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Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers

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¹Division of Cardiology, Department of Medicine, Columbia University, New York, New York; ²Divisions of Mathematical Biology and Cardiology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; and ³Research Institute, National Cardiovascular Center, Suita, Osaka, Japan

Burkhoff, Daniel, Israel Mirsky, and Hiroyuki Suga. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol* 289: H501–H512, 2005; doi:10.1152/ajpheart.00138.2005.—Assessment of left ventricular systolic and diastolic pump properties is fundamental to advancing the understanding of cardiovascular pathophysiology and therapeutics, especially for heart failure. The use of end-systolic and end-diastolic pressure-volume relationships derived from measurements of instantaneous left ventricular pressure-volume loops emerged in the 1970s as a comprehensive approach for this purpose. As invasive and noninvasive techniques for measuring ventricular volume improved over the past decades, these relations have become commonly used by basic, translational, and clinical researchers. This review summarizes 1) the basic concepts underlying pressure-volume analysis of ventricular and myocardial systolic and diastolic properties, 2) deviations from ideal conditions typically encountered in real-life applications, 3) how these relationships are appropriately analyzed, including statistical analyses, and 4) the most common problems encountered by investigators and the appropriate remedies. The goal is to provide practical information and simple guidelines for accurate application and interpretation of pressure-volume data as they pertain to characterization of ventricular and myocardial properties in health and disease.

systole; diastole; ventricular mechanics; end-systolic pressure-volume relationship; end-diastolic pressure-volume relationship

ASSESSMENT OF LEFT VENTRICULAR systolic and diastolic pump properties is fundamental to advancing the understanding of cardiovascular pathophysiology and therapeutics, especially for heart failure. The utility of the ventricular pressure-volume diagram for this purpose was evident from the earliest days of modern cardiovascular investigations, when Otto Frank (27) first documented that the strength of cardiac contraction increases with filling volume. Because of difficulties in measuring ventricular volume in intact animals and human subjects, however, research on pressure-volume relationships proceeded at a relatively slow pace during the first two-thirds of the twentieth century (7, 24, 74). With development of the isolated blood-perfused canine heart preparation (60, 80), echocardiography (26), and ventriculography (25) for studies in humans, there was a resurgence of activity in the 1970s and 1980s. These early efforts spawned a series of pivotal studies that established the end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively) as a meaningful and useful way of characterizing intrinsic ventricular pump properties (65, 67, 76, 80). Research in the 1980s and early 1990s elucidated detailed characteristics of these relations, clarified how they should be properly analyzed, and validated multiple techniques for measuring (or indexing)

ventricular volume (5) so that these concepts could be applied in basic and clinical research (5, 38, 39, 51). Furthermore, the physiological significance of the ESPVR and EDPVR was reinforced by their deterministic link to myocardial energy demand (77, 78). Because of the general applicability of the concepts to hearts of all species, pressure-volume analysis has become standard in studies of mice, humans, and animals of all sizes in between. Accordingly, an increasing number of investigators with varied backgrounds use this approach in their research. To move the respective fields forward, it is critical that the fundamental principles be applied rigorously.

This review summarizes 1) the basic concepts underlying pressure-volume analysis of ventricular systolic and diastolic properties and passive myocardial stiffness, 2) deviations from ideal conditions typically encountered in real-life applications, 3) how these relationships are appropriately analyzed, including statistical analyses, and 4) the most common problems encountered by investigators and the appropriate remedies. The goal is to provide practical information and simple guidelines for accurate application and interpretation of pressure-volume data and associated stress-strain analysis in preclinical and clinical studies.

It is important to appreciate at the outset that there are two distinct, although intimately interrelated, aspects of the assessment of cardiac properties. One is assessment of the properties of the ventricle as a hemodynamic pump; the other is assessment of the intrinsic properties of the cardiac muscle. Ventric-

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ular properties (systolic and diastolic) are dependent on myocardial properties (systolic and diastolic), the amount of muscle mass, chamber architecture, and chamber geometry. The pressure-volume construct is used to directly assess ventricular properties, which are the main focus of this review. Important parameters derivative of pressure-volume analysis that yield information about myocardial properties are also highlighted.

GENERAL OVERVIEW

The hemodynamic events occurring during the cardiac cycle are displayed by plotting instantaneous ventricular pressure vs. volume (Fig. 1A). Under steady-state conditions and with a constant time interval between beats, this loop is repeated with each contraction. For a given cardiac cycle, there is a single pressure-volume point that coincides with end diastole (which resides at the lower right corner of the loop) and a single pressure-volume point that coincides with end systole (which resides at the upper left corner of the loop). If an intervention is performed that acutely changes the loading conditions on the heart but has no effect on myocardial contractility¹ (e.g., transient inferior vena caval occlusion to reduce preload, administration of phenylephrine to increase afterload, etc.) a family of loops is obtained (Fig. 1, B and C). The end-systolic and end-diastolic points of these loops delineate two distinct boundaries. The EDPVR, constructed by connecting the end-diastolic pressure-volume points of each loop, is nonlinear and defines the passive physical properties of the chamber with the muscles in their most relaxed state. The ESPVR, constructed by connecting the end-systolic pressure-volume points of each loop, defines a reasonably linear relationship that characterizes properties of the chamber with the muscles in a state of maximal activation at a given contractile state. Additional didactic explanations of the pressure-volume loop are provided elsewhere (11).

SYSTOLIC PROPERTIES

Basic Concepts

Original studies suggested, as indicated in Fig. 1, B and C, that the ESPVR is reasonably linear and can be characterized by a slope (E_{es} , end-systolic elastance) and a volume axis intercept (V_o), so that $P_{es} = E_{es}(V_{es} - V_o)$, where P_{es} and V_{es} are end-systolic pressure and volume, respectively. Importantly, this relationship was initially shown to be independent of afterloading conditions (81). This means that, in principle, at a given contractile state, the ESPVR obtained by reducing filling volume with a fixed afterload resistance (Fig. 1B) would be the same as that obtained by reducing arterial resistance at a fixed preload (Fig. 1C). Furthermore, with inotropic agents that increase myocardial contractility (e.g., catecholamines,

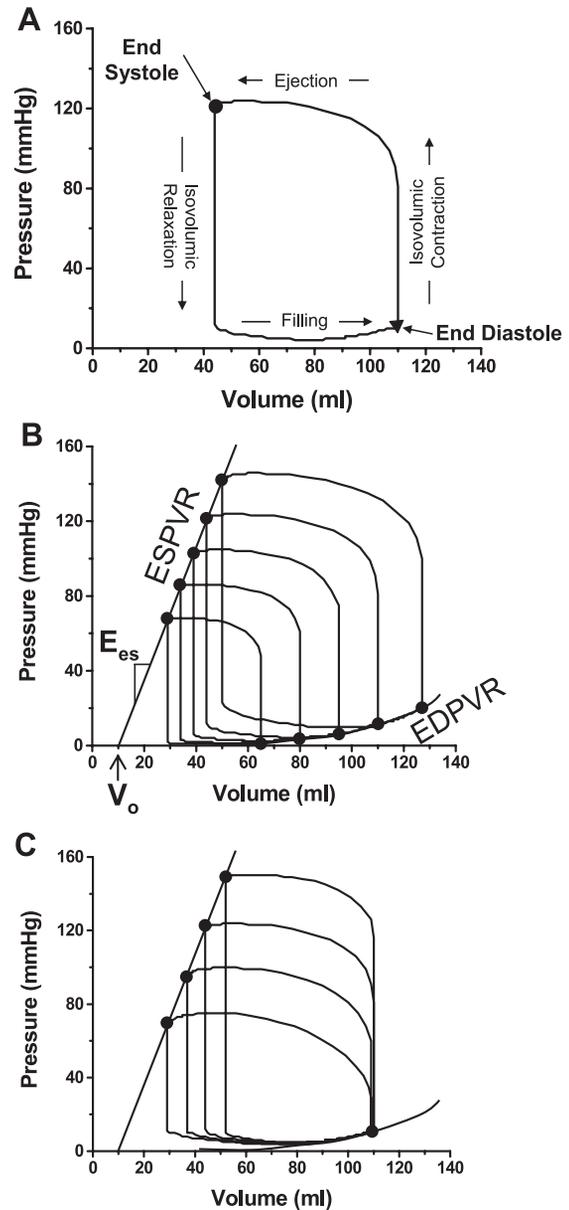


Fig. 1. A: the 4 phases of the cardiac cycle are readily displayed on the pressure-volume loop, which is constructed by plotting instantaneous pressure vs. volume. This loop repeats with each cardiac cycle and shows how the heart transitions from its end-diastolic state to the end-systolic state and back. B: with a constant contractile state and afterload resistance, a progressive reduction in ventricular filling pressure causes the loops to shift toward lower volumes at both end systole and end diastole. When the resulting end-systolic pressure-volume points are connected, a reasonably linear end-systolic pressure-volume relationship (ESPVR) is obtained. The linear ESPVR is characterized by a slope (E_{es}) and a volume axis intercept (V_o). In contrast, the diastolic pressure-volume points define a nonlinear end-diastolic pressure-volume relationship (EDPVR). C: when afterload resistance is increased at a constant preload pressure, the loops get narrower and longer and, under idealized conditions, the end-systolic pressure-volume points fall on the same ESPVR as obtained with preload reduction.

¹ A detailed discussion of the definition of the term "contractility" is beyond the scope of this review. To this day, this commonly used word has never been formally defined as far as it pertains to its use in the cardiac physiology literature (73). As deeper understanding of the molecular events underlying calcium-myofilament interactions emerged, including elucidation of how pre- and afterloading conditions influence those molecular events, the notion of a word whose definition would embody the concept of the load-independent measure of intrinsic strength of contraction (i.e., contractility) became more difficult. Therefore, the term is used presently in its vernacular sense as shorthand for "load-independent measure of intrinsic contractile strength" either of the heart or of cardiac muscle.

calcium), E_{es} was shown to increase with relatively little change in V_o (Fig. 2) (81). Conversely, with negative inotropic agents (e.g., acute β -blockade, high-dose calcium channel blockers), E_{es} was shown to decrease, again with relatively little influence on V_o . Appropriate changes in E_{es} are also observed when heart rate is varied (the so called force-fre-

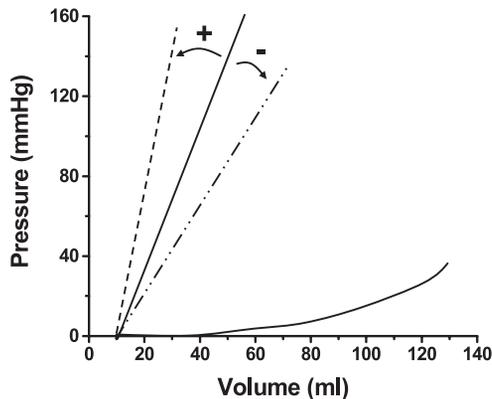


Fig. 2. Under idealized conditions, the ESPVR responds to acute changes in contractile state, increasing its slope, E_{es} , with positive inotropic interventions, with little change in V_o (dashed line), and decreasing its slope with negative inotropic interventions (dash-dotted line). With acute changes in contractility, the EDPVR is in general not influenced significantly.

quency relationship; Ref. 49) and even on a beat-to-beat basis when the interval between successive contractions is varied as on extrasystolic and postextrasystolic contractions (the so-called force-interval relationship; Refs. 14, 93). Because of these basic features (load independence and sensitivity to inotropic agents) that distinguished it from other measures [e.g., ejection fraction (EF) and maximum change of pressure with time (dp/dt_{max})], E_{es} was widely adopted as an index of ventricular contractility (64, 66).

Deviations from Ideal Conditions

The idealized characteristics of the ESPVR were mainly identified under well-defined conditions encountered in isolated canine heart preparations. When applied *in vivo* and over a broader range of conditions, however, several deviations are encountered that mandate more careful handling and interpretation of pressure-volume data.

First, it was shown that the ESPVR is influenced by afterload impedance (9, 16, 35, 69). The magnitude of this effect is relatively small, and this is generally ignored because in most studies (especially studies *in vivo*) afterload conditions do not vary over very wide ranges. The implication of this fact is more of theoretical importance, because it implies that in contrast to prior classic notions, loading conditions influence intrinsic myocardial contractility and metabolic efficiency (2, 6, 37), which is consistent with the notion of load-dependent actin-myosin interactions and load-dependent calcium sensitivity of the troponin regulatory proteins (6, 9, 10, 75).

Of more importance, however, are two interrelated phenomena. First, the ESPVR is in general nonlinear (Fig. 3; Refs. 13, 59, 87). Second, V_o is not totally independent of inotropic state. In large mammals (e.g., dogs, humans), the ESPVR becomes concave to the volume axis at high contractile states and convex to the volume axis at low contractile states. In other species, such as rats and mice, the ESPVR is generally nonlinear even at baseline levels of contractile state (28, 88). There are several important implications of nonlinear ESPVRs, particularly when applied to hearts *in vivo* (Fig. 4). First, when the nonlinear ESPVR is characterized by a single slope value, this is typically obtained by linear regression analysis applied to data obtained over limited pressure and volume ranges. The

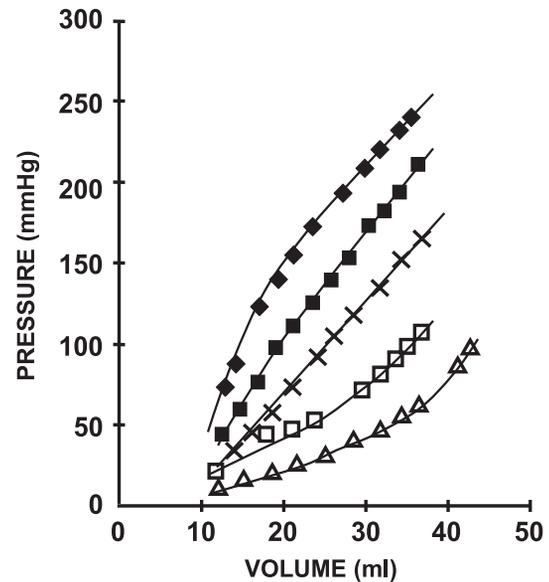


Fig. 3. Although the ESPVR is reasonably linear (e.g., ×), in reality, it is more commonly not linear over the entire range of pressures. These data obtained from an isolated dog heart show that at enhanced levels of contractility (◆, ■) the ESPVRs become concave to the volume axis, whereas at lower levels of contractility (▲, □) the curves become convex to the volume axis.

value of E_{es} obtained in this setting will obviously depend upon the specific pressure range of the available data, which invalidates the concept that this parameter uniquely characterizes the entire ESPVR and uniquely indexes contractile state. Second, the ESPVR V_o must now be estimated by linear extrapolation of the available end-systolic pressure-volume points instead of by direct measurement; in this case, extrapolated V_o (which may even take on negative values) will not equal true

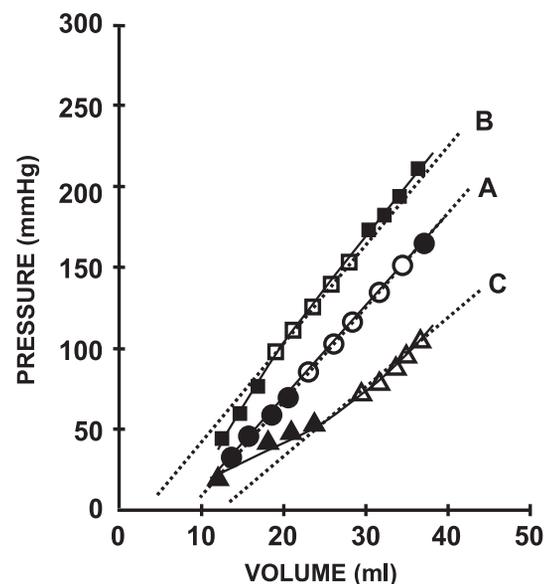


Fig. 4. In typical *in vivo* experiments, data for constructing the ESPVR are obtained over a limited pressure-volume range (open symbols). When characterized by a linear relation applied to the limited data (dotted lines), changes in contractility compared with a baseline state (line A) can manifest as relatively little or no change in slope with changes in the extrapolated volume axis intercept; this can be the case with either increases (line B) or decreases (line C) in contractility.

V_o and the degree of deviation will depend upon the degree of nonlinearity. Finally, because V_o and E_{es} measured from limited data are linear approximations obtained from only a portion of a nonlinear curve, the values of these parameters will covary when inotropic or loading conditions are varied (as detailed further below).

Common Problems and Remedies

The main implication of nonlinear ESPVR and inotropic variations in V_o is that when used to assess changes in ventricular contractility, a comparison of these relations between different states cannot be made simply by comparing values of E_{es} . This important point is illustrated in the hypothetical examples of Fig. 4, in which data are presumed to have been obtained over only a limited pressure range (points shown by the open symbols) and from which ESPVRs are then determined by linear regression analysis (dotted lines). Compared with the baseline condition (*line A*), an increased inotropic state (*line B*) in this scenario is manifest as a relatively unchanged E_{es} value with a decrease in extrapolated V_o (Fig. 4). A complimentary situation may arise with decreased contractile states (e.g., dilated cardiomyopathy) when baseline ESPVR is convex to the volume axis (*line C*, Fig. 4). Therefore, when the experimental question being asked is whether there are changes in chamber contractility between two groups, data concerning both E_{es} and V_o must be presented and accounted for in the interpretation. As observed in the examples of Fig. 4, even subtle nonlinearities may create a significant problem in relying only on E_{es} as the contractile index.

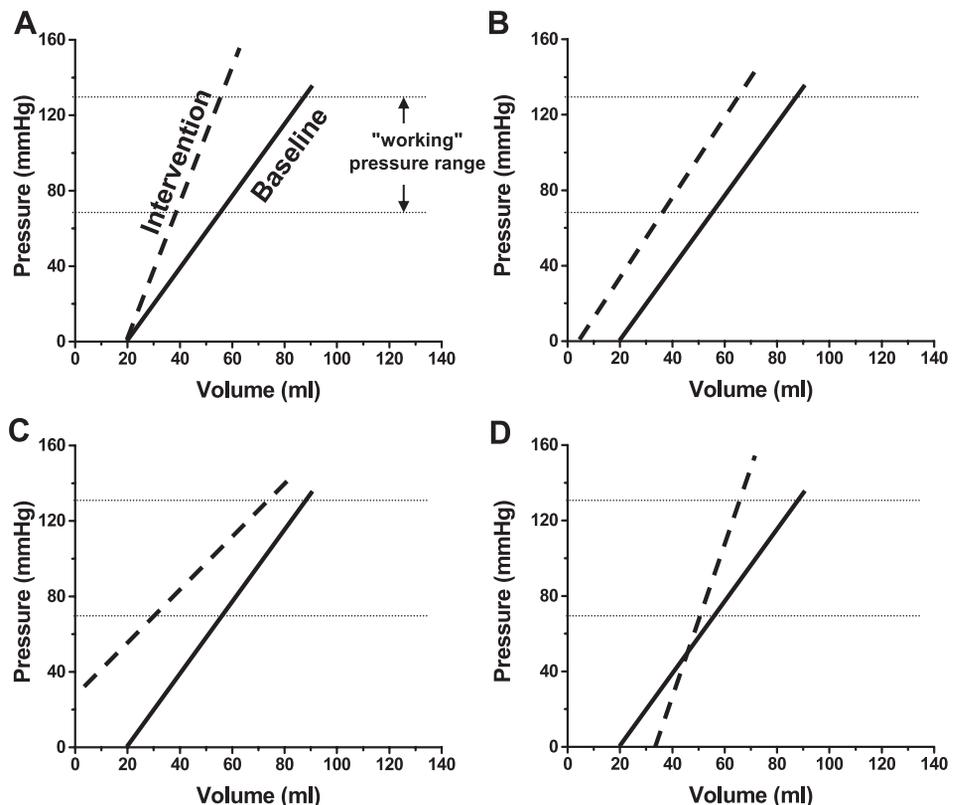
This also has important implications for the statistical approach used to test for a change of the ESPVR. Investigators have typically used a *t*-test to compare mean values of E_{es}

between groups or between treatments. Sometimes, when reported, a *t*-test is similarly applied to compare values of V_o . However, this approach fails to account for the intrinsic statistical covariance and interdependence between E_{es} and V_o .

The remedy to these problems is to use a more general statistical approach that addresses the question of whether the ESPVRs of two groups are different. Analysis of covariance or, more generally, a multiple linear regression analysis with dummy variables is the test of choice (70, 71). This approach simultaneously accounts for changes in slope and intercept (more specifically "elevation") of the data sets. Appropriate use of dummy variables allows detection of variations in the curves both between hearts and between experimental groups. If this test indicates a difference between groups, then the average slope and intercept values can be used to demonstrate which way the curves shift by superimposing the average relations on a common set of axes. In general, there are four possible outcomes that may indicate an increase in contractility as illustrated in Fig. 5 for a positive inotropic intervention. E_{es} may increase with little change in V_o (Fig. 5A), there may be no change in E_{es} with a decrease in V_o (Fig. 5B), E_{es} can decrease and V_o can decrease (Fig. 5C), or E_{es} and V_o can both increase (Fig. 5D). Each case indicates an increase in contractility (increased end-systolic pressure generation at a common volume) within the specified working range of pressures and volumes. The same arguments apply in reverse for situations in which contractility may be decreased.

The discussions above assume that pressure and volume measurements are accurate. Pressure measurements with high-fidelity micromanometers are widely available and have been shown to be accurate. The most widely used techniques for measuring volume are the conductance catheter (5), multicrys-

Fig. 5. Compared with an ESPVR measured under baseline conditions (solid lines) within a certain range of pressures (denoted by horizontal lines), an intervention that increases contractility within the measured range (dashed lines) may be manifest as an increase in E_{es} with no change in V_o (A), a decrease in V_o with little change in E_{es} (B), a decrease in both E_{es} and V_o (C), or an increase in both E_{es} and V_o (D).



tal sonomicrometry (30, 47, 72), echocardiography (2- or 3-dimensional; Refs. 20, 40), MRI (19), and radionuclide techniques (68); in general, with any of these techniques, a linear transformation is required to relate the raw measurement provided by the technique (V_{raw}) to the estimate of actual real volume (V_{real}): $V_{\text{real}} = aV_{\text{raw}} + b$. Although no technique is perfect, the tomographic techniques of MRI and three-dimensional echocardiography are generally considered as gold standards for measuring end-diastolic and end-systolic volumes under steady-state conditions. Real-time volume assessment, especially throughout a contraction and during transient load changes, is generally made with conductance or sonomicrometric techniques. For such techniques it is recognized that the relation between true and estimated volume may vary with changes in experimental conditions, even during the course of an acute intervention. Occasionally, data can be obtained that could potentially lead to nonsensical conclusions. For example, for the hypothetical situation depicted in Fig. 5D, one might be tempted to conclude that the intervention caused an increase in contractility in the high volume range and a reduction in the contractility in the low volume range, which, to our knowledge, is an unlikely scenario. Factors contributing to such a situation could include extrapolation of data measured over a limited pressure-volume range and a change in experimental conditions between the two measurements that alters the relation between V_{real} and V_{raw} . Unfortunately, if special efforts are not taken to assess a and b of the equation above under each condition, there is no definitive way to confirm that this is the source of the problem.

In addition to issues related to data analysis already reviewed, other experimental aspects should also be considered. Changes in autonomic tone encountered during load changes used to acquire pressure-volume data over a broad range of loads can also complicate the analysis of the ESPVR. For example, if a transient vena caval occlusion is used, accompanying drops in arterial pressure can lead to reflex-mediated increases in sympathetic tone that can have direct effects on myocardial contractility as well as secondary effects due to changes in heart rate. Changes in heart rate influence myocardial contractility by mechanisms that change calcium delivery to the myofilaments (32, 89, 92, 94). In the intact heart, this effect is most pronounced in the normal resting range, between ~ 60 and 100 beats/min (49). These effects can appear quickly (e.g., within 15–20 s), within the time it takes to complete a vena caval occlusion. If a pharmacological agent is used to modify afterload (e.g., phenylephrine), changes in sympathetic tone and heart rate can similarly be observed. Because the durations of drug infusions for this purpose are generally long, such changes may more likely occur with this approach. To minimize the impact of these phenomena, load changes should be performed as rapidly as possible. Data should be analyzed for changes in heart rate, and when significant changes are observed between the start and completion of the intervention, data should be excluded.

It is also common that arrhythmias (extra- and postextrasystoles or short bursts of supraventricular or ventricular tachycardias) can be induced during a vena caval occlusion. Although clinically benign in general, the underlying changes in the interval between beats profoundly modifies myocardial contractility on a beat-to-beat basis because of changes in calcium delivery to the myofilaments (89). The effect of even

a single premature beat on myocardial contractility can last for several beats (61, 90). Therefore, the presence of such arrhythmias should be detected during pressure-volume analysis and data should be excluded.

Finally, changes in coronary perfusion pressure are encountered during load changes, especially those achieved by a vena caval occlusion (83). When mean central aortic pressure (equivalent to coronary perfusion pressure) falls below a critical point (~ 60 mmHg) myocardial contractility may decline, and this effect can be observed within a few beats of the drop in pressure. This can generally be identified as a rather abrupt increase in the slope of the ESPVR near the termination of a prolonged caval occlusion (83). The remedy is to limit the duration of the load change to short time periods and, when this is not possible, to exclude data obtained below the abrupt change in ESPVR slope.

Other approaches to quantifying systolic ventricular properties derived from measurements of pressures and volumes include preload-recruitable stroke work (PRSW), the relationship between stroke work and end-diastolic volume (30), and the relationship between dP/dt_{max} and end-diastolic volume (46). Each of these is a reasonably linear, afterload-independent relationship characterized by a slope and an axis intercept value. As with the ESPVR, nonlinearities and afterload dependence can be observed (17), and assessment of changes in contractility by these approaches involves assessment of relative shifts of the relationships. In general, therefore, the same principles discussed above should be followed. PRSW has the advantage that the slope of the relationship has units of millimeters of mercury and is therefore independent of heart size, making it relatively easy to compare relationships between hearts of different sizes and species. The EDV- dP/dt_{max} relationship has the potential advantage that its slope is $\sim 50\%$ more sensitive to changes in contractile state than E_{es} (46). With each of these approaches, the analysis is limited to an assessment of systolic properties; there is no assessment of diastolic properties. A full discussion of the pros and cons of these approaches relative to the straight pressure-volume approach is beyond the scope of this review.

Myocardial Systolic Properties

Ventricular chamber properties depend on myocardial properties, muscle mass, and geometry. When mass and geometry are fixed, a shift of the ESPVR unambiguously signifies change in intrinsic myocardial contractility. Such observations would be typical, for example, of those observed during acute experiments in which inotropic agents (positive or negative) are administered (15, 81, 83). In the setting of chronic disease, however, geometry and muscle mass change. Important examples of this include the development of the eccentric hypertrophy in dilated cardiomyopathies and development of the concentric hypertrophy in idiopathic hypertrophic cardiomyopathy. In these cases, determination of the relative degree to which changes in the ESPVR reflect changes in chamber properties and changes in muscle properties is complex, with no single accepted standardized approach. One early proposal for indexing myocardial properties was simply to normalize E_{es} for muscle mass (79): $E_{\text{es},n} = E_{\text{es}} \cdot \text{LVM}$, where LVM is left ventricular mass in grams. With this approach, $E_{\text{es},n}$ in normal hearts of most species is relatively constant, assuming a value

between 400 and 700 mmHg·g·ml⁻¹ (or 4–7 mmHg·100 g·ml⁻¹). However, the limitations of this approach were recognized early, particularly when relative wall thickness (defined as the ratio between wall thickness and chamber radius) deviates from normal as in the examples provided above (65). Instead, investigators have resorted to derivation of parameters derived from estimated end-systolic myocardial stress-strain relations. This approach is similar for systole and diastole, has been applied more extensively to diastole and therefore is discussed below. It is noteworthy that in recent years this approach has been used successfully and the slope of the end-systolic myocardial stress-strain relationship has been shown to be load independent (84) and sensitive to changes in myocardial contractility when geometry is also changing (85).

DIASTOLIC PROPERTIES

Basic Concepts

The EDPVR is intrinsically nonlinear (Fig. 6), a characteristic attributed to the different types of structural fibers being stretched in different pressure-volume ranges (22). In the low pressure-volume range, where there is only a small increase in pressure for a given increment in volume, compliant elastin fibers and myocytes with sarcomeric titin molecules (42) being stretched are believed to account for stiffness. As volume is increased further to a higher range, pressure rises more steeply as slack lengths of collagen fibers and titin are exceeded and stretch is more strongly resisted by these stiff elements. Therefore, chamber stiffness (the change of pressure for a given change of volume, dP/dV) increases as end-diastolic pressure (or volume) is increased (Fig. 7A).

At subphysiological volume ranges, increasingly negative pressures are required to reduce volume (Fig. 6; Ref. 41). Data are not typically measured in this region in hearts studied in vivo and will not be discussed further, except to state that negative pressures have been observed in some patients with mitral stenosis (63).

In the past, a variety of curve fits have been applied to EDPVR data in an attempt to develop simple indexes of left ventricular chamber and myocardial stiffness. Table 1 displays

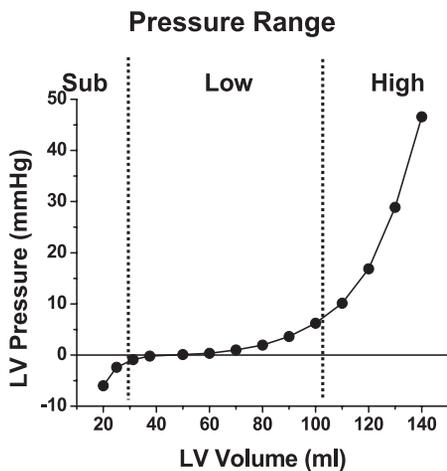


Fig. 6. The EDPVR is nonlinear, having a shallow slope at low left ventricular (LV) volume range and a steeper slope at higher LV volume range. At subphysiological (sub) volumes the EDPVR turns toward negative LV pressures.

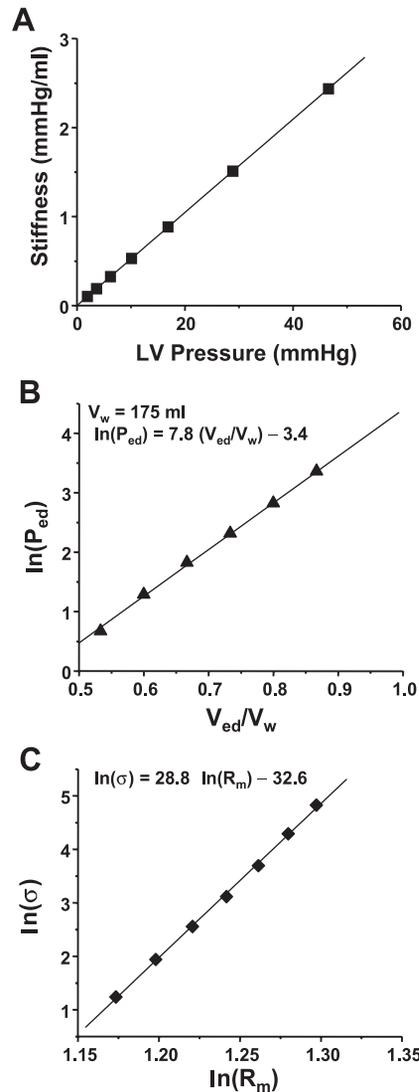


Fig. 7. A: as shown for the example in Fig. 6 in the low and high volume ranges (i.e., excluding the subphysiological range), absolute value of diastolic stiffness (change in end-diastolic pressure with change in end-diastolic volume, dP_{ed}/dV_{ed}) varies linearly with pressure. B: with logarithmic transformation of pressure and normalization of volume to myocardial wall volume (V_w) the EDPVR is linearized with a slope defined as the chamber stiffness index (β_w = 7.8). C: the relationship between natural logarithm of stress (σ) vs. natural logarithm of midwall radius (R_m) is also linear, with a slope μ = 28.8 that yields a myocardial stiffness index k = 14.4 (k = μ/2).

Table 1. Curve fits for EDPVR

Equation	Type of Fit	EDPVR Curve Fit	Chamber Stiffness (dP/dV)
1	Exponential	$P = A + Be^{\alpha V}$	$\alpha(P - A)$
2	Exponential	$P = Ce^{\beta V}$	βP
3	Cubic	$P = D + aV^3$	$3aV^2$
4	Cubic	$P = a_0 + a_1V + a_2V^2 + a_3V^3$	$a_1 + 2a_2V + 3a_3V^2$
5	Power	$P = b + cV^\gamma$	$\gamma(P - b)/V$
6	Power	$P = dV^\delta$	$\delta P/V$

EDPVR, end-systolic pressure (P)-volume (V) relationship; dP/dV, change of pressure with volume.

several such fits, each of which requires the use of nonlinear regression analysis. Although the EDPVR can be represented well by each of these (excluding the subphysiological pressure range), approaches to development of indexes of chamber and myocardial stiffness have met with limited success.

Inclusion of a constant term in curve-fit *Eqs. 1, 3, 4, and 5* (Table 1) signifies that, when measured *in vivo*, the curves may not asymptote to 0-mmHg pressure at low volumes, as is generally the case when measured *ex vivo* (as in Fig. 6). Factors such as pericardial restraints, interventricular interaction, and changes in intrathoracic pressure may cause the curves to be shifted upward or downward relative to their *ex vivo* position.

Shifts of the EDPVR may be reflective of changes in myocardial material properties (e.g., fibrosis, ischemia, edema), physiological remodeling (e.g., as with normal growth), or pathological remodeling (e.g., as observed during development of hypertrophy and chamber enlargement in heart failure). In all cases, however, the EDPVR reflects the net effect of all facets of myocardial material properties, chamber structural properties, and extracellular matrix.

Chamber stiffness constant. Chamber stiffness is the change in ventricular pressure relative to a change in volume of the ventricular chamber (dP/dV), i.e., the slope of the EDPVR. Because the EDPVR is nonlinear, chamber stiffness varies with filling pressure as shown in Table 1. For example, in the case of fit *Eq. 2* (Table 1), chamber stiffness increases linearly with pressure (Fig. 7A). The slope of this relationship, β , is termed a chamber stiffness constant and has been used by many investigators as a means for indexing diastolic chamber properties (53). In this case β has units of milliliters⁻¹ and is therefore dependent on chamber size. However, if β is multiplied by left ventricular wall volume (V_w) a dimensionless chamber stiffness index $\beta_w = \beta \cdot V_w$ is obtained, thus providing a means for comparing chamber stiffness of hearts having different sizes (e.g., different species or different states of disease). The rationale for the use of V_w as a normalization factor stems from the fact that chamber stiffness, dP/dV , has been shown to be related to myocardial stiffness and the V/V_w ratio (57). An example of the use of this approach is illustrated in Fig. 7B. In practice, V_w can be obtained by direct measurement [e.g., with magnetic resonance imaging (1) or tomographic 3-dimensional echocardiography (31)] or can be estimated from *in vivo* measurements of wall thickness and chamber diameter assuming a specific geometry. For example, one common approach is to assume a prolate ellipsoid model. Wall volume V_w is the difference between epicardial and endocardial volumes (V_{epi} and V_{endo} , respectively), so that:

$$\begin{aligned} V_w &= V_{\text{epi}} - V_{\text{endo}} \\ V_{\text{epi}} &= \pi(D_{\text{epi}}^2/6)L_{\text{epi}} \\ V_{\text{endo}} &= \pi(D_{\text{endo}}^2/6)L_{\text{endo}} \end{aligned} \quad (7)$$

where D_{epi} and D_{endo} are the epicardial and endocardial short-axis dimensions, respectively, and L_{epi} and L_{endo} are the long-axis dimensions, respectively. Various improvements on this simple approach are also available (20). Assuming again that curve-fit *Eq. 2* (Table 1) is the governing relationship for the EDPVR (namely, $P = Ce^{\beta V} = Ce^{\beta_w V/V_w}$), the constant C and dimensionless parameter β_w are determined by performing a

linear regression on the $\ln(P)$ vs. V/V_w relationship with the result:

$$\ln(P) = \ln(C) + \beta_w (V/V_w) \quad (8)$$

An example of this approach is illustrated in Fig. 7B. With concentric hypertrophy, where V_w increases out of proportion to chamber volume (and other factors remain constant), β_w would be increased, signifying an increase in chamber stiffness index. Conversely, with eccentric hypertrophy (as in dilated cardiomyopathy), β_w would be decreased. On the other hand, hearts whose volumes and wall masses are physiologically appropriate (e.g., normal mouse, rat, dog, and human) would have similar β_w values despite the marked differences in absolute heart sizes.

Caution should be exercised when interpreting the various chamber stiffness-pressure relationships cited in Table 1. First, in contrast to curve-fit *Eqs. 1 and 2*, where chamber stiffness is linearly related to filling pressure, *Eqs. 3–6* imply a nonlinear relationship. In particular, *Eqs. 3, 5, and 6* yield the results that $V \cdot dP/dV$ (defined as volume elasticity) are linear functions of the pressure P and should not be identified with chamber stiffness *per se*. Also, because a number of different equations have been used in the literature to represent the EDPVR (as noted in Table 1), it is sometimes difficult to compare results from different studies.

Myocardial diastolic stiffness. As was the case for E_{es} , the chamber stiffness index β_w is dependent upon myocardial material properties and ventricular chamber characteristics. However, indexes of intrinsic myocardial stiffness can also be estimated from the EDPVR. Analogous to the EDPVR, passive myocardial properties are characterized by the relation between stress (σ , force per unit cross-sectional area) and strain (ϵ , segment length relative to a specified standardized length). Unfortunately, one is faced with the challenging problem of assessing myocardial stiffness in the setting of the intact heart because the heart is subjected to a three-dimensional state of stress that, in the purest sense, requires calculation of LV wall stress and strain components in the radial, meridional, and circumferential directions. Few if any of these parameters are directly measurable in the intact heart. Relying on high-fidelity measurements of left ventricular end-diastolic pressure and dimension-based estimates of ventricular volumes, one must resort to the use of theoretical models for quantitation of stresses and strains.

RATIONALE FOR CHOICE OF SPHERICAL MODEL FOR LEFT VENTRICLE. Several geometric models of the left ventricle are used to estimate cavity volume and wall volume (V_w) as noted above (20, 21), the most common being ellipsoidal (*Eq. 7*) and spherical. With regard to stress calculations, many formulas have also been proposed. Huisman et al. (34), in their studies on patients with varied disease states, evaluated end-diastolic and end-systolic wall stresses based on nine different theoretical models, and significant disparities between models were noted. However, relative differences remained rather constant irrespective of the diseased state. In four of the thick-walled models examined [including that developed by Mirsky (52)], the circumferential and meridional stress distributions through the wall thickness differed markedly in both a qualitative and a quantitative manner. Yin (91), in his review article on ventricular wall stress, concluded that without experimental

verification the most accurate distribution remains undecided and that average or midwall stress is adequate for most clinical applications. Moreover, the theoretical studies by Janz et al. (36) and Mirsky (55) demonstrated that myocardial stiffness-stress relationships are not markedly altered by the assumed geometry (i.e., spherical vs. ellipsoidal).

EVALUATION OF SPHERICAL DIMENSIONS AND MIDWALL STRAIN. On the basis of all these studies, it is proposed at present to use the classic solutions for wall stresses in a sphere, which greatly simplifies the analysis (44, 57). To perform the analysis, one first obtains measures or estimates of the cavity volume V and wall volume V_w . Assuming a spherical geometry for the left ventricle, chamber inner radius (R_i), outer radius (R_o), and midwall radius (R_m) are obtained from relationships (Eq. 9)

$$\begin{aligned} R_i &= [(3/4\pi)V]^{1/3} \\ R_o &= [(3/4\pi)(V + V_w)]^{1/3} \\ R_m &= (R_i + R_o)/2 \end{aligned} \quad (9)$$

Note that this system of equations provides a means for interrelating chamber dimensions and volumes when the prolate ellipsoid long and short axes are unavailable (i.e., Eq. 7).

Estimates of midwall strains can be obtained from R_m because midwall length (L) is directly proportional. The two most commonly used definitions of strain in physiology and cardiology are Lagrangian and natural strain. Lagrangian strain (ϵ_L) is defined as $\epsilon_L = (L - L_o)/L_o$, whereas natural strain (ϵ_N) is defined as $\epsilon_N = \ln(L/L_o)$, where L is the stretched length and L_o is the length at zero stress (which would be determined at a transmural ventricular pressure of 0 mmHg, is designated as V_o , and generally differs from V_o of the ESPVR). Lagrangian strain is more often used in studies of metallic-like materials, where deformations are small. On the other hand, natural strain is more appropriate when large deformations are incurred, as is observed in heart muscle and other living tissues. Use of natural strain has additional advantages, as detailed immediately below, in that evaluations of myocardial stiffness constants become independent of L_o (and therefore of V_o), which is important because the measurement of V_o is not practical from measurements of the EDPVR in all settings.

Under the assumption of a thick-walled sphere, midwall stress difference can be estimated from measured pressure, cavity volume, wall volume, and R_m according to the following (57):

$$\sigma = (3/2)P*(V/V_w)*(R_o/R_m)^3 \quad (10)$$

On an empirical basis, the stress-strain relation has also been shown to be well represented by a power curve fit such as:

$$\sigma = gR_m^\mu \quad (11)$$

where g and μ are regression coefficients. This curve fit can be linearized by logarithmic transformation as follows:

$$\ln(\sigma) = \ln(g) + \mu \ln(R_m) \quad (12)$$

Thus, for each value of pressure and volume obtained during the measurement of the EDPVR, a value for σ and R_m can be obtained with Eqs. 9 and 10. After logarithmic transformation, a regression analysis is then performed on these data to arrive at values for g and μ according to Eq. 12.

EVALUATION OF DIASTOLIC MYOCARDIAL STIFFNESS. Finally, it remains to determine the myocardial stiffness, also called incremental modulus of elasticity E_{inc} , from the expression (57):

$$E_{inc} = (3/2)\Delta\sigma/\Delta\epsilon = (3/2)\Delta\sigma/3\Delta\epsilon_\theta = (1/2)\Delta\sigma/\Delta\epsilon_\theta \quad (13)$$

where ϵ_θ is the circumferential strain and the factor 3 in the denominator stems from the incompressibility conditions of heart muscle (58). Thus, from Eq. 11, it follows that

$$E_{inc} = \mu g R_m^{\mu-1} / 2 = (\mu/2)\sigma = k\sigma \quad (14)$$

This relationship is similar to that obtained by Laird (43), using a different model.

The factor k therefore represents a simple dimensionless index of myocardial stiffness in this linear E_{inc} vs. σ relationship, thus enabling stiffness to be compared between different hearts at common stress (σ) levels where $k = \mu/2$. An example of a myocardial stiffness index calculation is illustrated in Fig. 7C. Here it is determined that $\mu = 28.8$, so that $k = 14.4$. Furthermore, Pinto and Fung (62) and Mirsky and Parmley (56), in studies with papillary muscle, have demonstrated a linear relationship between elastic stiffness and stress. In the clinical setting it is observed that the k values are higher in patients with aortic stenosis than in aortic regurgitation (54).

This is but one approach that may be used. The references cited above provide more complex approaches. Whichever approach is adopted, the important message is that measurement of EDPVR and parameters derived from that relationship can provide a characterization of passive ventricular properties with respect to 1) chamber size (remodeling), 2) chamber stiffness, and 3) myocardial stiffness.

Deviations from Ideal Conditions

As noted above, when measured in vivo, factors extrinsic to the left ventricular myocardium may influence the EDPVR. Changes in intrathoracic pressure (as with spontaneous or assisted ventilation), pericardial constraints, and interventricular interactions may each influence ventricular diastolic pressure (when referenced to atmospheric pressure), which therefore influences the EDPVR. These factors, which may be difficult to measure (particularly in the clinical setting), should be considered, especially at high filling pressures, but may require special measurements (86). These factors in general will result in nonzero values for the constant terms if curve-fit Eqs. 1 and 4 (Table 1) are used and, if not accounted for, could influence the values for the other parameters.

Common Problems and Remedies

Although there is an extensive literature concerning how the EDPVR can be quantified and parameterized, there has been limited treatment in the literature of the proper statistical approach that should be used to compare these nonlinear curves between groups or between conditions (29). In assessing differences between groups, it is widely accepted practice to compare the mean values of the various parameters associated with the EDPVR, chamber stiffness, or myocardial stiffness. For example, if curve-fit Eq. 2 (Table 1) is used, the mean values of the chamber stiffness constant (β) or the chamber stiffness index (β_w) will be computed for the two groups and these mean values will then be compared with a t -test. This

approach however, has important limitations. First, for the nonlinear expressions used to describe the EDPVR, there is strong interdependence (i.e., covariance) among parameter values. Second, parameter values derived from the nonlinear regression analysis of different groups may differ if the data span different end-diastolic pressure ranges (as commonly occurs when comparing a normal state to a heart failure state), even if there is no significant difference in the regions where the data overlap.

Both these points are illustrated in the example of Fig. 8A, where the circles represent pressure-volume data obtained from a normal canine heart in vivo. The squares in Fig. 8A represent data obtained ~4 wk later after induction of heart failure; data obtained from the early heart failure state span a higher end-diastolic pressure-volume range. The solid lines show best-fit nonlinear regression according to curve-fit Eq. 2. These data yield the curve fits $P = 0.44e^{0.04V}$ for the normal condition and $P = 0.75e^{0.03V}$ for the heart failure state. Thus, even though the curves are virtually superimposable in the region of data overlap and appear to be extensions of each other, β of curve-fit Eq. 2 is significantly decreased and constant term C is significantly increased. As noted, these differences appear to be mainly a consequence of nonoverlapping data and covariance between parameter values. When this is repeated in additional

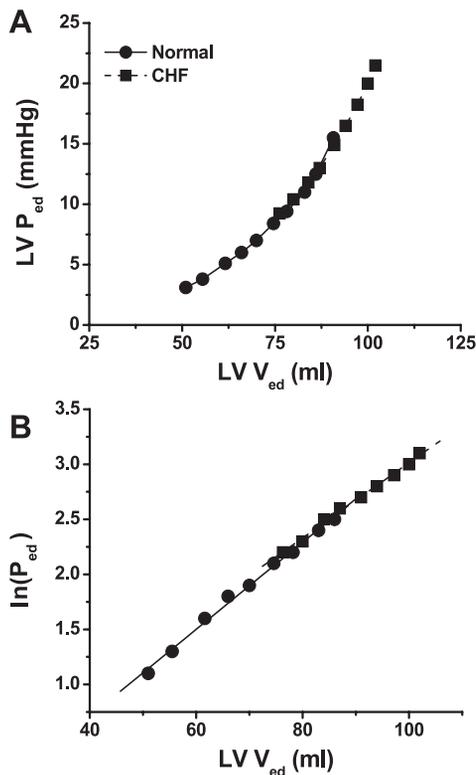


Fig. 8. A: EDPVR measured in a normal dog heart by vena-caval occlusion and then again after induction of mild heart failure with a rise in end-diastolic pressure (CHF). Although the data appear to delineate an identical curve in the overlapping pressure-volume ranges, actual curve fits provide very different parameter values because of the differences in the pressure ranges: $P = 0.44e^{0.04V}$ for the normal condition and $P = 0.75e^{0.03V}$ for the failure state. B: the curves can be linearized by logarithmic transformation of pressure and volume values, thus permitting application of a statistical method such as multiple linear regression analysis (or analysis of covariance) to be used to meaningfully to compare the curves for assessment of whether chamber stiffness has changed between conditions.

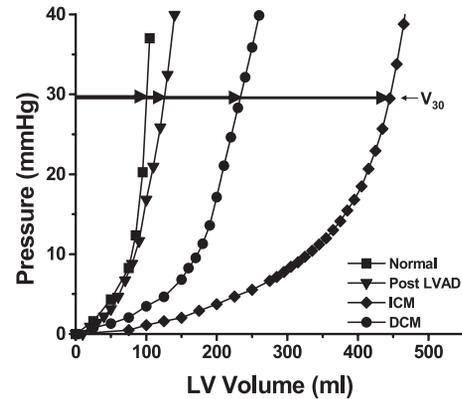


Fig. 9. Ventricular capacitance, the volume at a specified pressure, is a useful index for comparing the size of the heart. These examples obtained from explanted human hearts show how V_{30} , the volume at a pressure of 30 mmHg as indicated by arrows, can be used simply to index the amount of chamber dilation in the cardiomyopathic state and the return toward normal (reverse remodeling) following support with a left ventricular assist device (LVAD). ICM, idiopathic cardiomyopathy; DCM, dilated cardiomyopathy.

animals having a consistent bias in pressure ranges between groups, the parameter values may also have a consistent bias, which could result in a t -test on parameter values indicating inappropriately that a significant difference in EDPVRs exists between groups.

Unfortunately, there is no single agreed-upon statistical approach used to compare sets of nonlinear relationships obtained from different groups. One approach is to linearize the relationships and then use a standard approach for comparing linear relationships. For example, in the relationship $\ln(P) = \ln(C) + \beta_w(V/V_w)$, $\beta_w = 7.8$ (Fig. 7B) and represents the dimensionless chamber stiffness index. With a linear representation of the EDPVR, multiple linear regression analysis with dummy variables (or analysis of covariance) can be applied to compare relations, slopes, and elevations between groups in a manner similar to that recommended for statistical comparisons of the ESPVR (70, 71). Student's t -tests applied to one or another parameter may provide accurate results, but this is not ensured and would depend on the nature of the specific data sets.

A simpler approach can be used if the question is simply whether the left ventricular chamber has structurally changed in size. This is to quantify chamber capacitance, which is defined as the volume at a specified pressure. For example, this approach has been used to quantify changes in ventricular size of end-state cardiomyopathic hearts in response to prolonged unloading by ventricular assist devices (33, 45, 48). Passive diastolic pressure-volume curves obtained from an ischemic cardiomyopathic heart, an idiopathic dilated cardiomyopathic heart, and a cardiomyopathic heart supported with a left ventricular assist device (LVAD), each explanted at the time of orthotopic heart transplantation, along with a normal heart not suitable for transplantation, are shown in Fig. 9; the arrows show the respective volumes at a pressure of 30 mmHg (V_{30}). Relative to normal, the curves from the cardiomyopathic hearts are far right-shifted toward larger volumes, indicating chamber dilation or remodeling. The LVAD-supported heart has near-normal volume at 30 mmHg, indicative of reverse remodeling (45). Thus, independent of the parameter values of any curve

that may fit the data, it is evident that the value of V_{30} provides an extremely useful index of the size of the heart.

NEED FOR STANDARDIZED APPROACH TO PRESSURE-VOLUME ANALYSIS

With greater emphasis on molecular and cellular research, fewer researchers are devoting the time necessary to understand the nuances of how to measure, analyze, and interpret pressure-volume relationships. However, as the scope of cardiac papers has increased and focus has shifted toward discovery of new biochemical, molecular, and/or cellular principles, functional assays such as pressure-volume analysis take on a secondary role. Yet such data often constitute the critical information in proving the consequences and clinical or physiological relevance of primary biochemical, molecular, or cellular discoveries and may be, in the end, the basis for acceptance of a new concept. Needless to say, if the physiological portion of a study is flawed, the conclusions of an entire study may be in jeopardy, no matter how elegant and perfect the other aspects may be. Thus there is need for standardization of methodologies for analyzing and interpreting these relationships when measured, and a greater responsibility falls on peer reviewers for ensuring accuracy and appropriateness of analyses.

SUMMARY AND SUGGESTIONS

The use of pressure-volume analysis has been established as a powerful means of characterizing ventricular pump properties at end systole, end diastole, and throughout the entire cardiac cycle independent of loading conditions (65, 76). Nevertheless, this approach is not generally used in clinical practice because until recently, 1) highly specialized and invasive techniques have been required for its measurement, 2) techniques for measuring volume have been difficult and imprecise, and 3) a vast majority of clinical decision making can be made on the basis of other parameters such as EF and, less commonly, dP/dt_{max} . However, the utility of these alternate approaches in basic and clinical research is limited in explaining fundamental aspects of ventricular contraction. Furthermore, the pressure-volume approach also allows for detailed, quantitative understanding of ventricular-vascular coupling and the determinants of blood pressure, venous pressure, and cardiac output in health, in disease, and in response to complex therapeutic interventions in heart failure not possible with other approaches (3, 8, 12, 23, 82). With regard to diastole, the EDPVR and parameters derived from this relation (e.g., stiffness and capacitance) are the only means of directly characterizing passive ventricular properties. Other measures of diastolic properties commonly used in the clinical setting that generally involve assessments of mitral filling patterns provide indirect measures of stiffness, and their utility for this purpose is uncertain (4, 50). In addition to its established role in basic research, the pressure-volume approach could eventually assume a greater role in clinical research and clinical practice as techniques evolve for its measurement with noninvasive techniques (18). Accordingly, it is important that investigators are aware of how these relationships are appropriately measured and analyzed.

Even though the ESPVR is in general nonlinear, it is acceptable to parameterize this relationship with linear regression

analysis applied to limited ranges of data typically measurable in vivo. The EDPVR is nonlinear, even within relatively limited pressure and volume ranges. For the present, it is suggested that the following guidelines for analysis and interpretation of EDPVRs and ESPVRs be considered.

1) When using the ESPVR to compare contractility between conditions or between experimental groups, slope and volume axis intercept values should both be reported. Student's *t*-test is not the most appropriate statistical test for comparing slopes and/or intercept values of these relationships. Rather, use of multiple linear regression analysis (or analysis of covariance) is more appropriate to determine whether ESPVRs have shifted.

2) If the results of *step 1* indicate that the ESPVR has shifted, the average values of slopes and intercepts can be used to describe which way the curves have shifted. Final conclusions about changes in chamber contractility depend upon which way the curves shift within the range where pressure and volume data are measured, or with as little extrapolation outside of the measured data range as possible (Figs. 5 and 6).

3) Because approaches for normalizing E_{es} for chamber size and geometry are currently inadequate, myocardial contractility is most appropriately assessed by using the concept of the end-systolic myocardial stress-strain relation, which yields a measure of myocardial end-systolic stiffness.

4) The nonlinear EDPVR is a comprehensive means of characterizing passive ventricular diastolic properties. When using this relationship to compare chamber or myocardial diastolic properties of hearts in different experimental groups, it is not most appropriate to use *t*-tests to compare average parameter values associated with the various curve fits. Similar to the ESPVR, it is more appropriate to use a statistical test that accounts for covariance in parameter values and tests whether the curves are truly different. One approach is to linearize the curve-fit expressions (e.g., logarithmic transformation of pressure and/or volume data) and then apply multiple linear regression analysis with dummy variables (analysis of covariance).

5) Chamber stiffness index (β_w) and myocardial stiffness index (k) provide load- and chamber size-independent parameters of passive chamber and myocardial properties, respectively. Statistical comparisons of these parameters are also optimally accomplished with multiple linear regression analysis of the respective relationships (Eqs. 8, 12, and 14) from which they are derived.

6) When the experimental question relates to heart size, consider using a measure of ventricular capacitance, which is the volume at a specified filling pressure. This parameter is usually simple to measure, and the *t*-test is the appropriate approach for statistical comparisons between experimental groups.

The fact that these guidelines may not have been followed in prior studies does not mean that the conclusions are incorrect. However, depending upon the nature of the deviation, it does mean that the reader may have no means of independently evaluating the validity of conclusions presented.

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