Regional Myocardial Blood Flow during Exercise in Dogs with Chronic Left Ventricular Hypertrophy

ROBERT J. BACHE, THOMAS R. VROBEL, W. STEVES RING, ROBERT W. EMERY, AND ROBERT W. ANDERSEN

SUMMARY We compared the response of myocardial blood flow to exercise in normal dogs and in dogs with left ventricular hypertrophy (LVH) produced by banding the ascending aorta at 6-9 weeks of age. Blood flow was measured with 15-µm microspheres after the animals with LVH had reached adulthood when left ventricular body weight ratios were approximately 80% greater than normal. During resting conditions, left ventricular systolic pressure was 202 ± 18 mm Hg in the dogs with LVH and 119 ± 6 mm Hg in the normal dogs (P < 0.01). Three levels of treadmill exercise which increased heart rates to 190, 230 and 260 beats/min resulted in progressive increases in left ventricular systolic pressure to a maximum of 343 ± 18 mm Hg in the dogs with LVH as compared to 165 ± 10 mm Hg in the control dogs (P < 0.01). Unlike normal dogs which showed a significant transmural perfusion gradient favoring the subendocardium at rest (mean subendocardial:subepicardial ratio (endo:epi) = 1.25 ± 0.07), subendocardial flow did not significantly exceed subepicardial flow in the animals with LVH (mean endo:epi = 1.10 ± 0.08; P > 0.05 between normal and LVH). Myocardial blood flow increased as a direct linear function of heart rate during exercise in both groups of dogs. Exercise decreased the mean endo:epi ratio in both normal dogs (mean endo:epi = 1.10 ± 0.08 during heavy exercise; P < 0.01) and in the animals with LVH (mean endo:epi = 0.94 ± 0.03; P < 0.05), while the endo:epi ratios remained consistently less in the LVH dogs than in the normal animals (P < 0.05). The relative reduction of subendocardial flow in dogs with LVH was most apparent in the posterior papillary muscle region where the endo:epi ratio fell significantly below unity during heavy exercise (endo:epi = 0.79 ± 0.02; P < 0.01). These data demonstrate that relative blood flow to the subendocardium of the left ventricle is significantly less than normal, both at rest and during exercise, in dogs with LVH produced by supravalvular aortic stenosis. Circ Res 45: 76-87, 1981

MYOCARDIAL hypertrophy occurs in many forms of cardiac disease, often as an apparent compensatory mechanism by which the heart adapts to a chronically increased work load. As the ventricular wall hypertrophies in response to an increased systolic load, systolic wall stress decreases to normal or near normal levels, resulting in a stage of compensated hypertrophy which may be of long duration (Meerson, 1969; Goodwin, 1973; Grossman et al., 1975; Sasayma et al., 1976). Nevertheless, considerable data suggest that significant functional impairment eventually may occur in the chronically pressure-overloaded, hypertrophied ventricle which may lead ultimately to cardiac failure (Cooper et al., 1973; Pfeffer et al., 1976). It has been suggested that the basis for this functional abnormality may reside in the inability of the coronary vessels to perfuse the increased myocardial mass adequately (Linzbach, 1960). Thus, patients with left ventricular hypertrophy may have angina pectoris and electrocardiographic repolarization abnormalities that are suggestive of subendocardial ischemia despite normal coronary arterial anatomy (Goodwin, 1973).

In support of these clinical data, pathological studies have demonstrated that fibrosis of subendocardial myocardium or papillary muscles may occur despite anatomically normal coronary arteries (Moller et al., 1966). These observations have suggested that myocardial ischemia may exist in the hypertrophied left ventricle.

Although the above observations suggest that myocardial ischemia may accompany cardiac hypertrophy, studies of myocardial perfusion in patients and experimental animals with chronic left ventricular hypertrophy (LVH) generally have demonstrated that net blood flow per gram of muscle tissue is normal during resting conditions (Badder, 1971; O'Kane et al., 1973). However, several studies have suggested that the distribution of perfusion may not be normal. Thus, in dogs with LVH produced by banding the ascending aorta, a modest reduction in subendocardial blood flow relative to subepicardial flow has been reported (Rembert et al., 1978). In addition, it is possible that during
stress, when myocardial demands for arterial inflow are increased, perfusion deficits would become more prominent. In support of this, studies by Mueller and associates (1978) in dogs with renovascular hypertension, and by O’Keefe and associates (1978) and Holtz and associates (1977) in dogs with constriction of the ascending aorta, demonstrated that the minimum coronary vascular resistance produced by pharmacological coronary vasodilators was greater in dogs with cardiac hypertrophy than in normal dogs, suggesting that the cross-sectional area of the coronary vascular bed did not increase proportionately with the degree of hypertrophy. In addition, Rembert and associates (1978) reported that, during the reactive hyperemia which followed total occlusion of the circumflex coronary artery, flow to the subendocardium increased less in dogs with LVH than in normal animals, although the increase in subepicardial flow was similar in both groups. Because these previous studies have suggested that myocardial perfusion in the hypertrophied heart may be abnormal during high coronary flow states, the present study was designed to evaluate the ability of myocardial blood flow to respond to the stress of exercise in dogs with chronic LVH.

**Methods**

We studied eight adult mongrel dogs in which LVH had been produced by banding the ascending aorta while they were puppies, as well as nine normal adult mongrel dogs which served as a control group. At 6–9 weeks of age, the dogs in which LVH was to be produced were anesthetized with sodium pentobarbital (20 mg/kg, iv), ventilated with a respirator, and a right thoracotomy performed through the 3rd 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 connective tissue and fat pad. The aorta, then encircled with a polyethylene band 5.0 mm wide. While simultaneously measuring left ventricular and distal aortic pressures, the band was tightened until a 20–35 mm Hg peak systolic pressure gradient was achieved across the constriction. The chest then was closed, the right hemithorax evacuated of air with a chest tube, and the animal allowed to recover. At three months of age, the dogs were trained to run on a motor-driven treadmill. Thereafter, they were not exercised on the treadmill until approximately 2 weeks prior to the second surgical procedure, when both the dogs with LVH and the controls were subjected to a period of exercise training for approximately 1 hour daily to familiarize the animals with treadmill exercise.

After this period of training, when the dogs with LVH were 8–16 months old, the animals were anesthetized with sodium pentobarbital (25 mg/kg, iv) and ventilated with a respirator. A left thoracotomy was performed in the 4th intercostal space and the heart suspended in a pericardial cradle. A polyvinyl chloride catheter, 3.0 mm o.d., 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 root of the aorta distal to the aortic constriction via the left internal thoracic artery. A third catheter was inserted into the left ventricular cavity through a stab wound in the apical dimple and secured in place with a purse-string suture. The catheters were filled with a heparin-saline solution (200 U/ml) and tunneled into a subcutaneous pouch at the base of the neck. Re-training on the treadmill was begun 4–7 days after surgery, and the studies were performed 8–17 days after surgery. At the time of study all dogs were free from fever, anemia, or other evidence of ill health.

On the day prior to study, we used 2% lidocaine infiltration anesthesia and opened the subcutaneous pouch with a 1-cm skin incision and the catheters were exteriorized. At the time of study, the arterial and left ventricular catheters were attached to miniature pressure transducers (Ailtech Corp.) which were fastened at mid-chest level to a nylon vest that the dogs had been trained to wear (Alice King Chatham). In addition, the arterial catheter was attached to a polyethylene tube connected to a Statham P23Db pressure transducer (Statham Instruments Division, Gould, Inc.) mounted on the side of the treadmill cage at mid-chest level. Phasic and mean aortic and mean left atrial pressures, and left ventricular pressure at both normal and high gain for measurement of end-diastolic pressures, were recorded continuously on a Hewlett-Packard 8800 eight-channel direct writing oscillograph and a Carolina Medical Electronics model A eight-channel magnetic tape recorder.

Measurements of regional myocardial blood flow were made using serial injections of microspheres 15–μm in diameter and labeled with the γ-emitting radionuclides 114Ce, 85Sr, 89Yb, and 48Sc (3M Company). The microspheres were diluted in 10% low molecular weight dextran; during each intervention approximately 3 × 106 microspheres were delivered into the left atrium. Prior to administration into the dog, the injection vial containing the microspheres was counted in the γ spectrometer; this activity, less the residual radioactivity remaining in the vial after injection, was used for computation of cardiac output. Before injection, the microspheres were mixed thoroughly by alternate agitation for at least 15 minutes in an ultrasonic bath and a vortex agitator. During each intervention the microsphere suspension was injected into the left atrium and flushed in with 8.0 ml of isotonic saline over a 15-second interval. Beginning 5 seconds prior to the start of injection, a reference sample of arterial blood was withdrawn from the aortic catheter at a constant rate of 15.0 ml/min for 90 seconds.
Measurements of myocardial blood flow were made during quiet resting conditions, and during light, moderate, and heavy exercise on the treadmill. Light exercise was defined as the speed and grade necessary to increase heart rates to 160-200 beats/min. Moderate exercise was regulated to increase heart rates to 220-250 beats/min, and heavy exercise was the level of exertion necessary to achieve heart rates in excess of 200 beats/min. The mean speed and grade for each exercise level were: light exercise 2 mph at 4% grade, moderate exercise 4 mph at 4% grade, and heavy exercise 7 mph at 6% grade. There was no difference in the exercise load required to achieve the desired heart rate response between the control dogs and the animals with LVH. Microspheres were injected 3 minutes after the dog had achieved the desired speed and grade on the treadmill, and exercise was continued for 2 minutes after the injection of microspheres. Heart rate and all pressures were monitored continuously to ensure that a hemodynamic steady state existed prior to and following injection of microspheres.

After completion of the study, the dog was anesthetized with sodium pentobarbital (25 mg/kg, iv) and killed with a lethal dose of potassium chloride. The heart was removed and the left main coronary artery cannulated. The left ventricular catheter was attached to a bottle containing isotonic phosphate buffer suspended at a height equal to the left ventricular end-diastolic pressure measured during resting conditions during life. While this left ventricular distending pressure was maintained, the coronary artery cannula was perfused with 10% buffered formalin at a pressure of 150 mm Hg. After completion of fixation, the atria, great vessels, pericardial fat, and epicardial vessels were dissected from the left ventricle. The right ventricular free wall was removed and weighed. The left ventricle then was weighed and sectioned into four transverse rings of approximately equal thickness parallel to the mitral valve ring as previously described (Ball et al., 1975). Each ring was divided into six circumferential regions representing interventricular septum, posterior free wall, posterior papillary muscle region, lateral wall, anterior papillary muscle region, and anterior free wall. Each myocardial specimen was then divided into four transmural layers of equal thickness from epicardium to endocardium, weighed, and placed in vials for counting. For the remainder of this paper, these layers will be referred to as “layers 1 through 4,” layer 1 being the most epicardial layer and layer 4 the most endocardial layer. Individual myocardial sample weights ranged from 0.510 to 3.191 g with the most samples weighing 1.5 to 2.0 g. In addition, duplicate myocardial specimens were removed from the right ventricular free wall for blood flow determination. Because of the smaller wall thickness of the right ventricle, these specimens were divided into only two layers representing subepicardial and subendocardial myocardium.

Myocardial and blood reference samples were counted in a Packard model 5912 γ-counting system at window settings selected to correspond to the peak energies of each radionuclide. The counts per minute recorded in each energy window were corrected for background activity and overlapping counts contributed by the accompanying isotopes with a digital computer. Cardiac output (CO) was computed using the formula CO = Ci • Qr/Cr where Ci = counts per minute injected, Qr = reference blood flow (ml/min) and Cr = counts per minute of the reference blood specimen. Blood flow to each myocardial specimen was computed using the formula Qm = Qr • Cm/Cr where Qm = myocardial blood flow (ml/min), Qr = reference blood flow (ml/min), Cm = counts per minute of the myocardial specimen, and Cr = counts per minute of the reference blood flow specimen. Each myocardial sample blood flow (ml/min) was divided by the sample weight and expressed as ml/min per gram of myocardium. Mean left ventricular blood flow for each intervention was determined by averaging the flow to all left ventricular samples for each dog, and the regression equation for heart rate plotted against mean left ventricular blood flow was calculated. Data from individual myocardial segments were examined using a 3-way analysis of variance for significant effects of the experimental intervention (rest and three levels of exercise), the circumferential position, and transmural layer on blood flow. When significant differences were found, pairwise comparisons were performed for the intervention under study to determine within which myocardial segments significant differences existed. The resultant P values were adjusted using the Bonferroni method, which corrects for performing multiple tests on correlated data (Miller, 1966). Endocardial: epicardial blood flow ratios were obtained by dividing flow to layer 4 by flow to layer 1.

Results
Table 1 compares anatomic and resting hemodynamic data in the normal dogs and those with LVH. The left ventricular:body weight ratios ranged from 3.8 to 4.9 g/kg in the normal dogs, and were increased in the dogs with LVH to a mean value of 7.8 ± 0.5 g/kg (P < 0.01). Thus, aortic banding resulted in an approximately 80% relative increase in left ventricular mass. Regression analysis demonstrated that only a weak positive linear relationship existed between the resting left ventricular systolic pressure and left ventricular:body weight ratio (r = 0.48). The age of the animals at the time the study was carried out did not influence the degree of left ventricular hypertrophy. The average right ventricular:body weight ratio for the control group of dogs was 1.41 g/kg with 95% confidence limits extending from 0.86 to 1.97 g/kg. Although there was considerable overlap between the two groups of animals, so that no statistically
TABLE 1  Anatomic and Resting Hemodynamic Data from Eight Dogs with Chronic LVH and Nine Normal Dogs

<table>
<thead>
<tr>
<th></th>
<th>LVH dogs</th>
<th>Normal dogs†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo.)</td>
<td>12 ± 1.0</td>
<td>23.5 ± 1.7</td>
</tr>
<tr>
<td>Body wt. (kg)</td>
<td>20.6 ± 1.1</td>
<td>102 ± 1.7</td>
</tr>
<tr>
<td>LV wt. (g)</td>
<td>160* ± 8.3</td>
<td>102 ± 9.7</td>
</tr>
<tr>
<td>LV:BW (g/kg)</td>
<td>7.8* ± 0.5</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td>RV wt. (g)</td>
<td>36.1 ± 2.9</td>
<td>33.1 ± 3.3</td>
</tr>
<tr>
<td>RV:BW (g/kg)</td>
<td>1.80 ± 0.10</td>
<td>1.41 ± 0.11</td>
</tr>
<tr>
<td>LV pressure (mm Hg)</td>
<td>202* ± 11</td>
<td>119/5 ± 6/1</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>97/69 ± 7/7</td>
<td>119/77 ± 6/6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>102</td>
<td>81</td>
</tr>
</tbody>
</table>

* P < 0.05 in comparison with normal dogs.
† Two of the nine control dogs were littermates of the dogs subjected to aortic banding, and were studied at 12 and 13 months of age. The remaining seven control dogs were healthy adult mongrel dogs of unknown age.

significant difference could be demonstrated between the group means, examination of the individual data demonstrated that the right ventricular body weight ratio was more than two confidence limits removed from normal in three of the eight dogs with LVH.

Mean hemodynamic results at rest and during exercise are shown in Table 2. Resting heart rates ranged from 62 to 90 beats/min in the control dogs, and were significantly lower than in dogs with LVH (P < 0.01). In the dogs with LVH, heart rates ranged from 160 to 234 beats/min during light exercise, 215 to 255 beats/min during moderate exercise, and 240 to 302 beats/min during heavy exercise. These values were not different from those observed in the control animals. Left ventricular systolic pressure during resting conditions was elevated to 202 ± 18 mm Hg in the dogs with LVH, and each increasing level of exercise was accompanied by a further significant increase in systolic pressure (each P < 0.05). During resting conditions, there was no significant difference in mean aortic pressure between the control dogs and those with LVH. However, in the control dogs, the aortic pressure underwent a significant increase from rest to light exercise (mean increase = 30 ± 6 mm Hg; P < 0.01), and a further increase from light to moderate exercise (mean increase = 18 ± 5 mm Hg; P < 0.05). In contrast to this normal response, mean aortic pressure did not increase significantly at any exercise level in the dogs with LVH. During resting control conditions, there was no significant difference in cardiac output between the control dogs and the animals with LVH, and in both groups the cardiac output increased progressively with increasing exercise. Although the increment in cardiac output during exercise tended to be slightly greater in the normal dogs than in those with LVH, this difference did not achieve statistical significance. In addition, there was no significant difference in cardiac output between the two groups at any exercise level. In the control dogs, left ventricular end-diastolic pressure (measured after the A wave) did not increase significantly with exercise (Table 2). Left ventricular end-diastolic pressure was normal in seven of the eight dogs with LVH at rest, but increased significantly with each increasing level of exercise (Table 2).

Left ventricular regional blood flows for the control group of dogs at rest and during three levels of exercise are shown in Table 3. At rest, control mean left ventricular blood flow was 1.00 ± 0.10 ml/min per g. Since analysis of variance demonstrated that the circumferential position did not significantly affect blood flow either at rest or during exercise in the control group, blood flow data from all six regions were averaged and are presented in Figure 1. Since significant differences in flow were found across the four transmural layers, the ratio of subendocardial to subepicardial flow (endo:epi) was calculated. The mean endo:epi ratio for the entire left ventricle of the control dogs during resting

TABLE 2  Hemodynamic Data from Nine Normal Dogs (N) and Eight Dogs with LVH at Rest and during Three Levels of Treadmill Exercise

<table>
<thead>
<tr>
<th></th>
<th>LVH</th>
<th>Normal</th>
<th>LVH</th>
<th>Normal</th>
<th>LVH</th>
<th>Normal</th>
<th>LVH</th>
<th>Normal</th>
<th>LVH</th>
<th>Normal</th>
<th>LVH</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>81</td>
<td>102*</td>
<td>119</td>
<td>202*</td>
<td>5</td>
<td>8</td>
<td>87</td>
<td>80</td>
<td>105</td>
<td>2970</td>
<td>3300</td>
<td></td>
</tr>
<tr>
<td>Light exercise</td>
<td>±8</td>
<td>±7</td>
<td>±8</td>
<td>±12</td>
<td>±1</td>
<td>±2</td>
<td>±5</td>
<td>±3</td>
<td>±18</td>
<td>±410</td>
<td>±420</td>
<td></td>
</tr>
<tr>
<td>Moderate exercise</td>
<td>±2</td>
<td>±6</td>
<td>±2</td>
<td>±6</td>
<td>±1</td>
<td>±4</td>
<td>±6</td>
<td>±4</td>
<td>±14</td>
<td>±620</td>
<td>±630</td>
<td></td>
</tr>
<tr>
<td>Heavy exercise</td>
<td>±2</td>
<td>±7</td>
<td>±2</td>
<td>±10</td>
<td>±2</td>
<td>±6</td>
<td>±7</td>
<td>±9</td>
<td>±24</td>
<td>±1120</td>
<td>±1150</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.01 compared with normal dogs.
conditions was 1.25 ± 0.07, which was significantly greater than unity (P < 0.01). In addition, as shown in Table 3, in the control dogs mean endo:epi ratios calculated for individual myocardial regions were significantly greater than unity in the septal, posterior, lateral, and anterior papillary muscle regions (P < 0.05). Mean left ventricular blood flow in the control dogs increased to 2.44 ± 0.25 during light exercise, 3.27 ± 0.21 during moderate exercise, and 4.39 ± 0.21 ml/min per g of myocardium during heavy exercise. As shown in Figure 1, exercise resulted in progressive increases in blood flow to all transmural layers. However, the mean endo:epi ratio for the left ventricle fell from 1.25 ± 0.07 at rest to 1.14 ± 0.06 during light exercise (P < 0.05), then to 1.08 ± 0.08 during moderate exercise (P < 0.01 compared with rest) and, finally, to 1.01 ± 0.10 during heavy exercise (P < 0.01 compared with rest and P < 0.05 compared with light exercise). At each level of exercise, the endo:epi ratio was not significantly different from 1.0, except in the anterior papillary muscle region where the endo:epi ratio was 1.25 ± 0.05 during light exercise (P < 0.02).

In the dogs with LVH, mean left ventricular blood flow during resting conditions was 1.41 ± 0.07 ml/min per g, which was significantly higher than resting blood flow in the control group (P < 0.01). Since analysis of variance demonstrated that significant differences in blood flow existed across the four layers of the left ventricle, the ratio of subendocardial to subepicardial flow was also computed in these dogs with LVH. Unlike the control group, the endo:epi flow ratios in the dogs with LVH were not significantly different from unity in any of the six regions during resting conditions (Table 3). Since flow was generally greatest in layer 2 in the dogs with LVH (as shown in Fig. 2), blood flows to transmural layers 2 and 3 were compared.
EXERCISE IN LEFT VENTRICULAR HYPERTROPHY/Bache et al. 81

7.0 60 5.0 4.0 3.0 2.0 1.0 0.0

"3> 60 5.0 J 4.0 0 U S 3.0 i •3 20

Anterior Free Wall Anterior Papillary Muscle Region

Posterior Free Wall

0.0

6.0 - 5.0 4.0 30 2.0 1.0

Rest Posterior Papillary Muscle Region

12 3 4 Epicordium •• Endocordium

12 3 4 Epicordium•• Endocordium

FIGURE 2 Mean left ventricular myocardial blood flow (ml/min per g) ± SEM to each of the six circumferential regions and four transmural layers measured at rest and during three levels of treadmill exercise in eight dogs with left ventricular hypertrophy.

with flow to layer 1 for each of the six regions. This analysis demonstrated that blood flow was significantly greater in layer 2 than in layer 1 in the septal, posterior, and lateral regions of the hearts with LVH, whereas there was no significant difference in blood flow between layers 1 and 3 in any region.

In the dogs with LVH, mean left ventricular blood flow increased to 2.69 ± 0.31 during light exercise, 3.31 ± 0.42 during moderate exercise, and 5.00 ± 0.72 ml/min per g of myocardium during heavy exercise (Fig. 2). These values were not significantly different from the control group. The endo:epi ratios declined from an overall average of 1.10 ± 0.07 at rest to 0.94 ± 0.03 during heavy exercise ($P < 0.05$ compared with rest). These mean endo:epi ratios at rest and during light and moderate exercise were significantly lower in the LVH dogs than in the control group (each $P < 0.05$), whereas the value observed during heavy exercise was not significantly different. At each level of exercise the endo:epi ratios were not significantly different from unity, except in the posterior papillary region where the endo:epi ratio fell to 0.79 ± 0.02 during heavy exercise ($P < 0.01$) (Table 3).

To assess the relationship between heart rate and left ventricular myocardial blood flow in normal and hypertrophied hearts, mean blood flow for each dog was plotted against heart rate. As shown in Figure 3, a close positive correlation was observed between heart rate and blood flow in the control animals ($MBF = 0.0176 \text{ HR} – 0.459; r = 0.91$). Although the slope and intercept of the line describing the relationship between these variables was nearly identical in the dogs with LVH ($MBF = 0.0173 \text{ HR} – 0.388; r = 0.66$), the degree of scatter in the data from the hypertrophied hearts was greater than in the normal dogs, so that only 76% of

FIGURE 3 Mean left ventricular myocardial blood flow (ml/min per g) is plotted against heart rate (beats/min) for nine normal control dogs and eight dogs with left ventricular hypertrophy studied at rest and during three levels of treadmill exercise. The regression line describing the relationship between myocardial blood flow and heart rate for the nine control dogs is shown by the solid line. The broken lines represent 95% confidence limits for the relationship between myocardial blood flow and heart rate for the control dogs.
the data points for the hypertrophied ventricles fell within the 95% confidence limits previously derived from the normal dogs.

Mean right ventricular myocardial blood flow and the endo:epi ratios are shown in Table 4. There was no significant difference in mean myocardial blood flow to the right ventricle between the normal dogs and the animals with LVH at rest and during any level of exercise. Right ventricular myocardial blood flow (RVMBF) was found to increase as a linear function of heart rate (HR) in both groups of dogs; this relationship was similar in the normal dogs (RVMBF = 0.0150 HR - 0.846; r = 0.90) and in the dogs with LVH (RVMBF = 0.0137 HR - 0.730; r = 0.77). The right ventricular endo:epi ratios were significantly greater than unity at rest and during all levels of exercise in both the normal animals and in dogs with left ventricular hypertrophy (each P < 0.05), and the endo:epi ratios did not decrease significantly during exercise in either group. Although the endo:epi ratios tended to be slightly higher in the animals with LVH than in the normal dogs, this difference did not achieve statistical significance during any intervention.

Discussion

A summary of previous studies of regional myocardial blood flow in several different models of pressure-overload left ventricular hypertrophy is shown in Table 5. The degree of left ventricular hypertrophy obtained in these studies has been variable, depending on the experimental model used. Thus, in the present study, banding of the ascending aorta in puppies has consistently resulted in an 80–100% increase in relative left ventricular mass after the animals have reached adulthood (Holtz et al., 1977; Rembert et al., 1978) whereas a considerably lesser degree of hypertrophy has been found when banding of the ascending aorta is carried out in adult dogs (O'Keefe et al., 1978). However, because of increased vulnerability to rupture of the ascending aorta in adult dogs subjected to severe aortic constriction, banding of the ascending aorta in adult animals has been limited to resting systolic pressure gradients of only approximately 50 mm Hg, and dogs have been exposed to this pressure gradient for only 5–6 weeks to result in an approximately 30% increase in relative left ventricular mass (O'Keefe et al., 1978). The greater degree of hypertrophy observed when ascending aortic banding is produced in puppies thus may be related to: (1) the higher systolic pressure gradient achieved by the time the animals reached adulthood, (2) the longer duration that the animals are exposed to the pressure gradient, or (3) the fact that hypertrophy develops during the period of growth at a time when the ability of the heart to enlarge in response to systolic overload may be greater than in adult animals (Linzbach, 1960). Finally, experimental hypertension produced either by renal artery constriction or with the perinephritis model of Page (1939) resulted in an increase of approximately 50% in left ventricular mass relative to body weight (Mueller et al., 1978; Bache and Vrobel, 1979).

Myocardial blood flow per unit left ventricular mass during resting conditions was found to be normal in dogs with left ventricular hypertrophy secondary to arterial hypertension (Mueller et al., 1978; Bache and Vrobel, 1979) and in adult dogs subjected to banding of the ascending aorta (O'Keefe et al., 1978). Similarly, Holtz et al. (1977), using ascending aortic banding in puppies, found no difference in resting myocardial blood flow between normal and hypertrophied ventricles. In contrast to these reports, in the study of Rembert et al. (1978) and in the present study, blood flow per unit myocardial weight was significantly higher in the animals with left ventricular hypertrophy than in the control dogs during resting conditions. In both of these studies, however, resting heart rates were significantly faster in the dogs with left ventricular hypertrophy than in the normal dogs. It appears that the faster heart rates in the dogs with left ventricular hypertrophy contributed substantially to the difference in resting myocardial blood flow rates. Thus, in a separate group of six normal dogs not included in the present study, mean myocardial blood flow during atrial pacing at a rate of 100 beats/min was 1.30 ± 0.13, not significantly different from the value of 1.41 ± 0.07 ml/min per g observed in the hypertrophied hearts at a mean

### Table 4 Right Ventricular Myocardial Blood Flow and Subendocardial:

<table>
<thead>
<tr>
<th>Subepicardial Blood Flow Ratios (endo:epi) in Nine Normal Dogs and Eight Dogs with Chronic LVH at Rest and during Three Levels of Treadmill Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal LVH</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Values are mean ± SEM. There were no significant differences in flow or endo:epi ratios between normal and LVH dogs during any intervention.</td>
</tr>
</tbody>
</table>
heart rate of 102 beats/min. These data, indicating similar mean blood flow rates in normal and hypertrophied ventricles, provided that heart rates are similar, support the concept that, in the chronically pressure-overloaded left ventricle, hypertrophy occurs to result in normalization of systolic wall stress, and therefore oxygen consumption and blood flow per unit myocardial mass.

In the present study and in the study of Rembert et al. (1978), using a similar experimental model, the transmural distribution of perfusion during resting conditions was significantly different in the dogs with left ventricular hypertrophy than in the control animals. Thus, subendocardial blood flow significantly exceeded subepicardial flow in four of the six circumferential regions in the control dogs, whereas in the animals with left ventricular hypertrophy, subendocardial flow was not significantly different from subepicardial flow in any left ventricular region at rest. The absence of a transmural perfusion gradient favoring the subendocardium during resting conditions in the dogs with left ventricular hypertrophy did not appear to be caused by lack of further ability to vasodilate in the subendocardium, since blood flow in this area was able to increase during exercise. Since all of the dogs with left ventricular hypertrophy included in this study manifested electrocardiographic changes of left ventricular strain (greater than 0.1 mV of ST-segment depression in the leads overlying the left ventricle), the ability of subendocardial blood flow to increase further suggests that this electrocardiographic change did not result from subendocardial ischemia, at least during resting conditions. In contrast to the significant difference in endo:epi ratios between normal and hypertrophied left ventricles during resting conditions in the present study and in the report of Rembert et al. (1978), studies in dogs with less severe left ventricular hypertrophy produced by experimental arterial hypertension or by band-

**Table 5** Summary of Currently Available Data Concerning Myocardial Blood Flow and the Ratio of Subendocardial:Subepicardial Flow in Experimental Hypertrophy Produced by Left Ventricular Pressure Overload

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Experimental model</th>
<th>Increase in LV:BW (%)</th>
<th>MBF ratio</th>
<th>Exercise</th>
<th>Dipyridamole or adenosine</th>
<th>CVR during maximal vasodilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holtz et al. (1977)</td>
<td>Asc aortic band in pups</td>
<td>84</td>
<td>NS vs control</td>
<td>NS in LVH</td>
<td>NS</td>
<td>↑</td>
</tr>
<tr>
<td>Mueller et al. (1978)</td>
<td>Renovascular HT in adult dogs</td>
<td>49</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>↑</td>
</tr>
<tr>
<td>O'Keefe et al. (1978)</td>
<td>Asc aortic band in adult dogs</td>
<td>27</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>↑</td>
</tr>
<tr>
<td>Bache and Vrobel (1979)</td>
<td>Perinephritic HT in adult dogs</td>
<td>49</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>↑</td>
</tr>
<tr>
<td>Rembert et al. (1979)</td>
<td>Asc aortic band in pups</td>
<td>104</td>
<td>↑ in LVH</td>
<td>↑ in LVH</td>
<td>NS</td>
<td>↑</td>
</tr>
<tr>
<td>Present study</td>
<td>Asc aortic band in pups</td>
<td>80</td>
<td>↑ in LVH</td>
<td>↑ in LVH</td>
<td>NS</td>
<td>↑</td>
</tr>
</tbody>
</table>

Abbreviations: NS = no significant difference between control and LVH; LV:BW = left ventricular:body weight ratio; MBF = myocardial blood flow per unit left ventricular weight; endo:epi = endocardial:epicardial blood flow ratio; CVR = coronary vascular resistance per unit left ventricular weight; HT = hypertension; ASC = ascending.

*No data on concurrent controls.
ing the ascending aorta of adult dogs have demonstrated no abnormality in the transmural distribution of perfusion at rest (Mueller et al., 1978; O'Keefe et al., 1978; Bache and Vrobel, 1979). It is possible that the alteration of the transmural distribution of perfusion observed in the present study and by Rembert et al., (1978) relates to a change in the transmural pattern of systolic stress which occurs when the left ventricle becomes markedly hypertrophied. Since coronary autoregulation appears to regulate myocardial blood flow in response to local metabolic needs, blood flow may be expected to reflect local myocardial oxygen consumption (Katz and Feinberg, 1958). In the normal heart, the higher blood flow rate in the subendocardium appears to reflect the fact that systolic stress is greatest in this area, which in turn results in higher myocardial oxygen consumption (Weiss et al., 1978). This pattern does not appear to be altered in hearts with moderate degrees of left ventricular hypertrophy (Mueller et al., 1978; O'Keefe et al., 1978; Bache and Vrobel, 1979). In contrast, the markedly hypertrophied left ventricles in the present study, as well as those reported by Rembert et al. (1978), tended to have the highest flow rates in transmural layers 2 and 3, suggesting that the transmural pattern of systolic stress may be different from normal in these hearts, with the midwall of the left ventricle bearing the greatest systolic load. It must be acknowledged, however, that this hypothesis is weakened by the failure of Holtz et al. (1977) to find a significant abnormality in the resting endo:epi blood flow ratio in dogs with marked left ventricular hypertrophy produced by ascending aortic banding in puppies. The reason for this discrepancy is unclear.

Although blood flow per unit myocardial mass during basal conditions generally has been found to be within normal limits in previous studies of left ventricular hypertrophy (Badeer, 1971; Marchette, 1973; O'Keefe et al., 1978; Rembert et al., 1978; Mueller et al., 1978), the finding of normal myocardial perfusion at rest does not exclude the possibility that blood flow may be unable to increase adequately during periods of cardiac stress. For this reason, the response of myocardial blood flow to several different coronary vasodilator stimuli has been evaluated by several investigators. Holtz et al. (1977) and Rembert et al. (1978) examined myocardial perfusion during reactive hyperemia following a brief period of coronary artery occlusion (Table 5). Holtz et al. (1977) found that, although the maximum blood flow rates per unit left ventricular mass achieved during reactive hyperemia were normal in the hypertrophied left ventricle, a significant difference in the transmural distribution of perfusion occurred during reactive hyperemia with a reduction of the endo:epi blood flow ratio in the hypertrophied but not in the normal hearts. Although no data from concurrent control dogs were included in the study of Rembert et al. (1978), these investigators found similar results in dogs with left ventricular hypertrophy also produced by banding the ascending aorta in puppies.

Pharmacological vasodilation with adenosine, diprydamole, or carbocrome has been used to examine maximum blood flow rates and minimum coronary vascular resistance in dogs with left ventricular hypertrophy produced by aortic banding both in puppies (Holtz et al., 1977) and in adult dogs (O'Keefe et al., 1978), as well as in animals with renovascular hypertension (Mueller et al., 1978) (Table 5). In both groups of dogs with banding of the ascending aorta, the increase in myocardial blood flow during administration of adenosine or carbocrome tended to be less in hypertrophied hearts than in normal hearts, although this difference did not achieve statistical significance in the dogs subjected to aortic banding during adulthood (O'Keefe et al., 1978). In dogs with left ventricular hypertrophy secondary to renovascular hypertension, Muller et al. (1978) found that adenosine infusion produced an approximately 400% increase in mean myocardial blood flow in both normal and hypertrophied hearts, which was accompanied by a significant decrease in the endo:epi blood flow ratio which was similar in the control and hypertrophied groups. Although maximum blood flow rates were similar in both hypertrophied and normal hearts, these flow rates occurred at higher coronary perfusion pressures in the hypertensive dogs with left ventricular hypertrophy (Mueller et al., 1978). In all of these studies, computation of vascular resistance during pharmacological coronary vasodilation demonstrated that left ventricular hypertrophy was associated with significantly higher values for minimum coronary vascular resistance suggesting that during the hypertrophic process the functional cross-sectional area of the coronary vascular system did not increase in proportion to the increase in myocardial mass. In the present study, coronary vascular resistance could not be computed in the dogs with left ventricular hypertrophy since coronary driving pressure (i.e., pressure proximal to the aortic constriction) could not be measured regularly. Nevertheless, mean blood flow rates observed during heavy exercise were similar to those observed in the normal dogs during heavy exercise and were similar to the flow rates observed in normal dogs during maximal coronary vasodilation produced by adenosine administration (Bache and Cobb, 1977).

Two previous reports of myocardial blood flow during exercise in experimental left ventricular hypertrophy are available. Holtz et al. (1977), studying dogs with banding of the ascending aorta of puppies, found that mild exercise which increased heart rates to 160 ± 13 beats/min resulted in similar increases in blood flow per unit myocardial mass in normal dogs and in dogs with ventricular hypertrophy. The present study extends this finding by demonstrating that this similarity in mean myocardial blood flow...
between normal and hypertrophied ventricles persists throughout a wide range of exercise levels. However, unlike the present study and the report of Rembert et al. (1978), using a similar experimental model, Holtz et al. (1977) found that the endo:epi ratios were not decreased below normal in the hypertrophied ventricles during resting conditions. Nevertheless, since these investigators observed a greater than normal reduction of the endo:epi blood flow ratios during light exercise in the hypertrophied hearts, the endo:epi ratios were significantly decreased during exercise in the hypertrophied hearts, in agreement with the present study. The present study further demonstrated that the decrease in endo:epi ratio observed during light exercise became progressively more marked with increasing exercise loads. This was especially marked in the posterior papillary muscle region where the endo:epi blood flow ratio fell significantly below unity during heavy exercise. Thus, it is likely that the differences in transmural myocardial perfusion between the present study and the report of Holtz et al. (1977) are related in part to the heavier exercise loads used in the present study. In addition, several technical differences may have contributed to the variations in endo:epi ratios between the present study and the report of Holtz et al. (1977).

In that study, the left ventricular wall was cut into only three transmural layers, so that the resultant slightly lower transmural resolution could have concealed differences in the endo:epi blood flow ratios that were found in the present study. In addition, Holtz et al. (1977) carried out their studies using purebred German shorthaired pointers, whereas the present study was performed using mongrel dogs, so that some differences may be related to differences in breed of the experimental animals.

We have examined the transmural distribution of myocardial blood flow during treadmill exercise in dogs in which an approximately 50% increase in left ventricular mass had been produced by means of perinephritic hypertension (Bache and Vrobel, 1979). In contrast to the abnormally reduced endo:epi blood flow ratio in dogs with left ventricular hypertrophy produced by aortic banding in puppies, the endo:epi blood flow ratios were similar in normal dogs and dogs with left ventricular hypertrophy produced by arterial hypertension, with no tendency toward underperfusion of the subendocardium either at rest or during a range of treadmill exercise similar to that used in the present study (Table 5). This difference in the transmural distribution of perfusion between these two experimental models of left ventricular hypertrophy may be related to the greater degree of hypertrophy in the animals with aortic banding, or to differences in coronary perfusion dynamics between these two models. In experimental arterial hypertension, coronary pressure is elevated during diastole, when perfusion of the subendocardium principally occurs (Hess and Bache, 1976), whereas banding of the ascending aorta results in essentially normal diastolic coronary pressures. Thus, although systolic coronary perfusion pressure was elevated markedly in the banded dogs, pressure throughout diastole in the aortic segment proximal to the constriction was found to be within 10 mm Hg of distal aortic pressure both at rest and during exercise in one dog in which a catheter was placed in the proximal aortic segment. This finding of approximation of pressures across the aortic constriction during diastole is in agreement with studies of dogs with coarctation of the ascending aorta (Kleiman et al., 1978), as well as in patients with congenital supravalvular aortic stenosis (Morrow et al., 1959). Thus, unlike the situation in arterial hypertension in which coronary perfusion pressure is increased both in systole and diastole, diastolic coronary perfusion pressure does not appear to be increased in models involving supravalvular aortic stenosis. The increased diastolic coronary perfusion pressure in the hypertensive model would be expected to facilitate perfusion of the subendocardium of the hypertrophied left ventricle, and might thus prevent the decrease in endo:epi ratio observed in the dogs with left ventricular hypertrophy secondary to ascending aortic banding.

It is of interest that, unlike the control dogs, the animals with aortic stenosis and left ventricular hypertrophy did not significantly increase their aortic blood pressure during exercise, despite the finding that the increases in cardiac output during exercise were not significantly different in the two groups. It is possible that the lack of normal increase of aortic pressure during exercise may reflect activation of left ventricular baroreceptor reflexes in response to the increasing left ventricular systolic and diastolic intracavitary pressures during exercise (Mark et al., 1973a). These ventricular baroreceptor reflexes, which promote reflex vasodilation of the systemic vasculature, have been implicated in producing inappropriate systemic vasodilatation during exercise in human subjects with severe valvular aortic stenosis (Mark et al., 1973b).

It has been suggested that, in experimental models of left ventricular hypertrophy secondary to arterial hypertension, hypertrophy of the coronary arterial vasculature may occur in response to the elevated arterial pressures which could impair the ability of the coronary vessels to vasodilate (Mueller et al., 1978). Because of the high systolic pressures in the proximal aortic segment from which the coronary arteries arise in supravalvular aortic stenosis, such vascular changes might have occurred in the present study. Since any such changes in the coronary vasculature would be expected to occur throughout the entire coronary system, blood flow was examined in the right ventricle to determine whether the perfusion differences between the normal dogs and dogs with left ventricular hypertrophy would also be found in the right ventricles. These data demonstrated no significant differences
between either total flow or the transmural distribution of blood flow in the right ventricles of the normal dogs and the animals with left ventricular hypertrophy. Thus, it seems unlikely that structural changes in the coronary vasculature resulting from chronic exposure to elevated systolic pressures were responsible for the differences in left ventricular endo:epi ratios between the dogs with left ventricular hypertrophy and the normal dogs.

Since a gradient of intramyocardial tissue pressure appears to exist during diastole, increasing from the level of intrapleural pressure at the epicardial surface to cavity pressure at the endocardium, the elevated left ventricular diastolic pressures in the dogs with left ventricular hypertrophy might be expected selectively to impede blood flow to the subendocardium (Domenech, 1978). Thus, it is possible that the increasing left ventricular diastolic pressures during exercise in the animals with left ventricular hypertrophy could have contributed to the decreasing endo:epi blood flow ratios during exercise. The mechanism for the greater vulnerability in the hypertrophied heart of the subendocardium of the posterior papillary muscle to underperfusion observed during exercise is not entirely clear. Although the thickness of the left ventricular wall in this region was increased markedly in the hypertrophied hearts, it was not thicker than in the anterior papillary muscle region which showed no tendency for subendocardial underperfusion. It is possible that the posterior papillary muscle region is especially vulnerable to underperfusion merely because it is the region of the left ventricle most remote from its blood supply. Thus, underperfusion of the deepest layers of the most terminal portion of the coronary vascular bed may be the most sensitive indicator of the point at which total arterial inflow becomes insufficient to meet myocardial demands. It is probable that this perfusion abnormality would become increasingly severe and more generalized during more strenuous exercise, or in the presence of a greater degree of left ventricular hypertrophy.

In agreement with previous studies of left ventricular hypertrophy in the dog, left ventricular end-diastolic pressures at rest were normal or only slightly elevated in the animals with left ventricular hypertrophy in the present study (Sasayama et al., 1976; O’Keefe et al., 1978; Rembert et al., 1978). However, during exercise, left ventricular end-diastolic pressures underwent a substantial progressive increase. Although these increases in end-diastolic pressure may signify exercise-induced left ventricular decompensation, the lack of additional independent assessment of myocardial mechanical function does not permit evaluation of possible contributions of changes in left ventricular diastolic properties (Grossman et al., 1974; Peterson et al., 1978). It is clear, however, that ischemia of the subendocardial myocardium occurring during exercise would be expected to result in increased ventricular stiffness through alteration of diastolic myocardial tone or impaired relaxation (Grossman and Barry, 1980; Hanrath et al., 1980). This is of considerable interest, since Apstein et al. (1977) have shown that such ischemia-induced decreases in diastolic ventricular compliance are associated with parallel increases in coronary vascular resistance. This suggests a potential mechanism by which the decreased endo:epi blood flow ratio observed during exercise might be perpetuated and amplified; if exercise-induced impairment of subendocardial blood flow led to ischemia in this area, the resultant decrease in subendocardial compliance would be expected to increase further subendocardial coronary vascular resistance, thereby contributing to the decreased endo:epi blood flow ratio. Unfortunately, independent metabolic or electrocardiographic measurements which might be used to confirm the presence of subendocardial ischemia were not available in the present study. Clearly, however, it would be of importance to obtain such measurements in future studies to determine whether abnormalities of the transmural pattern of myocardial perfusion do in fact represent an imbalance between oxygen supply and demand in the subendocardium of the hypertrophied left ventricle.

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