The effect of vasoactive agents on the left ventricular end-systolic pressure-volume relation in closed-chest dogs

GREGORY L. FREEMAN, M.D., WILLIAM C. LITTLE, M.D., AND ROBERT A. O’ROURKE, M.D.

ABSTRACT The left ventricular end-systolic pressure-volume relation has received intense interest as a relatively load-insensitive measure of cardiac performance. In clinical studies, pharmacologic manipulation of blood pressure has been used to determine this relation. Since previous studies have shown that acute changes in the resistance and impedance of the arterial circulation influence the left ventricular end-systolic pressure-volume relation, the use of vasoactive drugs in its determination may affect the results achieved. This study was undertaken to determine whether clinically used vasoactive drugs influence the left ventricular end-systolic pressure-volume relation. Sixteen dogs were previously instrumented with micromanometer pressure transducers and three sets of piezoelectric crystals to permit determination of left ventricular pressure and volume. The dogs were studied after autonomic blockade and sedation. End-systolic pressure-volume relations were generated by caval occlusion at control levels of blood pressure, after infusion of a vasopressor (methoxamine, n = 6; angiotensin II, n = 10), and then after infusion of nitroprusside. A composite end-systolic pressure-volume relation was also constructed with the use of control, vasopressor, and vasodilator points in each dog. Angiotensin II resulted in a leftward shift in the relation (Ves decreased from 14.32 ± 7.3 to 8.04 ± 10.4 ml, p < .05) with no significant effect on slope. Methoxamine shifted the relation to the left (Ves decreased from 13.98 ± 8.74 to −0.47 ± 12.06 ml, p < .05) and also reduced the slope (5.41 ± 3.09 vs 8.28 ± 3.94 mm Hg/ml, p < .05). Nitroprusside shifted the relation to the right (Ves increased from 13.98 ± 8.74 to 17.35 ± 11.04 ml, p < .05), but did not significantly alter the slope. The composite end-systolic pressure-volume relations in the animals given angiotensin II had a steeper slope (11.22 ± 4.87 mm Hg/ml, p < .05) and were shifted to the right (17.99 ± 8.41 ml, p < .05) compared with those generated by control caval occlusion. The composite relations in the animals given methoxamine, on the other hand, had a flatter slope (7.15 ± 3.13 mm Hg/ml, p < .05), with no significant difference in Ves compared with control caval occlusion. We conclude that the technique used to generate the left ventricular end-systolic pressure-volume relation influences the results that are obtained. Results obtained through the use of pharmacologic alteration of load are different than those obtained with use of rapid caval occlusion, and vary depending on the vasoactive agents used. These factors should be considered when interpreting the findings of studies on this index of cardiac performance.


THE ASSESSMENT of left ventricular performance is important in both the clinical assessment of patients and in physiologic investigation. This process is difficult because conventional measures of left ventricular performance are influenced by the loading conditions of the ventricle. Isovolumetric indexes (maximum dP/dt and other variables derived from maximum dP/dt) are influenced by changes in preload, while the ejection phase indexes (ejection fraction, stroke volume) are influenced by changes in afterload. Since loading conditions are difficult to control both in patients and in intact animals and are variably altered by therapeutic interventions and pathologic conditions, the load dependence of conventional indexes of left ventricular performance is a serious limitation.

Recently, the left ventricular end-systolic pressure-volume (PES-VES) relation has received intense interest

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as a measure of left ventricular contractile function that is not substantially affected by the preload or afterload.\textsuperscript{3-6} Left ventricular end-systolic pressure and volume have been found to be linearly related in isolated canine hearts,\textsuperscript{3-6} intact dogs,\textsuperscript{7-9} and in man.\textsuperscript{10-14} This relation is described by the equation:

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

where \( P_{\text{ES}} \) is the left ventricular end-systolic pressure, \( V_{\text{ES}} \) is the left ventricular end-systolic volume, \( E_{\text{max}} \) is the slope of the \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relation, and \( V_o \) is the volume intercept of this relation. \( E_{\text{max}} \) is a measure of global inotropic state and is relatively insensitive to changes in loading conditions.

To determine the \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relation, a range of \( P_{\text{ES}} \), \( V_{\text{ES}} \) points must be determined. In clinical studies, this has been accomplished by pharmacologic manipulation of blood pressure with pressors and/or with vasodilators.\textsuperscript{10-14} The validity of this approach rests on the assumption that the vasoactive agents used to alter end-systolic pressure do not themselves affect the \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relation; if they do, the \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relations generated through their use may not provide an accurate index of left ventricular performance.

Several studies have indicated that acute changes in the properties of the arterial system influence the \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relation. Sodums et al.\textsuperscript{7} have shown that \( V_o \), the zero volume intercept of the relation, is shifted leftward in conscious dogs after the infusion of the vasoconstrictor angiotensin II. Maughan et al.,\textsuperscript{15} using isolated, perfused canine hearts connected to a servo-controlled loading system, demonstrated that \( V_o \) was influenced both by the resistance and the characteristic impedance of the arterial system. These observations suggest that \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relations obtained by the use of vasoactive drugs to manipulate loading conditions may represent a hybrid relation from two or more different \( P_{\text{ES}} \)-\( V_{\text{ES}} \) lines.

This study was undertaken to determine the effects of clinically used vasoactive agents on the \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relation in closed-chest animals. Individual \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relations were determined with the use of caval occlusions, first under control conditions, then after infusion of either methoxamine or angiotensin II to produce vasoconstriction, and then after infusion of nitroprusside to produce vasodilation. Composite \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relations were also constructed in each animal with the use of steady-state points obtained during control conditions and during infusion of the vasoactive agents. Our results suggest that the method of load alteration influences the \( P_{\text{ES}} \)-\( V_{\text{ES}} \) relation.

Materials and methods

Instrumentation. Sixteen conditioned mongrel dogs of both sexes were used for these studies. The surgical preparation has been previously described in detail.\textsuperscript{7-9} In brief, after administration of halothane (1% to 2%) anesthesia and under sterile conditions, three sets of piezoelectric crystals were implanted in the endocardium of the left ventricle of each dog (figure 1). These permitted continuous assessment of anterior-posterior, septal-lateral, and long-axis dimensions. A micromanometer-tipped catheter (Konigsberg Instruments) and a 1.1 mm inside diameter, fluid-filled polyvinyl catheter for calibration of the manometer were placed through the left ventricular apex and held in place by a purse-string suture. Balloon occluder cuffs were positioned around both the superior and inferior venae cavae, and the chest was closed.

Data collection. The animals were studied after full recovery from surgery, a period of at least 10 days, during which time they were trained to lay quietly in a sling. The left ventricular catheter was connected to a Statham P23Db pressure gauge calibrated against a mercury manometer. The signal from the manometer-tipped catheter was matched with the fluid-filled catheter. Lead II of the surface electrocardiogram was recorded. Left ventricular dimensions were obtained from the piezoelectric crystals assuming a constant velocity of sound in blood of 1.55 m/sec.

Analog recordings were made on an eight-channel forced-ink oscillograph (Beckman Instruments) at a paper speed of 25 mm/sec. The following variables were measured: left ventricular pressure, \( \Delta P/dt \), the electrocardiogram, and anterior-posterior, septal-lateral, and long-axis dimensions. These variables were also simultaneously analog-to-digital converted at a rate of either 100 or 200 Hz by a PDP 11/23 minicomputer and stored on floppy disks. Primary digital data were evaluated without the use of digital filtering.

Experimental protocol. On the day of the study the animals were sedated with fentanyl (0.03 to 0.06 mg/kg) and droperidol (1.5 to 3.0 mg/kg) to allow intubation. The dogs were ventilated with room air. Autonomic blockade was produced with 0.2 mg/kg iv atropine and 2 mg/kg propranolol (angiotensin II group) or 2 to 3 mg/kg hexamethonium (methoxamine group). The adequacy of autonomic blockade was documented by a less than 10 beat/min increase in heart rate over the course of any single caval occlusion, and by a less than 20 beat/min overall difference in heart rate during the vasopressor and vasodilator trials. To eliminate changes in intrathoracic pressure due to respiration the data were recorded during periods of posthyperventilation.
ventilation apnea, as previously described. Analog tracings from a typical caval occlusion are shown in figure 2A, and the derived pressure-volume loops from these signals are shown in figure 2B. One or two caval occlusions were performed at each animal’s baseline level of arterial pressure. Angiotensin II (0.5 to 2.5 μg/min, 10 dogs) or methoxamine (0.2 mg/kg/min, six dogs) was then administered, by constant-rate intravenous infusion with use of a Harvard pump, to elevate left ventricular pressure. When a stable increase (30 to 70 mm Hg) in arterial pressure was reached, caval occlusions were repeated. The angiotensin II or methoxamine infusion was then stopped, and pressures were allowed to return to control levels. At this point nitroprusside was administered in a similar fashion until a stable (20 to 50 mm Hg) decrease in arterial pressure was attained, and caval occlusions were then repeated. If arrhythmias occurred they were treated with bolus doses of 2 mg iv lidocaine.

Data analysis. The digital data were analyzed with the use of software developed in our laboratory. Ventricular volume was calculated from the three orthogonal dimensions (anterior-posterior, septal-lateral, and long-axis) with the formula V = π/6 (D_{AP}·D_{SL}·D_{LA}). We have previously demonstrated that this method gives a consistent measure of left ventricular volume, despite marked changes in left ventricular size and configuration.\(^7\)-\(^9\), \(^16\), \(^17\) End-systole was defined as the time of the peak instantaneous ratio of left ventricular pressure to volume.\(^18\) End-systolic data from each caval occlusion were fitted to the equation \(P = E_{max} (V-V_o)\) by the least squares method (BMPDIR\(^19\)). To determine the \(P_{ES-VES}\) relation resulting from data acquired under the three sets of loading conditions, the first point from each separate caval occlusion was used. A linear regression analysis was then performed on these three points by the same method, and \(E_{max}\) and \(V_o\) were again derived.

All results are summarized as the mean ± 1 SD, and a significant difference was assumed to be present at \(p < .05\). Data were analyzed by analysis of variance and intergroup com-

parisons were performed with use of paired two-tailed t tests and the Bonferroni correction (for multiple comparisons).\(^20\)

Results

Effect of angiotensin II and nitroprusside (n = 10). Angiotensin II increased \(P_{ES}\) by 55 ± 18 mm Hg (\(p < .05\)), while nitroprusside lowered it by 40 ± 16 mm Hg (\(p < .05\)). The effects of angiotensin II and nitroprusside on the \(P_{ES-VES}\) relation generated by caval occlusions and the composite \(P_{ES-VES}\) points (control, angiotensin II, and nitroprusside) are shown in table 1 and figure 3. Angiotensin II resulted in a leftward shift in the \(P_{ES-VES}\) relation, decreasing \(V_o\) from 14.32 ± 7.28 to 8.04 ± 10.44 ml (\(p < .05\)), while \(E_{max}\) was not significantly changed (8.84 ± 4.10 vs 7.07 ± 3.43 mm Hg/ml, \(p = NS\); table 1). Nitroprusside shifted the caval \(P_{ES-VES}\) relation in the opposite direction, increasing \(V_o\) to 17.47 ± 8.73 ml (\(p < .05\)), while \(E_{max}\) was not significantly altered. Compared with the \(P_{ES-VES}\) relation at the control caval occlusion, the composite relation determined with the control, angiotensin II, and nitroprusside points had a steeper slope (\(E_{max}\) increased to 11.22 ± 4.87 mm Hg/ml, \(p < .05\)) and was shifted to the right (\(V_o\) increased to 17.99 ± 8.41 ml, \(p < .05\)).

Effect of methoxamine and nitroprusside (n = 6). Methoxamine increased \(P_{ES}\) by 56 ± 19 mm Hg (\(p < .05\)), while nitroprusside lowered it by 37 ± 11 mm Hg (\(p < .05\)). The effects of methoxamine and nitroprusside on the \(P_{ES-VES}\) relation generated by caval occlusions and the composite \(P_{ES-VES}\) relation produced by connecting the three steady-state \(P_{ES-VES}\) points (control, methoxamine, and nitroprusside) are shown in table 2 and figure 4. Methoxamine produced a leftward shift in the \(P_{ES-VES}\) relation, reducing \(V_o\) from 13.98 ± 8.74 to \(-0.47 ± 12.06\) ml (\(p < .05\)). \(E_{max}\) was also decreased by methoxamine, from 8.28 ± 3.94 to 5.41 ± 3.09

FIGURE 2A. Recordings of left ventricular pressure (P_LV, mm Hg), dP/dt (mm Hg/sec), anterior-posterior, septal-lateral, and long-axis dimensions (D_{AP}, D_{SL}, D_{LA}), and aortic pressure (P_{AD}, mm Hg) after vena caval occlusion.

FIGURE 2B. Pressure-volume loops derived from the signals shown in figure 2A.
TABLE 1
Effects of angiotensin II and nitroprusside on the left ventricular PES-VES relation

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control</th>
<th>Angiotensin II</th>
<th>Nitroprusside</th>
<th>Composite</th>
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<td>V&lt;sub&gt;e&lt;/sub&gt;</td>
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r values are Pearson correlation coefficients. 
<sup>a</sup>p < .05 compared with the control value.

Nitroprusside produced a rightward shift in the P<sub>ES</sub>-V<sub>ES</sub> relation, increasing V<sub>e</sub> to 17.35 ± 11.04 ml (p < .05). Compared with the P<sub>ES</sub>-V<sub>ES</sub> relation at control caval occlusion, the composite P<sub>ES</sub>-V<sub>ES</sub> relation had a flatter E<sub>max</sub> (E<sub>max</sub> decreased to 7.15 ± 3.13 mm Hg/ml, p < .05), but there was no significant change in V<sub>e</sub>.  

**Discussion**

The P<sub>ES</sub>-V<sub>ES</sub> relation was initially described in the isolated, isovolumetric canine heart. In this preparation the relation was generated by varying preload while afterload was held constant at a maximal level. The observation that the upper left corner of the pressure-volume loops of variably loaded ejecting beats lay near the isovolumetric P<sub>ES</sub>-V<sub>ES</sub> relation suggests that the relation is relatively independent of the mode of ejection and afterload. Since global inotropic stimulation influences the slope of the relation, the P<sub>ES</sub>-V<sub>ES</sub> relation has received much attention as a load-independent measure of left ventricular contractile state.

The major practical difficulty in the clinical application of this relation is the need to use vasoactive drugs to alter systolic pressure so that enough points are generated to permit its definition. Vena caval occlusion, which produces a progressive drop in ventricular filling and end-systolic pressure, allows determination of the P<sub>ES</sub>-V<sub>ES</sub> relation in a relatively short period of time and provides multiple data points over a wide range of pressures. The brevity of the data acquisition period during caval occlusion minimizes reflex alterations in heart rate or contractility that might influence the P<sub>ES</sub>-V<sub>ES</sub> relation. Unfortunately, although it has been used in human subjects, caval occlusion is not a technique that is easily applied in clinical studies. While the commonly used technique of pharmacologic alteration of load offers a simpler way to generate P<sub>ES</sub>-V<sub>ES</sub> relations in patients, this study indicates that the method of load alteration may influence the resulting P<sub>ES</sub>-V<sub>ES</sub> relation.

In this study individual P<sub>ES</sub>-V<sub>ES</sub> relations were determined during caval occlusion under control conditions and during the infusion of a vasoconstrictor (angioten-
sin II or methoxamine) and a vasodilator (nitroprusside). To simulate clinically applied techniques, a composite $P_{ES} - V_{ES}$ relation was also determined from three steady-state points: control, vasopressor, and vasodilator. In each instance the relation was described very well by a straight line. Consistent with previous reports, angiotensin II shifted the $P_{ES} - V_{ES}$ relation to the left, decreasing $V_o$ without significantly altering $E_{max}$. Methoxamine's effect was somewhat different than that of angiotensin II. While it decreased the $V_o$ of the $P_{ES} - V_{ES}$ relation, it also significantly decreased the $E_{max}$. Vasodilation with nitroprusside, on the other hand, produced a parallel rightward shift in the $P_{ES} - V_{ES}$ relation. These results are consistent with the observation of Maughan et al., and verify the observation that the $P_{ES} - V_{ES}$ relation is influenced by acute changes in the mechanical properties of the arterial circulation. Although the precise mechanism for these shifts is not known, they may result from contractile inactivation related to the amount of shortening or from the rate of left ventricular ejection flow, factors altered by vasoactive drugs.

The slope of the $P_{ES} - V_{ES}$ relation is generally considered to reflect the overall contractile state of the left ventricle. Our finding of a reduction of the $E_{max}$ with methoxamine suggests that this drug has a negative inotropic effect. Although prior studies on the myocardial effects of methoxamine have produced variable results, data from studies of isolated cat papillary muscles and open-chest dogs suggest that methoxamine has a negative inotropic influence. Also consistent with our results is the recent observation in isolated isovolumetric rabbit hearts that methoxamine produces a direct myocardial depressant effect. The magnitude of change in the $E_{max}$ of the $P_{ES} - V_{ES}$ relation produced by methoxamine in our study suggests that there may be another mechanism in effect. Although the $P_{ES} - V_{ES}$ relation is considered to be linear over the normal range of left ventricular pressures, $P_{ES}$ cannot indefinitely continue to linearly increase with ever larger $V_{ES}$, but must at some point flatten out. While earlier studies in adult canine hearts have suggested that the peak isovolumetric left ventricular pressure-volume relation in hearts of adults is linear up to 225 mm Hg, a study by Cross et al. indicated that this relation reached a plateau value at approximately 140 mm Hg. Suga et al. recently reported that the $P_{ES} - V_{ES}$ relation in the isolated puppy left ventricle begins to plateau at 149 ± 61 mm Hg. In our animals

\[ \text{TABLE 2} \]

Effects of methoxamine and nitroprusside on the left ventricular $P_{ES} - V_{ES}$ relation

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control $r$ value</th>
<th>$E_{max}$</th>
<th>$V_o$</th>
<th>Methoxamine $r$ value</th>
<th>$E_{max}$</th>
<th>$V_o$</th>
<th>Nitroprusside $r$ value</th>
<th>$E_{max}$</th>
<th>$V_o$</th>
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$r$ values are Pearson correlation coefficients.

* $p < .05$ compared with the control value.

\[ \text{FIGURE 4.} \ P_{ES} - V_{ES} \text{ relations produced by vena caval occlusion during control, and after the infusions of methoxamine and nitroprusside in one dog. The} \ P_{ES} - V_{ES} \text{ relation calculated by linear regression of control, methoxamine, and nitroprusside points is also shown. LV = left ventricular.} \]
the peak level of $P_{ES}$ during the infusion of methoxa-
mine was $157 \pm 16.9$ mm Hg. Our finding of a reduc-
tion in the $E_{\text{max}}$ of the $P_{ES}^{-}V_{ES}$ relation dur-
ing the infusion of methoxamine suggests that at these levels of $P_{ES}$ the relation may no longer be linear, but may have begun to reach a plateau, and thus have a decreased slope. This is supported by our finding of such a marked reduction in the extrapolated $V_o$ during the infusion of methoxamine that three animals had a nega-
tive $V_o$. It is of interest that the $E_{\text{max}}$ of the $P_{ES}^{-}V_{ES}$ relation was not significantly different from control during the infusion of angiotensin II. While prior studies have shown that angiotensin II has a direct positive inotropic effect, 35.36 $E_{\text{max}}$ during the infusion of angio-
tensin II tended to be lower in our animals. This sug-
gests that the $P_{ES}^{-}V_{ES}$ relation was beginning to reach its plateau value, but that this effect was offset by the positive inotropic influence of angiotensin II.

The steady-state $P_{ES}^{-}V_{ES}$ relations resulting from the use of points obtained at control and during the infusion of vasoactive drugs were different from those generated by the control caval occlusions, whether angiotensin II or methoxamine was used. When angio-
tensin II was used as a vasoconstrictor, the composite $P_{ES}^{-}V_{ES}$ relation had a moderately steeper slope and slightly larger $V_o$ than that after the control caval occlusion. When methoxamine was used the composite relation had a moderately flatter slope while the $V_o$ was not significantly different. Thus, the results of studies using vasoactive drugs to generate the $P_{ES}^{-}V_{ES}$ relation may differ as a result of the particular agent used and may only approximate values that are obtained with the use of caval occlusion.

Although our data indicate that the method of load alteration influences the resulting $P_{ES}^{-}V_{ES}$ relation, the use of pharmacologic alteration of load is a valuable method of assessing this relationship. Borow et al. 12 have used peripheral arterial pressure and an echocardio-
graphic estimate of left ventricular diameter during the infusion of methoxamine to estimate a $P_{ES}^{-}$end-
systolic diameter relation. This relation responds ap-
propriately to positive inotropic stimulation and is useful in assessing left ventricular performance in patient groups. 12,13 Others have also found that the $P_{ES}^{-}V_{ES}$ relation determined by the use of both vasopressor and vasodilator drugs provides a useful method of determining left ventricular contractile state. 10, 11 Our results indicate that the method of load alteration should be considered when interpreting such data, and that $P_{ES}^{-}V_{ES}$ relations produced by different methods of load alteration may not be comparable.

Prior studies have shown that vasoactive drugs may influence the interaction of the right and left heart chambers. 35,36 It is possible that such effects may have contributed to the shifts we have seen in the $P_{ES}^{-}V_{ES}$ relation in this study. However, ventricular interde-
pendence predominantly affects diastolic filling, and the $P_{ES}^{-}V_{ES}$ relation is largely independent of diastolic volume. Thus, changes in ventricular coupling induced by the drugs used in this study should not have greatly influenced our results.

Several possible limitations of this study must be noted. While the animals were studied under a very controlled set of conditions, gradual alterations of myocardial contractile state could have taken place. Autonomic blockade with atropine and propranolol or hexamethonium was used to prevent such reflex changes in heart rate and contractility. The effects of autonomic reflexes and circulating catecholamines may play a role in animal or human studies in which autonomic blockade is not induced. The $P_{ES}^{-}V_{ES}$ data were acquired during apnea after a brief period of hyperventilation, a technique that eliminates changes in intrathoracic pressure that might influence absolute values of left ventricular pressure. 8 Our finding that the steady-state relations generated under these conditions differed from control caval occlusions suggests that even larger differences may have been found had these confounding influences been present. Finally, the results of this study depend on the determination of left ventricular volume from three left ventricular dimen-
sions. We have previously demonstrated that this method yields consistent results despite alterations in left ventricular configuration produced by caval occlusion, pulmonary arterial occlusion, volume loading, vasoconstriction, regional left ventricular ischemia, or pacing from either the right or left ventricle. 7-4, 16, 17 Since the application of volume data has been made only to end-systole, which occurs at the frequency of the heart rate, the signal content of the piezoelectric dimension gauges provides adequate information for the conclusions we have drawn. 37 Thus, the method of determination of left ventricular volume should not have influenced our results.

In conclusion, this study shows the $P_{ES}^{-}V_{ES}$ relation generated by caval occlusion under control conditions and that generated through the use of vasoactive drugs are not the same. The $P_{ES}^{-}V_{ES}$ relation produced by caval occlusion is influenced by the arterial system and is shifted to the left in response to vasoconstriction and to the right with vasodilation. Methoxamine decreases the slope of the $P_{ES}^{-}V_{ES}$ relation. These results indicate that the method of load alteration influences the $P_{ES}^{-}V_{ES}$ relation that is produced.
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