Preload-Induced Curvilinearity of Left Ventricular End-Systolic Pressure-Volume Relations
Effects on Derived Indexes in Closed-Chest Dogs

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With the technical assistance of Monique Laplace

End-systolic pressure-volume relations (ESPVRs) were analyzed in 10 closed-chest autononi-
ically blocked dogs before and after volume loading that restored end-diastolic volume to its
value measured in the control conscious state. Dogs had been previously instrumented with a left
ventricular pressure micromanometer and ultrasonic crystals for measurements of major,
anteroposterior, and septum-free wall diameters. Left ventricular volume was calculated with
an ellipsoidal model in the left ventricular cavity. ESPVRs obtained during caval occlusion after
volume loading were curvilinear as shown by the division of the relation into two parts. The
initial part of the relation had a significantly smaller ESPVR slope (Ees, 12.0±1.8 mm Hg/ml)
and ESPVR volume-axis intercept (Vd, −3.5±0.8 ml) than the final part of the relation
(19.5±3.1 mm Hg/ml and 0.0±0.6 ml, respectively, p < 0.01). The end-diastolic volume–peak
dP/dt relation showed a similar curvilinearity when end-diastolic volumes were larger than 1.5–
1.7 times the minimal end-diastolic volume reached during caval occlusion. ESPVRs were not
different during aortic constriction and caval occlusion when end-diastolic volume was small. In
contrast, with large end-diastolic volumes, Ees and Vd were significantly smaller during caval
occlusion than during aortic constriction. The final part of ESPVR (with small end-diastolic
volume) had the same slope and intercept as that during aortic constriction. We conclude that
preload produces a curvilinearity of ESPVR that significantly modifies derived indexes when the
range of preload changes is large. (Circulation 1989;79:431–440)

A number of indexes have been proposed for quantifying left ventricular function. Whereas iso-
volumic and ejection indexes of ventricular function are affected by changes in preload and afterload and inotropic state,1,2 the elastance model of ventricular function3 may theore-
tically define a load-independent index of inotropic state: the slope (Ees) of the end-systolic pressure-
volume relation (ESPVR). However, this load-independent feature of ESPVR has been questioned. For instance, an effect of arterial impedance changes on ESPVR has been shown in isolated4 and in situ5 hearts. An effect of stroke volume and velocity of ejection on end-
systolic pressure has also been demonstrated in isolated canine left ventricles.6 Thus, these factors
may produce a curvilinearity of ESPVR when the range of loading modifications is large.

The goal of our study was to determine the extent to which ESPVRs are curvilinear during loading
modifications induced either by an increase in afterload and aortic impedance (aortic constriction) or
by a decrease in preload and afterload (venal caval occlusion) before and after volume loading in closed-
chest dogs with autonomic blockade to avoid cardiovascular reflexes that significantly modify ESPVR
in the conscious state.7 A secondary goal was to determine whether or not the slopes and intercepts
of these relations were different with these different types of loading modifications.

Methods

Surgical Preparation

Ten male beagle dogs weighing 9.6–15.0 kg (average, 12.4±0.4 kg) were used for this study. They
were instrumented according to the tech-
niques of Sodums et al. After anesthesia with thiopental sodium (25 mg/kg i.v. with small additional doses given if necessary during the course of the intervention), dogs were ventilated by a Harvard respirator (South Natick, Massachusetts) delivering room air through an endotracheal tube. Under aseptic conditions, a thoracotomy was performed through the fifth left intercostal space. The pericardium was widely opened and a high-fidelity micromanometer (Model P7, Konigsberg Instruments, Pasadena, California) was inserted into the left ventricular chamber through the cardiac apex. Three pairs of piezoelectric crystals were implanted in the endocardium of the left ventricle, which permitted continuous measurement of left ventricular anteroposterior, septum-lateral free wall, and base-apex axis dimensions. An inflatable cuff occluder was placed around the ascending aorta previously dissected. In four dogs, a hydraulic cuff occluder was also positioned around the inferior vena cava. A polyvinyl catheter filled with heparinized saline solution was inserted in the left atrium through the left atrial appendage. The chest was then closed, and the pericardium was left open. The dogs were trained to lie on their right side in the conscious state, and experiments were performed after a period of recovery of 7–17 days (average, 11 days).

Experimental Protocol

Dogs were divided into two groups. In the first group of six animals (group 1), all hemodynamic variables and dimensional variables (heart rate, left atrial pressure, left ventricular pressure and its derivative, and left ventricular dimensions) were recorded as a control reference while dogs were lying quietly on their right side in the conscious, resting state. The animals were then sedated with fentanyl (0.03–0.06 mg/kg i.v.) and droperidol (1.5–3.0 mg/kg i.v.) to allow intubation. Ventilation was maintained by a Harvard respirator delivering room air to the animals. Autonomic blockade was accomplished with intravenous injections of propranolol (2.0 mg/kg) and atropine (0.2 mg/kg). The adequacy of autonomic blockade was judged by an increase of less than 10 beats/min or by a decrease in heart rate during any single inferior vena cava occlusion or ascending aortic constriction or both. An inferior caval occlusion was then performed by inflating the caval cuff occluder with saline solution. In dogs without caval cuff occluder, caval occlusions were performed by inflating with saline solution the balloon of a Swan-Ganz catheter introduced into the inferior vena cava through the femoral vein. To exclude the intervention of respiration, loading modifications were performed at the end of expiration by arresting the respirator. In a second period of the experiments, left ventricular dimensions were adjusted, by injecting dextran saline solution, to the level of left ventricular dimensions recorded in the control conscious state (Figure 1). After volume loading, caval occlusion was repeated. In addition, an aortic constriction was produced by inflation of the aortic cuff occluder after release of caval occlusion (Figure 1), which was followed by a caval occlusion. Cava occlusion and aortic constriction were considered adequate when they produced a minimum variation of 30 mm Hg of left ventricular end-systolic pressure.

In a second group of five animals (group 2, which included one dog of group 1), after recording control data in the conscious state, phenolamine (2 mg/kg i.v.), a nonselective α-adrenoceptor blocker, was given with propranolol (2 mg/kg i.v.) and atropine (0.2 mg/kg i.v.). The adequacy of complete autonomic blockade was tested with noradrenaline (0.5 μg/kg i.v. bolus). It was considered complete when heart rate and ventricular pressure were not significantly changed by noradrenaline injection. After autonomic blockade, aortic constriction and caval occlusion were performed before and after volume loading. In four dogs, data were also recorded during release of the aortic cuff occluder 2 minutes after its inflation to exclude the Anrep effect.

Data Collection and Analysis

Absolute values of left ventricular pressure were obtained by calibration of the micromanometer, performed before implantation in 37°C water against a Statham P23dB transducer (Cleveland, Ohio). The shift of left ventricular zero pressure was corrected with the end-diastolic atrial pressure simultaneously recorded with the Statham pressure transducer. In two dogs, micromanometers were calibrated in vivo with a Millar probe (Mikro-TP, PC-370, Houston, Texas) introduced into the left ventricle immediately before sacrifice of the animal. Ventricular dimensions were obtained by connecting the wires of the crystals to a sonomicrometer (Triton Technology, San Diego, California). All variables, including instantaneous left atrial pressure, heart rate, left ventricular pressure and its derivative, and left ventricular dimensions were monitored on an eight-channel graphic recorder (Model 7758A, Hewlett-Packard, Palo Alto, California) at a paper speed of 50 or 100 mm/sec and stored on a magnetic tape recorder (Model 3968 A, Hewlett-Packard) for subsequent analysis.

End diastole was defined as the time when left ventricular pressure began to rise rapidly just after the atrial contraction. End systole was defined as the time when the instantaneous left ventricular pressure volume ratio reached its maximum. Left ventricular volume was calculated according to a modified ellipsoidal model with ventricular dimensions:

\[ V_{LV} = \frac{(\pi/6) D_{AP} \cdot D_{SFW} \cdot D_{BA}} \]

where \( V_{LV} \) was left ventricular volume and \( D_{AP} \), \( D_{SFW} \), and \( D_{BA} \) were left ventricular anteroposterior, septum-lateral free wall, and base-apex diameters, respectively. Left ventricular ESPVRs were obtained by beat-to-beat least-squares linear regression analysis of data measured during each loading
modification with the time-varying elastance model of the left ventricle:

\[ P_{es} = E_{es} \cdot (V_{es} - V_d) \]

where \( P_{es} \) is end-systolic left ventricular pressure, \( E_{es} \) is end-systolic elastance of the left ventricle (slope of ESPVR), \( V_{es} \) is end-systolic volume, and \( V_d \) is volume-axis intercept of ESPVR, which was obtained by extrapolation of the relation.

To calculate left ventricular hemodynamic and dimensional data, a Digital Equipment computer (Model MINC 11-23, Marlboro, Massachusetts) was used. A 7-second sequence of cardiac contractions was analyzed for each loading intervention at a sampling rate of 200 Hz. The first time derivative of left ventricular pressure (dP/dt) was digitally obtained. Values were compared with analogically obtained dP/dt. Both methods led to similar values. At least two beats were taken into account for calculating mean values of left ventricular hemodynamic and dimensional data at the beginning and at the end of each loading modification.

### Table 1. Heart Rate, End-Diastolic Volume, and Ejection Fraction Changes During the Control Conscious State and Caval Occlusions Before and After Volume Loading

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>End-diastolic volume (ml)</th>
<th>Ejection fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
</tr>
<tr>
<td>Conscious state</td>
<td>111.4</td>
<td>120.8</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
<td>6.6</td>
<td>4.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Before volume loading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beginning</td>
<td>204.0*</td>
<td>150.1</td>
<td>10.2*</td>
</tr>
<tr>
<td></td>
<td>8.6</td>
<td>16.2</td>
<td>1.4</td>
</tr>
<tr>
<td>End</td>
<td>200.6</td>
<td>150.3</td>
<td>6.4†</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>13.2</td>
<td>0.9</td>
</tr>
<tr>
<td>After volume loading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beginning</td>
<td>129.4‡</td>
<td>122.6</td>
<td>15.7‡</td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>9.1</td>
<td>2.0</td>
</tr>
<tr>
<td>End</td>
<td>131.7</td>
<td>125.4</td>
<td>7.9‡</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>6.1</td>
<td>1.2</td>
</tr>
<tr>
<td>( F ) value</td>
<td>&lt;0.005</td>
<td>&lt;0.025</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Group 1, dogs received propranolol and atropine after recording of the control conscious state. Heart rate was markedly increased compared with the conscious state and was reduced by volume loading, but caval occlusions did not produce heart rate changes. Group 2, the addition of phenolamine to atropine and propranolol prevented heart rate changes.

*\( p < 0.005 \) with the control conscious state; †\( p < 0.01 \) with the beginning of the corresponding caval occlusion; ‡\( p < 0.01 \) with the beginning of caval occlusion before volume loading.
Figure 2. Curvilinearity of left ventricular end-systolic pressure-volume relations in six dogs of group 1 during caval occlusion after volume loading. Total relations were divided into two parts of equal magnitude of end-systolic pressure changes. Dotted lines are the calculated initial part of end-systolic pressure-volume relation (with large end-systolic pressure and volumes) and the solid lines are the final part of the end-systolic pressure-volume relation. Letters represent dogs' numbers.

Statistical Analysis

A two-way analysis of variance of repeated measures over time was used for statistical comparison of dimensional data and variables of ESPVR produced by different loading modifications. When a significant trend was found by the F test, a paired t test was used to compare two different interventions. To avoid errors due to repetitive t tests, a restrictive level of significance (p<0.01) was used. When only two measurements were compared (comparison between slopes and intercept of initial and final parts of ESPVR), statistical significance was defined by a p value less than 0.05. Values are given as mean±SEM.

Results

After sedation and intravenous administration of propranolol and atropine (group 1), there was a marked heart rate increase, which was associated with a significant left ventricular end-diastolic volume decrease compared with that obtained in the control conscious state (Figure 1 and Table 1). Heart rate was significantly reduced during volume loading with dextran injection, which restored end-diastolic volume to its control conscious value (Table 1). In contrast with these heart rate variations before and after volume loading, there were no significant variations in heart rate during caval occlusions (Table 1).

In group 2, dogs received not only propranolol and atropine but also phentolamine. This resulted in small variations in heart rate after autonomic blockade (Table 1). Heart rate was slightly larger before than after volume loading, but this change was not significant. End-diastolic volume changes during loading modifications were associated with changes of ejection fraction (Table 1).

Curvilinearity of End-Systolic Pressure-Volume Relations During Caval Occlusions After Volume Loading

During inferior vena caval occlusion performed after volume loading, the end-systolic pressure-volume relation appeared curvilinear as illustrated in Figure 2 in the six dogs of group 1. The total end-systolic pressure-volume relation was divided into two different parts with pressure changes of the same magnitude (an initial part with large end-systolic volumes and a terminal part). There were two closely rectilinear relations as indicated in Table 2 in both series of dogs. Compared with the slope of the ESPVR observed in the initial part of caval occlusion, the slope of the terminal part of ESPVR was larger with, in most dogs, a rightward shift of Vd that was negative when the total and initial parts of caval occlusion were considered. Left ventricular end-systolic pressure (122.8±6.2 mm Hg) measured at the onset of caval occlusion was significantly smaller than the theoretical value (135.7±8.5 mm Hg) estimated from the ESPVR of the terminal part of caval occlusion (p<0.05).

When ESPVR was divided into two parts with the same method in the first group of dogs before volume loading, there was a small (29.7%), non-significant difference between the initial part (Ees=26.9±5.6 mm Hg/ml, Vd=0.2±0.6 ml) and the final part (Ees=34.4±5.3 mm Hg/ml, Vd=2.1±0.6 ml) of the relation.

Curvilinearity of the Relation Between the Peak of the First Derivative of Left Ventricular Pressure and End-Diastolic Volume

The relation between peak dP/dt and end-diastolic volume was also curvilinear during vena caval occlusion after volume loading in both groups (group 1, Figure 3; group 2, Table 3). This relation produced by caval occlusion after volume loading was divided into two different parts according to the magnitude of end-diastolic volume. The chosen division point was the point when end-diastolic volume was equal to 1.5 times the minimal end-diastolic volume reached during inferior vena caval occlusion in eight dogs (1.7 times in two dogs with small end-diastolic volumes). There was no corre-
TABLE 2. Left Ventricular End-Systolic Pressure-Volume Relations During Vena Caval Occlusion After Volume Loading

<table>
<thead>
<tr>
<th>Dog</th>
<th>Total caval occlusion</th>
<th>Initial part</th>
<th>Final part</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E&lt;sub&gt;s&lt;/sub&gt; (mm Hg/ml)</td>
<td>V&lt;sub&gt;d&lt;/sub&gt; (ml)</td>
<td>r</td>
</tr>
<tr>
<td>N</td>
<td>14.3 ±2.0</td>
<td>-3.0 ±0.5</td>
<td>0.94 ±0.1</td>
</tr>
<tr>
<td>S</td>
<td>23.0 ±3.6</td>
<td>-2.1 ±1.2</td>
<td>1 ±0.2</td>
</tr>
<tr>
<td>G</td>
<td>13.8 ±2.0</td>
<td>-3.3 ±1.2</td>
<td>0.99 ±0.8</td>
</tr>
<tr>
<td>T</td>
<td>13.6 ±1.2</td>
<td>-0.8 ±0.8</td>
<td>0.99 ±0.7</td>
</tr>
<tr>
<td>R</td>
<td>16.0 ±1.7</td>
<td>1.0 ±0.9</td>
<td>0.99 ±0.7</td>
</tr>
<tr>
<td>Q</td>
<td>8.0 ±2.0</td>
<td>-0.2 ±0.5</td>
<td>0.97 ±0.3</td>
</tr>
<tr>
<td>Mean</td>
<td>14.8 ±2.0</td>
<td>-1.7 ±0.5</td>
<td>1.9 ±0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dog</th>
<th>Total caval occlusion</th>
<th>Initial part</th>
<th>Final part</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E&lt;sub&gt;s&lt;/sub&gt; (mm Hg/ml)</td>
<td>V&lt;sub&gt;d&lt;/sub&gt; (ml)</td>
<td>r</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>14.0 ±3.8</td>
<td>-2.0 ±1.6</td>
<td>11.8 ±2.9</td>
</tr>
<tr>
<td></td>
<td>±2.1 ±0.8</td>
<td>±1.7 ±0.8</td>
<td>±2.9 ±1.4</td>
</tr>
</tbody>
</table>

General mean representing the average of data obtained from the 10 dogs (with and without phentolamine) was calculated because heart rates were not significantly different in groups 1 and 2 after volume loading (Table 1). Dog R, which was in both groups, was included only once.

For total caval occlusion, all points obtained during caval occlusion were considered.

*p < 0.05 with total caval occlusion; †p < 0.05 with initial part of caval occlusion; §p < 0.01 with total caval occlusion; ¶p < 0.01 with initial part of caval occlusion.

lation between peak dP/dt and end-diastolic volume in the initial part. In this part, the range of peak dP/dt variations was very small although the end-diastolic volume was reduced by a large amount. The correlation coefficient of the end-diastolic volume–peak dP/dt relation was largest in most dogs in the final part of the relation than when the whole relation was considered.

When the 10 dogs were considered together (experiments with and without phentolamine), the mean slope of the final part was significantly steeper than that of the whole relation (166.6 ±24.2 vs. 93.7 ±11.7 mm Hg/ml, respectively; p < 0.005). The theoretical value of dP/dt estimated from the final part of the correlation (3,581 ±296 mm Hg/sec) was significantly larger than the value measured at the onset of caval occlusion (3,016 ±175 mm Hg/sec, p < 0.02).

Variations of E<sub>s</sub> and V<sub>d</sub> During Different Types of Loading Modifications

As illustrated in Figure 4 in one dog, aortic constriction after volume loading produced a larger E<sub>s</sub> than that produced by caval occlusion performed after volume loading. This was reproduced in all dogs of both series (Table 4) and associated with a marked rightward shift of V<sub>d</sub> compared with that obtained with caval occlusion. Compared with ESPVR obtained during caval occlusion after volume loading, caval occlusion after aortic constriction led to a similar E<sub>s</sub>, but this was associated with a significant leftward shift of V<sub>d</sub> (Table 4). Thus, ESPVRs obtained during caval occlusion after aortic constriction were shifted upward compared with ESPVR obtained during caval occlusion after volume loading (Figure 4).

There was a significant difference of E<sub>s</sub> values obtained from different interventions in both groups of dogs when all interventions were examined with two-way analysis of variance (Table 4). E<sub>s</sub> was larger during caval occlusion before volume loading than during caval occlusion after volume loading in group 1 (Table 4), but heart rates were significantly different (Table 1). Thus, ESPVRs obtained before and after volume loading were compared in group 2 animals where heart rate variations were small (Table 1). Before volume loading, slopes of ESPVR were the same during caval occlusion as those during aortic constriction with nearly identical values of V<sub>d</sub> that were close to zero (Table 4). In contrast, after volume loading, slopes of ESPVRs and calculated V<sub>d</sub> were smaller during caval occlusion than during aortic constriction. In addition, slopes obtained during caval occlusion after volume loading were smaller than those obtained before volume loading. Intercepts (V<sub>d</sub>) were also shifted to the left along the volume axis after
volume loading in all dogs (Table 4). In contrast, $E_{os}$ and $V_d$ of the terminal part of ESPVR obtained during caval occlusion after volume loading were not different from those obtained during aortic constriction before volume loading and aortic constriction after volume loading.

Effects of Loading Manipulations on the End-Diastolic Pressure-Volume Curve

Figure 5 shows an end-diastolic pressure-volume curve constructed from the mean values obtained in the five dogs of group 2 at the beginning and the end of each loading intervention (caval occlusion and aortic constriction before and after volume loading). Caval occlusions produced a displacement of end-diastolic pressure-volume points along the flat segment of the left ventricular passive pressure-volume curve. Aortic constriction after volume loading produced a large increase of end-diastolic pressure (from $24.2 \pm 5.1$ to $32.1 \pm 6.9$ mm Hg, $p < 0.005$) that was accompanied with a minimal increment in end-diastolic volume ($0.7 \pm 0.2$ ml). This change in end-diastolic volume was much smaller than that provoked by caval occlusion after volume loading ($5.8 \pm 0.5$ ml, $p < 0.001$). The end-diastolic pressure-volume point obtained in the conscious control state was situated close to the vertical segment of the passive pressure-volume curve.

Elimination of the Anrep Effect

To eliminate an effect of a subendocardial ischemia on end-systolic pressure-volume relations during rapid aortic constriction, ESPVRs were calculated also in four of five dogs of group 2 during release of aortic constriction 2 minutes after inflating the cuff. With low and high filling pressures, the slope of ESPVR was $14.3 \pm 2.6$ mm Hg/ml and $15.3 \pm 2.5$ mm Hg/ml, respectively, during inflation of the aortic cuff. During release of the aortic cuff, $E_{os}$ was slightly larger for both small and large end-diastolic volumes ($15.7 \pm 3.1$ and $16.2 \pm 3.4$ mm Hg/ml, respectively). These values were similar to those obtained during vena caval occlusion with small end-diastolic volume ($15.8 \pm 3.0$ mm Hg/ml) and were markedly larger than those measured when end-diastolic volume was large ($9.9 \pm 1.8$ mm Hg/ml).

Similarly, calculated $V_d$ was not different either during aortic constriction ($0.3 \pm 1.3$ and $1.5 \pm 2.0$ ml with low and high filling pressure, respectively) or during release of the aortic cuff ($1.1 \pm 1.5$ and

![Figure 3. Curvilinearity of the relation between left ventricular end-diastolic volume and peak dP/dt in the six dogs of group 1 during caval occlusion after volume loading. Heart size was small in these small dogs, particularly in dog S. Solid lines are the calculated correlation for end-diastolic volumes 1.5 times minimal end-diastolic volume reached during caval occlusion (1.7 times this value in dogs S and N). $y_1$ is the equation of this line, and $y_2$ is the equation of the total relation. Note that points obtained when end-diastolic volumes are large are below the solid line.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.79.2.436)

**Table 3.** Relations Between Left Ventricular End-Diastolic Volume and Peak dP/dt During CavaL Occlusion After Volume Loading in Group 2 Dogs

<table>
<thead>
<tr>
<th>Dog</th>
<th>Slope (mm Hg/sec/ml)</th>
<th>y-axis intercept (mm Hg/sec)</th>
<th>$r$</th>
<th>Slope (mm Hg/sec/ml)</th>
<th>y-axis intercept (mm Hg/sec)</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>112.9</td>
<td>1,059</td>
<td>0.948</td>
<td>124.1</td>
<td>933</td>
<td>0.883</td>
</tr>
<tr>
<td>R</td>
<td>46.6</td>
<td>2,306</td>
<td>0.719</td>
<td>127.8</td>
<td>1,584</td>
<td>0.935</td>
</tr>
<tr>
<td>V</td>
<td>43.9</td>
<td>1,184</td>
<td>0.863</td>
<td>95.3</td>
<td>687</td>
<td>0.906</td>
</tr>
<tr>
<td>O</td>
<td>111.7</td>
<td>2,682</td>
<td>0.730</td>
<td>261.8</td>
<td>1,498</td>
<td>0.886</td>
</tr>
<tr>
<td>I</td>
<td>64.5</td>
<td>1,644</td>
<td>0.893</td>
<td>81.8</td>
<td>1,357</td>
<td>0.878</td>
</tr>
<tr>
<td>Mean</td>
<td>75.9±15.3</td>
<td>1,775±315</td>
<td>0.878</td>
<td>138.2±32.1</td>
<td>1,212±172*</td>
<td>0.878</td>
</tr>
</tbody>
</table>

$n = 5$ dogs.

Slopes of relations between end-diastolic volume and peak dP/dt were smaller in all dogs when all points of the relation were considered (total caval occlusion) than when only the final point of the relation was considered (final part of caval occlusion) with a larger intercept with the y axis (*$p < 0.05$). $r$ is the individual correlation coefficient.
1.3 ± 2.0 ml for small and large end-diastolic volume, respectively. Values were not different from those measured during vena caval occlusion with small end-diastolic volume (1.0 ± 1.5 ml) but were markedly larger than those obtained with large end-diastolic volume (~2.8 ± 2.0 ml).

Discussion

This study shows that the slopes and intercepts of the ESPVR are different during aortic constriction and during caval occlusion when left ventricular end-diastolic volume is close to that measured during the control conscious state but not when heart size is small. This finding is attributed to the curvilinearity of ESPVR when the range of preload changes is large.

Possible Limitations of the Study

Calculated volumes of dogs in this study were smaller than volumes usually published. However, dogs used in this study were small. Using the same method that we used for measuring diameters, Sodums et al.18 showed an excellent correlation between calculated stroke volume and stroke volume obtained directly from angiocardiography. Nevertheless, major axis measurements could have been underestimated because the upper crystal was positioned immediately below the circumflex coronary artery, but a possible influence of an underestimation of end-diastolic volume on our results is unlikely because in the two dogs with the lowest end-diastolic volume curvilinearity of ESPVR was not observed (Figure 2).

The saturation of end-systolic clastance, convex to the volume axis, could be due in part to the depressant effect of fentanyl and droperidol. However, the slope of the final part of ESPVR was 62.5% larger than the slope of the initial part after volume loading, which is in contrast with an increase of 27.9% only before volume loading; this confirms a direct effect of preload.

Factors Affecting ESPVR

In conscious animals, the end-systolic pressure-volume relation is hampered by variability in $E_{es}$ and $V_d$ with changes in afterload because of an intact autonomic cardiovascular system.7 Autonomic reflexes produced by loading modifications were attenuated in our study by propranolol and atropine injections. Freeman et al.5 used the same procedure and showed a change in heart rate smaller than 10 beats/min during caval occlusion. In our study, caval occlusion did not produce significant heart rate changes, but volume loading induced a heart rate reduction, suggesting that all reflexes were not completely blocked. Horwitz and Bishop12 showed that the Bainbridge reflex could be blocked by $\beta$-blockade and atropine. Bainbridge reflex was not only blocked but inverted in group 1 dogs in our study. However, doses of propranolol and atropine in our study were larger than in Horwitz and Bishop's study. Phentolamine injection prevented the large tachycardia induced by $\beta$-sympathetic and vagal receptor blocking, and heart rate was not modified by volume loading after $\alpha$-blockade.

These heart rate changes could have affected the results of group 1 dogs because in isolated hearts13 and in closed-chest dogs14 heart rate increases have been shown to produce a rightward shift of $V_d$ and an increase of $E_{es}$. Heart rate changes, thus, could explain the differences in ESPVR obtained during caval occlusions with low and high preloads with markedly different heart rates in group 1 but not in group 2 dogs where heart rate changes were minimal before and after volume loading. Furthermore, heart rate changes could not explain the differences of ESPVRs measured during aortic constriction and caval occlusion at high preload.

Pressure and volume changes occurring in the right ventricle modify left ventricular function (ventricular interdependence).15 However, in situ heart
spontaneous baroreflexes were induced in this study and in the studies of others.10–12 Aortic constriction caused a decrease in both Ees and Vd and an increase in CO, which was also true in our study. However, the decrease in Ees and Vd during aortic constriction was less pronounced in our study than in studies of others.8,10 Small interanimal variability could be a reason for the discrepancy. Another possible reason is the different design of our study, which deals with conscious dogs, whereas most studies in the literature were performed in anesthetized dogs.10–13

In order to explain this discrepancy, we examined the linear relationship between Ees and Vd in the control state. In Figure 3, the data points obtained before aortic constriction and caval occlusion fall in a linear relation, which can be described by the regression equation Ees = 0.64Vd (r = 0.78, n = 6).

However, in the aortic constriction state, a linear relation was not present. This confirms that the linear relation was caused by aortic constriction. We therefore postulate that the linear relationship observed during control state is caused by a direct effect of the arterial baroreflexes on Ees. Thus, Ees might be determined by a factor other than Vd. In other words, the direct effect of baroreflexes on Ees might also explain the decrease in Ees during aortic constriction. However, the magnitude of the decrease in Ees during aortic constriction was not significantly different in control state and in the aortic constriction state. Thus, Ees was independent of Vd in both conditions. An effect of baroreflexes on Ees is not likely to account for the decrease in Ees during aortic constriction.

Recently, Berko et al.12 demonstrated that the linear relationship between Ees and Vd could be described by the regression equation Ees = 0.64Vd (r = 0.78, n = 6), whereas in the aortic constriction state, a linear relation was not present.

Changes in Ees and CO were observed during caval occlusion. In Figure 3, the data points obtained during caval occlusion fall in a linear relation, which can be described by the regression equation Ees = 0.64Vd (r = 0.78, n = 6). This is consistent with studies by other investigators.10,11,13 In the aortic constriction state, the decrease in Ees during caval occlusion was less pronounced than in the control state. Thus, Ees was independent of Vd in both conditions.

These results are consistent with the findings of other investigators.10,11,13 We therefore concluded that Ees is determined by the arterial baroreflexes and is not affected by Vd or end-diastolic pressure.

In conclusion, our results indicate that baroreflexes have a direct effect on Ees and can be described by the regression equation Ees = 0.64Vd (r = 0.78, n = 6), whereas in the aortic constriction state, a linear relation was not present.

FIGURE 3. Plot of mean end-diastolic pressure-volume points obtained during loading modifications. Circles, data obtained before aortic constriction (AC) or caval occlusion (CO) (control). Triangles and squares, data obtained when the maximal response after AC and CO were respectively reached. Point obtained in the control conscious state without autonomic blockade (X) appears close to the vertical portion of the relation.
variables is consistent with the predictions of the
time-varying elastance model. Our results (Figure
3) show the same linear relation until an end-
diastolic value is obtained, but beyond that peak dP/
dt is independent of end-diastolic volume, suggest-
ing that peak dP/dt could be a reliable index of
contractility in the in situ heart where end-diastolic
volumes are large. In Little’s study, only one example
of the curvilinear relation was shown. The difference
with our data probably lies in the dif-
f erent ranges of end-diastolic volumes because a
volume loading was produced in our study and not
in Little’s. The curvilinearity of the end-systolic
pressure-volume relation (Figure 2) is consistent
with the curvilinearity of the peak dP/dt—end-
diastolic relation. This produces a depression of
end-systolic pressure when end-diastolic volume is
large compared with the value that would be
expected from the ESPVR obtained with small
end-diastolic volumes. This agrees with results
obtained in isolated hearts by Suga and Yamakoshi,6
who showed that ESPVR is affected by ejection,
particularly when stroke volume is large. Kass and
Maughan18 recently insisted on the difference
between the true E\textsubscript{max} (obtained in isolated hearts from
different loaded beats synchronized in time)
and ESPVR obtained in the in situ heart, which can
lead to E\textsubscript{max} significantly steeper than E\textsubscript{es}. Among
possible mechanisms of depression of end-systolic
pressure from the isovolumic line, Suga and
Yamakoshi6 suggested an uncoupling effect of quick
shortening of heart muscles, contractility changes
with fiber length, and shortening velocity. The
concept of modulation of “contractility” by fiber
length was recently reviewed by Lakatta.23 This
could produce inotropic state changes when preload
was markedly modified. Some viscous resistance
against deformation among myocardial fibers and
layers may also affect ESPVR. The existence of a
series viscoelastic element has been suggested by
LeWinter et al24 as an explanation for a time-
dependent shift of the left ventricular diastolic filling
relation after methoxamine injection associated with
an end-systolic pressure-diameter shift. These results
are similar to those previously published by inves-
tigators from our laboratory22 where an end-systolic
pressure-dimension shift was shown during closure
of a fistula between the left carotid artery and the
left atrial appendage. A creep deformation is likely
to occur when end-diastolic pressure is high, par-
ticularly in this condition of chronic volume over-
load. It has been attributed to a slippage of
myofibrils.25 Our results (Figure 5) suggest that the
end-diastolic pressure-volume point is close to the
vertical portion of this relation in the conscious
resting state. Nearly 30 years ago, Rushmer et al26
observed that the end-diastolic ventricular size is
nearly maximal at rest in the intact conscious dog,
and these results were confirmed by Boeticher et
al.27 The left ventricle, thus, appears as operating
close to the Frank-Starling mechanism limit. Differ-
ences obtained in in situ and in isolated hearts
(where ESPVR was shown to be relatively insensitive
to preload changes) may be due to different
ranges of examined preloads in those models because
the in situ heart appears to operate on an end-
diastolic pressure-volume point close to the maxi-
mum preload reserve.

The absence of pericardium may have overdi-
lated the heart because a rightward shift of the end-
diastolic pressure-dimension has been shown after pericardectomy.28 Our results, thus, cannot be
directly extended to the clinical setting where the
pericardium is present, but they do indicate that,
along with other mechanisms such as heart rate and
arterial impedance, preload may affect the ESPVR,
particularly when the heart is dilated. Although
ESPVR has less of a curvilinear nature than the plot
of other indexes of ventricular function versus
load,29 our data show that, when preload is high,
ESPVR curvilinearity produces different E\textsubscript{es}
for different types of loading modifications.

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