Influence of Contractile State on Curvilinearity of In Situ End-Systolic Pressure-Volume Relations

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Although in situ end-systolic pressure-volume relations (ESPVRs) are approximately linear throughout a limited load range, they often yield seemingly “negative” volume axis intercepts ($V_0$) and $V_0$ shifts with inotropic interventions. We tested whether or not these findings could stem from in situ ESPVR nonlinearity, and we examined the physiologic meaning and limitations of linearized ESPVR variables frequently used for assessing contractile state. Continuous left ventricular pressures and volumes were obtained by micromanometer and conductance (volume) catheters in six open-chest dogs. Left ventricular loading was varied throughout a wide range by rapid left atrial hemorrhage into a reservoir. Propranolol and verapamil were administered to reduce inotropic state, with heart rate maintained by atrioventricular sequential pacing. ESPVRs were fit to nonlinear \( \text{ESPVR} = a(V_e - V_0)^2 + b(V_e - V_0') \) and linear \( \text{ESPVR} = \text{Ees} (V_e - V_0) \) models. Contractile state was assessed by the slope of the ESPVR at $V_0'$ (b, of nonlinear model) and by two other ESPVR model-independent measures: the slope of the $dP/dt_{max}$ and end-diastolic volume relation, and the slope of the stroke work and end-diastolic volume relation. ESPVR was frequently curvilinear, and a significant correlation existed between the extent of nonlinearity (a) and contractile state. Volume intercepts derived from linear fits to the high load ESPVR range were mostly negative and were dependent on changes in Ees. $V_0$ estimates derived from the low load portion were positive and relatively insensitive to Ees. Thus, in situ ESPVR displays contractility-dependent curvilinearity. The contractility range throughout which ESPVRs are essentially linear is typical for isolated hearts, but the range represents low values for in situ ventricles. Despite curvilinearity, Ees determined in situ throughout limited load ranges can accurately assess inotropic state; however, comparisons between ESPVRs should consider potential nonlinearity, and if possible, they should be made within similar end-systolic pressure ranges. (Circulation 1989;79:167–178)

Studies performed throughout the 1960s and 1970s established that in excised supported mammalian left ventricles, the end-systolic pressure-volume relation (ESPVR) is linear and provides a measure of chamber contractile state that is largely insensitive to steady-state loading conditions.\(^1\)\(^{-6}\) ESPVR linearity enables a simple description in terms of a slope (Ees) and volume axis intercept ($V_0$) and of a characterization of ventricular contraction by a time-varying elastance model. However, as techniques for ESPVR determination and the condition of experimental preparations have improved, nonlinearity of the relation has been increasingly observed.\(^7\)\(^{-9}\)

In a recent examination of this phenomenon, Burkhoff et al\(^7\) demonstrated contractility-dependent curvilinearity of ESPVRs in isovolumically contracting isolated canine ventricles. Throughout the range of Ees generally present in isolated heart preparations, ESPVR is adequately described by linear regression. However at higher or much lower contractile states (\(\geq 7.8\) or \(\leq 3.4\) mm Hg/ml), the former being typical of in situ ventricles, nonlinearity is significant. The influence of contractile state on ESPVR shape was likened to the behavior of force-length relations of cat papillary muscle\(^10\)\(^{-11}\) and intact and skinned rat trabeculae,\(^12\) which has been ascribed to length-dependent calcium activation.\(^10\)\(^{-12}\)
Studies performed in animal preparations that are more intact,\textsuperscript{13–16} as well as in humans,\textsuperscript{17–21} generally have reported linear ESPVRs. Frequently, however, in situ data yield apparent negative values for $V_o$, the estimated ventricular volume at zero end-systolic pressure. Furthermore, alterations in contractile state produced by pharmacologic agents have resulted in $V_o$ shifts and, at times, varying changes in $Ees$. These behaviors seem inconsistent with isolated heart data and models, and it is certainly difficult to attach any physiologic meaning to a negative $V_o$. Although curvilinearity of ESPVR could explain negative $V_o$ and $V_i$ shifts with inotropic interventions,\textsuperscript{7,22} most in situ ESPVRs (particularly in humans) have been derived from a few cardiac cycles generated throughout a limited load range, and these factors would reduce the likelihood of discerning nonlinearity in the data.

The purpose of this study was to examine whether or not ejecting in situ left ventricles demonstrated contractility-dependent curvilinearity of ESPVR similar to isolated isovolumic hearts and papillary muscle. We hypothesized that ESPVRs would be concave to the volume axis at high contractile states and that the degree of concavity would decrease as contractility fell. We assessed whether or not such curvilinearity could explain apparent negative extrapolated $V_o$, and consistent $V_i$ shifts with contractility change, observed when ESPVRs were fit by linear regression throughout a limited range. We used a conductance catheter technique to determine in situ pressure-volume relations and varied load throughout a wide range by left atrial hemorrhage. Contractility was systematically lowered by incremental doses of propranolol and verapamil.

Materials and Methods

Surgical Preparation

Six adult mongrel dogs were anesthetized with pentobarbital sodium (30 mg/kg) and ventilated on a volume respirator (Harvard Apparatus, South Natick, Massachusetts). The chest was opened through a left lateral thoracotomy. A micromanometer pressure transducer catheter (PC-550, Millar Instruments, Houston, Texas) was advanced to the left ventricle through a femoral artery to record cavity pressure. A second similar catheter was positioned in the proximal descending aorta for arterial pressure recording. An 8F multielectrode conductance (volume) catheter (Webster Labs, Baldwin Park, California) was advanced, through the left carotid artery, to the left ventricular apex. A 1-cm diameter cannula with multiple side holes was inserted in the left atrium through the atrial appendage. The cannula was attached to a 1.0 l reservoir that could be raised or lowered to rapidly alter left ventricular filling. The reservoir was primed with 500 ml 0.9% NaCl and 10% dextran, and the fluid was fully mixed with the blood before study. Fluid was added to the reservoir throughout the study if required for pressure maintenance. Central venous lines were placed for drug administration, and injection of hypertonic saline was used for volume signal calibration. An intravascular balloon-occluder catheter was placed in the inferior vena cava just below the right atrium. This was used only in combination with left atrial hemorrhage in three ESPVR determinations (all maximally depressed hearts) to facilitate adequate and rapid preload reduction. Finally, two pairs of pacing electrodes were sewn to the atrium and left ventricular apex for atrial and atrioventricular sequential pacing.

Volume Catheter System

The conductance catheter technique (Sigma V, Lecyom, Degaesta, The Netherlands) for continuous, instantaneous pressure-volume measurements has been previously described in detail.\textsuperscript{13,23} Briefly, a 40-\muA, 20-kHz alternating current passes between two source electrodes on the catheter positioned at the ventricular apex and just above the aortic valve, respectively. Multiple intervening electrodes are sequentially paired to measure segmental voltages, which because of constant current can be converted to conductances. Segment volume ($V_i$) is determined by the equation: $V_i = G_i \times \left( L^2 / \sigma \right) - V_{sp}$, where $G_i$ is the segmental conductance, $L$ is the interelectrode spacing, $\sigma$ is blood conductivity, and $V_{sp}$ is the volume offset due to parallel conductance of muscle wall and other structures. Total chamber volume ($V_t$) is the sum of the individual segment volumes:

$$V_t = \sum_{i=1}^{5} V_i$$

Proper placement of the catheter in the ventricular apex was confirmed by manual palpation and by inspection of individual segment pressure-volume loops. The length of the volume sensing portion of the catheter was adjusted so that all five subsegments were within the chamber (i.e., displayed counterclockwise pressure-volume trajectory). This was rechecked frequently throughout the experiment, and the catheter sense length was readjusted if required.

Volume Signal Calibration

The catheter volume signal was calibrated with the hypertonic saline technique,\textsuperscript{13,23} which enabled calculation of a steady-state estimate for the parallel conductance ($V_{sp}$). Two to 3 ml of highly concentrated saline (saturated solution) was rapidly injected into the right ventricle, maintaining ventilation at end expiration. The resulting change in blood conductivity increased the volume signal without actually altering volume (confirmed by little to no change in peak systolic pressure). The end-diastolic and end-systolic volumes (max/min) for the beats after the sodium chloride bolus were identified and were correlated linearly by perpendicular regression (which minimizes perpendicular distance between data point and regression line, thus no dependent and independent variable). This relation was extrapolated to the
line of identity (end-systolic volume = end-diastolic volume), and the intersection point provided a steady-state estimate of the parallel conductance volume. This was subsequently subtracted from the total volume signal to yield absolute volumes.

Parallel conductance was determined under steady-state resting conditions (upper range preload). At least three and often four separate estimates were made, and the results were averaged to determine parallel conductance. The mean coefficient of variance for repeat parallel conductance estimates under a given condition was 4.1±3%, with an overall average of 52±8 ml (n=51). Parallel conductance was reassessed two or three times during the experiment under differing inotropic and volume-loading conditions. In general, only small changes in parallel conductance occurred throughout an experiment (in the range of 5 ml), with no consistent relation to inotropic state or fluid loading. This was likely due to offsetting influences of lowered blood resistivity compared with chamber dilation.

Previous studies from our laboratory have suggested that reductions in right ventricular volume from inferior vena caval occlusion could lead to a small reduction in parallel conductance, and an initial shallow leftward shift of the ESPVR. These same experiments demonstrated that direct preload reduction through left atrial hemorrhage minimizes this artifactual “nonlinearity.” For this reason and for the extended loading range afforded by the latter technique, left atrial hemorrhage was used for the present study. Parallel conductance was not assessed at a low preload range in this study because of the lack of complete autonomic blockade. In other (fully blocked) preparations, however, parallel conductance has been found to fall by only 1–2 ml (n=27) during inferior vena caval occlusion.

Protocol

Baseline pressure-volume data were obtained first. The ESPVR was determined by rapid left atrial hemorrhage through the cannula and into the reservoir. On average, 15 consecutive cardiac cycles were used to determine each ESPVR with an average end-systolic pressure ranging from 104 to 54 mm Hg. Respirations were maintained at end expiration during each ESPVR determination, with 5 l/min oxygen provided to minimize changes in blood oxygenation. With this technique, data for ESPVR determination could be collected during 10–12 seconds. To eliminate any artifactual effects on the volume signal due to red cell sedimentation within the reservoir (this could alter blood conductance), ESPVRs were only assessed during blood removal and not return.

After baseline data collection, ventricular contractile state was progressively diminished by administration of two negative inotropic agents; a β-blocker (propranolol hydrochloride) and a calcium channel blocker (verapamil). Sequential doses of propranolol (10 mg/dose, or about 0.5 mg/kg) were administered, to a total of 40 mg. Ten minutes was provided for stabilization after each dose, and then, ESPVR determination was repeated. Atrial pacing was used if the heart rate fell below 90 beats/min. After a total dose of 40 mg propranolol, verapamil was administered intravenously at 5 mg/dose (0.25 mg/kg) to a total of 20 mg. Combining propranolol and verapamil frequently led to significant atrioventricular conduction blockade. Therefore, atrioventricular sequential pacing was used, maintaining a heart rate of 80–90 beats/min.

Because of the varying responses to the pharmacologic agents and the fluctuations in the level of anesthesia and sympathetic tone, not every dose produced a significantly different contractile state. Because the goal of these interventions was to examine ESPVR curvilinearity at differing contractile states, the final number of distinctly different ESPVRs for each animal varied (mean, 5). In addition, some animals required additional verapamil (10–15 mg) to adequately depress contractile state. The endpoint of the pharmacologic interventions was the marked reduction of developed pressure, usually to 30–40 mm Hg, after which hearts generally deteriorated rapidly terminating in cardiac arrest.

Data Analysis

Ventricular pressure and volume, arterial pressure, and electrocardiogram were monitored on a strip-chart recorder (Model 2800a, Gould, Cleveland, Ohio), digitized at 200 Hz with a portable sixteen-bit microcomputer acquisition system (Model 232A Halcom, Ft. Washington, Maryland), and stored on removable hard disks (Bernoulli Box, Iomega, Roy, Utah). The points of the ESPVR were determined by an iterative technique. The points of each cardiac cycle with the maximal pressure to volume ratio were first identified. Linear regression of these points with the expression

\[ \text{P}_{\text{es}} = \text{E}_{\text{es}} \cdot (V_{\text{es}} - V_0) \]  

yielded estimates for the slope, or end-systolic elastance (Ees), and the volume axis intercept (V₀). This initial V₀ estimate was used to identify the points of maximal P/(V – V₀) for each cardiac cycle, and these new points were again fit by linear regression, leading to new Ees and V₀ estimates. This procedure was iterated until convergence was achieved (usually three or four times).

ESPVRs were represented by two models. The linear model (Equation 1) was fit separately to upper and lower halves of the total load range of each ESPVR. Two sets of Ees and V₀ estimates were thus obtained. For the nonlinear representation, end-systolic pressure-volume points were first selected for each beat by maximizing P/(V – V₀) throughout the entire data range. These points were then fit to a parabolic curvilinear model:

\[ \text{P}_{\text{es}} = a \cdot (V_{\text{es}} - V_0)^2 + b \cdot (V_{\text{es}} - V_0) \]  

In this expression, a is the coefficient of curvilinearity, V₀ is the volume axis intercept of the curvi-
linear relation, and $b$ is the slope of the ESPVR at $V_0$. This latter point is easily demonstrated by evaluating the derivative of Equation 2 at $V_s = V_0$:

$$\frac{dP_{es}}{dV_{es}} = 2a(V_{es} - V_0) + b$$

$$= b(\text{at } V_{es} = V_0)$$

(3)

We chose this form of the parabolic equation, rather than the form used by Burkhoff et al. ($P_{es} = aV_{es}^2 + bV_{es} + c$) because the variables of interest ($a$, $b$, and $V_0$) are directly fitted, rather than being functions of the model variables. The end-systolic pressure-volume points were fit to Equation 2 by a Marquardt nonlinear least-squares algorithm.25

To test the relation between extent of curvilinearity and contractile state, a measure of contractility was needed. However, the curvilinear fit excluded use of a simple variable such as $E_{es}$ of Equation 1. Burkhoff et al.26 used the slope of the initial portion of the ESPVR (variable $b$, Equation 2). However, because the coefficients of the parabolic function are not orthogonal, changes in the linear term ($b$) are not totally independent of changes in the quadratic term ($a$). Thus, in addition to any physiologic correlation, some dependence between $a$ and $b$ could be expected based on the parabolic model alone.

To avoid this problem, an index of chamber contractile state was needed that was independent of the quadratic ESPVR model. Two such measures have been recently proposed; one is the slope of the stroke work and end-diastolic volume relation (preload recruitable stroke work) described by Glower et al.,26 and the other is the slope of the $dP/dt_{max}$ and end-diastolic volume relation described by Little.27 Stroke work was calculated digitally by the integrated area within each pressure-volume loop, and $dP/dt_{max}$ was determined by running a five-point weighted slope. End diastole was defined at the point of each cycle at which the rate of change of instantaneous elastance [dE/dt = d(P/V)/dt] exceeded 10% of dE/dt_{max}.24 End-diastolic volume was the volume at that point. Slopes of the relations between stroke work and end-diastolic volume and between $dP/dt_{max}$ and end-diastolic volume were estimated by linear regression. With these slopes as alternative contractility measures, the relation between the curvilinear shape variable $a$ and contractile state was reexamined.

To determine the statistical significance of curvilinearity, the standard error of the estimate was calculated with a general least-squares linear model.28 A $t$ test was used to assess the significance of a given variable estimate at the 95% level. That is, if $p$ is greater than 0.05, then the ESPVR was considered satisfactorily fit by the linear regression. Data are mean ± SD.

**Results**

**Curvilinearity of End-Systolic Pressure-Volume Relation**

An example of experimental pressure-volume loops during an ESPVR determination are shown in Figure 1. End-systolic pressure was reduced in this example by 60 mm Hg during left atrial hemorrhage, which was similar to the mean range from all animals (54.5 ± 13.8 mm Hg, mean ± SD). When examined throughout the entire range of altered loading, the ESPVR was curvilinear. Panel A displays two linear regression fits, one applied to the upper load range of the ESPVR (solid lines), and the other to the lower portion (dashed lines). The upper range linear ESPVR represented the fit to data commonly obtained during an inferior vena caval occlusion. It was shallower ($E_{es} = 4.7$ mm Hg/ml) than the ESPVR from the lower range and had an apparent negative extrapolated $V_0$ (~10.5 ml). The linear ESPVR derived from the lower load range had a steeper slope (10.9 mm Hg/ml) and a small, positive extrapolated $V_0$ (1.0 ml). Although throughout these more limited ranges, the ESPVR could satisfacto-

**Figure 1. Plots of curvilinearity of end-systolic pressure-volume relation (ESPVR) in situ.** Multiple pressure-volume loops obtained sequentially during preload reduction are displayed. Panel A: Two linear model fits to the data. Linear ESPVR fit to the upper load range (solid lines) was shallower ($E_{es} = 4.7$ mm Hg/ml) and had a more negative extrapolated volume axis intercept (~10.9 ml) than a similar linear fit to data from the lower ESPVR range (dashed lines; $E_{es} = 10.9$ mm Hg/ml, $V_0 = 1.0$ ml). Panel B: Same data but fit to the quadratic ESPVR model. Data are very well described by this simple nonlinear expression. See text for nonlinear variables.
by linear regression to the lower ESPVR range.

Table 1 provides upper and lower load range linear ESPVR variables (Ees, V0) and the nonlinear ESPVR variables (a, b, and V0*) for the control contractile state for each heart. The mean Ees and V0 of the higher load range (initial portion) were 6.5±2.4 mm Hg/ml and 3.7±2.8 ml, respectively, whereas Ees and V0 for the lower load range were 23.3±10.0 mm Hg/ml and 3.2±0.3 ml, respectively. Nonlinear ESPVR model fits to these same control data (Table 1) revealed statistically significant quadratic terms for each heart (−2.7±2.8 mm Hg/ml2). The linear term (b, 30.0±16.2 mm Hg/ml), representing the predicted ESPVR slope at V0, and V0* (3.9±2.3 ml) were similar to Ees and V0, respectively, derived by linear regression throughout the lower load range.

**Influence of Altered Contractile State**

Typical ESPVRs obtained throughout a broad range of altered contractile states are shown for three of the hearts (Figure 2). ESPVRs were generally concave to the volume axis, with a greater degree of curvilinearity for ventricles with the highest contractility (upper left for each series), and increasing linearity with progressive cardiac depression. In each example shown, inotropic state was substantially reduced to the point where ESPVRs displayed convex curvilinearity with respect to the volume axis. However, these hearts developed pressures of only 30 mm Hg and generally arrested shortly thereafter. Thus, convex curvilinearity will probably never be observed in vivo except in a premorbid state.

Linear ESPVRs were obtained for the upper and lower load ranges for each end-systolic pressure-volume data set, reflecting a wide spectrum of contractile states. The value of Ees for each ESPVR was plotted against the extrapolated V0. Extrapolated V0 estimates from ESPVRs derived from data in the upper load range (Figure 3, Panel A) were usually negative (−12.3±8.8 ml). In addition, the lower the Ees throughout this load range, the more negative the value of the extrapolated V0 (V0 = 3.2·Ees−26.3, r = 0.84, p < 0.001). This relation was fitted better by a nonlinear function: V0 = 1.03·[1−0.022·eEes]. In contrast to ESPVRs derived from data in the upper load range, ESPVRs derived from the lower pressure-volume range revealed no correlation between Ees and V0 estimates (Figure 3, Panel B). The extrapolated V0 was generally small and nearly always positive (+2.9±2.8 ml).

**Contractility Dependence of Curvilinearity**

The relation between ventricular contractile state and the extent of ESPVR curvilinearity was first examined by comparing the nonlinear variable a (Equation 2) to the slope of the ESPVR at V0 (variable b, Equation 2) as previously done by Burkhoff et al. Figure 4A displays the data from ESPVRs in which the b value fell between 1 and 12 mm Hg/ml, similar to the range reported for isolated canine ventricles. There was a significant correlation between contractile state and the curvilinear shape of the ESPVR, such that with higher values of b, the nonlinear term became increasingly negative (a = −0.028·b + 0.063; R2 = 0.92, p < 0.0001).

Figure 4B displays the same relation between variables a and b now with all of the data generated in this study. Values of b spanned a much broader range in these experiments compared with the values obtained in isolated ventricles. Rather than a linear correlation, the relations between variables a and b were clearly nonlinear and were fitted nearly perfectly by a parabolic expression:

\[
a = -b^2 \cdot (2.5 \cdot 10^{-3}) + b \cdot (4.6 \cdot 10^{-3}) + (1.7 \cdot 10^{-3})
\]

However, because the a and b variables were chosen purely to achieve the best statistical fit to a given ESPVR, but were themselves not totally orthogonal, some correlation could have entered into the
fitting process without any physiologic foundation. To minimize this potential effect, model-independent measures of chamber contractile state were required. Two indexes were calculated for this purpose: the slope of the stroke work and end-diastolic volume relation (preload recruitable stroke work), and the slope of the dP/dt\textsubscript{max} and end-diastolic volume relation. Both indexes have recently been reported\textsuperscript{26,27} to provide measures of ventricular contractile state that are also relatively load insensitive throughout a wide physiologic operating range.

Figure 5 displays preload recruitable stroke work and the dP/dt\textsubscript{max} and end-diastolic volume relation gain data for two of the hearts previously displayed (ESPVR data) in Figure 2. Both sets of relations were generally linear, demonstrated a slope reduction with the negative inotropic interventions, and had a relatively constant and common volume intercept. The slopes of each line were used as model-independent measures of ventricular contractility and were plotted against the nonlinear coefficient (a) of Equation 2. The results (Figures 6A and 6B) confirmed significant nonlinear relations between contractile state and ESPVR curvilinearity, which were both similar to the previous plot of a versus b (Figure 4B). Each relation could be well fitted by a monoeponential function (see figure legend for nonlinear fits).

The range of contractile states throughout which the nonlinear term a was found not to be statistically significant (i.e., a linear ESPVR) is demonstrated in Figure 7 (shaded zone). The value of the b coefficient (ESPVR slope at V\textsubscript{0}) represents Ees from the low load range (curve A), and the Ees slope from linear regression applied to the upper ESPVR range (curve B).
“Negative” Volume Axis Intercept

Since its description in isolated canine ventricles, many investigators have attempted to assess the ESPVR in more intact circulatory systems, including humans. These estimations have often used few cardiac cycles (2–4 in most human studies) collected within a limited loading range. Because even moderate nonlinearity may not be discerned throughout this limited range, it is not surprising that the observed ESPVRs have been reported as linear. This is true of our own data from previous reports in which we used measurement techniques similar to the present study but for which load change was limited to a narrower range (50% of the present study) due to the use of inferior vena caval occlusion. Extrapolation of the linear ESPVR in situ has frequently yielded negative volume axis intercepts. The reported range for negative VO estimates has varied from $-9^{18}$ to $-30^{20}$ ml for normal human ventricles. Similar negative VO values have been reported in open-chest,13 closed-chest,29 and conscious10 dogs. Although several investigators have suggested that ESPVR nonlinearity could explain “negative” VO values,12,22 the present study is the first to demonstrate the validity of this hypothesis in the in vivo heart.

When a linear model was fitted to the in situ ESPVR data in the upper load range, we found that the extrapolated VO was consistently negative and was shifted to the right with increases in contractility rather than remaining constant. Of note, this range of loading is similar to that generally obtained by techniques such as transient inferior vena caval occlusion or pharmacologic loading, which are used in many animal and human studies.8,13,14,16,20 In contrast, linear extrapolation from the lower load range yielded small positive VO values that were much less altered by contractile change.

These findings have several implications for the meaning of a linearly extrapolated VO. Certainly the “negative” values are physiologically nonsensical, and in view of the concavity of the in situ ESPVR, any extrapolated VO derived from a linear ESPVR model would be equal to or lower than the true volume at zero developed pressure. This problem could be compounded when loading increases are used to assess ESPVR as has been done in some studies.13,17-19 However, if care is taken to fit the ESPVR data with an appropriate model, then the VO variable may convey useful information regarding placement of the data along the volume axis. This is more likely applicable to human disease states such as ventricular aneurysm, in which markedly abnormal geometry can yield ESPVR shifts well outside even broad VO 95% confidence intervals. In general, it would be preferable to make statistical comparisons of ESPVR placement by contrasting end-systolic volumes measured at pressures common to the observed data.

Contractility Dependence of Curvilinearity

The contractile state for the isolated, denervated, cross-perfused left ventricle seems significantly lower

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**Figure 4.** Plots of dependence of end-systolic pressure-volume relation (ESPVR) curvilinearity assessed by the quadratic coefficient a and contractile state assessed by the slope (coefficient b) of the nonlinear ESPVR at V0 (volume axis intercept). Panel A: Data for b values between 0 and 12 mm Hg/ml are shown. Relation between a and b was highly significant and approximately linear. Panel B: Data for all b values obtained in the study. Examined throughout this much broader range, the codependence of a and b was clearly nonlinear and very well fit by a quadratic relation: a = \(-0.0025b^2 + 0.0046b + 0.0017\).
than that observed in situ as reflected by the smaller Ees values in the former. When the isolated heart contractile state is varied throughout a broader range by postextrasystolic potentiation and pharmacologic interventions, contractility-dependent curvilinearity of ESPVR is observed. In the study of Burkhoff et al,7 the initial slope of the curvilinear ESPVR (b coefficient in Equation 2) was used to assess contractile state and was found to bear a significant linear correlation with the coefficient a of the nonlinear term. A similar correlation was found in the present study (Figure 4A); however, when examined throughout the full range of contractile states (b values) obtained in situ, the relation was clearly parabolic. Some degree of codependence may have resulted from curve fitting a quadratic model, whose coefficients are not totally orthogonal; therefore, two additional model independent indexes (preload recruitable stroke work and dP/\( dt_{\text{max}} \) and end-diastolic volume relation) of contractile state were examined. There was still a strong correlation between nonlinear ESPVR shape indexed by the quadratic term a and contractile state (Figure 6). Furthermore, the data demonstrated that within a range of contractility (Ees ranging from 3.0 to 5.0 mm Hg/ml, preload recruitable stroke work ranging from 15 to 35 mm Hg) similar to that noted by Burkhoff et al,7 the ESPVR could be well represented by a linear model.

The ventricular ESPVR is a complex product of muscle properties, wall mass, fiber architecture, chamber geometry, and electrical activation. In a recent model relating myocardial stiffness, chamber geometry, and ESPVR, Mirsky et al22 predicted a curvilinear ESPVR (concave to the volume axis) assuming a linear muscle stiffness and natural strain relation. Thus, alterations in the shape of the ESPVR could occur from changes in chamber geometry (i.e., wall thickness relative to chamber diameter or chamber elongation) or muscle stiffness. Isolated papillary muscle studies have demonstrated that the force and sarcomere length relation is curvilinear and changes shape when the Ca\(^{2+}\) concentration of the bathing solution is altered.10,30 This change has been ascribed to length dependence of myofilament Ca\(^{2+}\) sensitivity12,31 and availability.11,32

In papillary muscles, as in isolated whole heart, low contractile states have been associated with

### Table 2. Alteration of ESPVR Curvilinearity With Changes in Contractile State

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<th>Dog</th>
<th>PRSW</th>
<th>dP/( dt_{\text{max}} ) and EDV</th>
<th>a</th>
<th>( p^* )</th>
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ESPVR, end-systolic pressure-volume relation; PRSW, preload recruitable stroke work; EDV end-diastolic volume; a, coefficient of curvilinearity; b, slope of the ESPVR curve at \( V_j \); Ees\(_{\text{high}} \), end-systolic elastance at high load. Data from each dog is shown. Contractile state was assessed by three different methods: the slope of the stroke work and end-diastolic volume relations (PRSW, mm Hg), and slope of the dP/\( dt_{\text{max}} \) and EDV relation (mm Hg/sec/ml), and the linear (b) coefficient (mm Hg/ml), the slope of the curvilinear ESPVR model at \( V_j \) (from Equation 2). Curvilinearity is assessed by the second-degree term (a, mm Hg/ml\(^2\)) also from Equation 2. The p value for the statistical significance of a \( \neq 0 \) is given for each data set. Also, the value of the linear ESPVR slope (Ees\(_{\text{high}} \)) derived from the upper range portion of each ESPVR is provided.
end-systolic force and sarcomere length relations that are convex to the dimension axis. Convex ESPVRs were observed in this study only at extreme levels of cardiac depression, with developed pressures of less than 40 mm Hg. Whereas the constant coronary perfusion of the isolated heart preparation enables such a condition to be sustained, such severe levels of cardiac depression in situ rapidly lead to terminal arrest by a vicious cycle of coronary perfusion feedback. Thus, convex ESPVR curvilinearity would probably never be observed in stable self-sustaining physiologic settings.

What does contractility-dependent curvilinearity of in situ ESPVR imply for the use of a linear ESPVR model in situ? Throughout most obtainable load ranges in situ, the ESPVR is usually well described by a linear relation, and the slope of the relation (Ees) can provide a measure of contractile state. This was demonstrated by the correlation between preload recruitable stroke work and Ees (determined from the upper ESPVR load range) (Figure 7). A similar correlation was present between Ees and the slope of the dP/dt_{max} and end-diastolic volume relation (y = 0.05x + 1.5; r = 0.91, p < 0.001). Effects of interventions in a given heart on Ees can be meaningfully compared if ESPVRs are determined throughout similar pressure ranges or if Ees changes in a direction opposite to that predicted by curvilinearity alone. Certainly, whether linear or not, the ESPVR provides a valid measure of the upper operating limits of systolic performance for a heart.

**Stroke Work and End-Diastolic Volume Relation and dP/dt_{max} and End-Diastolic Volume Relation**

Data from this study affirm and extend previous findings of Gower et al.26 concerning the slope of the relation between stroke work and end-diastolic volume and of Little27 who examined the dP/dt_{max} and end-diastolic volume relation. In the present study, both relations were generally linear, sensitive to changes in contractile state throughout a broad range, and displayed a fairly common volume intercept. Theoretical relations between each of these indexes and pressure-volume relations have been recently described.24 Although a parabolic curve was predicted for stroke work and the end-diastolic volume relation, the relation was effectively linear throughout a wide physiologic operating range and would predictably be even more so if a concave nonlinear ESPVR were assumed. The observed linearity of the dP/dt_{max} and end-diastolic volume relation, an isovolumetric rather than ejection phase index, suggests that a component of in situ ESPVR nonlinearity may arise from the ejection history.33,34 The relative linearity of these alternatives, compared with the ESPVR, suggests that they may be more easily used to index contractile state in vivo.35

**Limitations**

There are several limitations to this study intrinsic to the closed-loop physiology in situ. Left atrial hemorrhage was rapid; however, some potential reflex activation could have occurred altering the ESPVR under study. With a reduction in systolic pressure, however, reflex changes (primarily mediated by the carotid baroreceptors) would have enhanced contractile state,15,36 and this would have led to ESPVR curvilinearity that was convex to the volume axis, rather than to the concave shape we observed.

Coronary perfusion may have been compromised at low preloads, and combined with lowered hematocrit levels (due to volume loading), this could have reduced global myocardial contractile state. As shown in a previous isolated heart study37 (in which coronary perfusion was coupled to systolic pressure development), this effect could lead to a curvilinear steepening of the ESPVR in the lower load range. Although we cannot entirely rule out this effect, there are several reasons why it was not likely a
major factor. ESPVR nonlinearity was frequently observed over end-systolic pressure ranges well above 60 mm Hg, which is the critical coronary arterial pressure threshold found for isolated ventricles. Moreover, as ischemia-related ESPVR nonlinearity would represent end-systolic pressure-volume points derived from multiple steadily declining (linear) ESPVRs,37 similar nonlinearity should have been observed in preload recruitable stroke work or $dP/dt_{max}$ and end-diastolic volume relations. Yet, as Figure 5 demonstrates, these relations were essentially linear. Finally, ESPVRs with the greatest depression (and lowest end-systolic pressures) were more, not less, linear and eventually became convex to the volume axis. This is in the opposite direction predicted from a load-dependent ischemia mechanism.

**Volume Signal Calibration**

We assumed that the parallel conductance offset due largely to current leakage through the muscle wall and right ventricular chamber was constant during ESPVR determination. Certainly, this is a simplification because with preload reduction, parallel conductance will eventually fall, reflecting reduced venous return and thus right ventricular volumes. This reduction, however, tends to be quite small (1–2 ml), and if anything, it would shift the total volume signal leftward toward smaller (not larger) volumes and, therefore, not generate concave curvilinearity. As noted in “Materials and Methods,” the apparent nonlinearity that can be observed when inferior vena caval occlusion is used to reduce preload is effectively eliminated by direct left atrial hemorrhage. In the former case, the early rapid fall in parallel conductance (due to emptying of right-sided chambers) occurs before any left ventricular volume reduction, leading to an initial shallow ESPVR portion. With the use of left atrial hemorrhage, this initial shift is avoided, and only gradually does the reduced left ventricular output lead to a fall in right ventricular filling and thus small parallel conductance reduction (Figure 8A). Finally, use of a fixed parallel conductance would lessen apparent concave curvilinearity, not increase it. As shown schematically in Figure 8B, if parallel conductance is progressively reduced as end-systolic volume is lowered, an even steeper and more curvilinear ESPVR results.

**Choice of Nonlinear Model**

The quadratic nonlinear model was chosen because of its inherent simplicity, having a single nonlinear term whose value could be determined by linear least-squares procedures. For most ESPVRs, this model fits the data quite well. It appeared most useful for predicting the behavior in the low range of pressure-volume loading (Table 1). However, because the parabolic curve generally reached its vertex shortly above the highest end-systolic pressure-volume point of a given ESPVR (curving back down after this point), it would seem of little use in predicting systolic behavior at loads above the measured data.
FIGURE 8. Plots of influence of volume catheter parallel conductance ($V_p$) change during load reduction. Panel A: End-systolic pressure-volume relation (ESPVR) determined by left atrial hemorrhage (LAH) compared with transient inferior vena caval occlusion (IVCBO). IVCBO led to a short-term reduction in right ventricular volume; thus, there was a small initial fall in apparent volume unaccompanied by pressure change due to reduced $V_p$. This shifted the relation approximately 1 ml leftward of the LAH-ESPVR, and this shift was maintained until halfway down the load reduction range at which point the two relations converged. This likely represented the point at which LAH led to a similar right-sided fall in $V_p$ as produced on a short-term basis with IVCBO load reduction. Both ESPVRs, however, are quite similar and demonstrate the small impact of such $V_p$ shifts on the data. Panel B: Effect on curvilinearity data of using a diminishing rather than constant $V_p$ during load reduction. If a varying $V_p$ were used (rather than assuming $V_p$ constant as in the present study), the resulting ESPVRs would be even more, not less, curvilinear.

A clear drawback of the parabolic equation, however, is that it lacks any inherent theoretical basis. An alternative model was proposed recently \(^{22}\) based on a relation between myocardial stiffness and natural strain and chamber ESPVRs. By combining stiffness, several geometric variables, and empiric constants, a logarithmic equation was derived in the general form:

$$P_{es} = \frac{1}{\alpha + \beta V_{es}} \cdot \ln(V_{es}/V_0) \quad (4)$$

where $\alpha$ and $\beta$ combine myocardial stiffness, chamber geometry, and other empiric constants, and $V_0$ was the zero natural stress volume. This expression also fit the in situ ESPVR data of the present study very well (Figure 9). This expression has an advantage over Equation 2 because its variables have a theoretical basis and may provide a more “valid” estimate for $V_0$. However, both $\alpha$ and $\beta$ variables incorporate nonlinearity, making it more difficult to assess the contribution of either variable independently toward ESPVR shape change with contractile state. In addition, even by knowing $\alpha$, $\beta$, and $V_0$, it is not possible to derive myocardial stiffness without knowing the geometric and empiric constants.

Conclusions

We have demonstrated that the in situ left ventricular ESPVR displays contractility-dependent curvilinearity, much the same as the ESPVR in isolated canine ventricles, and the force and sarcomere length relations of papillary muscle. This curvilinearity is likely the principal cause of seemingly negative extrapolated $V_0$ values derived from linear fits of end-systolic pressure-volume data throughout normal but limited physiologic ranges and the cause of the shifts in $V_0$ often accompanying changes in inotropic state. Intrinsic nonlinearity may well contribute to Ees variability often seen between animal or human subjects and to differences in the response to inotropic agents. These data should emphasize the importance of presenting the actual pressure-volume data, rather than only reporting an “$E_{max}$” slope that may be derived from very few cardiac cycles throughout a limited load range. Despite potential nonlinearity, assessments of inotropic change can still be made by examining the relative position (left or rightward shift), shape, and local linear slope of in situ ESPVRs.

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KEY WORDS: ventricular function • pressure-volume relations • Frank-Starling relation • contractility • conductance (volume) catheter.
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