Evaluation of Left Ventricular Contractile Performance Utilizing End-Systolic Pressure-Volume Relationships in Conscious Dogs

Marcis T. Sodums, Frederick R. Badke, Mark R. Starling, William C. Little, and Robert A. O'Rourke

From the Department of Medicine, Division of Cardiology, The University of Texas Health Science Center at San Antonio, and The Audie L. Murphy Veterans' Administration Hospital, San Antonio, Texas

SUMMARY. The relationship between left ventricular end-systolic pressure and volume has been proposed as a model of left ventricular contraction which may be useful for quantifying inotropic state independent of preload and afterload. Although the model has been well-validated in isolated hearts, systematic evaluation in conscious animals with an intact peripheral circulation has been limited. Accordingly, we derived end-systolic pressure-volume relationships in twelve conscious dogs, chronically instrumented to measure left ventricular pressure and dimensions from endocardial ultrasonic crystals in three orthogonal axes. We examined the linearity of the end-systolic pressure-volume relationship, its response to alterations of inotropic state and the peripheral circulation, and the influence of β-adrenergic reflexes. End-systolic pressure-volume relationships were constructed by linear regression of end-systolic pressure-volume coordinates produced by transient inferior vena caval occlusions during atrial pacing. The relations were highly linear; of 127 inferior vena caval occlusions, the correlation coefficient was 0.96 ± 0.05 (mean ± SD). The slope of the end-systolic pressure-volume relationship was not significantly altered either by a moderate resistive afterload induced by angiotensin II infusion, or by a moderate increase in preload produced by dextran, but was increased from 4.7 ± 2.3 to 6.5 ± 2.2 mm Hg/ml (P < 0.05) in response to the positive inotropic stimulus of dobutamine. The volume intercept at zero end-systolic pressure was unaffected by dextran or dobutamine, but was decreased from 12 ± 8 to 5 ± 11 ml (P < 0.01) by angiotensin II infusion, indicating a leftward shift of the end-systolic pressure-volume relationship. Pretreatment with propranolol to block β-mediated adrenergic reflexes did not affect the response to angiotensin or dextran. We conclude that linear end-systolic pressure-volume relationships can be derived in conscious dogs with intact sympathetic reflexes. The slope appears to reflect left ventricular contractile function and is independent of the level of afterload and preload. However, the relation is shifted leftward by high levels of arterial resistance, indicating that end-systolic pressure is a function, not only of end-systolic volume and inotropic state, but also of the peripheral circulation, in this intact animal model. (Circ Res 54: 731-739, 1984)
This study was undertaken to evaluate systematically the behavior of the end-systolic P-V relationship in conscious dogs, chronically instrumented to measure simultaneous left ventricular (LV) pressure and volume. Our goals were to examine in this model: (1) the linearity of the relationship over a range of cardiac pressures and volumes, (2) the response of the parameters m and Vc to alterations of inotropic state and the peripheral circulation, and (3) the influence of the β-adrenergic nervous system on the definition and characteristics of the end-systolic P-V relation in the intact animals.

Methods

Instrumentation

Twelve healthy, adult mongrel dogs (20–35 kg) were instrumented under halothane anesthesia, through a left lateral thoracotomy, using sterile technique (Robotham et al., 1983). The instrumentation (Fig. 1) included left atrial pacing wires, a high fidelity pressure transducer (P-18, Konigsberg Instruments) in the LV apex, a polyvinyl small-bore catheter adjacent to the micromanometer for calibration, three pairs of endocardial (5 MHz) ultrasonic crystals in the anterior-posterior (AP), septal-lateral (SL), and apex-base (LA) dimensions, and a hydraulically occluder around the inferior vena cava (IVC). A small-bore polyvinyl catheter (not illustrated) was inserted into the left atrial appendage for drug administration. The wires and tubing were tunneled subcutaneously to the neck where they could be easily exposed for subsequent studies. Animals were allowed to recover from surgery for 1–2 weeks.

Data Collection

All studies were performed with the dogs lying quietly on their right side in a sling. The LV catheter was connected to a Statham P231D pressure transducer calibrated from a mercury manometer; the zero reference point was the vertebral column. The LV pressure signal from the micromanometer was adjusted to match that obtained from the fluid-filled catheter. The first derivation of LV pressure (dP/dt) was obtained electronically from the micromanometer signal using an RC circuit with a linear frequency response to 70 Hz and 3 dB down at 100 Hz. The transit time of 5 MHz sound between crystal pairs was determined using the electronics of Franklin et al. (1973), and converted to distance assuming a constant velocity of sound in blood of 1.55 mm//isec. High fidelity LV pressure, the first derivative of high fidelity LV pressure (dP/dt), and the dimensions of the three crystal pairs were recorded on an eight-channel, forced ink-pen oscillograph (Beckman Instruments), at a paper speed of 100 mm/sec. The six data channels were also A-to-D converted at 10-msec intervals and stored on floppy disk memory utilizing a minicomputer system (Zobex).

Data Analysis

The digitized, stored data were analyzed by means of a computer algorithm. End-diastole was defined as the Z-point of the high fidelity LV pressure tracing. Onset of ejection was taken at the time of maximum dP/dt. End-systole was defined as the maximum of the ratio of high fidelity LV pressure to volume (Sagawa, 1981), and end-ejection was defined as dP/dtm. Beats with similar heart rates from 10-second recordings of data during steady state conditions were averaged from measurement of peak LV pressure, end-diastolic pressure, end-diastolic volume, heart rate, and dP/dtm. Percent change of the end-diastolic volume was calculated as the end-diastolic dimension minus the end-ejection dimension, divided by the end-diastolic dimension, times 100; mean Vcf, as the percent change in AP diameter divided by the ejection time; and ejection fraction, as the end-diastolic volume minus the end-ejection volume, divided by the end-diastolic volume, times 100 (Mahler et al., 1975a). Volume was calculated by assuming that the left ventricle was a general ellipsoid and that the three dimensions formed the principal axes of this structure, using the equation:

\[
\text{Volume} = \pi/6 \times \text{AP} \times \text{SL} \times \text{LA}.
\]

Orientation of the crystal pairs in the three axes was confirmed by postmortem dissection of the left ventricle.

End-systolic P-V relations were constructed from end-systolic pressure-volume points obtained over a range of pressures and volumes produced by inflation of the IVC cuff occluder. During IVC occlusion, heart rate was kept constant by atrial pacing, utilizing small doses (0.1–0.5 mg) of atropine, as necessary, to prevent AV block. Individual beats with a heart rate 15% greater or less than the paced heart rate were excluded from the analysis. No effort was made to control for respiratory variation in pressure or volume. The end-systolic pressure-volume points from each IVC occlusion were subjected to least squared linear regression, starting with the highest end-systolic pressure-volume points and working downward.
systolic volume. The slope, m, volume intercept, \( V_o \), and correlation coefficient, \( r \), of the end-systolic P-V relationship were then derived from each IVC cuff inflation. The mean values of \( m \) and \( V_o \) for each study condition in each dog were then obtained by averaging the slopes and volume intercepts of at least two separate IVC occlusions (average 2.7 occlusions for each study condition).

One hundred and twenty-seven IVC cuff inflations were utilized to generate 127 end-systolic P-V relationships for this study. Of these 127 relationships, 115 (91\%) had an \( r \) value greater than or equal to 0.90; eleven had an \( r \) value greater than or equal to 0.82 but less than 0.90; and one had an \( r \) value of 0.77. The mean \( r \) value of the 127 relationships was 0.96 ± 0.05 (mean ± sd). The mean number of end-systolic pressure and volume coordinates for each of the 127 relationships was 12 ± 3.

Protocol

This study was performed in two portions. In the first, we obtained end-systolic P-V relationships during inotropic stimulation and during manipulation of preload and afterload in the presence of intact sympathetic reflexes in six dogs. In the second portion, the loading protocol was repeated in six additional dogs after pretreatment with 2 mg/kg propranolol (Ayerst Labs Inc.) to block \( \beta \)-mediated sympathetic effects (Vatner et al., 1972).

During the first part, inotropic state was enhanced with a dobutamine (Eli Lilly) infusion of 10 \( \mu \)g/kg per min, and arterial pressure loading was performed over 10–15 minutes with an infusion of angiotensin II (Ciba Geigy Corp.) (0.5–2.5 \( \mu \)g/min), and volume loading was accomplished with an infusion of dextran (Pharmacia Labs) (500 ml over 5 minutes). After each infusion, all parameters were allowed to return to control values before proceeding with the next intervention. IVC occlusions were performed during control and during enhanced inotropic state, volume loading, and arterial pressure loading. During the second portion, IVC cuff inflations were performed during control, after propranolol, and during pressure and volume loading following propranolol.

In three dogs, at low cardiac volumes during IVC occlusion, an entrapment artifact near end-systole developed on the LV pressure tracing from the micromanometer. In these dogs, LV pressure from the fluid system was used to obtain end-systolic pressure after suitable correction for transmission delay. In order to assess the reliability of pressure derived from the fluid system for the construction of the end-systolic P-V relationship, we compared the slopes and volume intercepts of the end-systolic P-V relations obtained from the two methods of pressure recording in four dogs with both suitable micromanometer and fluid pressure signals. Neither the slopes (mean difference, \( 0.3 ± 0.8 \) mg Hg/ml [mean ± sd]) nor volume intercepts (mean difference, \( 1 ± 3 \) ml) were significantly different. Accordingly, we included data in the \( \beta \)-blocked portion of this study from the three animals in which only pressure from the fluid system was usable.

Volume Validation

LV volume was computed utilizing the crystal-determined dimensions, assuming a general ellipsoidal model for LV shape. Because the geometrical assumptions of this method may be altered by the changes of inotropic state or loading conditions employed in this study, we compared LV volumes calculated by this method to volumes obtained from geometically independent techniques.

First, four dogs were additionally instrumented with an electromagnetic flow probe on the ascending aorta. In these animals, a range of steady state LV end-systolic volumes produced by incremental infusion of dobutamine and angiotensin II were calculated independent of geometry, using flow probe-derived measurements of stroke volume (SV) and radionuclide-derived measurements of ejection fraction (EF) by the formula:

\[
ESV = SV/EF - SV.
\]

Gated equilibrium radionuclide angiograms were obtained following in vivo red blood cell labeling with 20–30 mCi technetium-99m after the intravenous administration of stannous pyrophosphate. The dogs were positioned supine in a 30° right lateral position, and the γ camera was positioned in the 10° LAO/5° caudal tilt position which separated optimally the right and left ventricles in the plane of the interventricular septum. A 37 photomultiplier tube γ scintillation camera equipped with a low energy, all-purpose, parallel-hole collimator was used for image acquisition using a hardware zoom (2.0X). Image acquisition was such that count information in consecutive corresponding 30-msec frames of each cardiac cycle was summed and stored as images in the computer remote memory until each frame contained at least 2,000,000 counts. Using a semi-automated computer program (MDS MUGD), an LV region-of-interest for each image was defined, the activity in each LV region-of-interest during the cardiac cycle was determined, and an LV time-activity curve from these regions-of-interest was generated after background subtraction and temporal and spatial smoothing was completed. Background was obtained from an LV end-systolic paraventricular region. LV ejection fraction was calculated by subtracting end-systolic from end-diastolic counts and dividing by end-diastolic counts. This method of obtaining LV ejection fraction has been validated by comparison to the corresponding values obtained from simultaneous biplane contrast cineangiography (\( r = 0.93 \)) (Starling et al., 1981). End-systolic volumes measured by the crystal technique immediately after the radionuclide angiogram were compared to the radionuclide/flow probe-derived end-systolic volumes using least squares correlation. The results for the crystal-derived compared to the radionuclide-derived end-systolic volumes are contained in Table 1. For each dog there was a highly linear correlation between the values obtained by the two techniques (mean \( r \) value, 0.95 ± 0.02), although the relation was not that of the line-of-identity.

Next, four additional dogs were instrumented to allow

<table>
<thead>
<tr>
<th>Dog</th>
<th>Regression equation</th>
<th>( n )</th>
<th>( r )</th>
<th>SEE (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( V_c = 0.75 )</td>
<td>9</td>
<td>0.94</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>( V_c = 0.52 )</td>
<td>8</td>
<td>0.91</td>
<td>3</td>
</tr>
<tr>
<td>3 (#1)</td>
<td>( V_c = 0.41 )</td>
<td>6</td>
<td>0.95</td>
<td>2</td>
</tr>
<tr>
<td>3 (#2)</td>
<td>( V_c = 0.32 )</td>
<td>8</td>
<td>0.96</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>( V_c = 0.54 )</td>
<td>7</td>
<td>0.97</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 1**

Relation between Crystal-Derived and Radionuclide/Flow Probe-Derived End-Systolic Volumes in Four Dogs

Abbreviations: \( V_c \) = volume from ultrasonic crystals; \( V_R \) = volume from flow probe determined stroke volume and radionuclide determined ejection fraction; \( n \) = number of points; \( r \) = Pearson correlation coefficient; SEE = standard error of the estimate.

* Dog 3 was studied twice (on two separate days).
Circulation Research/Vol. 54, No. 6, June 1984

35-
30-
25-
20-
15-
r=0.99
SEE=0.9 ml
A CONTROL ANGIOTENSIN
10
—I—
15
—I—
20
—I—
25
—I—
30
—I—
35
—I—
40

Measured Stroke Volume (ml)

FIGURE 2. LV stroke volume calculated as the difference of the ultrasonically determined LV end-diastolic and end-ejection volumes compared to the simultaneously flow probe-measured stroke volume during IVC occlusions during control, infusion of angiotensin II, and following dextran infusion. The calculated and measured stroke volumes during these conditions are well described by a single linear regression.

the simultaneous measurement of ascending aortic flow with an electromagnetic flow probe and LV volume from the three orthogonal ultrasonically determined left ventricular dimensions. Similar to the protocol to produce the end-systolic pressure-volume relations, a range of ventricular volumes were produced by IVC occlusion in the control situation, and after the infusion of angiotensin II or volume loading with dextran. The crystal-derived stroke volume, calculated as end-diastolic left ventricular volume–end-ejection left ventricular volume, was compared with the simultaneously measured stroke volume from the aortic flow probe (Fig. 2; Table 2). In each animal, the calculated and flow probe-measured stroke volumes during IVC occlusions during control, angiotensin II infusion, or after dextran loading were related by a single linear regression (r ≥ 0.97, SEE ≤ 1.0 ml).

Statistical Analysis

Statistical analysis was performed by analysis of variance for repeated measures and paired t-tests, as appropriate. Where analysis of variance revealed a significant F-statistic, the Newman-Keuls test was utilized to determine significant difference of individual means from control (Winer, 1971). A P value of less than 0.05 was taken to signify statistical significance.

The study was approved by the Institutional Laboratory Animal Committee.

Results

Figure 3 is a sample analog recording of a single IVC occlusion. Depicted are LV dP/dt, high fidelity LV pressure, and the anteroposterior, septalateral, and the long axis dimensions. The arrow designates the time of cuff inflation, after which there was a progressive fall in dP/dtmax, LV pressure, and the three dimensions. The anteroposterior, septalateral, and long axis dimensions were utilized to calculate instantaneous LV volume assuming the formula for a general ellipsoid. During this cuff inflation, end-systolic pressure and volume coordinates from these beats with successively decreasing pressures and volumes were utilized to construct the end-systolic P-V relationship.

Figure 4 is an example of the end-systolic P-V relationships obtained during control and during the infusion of dextran, angiotensin II, and dobutamine.

TABLE 2

<table>
<thead>
<tr>
<th>Dog</th>
<th>Regression equation</th>
<th>n</th>
<th>r</th>
<th>SEE (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SVc = 1.24 SVe = 4.6</td>
<td>143</td>
<td>0.99</td>
<td>0.94</td>
</tr>
<tr>
<td>2</td>
<td>SVc = 0.87 SVe = 3.6</td>
<td>212</td>
<td>0.97</td>
<td>0.41</td>
</tr>
<tr>
<td>3</td>
<td>SVc = 0.97 SVe = 6.6</td>
<td>124</td>
<td>0.97</td>
<td>0.38</td>
</tr>
<tr>
<td>4</td>
<td>SVc = 1.1 SVe = 1.1</td>
<td>95</td>
<td>0.97</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Abbreviations: SVc = stroke volume calculated from ultrasonic crystals; SVe = stroke volume measured by the aortic flow probe; r = Pearson correlation coefficient; SEE = standard error of the estimate. The dog numbers do not correspond to those in Table 1.

TABLE 3

<table>
<thead>
<tr>
<th>Dog</th>
<th>Regression equation</th>
<th>n</th>
<th>r</th>
<th>SEE (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 3. Typical tracings obtained from a conscious animal in response to inferior vena caval cuff inflation. See text for details (dP/dt = first derivative of left ventricular pressure with respect to time)
demonstrated results similar to those in Figure 4. 

With angiotensin II, there was a significant increase in peak LV pressure from 113 ± 16 to 57 (Table 3). With angiotensin II, dextran, and dobutamine interventions, the dobutamine IVC occlusion had a steeper slope and a larger extrapolated volume intercept, compared with control. The group data from six dogs for control, angiotensin II, and dobutamine infusions in a conscious dog (see text for details) are listed for each cuff occlusion. During each intervention, it is apparent that the end-systolic P-V relation is quite linear. The control and dextran IVC occlusions resulted in similar slopes and volume intercepts, whereas the angiotensin II cuff inflation produced a similar slope, but a more negative volume intercept. In particular, 10 of the points on the angiotensin II regression line had overlapping end-systolic volumes with the control relationship, but at higher end-systolic pressures, consistent with the leftward displacement of \( V_0 \) during the angiotensin II infusion. The dobutamine IVC occlusion had a steeper slope and a larger extrapolated volume intercept, compared with control.

The group data from six dogs for control, angiotensin II, dextran, and dobutamine interventions demonstrated results similar to those in Figure 4 (Table 3). With angiotensin II, there was a significant increase in peak LV pressure from 113 ± 16 to 157 ± 18 mm Hg (\( P < 0.01 \)). LV end-diastolic pressure also rose from 3 ± 5 to 9 ± 7 mm Hg (\( P < 0.01 \)). The slope of the end-systolic P-V relationship did not change during the angiotensin II infusion; however, the volume at zero end-systolic pressure (\( V_0 \)) was decreased 62% from 12 ± 8 ml at control to 5 ± 11 ml with angiotensin II (\( P < 0.01 \)), indicating a leftward parallel shift of the end-systolic P-V relation during this intervention.

With dextran, LV end-diastolic pressure and volume rose significantly (from 3 ± 5 to 15 ± 6 mm Hg and 58 ± 20 to 68 ± 21 ml, respectively, \( P < 0.01 \)). Heart rate also increased from 121 ± 15 to 151 ± 25 beats/min (\( P < 0.05 \)) as the atrial pacemaker was overridden by the spontaneous sinus rate. However, with dextran, neither the slope nor the volume intercept of the end-systolic P-V relationship was changed from control values.

With dobutamine, there were significant increases in ejection fraction, \( \%AD \), mean Vcf, and \( dP/dt_{max} \) (all \( P < 0.05 \)), demonstrating a positive inotropic effect from the agent. The slope of the end-systolic P-V relationship increased significantly by 38% from 4.7 ± 2.3 to 6.5 ± 2.2 mm Hg/ml (\( P < 0.05 \)). \( V_0 \), although somewhat larger, did not change significantly from control.

In order to evaluate the effect of \( \beta \)-mediated sympathetic reflexes upon the end-systolic P-V relationship during the different states of the peripheral circulation, six additional animals were studied before and after propranolol and during the infusion of angiotensin II and dextran after \( \beta \)-blockade. The group results are listed in Table 4. The slope of the end-systolic P-V relationship was not significantly different from control after propranolol, during angiotensin II infusion, or dextran infusion, when compared by analysis of variance. Following propranolol, the infusion of angiotensin II or dextran did not significantly affect the slope of the end-systolic P-V relationship. The value of \( V_0 \) was significantly lower with angiotensin II, compared to control (—1 ± 4 vs. 6 ± 5 ml, \( P < 0.05 \)). In order to verify that the decrement in \( V_0 \) during the angiotensin II infusion represented a leftward shift of the end-systolic P-V relation, and was not due solely to extrapolation to zero pressure, we selected beats with similar end-systolic volumes from \( \beta \)-blocked control and \( \beta \)-blocked angiotensin II cuff occlusions, and then compared corresponding end-systolic pressures. End-systolic volume was matched within 1 ml from six beats in six dogs (31 ± 5 ml with propranolol and 31 ± 5 ml with angiotensin II). At these matched end-systolic volumes, the end-systolic pressure during the angiotensin II, \( \beta \)-blocked cuff inflations was significantly greater (144 ± 9 mm Hg) than during the \( \beta \)-blocked cuff inflations prior to angiotensin II (117 ± 14 mm Hg; \( P < 0.01 \)). Thus, the infusion of angiotensin II did indeed result in a leftward parallel shift of the end-systolic P-V relationship unrelated to an intact \( \beta \)-adrenergic nervous system.
To facilitate a qualitative comparison of the response of the slope of the end-systolic pressure-volume relation (m), the ejection fraction, and dP/dt max during the various interventions to alter inotropic state and the peripheral circulation, the data from Tables 3 and 4 are plotted as average percent change from control in Figure 5. The slope, m, was slightly, but not significantly, decreased in response to preload augmentation with dextran while dP/dt max and EF were increased. Although the change in m due to the positive inotropic stimulus of dobutamine appears less than that of dP/dt max, it is greater than that of the ejection fraction. A similar order of sensitivity of the three indices to the negative inotropic effect of propranolol is also evident.

**Discussion**

This study demonstrates that highly linear end-systolic P-V relationships can be obtained, irrespective of the respiratory cycle, and in the presence of intact sympathetic reflexes. Positive inotropic stimulation increases the steepness of the end-systolic P-V relationship without a change in the volume intercept. Moreover, the slope of the relationship remains relatively unchanged by maneuvers which alter the major determinants of the peripheral circulation (i.e., blood volume and arterial resistance). However, elevation of peripheral resistance with angiotensin II appears to shift the end-systolic P-V relation leftward, resulting in a higher end-systolic pressure for any end-systolic volume. With the exception of this parallel leftward shift induced by higher resistive afterload, these findings in the conscious dog are similar to the concepts proposed by Suga and Sagawa (1974), based on experiments in isolated hearts.

Blockade of β-mediated sympathetic reflexes by propranolol appears to have little influence upon the end-systolic P-V relationship or its response to alterations in the peripheral circulation. Although a
negative inotropic stimulus would have been expected to depress the value of \( m \), the decrement in the slope after \( \beta \)-blockade was not significant. In part, this failure to demonstrate a significant change with application of analysis of variance for repeated measures may relate to the intrinsic variation among animals within each treatment group. Alternatively, the small decrement may also reflect the low level of sympathetic tone in the resting, conscious dog (Vatner et al., 1972). Importantly, an increase in preload produced by dextran or afterload by angiotensin II did not significantly alter the slope of the relationship compared to the \( \beta \)-blocked control state, indicating that the effects seen in dogs without propranolol are not mediated by alterations in sympathetic drive to the ventricle. In particular, the infusion of angiotensin II during \( \beta \)-blockade produced a significant reduction in \( V_0 \), just as in the non-\( \beta \)-blocked state. Accordingly, this leftward parallel shift associated with an increase in arterial resistance does not result from sympathetically mediated changes in ventricular contractile function.

Although the slope of the end-systolic P-V relation appears to reflect LV contractile function, it is not obviously superior to the more traditional indices. However, compared to ejection fraction, percent change in AP diameter, mean Vcf, and \( dP/dt \max \), the slope, \( m \), was the only parameter which revealed a qualitative decrease in response to both augmentation of left ventricular preload and resistive afterload (Fig. 5, Table 3). This property of \( m \) may be of some value where LV preload, but not contractility, are augmented, and isovolumic and ejection phase indices are "spuriously" elevated (Mahler et al., 1975a). The ejection fractions in our study are somewhat lower than the angiographic ejection fraction in normal humans, but are consistent with previous results in instrumented, conscious dogs (Olsen et al., 1983; Visner et al., 1983).

Several potential limitations of this study need to be considered. The first potential limitation is the technique utilized for LV volume measurement. Although ultrasonic crystals in three dimensions and a general ellipsoidal model have been utilized and validated for the calculation of LV volume (Rankin et al., 1976), these calculations are based on geometric assumptions about LV shape at end-diastole and end-systole. In particular, LV internal shape at end-systole is less likely to be ellipsoidal, due to a variable amount of volume displacement by the papillary muscles. In our study, we validated the crystal method for calculating end-systolic volume by comparing it to geometrically independent techniques. Although the relationship between the calculated volumes and the measured volumes, using other techniques, was not the line of identity, the crystal technique and the geometrically independent approaches were linearly related, despite potential changes in LV geometry that may occur during the interventions employed in this study. Therefore, the crystal measurement of LV volume yields an index of LV volume. Since end-systolic pressure is linearly related to this index in these conscious animals, it follows that end-systolic pressure is also linearly related to true end-systolic volume, and that the behavior of the relationship in response to interventions will be similar.

A second potential limitation of our methods is that changes in preload or afterload altered the inotropic state through activation of baroreceptor reflexes. Most of these changes would have occurred through the \( \beta \)-adrenergic limb of the sympathetic nervous system (Sarnoff et al., 1960). Importantly, if baroreflex-derived changes in sympathetic tone were a significant factor in the generation of the end-systolic P-V relation in the autonomically intact animal, then end-systolic pressure-volume points during the later portion of IVC occlusions would be displaced leftward compared to the "ideal" end-systolic P-V line. Accordingly, \( V_0 \) should have been smaller prior to propranolol, compared to the value obtained after sympathetic reflex attenuation. In general, this was not observed; in fact, \( V_0 \) was slightly smaller after propranolol, although this change was not significant. Since our results were similar before and after pretreatment with propranolol, we suspect that such baroreceptor reflexes have little effect on the generation of the end-systolic P-V relation by IVC occlusion, or on the response of the relationship to changes in the peripheral circulation. This finding is consistent with the study of Vatner et al., who found little influence of the carotid sinus reflex on myocardial contractility in the conscious dog (Vatner et al., 1972). This may relate to the low basal level of sympathetic stimu-
The original formulation of the end-systolic pressure-volume model proposed that the time to $E_{\text{max}}$ was independent of cardiac loading and only a function of inotropic state (Sagawa et al., 1977; Sagawa, 1978). Subsequently, Elzinga and Westerhof have suggested that the time to $E_{\text{max}}$ is, in fact, load-dependent, and will increase in response to an elevation in afterload (Elzinga and Westerhof, 1981), perhaps shifting the end-systolic P-V relationship leftward. A second potential explanation relates to the difficulty in defining the time of end-systole in an isolated heart preparation ejecting into a model of the peripheral circulation. Thus, other non-inotropic factors would appear to be responsible for the leftward parallel shift of the end-systolic P-V relation seen during angiotensin II infusion.

The end-systolic P-V relationship is already been applied in the clinical arena, and our study has implications in this regard. In human studies employing angiography, only a small number of data points have been obtained in each subject due to the limitation of the contrast load (Grossman et al., 1977; Mehmel et al., 1981). In noninvasive studies, aortic pressure and echocardiographic measurements of LV dimensions have been utilized to construct end-systolic P-V relationships (Marsh et al., 1979; Borow et al., 1982a, 1982b). However, in none of these human studies has the reproducibility of the end-systolic P-V relation been assessed. Moreover, our study suggests that different end-systolic P-V lines are defined by maneuvers which change blood volume, as compared to those which alter arterial resistance. Accordingly, different slopes and intercepts may result when these relations are constructed by varying venous return, as opposed to changing arterial resistance (Sodums et al., 1982).

Some clinical investigations have combined both manipulations, in order to define a single “control” end-systolic P-V line, and our data suggest that this type of clinical application may require some modification.

In summary, end-systolic P-V relationships can be derived in conscious animals by IVC occlusion and atrial pacing. These relations are highly linear; their slope reflects contractility, and is unaffected by perturbations of the peripheral circulation. The volume intercept, $V_0$, is unaffected by manipulation of contractile state, but decreases in response to an increase in arterial resistive load. Thus, end-systolic pressure is not only a function of end-systolic volume and inotropic state, but also of the arterial circulation. Although the end-systolic P-V relation can detect acute changes in LV contractile function in an intact animal, our data also suggest that its usefulness may not be superior to conventional methods. Whether the relation will have greater value in the setting of chronic changes in either loading or function will require further study.

We express our gratitude to James Colston, Danny Escobedo, James Galloway and Don Watkins for their technical assistance, and to Donna Wallace and Joe Bingham for their expert secretarial support.

Supported in part by grants from the American Heart Association, Texas Affiliate, Inc.; National Heart, Lung, and Blood Institute Grants R01-H29368 and T32-HL07350; and a Veterans Administration Medical Research Grant.

Dr. Badke is a recipient of a Research Career Development Award from the National Heart, Lung, and Blood Institute.

Current address for Dr. Sodums is: Division of Cardiology, S.U.N.Y., Stony Brook, New York. Current address for Dr. Badke is: Boise Heart Clinic, Boise, Idaho.

Address for reprints: William C. Little, M.D., Division of Cardiology, University of Texas Health Science Center, at San Antonio, Texas, 7703 Floyd Curl Drive, San Antonio, Texas 78284.

Received June 27, 1983, accepted for publication April 10, 1984.
Sodums et al. / End-Systolic P-V Relations in Conscious Dogs

References


Franklin DL, Kemper W, Patrick T, McKnown D (1973) Technique for continuous measurement of regional myocardial segment dimensions in chronic animal preparations. Fed Proc 32: 343


Mahler F, Ross J Jr, O'Rourke RA, Covell JW (1975a) Effects of changes in preload, afterload, and inotropic state on ejection and isovolumic phase measures of contractility in the conscious dog. Am J Cardiol 35: 626-634


INDEX TERMS Contractility • End-systolic • Ventricular function • Conscious dogs
Evaluation of left ventricular contractile performance utilizing end-systolic pressure-volume relationships in conscious dogs.
M T Sodums, F R Badke, M R Starling, W C Little and R A O'Rourke

*Circ Res.* 1984;54:731-739
doi: 10.1161/01.RES.54.6.731

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/54/6/731

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org/subscriptions/