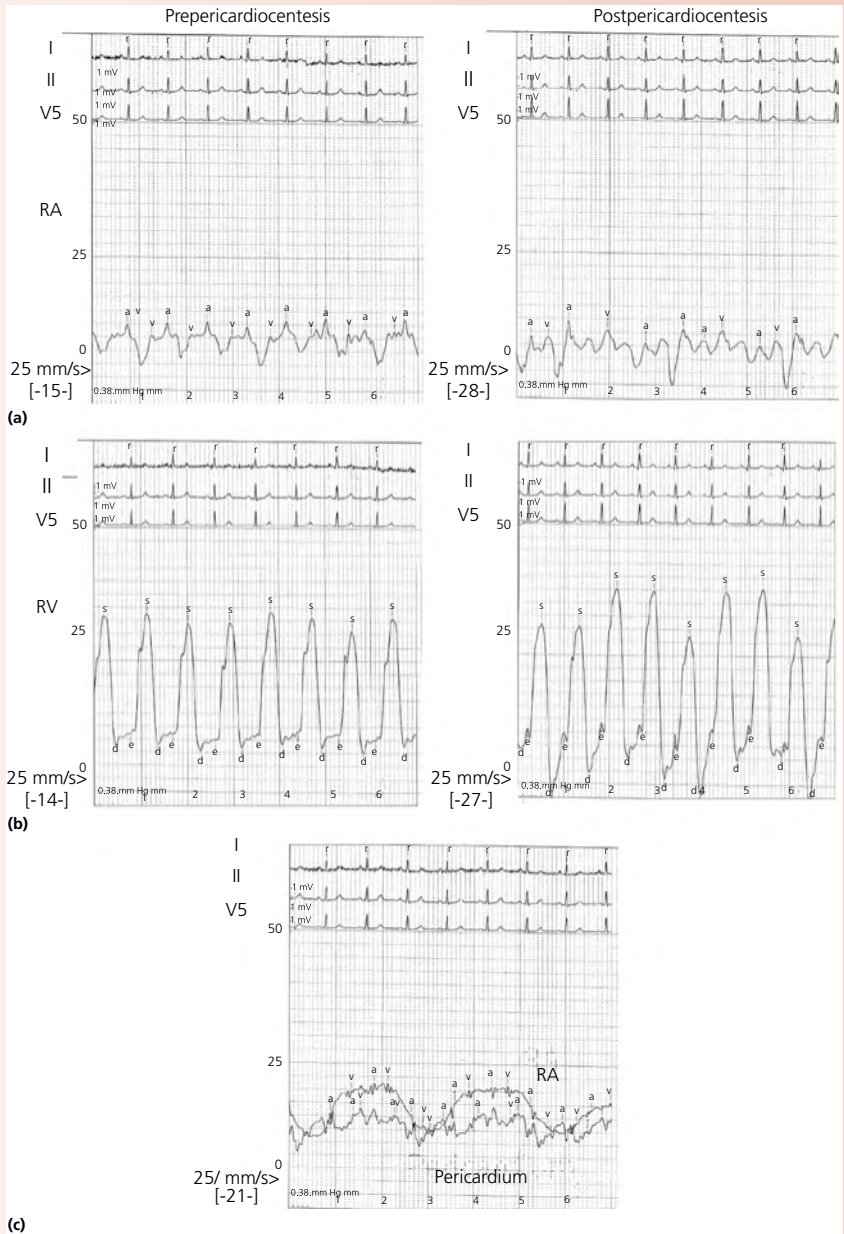


Figure 19.9 Pressure tracings from the patient described in the case study. RA (a) and RV (b) tracings before and after pericardiocentesis. Simultaneous RA and pericardial pressures after the removal of several hundred milliliters of pericardial fluid (c). Note that the scale is not accurate in (c) because the patient is no longer completely supine, but rather the thorax is partially inclined in order to facilitate pericardiocentesis.

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CHAPTER 20

Effusive–constrictive pericarditis

George A. Stouffer, Sidney C. Smith, Jr. and Faisal F. Syed

[This chapter is revised and modified from a chapter written for the first and second editions by Eric M. Crespo, Sidney C. Smith, Jr., and George A. Stouffer]

Effusive–constrictive pericarditis is an uncommon syndrome characterized by constriction of the heart by the visceral pericardium following the presence of a tense pericardial effusion. In these patients, pericardiocentesis converts the hemodynamics from those typical of tamponade to those of constriction. It is thought to be due to pericardial inflammation and is diagnosed when elevated right atrial pressures persist despite reduction of intrapericardial pressures to normal levels by pericardiocentesis. Although first observed in the 1960s [1], it was not well described until the publication of a 13-patient case series by Hancock in 1971 [2]. Since that time, there has been a paucity of medical literature on the topic, and it was not until the recent publication of a case series by Sagrista-Sauleda that more complete information about the etiology, incidence, and prognosis of effusive–constrictive pericarditis became known [3].

In their series, Sagrista-Sauleda and colleagues prospectively evaluated 1184 patients presenting to their institution with pericarditis of any type over a 15-year period. Based on their data, the authors estimated a prevalence of effusive–constrictive pericarditis of approximately 1.3% of all patients with pericarditis and 6.8% of patients with clinical tamponade [3]. Additionally, they found that although effusive–constrictive pericarditis can occur with all types of pericarditis, it is relatively more frequent with radiation-related pericardial disease and less often associated with postsurgical pericarditis. Other studies have shown a relatively higher frequency with tuberculous pericarditis [4].

The etiology and incidence vary between institutions and between different parts of the world based on the most common causes of pericarditis in each location [5]. Many patients diagnosed with effusive–constrictive pericarditis will progress to chronic constriction, but a proportion of those with idiopathic disease may have only temporary cardiac constriction and then go on to eventual

full resolution [3, 6]. One study employing a review of 5 published studies of 642 patients found that the pooled prevalence of effusive–constrictive pericarditis in patients with pericarditis of any type was 4.0–4.5%. The pericardiectomy rate was 65% with half of those managed conservatively having complete resolution [7].

Patients tend to have a subacute presentation and are often initially believed to have cardiac tamponade. The true diagnosis can only be made after constrictive physiology persists despite normal pericardial pressures. Thus, continuous monitoring of intracardiac filling pressures during pericardiocentesis is required to arrive at the correct diagnosis.

Hemodynamics of effusive–constrictive pericarditis

The hallmark of effusive–constrictive pericarditis is the persistence of elevated right atrial pressures after intrapericardial pressure has been reduced to normal levels by pericardiocentesis. As in both constrictive pericarditis and cardiac tamponade, the expansion of the cardiac chambers during diastole is limited and there are elevation and equalization of diastolic pressures in the atria and ventricles (Table 20.1). Prior to drainage of the effusion, the predominant hemodynamic findings are those of cardiac tamponade with a preserved X descent and an absent or attenuated Y descent on the right atrial pressure tracing. Once the effusion has been drained, constrictive physiology predominates, with return and exaggeration of the Y descent leading to a classic M- or W-shaped configuration of the right atrial pressure waveform. The ventricular pressure tracings demonstrate the square root sign due to rapid ventricular filling in early diastole.

Diagnostic criteria

The diagnostic criterion used by Sagrist-Sauleda et al was as follows: effusive-constrictive pericarditis was diagnosed in a patient with cardiac tamponade in whom right atrial pressure failed to fall by $\geq 50\%$ or to < 10 mm Hg after pericardiocentesis lowered intrapericardial pressure to near 0 mm Hg [3].

Table 20.1 Comparison of right atrial and intrapericardial pressures in various pericardial disease states.

	Effusive–constrictive pericarditis	Cardiac tamponade	Constrictive pericarditis
Intrapericardial pressure	Near 0 mm Hg	Elevated	Near 0 mm Hg
Right atrial pressure	Elevated; Failure of RAP to fall to < 10 mm Hg or by $\geq 50\%$ after pericardiocentesis	Elevated; approximates pericardial pressure	Elevated; approximates other intracardiac diastolic pressures
Y descent	Variable	Blunted	Exaggerated

In a study of 68 patients with tuberculous pericarditis, Ntsekhe *et al.* found that 36 patients (53%) had effusive–constrictive physiology as defined by these hemodynamic findings during combined pericardiocentesis and cardiac catheterization: (1) mean pericardial pressure of >8 mm Hg prior to fluid removal; (2) difference between right atrial pressure and intrapericardial pressure of ≤ 4 mm Hg; (3) mean pericardial pressure of 0 ± 4 mm Hg after pericardiocentesis; and (4) mean right atrial pressure of ≥ 11 mm Hg or failure to decrease by 50% or more of the pre-pericardiocentesis level [4].

Ohsawa *et al.* have suggested the following echocardiographic criteria for the diagnosis of effusive–constrictive pericarditis [1]: the absence of normalization in IVC dilatation and restoration of its respiratory changes [2]; persistently remaining significant respiratory variation of the mitral and tricuspid inflow Doppler pattern; and [3] the absence of disappearance of abnormal/paradoxical movement of the interventricular septum (“septal bounce”), immediately after the removal of tense pericardial fluid [8].

In a study of 205 patients undergoing pericardiocentesis at Mayo Clinic, Rochester, MN, Kim *et al.* reported 33 (16%) with residual constrictive physiology on Doppler echocardiography, defined by $>25\%$ respirophasic variation in early diastolic mitral inflow velocity (E) accompanied by at least 1 of the following: expiratory diastolic flow reversal of hepatic vein; respirophasic interventricular septal shift; or augmented early diastolic mitral septal annular velocity (e') and to a level higher than that of the lateral mitral e' [9].

For detailed descriptions of the hemodynamic principles and findings of constrictive pericarditis and cardiac tamponade, refer to Chapters 18 and 19.

Physical examination

The findings on physical examination are similar to those for a patient presenting with cardiac tamponade. Patients will have elevated jugular venous pressure (JVP), and careful examination of the neck veins may reveal a prominent X descent and an absent Y descent. Kussmaul’s sign, a failure of central venous pressure to decrease with inspiration, may be present and manifest as either increased or unchanged (i.e., failure to decrease) JVP during inspiration. Other sequelae of elevated right heart pressures may be noted, including hepatomegaly, ascites, and peripheral edema. Arterial pulsus paradoxus (inspiratory decrease in systolic pressure by ≥ 10 mm Hg) may also be noted. Additionally, a pericardial friction rub or pericardial knock may sometimes be auscultated. Following pericardiocentesis, the Y descent may be more pronounced. It should be kept in mind, however, that the sensitivity and specificity of different physical examination findings are not well defined.

Pericardial imaging techniques

A discussion of pericardial imaging can be found in Chapter 18. It is possible that pericardial calcification may be less common among patients with effusive–constrictive pericarditis than it is among those with strictly constrictive disease.

In the series by Sagrista-Sauleda and colleagues, none of the patients with effusive–constrictive pericarditis was noted to have pericardial calcification on radiographic examination [6]. In their study, Kim and colleagues found that a fibrinous or loculated pericardial effusion was more frequently present but not specific to effusive–constrictive pericarditis [9].

Findings on echocardiography

As with the hemodynamic findings during catheterization, the echocardiographic findings will fall somewhere on a spectrum between the findings of cardiac tamponade and those of constriction, depending on whether the effusion has been drained and intrapericardial pressure has normalized. In the series by Kim and colleagues, those with effusive–constrictive pericarditis had higher early diastolic mitral septal annular velocities (e' , 8.9 ± 2.5 cm/s vs. 6.9 ± 2.4 cm/s) and more frequent respirophasic septal shift (7/33 [21.2%] vs. 2/172 [1.2%]) on pre-pericardiocentesis echocardiography than those without [9].

Refer to Chapters 18 and 19 for further discussion of the echocardiographic findings in constrictive pericarditis and cardiac tamponade.

Case study

A 53-year-old previously healthy man presented to the hospital with a complaint of progressive dyspnea on exertion, mild pretibial edema, and pleuritic central chest pain. His symptoms had been progressing over the course of 2 weeks, and had only become prominent over the last few days. One week prior to the onset of symptoms, he had suffered a fall of approximately 8 feet in which he landed directly on his left chest and shoulder. Chest X-ray revealed cardiomegaly, but no pericardial calcification or pulmonary edema. Echocardiogram revealed a large (>2 cm) circumferential pericardial effusion with mild early diastolic collapse of the right ventricle and exaggerated respiratory variation in mitral inflow velocity. Right heart catheterization revealed the findings in Table 20.2.

Table 20.2 Findings on right heart catheterization.

	Before pericardiocentesis (mm Hg)	After pericardiocentesis (230 mL of serosanguinous fluid, mm Hg)
Right atrium	17	14
Right ventricular end-diastolic pressure	16	16
Pulmonary capillary wedge pressure	17	14
Pericardial pressure	13	0

The persistent elevation in right atrial pressure despite normalization of intrapericardial pressure is consistent with the diagnosis of effusive–constrictive pericarditis. In this case, the etiology was felt to be the patient's recent trauma, with bleeding into the pericardium leading to pericardial irritation and inflammation. Despite continued elevation of cardiac filling pressures, the patient's symptoms resolved completely. He was prescribed high-dose ibuprofen and scheduled for outpatient follow-up.

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PART V

Acute heart failure
and hemodynamic
support

 **2025** Edition

CHAPTER 21

Hemodynamics of cardiogenic shock

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Introduction

Cardiogenic shock (CS) is a life-threatening condition defined by hypotension with inadequate tissue perfusion due to ineffective cardiac output (CO). CS is most often caused by failure of myocardial contractile function but may also result from valvular disease, cardiac tamponade, structural heart abnormalities, or arrhythmias. The 30-day mortality rate of patients with CS remains >30% despite current management strategies that include infusion of vasopressor and inotropic medications, revascularization, and mechanical circulatory support (MCS) devices.

There are minor differences in the definition of CS used in clinical trials (Table 21.1) and in consensus documents (Table 21.2) but, in general, CS is defined as hypotension + clinical or biochemical evidence of inadequate perfusion. Hypotension is defined as a systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure (MAP) <60 mm Hg for >30 minutes or a need for vasopressors or MCS to maintain SBP $\geq$ 90 mm Hg or MAP $\geq$ 60 mm Hg. Impaired tissue perfusion can be defined by lactic acidosis or evidence of end-organ damage (acute kidney injury, acute hepatic injury, cool or mottled extremities, or altered mental status).

Normotensive cardiogenic shock (also referred to as nonhypotensive CS)

Normotensive CS is defined as inadequate tissue perfusion but without hypotension (SBP $\geq$ 90 mm Hg without the need for vasopressors, inotropes, or MCS). Patients with normotensive CS have greater systemic vascular resistance, but similar left ventricular (LV) ejection fraction, CO/cardiac index (CI), and pulmonary capillary

Table 21.1 Definition of cardiogenic shock from major clinical trials. [CI = cardiac index; CS = cardiogenic shock; HR = heart rate; SBP = systolic blood pressure.]

Clinical Study	SHOCK [1]	IABP – SHOCK II [2]	CULPRIT SHOCK [3]	ECLS-SHOCK [4]	DanGer Shock [5]
Year	1999	2012	2017	2023	2024
Criteria for CS	• SBP < 90 mm Hg for > 30 min or supportive measure to maintain SBP ≥ 90 mm Hg • Evidence of end-organ damage (urine output < 30 mL/hr, cool extremities, HR ≥ 60 bpm) • Hemodynamic criteria: CI < 2.2 and PCWP ≥ 15 mm Hg	• SBP < 90 mm Hg for > 30 min or need of catecholamines to maintain SBP > 90 mm Hg • Clinical signs of pulmonary congestion • Impaired end organ perfusion (altered mentation, cold/clammy skin and extremities, urine output < 30 mL/hr, or serum lactate > 2 mmol/L)	• SBP < 90 mm Hg for > 30 min or need of catecholamines to maintain SBP > 90 mm Hg • Clinical signs of pulmonary congestion • Impaired end organ perfusion (altered mentation, cold/clammy skin and extremities, urine output < 30 mL/hr, or serum lactate > 2 mmol/L)	• SBP < 90 mm Hg for > 30 min or need of catecholamines to maintain SBP > 90 mm Hg • Impaired end organ perfusion (altered mentation, cold/clammy skin and extremities, urine output < 30 mL/hr, or serum lactate > 3 mmol/L)	• SBP < 100 mm Hg or an ongoing need for vasopressor support • End organ hypoperfusion (arterial lactate ≥ 2.5 mmol/L)

Table 21.2 Definition of cardiogenic shock from Guidelines and Consensus Documents. [BNP = B-type natriuretic peptide; CI = cardiac index; CO = cardiac output; CPO = cardiac power output; Cr = creatinine; HR = heart rate; LFT = liver function tests; MAP = mean arterial pressure; PAPI = pulmonary artery pulsatility index; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; ULN = upper limit of normal.]

	Clinical criteria	Hypoperfusion	Hemodynamic criteria
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure [6]	SBP < 90 mm Hg for > 30 min or MAP < 60 mm Hg for > 30 min or the requirement of vasopressors to maintain SBP ≥ 90 mm Hg or MAP ≥ 60 mm Hg	Decreased mentation Cold extremities, livedo reticularis Urine output < 30 mL/h Lactate > 2 mmol/L	SBP < 90 mm Hg or MAP < 60 mm Hg CI < 2.2 L/min/m ² PCWP > 15 mm Hg CPO < 0.6 W Shock index (HR/systolic BP) > 1.0 For RV shock PAPI < 1.0 CVP > 15 mm Hg CVP/PCWP > 0.6
American Heart Association Cardiogenic Shock Registry [7]	Persistent hypotension (generally SBP < 90 mm Hg) for at least 30 min or the requirement for inotropic or vasopressor support to maintain an adequate SBP, in conjunction with evidence of end-organ malperfusion.	Altered mental status Cool or mottled extremities Oliguria, ischemic Liver injury Lactic acidosis.	Shock is classified as cardiogenic when tissue hypoperfusion is due to reduced CO in the absence of hypovolemia.
Shock Academic Research Consortium [8]	Cardiac disorder that results in an SBP < 90 mm Hg for ≥ 30 min (or the need for vasopressors, inotropes or mechanical circulatory support to maintain SBP ≥ 90 mm Hg) with evidence of hypoperfusion	Elevated arterial lactate (> 2 mmol/L) Acute kidney injury (creatinine ≥ 2 × ULN) or oliguria (e.g., urine output < 0.5 mL/kg-h) Acute hepatic injury (e.g., ALT > 3 × upper limit of normal) Cool or mottled extremities Altered mental status not explained by an alternative cause	CI ≤ 2.2 L/min/m ² Systemic vascular resistance index > 2200 dynes/(cm ² sec ⁻⁵)
SCAI Shock C [9]	Hypoperfusion requiring intervention (pharmacologic or mechanical) beyond volume resuscitation	Volume overload Altered mental status Cold and clammy Urine output < 30 mL/hr Lactate > 2 Cr > 1.5 × baseline or > 50% drop in GFR Increased LFTs Elevated BNP	CI < 2.2 L/min/m ² PCWP > 15 mm Hg

wedge pressure (PCWP) as patients with classic CS [10]. In some of these patients, compensatory mechanisms are activated that preserve blood pressure (BP) through vasoconstriction, while tissue perfusion and oxygenation may still be significantly decreased. In the Should We Emergently Revascularize Occluded Coronaries In Cardiogenic Shock? (SHOCK) registry, 4.6% of patients had normotensive CS with a mean BP of $104 \pm 34/62 \pm 23$ mm Hg and CI of 1.9 L/min/m^2 . Clinical signs of hypoperfusion were associated with a substantial risk of in-hospital mortality even in normotensive patients, suggesting that hypoperfusion identifies a “high-risk” group regardless of BP [11].

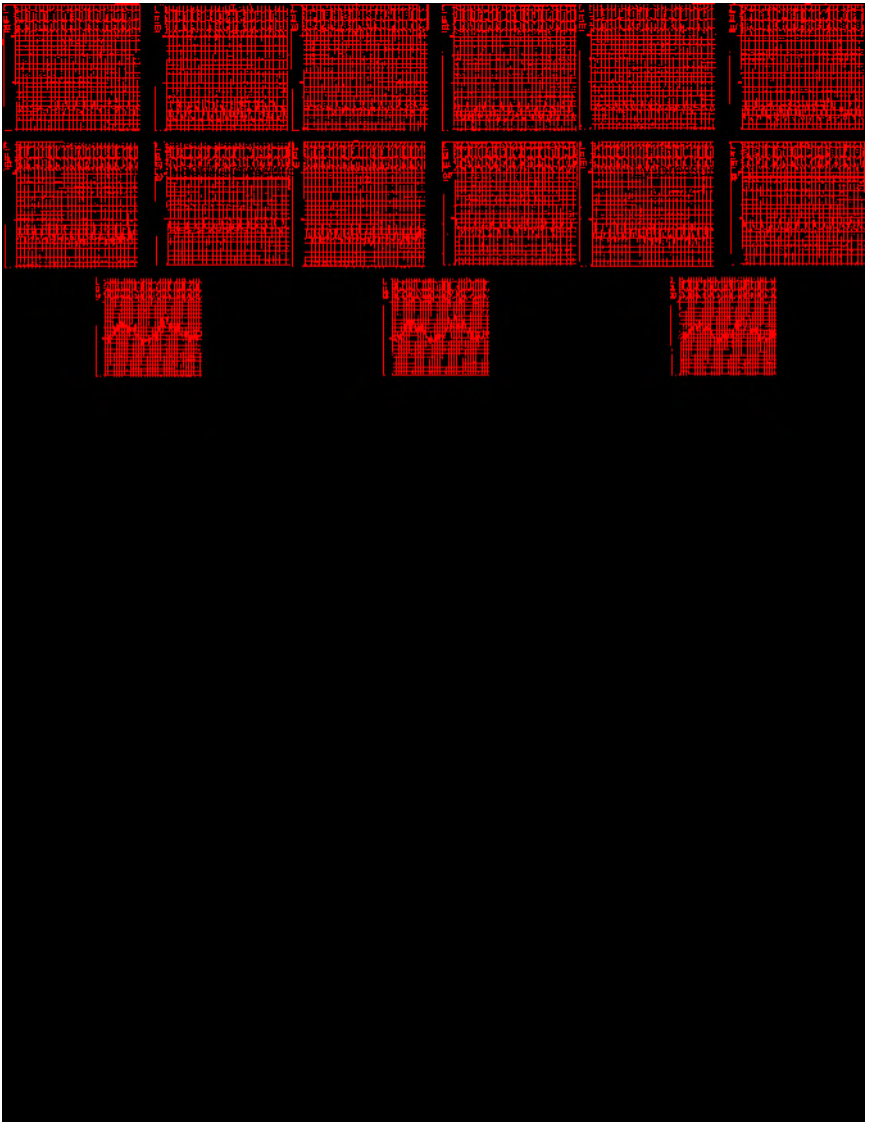
Causes of cardiogenic shock

The leading cause of acute CS is myocardial infarction (MI) where abrupt occlusion of a coronary artery leads to myocardial ischemia and myocyte death, causing a decrease in myocardial contractile forces which results in reduced stroke volume, decreased CO, and hypotension (Figure 21.1). This in turn can lead to a reduction in coronary perfusion, which then worsens the amount of myocardial ischemia. Peripheral vasoconstriction arises as a compensatory mechanism which increases afterload and can lead to a reduction in peripheral perfusion. In addition to causing substantial LV myocardial damage, MI can lead to CS by causing right ventricular (RV) ischemia (see Chapter 28 for a more detailed discussion) and/or causing MI-associated mechanical complications such as a papillary muscle rupture with acute mitral regurgitation, ventricular free wall rupture or ventricular septal rupture.

The second most common cause of CS is progression of chronic LV systolic failure. In contrast to the sudden drop in CO from acute MI, patients with chronic heart failure can reach a more subtle tipping point often precipitated by an acute insult (e.g. influenza infection, fluid overload) or maladaptation of compensatory neurohormonal mechanisms.

There are numerous other causes of CS. Cardiac arrest survivors and/or patients with Takotsubo cardiomyopathy can present with CS. Inflammatory cardiomyopathies, such as lymphocytic or giant cell myocarditis, can lead to abrupt ventricular (LV, RV or biventricular) failure. Infiltrative cardiomyopathies such as sarcoidosis, hemochromatosis, or amyloidosis can progress to CS in the later stages of disease. Severe valvular disease such as aortic stenosis or acute mitral or aortic insufficiency can cause CS. Tachyarrhythmias, such as prolonged atrial fibrillation with rapid ventricular rate or recurrent ventricular tachycardias, can cause CS. Rarely, a myocardial contusion (which most commonly affects the RV) can lead to CS.

CS can be caused by conditions affecting the LV, the RV, or both simultaneously. The leading cause of RV failure is LV failure. However, isolated RV failure can occur due to decreases in RV contractility (e.g. from RV ischemia), abrupt increases in RV afterload (e.g. pulmonary embolus), or acute-on-chronic RV failure in the setting of severe pulmonary hypertension due to a variety of causes



(e)

Figure 21.1 Pressures in a 61-year-old male with a long-standing history of smoking, diabetes, and hypertension who was brought to the Emergency Department by EMS with complaints of chest pain after a syncopal event at a grocery store. ECG showed anterior ST elevation and initial systolic blood pressure was 50 mm Hg. He was referred for emergency coronary angiography which showed occlusion of the proximal LAD. Pressure tracings including initial aortic pressure (a), left ventricular pressures (b), aortic pressure after insertion of an IABP (c), aortic pressure after insertion of an Impella (d) and pulmonary capillary wedge pressure (e).

including primary pulmonary arterial hypertension, severe pulmonary disease, chronically elevated left atrial (LA) pressures, chronic thromboembolic pulmonary hypertension or Eisenmenger's syndrome. A reduction in RV contractility can rarely be caused by cardiomyopathies, which predominantly affect the RV such as arrhythmogenic RV cardiomyopathy.

Isolated RV infarction occurred in 49 of 893 patients (5.5%) in the SHOCK registry [12]. Patients with CS due to RV infarction were younger, were less likely to have a history of prior MI, had less multivessel coronary artery disease, and had less time between the index MI and the diagnosis of shock.

Classification of cardiogenic shock

The Society for Cardiovascular Angiography and Interventions (SCAI) developed a classification scheme that includes five stages of CS: A (patients At risk), B (Beginning of CS), C (Classical CS), D (Deteriorating patients), and E (those in Extremis). These criteria incorporate physical exam findings, biochemical markers, and hemodynamic parameters to characterize the severity of CS and are associated with in-hospital mortality (Table 21.3) [14].

Here is a brief summary of the SCAI stages:

- Stage A: "At Risk" for CS—a patient who is not experiencing signs or symptoms of CS but is at risk for its development.
- Stage B: "Beginning" CS (Pre-shock/compensated shock)—a patient who has clinical evidence of relative hypotension or tachycardia without hypoperfusion.
- Stage C: "Classic" CS—a patient with hypoperfusion that requires an initial set of interventions (inotropes, pressor, mechanical support, or ECMO) beyond volume resuscitation to restore perfusion.
- Stage D: "Deteriorating" or "Doom" CS—a patient who has failed to stabilize despite intense initial efforts and further escalation is required.
- Stage E: "Extremis" CS—a patient with circulatory collapse

The SCAI stages were later updated and modified by the Cardiogenic Shock Working Group with the application of more clinically relevant vital signs and biological markers: [15]

- SCAI Stage B patients were defined as having either isolated hypoperfusion (lactate 2–5 mmol/L or ALT 200–500 U/L) or hypotension (SBP 60–90 mm Hg or MAP 50–65 mm Hg) without the need for drug or device therapy.
- SCAI stage C patients were defined as having hypoperfusion *and* hypotension using the same criteria as for SCAI stage B or those patients who are being treated for CS with 1 drug (i.e., vasopressor or inotrope) or 1 circulatory support device.
- SCAI stage D patients were defined as having hypotension (SBP 60–90 mm Hg or MAP 50–65 mm Hg) *and* hypoperfusion (lactate 5–10 mmol/L or ALT >500 U/L) or the need for 2–5 drugs or devices. Stage D also included patients on 1 drug or device with hypotension or hypoperfusion that persisted despite treatment.

Table 21.3 SCAI stages of shock.

SCAI Shock Stage	Physical examination findings	Biochemical markers	Hemodynamics	In-hospital mortality
Stage A At risk	Normal JVP Warm and well-perfused Strong distal pulses Normal mentation Clear lung sounds	Normal lactate Baseline renal function	SBP > 100 mm Hg (or at baseline) CI > 2.5 (if acute) CVP ≤ 10 mm Hg PCWP ≤ 15 mm Hg PA sat ≥ 65%	
Stage B Beginning CS	Elevated JVP Warm and well-perfused Strong distal pulses Normal mentation Rales in lung fields	Normal lactate Minimal acute renal function impairment Elevated BNP	SBP < 90 mm Hg or MAP < 60 mm Hg or 30 mm drop from baseline HR > 100 bpm	0
Stage C Classic CS	Volume overload Altered mental status Cold and clammy May look unwell, ashen Rales assisted ventilation; low urine output	Lactate > 2 CR 1.5 × baseline or > 50% drop in GFR Increased LFTs Elevated BNP	CI > 2.2 PCWP > 15 mm Hg	11%
Stage D Deteriorating	Any of stage C and worsening (or not improving) signs/sx of hypoperfusion despite initial therapy	Any of stage C and lactate rising and persistently > 2 Deteriorating renal function, Worsening LFTs Rising BNP	Any of stage C and requiring escalating doses or increasing numbers of pressors or addition of MCS device to maintain perfusion	33%
Stage E Extremis	Typically unconscious Near pulselessness Cardiac collapse Multiple defibrillations	Lactate > 5 CPR Severe acidosis (pH < 7.2)	Profound hypotension despite maximal hemodynamic support Need for bolus doses of vasopressors	55%

Source: Modified from SCAI Shock Classification Checklist [9]. Mortality data is from Hsu *et al.* [13]

- SCAI stage E patients were defined as having hypotension (SBP < 60 mm Hg or MAP < 50 mm Hg) or hypoperfusion (lactate > 10 mmol/L or pH $\leq$ 7.2) or the need for > 3 drugs or 3 devices. All patients who experienced OHCA were included in stage E.

Pathophysiology

The pathophysiology of CS is characterized by an initial insult that decreases CO, followed by a decrease in BP and increases in LV and RV filling pressures, microcirculatory dysfunction, a systemic inflammatory response syndrome and multi-organ dysfunction. Decreased perfusion leads to activation of compensatory mechanisms including neurohormonal pathways such as the sympathetic nervous system and the renin-angiotensin-aldosterone system. Activation of the sympathetic nervous system and neurohormonal pathways results in increased levels of circulating catecholamines (leading to an increase in vasoconstriction, heart rate, myocardial contractility and venoconstriction shifting intravascular volume from the splanchnic circulation to the venous system). Activation of the renin-angiotensin-aldosterone cascade results in increased salt and water retention. These compensatory mechanisms work to increase BP and CO but have deleterious effects including increasing myocardial afterload and circulating plasma volume, which can lead to pulmonary edema. This, in turn, can result in a downward spiral where a reduction in coronary artery perfusion leads to myocardial ischemia, which results in worsening cardiac function, and eventually in circulatory collapse.

Microcirculatory dysfunction is present in CS patients and is associated with the development of multi-organ failure. In a sub-analysis of the CULPRIT-SHOCK trial, video microscopy of the sublingual capillary network in 66 patients showed an association between microcirculatory perfusion parameters and the combined clinical endpoint of 30-day all-cause death and renal replacement therapy [16]. Clinically, overt inflammation is seen in 20–40% of CS patients with elevated levels of various cytokines (interleukin-1 β , 6, 7, 8, and 10). Multi-organ dysfunction can result from both hemodynamic compromise and microcirculatory dysfunction.

The hemodynamic consequences of CS are reflected in changes in LV pressure-volume (PV) loops (Figure 21.2). As discussed in Chapter 3, PV loops are a useful method to display the relationship between ventricular volume and pressure during the cardiac cycle. Stroke volume (change in volume) and stroke work (stroke volume $\times$ MAP or alternatively the area inscribed by the PV loop) can be calculated using PV loops. Different PV loops are obtained following changes in preload, afterload, or contractility (Figure 3.13). A PV loop diagram can aid in characterizing the hemodynamic effects of acutely decreased ventricular contractility in CS. In the initial stages of decompensated CS due to acute MI (AMI), the end-systolic PV relationship (ESPVR) shifts rightward and downward, while a small elevation is observed in the end-diastolic PV relationship (EDPVR). These changes produce a drop in stroke work and CO.

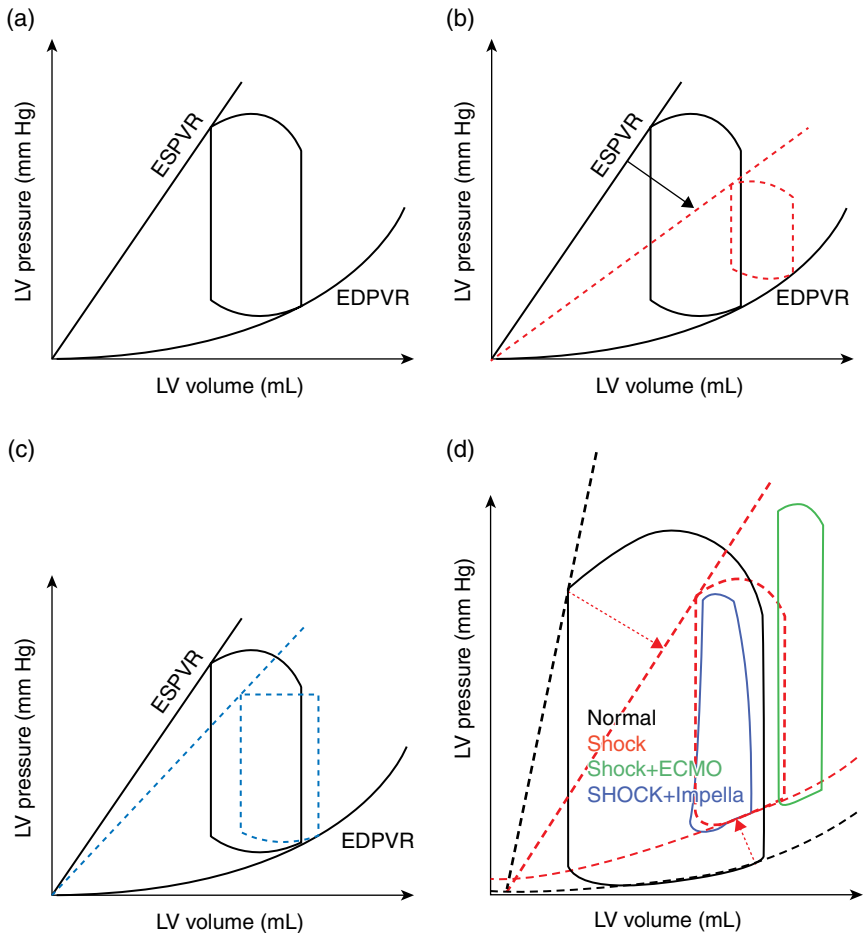


Figure 21.2 PV loops in the normal heart (a), in cardiogenic shock from an acute MI (b), in cardiogenic shock from progressive heart failure (c) and in cardiogenic shock from acute MI with various support devices (d).

Invasive evaluation of cardiogenic shock

In addition to confirming the diagnosis of CS (e.g. SBP < 90 mm Hg, elevated ventricular filling pressures and $CI < 2.2 \text{ L/min/m}^2$), invasive hemodynamic parameters can help risk stratify critically ill patients and guide the use of MCS devices.

While randomized controlled trials of pulmonary artery catheters (PAC) have not shown any benefit in heart failure, acute respiratory distress syndrome (ARDS) or sepsis (see Chapter 2 for a more detailed discussion), there are no randomized controlled trials of PAC use in CS. There are observational studies, however, that suggest hemodynamically guided decision making may be associated with improved outcomes in CS [10, 17]. A study of 1414 patients with CS from

the Cardiogenic Shock Working Group registry found that PAC use was associated with improved survival in the overall cohort and in SCAI Stage C, Stage D and Stage E patients [18]. The AHA Contemporary Management of Cardiogenic Shock Scientific Statement recommends the use of PACs if there is any uncertainty in management, or in cases of moderate to severe CS, with an initial poor response to therapy [19]. The Pulmonary Artery Catheter in Cardiogenic Shock Trial (PACCS) is ongoing and will help determine whether early use of PACs and management of CS with PACs is associated with lower in-hospital mortality compared to standard of care.

Typical hemodynamic metrics measured in patients with CS include BP, heart rate, right atrial (RA) pressure, pulmonary artery (PA) pressure, PCWP, and CO/CI.

There are several calculated hemodynamic parameters useful in CS (Table 21.4).

• Systemic vascular resistance $SVR = \frac{(MAP - RAP) \times 80}{CO}$

The normal values of SVR range from 800 to 1200 dynes s/cm⁵

Table 21.4 Calculated hemodynamic parameters that are useful in CS. [CO = cardiac output; HR = heart rate; LVEDP = LV end-diastolic pressure; MAP = mean arterial pressure; MI = myocardial infarction; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.]

Parameter	Calculation	Interpretation
Systemic vascular resistance (SVR)	$= (MAP - RAP) \times 80 / CO$	Normal values of SVR range from 800 to 1200 dynes s/cm ⁵
Cardiac power output (CPO)	$= MAP \times CO / 451$	CPO < 0.6 W is suggestive of an increase in in-hospital mortality and has been used to gauge whether MCS might be beneficial [20].
Pulmonary Artery Pulsatility Index (PAPi)	$= (PA \text{ systolic pressure} - PA \text{ diastolic pressure}) / RA \text{ pressure}$	PAPi < 2 = RV dysfunction after LVAD [21] PAPi < 1.5 = severe RV dysfunction [22] PAPi < 1 = indication for percutaneous RVAD in inferior MI [23]
RAP/PCWP ratio		Typically will be < 0.86 in LV dominant shock, and > 0.86 in RV or biventricular dominant shock.
Stroke volume (SV)	$= CO / (HR \times 1000)$	Normal value is 60–100 mL
LV stroke work	$= SV \times LV \text{ pressure difference}$ [variously defined as (MAP-PCWP) or (LV systolic pressure – LVEDP)]	4.5–7.9 mm Hg/L

- Cardiac power output $CPO = \frac{MAP \times CO}{451}$

$CPO < 0.6$ W is suggestive of an increase in in-hospital mortality and has been used to gauge whether MCS might be beneficial [20].

An analysis of 541 patients enrolled in the Shock Trial Registry showed that CPO was the strongest independent hemodynamic correlate of in-hospital mortality in CS [24]. On univariate analysis, CPO, cardiac power index (CPI), CO, CI stroke volume, LV work, LV work index, stroke work, MAP, systolic and diastolic BP (all $p < 0.001$), coronary perfusion pressure ($p = 0.002$), ejection fraction ($p = 0.013$), and pulmonary artery systolic pressure ($p = 0.047$) were associated with in-hospital mortality.

In the National Cardiogenic Shock Initiative (NCSI) dataset, CPO (>0.6 or <0.6 W) and lactate (>4 or <4 mg/dL) at 12–24 hours were the best predictors of survival [25].

- Pulmonary Artery Pulsatility Index (PAPi) = (PA systolic pressure – PA diastolic pressure)/RA pressure

PAPi is used to evaluate the presence of isolated RV failure compared to LV and biventricular failure. PAPi has been validated in multiple settings including following acute inferior wall MI and post-LVAD implantation and can be used to assist in deciding whether to employ percutaneous RVAD support or VA-ECMO.

A PAPi < 0.9 can identify significant RV failure (see Chapter 28).

RAP/PCWP ratio will typically be <0.86 in LV dominant shock, and >0.86 in RV or biventricular dominant shock.

LV stroke work is the amount of work done by the LV to eject a volume of blood and thus is the stroke volume $\times$ the force that is applied to send the blood from the LV into the aorta. LV stroke work can be estimated as stroke volume $\times$ MAP – PCWP or stroke volume $\times$ LV systolic pressure – LVEDP. The LV stroke work is the area inscribed on the PV loop by the cardiac cycle.

Shock indices

Various hemodynamic parameters and shock indices (SI) have been developed to rapidly identify STEMI patients who are at high risk of death and thus may benefit from early initiation of MCS. SI were originally developed to identify high-risk trauma patients and are easily calculated at the bedside. Studies have found significant prognostic value in predicting short-term all-cause mortality in patients with STEMI using SBP/LVEDP, Admission-shock index (SI), Modified shock index (MSI), Age-SI, Age-MSI and STEMI-SI (Table 21.5) [26–31]. The age, creatinine, ejection fraction (ACEF) score ($= \frac{\text{age}}{\text{ejection fraction (EF)}} + 1$ if the creatinine level is

>2 mg/dL) was tested in STEMI patients with CS and found to predict in-hospital mortality in one study [32].

Table 21.5 Shock indices and hemodynamic parameters predicting short-term outcomes in STEMI patients. [GRACE = Global Registry of Acute Coronary Events; HR = heart rate; IABP = intra-aortic balloon pump; MAP = mean arterial pressure; MCS = mechanical circulatory support; SBP = systolic blood pressure.]

Indices	Definition	Outcomes
SBP/LVEDP		STEMI patients with SBP/LVEDP ≤ 4 had increased risk of in-hospital death and IABP compared to patients with SBP/LVEDP > 4 [26].
Admission-shock index (SI)	= HR/SBP	An SI ≥ 0.7 in STEMI patients was an independent risk factor for 7-day all-cause mortality and 30-day all-cause mortality compared to patients with an SI of <0.7 [27].
Modified shock index (MSI)	= HR/MAP	An MSI ≥ 1.4 predicted 7-day all-cause mortality [28]
Age-SI	= SI multiplied by age = age $\times$ HR/SBP	Age-SI was similar to the GRACE score and better than SI and MSI at predicting all-cause mortality at mean duration of follow-up of 32 months (12–69 months) [29]
Age-MSI	= MSI multiplied by age = age $\times$ HR/MAP	The predictive values of Age-SI and Age-MSI were comparable to that of the GRACE score, but superior to those of SI and MSI for in-hospital cardiac mortality [30]
STEMI-SI	= age $\times$ HR divided by coronary perfusion pressure (aortic diastolic BP – LVEDP).	Patients with STEMI-SI ≥ 182 were more likely to have a cardiac arrest in the catheterization laboratory, require MCS and be treated with vasopressors compared to STEMI SI < 182 [31].

Using hemodynamics to guide treatment in CS

Rapid correction of the acute insult leading to CS is a cornerstone of treatment. In the setting of acute MI, early revascularization with primary percutaneous coronary intervention is associated with improved outcomes [33]. Similarly, correction of structural and valvular dysfunction helps restore normal cardiac function. For the purposes of this chapter, we will concentrate on managing CS independent of the cause and discuss treatment of CS with pharmacologic measures and/or by using temporary MCS devices.

The cornerstone of pharmacological treatment for patients with CS is augmentation of CO and support of BP. While vasoactive medications can improve CO and BP, they also increase myocardial oxygen consumption and the risk of arrhythmias. Pure inotropic agents commonly used include dobutamine and milrinone, while medications that have combined vasopressor effects and inotropic effects include dopamine, norepinephrine, and epinephrine. Table 21.6 compares the physiologic effect of different vasoactive and ionotropic medications used in the treatment of CS.

Table 21.6 Hemodynamic effect of vasoactive medications used in C. [CO = cardiac output; PD = phosphodiesterase; SVR = systemic vascular resistance.]

Agents	Mechanism	Hemodynamic Effect
Phenylephrine	+++ $\alpha 1$ agonist	Vasoconstriction causing increased SVR
Norepinephrine	++++ $\alpha 1$ agonist ++ $\beta 1$ agonist + $\beta 2$ agonist	Vasoconstriction causing increased SVR Inotropy causing mild increase in CO
Epinephrine	++++ $\alpha 1$ agonist ++++ $\beta 1$ agonist +++ $\beta 2$ agonist	Vasoconstriction causing increased SVR Inotropy causing increased CO
Very low dose dopamine	+ $\beta 1$ agonist	Inotropy causing increased CO
Low dose dopamine	+ $\alpha 1$ agonist +++ $\beta 1$ agonist + $\beta 2$ agonist	Inotropy causing increased CO Mild vasoconstrictive effect causing increased SVR
High dose dopamine	+++ $\alpha 1$ agonist ++ $\beta 1$ agonist	Vasoconstriction causing increased SVR Inotropy causing increased CO
Vasopressin	V1 agonist	Vasoconstriction causing increased SVR
Dobutamine	+ $\alpha 1$ agonist ++++ $\beta 1$ agonist ++ $\beta 2$ agonist	Main effect is increasing inotropy and thus CO Mild vasodilation with decreased SVR
Milrinone	PD3 inhibitor	Main effect is increasing inotropy and thus CO Mild vasodilation with decreased SVR
Isoproterenol	++++ $\beta 1$ agonist +++ $\beta 2$ agonist	Increased heart rate and CO Decreased SVR

Options for acute MCS include the intra-aortic balloon pump (IABP), microaxial flow pumps (Impella RP, CP, and 5.5), left atrial-to-femoral arterial ventricular assist devices (Tandem Heart) and venous-arterial extracorporeal membrane oxygenation (VA-ECMO) [34]. The hemodynamics of IABP and VA-ECMO are discussed in more detail in Chapters 22 and 24, respectively.

Impella is a microaxial pump that is available in both LV and RV configurations. The Impella device unloads the ventricle by withdrawing blood and then expelling at a higher pressure into the aorta (for the LV device) or PA (for the RV device). Impella CP and RP can be rapidly inserted percutaneously in the catheterization laboratory while Impella 5.5 requires surgical insertion [35]. Unlike IABP, Impella does not require electrocardiographic or arterial waveform triggering, which enables it to provide hemodynamic support independent of the cardiac rhythm.

TandemHeart provides a continuous flow via a centrifugal pump. The venous cannula is inserted through the venous system into the LA via a transseptal puncture with the arterial cannula returning oxygenated blood into the abdominal

aorta. TandemHeart increases CO and MAP and decreases LV filling pressures by venting the LA.

Both Impella and TandemHeart reduce LVEDP, whereas VA-ECMO can increase LVEDP unless the LA or the LV are vented. Increased LVEDP can result in greater wall stress and myocardial oxygen demand. After active unloading by an Impella device, the area of the PV loop, and thus the amount of work performed by the myocardium, decreases (Figure 21.2). A reduction in EDV and EDP increases coronary blood flow and decreases myocardial oxygen demand—impacting both sides of the supply-demand equation.

In acute isolated RV CS, the RV is very sensitive to preload and afterload. Fluid administration is recommended to ensure adequate central venous pressure from 10 to 14 mm Hg (see Chapter 28 for a more detailed discussion of management of RV MI). As seen in massive pulmonary emboli or decompensated pulmonary hypertension, slight changes in afterload can cause a dramatic decrease in RV stroke volume. This can be further demonstrated by the addition of positive pressure ventilation which can lead to a severe drop in stroke volume in those with severe RV dysfunction, leading to shock and/or cardiac arrest.

Several management algorithms have been proposed to guide therapy [10, 13, 25]. These algorithms won't be discussed in detail as they are evolving rapidly, but in general, these algorithms incorporate a multidisciplinary shock team approach and utilize PAC data to guide therapy with vasopressor and inotropic agents followed by escalation to MCS if necessary.

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CHAPTER 22

Hemodynamics of intra-aortic balloon counterpulsation

Richard A. Santa-Cruz and George A. Stouffer

History and uses

The idea of using diastolic augmentation to treat left ventricular failure was first proposed in the 1950s. The earliest method involved removing blood from the femoral artery during systole and replacing this volume rapidly during diastole. In the early 1960s, an experimental prototype of the intra-aortic balloon pump (IABP) was developed, in which inflation and deflation were triggered by the electrocardiogram (ECG). The initial use of IABP in clinical practice was in 1968. The early devices were 15 French in size and required surgical insertion and removal. Subsequent improvements included a dramatic reduction in size, enabling percutaneous insertion.

Current indications for IABP include cardiogenic shock or left ventricular failure, unstable ischemic syndromes, mechanical complications of acute myocardial infarction, ischemic ventricular arrhythmias, severe mitral regurgitation, stabilization of patients undergoing coronary artery bypass grafting with high-risk anatomy (e.g., severe left main disease), failure to separate a patient from cardiopulmonary bypass, high-risk coronary intervention, or as a bridge to a left ventricular assist device (LVAD) or heart transplantation (Table 22.1). Relative contraindications to IABP usage are listed in Table 22.2.

Description

The IABP consists of a polyurethane balloon placed in the patient's descending aorta and a console that rapidly shuttles a gas, either helium or carbon dioxide, into and out of the balloon. Helium is most commonly used and has the advantage of a lower density and therefore a better rapid diffusion coefficient. Carbon dioxide, on the other hand, has an increased solubility in blood and

Table 22.1 Indications for IABP.

Complicated acute myocardial infarction
Refractory unstable angina
Cardiogenic shock (including right ventricular failure)
Mechanical complications of acute myocardial infarction or trauma
Severe coronary artery disease with hemodynamic compromise
Severe left main disease
Support of high-risk coronary interventions
Induction and weaning of cardiopulmonary bypass
Bridge to cardiac transplantation
Refractory ventricular arrhythmias
Noncardiac surgery for high-risk cardiovascular patients
Severe mitral regurgitation

Table 22.2 Relative contraindications for IABP.

Severe peripheral vascular disease
Active hemorrhage
Bleeding diatheses including severe thrombocytopenia
Contraindication to anticoagulation
Moderate to severe aortic insufficiency

thereby reduces the potential consequences of gas embolization following a balloon rupture.

The IABP is placed with one tip below the origin of the left subclavian artery (a useful angiographic marker is the left main stem bronchus). The other tip should be positioned above the renal arteries. It is important to match the appropriate balloon size to patient size since mismatches can cause either ineffective counterpulsation and/or possible mechanical trauma to the aorta. In general, a 40 cc balloon size is used, although sizes from 25 to 50 cc are available.

Hemodynamic effects

In theory, hemodynamic effects of IABP can be predicted by realizing that the balloon inflates during diastole, leading to increased coronary and visceral perfusion pressures, and deflates during systole resulting in decreased afterload.

Thus, an IABP produces hemodynamic effects through the cardiac cycle. During diastole, the IABP inflates, thereby displacing blood from the descending aorta. The balloon deflates immediately before systole, resulting in decreased aortic impedance (Figure 22.1). The primary hemodynamic benefits of IABP treatment are diastolic pressure augmentation and afterload reduction (Table 22.3). Diastolic

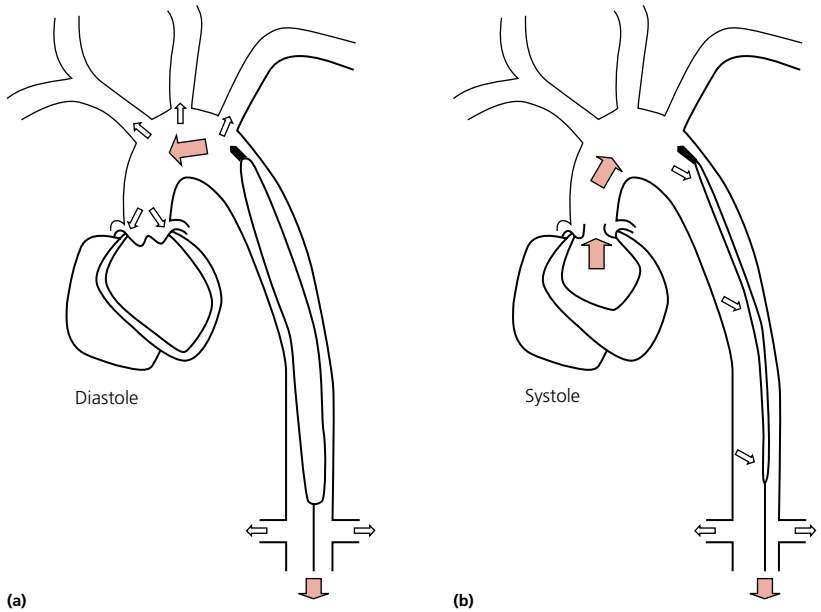


Figure 22.1 IABP inflation and deflation. During diastole, the IABP is inflated, increasing diastolic pressure, thus augmenting flow not only into the coronary arteries but also the great vessels and the renal arteries (a). Just prior to systole, the IABP is deflated, creating a void where the inflated balloon was, thus increasing forward flow into the aorta and to the periphery (b).

Table 22.3 Hemodynamic effects of IABP therapy.

Decreased left ventricular afterload
Decreased aortic systolic blood pressure
Increased aortic diastolic blood pressure
Decreased pulmonary capillary wedge pressure
Decreased LV volume
Decreased LV end-diastolic pressure
Increased coronary blood flow
Increased cardiac output

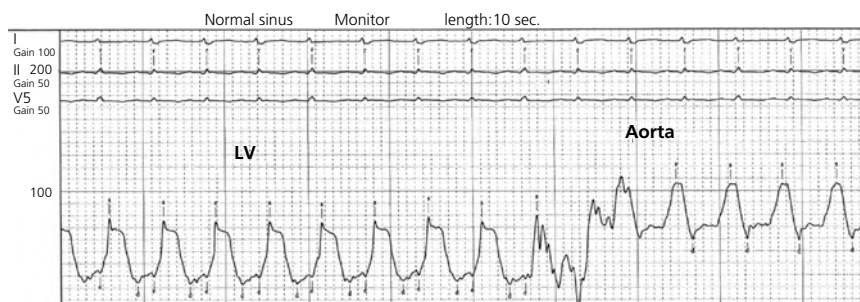


Figure 22.2 Aortic counterpulsation in a patient with cardiogenic shock, left ventricle to aortic pullback. The patient was a 48-year-old male who presented with an extensive anterior–lateral myocardial infarction. An IABP was placed via the left femoral artery. An end-hole catheter was inserted into the left ventricle and pressures were recorded as the catheter was withdrawn into the aorta. Note the decreased left ventricular systolic pressure and increased LVEDP. IABP diastolic augmentation is a major contributor to aortic pressure.

augmentation can increase coronary perfusion pressure, mean arterial blood pressure, and systemic perfusion, although these effects have not been consistently found in all studies. As shown in Figure 22.2, diastolic pressure augmentation by aortic counterpulsation can be a major support of mean arterial blood pressure in patients with cardiogenic shock. Afterload reduction can decrease left ventricular filling pressures and decrease myocardial oxygen demand. The decrease in afterload generally results in a decrease in left ventricular end-diastolic pressure (LVEDP) during counterpulsation, with preservation or increase of the left ventricular stroke volume and ejection fraction. Left ventricular work is decreased by a reduction in afterload, which results in lower myocardial oxygen demand. The decrease in systolic pressure is generally less than the increase in diastolic pressure, resulting in an increase in mean arterial blood pressure.

Because an IABP works via diastolic pressure augmentation and afterload reduction, the beneficial effects are dependent on heart rate, cardiac output, and blood pressure. Diastolic augmentation is limited in patients with poor cardiac output independent of how well the IABP is functioning. This is in contradistinction from extracorporeal membrane oxygenation (ECMO) or LVAD, in which hemodynamic support is generally independent of intrinsic cardiac activity.

Counterpulsation has many metabolic effects on both ischemic and nonischemic myocardium. In general, aortic counterpulsation results in decreased myocardial metabolic demands. Increased end-organ perfusion is probably an important contributor to the overall improvement in patient status associated with aortic counterpulsation among those with hemodynamic compromise, such as in cardiogenic shock.

There is a surprisingly limited amount of data on the hemodynamic effects of IABP but some data are provided by various studies. In a study of 41 patients with

cardiogenic shock with acute myocardial infarction randomized to IABP vs. LVAD, the IABP group ($n = 20$) showed an increase in cardiac power index, from 0.22 (IQR 0.18–0.30) to 0.28 W/m² (IQR 0.24–0.36), cardiac output, from 3.0 (2.5–4.0) to 3.3 (2.9–4.3) L/min; and mean arterial pressure, from 64 (57–74) to 67 (62–84) mm Hg; and a decrease in pulmonary capillary wedge pressure, from 27.0 (20.0–30.0) to 21.5 (17.0–26.0) mm Hg. This study found that a percutaneous LVAD (Tandem Heart™, Cardiac Assist, Pittsburgh, PA, United States) provided more hemodynamic support but resulted in more complications [1].

The IABP Cardiogenic Shock Trial was a prospective, randomized, single-center trial looking at the effects of IABP vs. inotropic therapy (i.e., dobutamine and/or norepinephrine) in 40 patients with acute myocardial infarction complicated by cardiogenic shock, treated by PCI within 12 hours of onset of hemodynamic instability. There was significant improvement in both groups in cardiac output, systemic vascular resistance, and cardiac power output, and no significant differences between the IABP group and the medical-alone group in cardiac output or systemic vascular resistance after 24, 48, 72, or 96 hours [2].

A retrospective observational study of hemodynamics in 132 patients who had an IABP placed for acute decompensated heart failure-cardiogenic shock (ADHF-CS) found improvement in mean arterial pressure, cardiac output, and pulmonary artery pressures [3].

Finally, an interesting retrospective observational study of 205 patients found differential hemodynamic responses in patients with ADHF ($n = 132$) vs cardiogenic shock due to an acute myocardial infarction ($N = 73$). Both groups were compromised at baseline with a mean (SD) cardiac output of 3.0 ± 0.8 L/min and cardiac power index of 0.26 ± 0.06 W/m². An IABP increased cardiac output by 0.6 ± 0.8 L/min in the ADHF group vs 0.1 ± 1.0 L/min for the myocardial infarction group [4].

Intra-aortic balloon pump timing

To achieve optimal effects of counterpulsation, inflation and deflation need to be correctly timed to the patient's cardiac cycle. This can be accomplished by using the patient's ECG signal, the patient's arterial waveform, or an intrinsic pump rate. The most common method of triggering the IABP is from the R wave of the patient's ECG (Figure 22.3). On identification of the R wave the balloon deflates. Balloon inflation is generally set to start automatically in the middle of the T wave. Tachyarrhythmias, cardiac pacemakers, and poor ECG signals may cause difficulties in obtaining synchronization when the ECG mode is used. In such cases, the arterial waveform may be useful for triggering.

For optimal efficacy, the IABP should inflate during early diastole (after the aortic valve closes, which is identified by the dicrotic notch) and deflate just prior to systole (just before the aortic valve opens). IABP inflation and deflation timing,

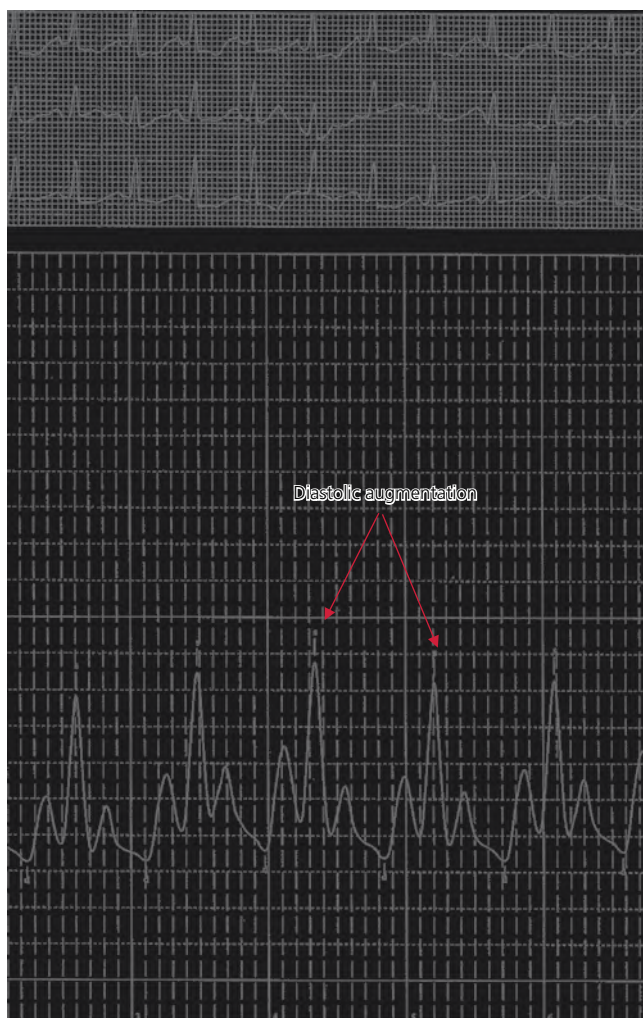


Figure 22.3 IABP set on a 1:2 ratio in a 60-year-old male with cardiogenic shock in the setting of acute myocardial infarction (200 mm Hg scale).

as well as ratio of counterpulsations to cardiac cycles, can be adjusted to optimize performance (Figures 22.4 and 22.5). In general, optimal assistance from the IABP occurs when each cardiac cycle is augmented in a 1:1 ratio. In patients with tachycardia (e.g., rapid atrial fibrillation), a lower assist ratio (1:2 or 1:3) can be used to allow gas delivery to and removal from the balloon.

The most common cause of inadequate balloon counterpulsation is the inaccurate timing of inflation and deflation. Some errors associated with IABP timing will simply result in poor hemodynamic response to IABP, but others are more dangerous for patients with already tenuous cardiovascular situations. Understanding IABP pressure waveforms is critical to use this device properly. The

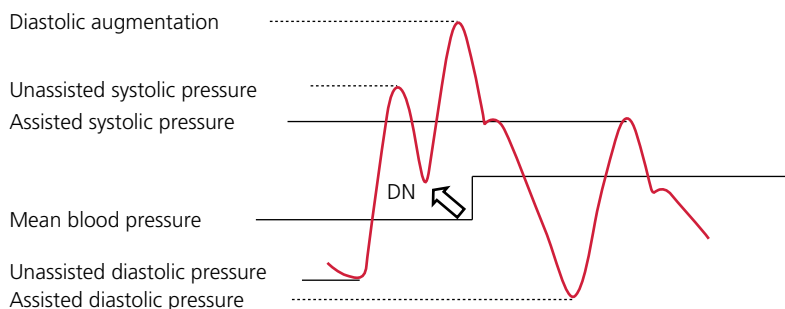


Figure 22.4 Correct IABP timing and hemodynamic effects. Normal timing of the IABP (arrow) with inflation at the dicrotic notch (DN) and good diastolic augmentation, which increases coronary blood flow and increases mean blood pressure. Assisted systolic and end-diastolic pressures are lower than unassisted systolic and end-diastolic pressures.

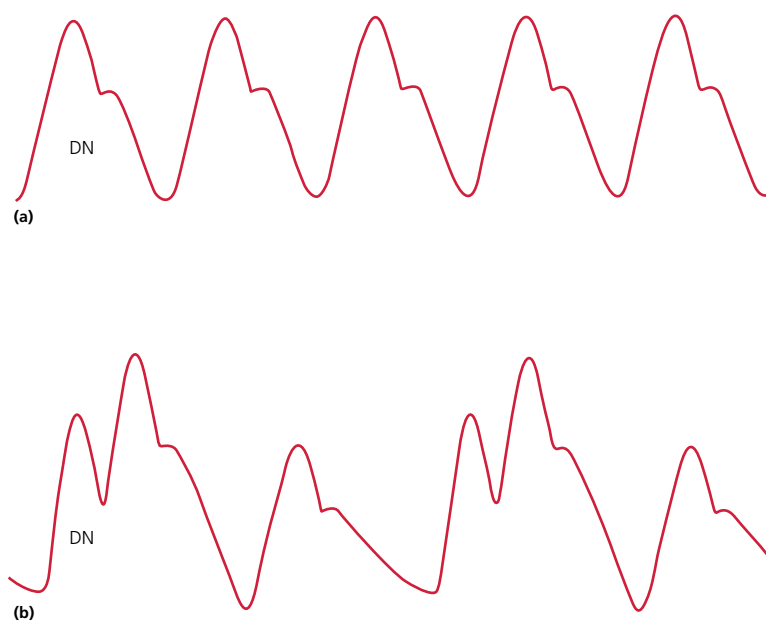


Figure 22.5 Aortic pressure with and without IABP. Aortic pressure waveforms prior to (a) and after initiation of IABP at 1:2 ratio (b). [DN = dicrotic notch.]

timing errors can be divided into two groups: systolic errors (early and late inflation) and diastolic errors (early and late deflation).

Early inflation

Inflation of the IABP prior to aortic valve closure will increase afterload since the heart must eject blood against an inflated balloon. This increases myocardial wall stress and LVEDP, thereby increasing LV work, reducing cardiac output, and potentially precipitating early closure of the aortic valve. On the hemodynamic

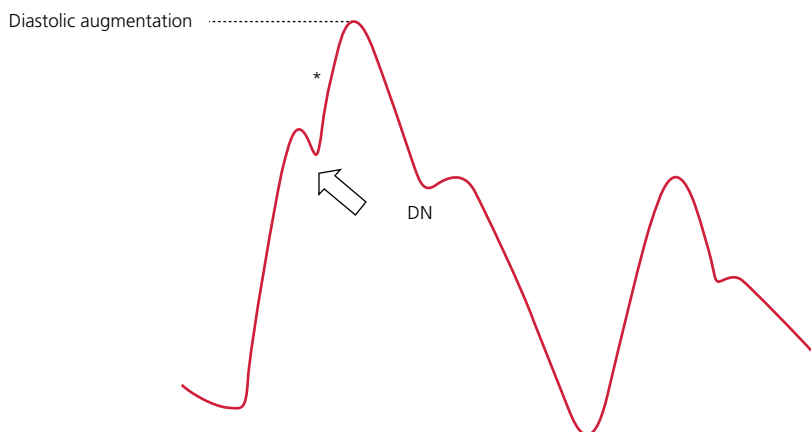


Figure 22.6 Incorrect IABP timing—early inflation. Aortic pressure waveform demonstrating early inflation of the IABP (arrow) prior to the diastolic notch (DN) and prior to the closure of the aortic valve. There is a rapid rise in augmented diastolic pressure (*) with the aortic valve still open, which causes a dramatic increase in afterload and reduces cardiac output.

tracing, a sharp or rapid rise in the augmented pressure will be seen prior to the diastolic notch (Figure 22.6).

Late inflation

Although probably the least dangerous error, late IABP inflation can preclude the patient from obtaining optimal hemodynamic support. Here, the IABP inflates too long after the aortic valve closes. This delay does not allow for adequate diastolic augmentation. There is a blunting or complete lack of the diastolic augmentation waveform (Figure 22.7). Associated with this is a lack of end-diastolic pressure decrease (afterload reduction) and no increase in diastolic perfusion pressure.

Early deflation

Early deflation, similar to late inflation, is not a particularly dangerous situation, although the patient will not receive optimal balloon counterpulsation. The hemodynamic tracing reveals a normal diastolic augmentation, but then a long-drawn-out U-shaped wave prior to the assisted systolic waveform (Figure 22.8). Notice that there is inadequate preload reduction and therefore no change in assisted and unassisted systolic pressure. Simply prolonging the balloon inflation will quickly improve the hemodynamic support that the balloon pump can provide.

Late deflation

Late IABP deflation is potentially the most critical timing error. If the balloon remains inflated when the left ventricle enters systole, the left ventricle is forced to contract against the inflated balloon. The result can be acute hypotension and cardiac arrest. The hemodynamic tracing reveals a long inflation time with elevated end-diastolic pressure and a severely reduced assisted systolic pressure (Figure 22.9).

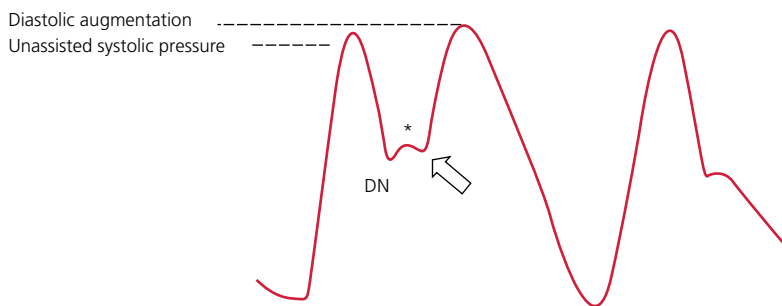


Figure 22.7 Incorrect IABP timing—late inflation. Aortic pressure waveform demonstrating late inflation of the IABP. The notable hemodynamic changes are the clearly visible dirotic notch (DN) with the IABP inflation following (arrow). There is a prolonged dip or U wave (*), then a blunted or decreased diastolic augmentation.

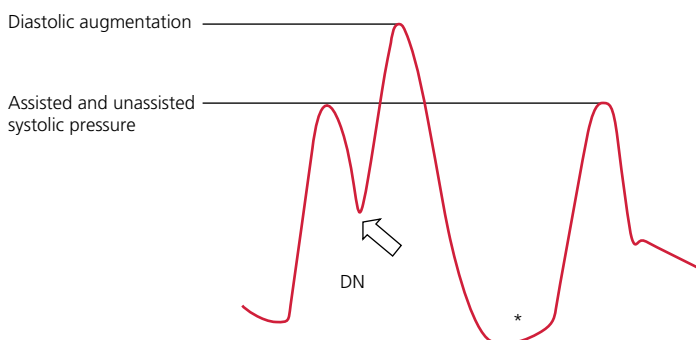


Figure 22.8 Incorrect IABP timing—early deflation. Aortic pressure waveform demonstrating early deflation of the IABP. Early deflation of the IABP in diastole does not affect diastolic augmentation but does prevent optimal end-diastolic pressure decrease. This is evident by a prolonged dip and U wave (*) post augmentation. There is no reduction in assisted systolic pressure, which is equal to the unassisted systolic pressure, representing a lack of afterload reduction. Large arrow denotes beginning of IABP inflation.

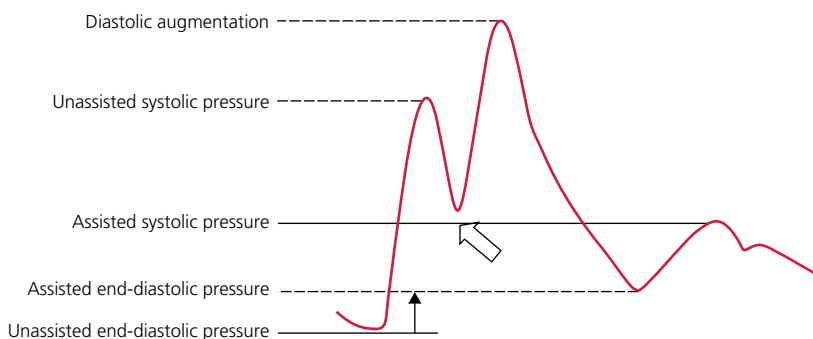


Figure 22.9 Incorrect IABP timing—late deflation. Aortic pressure waveform demonstrating late deflation of the IABP. Late deflation of the IABP in diastole causes a dramatic increase in afterload since systole begins with higher intra-aortic pressure. This causes late opening of the aortic valve and severely reduces the cardiac output. The pressure waveform reveals an assisted end-diastolic pressure that is higher than the unassisted end-diastolic pressure and a drastically reduced assisted systolic pressure. Large arrow denotes beginning of IABP inflation.

Conclusion

The IABP is a widely used device in the management of patients suffering from the ill effects of acute and chronic cardiovascular disease. Understanding the characteristic hemodynamic tracings of balloon counterpulsation is critical for proper functioning and ensuring maximal therapeutic benefit. In turn, recognizing the possible complications and pitfalls of IABP timing is crucial to minimizing potential adverse effects.

Since IABP is widely used, it is surprising that there are so little data demonstrating clinical efficacy in acute coronary syndromes. In particular, IABP has not been shown to be beneficial in high-risk PCI, acute MI complicated by cardiogenic shock, and acute MI without cardiogenic shock [5, 6]. IABP use during revascularization has a Class IIb recommendation in American guidelines and a Class III recommendation in European guidelines.

Review of IABP tracings

Match the tracing with the diagnosis. All tracings are taken with the IABP on a 1:2 ratio.

- (a) Accurate timing
- (b) Early balloon inflation
- (c) Early balloon deflation
- (d) Late balloon inflation
- (e) Late balloon deflation



Tracing 1



Tracing 2



Tracing 3



Tracing 4



Tracing 5

Answers

- 1 Early balloon deflation
- 2 Late balloon deflation
- 3 Accurate timing
- 4 Early balloon inflation
- 5 Late balloon inflation

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CHAPTER 23

Hemodynamics of left ventricular assist device implantation

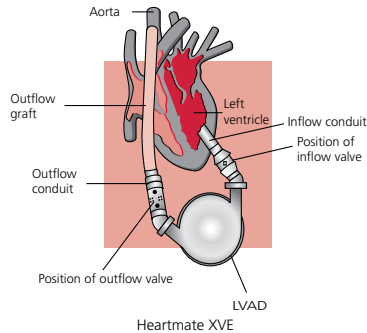
Mason G. Sanders, Jason N. Katz and Mirmela Byku

The modern history of left ventricular (LV) assist devices (LVAD) dates back to the late 1970s and early 1980s with the development of the Jarvik artificial heart. In 1982, surgeons at the University of Utah implanted the Jarvik 7 prototype (Figure 23.1) in a patient named Barney Clark, who ultimately survived 112 days on mechanical support [1]. At the same time, Dr. Norman Shumway and his group at Stanford University were improving the surgical technique for cardiac transplantation and found durable success thanks in large part to the pharmacologic discovery of inducible immune tolerance. Research and development resources were concentrated on improving outcomes on the early promise of heart transplantation as the primary strategy for treating end-stage heart failure, given its biologic symmetry compared to the Frankensteinian connotations of mechanical support alternatives. This slowed the evolution of mechanical support technologies throughout the 1980s and into the 1990s.

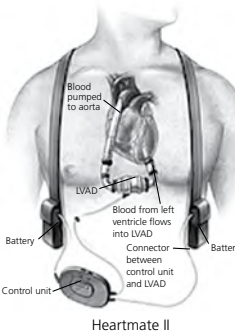
The conventional wisdom at the time was that mechanical heart replacement therapy would require two pumps to support both the LV and RV chambers, and this concept created additional barriers to the maturation of mechanical circulatory support (MCS) as a field. A turning point came in 2001 with the publication of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial [2]. This pivotal study was the first to demonstrate a durable advantage of LVAD therapy for transplant-ineligible patients with advanced heart failure. With a pneumatically driven pulsatile LV support system (Figure 23.1; HeartMate XVE, Thoratec Corp., Pleasanton, CA, United States), investigators showed a nearly 50% reduction in all-cause mortality compared to optimal medical management alone. These results validated two critical concepts: (1) that univentricular (i.e., left-sided) support could work in advanced, biventricular heart failure; and (2) that MCS could improve outcomes versus medical therapy for individuals with extremely advanced heart failure.



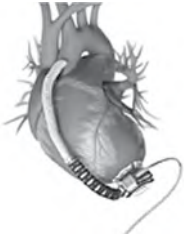
Jarvik-7



Heartmate XVE



Heartmate II



HeartWare Ventricular Assist Device



Jarvik 2000 Ventricular Assist Device



Heartmate 3

Figure 23.1 Different types of mechanical cardiac support devices.

Although the utilization of LVAD therapy slowly increased following REMATCH, it became apparent that the early pulsatile devices (e.g., HeartMate XVE; Novacor, World Heart Corp., CA, United States) were imperfect solutions to the heart failure epidemic. Limitations of these first-generation LVADs included their large size and limited durability. Many of these barriers were addressed with the creation of second-generation, axial-flow pumps (Figure 23.1; HeartMate II, Thoratec Corp., CA, United States). Results from a multicenter trial of 133 non-randomized patients receiving the HeartMate II device as a bridge to transplantation, published in 2007 [3], demonstrated that patients could be successfully stabilized until cardiac transplantation with the use of a continuous-flow (CF) LVAD. In addition, the HeartMate II device was found to be easier to implant, more durable, and had fewer complications than its pulsatile predecessors. The HeartMate II was also tested as an alternative to the first-generation HeartMate XVE in a transplant-ineligible heart failure population, often referred to as “destination therapy.” Although both devices improved quality of life, the axial-flow HeartMate II device allowed for greater survival free from stroke, with less risk of device failure [4].

With validation of LVAD therapy as both a bridge to transplantation and a destination-therapy option, other industry participants began to enter the MCS space. The HeartWare ventricular assist device (HVAD, Medtronic, Mounds View, MN) was another axial, CF LVAD initially approved in 2012, which was shown in the ENDURANCE trial [5] to be noninferior to the HeartMate II in terms of survival, albeit with a higher risk of stroke. Ultimately, given concerns for device failure, risk of thrombosis, and increased stroke risk, this device was withdrawn in June 2021, recalling 4620 implanted devices in the process [6].

The current standard of care is the third-generation, magnetically levitated, centrifugal-flow HeartMate III device, developed by the St. Jude Corporation, now Abbott Medical. The MOMENTUM 3 trial [7], published in April 2021, evaluated the HeartMate III as either a bridge to transplant or as destination therapy. This study demonstrated superiority of the HeartMate III centrifugal-flow device compared to the HeartMate II axial-flow LVAD with decreased frequency of pump replacement as well as lower rates of stroke and significant bleeding. Since then, HeartMate III has become the dominant player in terms of market share, with 92.7% of LVADs implanted in 2021 being the magnetically levitated device [8].

Predictably, the utilization of LVAD therapy has increased since 2008, thanks in large part to rapidly evolving technology, improved outcomes and a burgeoning population of aging heart failure patients. The number of LVADs implanted peaked in 2019 with 3219 implants performed, decreasing by 23.5% by 2021, felt to be in part due to the COVID-19 epidemic as well as changes to the United States organ allocation system. The proportion of LVADs implanted as destination therapy has continued to increase to 92.7% in 2021, also likely driven by changes in organ allocation. LVAD remains an important therapy moving forward as the population with heart failure grows and ages, and as donor heart organ shortage issues remain. As technology evolves, the number of LVAD implantation centers

increases, and familiarity with LVAD grows both for potential candidates and for operators, this therapy is expected to continue to grow in importance and utilization. To better understand patient eligibility, appropriate timing of implantation, and the management of LVAD-supported individuals in both the acute and chronic post-operative settings, it is critical to understand their hemodynamic profiles.

Initial evaluation

There are multiple factors that should be considered when assessing a patient's eligibility for LVAD. It is critical to evaluate not only their expected tolerability of the initial operative insult but also the likelihood that the patient will reap durable benefits from mechanical support. Those individuals most likely to thrive with univentricular support include those with pre-operative hemodynamics most suggestive of predominant left-sided cardiac dysfunction. Individuals with isolated right-sided heart failure, or those with biventricular failure in whom right ventricular (RV) dysfunction is not modifiable, are poor candidates for LVAD therapy and should not undergo device implantation. The following are some hemodynamic examples to guide operative assessment.

Left-sided heart failure

The ideal LVAD patient has predominantly advanced LV dysfunction. These individuals will have elevated left-sided cardiac filling pressures, and often secondarily increased right-sided filling pressures (Table 23.1). As stroke volume diminishes, mean systemic perfusion (mean arterial pressure, MAP) will decrease as well. In addition, mixed venous oxygen saturation (SVO_2) will be low. If, on the other hand, left-sided filling pressures are not elevated, it can be surmised that the LVAD will be unlikely to provide incremental LV unloading, and hence device implantation would result in little benefit at the expense of increased complications.

Right-sided heart failure

While RV function does not have to be normal for LVAD support, the RV does have to be strong enough to deliver blood across the usually low-pressure, low-resistance pulmonary arterial circulation to the left heart. For those with either pure right-sided heart failure (with no LV failure) or biventricular failure and unmodifiable RV dysfunction, suboptimal left-sided preload will lead to device complications if LVAD implantation is pursued (Table 23.1). The concept of ventricular interdependence is crucial in understanding the function of the RV, particularly in assessing and predicting whether the right heart circulation will be able to match the output of the augmented left ventricle output in various time frames post-LVAD.

While it can be challenging to define the severity of RV failure, those most likely to fail left-sided, univentricular support include those with markedly elevated central venous pressures (e.g., $\text{CVP} \geq 20\text{mm Hg}$) and those with narrow

Table 23.1 Hemodynamic parameters of ventricular failure and VAD complications.

[RA = right atrial; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; MAP = mean arterial pressure; SVO₂ = mixed venous oxygen saturation.]

Condition	RA	PAP	PCWP	MAP	SVO ₂
LV failure	↑	↑	↑	↓	↓
RV failure	↑ or ↓	↑ or ↓	↓	↓	↓
Hypovolemia	↓	↓	↓	↓	↓
Hypertension	↔	↑	↑	↑	↔
Tamponade	↑	↑	↑	↓	↓
Device failure	↑	↑	↑	↓	↓
LVAD thrombosis	↑	↑	↑	↓	↓
Aortic insufficiency	↔	↑	↑	↓	↓

gradients between the CVP and the PCWP (e.g., $\text{PCWP} - \text{CVP} < 5 \text{ mm Hg}$ or $\text{CVP}/\text{PCWP} \geq 0.8$). In addition, the Pulmonary Arterial Pulsatility Index (PAPi) defined as the ratio of pulmonary artery pulse pressure to mean right atrial pressure is a hemodynamic parameter of RV function, that couples right heart preload with contractility, and is an easily calculable tool that is often determined in the pre-LVAD setting and used to assist in management perioperatively. A $\text{PAPi} < 2.0$ has been shown to predict RV failure and need for RVAD support post-LVAD [9].

$$\text{PAPi} = \frac{(\text{PA systolic} - \text{PA diastolic pressure})}{\text{mean RA pressure}}$$

where:

PA = pulmonary artery

RA = right atrial

Similarly, the Right Ventricular Stroke Work is another hemodynamic index that provides useful information. If RVSWI is less than approximately 300 mm Hg, the risk of complications after LVAD implantation goes up considerably [10].

$$\text{RVSWI} = \frac{(\text{mean PA pressure} - \text{mean RA pressure}) \times \text{HR}}{\text{CI}}$$

where:

PA = pulmonary artery

RA = right atrial

HR = heart rate

CI = cardiac index

Hemodynamic changes seen in early post-implantation period complications

After LVAD implantation, the time course of hemodynamic stabilization and homeostasis of end-organ perfusion is usually longer than the typical cardiac surgical case. A myriad of confounding variables contribute to this observation, but one factor that always generates discussion is the alteration in the arterial waveform post-implant. Patients supported with CF ventricular support pumps persistently demonstrate pulsatility even with complete closure of the aortic valve (Figure 23.2). This pulsatility is explained by the physics of wave generation. The RV and even the unloaded LV continue to beat, creating a wave that varies in height depending on preload conditions and the intrinsic contractility of the left ventricle, interacting with the degree of LV unloading contributed by the LVAD. Once created, this wave is continuously transmitted through the column of fluid present within the pump and to the systemic aortic circulation, albeit in a muted fashion.

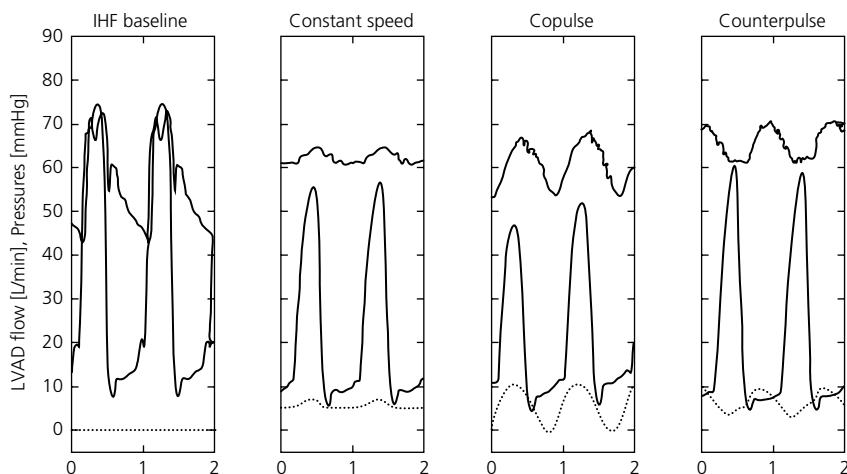
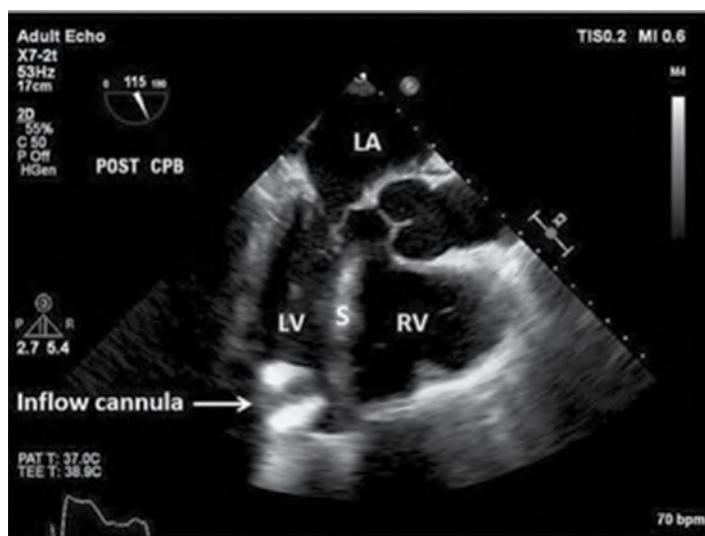


Figure 23.2 LV pressure, aortic pressure, and cardiac output in advanced systolic heart failure and with various types of mechanical support.

The majority of patients are weaned from cardiopulmonary bypass with the simultaneous support of parenteral vasoactive agents. These medications are then slowly withdrawn with invasive hemodynamic guidance in the intensive care unit setting. Several potential complications must be identified quickly and immediately rectified in order to avoid additional patient or device complications. Of note is that echocardiographic evaluation of the heart and LVAD, either by transthoracic or transesophageal modalities, provides complementary information to invasive monitoring of hemodynamics. Some frequently encountered clinical situations where invasive hemodynamics and echocardiographic imaging are helpful are hypovolemia, RV failure, hypertension, tamponade, and device failure.

Hypovolemia

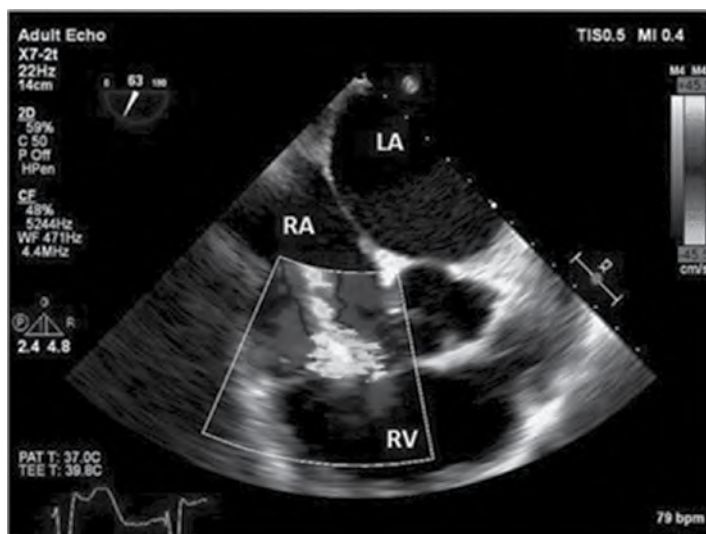
Volume loss is common during the perioperative period and occurs secondary to hemodilution (as seen with cardiopulmonary bypass), bleeding and coagulopathy, and third spacing. When identified, rapid volume resuscitation and/or transfusion of blood products are mandatory. In addition, the cause of volume loss should be identified and corrected where appropriate. From an LVAD perspective, hypovolemia will often result in diminished pump flows and reduced power consumption, along with decreased blood pulsatility within the device (Figure 23.3a).



Hypovolemia and a suction event

(a)

Figure 23.3 TEE findings in patients with hemodynamic changes after VAD implantation. (a) Hypovolemia and suction event. 2D TEE mid-esophageal long-axis view showing a suction event due to high pump speed relative to volume. The inflow cannula turned and faced the interventricular septum.



(b) RV failure



(c) Tamponade

Figure 23.3 (Continued) (b) RV failure. 2D mid-esophageal RV inflow–outflow view with color flow Doppler demonstrating moderate to severe tricuspid regurgitation (TR). (c) A localized apical thrombus resulting in tamponade. Post-LVAD implantation, there was a hemodynamic compromise. An apical thrombus (arrow) compressing the LV cavity resulted in cardiac tamponade. Surgical removal of the thrombus resulted in restoration of normal hemodynamics. [LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; S = interventricular septum; TEE = transesophageal echocardiography.]

Right ventricular failure

It is critical to monitor for RV failure, whether induced by elevated pulmonary vascular resistance, volume overload, or inadequate inotropic support. The short- and longer-term mortality of patients after durable LVAD implantation increases considerably if mechanical RV support (i.e., RVAD placement) is necessary [11].

In addition to the hemodynamic changes outlined in Table 23.1, there will often be declining LVAD flows, reduced power consumption, and decreasing device pulsatility in the setting of progressive RV failure (Figure 23.3b). Monitoring trends in hemodynamic indices including RV stroke work index (RVSWI) and PAPi are useful to detect and expeditiously address RV dysfunction by pharmacologic means, adjustment in LVAD speed, or addition of MCS (Figure 23.4). Early detection and prompt institution of RV mechanical support with a temporary device such as an RVAD can improve overall outcomes in such patients [11, 12].

Hypertension

The majority of contemporary LVAD pumps are highly sensitive to increasing afterload. As a result, marked systemic hypertension can result in decreased device flow and hence less robust LV unloading. If LVAD flows diminish due to acute hypertension, pharmacologic vasodilator therapy may be needed as RV inotropic support is weaned.

Cardiac tamponade

When present, cardiac tamponade can result in hemodynamics characterized by a rise in and equalization of diastolic pressures. If not treated rapidly, hypotension and end-organ dysfunction often ensue. In addition to the classic invasive hemodynamic changes, LVAD flows will decrease in the setting of cardiac tamponade (Figure 23.3c and Table 23.1).

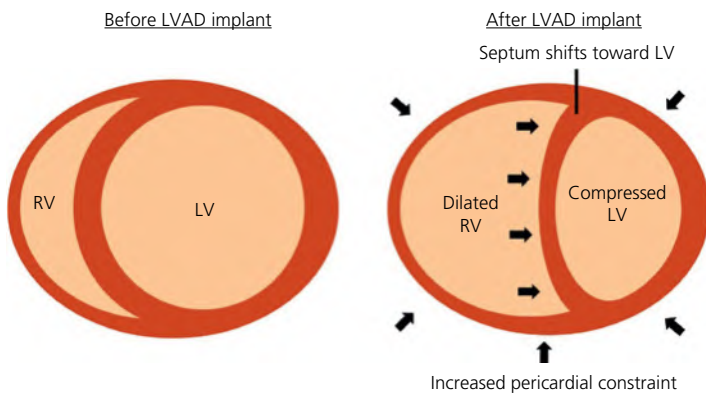


Figure 23.4 Ventricular interdependence in LVAD implantation. With left ventricular (LV) unloading, there is a leftward shift of the interventricular septum, along with an increase in RV preload. Decreased LV preload and RV volume overload can result in congestion, systemic hypotension, and overt RV failure. Source: Lin *et al.* [12] / Reproduced with permission of Springer Nature.

Pump failure

The hemodynamic picture of a patient with LVAD failure will look similar to that of a patient with cardiogenic shock and LV dysfunction. The failing LVAD will be unable to unload the congested left heart adequately. Depending on the cause of device malfunction, LVAD interrogation may show elevated or normal power consumption, elevated or low estimated device flows, and diminished pulsatility.

Hemodynamic changes in long-term LVAD complications

After an LVAD patient leaves the hospital following their implant, careful outpatient follow-up is still necessary. These individuals remain susceptible to complications secondary to both patient factors and abnormal patient–device interactions. The following are examples of conditions that may arise during chronic LVAD support.

Hypovolemia

LVAD patients are at risk for hypovolemia both during the early postoperative period and during the chronic phase of their care. This is particularly true when robust LVAD unloading leads to enhanced renal perfusion and frequent urination. It is also a common complication of excessive diuretic therapy. As already discussed, hypovolemia can result in decreased LVAD flows, diminished pulsatility, and an associated decrease in power consumption. If the LV preload is low enough, suction events—in which the LVAD inflow cannula directly contacts the opposing interventricular septum—may occur.

Late right ventricular failure

Even if LVAD patients tolerate device implantation without requiring RV mechanical support, they can occasionally develop late RV dysfunction. These individuals will often present with right heart failure symptoms, including hepatic congestion, ascites, peripheral edema, fatigue, and end-organ dysfunction. Progressive right heart failure can also lead to impaired LV filling, diminished LVAD flows, suction events, and electrical instability (generally in the form of ventricular arrhythmias).

LVAD thrombosis

Although LVAD pump thrombosis rates are markedly lower with the HeartMate III device (0% and 1.1% at 6 and 24 months after implantation, respectively) [7], thrombosis remains a clinically relevant phenomenon. This can lead to LVAD failure, hemolysis and its sequelae, cerebrovascular events, and even death. If a clot forms directly on the pump rotor, power consumption will increase and calculated flows will often rise (then ultimately decline with subsequent pump failure). As device malfunction ensues, invasive hemodynamics will reflect cardiac decompensation and a state of volume overload (Table 23.1).

Aortic valve insufficiency

In some patients, destruction and invagination of the aortic valve leaflets can result from chronic LVAD unloading. This aortic valvopathy may lead to progressive aortic regurgitation. The presence of progressive aortic insufficiency may be suggested by an LVAD interrogation that reveals escalating power, rising flows, and diminishing device pulsatility (Table 23.1).

Conclusions

Hemodynamic assessment will continue to be a pivotal tool for guiding appropriate patient selection, assisting with patient management, and monitoring for potential sequelae of LVAD therapy. Combining invasive hemodynamic data with LVAD interrogation and selected imaging studies can help ensure that patients continue to derive the greatest benefit possible from durable mechanical support.

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CHAPTER 24

Extracorporeal Life Support

Brian Kelley and Joseph S. Rossi

Extracorporeal life support (ECLS)—also described as extracorporeal membrane oxygenation (ECMO)—is an essential tool to rescue patients from cardiovascular collapse. There has been a dramatic increase in popularity within the cardiac catheterization lab over the last 10 years [1]. Although catheter-based, the techniques required for application of peripheral veno-arterial ECLS (VA-ECLS) are highly invasive with a significant risk of complications including bleeding, stroke, limb ischemia, and death. It is imperative that clinicians be familiar with not only the techniques and complications of ECLS but also the hemodynamic changes associated with cannulation and important parameters for safe weaning and decannulation. This chapter will review the desired hemodynamic benefits of ECLS and discuss the challenges that must be overcome to ensure appropriate end-organ perfusion and minimize the risk of ischemic complications.

Indications for veno-arterial extracorporeal life support (VA-ECLS)

VA-ECLS can be accomplished with different methods of cannulation (central versus peripheral), circuit components, and parameters (Figure 24.1). Unlike other temporary mechanical circulatory support devices, it provides full hemodynamic support as well as concomitant gas exchange. A simplified explanation of the circuit is that deoxygenated blood continuously is drained from the central venous system, exposed to gas exchange by way of a membrane oxygenator, and then returned to the systemic arterial circulation via an extracorporeal pump (Figure 24.2). Venovenous ECLS (VV-ECLS) is primarily used for acute lung injury to provide oxygenated blood back into the venous circulation and will not be described in detail in this review.

Main indications for VA-ECLS
Cardiogenic shock related to the following: ▪ Acute myocardial infarction (AMI) ▪ Acute decompensated heart failure ▪ Acute pulmonary embolism (PE)

Figure 24.3 Main indications for VA-ECLS.

Complications
Thrombosis
Bleeding/coagulopathy (including hemolysis)
Vascular injury
Lower limb ischemia
Pulmonary edema
Neurologic events (e.g., stroke)
Infection
Differential hypoxemia (North-South or Harlequin syndrome)

Figure 24.4 Complications associated with peripheral VA-ECLS (right).

Selection of patients for VA-ECLS cannulation

- a** AMI is a common indication for VA-ECLS support. Patients with acute ischemia can develop pump failure involving the left ventricle (LV), right ventricle (RV), or both ventricles causing refractory hypotension or arrhythmia. Typically, mechanical support should be considered early in the setting of refractory shock and is considered a temporary measure to safely facilitate high-risk percutaneous coronary intervention (PCI). A common protocol is described in the National Cardiogenic Shock Initiative [2]. VA-ECLS can provide support for both RV and LV failure and as can percutaneous RV and LV support. But while the latter can be provided quickly via insertion of axial-flow pumps, these devices are often inadequate for patients requiring more than 3.5 L/min of circulatory support. A note of caution is that patients with AMI can have other significant comorbidities that render VA-ECLS cannulation futile, and care should be taken to apply this therapy for patients where the provider anticipates a high likelihood of survival to recovery or another endpoint such as transplantation or LVAD surgery.

- b** Worsening CHF leading to cardiogenic shock can occur upon initial presentation or later during hospitalization among patients presenting with acute heart failure. Similar to AMI, presentation can be primarily LV or RV failure, or mixed etiology. Hemodynamic risk stratification with pulmonary artery (PA) catheterization is the standard of care to determine appropriate escalation of therapies. For patients with worsening CHF requiring VA-ECLS, careful consideration of definitive therapies is essential due to the low likelihood of meaningful recovery of native cardiac function. ECLS should only be considered when the likelihood of recovery is high (e.g., acute myocarditis, transplant rejection), or if the patient is deemed to be a good candidate for advanced heart failure therapies (i.e., transplantation and/or durable left ventricular assist device (LVAD)).
- c** Acute PE is becoming a more common indication for VA-ECLS cannulation. Unlike AMI and worsening CHF, acute PE almost always results in acute RV failure with relative sparing of the LV. Generally, preservation of LV function obviates the need for direct LV venting, and less hemodynamic support is typically required, especially when immediate relief of obstruction can be achieved with mechanical embolectomy. Unlike AMI and worsening CHF, almost all patients with massive PE recover to decannulation if appropriate relief of pulmonary vascular obstruction is achieved.

Cannulation technique

Among cardiology patients, the most common method of cannulation for VA-ECLS requires the placement of a central venous (drainage) cannula and an arterial (return) cannula placed in the common femoral artery (CFA) to return oxygenated blood to the systemic circulation. These catheters are connected to a centrifugal pump that circulates the blood and an oxygenator which comprise the VA-ECLS circuit. Cannulation for peripheral VA-ECLS is almost always performed urgently or emergently. When a patient is actively receiving CPR, the immediate need is to obtain femoral arterial and venous access efficiently, ideally using ultrasound guidance to ensure puncture in the CFA and common femoral vein (CFV) in order to use the most appropriate cannula sizes. Ultrasound guidance is essential to measure the diameter of the CFA and evaluate for atherosclerosis. Measurement of the vessel lumen ensures that the arterial cannula is not oversized, which is associated with an increased risk of vascular trauma and acute limb ischemia.

Although smaller cannulas are likely associated with a lower incidence of limb ischemia and vascular injury, larger cannulas provide a significantly greater amount of flow in the circuit. Factors to consider include not only catheter size and length but also blood viscosity, catheter material, and patient anatomy. The cross-sectional area of typical cannula sizes is shown in table 1. For adults, the standard venous cannula size is between 21 and 25F in diameter, while the arterial cannula is often between 17 and 21F (Figure 24.5). The venous cannula is typically inserted into a CFV and advanced to the superior cavoatrial junction. The

Cannulas	Size	Length	Insertion site	Tip location
Venous (drainage) cannula	21–25 F	50–55 cm	CFV	SVC/RA/LA
Arterial (return) cannula	17–21 F	15–25 cm	CFA	Common iliac/lower aorta
Distal reperfusion cannula (DRC)	5–8 F	11 cm	SFA	SFA

Figure 24.5 Standard cannula settings used for femoro-femoral peripheral VA-ECLS.

arterial cannula is inserted into either the ipsilateral or contralateral CFA with its tip positioned in the iliac artery or lower abdominal aorta.

Because of the size of the arterial catheter, most patients cannulated for peripheral VA-ECLS will require perfusion of the superficial femoral artery (SFA) via a sheath or catheter that is referred to as the “distal reperfusion cannula” (DRC). When cannulating during CPR, this DRC (typically a stiff braided sheath that is 5–6F in size) can be placed following initiation of the VA-ECLS circuit. For patients cannulated urgently with supported blood pressure and a few minutes to spare, it is ideal to place the DRC in the SFA antegrade first before flow is disrupted by cannulation.

When LV venting is indicated, one of the techniques utilized is transseptal puncture with direct insertion of the drainage cannula within the left atrium (LA), which allows for pulmonary decongestion and equalization of the LA and right atrial (RA) pressures. A relatively new technique referred to as left atrial-veno-arterial ECMO (LAVA ECMO) has been described, which involves placement of a 25F multi-fenestrated cannula that provides bi-atrial drainage [3]. Alternatively, LV venting can be accomplished with axial flow pumps, intra-aortic balloon pumps, or inotropic support.

Post-cannulation hemodynamics

VA-ECLS cannulation immediately increases mean arterial pressure (MAP), with a resultant decrease in stroke volume due to increased afterload. When the LV is failing, VA-ECLS will likely lead to increased LV wall tension and myocardial oxygen consumption, and this should be considered when deployed as a bridge to recovery. Patients with LV failure requiring VA-ECLS support are more likely to benefit from direct LV drainage (*venting*) using an Impella device to allow for decompression and additional support after decannulation. The following guidance can be considered for most patients after cannulation, regardless of the underlying etiology of cardiovascular collapse:

- a** MAP should be maintained >65 mm Hg to support urine output and end-organ perfusion. Overall, a MAP goal between 65 and 90 mm Hg is often recommended during VA-ECLS. Vasopressors can be utilized as needed to overcome vasoplegia following cannulation. It is also common to administer vasodilators (e.g., clevidipine, nitroprusside) to lower systemic vascular resistance in the setting of an elevated MAP.

- b** Central venous pressure (CVP) should be maintained >10 mm Hg to ensure adequate venous drainage. Lower CVP can result in decreased venous drainage due to catheter interaction with venous structures. This may manifest as visible shaking (“chatter” or “chugging”) of the tubing from variable venous drainage when the pump is trying to drain more than what the native venous return allows. Given that this venous “chatter” is commonly associated with low central venous volume, improvement is often achieved with the administration of intravenous fluids or blood transfusion.
- c** LV performance does not improve with VA-ECLS cannulation. Pressure-volume loops demonstrate a reduction in the LV stroke volume with increased LV afterload and wall tension (Figure 24.6). Although the increased MAP provided by VA-ECLS is favorable in these patients, it comes at the expense of detrimental hemodynamic effects on the LV such as increased left-sided filling pressures (Figure 24.7) as well as decreased arterial pulsatility (Figure 24.8). The subsequent elevation in afterload can result in progressive LV failure with inadequate opening of the aortic valve. This causes stasis within the left-sided cardiac chambers with the risk of thromboembolism, which can be detected on echocardiography (Figure 24.9). Ideally, appropriate afterload is maintained at a point that allows for aortic pulsation to be visible on invasive hemodynamic monitoring to ensure aortic valve opening and promote myocardial recovery (Figure 24.10).
- d** LV decompression (“venting” or “unloading”) can help mitigate LV strain and reduce the likelihood of acute LV and LA thrombus formation due to stasis. A key is to strike the right balance between LV depression and systemic perfusion

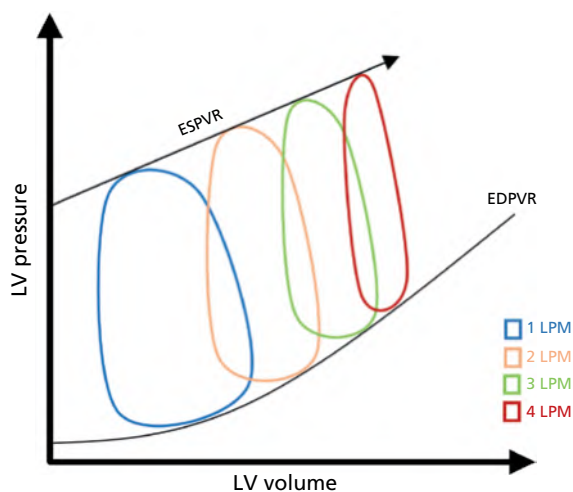


Figure 24.6 P-V loops at different ECMO flows. ESPVR = end-systolic pressure-volume relationship which represents the maximal pressure developed by the LV at a given volume. EDPVR = end-diastolic pressure-volume relationship and provides information about compliance of the heart.

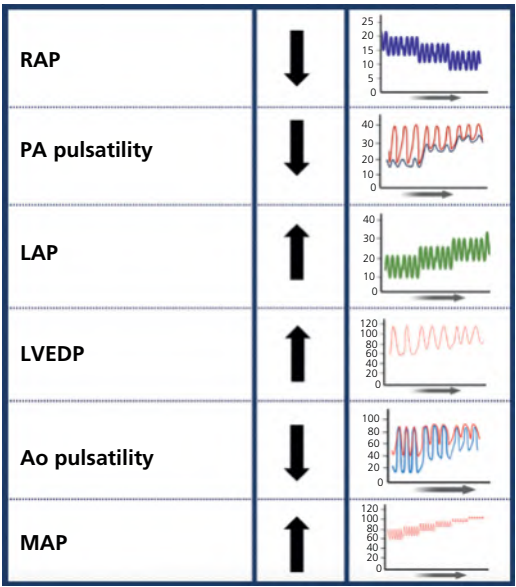


Figure 24.7 Hemodynamic effects of peripheral VA-ECLS. [Ao = aorta; LAP = left atrial pressure; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; PA = pulmonary artery; RAP = right atrial pressure]. Source: Adapted from [4].

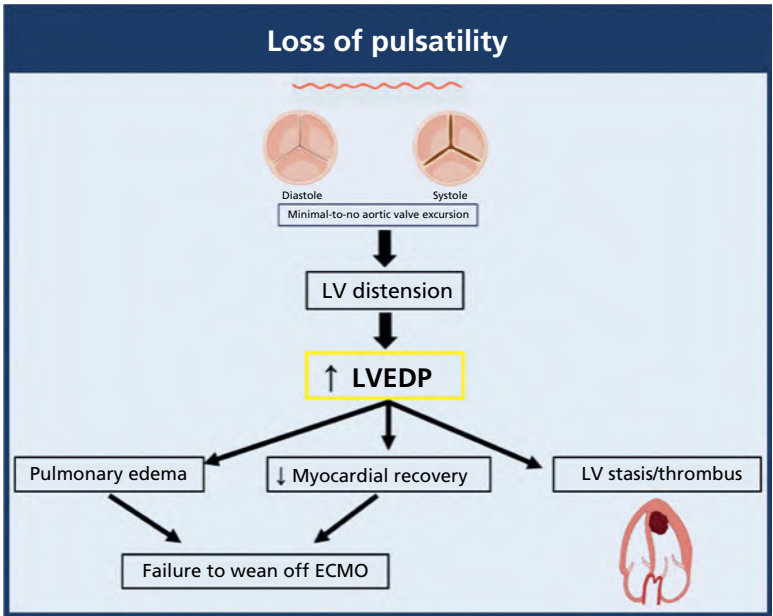


Figure 24.8 Lack of pulsatility and aortic valve opening lead to an increase in LVEDP which has several unfavorable consequences including pulmonary edema, lower likelihood of myocardial recovery, and stagnation of blood flow within the LV cavity.

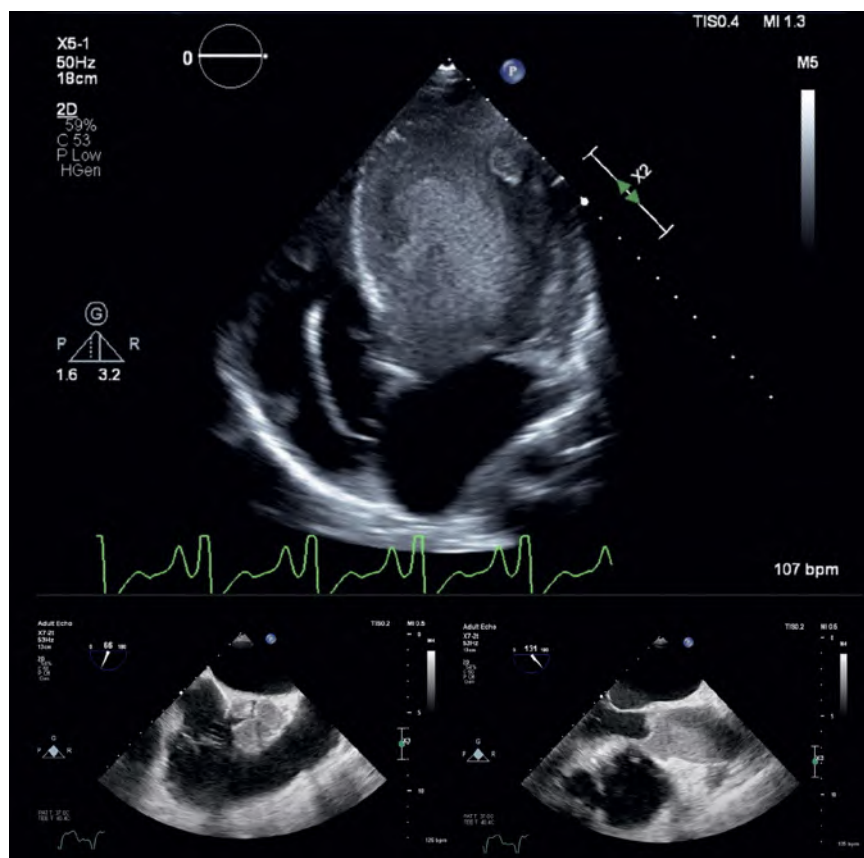


Figure 24.9 TTE demonstrating stasis, sludge, and thrombus within the LV cavity (top). TEE showing significant stasis and sludge in the aorta (bottom).

(Figure 24.11). Multiple strategies to decompress the LV during VA-ECLS have been described (Figure 24.12). Inotropic therapy to increase LV ejection is the simplest and least invasive solution. Placement of an LV Impella device in the presence of an ECLS circuit (*EC-Pella*) has been advocated as an immediate solution to reduce LV volume and stasis, although this required a separate large-bore arterial cannula and the associated risk of vascular complications [4]. However, a single arterial access technique has been described in which a Y-shaped prosthesis is anastomosed to the axillary artery for placement of both the Impella and the arterial cannula of the ECLS circuit [5]. Patients with acute RV failure typically have preserved LV ejection and invasive venting strategies can be deferred. Transesophageal echocardiography is a valuable tool to confirm appropriate LV decompression, rule out the presence of intracardiac thrombus, and monitor aortic valve motion in real time optimization of the ECMO circuit.

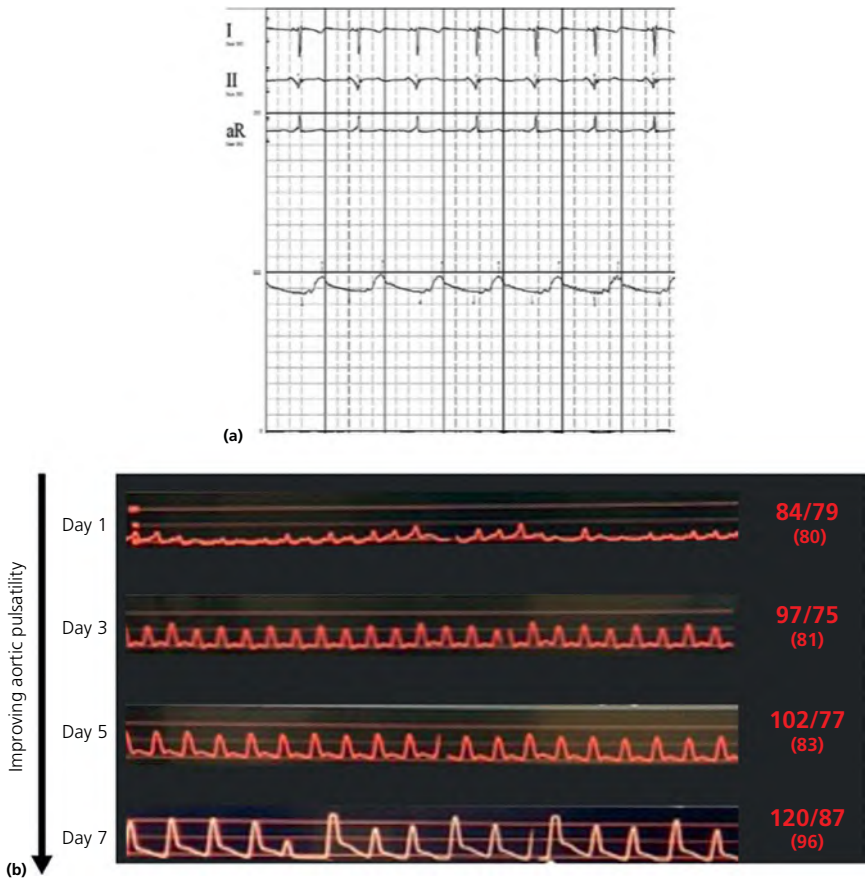


Figure 24.10 Cardiogenic shock patient placed on peripheral VA-ECLS with no pulsatility present on arterial waveform (a). Increasing pulsatility on the arterial waveform of a different patient as resolution of the cardiogenic shock occurs over 7 days (b).

- e Differential hypoxemia (also termed “North-South” or “Harlequin” syndrome) is a complication unique to peripheral VA-ECLS that occurs when lung pathology leads to poorly oxygenated blood reaching the systemic circulation. It is most often encountered when the native cardiac function recovers pulsatility, but pulmonary function remains inadequate. Antegrade (deoxygenated) perfusion from native cardiac function will typically mix with the retrograde (oxygenated) perfusion from the ECMO circuit somewhere along the aortic arch (sometimes referred to as a “mixing cloud” or the “watershed phenomenon”). This can usually be easily detected with pulse oximetry monitoring of the right upper extremity. If unable to be resolved with adjustments to flow of the circuit, then placement of an additional cannula into an internal jugular

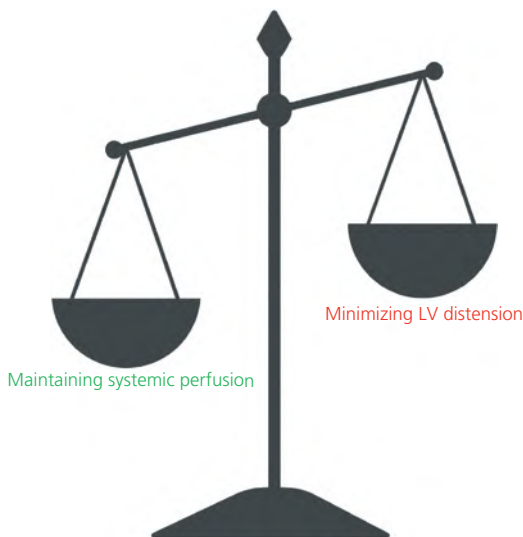


Figure 24.11 Striking a balance between maintaining systemic perfusion versus minimizing LV distension is key in ECLS management.

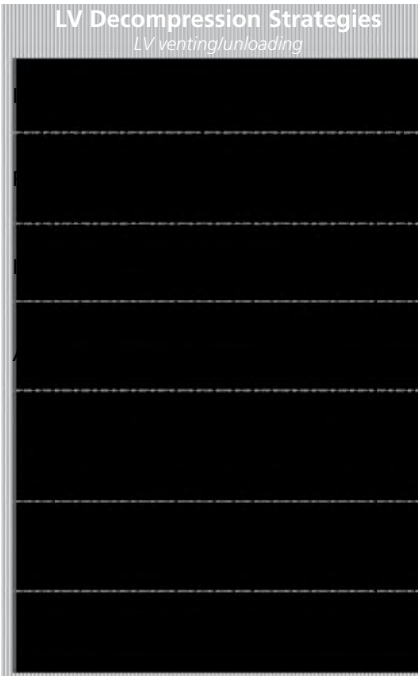


Figure 24.12 Techniques used to decompress (“vent” or “unload”) the LV in order to avoid the unfavorable consequences of LV distension. [IABP = intra-aortic balloon pump; PA = pulmonary artery]. Source: Adapted from [4].

vein may be considered in order to achieve a hybrid configuration referred to as veno-arterial-venous (VAV) ECLS.

- f** As mentioned previously, VA-ECLS provides full hemodynamic support with flow rates ranging between 3 and 7 L/min [6]. Flow is generated by the speed (measured in revolutions/minute [RPMs]) of the centrifugal pump. Target flow rate for adult patients placed on VA-ECLS is often recommended to be set between 60 and 80 mL/kg/min [7]. Extracorporeal gas exchange is achieved by an oxygenator (“membrane lung”) with a long microporous tube as well as a gas blender. The “sweep” gas flow rate (in L/min) determines the removal of carbon dioxide (CO₂), with a higher sweep rate leading to greater CO₂ clearance. The ECLS circuit has a fixed thickness and surface area, and the amount of gas exchange can therefore be precisely controlled by the ECLS technologist by simply controlling the flow through the oxygenator and pump. The pressure gradient between the patient’s blood flow and the sweep gas flow allows the ECLS circuit to control gas exchange [8].

Decannulation

Criteria for decannulation typically involve recovery of native cardiac output. Following AMI, this can occur anywhere from 3 to 14 days depending on the severity of initial injury. Recovery of native cardiac output can occur sooner for patients with rapidly treatable etiology of shock such as PE. Weaning strategies typically involve a daily weaning trial where ECLS support is decreased by 0.5 L/min every 15–20 minutes until achieving the lowest allowable flow to prevent pump thrombosis, generally accepted to be 1.5–2.0 L/min. It is important that patients remain on systemic heparin when considering a weaning trial in order to minimize the risk of pump thrombosis. Decannulation can be accomplished using percutaneous techniques although, depending on cannula size, underlying peripheral vascular disease, and patient body habitus, some providers will choose surgical decannulation with direct visualization and surgical closure. This technique can ensure vessel patency and avoid the need for emergency limb salvage surgery which can occur following percutaneous closure.

Summary

VA-ECLS is a life-saving therapy that can rescue patients from cardiovascular collapse by maintaining end-organ perfusion and gas exchange. Appropriate patient selection includes consideration of comorbidities and ability to recover from major hemodynamic insult associated with this highly invasive endovascular procedure. The hemodynamic benefits of VA-ECLS, appropriate hemodynamic monitoring, the need for LV venting, and criteria for decannulation vary from patient to patient.

Table 1 – Cross-sectional area of typically used arterial and venous catheters

French Size	Diameter (mm)	Area (mm ²)
6	2.00	3.14
7	2.33	4.28
8	2.67	5.59
9	3.00	7.07
10	3.33	8.73
11	3.67	10.56
12	4.00	12.57
13	4.33	14.75
14	4.67	17.10
15	5.00	19.63
16	5.33	22.34
17	5.67	25.22
18	6.00	28.27
19	6.33	31.50
20	6.67	34.91
21	7.00	38.48
22	7.33	42.24
23	7.67	46.16
24	8.00	50.27
25	8.33	54.54

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PART VI

Coronary hemodynamics

 **2025** Edition

CHAPTER 25

Basics of coronary blood flow

David P. McLaughlin, Samuel S. Wu and George A. Stouffer

[This is a modification of a chapter written by David P. McLaughlin, Samuel S. Wu and George A. Stouffer]

The coronary arteries are the first vessels to branch off the aorta and through them, the heart receives about 5% of the cardiac output when the body is at rest, or 250 mL/min.

The heart has the highest oxygen (O_2) consumption per tissue mass of all human organs. Under basal conditions, myocardium extracts approximately 75–80% of delivered O_2 with the myocardium having a basal metabolic requirement that is approximately 15–20 times that of resting skeletal muscle and approximately equal to that of skeletal muscle under severe acidotic conditions. The heart has the highest arterial–venous O_2 difference of any major organ (10–13 mL/100 mL) and the O_2 saturation in the coronary sinus is one of the lowest in the body (Figure 25.1).

Determinants of myocardial O_2 demands include preload, afterload, heart rate, contractility, and basal metabolic rate. Other than basal metabolic rate, these are factors that influence stroke volume. Systolic wall tension uses approximately 30% of myocardial O_2 demand. Wall tension itself is affected by intra-ventricular pressure, afterload, end-diastolic volume, and myocardial wall thickness.

Because there is little room for increased O_2 extraction and the heart has minimal capacity for anaerobic metabolism, increased metabolic demands of the heart are met primarily via increases in coronary blood flow, or stated in other words, flow is tightly coupled to O_2 demand. In the absence of obstructive epicardial coronary artery disease, coronary blood flow is primarily controlled by changes in resistance in the microvasculature (prearterioles, arterioles and capillaries). Resistance within the microvessels plays an important role in myocardial perfusion in general and in regional and transmural distribution.

Camici and Crea describe a three-compartment system in the coronary circulation [1]. The proximal compartment includes the large epicardial coronary arteries, which offer little resistance to coronary blood flow in the absence of

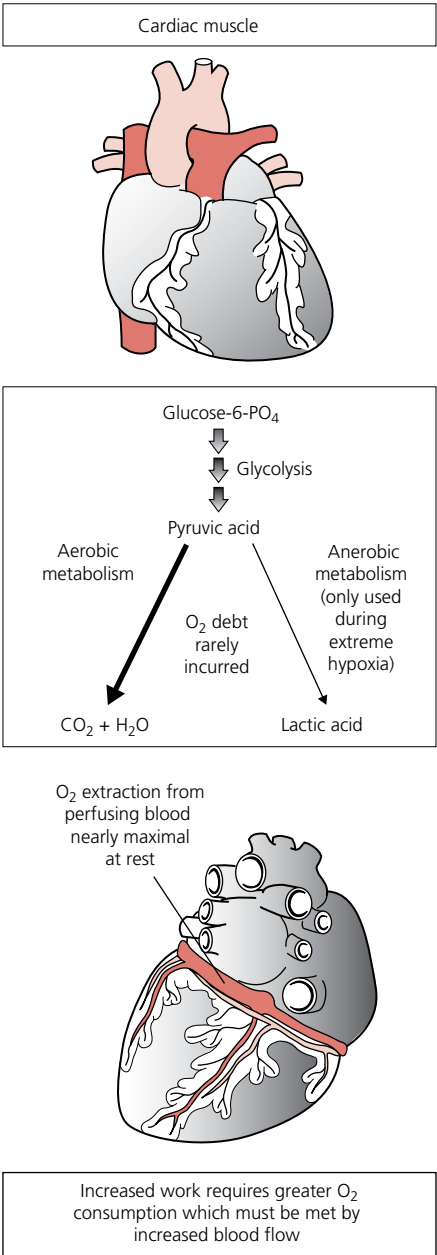


Figure 25.1 Oxygen (O₂) extraction in cardiac muscle.

obstructive disease. The intermediate compartment includes prearterioles, which offer some resistance to flow resulting in a measurable pressure drop along their length. The specific function of the prearterioles is to maintain pressure at the origin of arterioles within a narrow range despite changes in perfusion pressure or flow (important in autoregulation). The more distal compartment includes intramural arterioles and capillaries and is associated with a considerable drop in pressure. The function of the distal compartment is to match myocardial blood supply and O_2 consumption.

For the purpose of understanding clinical applications of physiologic testing of coronary blood flow, the intermediate and distal compartments can be lumped together and labelled as the microvasculature, creating a two-component model. Normal epicardial coronary arteries provide little if any resistance to myocardial blood flow even at maximal flow and are commonly referred to as conductance vessels. In contrast, the microcirculation provides the majority of resistance to flow under normal resting conditions. Microvascular dysfunction will be discussed in Chapter 27.

Five important principles of coronary physiology

- 1 Myocardial cell contraction and relaxation are aerobic, O_2 -requiring processes.
- 2 O_2 extraction in the coronary bed is near maximal in the baseline state (75–80% in the heart versus 30–40% in skeletal muscle). Therefore, to increase O_2 delivery, flow must increase.
- 3 In the normal heart, the major resistance to coronary flow occurs in the microvasculature (prearterioles, arterioles, and capillaries). There is little resistance to flow in the epicardial arteries visible on coronary angiography.
- 4 The primary mechanism to increase coronary flow is via a decrease in microvascular resistance (primarily regulated by metabolic demands).
- 5 The presence of hemodynamically significant epicardial disease leads to a decrease in microvasculature resistance at baseline so that coronary blood flow is maintained. This limits the ability of the microvasculature to increase myocardial blood flow in response to increased demand.

Regulation of coronary blood flow

Coronary blood flow is primarily controlled by release of local metabolites such as adenosine or nitric oxide. Hypoxia is a more potent coronary vasodilator than either hypercapnia or acidosis. Neural influences on coronary blood flow are relatively minor. Sympathetic activation of the heart can result in transient vasoconstriction, followed by coronary vasodilation due to increased metabolic activity. Parasympathetic stimulation of the heart directly stimulates coronary vasodilation, but this effect is modest.

Coronary blood flow is unique in that it primarily occurs during diastole because of systolic compression of myocardial arterioles and capillaries by the contracting

myocardium. Systolic compressional forces are much greater in the subendocardial layers than in the epicardial arteries. Flow in the left coronary artery has a greater diastolic predominance than the right coronary artery because the compressive forces of the right ventricle (underlying a portion of the right coronary artery) are less than those of the left ventricle. At least 85% of coronary flow in the left anterior descending occurs in diastole, whereas the right coronary artery blood flow is more or less equal in systole and diastole. The predominance of flow during diastole exacerbates myocardial ischemia during tachycardia. With increased heart rates, O_2 supply is reduced (because diastole is shortened) while demand increases.

It was observed many years ago that coronary flow is largely independent of arterial pressure at constant O_2 consumption, referred to as coronary autoregulation. Autoregulation maintains consistent coronary flow over a range of perfusion pressures from 60 to 150 mm Hg (Figure 25.2), although there is evidence that autoregulation is exhausted at higher pressures in patients with left ventricular hypertrophy [2]. In the setting of maximum vasodilation of coronary resistance vessels, coronary blood flow is no longer autoregulated and varies linearly with

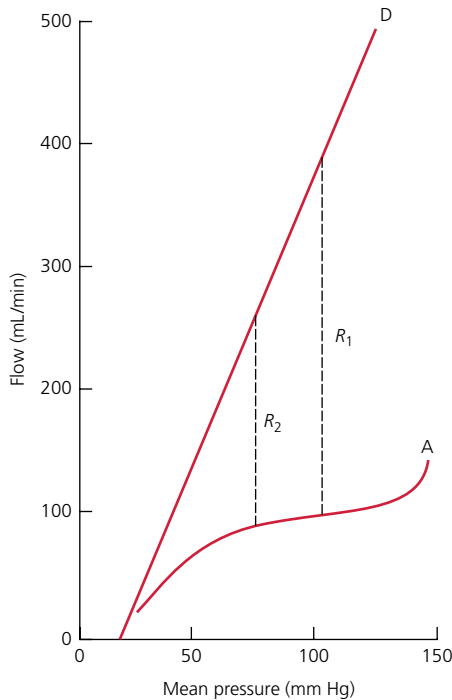


Figure 25.2 Coronary autoregulation. Note that flow is maintained at a relatively constant level despite significant changes in mean arterial pressure via autoregulatory mechanisms in the normal heart (A) whereas the relationship between pressure and flow is much steeper during maximal vasodilatation (D). Source: Polese et al. [2]. Reproduced with permission of Wolters Kluwer.

perfusion pressure. One example of an autoregulatory mechanism is the Bayliss phenomenon in which increased perfusion pressure causes reflex vasoconstriction. The ability of autoregulation to maintain flow when perfusion pressures are decreased is especially important in the presence of epicardial coronary stenoses.

The garden hose analogy

One way to understand coronary blood flow is to think of the coronary circulation as a garden hose with a nozzle on the end (Figure 25.3). Under regular conditions, the nozzle is used to adjust flow through the hose, opening further when more flow is needed and partially closing when less flow is needed. If someone is stepping on the hose, the nozzle loses some of its ability to regulate flow. The nozzle has to be opened further to maintain basal flow and the maximal flow that can be obtained when the nozzle is wide open is reduced. In the presence of a severe obstruction in the garden hose, it becomes difficult to maintain basal flow and there is no way to increase flow as the nozzle is already wide open. The more resistance to flow from the person stepping on the hose, the less control you have at the nozzle. The impact of someone stepping on a garden hose is similar to the presence of a stenosis in an epicardial coronary artery.

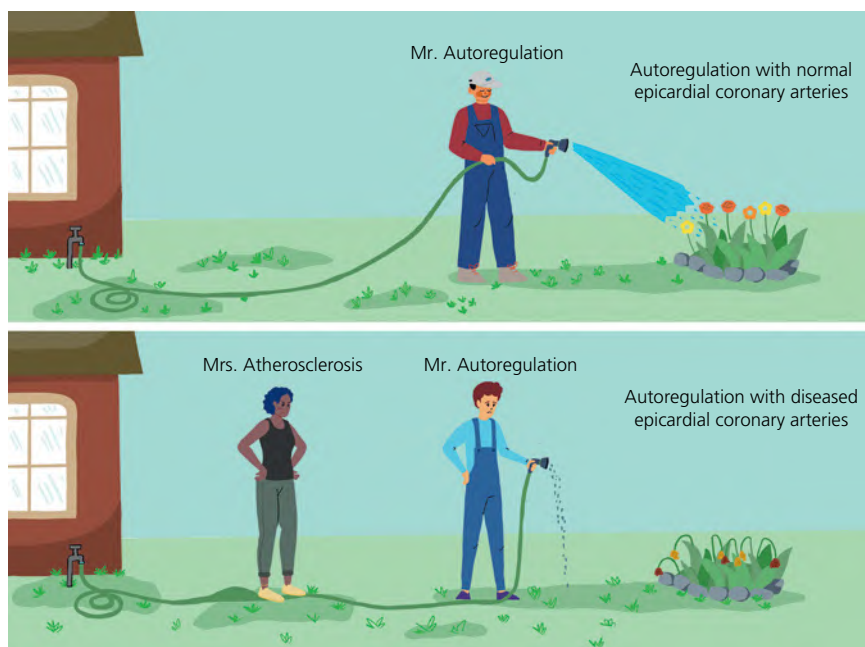


Figure 25.3 The effect of epicardial atherosclerosis on myocardial autoregulation.

Source: Courtesy of Nikki Wong.

Coronary flow reserve

Coronary blood flow can increase two- to fivefold in the normal heart with the ratio of maximal coronary flow to resting coronary blood flow being labelled as the coronary flow reserve (CFR; Figure 25.4). The range of CFRs found in humans will vary depending on the patient population and the method used to determine CFR. In one study of adult patients with angiographically normal vessels and coronary artery disease risk factors that utilized an intracoronary Doppler wire and adenosine, coronary blood flow increased by 2.7 ± 0.6 times with maximal coronary vasodilation [3]. A study of 20 endurance athletes and 19 controls using transthoracic doppler of left anterior descending flow found $\text{CFR} = 5.9 \pm 1.0$ vs 3.7 ± 0.7 , respectively [4].

Maximal coronary blood flow can be achieved experimentally using any one of three different mechanisms. First, reactive hyperemic flow is coronary flow that occurs following a transient period of flow cessation. Metabolites of ischemia accumulate during interruption of flow and cause vasodilation of the microcirculation. When flow is re-established, the resistance of the microcirculation is markedly diminished and coronary blood flow increases. Second, maximal coronary blood flow can be achieved using exercise or another physiologic stimulus to increase flow. Lastly, maximal coronary flow can be achieved by intracoronary administration of potent microcirculation vasodilators such as adenosine, papaverine, nicorandil, or nitroglycerin.

The physiologic principle underlying the clinical use of CFR is that significant atherosclerosis will impair coronary blood flow responses during hyperemic stresses. As atherosclerosis progresses, maximal coronary blood flow is initially reduced, followed in the severe stages by a reduction in resting coronary blood flow. CFR, the ratio of maximal blood flow to basal blood flow, will decrease with

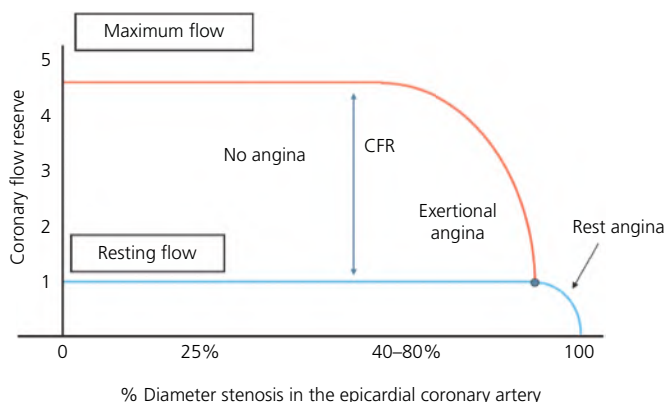


Figure 25.4 Schematic of coronary flow under basal conditions and with hyperemic stimuli. [CFR = coronary flow reserve.]

progressive obstruction of the lumen of an epicardial coronary artery by atherosclerosis. The diagnostic and prognostic ability of CFR has been evaluated in hundreds of studies and a meta-analysis found that an abnormal CFR conferred a 3.7 times increased risk of death and a 3.4 times increased risk of major adverse cardiovascular events [5].

Although CFR has great theoretical potential, several limitations have to be kept in mind. First, conditions other than atherosclerosis can affect CFR. These include factors that raise basal coronary blood flow (e.g., fever, hypoxia, tachycardia, anemia, or ventricular hypertrophy) and factors that impair vasodilatory responses of the microvasculature (e.g., ventricular hypertrophy or diabetes mellitus). Second, there is a lack of consensus on what value of CFR is consistent with a hemodynamically significant lesion. In various clinical studies, CFR cutoff values between 1.6 and 2.5 were used to determine ischemia-causing lesions [6]. Third, there is a discrepancy between CFR as derived by Doppler wire and CFR derived by thermodilution. In an international multicenter study of 250 arteries in 149 patients, CFR calculated by thermodilution was greater than Doppler-derived CFR (mean 2.59 ± 1.46 vs 2.05 ± 0.89 ; $P < 0.0001$) and there was only a modest correlation between the two techniques ($r^2 = 0.36$) [7].

Since CFR cannot discriminate between epicardial lesions and microvascular dysfunction, the concept of “relative CFR” (rCFR) was developed. This approach requires that CFR be measured in a coronary artery without epicardial disease in order to interpret the value of CFR in an artery with epicardial disease. If CFR is abnormal in the artery without disease, this result implies an impaired microvasculature. The use of rCFR has several caveats, including the requirement for a vessel without significant epicardial disease and the assumption that microvasculature function is consistent across different vascular beds (an obvious problem in the case of prior myocardial infarction).

Clinical measurement of coronary blood flow in the cardiac catheterization laboratory

Clinically, adenosine is commonly used to induce hyperemia, since it causes less hemodynamic and ECG changes than papaverine [8]. But no matter how maximal coronary flow is elicited, CFR is calculated as the ratio of maximal coronary flow to resting coronary blood flow (Figure 25.4).

In the cardiac catheterization laboratory, CFR is measured either with a 0.014-inch guidewire with a 12 MHz piezoelectric transducer mounted on its tip (Doppler wire; Figure 25.5) or by a thermodilution method. When using the Doppler wire, it is important to remember that accurate measurements are dependent on correct positioning of the Doppler flow wire. The transducer should be pointing away from the vessel wall and into the flow stream to avoid vessel wall artifacts. Gray scale signal amplitude and peak velocity can be used as indicators of proper positioning.

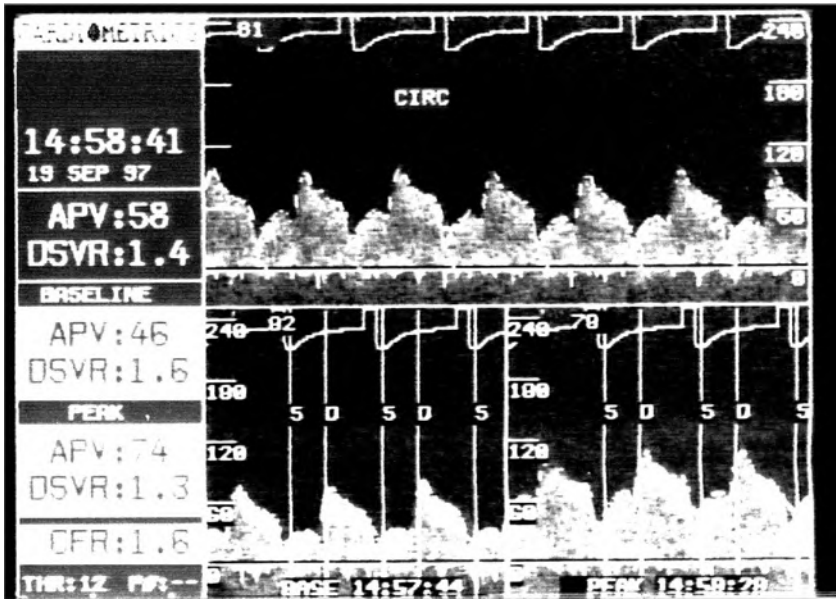


Figure 25.5 Measurement of CFR in the left circumflex with a Doppler FloWire following the administration of adenosine. The top window represents a real-time measurement of coronary velocity. The bottom left window is a “baseline” measurement and the bottom right window is velocity as measured after administration of adenosine. [APV = time-averaged distal peak velocity; CFR = coronary flow reserve; D = diastole; DSVR = diastolic/systolic flow-velocity ratio; S = systole.]

Currently, the two primary thermodilution methods used clinically employ either a bolus injection or continuous infusion of room-temperature saline into a coronary artery. For bolus injections, coronary blood flow is estimated based on transit time of a bolus of room temperature saline between two thermistors on a 0.014 inch interventional guidewire (thermodilution wire). It is assumed that there are minimal changes in coronary diameter (and area), thus enabling velocity to be used in place of flow (flow = velocity $\times$ area). Transit time is measured under basal conditions and then the patient is given a hyperemic stimulus and transit time is remeasured. Estimation of coronary flow under basal and hyperemic conditions enables the calculation of CFR.

This approach requires the use of a coronary wire (PressureWire XTM, Abbott Vascular, Santa Clara, CA, United States) with three sensors (proximal temperature, distal pressure, and distal temperature). Coronary flow is estimated by intra-coronary injections of room-temperature saline under basal conditions and during administration of intravenous adenosine. The mean transit time (Tmn) is the time needed for the saline bolus to travel from the tip of the guiding catheter to the distal temperature sensor of the pressure wire and CFR is equal to the resting Tmn divided by the hyperemic Tmn.

Recently, investigators have begun using a continuous thermodilution method to measure coronary flow [9]. This method involves placing the tip of a special guidewire in the distal part of the coronary artery. A monorail infusion catheter is advanced over the guide wire and its tip is placed in the proximal portion of the coronary artery. Room-temperature saline infusion is infused at a rate of 15–25 mL/min with steady-state maximum hyperemia induced by the saline infusion itself within 10–20 seconds. After steady-state is reached, the distal temperature (T) can be recorded by the guidewire. Then the temperature sensor is pulled back to the tip of the infusion catheter, and infusion temperature is measured. Coronary flow is calculated by a computer algorithm.

Pressure wire and fractional flow reserve

Pressure changes are used as surrogates for coronary flow changes when measuring fractional flow reserve (FFR). The development of a pressure transducer mounted on an angioplasty guidewire allows measurement of the pressure distal to a coronary stenosis (Figure 25.6). The concept of using pressure gradient as a

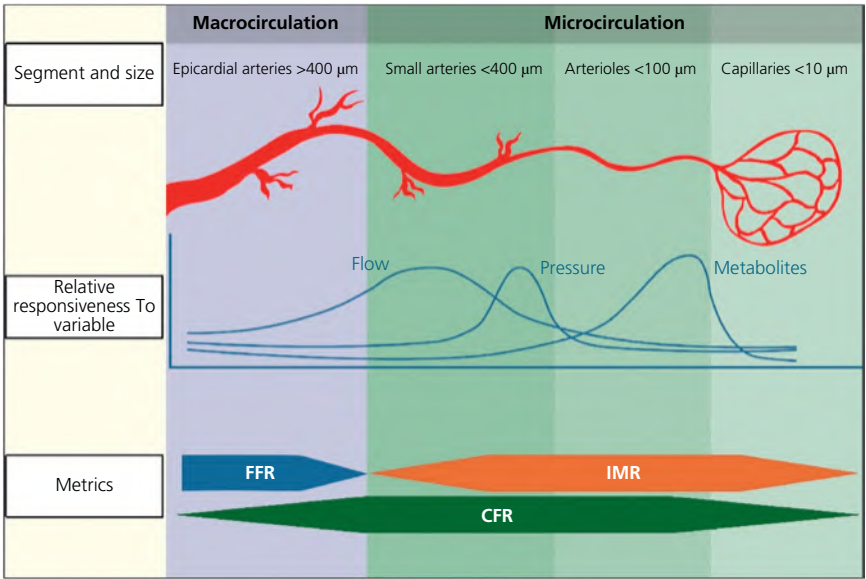


Figure 25.6 Use of CFR, FFR and index of microvascular resistance (IMR) in assessing patients with chest pain. Source: From reference [10] / MDPI / CC-BY-4.0. IMR is the most widely used measurement of microvascular function and is equal to the pressure difference across the microvasculature (ΔP) divided by the flow rate (Q): $R = \Delta P/Q$. ΔP is estimated using the pressure measured by a wire in the distal portion of the coronary artery and Q represents coronary flow as measured by thermodilution.

technique to assess stenosis severity has existed since the early days of endovascular intervention. It is of historical interest that the original description of percutaneous transluminal coronary angioplasty (PTCA) reported a decrease in translesional pressure gradients from 58 to 19 mm Hg in the 32 patients in whom PTCA was successful [11]. Early attempts to measure pressures distal to stenosis were hampered by the use of fluid-filled tubes, which, because of their size, increased the translesional gradient. The advent of a pressure transducer mounted on a 0.014-inch angioplasty wire overcame these difficulties and enabled the introduction of the concept of pressure-derived FFR [12, 13].

The concept of pressure as a surrogate for flow is based on Ohm's law:

$$\text{Flow} = \frac{\text{Pressure}}{\text{Resistance}}$$

FFR is defined as maximum myocardial blood flow in the presence of a stenosis divided by the theoretical maximum flow in a normal vessel (i.e., the absence of any stenosis). Under maximum arteriolar vasodilatation, the resistance imposed by the normal myocardial bed is minimal and blood flow is proportional to driving pressure. Thus, FFR represents that fraction of normal maximum flow that is achievable in the presence of epicardial coronary stenosis. Since myocardial ischemia occurs in a patient when maximum blood flow is insufficient to meet myocardial demands, FFR aims to measure perfusion pressure during maximum coronary flow to establish the physiologic significance of a stenosis. FFR is independent of changes in systemic blood pressure, heart rate, or myocardial contractility.

A full description of the theoretical basis of FFR and its clinical utility is included in Chapter 26.

Definitions of coronary hemodynamic measurements used clinically

- **Coronary flow reserve (CFR)**—Ratio of maximal coronary flow to basal coronary flow.
- **Relative coronary flow reserve (rCFR)**—Used to minimize the influence of microvasculature on assessment of the hemodynamic severity of an epicardial stenosis. It is the ratio of CFR in the diseased vessel to CFR in a "normal" vessel ($\text{rCFR} = \text{CFR}_{\text{target}} / \text{CFR}_{\text{reference}}$).
- **Fractional flow reserve (FFR)**—Maximum myocardial blood flow in the presence of a stenosis divided by the theoretical maximum flow in the absence of the stenosis.

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CHAPTER 26

Fractional flow reserve

Paul M. Johnson, Shriti Mehta, Prashant Kaul and George A. Stouffer

[Original chapter by: Paul M. Johnson, Shriti Mehta, Prashant Kaul, and George A. Stouffer]

Concept of fractional flow reserve

The ability to accurately assess the physiologic significance of coronary stenosis in clinical practice is critical. Lesions that are responsible for inducible ischemia are associated with worse outcomes, and those patients may benefit from revascularization, either by percutaneous intervention (PCI) or coronary artery bypass grafting (CABG). For clinicians in the cardiac catheterization laboratory, it is difficult to determine by angiography alone if an intermediate coronary lesion (40–70% stenotic by angiography) is responsible for ischemic symptoms. On the other hand, lesions that do not produce inducible ischemia are associated with a favorable prognosis and medical treatment alone is reasonable.

Due to the practical limitations of the Doppler wire and other methods to calculate coronary flow reserve (CFR; Chapter 25), the use of a pressure transducer to measure pressure-derived fractional flow reserve (FFR) has gained wide acceptance as a clinically useful tool to assess the hemodynamic significance of coronary stenosis. Early efforts to measure pressure gradients across stenosis with small fluid-filled catheters were limited because the catheters were large enough to artifactually increase the translesional gradient in diseased arteries. The development of a pressure transducer mounted on a 0.014-inch coronary guidewire overcame this limitation and made measurement of the pressure gradient across a coronary lesion efficient and safe. Current technology measures pressure differences using either piezoelectrical or optical sensors on the wire.

The basic principle of FFR is that when resistance is constant, changes in pressure are proportional to changes in flow. Since pressure is easier to measure

than flow, FFR has replaced CFR for clinical use. Ohm's Law, which describes the relationship between pressure, flow, and resistance, forms the hemodynamic basis for FFR:

Ohm's Law

$$\text{Flow} = \frac{\text{Pressure difference}}{\text{Resistance}}$$

As described in Chapter 25, the heart has the ability to maintain adequate coronary blood flow across a range of perfusion pressures because of the autoregulatory system. The resistance of the myocardial microcirculation is regulated to vary coronary blood flow based on the oxygen demand of the myocardium. FFR is measured when microvasculature resistance is at a minimum and coronary flow is at a maximum, which enables determination of maximal pressure loss across a stenosis in an epicardial coronary artery (Figure 26.1). FFR is defined as the maximum myocardial blood flow in the presence of a stenosis divided by the theoretical maximum myocardial blood flow in a normal coronary vessel (i.e., in the absence of a stenosis). Thus, it represents the fraction of normal coronary blood flow that is achievable in the presence of epicardial coronary stenosis. This index is generally independent of heart rate, systemic blood pressure, or myocardial contractility [1].

FFR can be represented in the following equation:

$$\text{FFR} = \frac{(P_d - P_v) / R_{\min}}{(P_a - P_v) / R_{\min}}$$

where:

P_a = mean aortic pressure as measured by the guide catheter

P_d = mean pressure in the coronary artery as measured by the pressure-wire distal to the stenosis

P_v = mean central venous pressure

$R_{\min}$ = minimum resistance to blood flow in the microvasculature

At maximal hyperemia, resistance of the microvasculature is minimal, $R_{\min}$, and can thus be removed from the equation:

$$\text{FFR} = \frac{(P_d - P_v)}{(P_a - P_v)}$$

Furthermore, if the venous pressure is assumed to be minimal compared to the arterial pressure, it can be removed from the equation:

$$\text{FFR} = \frac{P_d}{P_a}$$

Thus, in practical terms, FFR is obtained by simultaneously measuring the mean aortic pressure (from the distal tip of a coronary guide catheter) and intracoronary

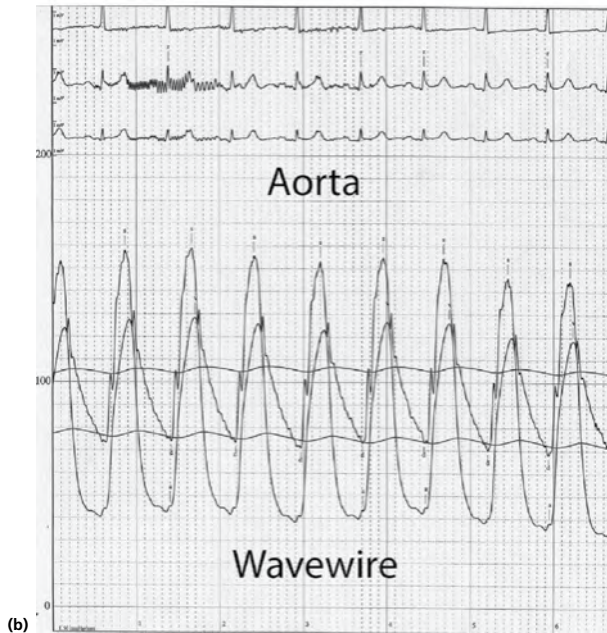
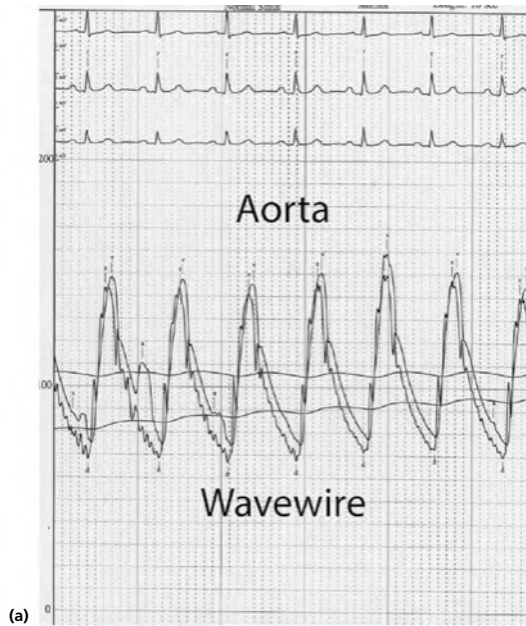


Figure 26.1 Measurement of Pd/Pa and FFR. Simultaneous measurement of pressure in aorta and distal left anterior descending (LAD) coronary artery (labelled pressure wire) at rest (a) and following intracoronary administration of adenosine (b) in a 63-year-old male with chest pain and an intermediate lesion on angiography. Under basal conditions, there is a 7 mm Hg difference in mean pressures between the distal LAD coronary artery (measured with the pressure wire) and the aorta (measured with the guide catheter) and the Pd/Pa was 0.94. Following administration of 60 μ g of adenosine, distal perfusion pressure decreased, the difference in mean pressures increased, and FFR was measured at 0.58.

pressure distal to a stenosis (from the pressure transducer of the guidewire distal to a lesion) at maximal hyperemia. Various vasodilators can be used to induce maximal hyperemia, including adenosine, nitroglycerin, regadenoson, or papaverine. Adenosine, which is safe and effective at producing maximal hyperemia, is the most frequently used vasodilator in clinical practice. It can be administered either by intracoronary bolus or intravenously, with most clinical studies requiring the IV route to ensure that a steady state of hyperemia is achieved.

Some investigators advocate using contrast FFR (cFFR), which is defined as the lowest Pd/Pa after injection of contrast. Studies have shown that a cFFR of 0.83 correlates well with an adenosine-induced FFR of 0.80 [2].

A description of some clinical scenarios (see also Figure 26.2) illustrates the relationship between FFR and coronary flow:

- A 70% stenosis in a large artery is more likely to be hemodynamically significant than a 90% stenosis in a small artery.
- Given the same degree of stenosis, flow will be decreased and FFR will be increased in an area of the heart following myocardial infarction (MI).
- The presence of collaterals supplied by a stenosed artery will result in a decrease in FFR because of the increased flow through the stenosis to supply the collaterals.

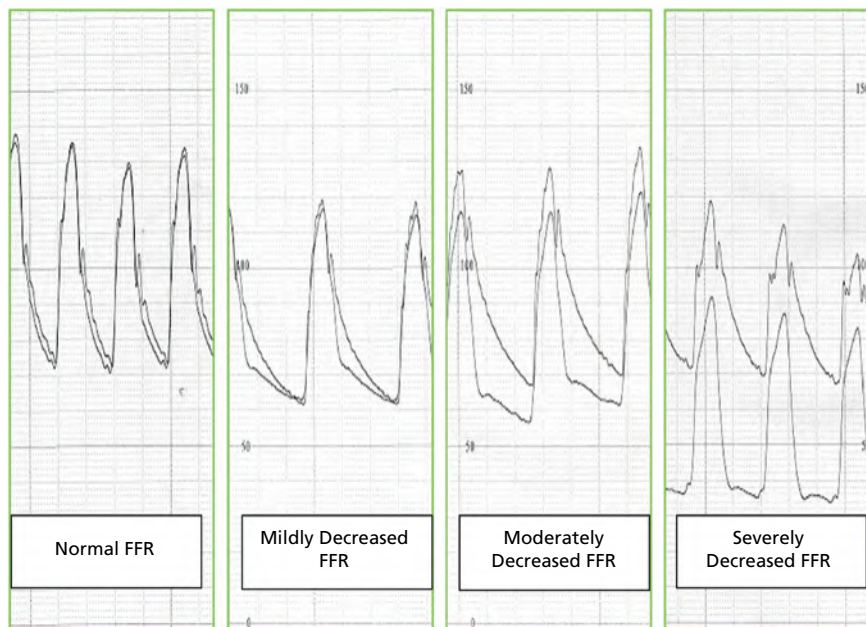


Figure 26.2 Examples of FFR measurements in four patients with coronary disease of different hemodynamic severity. Simultaneous pressure recordings, following intracoronary administration of adenosine, from the aorta and distal coronary artery in four different patients showing normal FFR and mildly, moderately, and severely decreased FFR.

It is important to remember that several assumptions have to be made to enable the use of pressure data as a surrogate for coronary flow.

While in the vast majority of cases, the assumptions underlying the calculation of FFR don't affect clinical decision making, there are scenarios where it is important to understand the impact of these assumptions.

RA pressure is unimportant

RA pressure (P_{RA}) is considered to have little impact if it is within normal range, so it is neglected in the formula. To test this assumption, Toth et al. evaluated 1676 stenoses in 1235 patients undergoing left and right heart catheterization for ischemic (52%) or valvular heart disease (48%) [3]. The median RA pressure (P_{RA}) was 7 [IQR: 5–10] mm Hg. FFR values calculated using the standard formula ($FFR = P_D/P_A$) were compared to FFR values calculated using RA pressure ($FFR_{RA} = P_D - P_{RA}/P_A - P_{RA}$). There was a good correlation between FFR and FFR_{RA} ($R^2 = 0.987$). The median FFR was slightly higher than the median FFR_{RA} (0.85 [IQR: 0.78–0.91] vs. 0.83 [IQR: 0.76–0.90]; $p < 0.001$) with a median difference of 0.01 [IQR: 0.01–0.02]. Values of FFR above the cutoff of 0.80 were associated with an $FFR_{RA} \leq 0.80$ in 110 (9%) stenoses.

Hypotension is unimportant

FFR is generally independent of systemic blood pressure and heart rate [1] but there are studies suggesting that extremes of blood pressure do influence FFR measurements. Theoretically, hypotension could have an effect as the pressure-flow relationship during maximal vasodilation is curvilinear at low pressures implying an increase in the hyperemic microvascular resistance at low perfusion pressures.

Verdier-Watts *et al.* [4] enrolled 12 patients with stable angina with a mean arterial blood pressure of 70 mm Hg and an average coronary lesion severity of $58 \pm 21\%$. FFR measured under baseline conditions (0.81 ± 0.11) was significantly higher than FFR measured during infusion of phenylephrine (mean arterial pressure of 101 mm Hg; $FFR = 0.75 \pm 0.12$).

In contrast, de Bruyne *et al.* found no effect on FFR of nitroprusside infusion in 10 stenoses. Systolic blood pressure decreased from 136 ± 12 mm Hg to 100 ± 9 mm Hg during nitroprusside infusion and resulted in a reflex tachycardia. Resting and hyperemic distal coronary pressures were significantly lower during nitroprusside infusion but FFR was unchanged [1].

Hydrostatic pressure gradient is unimportant

When FFR is measured, there is the assumption that both distal and proximal pressures are measured at the same height. But in a patient lying on their back, the left anterior descending (LAD) coronary artery is generally higher than the right coronary artery (RCA) or circumflex. Since the FFR wire is normalized in the left main or proximal RCA, it may not account for the effect of the hydrostatic

pressure created by the height difference between the distal position of the pressure wire sensor and the coronary ostium. This can lead to pressures in the distal LAD being lower (and thus FFR being lower), on average, than pressures in the distal RCA or distal circumflex [5].

Härle *et al.* [6], in their study utilizing coronary CT angiography, found that the distal LAD and the distal right posterior descending artery (rPDA) were at the highest point, and the distal circumflex and distal right posterolateral branch (rPL) at the lowest point, in patients in a supine position. They estimated that with a mean arterial pressure of 100 mm Hg, “normal” FFR would be 0.96, 0.97, 1.03, and 1.02 in LAD, RPDA, circumflex, and rPL, respectively. Thus, in the normal clinical scenario, a decrease in FFR of 0.16 would be indicative of ischemia in the LAD ($0.96 - 0.16 = 0.80$) but not in the circumflex ($1.03 - 0.16 = 0.87$).

Heart rate is unimportant

As the HR increases, the ratio of time in systole to time in diastole increases. Thus, the FFR index, calculated as the mean Pd/Pa over the whole cardiac cycle, might be biased by an elevated HR. No clinical study however has convincingly shown that heart rate affects FFR [1].

Key clinical studies of FFR

Initial studies were done to determine the appropriate threshold of FFR for identifying patients who would benefit from revascularization compared FFR to non-invasive stress testing. Pijls *et al.* performed bicycle stress testing, thallium scintigraphy, and stress echocardiography in 45 consecutive patients with chest pain and moderate coronary stenosis. In the 21 patients with $\text{FFR} < 0.75$, all had at least one stress test with a positive result [7]. Using a cutoff of 0.75 for FFR produced a sensitivity of 88%, specificity of 100%, and accuracy of 93% in this population. Furthermore, after revascularization of patients with $\text{FFR} < 0.75$, all of the positive stress test results reverted to normal. Subsequent studies (most noticeably the FAME studies) modified the FFR threshold to 0.80, which is used in clinical practice today. It is important to mention however that studies suggest that FFR has a continuous and independent relationship with clinical outcomes rather than a defined threshold value [8].

There are many clinical scenarios in which measurement of FFR has been shown to be clinically useful. Some of the most important studies are summarized here:

- 1 *Use of FFR to guide PCI in patients with multivessel coronary artery disease (CAD).* Use of FFR, compared to angiography, to determine lesions needing revascularization in patients with multivessel CAD reduced major adverse cardiovascular events in the FAME I trial. In this study, 1005 patients with multivessel CAD were randomized to undergo PCI guided by angiography or by FFR. Patients in the angiography group received drug-eluting stents in all angiographically

significant lesions, whereas those in the FFR group received stents only if FFR was ≤ 0.80 . The event rate at one year for the combined primary end-point of death, nonfatal MI, and repeat revascularization was 18.3% in the angiography group versus 13.2% in the FFR-guided group ($p = 0.02$). There was also a significant reduction in the number of stents placed in the FFR group [9].

- 2 *Revascularization in patients with stable ischemic heart disease and intermediate angiographic stenosis with FFR ≤ 0.80 .* In the FAME 2 trial, patients with stable ischemic heart disease referred for PCI with at least one lesion with FFR ≤ 0.8 were randomized to PCI plus optimal medical therapy versus optimal medical therapy alone. The primary outcome of death, MI, or urgent revascularization occurred in 12.7% of patients in the medical therapy group, and only 4.3% of the PCI plus medical therapy group at one year; HR 0.32 (0.19–0.53 for 95% CI). It should be noted that the study was stopped early and that primary outcome event rate was largely driven by the need for urgent revascularization [10].
- 3 *Safe deferral of PCI in patients with intermediate lesions and nonsignificant FFR.* In the DEFER trial, Bech *et al.* measured FFR in 325 patients with moderate coronary stenosis referred for coronary intervention. PCI was performed in all patients with FFR < 0.75 , but patients with FFR ≥ 0.75 were randomized to receive either PCI or medical management (deferral of PCI). The rate of adverse cardiovascular events in those with FFR ≥ 0.75 was numerically lower in the medical management group compared to the performance of the PCI group (but did not reach statistical significance). Furthermore, in long-term follow-up, those with FFR ≥ 0.75 who received medical management had a very low event rate [11].
- 4 *Left main lesions.* A meta-analysis of 525 patients showed that patients who did not undergo revascularization based on FFR > 0.75 (one study with FFR > 0.80) had similar rates of all-cause mortality and nonfatal MI, but higher rates of subsequent revascularization compared to patients who had FFR ≤ 0.75 and underwent revascularization [12]. A technical note: to measure FFR of a left main lesion, intravenous adenosine should be used to induce maximal hyperemia and the guide should be disengaged to avoid ostial narrowing causing obstruction of blood flow with pressure damping in the aortic tracing and false elevation of the FFR value.
- 5 *Determining the success of PCI.* The prognostic value of FFR after PCI is controversial but a meta-analysis of 5277 patients found that lower post-PCI FFR was associated with an increased risk of target vessel failure and cardiac death or MI and that these associations were consistent regardless of age, sex, the presence of hypertension or diabetes, and clinical diagnosis [13]. A low FFR post-PCI can be due to inadequate dilation of the treated segment and/or disease within the rest of the artery.
- 6 *Tandem lesions.* Theoretically, in the presence of serial lesions, the flow through each lesion is affected by other lesions and thus overestimates the FFR value. However, a gradual pullback of the distal pressure sensor toward the guide under maximal hyperemia can be used to identify the area of maximum

pressure drop. FFR can be measured again in the vessel after PCI of the primary lesion to determine if PCI of other lesions needs to be performed. It has been shown that the technique of measuring FFR during wire pullback to guide revascularization is safe and effective [14].

7 *Bifurcation lesions.* Use of FFR to guide side branch revascularization has been shown to reduce the need for intervention of short ostial side branch lesions after main branch stenting, with comparable clinical outcomes to an angiograph-guided strategy [15].

Nonhyperemic pressure ratios

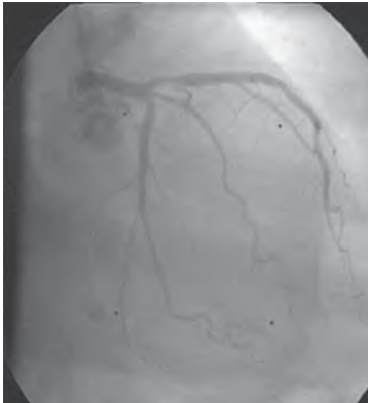
In order to avoid the time, cost, and potential (albeit very rare) side effects of administering a vasodilator, numerous non-hyperemic pressure ratios (NHPR) have been devised (Table 26.1). All compare the pressure in the distal portion of the coronary artery measured from the wire to the pressure in the aorta measured from the guide but vary depending on which part of the cardiac cycle is sampled. They can be divided into whole cycle (resting Pd/Pa and RFR) vs. phase-specific ratios (iFR, dPR, and DFR) [16].

As a general rule, resting indices are highly correlated and none of them have been shown to be superior. Compared to hyperemic indices (e.g., FFR), the pressure gradients with NHPR are smaller, which makes them more susceptible to pressure drift, hydrostatic effects, hemodynamic changes, and noise in the electronics.

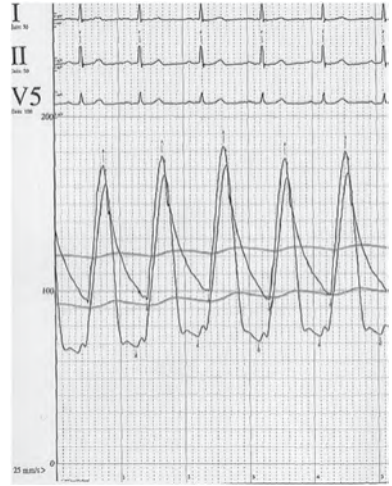
Instantaneous wave-free ratio (iFR) is the best-studied NHPR. It is measured during the wave-free period of mid to late diastole when flow during the cardiac cycle is the highest and the microcirculatory resistance is the lowest. During this period, pressure and flow velocity are linearly related, allowing pressure ratios to be used to determine the limitation to flow of a lesion. DEFINE-FLAIR and

Table 26.1 Nonhyperemic pressure ratios.

Index	Definition	Cutoff for ischemia
Resting Pd/Pa	Lowest mean Pd/Pa over entire cardiac cycle	0.91 or 0.92
Instantaneous wavefree ratio (iFR)	Pd/Pa during the wavefree period of diastole	0.89 or 0.90
Diastolic pressure ratio (dPR)	Pd/Pa during diastole	0.89
Diastolic hyperemia-free ratio (DFR)	Average Pa/Pd during the period when Pa < mean Pa	0.89
Resting full cycle ratio (RFR)	Lowest instantaneous Pd/Pa over entire cardiac cycle	0.89



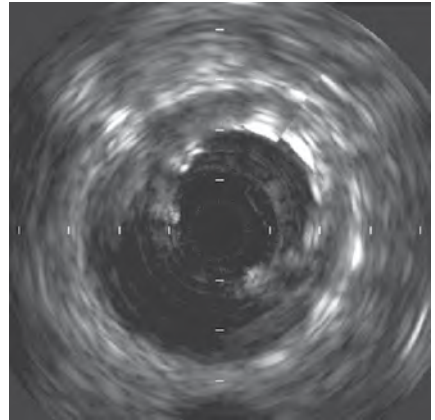
(a)



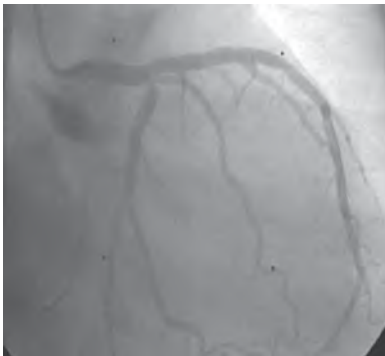
(b)



(c)



(d)



(e)

Figure 26.3 Angiograms, IVUS, and FFR measurements from the case study. Initial coronary angiogram is shown in A, FFR prior to stent placement in B, coronary angiogram after stent placement in C, IVUS after stent placement in D and final coronary angiogram after stent post-dilation in E.

Case study

A 61-year-old female with diabetes and hypertension reported the recent onset of exertional angina. An exercise treadmill test was performed, during which she developed chest pain and 2 mm of ST depression 2 minutes into the Bruce protocol. At angiography, her coronary arteries were unremarkable except for a 60% lesion involving the ostium of the LAD coronary artery (Figure 26.3a). Because of the intermediate nature of the lesion, FFR analysis was performed using the pressure wire. Pd/Pa was 0.94 at baseline and FFR was 0.73 following intracoronary administration of 60 µg of adenosine (Figure 26.3b). QCA of the proximal LAD revealed a size of 3.3 mm and therefore a 3.0 mm Cypher drug-eluting stent was placed at 12 atmospheres. Angiography revealed a satisfactory result (Figure 26.3c); however, FFR was 0.82 following intracoronary administration of 60 µg of adenosine. Intravascular ultrasound showed that the vessel diameter was much larger than it appeared on angiography and that the stent was underdeployed (Figure 26.3d). The Cypher stent was dilated to 3.8 mm and angiography repeated (Figure 26.3e). Pressure wire analysis showed that the FFR was now 0.98 at baseline and 0.95 following intracoronary administration of 60 µg of adenosine.

iFR-SWEDEHEART were large, randomized trials comparing outcomes in patients undergoing iFR-guided PCI vs. FFR-guided PCI [17, 18]. These studies showed no difference in major adverse cardiovascular outcomes (death from any cause, non-fatal myocardial infarction, or unplanned revascularization) in stable patients with intermediate coronary lesions. Unfortunately, neither study used relief of stable ischemic symptoms, the primary reason for doing a PCI in a stable patient, as a primary outcome.

Interestingly, there is a 15–20% rate of discordance between resting indices and hyperemic indices. Resting indices and hyperemic indices don't measure the same thing and thus discrepancies are not surprising. The reasons for the discrepancies are not well understood but various factors have been shown to play a role including procedural factors (e.g., guide engagement) and patient factors (e.g., sex, age, specific artery, amount of disease, LVEDP). The clinical outcomes of these patients have not been well-studied.

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CHAPTER 27

Assessment of coronary microvasculature

George A. Stouffer

The coronary circulation can be divided into a three-compartment system (Figure 27.1) [1]. The proximal compartment includes the large epicardial coronary arteries, usually with a diameter $>500\mu\text{m}$ and visible on coronary angiography. The epicardial vessels offer little resistance to coronary blood flow in the absence of obstructive disease. The intermediate compartment includes prearterioles (diameter $100\text{--}500\mu\text{m}$) and regulates pressure at the origin of arterioles within a narrow range despite changes in perfusion pressure or flow (important in autoregulation). The distal compartment includes arterioles (diameter $<100\mu\text{m}$) and capillaries and is the primary site of regulation for matching myocardial blood supply with oxygen requirements. The arterioles are far more responsive to metabolites than prearterioles and thus the distal compartment is mainly responsible for the metabolic regulation of coronary blood flow.

The microvasculature is generally defined as the intermediate and distal compartments (i.e. the prearterioles, arterioles, and capillaries). The microvasculature regulates myocardial blood flow and provides the majority of resistance to flow under normal resting conditions in the absence of epicardial disease.

Numerous noninvasive techniques have been developed to evaluate microvascular function that generally assess perfusion at rest and after administration of a vasodilator to induce hyperemia. Imaging can be performed with echocardiography, positron emission tomography (PET), coronary computed tomographic angiography (CCTA), or cardiac magnetic resonance imaging (CMR). PET scans can be used to measure levels of a radionuclide tracer at baseline and with a hyperemic stimulus in order to estimate resting and hyperemic myocardial blood flow and thus calculate coronary flow reserve (CFR). There are several CMR techniques that can be used to estimate microvascular function including stress perfusion and stress T1 mapping. Transthoracic Doppler echocardiography can be used to measure velocity in the proximal left anterior descending (LAD) coronary

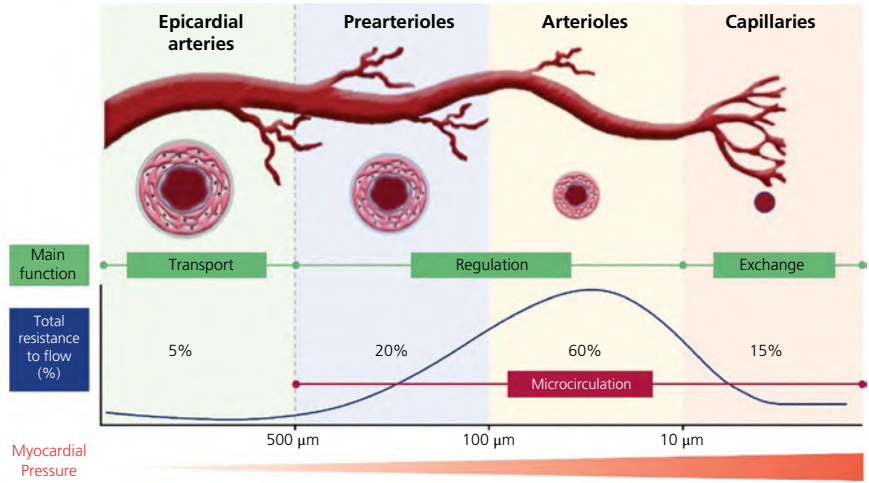


Figure 27.1 Coronary circulation. Source: Adapted from reference [2].

artery but an appropriate signal can be difficult to acquire. Various techniques are being developed to measure flow using CCTA. It is important to remember that most noninvasive techniques measure surrogates of coronary flow.

In the cardiac catheterization laboratory, prearterioles and arterioles are below the resolution of current angiographic systems and thus coronary microvascular function is assessed indirectly by measurement of changes in flow in response to various stimuli. The most commonly used invasive indices of microvascular function are CFR, thrombolysis in myocardial infarction (TIMI) frame count and flow grade, TIMI myocardial perfusion grade (TMPG) and the index of microcirculatory resistance (IMR). CFR is discussed in detail in chapter 25. Angiographic measures such as TIMI flow grade and TMPG were used in older studies but have largely been supplanted by more sensitive techniques [2, 3].

Index of microvascular resistance (IMR)

The most widely used measurement of microvascular function is IMR. IMR is derived from Ohm's law in which the microvasculature resistance (R) is equal to the pressure difference across the microvasculature (ΔP) divided by the flow rate (Q): $R = \Delta P / Q$. ΔP is estimated using the pressure measured by a wire in the distal portion of the coronary artery; the venous pressure is assumed to be zero. Q represents the coronary flow as measured by thermodilution. Therefore, IMR is calculated as the distal coronary pressures (P_d) $\times$ thermodilution-derived mean transit time (T_{mn}) during maximal hyperemia.

$$\text{IMR} = P_d \times T_{mn}$$

where:

IMR = the index of microcirculatory resistance

Pd = distal coronary pressure

Tmn = thermodilution-derived mean transit time during maximal hyperemia

Although IMR is theoretically measuring only the function of the microvasculature, studies have shown that microvascular resistance will be overestimated in the presence of critical epicardial stenosis. This is thought to be due to the fact that microvascular blood flow is equal to epicardial coronary flow plus a contribution from collateral flow when there is severe epicardial stenosis. In these cases, collateral flow needs to be taken into account by incorporating the coronary wedge pressure (Pcw) and aortic pressure (Pa) into a more complex formula:

$$\text{IMR} = \text{Pa} \times \text{Tmn} \times \left(\frac{\text{Pd} - \text{Pcw}}{\text{Pa} - \text{Pcw}} \right)$$

There is controversy regarding what IMR values are normal but in general, microvascular dysfunction (MVD) is defined as an $\text{IMR} \geq 25$.

Other invasive indices of microvascular function

- Hyperemic microvascular resistance (HMR) is defined as the ratio of the mean distal pressure (Pd) to the average peak flow velocity (APV) during maximal hyperemia and is measured using an intracoronary Doppler wire.
- Minimal microvascular resistance is defined as the ratio between the distal coronary pressure and the flow velocity during the hyperemic wave-free period.
- Resistive reserve ratio (RRR) is defined as the ratio between the basal and hyperemic microcirculatory resistances. This index evaluates response of the coronary microcirculation to vasodilation with a higher RRR value indicating a greater vasodilatation of the microcirculation in response to hyperemia.

$$\text{RRR} = \text{CFR} \times \left(\frac{\text{resting Pd}}{\text{hyperemic Pd}} \right)$$

- Microvascular resistance reserve (MRR) is similar to RRR but uses aortic pressure rather than distal coronary pressure. In its general form, the MRR is expressed as the ratio of the CFR to the FFR, corrected for the driving pressures.

$$\text{MRR} = \text{CFR} \times \left(\frac{\text{resting Pa}}{\text{hyperemic Pd}} \right) = \text{RRR} \times \left(\frac{\text{resting Pa}}{\text{resting Pd}} \right)$$

Coronary microvascular dysfunction (CMD)

CMD occurs in a wide variety of cardiovascular disease states and is generally due to either: (1) impaired vasodilatory mechanisms; or (2) increased resistance to flow due to structural factors. CMD was originally studied in patients with angina

without obstructive coronary artery disease but has also been shown to play a role in obstructive coronary artery disease; restrictive, hypertrophic, and stress-induced cardiomyopathies; aortic stenosis; and heart failure with preserved ejection fraction (HFpEF). CMD is found at a higher rate in patients with coronary artery disease risk factors (e.g., hypertension, dyslipidemia, obesity and metabolic syndrome, smoking, and diabetes) [4].

The COVADIS (Coronary Vasomotion Disorders International Study Group) has published international standardized diagnostic criteria for CMD [5]. They recommend using CFR and IMR to assess microvasculature function with a major advantage of IMR compared to CFR being that IMR does not depend on resting physiology. Their criteria for CMD are:

- Impaired CFR which is defined differently in various studies with cutoff values between ≤ 2.0 and ≤ 2.5
- Abnormal coronary microvascular resistance indices (e.g., $\text{IMR} > 25$)
- Coronary slow flow phenomenon, defined as TIMI frame count > 25 .

The 2019 ESC guidelines for the Diagnosis and Management of Chronic Coronary Syndromes [6] and the 2020 EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries [7] both proposed that values of $\text{CFR} < 2.0$ or index of microcirculatory resistance ($\text{IMR} \geq 25$ units) are indicative of CMD.

Clinical implications

The clinical measurement of IMR in the United States became possible with the availability of a specific pressure wire (PressureWire XTM, Abbott Vascular, Santa Clara, CA, United States) with three sensors (proximal temperature, distal pressure, and distal temperature), which enables the measurement of CFR, FFR, and IMR (Figure 27.2). Coronary flow is estimated using thermodilution by intracoronary injections of room-temperature saline under basal conditions and during administration of intravenous adenosine. The mean transit time (T_{mn}) is the time needed for the saline bolus to travel from the tip of the guiding catheter to the distal temperature sensor of the pressure wire and CFR is equal to the resting T_{mn} divided by the hyperemic T_{mn} . IMR is calculated by simultaneous measurement of the distal coronary pressure (P_d) and thermodilution-derived mean transit time (T_{mn}) during maximal hyperemia with $\text{IMR} = P_d \times T_{mn}$. T_{mn} is calculated based on thermodilution curves measured following 3 injections of room-temperature saline. A correction is employed when hemodynamically significant epicardial disease is present.

A comprehensive assessment of coronary circulation using FFR (described in Chapter 26) to assess the hemodynamic significance of epicardial disease and IMR as an index of CMD enables a stratification of patients with chest pain. Patients can be classified according to the schema outlined in Figure 27.3.



Figure 27.2 Invasive evaluation of a 73-year-old female with hypertension and history of placement of a 3.5×12 mm drug-eluting stent in the proximal LAD 4 years previously. She presented with chest pain and an echocardiogram showed mild anterior and apical hypokinesis. Coronary angiography showed a patent stent in the proximal LAD (arrow) and diffuse, moderate disease in the mid-LAD. To perform a comprehensive physiologic assessment, a 6F guide catheter was engaged in the left main coronary artery and a wireless pressure-temperature sensor guidewire (Abbott) was placed in the coronary artery in the distal LAD. Pd/Pa was measured. Three injections of 3 mL of room-temperature saline were made in the coronary artery via the guide, and the transit times were averaged to calculate the resting mean transit time. An intravenous infusion of adenosine (140 µg/kg/min) was then started via a large peripheral IV to induce steady-state maximal hyperemia, and two minutes later 3 more injections of 3 mL of room-temperature saline were made. The transit times were averaged to calculate the hyperemic mean transit time. Simultaneous measurements of mean aortic pressure (by guiding catheter) and mean distal coronary pressure (by pressure wire) were also made during maximal hyperemia and FFR was determined. FFR, CFR and IMR values are shown on the screen and were consistent with a nonischemic etiology of her chest pain.

	FFR ≤ 0.80	Flow-limiting epicardial coronary artery disease + normal microvascular function	Flow-limiting epicardial coronary artery disease + microvascular dysfunction
Epicardial disease			
	FFR > 0.80	Nonflow-limiting epicardial coronary artery disease + normal microvascular function	Nonflow-limiting epicardial coronary artery disease + microvascular dysfunction
		IMR < 25	IMR ≥ 25
		Microvasculature disease	

Figure 27.3 Invasive evaluation of epicardial disease and microvascular function.

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PART VII

Miscellaneous

 **2025** Edition

CHAPTER 28

Right ventricular myocardial infarction

Robert V. Kelly, Mauricio G. Cohen and George A. Stouffer

[This chapter is revised and modified from a chapter written for the first and second editions by Robert V. Kelly, Mauricio G. Cohen, and George A. Stouffer]

Right ventricular (RV) dysfunction occurs to some degree in approximately 30–50% of inferior wall and 10% of anterior wall infarcts [1]. Severe RV dysfunction leading to the classic hemodynamic changes occurs in approximately 10% of inferior myocardial infarctions and is associated with higher rates of mortality, cardiogenic shock, sustained ventricular arrhythmias, and advanced atrioventricular (AV) block. Patients in cardiogenic shock with RV involvement have significantly higher in-hospital mortality compared to patients without RV involvement. While RV dysfunction during acute arterial occlusion has classically been labelled RV infarction, profound RV ischemia may be more accurate, since patients with RV infarctions who survive their initial hospitalization tend to do well in the long term and RV function generally recovers.

Effects of ischemia on the right ventricle

The RV is pyramidal-shaped with a triangular base and a thin crescentic free wall. It is designed as a volume pump ejecting into the low-resistance pulmonary circulation. The RV is less susceptible to ischemia than the left ventricle (LV) for two reasons: oxygen demand is less and the blood supply is more redundant. Oxygen demand is lower due to the smaller muscle mass of the RV (approximately 15% of muscle mass of LV), lower preload, and lower afterload. Less oxygen extraction at rest means that the RV has a greater extraction reserve during stress.

The RV receives its blood supply from several sources. The septum is perfused by the left anterior descending (LAD) artery and posterior descending artery, the lateral wall by marginal branches of the right coronary artery (RCA), and the anterior free wall by the conus branch of the RCA and the moderator branch artery of the LAD. The RV is also thought to receive oxygen directly from the ventricular cavity by diffusion.

Coronary perfusion to the RV occurs approximately equally during systole and diastole, both under normal conditions and with collateral perfusion during RCA occlusion. RV perfusion during systole is greater than LV perfusion because of lower systolic intramyocardial pressure and less diastolic intracavitary pressure.

The vast majority of RV infarcts occur with occlusion of the RCA (Figure 28.1), although the LAD and circumflex can also cause RV infarcts. There is a large inter-individual variation in the number and origin of RV branches from the RCA (Figure 28.2), but a direct correlation exists between more proximal occlusion of the RCA occlusion and a larger extent of RV infarction.

Abrupt cessation of epicardial blood supply to the RV causes the ischemic RV to become stiff, which results in diastolic pressure elevation. The RV dilates acutely which results in impaired filling of the other chambers due to pericardial constraint (which can lead to ‘pseudo-constriction’ hemodynamics; see Chapter 18). RV dilation, along with elevated RV diastolic pressures, causes the interventricular septum to shift towards the underfilled LV, which further impairs LV filling. These changes can lead to decreased cardiac output +/- hypotension.

Clinical presentation, ECG changes, and echocardiographic findings in RV infarction

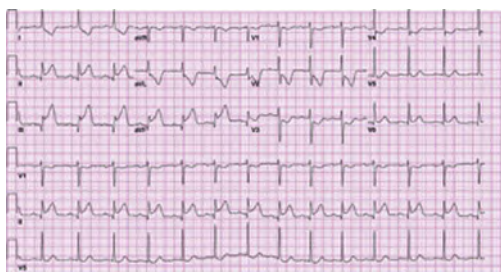
The diagnosis of RV myocardial infarction is made using the clinical presentation in combination with echocardiogram (ECG), echocardiographic, and/or hemodynamic criteria. The classic clinical triad described with RV infarction is hypotension, clear lung fields, and elevated jugular venous pressure in the setting of an inferior wall myocardial infarction.

The ECG with right-sided leads is very useful in the diagnosis of RV myocardial infarction. The sensitivity of ST elevation in V4R, V3R, and V1 is 93%, 69%, and 28%, respectively, while the specificity is 95%, 97%, and 92%.

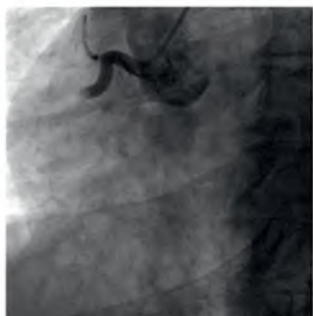
Echocardiographic findings that support the diagnosis of RV infarction include RV dilation, RV wall motion abnormalities, paradoxical motion of the interventricular septum, tricuspid regurgitation, decreased descent of the RV base, and plethora of the inferior vena cave (IVC).

Hemodynamics of RV infarction

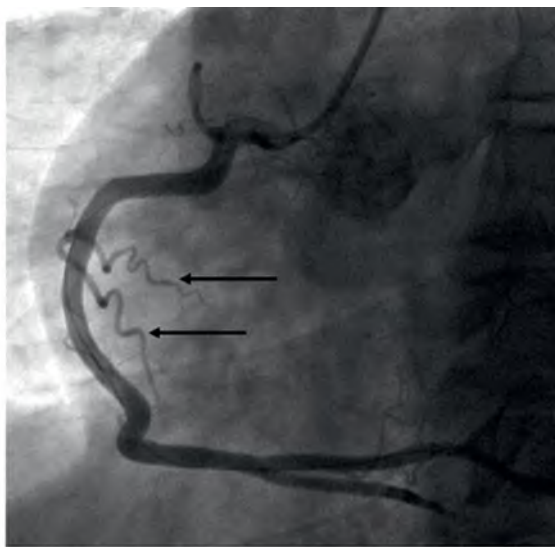
In proximal RCA occlusion, there is compromised perfusion to the RV free wall, with RV dyskinesia and depressed RV function, which is reflected in the RV waveform as a sluggish upstroke, depressed broadened systolic peak, delayed relaxation phase, and diminished RV stroke work (Figure 28.3). RV systolic dysfunction reduces transpulmonary delivery of LV preload, leading to decreased cardiac output despite intact LV contractility. RV dysfunction is compensated for by augmented RA contraction and by left ventricular septal contraction, which



(a)



(b)



(c)

Figure 28.1 ECG (a), initial RCA angiogram (b) and final RCA angiogram (c) in a 43-year-old male who presented with an inferior ST-elevation myocardial infarction and hypotension. The arrows in panel C show RV marginal branches. The patient's blood pressure improved with restoration flow in the RCA.

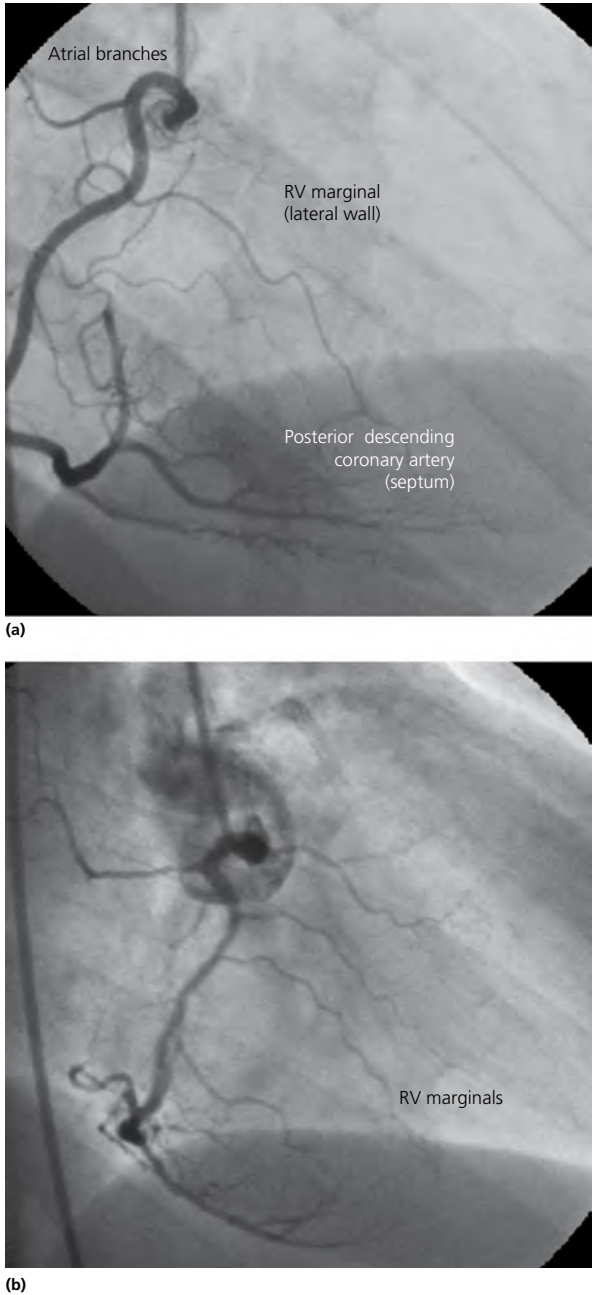


Figure 28.2 Right ventricular blood supply. Panel (a) is an AP cranial projection of RCA demonstrating RA branches, a large RV marginal branch, and the posterior descending coronary artery. Panel (b) is an RAO projection of RCA from a different patient and demonstrates several RV marginal branches originating from the mid-portion of the RCA. From this angiogram, it is easy to see that the more proximal the occlusion in the RCA, the greater the extent of RV ischemia.



Figure 28.3 RV pressure tracing in a patient with RV ischemia.

bulges in a piston-like fashion into the RV during systole and generates force against a stiff RV-free wall.

In acute RV ischemia, diastolic biventricular function is key. Depressed RV contractility results in RV dilation and ischemia impairs RV relaxation. The RV becomes stiff and dilated in early diastole, resulting in increased impedance to initial RV inflow. As filling progresses during diastole, the noncompliant RV ascends a steep pressure–volume curve, leading to the pattern of rapid diastolic pressure elevation (Figure 25.2). Acute RV dilation and elevated RV diastolic pressure cause the interventricular septum to bulge into the LV during diastole, leading to impaired LV compliance and potentially limiting LV filling.

Abrupt RV dilatation within a noncompliant pericardium leads to elevated intrapericardial pressure. As both ventricles fill during diastole and compete for space within the pericardium, the effects of pericardial constraint cause a pattern of equalized diastolic pressures and the RV “dip and plateau” pattern suggestive of constrictive pericarditis.

Right atrial (RA) waveforms in RV infarction are characterized by diastolic impedance imposed by a stiff dilated RV. The ischemic RV causes preload and afterload of the right atrium to increase, resulting in enhanced RA contractility, reflected in a “W” pattern in the RA waveform characterized by a rapid upstroke

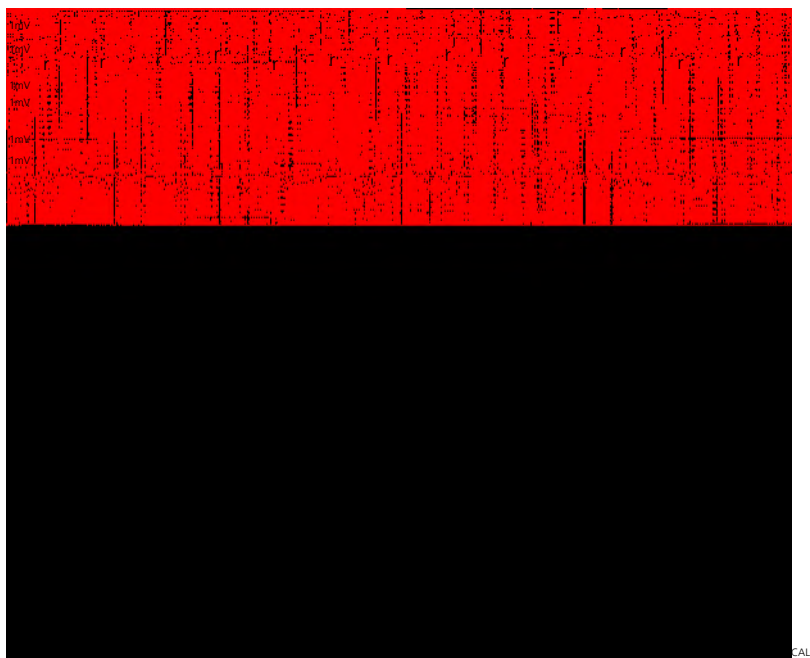


Figure 28.4 RA pressure tracing in a patient with RV ischemia. Note the “W” configuration.

and increased peak A wave amplitude, sharp X descent reflecting atrial relaxation, and blunted Y descent of pandiastolic RV dysfunction. Reduced inflow velocity across the tricuspid valve gives rise to a blunted Y descent (more prominent in expiration) rather than a rapid Y descent, as seen in constrictive pericarditis. In the RA, the blunted Y descent signifies pandiastolic RV dysfunction as opposed to constrictive pericarditis where the diastolic ‘dysfunction’ is limited to the terminal phase of diastole (Figure 28.4).

Early studies reported that a prominent Y descent was frequently found in RV infarction; however, later studies that timed RA events to RV events (rather than to the ECG) showed that the X descent was predominant [2]. Patients with intact RA function demonstrate prominent A waves and X descents and diminished Y descents. An exception will be patients with tricuspid regurgitation, in whom V waves and Y descent will be prominent.

Very proximal RCA occlusions which compromise atrial blood supply result in atrial as well as ventricular ischemia. Atrial dysfunction results in a further elevation in mean RA pressure and an “M” waveform pattern in the RA tracing characterized by depressed A wave and blunted X and Y descents. In proximal occlusion of the RCA resulting in acute ischemia involving both the RA and RV, there is RA dysfunction and decreased RV filling, with resultant decrements in LV preload and cardiac output.

Findings at cardiac catheterization

RV infarction is characterized by increased RA and RV diastolic pressures, low cardiac output, and systolic hypotension (Table 28.1). LV dysfunction (which will be proportional to the amount of the LV perfused by the LV branches originating from the RCA) increases RV afterload, which can further reduce cardiac output. In right dominant circulation (80–85% of individuals), the RCA supplies the posterior descending artery. The RCA can also give off branches supplying the posterior and lateral walls of the LV. The RCA is nondominant in 5–10% of patients in which RCA only supplies blood to the RV lateral wall and RA. Approximately 5–10% of individuals have a co-dominant circulation in which the PDA arteries originate from both the RCA and left coronary artery.

1 RA waveform:

- Pressure is elevated
- Y descent is impaired
- Failure of RA pressure to decrease with inspiration (Kussmaul's sign) has been shown in small studies to be sensitive and specific for RV infarction.
- Comparison of X and Y descents approximates degree of RA impairment:
 - (a) RV infarction with intact RA function—RA pressure tracing demonstrates increased A wave, steep X descent, and impaired Y descent ("W" pattern; Figure 28.4).
 - (b) Combined RA and RV infarction—RA pressure tracing demonstrates decreased A wave and impaired X and Y descents ("M" pattern; Figure 28.5).

2 RV waveform:

- Elevated diastolic pressures
- Rapid rise in diastolic pressures
- Slow upstroke in systole
- Diminished peak pressure
- Delayed relaxation

Table 28.1 Hemodynamic principles of RV infarction.

RV systolic and diastole function are impaired.

In the setting of a large area of RV ischemia, the RV becomes merely a conduit (and a stiff one at that) from the systemic veins to the pulmonary circulation.

In the setting of a large area of RV ischemia, the difference between RA and LA pressure becomes the driving force between the systemic veins and the LV. RA transport is important in maintaining LV preload and cardiac output.

RA pressure increases and PA pulse pressure decreases.

Dilation of RV can impair LV function.

Abrupt dilation of RV can give rise to a "pseudo" constrictive pericarditis appearance to hemodynamics, including a "dip and plateau" configuration in RV tracing and a positive Kussmaul's sign.

Cardiac output is reduced.

Systemic hypotension and reduced pulse pressure are common.

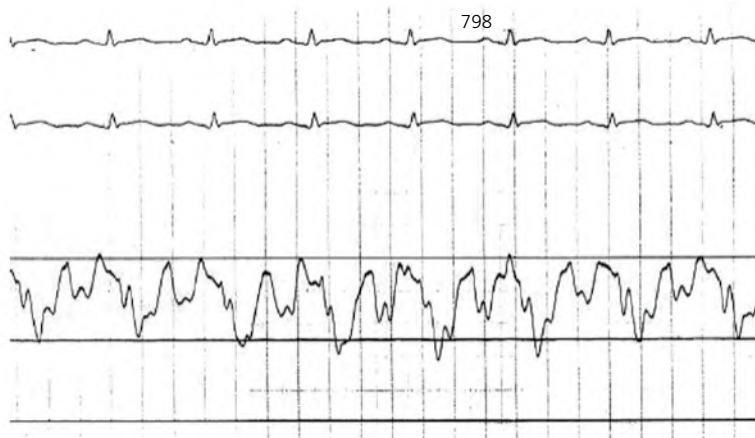


Figure 28.5 RA pressure tracing in a patient with RA and RV ischemia. Note the “M” configuration.

- In severe, abrupt RV dilation, RV and LV diastolic pressures are elevated and equalized and demonstrate a “dip and plateau” configuration (similar to constrictive pericarditis). The Y descent is blunted, unlike the accentuated Y descent seen in constrictive pericarditis
- 3 Pulmonary artery (PA) waveform:
 - Decreased PA systolic pressure
 - Pulse pressure is reduced
- 4 Aortic pressure
 - Relative hypotension (Figure 28.6)
 - Pulse pressure is reduced
 - Pulsus paradoxus may be present

Diagnosis of RV infarction with hemodynamics

Various criteria have been advanced to aid in the diagnosis of RV infarction:

- 1 Both mean RA pressure of ≥ 10 mm Hg and an RA/pulmonary capillary wedge pressure (PCWP) ratio of 0.8 or more are suggestive of RV infarction in the proper clinical situation. Occasionally these findings may be unmasked by volume loading. An abnormal RV radionuclide angiogram was observed in 12 of 13 patients with these hemodynamic measurements in a study of 53 patients with acute inferior myocardial infarction [3].
- 2 RA pressure greater than 10 mm Hg and within 1–5 mm Hg of PCWP had a sensitivity of 73% and a specificity of 100% in identifying RV infarction in 60 patients with acute myocardial infarction (22 with RV involvement) [4].
- 3 A severe noncompliant pattern, defined as a Y descent deeper than the X descent in RA pressure tracing, was present in 55% of patients with, and 3% of

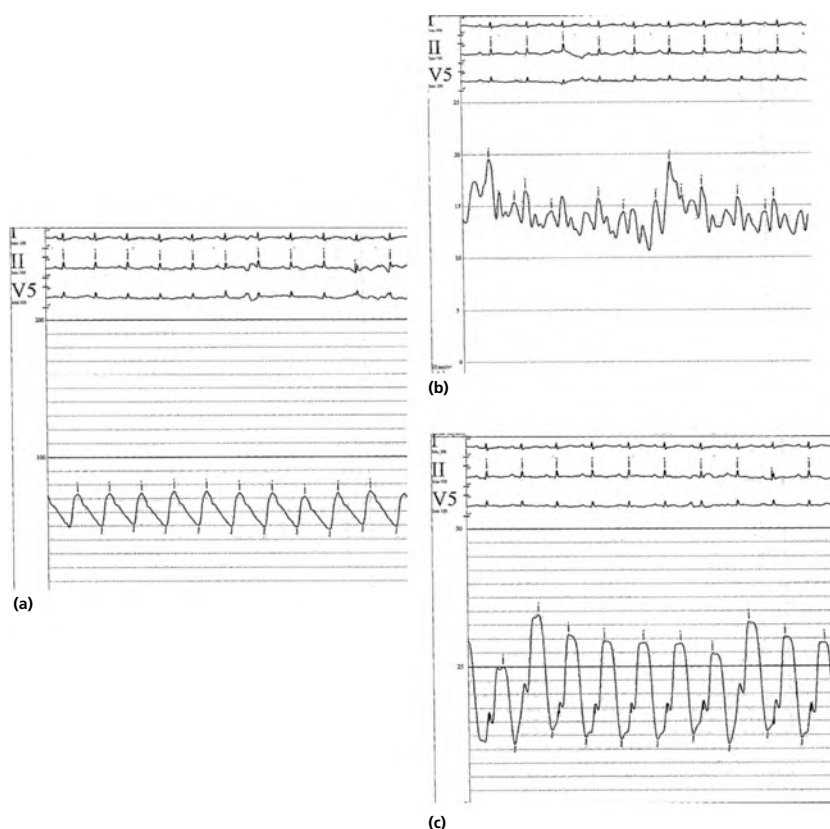


Figure 28.6 Aortic (a), RA (b), and RV (c) pressure tracings in a 64-year-old female with RV ischemia in the setting of an inferior myocardial infarction. Note the relative hypotension, increased RA pressure, and increased RV end-diastolic pressure.

patients without, RV infarction (sensitivity of 54.5% and specificity of 97.4%) in 60 patients with acute myocardial infarction [4].

- 4 RA > PCWP. The sensitivity and specificity of this criteria were 45% and 100%, respectively, in a study of 60 patients with acute myocardial infarction [4].
- 5 Pulmonary artery pulsatility index (PAPi) is defined as the ratio of PA pulse pressure to RA pressure. In a study of 20 patients with angiographically confirmed proximal RCA occlusion, compared to 50 patients with nonobstructive coronary artery disease and 14 patients presenting with acute coronary syndrome involving the left coronary artery, $\text{PAPi} \leq 0.9$ demonstrated a sensitivity of 88.9% and a specificity of 98.3% for predicting in-hospital mortality and/or requirement of a percutaneous RV support device. Patients with RV dysfunction had a significantly lower ratio of PA pulse pressure to RA pressure (1.1 ± 0.6 vs. 4.3 ± 3.0 vs. 5.5 ± 4.4 , respectively, $p < 0.01$) and a higher RA:PCWP ratio (0.8 ± 0.3 vs. 0.5 ± 0.2 vs. 0.5 ± 0.3 , respectively, $p < 0.05$) [5].

Management

Management of RV infarction can be summarized as follows: early recognition + reperfusion + volume expansion $\pm$ dobutamine or a mechanical support device. The cornerstone of treatment of myocardial infarction is reperfusion, either via primary percutaneous coronary intervention or thrombolytic therapy.

The hemodynamic management of patients with RV infarction includes aggressive fluid resuscitation, which is vital to restore preload and raise RV filling pressure in order to maximize cardiac output. This can require several liters of saline. Once PCWP increases above 15 mm Hg, further fluid expansion is unlikely to improve hemodynamics, since this can lead to further dilation of the RV compromising LV filling.

Once RV preload is optimized, dobutamine may improve RV function and cardiac output. In one small study of patients with RV infarction, volume loading increased RA and PCWP pressure but did not improve cardiac index. Addition of dobutamine, but not nitroprusside, increased cardiac index (by an average of 35%) and RV ejection fraction [6]. Other therapeutic options to support blood pressure include intra-aortic balloon pumping and cardiac pacing to maintain AV synchrony in the setting of advanced AV block.

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CHAPTER 29

Acute right ventricular strain

Kevin A. Friede

Introduction

While most of our clinical energy and effort in heart failure is devoted to left ventricular (LV) failure, the right ventricle (RV) plays a critical role in hemodynamics and maintenance of cardiac output. The RV has been labeled the “People’s Ventricle,” and RV dysfunction is an important clinical entity with which every cardiologist and critical care specialist must be familiar. In this chapter, we will explore the physiology of the RV; review diseases that result in dysfunction or failure of the RV, both in isolation and in combination with LV failure; and discuss important treatment modalities to improve RV function and/or support the RV in critically ill patients.

Right ventricular morphology and physiology

The RV is the most anterior structure of the heart. It is anatomically continuous with the LV in the region of the intraventricular septum (IVS). For this reason, the RV has two different patterns of muscle fibers: in the septum, the fibers are helically arranged, as in the rest of the LV, exhibiting a longitudinal contractile pattern; while in the RV free wall, the muscle fibers are arranged circumferentially, with a transverse shortening pattern.

Disorders that affect the RV can be categorized based on their effects on four principles of RV function: preload, afterload, chronotropy, and lusitropy (Figure 29.1) [1].

- **Preload.** Defined either as wall stress or stretch experienced by muscle cells during diastole, preload is closely related to end-diastolic volume. The thin-walled RV can generally accommodate a large increase in preload, even when it occurs rapidly; however, in extreme cases, this can cause leftward shift of the IVS and

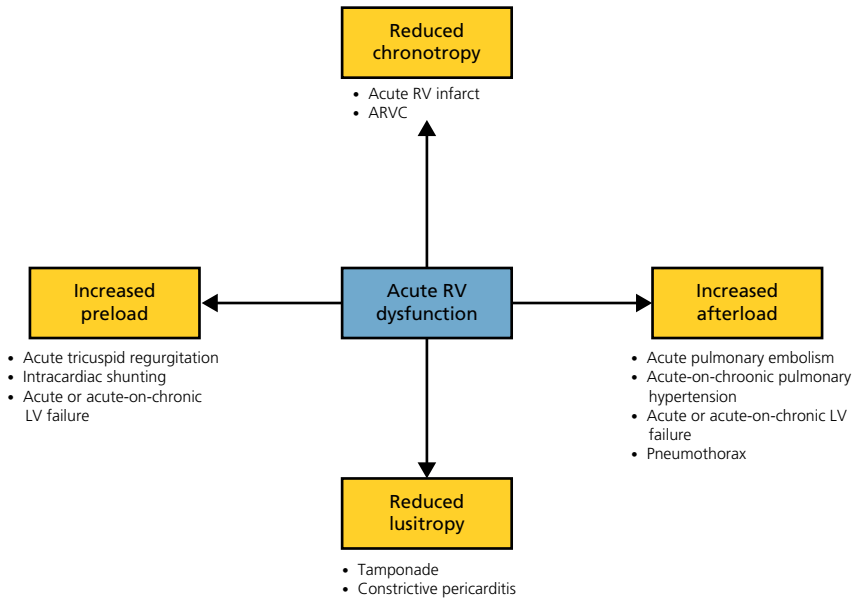


Figure 29.1 Causes of acute right ventricular failure, by mechanism. [ARVC = arrhythmogenic right ventricular cardiomyopathy; LV = left ventricle; RV = right ventricle.] Source: Adapted from Houston *et al.* [1].

signs of ventricular interdependence. Over longer periods of time, increases in RV preload manifest as peripheral venous congestion, ex., peripheral edema, hepatic congestion, or cardiorenal syndrome.

- **Afterload.** Defined as the wall stress experienced by muscle cells during systole, RV afterload is closely related to impedance and resistance in the pulmonary artery (PA). Because the heart and pulmonary circuit are both completely contained within the thoracic cavity, afterload is also affected by respiratory mechanics; most notably, there is an increase in afterload in response to positive pressure ventilation (continuous or bilevel positive airway pressure, or endotracheal intubation). The RV is more sensitive to changes in afterload than the thick-walled LV and an acute increase in RV afterload can result in rapid hemodynamic collapse. RV afterload is generally measured in terms of mean PA pressure (mPAP). The most recent updated pulmonary hypertension (PH) guidelines [2] define a mPAP >20 mm Hg at rest as mild PH, with mPAP of >30 mm Hg and >40 mm Hg defined as moderate and severe, respectively.
- **Contractility.** Defined as the ability of the ventricle to contract and eject a stroke volume at a given level of preload and afterload. The gold-standard metric to express RV contractility is end-systolic elastance (Ees). Conditions which affect the tension and velocity of muscle fiber shortening generally affect contractility.
- **Lusitropy.** Defined as the ability of the ventricle to relax. Conditions which cause chronic pressure or volume overload, extrinsic compression (e.g., constrictive

pericarditis), or infiltration of the muscle tissue (e.g., restrictive cardiomyopathy) generally affect lusitropy.

Assessment of RV function by echocardiography

There are multiple assessments of RV structure and function that can be made using echocardiography. Subjectively, echocardiography can assess gross contractile function as well as whether the RV appears thickened or dilated. Classically, flattening of the IVS in diastole suggests RV volume overload, while flattening in systole suggests RV pressure overload. A concomitantly dilated right atrium (RA) suggests that RV dysfunction is chronic.

Other echo parameters that are useful in assessing RV function include:

- Tricuspid annular plane systolic excursion (TAPSE), measured using M-mode as the distance that the lateral tricuspid annulus moves toward the RV apex in systole, is closely connected to RV contractile function but only assesses the function of the basal RV free wall and not global RV function [3].
- RV systolic excursion velocity, usually denoted as S' , is measured using tissue Doppler at the lateral tricuspid annulus and is readily reproducible.
- RV index of myocardial performance (RIMP) is determined by measuring isovolumic contraction and relaxation times (IVCT and IVRT), as well as ejection time (ET) on a tissue Doppler assessment of the lateral tricuspid valve annulus, and then calculated using the formula $RIMP = (IVCT + IVRT) / ET$.
- RV free wall longitudinal strain is another assessment of global RV performance calculated based on two-dimensional speckle-tracking echocardiography as the mean of the strain values in the basal, mid, and apical segments of the RV [4].
- In the absence of tricuspid and/or pulmonary valve stenosis, RV and PA systolic pressures (RVSP and PASP) can be assessed by measuring the maximum velocity of the jet of tricuspid regurgitation which reflects the pressure gradient between the RA and RV and then adding RA pressure (RAP) based on assessment of IVC size and collapsibility. Plugging these values into the Bernoulli equation gives $RVSP = 4v^2 + RAP$ where v = velocity of flow across the TV.
- The ratio of TAPSE to PASP can be used as a surrogate for invasive pressure-volume loop-derived end-systolic elastance. This value is an estimate of the extent of RV-PA arterial coupling, and lower values are associated with a worse prognosis [5].
- The LV eccentricity index, measured in a parasternal short-axis view as the ratio of LV diameter measurements perpendicular and parallel to the IVS, is a well-validated method for assessing the degree of RV pressure and volume overload [6].

Last, echocardiographic assessment of RV function is incomplete without careful assessment of LV and left atrial (LA) size, LV diastolic function, cardiac valve function, and characteristics of the pericardium.

Assessment of RV function by cardiac MRI

While MRI evaluation takes longer and involves more patient-initiated maneuvers (e.g., breath holds) than echocardiography and cannot be performed at the bedside, there are several situations in which it can be a valuable method for assessing the RV.

- Because of the complex geometry of the RV, its exaggerated motion compared to the LV, and potential issues with acoustic windows with echocardiography, MRI is considered the gold standard for assessment of RV ejection fraction. The ability of cardiac MRI to assess the entire RV in three dimensions in each part of the cardiac cycle provides a straightforward method to measure end-systolic and end-diastolic volumes, from which stroke volume index can be easily calculated.
- The ratio of stroke volume index to end-systolic volume can be used as a surrogate for the assessment of RV to PA coupling.
- Contrast MRI is an excellent method for assessing the presence of, and differentiating between, fibrosis, inflammation, or infiltration of the RV wall, which can be characteristic of several diseases that affect the RV [7].

Assessment of RV function by right heart catheterization (RHC)

RHC directly measures right-sided filling pressures and cardiac output and can be performed either in the cardiac catheterization laboratory or intensive care unit. While historical studies showed that routine use of PA catheters does not improve outcomes [8], their use in selected patients with decompensated heart failure carries a IIa recommendation in the most recent ACC/AHA heart failure guidelines [9] due to the potential for invasive hemodynamic data to guide therapy. Because right-sided pressures are particularly sensitive to respiratory variation, proper technique is critical for accurate measurements. In addition to the standard pressure and output measurements, RV stroke volume and stroke work index, PA pulsatility index (PAPi; which has important prognostic value), and flow-volume loops can be measured during RHC.

Characteristic findings of acute RV failure include elevated RA pressure and elevated RV end-diastolic pressure with normal pulmonary capillary wedge pressure (PCWP) (Figure 29.2). RV systolic pressure and PA systolic pressure may be mildly elevated but moderate or severe PH suggests an acute or chronic process.

Traditionally, a ratio of the RA pressure to PCWP >0.6 was used to indicate RV dysfunction (a normal RA/PCWP ratio is ~ 0.5) but more recently, other values (e.g., >0.8 or >0.86) have been proposed to identify RV dysfunction. Several other, more sophisticated indices have also been derived (box). One of the most

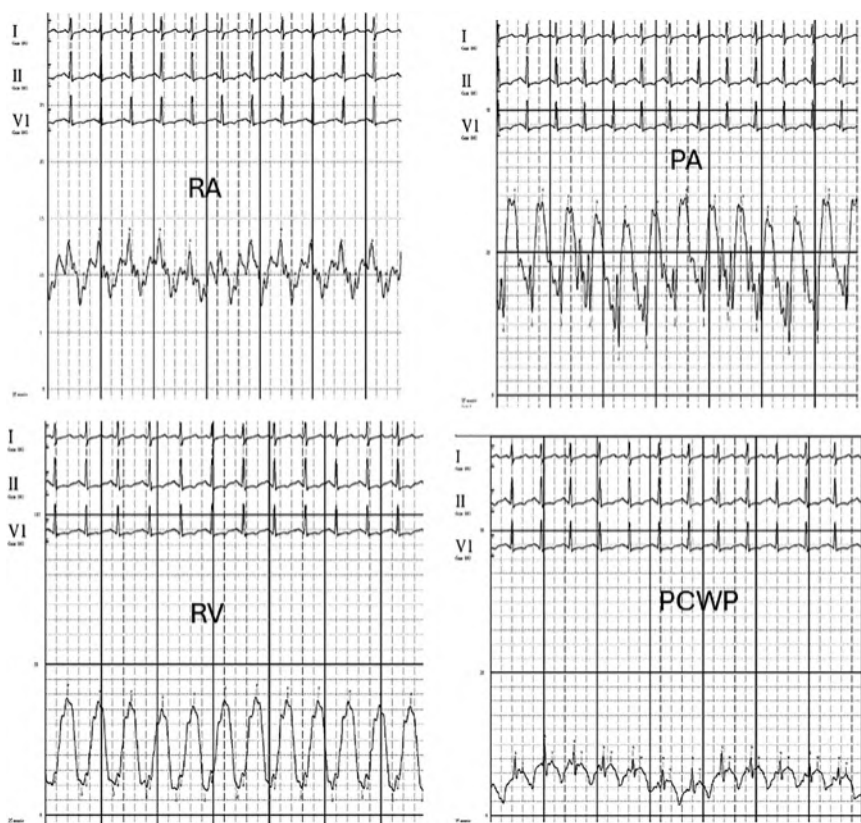


Figure 29.2 Right heart, pulmonary artery, and pulmonary capillary wedge pressures in a 51-year-old female who presented with acute, submassive pulmonary embolus. She suddenly felt short of breath while brushing her teeth and presented to her local Emergency Department where a PA CT angiogram showed a large saddle PE and evidence of right heart strain. Bedside point of care ultrasound showed evidence of right heart strain and troponin was mildly elevated. Of note is that she was recently in a car accident and was in a cast for a right navicular fracture.

useful is PAPI which is equal to PA pulse pressure divided by RA pressure. In various studies, PAPI has been reported to provide prognostic information on RV function in patients with cardiogenic shock, acute inferior myocardial infarction, undergoing LV assist device placement, pulmonary arterial hypertension (PAH), postcardiopulmonary bypass RV dysfunction, New York Heart Association class IV patients with heart failure and ambulatory patients with heart failure. There is no consensus on what constitutes a normal PAPI, although most studies have found that adverse events increase at $PAPi < 2$.

Invasive hemodynamic parameters that have been proposed to reflect RV performance:

Ratio of mean RA pressure to mean PCWP ratio with studies suggesting various cutoffs (including >0.6 or >0.8) are suggestive of RV dysfunction.

Pulmonary vascular resistance (PVR)

$$PVR = \frac{(mPAP - \text{mean PCWP})}{CO}$$

Pulmonary artery pulsatility index (PAPi)

$$PAPi = \frac{PA \text{ pulse pressure}}{mRAP} = \frac{PA \text{ systolic pressure minus } PA \text{ diastolic pressure}}{mRAP}$$

Pulmonary arterial compliance (PAC)

$$PAC = \frac{\text{Stroke volume}}{(PA \text{ systolic pressure} - PA \text{ diastolic pressure})}$$

Pulmonary effective arterial elastance can be estimated as RV end-systolic pressure/stroke volume where end-systolic pressure is estimated as $1.65 \times mPAP - 7.79$.

RV stroke work index (RVSWI)

$$RVSWI = SVI \times (mPAP - mRAP) \times 0.0136$$

where:

$$SVI = \text{stroke volume index} = \frac{\text{cardiac index (L/min/m}^2\text{)} \times 1000}{\text{heart rate (bpm)}}$$

mPAP = mean pulmonary artery pressure (mm Hg)

mRAP = mean RA pressure (mm Hg)

CO = cardiac output (L/min)

Etiologies of RV failure

There are a number of causes of acute RV failure and representative RHC findings are shown in Table 29.1. Potential etiologies include:

- *Acute RV infarction.* While this occurs most commonly during or immediately after acute occlusion of the right coronary artery (RCA), as in ST-elevation myocardial infarction (STEMI), it can also occur due to distal occlusion of a dominant left circumflex artery or a “wraparound” left anterior descending artery. The classic findings of hypotension, elevated jugular venous pressure, and lack of pulmonary congestion are suggestive of, though not pathognomonic for, this diagnosis [10]. More information on RV infarction can be found in Chapter 28.
- *Acute PH due to pulmonary embolism (PE) or pneumothorax (PTX).* Both PE and PTX result in an acute rise in RV afterload. In PE, this occurs both due to mechanical obstruction of the pulmonary vasculature as well as hypoxia-induced vasoconstriction. In PTX, acute external compression of the lung results in similar physiology. When these processes reach a critical level, the RV dilates, and the resulting pressure and volume overload result in LV underfilling and underperfusion of the coronary arteries. Massive PE is defined as an acute PE

Table 29.1 Causes of acute right ventricular failure with representative right heart catheterization findings. [CO/CI = cardiac output/cardiac index; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; RA = right atrium; RV = right ventricle.]

Cause	RA	RV	PA	PCWP	CO/CI
Acute RV infarction	↑	↑	↔	↔	↓
Acute (or acute-on-chronic) pulmonary hypertension	↑	↑	↑	↔	↓
Acute tricuspid regurgitation	↑	↑	↔	↔	↓
Complications of acute myocardial infarction (ventricular septal defect, RV free wall rupture)	↑	↑	↑	↑	↓
Pericardial effusion/tamponade	↑	↑	↑	↑	↓

accompanied by obstructive shock, systolic blood pressure (SBP) of <90 mm Hg, and/or cardiac arrest; in contrast, submassive PE is characterized by acute PE without systemic hypotension, but with evidence of RV dysfunction or strain or myocardial necrosis seen either on imaging or blood levels of cardiac troponin or B-type natriuretic peptides [11].

- *Acute tricuspid regurgitation (TR)*. While chronic TR can occur as a result of chronic RV failure, acute TR is most common in the setting of bacterial endocarditis resulting in valve damage or perforation. Alternatively, acute TR can have a non-infectious etiology – notably, valve damage related to endomyocardial biopsy or placement of a temporary or permanent transvenous pacemaker lead in the RV. Regardless of etiology, severe TR is associated with a very high mortality rate [12].
- *Mechanical complications of acute myocardial infarction (MI)*. While less common in the era of emergency primary percutaneous coronary intervention (PCI) for acute coronary syndromes including STEMI, mechanical complications of RCA MI such as acute ventricular septal defect (VSD) or RV free wall rupture can still occur, especially in patients whose presentation to the hospital is delayed. Post-MI VSD results in an acute left-to-right shunt with resulting pressure and volume overload of the RV.

There are several other situations in which acute RV failure can occur as a progression or exacerbation of diseases which cause chronic RV failure:

- *Pulmonary arterial hypertension (PAH)*. While the increased RV afterload characteristic of PAH is generally a chronic process, RV adaptation can, in some patients, be maladaptive, with RV dilatation and systolic dysfunction. Eventually, these maladaptive responses result in incomplete tricuspid valve leaflet coaptation, RV pressure and volume overload, changes in the metabolic profile of the RV cardiomyocytes, RV ischemia, and heightened adrenergic tone.
- *Arrhythmic right ventricular cardiomyopathy (ARVC)*. ARVC is a rare, inherited cause of cardiomyopathy characterized by mutations in the genes coding for desmosomes. Classically, there is fibrofatty infiltration of the RV inflow tract,

outflow tract, and apex, and LV involvement is often also affected. While ARVC mostly results in arrhythmic issues, heart failure, including isolated RV failure, is usually a late manifestation of ARVC. Because there is no direct treatment or cure for ARVC, fulminant disease can sometimes require transplantation [13].

- Constrictive pericarditis. Constrictive pericarditis occurs when a thickened pericardium (due to prior surgery or radiation, tuberculosis, acute pericarditis, or other rheumatologic or inflammatory diseases; see chapter 18) inhibits filling of the RV and LV during diastole. Noninvasive imaging and invasive hemodynamics will, classically, demonstrate ventricular interdependence with near equalization of right and left heart-filling pressures and discordance of RV and LV pressure during the respiratory cycle. Patients whose disease is not adequately manageable with medical therapy (i.e., diuretics) may develop fulminant disease for which the only definitive treatment is surgical pericardiectomy [14].
- Congenital heart disease with intracardiac shunts. These diseases, including atrial and ventricular septal defects (ASD/VSD) and patent ductus arteriosus, are often characterized by left-to-right shunting early in life. However, chronic RV pressure and volume overload can result in RV failure and PH, which can cause the shunt to reverse to become right-to-left shunting in late-stage disease, leading to cyanosis and RV failure [15].

Management of acute RV failure

It should not come as a surprise that the treatment of acute RV failure depends on its etiology and the specific hemodynamic profile in an individual patient. The best treatment of RV failure is to relieve the underlying cause (i.e. acute PE, RV infarction, etc.) but some general recommendations regarding medical and interventional management of acute RV failure can be made. It is important to realize that the evidence for each of these therapies is generally of low quality [16].

Patients with chronic RV failure often have elevated right-sided pressures requiring treatment with diuretics. However, patients in shock may actually benefit from volume expansion to augment RV stroke volume. For patients with PAH, pharmacotherapy targeting the endothelin, prostacyclin, and nitric oxide pathways is the mainstay of both acute and chronic treatment. In more severe or refractory acute cases of RV failure, augmentation of cardiac output with inotropes such as dobutamine or milrinone may be necessary although milrinone must be used with caution to avoid excessive systemic vasodilation [1, 17].

For patients with severe acute right heart failure refractory to medical management, temporary mechanical circulatory support (MCS) with a right ventricular assist device (RVAD) is sometimes required. While the available devices have improved considerably over the last 10–20 years, they all still require large-bore vascular access and so carry a high risk of peri- and post-procedural bleeding [18]. It should be noted that in patients with severe decompensated PAH, RVAD

implantation often leads to pulmonary hemorrhage and should not be used. Available right-sided temporary MCS devices include [19]:

- The Impella RP temporary extracorporeal RVAD (Abiomed, Inc., Danvers, MA, United States), inserted via the femoral vein, consists of a microaxial pump which drains blood from the RA and ejects it into the PA. The RECOVER RIGHT single-arm outcomes trial [20], which consisted of only 30 patients, showed a 30-day survival of 73%.
- The PROTEK Duo RVAD (LivaNova, PLC, London, United Kingdom) is a dual-lumen cannula, which is inserted via the IJ vein and advanced to the distal PA. The device is connected to an extracorporeal centrifugal flow pump that aspirates blood from the RA and delivers it to the PA. One potential benefit of this device is that, because it is inserted via the IJ vein, it allows for ambulation while awaiting recovery or transplantation [21].
- Intermediate-term RV support can be provided with surgical RVAD devices such as the CentriMag (Abbott Cardiovascular) extracorporeal centrifugal flow pump, which is centrally inserted via a sternotomy or thoracotomy with the inflow cannula positioned in the RA and the outflow cannula positioned in the PA.
- Extracorporeal membrane oxygenation (ECMO) provides perfusion and oxygenation and can be used to support the heart while awaiting a definitive therapy such as mechanical thrombectomy or as a bridge to heart transplantation [22]. Venovenous ECMO (VV-ECMO) can be used in cases of isolated RV failure related to acute respiratory failure but does not provide circulatory support. Venoarterial ECMO (VA-ECMO) is the preferred modality in primary RV failure with or without concomitant LV failure. VA-ECMO can decompress the failing RV and restore adequate cardiac output; however, VA-ECMO also results in an increase in LV afterload which can be transmitted backward through the pulmonary vasculature resulting in pulmonary edema. A triple cannulation strategy (venoarterial-venous or VAV-ECMO) can be used in cases where a patient initially cannulated for VV-ECMO experiences progressive RV failure. Peripheral cannulation via the femoral artery and vein, with catheters terminating in the descending aorta and inferior vena cava, respectively, is the most common approach for emergency cases. While ECMO is a very effective therapy for supporting the failing RV, there is a high rate of vascular and bleeding complications and should be reserved for only the most refractory cases [23].

Conclusions

Treatment of isolated acute RV failure remains challenging, and much remains to be improved in our knowledge of the “forgotten” ventricle. We have, in this chapter, described a multitude of new invasive and noninvasive techniques for assessment of RV function; however, we do not yet fully understand which of these is

the best measurement in individual situations. Finally, while much of our treatment of acute RV failure is focused on improving the loading conditions of the RV, rather than RV contractility directly, future therapies may directly target RV function on a molecular level.

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CHAPTER 30

Pulmonary hypertension

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[This is a revision of a chapter from the second edition: Pulmonary hypertension by Lisa J. Rose-Jones, Daniel Fox, David P. McLaughlin and George A. Stouffer]

The normal pulmonary circulation consists of the pulmonary arteries, which receive deoxygenated blood from the thin-walled, compliant right ventricle (RV). The pulmonary arteries deliver this blood to the capillary beds of the respiratory parenchyma where carbon dioxide is exchanged for oxygen. Oxygen-rich blood is then delivered to the left atrium via the pulmonary veins (Figure 30.1). This circulation is characterized by high blood flow, low pressure, and low resistance. The normal adult pulmonary vascular bed is highly distensible and capable of accommodating large increases in blood flow with minimal elevations of pressure. Normal peak systolic pressures in the pulmonary arteries range from 18 to 25 mm Hg and end-diastolic pressures range from 6 to 10 mm Hg, with a normal mean pressure of less than 20 mm Hg.

Pulmonary hypertension is quite simply elevated pressure in the pulmonary arteries. Right heart catheterization plays a crucial role in further defining the cause of the pulmonary pressure elevation and determining its severity. Pulmonary hypertension is defined as a mean pulmonary artery pressure (PAP) >20 mm Hg [1, 2]. Pulmonary arterial hypertension (PAH), a true resistance in the pulmonary vascular bed due to vasculopathy, is further defined by a mean PCWP ≤ 15 mm Hg and PVR ≥ 2 Wood units based on the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines [1].

Hemodynamic profiles help group patients into the World Health Organization (WHO) classification scheme (Table 30.1) [3]. This allows for patients to be categorized based on similar pathologic findings and guides the clinician as to what therapeutic strategies should be pursued. Pulmonary hypertension may be the consequence of increased pulmonary blood flow (e.g., anemia, pregnancy, thyrotoxicosis), increased pulmonary vascular resistance (PVR), or elevated left heart pressure.

WHO Group 1 PAH is a panvasculopathy of the distal pulmonary arteries that is characterized by medial hypertrophy, intimal proliferation, and fibrosis with

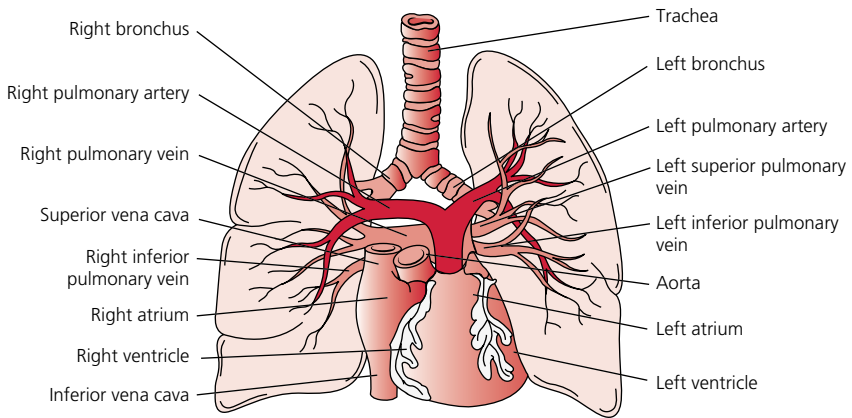


Figure 30.1 Pulmonary arteries and veins.

Table 30.1 5th World Health Organization classification of pulmonary hypertension.

WHO Group 1: Pulmonary arterial hypertension (PAH)

- Idiopathic
- Heritable: BMPR2, ALK-1, ENG, SMAD9, CVA1, KCN3
- Drug/toxin: fenfluramine, aminorex
- Associated with congenital heart disease (systemic to pulmonary shunt lesions), connective tissue disease (esp. scleroderma), portal hypertension, HIV infection, and schistosomiasis

WHO Group 2: Pulmonary hypertension owing to left heart disease

- Left ventricular systolic or diastolic dysfunction, valvular heart disease, and congenital/acquired left heart inflow/outflow tract obstructions

WHO Group 3: Pulmonary hypertension owing to lung diseases and/or hypoxia

- Chronic obstructive lung disease, interstitial lung disease, sleep-disordered breathing, mixed obstructive and restrictive lung diseases, alveolar hypoventilation disorders, chronic high altitude exposure, and developmental lung disease

WHO Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)

WHO Group 5: Pulmonary hypertension with unclear and multifactorial mechanisms

- Sarcoid, chronic hemolytic anemia, myeloproliferative disorders, metabolic disorders, chronic renal failure, etc.

ultimate plexiform lesion formation. There are numerous systemic conditions and heritable genetic mutations that are associated with the development of PAH.

WHO Group 2 pulmonary hypertension is far and away the most prevalent. It is pulmonary hypertension as a result of left heart disease.

Chronic lung disease and/or hypoxia represent the causative nature in WHO Group 3 pulmonary hypertension. This is felt to be secondary to hypoxia-triggered vasoconstriction and vascular remodelling, as well as hyperinflation-induced compression and obliteration of alveolar vessels.

Chronic thromboembolic disease makes up WHO Group 4. It is hemodynamically similar to PAH but results in arteriopathy as a consequence of thromboembolic

material. There is some variability in reported incidences, but recent meta-analysis data estimates the development of chronic thromboembolic disease to be about 3% [4–6]. This patient population is increasing making it essential to identify as it is potentially curable with surgical intervention [7].

Last, WHO Group 5 is composed of several different disorders that have not been as well studied. This collection of disorders has unclear and/or multifactorial mechanisms as to the causation of pulmonary hypertension.

Hemodynamic changes associated with pulmonary hypertension

The hemodynamic hallmark of pulmonary hypertension is elevated PAPs. A mean PAP > 20 mm Hg is the current definition of pulmonary hypertension based on recent data [1]. Historically, this cutoff had been arbitrarily defined as a mean PAP $\geq$ 25 mm Hg and was accepted by the pulmonary hypertension community and used in all major multi-center trials. However, more recent data has shown that a normal mean PAP is 14.0 ± 3.3 mm Hg and thus two standard deviations above that gives the upper limit of normal now used in the updated definition [8].

PAPs increase in response to elevated left atrial pressure, cardiac output, or true changes in PVR from arterial remodelling. The latter, which represents PAH, has the most evidence base behind targeting management through treatment with pulmonary-specific vasodilator therapy. Thus, hemodynamics obtained through right heart catheterization are imperative to guide diagnosis and treatment options.

Hemodynamic changes in patients with elevated pulmonary pressures depend on the extent of the pulmonary hypertension. The sheer magnitude to which the pulmonary pressures are elevated is important to note—the higher the pressure, the more afterload on the RV. The thin-walled, highly compliant RV can accommodate acute increases in volumes at physiologic pressures (i.e., during exercise), but it is not designed to overcome abrupt increases in afterload. Thus, acute RV dilation and failure can accompany sudden increases in pulmonary pressure (i.e., with acute pulmonary embolus). In chronic pulmonary hypertension, RV wall thickness increases to normalize wall stress and myocardial oxygen consumption. However, over time, as PVR increases with obliterative pulmonary artery remodelling, the RV reaches a point where it can no longer overcome this afterload. It dilates and starts to fail. As RV failure ensues and forward flow is impaired, the mean PAP will decrease. It is important not to be fooled by these “lower-” than-expected mean PAPs. This end-stage disease progression is best detected by significant elevations in right atrial (RA) pressures (generally > 20 mm Hg) associated with a low cardiac index (< 2.0 L/min/m²). Both of these have been associated with worse survival [9].

In moderate cases of pulmonary hypertension, it is not uncommon to see very prominent A waves in the RA pressure tracings (Figure 30.2). This is a reflection of impaired RV compliance and an increase in RV end-diastolic pressure. In more

severe cases with significant tricuspid regurgitation, prominent V waves may be present on RA pressure tracings. Occasionally, with severe cases of RV failure and tricuspid regurgitation, RA pressure tracings take on characteristics similar to ventricular pressure tracings (see Chapter 13).

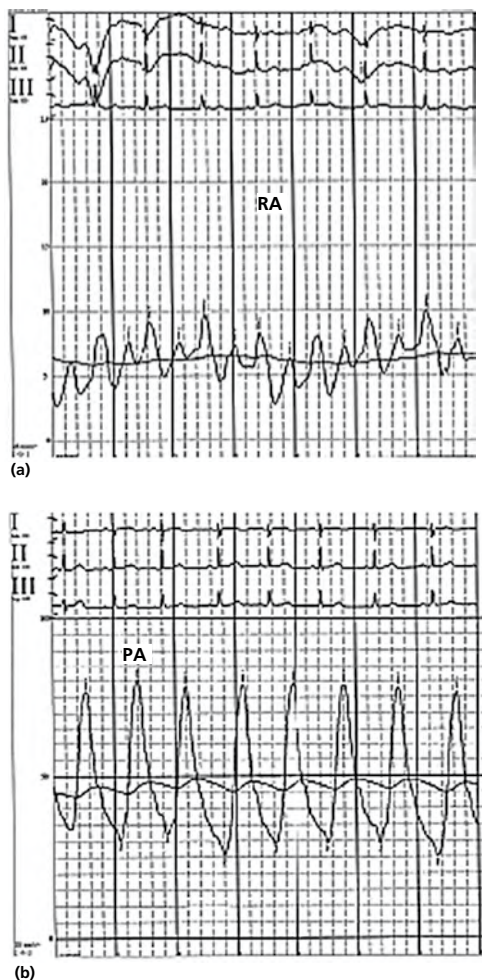


Figure 30.2 Pressure tracings in a patient with pulmonary arterial hypertension associated with scleroderma. Panel (a) shows a right atrial hemodynamic tracing. Note the prominent A waves due to a noncompliant, hypertrophied right ventricle. Panel (b) shows a pulmonary artery pressure waveform on a 100 mm Hg scale. Note the peak systolic pressure of 96 mm Hg and mean pressures of around 67 mm Hg. Panel (c) shows pulmonary capillary wedge pressures (PCWP) via a balloon-tipped pulmonary artery catheter. The PCWP is crucial in excluding left heart disease as an etiology of elevated pulmonary pressure. It is also necessary for calculating pulmonary vascular resistance, which is included in the hemodynamic definition of PAH. PCWP at end-expiration: (Mean): 9 (a-wave): 10 (v-wave): 10 mm Hg.

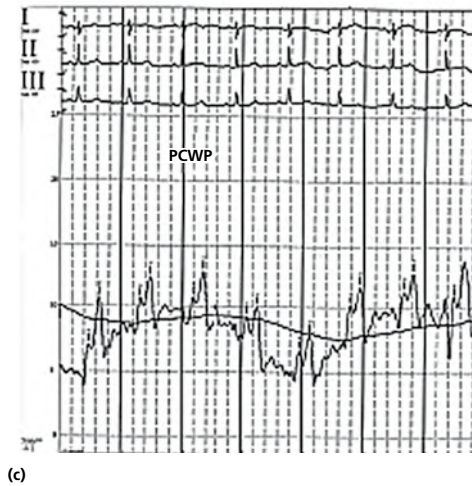


Figure 30.2 (Continued)

In addition to mean PAP ≥ 20 mm Hg and mean PCWP ≤ 15 mm Hg, the amount of PVR is another important consideration when defining pulmonary hypertension [1]. PVR is calculated by dividing the transpulmonary pressure gradient (mm Hg) by the cardiac output (CO; liters/min).

$$\text{PVR} = \frac{(\text{mean PAP} - \text{mean PCWP})}{\text{CO}}$$

PVR is generally expressed in Wood units (1 WU = 1 mm Hg min/L = 80 dyne s/cm⁵). All pressure measurements in the equation should be assessed at end expiration. However, in the subset of patients that have large intrathoracic pressure changes during a respiratory cycle (i.e., chronic obstructive pulmonary disease or obesity), it is appropriate to average pressures over three to four respiratory cycles [1]. Thermodilution is the preferred method for measuring CO in this setting.

PVR has two components: the fixed component that results from vascular remodelling and cannot change acutely, as well as the dynamic component from vasoconstriction. PVR is mainly determined by the geometry of small distal resistive pulmonary arterioles, and according to Poiseuille's law, PVR is inversely related to the fourth power of arterial radius.

Hemodynamic changes detected by history and physical exam

The most common symptom attributable to pulmonary hypertension is exertional dyspnea, though angina can also occur. This results from increased RV myocardial oxygen demand due to high wall stress. The RV is generally perfused during both

systole and diastole; however, in pulmonary hypertension, there is a drop in systolic coronary blood flow due to high RV systolic pressures in response to elevated pulmonary pressures. There can also occasionally be compression of the left main coronary by a dilated main pulmonary artery. Other common symptoms include fatigue and peripheral edema. Syncope is a sign of very advanced disease. On physical exam, increased jugular venous pressure with visually prominent A waves is typical. A left parasternal lift produced by the impulse of the hypertrophied high-pressure RV is sometimes palpable. On auscultation, patients with pulmonary hypertension will have an increased pulmonic component of the second heart sound and may have a right-sided S4 heart sound and/or an early systolic ejection click due to sudden interruption of the pulmonary valve opening. A mid-systolic ejection murmur caused by turbulent transvalvular pulmonary flow may also be audible.

The Graham Steell murmur of pulmonary regurgitation, an early diastolic decrescendo murmur at the left sternal border, is not uncommon in advanced cases. Other findings in patients with severe pulmonary hypertension include those associated with tricuspid regurgitation (a holosystolic murmur that augments with inspiration and prominent V waves in the jugular veins) and right ventricular failure (hepatojugular reflux, a pulsatile liver, a right ventricular S3 gallop, and peripheral edema).

Pulmonary vasoreactivity testing

Assessing pulmonary vasoreactivity with pharmacologic vasodilator therapy is indicated in several clinical settings. Patients with WHO Group 1 PAH whose etiology is felt to be idiopathic, heritable, or anorexigen-induced should undergo a vasodilator challenge [10]. This test predicts short-term response to oral calcium channel blocker therapy and has the most evidence for treatment effect among the aforementioned groups. Vasoreactivity testing is most easily accomplished with inhaled nitric oxide, although occasionally intravenous epoprostenol or inhaled iloprost is employed [1]. A positive vasodilator response is defined as a reduction of the mean PAP of at least 10mm Hg to an absolute value of less than 40mm Hg without a decline in the CO [11]. Less than 10% of patients will respond. However, positive vasoreactivity testing does not predict long-term response to calcium channel blocker therapy [1]. Limitations to vasoreactivity testing include increased time during the procedure itself, cost of the medication, logistical barriers to obtaining the vasodilator medication of choice (in many insitutions, inhaled nitric oxide can only be administered by a Respiratory Therapist), and adverse reactions during its administration.

Special population: pulmonary hypertension in congenital heart disease

Some of the highest PAPs will be seen in a rare condition termed Eisenmenger's syndrome. This results from longstanding, untreated large intra- and extracardiac defects that initially begin as systemic to pulmonary shunts. It is felt that

high-pressure pulmonary blood flow results in vascular endothelial damage that incites the milieu to shift into the remodelling process of vasoconstriction, inflammation, and thrombosis. Eventually, resistance in the pulmonary arteries leads to elevation in right heart pressure (Figure 30.3). This leads to a reversal of flow resulting in right-to-left shunting (Eisenmenger's physiology). Patients with Eisenmenger's syndrome develop cyanosis, hypoxemia, and secondary erythrocytosis.

Special population: pulmonary hypertension in patients being evaluated for cardiac transplantation

The contribution of reversible and fixed components of PVR is best illustrated in patients being evaluated for cardiac transplantation. It remains important to distinguish these components because donor hearts are unable to pump against significant PVR for any length of time. If there is a large component of fixed resistance, the cardiac allograft will fail because the donor RV cannot acclimate and overcome the elevated afterload. On the other hand, if the PVR is high but consists primarily of a dynamic component of vasoconstriction triggered as a response to elevated left heart pressures, the patient's pulmonary resistance will drop dramatically following transplantation as left heart pressures normalize.

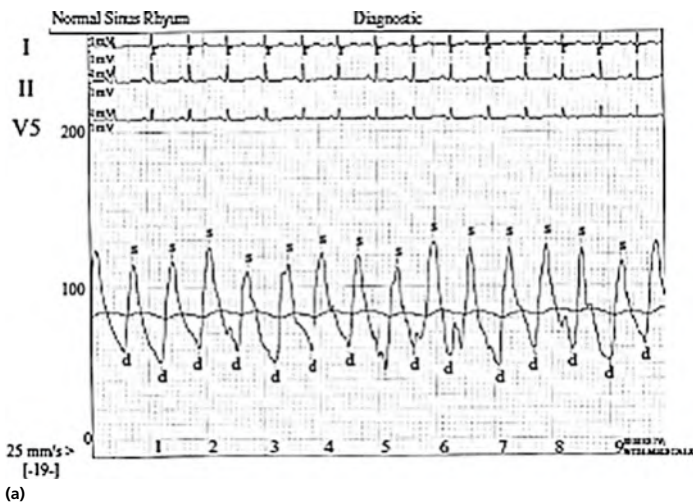


Figure 30.3 Pressure tracings from a patient with Eisenmenger's syndrome. Panel (a) shows pulmonary artery pressures on a 200 mm-Hg scale. Peak systolic and mean pressures of 120 mm Hg and 82 mm Hg are indicative of severe pulmonary hypertension. Panel (b) shows simultaneous left ventricular and PA pressures. Panel (c) shows simultaneous measurements of right and left ventricular pressures. At this point in time, the pressures are equal in the two ventricles.

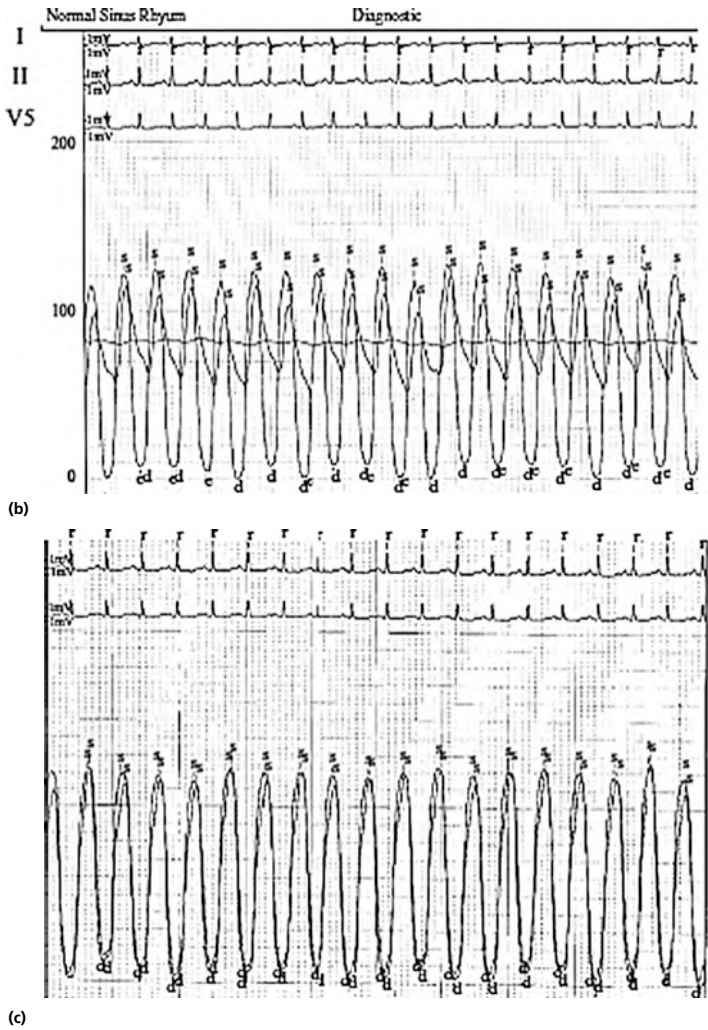


Figure 30.3 (Continued)

The International Society of Heart and Lung Transplantation (ISHLT) recommends determining the relative contributions of fixed and dynamic components. Assessment of reversibility is generally indicated when PA systolic pressure ≥ 50 mm Hg and the transpulmonary gradient ≥ 15 mm Hg and/or PVR > 3 Wood units [12]. Nitroprusside is the preferred agent of choice since it induces a simultaneous decrease in both pulmonary and systemic afterload. Nitroprusside can result in a reduction in left atrial pressure, which will decrease PAPs and theoretically reduce the possibility of pulmonary edema from selective pulmonary vasodilatation in the setting of elevated left-sided filling pressures. Inability to

“reverse” pulmonary hypertension is associated with a high incidence of post-transplant mortality from right heart failure and is thus a contraindication to heart transplantation.

Case study

The patient is a 54-year-old female with a history of end-stage ischemic cardiomyopathy and coronary artery bypass grafting 8 years prior. The left ventricular ejection fraction was severely reduced at 10–15%. She presented for evaluation for cardiac transplantation as she had worsening exertional dyspnea and frequent hospitalizations for decompensated heart failure. Right heart catheterization revealed significant pulmonary hypertension that would otherwise preclude transplantation (see Table 30.2). After graduated administration of nitroprusside, the patient’s pulmonary pressures were deemed “reversible” and she was cleared to proceed with transplantation.

Table 30.2 Pressures in a patient with severe systolic LV dysfunction at baseline and during nitroprusside infusion.

	Baseline	Nitroprusside infusion
Systemic BP	106/73	92/60
Mean PCWP	24	8
PA (mean)	65/34(44)	32/10 (17)
Cardiac output	2.9	4.4
PVR (Wood units)	7.0	2.0

Two-dimensional echocardiography in pulmonary hypertension

While right heart catheterization remains the gold standard for the diagnosis of pulmonary hypertension, two-dimensional echocardiography is a reasonable initial noninvasive diagnostic study when the history, symptoms, or physical exam suggest pulmonary hypertension. Estimating the pulmonary artery systolic pressure on echocardiography is typically done via the use of a modified Bernoulli equation. The velocity of the TR jet (an estimation of the difference in pressure between the RV and RA during systole) is added to the RA pressure estimation as seen below.

Pulmonary artery systolic pressure = $4v^2$ + RA pressure

However, it is now recommended that the peak velocity of the TR jet (Figure 30.4) be used instead of the estimated pulmonary artery systolic pressure to reduce the

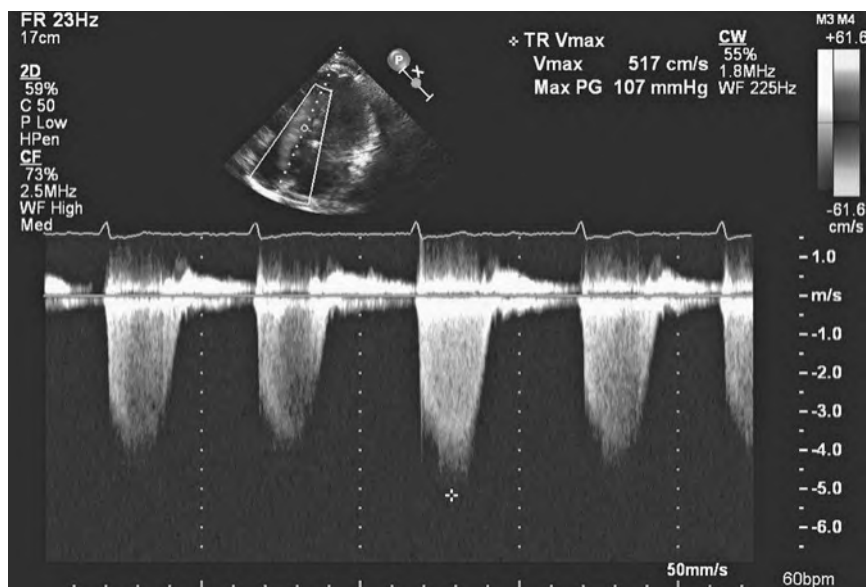


Figure 30.4 Using echocardiography to measure peak TR jet velocity. An example of pulsed-wave Doppler obtained at the level of the tricuspid valve in a patient with pulmonary hypertension.

inaccuracies of the noninvasive RA pressure estimations that then get amplified by measurement errors in the equation [1, 13, 14]. A peak TR velocity >2.8 m/sec may suggest pulmonary hypertension when coupled with other concomitant echocardiographic abnormalities and the appropriate clinical context.

The transthoracic echocardiogram is important not only to get to an assessment of the pulmonary artery systolic pressure but also to look for signs of remodeling of the right atrium and ventricle in response to increased afterload. Furthermore, it is also extremely useful to look for the most common cause of pulmonary hypertension: left-sided heart failure.

Take home message

Pulmonary hypertension is a broad term that purely reflects elevated pulmonary pressures. While a good history and physical exam are necessary, echocardiography can provide an initial assessment of pulmonary pressures. Invasive hemodynamic testing remains the gold standard in diagnosing pulmonary hypertension. Hemodynamics helps specifically tease out if PAH is present, defined as mean PAP >20 mm Hg, mean PCWP ≤ 15 mm Hg, and PVR >2 Wood units. PAH is a pan vasculopathy that has data to support the use of treatment with pulmonary vasodilators.

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CHAPTER 31

Hemodynamics of arrhythmias and pacemakers

Revised and updated by George A. Stouffer

[Original chapter by Rodrigo Bolanos, Kimberly A. Selzman, Lukas Jantac, and George A. Stouffer]

The cardiac rhythm is integral to the development of physiologic pressure waveforms. Disturbances in electrical conduction can change atrial and ventricular filling and contraction and, hence, hemodynamic parameters. This chapter will describe changes that take place as a result of some of the most common arrhythmias encountered in the coronary intensive care unit or cardiac catheterization laboratory. Although sinus tachycardia and sinus bradycardia usually represent normal cardiac physiology, they will also be discussed in this chapter because of their effects on pressure tracings and hemodynamic parameters. Last, we will discuss the hemodynamic effects of pacemakers.

Premature atrial and ventricular contractions

Perhaps the most frequently encountered cardiac arrhythmia is a premature beat, either a premature atrial contraction (PAC) or a premature ventricular contraction (PVC). Although a single ectopic beat is unlikely to have a clinically significant hemodynamic effect, the pressure tracings associated with it are interesting. As a result of the earlier-than-normal ventricular contraction and shortened diastolic filling time, the stroke volume and arterial pulse pressure are substantially reduced. The post-ectopic beat tends to produce an increased stroke volume secondary to enhanced ventricular filling during the compensatory pause (Figure 31.1). An increase in arterial pulse pressure will also be evident.

A PVC can serve as an aid in diagnosing hypertrophic obstructive cardiomyopathy (HOCM). This finding was first described in 1961 and is termed the Brockenbrough–Braunwald–Morrow sign (see Chapter 15 for a further description of this sign). It is defined as a decrease in aortic pulse pressure during the

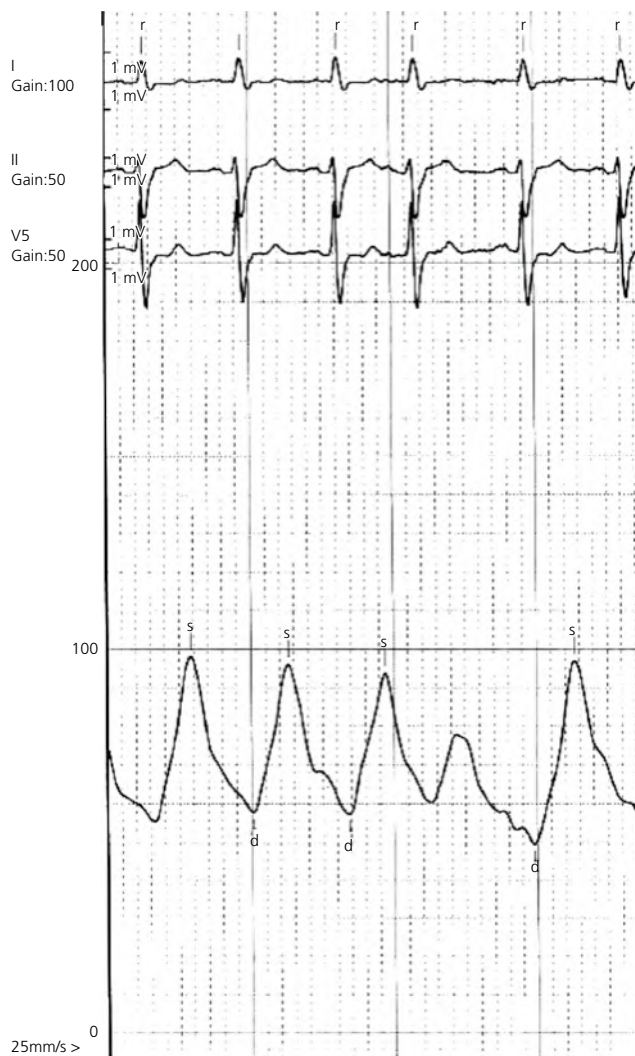


Figure 31.1 Aortic pressure tracing during PAC.

sinus beat immediately following a PVC (Figure 31.2). A decrease in pulse pressure post-PVC is much more specific for HOCM than other post-PVC hemodynamic findings (e.g. an increase in the left ventricular systolic pressure or an increase in the systolic gradient between the left ventricle and aorta), which can also be seen with aortic valve stenosis. On palpation of the carotid pulse, a reduced impulse on the beat following an ectopic beat may be noted in patients with HOCM in contrast to the usual finding of an increased impulse (i.e., increased pulse pressure).



Figure 31.2 Brockenbrough–Braunwald–Morrow sign. Simultaneous recordings of LV and aortic pressures in a patient with HOCM (a) and a patient with aortic stenosis (b). Note that pulse pressure falls in the post-PVC beat in HOCM (arrow), but increases in the post-PVC beat in aortic stenosis.

Heart block

Complete heart block (CHB) causes dissociation of the electrical activity of the atria and ventricles. CHB is generally associated with a slowing in ventricular rate with the resulting ventricular rate being dependent on the site of pacemaker activity (i.e., junctional or ventricular) that serves as an escape rhythm. Systolic blood

pressure may be preserved, but the long periods between ventricular contractions are associated with lower diastolic blood pressure and lower mean arterial pressure (Figure 31.3). Note that systolic pressure may be increased in heart block to maintain mean arterial pressure in the setting of bradycardia (Figure 31.4).

Cannon A waves

Large A waves on atrial pressure tracings that result from atrial contraction when the mitral or tricuspid valves are closed are termed “cannon A” waves. Cannon A waves result when ventricular contraction takes place during or just prior to atrial contraction. This increases ventricular pressure to the point where the tricuspid or mitral valve does not open during atrial contraction, which results in increased atrial pressure. Any arrhythmia that causes atrioventricular (AV) dissociation (e.g., CHB, pacemaker syndrome, or ventricular tachycardia) can cause random cannon A waves (Figure 31.5). More rarely seen are arrhythmias in which the atrium is activated via retrograde conduction (e.g., AV nodal re-entry or some forms of ventricular tachycardia), which can cause regular cannon A waves.

Ventricular tachycardia

Much like a PVC, ventricular tachycardia originates in the ventricles and represents an abnormal sequence of electrical as well as mechanical events. The P wave on an electrocardiogram (ECG) representing atrial activation may or may not be visible during ventricular tachycardia. Atrial activation during this arrhythmia may take place as a result of normal antegrade activation from the sinus node or via retrograde conduction from the ventricles. Ventricular tachycardia resulting in complete AV dissociation will produce random cannon A waves. Less commonly, when atrial activation during ventricular tachycardia occurs via retrograde activation, cannon A waves will be observed in a regular fashion.

The rapid rate and loss of atrial contribution to ventricular filling that are seen in ventricular tachycardia can lead to hemodynamic deterioration (Figure 31.6). As shown in Figure 31.7, the sudden onset of ventricular tachycardia in this patient resulted in the loss of systolic pressure generation and thus a steady decay in mean blood pressure.

Junctional rhythm

During junctional rhythm, atria may be activated via retrograde impulse originating in or around the AV node. The retrograde atrial activation is evident in leads I and II on the standard 12-lead ECG, as the P waves, if seen at all, will be inverted. Atrial systole may occur during, before, or after ventricular systole in this setting.

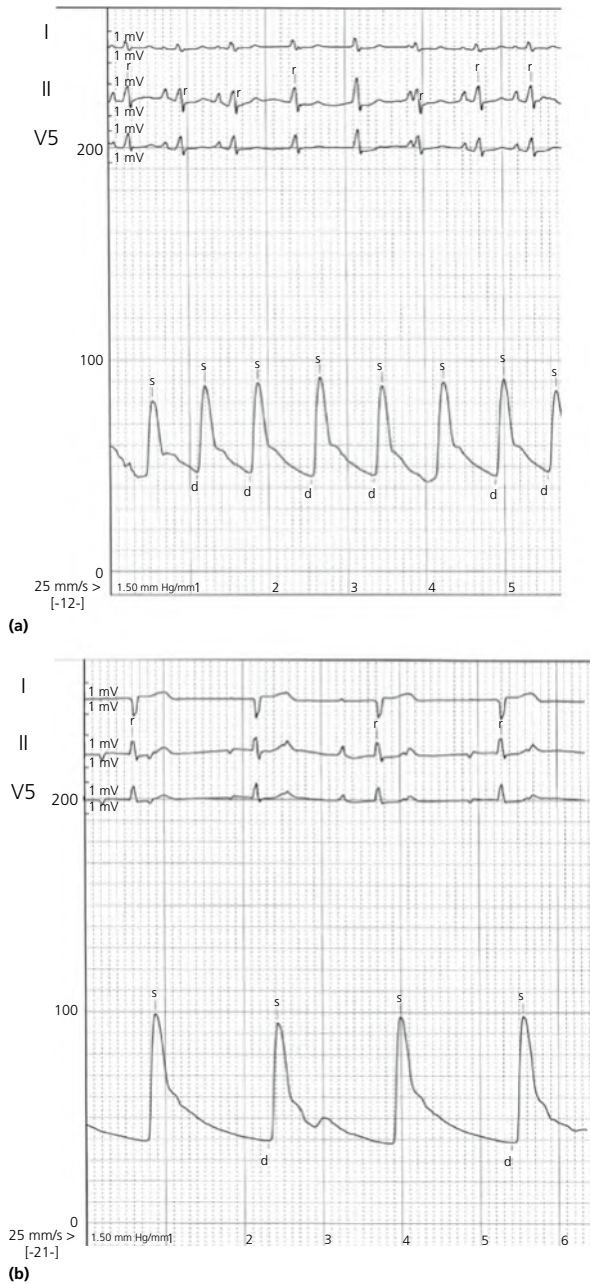
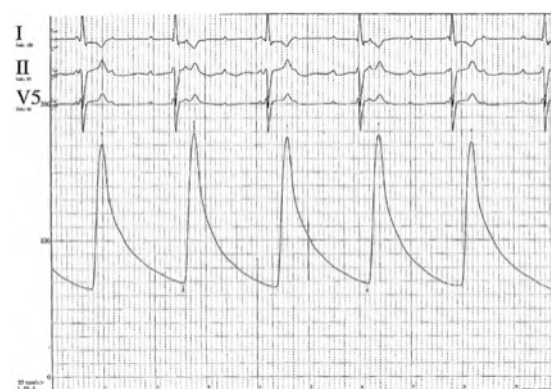


Figure 31.3 Aortic pressure tracings in a patient who developed CHB. Aortic pressures during a brief period (a) and sustained episode (b) of CHB are shown.



(a)



(b)

Figure 31.4 Aortic blood pressure pre- (a) and post- (b) development of CHB with a junctional escape rhythm. Note that systolic pressure increased and diastolic pressure decreased with development of CHB with minimal change in mean arterial pressure.



Figure 31.5 Right atrial pressure in a patient with CHB. Note the increase in A wave amplitude when the atrium contracts against a closed tricuspid valve (cannon A waves represented by arrows).

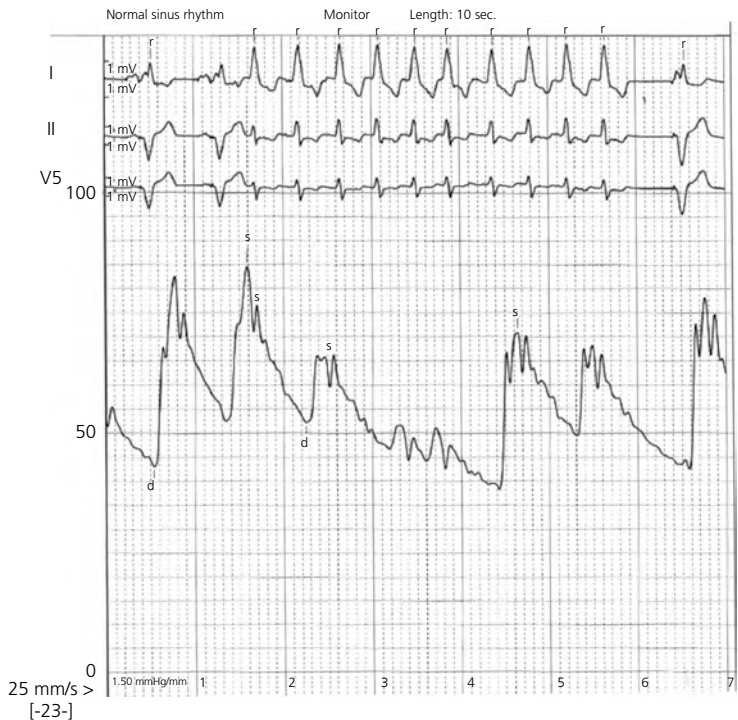


Figure 31.6 Aortic pressure in an elderly woman with a permanent pacemaker and a transient episode of ventricular tachycardia.

As seen with ventricular tachycardia, complete AV dissociation may also be present during a junctional rhythm. Because atria may be activated immediately following ventricular systole, cannon A waves can be observed on the right atrial (RA) hemodynamic recording. Although junctional rhythm is in general slow (40–60bpm), accelerated junctional rhythm may compromise systolic pressure generation (Figure 31.8).

Atrial fibrillation and atrial flutter

Because atrial fibrillation results in the lack of organized atrial contraction, the A wave will be absent from the pressure tracings. Depending on the size of the atrium, V waves may also be lacking if the atrium is large enough to serve as a distensible, compliant reservoir (Figure 31.9a). Occasionally, atrial activity may produce enough pressure to open and close the mitral and tricuspid valves and give rise to a C wave on the RA pressure recording. The rhythm in atrial fibrillation is irregular, with a varying length of time spent in diastole. As a result, the stroke volume and hence arterial pulse pressure may vary greatly from beat to

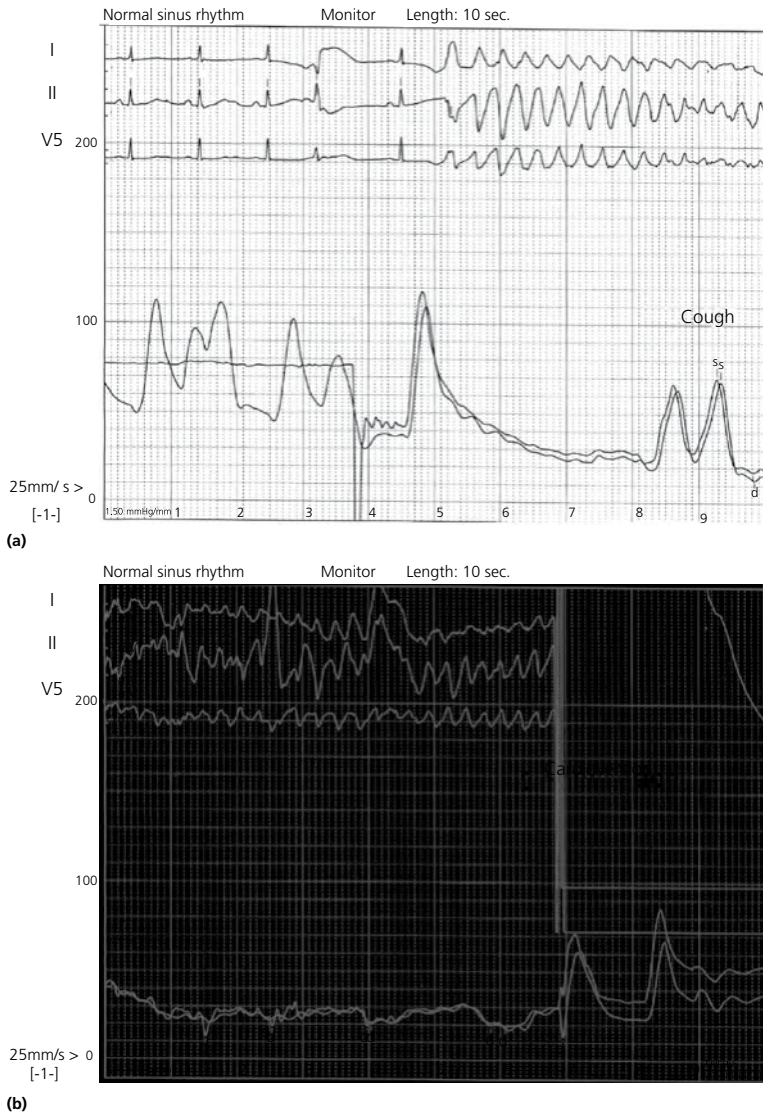


Figure 31.7 Aortic and distal left anterior descending (LAD) coronary artery pressure in a patient who developed ventricular tachycardia following intracoronary adenosine administration. The patient was undergoing fractional flow reserve evaluation of a lesion in the LAD when ventricular tachycardia developed (a). The increase in aortic pressure with a cough can be seen. In panel (b), the return of pulsatile blood pressure can be seen following electrical cardioversion.

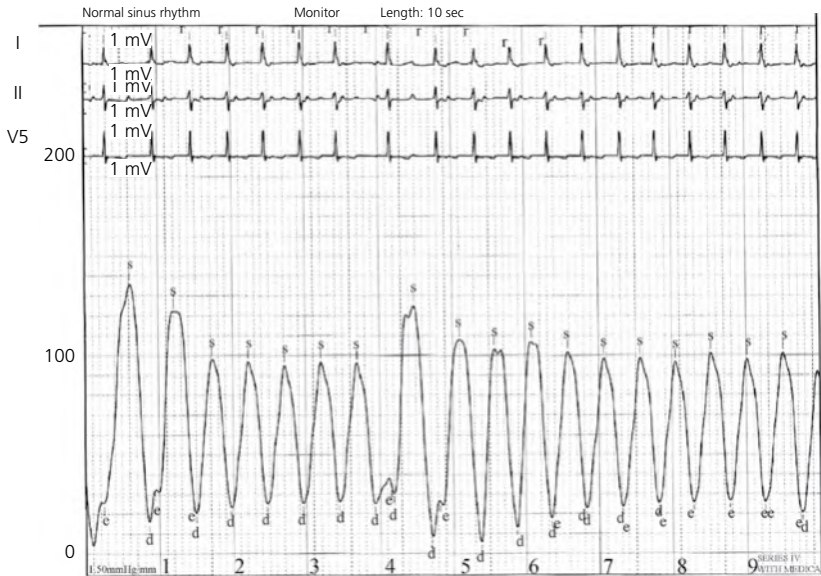


Figure 31.8 Left ventricular pressure during an episode of junctional tachycardia.

beat. In general, the longer the diastolic period, the higher the pulse pressure (Figure 31.9b).

In atrial flutter, atrial activity is more organized than in atrial fibrillation and atrial systole can occur (usually at a rate of approximately 300 bpm). The regular atrial activity is reflected on RA pressure tracings as flutter waves (Figure 31.10). Systolic pressure will vary with left ventricular filling. Almost always, atrial-ventricular block exists, whereby not every atrial impulse is conducted to the ventricles. Because atrial contraction can take place against a closed mitral or tricuspid valve, an exaggerated flutter wave similar to a cannon A wave may be seen. For a detailed description of the hemodynamic importance of atrial contraction, see Chapter 5.

Sinus bradycardia or tachycardia

Sinus bradycardia or tachycardia may result in hemodynamic effects and pressure tracings that mimic other arrhythmias. During sinus tachycardia, for example, the cardiac cycle length is shortened, as evidenced by a decreased R-R interval (Figure 31.11). On the RA pressure waveform, one may not be able to distinguish separate A and V waves, because the A wave of one cycle comes progressively closer to the V wave of the preceding cycle as the heart rate increases. As a result, the tracing may resemble that of cardiac tamponade, because the Y descent will not be evident. As a result of the reduced diastolic filling time, stroke volume may

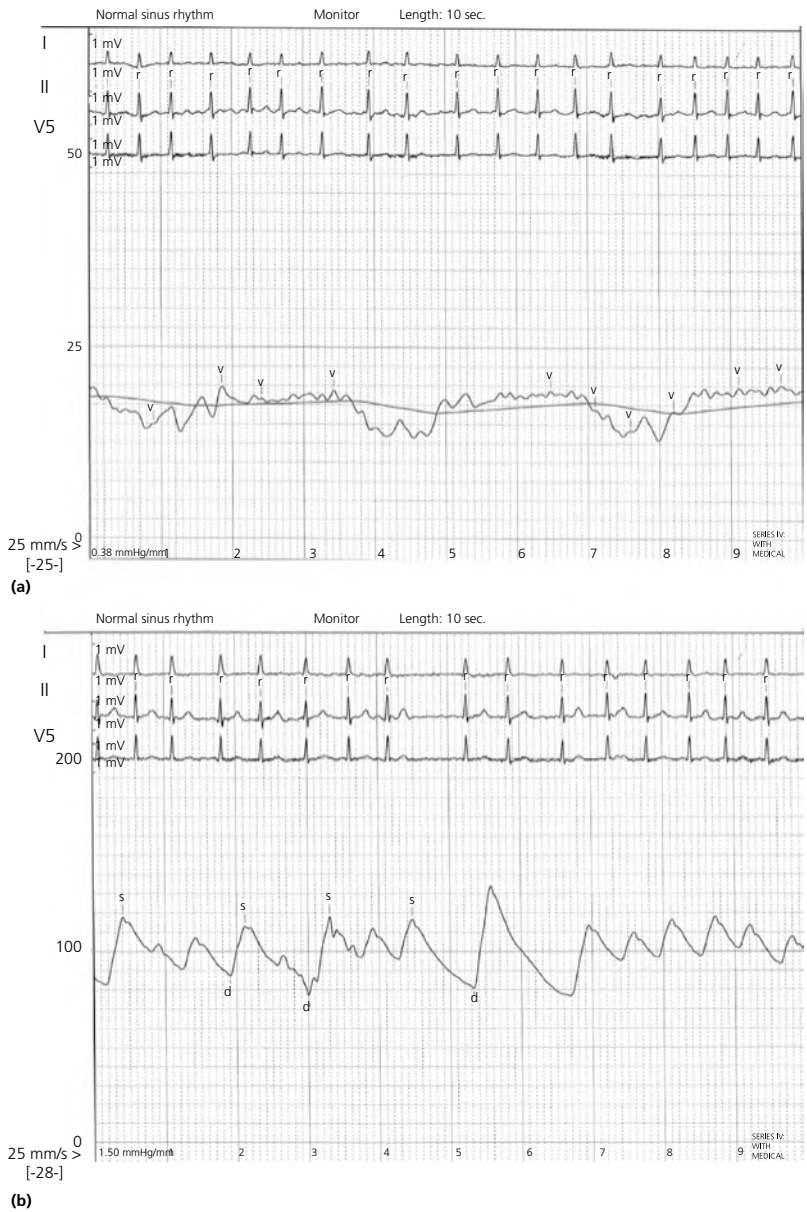


Figure 31.9 Pressure tracings in a patient with atrial fibrillation. Right atrial (a) and aortic (b) pressure tracings during atrial fibrillation. Note the increase in aortic systolic and pulse pressure when the diastolic filling period is increased.

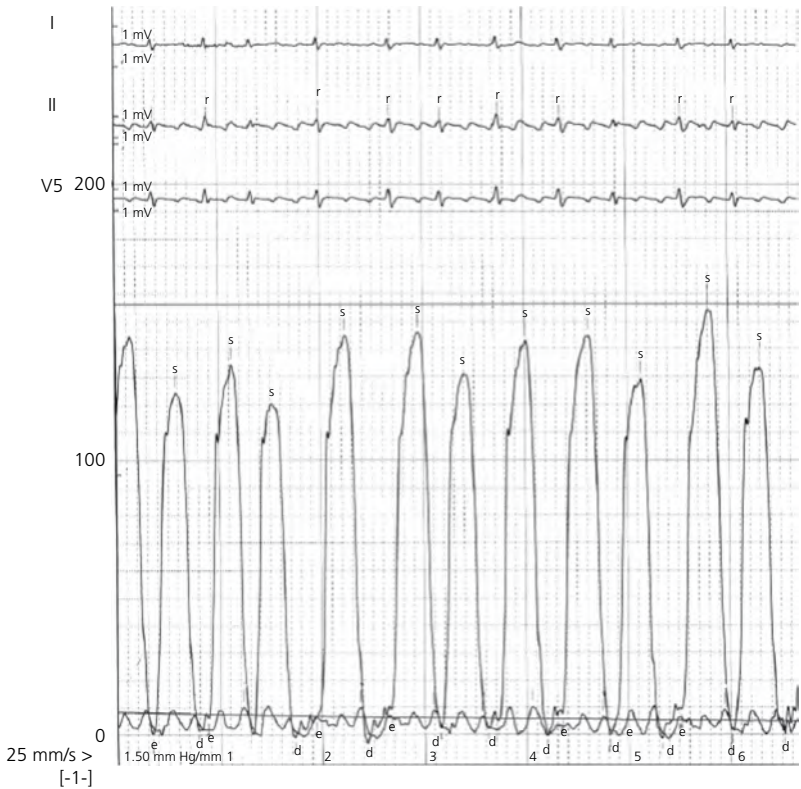


Figure 31.10 Left ventricular and right atrial pressure in a patient with atrial flutter.

be significantly reduced (although cardiac output may increase because of the increase in heart rate).

During sinus bradycardia, the R–R interval on an ECG is lengthened. As a result, an RA pressure tracing will reveal a longer diastolic period, evidenced by lengthening the interval between the V wave of one cycle and the A wave of the next cycle. On careful observation, one may be able to distinguish an additional positive deflection following the Y descent on the RA pressure waveform tracing. The etiology and significance of this waveform, termed the H wave, are unclear.

Cardiac pacing

Optimal cardiac performance is dependent on the proper timing of atrial and ventricular contraction. When the cardiac electrical conduction system becomes diseased, typically from ischemic heart disease, calcification, or a degenerative

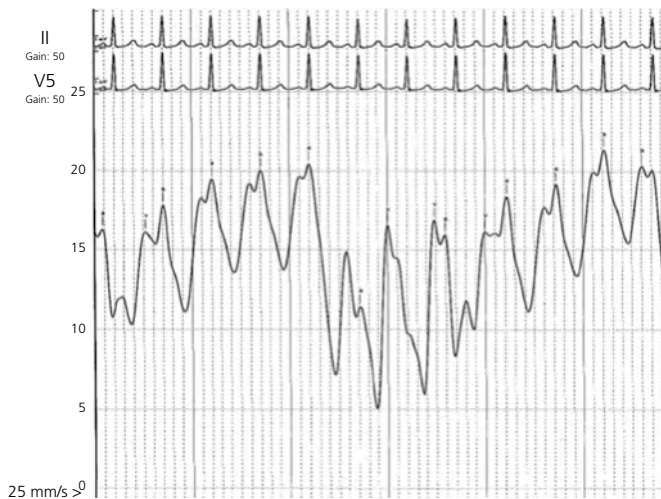


Figure 31.11 Right atrial pressure in a patient with sinus tachycardia. Notice the short time between A waves and V waves and the lack of a Y descent.

process, bradycardia or heart block may occur. These patients often require the placement of a temporary or permanent pacemaker. The first cardiac pacemaker was implanted in 1958 by Elmqvist and Senning via thoracotomy. Since that time, pacemakers have become smaller, more reliable, and more capable of mimicking natural conduction. Despite these improvements, there remain acute and chronic hemodynamic effects of pacemakers and understanding these changes in various patient populations is important in optimizing patient care and outcomes.

The most common type of pacing is a dual-chamber system in which both the RA and right ventricle (RV) are paced. Single-chamber pacemakers pace only the RA or only the RV (Figure 31.12). With biventricular (BiV) pacemakers, the left ventricle (LV) is also paced, usually via a posterior lateral branch of the coronary sinus (triple-chamber pacing systems). The primary goal of pacemakers is to achieve “physiologic pacing.” The key components of physiologic pacing are optimization of AV synchrony, rate responsiveness, and interventricular synchrony.

AV synchrony involves the proper timing of atrial diastole and systole in relation to ventricular diastole and systole so that ventricular preload is maximized, atrial pressures are optimal, and closure of AV valves occurs prior to ventricular systole. This is adjusted by varying the AV delay, which is programmable in all dual-chamber and BiV pacemakers. Rate responsiveness refers to the ability of a pacemaker to increase the rate appropriately to changing physiologic demands. This is typically achieved with an accelerometer or minute ventilation sensor built into the pacemaker. Interventricular synchrony addresses the coordination of contraction between RV and LV to optimize cardiac function.

Transvenous endocardiac electrodes with implanted pacemaker

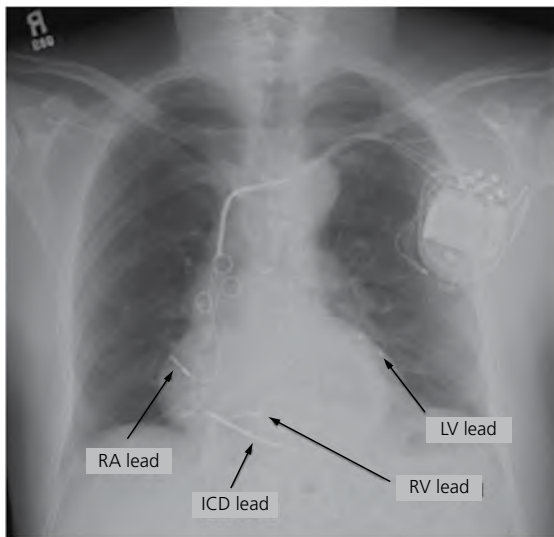
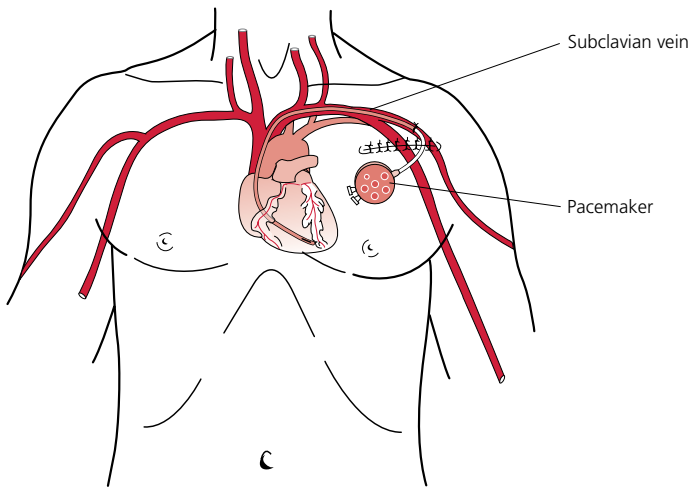


Figure 31.12 Schematic of where a permanent transvenous pacemaker lies in the chest and a chest X-ray showing four cardiac leads in a patient with an ICD and BiV pacemaker.

Physiology and pathophysiology of AV synchrony

Atrial contraction and AV synchrony influence cardiac output and diastolic filling pressures (Figure 31.13). Dyssynchronous or asynchronous atrial contraction results in reduced ventricular end-diastolic volume at a given end-diastolic

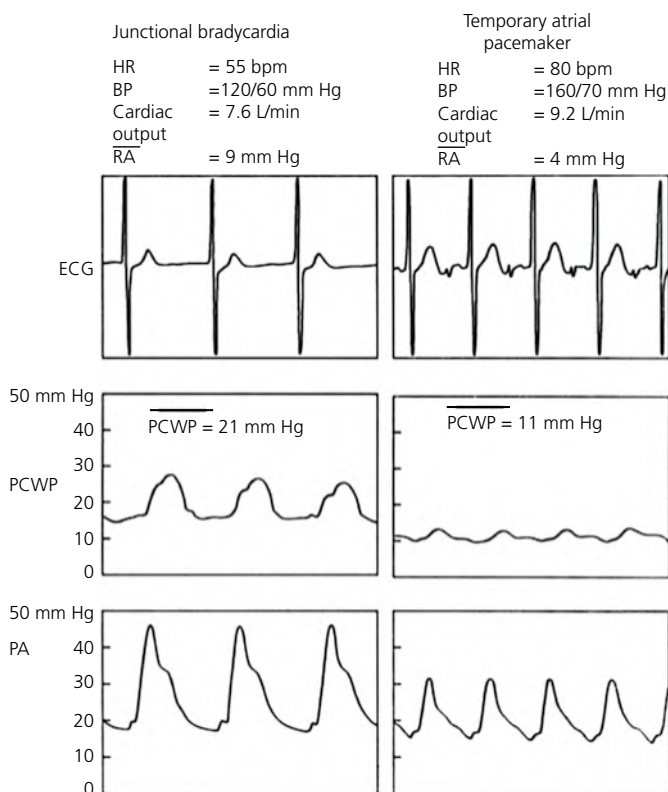


Figure 31.13 PCWP and PA pressure tracings during junctional bradycardia and atrial pacing. Source: Courtesy of WG Sanders, Jr.

pressure, reduced LV stroke volume, and reduced cardiac output. Two mechanisms have been implicated in the shift in the LV pressure-volume curve that is observed during impaired atrial activity: (1) the loss of atrial contraction directly influences ventricular diastolic filling; and (2) failure of the atria to empty during ventricular diastole increases volume within the pericardium and thus filling pressures [1]. In a given patient, the absence of atrial contraction and/or loss of AV synchrony may result in altered hemodynamics, with important clinical implications.

The loss of “atrial kick,” or ventricular diastolic filling from atrial contraction, may be particularly detrimental to patients with decreased ejection fractions or noncompliant ventricles. Atrial contraction may contribute up to 25–30% of diastolic filling in these individuals. This scenario may be observed in patients with bradycardia but preserved AV synchrony who are paced from the RV at a rate higher than the intrinsic rate (e.g., with a temporary pacing wire or a permanent single-chamber pacemaker). The loss of atrial contraction may be evident as a non-distinct atrial pressure waveform and as lower RV and LV end-diastolic pressures.

If atrial contraction is present but occurs after ventricular contraction has begun, then the atria will contract against closed AV valves, often resulting in prominent A waves or cannon A waves on atrial pressure tracings. This scenario can occur when atrial activity does not precede ventricular activity (sinus node dysfunction), atrial activity is asynchronous with ventricular systole (CHB with AV dissociation), or there is conduction retrograde from the ventricles to the atria (VA conduction), resulting in contraction of the atria against closed AV valves. This lack of AV synchrony may lead to impaired ventricular filling and thus increase the mean RA pressure and pulmonary capillary wedge pressure (PCWP).

Pacemaker syndrome is used to describe patients who respond adversely to the loss of AV synchrony during pacing. Symptoms of pacemaker syndrome range from pulsatile sensations in the neck to malaise, presyncope, or syncope in severe cases due to hypotension. This syndrome is most often seen in patients with a single lead pacing the RV apex (VVI pacing mode) and intact sinus node function. The pacemaker will neither sense atrial activity nor time ventricular pacing based on atrial contractions. The development of dual-chamber pacemaker systems that sense and pace both the atrium and ventricle has decreased but not eliminated pacemaker syndrome. Symptoms can occur in patients with dual-chamber devices if the programmed parameters are inappropriate and allow asynchronous atrial and ventricular pacing. Similar to a single-lead system, a dual-chamber device with a nonfunctioning atrial lead can also lead to pacemaker syndrome symptoms.

Patients exhibit a wide range of clinical sensitivity to the loss of AV synchrony. Some patients are asymptomatic, while others are completely intolerant. Likewise, the expected clinical benefit of re-establishing AV synchrony in patients through placement of a pacemaker is quite variable. Although multiple invasive and non-invasive studies have shown significant improvement in cardiac output with AV sequential pacing, the expected benefits have not been consistently borne out in clinical trials.

Patient response is heterogeneous and it appears that patients with low or normal filling pressures benefit most from the "atrial kick" due to their position on the upslope of the Starling curve. Interestingly, patients with significantly increased filling volumes may be the least likely to have a correlation between "atrial kick" and increased cardiac output. These patients still appear to benefit from AV synchrony but through other mechanisms, such as re-establishment of the optimal diastolic filling period and abolition of mitral regurgitation [2].

Numerous clinical trials have examined the benefits of atrial-based pacing systems that promote AV synchrony versus single-lead systems that only pace the RV (VVI). Generally accepted benefits of AV pacing include improved symptoms, a likely reduction in the risk of developing persistent atrial fibrillation, and possible trends toward fewer incidents of pacemaker syndrome and heart failure.

One of the risks of frequent RV pacing is the development of a cardiomyopathy and/or worsening heart failure. Sweeney *et al.* showed in a population of patients with sinus node dysfunction and narrow QRS that DDR pacing resulting in RV pacing >40% of the time was a strong predictor of heart failure hospitalization

and atrial fibrillation, despite maintenance of AV synchrony [3]. In the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial, DDDR pacing at 70 bpm versus backup VVI pacing at 40 bpm resulted in a 10.6% absolute increase in risk at 1 year of the composite endpoint of mortality and hospitalization for heart failure, likely as a result of the ventricular dyssynchrony imposed by ventricular pacing even when AV synchrony is preserved [4].

Role of AV synchrony: Key points

- Loss of AV synchrony may result in ↑ PCWP, ↓ BP, and ↓ CO. Symptoms may include pulsatile sensations in the neck, malaise, presyncope, or syncope
- Loss of atrial contraction may be evident as non-distinct atrial pressure waveforms, ↓ LVEDP on ventricular pressure tracings, and ↓ BP on LV/aortic pressure waveforms
- Atrial contraction occurring against closed AV valves may be evident as cannon A waves, ↑ mean atrial pressure, and ↑ PCWP
- Pacemaker syndrome incidence can be decreased by using dual-chamber pacing rather than RV single-chamber pacing (VVI pacing)

Pacemakers in specific patient populations

There are specific patient populations where pacemakers often have distinctive hemodynamic effects. These include RV myocardial infarctions requiring temporary pacing, HOCM, and severe congestive heart failure from dilated cardiomyopathy with left ventricular dysfunction.

Right ventricular infarction

Myocardial infarction involving the RV is complicated by bradyarrhythmias (usually in the form of sinus bradycardia or AV block) in 10–33% of cases. CHB due to an RV infarction is most often transient; however, it can last several days or longer. Correction of bradycardia is occasionally necessary to maintain hemodynamic stability. Although some patients may respond to atropine or aminophylline, most patients with RV infarction and heart block require temporary pacing during the peri-infarct period. This is typically done with a temporary transvenous pacing wire, which is placed in the RV.

Some patients may experience hemodynamic deterioration with the initiation of VVI pacing, possibly due to loss of AV synchrony with loss of atrial contribution to ventricular filling, development of tricuspid regurgitation, or development of asynchronous contraction between the right and left ventricles. These patients may be better served by temporary pacing of both the atrium and ventricle with maintenance of AV synchrony. Topol *et al.* reported four patients who had low

cardiac output during RV infarctions. Ventricular pacing resulted in increased heart rates, but had no effect on cardiac output. In contrast, atrial pacing increased cardiac output by 25–63% [5]. Love *et al.* subsequently reported seven patients with loss of AV synchrony during RV infarction in which restoration of AV synchrony resulted in increased systolic blood pressure, cardiac output (by an average of 50%), and stroke volume [6].

Hypertrophic obstructive cardiomyopathy

Dual-chamber pacemakers have been advocated as a therapeutic treatment option for patients with HOCM. The theory underlying the use of dual-chamber pacing with a short-programmed AV delay resulting in continuous RV pacing in these patients is that activation of the RV will cause asynchronous contraction of the septum and LV free wall, with resultant increased LV outflow tract diameter, decreased pressure gradient, and decreased systolic anterior motion of the mitral valve. Early studies reported marked decreases in LV outflow tract gradients and improvement in symptoms in most patients with dual-chamber pacing (an example of a dramatic response to pacing is shown in Figure 31.14). The initial enthusiasm was dampened by subsequent randomized crossover trials, which revealed that reductions in LVOT gradients varied significantly from patient to patient and were more modest than initially reported. A significant placebo effect emerged, with subjective symptom improvement but no difference in objective measures of exercise capacity between periods of active pacing and periods when the pacemaker was set to backup mode. Based on available data at this time, dual-chamber pacing for HOCM is not recommended as first-line therapy for relief of symptoms and outflow tract obstruction [7]. In patients with significant LVOT gradient and severe symptoms (NYHA class III or IV), surgical myectomy or alcohol septal

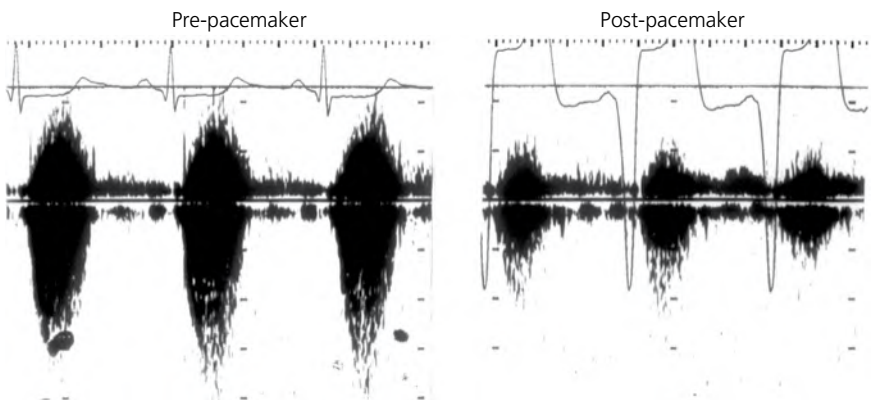


Figure 31.14 Effect of pacing on outflow tract gradient (as determined by Doppler interrogation) in a patient with HOCM. Source: Courtesy of WG Sanders, Jr.

ablation is considered prior to pacing. Pacing is generally reserved for selected patient subgroups such as those >65 years old who may not be good candidates for invasive treatment, or perhaps in patients who receive an implantable cardiac defibrillator (ICD) for prevention of sudden cardiac death.

Role of pacemakers in HOCM: Key points

- Dual-chamber pacemakers with continuous pacing of the RV apex may result in 25–40% reduction in LVOT gradient
- Reduction of LVOT and symptom relief varies widely between patients
- Use of permanent pacemakers in HOCM is reserved for patients with significant outflow gradient and severe symptoms who are not candidates for myectomy or alcohol septal ablation and/or who have another indication for permanent pacing or ICD therapy

Biventricular pacing in patients with heart failure and dilated cardiomyopathy

As the LV dilates in the setting of impaired systolic function, progressive adverse changes in cardiac geometry and structure can occur, resulting in increased wall stress, decreased mechanical performance, and worsening mitral regurgitation. Often accompanying the mechanical changes is the development of disordered electrical timing, resulting in a prolonged AV delay and asynchronous contraction between the ventricles of the heart. These electrical changes are manifest on the ECG as a prolonged PR interval and widened QRS duration or bundle branch block. Pacemaker therapy in dilated cardiomyopathy has thus evolved not only to correct coexisting sinus node and AV node dysfunction but also directly to address interventricular dyssynchrony from disordered electrical timing.

Role of pacemakers in heart failure from systolic dysfunction: Key points

- Dual-chamber pacing can acutely increase CO and contractility
- Dual-chamber pacemakers with chronic, frequent (i.e., >40%) pacing of the RV may exacerbate heart failure
- Cardiac resynchronization therapy leads to ↓ PCWP, ↑ CI, and ↑ stroke work
- Patients with class III/IV experience ↑ exercise capacity, improved functional capacity, and quality of life with cardiac resynchronization therapy (CRT) with a 75–80% patient response rate
- CRT decreases hospitalizations and mortality in patients with class III/IV HF who have evidence of dyssynchrony and who are on optimal medical therapy

Initial pacing efforts in patients with decreased LV ejection fraction focused on reducing AV conduction delay using dual-chamber devices pacing the RA and RV

(AV synchronous pacing). Shortening the AV interval has several theoretical advantages, including lengthening the diastolic filling time, changing the diastolic filling pattern to more physiologically balanced early and late (atrial) filling components compared to primarily early filling (resulting in lower mean atrial pressures), and reducing mitral regurgitation. Initial studies of acute effects revealed improved hemodynamics, improved contractility, increased cardiac output, and, in some patients, decreased mitral regurgitation. Early enthusiasm for pacing strategies that reduced AV delay but only paced the RA and RV in patients with dilated cardiomyopathy was dampened by several large trials that failed to show improved outcomes.

The focus has now shifted to addressing directly the interventricular asynchrony that exists in patients with dilated cardiomyopathy and a wide QRS complex. The wide QRS is felt to be an electrical marker for mechanical dyssynchrony between the two ventricles. The re-establishment of concerted LV and RV contraction via simultaneous electrical stimulation of the RV and LV is known as CRT. The concept of CRT is that simultaneous pacing of the RV and LV will eliminate interventricular conduction delays, enable the ventricles to contract simultaneously and lead to improved hemodynamics and LV contraction. The term CRT was coined by Cazeau and colleagues in 1994 when they placed four epicardial leads in a 54-year-old man with LBBB, dilated cardiomyopathy, and class IV congestive heart failure, with an immediate decrease in PCWP and increase in cardiac output [8]. Six weeks later the patient's symptoms had improved to class II, accompanied by drastic weight loss and resolution of peripheral edema.

Acute hemodynamic improvements are seen with LV pacing in patients with dilated cardiomyopathy, decreased systolic function, and left bundle branch block (LBBB; Figure 31.15). For example, Kass *et al.*, in a study of 18 patients with dilated cardiomyopathy and prolonged QRS, found that LV free-wall pacing increased $dP/dt_{\max}$ (a measurement of LV contractile performance) by $23.7 \pm 19.0\%$,

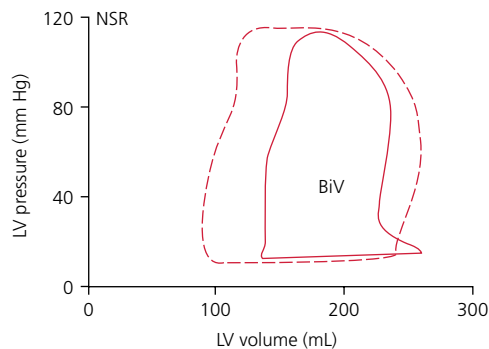


Figure 31.15 Pressure–volume loops in a patient with left bundle branch block and dilated cardiomyopathy taken during normal sinus rhythm (NSR) and during BiV pacing. Source: Kass *et al.* [9] / The American Heart Association, Inc.

pulse pressure (by $18.0 \pm 18.4\%$), and stroke work. BiV pacing yielded less improvement, whereas RV apical or mid-septal pacing had negligible effects [9]. AV delay had less influence on LV function than the ventricular pacing site. Nelson *et al.* found that LV pacing and BiV pacing improved arterial pulse pressure, cardiac output, and $dP/dt_{\max}$, while simultaneously reducing energy demands (8% reduction in myocardial oxygen consumption; MVO_2). In contrast, administration of dobutamine at a level to achieve a similar effect on $dP/dt_{\max}$ increased MVO_2 by 22% [10].

BiV pacing has been shown to have various and variable effects on hemodynamics. In patients with left bundle-branch block (LBBB) and ejection fraction $<35\%$, initial studies showed an increase in arterial blood pressure and cardiac output, and decreased filling pressures with BiV pacing [11]. Steendijk *et al.* in their study of 22 patients using pressure-volume loops found improved LV ejection fraction, decreased LV end-diastolic pressure, increased LV $dP/dt_{\max}$ (the maximum rate of LV pressure rise) and increased LV stroke work (LVSW) at 6 months [12]. A study of 10 patients found that BiV pacing enhanced coronary flow velocity time integral by 15% and LV $dP/dt_{\max}$ by 15% [13]. A study of 82 patients found improvement in LV $dP/dt_{\max}$ and LVSW calculated using pressure-volume loops in some but not all patients and that improvements in LVSW were associated with better clinical outcomes [14].

While CRT is usually accomplished by simultaneous pacing of the RV and the LV lateral wall (BiV pacing), other sites of LV pacing have been studied including his-bundle pacing and interventricular pacing. The hemodynamic effects are not well studied but, at least in the short term, seem to be comparable [15]. Additional patient populations that could benefit from CRT are also being evaluated. For example, in a study of 15 patients with left ventricular assist devices who were in sinus rhythm, BiV pacing acutely improved load-independent RV contractility and cardiac output [16].

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CHAPTER 32

Systematic evaluation of hemodynamic tracings

George A. Stouffer

This chapter includes hemodynamic tracings taken from 15 patients. Extract as much information as you can from these tracings and then check your answers at the end of the chapter. Remember that it is rare to arrive at a specific diagnosis based on hemodynamic tracings. Thus, the goal is not to come up with a diagnosis, but rather to list the useful hemodynamic findings present in each tracing.

In assessing the hemodynamic status of a patient, it is important to use a systematic approach so that the maximal useful information is obtained. Here are 10 suggested steps to use in analyzing hemodynamic data:

- 1** *Make sure that the hemodynamic data are accurate.* It goes without saying that making clinical decisions based on incorrect data can have disastrous consequences (Figure 32.1). The equipment should be calibrated and leveled properly and the minimum amount of tubing and stop-cocks should be used. Other sources of errors in hemodynamic measurements are discussed in Chapter 2.
- 2** *Avoid artifacts.* Examine the pressure tracings to make sure that the pressures are not damped or distorted by incorrect catheter position (e.g., when a pigtail catheter has a side hole above the aortic valve during recording of left ventricular pressures). A common artifact is shown in Figure 32.1.
- 3** *Note whether intracardiac pressures are elevated.* Elevation in diastolic pressures is a sensitive indicator that pathology is present. Conversely, “normal” diastolic pressures may mask characteristic hemodynamic findings (e.g., in restrictive cardiomyopathy or constrictive pericarditis) and should elicit a fluid bolus if there is a high degree of clinical suspicion.
- 4** *Examine pressure waveforms from each cardiac chamber, the aorta, and the pulmonary artery.* Examine A and V waves and X and Y descents in atrial tracings and determine whether characteristic waveforms (e.g., W or M configuration) are present. Similarly, in ventricular tracings, pay special attention to whether a

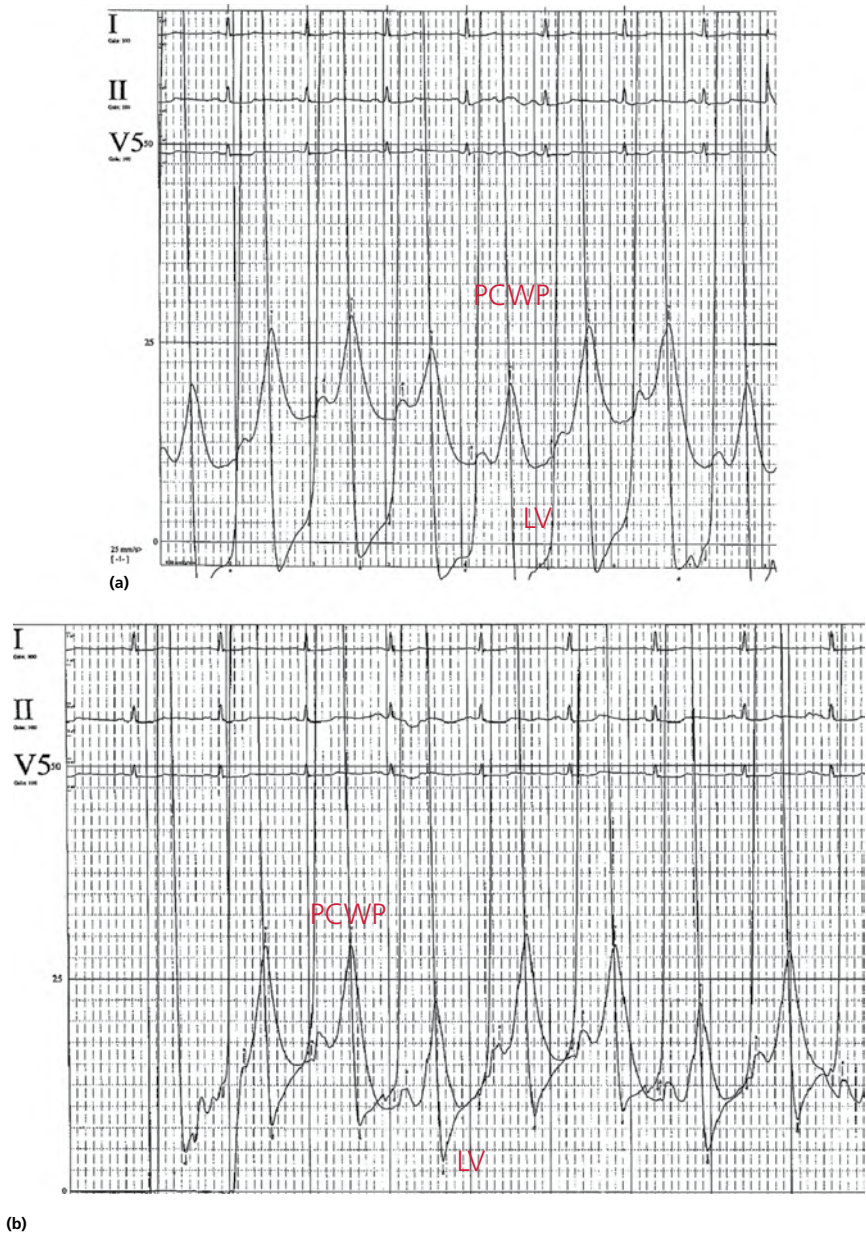


Figure 32.1 These tracings are taken from a 40-year-old female who presented with exertional dyspnea. The tracing in panel (a) is consistent with mitral stenosis, with a persistent gradient between pulmonary capillary wedge pressure and left ventricular pressure during diastole. This difference was artefactual and due to incorrect zeroing of the LV pressure transducer. Accurate tracings are shown in panel (b).

“dip and plateau” configuration is present and to the slope of the rise in pressure during diastole. Note the contour of the aortic pressure tracing as well as systolic, diastolic, and pulse pressures. These findings can provide helpful clues to many diseases, as discussed in Chapter 4.

- 5 *Take note of the effect of respiration.* In the normal heart, the decrease in intrathoracic pressure with inspiration is transmitted to the heart with characteristic results. If right atrial pressure does not decrease with inspiration (i.e., Kussmaul’s sign), this suggests constrictive pericarditis but can also be found in other diseases.
- 6 *Characterize diastolic filling.* Examination of the atrial and ventricular pressure tracings can give an indication of diastolic filling patterns. An exaggerated Y descent implies that significant ventricular filling occurs in early diastole, whereas an exaggerated X descent signifies late diastolic filling. For each patient determine whether diastolic filling occurs primarily in early diastole (e.g., constrictive pericarditis or aortic regurgitation), throughout diastole, or in late diastole (e.g., cardiac tamponade).
- 7 *Interpret cardiac output based on filling pressures.* Cardiac output is a function of left ventricular filling pressure. Low cardiac output in the setting of an elevated left ventricular end-diastolic pressure (LVEDP) is an ominous finding, whereas low cardiac output with low LVEDP is an expected consequence of dehydration. An elevated cardiac output can be a clue to anemia, arteriovenous shunt (e.g., dialysis graft), high-output heart failure, anxiety, and so on. Note also that pulmonary artery pressure and pressure gradients across stenotic valves increase in proportion to cardiac output. For example, exercise during right heart catheterization can be a useful technique to unmask symptomatic mitral stenosis.
- 8 *Compare pressures measured simultaneously from two sites within the heart or major vessels.* There are numerous benefits to measuring pressures at two sites simultaneously. Comparison of pressures measured proximal and distal to a diseased valve provides information useful in determining the degree of stenosis or regurgitation. Simultaneous measurement of left ventricular and left atrial pressures (or pulmonary capillary wedge pressure (PCWP)) is useful in determining diastolic filling characteristics as well as mitral valve pathology. Also, simultaneous measurement of left ventricular/right ventricular pressures or left ventricular/right atrial pressures gives an indication of whether pressures in these chambers are independent or interdependent (e.g., in constrictive pericarditis).
- 9 *Perform any necessary calculations.* Calculate valve area, intracardiac shunt fraction, systemic vascular resistance, and so on as needed. Treatment decisions are often based on the severity of the condition as reflected in these calculations.
- 10 *Synthesize hemodynamic information with clinical presentation, ECG, past medical history, echocardiographic data, other imaging data and so on to arrive at a working diagnosis.*

Unknowns

In the following images are hemodynamic data from 15 patients. See how well you do at identifying the relevant information and answering the questions.

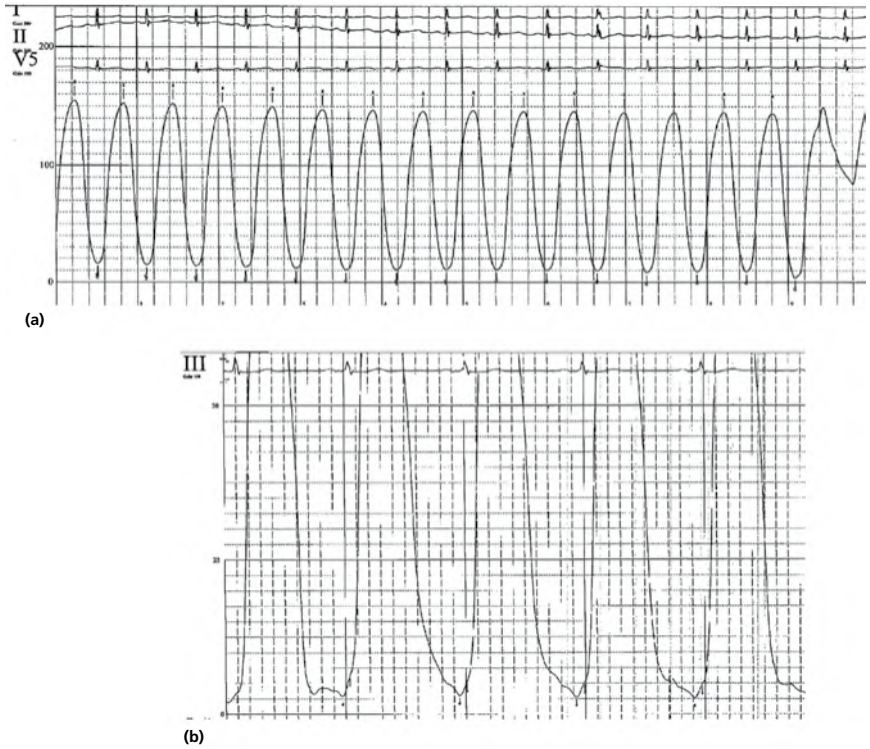


Figure 32.2 Examples of hemodynamic tracings with artifacts. The LV pressure tracing in panel (a) is a damped tracing due to an air bubble being in the line. Note the rounded appearance and lack of definition in the peak systolic and diastolic phases of the tracing. In panel (b), the LV pressure is decreasing during diastole. This is nonphysiologic and is due to a side hole of the pigtail catheter being above the aortic valve. The right atrial tracing in panel (c) has an artifact from periodically going in and out of the tricuspid valve. At first glance, it appears that RA pressures are elevated and that there is a large V wave, consistent with tricuspid regurgitation. An accurate RA tracing is shown in (d).

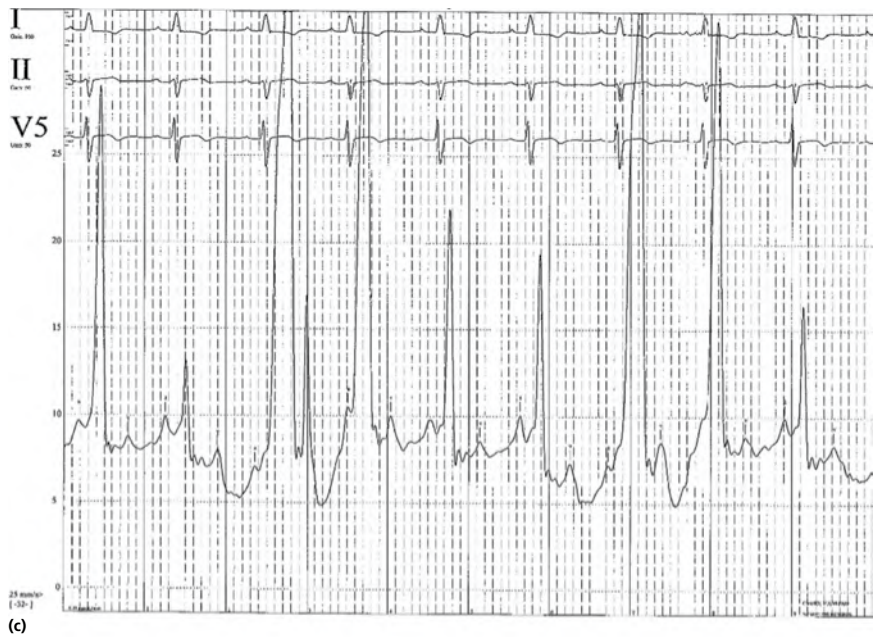


Figure 32.2 (Continued)

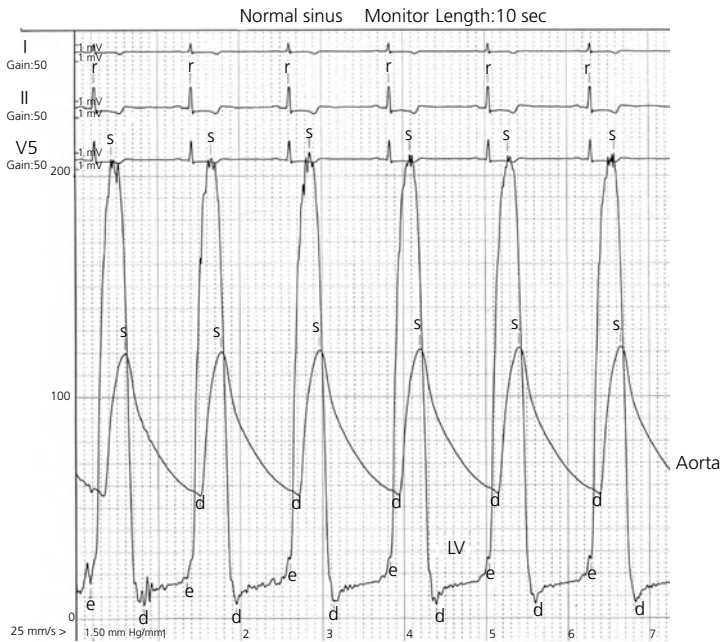


Figure 32.3 A 66-year-old male presents with exertional dyspnea and one episode of syncope. What is the diagnosis?

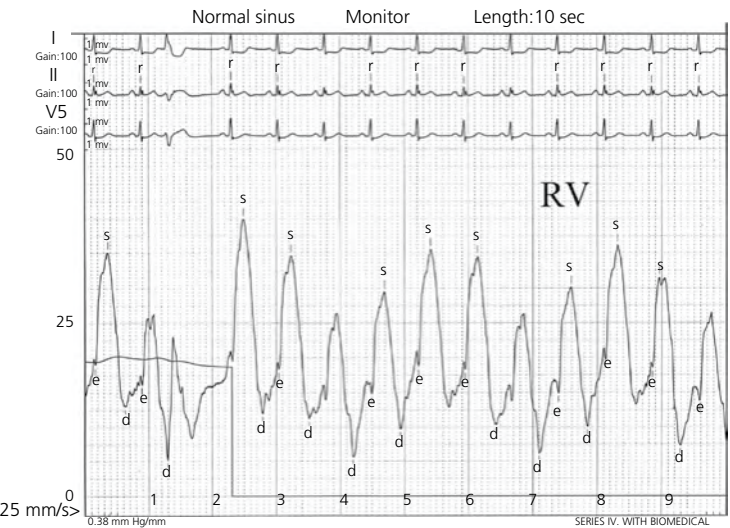


Figure 32.4 A 62-year-old female presents with acute ST elevation inferior MI. Mean RA pressure = 13 mm Hg and mean PCW pressure = 12 mm Hg. Does this patient have hemodynamic evidence of RV ischemia?



Figure 32.5 Pulmonary artery pressure in a 52-year-old female with a recent episode of endocarditis who now presents with exertional dyspnea. What is the diagnosis?

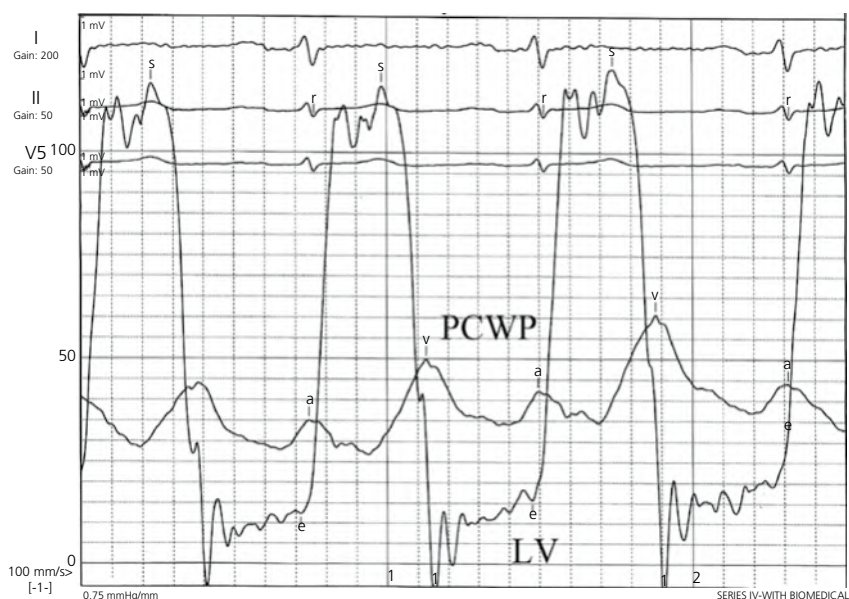


Figure 32.6 A 50-year-old male who is being evaluated after a recent hospital admission for "pneumonia." What is the diagnosis?

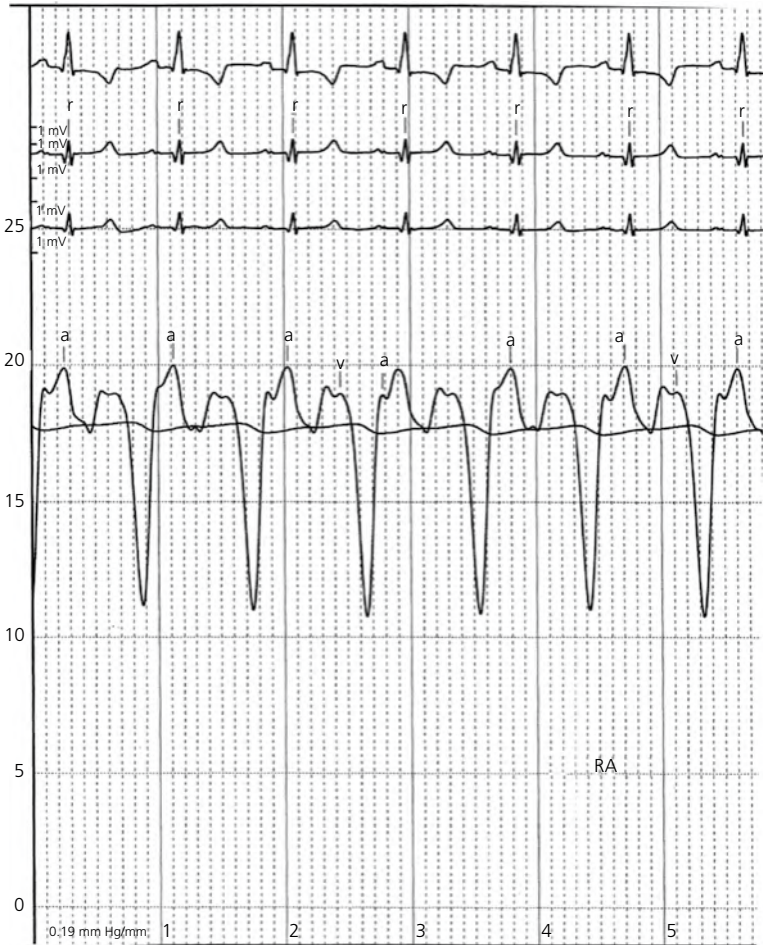


Figure 32.7 A 54-year-old male with end-stage renal disease is admitted with congestive heart failure. Past medical history was remarkable for an episode of pericarditis requiring pericardiocentesis 10 years ago. What is the diagnosis?

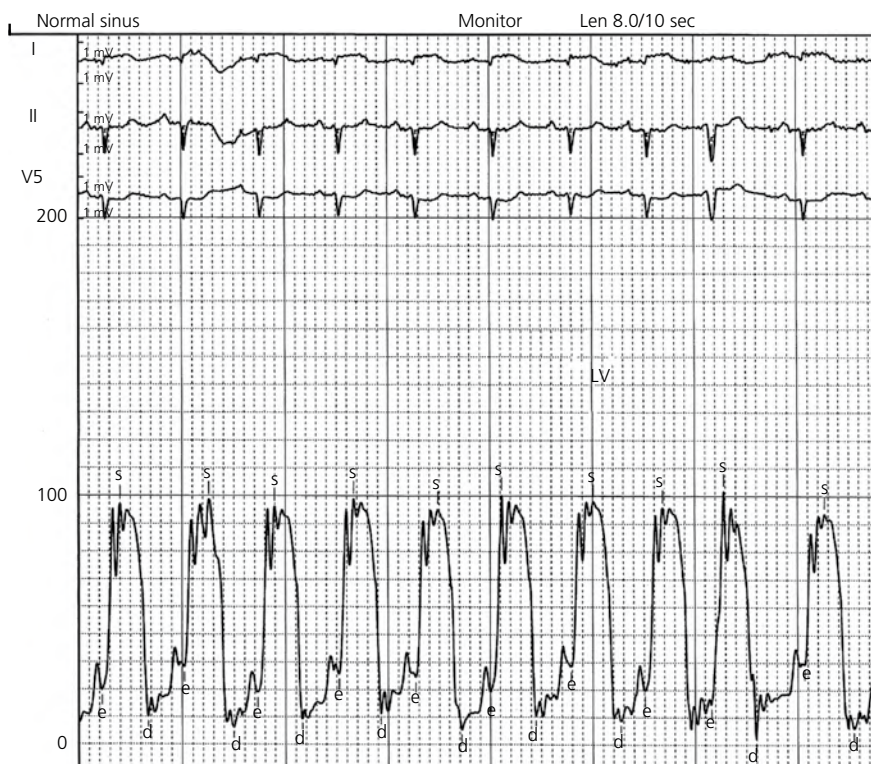


Figure 32.8 A 77-year-old female with acute anterior wall, ST elevation MI. What information is available from this pressure tracing?

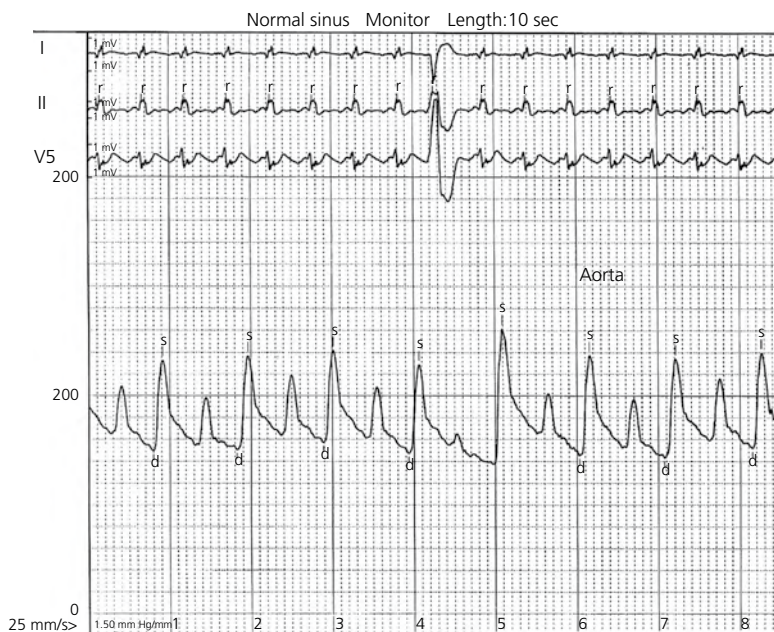


Figure 32.9 A 56-year-old male with a history of hypertension who now presents with congestive heart failure. What does the aortic pressure tracing show?

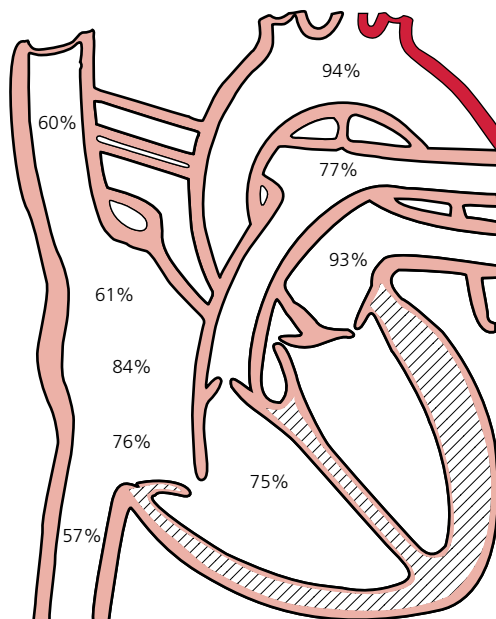


Figure 32.10 A 53-year-old female with cough and shortness of breath. The oxygen saturations obtained in various chambers are listed. What is the diagnosis?

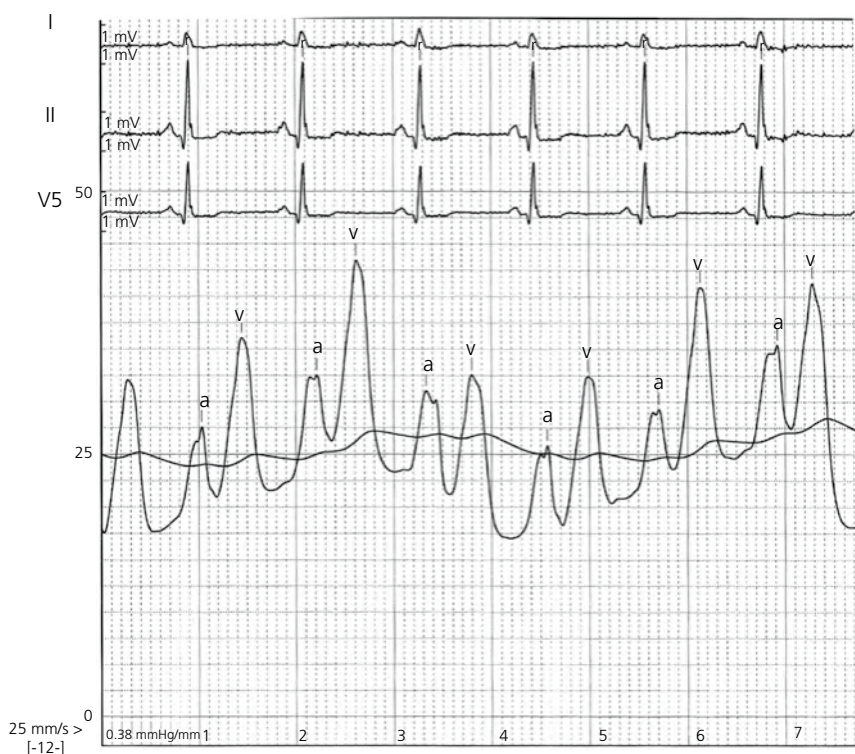


Figure 32.11 Where is this pressure tracing obtained from?



Figure 32.12 A 73-year-old white male with a history of atrial fibrillation who complains of dyspnea on exertion. What is the diagnosis?

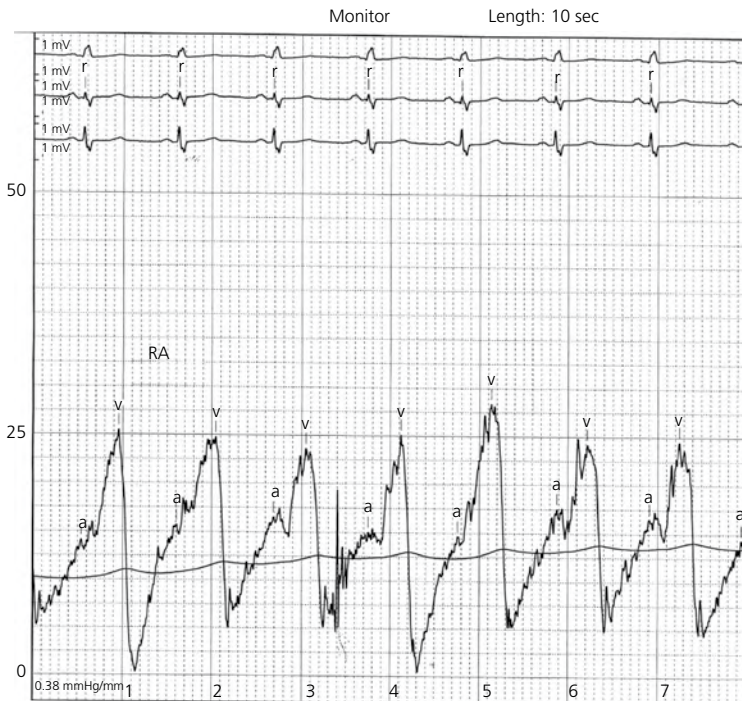


Figure 32.13 A 72-year-old female who has had recurrent episodes of “congestive heart failure.” What is the diagnosis?

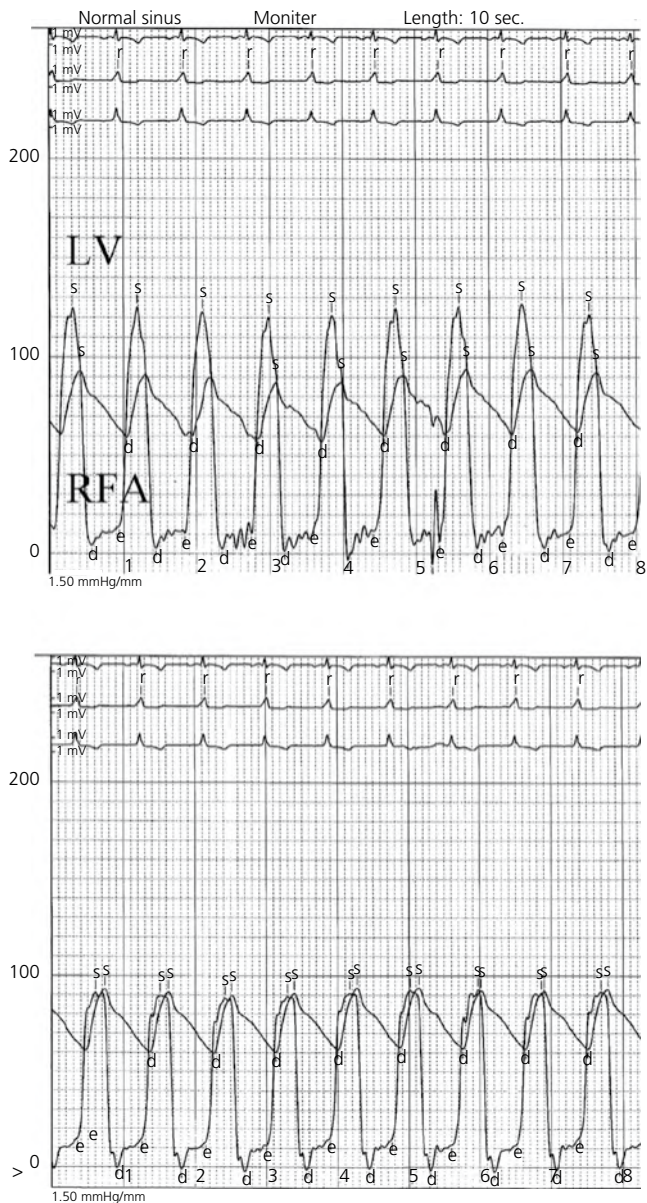


Figure 32.14 These two tracings are obtained as an end-hole catheter (marked LV) is slowly withdrawn from the LV apex to the aorta (while right femoral artery pressure is continuously recorded) in a 29-year-old female who presented with dyspnea on exertion. What is the diagnosis?

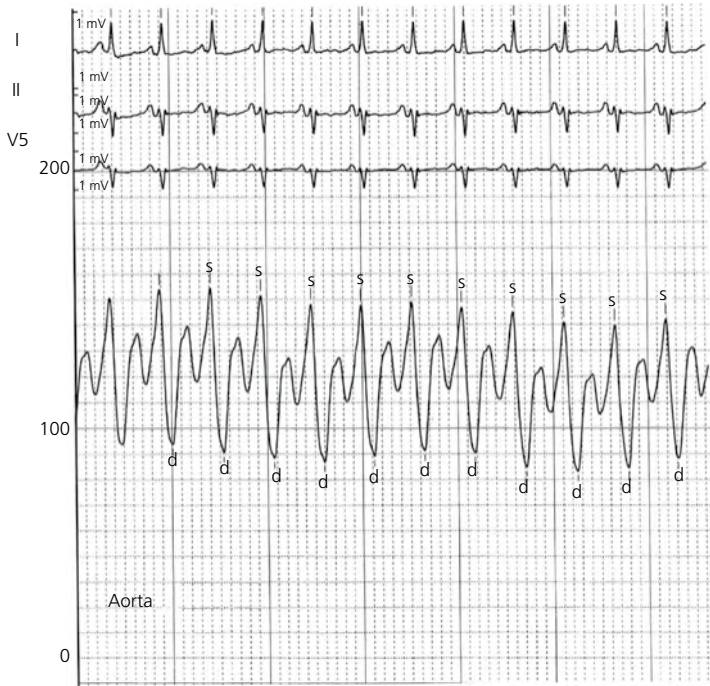


Figure 32.15 What does this aortic pressure tracing represent?

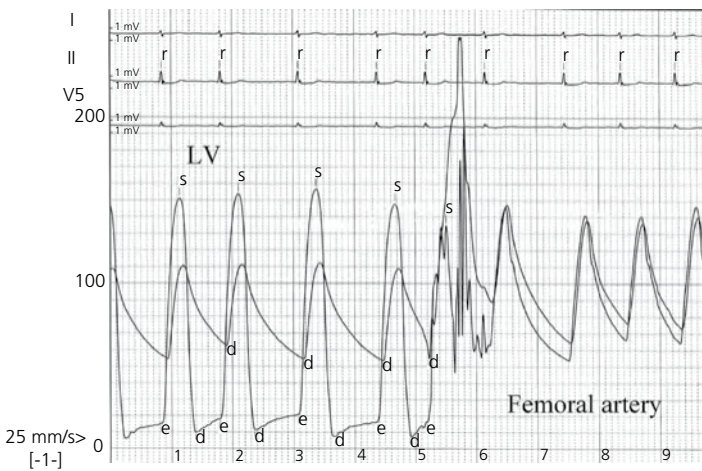


Figure 32.16 An 82-year-old man with chest discomfort on exertion. What is the diagnosis?

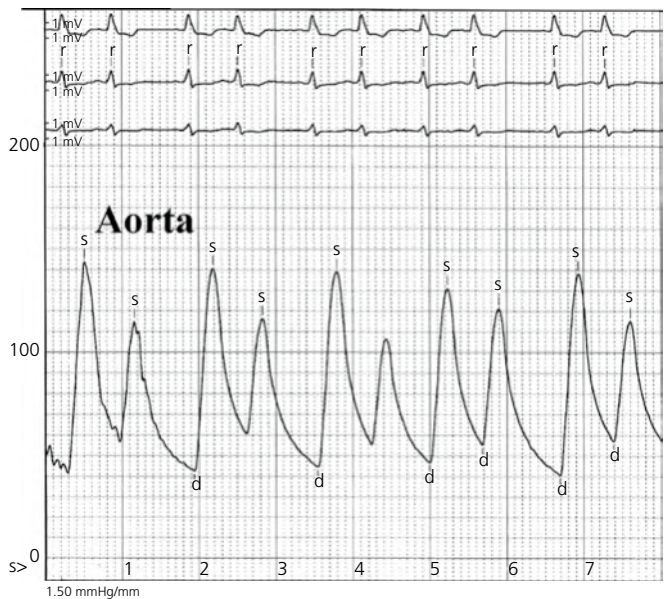


Figure 32.17 An 81-year-old female with hypertension and diabetes mellitus who presented with complaints of substernal chest pain awakening her from sleep. Cardiac enzymes are elevated. What information is available from the aortic pressure tracing?

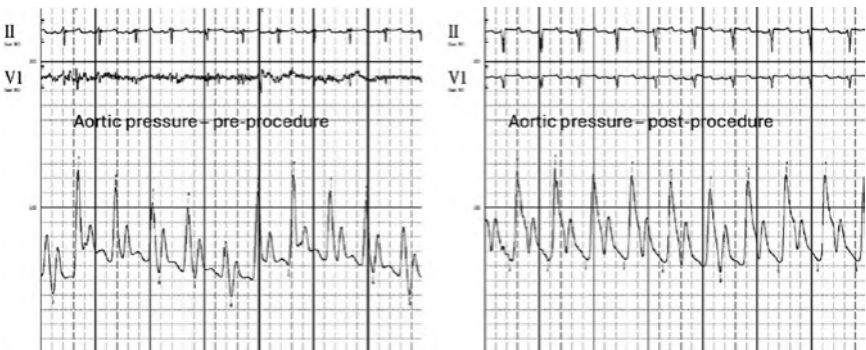


Figure 32.18 A 28-year-old female with end-stage renal disease, hypertension and systemic lupus erythematosus presented with progressive dyspnea and hypotension. These aortic pressure tracings were recorded from a radial arterial line before and after a procedure was performed. What was the procedure?

Answers

- 32.3** The pressure tracings show a large gradient (approximately 90 mm Hg) between the left ventricle (LV) and the aorta. These tracings could be found in a number of conditions, including valvular aortic stenosis, hypertrophic obstructive cardiomyopathy, subvalvular aortic stenosis, or supra-aortic stenosis. The contour of the aortic pressure will occasionally provide some help in the diagnosis, but here there is neither bisferiens pulse seen in hypertrophic obstructive cardiomyopathy nor pulsus parvus et tardus seen in aortic stenosis (although neither of these findings is a sensitive indicator). Statistically, the most likely diagnosis in a 66-year-old patient is valvular aortic stenosis, which was the case here. The aortic valve area was calculated to be 0.5 cm². Also note in this tracing the elevated LVEDP (approximately 25 mm Hg).
- 32.4** The pressure tracing shows elevated right ventricular (RV) diastolic pressure, consistent with RV ischemia. The diagnosis is confirmed by findings that RA pressure was greater than PCWP (specificity of 100% for diagnosis of RV infarction in one study), RA pressure greater than 10 mm Hg and within 1–5 mm Hg of the PCWP (specificity of 100% for diagnosis of RV ischemia in another study), and a mean RA pressure of 10 mm Hg or more and an RA/pulmonary capillary wedge pressure ratio of 0.8 or more (specificity of 92% in a third study).
- 32.5** The tracing is taken from a catheter placed in the pulmonary artery (PA). Note, however, the ventricular-like appearance, with a rise in pressure during diastole. This tracing is suggestive of severe pulmonary insufficiency (presumably from endocarditis). Also consistent with this diagnosis was the elevated RVEDP at 21 mm Hg. With severe pulmonic valve incompetence, RV and PA pressures become similar in diastole.
- 32.6** The pressure tracings show a gradient between PCWP and LV that persists throughout diastole. Resistance (and thus pressure gradient) between PCWP and LV can occur either in the pulmonary venous system (e.g., veno-occlusive disease or pulmonary venous stenosis following atrial fibrillation ablation) or at the level of the mitral valve. The PCWP tracing shows distinct A and V waves (implying that the PCWP is a good surrogate for left atrial pressure) and thus the most likely diagnosis is mitral stenosis. That was the case in this patient, who had rheumatic mitral stenosis with a valve area calculated to be 0.7 cm².
- 32.7** RA pressure is elevated and the tracing shows characteristic findings of constrictive pericarditis. Note the exaggerated Y descent with a preserved X descent. Although the tracing is too short to make definitive conclusions, there also appears to be minimal variation with respiration.
- 32.8** This tracing shows elevated LV end-diastolic pressure (32 mm Hg) and reduced LV systolic pressure (95 mm Hg). In the setting of acute myocardial infarction, this relationship can provide important information regarding LV

function. In this case, LV systolic pressure is low despite elevated filling pressures, suggesting that LV contractility is severely reduced (based on the Frank–Starling principle). The prognostic importance of LV systolic and end-diastolic pressures has been known since at least 1967 when Killip and Kimball demonstrated that mortality in the setting of acute MI was a function of LV filling pressures (in their case using physical exam findings of pulmonary edema) and aortic systolic pressure. This patient would be Killip class IV [1].

32.9 Systolic pressure alternates in a beat-to-beat fashion in this aortic pressure tracing. This is characteristic of pulsus alternans, which is found in patients with failing left ventricles. This patient had a severe nonischemic cardiomyopathy with an ejection fraction of less than 20%. Be aware of pseudo-pulsus alternans that can occur due to atrial arrhythmias and also cause beat-to-beat variation in systolic pressure.

32.10 This patient has an atrial septal defect (ASD). There is a significant “step up” in oxygen saturation between the vena cava and right ventricle. To estimate Q_p/Q_s using the short equation, first calculate mixed venous (MV) oxygen saturation. In the case of an ASD, MV oxygen saturation can be calculated using the equation:

$$MV O_2 = (3 \times SVC + IVC)/4$$

In this case, $MV O_2 = 59.25\%$ rounded to 59%.

$$Q_p/Q_s = (SAO_2 - MVO_2)/(PVO_2 - PAO_2).$$

If we assume $SAO_2 = PVO_2$ (a valid assumption in the absence of right-to-left shunting):

$$Q_p/Q_s = (94 - 59)/(94 - 77) = 2.1$$

32.11 This tracing shows pulmonary capillary wedge pressure as a surrogate for left atrial pressure. Note that the mean pressure is 25 mm Hg and that there is significant respiratory variation, both consistent with atrial pressure. In the left atrium, the V wave is generally larger than the A wave; the opposite is generally true in the right atrium. These pressures were obtained from the pulmonary capillary wedge position, which explains the delay between the ECG and pressure deflections (compare the P wave on the ECG and A wave on the tracing).

32.12 This aortic pressure tracing shows findings consistent with hypertrophic obstructive cardiomyopathy. There is a minimal gradient between right femoral artery (RFA) and left ventricle (LV) at rest, but a gradient >100 mm Hg is present post-PVC. Also present is a Brockenbrough–Braunwald–Morrow sign [2]. This sign, originally described in 1961, is defined as diminished pulse pressure in a post-extrasystolic beat compared to the beat immediately preceding the premature ventricular contraction (PVC).

32.13 The RA tracings show “ventriculization,” that is, the atrial pressure takes on characteristics of a ventricular pressure (an exaggerated Y descent, rapid rise in pressure during ventricular diastole, and lack of X descent). This patient had severe tricuspid regurgitation.

- 32.14** This patient had congenital subvalvular stenosis. The tracing on the left shows a pressure difference between the LV apex and femoral artery, with a mean gradient of 29 mm Hg. The tracing on the right was taken with an end-hole catheter just below the aortic valve. It identifies the obstruction as being subvalvular since there is no gradient between the ventricle at this location (note the ventricular contour of the tracing) and the femoral artery.
- 32.15** This patient has an intra-aortic balloon pump. Note the diastolic augmentation.
- 32.16** At first glance, this looks like aortic stenosis since there is a pressure gradient between LV and femoral artery. Note, however, that the femoral artery pressure increases during the catheter pullback and that there is no difference between LV systolic and aortic systolic pressure. Presumably, this patient had a thrombus in the sheath that was dislodged during pullback. The cause of the chest symptoms was coronary artery disease.
- 32.17** At first glance, this tracing looks like pulsus alternans. Note, however, that the ECG shows type 1, second-degree heart block (Wenckebach). The beat-to-beat variability in aortic systolic pressure is explained by shortened diastolic filling times in alternate beats and does not indicate severe LV failure.
- 32.18** These pressure tracings were taken before and after pericardiocentesis. In the pre-procedure tracing, note the marked pulsus paradoxus with a decrease in systolic pressure from ~125 mm Hg to <80 mm Hg with inspiration. Note also the very rapid decrease in aortic pressure during diastole which is consistent with a low cardiac output.

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