Changes of Left Ventricular Diastolic Function in Exercising Dogs Without and With Ischemia

Shunichi Miyazaki, MD, Brian D. Guth, PhD, Toshiro Miura, MD, Ciro Indolfi, MD, Rainer Schulz, MD, and John Ross Jr., MD

Left ventricular (LV) diastolic function in the absence and presence of regional ischemia was examined in eight conscious dogs chronically instrumented with ultrasonic devices for measuring LV wall thickness and volume. During treadmill exercise, ischemia was induced (hydraulic occluder) to produce less than 10% systolic wall thickening in the ischemic zone. LV filling was assessed by the peak filling rate (PFR), mean filling rates in the first and second halves of filling (mFR, and mFR2), an early filling index from mitral valve opening to minimal diastolic pressure (PDM), and the percentage of atrial filling. Also, LV relaxation (τ) and wall thinning rates during isovolumetric relaxation and the first and second halves of the filling phase were assessed. During control exercise without ischemia, PDM decreased by 2.61 mm Hg (p<0.05) to ~1.1 mm Hg and there was a downward shift of the entire LV diastolic pressure-volume (P-V) curve. The LV relaxation rate, PFR, mFR1, and mFR2 were enhanced. Early filling was increased by 116%, the percentage of atrial filling by 118%, and overall diastolic filling by 23% despite a 63% decrease in the filling period. During ischemic exercise, systolic function was depressed compared with the resting state, PDM increased by 4.84 mm Hg (p<0.005) associated with a pronounced rightward and upward shift of the early portion of the P-V curve. LV relaxation rate, PFR, and mFR were reduced, the early filling index fell sharply by 62% but percentage of atrial filling was unchanged, while overall diastolic filling decreased by 30%. The thinning rate of the control wall was enhanced, whereas that of ischemic wall was depressed. Multiple factors contributed to the markedly impaired early and overall diastolic LV filling during ischemia, including impaired systolic function, reduced relaxation rate, nonuniformity of wall motion, an upward shift of the early diastolic P-V curve, and absence of a compensatory increase in late diastolic filling. (Circulation 1990;81:1058–1070)

Under resting conditions, left ventricular filling dynamics can be altered by such factors as changing loading conditions, the atrial driving pressure, and the ventricular relaxation rate.1–3 During physiological stress such as exercise, alterations also occur but there have been few studies of such responses in normal animals or normal human subjects. The stress of rapid pacing has been examined in the presence of clinical coronary heart disease and experimental ischemia, and effects on early filling accompanied by an upward shift of the diastolic pressure-volume (P-V) curve after pacing have been described.4–6 There have been no detailed studies of left ventricular (LV) filling dynamics during regional ischemia induced by exercise in experimental animals. A few clinical studies on exercise filling dynamics in patients with coronary heart disease have been performed that show abnormal diastolic filling but the types of filling patterns have varied.7,8 Accordingly, we undertook to examine several measures of diastolic LV filling, including the diastolic P-V curve, in healthy normal dogs before and during strenuous submaximal exercise, and to compare these responses to those in the same dogs after the induction of regional ischemia during exercise. The dogs were chronically instrumented with multiple ultrasonic dimension devices on the left...
ventricle and a high-fidelity micromanometer. In some dogs, intrapleural pressure was measured, and all the dogs were trained to run on a treadmill in the absence and presence of severe regional ischemia.

Methods

The dogs in this study were handled according to the animal welfare regulations of the University of California, San Diego, and the protocol was approved by the animal use committee of this institution. These procedures were in accordance with the animal use principles of the American Heart Association.

Animal Preparation

Eight dogs weighing 24–37 kg were trained to run on a motor-driven treadmill before instrumentation. Before surgery, they were premedicated with atropine sulfate (0.06 mg/kg i.m.) and morphine sulfate (1 mg/kg i.m.), and then anesthetized with sodium thiopental (25 mg/kg i.v.). An antibiotic (cefazolin 0.5 g) was given before and during surgery. Respiration and further anesthesia were maintained with a mixture of oxygen and isoflurane (1.5%) through an endotracheal tube. A left thoracotomy was performed in the fifth intercostal space. The pericardium was opened, and pacing wires were sutured to the left atrial appendage. A high-fidelity micromanometer (Konigsberg P-7, Pasadena, California) was introduced into the LV chamber through the apex together with a Tygon fluid-filled catheter (Norton, Akron, Ohio) for zero pressure reference and for calibration of the micromanometer. In five of eight dogs, intrapleural pressure was measured using 2×6-cm silicone rubber sheeting formed into a cuff and placed around the inferior vena cava; its tubing was connected to a Statham P-23Db pressure transducer (Statham Instruments, Oxnard, Massachusetts). Mean left atrial pressure was measured through a fluid-filled catheter attached to an external Statham P-23Db transducer.

The proximal left circumflex coronary artery was dissected free, a single crystal (10 MHz) Doppler flow probe was placed around the vessel, and a pneumatic occlusive cuff was positioned distal to the flow probe. LV external short axis, long axis, anterior wall thickness, and posterior wall thickness were measured with ultrasonic crystals by methods reported previously from this laboratory.9,10 The pericardium was left open, and all wires and catheters were exteriorized to the back. The chest was closed, and the dog was allowed to recover.

At necropsy, appropriate positioning of all crystals was confirmed in the eight dogs reported. All subendocardial crystals were within the inner third of the left ventricular wall and within the transmural projection of the larger epicardial crystal.

Experimental Protocol

Experiments were conducted 7–14 days postoperatively when dogs had fully recovered from surgery. Control recordings were performed with the dogs standing quietly on the treadmill. If significant sinus arrhythmia was observed, the left atrium was paced just above the spontaneous rhythm to facilitate later digitization of the analog signals. The dogs were then run for 5–6 minutes on the treadmill at 6 mph and 8% inclination without coronary stenosis. Ischemic exercise runs were performed on a separate day. After 1–2 minutes of running, when the hemodynamic and dimension data appeared stable, coronary stenosis was produced by adjustment of the pneumatic occluder to reduce systolic wall thickening in the ischemia wall to less than 10% (but without dyskinesia, to prevent ventricular fibrillation). The Doppler flow signal was monitored to prevent complete obstruction of the coronary artery and to maintain a constant level of stenosis.11,12 After a steady level of ischemia was achieved, the dogs were run for an additional 2–3 minutes for a total running time of 6–7 minutes, which is near the maximum run duration tolerable to the dog during severe ischemia. Because the 1–2 minutes of running before coronary stenosis might not represent a complete steady state, the nonischemic run at 5–6 minutes on a different day was performed, and these data were analyzed separately as control exercise without ischemia; also, these data at 5–6 minutes were compared with the first 1–2 minutes of the ischemic run and shown not to differ significantly for almost all measurements although a few changes did reach statistical significance (e.g., end-diastolic volume [EDV] and minimal diastolic pressure [PDM]) in the 2-minute run. To avoid slight differences in pressure calibration and zero references on different days, the 2-minute data were used in directly comparing filling dynamics and diastolic P-V curve shifts during exercise without and with ischemia.

LV pressure was calibrated both before and after running. Calibration of the micromanometer was performed by matching it to the pressure obtained through the fluid-filled catheter at end diastole and end systole. Each micromanometer was characterized before implantation; the temperature sensitivity was verified to be less than 1°C over the range of 32–42°C, pressure sensitivity was established, and the zero pressure electrical output signal was determined using the excitation voltage.

Data Analysis

All data were recorded on an eight-channel Brush chart recorder and on magnetic tape using a magnetic tape recorder (Hewlett-Packard model 3955D, Waltham, Massachusetts). The taped data were played back and digitized at 3-msec intervals using a computer-assisted system (DEC PDP 11/03). For the control recordings, 10–15 beats were averaged, and during exercise, 20 beats were averaged. The peak positive first derivative of LV pressure (dP/dt) served as the reference signal for the computer, and all beats 25 msec longer or shorter than the mean R-R interval were excluded from the computation.
In most clinical studies concerning diastolic function, analysis of P-V or pressure-dimension curves have used single-beat analyses.\textsuperscript{13-16} Because the diastolic pressure is relatively low, the effects of respiration could contribute to any observed changes of pressure with this approach, especially during exercise. The measured changes in mean intrapleural pressure in our study were minimal and not significantly different before and during exercise, as shown in Table 1 and Figure 1. Therefore, all analyses during diastole were performed using averaged beats, which minimized such intrapleural pressure effects, and intrapleural pressure was not subtracted from the measured LV pressure.

Calculations

LV volume (V) was calculated using the equations described by Rankin et al\textsuperscript{17} and previously used in this laboratory.\textsuperscript{9} To avoid problems with asymmetrical shape changes during systole in the presence of ischemia, volumes were calculated only from estimated mitral valve opening (MVO) to end diastole as follows:

\[
\begin{align*}
\text{LAD} &= \text{LAD}_{\text{ext}} - 1.1 \times cWth \\
\text{SAD} &= \text{SAD}_{\text{ext}} - (cWth + iWth) \\
V &= \pi/6,000 \times \text{LAD} \times \text{SAD}^2
\end{align*}
\]

where LAD is LV internal long axis; LAD\textsubscript{ext} is LV external long axis; cWth is the control region wall thickness; iWth is ischemic wall thickness; SAD is LV internal short axis, V is volume (ml); and, SAD\textsubscript{ext} is LV external short axis. Dimensions are in millimeters.

An average diastolic P-V curve was constructed using four points, that is, MVO estimated as the point on the LV pressure tracing during relaxation at a value 5 mm Hg above the end-diastolic pressure,\textsuperscript{4,13,18-20} minimal LV diastolic pressure, P-V value at the midpoint in time between minimal pressure and end-diastolic pressure, and end-diastolic pressure. It is recognized that if mitral regurgitation were present, the above estimate of MVO would be less accurate.

The LV pressure dP/dt, LV filling rates, and LV wall thinning rates were calculated by the differentiation of LV pressure and LV volume, using commercially available computer software (\textsc{Lotus} 1-2-3, Lotus Development Corp., Cambridge, Massachusetts). The time constant of isovolumetric LV pressure decrease (\(\tau\)) was calculated using LV pressure data between maximum (-)LV dP/dt and MVO. There has been some controversy about methods for calculating \(\tau\), and the several available formulas are described as follows: 1) a monoexponential model with zero asymptote,\textsuperscript{21,22} 2) a monoexponential model with a variable asymptote,\textsuperscript{18} 3) a biexponential model,\textsuperscript{23} and 4) a polynomial model.\textsuperscript{19,24} Equation 3 does not describe a continuous process of relaxation, and Equation 4 might have questionable physiological relevance; therefore, we calculated \(\tau\) using Equations 1 and 2. Equation 1 provided good correlations between time and the logarithm of LV pressure (correlation coefficients were from 0.9900 to 0.9998, mean+SD=99.90±0.10), whereas Equation 2 provided poorer correlation between LV pressure and LV (-)dP/dt (correlation coefficients were from
### Table 1. Summary of Hemodynamic and Dimensional Data During Control Nonischemic Exercise

<table>
<thead>
<tr>
<th>Measure</th>
<th>Standing (5 min)</th>
<th>Exercise (5 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>118±6</td>
<td>214±16*</td>
</tr>
<tr>
<td>PDM (mm Hg)</td>
<td>1.48±2.72</td>
<td>−1.13±3.75†</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>9.23±2.45</td>
<td>8.95±5.11</td>
</tr>
<tr>
<td>PLVP (mm Hg)</td>
<td>127±11</td>
<td>152±15*</td>
</tr>
<tr>
<td>(+)dP/dt (mm Hg/sec)</td>
<td>3.352±404</td>
<td>5,699±825*</td>
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<td>(−)dP/dt (mm Hg/sec)</td>
<td>−2,267±360</td>
<td>−3,979±593*</td>
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<tr>
<td>CWed (mm)</td>
<td>9.24±0.96</td>
<td>9.13±0.87†</td>
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<tr>
<td>CWes (mm)</td>
<td>12.08±1.79</td>
<td>12.54±1.92†</td>
</tr>
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<td>%CW (%)</td>
<td>30.55±11.46</td>
<td>36.93±12.14*</td>
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<td>IWed (mm)</td>
<td>9.53±1.67</td>
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<td>IWed (mm)</td>
<td>12.30±2.68</td>
<td>12.57±2.63</td>
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<td>%IW (%)</td>
<td>28.31±8.19</td>
<td>30.24±8.68†</td>
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<tr>
<td>S ed (mm)</td>
<td>48.24±7.53</td>
<td>49.78±7.40*</td>
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<td>S es (mm)</td>
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<td>24.52±5.07*</td>
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<tr>
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<td>64.14±6.46</td>
</tr>
<tr>
<td>% L (%)</td>
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<td>9.31±3.33</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>87.89±31.33</td>
<td>94.31±32.27†</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>53.04±27.22</td>
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</tr>
<tr>
<td>EF (%)</td>
<td>42.27±8.93</td>
<td>47.95±8.43*</td>
</tr>
<tr>
<td>DFP (msec)</td>
<td>274±33</td>
<td>108±19**</td>
</tr>
<tr>
<td>τ (msec)</td>
<td>22.02±2.32</td>
<td>13.01±2.18*</td>
</tr>
<tr>
<td>IPP (mm Hg)</td>
<td>−0.25±0.86</td>
<td>−1.02±1.54</td>
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n=8. All values are given as mean±SD.

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The peak filling rates (PFR) are presented as absolute values and also normalized by dividing by the diastolic filling volume (used to estimate the total stroke volume, assuming absence of mitral regurgitation). This approach has been used by other investigators to normalize for the influence of cardiac output or reduced end-diastolic volume.

The mean rates of change of thickness in the control and ischemic walls were also calculated in the isovolumetric relaxation and filling phases during exercise with ischemia.

**Diastolic filling.** Several measures of diastolic filling were used, including the peak filling rates (absolute and normalized), mean filling rates and filling fractions in the first and second halves of diastole, a new filling index, and the percentage of filling during atrial contraction. As noted previously, wall thinning rates during filling were also calculated.

The peak filling rates (PFR) are presented as absolute values and also normalized by dividing by the diastolic filling volume (used to estimate the total stroke volume, assuming absence of mitral regurgitation). This approach has been used by other investigators to normalize for the influence of cardiac output or reduced end-diastolic volume.

Diastolic filling was also divided into two periods, the first (early) and second (late) halves of the filling phase, for calculation of mean filling rates. The filling volumes during the first and second halves of diastole were calculated and expressed as early and late filling fractions by dividing by the total diastolic filling volume. The peak filling rates during normal and ischemic exercise were not significantly different, filling times during these phases were comparable.

In a new approach for assessing diastolic filling dynamics in the rapid phase of early ventricular filling, during control exercise without ischemia we calculated the actual volume increment from MVO to the volume at PDM with the animal standing at rest (from M2 to A in Figure 2) and compared it to that from MVO to the volume at an equivalent pressure (from M1 to B in Figure 2) during exercise. To compare exercise during ischemia with normal exercise, because the minimum pressure was markedly increased during ischemia, we used a different approach and calculated the actual volume increment from MVO to the minimal pressure during ischemic exercise (from M3 to C in Figure 2) and compared it with the volume increment from MVO to an equivalent pressure during control exercise (from M1 to D in Figure 2). Each of these volume increments was expressed as a percentage of the total
filling volume at each exercise state and termed the early ventricular filling index (EVF index). Thus, for analyzing the effects of control exercise, the EVF index at rest is measured at the minimum LV pressure and compared with the index calculated during exercise at the same pressure as the minimum LV pressure at rest (reflecting the benefit of the observed outward displacement of the diastolic P-V relation during exercise). On the other hand, for analyzing the effects of ischemic exercise compared with control exercise, the EVF index is assessed at the minimum LV pressure during ischemic running and compared with the index during control exercise, calculated at the same pressure as the minimum LV pressure during the ischemic run (reflecting the detrimental effect of the observed upward and rightward displacement of the diastolic P-V relation during ischemia).

The effect of atrial contraction on LV filling dynamics was assessed from the ventricular volume increment from 75 msec before end diastole up to the EDV during control standing and from 50 msec before EDV during exercise. These time values were taken as the starting points of atrial contraction; they were derived from continuous calculations of filling rates and manifested in many tracings by abrupt increases in late diastolic filling (Figure 3). At rest, the abrupt change was discernible in all eight dogs; during exercise, it was possible to observe the abrupt increase in four of eight dogs without ischemia and three of eight with ischemia. Based on these observations, we defined the atrial filling periods as previously indicated. The percentage of filling during atrial contraction (% atrial filling) was then calculated as the ventricular volume change during this period divided by the total diastolic filling.

**Determination of End Diastole and End Systole**

End diastole was defined as the time the LV dp/dt began its rapid upstroke before its maximum value. End systole (end ejection) was taken at the time approximately 20 msec before the minimum (−)dp/dt. The shape of the LV chamber can be deformed during systole by ischemia, leading to unreliable calculated volumes. During diastole (from MVO to end diastole), however, the shape change is considered to be minimally different from normal. Therefore, as mentioned earlier, we used only calculated values of volume during diastole beginning at MVO in the runs with ischemia; the values at MVO and at end diastole were used in estimating the stroke volume and ejection fraction, assuming that mitral regurgitation was absent.

A paired t test was used to compare variables during control standing with those during control exercise (5 minutes of exercise) in the absence of ischemia. Measurements of the run with regional ischemia were compared at three times, that is, control standing at rest, control exercise (early, 1–2 minutes of exercise) without ischemia, and exercise with ischemia (5 minutes of exercise); a repeated measure, one-way analysis of variance followed by Tukey's multiple comparison test was used. Differences were considered significant when the value of p was less than 0.05. Values are given as mean ± SD.

**Results**

**Effects of Control Exercise Without Ischemia**

*Global systolic exercise*. During 5 minutes of exercise, heart rate, and peak LV pressure increased (Table 1). Both isovolumetric and ejection phase indexes of LV contractility increased, and peak (+)LV dp/dt increased by 70%. Estimated ejection fraction increased by 14% (Table 1).

*Global diastolic function*. LV end-diastolic pressure was unchanged. The time constant of LV isovolumetric pressure decay (τ) decreased significantly from 22 to 13, and peak (−)dp/dt also increased significantly (Table 1). The total diastolic filling period decreased significantly by 61% (Table 1), and the time to peak filling was abbreviated (Table 2). Both peak and mean filling rates in the first and the second halves of the filling phase increased significantly (Figure 3, Table 2), whereas the early and late filling fractions (EFF and LFF, respectively) were unchanged (Table 2).
The EVF index increased substantially (by 116%) from rest to exercise as shown in Figure 4 (mean, from 25.54±6.79% to 60.37±28.07%; p<0.01). The percentage of atrial filling was also significantly enhanced (by 118%) from 17.26±6.92% to 37.56±19.98% (p<0.05).

**Diastolic pressure-volume curves.** These changes were accompanied by a shift downward of the LV diastolic P-V curve. The LV diastolic P-V curves in four animals representative of the range of observed responses are shown in Figure 5A, and the averaged diastolic P-V curves at rest and during exercise in all animals are shown in Figure 6A.

**Regional systolic function.** Regional systolic wall thickening during ejection of the anterior and posterior walls increased by 25% and by 11%, respectively (Table 1).

**Regional diastolic function.** End-diastolic wall thickness of both walls showed no significant change during exercise. The thinning rates of both walls were markedly increased in the first half of the filling phase (anterior wall by 250% and posterior wall by 220%) (Table 3). The wall thinning rates in the second half of the filling phase did not change significantly (Table 3).

**Effects of Exercise With Ischemia**

During the first 2 minutes of running before induction of ischemia, all variables changed in the same direction as during the control run at 5 minutes of exercise on a different day although the minimal diastolic pressure and the end-diastolic volume did not attain statistical significance. Therefore, in the following comparisons between control and ischemic exercise, the data obtained during early exercise in the same run were used for the comparative analyses.

**Global systolic function.** Compared with control exercise at 2 minutes, peak LV pressure and maximal dP/dt were decreased during ischemia, with no significant difference in heart rates (Table 4). The volume at MVO was greatly increased by 51%. The total diastolic filling volume and, hence, the estimated stroke volume were reduced, and the ejection fraction decreased by 42% from control exercise to ischemic exercise (Table 4).

**Global diastolic function.** During ischemic exercise, the LV end-diastolic pressure and volume were significantly higher and the mean left atrial pressure was also increased substantially, as compared with control exercise (Table 4). The peak (-)dP/dt decreased by 12%, and τ was significantly increased by 18% (Table 4). The diastolic filling period was not significantly different from control exercise.

During ischemic exercise, the PFR in the first half of the filling phase was increased relative to the resting value but, as compared with control exercise, it was decreased significantly (Figure 3); however, the PFR normalized by stroke volume was unchanged (Table 2). The time to PFR was prolonged as compared with control exercise (Table 2). Mean filling rates in the second halves of the filling phase were increased both during control and ischemic running; however, the rate in the first half was significantly

![Figure 4](http://circ.ahajournals.org/)
FIGURE 5. Responses of diastolic pressure-volume curves that were selected to illustrate full range of responses. Panel A: Diastolic pressure-volume curves in four representative dogs standing at rest (○) and during control (nonischemic) exercise (△) at 5 minutes. Panel B: Diastolic pressure-volume curves in four representative dogs standing at rest (○) and during ischemic exercise (△). Control exercise (Panel A) caused downward and leftward shifts of pressure-volume curves, whereas ischemic exercise (Panel B) caused upward and rightward shifts of early portions of pressure-volume curves. Curves in panel B4 show one of two animals in which entire curve was displaced upward. LV, left ventricular, LVP, left ventricular pressure.
lower during ischemic compared with control exercise, whereas the decrease in the second half was not statistically significant (Table 2). The EFF and LFF did not change significantly from rest to exercise or between control and ischemic runs (Table 2). Because the total diastolic filling periods were not significantly different between control and ischemic exercise (Table 4), the first and second half filling periods were comparable. The lack of change of the filling fractions during the two exercise periods indicate that the decrease in total diastolic filling volume during ischemia was equally distributed between the two periods when expressed in this manner.

The EVF index was decreased markedly during ischemic compared with control exercise, as shown in the right panel of Figure 7 (from 73.29±21.93 to 7.78±13.13). The percentage of atrial filling was increased during both exercise periods but there was no change between control and ischemic running (Table 2).

**Diastolic pressure-volume curves.** During ischemic exercise, there was a shift upward and to the right of the early portion of the diastolic P-V curve but the remainder of the averaged curves seemed to form an extension of the control curve with pronounced elevation of the end-diastolic pressure (Figure 6B). Two dogs exhibited mild upward displacement of the entire curve (example shown in Figure 5B).

**Regional systolic function.** Compared with control exercise, regional systolic wall thickening in the ischemic zone was greatly decreased (5.7%), and all dogs showed less than 10% wall thickening during regional ischemia. The control wall showed a compensatory increase of percentage of wall thickening (Table 4).

**Regional diastolic function.** During isovolumetric relaxation, the thinning rate of the control wall (dCW/dt) was increased during ischemia compared with control exercise, whereas during this phase, the ischemic wall showed thickening (Table 3). The thinning rate of the ischemic wall (dW/dt) in the first and second halves of filling during ischemic exercise was decreased compared with control exercise (Table 3).

**Discussion**

In these experiments, a dog model was used that allowed investigation of the effects of exercise in the absence and presence of regional ischemia in the same dog. The ultrasonic instrumentation obviated

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**TABLE 3. Mean Wall Thinning Rates**

<table>
<thead>
<tr>
<th></th>
<th>dCW/dt (mm/sec)</th>
<th>dW/dt (mm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standing</td>
<td></td>
<td></td>
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<tr>
<td>First</td>
<td>−11.23±5.10</td>
<td>−15.08±6.81</td>
</tr>
<tr>
<td>Second</td>
<td>−2.76±1.39</td>
<td>−3.07±1.08</td>
</tr>
<tr>
<td>Control exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>−39.81±15.81*</td>
<td>−48.09±15.15†</td>
</tr>
<tr>
<td>Second</td>
<td>−12.02±8.16</td>
<td>−12.24±7.12</td>
</tr>
<tr>
<td>Ischemic exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iso</td>
<td>−60.93±32.59†‡</td>
<td>+12.92±16.77§</td>
</tr>
<tr>
<td>First</td>
<td>−38.20±19.25†</td>
<td>−14.92±13.84‡</td>
</tr>
<tr>
<td>Second</td>
<td>−9.09±8.73</td>
<td>−3.58±3.86§</td>
</tr>
</tbody>
</table>

n=8. All values are expressed as mean±SD.

dCW/dt, thinning rate of nonischemic wall; dW/dt, thinning rate of ischemic wall; Standing, control standing before run; First, first half of diastolic filling phase; Second, second half of diastolic filling phase; Control exercise, running (2 min) without ischemia; Ischemic exercise, running with ischemia; Iso, isovolumetric relaxation phase.

*p<0.05, †p<0.005, as compared with Standing; ‡p<0.005, §p<0.05, as compared with Control exercise.
the need for repeated angiographic injections and permitted vigorous treadmill exercise to a comparable degree, with similar hemodynamic responses among dogs. Additionally, a comparable degree of regional ischemia could be produced among dogs, and long-term changes because of generalized fibrosis or regional scarring often observed in patients with coronary heart disease were absent. Also, the pericardium was removed, and the potential effects of intrapleural pressure changes could be assessed.

In previous studies concerning the effects of very severe exercise in conscious untethered dogs, the heart rates increased to approximately 300 beats/min.29 In our treadmill studies, the average heart rate increased to approximately 210 beats/min both during early (1–2 minutes) and late (5 minutes) exercise, indicating a strenuous but submaximal level of exercise for the dog.

**Effects of normal exercise on filling dynamics.** We have demonstrated that during normal strenuous exercise, early filling relative to LV diastolic pressure (EVF index) is enhanced more than twofold (116%) from the standing value (Figure 4), in association with a downward shift of the entire diastolic P-V curve (Figure 6A). Thus, a decrease in the PDM occurred, despite an increased filling rate that per se would tend to increase the minimal pressure,30
emphasizing the highly important role of enhanced LV relaxation, an energy-dependent process.\(^{31}\) This downward shift of the LV P-V curve, which was not due to a significant intrapleural pressure change, should provide an advantage for LV filling from the left atrium. Although we were unable to measure phasic left atrial pressure in these studies to assess the dynamic filling pressure, mean left atrial pressure did not change significantly during normal exercise. Determination of whether this downward displacement, which can reflect increased chamber compliance, represents a true alteration of passive muscle properties will require further studies.

Brutsaert et al\(^{32}\) proposed that the rate of relaxation is influenced by the following three factors: 1) loading conditions, 2) muscle inactivation, and 3) nonuniformity. Increased afterload placed in early systole or midsystole (contraction loading) decreases the relaxation rate, whereas late contraction loading increases it.\(^{2,18,32}\) Recent evidence indicates that isolated changes in preload do not affect relaxation rate.\(^{33,34}\) and Starling et al\(^{34}\) reported the effect of increased systolic pressure to be small in conscious human subjects. Because LV EDV and systolic pressure both increased during normal exercise, afterload probably increased, and this effect alone might have tended to delay relaxation. Inotropic stimulation during exercise would have the opposite effect, however, and hasten muscle inactivation. Blaustein et al\(^{22}\) reported that \(\beta\)-adrenergic receptor stimulation decreases the time constant of LV pressure decay, and during exercise, the pronounced sympathetic response together with the positive inotropic effect of increased heart rate per \(\text{s}^{-1}\) would also increase the relaxation rate. Recently, Heyndrickx et al\(^{36}\) reported that, during exercise, the increase of heart rate with a normal activation sequence (right atrial pacing) decreased \(\tau\), whereas exercise during right ventricular pacing caused an increase in \(\tau\) because of nonuniformity. The markedly enhanced relaxation rate and augmented early filling during normal exercise in our studies seem predominantly because of increased sympathetic tone to the ventricle,\(^{22}\) increased heart rate, and a decrease in “normal” resting nonuniformity.\(^{22}\) LV volume at MVO was also slightly lower with a negative minimum pressure during the 5-minute run (Table 1), and increased recoil (an energy-independent mechanism) should also be considered.

The net effect of all these changes during normal exercise is a remarkable increase in early filling, elimination of diastolic filling, and increased late filling with augmented atrial contractility, leading to a 23% increase in total filling per beat despite a 60% decrease in diastolic filling time.

**Effects of regional ischemia on filling dynamics during exercise.** During exercise with regional ischemia, relaxation was delayed (\(\tau\) increased), there was increased ventricular volume at MVO compared with resting control and control exercise, early filling relative to diastolic pressure (EVF index) was markedly diminished compared with control exercise, and minimum diastolic pressure was greatly increased. The negative inotropic effect of regional ischemia slowed the regional relaxation rate, and this likely contributed to the slowed LV pressure decay. Although the entire averaged diastolic P-V curve was usually not displaced, the early diastolic portion was prominently shifted rightward and upward (Figure 6B). Impaired systolic function resulted in increased residual ventricular volume, and the increased filling volume from the left atrium during exercise led to a further increase of intracavitary diastolic pressures.

There have been many studies concerning diastolic function during ischemia in the resting state but few have analyzed ventricular filling dynamics during exercise-induced ischemia. In a clinical study using angiography, Carroll et al\(^{8}\) reported that the peak and mean early filling rates during exercise were not reduced in patients with coronary artery disease and ischemia compared with control patients although \(\tau\) was increased. On the other hand, Reduto and coworkers,\(^{7}\) using a radionuclide angiographic technique, estimated that filling in the first third of diastole was diminished during exercise, in patients with coronary heart disease, compared with that during exercise in normal subjects. The reasons for these differing observations are not clear, although in Carroll et al's study, data were obtained during supine exercise, whereas data were obtained just after exercise in Reduto's study. Additionally, in such clinical studies, the “control” group is not necessarily a normal population. In another clinical study, Carroll et al\(^{37}\) reported that delayed early diastolic filling observed in patients with coronary heart disease before coronary artery bypass graft surgery was improved at the postoperative study. Bonow et al\(^{38}\) have reported that abnormal filling at rest can be found in a high percentage of patients with coronary artery disease, even without evidence of ischemia on the ECG or impaired systolic function at rest. In our study, in which it was possible to compare ischemic with normal exercise in the same animal on the same day, early filling relative to diastolic pressure was
greatly impaired during exercise-induced ischemia (Figure 7). Absolute peak and mean early filling rates, although increased compared with rest, were reduced in ischemia as compared with control exercise although, when normalized to stroke volume or when expressed as a filling fraction in the first half of diastole, no change was detected from control exercise; this undoubtedly reflected the decrease in stroke volume during ischemia, which, in turn, was related to both decreased regional contractility and impaired LV filling.

We found that the mean filling rate in the second half of the filling phase was not significantly different during ischemic compared with control exercise. Also, whether expressed as percentage of atrial filling or as the second half filling fraction, late filling was unchanged, indicating no compensatory increase in filling due to atrial contraction in the run with ischemia. Carroll et al reported a reduction of late filling rates in patients with exercise-induced ischemia compared with normal patients and suggested that it might be related to increased impedance to ventricular filling. There could be several factors involved in the failure of the left atrium to increase the filling rate further during ischemia despite a likely increase in atrial volume. Increased afterload on the left atrium during ischemic exercise could have limited its response; as shown in Figure 6B, the P-V curves showed no consistent displacement in late diastole but, during ischemia, the left ventricle was operating on a steeper portion of its P-V relation at the time of atrial systole, thereby augmenting the systolic load on the left atrium, which could have prevented improved performance. Additionally, because ischemia was produced by constricting the proximal left circumflex coronary artery in our dog model, left atrial branches might have been affected, rendering the left atrium ischemic and unable to increase its booster pump function.

**Diastolic pressure-volume curves during ischemia.**

Numerous studies have examined shifts of the diastolic P-V curve or pressure-dimension curve during ischemia at rest. In two clinical studies that used cineangiography, a shift upward of the LV P-V curves were described during exercise-induced ischemia; however, the degree of acute ischemia induced is not clear, and the role of external mechanical constraints such as the pericardium, and of altered intrapleural pressure, during supine exercise in these studies is unknown. The individual LV diastolic P-V curves in our study exhibited a rightward and upward shift in early diastole but no consistent displacement of the entire curve during ischemic exercise although, in one dog, there was a clear upward shift (Figure 5B) and in another a mild upward displacement was apparent, whereas the averaged P-V curves demonstrated no upward shift (Figure 6B).

A shift upward of the diastolic P-V curve after pacing-induced ischemia in humans has been described. Delayed relaxation and increased LV stiffness just after the cessation of pacing in patients with angina pectoris have also been noted, and it was suggested that the latter shift was related to a change in myocardial stiffness, which might be caused by impaired calcium sequestration or increased net calcium influx. Our finding that the entire P-V relation curve during exercise with regional ischemia does not show consistent displacement might relate, in part, to differing hemodynamic variables during exercise stress, compared with those after pacing. Thus, during exercise, there is markedly increased myocardial contractility in normal regions, venous return is greatly augmented, and peak LV pressure is increased. Moreover, during experimental exercise-induced ischemia there is subendocardial hypoperfusion in the ischemic region, whereas after pacing or after exercise, normal or increased blood flow to the ischemic region is expected. Such differences can explain, in part, the lack of displacement of the entire P-V curve upward during exercise, as observed after pacing. It can be further postulated that the increased cardiac distension imposed by the enhanced venous return of exercise might serve to prevent an upward displacement of the entire curve.

**Regional wall dimensions.** Kumada et al reported that during 1 minute of coronary occlusion, dysynchrony because of late systolic contraction and relaxation in different regions produced pronounced effects on the rate of isovolumetric ventricular pressure fall. In the present study, thinning of the control wall was accompanied by thickening of the ischemic wall during the isovolumic relaxation phase (Table 3), documenting that asynchrony (nonuniformity) occurred during isovolumic relaxation in exercise-induced ischemia. Therefore, the observed decrease in relaxation rate (\(\tau\)) could be, in part, responsible for such asynchrony caused by regional ischemia, although the negative inotropic effect of regional ischemia per se also undoubtedly further contributed to impaired relaxation. We propose that the ischemic wall, by generating force or stretch on the nonischemic wall during the isovolumic relaxation phase, could lead to late-systolic loading and, thereby, contribute to the enhanced thinning rate of the normal region.

**Potential Limitations of Methods**

**Pericardial pressure.** Tyberg et al and Shirato et al reported that an upward shift in the LV diastolic filling curve can be caused by an increase in pericardial pressure, in turn, caused by volume loading. In our dogs, the pericardium was left open at operation, and we consider it unlikely that this factor affected the P-V curves although it is possible that some degree of ventricular interaction could have occurred. Moreover, we cannot exclude the possibility that postoperative changes could have placed some external constraint on the heart.

**Intrapleural pressure.** We measured the mean intrapleural pressure using a fluid-filled system in most dogs. Although large respiratory excursions and
increased high-frequency noise on the pressure signal occurred during exercise, the changes in mean pressure were minimal. Therefore, we believe that the mean intrapleural pressure reflected the effects of true intrapleural pressure; the close agreement of the data when intrapleural pressure was considered with beat-averaged data suggests that intrapleural pressure changes were not a major factor affecting intracardiac pressures with the techniques used.

Useful information would have been obtained from high-fidelity left and right atrial pressure measurements but, because of the large amount of instrumentation implanted in these dogs, we chose not to place additional devices.

*Volume calculations.* During ischemia, the shape of the left ventricle can be considerably deformed. These systolic changes with asynchronous motion, however, occur before the mitral valve opens; therefore, we used the standard formulas to calculate LV volumes only from MVO up to end diastole, a procedure that we have previously used to describe diastolic events in ischemic hearts. Placement of the crystals (particularly the endocardial crystal) undoubtedly introduces some error into the calculation of absolute LV volumes by the technique used and might explain the relatively low ejection fractions, also reported in normal dogs by Rankin et al.¹⁷

We cannot exclude the occurrence of some mitral regurgitation during exercise with ischemia. Because hypokinesia (rather than dyskinesia) of the wall was induced, however, it seems unlikely that significant papillary muscle dysfunction occurred. Moreover, the increase of LV EDV during ischemic exercise was less than 10% above that during normal exercise, whereas the total filling volume was lower and associated with an increased ventricular volume (residual volume) at the onset of filling during ischemic exercise, making a significant degree of mitral regurgitation seem unlikely.

**Severity and size of the ischemic region.** In this study, ischemia was produced during exercise with the criterion of causing less than 10% thickening of the ischemic wall, a value that is associated with sharply reduced subendocardial blood flow.¹¹,⁴⁴ This level was chosen to avoid ventricular fibrillation, which often occurs during exercise with very severe ischemia.

Because the dog has a dominant circumflex coronary artery, the size of the ischemic region generally is large but can vary because of differences in the collateral circulation. Whether methodological differences or, perhaps, a larger ischemic area are responsible for the upward shift of the entire diastolic P-V relation during exercise in some clinical studies is uncertain. However, it is possible that, with a larger area and a more severe ischemia, different results would have been obtained in our study.

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