Alterations of Myocardial Blood Flow Associated with Experimental Canine Left Ventricular Hypertrophy Secondary to Valvular Aortic Stenosis


SUMMARY. Experimental renovascular hypertension or supravalvular aortic constriction results in left ventricular hypertrophy and impaired minimum coronary vascular resistance. However, these experimental models expose the coronary arteries to increased intra-arterial pressure, so that hypertensive vascular changes might be responsible for the impaired minimum coronary resistance. This study was performed to test the hypothesis that left ventricular hypertrophy in the absence of increased coronary pressure results in abnormalities of myocardial perfusion. Aortic valve stenosis was produced by plication of the noncoronary aortic cusp of 11 dogs at 6–8 weeks of age. Studies were carried out when the animals reached adulthood; mean left ventricular:body weight ratio was 7.1 ± 0.4 as compared to 4.4 ± 0.3 g/kg in 11 normal dogs (P < 0.01). Under quiet resting conditions, myocardial blood flow measured with microspheres was significantly greater than normal in dogs with aortic stenosis. However, during maximum coronary vasodilation with adenosine, mean left ventricular blood flow in dogs with hypertrophy (3.29 ± 0.39) was substantially less than in normal dogs (6.19 ± 0.54 ml/min per g; P < 0.01), whereas minimum coronary resistance was increased from 14.1 ± 1.7 in normal dogs to 23.7 ± 5.4 mmHg-min-g/ml (P < 0.01). To examine the response of myocardial perfusion to cardiac stress, blood flow was measured during pacing at 200 and 250 beats/min. Compared with normal dogs, animals with hypertrophy had a subnormal increase in myocardial blood flow during tachycardia; this perfusion deficit was most marked in the subendocardium. These data demonstrate that left ventricular hypertrophy alone, without increased coronary artery pressure, is associated with impaired minimum coronary vascular resistance and with abnormalities of myocardial blood flow during pacing stress. (Circ Res 58: 47–57, 1986)

ALTHOUGH cardiac hypertrophy is a useful compensatory mechanism by which the heart adapts to an increased workload, clinical findings suggest that the hypertrophied heart has increased vulnerability to myocardial ischemia. Thus, patients with left ventricular hypertrophy may experience exertional angina pectoris and develop electrocardiographic repolarization abnormalities which are suggestive of subendocardial ischemia despite normal coronary artery anatomy (Goodwin, 1973; Harris et al., 1973). In support of these clinical observations, experimental studies have shown that, during drug-induced vasodilation, minimum coronary vascular resistance is increased in hypertrophied left ventricles (Holtz et al., 1977; Mueller et al., 1978; O’Keefe et al., 1978; Mittmann et al., 1980; Bache et al., 1981a; Marcus et al., 1981). These previous studies have been performed in animals in which left ventricular hypertrophy was produced by means of arterial hypertension or by banding the ascending aorta. Although these experimental interventions produce systolic overload which leads to the development of left ventricular hypertrophy, they also result in exposure of the coronary vasculature to markedly increased intra-arterial pressures. Consequently, the observed impairment of minimum coronary vascular resistance could result not only from the effects of increased myocardial mass, but also from changes in the coronary resistance vessels secondary to the increased blood pressure (Folkow et al., 1970; Mueller et al., 1978; O’Keefe et al., 1978). Thus, hypertrophy of the vessel walls could act to limit the maximum cross-sectional area of the coronary resistance vessels achieved during maximal vasodilation (Folkow et al., 1970; O’Keefe et al., 1978). The present study was carried out to separate these two effects. Left ventricular systolic overload was produced by surgically creating stenosis of the aortic valve. By causing left ventricular outflow obstruction in a subcoronary position, the coronary vessels were protected from the increased pressure to which the left ventricle was exposed. This allowed separation of the effects of left ventricular hypertrophy from the direct effects of increased pressure on the coronary vasculature. Studies were carried out in the awake state to eliminate possible interfering effects of general anesthesia and acute surgical trauma.
Methods

We studied 11 mongrel dogs in which left ventricular hypertrophy had been produced by plicating the noncoronary aortic valve cusp, as well as 11 normal adult mongrel dogs which served as a control group. At 6–8 weeks of age, the dogs in which left ventricular hypertrophy was produced were anesthetized with sodium thiopental, 15–20 mg/kg, iv, ventilated with a respirator, and a right thoracotomy was performed through the 4th intercostal space. A pericardial cradle was created and dissection was performed between the right atrium and the aorta until the two commissures of the noncoronary aortic valve cusp were visualized. Pledged sutures were then placed to plicate the noncoronary cusp of the aortic valve, under temporary inflow occlusion of both superior and inferior vena cava. A systolic thrill was palpated in the ascending aorta following plication. The pericardium was carefully closed using interrupted sutures, the thoracotomy was repaired, and the animal allowed to recover.

After 8–14 months had been allowed for the development of left ventricular hypertrophy, the animals were instrumented for study. Surgical anesthesia was induced with sodium thiopental 25–30 mg/kg, iv, and maintained with anesthetic gas (1% halothane and 99% oxygen). A left thoracotomy was performed through the 5th intercostal space, and the heart was suspended in a pericardial cradle. A silicone rubber catheter, 6.0 mm o.d., was implanted in the left atrium through the atrial appendage and secured with a pursestring suture. A polyvinyl chloride catheter, 3.0 mm o.d., was inserted into the root of the aorta through the left internal mammary artery. A bipolar epicardial pacing electrode was sutured to the area of the right ventricular outflow tract. The catheters and pacing wire were exteriorized dorsally and protected with a nylon vest (Alice King Chatham). Eleven normal adult mongrel dogs underwent the identical surgical procedure and served as a control group. The dogs were allowed to recover from the effects of surgery and were studied in the resting awake state.

Dogs were trained to lie quietly on their right sides during study. Lead III of a standard electrocardiogram was recorded. Aortic pressure was recorded with a Statham P23Db pressure transducer. A Millar PC350 micromanometer catheter was inserted into the left ventricle via the previously implanted left atrial catheter to allow measurement of left ventricular pressure. A side arm attached to the left atrial catheter allowed access to the left atrium for injection of microspheres. Data were recorded on a Hewlett-Packard model 7758-A direct-writing oscillograph. The laboratory was dimly illuminated and kept free from noise or other activity which might disturb the dog.

Regional myocardial blood flow was measured with left atrial injections of microspheres, 15 μm in diameter, labeled with γ-emitting radionuclides 125I, 51Cr, 95Nb, 113Sn, 85Sr, or 45Sc (3M Company and New England Nuclear). Before injection, microspheres were agitated for at least 15 minutes in an ultrasonic bath and vortex agitator. Blood flow measurements were performed by injecting 3 × 10⁶ microspheres into the left atrium over a 15-second interval. Beginning 5 seconds before 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.

After all recording instruments had been connected, a 45- to 60-minute period was allowed for the dog to adjust to laboratory conditions. Data were recorded continuously during this interval to ensure that a control steady state had been achieved. Microspheres were then injected for measurement of myocardial blood flow during quiet resting conditions in all dogs. To assess minimum coronary vascular resistance, a second injection of microspheres was performed during maximum coronary vasodilation produced by intravenous infusion of adenosine, 4 μg/kg of body weight per minute (1.07 mg/kg per min) in nine dogs with aortic stenosis as well as in all the normal animals. This dosage of adenosine has been demonstrated to result in maximum coronary vasodilation since (1) no further increase in coronary blood flow was observed during infusion of larger dosages of adenosine, and (2) no further increase in blood flow occurred during reactive hyperemia following 10- to 15-second periods of coronary occlusion (Cobb et al., 1974; Rembert et al., 1980). Adenosine was dissolved in warm saline so that the desired dosage was delivered by an infusion rate of 0.7 ml/min. Infusion of adenosine was begun 5 minutes before injection of microspheres and continued until completion of reference blood sampling. A 20- to 30-minute interval was allowed for dissipation of the adenosine effect before subsequent measurements were performed.

Myocardial blood flow was then measured during two separate periods of ventricular pacing at heart rates of 200 and 250 beats/min in all dogs. Pacing was accomplished with a Grass model 588 physiological stimulator delivering 3-msec rectangular pulses 25% above threshold voltage through a stimulus isolation unit. Pressures were recorded continuously to ensure that steady state hemodynamic conditions were achieved. Microspheres were injected after 3 minutes at each pacing rate, and pacing was continued until completion of reference blood sampling. A 10-minute interval was allowed between pacing periods, and the order in which pacing rates were performed was randomized.

After completion of the study, the dog was killed with a lethal dose of sodium pentobarbital. The heart was removed and fixed in 10% buffered formalin. After fixation, the atria and great vessels were dissected from the ventricles, and the right ventricular free wall was removed and weighed. The left ventricle was then weighed and sectioned into four transverse rings of equal thickness parallel to mitral valve ring. The two central sections, which constituted 61 ± 3% of the left ventricular weight for the combined groups, were divided into six regions: anterior free wall, interventricular septum, posterior free wall, and anterior papillary muscle region as previously described (Bache et al., 1981a). Each regional specimen was then divided into four equal layers 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 1-4" with layer 1 being closest to the epicardium and layer 4 closest to the endocardium. Sample weights ranged from 0.55–3.8 g, with most samples weighing 1.5–2.0 g. Myocardial specimens were removed from the right ventricular free wall for blood flow determination. Because of the thinner wall of the right ventricle, these specimens were divided into only two layers for determination of subepicardial and subendocardial blood flow.

Myocardial and blood reference samples were counted in a Hewlett-Packard model 5912 γ-counting system with multichannel analyzer at window settings corresponding to the peak energy of each radionuclide. The activities recorded in each energy window were entered into a digital computer programed to correct for contaminant
Activity contributed by the associated nuclides and for background activity (Domenech et al., 1969). Blood flow to each myocardial specimen was computed using the formula: \( Q_m = Q_r \times C_m/C_r \) where \( Q_m \) = myocardial blood flow (mL/min), \( Q_r \) = reference blood flow (mL/min), \( C_m \) = counts/min of myocardial specimen, and \( C_r \) = counts/min of reference blood specimen. Each myocardial sample blood flow (mL/min) was divided by the sample weight and expressed as mL/min per g of myocardium.

Heart rate, arterial pressure, and left ventricular pressure were measured directly from the strip-chart recordings. Analysis of the effect of adenosine and pacing on each of these variables was performed by Student’s t-test for paired and unpaired data, and analysis of variance for multiple comparisons as appropriate. Myocardial blood flows from the corresponding transmural layers of each of the six circumferential regions were compared by multivariate analysis. Both the circumferential region and transmural layer were found to exert a significant effect on blood flow; therefore, multiple contrasts were performed between the layers and regions. The ratio of subendocardial:subepicardial blood flow was determined by dividing flow to layer 4 by the corresponding flow to layer 1.

**Results**

Anatomic data are shown in Table 1. Body weight was not different between the normal dogs and dogs with aortic stenosis. Mean left ventricular weight was significantly increased in dogs with aortic stenosis, yielding a left ventricular-to-body weight ratio of 7.1 ± 0.4 g/kg as compared with 4.3 ± 0.3 g/kg in the normal animals (P < 0.01). Mean right ventricular myocardial blood flow in the dogs with hypertrophy was significantly greater than control during resting conditions. Subendocardial flow was significantly greater than subepicardial flow in both groups of animals (Fig. 1). During maximum coronary vasodilation with adenosine, mean left ventricular blood flow per gram increased 601% in the normal dogs but only 286% in the dogs with aortic stenosis (P < 0.01) (Fig. 2). In dogs with hypertrophy, myocardial blood flow during adenosine infusion was significantly less than control in each circumferential region of the left ventricle. The mean subendocardial:subepicardial blood flow ratio decreased significantly during adenosine infusion in both normal dogs and dogs with aortic stenosis. During adenosine infusion, the mean subendocardial:subepicardial blood flow ratio for the normal dogs was not significantly different from unity, but for the dogs with aortic stenosis, the subendocardial:subepicardial blood flow ratio was significantly less than 1.0 and significantly less than in the normal dogs. Examination of data from the six left ventricular regions demonstrated that this difference of subendocardial:subepicardial blood flow ratio between aortic stenosis dogs and normal dogs during adenosine infusion was confined to the posterior free wall and posterior papillary muscle regions (Table 3).

Increasing heart rates produced by cardiac pacing were associated with increased mean left ventricular myocardial blood flow in both normal dogs and dogs with aortic stenosis (Table 3; Fig. 3). At a heart rate of 200 beats/min, mean blood flow per gram of myocardium was significantly less than control in dogs with aortic stenosis; individual significant dif-

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Aortic stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mos)</td>
<td>22 ± 2</td>
<td>12 ± 3</td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td>96 ± 8.4</td>
<td>149 ± 12.4†</td>
</tr>
<tr>
<td>LV wt (g)</td>
<td>4.3 ± 0.3</td>
<td>7.1 ± 0.4</td>
</tr>
<tr>
<td>LV/BW (g/kg)</td>
<td>33 ± 3.1</td>
<td>39 ± 3.4</td>
</tr>
<tr>
<td>RV wt (g)</td>
<td>1.48 ± 0.11</td>
<td>1.86 ± 0.14*</td>
</tr>
<tr>
<td>RV/BW (g/kg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed as mean ± se. LV = left ventricle; RV = right ventricle; BW = body weight. *P < 0.05; †P < 0.01, compared with the corresponding control values.
Hemodynamic Data

<table>
<thead>
<tr>
<th>Heart rate (beat/min)</th>
<th>Left ventricular systolic pressure (mm Hg)</th>
<th>Left ventricular end-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NL</td>
<td>AVS</td>
</tr>
<tr>
<td>Control</td>
<td>105 ± 9</td>
<td>125 ± 8</td>
</tr>
<tr>
<td>Pace 200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Pace 250</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Adenosine</td>
<td>133 ± 8†</td>
<td>155 ± 12†</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SE. NL = normal control dogs; AVS = dogs with aortic stenosis.

* P < 0.05, compared with the respective NL value.
† P < 0.05, compared with the corresponding value measured during control conditions.

Differences in flow were found in the posterior papillary muscle region and the lateral wall regions. At 250 beats/min, mean left ventricular blood flow per gram of myocardium was significantly less in the dogs with aortic stenosis than in the normal dogs; individual significant differences were found in the posterior, posterior papillary muscle, and lateral regions, whereas blood flow in anterior, septal, and anterior papillary muscle regions was insignificantly different from control. In dogs with aortic stenosis, the mean subendocardial/subepicardial blood flow ratio decreased significantly during ventricular pacing. In contrast, in the normal dogs, the mean subendocardial/subepicardial blood flow ratio at paced rates of 200 and 250 beats/min was not significantly different from that during sinus rhythm. The mean subendocardial/subepicardial ratio was significantly less in the aortic stenosis dogs, compared to the normal dogs at both 200 and 250 beats/min. The decrease in subendocardial/subepicardial ratio during pacing in dogs with aortic stenosis was most marked in the posterior papillary muscle region, but this ratio did not decrease significantly in the anterior or septal regions.

Right ventricular myocardial blood flow data are shown in Table 4. Mean right ventricular blood flow per gram of myocardium was not significantly different from control in dogs with aortic stenosis during resting conditions, and the increase in flow during adenosine infusion was similar in both groups. There was no difference in right ventricular myocardial blood flow between control animals and dogs with aortic stenosis at pacing rates of 200 and 250 beats/min. Right ventricular subendocardial/subepicardial blood flow ratios were significantly greater than unity at all paced rates for both normal dogs and dogs with aortic stenosis.

Minimum coronary vascular resistance during maximum vasodilation with adenosine is shown in Table 5. Minimum vascular resistance was computed for the entire left and right ventricles as well as per gram of myocardium. Maximum myocardial blood flow...
flow rates and minimum coronary vascular resistance for the total left ventricle were not significantly different between normal and hypertrophied hearts. Because of the greater left ventricle weights in animals with aortic stenosis, blood flow per gram of myocardium was significantly reduced in animals with hypertrophy, whereas minimum coronary vascular resistance per gram of myocardium was significantly greater than normal. In contrast, maximum myocardial blood flow rates and minimum coronary vascular resistance expressed for the total right ventricle or per gram of right ventricular myocardium were not different between normal dogs and animals with aortic stenosis.

Discussion
The most important finding of this study is that left ventricular hypertrophy alone, without exposure of the coronary vessels to increased pressure, is associated with impaired coronary vasodilator capacity. Previous studies of concentric left ventricular hypertrophy produced by prolonged systolic overload have demonstrated impaired minimum coronary vascular resistance during maximum pharmacological vasodilation (Holtz et al., 1977; Mueller et al., 1978; O'Keefe et al., 1978; Mittmann et al., 1981; Bache et al., 1981a; Marcus et al., 1981). However, these studies employed renovascular hypertension or supravalvular aortic stenosis as the stimulus for left ventricular hypertrophy. Both of these procedures result in exposure of the coronary vessels to increased arterial pressure; in hypertensive animals throughout the entire cardiac cycle and in animals with supravalvular aortic stenosis during systole, when the coronary vessels which arise from the proximal aortic segment are subjected to systolic left ventricular pressure. It has been suggested that, in these models of left ventricular hypertrophy, the increased intra-arterial pressure may cause vascular changes which could impair coronary vasodilator capacity (Mueller et al., 1978). This suggestion is supported by the finding of O'Keefe et al. (1978) that in adult dogs in which supravalvular aortic stenosis was used to produce left ventricular hypertrophy, minimum coronary vascular resistance was...
impaired not only in the left ventricle, but also in
the right ventricle, despite minimal hypertrophy of
the right ventricle. Furthermore, histological exami-
nation of the hearts from these animals demon-
strated abnormal thickening of the media of intra-
myocardial arteries from 100-300 μm in external
diameter. These investigators proposed that the in-
creased vessel wall thickness could have accounted
for, at least in part, the elevated minimum vascular
resistance of the fully dilated coronary system.

In contrast to these previous experimental models,
in the present study the site of the left ventricular
outflow obstruction was proximal to the origin of
the coronary vessels so that the coronary vasculature
was not exposed to increased arterial pressure.
Nevertheless, minimum left ventricular coronary
vascular resistance per gram of myocardium was
substantially impaired in the animals with left ven-
tricular hypertrophy. It is of interest that when
minimum coronary vascular resistance was calcu-
lated for the entire left ventricle, there was no sig-
nificant difference between normal and hypertro-
phied hearts. This finding suggests that during the
development of hypertrophy, coronary vascular
growth did not occur in concert with myocardial
growth. Alternatively, coronary vasodilator reserve
capacity could be compromised by increased extra-
vascular factors in the hypertrophied heart. Abnor-
malities of diastolic relaxation have been reported
in the hypertrophied left ventricle which could act
to compress the intramural coronary vessels, thereby
limiting maximum blood flow rates (Grossman et

![Figure 1](image1.png)

**FIGURE 1.** Left ventricular myocardial blood flow to four
layers from subepicardium (layer 1) to subendocardium
(layer 4) in normal control dogs and in dogs with left
ventricular hypertrophy (LVH) during quiet resting con-
ditions. *P < 0.05, compared with the corresponding value
in the normal control dogs.

![Figure 2](image2.png)

**FIGURE 2.** Left ventricular myocardial blood flow to four
layers from epicardium (layer 1) to endocardium (layer 4)
in normal control dogs and dogs with left ventricular
hypertrophy (LVH) during infusion of adenosine, 1.0 mg/
kg per min. *P < 0.01, compared with the corresponding
value in the normal control dogs.
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Heart Rate 200

Heart Rate 250

FIGURE 3. Left ventricular myocardial blood flow to four layers from epicardium (layer 1) to endocardium (layer 4) in normal control dogs and dogs with left ventricular hypertrophy (LVH) during pacing at 200 and 250 beats/min. *P < 0.05, compared with the corresponding value in the normal control dogs.

al., 1979; Grossman and Berry, 1980). Impairment of coronary vasodilator reserve capacity appeared to be related to the presence of myocardial hypertrophy, since minimum coronary vascular resistance in the right ventricle was not significantly different from normal. These data indicate that myocardial hypertrophy alone, without exposure of the arterial system to increased intravascular pressure, resulted in impaired minimum coronary vascular resistance.

Bishop and Melsen (1976) found that severe acute systolic overload of the right ventricle produced myocardial damage, with focal necrosis and healing by fibrosis. Although the systolic pressure gradient across the area of constriction was not measured at the time of aortic valve plication in the present study, it is likely that only a moderate acute elevation in left ventricular systolic pressure was produced. In preliminary studies developing the plication technique in which left ventricular and ascending aortic pressures were measured, it was found that systolic gradients greater than 15 mm Hg were associated with a palpable thrill in the ascending aorta, while pressure gradients greater than 35 mm Hg resulted in acute left ventricular failure and death within less than 1 week. Animals with initial systolic pressure gradients of 15 mm Hg or more that survived to adulthood invariably had significant left ventricular hypertrophy. Because of the technical difficulty of the plication procedure, the additional manipulation required for measurement of left ventricular pressures was associated with an increased complication rate and increased surgical mortality. Since the presence of a systolic thrill indicated an adequate degree of obstruction which would result in left ventricular hypertrophy if the animals lived to adulthood, and because of the irreversibility of the plication procedure even if excessive degrees of aortic stenosis were produced, aortic valve plication was performed to produce a thrill but without measurement of left ventricular pressures for animals used in the present study. Histological study for assessment of myocardial fibrosis was not performed, but our initial experience suggests that the degree of acute systolic overload was modest, and that left ventricular systolic pressures increased as normal body growth occurred in the presence of aortic stenosis. Although no diastolic murmur of aortic regurgitation was heard in any of the animals included in this study, aortograms were not routinely performed for assessment of aortic insufficiency. However, aortic pulse pressures were not increased and pathological examination of the left ventricles showed concentric hypertrophy, with increased wall thickness and normal-to-decreased cavity diameter. Thus, although a trivial degree of aortic regurgitation might not have been detected, the hemodynamic and pathological findings indicated that aortic stenosis was the principle valvular abnormality.

In the present study, myocardial blood flow during quiet resting conditions was significantly higher in animals with aortic stenosis than in normal dogs. This finding is similar to the report by Rembert et al. (1978) and Bache et al. (1981b) who found that

### Table 4

Right Ventricular Myocardial Blood Flow (ml/min per g) and the Ratio of Subendocardial to Subepicardial Blood Flow (Endo:Epi) during Control Sinus Rhythm, Adenosine Infusion (1.0 mg/kg per min., iv), and Ventricular Pacing at 200 and 250 Beats/Min

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Adenosine</th>
<th>Pace 200</th>
<th>Pace 250</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flow</td>
<td>Endo:Epi</td>
<td>Flow</td>
<td>Endo:Epi</td>
</tr>
<tr>
<td>Normal</td>
<td>0.65 ± 0.17</td>
<td>1.12 ± 0.11</td>
<td>5.84 ± 0.67</td>
<td>1.12 ± 0.09</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>0.70 ± 0.08</td>
<td>1.15 ± 0.08</td>
<td>5.57 ± 0.38</td>
<td>1.25 ± 0.13</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SE.  
* P < 0.05 compared with the respective value during control sinus rhythm.  
† P < 0.05 Endo:Epi ratio significantly different from a value of 1.00.
blood flow per unit myocardial mass was significantly higher in dogs with left ventricular hypertrophy produced by constricting the ascending aorta than in normal dogs during control sinus rhythm. The difference in blood flow reported by these investigators appeared to be related, at least in part, to significantly faster resting heart rates in the dogs with left ventricular hypertrophy than in normal dogs. Thus, when the normal dogs were paced at heart rates similar to the sinus rates in the dogs with left ventricular hypertrophy, the significant difference in resting myocardial blood flow disappeared (Bache et al., 1981). These observations suggest that greater oxygen requirements due to faster heart rates and perhaps to abnormalities of ventricular geometry may, at least in part, account for the increased resting myocardial blood flow rate in animals with aortic stenosis.

Table 6 summarizes previously published studies of experimental pressure overload left ventricular hypertrophy in which myocardial blood flow was measured during maximum coronary vasodilation. The degree of left ventricular hypertrophy produced in these previous studies has been variable, depending on the experimental model used. The present model of aortic valvular stenosis produced an approximately 65% increase in relative left ventricular mass. Lesser degrees of hypertrophy have generally been produced with renovascular hypertensive models, as well as ascending aortic banding in the adult dogs. However, the ascending aortic banding model in the puppy is similar to the present model, in that the pressure overload was created at age 6–9 weeks, and animals were studied after reaching adulthood when left ventricular mass had increased substantially more than 50%. In all of these previous studies, minimum coronary vascular resistance per gram of myocardium was impaired in the hypertrophied left ventricle, while minimum coronary resistance for the entire left ventricle was not significantly different from normal hearts.

Previous studies of dogs with experimental left ventricular hypertrophy have reported that during maximum pharmacological coronary vasodilation with adenosine, dipyridamole, or carbochrome, left ventricular blood flow per gram of myocardium was either normal or decreased in comparison with normal animals. Whether myocardial blood flow rates during maximum coronary vasodilation are normal or decreased may be related to the different models used and the degree of hypertrophy. In dogs in which the ascending aorta was banded in adulthood, the increase in myocardial blood flow during maximum coronary vasodilation with adenosine or dipyridamole tended to be less in hypertrophied than in normal hearts, although this difference did not achieve statistical significance (O’Keefe et al., 1978; Breisch et al., 1980). In dogs with left ventricular hypertrophy secondary to renovascular hypertension, Mueller et al. (1978) found that adenosine

### Table 5

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Experimental model</th>
<th>Duration of systolic overload</th>
<th>LV/body (g/kg)</th>
<th>Vasodilator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holtz et al. (1977)</td>
<td>Asc Ao band in puppies</td>
<td>1 yr</td>
<td>8.5 ± 0.5</td>
<td>Dipyridamole</td>
</tr>
<tr>
<td>Mueller et al. (1978)</td>
<td>Renovascular hypertension in adult dogs</td>
<td>6–7 wk</td>
<td>6.1 ± 0.2</td>
<td>Adenosine</td>
</tr>
<tr>
<td>O’Keefe et al. (1978)</td>
<td>Asc Ao band in adult dogs</td>
<td>6 wk</td>
<td>5.1 ± 0.3</td>
<td>Adenosine or carbochrome</td>
</tr>
<tr>
<td>Bache et al. (1981)</td>
<td>Asc Ao band in puppies</td>
<td>10–15 mo</td>
<td>8.3 ± 0.4</td>
<td>Adenosine</td>
</tr>
<tr>
<td>Marcus et al. (1981)</td>
<td>Renovascular hypertension in adult dogs</td>
<td>6 wk</td>
<td>5.1 ± 0.1</td>
<td>Adenosine</td>
</tr>
<tr>
<td>Present</td>
<td>Aortic valve stenosis in puppies</td>
<td>8–14 mo</td>
<td>7.1 ± 0.4</td>
<td>Adenosine</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± se. Asc Ao = ascending aorta.

*P < 0.05, compared with the respective control value.
infusion produced an approximately 400% increase in left ventricular myocardial blood flow in both normal and hypertrophied hearts. In a later study using the same experimental model, Marcus et al. (1981) reported that mean myocardial blood flow was significantly less in dogs with left ventricular hypertrophy during adenosine infusion, compared to normal dogs, but in that study, adenosine caused a significantly greater fall in arterial pressure in hypertensive dogs than in normal dogs. For dogs with left ventricular hypertrophy produced by ascending aortic banding at 6–8 weeks of age, Bache et al. (1981) showed that the maximum left ventricular myocardial blood flow with adenosine infusion was not significantly different from normal. Using a similar experimental model, Holtz et al. (1977) and Mittmann et al. (1980) showed a significantly smaller increase in mean blood flow during maximum coronary vasodilation with dipyridamole in hypertrophied as compared with normal hearts. In all of these previous studies, the calculated mean minimum coronary vascular resistance per gram of myocardium was significantly increased during pharmacological coronary vasodilation in the dogs with left ventricular hypertrophy from pressure overload, compared with normal dogs.

Substantial regional variability in the transmural distribution of perfusion was observed in the hypertrophied heart during adenosine infusion. Thus, in the septum and anterior papillary muscle region, subendocardial-to-subepicardial blood flow ratios were not significantly different from normal, and not different from unity, whereas these ratios were significantly decreased in the lateral wall and posterior papillary muscle regions. Similar regional alterations of the transmural distribution of myocardial blood flow were observed during coronary vasodilation associated with treadmill exercise in dogs with left ventricular hypertrophy secondary to banding of the ascending aorta (Bache et al., 1981). This finding does not appear unique to the hypertrophied heart, since regional differences of the transmural distribution of blood flow of lesser magnitude have also been reported in normal hearts during maximum coronary vasodilation. Thus, Cobb et al. (1974) reported that, in normal dogs, subendocardial-to-subepicardial blood flow ratios were significantly lower in the posterior papillary muscle region than in the anterior left ventricular wall during adenosine infusion. Similarly, in the present study, the ratio of subendocardial to subepicardial flow in the normal dogs was significantly lower in the posterior papillary muscle region than in the anterior papillary muscle region during adenosine infusion ($P < 0.05$). Although the mechanisms responsible for this regional variability in the transmural distribution of myocardial blood flow during maximum coronary vasodilation are unknown, these differences are magnified in the hypertrophied left ventricle.

The effects of heart rate on myocardial blood flow have previously been studied in left ventricular hypertrophy secondary to renovascular hypertension and supravalvular aortic stenosis. Mueller et al. (1978), using renovascular hypertension in adult dogs, found that at a paced rate of 200 beats/min, left ventricular myocardial blood flow, the subendocardial-to-subepicardial blood flow ratio, and coronary vascular resistance per gram of myocardium were normal for the hypertensive dogs as compared to normal dogs. However, Vrobel et al. (1980), in a study of left ventricular hypertrophy produced by ascending aortic banding in puppies, found that although mean left ventricular myocardial blood flow was not significantly different from control, the subendocardial-to-subepicardial blood flow ratio decreased below control values at paced rates of 200 and 250 beats/min. In contrast to these previous reports, the present study demonstrated that pacing at 200 or 250 beats/min was associated with significantly lower blood flow rates in hypertrophied than in normal left ventricles. Unlike the normal hearts in which myocardial blood flow increased significantly from sinus rhythm to pacing at 200 beats/min, blood flow did not increase during this intervention in animals with aortic stenosis. Furthermore, the subendocardial-to-subepicardial blood flow ratios were significantly less than normal at both 200

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<th>Minimum Coronary Vascular Resistance Achieved during Maximum Pharmacological Coronary Vasodilation in Dogs</th>
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and 250 beats/min. This relative decrease in subendocardial blood flow was most marked in the posterior papillary muscle region.

The mechanism for decreased myocardial blood flow in animals with aortic stenosis during pacing-induced tachycardia may involve several separate factors. Pacing at 250 beats/min resulted in a significant increase in left ventricular end-diastolic pressure in the dogs with aortic stenosis, but not in the normal animals. This increase in left ventricular pressure during diastole would be expected to oppose subendocardial perfusion, and might thereby contribute to the decreased ratio of subendocardial:subepicardial blood flow seen in the animals with aortic stenosis during pacing. Bache et al. (1984) previously demonstrated that similar abnormalities of the transmural distribution of myocardial perfusion during pacing in animals with left ventricular hypertrophy secondary to supravalvar aortic stenosis may be associated with metabolic evidence of myocardial ischemia. Ischemia occurring during tachycardia might become self-perpetuating, since ischemia would further increase left ventricular diastolic pressure and prolong the isovolumic relaxation phase of systole, thereby augmenting the extra-vascular compressive forces acting on the intramural coronary vessels (McLaurin et al., 1973; Palacios et al., 1978; Mann et al., 1979; Grossman and Barry, 1980). Unfortunately, neither metabolic nor electrocardiographic data were available in the present study to determine whether ischemia occurred in the hypertrophied hearts during pacing at 250 beats/min.

In summary, this study has demonstrated that left ventricular hypertrophy produced by chronic pressure overload results in impaired minimum coronary vascular resistance, even when the coronary arteries are not exposed to increased intravascular pressure. These findings support the concept that during the hypertrophic process coronary cross-sectional area does not increase in parallel with the increased myocardial mass, and that this effect is not dependent upon vascular changes resulting from increased intra-arterial pressure. In addition, cardiac pacing was associated with abnormal perfusion in the hypertrophied heart, with lower total myocardial blood flow and a decreased ratio of subendocardial:subepicardial blood flow compared to normal animals. This perfusion abnormality appeared to be related to functional changes occurring during pacing in the animals with hypertrophy.

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Address for reprints: Robert J. Bache, M.D., University of Minnesota, Box 338—Mayo Memorial Building, University of Minnesota Medical School, Minneapolis, Minnesota 55455.

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INDEX TERMS: Coronary reserve • Coronary vasodilation • Adenosine • Tachycardia • Cardiac pacing
Alterations of myocardial blood flow associated with experimental canine left ventricular hypertrophy secondary to valvular aortic stenosis.

D Alyono, R W Anderson, D G Parrish, X Z Dai and R J Bache

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