The end-systolic pressure-volume relationship in conscious dogs

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ABSTRACT The end-systolic pressure-volume relationship (ESPVR) has been shown to be an afterload-insensitive descriptor of ventricular inotropic state in the isolated heart. The purpose of this study was to examine the effects of changes in afterload, heart rate, intravascular volume, autonomic tone, and inotropic state on the ESPVR in conscious dogs. In 30 dogs, left ventricular and pleural pressures were measured with micromanometers, and left ventricular volume was assessed with global ultrasonic crystals. The ESPVR was obtained during vena caval occlusions in each dog during pharmacologic afterload interventions at control and after autonomic blockade. Analysis of variance techniques were used to compare the slopes (E_{max}) and intercepts (V_d) of ESPVR regression lines in a given study. All estimates of the ESPVR in conscious dogs involved large extrapolations to obtain estimates of V_d. Repeat determinations of E_{max} at control in the unblocked state were significantly different in six of eight dogs (p < .05). After autonomic blockade, these differences were significant in only one of eight dogs. Changes in heart rate and volume loading had minimal effects on the ESPVR. In the absence of autonomic blockade, increases in inotropic state with either calcium or dobutamine tended to cause parallel shifts in the ESPVR. After autonomic blockade, E_{max} increased with augmentation of inotropic state, while V_d was unchanged. ESPVRs obtained at different afterloads showed statistically significant differences in E_{max} and in V_d in 12 of 14 dogs. However, no statistically significant relationship of E_{max} to afterload was observed. Thus, the ESPVR is probably valid in conscious dogs, but measurement with an intact cardiovascular system is hampered by statistically significant variability in E_{max} and V_d with changes in afterload. Baseline variability is magnified by the autonomic nervous system, probably mediated through sympathetic reflexes.


THE END-SYSTOLIC pressure-volume relationship (ESPVR) as proposed originally by Suga and Sagawa has been shown to be insensitive to changes in afterload and sensitive to alterations in inotropic state in the isolated heart. Recently, a modification of this index using end-systolic length instead of volume has been used clinically as an index of ventricular inotropism. Further modifications using end-systolic stress, peak left ventricular systolic pressure, and the ratio of left ventricular stress to volume at end-systole have been used clinically. This relationship has been applied to pathologic conditions for characterization of inotropic state in patients with valvular heart disease, congestive heart failure, ischemia and recovery from cardiopulmonary bypass.

In general, these studies represent an extension of the ESPVR beyond experimental validation. Only one detailed experimental analysis of the ESPVR during ischemia has been performed in isolated hearts, and the results of that study did not correlate with the clinical data. Recent editorials have emphasized both the limitations of this index as a measure of inotropic state in humans and the differences between the relationship defined by Suga and Sagawa and those used clinically. A recent letter to the editor has characterized the artificial nature of the end-systolic stress-volume relationship reported in several clinical reports. In isolated heart preparations, some degree of global insufficiency is almost certainly imposed as a result of establish-
ing the preparation. In addition, the peripheral vasculature is modeled as a three-element Windkessel system, which may not accurately represent the vascular response characteristics of intact animals. Finally, the range of pressures and volumes over which data can be obtained in isolated hearts is much greater than in intact preparations. The amount of data available and the range over which the data are acquired also are different in isolated and intact situations.

Few studies of the ESPVR have been performed in conscious dogs, and existing reports either have been preliminary investigations or have focused on particular aspects of the measurement. Only one study has systematically examined the responses of the ESPVR to volume loading, afterload, and perturbations of inotropic state. The purpose of the present study was to evaluate the ESPVR in conscious dogs under a variety of hemodynamic conditions. The effects of autonomic blockade, heart rate, volume loading, and reproducibility of measurements were investigated. Alterations in afterload were examined, along with influences of inotropic interventions, in both autonomically blocked and unblocked states. Finally, the importance of the range of data was evaluated, and the statistical problems involved with the use of the ESPVR were assessed.

Methods

Experimental preparation. The details of the experimental preparation have been presented elsewhere. Briefly, 30 healthy adult mongrel dogs (weight 18.5 to 27 kg) received sterile implantations for subsequent study (figure 1). Each dog was anesthetized with intravenous thiamylal sodium (25 mg/kg) and ventilated with an MA-1 respirator (Puritan-Bennett, Los Angeles). A thoracotomy was performed through the left fifth intercostal space of each dog, and hemispheric pulse transit ultrasonic dimension transducers were positioned across the minor- and major-axis diameters of the left ventricle. Silicone rubber pneumatic occluders were placed around the vena cavae, and a silicone rubber tube (2.5 mm inside diameter) was implanted in the posterior left atrium. A bipolar pacing electrode was sutured to the left atrial appendage, and a second silicone rubber tube with multiple side holes was sutured to the superior mediastinum at the midventricular level. The pericardium was left widely open, and all tubing, transducer leads, and electrode wires were placed in a subcutaneous pouch as the thoracotomy was repaired in layers. At least 7 days were allowed before data acquisition, and on the day before study, the subcutaneous pouch was anesthetized with lidocaine, opened with a small incision, and the hardware was exteriorized.

Data acquisition. On the day after exteriorization, each dog was sedated with morphine sulfate (10 to 15 mg intramuscularly) and studied in the conscious state. The dimension transducers were coupled directly to a sonomicrometer designed in our laboratory. Micromanometers (PC-350, Millar Instruments) were passed into the left ventricle through the implanted left atrial introducer and into the thoracic cavity through the pleural introducer. All manometers were prewarmed in a constant-temperature bath (38°C) and electrically excited by pressure amplifiers (Model 8805-C, Hewlett-Packard) for 24 hr before each study. Each manometer was balanced and calibrated against a water column just before passage into the dog. All pressure calibrations were repeated at the conclusion of each study, and data were not accepted unless the drift was less than 1.0 mm Hg throughout the study. The cardiac dimension and pressure data were filtered once with a 50 Hz analog filter and digitized at 200 Hz with use of an interactive computer program run on a digital computer (LSI 11/23, Digital Equipment Corporation).

The progress of each experiment was monitored in several ways. A paper strip-chart recorder ran at a slow speed throughout the experiment to assess trends in pressures and dimensions over time and to establish when the values had returned to the control level after each intervention. Individual pressure and dimension waveforms were monitored on a storage oscilloscope, allowing precise assessment of dimension transducer tracking and the pressure waveforms. Spontaneous sinus heart rate was monitored as an index of autonomic tone, and a continuous evaluation of heart rate was provided by the computer program. When data were digitized for later analysis, video- graphic plots of pressure–minor axis diameter loops were displayed.

Experimental protocols. Four protocols were used in the study. Throughout each protocol, preload was varied by transient vena caval occlusions that lasted approximately 20 sec each. The first protocol was designed to test the reproducibility of measurements of ESPVR over time and also to evaluate the effects of autonomic blockade; nine dogs were used for this protocol. After sedation with morphine, the dogs underwent multiple repeat measurements of ESPVR in the control, unblocked state. Repeat measurements of ESPVR then were made after establishing autonomic blockade with intravenous propranolol (1 mg/kg) and atropine (0.01 mg/kg). Additional doses of atropine were administered as necessary to maintain heart rate within ±10% of the unblocked control value. The second
protocol involved examining the effects of changes in heart rate on ESPVR. After establishing sympathetic blockade with intravenous propranolol (1 mg/kg), five dogs underwent atrial pacing at rates of 100, 120, 140, and 160 beats/min. Vena caval occlusions were performed at each of these heart rates to measure ESPVR, and the results were compared. Sympathetic blockade alone was used in this protocol to minimize changes in heart rate during vena caval occlusion as compared with the unblocked state.

In the third protocol, the effects of changes in afterload on the ESPVR were investigated. Fourteen dogs underwent autonomic blockade with intravenous propranolol (1 mg/kg) and atropine (0.01 mg/kg). Afterload was varied by continuous infusion of either phenylephrine (0.1 to 1.0 μg/kg/min) or sodium nitroprusside (10 to 20 μg/kg/min). Vena caval occlusions were obtained at control, at increasing levels of systolic arterial pressure, again at control, and then at decreasing levels of systolic pressure. The order of phenylephrine and nitroprusside administration was randomized for each study. Only beats from each vena caval occlusion in which heart rate varied by less than 10% from steady-state values before occlusion were used. The coefficients of ESPVR regressions at each afterload were compared as described in subsequent sections. The data from all of the variably afterloaded determinations then were pooled, and comparisons were made between the pooled determinations of ESPVR and the individual determinations.

The effects of blood volume expansion and inotropic interventions were studied in the fourth protocol. Eight dogs underwent volume loading with 500 ml of lactated Ringer’s solution, and inotropic state was varied with an intravenous infusion of either phenylephrine (0.1 to 1.0 μg/kg/min) or sodium nitroprusside. Vena caval occlusions were obtained at control, at increasing levels of systolic arterial pressure, again at control, and then at decreasing levels of systolic pressure. The order of phenylephrine and nitroprusside administration was randomized for each study. Only beats from each vena caval occlusion in which heart rate varied by less than 10% from steady-state values before occlusion were used. The coefficients of ESPVR regressions at each afterload were compared as described in subsequent sections. The data from all of the variably afterloaded determinations then were pooled, and comparisons were made between the pooled determinations of ESPVR and the individual determinations.

Data analysis. From each study, segments of digitized data were selected during each intervention and analyzed. Transmural left ventricular pressure was calculated as the difference between left ventricular intracavitary volume and pleural pressure. The first derivative of left ventricular transmural pressure was calculated as a running five-point, polygonal orthogonal transformation of the digitized left ventricular pressure waveform. End-systole was defined as the point of maximal elastance calculated as the ratio of instantaneous left ventricular transmural pressure to instantaneous left ventricular volume. End-diastole was defined as the point just before the beginning of the systolic upstroke of left ventricular transmural pressure. Ejection was defined as that portion of the cardiac cycle between peak positive and peak negative dP/dt. 29

The left ventricle was modeled as a prolate spheroid. The anterior-posterior and septal–free wall equatorial diameters were assumed to deform similarly under the conditions examined in this study, 30 and were assessed by the epicardial anterior-posterior minor-axis diameter. The major diameter was measured as the epicardial base-apex diameter. 31 At the conclusion of each study, the heart was excised, and the right ventricle, atria, and valvular apparatus were removed. Left ventricular myocardial volume was determined by displacement of saline in a graduated cylinder, and left ventricular cavity volume was computed subsequently as the difference between the calculated epicardial volume and left ventricular myocardial volume. Stroke volume was calculated as the difference between left ventricular intracavitary volume at end-diastole and at peak elastance. Mean ejection pressure, computed as the mean of all left ventricular transmural pressure points during ejection, was used as the index of arterial afterload.

The ESPVR as originally defined by Suga and Sagawa 1, 2 was

\[ E(t) = P(t)/[V(t) - V_d] \]

where \( E(t) \) is a function of time, and \( V_d \) is an empirically determined correction factor. The point of maximal elastance, \( E_{\text{max}} \), was defined as the instantaneous pressure-to-volume ratio at a specified time \( t \) when the ratio was maximal. More recently this relationship has been expressed as

\[ P_{\text{ES}} = E_{\text{ES}}(V_{\text{ES}} - V_d) \]

where \( P_{\text{ES}} \) is the slope of the ESPVR. \( V_d \) is the corresponding value at end-systole and was so termed because at this volume the isolated ventricle cannot generate any pressure.

The ESPVR was defined by a linear regression performed on the pressure and volume points occurring at peak elastance during each beat of a vena caval occlusion. The slope of this regression line was termed \( E_{\text{max}} \), and the intercept of the regression line with the volume axis was termed \( V_d \). The regression was done using end-systolic pressure as the independent variable and end-systolic volume as the dependent variable because of statistical considerations (appendix 1).

In previous studies of the isolated heart, the time to peak elastance was by definition constant for all beats examined, but this was not the case in the present method of determination. The time to instantaneous peak elastance averaged 40 msec before peak negative dP/dt, but this time interval did vary to a slight degree so that the interval tended to increase at lower afterloads. Nevertheless, this technique of determining \( E_{\text{max}} \) is most feasible with current methods and probably is a close approximation of that used in the isolated heart. One study has demonstrated that correlation of peak ejection or end-ejection pressure with end-ejection volume provided an accurate estimate of the ESPVR, 32 but another comparative study 33 showed that the calculation of peak elastance was the most accurate method. The old terminology of Suga and Sagawa was used to define the volume axis intercept of the ESPVR as \( V_d \) because \( V_d \) has been used to describe the unstressed volume of the ventricle at end vena caval occlusion in previous publications from our group. 29

Comparisons of the slopes of individual estimates of \( E_{\text{max}} \) were performed with an analysis of covariance. 34, 35 Comparisons of groups of regression slopes and intercepts were accomplished with the method of contrast matrices in a general linear statistical model (appendix 2). The majority of the statistical analyses were done with the use of commercially available software 36 at the Triangle Universities Computation Center. The power of statistical tests was estimated with the use of standard tables. 37 Other tests of group means were made with the Wilcoxon test, Student’s t test, or an analysis of variance design, as appropriate.

Results

Typical recordings of digitized raw data obtained during the control state and during nitroprusside and phenylephrine infusions are shown in figure 2. Shortening in each of the two diameters was maximal at low afterloads and progressively decreased with higher afterloads. The effects of each intervention on mean left ventricular ejection pressure can be appreciated on the transmural pressure waveform. With nitroprusside,
left ventricular transmural pressure diminished rapidly at end-ejection due to the lower arterial resistance. The elastance waveform with nitroprusside was seen to be more rounded, with the point of peak elastance occurring relatively early in systole. With the infusion of nitroprusside, left ventricular pressure decreased progressively during ejection, whereas during afterload augmentation, left ventricular pressure was maintained nearly constant or even increased throughout ejection. Representative pressure-volume loops at each of the three afterload conditions are shown in figure 3 with ESPVR lines superimposed. The mean correlation coefficient for any given ESPVR determination averaged .94, and an average of 15 beats was used for each determination of ESPVR.

**Steady-state variability and autonomic blockade.** Data from the autonomic blockade protocol are shown in table 1, and a representative illustration of raw data from one dog together with superimposed regression lines are depicted in figure 4. In the unblocked state, a moderate scatter of ESPVR measurements was observed, even when they were obtained in the same dog over a relatively short period of time. The overall mean $E_{\text{max}}$ in the unblocked state was 6.7 mm Hg/ml, with a range of $E_{\text{max}}$ estimates from 15.5 to 2.8 mm Hg/ml. The mean range of $E_{\text{max}}$ estimates within a given dog was 4.9 mm Hg/ml and represented a variability of 73% as compared with the overall $E_{\text{max}}$ value of 6.7 mm Hg/ml. The mean correlation of multiple ESPVRs in a given dog in the unblocked state was .90. The mean $E_{\text{max}}$ after autonomic blockade was 5.1 mm Hg/ml and was not significantly different from the unblocked value. With autonomic blockade, however, the amount of scatter in $E_{\text{max}}$ was less, with an average range of 1.8 mm Hg/ml. This variability of 35% as compared with the overall mean of 5.1 mm Hg/ml was statistically significantly decreased from that in the unblocked state ($p < .05$). After blockade, the estimate of any individual ESPVR was improved since the mean correlation coefficient increased to .95; this increase also was statistically significant as compared with unblocked determinations ($p < .05$). Equality of $E_{\text{max}}$ estimates was tested with an analysis of covariance. This analysis showed statistically significant differences in the slope of the ESPVR in six of nine dogs before blockade, but in only two of nine dogs after blockade. Differences in heart rate, $E_{\text{max}}$, $V_d$, and the range of end-systolic pressures and end-systolic volumes achieved were not significant after blockade. Although the range of $V_d$ estimates was decreased after
blockade, this difference was not significant due to the large amount of variability present.

**Effects on heart rate.** In the second part of this study, the effects of heart rate on $E_{\text{max}}$ were compared during autonomic blockade (table 2). The relationship between heart rate and $E_{\text{max}}$ was evaluated with a two-way analysis of variance and was highly significant ($p < .001$). The overall estimate of the slope of this relationship based on values from seven dogs was 0.04 mm Hg/min/ml. This finding indicates that $E_{\text{max}}$ increased by an average of 2.4 mm Hg/ml for an increase in heart rate from 100 to 160 min$^{-1}$. A similar analysis for $V_d$

**TABLE 1**
Results of repeated vena caval occlusions (VCOs) and autonomic blockade

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>No. of VCOs</th>
<th>Blockade</th>
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<th>Range $E_{\text{max}}$ (mm Hg/ml)</th>
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<th>Mean $V_d$ (ml)</th>
<th>Range $V_d$ (ml)</th>
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- $t$ test: $-0.92$, $p = .03$
- $t$ test: $-0.92$, $p = .03$

No automatic blockade is indicated by Un, whereas autonomic blockade is indicated by Bl. Mean $E_{\text{max}}$ is the mean of each of the individual estimates of $E_{\text{max}}$, $p$ equal $E_{\text{max}}$ is the result of the covariance analysis for equality of $E_{\text{max}}$ determinations. Similar results for $V_d$ and the mean correlation coefficient also are given.
as a function of heart rate showed no significant differences, again due to the large variability in individual $V_d$ determinations.

**Effects of changes in afterload.** In the third part of this study, the effects of changes in afterload on the ESPVR were assessed (table 3). The dogs were subjected to autonomic blockade, and heart rate varied by less than 10% from steady state. The mean extremes of end-systolic pressures achieved throughout each study were from 188 to 69 mm Hg (range 119), and the mean range of end-systolic volumes was 26.7 ml. The mean individual $E_{\text{max}}$ was 4.3 mm Hg/ml, with a mean range of 5.9 to 3.0 mm Hg/ml. If the 95% confidence interval estimates for $E_{\text{max}}$ determination were used, the

![Figure 4](http://circ.ahajournals.org/)

**FIGURE 4.** Representative raw data from dogs in the unblocked state and during autonomic blockade. Raw data points are shown in the upper panels and the individual ESPVR regression lines are illustrated in the lower panels.

<table>
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<th>Dog No.</th>
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<th>120 (min⁻¹)</th>
<th>140 (min⁻¹)</th>
<th>160 (min⁻¹)</th>
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**TABLE 2**  
Influence of heart rate of $E_{\text{max}}$ and $V_d$

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Means indicated by equal numbers of asterisks are not significantly different. All other means are significantly different at $p < 0.05$. 

**TABLE 2**  
Influence of heart rate of $E_{\text{max}}$ and $V_d$
range increased to 7.1 to 2.4 mm Hg/ml. The mean individual $V_d$ was 2.2 ml and ranged from a mean maximum of 11.8 to a mean minimum of $-13.2$ ml. The representative 95% confidence limit values were 19.0 to $-22.6$ ml.

A general linear model was used to test equality of $E_{\text{max}}$ estimates at different afterloads in a given dog (appendix 2). This analysis showed that the $E_{\text{max}}$ estimates were significantly different in 12 of 14 dogs. $V_d$ estimates, when compared with linear contrasts in the two dogs without significant differences in $E_{\text{max}}$ values, were different in one of the two cases. In figure 5, A, the $E_{\text{max}}$ estimates for each afterload in each dog were plotted as percent control against steady-state mean ejection pressure. Only seven dots are shown on the horizontal control line because of overlap. If $E_{\text{max}}$ was afterload insensitive and could be accurately measured, then all $E_{\text{max}}$ values would cluster near the horizontal control line. Most points were clustered near the line, but a large amount of variability was noted over the entire range of mean ejection pressures. The relationship of $E_{\text{max}}$ to steady-state mean ejection pressure was tested in each dog by analysis of covariance. The overall slope of this relationship based on the 14 dogs was 0.0003. This test has a power of slightly more than 0.9 to detect a change in $E_{\text{max}}$ of 1 mm Hg/ml over a pressure range of 100 mm Hg. No significant relationship between $E_{\text{max}}$ and steady-state mean ejection pressure was demonstrated.

In a similar analysis for $V_d$ (figure 5, B), the range of variability was much greater than that for $E_{\text{max}}$. When the slope of the lines relating $V_d$ to mean ejection pressure for each dog were compared, the overall estimate of the slope of this relationship was $-0.011$. This line also was not statistically significantly different from zero. This test has a power of 0.9 to detect a change in $V_d$ of 7 ml over a pressure range of 100 mm Hg in steady-state mean ejection pressure.

In figure 6, A, are shown the pooled data from a complete afterload study in a representative dog. The pooled data form a linear relationship with a correlation coefficient of 0.93, which might be said to be an estimate of the ESPVR; however, when the individual regression lines for each vena caval occlusion are superimposed (figure 6, B), the large variability in these individual estimates becomes readily apparent. Figure 6, C, illustrates the tendency for $E_{\text{max}}$ to remain relatively constant but for $V_d$ to shift with changes in afterload. A representative ESPVR for phenylephrine was approximately parallel to, but above, that of control while the opposite effect, usually of smaller degree, was seen after nitroprusside. In figure 6, D, the individual regression lines from figure 6, C, are shown, but the regression line for the pooled data is superimposed. The $E_{\text{max}}$ for the pooled data was greater than that for any given individual determination of $E_{\text{max}}$; this type of effect was seen to varying degrees in

### Table 3

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<th>Dog No.</th>
<th>Vd Mean (ml)</th>
<th>Vd Max (ml)</th>
<th>Vd Min (ml)</th>
<th>Range (ml)</th>
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ESP = end-systolic pressure; ESV = end-systolic volume; ind $r$ = mean correlation coefficient for each individual regression; others are as in table 1.

Pooled values are those obtained when one regression was run on the combined afterload data for each dog treated as a single group.

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LABORATORY INVESTIGATION—VENTRICULAR PERFORMANCE
12 of the 14 dogs studied. Thus, although the pooled data form a linear relationship in any given dog, the 
$E_{max}$ and $V_d$ of this relationship usually differed from those seen with individual measurements of the 
ESPVR.

The effect of each pharmacologic intervention on $E_{max}$ and $V_d$ was tested with an analysis of variance 
design with the use of drug, dog, and drug-dog interaction terms as independent effects. No significant effect 
of drug on either $E_{max}$ ($p = .90$) or $V_d$ ($p = .69$) was seen. This was due to the large variability of these 
variables within a given dog and between dogs. No overall effect was seen on heart rate ($p = .73$), but a 
marked effect was seen on mean ejection pressure ($p = .0003$).

**Statistical considerations.** The statistical problem of estimating ESPVR from data from one vena caval occlusion as compared with the pooled data is shown in figure 7. Panel A shows the 95% confidence intervals for the mean from an individual vena caval occlusion and panel B shows the same intervals for the pooled data. The pooled data provide a statistically better estimate of $E_{max}$ and hence $V_d$ because of the much wider range of points as compared with a single vena caval occlusion. The mean range of end-systolic pressure change with a single vena caval occlusion was 37.8 mm Hg and the mean change in end-systolic volume was 9.8 ml. The ranges for the pooled data were much larger and averaged 120.1 mm Hg for end-systolic pressure and 24.2 ml for end-systolic volume. For an individual vena caval occlusion, estimation of the volume intercept necessitates an extrapolation averaging 3.2 times the range of existing volume data while the extrapolation outside the pressure range is 3.3-fold. The mean 95% confidence interval for the pooled $E_{max}$ was 0.5 mm Hg/ml and that for $V_d$ was 1.6 ml. The corresponding values for individual determinations were 2.3 mm Hg/ml for $E_{max}$ and 20.8 ml for $V_d$. This represented a fivefold loss in the accuracy of the estimate of $E_{max}$ and a 13-fold loss in the accuracy of the estimate of $V_d$ when individual vena caval occlusions were used.

**Effects of volume loading and changes in inotropic state.** The effects of volume loading and autonomic blockade on changes in inotropic state were investigated next. Summary data are shown in tables 4A and 4B. The mean value of $E_{max}$ at control in the unblocked state was 4.2 mm Hg/ml and changed insignificantly to 4.4 mm Hg/ml after volume loading with 500 ml of crystalloid intravenously. The corresponding changes in $V_d$ were 7.7 ml to 9.8 ml (NS). In the unblocked state, $E_{max}$ increased to 10.1 mm Hg/ml with dobutamine.

![Figure 5](http://circ.ahajournals.org/)

**FIGURE 5.** Individual estimates of $E_{max}$ and $V_d$ as percent control are represented as a function of afterload. Control points are illustrated as solid circles, while those obtained during sodium nitroprusside and phenylephrine are hollow squares and triangles, respectively.
FIGURE 6. Pooled afterload data from one dog. The individual data points are shown in (A) along with the individual estimates of the ESPVR for each vena caval occlusion (B). C, A representative ESPVR after phentylephrine together with estimates for control and postnitroprusside ESPVR. D, The same individual estimates as in C, together with an estimate of the ESPVR run on the pooled data (dark line).

FIGURE 7. Individual end-systolic pressure-volume points are illustrated together with the ESPVR determined by linear regression and the ±95% confidence intervals for an individual observation. A, Data points from one vena caval occlusion at control. B, The pooled data points from all vena caval occlusions comprising a complete afterload study in one dog. The end-systolic pressure and volume ranges for this dog were 167 mm Hg and 46.8 ml, respectively.
infusion and 7.9 mm Hg/ml with an intravenous calcium bolus. Each of these values was statistically significantly different as compared with control (p < .05). Significant increases in Vd also were observed with calcium and dobutamine infusions (figure 8, A) in the unblocked state (p < .05). After autonomic blockade, however, significant changes were seen in Emax but not in Vd with the same interventions (figure 8, B). Thus, the ESPVR tended to undergo a shift in the intercept as well as the slope with augmentation of inotropic state in the absence of autonomic blockade. After blockade, Emax increased with augmentation of inotropic state while Vd was relatively unaffected. With the infusion of nifedipine in the autonomically blocked state, both Emax and Vd decreased significantly. The mean ESPVR for each intervention in the blocked state is shown in figure 9.

Discussion

Since the ESPVR has come into more widespread use, many reports of the use of modifications of the actual relationship as defined by Suga and Sagawa and of the use of approximations to the original measurement techniques have appeared. Before the validity of these studies can be estimated, a detailed examination of the ESPVR in the intact heart, and an assessment of the measurement ranges required for the application of this relationship to the intact cardiovascular system was needed. For this purpose, the instrumented conscious dog preparation was employed along with analytic techniques that have been shown to be precise and reproducible. The pressure determinations in this study were highly accurate, and errors in volume calculation (modeling the left ventricle as a prolate spheroid) probably were not more than a few percent.26 This method has been extensively validated against balloon volumes38, 39 and against volume calculated with a third pair of crystals in the septal–free wall axis throughout the physiologic range, and has been found to be accurate for the purposes of this study. Since myocardial transmural pressure affects diastolic loading in closed-chest preparations, it was included in this analysis.

### TABLE 4A

Results of inotropic interventions in autonomically unblocked dogs

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<th>Dog No.</th>
<th>Control Emax (mm Hg/ml)</th>
<th>Dobutamine Emax (mm Hg/ml)</th>
<th>Calcium Emax (mm Hg/ml)</th>
<th>Vol. load Emax (mm Hg/ml)</th>
<th>Control Vd (ml)</th>
<th>Dobutamine Vd (ml)</th>
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^p < .05 vs control by paired Student’s t test.

### TABLE 4B

Results of inotropic interventions in autonomically blocked dogs

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^p < .05 vs control by Student’s t test.
The first protocol investigated the reproducibility of successive determinations of E\textsubscript{max} in the same preparation. As shown in table 1, repeated measures of E\textsubscript{max} in unblocked dogs varied by an average of 73% as compared with control values. After autonomic blockade, this variability decreased significantly but still averaged 35%. The variability seemed to arise because of the limited range of pressure and volume measurements available. This problem seemed to be an intrinsic characteristic of the intact circulation, and it is difficult to imagine how reproducibility could be improved. The relationship of V\textsubscript{A} to E\textsubscript{max} certainly was important, but errors in estimation of V\textsubscript{A} were much larger than those for E\textsubscript{max}. These problems may prove to be permanent limitations to the application of the ESPVR in the intact circulation.

The effects of heart rate on the ESPVR were investigated next. As shown in table 2, a slight increase in E\textsubscript{max} was observed with relatively large increases in heart rate. Based on these data, the ESPVR seems to be affected minimally by changes in heart rate, and differences in contraction frequency should not interfere significantly with determination of ESPVR over the physiologic range of rates. This conclusion has been substantiated by other studies\textsuperscript{23} in conscious dogs and isolated hearts.\textsuperscript{40} This rate independence, however, is somewhat paradoxical, since heart rate has been shown in several studies to influence inotropic state significantly.\textsuperscript{20, 41, 42}

The ESPVR has been found to be afterload insensitive in the isolated heart over the physiologic range of simulated arterial pressures in the study of Suga and Sagawa.\textsuperscript{7} Of nine dogs studied in their series, a mean range in E\textsubscript{max} of 1.1 mm Hg/ml was observed as compared with an overall mean value of 6.7 mm Hg/ml, resulting in a variability of 17%. This variability was seen with a mean pressure range of 80 mm Hg. The situation in the intact animal, however, appeared to be somewhat different. A variability in E\textsubscript{max} of twice this
degree was observed, even though a significant dependence of $E_{max}$ on afterload was not demonstrated. The marked variability in $V_d$ also detected with changes in afterload was due partly to the variability in $E_{max}$ but was compounded by the large extrapolation distances. There was a tendency, although not a statistically significant one, for $V_d$ to increase with augmentation of afterload. A possible explanation is that the afterload impedance of the peripheral vasculature continued to increase during infusion of phenylephrine, despite stable but elevated mean ejection pressure. Changes in $V_d$ have been shown in isolated hearts with changes in characteristic impedance. Another explanation is that our current understanding of ventricular-arterial interaction is inadequate and that differences exist between observations in the isolated heart and the conscious dog. A third but unlikely possibility is that the heart underwent creep or stress relaxation with increases in afterload. ESPVR determinations made during the same inotropic state would then be seen as parallel shifts, or changes in $V_d$ with the same $E_{max}$. 

In the final portion of this study, the effects of changes in inotropic state on the ESPVR were investigated as a function of autonomic blockade. With autonomic reflexes intact, the responses to inotropic interventions were highly variable; however, after blockade, the results more closely approximated those reported from isolated heart studies in that $E_{max}$ significantly increased but $V_d$ was unchanged with augmentation of inotropic state. This sensitivity of the ESPVR to autonomic tone is another factor that may limit its applicability to intact cardiovascular systems. The degree of autonomic tone can vary markedly in clinical as well as experimental settings. Sufficient autonomic attenuation may not be obtainable in many clinical situations, such as in patients with borderline myocardial function.

The statistical problems associated with the estimation of ESPVR have been largely ignored in previous studies. Assuming that a measure of inotropic state exists in a given animal or patient, it would be necessary to perform measurements to determine ESPVR. The index being measured may be a good approximation over a certain range but may deviate at the extremes, or it may consistently over- or underestimate the true inotropic state. This systematic error and the limits of sensitivity for repeated measurements or to small, essentially random, changes in inotropic state must be known. Assuming that an ideal index exists and that its reproducibility is suitable, it remains to be estimated. Measurements must be obtained and as-

sumptions about cardiac geometry must be made, both of which are subject to random and systematic error. The amount of data used for a measurement of this index and the range over which these data are obtained are final considerations. If data are collected over a narrow range, even small differences in the actual measurements could lead to large differences in the estimate of the index. With a large range of data, a given index can be estimated reproducibly despite variation in the individual measurements. This later problem is the one that is most obvious in the estimation of ESPVR in conscious animals (appendix 1). In isolated hearts, the end-systolic pressure can be varied from the steady-state value, which is essentially normal, to zero. In intact dogs, the range over which pressure can be varied is a function of the steady-state pressure and decreases with decreasing end-systolic pressure. The average range is 40 mm Hg. In clinical studies this range is usually smaller and has been reported to be as small as 10 mm Hg. Even though $E_{max}$ can be estimated from any range of data, the statistical accuracy of the estimate varies directly with the range over which data exist. Estimates of $E_{max}$ in isolated hearts are therefore more accurate because of this factor. The problem of reproducibly estimating $V_d$ is even more evident. In isolated hearts, an extrapolation of only a few percent is all that is typically necessary to estimate $V_d$, but in conscious dogs, an extrapolation averaging three times the range of existing data is required. Some statistical considerations of linear extrapolation are outlined in appendix 1.

Many important methodologic differences exist between the isolated heart preparation and the intact animal. In most isolated heart preparations, the dogs are anesthetized with barbiturate derivatives that are known to have a depressant effect on myocardial function. While the preparation is being established, the heart frequently undergoes a period of global ischemia that might alter myocardial properties. Although the isolated heart is physically separated from the donor dog, it should not be considered autonically inert. Catecholamines freely circulate from the support dog to the isolated heart and can modify the contractile state. The amount of catecholamine circulating is probably closely related to the depth of sedation of the support dog.

In conscious dog preparations, phenylephrine is known to have some $\beta_1$-adrenergic effect that could independently influence contractility in the third protocol. If this were occurring, however, one might expect a change in $E_{max}$, but no statistically significant alteration as a result of the infusion of phenylephrine
was detected. In addition, direct inotropic effects of this drug probably are minimal during autonomic blockade.\textsuperscript{29} Coronary artery pressure is fixed in most isolated heart preparations, but in intact animals it is a function of the mean aortic pressure, especially at lower pressures. While coronary blood flow in both preparations should be relatively independent of perfusion pressure because of intact vasomotor regulation, it is possible that minor functional differences occur because of disparate coronary perfusion characteristics. Finally, the peripheral vasculature in the isolated heart is modelled as an electrical circuit. Although extensive validation of this analog has been performed,\textsuperscript{20} it may not provide an accurate model of the intact cardiovascular system in all instances.\textsuperscript{49, 50} In particular, the minimum pressure of the vasculature with zero stroke volume, $P_{\text{min}}$, is assumed to be zero in the three-element Windkessel model regardless of afterload. Data from this study in conscious dogs suggest that $P_{\text{min}}$ has a quite significant magnitude in the intact circulation, seems to be somewhat determined by steady-state pressure, and decays to zero only over prolonged periods of time. For example, the mean end-vena caval occlusion end-systolic pressure for the dogs used in the afterload protocol was 69 mm Hg.

All determinations of the ESPVR were done by varying the preload with vena caval occlusions. This technique has been shown to give the same results as steady-state reductions in preload and is therefore valid in intact animals.\textsuperscript{51} Others have reported measuring the ESPVR with bolus infusions of phenylephrine.\textsuperscript{7, 8, 10, 21} This technique was attempted in several animals but was found to be extremely unproductive. The variability of repeated ESPVR measurements was much greater than that seen with repeated vena caval occlusions, the animals became tachyphylactic to multiple injections, and the method was further limited by the fact that good ESPVR measurements could not be made at different steady-state afterloads.

Mean ejection pressure was used as a measure of afterload in this study rather than peripheral vascular resistance or arterial impedance. Although this approximation is not strictly correct, it does provide a useful estimate of directional changes in impedance variables. Determination of vascular impedance in an intact organism involves making simultaneous pressure and flow measurements at the aortic root, a procedure that is difficult in either conscious animals or man. In addition, the mathematic analysis of impedance spectra is generally not reducible in a form useful for the assessment of ventricular function,\textsuperscript{52} so that readily measurable variables of ventricular pressures and dimensions were examined in this study to minimize the number of modeling assumptions.

Existing clinical studies represent important attempts at application of the ESPVR, but considerably more experimental validation needs to be done, particularly in pathologic states, before this index can be considered as a useful indicator of inotropic state in man. Heart rate and afterload sensitivity of the ESPVR have not been investigated in humans, the conclusions from clinical studies of ischemic heart disease are at odds with existing experimental data, and no information exists validating use of the ESPVR in heart failure or in the setting of valvular heart disease. Changes in $V_d$ are largely ignored even though they should be considered to be as important as changes in $E_{\text{max}}$.\textsuperscript{3} In addition, the ESPVR has the theoretical limitation of being dependent on myocardial size. Since end-systolic pressure remains relatively constant, changes in left ventricular size will affect the absolute value of the ESPVR. Therefore, one must conclude that application of the ESPVR to studies of patients with heart disease is premature at the present time.

In summary, the ESPVR is probably a valid measurement of inotropic state in intact animals, but it is difficult to measure accurately and must be interpreted with caution. Although the isolated heart has proven to be an extremely useful method of investigating cardiac function, results obtained in isolated hearts do not readily translate to the intact animal. Repeated measurements of $E_{\text{max}}$ in the intact circulation vary significantly, and measures of $V_d$ are even less reproducible. No significant dependence of $E_{\text{max}}$ on changes in afterload is evident, but a large random variability in the ESPVR is consistently observed. The effects of changes in inotropic state seem to be modified to some extent by autonomic tone, and finally, an inordinately wide range of absolute $E_{\text{max}}$ values is observed even in healthy autonomically blocked dogs. Thus, the ESPVR has limited utility in the intact circulation unless the problems of autonomic tone, range of values, statistical extrapolation, and reproducibility are carefully identified and controlled.

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Appendix 1

Most estimates of the ESPVR in vivo involve relatively small amounts of data and large extrapolation distances. Statistical considerations become important in this setting. The ESPVR is...
customarily displayed with end-systolic pressure (ESP) on the ordinate and end-systolic volume (ESV) on the abscissa. The slope of this relationship, $E_{\text{max}}$, is expressed as

$$\frac{\Delta \text{ESP}}{\Delta \text{ESV}}$$

The intercept, $V_0$, is defined by the intersection of the ESPVR with the abscissa. Regression analyses usually are illustrated with the dependent variable on the ordinate and the independent variable on the abscissa. The independent variable is assumed to be known without error. In practice, this can never be known. Therefore assumed to be accurate. In the case of the ESPVR, as customarily applied, the ESV measurements are therefore assumed to be known more accurately than is ESP. This is usually not the case in intact subjects. The left ventricular pressure can be measured accurately with micromanometers, but left ventricular volume measurements rely on geometric modeling assumptions as well as the errors introduced by the actual dimension or volume measurement techniques.

The regression was performed with ESP as the independent variable since it is known more accurately. Our model was then:

$$\hat{X} = \bar{X} + \bar{b}_{x,y} (Y - \bar{Y})$$  \hspace{1cm}  \text{For } Y = 0, V_{d_{x,y}} = \bar{X} - \bar{b}_{x,y} \bar{Y}$$

The 95% confidence interval for an estimate of $V_{d_{x,y}}$ is:

$$\pm t_{0.05} \frac{s_{x,y}}{\sqrt{1 + \frac{(\bar{Y} - \bar{Y})^2}{\Sigma(Y - \bar{Y})^2}}}$$

On the other hand, the regression is usually done with ESP on ESV. To determine $V_0$, the regression line was used to predict $X(ESV)$ from $Y(ESP)$, even though it was constructed in the opposite manner. In this instance, the confidence interval for an estimate of $V_0$ is larger. This model was:

$$\hat{Y} = \bar{Y} + \bar{b}_{y,x} (X - \bar{X})$$  \hspace{1cm}  \text{For } \hat{Y} = 0, V_{d_{y,x}} = \bar{X} - \bar{Y}$$

The 95% confidence interval for an estimate of $V_{d_{y,x}}$ was then:

$$\pm t_{0.05} \frac{s_{Y,X}}{\sqrt{\left(1 + \frac{n - 2}{n} - \frac{\bar{Y}^2}{\Sigma(Y - \bar{Y})^2}\right)}}$$

The confidence interval for $V_{d_{x,y}}$ is larger than that for $V_{d_{y,x}}$. A similar conclusion can be drawn for the confidence intervals of $E_{\text{max},x,y}$ and $E_{\text{max},y,x}$. Thus, what are usually thought to be the confidence intervals for the slope and intercept of the ESPVR are actually smaller than the true values.

When the regression is performed as $X$ on $Y$ and $0 < r < 1$, both $V_{d_{x,y}}$ and $E_{\text{max},x,y}$ are larger than when the regression is performed in the opposite manner. The magnitude of this increase depends on the variance of $X$ and $Y$ as well as the correlation coefficient $r$.

**Appendix 2**

Comparisons of slopes and intercepts of individual vena caval occlusions with control were made in each dog by use of a statistical general linear model. ESV was the dependent variable and ESP was the independent variable, while individual vena caval occlusions appeared as separate terms. The model was as follows, where $P$ was ESP, and $F_i$ was vena caval occlusion $i$ being compared to a steady-state control vena caval occlusion C:

$$\text{ESV} = \beta_0 + \beta_1 P + \beta_2 F_1 + \beta_3 F_2 + \cdots + \beta_{1+r} F_i + \beta_{1+r+1} P F_i + \beta_{1+r+2} P F_1 + \cdots + \beta_{2+r+1} P F_{i-1}$$

Slopes and intercepts of individual $F_i$ were compared with $C$ by testing the estimates of $\beta$ as being significantly different from zero. A significant difference in $\beta_{1+r} - \beta_{2+r}$ showed that the slope of vena caval occlusion $F_i$ was different from control. A separate test allowed the comparison of all of the $F_i$ to control. If this test was not significant, then the slopes were said to be parallel, and the intercepts could be compared. A significant difference in $\beta_1 - \beta_{1+1}$ showed that the intercept of vena caval occlusion $F_i$ was different from control, given that the slopes were parallel.

Comparisons of groups of vena caval occlusions (e.g., all vena caval occlusions induced during infusion of nitroprusside) with control were done with contrast matrices. Linear combinations of the $\beta_i$ were used to make these tests.
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