From ‘Emax’ to pressure-volume relations: a broader view

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THE REQUIREMENT for making accurate and detailed assessments of organ function has always depended on the scope and capabilities of available therapies. Over the past decade, we have witnessed an explosion in the pharmacologic and interventional treatment options for coronary artery, myocardial, and valvular heart disease, and with that has come a growing need for more precise measurements of cardiac performance. A complete evaluation of ventricular performance ideally includes relatively load insensitive measures of both systolic and diastolic pump properties, assessments of inotropic state and contractile reserve, and an evaluation of the cardiac response to altered vascular loading conditions. However, routine clinical hemodynamic evaluation falls short of this mark, being generally limited to the determination of steady-state end-diastolic and peak systolic pressures, ejection fraction, and occasionally maximum dP/dt.

In his recent review, Arnold Katz described the utility of pressure-volume loops and relationships to assess “the effects of different forms of heart disease and to predict responses to the many therapeutic options now available for the treatment of the patient with cardiac disease.” This approach was originally studied as a means of integrating and modeling the heart and vascular systems. Two principal observations were made: (1) that the left upper corners of pressure-volume loops (“the end-systolic pressure-volume points”) obtained at various loads at a constant inotropic state appeared to reach the same straight line, and (2) that this linear relation between pressure-volume points was in effect at all times in the cardiac cycle, giving rise to the concept that cardiac contraction could be modeled as a “time-varying volume elastance.”

The end of systole was defined as the time at which this elastance reached a maximal value, termed Emax. For a given set of systolic and diastolic properties, cardiac contraction was bounded by the end-diastolic and end-systolic pressure-volume relations (EDPVR and ESPVR).

The pressure-volume framework has provided physiologists with a single approach with which ventricular properties, myocardial energetics, and pump performance predictions through ventriculovascular coupling (recently reviewed by Sunagawa et al.) can all be studied. It has proven to be a fertile area of research, and has significantly helped broaden our understanding of cardiac mechanics and hemodynamics. The clinical application of this approach, however, has tended to be more narrowly focused primarily on the use of Emax as an “index of contractile state.” This particular application has encountered some difficulties; studies of the ESPVR have revealed afterload dependencies, measurement variability, nonlinearity of ESPVRs, and dependence of ESPVR on chamber size and possibly cavity shape.

However, these potential complicating features of the ESPVR primarily frustrate attempts at deriving a single number, Emax. By adopting a broader view that uses all of the information conveyed by pressure-volume relations, the approach provides a powerful tool for understanding and quantifying the function of the heart and its interactions with the vascular system. Furthermore, with the development of new techniques such as the multielectrode conductance catheter providing on-line continuous left ventricular volumes, and methods of rapid, reversible load alteration such as inferior vena caval occlusion, clinical applications may finally be practical.

Amid concerns regarding Emax, there has been a growing interest in the use of pressure-volume relations. Thus we believed it timely to review the current status of these relations and their potential uses. We first present a clinical example: that of assessing the influence of coronary occlusion and reperfusion on global chamber performance. Next several current concerns regarding Emax and the assessment of chamber contractile state are discussed and put in perspective. Finally, pressure-volume relations are applied to...
the evaluation of pump performance of patients with congestive heart failure, and the utility of the approach for predicting the response to alterations in volume status, vasodilation, and inotropic state, is shown.

A clinical example. Determining the influence of a coronary occlusion on global left ventricular function is important to many clinical studies of coronary heart disease. The ultimate efficacy of reperfusion techniques, whether thrombolytic agents or angioplasty, often relies on a demonstration of improved pump performance. Yet characterization of global systolic and diastolic dysfunction with coronary occlusion and reperfusion in man has been limited.

Figure 1 displays a series of pressure-volume loops and relations in a patient with a single-vessel coronary artery stenosis (proximal left anterior descending artery [LAD]), and no prior myocardial infarction. The patient underwent percutaneous coronary angioplasty of the LAD lesion. Continuous pressure-volume loops were obtained before, during, and after angioplasty by the conductance catheter technique. Baseline ESPVR and EDPVR were generated by transient re-
duction of left ventricular filling volume via inferior vena caval occlusion with a balloon catheter.

Panel A shows the baseline pressure-volume loops and ESPVR and EDPVR. The cardiac performance was essentially normal at rest despite the critical steno-
sis. The ejection fraction was 59%, with an end-diastolic volume of 100 ml. The control relationships are reproduced in subsequent panels for comparison.

Panel B displays every third beat after the complete occlusion of the LAD by the angioplasty balloon. Over a 30 sec period, the pressure-volume loops shifted markedly to the right and displayed a fall in systolic pressure. Panel C shows a steady-state pressure-volume loop after 90 sec of coronary occlusion. Two major changes in pump performance are easily discerned: (1) the end-systolic pressure-volume point has shifted markedly to the right from baseline, demonstrating a substantial reduction in systolic pump properties, and (2) the EDPVR is markedly elevated above control, consistent with a significant alteration in chamber compliance. The latter change was likely critical in limiting further increases in end-diastolic

FIGURE 1. Pressure-volume loops and relations obtained before, during, and after balloon angioplasty of a LAD stenosis in man. Left ventricular volume data were obtained with a multielectrode conductance catheter, with an intraluminal high-fidelity micromanometer catheter for pressure recording. Pressure-volume relations were assessed by transient IVC occlusion with a balloon catheter. A, Baseline ESPVR, EDPVR, and pressure-volume loops. B, Pressure-volume loops during the first 30 sec of coronary occlusion. The ESPV point shifted significantly rightward while the DPVR shifted up and became steeper. C, Steady-state pressure-volume loop after 90 sec of coronary occlusion displaying both systolic and diastolic changes. D, Pressure volume loops during the initial 15 sec of reperfusion. The ESPV point shifted back up and to the left, while the DPVR shifted back down essentially back to control. E, Steady-state loop before and after reperfusion. There is no indication of residual dysfunction.
volume and thus stroke volume during coronary occlusion. Should further study reveal a relation between the extent of rightward ESPVR shift and ischemic mass, similar to that previously demonstrated in animals, this approach could provide important clinical information regarding anatomic-functional correlates.

Panel D displays every other beat after deflation of the angioplasty balloon. The pressure-volume loops returned to normal within seconds of reperfusion, and if anything slightly exceeded the baseline condition (panel E). There was no evidence for myocardial "stunning," and the demonstration of functional recovery with reperfusion was as clear as the initial display of dysfunction during coronary occlusion.

We chose this example because it demonstrated the overall use of pressure-volume relations to describe a complex setting of altered loading and mechanical performance, without actually requiring mention of chamber contractility or Emax. In the next few sections, however, we specifically examine some of the issues and controversies regarding Emax determination.

Assessing Emax: definitions and issues

ESPVR vs Emax. Some of the controversy surrounding Emax has resulted from confusion over its definition. Emax [the maximal value of the time-varying elastance, E(t)] was originally considered to be identical to the slope of the ESPVR. To measure Emax one had to determine E(t) [E(t) = P(t)/(V(t) - Vo(t))] using differently loaded beats synchronized in time, and obtain its maximal value. The ESPVR, on the other hand, was comprised of the set of individual end-systolic points, one from each beat, [point of maximal P/(V - Vo)] chosen regardless of timing. The slope of this relationship is called the end-systolic elastance, Ees.

Why is the distinction between Ees and Emax important? In isolated hearts with isovolumetric or ejecting beats determined over a range of preloads, Emax and Ees are nearly identical. However, when the afterload is significantly altered among the cardiac cycles used for Ees or Emax determination, the two can be very different. In vivo, afterload and preload are interrelated, and Emax and Ees frequently differ (figure 2). The differences likely relate to resistive and inertial influences on end-systolic pressures, as well as changes in the time to reach end-systole (t_e) as a function of load. These influences can often lead to an Emax that is significantly steeper, and in contrast to Ees, does not fall at the corners of the pressure-volume loops.

Most experimental and clinical studies of ESPVRs have determined Ees rather than Emax, although the latter notation is frequently used regardless. Ees is the more useful measure of systolic properties for the purpose of assessing pump function. While estimation of Emax modified with internal resistances and other components will continue to be a useful concept for ventricular modeling, it is less likely to be of clinical utility in characterizing systolic performance in man.

ESPVR nonlinearity. Most studies performed in the 1970s revealed the ESPVR to be approximately linear over a reasonably wide range of loading conditions. This linearity was convenient as it allowed a simple description of the ESPVR with only two parameters: a slope (Ees) and intercept (Vo).

While earlier studies often stressed the importance of ESPVR linearity, recent evidence has shown that the ESPVR becomes significantly nonlinear under a variety of conditions. One example of this was provided by the study of Sunagawa et al. on the effects of regional ischemia on ESPVR. Coronary occlusion produced an ESPVR convex to the volume axis, with a net rightward shift of the relation in the high-pressure range. Thus, the local slope of the ESPVR varied somewhat as a function of the end-systolic pressure, making a linear model inadequate for describing the entire relation (figure 3).

Even homogeneous conditions can yield nonlinearity of ESPVRs. Burkoff et al. examined ESPVRs from isovolumetrically contracting isolated canine left ventricles, varying contractile state over a wide range with the use of pharmacologic agents, lowered coronary perfusion, and extrasystolic premature and potentiated beats (figure 4, A). Within the inotropic range
Recent studies into the underlying mechanisms for the myocardial force-length relation have revealed curvilinear relations in a variety of preparations. The shape and degree of curvilinearity have been found to vary depending on the Ca\(^{2+}\) concentration in the bathing solutions, and have been ascribed to length dependence of the affinity of myofilaments to Ca\(^{2+}\) as well as the Ca\(^{2+}\) available to them. In addition,

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**FIGURE 3.** Top, Isolated canine heart data showing the effects of regional ischemia on ESPVR (from Sunagawa et al.). With increasing extents of ischemia, the ESPVR becomes more curvilinear. Bottom, Intact canine heart data (Kass DA: unpublished data) displaying shift in ESPVR with distal LAD occlusion. Over the range of data obtained, the ESPVR appears shifted rightward with little change in Ees. The dashed line represents the theoretical ESPVR based on isolated heart data. LCX = left circumflex artery.

Typical of isolated hearts (Ees from 3.5 to 7.0 mm Hg/ml), the ESPVR was essentially linear; however, at higher contractile states, such as those accompanying conditions in situ, ESPVRs were concave to the volume axis (much lower contractile states led to convex ESPVRs). Data we have recently obtained from canine hearts in situ over a broad range of contractile states have shown results similar to those reported by Burkhoff et al. ESPVRs were frequently concave to the volume axis, (figure 4, B), and the degree of nonlinearity depended on contractile state.

Experimental and clinical studies in vivo often determine ESPVR over a limited range of altered loading, with few individual pressure-volume loops (the latter particularly true in human studies). Even considerable nonlinearity may not be discerned with these limited data. However, it is common to observe seemingly negative values for the volume axis intercept (Vo), which could be explained by ESPVR nonlinearity (figure 4, B).

![Diagram](image)

**FIGURE 4.** A, Curvilinearity of ESPVR in isolated canine hearts (data from Burkhoff et al.). Five different contractile states varied by dobutamine or altered coronary perfusion pressure (CPP) are shown. Each set of data are fit by a quadratic equation. The shape of ESPVR nonlinearity was dependent on contractile state. B, Curvilinearity of ESPVR in situ. Data were again obtained by conductance catheter technique. Linear approximation was inadequate to properly describe the ESPVR and led to a negative extrapolated Vo (dashed line), while curvilinear fit (solid line) predicted a small positive Vo.
ESPVR nonlinearity has been predicted by models relating the ESPVR to myocardial stiffness—natural strain relations. However, the ESPVR was never intended to directly define myocardial properties. Rather, it was thought to provide a useful measure of chamber systolic properties. Thus, in addition to reflecting the status of the myofilaments, the ESPVR is likely sensitive to the architectural arrangement of fibers, chamber geometry, left ventricular mass, and connective tissue elements. Given the complex three-dimensional geometry of the ventricle, it is not surprising that ESPVR is nonlinear.

It is important to recognize that linearity is a convenience that enables the relationship to be described in simple terms. Lack of linearity does not change the fact that the relationship defines the limits of systolic performance for a given heart in a given state. It does mean that investigators who wish to use the ESPVR to assess systolic properties must carefully consider whether the model they choose to fit to the relationship adequately describes the data in the pressure-volume range of interest. Comparisons between ESPVRs obtained over very different pressure loads should be carefully interpreted, taking potential nonlinearity into account.

Afterload and ESPVR. Otto Frank's experiments on pressure-volume relations of the frog ventricle, performed near the turn of the century, revealed a substantial influence of afterloading conditions on the ESPVR. For several decades, concern about this dependence led many investigators away from pressure-volume descriptions of ventricular performance. However, when pressure-volume relations were re-examined in mammalian ventricles in the 1960s and 1970s, it became apparent that the degree of afterload sensitivity was much less than that in the amphibian heart. Evidence provided from a number of different laboratories using a variety of experimental preparations demonstrated that the ESPVR was relatively insensitive to afterloading conditions.

Yet, it has been well appreciated that ESPVR load insensitivity is relative, and that substantial alterations in afterload impedance or ejection pattern can change the ESPVR. Suga et al. examined ESPVRs under a wide variety of ejecting conditions, and found that if the end-diastolic and end-systolic volumes were kept constant, the end-systolic pressure points clustered together independent from the ejection pattern. However, if the stroke volume was widely varied, then an effect on the end-systolic pressure-volume point was observed, with the end-systolic pressure being slightly lower if preceded by a large stroke volume.

Maughan et al. subsequently compared ESPVRs determined at multiple combinations of different arterial resistances, compliances, and characteristic impedances, each independently varied over a fourfold range. Each ESPVR was obtained by varying preload at a fixed afterload impedance. These data showed that the slope of the ESPVR (Ees) was not significantly altered by changes in any of the parameters; however, the ESPVR shifted rightward by as much as 5 ml with a marked increase in resistance. Similar rightward parallel shifts of the ESPVR were demonstrated by Freeman et al. in closed-chest dogs in a study in which steady-state afterload was altered by infusion of angiotensin II or nitroprusside, and ESPVRs were determined by transient inferior vena caval (IVC) occlusion.

Parallel ESPVR shifts with marked changes in afterload could result in a much greater change in ESPVR slope (Ees) if the loading sequence consists of beat-to-beat changes in afterload resistance with relatively constant preload. With a reduction in afterload resistance, ejection fraction would increase, and the end-systolic pressure-volume points would fall on ESPVRs that are shifting slightly to the right. This would result in a steeper ESPVR than that obtained at any of the afterloads at steady state with use of preload reduction as the means of constructing the ESPVR (figure 5). Such a phenomenon has been recently demonstrated by Baan and van der Velde for canine ventricles in situ.

Afterload influences on ESPVR are consistent with data from papillary muscle and whole hearts for which greater shortening from the same starting length or volume results in a force-length (or pressure-volume) trajectory that falls short of the end-systolic point achieved by isometric (or isovolumetric) contraction. Some of this reduction has been attributed

![FIGURE 5. Schematic diagram showing the disparity between ESPVR obtained by preload reduction at three different fixed afterloads (dotted lines) and one obtained by afterload reduction at a fixed preload (solid line). The latter ESPVR will most often be steeper.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.77.6.1207)
to a ventricular internal resistance, as well as shortening deactivation. Recent studies have further suggested potential positive effects of ejection on end-systolic pressure under certain conditions. This positive effect may relate to the total integrated time spent at longer muscle lengths for ejecting beats (particularly those at high afterloads), thereby enhancing contractile state via length-dependent Ca$^{2+}$. activation.

Since ejection history dependence is likely to influence the ESPVR more if differently afterloaded beats are used, these results support a preference for the use of preload reduction to determine the ESPVR. It remains possible that there are significant differences between man and canine preparations regarding the influence of afterload on ESPVR. In this regard, several clinical studies we have performed have failed to demonstrate any significant ESPVR shift or alteration between relations generated during IVC occlusion versus increased afterload produced by isometric handgrip (figure 6, A). Thus, despite the potential load dependence, changes in pressure-volume relations due to physiologic alterations in load have thus far appeared tiny compared with the substantial changes brought about by varying inotropic state (figure 6, B).

Statistical uncertainties. Assessment of ESPVR in situ may yield data limited to a relatively small range of altered loading, with few individual cardiac cycles. This is particularly true for patient studies, in which many ESPVRs first reported were based on 2 or at most 3 beats. Even now, studies are performed in which the Ees parameter is based on limited data. Clearly, the statistical confidence of a given slope will be poor if only a few points are determined over a limited range. Even a small degree of noise in the pressure or volume data can yield different estimates for Ees and Vo. Reliance on a given slope and intercept as if they were exact measured parameters can easily mislead us.

Some investigators have expressed concern over the statistical difficulties surrounding ESPVR characterization. They emphasize that as the range of altered end-systolic pressures and volumes is fairly small with the usually obtainable range of data in situ, the relationship is difficult to characterize in a statistically meaningful way. While true to some extent, it is often this attempt to boil down the description of an ESPVR into two linear parameters that can obscure clear differences between pressure-volume relations. Instead of fixing on a slope and intercept, the actual pressure-volume data should be more frequently displayed. As many individual cardiac cycles as possible should be used over as wide a loading range as practically obtainable. Alternative statistical approaches such as analysis of covariance, or comparisons of Ves measured within the data range (rather than Vo) should be used. Assuming the data are not exceedingly corrupted by noise, the end-systolic pressure-volume points, whether linear or not, provide important information concerning the limits of systolic performance for a given heart. The ability to reasonably distill the data into two parameters with a high degree of statistical confidence is certainly convenient, but not a necessity.

Contractility: alternative views. The slope of the ESPVR provides a measure of the end-systolic chamber stiffness over a given loading range; however, whether chamber stiffness is what we mean by "contractile
state" remains debatable. Certainly end-systolic elastance can be influenced by chamber geometry, again stressing that the variable assesses a chamber and not a muscle property. Several attempts have been made to normalize Ees by muscle mass and/or cavity volume. However, while these "corrections" may be applicable under controlled conditions, it is unlikely that given the wide clinical spectrum of myocardial disease, large ventricles, for example, will always have lower Ees values (see example in figure 8, B).

In isolated hearts with homogeneous wall properties, the end-systolic elastance is highly correlated with inotropic state. However, in regionally ischemic or locally paced ventricles, heterogeneity of mechanical properties or systolic timing can render the correlation between net chamber contractility and Ees much less direct. A rightward shift of ESPVR placement, for example, certainly indicates reduced mechanical performance in that lower end-systolic pressures and stroke work are obtained for any given starting volume. However, the end-systolic elastance can appear unchanged (figure 3, bottom).

The potentially complex relationship between ESPVR and contractile state is not unique to this measurement. Another measure of systolic chamber function is the slope of the relation between the maximal value of the first derivative of left ventricular pressure (dP/dtmax) and end-diastolic volume. It is fairly simple to predict a correlation between this slope and Ees, and it is thus not surprising that interventions that shift ESPVR without altering Ees have been found to also shift the dP/dtmax-end-diastolic relation without altering its slope.

Yet another proposed measure of chamber contractile state is the preload-recruitable stroke work (PRSW), or the slope of the stroke work–end-diastolic relationship. First suggested by Sarnoff and Mitchell, this relation was recently demonstrated in closed-chest dogs by Glower et al. The PRSW is attractive for several reasons. It is quite linear over a wide range of physiologic conditions. The dependent variable (stroke work) varies more with changes in end-diastolic volume than end-systolic pressure does with end-systolic volume; therefore, from a statistical standpoint, this relation may be easier to quantify in situ. Despite the clear potential for afterload sensitivity (stroke work declines to zero at both no load and infinite load), PRSW is quite stable over a range of physiologic afterloads.

However, PRSW does not separate systolic and diastolic properties, but rather integrates them. In animal studies, in which the greatest degree of testing of PRSW has been done, EDVPRs are generally so flat that this interdependence is of little significance. However, in patients with chronic hypertension in whom diastolic properties may be very abnormal, the interplay between systolic and diastolic properties may render PRSW difficult to interpret as a pure systolic index. In addition, stroke work is at some level ejection-history dependent, and some care should be taken to derive PRSW from cardiac cycles under different preloads but with relatively stable ejection patterns. We emphasize that all of the indexes discussed above are easily obtainable from the same set of pressure-volume data used in assessing the ESPVR (figure 7).

**FIGURE 7.** Multiple assessments of systolic performance from same set of pressure-volume loops obtained during IVC occlusion in a patient. Left, The pressure-volume loops and ESPVR. Right, the stroke work–end-diastolic volume and dP/dtmax–end-diastolic volume relations.
The pressure-volume diagram: a broader view. Thus far we have concentrated on several of the issues and controversies surrounding ESPVR and Ees as assessments of ventricular contractile state. However, the strengths of the pressure-volume description of ventricular performance do not depend on a complete resolution of these issues. The preoccupation with making Ees the ultimate index of contractility as sort of a "holy grail" is unfortunate. What is important, however, is that the steepness of an ESPVR combined with the EDPVR enables the clinician to appreciate the influence of afterload changes on systolic pressure and stroke volume, or the dependence of both variables on changes in ventricular filling. Focusing on the entire pressure-volume description, particularly on the interrelation between diastolic and systolic properties, rather than on the determination of Ees alone, is much more likely to provide clinically useful insights into cardiac function and the outcome of drug therapy.

Two clinical examples drawn from recent patient studies are shown to demonstrate this utility (figure 8). Left ventricular pressure-volume relationships were obtained by use of a multielectrode conductance catheter system, while loading was again rapidly (and reversibly) altered by transient IVC occlusion.

Both patients had a 1 year history of dyspnea on exertion, without any coronary or valvular disease. Cardiac catheterization confirmed normal coronary arteries, and ventriculography demonstrated diffuse hypokinesis with cavity enlargement. Patient A had normal systolic pressures (100 mm Hg), while patient B had high pressures (180 mm Hg). Thus, patient B might have been anticipated to respond more to vasodilator therapy (with an improvement in stroke volume) than patient A; however, the exact opposite proved true. Patient A had a very shallow ESPVR, and thus the reduction in afterload (solid lines) would have substantially improved forward output (by 30% in this case). However, the left ventricle in patient B, while dilated, had a very steep ESPVR, and similar afterload reduction would not have substantially improved stroke volume (+10% at most). Furthermore, he would be unlikely to benefit from inotropic agents, since his ESPVR was already quite steep, while patient A might benefit a great deal. This was confirmed by administering dobutamine to patient A (figure 9), which produced a marked leftward shift and steepening of the ESPVR, increasing stroke volume at any given preload. Neither patient had significant preload reserve, because both were operating at end-diastolic pressures of 20 to 22 mm Hg. Thus, simply by generating the diastolic and systolic pressure-volume relations, a much more precise characterization of cardiac performance was obtained, and pharmacologic therapy was better targeted.

In this perspective, we have tried to review the status of the ESPVR and pressure-volume relations for the characterization of ventricular performance. Many of the current concerns regarding ESPVR primarily impact on attempts to reduce pressure-volume data to a single number, Ees, as an index of contractility. Rather than dwell on these issues, we believe the focus should

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be reoriented toward use of the entire pressure-volume description for its many strengths: (1) that it provides a characterization of pump performance that allows loading factors to be reasonably separated from ventricular properties, (2) that it identifies both diastolic and systolic properties in common terms and therefore helps clarify their interrelationship, and (3) that it provides a description of coupling between ventricle and vasculature, which enables predictions of stroke volume and stroke work response to various loading interventions.

We thank Dr. Kiichi Sagawa for his thoughtful insights, suggestions, and encouragement in the writing of this perspective.

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Circulation. 1988;77:1203-1212
doi: 10.1161/01.CIR.77.6.1203

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