Abnormalities in myocardial perfusion during tachycardia in dogs with left ventricular hypertrophy: metabolic evidence for myocardial ischemia

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ABSTRACT This study tested the hypothesis that in the chronically hypertrophied left ventricle pacing stress may cause abnormalities of perfusion that result in myocardial ischemia. Left ventricular hypertrophy (LVH) was produced by banding the ascending aorta of 10 dogs at 6 weeks of age, and studies were carried out after the animals had reached adulthood and when mean left ventricular/body weight ratio was 74% greater than in eight control dogs. Myocardial blood flow was measured with microspheres during pacing at 100, 200, and 250 beats/min, while aortic and coronary sinus blood samples were obtained for determination of concentrations of lactate and the adenosine metabolites inosine and hypoxanthine. In the control dogs, increasing heart rates were associated with an increase in mean myocardial blood flow while subendocardial flow was maintained at a level equal to or greater than subepicardial flow. Myocardial lactate uptake ranged from +60% to −5%, and adenosine metabolites were not detected in coronary sinus blood (<0.5 μM/l). In four dogs that underwent aortic banding no production of lactate or adenosine metabolites was observed at any heart rate; in these animals subendocardial flow was maintained at a level equal to or greater than subepicardial flow at all pacing rates. The remaining six dogs with LVH demonstrated net lactate production significantly greater than control during pacing at 250 beats/min; five of these six animals also produced adenosine metabolites. In these six animals mean myocardial blood flow failed to increase as the pacing rate was increased from 200 to 250 beats/min, and pacing at 250 beats/min was associated with a transmural redistribution of perfusion away from the subendocardium (subendocardial/subepicardial blood flow ratio = 0.50 ± 0.05). These findings demonstrate that perfusion abnormalities may occur in the chronically hypertrophied heart during rapid cardiac pacing and that these result in myocardial ischemia. Circulation 69, No. 2, 409–417, 1984.

SEVERAL OBSERVATIONS suggest that the hypertrophied left ventricle may have increased vulnerability to ischemia. Thus, patients with severe left ventricular hypertrophy may experience angina pectoris and develop electrocardiographic repolarization abnormalities that are suggestive of myocardial ischemia. These findings may be accompanied by pathologic evidence of fibrosis or infarction of subendocardial myocardium or papillary muscle even in the presence of anatomically normal coronary arteries.1,2 Although previous studies in the pressure-overloaded hypertrophied left ventricle have generally demonstrated a normal or slightly increased volume of blood flow per unit myocardial mass and a normal transmural distribution of perfusion under basal conditions,3–10 several investigators have reported that during the stress of exercise or rapid cardiac pacing, the hypertrophied heart may develop relative subendocardial hypoperfusion.5,6,11,12 However, it is possible that alterations in the transmural distribution of myocardial blood flow could be related in part to changes in the transmural pattern of systolic stress (and therefore myocardial oxygen consumption) in the hypertrophied heart.9 For this reason, without information regarding myocardial metabolic demands it is not possible to determine whether relative subendocardial underperfusion in the hypertrophied heart represents inadequate subendocardial blood flow, or whether it results from a reduction of systolic stress in the subendocardium, thus represent-
ing an appropriate response to a change in the transmural pattern of myocardial metabolic requirements. Consequently, our study was carried out to examine the response of net myocardial metabolism of lactate and adenosine during rapid pacing in the chronically pressure-overloaded hypertrophied left ventricle.

Methods

Studies were performed in 10 adult mongrel dogs in which left ventricular hypertrophy (LVH) had been produced by banding the ascending aorta when they were puppies, and in eight adult mongrel dogs that served as a control group. At 6 weeks of age, each animal in which LVH was to be produced was anesthetized with sodium pentobarbital (20 to 25 mg/kg) and ventilated with a respirator, and a right thoracotomy was performed in the third intercostal space. A pericardial cradle was created and the ascending aorta, approximately 1.5 cm above the aortic valve, was dissected free from the surrounding fat and connective tissue. The aorta was then encircled with a polyethylene band, 3 mm in width. While simultaneously measuring left ventricular and distal aortic pressures, the band was tightened until a 20 to 30 mm Hg peak systolic gradient was achieved across the constriction. The pericardium was then closed with interrupted 4-0 silk sutures, the thoracotomy repaired, the right hemithorax evacuated of air with a chest tube, and the animal allowed to recover. When the animals were 12 months of age, a second surgical procedure was performed for placement of catheters and pacing electrodes. Each animal was anesthetized with sodium pentobarbital (25 to 30 mg/kg iv) and ventilated with a respirator, and a left thoracotomy was performed in the fourth intercostal space. The heart was suspended in a pericardial cradle and a PVC catheter of a 3 mm outer diameter that was filled with heparin saline solution (200 U/ml) was inserted into the left atrial cavity via the atrial appendage and secured with a purse string suture. A similar catheter was inserted into the left ventricular cavity through a stab wound at the apical dimple and secured with a purse string suture. A third catheter was introduced into the ascending aorta distal to the aortic constriction via the left internal thoracic artery. A bipolar epicardial pacing electrode was sutured to the region of the right ventricular outflow tract. The catheters and pacing wire were tunneled dorsally into a subcutaneous pouch at the base of the neck, but were not exteriorized to protect them from damage. The pericardium was loosely closed, the thoracotomy incision repaired, and the animal allowed to recover. An identical surgical procedure was carried out in eight adult mongrel control dogs.

Studies were performed 10 to 14 days after surgery. At the time of study the dogs were active, free of fever or anemia, and appeared to be fully recovered from the effects of surgery. On the day before study, the dogs were sedated with fentanyl (0.01 mg/kg) and droperidol (0.4 mg/kg im) and, with 2% lidocaine infiltration anesthesia, a No. 7F NIH catheter was inserted into the right jugular vein under sterile conditions and advanced under fluoroscopic guidance into the coronary sinus with the catheter tip 3 cm past the coronary sinus ostium. The catheter was then tunneled subcutaneously to exit from the skin at the base of the neck. Subsequently, with 2% lidocaine infiltration anesthesia, the catheters and pacing wire that had been implanted when the dogs were puppies were exteriorized from the subcutaneous pouch. These devices were protected by nylon vests that the dogs had been trained to wear. On the morning of study, the position of the coronary sinus catheter was confirmed with fluoroscopy by injecting 1 to 2 ml of diatrizoate meglumine to opacify the coronary sinus. At least 2 hr elapsed after this injection before hemodynamic and myocardial blood flow measurements were obtained. Pressures from the aortic, left atrial, and left ventricular catheters were obtained with Statham P23D b pressure transducers. Lead II of a standard electrocardiogram was obtained. Data were recorded on a Hewlett-Packard Model 8800 direct-writing oscillograph. The laboratory was dimly illuminated and kept free from noise or activity that might have disturbed the dogs.

Measurements of myocardial blood flow were made with left atrial injections of microspheres, 15 ± 3 μm in diameter, labeled with gamma-emitting radionuclides 125I, 141Ce, 51Cr, 46Sc, 85Sr, or 95Nb (3M Company, St. Paul, MN). The microspheres were obtained as 1.0 mCi of each nuclide in 10 ml of 10% dextran. Before injection, the microspheres were thoroughly mixed for at least 15 min in an ultrasonic bath. Myocardial blood flow measurements were performed in each dog during three separate periods of ventricular pacing at rates of 100, 200, and 250 beats/min. Pacing was performed with a Grass Model S-88 physiologic stimulator delivering square-wave impulses 3 msec in duration at 25% above threshold current through a stimulus isolation unit. Arterial, left atrial, and left ventricular pressures were recorded continuously to ensure that steady-state hemodynamic conditions had been achieved. After 4 min of pacing at each rate, aortic and coronary sinus blood samples, 5.0 ml each, were withdrawn for determination of concentrations of lactate and adenosine metabolites. Immediately thereafter, 3 × 106 microspheres were injected into the left atrium for measurement of myocardial blood flow. This and all subsequent microsphere injections were performed over a 15 sec interval. Beginning 5 sec before each microsphere injection and continuing for 90 sec, a reference sample of arterial blood was collected from the aortic catheter at a constant rate of 15 ml/min with a Harvard Model 1210 withdrawal pump. Pacing was continued 2 min after microsphere injection. A minimum of 30 min was allowed between pacing interventions, and the order in which pacing rates were applied was randomized. A different radionuclide was used for each of the three pacing rates. Immediately before beginning each pacing intervention, control blood samples were obtained from the aortic and coronary sinus catheters.

After completion of the study, the dogs were anesthetized with sodium pentobarbital (25 to 30 mg/kg iv) and fluoroscopy was again performed to confirm the position of the coronary sinus catheter. There was no change in catheter position in any of the dogs included in this report. The dogs were then killed with a lethal dose of pentobarbital and the hearts were removed, weighed, and fixed in a 10% buffered formalin. The atria, right ventricle, aorta, and large epicardial vessels were dissected from the left ventricle. The left ventricle was then sectioned into four transverse rings of approximately equal thickness parallel to the mitral valve ring. The two central rings were then divided into six circumferential regions corresponding to the anterior free wall, interventricular septum, posterior free wall, posterior papillary muscle region, lateral wall, and anterior papillary muscle region, as previously described. The resultant specimens were then divided into four transmural layers of equal thickness from epicardium to endocardium, weighed, and placed in vials for counting. These layers will be referred to as layers 1 to 4, layer 1 being closest to the epicardium and layer 4 closest to the endocardium. Individual sample weights ranged from 1 to 3 g.

Myocardial and blood reference specimen radioactivity was determined with a Packard Model 5812 gamma spectrometer with multichannel analyzer with the use of window settings selected to correspond to the peak energies emitted by each radionuclide. The activities recorded in each energy window and the corresponding sample weights were entered into a digital computer programmed to correct for contaminant activity contributed by the associated radionuclides and for background
activity, and to compute the corrected counts per minute per gram of myocardium. Blood flow to each myocardial specimen (Q_m) was computed with the formula: 
\[
Q_m = \frac{Q_c}{C_m/C_r}
\]
where \(Q_c\) = reference blood flow rate (ml/min), \(C_m\) = counts per minute of the myocardial specimen, and \(C_r\) = counts per minute of the reference blood specimen. Blood flow to each myocardial specimen was then divided by sample weight and expressed as milliliters per minute per gram of myocardium.

Heart rate and arterial, left atrial, and left ventricular pressures were measured directly from the strip-chart recordings. Analysis of the effect of pacing on each of these variables was examined with one-way analysis of variance testing. Myocardial blood flows from the corresponding transmural layers of each of the six circumferential regions were compared by multivariate analysis. A p value of less than .05 was required for statistical significance. When significant differences were found to exist, multiple contrasts were performed between layers and regions. The ratio of subendocardial/subepicardial blood flow (endo/epi) was obtained by dividing flow to layer 4 by the corresponding flow to layer 1. Comparisons of data from normal control animals and from dogs with LVH at each of the three heart rates were performed with Student’s t test for unpaired data. P values were corrected by the Bonferroni method.

Specimens of whole blood obtained for determination of lactate and adenosine metabolites were immediately deproteinized by rapidly adding 2.5 ml of 2M iced perchloric acid. After centrifugation at 6000 g for 20 min in a refrigerated centrifuge, the protein-free supernatant was removed and neutralized. Lactate was measured enzymatically by conversion to pyruvate by lactic dehydrogenase according to the spectrophotometric method of Hadjivassiliou and Reider. The percentage lactate extraction was calculated as arterial minus coronary sinus lactate concentration divided by the arterial concentration times 100. A negative percentage therefore indicated myocardial production of lactate. Adenosine metabolites were measured by sequential enzymatic degradation to uric acid by the addition of xanthine oxidase, nucleoside phosphorylase, and finally adenosine deaminase in a single cuvette of an Aminco DW-2 dual-beam, dual wave length-recording spectrophotometer at wave lengths of 292 and 320 mm. The threshold of sensitivity for this method for determination of adenosine and xypurines in our laboratory is 0.5 μM/l, with a coefficient of variation for reproducibility of 4.4%.

**Results**

Anatomic data for eight normal control dogs and 10 animals with aortic banding are shown in table 1. Dogs with aortic banding were divided into two groups. Group LVH-I includes four dogs in which no production of lactate or adenosine metabolite occurred at any pacing rate, while group LVH-II includes six dogs in which production of lactate and/or adenosine metabolite indicative of myocardial ischemia occurred during pacing at 250 beats/min. All dogs with aortic banding had significant LVH, with the mean left ventricular/body weight ratio increased 77% above control in group LVH-I and 65% above control in group LVH-II. Although mean body weight tended to be lower in group LVH-II, this value was not significantly different from that for either the control group or group LVH-I. Mean right ventricular/body weight ratios were not significantly different from control in either group of animals with LVH.

Hemodynamic data are shown in table 2. The normal control dogs and both groups of animals with aortic banding had resting heart rates of less than 100 beats/min. At a pacing rate of 100 beats/min, mean left ventricular systolic pressure was 68 mm Hg higher than control in group LVH-I (p < .01) and 91 mm Hg higher than control in group LVH-II (p < .01). This increase in left ventricular systolic pressure was accounted for by a peak systolic pressure gradient between the left ventricle and the aorta distal to the constriction of 88 ± 7 mm Hg in group LVH-I and of 116 ± 16 mm Hg in group LVH-II; this difference in systolic pressure gradient between the two groups of dogs with aortic banding was of borderline significance (p < .1). In the normal control dogs mean aortic pressure and left ventricular end-diastolic pressure did not change significantly as heart rates were increased to 200 and 250 beats/min, while left ventricular systolic pressure decreased from 117 ± 10 at 100 beats/min to 95 ± 9 mm Hg at 250 beats/min (p < .05). In both groups of dogs with aortic banding, increasing pacing rates were associated with similar progressive reductions in left ventricular systolic pressure (p < .05), while mean aortic pressure did not change significantly. Left ventricular end-diastolic pressure was not significantly different from control in group LVH-I; in-

**Table 1**

<table>
<thead>
<tr>
<th>Anatomic data</th>
<th>Body weight (kg)</th>
<th>LV weight (g)</th>
<th>LV/body weight (g/kg)</th>
<th>RV weight (g)</th>
<th>RV/body weight (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>20.4 ± 2.2</td>
<td>89.7 ± 10.2</td>
<td>4.40 ± 0.24</td>
<td>26.0 ± 2.3</td>
<td>1.33 ± 0.11</td>
</tr>
<tr>
<td>Group LVH-I</td>
<td>16.0 ± 1.8</td>
<td>93 ± 22.2</td>
<td>5.81 ± 0.64</td>
<td>25.5 ± 3.3</td>
<td>1.59 ± 0.07</td>
</tr>
<tr>
<td>Group LVH-II</td>
<td>15.3 ± 1.7</td>
<td>113 ± 18.3</td>
<td>7.27 ± 1.08</td>
<td>23.6 ± 3.7</td>
<td>1.53 ± 0.12</td>
</tr>
</tbody>
</table>

LV = left ventricular; RV = right ventricular.

*p < .05 in comparison with the corresponding control value.
TABLE 2
Mean aortic pressure and left ventricular systolic and end-diastolic pressures in eight normal control dogs and 10 dogs with LVH during ventricular pacing at 100, 200, and 250 beats/min

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Mean aortic pressure (mm Hg)</th>
<th>LV systolic pressure (mm Hg)</th>
<th>LV end-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>LVH-I</td>
<td>LVH-II</td>
</tr>
<tr>
<td>100</td>
<td>93 ± 7</td>
<td>84 ± 4</td>
<td>82 ± 3</td>
</tr>
<tr>
<td>200</td>
<td>88 ± 9</td>
<td>78 ± 8</td>
<td>82 ± 4</td>
</tr>
<tr>
<td>250</td>
<td>81 ± 8</td>
<td>76 ± 3</td>
<td>76 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*p < .05 in comparison with the corresponding control value; p < .05 in comparison with the corresponding value measured at a heart rate of 100 beats/min.

Increasing pacing rates did not cause a significant increase in end-diastolic pressure in these animals. Left ventricular end-diastolic pressure was significantly higher than control in group LVH-II at a heart rate of 100 beats/min. In these dogs, pacing at 250 beats/min was associated with a further significant increase in left ventricular end-diastolic pressure to 23 ± 4 mm Hg (p < .01).

Aortic and coronary sinus lactate concentrations and myocardial lactate extraction are shown in figure 1 and table 3. In the control animals, myocardial lactate extraction ranged from 2.3% to 52% at a heart rate of 100 beats/min. There was no significant change in mean lactate extraction as heart rates were increased to 200 and 250 beats/min; at a heart rate of 250 beats/min, lactate extraction ranged from -4.4% to 47%. Aortic and coronary sinus lactate concentrations and myocardial extraction in group LVH-I were not significantly different from control. In group LVH-II, aortic and coronary sinus lactate concentrations and myocardial lactate extraction were not significantly different from in the control animals at a heart rate of 100 beats/min. At a heart rate of 200 beats/min, one of six dogs in group LVH-II demonstrated frank lactate production (figure 1), while at 250 beats/min the dogs in group LVH-II had arteriovenous lactate values greater than 2 SDs removed from those in the control group.

Total concentrations of adenosine metabolites (inosine, hypoxanthine, and xanthine) were less than 0.5 μM/l in all arterial and coronary sinus blood samples in the control animals and in group LVH-I at all three heart rates. During pacing at 200 beats/min, five of the
six dogs in group LVH-II demonstrated no detectable adenosine metabolites in coronary sinus blood. The single dog in group LVH-II that produced lactate during pacing at 200 beats/min also produced inosine and hypoxanthine. During pacing at 250 beats/min, five of the six dogs in group LVH-II demonstrated adenosine metabolite production at levels greater than 0.5 μM/l (range 1.69 to 18.51 μM/l). Mean coronary sinus inosine concentration in these five dogs was 3.16 ± 1.84 μM/l and mean hypoxanthine concentration was 3.46 ± 1.25 μM/l during pacing at 250 beats/min.

Myocardial blood flow data are shown in table 4 and figure 2. In the normal control dogs, mean blood flow was 0.98 ± 0.08 ml/min·g of myocardium at a heart rate of 100 beats/min, and subendocardial flow significantly exceeded subepicardial flow (endo/epi = 1.36 ± 0.07). Mean myocardial blood flow was significantly higher in both groups of animals with LVH than in the control dogs at a heart rate of 100 beats/min. The endo/epi blood flow ratio was not different from control in dogs in group LVH-I, but was significantly decreased to 1.12 ± 0.08 in those in group LVH-II (p < .05 vs control).

Increasing the pacing rate to 200 beats/min resulted in a 61 ± 10% increase in mean myocardial blood flow in the control animals (p < .01), with no change in the transmural distribution of perfusion. Mean myocardial blood flow remained significantly higher than control in both groups of animals with aortic banding during pacing at 200 beats/min. In group LVH-I, the endo/epi blood flow ratio did not change significantly as pacing rates were increased from 100 to 200 beats/min, and was not different from that in the control group. In group LVH-II, the endo/epi ratio fell to 0.99 ± 0.16 during pacing at 200 beats/min as compared with 1.41 ± 0.08 in the control group (p < .05).

In the control group increasing the pacing rate from 200 to 250 beats/min resulted in an insignificant increase in mean myocardial blood flow; during pacing at 250 beats/min the endo/epi ratio was not significantly different from unity. In group LVH-I, pacing at 250 beats/min resulted in a significant further increase in

### TABLE 3

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Control</th>
<th></th>
<th></th>
<th></th>
<th>LVH-I</th>
<th></th>
<th></th>
<th></th>
<th>LVH-II</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ao</td>
<td>CS</td>
<td>%</td>
<td>Ao</td>
<td>CS</td>
<td>%</td>
<td>Ao</td>
<td>CS</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>1.202</td>
<td>0.780</td>
<td>33</td>
<td>2.007</td>
<td>1.389</td>
<td>33</td>
<td>0.970</td>
<td>0.590</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>±0.227</td>
<td>±0.159</td>
<td>±7</td>
<td></td>
<td>±0.359</td>
<td>±0.324</td>
<td>±6</td>
<td>±0.168</td>
<td>±0.088</td>
<td>±0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>1.324</td>
<td>0.817</td>
<td>37</td>
<td>1.848</td>
<td>1.224</td>
<td>34</td>
<td>0.930</td>
<td>0.764</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>±0.211</td>
<td>±0.094</td>
<td>±6</td>
<td></td>
<td>±0.486</td>
<td>±0.318</td>
<td>±3</td>
<td>±0.163</td>
<td>±0.162</td>
<td>±11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>1.324</td>
<td>0.883</td>
<td>28</td>
<td>1.658</td>
<td>1.163</td>
<td>28</td>
<td>1.110</td>
<td>1.347^B</td>
<td>16^AB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>±0.222</td>
<td>±0.106</td>
<td>±6</td>
<td></td>
<td>±0.407</td>
<td>±0.239</td>
<td>±5</td>
<td>±0.259</td>
<td>±0.332</td>
<td>±2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE.

Ao = aortic concentration of lactate; CS = coronary sinus concentration of lactate; % = percent myocardial lactate extraction [(Ao - CS)/Ao]x 100.

^p < .05 in comparison with the control group; ^p < .05 in comparison with the corresponding value at a heart rate of 100 beats/min.

### TABLE 4

Mean left ventricular blood flow and the ratio Endo/Epi for eight normal dogs (control), four dogs with LVH that demonstrated no biochemical evidence of ischemia at any pacing rate (LVH-I), and six dogs with LVH that developed evidence of ischemia at a heart rate of 250 beats/min

<table>
<thead>
<tr>
<th>Heart rate 100 beats/min</th>
<th>Flow (ml/min·g)</th>
<th>Endo/Epi</th>
<th></th>
<th>Heart rate 200 beats/min</th>
<th>Flow (ml/min·g)</th>
<th>Endo/Epi</th>
<th></th>
<th>Heart rate 250 beats/min</th>
<th>Flow (ml/min·g)</th>
<th>Endo/Epi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.96 ±0.08^BD</td>
<td>1.36 ±0.07</td>
<td></td>
<td>1.50 ±0.07^BC</td>
<td>1.41 ±0.08</td>
<td></td>
<td>1.59 ±0.15^BC</td>
<td>1.13 ±0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH-I</td>
<td>1.60 ±0.22^A</td>
<td>1.28 ±0.17</td>
<td>1.93 ±0.15^A</td>
<td>1.39 ±0.19</td>
<td>2.88 ±0.51^ACD</td>
<td>1.00 ±0.12</td>
<td></td>
<td>1.53 ±0.15^BD</td>
<td>0.50 ±0.05^A-D</td>
<td></td>
</tr>
<tr>
<td>LVH-II</td>
<td>1.64 ±0.12^A</td>
<td>1.12 ±0.08^AB</td>
<td>2.04 ±0.23^A</td>
<td>0.99 ±0.16^AB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE.

^p < .05 vs the corresponding control value; ^p < .05 vs LVH-I; ^p < .05 vs the corresponding value at a heart rate of 100 beats/min; ^p < .05 vs the corresponding value at a heart rate of 200 beats/min.
mean myocardial blood flow to 2.88 ± 0.51 ml/min·g (p < .01); the endo/epi blood flow ratio during pacing at 250 beats/min was not different from unity or from the control value. In group LVH-II, increasing the pacing rate from 200 to 250 beats/min was associated with a significant reduction in mean myocardial blood flow from 2.04 ± 0.23 to 1.53 ± 0.15 ml/min·g (p < .05) and with a transmural redistribution of perfusion with a significant reduction from control in flow to layers 3 and 4 (p < .05). Blood flow to each of the four transmural layers was significantly less than in the dogs in group LVH-I (p < .05). This change in the transmural distribution of perfusion resulted in a decrease in the endo/epi blood flow ratio to 0.50 ± 0.05, which was significantly less than in both the control dogs (1.13 ± 0.09; p < .05) and the dogs in group LVH-I (1.00 ± 0.12; p < .05) during pacing at 250 beats/min.

**Discussion**

The experimental preparation used in this study resulted in substantial LVH with a 74% mean increase in the left ventricular/body weight ratio. This degree of hypertrophy is similar to that reported from other laboratories in which ascending aortic constriction was used in puppies.\(^4\)\(^-\)\(^6\)\(^-\)\(^8\) but is greater than that when aortic constriction has been produced in adult dogs. When aortic constriction is produced as a single stage in adult dogs, abrupt increases of left ventricular systolic pressure of no more than 50 mm Hg are tolerated, and exposure to this pressure gradient has generally been from 4 to 6 weeks, resulting in an approximately 30% increase in relative left ventricular mass.\(^7\)\(^-\)\(^8\) In our study aortic banding was carried out to produce a modest systolic pressure gradient that was well tolerated; the degree of pressure overload increased progressively as the aortic constriction remained fixed in the face of normal body growth, thereby resulting in marked systolic overload at the time of study.

In this study, blood flow per unit myocardial mass at a heart rate of 100 beats/min was significantly higher in dogs with LVH than in the control animals. Using this experimental preparation, we have previously found that blood flow tended to be higher in dogs with
hypertrophy than in normal animals, although this difference did not always achieve statistical significance.\textsuperscript{10-12} Similarly, Rembert et al.\textsuperscript{9} reported that myocardial blood flow was significantly higher than control in animals with LVH produced by ascending aortic coarctation in puppies while Holtz et al.\textsuperscript{5} found no difference in resting myocardial blood flow between normal and hypertrophied ventricles. The reason for this difference is unclear. In response to an elevated pressure, hypertrophy occurs to distribute the increased systolic load over a larger cross-sectional area, thereby reducing systolic stress and oxygen consumption per unit myocardial mass to near normal levels.\textsuperscript{19} Strauer\textsuperscript{20} has suggested that variations in oxygen consumption per unit myocardial mass in the hypertrophied heart may relate to the appropriateness of the degree of hypertrophy, with some hearts having appropriate hypertrophy and normal oxygen consumption per unit myocardial mass, while others may have a suboptimal degree of hypertrophy that results in persistently increased systolic wall stress and increased oxygen requirements. Unfortunately, measurements of myocardial oxygen consumption could not be obtained in our study to determine whether the increase in myocardial blood flow in the hypertrophied hearts resulted from an increase in myocardial oxygen consumption.

Coronary vasodilator reserve capacity during maximum pharmacologic vasodilation has been shown to be impaired in dogs with LVH due to both arterial hypertension and ascending aortic banding, suggesting that growth of the coronary vasculature does not keep pace with the increasing myocardial mass during the hypertrophic process.\textsuperscript{5, 6, 12} However, in our study the myocardial perfusion abnormality was expressed most strikingly by an abnormal transmural distribution of blood flow that became apparent at a heart rate of 250 beats/min. Thus, at pacing rates of 100 and 200 beats/min, mean blood flow in group LVH-II was significantly greater than control and similar to that in group LVH-I. Even during pacing at 250 beats/min, mean myocardial blood flow in group LVH-II was similar to that in the control animals, although a marked transmural maldistribution of perfusion became apparent.

The abnormal transmural distribution of perfusion in group LVH-II dogs during pacing at 250 beats/min was associated with metabolic evidence of myocardial ischemia. In the control animals increasing pacing rates resulted in no significant change in mean lactate metabolism, although one dog showed modest lactate production at a heart rate of 250 beats/min, resulting in 95% confidence limits for lactate extraction of +60% to −5.0%. The dogs in group LVH-II showed lactate production at values outside the 95% confidence limits for the control group during pacing at 250 beats/min. This response is strongly suggestive of anaerobic metabolism during rapid cardiac pacing. The presence of myocardial ischemia was further supported by the finding of myocardial production of the adenosine metabolites inosine and hypoxanthine in five of these six dogs during pacing at 250 beats/min. Previous studies have demonstrated that coronary venous concentrations of adenosine and its metabolites increase in response to myocardial ischemia both in experimental animals and in human subjects with coronary artery disease.\textsuperscript{21-24} In our study adenosine metabolites were not detected in coronary sinus blood at any pacing rate in the control dogs or the dogs in group LVH-I. In these animals the endo/epi blood flow ratios did not fall below 0.75. In the animals in group LVH-II, endo/epi ratios of 0.63 or below were associated with production of inosine and hypoxanthine. This finding is in agreement with a previous study from our laboratory in which a coronary stenosis that resulted in hypoperfusion confined to the subendocardium resulted in production of adenosine metabolites.\textsuperscript{24}

It is of interest that results in the animals with hypertrophy differed during pacing at 250 beats/min, with some dogs showing an abnormal transmural distribution of perfusion and metabolic evidence of ischemia, while others maintained a uniform transmural distribution of perfusion. Differences between groups LVH-I and LVH-II that might explain this difference were sought. There was no difference in the degree of hypertrophy as judged by left ventricular/body weight ratios between the two groups of animals. In addition, aortic pressures were similar in the two groups. The systolic pressure gradient across the area of constriction tended to be greater in the dogs in group LVH-II (116 ± 16 mm Hg) than in those in LVH-I (88 ± 7 mm Hg; p < .1) at a heart rate of 100 beats/min. Although mean myocardial blood flow was essentially identical in groups LVH-I and LVH-II at a heart rate of 100 beats/min, even at this heart rate a significant difference in transmural distribution of perfusion existed between these two groups. Thus, at 100 beats/min, the endo/epi ratio was lower in group LVH-II (1.12 ± 0.08) than in LVH-I (1.28 ± 0.17; p < .05). This lower endo/epi ratio in group LVH-II did not appear to result from inability of subendocardial flow to increase further since flow to layer 4 did increase as pacing rates were increased from 100 to 200 beats/min. At a pacing rate of 250 beats/min, blood flow to layer 4 not only failed to increase, but actually decreased below the level observed at heart rates of 100 and 200 beats/min. This
indicates that the abnormal transmural distribution of perfusion observed at a heart rate of 250 beats/min resulted from a functional abnormality that occurred during pacing at 250 beats/min, resulting in depression of subendocardial flow below that observed during heart rates of 100 and 200 beats/min. The concept of a functional maldistribution of perfusion during pacing at 250 beats/min in group LVH-II is supported by results of a previous study in our laboratory that demonstrated that vasodilator reserve capacity in response to adenosine infusion was similar in normal and hypertrophied hearts at a heart rate of 100 beats/min, but was markedly compromised during pacing at 250 beats/min.12

The development of metabolic evidence of ischemia during pacing at 250 beats/min in group LVH-II was associated with a substantial increase in left ventricular end-diastolic pressure. Similarly, in patients with coronary artery disease, myocardial ischemia produced by cardiac pacing has been shown to cause increased diastolic ventricular stiffness as a result of increased diastolic tone and residual diastolic interaction of contractile elements.25-27 Such an alteration in diastolic mechanical function during pacing-induced ischemia in the hypertrophied heart could directly impair myocardial perfusion since, as demonstrated by Alpstein et al.,28 ischemia-induced decreases in ventricular compliance are associated with parallel increases in coronary vascular resistance. In addition, the increased diastolic left ventricular cavity pressure observed in dogs in group LVH-II at a heart rate of 250 beats/min would contribute to the intramyocardial tissue pressure acting to compress the intramural coronary vessels; since cavity pressure is transmitted into the ventricular wall as a decreasing gradient from endocardium to epicardium, greatest impedance to blood flow would occur in the subendocardium.29 In addition, prolongation of the isovolumetric relaxation phase of systole by myocardial ischemia would encroach upon the interval of diastole available for perfusion of the subendocardium.25,30 These findings suggest that subendocardial underperfusion during tachycardia in the hypertrophied heart may initiate positive feedback mechanisms that could perpetuate and aggravate the resultant ischemia. Thus, myocardial ischemia may lead to impaired diastolic relaxation, thereby increasing the extravascular forces acting on the intramural coronary vasculature and further impairing subendocardial blood flow. In this way, subendocardial ischemia could result in progressive abnormalities of myocardial function that would act to further impede subendocardial blood flow.

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