ABSTRACT   We tested the ability of the slope (E_max) and the volume intercept (V_o) of the end-systolic pressure-volume relationship (ESPVR) to indicate contractility changes in conscious dogs instrumented with sonomicrometers measuring left ventricular diameter in three orthogonal axes and a left ventricular pressure microtransducer. ESPVRs were generated by inferior vena caval occlusion under control conditions (C_1 and C_2) and during enhanced (I^+) and depressed (I^-) inotropic states achieved by infusion of dobutamine and injection of propranolol, respectively. No significant difference between the first control (C_1) and I^+ or between the second control (C_2) and I^- were found for either E_max (C_1, 5.31 ± 1.68 mm Hg/ml, mean ± SD; I^+, 5.37 ± 1.44; C_2, 5.20 ± 1.62; I^-, 4.18 ± 1.32) or V_o (C_1, 10.3 ± 9.6 ml; I^+, 7.3 ± 9.1; C_2, 9.9 ± 9.0; I^-, 12.7 ± 12.5), despite significant changes in other indexes of contractility. Comparison of changes in E_max in individual animals in response to I^+ and I^- revealed that 63% were nonsignificant, 28% were significant and expected, and 9% were significant and paradoxical. Within defined volume limits and irrespective of individual changes in E_max and V_o, in all animals I^- shifted the ESPVR above and to the left of C_1 and I^+ shifted the ESPVR below and to the right of C_2. We thus integrated the changes in E_max and V_o by measuring the area beneath each ESPVR between defined limits of end-systolic volume. The values for area were: C_1, 612 ± 150 mm Hg/ml; I^+, 745 ± 191 (p < .001); C_2, 520 ± 198; I^-, 420 ± 139 (p < .001). We conclude that (1) neither E_max nor V_o are individually reliable indexes of changed contractility, and (2) the area beneath the ESPVR between defined end-systolic volume limits is a consistent indicator of variations in inotropic state.


THE RELATIONSHIP between left ventricular pressure and volume at end-systole has been shown to be linear within the physiologic range. \(^1-10\) Both in vitro\(^1-4, 10, 11\) and in vivo,\(^5, 7, 12\) the end-systolic pressure-volume relationship (ESPVR) is sensitive to changes in inotropic state and relatively insensitive to left ventricular loading conditions. This load independency represents the major advantage of the ESPVR over the traditional ejection phase and isovolumetric phase indexes of contractility, which are variably influenced by preload and afterload.\(^13\) The variables defining the ESPVR are its slope (E_max) and its intercept (V_o) on the volume axis. Controversy exists as to which of these two variables is the more reliable indicator of inotropic state. In isolated canine left ventricles,\(^1-3, 10\) as well as in open-chest dogs,\(^14\) changed inotropic state was shown to affect E_max with no significant alteration in V_o. Similar results were reported by Sodums et al.\(^7\) and Lee et al.\(^15\) in conscious dogs and by Mehmel et al.\(^16\) in humans. In conscious dogs, in which end-systolic diameter was used instead of volume, Mahler et al.\(^5\) found no significant changes in the E_max, but did find significant displacements of the diameter intercept when varying inotropic state. Using the same approach, Sagawa et al.\(^17\) observed that some conscious dogs of his series showed changed E_max, whereas others
showed a parallel shift of the end-systolic pressure-diameter relationship with varying contractility. In patients, Grossman et al.\textsuperscript{18} reported significant changes in both $E_{\text{max}}$ and $V_0$ with varying contractile state. Again in humans, Borow et al.\textsuperscript{19} found significant changes in $E_{\text{max}}$ when using either left ventricular volume or diameter to study the end-systolic relationship. In the latter case, however, the diameter intercept also varied significantly. Significant variations of the slope and the intercept of the ESPVR were also reported by Kass et al.\textsuperscript{20} in a recent article, who used a conductance catheter to estimate continuous left ventricular volume in open-chest dogs.

In experiments performed on anesthetized, intact dogs with $\beta$-adrenergic and muscarinic receptor blockade undergoing pharmacologically induced contractility changes, we observed\textsuperscript{21} that the values for $E_{\text{max}}$ and $V_0$ changed inconsistently, and therefore could not be considered to be reliable individual indexes of changed inotropic state. However, combining the changes in both variables by measurement of the area beneath the ESPVR within defined limits of end-systolic volume (ESV) allowed reliable assessment of changed contractility.

In the present study we decided to evaluate the response of $E_{\text{max}}$ and $V_0$ to acute positive and negative inotropic stimulation ($+\Gamma$ and $-\Gamma$) in conscious, unsedated, unrestrained dogs without pharmacologic autonomic blockade and without any effort to control preload or afterload.

The results are consistent with our observations in anesthetized dogs in that neither $E_{\text{max}}$ nor $V_0$ alone is a reliable index of changed contractility. By contrast, the area under the ESPVR within defined limits of ESV provides a consistent, reliable indication of changed inotropic state.

**Methods**

**Animal preparation.** Eighteen healthy mongrel dogs of both sexes and weighing between 18 and 28 kg (22 ± 3.2 kg, mean ± SD) were prepared for this study. Anesthesia was induced by intravenous thiopental sodium (25 mg/kg). After intubation, anesthesia was maintained with 2% enflurane carried in pure oxygen (4 liters/min) via a Bain tube. Ventilation was maintained with a Bird Mark VIII respirator. Under sterile conditions, a left lateral thoracotomy was made at the fifth intercostal space of each dog. The pericardium was opened to form a cradle supporting the heart. A pressure microtransducer (Königsberg P7) and a Tygon catheter for the microtransducer’s calibration were inserted into the left ventricle via a stab incision near the apex. Three pairs of 3 MHz piezoelectric crystals of 5 mm in diameter were introduced through the left ventricular walls to rest on the endocardial surface for later measurement of apexbase (ABD), septum–free wall (SFWD), and anteroposterior (APD) diameters. A hydraulic occluding cuff made from silicone rubber was placed around the inferior vena cava. A pair of wires was tied onto the left atrial appendage for cardiac pacing and a Tygon catheter was advanced through the mammary vein to rest in the right atrium for drug infusion. All cables and catheters were tunneled subcutaneously to emerge between the scapulae. Figure 1 depicts the instrumentation. The thoracotomy was closed without pericardial closure and the animals were allowed to recover from anesthesia. Prophylactic antibiotic therapy (ampicillin, 100 mg/kg/day im) was maintained for 5 days. The right atrial and left ventricular catheters were flushed daily with sterile heparin solution. All animals were monitored by professional veterinary staff throughout the period of the study.

**Experimental protocol.** Animals were studied in the conscious, unsedated state, starting about 10 days after surgery. Each study was performed with the animal resting quietly on its right side. The pressure microtransducer was calibrated against a Statham P23 transducer connected to the left ventricular fluid-filled catheter. The zero reference point was set at the level of the vertebral column. The Statham P23 had previously been calibrated with a mercury manometer. The pressure signal and the three left ventricular diameter signals were displayed on a six-channel chart recorder (Gould Brush 2600, Cleveland). The diameter signals were first centered in their respective recorder channels, which were then individually calibrated between the channel margins with the 1 mm step calibration facility of the sonomicrometer (Triton Technology Inc., San Diego). The time derivative of left ventricular pressure ($dP/dt$) was derived from the left ventricular pressure signal by use of an amplifier with a high cutoff frequency of 300 Hz (Gould model 13-4615-71). Heart rate (HR) was also derived from the left ventricular pressure signal (Gould Biotach amplifier model 13-4615-65). HR and $dP/dt$ were displayed on the remaining two channels of the chart recorder. All signals were stored on FM tape (Hewlett-Packard 3968A, San Diego) for later analysis. In each experimental session, four ESPVRs were generated. The first was obtained during control ($C_1$) and the second was obtained under $+\Gamma$ (dobutamine infusion, 5 to 35 μg/kg/min), causing maximum $dP/dt$ to increase at least 25%. Subsequently, the infusion of dobutamine was discontinued and after 10 to 15 min, when all variables had returned to basal values, a second control ESPVR was recorded ($C_2$). The last ESPVR was obtained under negative

**FIGURE 1.** Instrumentation. Microcrystal pairs measure (1) ABD, (2) APD, (3) SFWD. PW = pacing wires; FFC = fluid-filled catheter; PM = pressure microtransducer; IVCO = inferior vena caval occluder. Not shown is right atrial catheter.
inotropic stimulation (I−) (propranolol, 3 mg/kg iv); with this dose, maximum dP/dt decreased at least 15% in all dogs. All four ESPVRs were obtained under steady-state conditions.

In one dog this protocol was repeated on five different days, allowing at least 2 days between experiments.

Each ESPVR was obtained by restricting venous inflow to the heart by inflation of the inferior vena cava (IVC) occluder while heart rate was held constant by atrial pacing (Medtronic 5325, Minneapolis). The maneuver lasted 12 sec at most and its success was visually estimated from the screen of a computer (Apple II, Cupertino, CA) displaying on-line real-time pressure-volume loops by means of an analog-to-digital converter and a computer program written in our laboratory and reported upon elsewhere. Examples are shown in figure 2. Success was defined as the absence of arrhythmias and artifacts in the pressure and volume signals. Any unsuccessful maneuver was repeated after recovery to a steady hemodynamic state. No effort was made to synchronize the inflation of the cuff occluder with the respiratory cycle of the dog. On termination of their individual protocols, all animals were killed by an overdose of thiopental sodium and crystal positioning was verified at autopsy.

This study was conducted in accordance with the guiding principles of the American Physiological Society.

**Data analysis.** Using an Apple II Europlus computer system, the recorded signals were digitized every 5 msec and stored on floppy disks.

Assuming the left ventricular cavity to have the shape of a general ellipsoid, left ventricular (LV) volume was calculated with the following equation:

\[
LV \text{ volume} = ABD \cdot SFWD \cdot \text{APD} \cdot \pi / 6
\]

This method of volume calculation has been previously used and validated. End-diastole was defined as the moment at which dP/dt started its rapid upstroke, and end-systole as the maximum pressure-to-volume ratio. Onset of ejection was defined to occur at maximum dP/dt and end of ejection as peak negative dP/dt. For each steady-state condition 3 to 10 beats before IVC occlusion were averaged for calculation of end-systolic pressure (ESP) and volume (ESV), end-diastolic pressure (EDP) and volume, (EDV), volume at onset of ejection (OEV) and at end-ejection (EEV), peak systolic pressure (PSP), APD at onset of ejection and end-ejection, maximum dP/dt, and ejection time (ET). Stroke volume (SV) was calculated as the difference between OEV and EEV, and cardiac output (CO) was calculated as SV \times HR. Mean velocity of circumferential fiber shortening (Vcf) was calculated according to the following equation:

\[
Vcf = \frac{\text{APD at ejection onset} - \text{APD at ejection end}}{\text{APD at ejection onset} \times ET}
\]

Ejection fraction (EF) as a percentage was calculated as: 100 \times SV divided by EDV. The end-systolic pressure-volume points of 7 to 19 (13 ± 3) consecutive beats of each IVC occlusion were used to construct the corresponding ESPVR by least squares linear regression. The beats used were those occurring after an initial phase during which EDV decreased with little change in ESP and ESV. The beats used thus occurred in that part of the response to IVC occlusion during which notable changes of both ESV and ESP were observed from beat to beat. From each ESPVR the slope E_{max}, the volume intercept V_o, the pressure intercept P_o, and the correlation coefficient r were determined. To measure any vertical shift of the test ESPVR (I+ or I−) away from its respective control we calculated the difference between ESP (test) and ESP (control) at the ESV corresponding to the mean ESV of the control set of SV data used in calculating the control regression equation. This difference will be referred to as the isovolumetric shift.

The percent change (%Δ) in E_{max}, V_o, area (which is explained in the next section), and Vcf in I− with respect to C, and in I+ with respect to C+ was calculated according to the equation %Δ variable = (test value − control value) \times 100/control value.

**FIGURE 2.** On-line monitoring of pressure-volume loops during vena caval occlusion in dog 3. A. Control; B. I+; C. I−. P = pressure (mm Hg); V = volume (ml).
Calculation of the area beneath the ESPVR. The maximum and minimum ESVs observed during the acquisition of each control ESPVR were determined and named VM and Vm, respectively.

We then integrated each control ESPVR between its VM and Vm, according to the equation for the area of a trapezoid:

\[ A = \frac{L}{2} (h_1 + h_2) \]

where L is the base length, and h1 and h2 are the heights. In this case, L is (VM - Vm), h1 is (P_o + VM \cdot E_{max}), and h2 is (P_o + Vm \cdot E_{max}), P_o being the pressure axis intercept.

Thus,

\[ A = (VM - Vm) \left( \frac{(P_o + VM \cdot E_{max}) + (P_o + Vm \cdot E_{max})}{2} \right) \]

Then,

\[ A = (VM - Vm) \left( \frac{2P_o + E_{max} (VM + Vm)}{2} \right) \]

The areas corresponding to I^+ and I^- were calculated by substituting into the equation their respective E_{max} and P_o values.

Figure 3 shows an example of area determination. Depicted are the ESPVRs corresponding to C1 and I^+. Within the limits of volume yields by the control IVC occlusion, two trapezoidal areas are determined. The largest (trapezoid AEFD) is obtained during dobutamine infusion and the trapezoid ABCD corresponds to the control situation. The difference between areas is equal to summation of isovolumetric shifts at all volumes lying between VM and Vm and thus acts as a method for reducing the inherent “noise” associated with a single point measurement.

Statistics. All hemodynamic variables and indexes derived from the ESPVRs from C1 and I^+ and C2 and I^- were compared with the use of the paired difference t test. Individual E_{max} values from C1 and I^+ and C2 and I^- periods were compared with use of the appropriate t test. A similar analysis was used to test for vertical shift of the I^+ and I^- lines with respect to their controls. Least squares linear regression analysis was used to study the correlation between percent changes in Vcf and percent changes in E_{max}, V_o, and area. The repeatability of the direction of change of E_{max}, V_o, and area in response to I^+ and I^- in one dog was analyzed nonparametrically with the Wald-Wolfowitz one-sample-runs test. In all cases a p value less than .05 was considered indicative of a statistically significant difference. All values are expressed as the mean ± SD.

Results

Of 18 dogs operated on, two died postoperatively and one was excluded because of clotting of the left ventricular catheter preventing calibration of the pressure microtransducer, two were excluded because of poor diameter signal quality, and two were excluded because of incorrect crystal positioning. Data from 11 dogs are thus reported. Figure 4 shows a typical example of a low-speed recording from a dog during IVC occlusion. Left ventricular pressure, ABD, SFWD, APD, left ventricular dP/dt, and HR are shown.

Hemodynamic variables. Absolute values for HR, CO, PSP, EDP, EDV, ESV, EF, maximum dP/dt, and Vcf in C1, I^+, C2, and I^- periods are listed in table 1. HR did not vary under either condition with respect to control. PSP during dobutamine infusion was significantly higher than control (p < .005), but not during I^- ESP increased after dobutamine and after propranolol, but only in the latter case did the increase achieve significance (p < .05). EDP did not change significantly during dobutamine infusion but increased significantly (p < .005) after the injection of propranolol, as did EDV (p < .001). ESV as well as EEV and EF reached significantly with the infusion of dobutamine (p < .001), and increased significantly after the injection of propranolol (p < .001). As expected, CO, EF, maximum dP/dt, and Vcf rose significantly during the infusion of dobutamine and fell significantly after the injection of propranolol.

End-systolic pressure-volume relationships. The correlation coefficients from 44 IVC occlusions ranged from 0.836 to 0.997 (0.953 ± 0.037).

Table 2 lists the absolute values, means, and stan-

FIGURE 3. Control and positive inotropic ESPVRs from dog 1. The vertical bars indicate the volume limits within which the areas were calculated. The end-systolic pressure-volume points used to generate each ESPVR are marked as closed circles for the control ESPVR and as open circles for the positive inotropic ESPVR. LVP = left ventricular pressure; LVV = left ventricular volume. See text for further details.
standard deviations of $E_{\text{max}}$, $V_o$, area, and isovolumetric shift in all dogs during $C_1$, dobutamine infusion, $C_2$, and propranolol injection. The mean values of neither $E_{\text{max}}$ nor $V_o$ show significant differences between $C_1$ and $I^+$ or between $C_2$ and $I^-$. By contrast, the mean values for area and isovolumetric shift show highly significant differences between $C_1$ and $I^+$ ($p < .001$) and $C_2$ and $I^-$ ($p < .001$).

Figure 5 shows the ESPVRs of all dogs in $C_1$ and $I^+$. In each panel, the dotted area between the line marked $C$ and the abscissa is the control area and that between the line marked $+$ and the abscissa is the $I^+$ area. Figure 6 shows the ESPVRs of all dogs in $C_2$ and $I^-$. In this case, the dotted area between the line marked $C$ and the abscissa is the control area and that between the line marked with the minus sign and the abscissa is the $I^-$ area.

The proposed index $A$ (area) correlates well ($r = .88$) with $V_{cf}$, which despite its load dependency, is accepted as a reliable index of contractility.13, 31, 32 This correlation is illustrated in figure 7, where the percent changes in $A$ ($\%\Delta A$) and $V_{cf}$ ($\%\Delta V_{cf}$) are plotted against each other. By contrast, a low correlation was found between $\%\Delta V_{cf}$ and $\%\Delta E_{\text{max}} (r = .31)$ and $\%\Delta V_{cf}$ and $\%\Delta V_o (r = .48)$.

The lack of significant changes in $E_{\text{max}}$ and $V_o$ when the animals were analyzed on a group basis led us to analyze the ESPVRs on an individual animal basis, as explained above (statistical analysis). The results are presented in table 3, from which it is seen that for $E_{\text{max}}$, six of 22 responses (28%) were significant and expected, two (9%) significant and paradoxical, and the remaining 14 (63%) insignificant. Analysis of the changes in pressure at constant ESV (table 2) revealed that all of these shifts were significant ($p < .001$, except for dog 4 $I^+$, where $p < .005$) and occurred in the expected direction.

Repeatability. The day-to-day variation of $E_{\text{max}}$, $V_o$, and area in one dog is shown in figure 8. Neither $E_{\text{max}}$ nor $V_o$ responded repeatably to the inotropic interventions, whereas area showed a highly significant repeatability ($p < .025$, Wald-Wolfowitz test) in terms of its direction of change.

### Table 1

<p>| Hemodynamics at control and with $I^+$ and $I^-$ |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>$C_1$</th>
<th>Dobutamine</th>
<th>$C_2$</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>145 ± 12</td>
<td>147 ± 15</td>
<td>146 ± 13</td>
<td>148 ± 15</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>2.78 ± 1.08</td>
<td>3.31 ± 1.02</td>
<td>2.86 ± 0.95</td>
<td>2.43 ± 0.87</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>4.9 ± 3.9</td>
<td>4.5 ± 3.3</td>
<td>5.3 ± 3.5</td>
<td>9.8 ± 6.6</td>
</tr>
<tr>
<td>ESP (mm Hg)</td>
<td>112 ± 13</td>
<td>117 ± 20</td>
<td>108 ± 12</td>
<td>118 ± 15 \text{A}</td>
</tr>
<tr>
<td>PSP (mm Hg)</td>
<td>122 ± 13</td>
<td>132 ± 17 \text{B}</td>
<td>120 ± 12</td>
<td>122 ± 15</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>46.7 ± 12.6</td>
<td>44.4 ± 12.2</td>
<td>45.6 ± 12.5</td>
<td>55.5 ± 13.1 \text{C}</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>34.1 ± 10.7</td>
<td>30.1 ± 10 \text{C}</td>
<td>33.0 ± 10.9</td>
<td>43.7 ± 12 \text{C}</td>
</tr>
<tr>
<td>EEE (ml)</td>
<td>30.8 ± 9</td>
<td>26.1 ± 8 \text{C}</td>
<td>29.6 ± 9</td>
<td>40.8 ± 10.6 \text{C}</td>
</tr>
<tr>
<td>Maximum dP/dt (mm Hg/sec)</td>
<td>1798 ± 491</td>
<td>2735 ± 726 \text{C}</td>
<td>1856 ± 494</td>
<td>1237 ± 328 \text{C}</td>
</tr>
<tr>
<td>EF (%)</td>
<td>41 ± 10</td>
<td>51 ± 10 \text{C}</td>
<td>43 ± 9</td>
<td>30 ± 8 \text{C}</td>
</tr>
<tr>
<td>$V_{cf}$ (sec⁻¹)</td>
<td>2.57 ± 0.86</td>
<td>3.53 ± 1.1 \text{C}</td>
<td>2.67 ± 0.85</td>
<td>1.71 ± 0.62 \text{C}</td>
</tr>
</tbody>
</table>

\*p < .05; \*p < .005; \*p < .001.
TABLE 2
Variables of the ESPVR, area beneath the ESPVR, and isovolumetric shifts in 11 dogs

<table>
<thead>
<tr>
<th>No.</th>
<th>E_max (mm Hg/ml)</th>
<th>V_o (ml)</th>
<th>Area (mm Hg ml)</th>
<th>IVS (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C_1</td>
<td>I^-</td>
<td>C_2</td>
<td>I^-</td>
</tr>
<tr>
<td>1</td>
<td>7.42</td>
<td>6.87</td>
<td>6.92</td>
<td>3.64</td>
</tr>
<tr>
<td>2</td>
<td>3.56</td>
<td>4.46</td>
<td>3.23</td>
<td>5.55</td>
</tr>
<tr>
<td>3</td>
<td>3.08</td>
<td>4.35</td>
<td>2.89</td>
<td>2.32</td>
</tr>
<tr>
<td>4</td>
<td>6.58</td>
<td>5.18</td>
<td>7.39</td>
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<td>5</td>
<td>2.63</td>
<td>3.74</td>
<td>2.91</td>
<td>2.68</td>
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<tr>
<td>6</td>
<td>6.26</td>
<td>7.13</td>
<td>6.14</td>
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</tr>
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<td>7</td>
<td>5.88</td>
<td>4.33</td>
<td>4.76</td>
<td>3.83</td>
</tr>
<tr>
<td>8</td>
<td>6.69</td>
<td>7.45</td>
<td>6.30</td>
<td>3.08</td>
</tr>
<tr>
<td>9</td>
<td>3.83</td>
<td>3.31</td>
<td>4.62</td>
<td>3.62</td>
</tr>
<tr>
<td>10</td>
<td>6.39</td>
<td>6.26</td>
<td>6.01</td>
<td>6.19</td>
</tr>
<tr>
<td>11</td>
<td>6.03</td>
<td>6.04</td>
<td>5.97</td>
<td>5.44</td>
</tr>
<tr>
<td>Mean</td>
<td>5.31</td>
<td>5.37</td>
<td>5.20</td>
<td>4.18</td>
</tr>
<tr>
<td>SD</td>
<td>1.68</td>
<td>1.44</td>
<td>1.62</td>
<td>1.32</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

IVS = isovolumetric shift; NS = nonsignificant (paired difference t test).

Discussion

Method. Despite the accuracy and reproducibility of measurements obtained by the use of sonomicrometry, the assessment of intraventricular volume from dimension measurements depends on the geometrical model used to link these variables. The model that we selected assumes that the left ventricle has the shape of a general ellipsoid. Although we did not directly validate this model, studies by Rankin et al.33 (using epicardial sonomicrometers) and by Sodums et al.7 (using endo-

FIGURE 5. ESPVRs of all dogs during first control (C) and positive inotropic stimulation (+). P = pressure; V = volume. See text for details.
cardiac sonomicrometers) in conscious dogs have demonstrated that there is a highly linear correlation between microcrystal-derived volume and values for volume obtained by techniques independent of left ventricular geometry, even when maneuvers that may change that geometry are used. The somewhat smaller EDVs from our study (47 ± 13 ml) with respect to those reported by Sodums et al. (58 ± 20 ml) could be attributed to the smaller range of weights of the dogs we used. In a recent study using the same method, Little reported EDV and ESV values almost identical to ours.

The construction of the ESPVR presents its own problems. The first of these refers to the definition of end-systole. As a definition of the end-systolic pres-

FIGURE 6. ESPVRs of all dogs during second control (C) and negative inotropic stimulation (-). P = pressure; V = volume. See text for details.

FIGURE 7. Correlation between %ΔA and %ΔVcf. n = 22 responses.

TABLE 3
Significant and nonsignificant changes in the Emax of the ESPVR (n = 22 responses)

<table>
<thead>
<tr>
<th></th>
<th>Significant</th>
<th>Nonsignificant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>2 (3, 5)</td>
<td>4 (2, 6, 8, 11)</td>
</tr>
<tr>
<td>1-</td>
<td>4 (1, 3, 4, 8)</td>
<td>2 (6, 9)</td>
</tr>
<tr>
<td>Total</td>
<td>6 = 28%</td>
<td>6 = 28%</td>
</tr>
<tr>
<td>Paradoxical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>1 (7)</td>
<td>4 (1, 4, 9, 10)</td>
</tr>
<tr>
<td>1-</td>
<td>1 (2)</td>
<td>4 (5, 7, 10, 11)</td>
</tr>
<tr>
<td>Total</td>
<td>2 = 9%</td>
<td>8 = 35%</td>
</tr>
</tbody>
</table>

Dog Nos. are in parentheses. See text for further explanation.
FIGURE 8. Day-to-day response of $E_{\text{max}}$, $V_o$, and area to $I^+$ and $I^-$ with respect to their controls ($C_1$ and $C_2$) in one dog. 

$\bigcirc = \text{day 1}; \bullet = \text{day 2}; \Box = \text{day 3}; \blacksquare = \text{day 4}; \triangle = \text{day 5}.$

sure-volume point on a given loop we used the maximum pressure/volume ratio, as recommended by Sagawa and used in recent publications. This criterion is in accordance with the definition that end-systole is the instant at which the contractile process reaches its maximum, and is clearly different from end-ejection. In effect, ejection can end far beyond the instant of maximum elastance, as shown by Maughan et al. for the right ventricle and by Suga using a computer simulation of human ventricular ejection. To produce ESPVRs, left ventricular loading must be changed. We have used the method of acutely restricting venous return to the heart by occluding the inferior vena cava. This method allows the ESPVR to be generated by a considerably larger number of individual beats than would be the case for changing afterload by abrupt aortic occlusion, thus permitting a more accurate estimate of the slope and intercept of the ESPVR. It has been shown in the presence of intact reflexes that a small increase in slope can occur after repeated IVC occlusions. Thus, despite the fact that the recorded variables returned to their prestimulus levels after the positive inotropic stimulus, the possibility existed that the slope of the control ESPVR had been increased by the mechanism mentioned above. Inspection of the slope values for the second control ESPVR shows that this was not the case. The fall in arterial pressure during the IVC occlusion could induce chronotropic and inotropic reflex effects in addition to the effects of reduced coronary perfusion pressure. We prevented changes in HR by atrial pacing during the maneuver and kept the maneuver short (see below).

Next, we should consider whether the inotropic state had changed with respect to control. During the experiments, the variable selected to assess the change in contractility was maximum $dP/dt$. The percent variation in maximum $dP/dt$ as a result of dobutamine infusion ranged from 32% to 112% (54 ± 22%). Because of the well-known sensitivity of maximum $dP/dt$ to changes in preload and afterload, it could be argued that this change was largely due to increased afterload, especially if the significant increase in PSP that occurred after the infusion of dobutamine is considered. However, the magnitude of the change in maximum $dP/dt$ was too large to have been caused only by increased afterload, and in addition Vcf, which despite its load dependency has been shown to be a good index of contractility, displayed a 39% increase after the infusion of dobutamine ($p < .001$). Other indicators of contractility (EF, SV, and CO) also showed significant increases. Moreover, dobutamine administered in similar doses has been used to produce a positive inotropic stimulation in studies involving humans as well as experimental animals.

The evidence for a negative inotropic effect induced by the injection of propranolol is of a similar nature, that is to say, significantly reduced maximum $dP/dt$, $V_c$, EF, SV, and CO and significantly increased EDP, EDV, and ESV. We therefore conclude that the dogs' hearts were subjected to genuine increases and decreases in contractile state during the experiments.

Slope of the ESPVR. Given that $I^+$ and $I^-$ resulted in marked changes in maximum $dP/dt$, $V_c$, and other indexes as mentioned above, we were surprised to find...
that the group mean values for $E_{\text{max}}$ (I$^+$ and I$^-$) were not statistically significantly different from the group mean control values, despite the fact that the numerical trend in $E_{\text{max}}$ exhibited the expected behavior.

The lack of change of $E_{\text{max}}$ could have resulted from each animal showing nonsignificant responses to the stimuli, or from a large spread of changes in $E_{\text{max}}$ among individual animals, some showing the expected result, some showing a paradoxical result (decreased $E_{\text{max}}$ during I$^+$, increased $E_{\text{max}}$ during I$^-$), and some showing individually insignificant changes. That this latter explanation may be correct is evidenced by inspection of table 3, where the three groups are clearly delineated: 63% of the responses were nonsignificant, 28% were as expected and significant, and the remaining 9% were paradoxical and significant. That is to say, 72% of the time the responses did not correctly identify the change in inotropic state. These results suggest that changes in $E_{\text{max}}$ alone cannot be relied on as an indicator of changed contractility.

In the literature, changes in $E_{\text{max}}$ produced by dobutamine and propranolol have been reported in both anesthetized and conscious dogs. In neither case did propranolol significantly reduce $E_{\text{max}}$, in general agreement with our own findings. Dobutamine, on the other hand, produced a significant increase in $E_{\text{max}}$ in all three studies. Inspection of the results of Sodums et al. reveals that dobutamine doubled maximum dP/dt, whereas in our animals the increase was more moderate (54%). This indicates that contractile state was not as elevated in our animals as it was in those of Sodums. Changes in maximum dP/dt reported by Kasenda et al. were similar to our findings. However, the results are not strictly comparable, due to the use of anesthesia and to the selection of end-ejection rather than end-systole to generate the ESPVR in the mentioned study. In neither the study of Sodums et al. nor that of Kasenda et al. were individual animal values for $E_{\text{max}}$ reported. Individual values were reported by Little, who used heavily sedated dogs in which the ESPVR was generated in the same way as in the present study. He found a highly significant increase in $E_{\text{max}}$ compared with control in six animals in which inotropic state was increased by dobutamine infusion. The rise observed in maximum dP/dt (60%) was similar to that in our experiments, but the increase in $E_{\text{max}}$ was considerably greater (140%). We are unable to explain the differences between the results of Little and our own, but suspect that in our conscious dogs, their ability to reflexly withdraw sympathetic drive to the heart in the face of the dobutamine challenge should be much greater than in the heavily sedated animals used by Little. The resulting change in inotropic state induced by similar doses of dobutamine should then be smaller in our animals than in those of Little.

Individual values for slope and intercept were also reported by Lee et al. in a recent study in which end-systolic pressure-volume and pressure-wall thickness relations during the infusion of dobutamine and after injection of propranolol were analyzed in conscious dogs. In agreement with our results, decreased inotropic state produced inconsistent changes in both $E_{\text{max}}$ and $V_o$, despite the fact that in four of five animals the expected increase in ESV at a constant ESP achieved statistical significance.

By contrast, the individual $E_{\text{max}}$ values under low-dose and high-dose dobutamine infusion showed the expected increases, confirmed in all cases by a significant decrease in ESV at constant ESP, despite inconsistent changes in $V_o$. Unfortunately, although the values for $E_{\text{max}}$ under control and low and high doses of dobutamine are reported in the study of Lee et al., no direct statistical comparison of slopes was made, emphasis being placed on the shift in ESV at constant ESP. Our study therefore remains the first to directly examine the significance of changed $E_{\text{max}}$ under positive and negative inotropic interventions. It should be emphasized that Lee et al. define end-systole as ejectation, and as already discussed above, the difference between end-ejection and end-systole as we and others define it varies with loading conditions, leading to difficulties in the interpretation of the shifts in ESV reported by Lee et al.

$V_o$ of the ESPVR. Changes in the $V_o$ of the ESPVR have been described as a consequence of changes in afterload, regional myocardial ischemia, and dyssynchronous ventricular activation. The influence of changes in inotropic state on $V_o$ is a matter of controversy. Whereas some studies show that $V_o$ is unaffected by inotropic intervention, others show significant changes. In two of these studies, left ventricular diameter rather than left ventricular volume was used to generate the end-systolic relationship.

In the majority of our dogs, $V_o$ showed large changes in response to manipulation of inotropic state. The inconsistency of these changes in relation to the direction of the inotropic variation rendered the variations nonsignificant when studied statistically as a group. In effect, whereas in some cases (dogs 1, 4, 7, 9, 10) I$^+$ caused an important leftward shift of $V_o$, in other animals (dogs 2, 3, 5) I$^+$ provoked the opposite shift.

Similarly, I$^-$ displaced $V_o$ to the right in dogs 2, 5, 9, 10, and 11, and to the left in dogs 1, 3, 6, and 8.
In some cases, the rightward or leftward \( V_o \) shift was slight and could be practically disregarded (dogs 6, 8, and 11 for \( I^+ \) and dogs 4 and 7 for \( I^- \)). However, in no case did \( V_o \) remain constant for both \( I^+ \) and \( I^- \) with respect to the control values. These results, although not supporting the invariability of \( V_o \) reported especially for hearts in vitro, are in agreement with the previously reported unreliability of \( V_o \) as an index of changed contractility.

**Area beneath the ESPVR.** Whatever the changes in \( E_{\text{max}} \) and \( V_o \), within defined volume limits the ESPVR representing an enhanced inotropic state was always observed to be located above and to the left of the control ESPVR and that corresponding to a depressed contractility was always observed to be located below and to the right of the control ESPVR. Thus, to detect a change in contractility from the ESPVR it was necessary to combine \( E_{\text{max}} \) and \( V_o \). This was achieved numerically by measurement of the area below the ESPVR between defined volume limits. These limits were not arbitrarily selected. The upper limit was the maximum ESV observed during the obtention of the control ESPVR and therefore reflected the resting hemodynamic state of the animal. The lower limit (minimum ESV observed during the obtention of the control ESPVR) depended not only on the IVC flow but also on the duration of the IVC occlusion. The longer the IVC occlusion, the closer ESV will be to \( V_o \). This implies that the IVC occlusion should be maintained for as long as possible to cover a wide range of pressure and volume. However, the duration of IVC occlusion is limited by the possibility of the arterial baroreflex altering inotropic state as a result of the fall in arterial pressure, and also by that of impairment of coronary perfusion, again due to a fall in arterial pressure, with consequent effects on the ESPVR. We limited the period of IVC occlusion to 8 to 12 sec and thereby limited the possibility of changed inotropic state during the maneuver, caused by the factors mentioned above. Selection of the volume limits in this way has the disadvantage of making the area index unique for each maneuver, but on the other hand, it has the advantage that at least one of the limits is fixed by the animal, thus resulting in a volume interval that is well within the physiologic range. Within this range, whatever the changes in \( E_{\text{max}} \) and \( V_o \), the ESPVR \( (I^+) \) is located above and to the left of the ESPVR \( (C_1) \) and the ESPVR \( (I^-) \) is located below and to the right of the ESPVR \( (C_2) \). Thus, within this range, irrespective of any change in slope or intercept, the resulting position of the ESPVR satisfies the general concept of enhanced or depressed inotropism, that is, increased or decreased pressure development from a given ventricular volume.

It should be emphasized that the numerical value assigned to area could be expressed equally well in square centimeters or, as we calculated it, in millimeters of mercury \( \times \) milliliter. The fact that the units we used are dimensionally equivalent to work arises from the inherent nature of a pressure-volume diagram. Area should not be confused with a work diagram. It is merely a numerical description of what the eye sees when inspecting the diagram. An equivalent exists for the pressure-diameter relationship or the pressure-wall thickness relationship. The units in which area would be calculated in these cases are dimensionally different but would express the same thing.

We did not test the ability of the area to detect changes in ventricular loading. Whether or not the area is sensitive to changes in ventricular load depends on the load sensitivity of the ESPVR itself. Since the area incorporates variations in \( V_o \) and in \( E_{\text{max}} \), conditions affecting these variables should also influence the value for area. As stated, a slight but significant leftward shift as a result of afterload increases has been reported in vitro, in sedated dogs, and in conscious dogs. In isolated hearts, this afterload dependency was demonstrated with the use of mechanical maneuvers to change afterload. In sedated and conscious dogs, the afterload increase was induced by infusion of angiotensin II. Since there is evidence for a direct positive inotropic effect of angiotensin II on the ventricular myocardium and since angiotensin II receptors have been described in the rabbit aтриa, the question still remains as to whether the leftward shift of the ESPVR induced by angiotensin II was due to a pure afterload change or to a combined increase in afterload and contractility. In any case, further studies are needed to test the specificity of the area as an index of changed inotropic state.

**Reproducibility.** To study reproducibility, we imposed the \( I^+ \) - \( I^- \) stimulus pair on five successive occasions and used the Wald-Wolfowitz test to detect alternation of the response. The fact that \( E_{\text{max}} \) and \( V_o \) did not display statistically significant responses indicates that not only are they poor indicators of inotropic state as mentioned above, but also that their behavior when subject to changed contractility is apparently random in nature. This was not the case for area, which correctly indicated the direction of the stimulus on all five occasions. The only previously published report of repeatability is the recent one of Lee et al. They conducted two studies on the same day with an average time difference of 55 min. In seven dogs neither \( E_{\text{max}} \) nor \( V_o \) changed significantly. However, slight ESV
displacement at a common ESP was found to be significant in two of these dogs. These results are in agreement with our own finding of similar values for \( C_1 \) and \( C_2 \) and suggest stability of response only over the short term.

**Alternative indexes.** Although changes in area have been shown to adequately reflect changes in contractile state both parametrically (t test) and nonparametrically (Wald-Wolfowitz test), the problem still remains that despite the ease with which area may be calculated, its use is restricted principally to indication of the direction of change in contractility. On occasion it would be useful to have a parametric index that expresses physiologic information. Two such indexes are change in ESP at constant ESV (isovolumetric index) and change in ESV at constant ESP (isobaric index). These indexes are especially useful when presented as absolute values because they allow statistical testing of individual pairs of results, a situation in which area can be used only on a nonparametric basis. The isovolumetric index is effectively the same as area with the difference between the volume limits reduced to zero, and the resulting isovolumetric shifts are seen to behave in exactly the same was as changes in area, reliably indicating changed contractility. The isobaric index has been reported by Lee et al.\(^{15}\) and shows equal sensitivity to changed contractility. In our study, the isovolumetric shift was capable of assigning statistical significance to a pressure change of as little as 5 mm Hg (dog 4, \( I^* \) vs \( C_1 \)).

The final choice of index will obviously depend on the individual application. Area is quick to calculate and highly reliable as a nonparametric index, the isovolumetric and isobaric indexes must be more painstakingly calculated if their true potential is to be exploited. A choice between the two would depend on the expected outcome of the proposed treatment. Therapy for heart failure, for example, may well be expected to reduce ESV with little change in ESP, thus suggesting usefulness of the isobaric index.

In conclusion, our results show that the ESPVR continues to possess physiologic relevance as an indicator of contractile state, despite the fact that the variables defining the line mathematically are themselves poor indicators of variations in contractility. For this reason, we have proposed alternative indexes, each based on the concept of the ESPVR, which do faithfully reflect changed contractility.

We thank Dr. Brian Guth (Division of Cardiology, Department of Medicine, University of California, San Diego) and Eng. Marcelo Rodriguez Chatruc (Favaloro Foundation, Buenos Aires) for their contribution in the early stages of the study. We are grateful to Jorge Negroni for suggesting the use of isovolumetric shift and to Ms. Elizabeth de Balázs for typing the manuscript. We also thank Richmond Laboratories, Buenos Aires, Argentina, for providing propranolol.

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