Effects of global ischemia on the diastolic properties of the left ventricle in the conscious dog


ABSTRACT The alterations in regional diastolic mechanics that occur during regional myocardial ischemia (creep and increased myocardial stiffness) may be the result of interactions between the ischemic and surrounding nonischemic myocardium rather than the direct result of ischemia. Thus similar changes may not occur when the entire left ventricle is ischemic. To investigate this proposition, left ventricular diastolic mechanics were studied in seven chronically instrumented conscious dogs during global left ventricular ischemia. The anterior-posterior, septal-free, and base-apex axes of the left ventricle were measured with ultrasonic dimension transducers. Left and right ventricular pressures were measured with micromanometers. Myocardial blood flows were measured with left atrial injections of 15 μm radioactive microspheres. Global left ventricular ischemia was induced by hydraulic constriction of the left main coronary artery, which resulted in a 54% decrease in mean left ventricular subendocardial blood flow. Left ventricular volume, midwall circumference, and midwall circumferential stress were calculated from ellipsoidal shell theory. To construct pressure-strain and stress-strain relationships from diastolic data collected during vena caval occlusions, all measured and calculated dimensions were normalized to Lagrangian strains (fractional extension from unstressed dimension). During ischemia, creep (elongation of unstressed dimension) occurred in each of the three left ventricular axes. The mean unstressed dimension of the anterior-posterior axis increased from 5.39 ± 0.53 to 5.85 ± 0.50 cm (p < .05); the septal-free wall unstressed dimension increased from 5.11 ± 0.53 to 5.72 ± 0.80 cm (p < .05); and the base-apex unstressed dimension increased from 7.04 ± 0.61 to 7.25 ± 0.65 cm (p < .05). The relationship between diastolic midwall circumferential stress and strain shifted upward and to the left with ischemia, indicating that an increase in intrinsic myocardial stiffness had occurred. As a result of these mechanical alterations, there was a decrease in left ventricular chamber compliance that was manifested by a leftward shift of the diastolic pressure-volume strain relationship. Neither systolic bulging nor dysynchronous systolic shortening occurred in any of the three left ventricular spatial axes during ischemia. Thus, during global left ventricular ischemia, changes in diastolic mechanics identical to those that occur during regional ischemia account for a loss of left ventricular chamber compliance. This suggests that although systolic dyskinesia during regional ischemia may result from interactions between areas of ischemic and nonischemic myocardium, changes in regional diastolic mechanics are the direct result of ischemia.


THE RESULTS of clinical and experimental studies have suggested that diastolic relationships between left ventricular pressure and dimension are altered by ischemia. Although the effects of ischemia on regional diastolic properties have been well documented,1-2 less is known about the effects of global left ventricular ischemia on the diastolic pressure-volume relationship of the left ventricle. Data collected from patients with coronary artery disease3-9 have demonstrated that left ventricular end-diastolic pressure and volume both increase when there is an increased demand for cardiac output. Because left ventricular diastolic pressures at any given volume have been observed to be higher during ischemia, these data have been interpreted as demonstrating a decrease in the distensibility of the left ventricular chamber. Changes in the elastic properties of the myocardium, increases in right ventricular pressure, and incomplete ventricular relaxation are the most frequently invoked causes of this abnormality. On the other hand, there have been disparate results
from experiments in animal preparations of global left ventricular ischemia. In dogs with coronary stenoses, left ventricular compliance has been shown to decrease during rapid atrial pacing. Experiments in isolated heart preparations, however, have shown left ventricular compliance to be either unchanged or increased during acute global ischemia.

The analysis of regional diastolic mechanics during regional left ventricular ischemia has emphasized the importance of characterizing the elasticity of the myocardium with rigorous mechanical theory and methodology. This type of methodology has not been used previously to analyze the changes in left ventricular compliance that occur during acute global left ventricular ischemia. The proper normalization of dimensions is essential if diastolic pressure-dimension data are to be interpreted meaningfully. When the resting or unstressed dimensions of an elastic material are variable, the analysis of elasticity must take into account this variability. As the left ventricle fills during diastole, changes in its dimensions must be referred to unstressed dimensions to determine to what extent the ventricle is being deformed from its unstressed configuration. One method of accomplishing this is to convert raw dimensions to Lagrangian strain, which is the fractional change in dimension from unstressed dimension. It has been shown that the unstressed dimension of myocardial segment length increases during regional ischemia (the creep phenomenon). For this reason, linear segments within ischemic regions become longer at any given left ventricular diastolic pressure. When myocardial segment length is not expressed as strain, regions of the left ventricle may appear to become more compliant rather than less compliant during ischemia. However, when segment length is properly normalized with respect to unstressed dimension, it has been observed that regions of the left ventricle actually become less compliant during ischemia.

If the same changes in myocardial mechanics that occur during left ventricular regional ischemia occur globally when the entire ventricle is ischemic, it would dictate that during global ischemia, pressure and dimension data must be analyzed with the same rigorous methodology previously used to analyze regional data. It would also suggest that the abnormalities that occur during regional ischemia are the direct result of ischemia rather than the result of interactions between the ischemic region and surrounding areas of nonischemic myocardium. The purpose of the present study was to examine the changes in diastolic mechanics that occur during global left ventricular ischemia induced by constriction of the left main coronary artery in the conscious dog. We also investigated to what extent altered myocardial elasticity, abnormal right ventricular loading, and prolonged left ventricular relaxation contribute to changes in left ventricular compliance during global ischemia.

**Materials and methods**

**Experimental preparation.** Seven healthy adult dogs (20 to 30 kg) were subjected to left thoracotomy under general anesthesia (30 mg/kg pentobarbital) for the implantation of instrumentation to collect ventricular pressure and dimension data (figure 1). The experimental preparation has been described previously. In brief, three pairs of ultrasonic dimension transducers were implanted to measure the anterior-posterior minor axis, septal–free wall minor axis, and base-apex major axis of the left ventricle. The anterior-posterior and base-apex axes were measured as external diameters, with their respective transducers sewn to the left ventricular epicardium. The septal–free wall diameter was measured from the midwall of the interventricular septum to the epicardium of the lateral free wall.

Silicone rubber catheters were implanted in the right ventricle and left atrium so that during subsequent studies, micromanometers could be introduced to measure right and left ventricular pressures. A third silicone rubber catheter, closed at its distal end by a compliant silicone rubber balloon (1/100 inch thickness), was positioned in the chest at the level of the aortic arch to measure intraluminal pressure. Bipolar pacing electrodes were sewn onto the right atrial appendage. Inflatable silicone rubber occluders were placed around the two vena cavae, and the azygos vein was ligated. A fluid-filled polyvinyl chloride catheter was inserted through the left internal mammary artery into the aortic arch to measure aortic pressure.

A 6 mm inflatable silicone rubber occluder was positioned around the left main coronary artery. A 3.5 mm Statham electromagnetic flow probe was positioned around the anterior descending coronary artery proximal to its first major diagonal branch. The electrical leads, catheters, and occluders were all exteriorized dorsal to the thoracotomy incision. The pericardium was left open, and the chest was closed. Postoperatively the dogs received intramuscular injections of dihydrostreptomycin (0.75 g) and penicillin (6 × 10⁶ U) for 3 days.

**Instrumentation and data acquisition.** The dogs were allowed to recover from surgery for 7 days before they were studied. Data were collected while the dogs were awake and

**FIGURE 1.** Experimental preparation. See text for details.
unsedated. The sonomicrometer used in these experiments was constructed in this laboratory and has been described previously.\textsuperscript{16} It converts the transit time of a pulse of ultrasound between two piezoelectric crystals into an analog signal.\textsuperscript{17} Since the velocity of sound is constant in tissues and blood, the measured transit time is directly proportional to the distance between the transducers. The sampling rate of the device is 1 kHz, and its resolution is 0.05 mm.

Left and right ventricular pressures were measured with catheter-tipped micromanometers (Millar PC-350). They were driven with Hewlett-Packard 8805C carrier preamplifiers and were zeroed and balanced to atmospheric pressure at 38°C. The zero drift of each transducer did not exceed 0.5 mm Hg during the course of any study. The resonant frequency of the Millar micromanometer is 25 to 35 kHz.

Pleural and aortic pressures were measured with external transducers (Statham P23Db) connected to fluid-filled catheters. A No. 6F catheter (U.S.C.I.) was inserted through the previously implanted pleural catheter to measure pleural pressure. The catheter-balloon system was filled with between 0.5 and 1.0 ml of saline before insertion of the No. 6F catheter. This volume was enough to fill the system with the No. 6F catheter inserted and to measure 0.0 mm Hg pressure during testing before implantation. Aortic pressure was measured with the fluid-filled polyvinyl chloride catheter previously implanted in the aortic arch. The external transducers were zeroed and balanced to atmospheric pressure at the midchest level. The zero drift of the pleural pressure transducer did not exceed 0.5 mm Hg during any study.

The flow probe encircling the anterior descending coronary artery was connected to a Gould-Statham SP2202 square-wave flowmeter. The analog signal from the flowmeter was passed through a Hewlett-Packard 8811A bioelectric preamplifier and displayed on a Hewlett-Packard 13909A oscilloscope.

Analog data representing pressures and dimensions were recorded on magnetic tape with a Hewlett-Packard 3968A tape recorder. Data were collected from each dog during a control period and at the end of a 5 min period of constriction of the left main coronary artery. The coronary occluder was inflated until either a 50% decrease in flow was noted on the tracing from the coronary flow probe or until a change in left ventricular pressure (increased left ventricular end-diastolic pressure or decreased left ventricular peak systolic pressure) was observed. Transient vena caval occlusions were produced both during the control period of data collection and during the ischemic period by inflating the vena caval occluders so that peak systolic left ventricular and aortic pressure were gradually reduced to 25 mm Hg over a 30 sec period. The data collected during these occlusions were used to determine the unstressed dimensions of the left ventricle and to generate diastolic pressure-dimension relationships over a wide range of left ventricular loading.

Injections of 15 μm radioactive microspheres were administered through the left atrial catheter before and 5 min after constriction of the left main coronary artery. Reference samples of blood were withdrawn through the aortic catheter during each microsphere injection. To control for changes in myocardial blood flow caused by tachycardia, each control injection of microspheres was performed during atrial pacing at a rate of 150 beats/min.

Each dog was killed at the conclusion of the experiment and examined at autopsy. The position of the septal transducer was ascertained to be within 2 mm of the midwall position in each of the dogs. The mass of the left ventricle, including the interventricular septum, was determined. The left ventricle was fixed in 3% formaldehyde for 1 week before samples were taken for radioactive counting.

For the purpose of determining myocardial blood flows, the left ventricle was divided along the long axis into four slices of approximately equal thickness. Only samples from the middle two rings were counted. These two rings were divided into six circumferential regions representing the interventricular septum, posterior free wall, posterior papillary muscle, lateral wall, anterior papillary muscle, and anterior free wall. Each of these specimens was then divided into four samples of approximately equal thickness from epicardium to endocardium. Myocardial and blood reference samples were counted in a Packard 5912 gamma-counting system at window settings selected to correspond to the peak energies of each radionuclide.

Data analysis. The analog data representing pressures and dimensions were digitized at 5 msec intervals on a PDP 11/34 computer (Digital Equipment Corp.). The left ventricle was modeled as a generalized ellipsoidal shell with three unequal orthogonal axes. The measured base-apex was considered the external major axis diameter of the shell. The measured anterior-posterior dimension was considered one of the two external equatorial minor axes. The measured septal-free wall dimension was set equal to the external equatorial septal–free wall diameter minus one-half of the equatorial wall thickness.

The equatorial left ventricular wall thickness dimension was calculated from the three measured left ventricular axis dimensions and the postmortem mass of the left ventricle with its papillary muscles excised. This single estimate ignores circumferential variability and was obtained in the following manner: The external volume (Ve) of the shell is equal to

\[
Ve = \frac{\pi}{6} (a) (b) (c + .5h) \tag{1}
\]

where \(a\), \(b\), and \(c\) are the measured major axis, anterior-posterior minor axis, and septal–free wall minor axis, respectively, and \(h\) is equatorial wall thickness.

The inner volume of the shell (Vi) is equal to

\[
Vi = \frac{\pi}{6} (a - 1.1h) (b - 2h) (c - 1.5h) \tag{2}
\]

Equation 2 assumes that the thickness of the shell at the base and apex (beneath the major axis transducers) is 55% of equatorial wall thickness, a relationship previously validated by postmortem studies.\textsuperscript{18} The mass (M) of the shell is equal to its volume multiplied by its specific gravity (1.07 g/cm³):

\[
M = 1.07 (Ve - Vi) \tag{3}
\]

By substituting the postmortem left ventricular mass for \(M\), \(h\) can be calculated from equations 1, 2, and 3.

The chamber volume of the left ventricle was considered to be the inner volume of the shell (Vi, equation 2). Midwall equatorial circumference (L) was calculated as

\[
L = 2(b - h) \int \sqrt{1 - k^2 \sin^2 \theta} \ d\theta \tag{4}
\]

where

\[
k^2 = \frac{(b - h)^2 - (c - .5h)^2}{(b - h)^2} \tag{5}
\]

Left ventricular transmural pressure (TMP) was calculated as the difference between left ventricular intracavitary pressure (LVP) and pleural pressure (PP):

\[
TMP = LVP - PP \tag{6}
\]

To estimate midwall circumferential stress at the left ventricular equator, an external left ventricular pressure (ELVP) was calculated by assuming that two-thirds of the outer surface area of the left ventricle are surrounded by the pleural cavity and one-third...
is surrounded by the right ventricle:\(^1\):

\[
	ext{ELVP} = (2\text{PP} + \text{RVP})/3
\]  

(7)

The midwall circumferential stress at the left ventricular equator was then calculated for a thin-walled ellipsoidal shell:\(^2\):

\[
\text{LV P} \left( \frac{b - 2h}{4h} \right) \left( \frac{c - 1.5h}{b} \right) + \left( \frac{b - 2h}{a - 1.5h} \right) - \text{ELVP} \left( \frac{b + 2h}{4h} \right) \left( \frac{c + 5h}{a} \right) = \frac{b c + (c + 0.5h) h}{a^2}
\]

(8)

A computerized algorithm was used to identify the diastolic and ejection phases of the cardiac cycle. The beginning of diastole was marked at the minimum left ventricular pressure after ventricular systole. The end of diastole was marked at the minimum left ventricular pressure after atrial systole. The beginning of systolic ejection was marked at the first time during systole that left ventricular pressure was equal to aortic pressure. End-ejection was marked during the rapid descent of left ventricular pressure (-\(dP/dt\) \(\geq 200\) mm Hg/sec) at the first point in time when aortic pressure exceeded left ventricular pressure by more than 5 mm Hg.

For the purpose of analyzing diastolic force-dimension relationships, each measured and calculated left ventricular dimension was normalized to a Lagrangian strain, \(\varepsilon\) (fractional extension from unstressed dimension):

\[
\varepsilon D = (D - Do)/Do
\]

(9)

where \(\varepsilon D\) is the Lagrangian strain of dimension \(D\) and \(Do\) is the unstressed dimension of \(D\). The unstressed dimensions of the three left ventricular axes, left ventricular volume, midwall circumference, and equatorial wall thickness were determined at maximal vena caval occlusion when left ventricular transmural pressure was equal to 0 mm Hg.

To characterize the static elastic diastolic properties of the left ventricle, pressure-strain and stress-strain data were selected from multiple (20 to 30) cardiac cycles during vena caval occlusions. Data were selected from the midexpiratory phase of the respiratory cycle to minimize respiratory variation in the ventricular pressure and dimension data. Pleural pressures were usually between 0.0 and \(-5.0\) mm Hg during this phase of the respiratory cycle. Only data of low strain velocity (\(d\varepsilon/dt \leq 0.01\) sec for each left ventricular axis, \(\leq 0.03\) sec for left ventricular midwall circumference, and \(\leq 0.1\) sec for left ventricular volume) were analyzed, thereby minimizing the effects of the viscous filling properties of the left ventricle. These data were fit by nonlinear least squares regression to the Kelvin viscoelastic equation:

\[
\text{TMP or } \sigma = \alpha(\varepsilon^\beta - 1) + \eta \varepsilon/dt
\]

(10)

where \(\alpha\), \(\beta\), and \(\eta\) are parameters determined from the curve fit and \(\varepsilon/dt\) is strain velocity. Since only data of low strain velocity were selected for analysis, the viscous term of equation 10, \(\eta \varepsilon/dt\), was set equal to zero:

\[
\text{TMP or } \sigma = \alpha(\varepsilon^\beta - 1)
\]

(11)

Thus, only the elastic component of the Kelvin equation was used to account for the forces generated in filling the ventricle. The suitability of equation 11 as a descriptor of the static elastic relationship between midwall circumferential stress and strain has been established previously.\(^2\) This modification of the Kelvin model has also been used empirically to characterize the relationships between left ventricular transmural pressure and volume strain and between transmural pressure and axis length strain.\(^2\) For the purpose of demonstrating the relationship between left ventricular transmural pressure and unstressed dimension.
distribution, manifested by a significant decrease in the endocardial-to-epicardial flow ratio, occurred during ischemia.

To assess the homogeneity of the decreases in blood flow during coronary constriction, flow was segregated onto its anterior and posterior components (table 1). The anterior measurements are averages from the anterior free wall and anterior papillary muscle regions. The posterior flows are averages from the posterior free wall and posterior papillary muscle regions. The decreases in flow posteriorly exceeded the decreases in anterior flow. During ischemia there were substantial decreases in endocardial flow in both the anterior and posterior circulations. Significant changes in mural flow distribution occurred both anteriorly and posteriorly, as manifested by decreases in the ratio of endocardial to epicardial flow.

Hemodynamics. The hemodynamic parameters measured during the control period and after 5 min of constriction of the left main coronary artery are presented in table 2. The parameters from each dog are represented by mean values obtained from 10 cardiac cycles. The significant increase in heart rate during ischemia compensated for the decreases in stroke volume and ejection fraction to maintain cardiac output. The decline in peak systolic left ventricular transmural pressure was not statistically significant. End-diastolic left ventricular transmural pressure and end-diastolic volume were both significantly increased during ischemia. The changes in right ventricular pressure that were observed were not statistically significant. The time constant describing the decay of left ventricular pressure during relaxation was significantly prolonged during ischemia. In each dog, however, the diastolic interval exceeded 3.5 time constants during both the control and ischemic periods. Thus near-complete relaxation occurred by end-diastole during both the control and ischemic periods.

Left ventricular diastolic mechanics. Representative analog data collected from vena caval occlusions performed during a control period and after 5 min of ischemia are illustrated in figure 2. During ischemia, heart rate and end-diastolic left ventricular pressure were higher than control values. Left ventricular peak systolic pressure was somewhat lower during ischemia. During each vena caval occlusion, progressive decreases in all three left ventricular diastolic dimensions occurred until they reached their unstressed values. During ischemia the unstressed dimensions of each of the three left ventricular axes were increased compared with control values. All seven dogs behaved similarly.

The increases in the unstressed dimensions of the left ventricle that occurred after 5 min of ischemia are documented in table 3. On the basis of the increases in the unstressed dimensions of the three left ventricular axes, there were also significant increases in the unstressed dimensions of left ventricular midwall circumference and left ventricular volume during ischemia. The calculated unstressed dimension of equatorial wall thickness decreased significantly during ischemia.

Figure 3 illustrates the diastolic pressure-strain and stress-strain relationships for a single animal. In the experiment depicted in figure 3, left ventricular end-diastolic pressure exceeded 40 mm Hg during ischemia. This increase in end-diastolic pressure was by far

<p>| TABLE 1 |
| Myocardial blood flows |
| Mean blood flow | Endocardial flow | Epicardial flow | Endocardial/epicardial |</p>
<table>
<thead>
<tr>
<th>Control</th>
<th>Ischemia</th>
<th>Control</th>
<th>Ischemia</th>
<th>Control</th>
<th>Ischemia</th>
<th>Control</th>
<th>Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total circumferential flow</td>
<td>1.23 ± 0.20</td>
<td>0.80 ± 0.28</td>
<td>1.41 ± 0.26</td>
<td>0.65 ± 0.28</td>
<td>0.89 ± 0.18</td>
<td>0.82 ± 0.37</td>
<td>1.60 ± 0.18</td>
</tr>
<tr>
<td>Anterior flow</td>
<td>1.24 ± 0.14</td>
<td>0.95 ± 0.33</td>
<td>1.48 ± 0.19</td>
<td>0.83 ± 0.57</td>
<td>0.79 ± 0.19</td>
<td>0.82 ± 0.30</td>
<td>1.94 ± 0.33</td>
</tr>
<tr>
<td>Posterior flow</td>
<td>1.29 ± 0.26</td>
<td>0.71 ± 0.45</td>
<td>1.48 ± 0.33</td>
<td>0.59 ± 0.59</td>
<td>0.95 ± 0.22</td>
<td>0.80 ± 0.52</td>
<td>1.58 ± 0.21</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

*p ≤ 0.05 by paired t-test.

<p>| TABLE 2 |
| Hemodynamic data |</p>
<table>
<thead>
<tr>
<th>Control</th>
<th>Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>114 ± 19</td>
</tr>
<tr>
<td>Peak systolic TMP (mm Hg)</td>
<td>125 ± 11</td>
</tr>
<tr>
<td>End-diastolic TMP (mm Hg)</td>
<td>13 ± 2</td>
</tr>
<tr>
<td>Peak systolic RVP (mm Hg)</td>
<td>26 ± 6</td>
</tr>
<tr>
<td>End-diastolic RVP (mm Hg)</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>End-diastolic LV volume (cm³)</td>
<td>79.8 ± 28.0</td>
</tr>
<tr>
<td>LV systolic stroke volume (cm³)</td>
<td>27.2 ± 16.5</td>
</tr>
<tr>
<td>LV systolic ejection fraction</td>
<td>0.34 ± 0.10</td>
</tr>
<tr>
<td>Cardiac output (cm³/min)</td>
<td>3030 ± 1583</td>
</tr>
<tr>
<td>Relaxation time constant (msec)</td>
<td>19 ± 4</td>
</tr>
</tbody>
</table>

LV = left ventricular; RVP = right ventricular pressure; TMP = left ventricular transmural pressure.

Data are mean ± SD.

*p ≤ 0.05 by paired t-test.
the largest among the six dogs but provided the greatest range of data for the purpose of illustration. The mean value among the six dogs for left ventricular end-diastolic pressure during ischemia was 18 ± 7 mm Hg (table 2). The exponential curves labeled with equations were fit to data of low strain velocity during vena caval occlusions. Superimposed on these static curves are dynamic data collected from individual diastoles preceding the vena caval occlusions. The relationships between transmural pressure and strain in each of the three left ventricular axes were shifted to the left and upward during ischemia (figure 3, A to C). Similarly the transmural pressure-volume strain relationship, a descriptor of left ventricular chamber compliance, was shifted to the left and upward (figure 3, D), as was the relationship between midwall circumferential stress and strain (figure 3, E).

Figure 4 illustrates the effects of global ischemia on the relationship between left ventricular transmural pressure and unnormalized left ventricular volume. The dynamic data collected from a single diastole during ischemia is displaced upward and slightly to the right of the dynamic data collected during the control period. The static curve fit through data of low strain velocity from a vena caval occlusion during ischemia lies slightly to the right of the control curve and extends to higher pressures than the control.

The shifts in the diastolic relationships illustrated in figure 3 occurred in each of the seven dogs studied.

The changes that occurred during ischemia are quantified in table 4. At designated left ventricular transmural pressures, mean values of strain are given for each left ventricular axis and for left ventricular volume. At designated midwall circumferential stresses, mean values of midwall circumferential strain are shown. During ischemia, significant decreases in the mean value of anterior-posterior minor axis strain occurred at left ventricular transmural pressures of 12, 8, and 4 mm Hg. The strains in the base-apex major axis were significantly smaller at 12 mm Hg only. Significant decreases in septal–free wall minor axis strains occurred at all three left ventricular transmural pressures. During ischemia, left ventricular volume strains were also significantly decreased at each transmural pressure. Midwall circumferential strains were de-

**TABLE 3**

**Unstressed left ventricular dimensions**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior-posterior minor axis (cm)</td>
<td>5.39 ± 0.53</td>
<td>5.85 ± 0.50^a</td>
</tr>
<tr>
<td>Base-apex major axis (cm)</td>
<td>7.04 ± 0.61</td>
<td>7.25 ± 0.65^a</td>
</tr>
<tr>
<td>Septal–free wall minor axis (cm)</td>
<td>5.11 ± 0.53</td>
<td>5.72 ± 0.80^a</td>
</tr>
<tr>
<td>Equatorial wall thickness (cm)</td>
<td>1.46 ± 0.06</td>
<td>1.17 ± 0.09^a</td>
</tr>
<tr>
<td>Midwall equatorial circumference</td>
<td>13.3 ± 1.4</td>
<td>15.6 ± 2.0^a</td>
</tr>
<tr>
<td>(cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume (cm^3)</td>
<td>22.5 ± 8.0</td>
<td>44.4 ± 20.7^a</td>
</tr>
</tbody>
</table>

Data are mean ± SD.

^a p ≤ .05 by paired t test.
increased at stresses of 40, 25, and 10 dynes \( \times 10^3/\text{cm}^2 \), consistent with the leftward shift of this relationship during ischemia.

**Discussion**

These data clarify the analysis of the results of previous studies of global left ventricular ischemia. The findings of these previous studies are difficult to interpret because (1) the pressure-dimension relationships were not normalized, (2) the data were not selected to minimize or account for the viscous properties of left ventricular filling, and (3) many of the data were collected from a steep region of the pressure-dimension relationship, where under nonischemic conditions large increases in pressure are accompanied by only very small changes in dimension.

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**FIGURE 3.** Diastolic pressure-strain and stress-strain relationships constructed from control data and ischemic data. The heavy black curves, labeled with their respective equations, were constructed from static elastic data collected from vena caval occlusions. The lighter curves are dynamic data collected from individual diastoles preceding the vena caval occlusions.
the left, indicating that the loss of left ventricular compliance was truly a global process, measurable in each of the three orthogonal axes of the ventricle. Finally, the circumferential stress-strain relationship was shifted to the left, indicating that the loss of left ventricular chamber compliance was the result, at least in part, of a decrease in compliance of the left ventricular myocardium itself.

With the type and degree of ischemia induced by constriction of the left main coronary artery, we could not demonstrate a decrease in left ventricular chamber compliance in our analysis of unnormalized left ventricular volumes (figure 4). This is in contradistinction to the results of clinical studies in which left ventricular ischemia was induced by pacing at rapid heart rates. In these studies and in a study of pacing in dogs with experimental coronary stenoses, unnormalized left ventricular volumes were smaller at specified diastolic pressures during ischemia. Whether or not the relationship between diastolic pressure and unnormalized volume is shifted to the left by increases in intrinsic myocardial stiffness during ischemia depends on how much unstressed volume is increased by the creep phenomenon. The unnormalized volumes in our study may have been relatively larger because in our preparation more creep was induced by the ischemia resulting from the constriction of the left main coronary artery. Alternatively, the increases in the intrinsic stiffness of the left ventricular myocardium were less substantial in our preparation. In either case, the loss of left ventricular distensibility demonstrated in the previous studies might have been more dramatic had normalization of volumes to unstressed volume been feasible.

Previous investigators have recognized several factors that may contribute to the loss of left ventricular chamber compliance during ischemia. Incomplete re-

### TABLE 4

<table>
<thead>
<tr>
<th>Left ventricular diastolic data: strain</th>
<th>At TMP = 12 mm Hg</th>
<th>At TMP = 8 mm Hg</th>
<th>At TMP = 4 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Ischemia</td>
<td>Control</td>
<td>Ischemia</td>
</tr>
<tr>
<td>Anterior-posterior minor axis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.217 ± 0.082</td>
<td>0.105 ± 0.031(^a)</td>
<td>0.181 ± 0.083</td>
<td>0.089 ± 0.027(^a)</td>
</tr>
<tr>
<td>Base-apex major axis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.086 ± 0.031</td>
<td>0.066 ± 0.014(^a)</td>
<td>0.069 ± 0.026</td>
<td>0.056 ± 0.013</td>
</tr>
<tr>
<td>Septal-free wall minor axis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.284 ± 0.090</td>
<td>0.162 ± 0.048(^a)</td>
<td>0.239 ± 0.069</td>
<td>0.142 ± 0.044(^a)</td>
</tr>
<tr>
<td>Volume</td>
<td>2.68 ± 0.89</td>
<td>0.91 ± 0.028(^a)</td>
<td>2.20 ± 0.76</td>
</tr>
</tbody>
</table>

At \(\sigma = 40\) dynes \(\times 10^3/cm^2\) at \(\sigma = 25\) dynes \(\times 10^3/cm^2\) at \(\sigma = 10\) dynes \(\times 10^3/cm^2\)

| Midwall circumference                  |                   |                   |                   |
| Control                                | Ischemia          | Control           | Ischemia          | Control           | Ischemia          |
| 0.395 ± 0.083                          | 0.198 ± 0.051\(^a\) | 0.341 ± 0.059     | 0.171 ± 0.047\(^a\) | 0.239 ± 0.062     | 0.116 ± 0.049\(^a\) |

\(\text{TMP} = \) left ventricular transmural pressure; \(\sigma = \) left ventricular equatorial midwall circumferential stress.

\(^a\)Data are mean ± SD.

\(^a\) \(p \leq 0.05\) by paired t test.
Relaxation of the left ventricle is one such factor. The time constant of relaxation was significantly prolonged during ischemia in this study. However, as has been emphasized previously, a small prolongation of relaxation cannot account for upward or leftward displacement of the pressure-dimension relationship throughout diastole, since relaxation is nearly complete after 3.5 time constants elapse. In this study, at least 3.5 time constants elapsed before end-diastole during both the control and ischemic periods in each of the dogs.

Short-term changes in right ventricular loading can alter the distensibility of the left ventricle. It has been suggested, for example, that the increases in the left ventricular end-diastolic pressure observed during handgrip exercise in patients with coronary disease are the result of increases in right ventricular pressure. Leftward septal displacement with encroachment on left ventricular diastolic volume has been demonstrated previously in this laboratory during acute right ventricular hypertension induced by pulmonary arterial constriction. However, right ventricular peak systolic pressures in excess of 60 mm Hg were necessary to demonstrate this ventricular interaction. In this study, neither peak systolic nor end-diastolic right ventricular pressures were significantly increased during left ventricular ischemia. Previous investigators have demonstrated that changes in the unnormalized pressure-volume relationship during left ventricular ischemia in dogs with coronary stenoses cannot be mimicked by constricting the pulmonary artery and raising end-diastolic right ventricular pressures to nearly twice the level observed during ischemia.

Changes in the intrinsic mechanical properties of the left ventricular myocardium have usually been implicated as the cause of alterations in the left ventricular diastolic pressure-volume relationship during ischemia when other factors have been eliminated. In this study, the static elastic relationship between diastolic circumferential stress and strain was used to characterize the intrinsic stiffness of the myocardium comprising the equator of the left ventricle. The leftward shift of the stress-strain relationship documented in this study demonstrates that an increase in myocardial stiffness occurs during acute global left ventricular ischemia. Thus the findings suggest that changes in the intrinsic material properties of the left ventricular myocardium (creep and increased myocardial stiffness) account for the alterations in left ventricular chamber compliance during global left ventricular ischemia. These changes in mechanics are identical to those that have been proposed to explain the alterations in regional diastolic properties during regional left ventricular ischemia.

Because the entire left ventricle was made ischemic in this study, it follows that the mechanical changes observed are the direct result of ischemia rather than the result of interactions between ischemic and nonischemic regions of myocardium. The finding that the mechanical changes during diastole induced by global left ventricular ischemia (creep and increased myocardial stiffness) are identical to those that occur during regional ischemia suggests that the regional abnormalities are also the direct result of ischemia rather than the result of mechanical interactions between ischemic and nonischemic regions of the left ventricle. There may have been some inhomogeneity in the degree of ischemia throughout the ventricle, but the ischemia was extensive enough for creep to occur in each global axis of the left ventricle and for a significant change in transmural flow distribution to occur everywhere in the ventricle. It could be argued that interactions occurred between the ischemic left ventricular myocardium and the nonischemic right ventricular myocardium. However, if these interactions had contributed significantly to the mechanical alterations observed during ischemia, it is unlikely that the changes in unstressed dimension and the relationships between pressure and strain would have been observed uniformly in the three left ventricular axes.

Because the holosystolic bulging of severely ischemic left ventricular regions appears to resemble the passive extension of these regions during diastole, it could be argued that this systolic abnormality is the result of the ischemic region being passively deformed by the surrounding nonischemic regions of the left ventricle. If the equivalent of regional bulging occurred in each axis of the left ventricle during global ischemia, there could be no effective systolic contraction or cardiac output. No dysynchronous systolic shortening was observed in any left ventricular axis during global ischemia. This finding is consistent with the hypothesis that regional systolic dyskinesia is the result of interactions of the ischemic region with surrounding nonischemic regions of myocardium. However, it is possible that during global ischemia, the appearance of diastolic abnormalities precedes the onset of systolic dyskinesia and that more severe global ischemia would have resulted in global dyskinesia and failure of left ventricular contraction.

There are several analytical difficulties in assessing the diastolic stress-strain relationships in this study. The geometry of the left ventricle was assumed to be ellipsoidal. Although this may be valid under normal circumstances, regional deformations of the left ven-
tricular wall may occur during ischemia, particularly if the severity of ischemia is not homogeneous throughout the ventricle. Similarly, the model assumes uniform thickness of the left ventricular shell circumferentially at the equator. This single wall thickness dimension is computed rather than measured. During ischemia, local variations in wall thickness may occur, particularly if the ischemia is not of a uniform degree. Local deformations in the shape and thickness of the left ventricle would limit the validity of computing single values of stress and strain for an entire equatorial slice of the ventricle from three global dimensions.

Although an attempt was made to induce global and homogenous ischemia throughout the left ventricle, the myocardial blood flow data suggest that this was not always achieved. It would appear that hypoperfusion was slightly more severe in the posterior left ventricular coronary circulation than in the anterior circulation. In response to coronary constriction, distal vasodilation in the coronary system may have permitted mean myocardial flow to be maintained at higher levels in the anterior circulation than in the posterior circulation. However, these data do not describe the matching of mechanical work with myocardial blood flow. Without a significant decrease in mean blood flow, the anterior regions of the left ventricle may have been severely ischemic when faced with an increased demand for systolic work and increased diastolic wall stress. The decrease in endocardial flow and the change in endocardial-epicardial flow distribution in the anterior regions suggest that they were subjected to a significant degree of ischemia. It should also be emphasized that because there were no significant decreases in left ventricular epicardial blood flows, the results of this study can be said to pertain primarily to subendocardial left ventricular ischemia as opposed to truly transmural ischemia.

In summary, during global ischemia the chamber compliance of the left ventricle is decreased. Alterations in the intrinsic mechanical properties of the myocardium account for this alteration. These changes (creep and increased myocardial stiffness) are identical to those that have been implicated in the loss of regional compliance during regional ischemia, which suggests that regional abnormalities during regional ischemia are the direct result of ischemia rather than the result of interactions between ischemic and nonischemic myocardium.

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