Evaluation of Systolic and Diastolic Function of the Ventricles and Myocardium

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A critical aspect of most cardiac catheterization procedures is the evaluation of myocardial function. At its simplest, this consists of a visual assessment of the left ventricular (LV) contractile pattern from the left ventriculogram, together with measurements of LV end-diastolic pressure. In laboratories where most patients have right-sided heart catheterization and cardiac output measurement as part of a standard cardiac catheterization procedure, additional information about LV function may be gleaned from the cardiac output, stroke volume, and pulmonary capillary wedge pressure, whereas right ventricular (RV) function is reflected in the values for right ventricular end-diastolic pressure (RVEDP) and right atrial pressure. Measurements of pressures and cardiac output give important information about overall cardiac function but may shed little light on whether dysfunction is caused by abnormal systolic or diastolic myocardial performance. This chapter describes some of the specific methods that can be used in the cardiac catheterization laboratory to examine myocardial performance in systole and diastole.

SYSTOLIC FUNCTION

Preload, Afterload, and Contractility

Systolic function of the myocardium is a reflection of the interaction of myocardial preload, afterload, and contractility. **Preload** is the load that stretches myofibrils during diastole and determines the end-diastolic sarcomere length. For the left ventricle, this load is often quantified as the LV end-diastolic pressure (LVEDP). This pressure, taken together with LV wall thickness (h) and radius (R), determines LV end-diastolic wall stress (\( \sigma \)). End-diastolic stress or “stretching force” is resisted by the intrinsic stiffness or elasticity of the myocardium, and the interaction of end-diastolic stretching force and myocardial stiffness determines the extent of end-diastolic sarcomere stretch. If the myocardium is diffusely fibrotic or infiltrated with amyloid, a very high end-diastolic stretching force may be required to produce a normal end-diastolic sarcomere length. In such a case, LVEDP may be very high (e.g., more than 25 mm Hg), and attempts to lower it by diuretic or venodilator therapy may lead to reduction in end-diastolic sarcomere stretch to subnormal values and a concomitant fall in cardiac output.

Changes in preload influence both the extent and velocity of myocardial shortening in experiments using isolated cardiac muscle preparations. Increased preload augments the extent and velocity of myocardial shortening at any given afterload. In the intact heart, the relationship is more complex because increases in preload generally produce increases in LV chamber size and LV systolic pressure. Therefore, **afterload** (the force resisting systolic shortening of the myofibrils) is also increased, and this increase tends to blunt the increases in extent and velocity of myocardial shortening caused by increased diastolic fiber stretch. This point is discussed in more detail later in this chapter, under the section on ejection phase indices of systolic function.

Afterload varies throughout systole as the ventricular systolic pressure rises and blood is ejected from the ventricular chamber. LV systolic stress approximates the force resisting myocardial fiber shortening within the wall of the ventricle. The theory and methods for calculation of wall stress are described in Chapter 16. End-systolic wall stress is considered by many to be the final afterload that determines the extent of myocardial fiber shortening, when preload and contractility are constant. An increase in end-systolic wall stress results in a decrease in myocardial fiber shortening. For the intact ventricle, an increase in afterload (end-systolic wall stress) therefore results in a fall in stroke volume and ejection fraction.

**Contractility** refers to the property of heart muscle that accounts for alterations in performance induced by...
biochemical and hormonal changes; it has classically been regarded as independent of preload and afterload. Contractility is generally used as a synonym for inotropy; both terms refer to the level of activation of cross-bridge cycling during systole. Contractility changes are assessed in the experimental laboratory by measuring myocardial function (extent or speed of shortening, maximum force generation) while preload and afterload are held constant. In contrast to skeletal muscle, the strength of contraction of heart muscle can be increased readily by a variety of biochemical and hormonal stimuli, some of which are listed in Table 17.1.

Increased myocardial contractility may be present in patients with hyperadrenergic states, thyrotoxicosis, or hypertrophic cardiomyopathy or in response to a variety of drugs. It is manifested by an increase in the speed and extent of myocardial contraction at constant afterload and preload.

Experiments with isolated myocardial tissue have demonstrated that contractility is not truly independent of preload. Increased end-diastolic sarcomere stretch leads to an immediate increase in the strength of contraction due to the Frank-Starling mechanism, followed by a gradual further increase in contractile strength over 5 to 10 minutes (1–3). Evidence supports a role for both increased intracellular calcium (Ca++) release and increased myofilament sensitivity to any given level of cytosolic Ca++ as underlying factors in the length-dependent activation seen with increased preload (2).

FIG. 17.1.

Micromanometer recordings of left ventricular pressure and its first derivative, dP/dt, in a patient with normal left ventricular function. Isoproterenol markedly increases contractility with large increments in positive \( +dP/dt \). Atropine produces tachycardia, which results in a treppe effect and a rise in \( +dP/dt \) above control. (From Gleason WL, Braunwald E. Studies on the first derivative of the ventricular pressure pulse in man. J Clin Invest 1962;41:80, with permission.)

Assessment of systolic function requires consideration of the simultaneous influence of afterload, preload, and contractility. Systolic function should not be regarded as synonymous with contractility. Major depression of systolic function can occur with normal contractility, as in conditions with so-called afterload excess (see later discussion).

Isovolumic Indices

One of the oldest and most widely used measures of myocardial contractility is the maximum rate of rise of LV systolic pressure, \( dP/dt \). Wiggers noted more than 70 years ago that in animal experiments the failing ventricle showed a reduced steepness of the upslope of the ventricular pressure pulse (4). In 1962, Gleason and Braunwald first reported measurement of \( dP/dt \) in humans (5). They studied 40 patients with micromanometer catheters. Maximum \( dP/dt \) in those patients without hemodynamic abnormalities ranged from 841 to 1,696 mm Hg/sec in the left ventricle and 223 to 296 mm Hg/sec in the right ventricle. Interventions known to increase myocardial contractility, such as exercise and infusion of norepinephrine or isoproterenol, caused major increases in \( dP/dt \). Increased heart rate produced by intravenous atropine also caused a rise in maximum \( dP/dt \), and the authors attributed this to the treppe phenomenon described by Bowditch. Acute increases in arterial pressure and afterload produced by infusion of the \textit{ALPHA}-adrenergic vasoconstricting agent methoxamine produced little change in \( dP/dt \). These points are illustrated in Figs. 17.1 and 17.2.

FIG. 17.2.

Micromanometer recordings of left ventricular (LV) pressure and \( dP/dt \), as in Fig. 17.1. Methoxamine raises arterial and LV systolic pressure but does not increase \( +dP/dt \). In contrast, the combined \textit{ALPHA}- and \textit{BETA}-adrenergic effects of norepinephrine increase LV systolic pressure and \( +dP/dt \). (From Gleason WL, Braunwald E. Studies on the first derivative of the ventricular pressure pulse in man. J Clin Invest 1962;41:80, with permission.)

In normal subjects and in patients with no significant cardiac abnormality, maximum \( dP/dt \) increases significantly in
response to isometric exercise (6), dynamic exercise (5), tachycardia by atrial pacing (7),(8) or atropine (5), BETA-agonists (5), and digitalis glycosides (9). Relatively few studies have been done in humans to assess the changes in dP/dt induced by alterations in afterload and preload, but some studies do indicate that maximum positive dP/dt tends to increase slightly (6% to 8%) with moderate increases in LV preload (10) and shows little change with methoxamine-induced increases (5) or nitroprusside-induced decreases (11) in mean arterial pressure of 25 to 30 mm Hg. Extensive studies in animals have examined the influence of changes in afterload, preload, and contractility on maximum dP/dt (10,12–15). These studies generally show that maximum dP/dt rises with increases in afterload and preload, but the changes were quite small (less than 10%) in the physiologic range.

As discussed in Chapter 7, accurate measurement of dP/dt requires a pressure measurement system with excellent frequency-response characteristics. Micromanometer catheters are usually required to achieve this frequency-response range (16). Differentiation of the ventricular pressure signal can be achieved by (a) analog techniques on-line (Figs. 17.1 and 17.2), using a resistance capacitor (RC) differentiating circuit (5),(10); (b) computer digitization of the analog LV pressure tracing and subsequent differentiation of a polynomial best fit to the averaged LV isovolumic pressure (17); or (c) computer digitization of the analog LV pressure tracing with subsequent Fourier analysis and differentiation (18).

In addition to dP/dt, several other isovolumic indices have been introduced in an attempt to obtain a “pure” contractility index, completely independent of alterations in preload and afterload (10,19,20). These indices include the maximum value of (dP/dt)/P, where P is LV pressure (the maximum value of (dP/dt)/P is sometimes called V_p,Max); (peak dP/dt)/IIT, where IIT is the integrated isovolumic tension; (dP/dt)/CPIP, where CPIP is the common developed isovolumic pressure; V_max, the extrapolated value of (dP/dt)/P versus P, when P = 0; (dP/dt)/P_P, when the developed LV pressure, P_P, equals 5, 10, or 40 mm Hg; and the fractional rate of change of power, which involves the second derivative of LV pressure.

Although changes in dP/dt reflect acute changes in inotropy in a given individual, the usefulness of dP/dt is reduced in comparisons between individuals, especially when there has been chronic LV pressure or volume overload. Peak dP/dt is generally increased in patients with chronic aortic stenosis, even though contractility is normal or decreased in most of these patients. To account for chronic changes in LV geometry and mass that occur with chronic LV overload, some investigators have examined the rate of rise of systolic wall stress (17). The peak value of dsigma/dt may be used as a contractility index, as may the spectrum plot that relates d(sigma)/dt to instantaneous sigma (Fig. 17.3).

FIG. 17.3.

Left ventricular (LV) isovolumic indices of contractility. A: Rate of pressure development (dP/dt) as a function of LV-developed pressure (P_P). Mean values in control subjects (open circles), patients with aortic stenosis (AS, closed circles), and patients with dilated cardiomyopathy (CMP, crosses) are shown. Brackets represent standard errors of the mean (SEM). B: Rate of wall stress development (dsigma/dt) as a function of LV-developed stress (sigma_P) for the same groups. There are no significant differences for patients with AS compared with controls, although patients with CMP clearly show depressed values for dP/dt and dsigma/dt at all levels of P_P and sigma_P. (From Ififer MA, Gunther S, Grossman W, et al. Myocardial contractile function in aortic stenosis as determined from the rate of stress development during isovolumic systole. Am J Cardiol 1979;44:1318, with permission.)

Pressure-Volume Analysis

Since the time of Frank and Starling, pressure-volume (PV) diagrams have been used to analyze ventricular function. The normally contracting left ventricle ejects blood under pressure, and the relationship of its pressure generation and ejection can be expressed in a plot of LV pressure against volume. As can be seen in Fig. 17.4, end-diastole is represented by point A, isovolumic contraction by line AB, aortic valve opening by point B, ejection by line BC, end-ejection and aortic valve closure by point C, isovolumic relaxation by line CD, mitral valve opening by point D, and LV diastolic filling by line DA.
Diagram of ventricular pressure \( (P) \) plotted against simultaneous ventricular volume \( (V) \) for a single cardiac contraction. For the left ventricle, point A represents end-diastole, segment AB is isovolumic contraction, point B is aortic valve opening, segment BC is LV ejection, point C is aortic valve closure and represents end-ejection, segment CD is isovolumic relaxation, point D is mitral valve opening, and segment DA is LV filling. LV stroke work (SW) is the cross-hatched area, and the stippled area is diastolic work done on the left ventricle by right ventricle and left atrium. (See text for details.)

**Stroke Work**

The area ABCD enclosed within the PV diagram in Fig. 17.4 is the external LV stroke work (SW), represented mathematically as integral \( PdV \). Although the calculation of LVSW is most accurate when it is derived by integrating the area within complete PV diagrams, a practical approximation can be obtained as follows:

\[
\text{LVSW} = (\overline{\text{LVSP}} - \overline{\text{LVDP}}) \text{SV}(0.0136) \quad (17.1)
\]

where LVSP and LVDP are, respectively, the mean LV systolic and diastolic pressures (in mm Hg), SV is the LV total stroke volume (in mL), and 0.0136 is a constant for converting mm Hg-mL into g-m. LVSP and LVDP may be obtained from planimetry of direct pressure tracings, as shown in Fig. 17.5. When the total LV stroke volume is the same as the forward stroke volume, SV may be calculated as cardiac output divided by heart rate. In cases where LV total stroke volume differs from forward stroke volume (e.g., mitral or aortic regurgitation, ventricular septal defect), the PV diagram may differ substantially in configuration from that shown in Fig. 17.4, and LVSW cannot be calculated from Eq. (17.1). Instead, planimetric integration of the entire PV plot is required.

**FIG. 17.5.**

Left ventricular (LV) and aortic pressure tracings illustrate areas planimetered to measure LV mean systolic pressure (LVSP), LV mean diastolic pressure (LVDP), and aortic mean systolic pressure (AoSP). LVSP is the area contained under the LV pressure curve, bounded by perpendicular lines defining end-diastole and mitral valve opening; LVDP is the diastolic area, similarly defined. AoSP is the area contained under the aortic pressure curve, bounded by perpendicular lines defining aortic valve opening and closure.

If LV pressure tracings are not available, in the absence of major regurgitation SW can be approximated from the aortic and pulmonary capillary wedge pressures as follows:

\[
\text{LVSW} = (\overline{\text{AoSP}} - \overline{\text{PCW}}) \text{SV}(0.0136) \quad (17.2)
\]

where AoSP is the aortic systolic mean pressure (planimetered from the aortic pressure tracing, Fig. 17.5) and PCW is the mean pulmonary capillary wedge pressure. A further approximation may be made by substituting mean systemic arterial pressure for AoSP, which it closely approximates.

LVSW is a reasonably good measure of LV systolic function in the absence of volume or pressure overload conditions, both of which may substantially increase calculated LVSW. The normal LVSW in adults is approximately 90 ± 30 g-m (mean ± SD); in adult patients with dilated cardiomyopathy or heart failure from extensive prior myocardial infarction, LVSW is often less than 40 g-m. Values less than 25 g-m indicate severe LV systolic failure, and when LVSW is less than 20 g-m the prognosis is grave.

LVSW is a measure of total LV chamber function and can be considered to reflect myocardial contractility only when the ventricle is reasonably homogeneous in its composition, as in most patients with dilated cardiomyopathy.
For patients with coronary artery disease and extensive myocardial infarction, LVSW may be depressed even though well-perfused areas of the myocardium with normal contractility remain.

Because power is the rate at which work is done, LV power in the normal heart is the integral of the product of LV pressure during ejection and aortic flow. LV power may be regarded as a measure of overall LV contractile function; with refinement (such as the measurement of preload-adjusted maximal power), it can be used as a measure of inotropic state (21).

**Ejection Phase Indices**

LV systolic function can be assessed using only the volume data from the PV diagram. One of the most widely used indices of LV systolic performance is the ejection fraction (EF), which is defined as follows:

$$\text{EF} = \frac{LVEDV - LVESV}{LVEDV} \quad (17.3)$$

where LVEDV and LVESV are the LV end-diastolic and end-systolic volumes, respectively. In the cardiac catheterization laboratory, left ventricular EF (LVEF) is most often derived from the LV angiogram, as discussed in Chapter 16. If the EF is divided by the ejection time (ET), measured from the aortic pressure tracing, the quotient is called mean normalized systolic ejection rate (MNSER).

$$\text{MNSER} = \frac{LVEDV - LVESV}{(LVEDV)(ET)} \quad (17.4)$$

Finally, another ejection phase index of LV systolic function is the velocity of circumferential fiber shortening, $V_{CF}$ (22). This is calculated as the rate of shortening of a theoretic LV myocardial fiber in a circumferential plane at the midpoint of the long axis of the ventricle. For convenience, mean $V_{CF}$ is used most often, rather than instantaneous or peak $V_{CF}$. Mean $V_{CF}$ is obtained by subtracting the end-systolic endocardial circumferential fiber length ($PID_{ES}$) from the end-diastolic endocardial circumferential fiber length ($PID_{ED}$), then dividing by ET and normalizing for end-diastolic circumferential fiber length:

$$V_{CF} = \frac{(\pi D_{ED} - \pi D_{ES})}{\pi D_{ED}(ET)} = \frac{(D_{ED} - D_{ES})}{D_{ED}(ET)} \quad (17.5)$$

$D_{ED}$ and $D_{ES}$ are end-diastolic and end-systolic minor axis dimensions. Although $V_{CF}$ can be calculated from angiographic data using the area-length method ($D = 4 A/PIL$), it is most commonly calculated from values for $D$ measured by M-mode echocardiography. Normal values for isovolumic and ejection phase indices are given in Table 17.2.

Ejection phase indices are obtained easily from LV angiography and can also be derived reliably from a variety of noninvasive techniques such as radionuclide ventriculography and echocardiography. The most widely used ejection phase index, the EF, is generally depressed when myocardial contractility is diminished. However, the ejection indices depend heavily on preload and afterload and cannot be regarded as reliable indices of contractility in conditions associated with altered loading conditions. For example, increases in preload cause the EF (and other ejection indices) to rise; consequently, LVEF may be increased in patients with mitral or aortic regurgitation, severe anemia, or other causes of increased diastolic LV inflow and may mask underlying deterioration of myocardial contractility. Conversely, increases in afterload cause the EF to fall; consequently, LVEF may be low in patients with severe aortic stenosis or other causes of increased resistance to systolic ejection and may falsely suggest underlying depression of myocardial contractility.
In practice, acute elevation of LV preload causes some increase in LV chamber size and aortic pressure, and these increases in afterload (systolic \( \sigma \) resisting shortening) tend to decrease the EF and other ejection indices, offsetting the rise in EF that a pure rise in preload would produce. Rankin and coworkers (28) produced changes in venous return by total body tilt in normal subjects; despite substantial changes in LV end-diastolic dimension and volume, there were no significant changes in EF, MNSER, or \( V_{CF} \). Similarly, acute elevation of afterload caused by raising aortic pressure causes an increase in LVEDP, and the resultant rise in preload (end-diastolic fiber stretch) tends to increase the EF and other ejection indices, offsetting the fall in EF produced by a pure rise in afterload. These physiologic adjustments explain why the ejection indices are much more useful clinically than might be expected on the basis of studies in the isolated heart or muscle preparation.

An LVEF of less than 0.40 indicates depressed LV systolic pump function, and if there is no abnormal loading to account for it, an LVEF of 0.40 or less can be taken to signify depressed myocardial contractility. An LVEF of less than 0.20 corresponds to severe depression of LV systolic performance and is usually associated with a poor prognosis. Interpretation of EF and other ejection indices is improved by consideration of the ventricular preload and afterload, and the latter values are defined most precisely by end-diastolic and end-systolic wall stresses, respectively.

**End-Systolic Pressure-Volume and \( \sigma \)-Length Relations**

Over the past 20 years, several groups have shown that the LV end-systolic PV, pressure-diameter, and \( \sigma \)-length relationships accurately reflect myocardial contractility, independent of changes in ventricular loading. This has been established in a series of studies in animals (29–35) and humans (36–42). The fundamental principle of end-systolic PV analysis is that at end-systole there is a single line relating LV chamber pressure to volume, unique for the level of contractility and independent of loading conditions. The LV end-systolic PV line can be generated by producing a series of PV loops (such as the one in Fig. 17.4) over a range of loading conditions (Figs. 17.6 and 17.7). The line connecting the upper left corners of the individual PV diagrams is the end-systolic PV line, characterized by a slope and by an x-axis intercept, called \( V_0 \) (the extrapolated end-systolic volume when end-systolic pressure is zero).

Current evidence indicates that an increase in contractility shifts the end-systolic PV line to the left with a steeper slope, and a depression in contractility is associated with a displacement of the line downward and to the right, with a reduced slope. Although there is some uncertainty as to the meaning of \( V_0 \), it is generally agreed that an increase in slope of the end-systolic PV line is a sensitive indicator of an increase in contractility. However, the technique of end-systolic analysis may not be as useful in comparisons among subjects as it is in comparisons of values in a single subject measured before and after an intervention. The end-systolic PV lines for groups of patients with normal, intermediate, and depressed LV contractility are shown in Fig. 17.8.

**FIG. 17.6.**

Left ventricular (LV) pressure-volume (PV) plots constructed using radionuclide ventriculography to measure LV volume simultaneously with measurement of LV pressure during cardiac catheterization. A: Three sequential plots measured during baseline and at two sequential doses of intravenous nitroglycerin to lower LV pressure. B: Similar plots in a patient whose baseline LV systolic pressure was low: In this case, phenylephrine was used in increasing doses to produce three levels of systolic loading. The upper left (end-systolic) corners of the three PV plots in each panel define a straight line, the LV end-systolic PV line. (See text for discussion.) (From McKay RG, Aroesty JM, Heller GV, et al. Left ventricular pressure-volume diagrams and end-systolic pressure relations in human beings. J Am Coll Cardiol 1984;3:301, with permission.)

**FIG. 17.7.**

The left panel shows left ventricular (LV) pressure-volume loops obtained during rapid LV unloading achieved by inferior vena cava (IVC) balloon occlusion in a patient undergoing cardiac catheterization. Volume was obtained by a conductance catheter technique. The right panels show relationships between stroke work (upper right), maximum rate of rise of LV systolic pressure, \( dP/dt \) (lower right), and LV end-diastolic volume. (From Kass DA, Maughan WL. From E to pressure-volume relations: a broader view. Circulation 1988;77:1203, with permission.)
Left ventricular (LV) end-systolic pressure ($P_{ES}$) plotted against end-systolic volume index ($V_{ES}$) at two levels of loading for each of three patient groups: Group A, patients with normal LV contractile function; Group B, patients with moderate depression of LV contractile performance; Group C, patients with marked depression of LV contractility. Depressed contractility shifts the $P_{ES}-V_{ES}$ relation to the right, with a reduced slope ($m$) and increased intercept ($V_0$). (From Grossman W, Braunwald E, Mann JT, et al. Contractile state of the left ventricle in man as evaluated from end-systolic pressure relations. *Circulation* 1977;45:845, with permission.)

To measure the end-systolic PV line, one can use aortic dicrotic notch pressure as end-systolic LV pressure and minimum LV chamber volume as end-systolic volume. LV volume can be measured by angiography, using either direct LV injection or right-sided injection with image enhancement by digital subtraction angiography. Alternatively, LV volume can be measured by radionuclide techniques, ultrasonic techniques, or a specially designed impedance (conductance) catheter (42),(43).

**Relationship Between Peak dP/dt and End-diastolic Volume**

Little and coworkers (44) have examined the relationship between LV $dP/dt_{max}$ and end-diastolic volume and have proposed the slope of this relationship as an index of contractile state. They have shown that, on theoretic grounds, this relationship can be derived from the LV end-systolic PV relationship; both provide estimates of maximal myocardial elastance. This relationship is simpler to derive because both LV end-diastolic volume and $dP/dt_{max}$ are more readily defined than either end-systolic pressure or volume. One does not need to be concerned about a lack of coincidence between end-systole and maximal elastance, as with the end-systolic PV relationship. The $dP/dt_{max}$–end-diastolic volume relationship, however, has yet to be evaluated extensively in the clinical setting. Also, the end-systolic PV relationship can be estimated clinically by entirely noninvasive methods (45). Nevertheless, the $dP/dt_{max}$–end-diastolic volume relationship represents an intriguing concept and may prove a valuable index of contractile state.

**FIG. 17.8.**

Relationship between left ventricular (LV) end-systolic wall stress ($\sigma_{ES}$) and % fractional shortening (%DELTAD) measured by echocardiography for 130 control points, at rest (open dots) or during methoxamine infusion (solid dots). The inverse relationship defines normal LV myocardial contractility. (From Borow KM, Green LH, Grossman W, et al. Left ventricular end-systolic stress-shortening and stress-length relations in humans. *Am J Cardiol* 1982;50:1301, with permission.)

**Stress-shortening Relationships**

Another approach to the assessment of LV systolic performance and myocardial contractility involves measuring the extent of cardiac muscle shortening and relating this shortening to the systolic wall stress ($\sigma$) resisting shortening.

If a ventricle is presented with progressively increasing resistance to ejection, $\sigma$ rises while the extent of myocardial shortening declines. Therefore, a plot of systolic $\sigma$ on the horizontal axis against myocardial shortening expressed as EF, $V_{CF}$, or percent fractional shortening (%DELTAD) on the vertical axis yields a tight inverse relationship (Fig. 17.9). Data from studies of individual patients may then be compared with these normal values. In Fig. 17.9, if the point relating end-systolic $\sigma$ ($\sigma_{ES}$) and %DELTAD for a given patient lies within the confidence lines of the normal population, myocardial contractility is likely to be normal; however, if the $\sigma_{ES}$-%DELTAD point lies below the normal range, contractility is depressed even if %DELTAD is normal. Fig. 17.10 shows that the $\sigma_{ES}$-%DELTAD relationship is shifted upward by an increase in contractility.
resulting from a dobutamine infusion. One caution concerning the $\sigma_{ES}$-$\%$DELTAD relationship is that it is preload sensitive. That is, increases in preload will increase $\%$DELTAD for any level of $\sigma_{ES}$. There is some evidence that when $V_{CF}$ is substituted for $\%$DELTAD the preload dependence of the stress-shortening relationship is attenuated or abolished.

FIG. 17.10.

Upward shift in the left ventricular (LV) end-systolic stress-shortening relation resulting from dobutamine infusion. (See text.) (From Borow KM, et al. Left ventricular end-systolic stress-shortening and stress-length relations in humans. Am J Cardiol 1982;50:1301, with permission.)

Plots of systolic wall stress against LVEF have been analyzed for patients with a variety of conditions, including LV pressure overload (Fig. 17.11). In these plots, comprised of multiple individual data points (each point relating LV wall $\sigma$ and EF for an individual patient) an inverse systolic $\sigma$-EF relationship is apparent for patients with chronic LV pressure overload. This suggests that the depressed LVEF in some of these individuals is caused by excessive systolic $\sigma$; that is, the load resisting systolic shortening is abnormally high and is responsible for a reduced extent of shortening. This combination of high $\sigma$ and low EF is sometimes referred to as afterload mismatch (46–48), and it implies that hypertrophy has been inadequate to return systolic wall stress to its relatively low normal level. Patients in whom LVEF is diminished out of proportion to any increase in systolic wall stress can be assumed to have depressed myocardial contractility (Fig. 17.12).

FIG. 17.11.

Left ventricular (LV) ejection fraction plotted against mean systolic circumferential wall stress, $\sigma$, for 14 patients with pure aortic stenosis (normal coronary arteries, no other valve disease) and varying degrees of LV decompensation. The inverse relationship is consistent with afterload excess as a principal cause of the decreased ejection fraction. (From Gunther S, Grossman W. Determinants of ventricular function in pressure-overload hypertrophy in man. Circulation 1979;59:679, with permission.)

FIG. 17.12.

Plot of left ventricular (LV) ejection fraction against systolic $\sigma$, similar to Fig. 17.11 but including patients with aortic stenosis (solid dots), dilated cardiomyopathy (crosses), and normal ventricular function (open squares). The regression line was constructed from the patients with normal LV function and those with aortic stenosis. (See text for discussion.) (From Gunther S, Grossman W. Determination of ventricular function in pressure overload hypertrophy in man. Circulation 1979;5:679, with permission.)

A refinement of this approach involves measuring the relation between end-systolic LV wall stress and the heart rate–corrected velocity of fiber shortening. This approach was found to be sensitive and preload independent in an assessment of LV response to nitroprusside and dopamine infusions in patients with dilated cardiomyopathy (49). In that study, this approach was more sensitive to detecting increased contractility than was LV $dP/dt$.

The advantage of $\sigma$-shortening analysis over PV diagram analysis is that wall $\sigma$ takes into consideration changes in LV geometry and muscle mass that occur in response to chronic alterations in loading. For example, a systolic pressure of 250 to 300 mm Hg imposed acutely on a normal left ventricle would result in considerable reduction in LVEF, perhaps down to the 20% to 30% range. This change occurs because, in the absence of any increase in LV wall thickness or decrease in chamber radius, systolic $\sigma$ would more than double in response to such an acute pressure overload, and this would lead to a major reduction in LVEF. However, if the increase in systolic pressure to 250 to 300 mm Hg occurs gradually and is matched by the development of sufficient hypertrophy in the appropriate pattern, systolic wall $\sigma$ remains normal and fiber shortening and LVEF do not decrease. Therefore, in the presence of significant hypertrophy and/or altered LV geometry, $\sigma$-shortening analysis may have considerable value.
DIASTOLIC FUNCTION

Left Ventricular Diastolic Distensibility: Pressure-Volume Relationship

As pointed out by Henderson in 1923, “In the heart, diastolic relaxation is a vital factor and not merely the passive stretching of a rubber bag. Being vital, it is variable” (50). Analysis of diastolic function today requires appreciation that diastolic compliance is variable and may change substantially in a given patient from one minute to the next. Diastolic function is summated physiologically in the relation between LV pressure and volume during diastole (Fig. 17.4, segment DA). Traditionally, an upward shift in this diastolic PV relation is regarded as indicating increased LV diastolic chamber stiffness, and a downward shift indicates decreased stiffness or increased LV diastolic chamber compliance. In the terminology of physics and engineering, stiffness, and its opposite, compliance, relate a change in pressure (DELTAP) to a change in volume (DELTAV); therefore, some investigators have restricted these terms to refer to the slope of the diastolic PV relation. In this regard, as seen in segment DA of Fig. 17.4, LV diastolic stiffness (DELTAP/DELTAV) is low early in diastole and rises steadily throughout diastolic filling.

Figure 17.13 shows theoretic LV diastolic PV plots for patients with normal, stiff, and compliant ventricular chambers. Several problems arise when stiffness and compliance are defined strictly in terms of the slope of the diastolic PV diagram, and these problems are illustrated in Fig. 17.14. First, in some clinical conditions (e.g., angina pectoris), the LV diastolic PV plot shifts upward in a parallel fashion, without a noticeable change in slope. These patients have increased LV filling pressure, often with normal chamber volumes, and from a hydrodynamic point of view the LV chamber must be regarded as presenting increased resistance to diastolic filling. To say that LV diastolic stiffness and compliance are normal in such patients because the upward shift has been a parallel one (without slope change) seems inappropriate. In other cases (e.g., after nitroprusside infusion in patients with heart failure), there is a downward shift in the LV diastolic PV plot, with an increase in the steepness of the plot; again, to say that such patients exhibit increased LV diastolic stiffness seems inappropriate, because they require a lower filling pressure to achieve the same diastolic chamber dimension and fiber stretch. Therefore, the LV diastolic PV plot can show changes of two types: displacement (movement of the entire relationship upward, downward, or laterally) and configuration change (including change in curvature). In our studies, we have referred to upward or downward displacement changes as being associated with a change in ventricular distensibility (51). Therefore, if the LV diastolic PV plot shifts upward, we would say that the LV chamber has become less distensible; a higher diastolic pressure is required to fill or distend the chamber to its earlier volume (Fig. 17.14). Similarly, a downward shift in the diastolic PV plot would be said to indicate an increase in LV diastolic distensibility. The changes in curvature and/or configuration that may accompany these displacement changes are difficult to quantify and to interpret.

FIG. 17.13.

Diagrammatic representation of ventricular diastolic pressure-volume relations for normal, stiff, and compliant ventricles. (See text for discussion.)

FIG. 17.14.

Schematic illustration of the difference between diastolic distensibility and compliance. On the left, the left ventricular diastolic pressure-volume (PV) relation has undergone a parallel upward shift. Distensibility is decreased (higher diastolic pressure required to fill the ventricle to the same chamber volume), but compliance, defined as the slope of the PV relation, is unchanged. On the right, superimposed on the parallel upward shift, are curves whose slopes are steeper (decreased compliance) or less steep (increased compliance) than either of the two parallel PV curves. This illustrates the importance of distinguishing distensibility from compliance, because the curve labeled “increased compliance” nevertheless exhibits decreased diastolic distensibility, compared with the normal PV relation. (From Grossman W. Relaxation and diastolic distensibility of the regionally ischemic left ventricle. In: Grossman W, Lorell BH, eds. Diastolic Relaxation of the Heart. Boston: Martinus Nijhoff, 1988:193.)

Various formulas have been developed for analyzing the curvature of the LV diastolic PV plot (52–55). These
generally assume that the curvature is exponential, an assumption that is often but not always reasonable. Diastolic PV and P-segment length (SL) plots constructed from a series of end-diastolic points have been used in animal experiments to assess LV diastolic compliance (56), and this technique has been applied to clinical studies. When a series of end-diastolic PV or P-SL points are plotted, the relation is more strictly exponential, and application of mathematical models and analysis is more easily justified by the good agreement of measured data and mathematical predictions.

Clinical Conditions Influencing Diastolic Distensibility

Factors that influence the position of the LV diastolic PV plot (that is, factors that influence LV diastolic distensibility) are listed in Table 17.3. Constrictive pericarditis and pericardial tamponade are associated with a striking upward shift in the diastolic PV relation. This upward shift is a parallel shift, without substantial change in curvature. Pericardial restraint is also important in the mechanism whereby altered RV loading can alter the LV diastolic PV relation. When distended, the right ventricle can decrease LV diastolic distensibility by exerting an extrinsic pressure on the LV chamber in diastole through the shared interventricular septum, which may actually bulge into the LV chamber. Acute RV infarction causes dilatation of the RV chamber that, in the presence of an intact, previously unstressed pericardium, may lead to extrinsic compression of the LV in diastole with a hemodynamic pattern resembling cardiac tamponade (57). The effect of increased RV loading on LV diastolic distensibility is an example of ventricular interaction, which is more prominent in the presence of an intact and relatively snug pericardium. In animal experiments, it is difficult to demonstrate diastolic ventricular interaction once the pericardium has been opened wide (55).

Coronary vascular turgor can influence LV diastolic chamber stiffness (58). The LV wall has a rich blood supply, and engorgement of the capillaries and venules with blood makes the wall relatively stiff: for obvious reasons, this has been referred to as the erectile effect. Although the erectile effect is probably not of much importance when coronary blood flow and pressure (the two components determining the degree of turgor) are in the physiologic range, a marked fall in coronary flow and pressure (as occurs distal to a coronary occlusion when collateral flow is poor or absent) is associated with a decrease in stiffness of the affected myocardium and an increase in LV diastolic distensibility.

Experimental evidence (59) supports an important role for increased coronary venous pressure as a major determinant of coronary vascular turgor. Increases in right atrial pressure from 0 to 15 and 30 mm Hg led to substantial upward shifts in the LV end-diastolic PV relation that could not be attributed to right ventricular distention and a shift in the interventricular septum.

Extrinsic compression of the heart by tumor may cause decreased LV diastolic distensibility and may mimic cardiac tamponade.

When an upward shift in the diastolic PV relation is present and the extrinsic factors listed in Table 17.3 cannot clearly explain the altered distensibility, a change in one of the intrinsic determinants of LV distensibility is likely to be present. Altered passive elasticity caused by amyloidosis, edema, or diffuse fibrosis may cause a restrictive cardiomyopathic pattern, with high LV diastolic pressure relative to volume in the presence of reasonably well-preserved systolic function. Clinically, heart failure may be present. Endomyocardial biopsy of the right or left ventricle may be needed to establish the diagnosis (see Chapter 20).

Myocardial Ischemia

Abnormal diastolic relaxation can cause the diastolic PV relation to shift upward strikingly. During angina pectoris, a 10 to 15 mm Hg rise in average LV diastolic pressure may occur with little or no change in diastolic volume; if this persists for a sufficient duration (more than 10 to 20 minutes), pulmonary edema may occur. Such episodes of flash pulmonary edema in patients with essentially normal LV systolic function and normal LV chamber size generally indicate a large mass of ischemic myocardium (60) and suggest three-vessel or left main coronary artery obstruction. The decreased LV distensibility during ischemia may be prevented in many patients by a Ca++ channel blocking agent (61). The mechanism of impaired myocardial relaxation during the ischemia of angina pectoris is not ++
understood completely but may be associated with diastolic Ca overload of the ischemic myocytes, in part related to ischemic dysfunction of the sarcoplasmic reticulum (62). During the ischemia of acute coronary occlusion, an upward shift of the diastolic PV relation may occur if sufficient collateral blood flow is present to permit continued systolic contraction of the ischemic segment. If ischemia is sufficiently severe to cause complete akinesis of the affected myocardium, however, altered distensibility does not occur: incomplete relaxation can occur only in myocytes when there has been systolic cross-bridge activation. Also, the marked decrease in coronary vascular turgor distal to a coronary occlusion with poor or absent collaterals, together with local accumulation of hydrogen ion (H\(^+\)), contributes to an increase in regional distensibility, so that the net effect on the ventricular diastolic PV relation may be one of no change.

Cardiac Hypertrophy

Impaired relaxation with decreased LV diastolic distensibility is also seen in patients with hypertrophic cardiomyopathy and during angina pectoris in patients with aortic stenosis and normal coronary arteries.

Indices of Left Ventricular Diastolic Relaxation Rate

Much attention has been given to measures of LV diastolic relaxation during the isovolumic relaxation period and during early, middle, and late diastolic filling. These indices may be considered as either pressure-derived or volume flow-derived and may assess either global or regional diastolic relaxation (63–83). A listing of some of these indices and their normal values is given in Table 17.4.

The time course of LV pressure decline after aortic valve closure is altered in conditions known to be associated with abnormalities of myocardial relaxation. One of the simplest ways of quantifying the time course of LV pressure decline is to measure the maximum rate of pressure fall, peak -dP/dt. Although peak negative dP/dt is altered by conditions that change myocardial relaxation, it is also altered by changes in loading conditions. For example, LV peak -dP/dt increases (i.e., rises in absolute value) when aortic pressure rises. For example, an increase in LV peak -dP/dt from -1,500 to -1,800 mm Hg/sec could be caused by an increase in the rate of myocardial relaxation, a rise in aortic pressure, or both. An increase in peak negative dP/dt when aortic pressure is unchanged or declining, however, signifies an improvement of LV relaxation. LV peak -dP/dt is decreased during the myocardial ischemia of either angina pectoris or infarction and is increased in response to BETA-adrenergic stimulation and the phosphodiesterase inhibitor milrinone (63). It is not increased by digitalis glycosides.

Time Constant of Relaxation

Because of the load dependency of peak negative dP/dt and the fact that it uses information from only one point on the LV pressure-time plot, other indices have been introduced that analyze the time course of LV isovolumic pressure fall more completely. In 1976, Weiss and coworkers introduced the time constant T (or tau) of LV isovolumic pressure decline (64). They pointed out that LV isovolumic pressure decline could be fit by the equation

\[
P = e^{At+B}
\]  
(17.6)

where \(P\) is LV isovolumic pressure, \(t\) is time after peak negative dP/dt, and A and B are constants. This can also be expressed as

\[
\ln P = At + B
\]  
(17.7)

A plot of the natural logarithm of LV pressure versus time allows calculation of the slope A, a negative number whose units are sec\(^{-1}\). The time constant \(T\) of isovolumic pressure fall is then defined as -1/A, expressed in
milliseconds, and is the time that it takes $P$ to decline $1/e$ of its value. Studies by the Johns Hopkins group have suggested that myocardial relaxation is normally complete by approximately $3.5 T$ after the onset of isovolumic relaxation. The normal value for $T$ as calculated using a plot of $\ln P$ versus $t$ is 25 to 40 msec in humans. Therefore, by 140 msec after the dicrotic notch, LV diastolic PV relations should be determined primarily by passive elastic properties of the myocardium. Because the normal LV diastolic filling period is more than 400 msec, it is unlikely, according to this concept, that late- and end-diastolic PV relations are still influenced by the relaxation process. However, there is now considerable evidence that even in the normal myocardium cross-bridge cycling persists to some extent throughout diastole. This resting myocardial activity or tone makes it difficult to know what significance to apply to the concept that relaxation is complete at $3.5 T$. Nevertheless, it is important to emphasize that the relaxation process does progress with time through diastole, so that slowing of the process (prolongation of $T$) or shortening of the diastolic filling period (e.g., tachycardia) results in a greater resistance to early and even late diastolic filling.

Another approach to the measurement of $T$ uses a more general equation to describe LV isovolumic pressure decline:

$$ P = P_o e^{-t/T} + P_B \tag{17.8} $$

In this formulation, if diastole were infinite in duration ($t = infinite$), $P$ would decay to a residual pressure, $P_B$. In the initial formulation by Weiss and coworkers (64), $P$ always declines toward zero in long diastoles. The more general formula allows for two variables: $T$ (which equals $-1/A$) and $P_B$. Work by Carroll and coworkers (66), as well other groups (63), has shown that both $P_B$ and $T$ can vary with physiologic maneuvers (e.g., exercise, ischemia). The biologic meaning of $P_B$ is uncertain, although there has been speculation that it may reflect the level of diastolic myocardial tone. A problem with both $P_B$ and $T$ is that there is experimental evidence that the speed of the relaxation process itself is altered by myofiber stretch that occurs after mitral valve opening.

When $T$ is to be derived from the formulas that assume a variable pressure intercept ($P_B$), the calculation is often accomplished by taking the first derivative (65):

$$ \frac{dP}{dt} = -\frac{1}{T} (P - P_B) \tag{17.9} $$

Here, a plot of $dP/dt$ versus ($P - P_B$) has the slope $-1/T$.

Normal values in humans for $T$ calculated by either the logarithmic method (asymptote = 0) or the derivative method (variable asymptote) are listed in Table 17.4.

Interesting experimental data comparing the two methods of calculating $T$ with a “gold standard” were published by Paulus and coworkers (67). They measured LV pressure decay with a micromanometer catheter during isovolumic beats generated using an Inoue balloon to occlude the mitral valve orifice in patients with mitral stenosis who were undergoing balloon valvuloplasty. LV pressure declined to an asymptote of $2 \pm 3$ mm Hg, and $T$ was calculated from a monoexponential curve fit using the measured asymptote pressure. This $T$ was considerably shorter than the $T$ calculated by the derivative (variable asymptote) method and was much closer to the value obtained by the original Weiss logarithmic method (64), which assumes a zero asymptote.
Not only slow myocardial relaxation but also asynchrony of the relaxation process within the ventricular chamber results in a prolongation of $T$. In addition, $T$ is probably not completely independent of loading conditions, although the influence of altered loading is relatively small. Measurement of $T$ should be attempted only from LV pressure tracings obtained with high-fidelity, micromanometer-tipped catheters, or from fluid-filled systems with demonstrated optimal damping and high (more than 25 Hz) natural frequencies (see Chapter 7). Of interest, investigators have reported the noninvasive assessment of LV relaxation by continuous wave Doppler echocardiography in patients with some degree of mitral regurgitation (68). (69). The Doppler mitral regurgitant velocity profile is recorded, digitized, and converted to ventriculoatrial pressure gradient curves with the use of the simplified Bernoulli equation and differentiated into instantaneous $dP/dt$. The relaxation time constant is then calculated assuming a zero-pressure asymptote (Fig. 17.15). In general, close correlations are seen between measurements of $T$ made by this technique and those made from simultaneous LV micromanometer pressure measurements (68), (69). However, accurate prediction of actual $T$ was improved substantially when a measure of left atrial pressure was incorporated in the analysis.

**FIG. 17.15.**

Doppler technique for measuring left ventricular (LV) rate of pressure fall, $dP/dt$, and the time constant of LV relaxation ($T$), using Doppler mitral regurgitant velocity spectrum (A, top), LV–left atrial pressure gradient and its first derivative (A, bottom), and linear plot of log LV-estimated pressure ($p$) versus time (B), with $T = 1/slope$. (From C Chen et al. Doppler derived $dP/dt$ and $T$ in mitral regurgitation. *J Am Coll Cardiol* 1994;23:970, with permission.)

**Volume-Derived Indices of Relaxation**

**Peak Filling Rate**

After mitral valve opening, ventricular filling usually proceeds briskly with an initial rapid filling phase, a middle slow filling phase, and a terminal increase in filling rate associated with atrial systole. The rapid filling phase may be characterized by a maximum or peak filling rate (PFR) and time-to-PFR. PFR is usually determined by plotting LV volume against time, fitting the initial portion of this plot after mitral valve opening to a third- (or higher-) order polynomial, and solving for the first derivative of this polynomial. LV volume for this calculation may be obtained from the LV cineangiogram or from radionuclide techniques. As one might expect, PFR is preload dependent: interventions that raise left atrial pressure increase PFR, and interventions that reduce pulmonary venous return and left atrial pressure cause PFR to decrease (70). However, an increase in PFR that occurs when LV filling pressure (pulmonary capillary wedge pressure, left atrial pressure, or LV diastolic pressure) is unchanged or falling can reasonably be taken as an indication that LV relaxation has improved. For example, PFR has been shown to decrease during angina pectoris (71) when LV filling pressure is increasing. Because the rise in LV filling pressure by itself would cause an increase in PFR, the fall in PFR that is actually observed most likely indicates slowed relaxation of the myocardium, consistent with the other findings in this condition (fall in peak negative $dP/dt$, prolongation of $T$) that suggest impaired relaxation of the ischemic myocardium. PFR is reduced in patients with coronary stenoses, even in the absence of overt ischemia, and improves after coronary angioplasty (72). PFR is also reduced in patients with hypertrophic cardiomyopathy and improves after administration of a calcium-blocking agent (73). PFR is usually normalized for end-diastolic volume (EDV) and expressed as EDV/sec. Cardiac dilatation by itself tends to depress PFR, exaggerating its preload dependence.

**FIG. 17.16.**

Analysis of diastolic left ventricular (LV) regional wall motion. **A:** The LV silhouette is divided into eight segments. **B:** Regional area is plotted throughout the cardiac cycle, and the change in area (DELTAA) during isovolumic relaxation (defined as the first 80 msec after peak rate of LV pressure fall) and regional peak filling rate are calculated. $-dP/dt$, maximum rate of LV pressure fall; ED, end-diastolic. (From Friedrich S, Lorell BH, Rousseau M, et al. Intracardiac angiotensin-converting enzyme inhibition improves diastolic function in patients with LV hypertrophy due to aortic stenosis. *Circulation* 1994;90:2761, with permission.)
Regional Diastolic Dysfunction

Diastolic dysfunction of specific regions of the left ventricle may be difficult to assess solely by examination of a global parameter of LV diastolic function such as the time constant of relaxation or the PFR. As pointed out by Pouleur and Rousseau (74), the time course of LV isovolumic pressure decline underestimates the severity of regional impairment in the rate of relaxation. Marked slowing of regional relaxation in an area of myocardial ischemia is partially masked by normal or enhanced rates of relaxation in adjacent normal regions of myocardium. Regional wall stress measurements have been proposed as an ideal way to assess regional rates of relaxation, but these can be made only by having knowledge of simultaneous LV pressure wall thickness and geometry (74).

A more practical way of assessing regional LV myocardial relaxation involves measurement of changes in regional LV chamber volume during isovolumic relaxation (Fig. 17.16) as well as regional PFR (75–77). Regional LV area may not be constant for each segmental area during “isovolumic” relaxation in the dysfunctional ventricle. Instead, some regions may increase while others decrease in area, due to either asynchrony or regional slowing of the relaxation process, with resultant differences in active wall tension in different parts of the left ventricle. An example of the application of this approach to measurement of regional myocardial relaxation is seen in a hemodynamic study by Friedrich and coworkers (75) of 20 adult patients with LV hypertrophy resulting from aortic stenosis (mean aortic valve area, 0.7 ± 0.2 cm²). LV global diastolic function was abnormal, with a T of 58 ± 4 msec, and a time-to-PFR of 378 ± 63 msec. Enalaprilat, an angiotensin-converting enzyme inhibitor, was infused into the left coronary artery, and regional LV diastolic function was assessed in both the anterior wall (perfused by enalaprilat) and the inferior wall. LV area change during isovolumic relaxation increased in anterior segments and decreased in inferior segments (Fig. 17.17), suggesting improved diastolic relaxation of the hypertrophied myocardium in response to angiotensin-converting enzyme inhibition (75), something seen previously only in animal experiments (76).

FIG. 17.17.

Left ventricular (LV) regional area change during isovolumic relaxation before and after selective left intracoronary angiotensin-converting-enzyme (ACE) inhibition with enalaprilat in patients with marked LV hypertrophy and normal coronary arteries. Because total LV volume is constant during isovolumic relaxation, the increase in anterior segment area (presumably caused by improved myocardial relaxation due to regional ACE inhibition) is exactly counterbalanced by a decrease in inferior segment area. (From Friedrich S, et al. Intracardiac angiotensin-converting-enzyme inhibition improves diastolic function in patients with LV hypertrophy due to aortic stenosis. Circulation 1994;90:2761, with permission.)

Rate of Wall Thinning

Another index of diastolic function, similar in some ways to PFR, is the peak rate of diastolic LV wall thinning. This can be measured echocardiographically by plotting posterior or septal wall thickness against time, fitting the data to a polynomial, and taking the first derivative (77–79). The posterior wall thickness, h, and its first derivative, dh/dt, reflect regional diastolic function of the posterior wall myocardium. An advantage of peak negative dh/dt over PFR is that it assesses regional myocardial function, whereas PFR describes behavior for the whole ventricle and is insensitive when equal and opposite changes in diastolic function are occurring in different parts of the LV chamber. Peak negative dh/dt decreases during angina, even though LV filling pressure rises (79).

Various other indices of diastolic myocardial relaxation have been proposed. Most are imperfect, as are the ones discussed here. However, important information about diastolic relaxation and distensibility usually can be gleaned from examination of the parameters discussed in this chapter, taken in the context of the clinical setting and other hemodynamic findings in an individual patient.