Systolic and Diastolic Dysfunction During Atrial Pacing in Conscious Dogs With Left Ventricular Hypertrophy

Alan M. Fujii, Ricardo J. Gelpi, Israel Mirsky, and Stephen F. Vatner

To determine the extent to which the hypertrophied left ventricle responds to the chronotropic stress induced by graded atrial pacing rates, we studied conscious, chronically instrumented dogs with severe compensated pressure overload left ventricular (LV) hypertrophy induced by aortic banding in puppies 8–10 weeks of age. At 1–2 years, dogs with severe LV hypertrophy (LV free wall/body wt ratio 6.8 ± 0.6 g/kg) and sham-operated littermates (LV free wall/body wt ratio 4.0 ± 0.3 g/kg) were instrumented with ultrasonic dimension crystals to measure LV short axis internal diameter and wall thickness, miniature LV pressure transducers, and aortic and LV catheters. During atrial pacing (240 beats/min) in eight control dogs, LV pressure did not change from 119 ± 2 mm Hg, and mean velocity of circumferential fiber shortening (VCF) did not change from 1.25 ± 0.09/sec. In seven dogs with LV hypertrophy, atrial pacing (240 beats/min) decreased systolic LV function; that is, LV systolic pressure decreased (p < 0.01) by 65 ± 12 from 254 ± 14 mm Hg, and VCF decreased (p < 0.01) by 0.19 ± 0.03 from 0.97 ± 0.15/sec. Diastolic dysfunction was also observed in the dogs with LV hypertrophy. In the control dogs during atrial pacing (240 beats/min), LV end-diastolic pressure decreased (p < 0.01) by 8 ± 1 from 9 ± 1 mm Hg, end-diastolic stress decreased (p < 0.01) by 18 ± 2 from 22 ± 2 g/cm², and the radial myocardial stiffness constant did not change from 5.6 ± 1.0. In contrast, during atrial pacing (240 beats/min) in dogs with LV hypertrophy, LV end-diastolic pressure increased (p < 0.01) by 21 ± 4 from 12 ± 1 mm Hg, end-diastolic stress increased (p < 0.01) by 10 ± 5 from 17 ± 1 g/cm², and the stiffness constant increased (p < 0.01) by 12.1 ± 3.7 from 8.4 ± 2.0. These data demonstrate that rapid atrial pacing impairs ejection phase indexes of LV function and increases diastolic myocardial stiffness in the dogs with severe LV hypertrophy. Thus, while baseline LV function in the dogs with LV hypertrophy was not depressed, systolic and diastolic decompensation occurred during the chronotropic stress induced by rapid pacing rates. (Circulation Research 1988;62:462–470)

In animals and man, the effects of severe pressure overload left ventricular (LV) hypertrophy on LV function remain controversial. However, the natural history of pressure overload LV hypertrophy is the progressive decline in LV function with the eventual development of irreversible heart failure with a reduced capacity to respond to stress. One hypothesis for the deterioration of left ventricle function and the limited reserve of the hypertrophied left ventricle is the diminished myocardial perfusion reserve. During the chronotropic stress induced by pacing, several investigators have reported relative subendocardial hypoperfusion in the hypertrophied left ventricle and biochemical evidence of myocardial anaerobic metabolism. The effects of the chronotropic stress on systolic and diastolic function in the hypertrophied left ventricle have not been reported. Our study was designed to determine the effect of the chronotropic stress induced by atrial pacing on both systolic and diastolic LV function in conscious, chronically instrumented dogs with severe LV hypertrophy and in sham-operated littermates. Atrial pacing was used since it is a more physiological chronotropic stress than occurs during ventricular pacing. The pacing rates used (120–270 beats/min) were in the physiological range because heart rates of 300 beats/min are routinely observed in dogs during maximal free ranging exercise. In addition, use of conscious dogs eliminated the complicating effects of anesthetics, and use of sham-operated littermates eliminated possible genetic and environmental factors that could affect the responses.

Materials and Methods

Aortic Constriction–Induced Left Ventricular Hypertrophy

Pressure overload LV hypertrophy was induced by implanting a 1-cm wide Teflon band around the ascending aorta, distal to the coronary arteries in mongrel puppies 8–10 weeks of age. The band was implanted through a thoracotomy in the fourth right intercostal space using sterile surgical technique and
sodium thiamylal anesthesia (25 mg/kg). The bands were tightened until a thrill could be palpated over the aortic arch. In the littermates designated as controls, a right thoracotomy was performed, the aortic root dissected, and the chest closed without implantation of a band. Both groups of puppies were allowed to recover from surgery and grow to maturity. The Teflon band created a fixed supravalvar aortic lesion that became relatively more stenotic as the puppies grew. None of the puppies died during the banding procedure itself. Two dogs died prior to instrumentation during the development of hypertrophy: one from heart failure and one from aortic rupture at the band site.

Implication of Instrumentation

At 1–2 years of age, 16 dogs were instrumented through a thoracotomy in the fifth left intercostal space using sterile surgical technique and sodium pentobarbital anesthesia (30 mg/kg i.v.). Tygon (Norton Plastics and Synthetic Division, Akron, Ohio) catheters were implanted in the descending thoracic aorta, LV apex, and left atrium. Piezoelectric ultrasonic dimension crystals were implanted on opposing anterior and posterior endocardial surfaces of the left ventricle to measure the short axis internal diameter and on opposing endocardial and epicardial surfaces in the same equatorial plane as the internal diameter crystals to measure wall thickness. A solid-state miniature pressure transducer (model P22, Konigsberg Instruments, Pasadena, California) was implanted in the apex to measure LV pressure. Pacing electrodes were sutured to the left atrial appendage. The thoracotomy incision was closed in layers, and the animals were allowed to recover for 2–4 weeks prior to study. The animals used in this study were maintained in accordance with the guidelines for the “Care and Use of Laboratory Animals” of the Institute of Laboratory Animal Resources, National Council [DHHS publication No. (NIH) 85-23, revised 1985].

Statham strain gauge manometers (model P23ID Statham Instruments, Oxnard, California) were calibrated with a mercury manometer and used to sample aortic and LV pressures from chronically implanted catheters. LV pressure was measured using the solid-state miniature pressure gauge calibrated in vitro with a mercury manometer and in vivo using the LV catheter and Statham strain gauge manometer. The solid-state Konigsberg pressure transducer has a high frequency response necessary for the accurate measurement of LV dP/dt as well as for the timing of events during the cardiac cycle.19,20 LV internal diameter and wall thickness were measured using an ultrasonic transit-time dimension gauge.21 The dimension gauge generates a voltage linearly proportional to the transit time of the ultrasonic impulses traveling at the velocity of $1.58 \times 10^6$ mm/sec between the 3-MHz crystals. The frequency response of the dimension gauge is flat to 60 Hz. At constant room temperature, the thermal drift of

![Figure 1](responses-to-graded-atrial-pacing-rates-in-a-conscious-dog-with-severe-left-ventricular-hypertrophy-image.jpg)

**Figure 1.** Responses to graded atrial pacing rates in a conscious dog with severe left ventricular hypertrophy. There is a rate-related decrease in systolic left-ventricular pressure (LVP). The LV end-diastolic pressure initially decreases with increasing atrial rates, then increases at pacing rates greater than 210 beats/min. LV end-diastolic internal diameter decreases and end-diastolic wall thickness increases as the pacing rate is increased. LV end-systolic internal diameter decreases and wall thickness increases only slightly with increasing pacing rates. The end-diastolic point is indicated by a vertical line for each pacing rate. The waveform at atrial pacing rate of 240 beats/min is expanded to clarify the end-diastolic point.
the instrument is minimal (i.e., less than 0.02 mm in 6 hours). Any drift in the measurement system was eliminated during the experiment by periodic calibrations accomplished by substituting impulses of known duration from a crystal-controlled pulse generator having a stability of 0.001%. The position of all transducers was confirmed at autopsy. In eight of the animals studied, the position of the crystals was also confirmed in vivo using fluoroscopic visualization.

Data Analysis

The data were recorded on a multichannel tape recorder (model 101, Honeywell, Denver, Colorado) and played back on a direct-writing oscillograph (Gould-Brush Mark 200, Cleveland, Ohio). A cardiotorahometer (model 9857B, Beckman Instruments, Fullerton, California) triggered by the LV pressure pulse, provided instantaneous and continuous records of heart rate. Continuous records of LV dP/dt were derived from the LV pressure signals using Philbrick operational amplifiers (Teledyne Philbrick, Dedham, Massachusetts), operated as differentiators and having a frequency response of 700 Hz. A triangular wave signal was substituted for the pressure signals to directly calibrate the differentiator. End-diastolic LV dimensions were measured at the onset of LV contraction, indicated by the initial increase in LV dP/dt. At atrial pacing rates ≥ 180 beats/min, the end-diastolic point corresponds with maximum internal diameter and minimum wall thickness (Figures 1 and 2). End-systolic dimension was measured at the time of minimum internal diameter and maximum wall thickness. Ejection time was taken as the interval between maximum and minimum LV dP/dt. The derived ejection phase index was calculated as follows:

\[ VCF = \frac{(EDD - ESD/EDD)}{ET} \]

where VCF is the mean velocity of circumferential fiber shortening, EDD is the end-diastolic internal diameter, ESD is the end-systolic internal diameter, and ET is the ejection time. The analog signals of LV pressure and dimensions were digitized at 4-msec intervals, using a digital computer (PDP 11/34, Digital Equipment, Maynard, Massachusetts). The computer was used to calculate global LV circumferential wall stress using a cylindrical model,

\[ \text{stress} = 1.36 \left( \frac{PD}{2h} \right) \]

where P is LV pressure, D is internal short axis diameter, and h is wall thickness. The integrated area under the systolic wall stress-time curve was divided by the ejection time so that average global systolic wall stress was determined. Radial diastolic myocardial stiffness was assessed using a modification of the
formula developed by Mirsky22-24 (see "Appendix"). The radial diastolic myocardial stiffness constant, \( a \), was determined from an average of at least five beats.

Statistical and linear regression analyses were performed using an IBM PC/AT or a Digital PRO 350 computer. The data are reported as the mean \pm SEM. Analysis of variance was used to determine whether there were differences between the values in the control dogs and the dogs with LV hypertrophy.\(^25\) A \( t \) test with a Bonferroni correction\(^26\) was used to determine whether there were differences at each pacing rate. For example, if five simultaneous comparisons were made, \( p < 0.01 \) was considered significant at the \( p < 0.05 \) level of significance.

**Protocols**

The dogs were studied beginning 2–4 weeks after instrumentation, when they were healthy and had completely recovered from the effects of surgery. All dogs studied were vigorous and without signs of heart failure. Graded rates of atrial pacing (range 120–270 beats/min) after pretreatment with atropine (0.04 mg/kg) were used. The pacing rate was increased in 30-beat/min increments at 5-minute intervals. Atropine sulfate was used to decrease the amount of rate-dependent atroventricular block and allow atrial pacing at rates up to 270 beats/min. Atropine increased baseline heart rate to 110–120 from approximately 90 beats/min (Table 1) without inducing changes in mean aortic pressure, LV systolic pressure, or LV dp/dt. The baseline control data were taken prior to atropine administration. The radioactive microsphere technique was also utilized to measure regional myocardial blood flow in five dogs with LV hypertrophy. In this study, 15 ± 1-\(^{\mu}\)m microspheres labeled with \( ^{141}\)Ce, \( ^{99}\)Nb, \( ^{85}\)Sr, \( ^{85}\)Sc, \( ^{103}\)Ru, \( ^{113}\)Sn, or \( ^{111}\)In were used (New England Nuclear, Boston, Massachusetts). Two of these isotopes were administered to each animal under baseline conditions and then with heart rate elevated to 240 beats/min by atrial pacing.

**Results**

In postmortem studies, the LV free wall-to-body weight ratio in dogs with LV hypertrophy (6.8 ± 0.6 g/kg) was found to be 70% greater (\( p < 0.01 \)) than in sham-operated control dogs (4.0 ± 0.3 g/kg). LV free wall-to-body weight ratio was measured in all eight dogs with LV hypertrophy and in four sham-operated control dogs. The body weights of dogs with LV hypertrophy (21 ± 1 kg) were similar to the control animals (23 ± 1 kg).

**Effects of Atrial Pacing on Systolic Function**

**(Table 1)**

Representative responses to graded atrial pacing rates in a dog with severe LV hypertrophy and in a control dog are shown in Figures 1 and 2. A summary of the responses to atrial pacing are shown in Tables 1 and 2. Paired data at baseline and during atrial pacing were obtained in eight dogs with LV hypertrophy and eight control dogs. In one dog with LV hypertrophy, atrial pacing could not be maintained at rates ≥240 beats/min. Thus, while data from seven dogs with LV hypertrophy are presented in the table, data from eight dogs with LV hypertrophy are presented in the figures. The baseline LV systolic pressure in seven dogs with LV hypertrophy was greater (254 ± 14 versus 119 ± 2 mm Hg, \( p < 0.01 \)), while the baseline mean arterial pressures were similar (92 ± 5 versus 97 ± 3 mm Hg) to eight control animals. In the dogs with LV hypertrophy, there was a baseline peak-to-peak LV to aortic systolic gradient of 143 ± 17 mm Hg. The baseline internal short axis diameters were similar in the two groups, while the LV end-diastolic wall thickness in the dogs with LV hypertrophy was 57% greater (\( p < 0.01 \)) than in the sham-operated controls. The baseline LV systolic wall stress in the dogs with LV hypertrophy (249 ± 26 g/cm\(^2\)) was similar to the sham-operated controls (204 ± 17 g/cm\(^2\)). Baseline indexes of LV function were similar in the dogs with hypertrophy and the sham-operated control dogs: percentage change in internal short axis diameter was 20.8 ± 3.8% versus 22.5 ± 2.3%, and mean velocity of circumferential fiber shortening (VCF) was 0.97 ± 0.15 versus 1.25 ± 0.09/sec.

Atrial pacing at 240 beats/min decreased (\( p < 0.01 \)) LV systolic pressure in the dogs with LV hypertrophy by 65 ± 12 to 187 ± 20 mm Hg, while the LV systolic pressure in the control animals did not change (Figure 3). In the dogs with LV hypertrophy, the peak-to-peak LV to aortic systolic gradient decreased (\( p < 0.01 \)) by 58 ± 14 mm Hg during atrial pacing (240 beats/min). The LV end-diastolic internal diameter decreased similarly in the two groups. LV end-diastolic internal diameters did not change in the dogs with hypertrophy but decreased (\( p < 0.01 \)) by 2.8 ± 0.4 mm in the control animals. Thus, rapid atrial pacing decreased the extent to which the left ventricle contracted in the dogs with LV hypertrophy when compared with the control animals. The percentage change in internal diameter decreased (\( p < 0.01 \)) by 9.8 ± 1.7% in the dogs with LV hypertrophy and decreased (\( p < 0.01 \)) by 7.3 ± 1.4% in the control animals. VCF decreased (\( p < 0.01 \)) by 0.19 ± 0.03/sec (Figure 4) in the dogs with LV hypertrophy, while VCF did not change in the control dogs. The average global LV systolic wall stress decreased (\( p < 0.01 \)) by 86 ± 19 g/cm\(^2\) in the dogs with LV hypertrophy and decreased (\( p < 0.01 \)) by 52 ± 7 g/cm\(^2\) in the control dogs. Atrial pacing was associated with a greater decrease in VCF (\( p < 0.01 \)) and similar decreases in wall stress in the dogs with LV hypertrophy when compared with the control dogs (Figure 4). Thus, while systolic function was similar in the two groups of animals in the baseline state and at low pacing rates, rapid atrial pacing rates induced LV systolic dysfunction in the dogs with hypertrophy.

**Effects of Atrial Pacing on Diastolic Function**

**(Table 2)**

The baseline indexes of LV diastolic function were generally similar in the two groups of animals. LV end-diastolic pressure (12 ± 1 versus 9 ± 1 mm Hg) and...
### Table 1. Effects of Pacing on Left Ventricular Systolic Function

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>240 beats/min</th>
<th>Change</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean arterial pressure (mm Hg)</strong></td>
<td></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>97 ± 3</td>
<td>102 ± 4</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>92 ± 5</td>
<td>96 ± 5</td>
<td>4 ± 2</td>
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<tr>
<td><strong>LV systolic pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>119 ± 2</td>
<td>119 ± 3</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>254 ± 14*</td>
<td>187 ± 20*†</td>
<td>−65 ± 12*</td>
</tr>
<tr>
<td><strong>LV dP/dt (mm Hg/sec)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control dogs (n = 8)</td>
<td>3,179 ± 151</td>
<td>2,989 ± 115</td>
<td>−190 ± 138</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>3,379 ± 121</td>
<td>3,512 ± 156</td>
<td>133 ± 120</td>
</tr>
<tr>
<td><strong>LV end-diastolic diameter (mm)</strong></td>
<td></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>39.6 ± 1.6</td>
<td>33.0 ± 1.7†</td>
<td>−6.7 ± 0.9</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>38.0 ± 1.1</td>
<td>33.1 ± 1.9†</td>
<td>−4.8 ± 1.1</td>
</tr>
<tr>
<td><strong>LV end-systolic diameter (mm)</strong></td>
<td></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>30.8 ± 1.8</td>
<td>28.0 ± 1.7†</td>
<td>−2.8 ± 0.4</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>30.3 ± 2.0</td>
<td>29.7 ± 2.3</td>
<td>−0.6 ± 0.3*</td>
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<tr>
<td><strong>LV shortening (mm)</strong></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>8.8 ± 0.9</td>
<td>4.9 ± 0.3†</td>
<td>−3.9 ± 0.8</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>7.8 ± 1.3</td>
<td>3.4 ± 0.5††</td>
<td>−4.2 ± 0.8</td>
</tr>
<tr>
<td>Change in internal diameter (%)</td>
<td></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>22.5 ± 2.3</td>
<td>15.1 ± 1.1†</td>
<td>−7.3 ± 1.4</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>20.8 ± 3.8</td>
<td>11.0 ± 2.3††</td>
<td>−9.8 ± 1.7</td>
</tr>
<tr>
<td><strong>Ejection time (msec)</strong></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>178 ± 7</td>
<td>114 ± 2†</td>
<td>−64 ± 6</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>210 ± 8*</td>
<td>139 ± 2*†</td>
<td>−68 ± 8</td>
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<tr>
<td><strong>VCF (sec⁻¹)</strong></td>
<td></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>1.25 ± 0.09</td>
<td>1.33 ± 0.08</td>
<td>0.08 ± 0.06</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>0.97 ± 0.15</td>
<td>0.79 ± 0.15* †</td>
<td>−0.19 ± 0.03*</td>
</tr>
<tr>
<td><strong>LV end-diastolic wall thickness (mm)</strong></td>
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<td></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>11.7 ± 0.5</td>
<td>13.0 ± 0.5†</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>18.4 ± 1.2*</td>
<td>19.9 ± 1.2*†</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td><strong>LV end-systolic wall thickness (mm)</strong></td>
<td></td>
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</tr>
<tr>
<td>Control dogs (n = 8)</td>
<td>13.9 ± 0.5</td>
<td>14.7 ± 0.5†</td>
<td>0.8 ± 0.2</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>20.7 ± 1.3*</td>
<td>21.0 ± 1.4*</td>
<td>0.3 ± 0.2</td>
</tr>
<tr>
<td><strong>LV wall thickening (mm)</strong></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>2.2 ± 0.3</td>
<td>1.6 ± 0.4†</td>
<td>−0.6 ± 0.1</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>2.3 ± 0.5</td>
<td>1.2 ± 0.3†</td>
<td>−1.1 ± 0.2</td>
</tr>
<tr>
<td><strong>LV average global systolic wall stress (g/cm²)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Control dogs (n = 8)</td>
<td>204 ± 17</td>
<td>152 ± 12†</td>
<td>−52 ± 7</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>249 ± 26</td>
<td>162 ± 26†</td>
<td>−86 ± 19</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control dogs (n = 8)</td>
<td>87 ± 3</td>
<td>240 ± 0†</td>
<td>153 ± 3</td>
</tr>
<tr>
<td>Hypertrophy dogs (n = 7)</td>
<td>91 ± 6</td>
<td>240 ± 0†</td>
<td>149 ± 6</td>
</tr>
</tbody>
</table>

LV, left ventricular; VCF, mean velocity of circumferential fiber shortening.

*Hypertrophy dogs different from control dogs (p<0.01).

†Values at 240 beats/min different from baseline (p<0.01).

LV end-diastolic wall stress (17 ± 1 versus 22 ± 2 g/cm²) were similar in the two groups of dogs. The radial myocardial stiffness constant, α, (see "Appendix"), as obtained from the pressure-thickness relation, P = Ah⁻⁸, was similar in dogs with LV hypertrophy and in the control dogs (α = 8.4 ± 2.0 versus 5.6 ± 1.0).

At rapid atrial pacing rates, there was a striking difference in the indexes of LV diastolic function in the two groups. At an atrial pacing rate of 240 beats/min,
Effects of Atrial Pacing on Regional Myocardial Blood Flow

Radioactive microspheres were administered into the left atrium in five dogs with LV hypertrophy under baseline conditions and after heart rate was elevated to 240 beats/min by atrial pacing. Under baseline conditions, regional myocardial blood flow in the LV free wall was 1.42 ± 0.43 ml/min/g in the endocardium and 1.29 ± 0.19 ml/min/g in the epicardium. At a heart rate of 240 beats/min, blood flow rose in the endocardium to 2.08 ± 0.31 ml/min/g and in the epicardium to 2.56 ± 0.52 ml/min/g. The endocardial-to-epicardial ratio fell from 1.07 ± 0.18 to 0.85 ± 0.06 with pacing.

Discussion

In this study, aortic banding in the puppies resulted in a 70% increase in the LV free wall-to-body weight ratio when compared with sham-operated littermates. This degree of LV hypertrophy was similar to previous reports in which banding of the ascending aorta of puppies was performed but was greater than that observed when the supracoronary aortic stenosis was produced in adult dogs. Since the body weights were similar in the two groups of animals, the LV-to-body weight ratio is a useful indicator of the degree of LV hypertrophy developed. In our study, the hypertrophied left ventricle remained well compensated. The baseline values for LV systolic function in the dogs with LV hypertrophy were generally similar to the sham-operated control dogs. In particular, baseline systolic wall stress in the two groups of animals was similar, as were the ejection phase indexes. There were, however, slight differences in the baseline parameters of diastolic function. In the dogs with LV hypertrophy, the slight elevation of the LV end-diastolic pressure was compensated for by the increase in end-diastolic wall thickness. The LV diastolic radial stiffness constant was similar in the two groups of dogs. Thus, parameters of both systolic and diastolic function in the dogs with LV hypertrophy in baseline conditions suggested adequate compensation for the large pressure overload induced by the aortic band.

A recent study by Fujii et al demonstrated that in conscious, chronically instrumented dogs with severe LV hypertrophy, the LV mechanical and inotropic responses to infusions of norepinephrine and prenalin...
FIGURE 3. Responses of left ventricular (LV) systolic (upper panel) and end-diastolic (lower panel) pressure to graded rates of atrial pacing. In the eight dogs with LV hypertrophy, there is a rate-related decrease in LV systolic pressure, while LV systolic pressure does not change in eight control dogs. LV end-diastolic pressure initially decreases in both groups of dogs, which reaches a nadir at pacing rates of 180 beats/min in the dogs with LV hypertrophy. At higher pacing rates, the LV end-diastolic pressure increases in the dogs with LV hypertrophy, while it remains low in the control dogs. The broken lines indicate incomplete data due to inability to sustain atrial pacing at high rates. Thus, at pacing rates of 240 beats/min, there are seven dogs with LV hypertrophy and eight controls. At 270 beats/min, there are five dogs with LV hypertrophy and six control dogs.

trol were normal. During infusions of norepinephrine, the hypertrophied left ventricle developed and sustained systolic pressures over 300 mm Hg while maintaining a normal inotropic response. These data demonstrate that the hypertrophied left ventricle not only functions normally at rest but also has a substantial reserve to respond to certain types of stress.

In contrast, in the current investigation, the chronotropic stress of rapid atrial pacing induced a rate-related impairment in both systolic and diastolic LV function. At low atrial pacing rates, in the presence of atropine, both systolic and diastolic function parameters remained similar in the two groups of animals, demonstrating that atrial pacing itself was not responsible for the differences observed at the higher pacing rates. The rate-related reduction in LV systolic pressure in the dogs with supracoronary aortic bands was probably due to a combination of reduced stroke volume and depressed LV systolic function. Although LV diastolic chamber and myocardial stiffness have been studied in pressure overload hypertrophy, the effect of chronotropic stress on diastolic myocardial stiffness has not been reported. In the dogs with LV hypertrophy, myocardial stiffness increased at rapid pacing rates. The threshold for systolic and diastolic dysfunction occurred at pacing rates between 210 and 240 beats/min. Thus, while the hypertrophied left ventricle has substantial inotropic and mechanical

FIGURE 4. Responses of average global systolic wall stress (upper panel) and end-diastolic wall stress (lower panel) and mean left ventricular (LV) velocity of circumferential fiber shortening (VCF) (middle panel). In both the control dogs and in the dogs with LV hypertrophy, there is a rate-related decrease in the average global LV systolic wall stress. In the dogs with LV hypertrophy, VCF decreases with increasing atrial pacing rates, while VCF remains relatively constant in the control dogs. There is a rate-related decrease in the end-diastolic wall stress with atrial pacing rates of 120–180 beats/min in both groups of animals. At atrial pacing rates ≥210 beats/min, end-diastolic wall stress increases with increasing pacing rates in the dogs with LV hypertrophy, while it remains low in the control animals.
dial stiffness during rapid atrial pacing. An alternate systolic function and an increase in diastolic myocardial hypertrophy during the stress induced by hemorrhage, the relation is dramatically disrupted during rapid atrial pacing. The broken lines indicate fewer numbers of animals for the indicated response.

One hypothesis to explain reduced capacity of the hypertrophied left ventricle to respond to chronotropic stress is an impairment of myocardial perfusion resulting in myocardial ischemia and LV dysfunction. With an increase in the heart rate, diastolic perfusion time is reduced, and time-tension index is increased. Bache and his colleagues have shown that in dogs with severe LV hypertrophy, pacing induces subendocardial myocardial hypoperfusion, which is associated with biochemical evidence of myocardial anaerobic metabolism. In the current investigation, relative subendocardial hypoperfusion was also observed in response to pacing in the dogs with LV hypertrophy. Other studies have demonstrated a reduced LV myocardial perfusion reserve in the hypertrophied left ventricle in response to pharmacological vasodilation and a reduced coronary vasodilator reserve during rapid pacing. The response of various LV function parameters to myocardial ischemia has been investigated for many years. In patients with coronary artery disease, several investigators have found that pacing-induced angina caused marked diastolic dysfunction. In our study, we have demonstrated both a reduction in ejection phase indexes of LV systolic function and an increase in diastolic myocardial stiffness during rapid atrial pacing. An alternate hypothesis is that the diastolic dysfunction and increased LV diastolic pressure at high heart rates may contribute to the subendocardial myocardial hypoperfusion. The cause and effect relation between diastolic function and myocardial perfusion was beyond the scope of the present study and will require further investigation.

In conclusion, we have demonstrated that in conscious dogs with severe compensated pressure overload LV hypertrophy, there is a diminished capacity to respond to chronotropic stress. At rapid pacing rates (240 beats/min), there was both systolic and diastolic LV dysfunction in the hypertrophied hearts.

**References**


34. Hoffman JIE, Buckberg GD: Transmural variations in myocardial perfusion. Prog Cardiol 1976;5:37—89


42. Spaan JAE: Coronary diastolic pressure—flow relation and zero flow pressure explained on the basis of intramyocardial compliance. Circ Res 1985;56:293—309

KEY WORDS • left ventricular hypertrophy • systolic function • diastolic function • pacing • heart rate
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