Effect of Coronary Stenosis on Myocardial Blood Flow During Exercise in the Chronically Pressure-Overloaded Hypertrophied Left Ventricle

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This study was performed to determine if a coronary artery stenosis would result in more-severe perfusion abnormalities in hypertrophied compared with normal canine hearts during exercise. Studies were performed in eight normal control dogs and in seven adult dogs in which a 67% increase in left ventricular mass was produced by banding the ascending aorta at 9 weeks of age. Myocardial blood flow was measured by the microsphere method during treadmill exercise in the presence of a coronary artery stenosis that decreased distal coronary perfusion pressure to 55 or 42 mm Hg. At a coronary pressure of 55 mm Hg, mean myocardial blood flow was decreased by 23±5% in normal control dogs but was decreased by 53±10% in dogs with left ventricular hypertrophy (LVH) (p<0.05, comparing normal vs. LVH dogs). Similarly, at a coronary pressure of 42 mm Hg, mean blood flow was decreased by 53±6% below control in normal dogs but was decreased by 76±5% below control values in dogs with LVH (p<0.01, comparing normal vs. LVH dogs). In both groups of dogs, the stenosis caused a gradient of hypoperfusion, worsening from epicardium to endocardium. However, for each level of stenosis, subendocardial blood flow and the ratio of subendocardial to subepicardial blood flow was less in LVH than in normal canine hearts. These findings demonstrate that the presence of LVH secondary to long-term pressure overload is associated with an increased vulnerability to myocardial hypoperfusion during exercise in the presence of a coronary artery stenosis. (Circulation 1990;81:1967–1973)

Left ventricular hypertrophy (LVH) secondary to long-term pressure overload is associated with increased vulnerability to abnormalities of myocardial perfusion. Thus, exercise or pacing-induced tachycardia may result in perfusion deficits that are especially prominent in the subendocardium of the hypertrophied left ventricle.1–4 These stress-induced abnormalities of subendocardial perfusion are physiologically significant since they may be associated with evidence of myocardial ischemia, including myocardial lactate production and systolic and diastolic contractile dysfunction.5,6

When an arterial stenosis limits the increase in coronary blood flow that may occur during exercise, the resultant perfusion abnormality is most pronounced in the left ventricular subendocardium.7,8 Because of the increased vulnerability to subendocardial underperfusion in the habitually pressure-overloaded hypertrophied left ventricle, the effects of a coronary artery stenosis could be especially prominent in the hypertrophied left ventricle. Consequently, the present study was performed to determine if LVH aggravates the perfusion abnormality that occurs when a coronary artery stenosis limits arterial inflow during exercise.

Methods

We performed these studies in seven adult mongrel dogs, in which LVH had been produced by banding the ascending aorta, as well as in eight normal dogs that served as a control group. Studies were performed in accordance with the position of the American Heart Association on research animal use adopted November 11, 1984, and under the regulations of the Animal Care Committee of the University of Minnesota. Dogs in which LVH was produced underwent banding of the ascending aorta at 9 weeks of age. The dogs were anesthetized with...
sodium pentobarbital (20–25 mg/kg i.v.), intubated, and ventilated with a respirator. A right thoracotomy was performed in the third intercostal space. At approximately 1.5 cm above the aortic valve, the ascending aorta was dissected from the surrounding fat and connective tissue. The aorta was encircled with a 2.5-mm wide polyethylene band. While left ventricular and distal aortic pressure measurements were made, the polyethylene band was tightened until a 20–25 mm Hg peak systolic pressure gradient was achieved across the area of narrowing. The chest was then closed, the pneumothorax was evacuated with a chest tube, and the dog was allowed to recover. The dogs were subsequently maintained in enclosed runs and fed a standard laboratory diet. At 3 months of age, the dogs were trained to run on a motor-driven treadmill.

At 12–14 months of age, the dogs were returned to the laboratory. After premedication with fentanyl (0.4 mg i.m.) and droperidol (20 mg i.m.), they were anesthetized with sodium pentobarbital (30–35 mg/kg i.v.), intubated, and ventilated with a respirator. A left thoracotomy was performed in the fifth intercostal space. A heparin-filled polyvinyl chloride catheter (3.0 mm o.d.) was introduced into the left internal thoracic artery and advanced into the ascending aorta. A similar catheter was introduced into the left ventricle in the region of the apical dimple and secured with a purse-string suture. A third catheter was introduced into the left atrium through the atrial appendage. The proximal left circumflex coronary artery was dissected free, and a hydraulic occluder of polyvinyl chloride tubing (2.7 mm o.d.) was placed around the artery. A heparin-filled catheter of silicone rubber tubing (0.3 mm i.d.) was introduced into the left circumflex artery distal to the hydraulic occluder according to the method of Gwirtz.9 The catheters were tunneled subcutaneously to exit at the base of the neck. The chest was closed in layers, the pneumothorax was evacuated, and the dogs were allowed to recover. Catheters were flushed daily with heparin-saline solution to maintain patency. This instrumentation procedure was performed in all animals with aortic banding, as well as in eight normal dogs that served as a control group.

Studies were performed 10–14 days after surgery when the dogs were vigorous and in good health. Phasic and mean aortic pressures, left ventricular pressure, and distal coronary perfusion pressure were measured with Gould Model P23XL pressure transducers (Gould Inc., Glen Burnie, Maryland) affixed to the nylon vest at the level of the heart. Data were recorded on a Coulbourn Model R14-28 eight-channel direct-writing recorder (Coulbourn Instrs., Inc., Lehigh Valley, Pennsylvania).

**Measurement of Myocardial Blood Flow**

Myocardial blood flow was measured with radioactive microspheres, 15-μm diameter, labeled with one of the following radionuclides: 125I, 141Ce, 51Cr, 85Sr, 95Nb, or 46Sc (3M Co., St. Paul, Minnesota and New England Nuclear, Boston, Massachusetts). Microspheres were mixed in an ultrasonic bath for 15 minutes before injection. Blood flow measurements were performed by injecting 3 × 10⁶ microspheres into the left atrial catheter, which was then flushed with 8 ml normal saline solution. A reference sample of arterial blood was withdrawn from the aortic catheter at a rate of 15 ml/min beginning at the time of microsphere injection and continuing for 90 seconds.

**Experimental Protocol**

After resting control measurements were made, exercise was begun and was increased to a level that produced a heart rate of 190–200 beats/min (approximately 6 km/hr at a 5% grade). After the desired heart rate was achieved, the coronary artery occluder was inflated with a micrometer-driven syringe to produce a stenosis that resulted in a mean distal coronary artery perfusion pressure of 55 mm Hg. After a stable level of stenosis had been maintained for 2 minutes, microspheres were injected for measurement of myocardial blood flow. After completion of reference blood sampling, the coronary artery occluder was further inflated until a distal coronary artery perfusion pressure of 42 mm Hg was achieved. After this level of stenosis had been maintained for 2 minutes, a second injection of microspheres was performed for measurement of myocardial blood flow. After completion of reference blood sampling, the stenosis was released, and exercise was discontinued.

**Tissue Sampling**

After completion of the study, 10 ml Evans blue dye was injected into the coronary artery catheter to stain the area of myocardium perfused by the stenotic artery. Immediately thereafter, a lethal dose of sodium pentobarbital was administered. The heart was removed and fixed in 10% buffered formalin. After fixation, the left ventricle was divided into four transverse rings from base to apex. Duplicate myocardial specimens from the midportion of the blue-stained region were obtained, representing the area perfused by the stenotic left circumflex coronary artery. Each specimen was divided into four layers of equal thickness from epicardium to endocardium, weighed on an analytical balance, and placed into vials for counting. Similar duplicate myocardial specimens were obtained from the anterior left ventricular wall to serve as controls.

The radioactivities of myocardial and blood reference specimens were determined with a Packard Model 5912 gamma spectrometer (Packard Instr. Co., Inc., Meriden, Connecticut) with a multichannel analyzer with window settings corresponding to the peak emission energies of the radioisotopes used during the study. The activity recorded in each energy window, background activity, and sample weight were entered into a digital computer programmed to correct for contaminant activity between the isotopes, as well as for background activity, and to compute the corrected cpm per gram of myocardium.
Knowing the rate of withdrawal of the reference sample (Qr) and the radioactivity in the reference sample (Cr), we used myocardial radioactivity (Cm) to compute myocardial blood flow (Qm) as

\[ Q_m = \frac{Q_r \times C_m}{C_r} \]

Blood flows were expressed in milliliters per minute per gram of myocardium.

**Data Analysis**

Hemodynamic data were measured directly from the strip-chart recordings. Comparisons between normal dogs and dogs with LVH were performed with Student’s t test for paired data. Comparisons of blood flow across the four transmural layers were made with an analysis of variance for repeated measures. A p value of less than 0.05 was required for statistical significance. When a statistically significant result was found, individual comparisons were made with Scheffe’s test.10

**Results**

Dogs with banding of the ascending aorta had substantial LVH as indicated by a mean left ventricular–body weight ratio of 7.46±0.89, compared with a value of 4.47±0.28 in the normal group (p<0.02). Hemodynamic data are shown in Table 1. Heart rates during exercise were similar in normal dogs and in dogs with LVH. The addition of a coronary artery stenosis did not significantly alter the exercising heart rate in either group of dogs.

In normal dogs, left ventricular systolic pressure significantly increased during control exercise from resting values. There was a trend toward a decrease in left ventricular systolic pressure during exercise with application of both levels of coronary artery stenosis, but this trend did not achieve statistical significance. Left ventricular systolic pressure increased significantly during control exercise from resting values in dogs with LVH and was significantly greater than normal in dogs with aortic banding both at rest and during each exercise intervention (each, p<0.01). In dogs with aortic banding, left ventricular systolic pressure decreased significantly with application of both levels of coronary artery stenosis (p<0.01).

In normal dogs, left ventricular end-diastolic pressure did not change significantly during control exercise, from resting values nor did it change with the addition of a coronary artery stenosis. Left ventricular end-diastolic pressure was significantly greater than normal in dogs with LVH both at rest and during each exercise trial (each, p<0.05). Unlike the normal dogs, in dogs with LVH, left ventricular end-diastolic pressure increased significantly from rest during control exercise (p<0.01). There was a trend toward a further increase in left ventricular end-diastolic pressure with application of the coronary artery stenosis during exercise, but this trend did not achieve statistical significance. In the normal dogs, mean aortic pressure did not vary significantly throughout the experimental interventions. In animals with LVH, mean aortic pressure tended to decrease during exercise; this decrease was significant during exercise in the presence of a coronary artery stenosis with the coronary pressure at 42 mm Hg.

Myocardial blood flow values measured with microspheres during exercise in the presence of two levels of coronary artery stenosis are shown in Table 2 and Figures 1 and 2. In the area of the left ventricle perfused by the normal left anterior descending coronary artery, there was no significant difference in mean myocardial blood flow between normal and hypertrophied hearts. However, there was a difference in the transmural distribution of perfusion, with the highest flow rates confined to the inner half of the left ventricular wall in normal hearts and the highest flow rates found in the midwall of hypertrophied ventricles. As a result, the ratio of subendocardial to subepicardial flow was significantly less in normally perfused areas of hypertrophied than of normal ventricles (p<0.01). As shown in Figure 1, in the normal hearts, a coronary artery stenosis that decreased distal coronary perfusion pressure to 55 mm Hg caused a 23±5% reduction in mean myocardial blood flow (p<0.05). During this level of stenosis, blood flow was not significantly altered in layers 1 and 2 of the left ventricular wall, while blood flow to the inner two layers was significantly decreased below the anterior control region (each, p<0.05). When the severity of coronary artery stenosis was increased to produce a

**TABLE 1. Hemodynamic Data**

<table>
<thead>
<tr>
<th>Time of measurement</th>
<th>Heart rate (beats/min)</th>
<th>LV systolic pressure (mm Hg)</th>
<th>LV end-diastolic pressure (mm Hg)</th>
<th>Mean aortic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>LVH</td>
<td>Normal</td>
<td>LVH</td>
</tr>
<tr>
<td>Rest</td>
<td>126±7</td>
<td>121±6</td>
<td>129±6</td>
<td>230±13*</td>
</tr>
<tr>
<td>Control exercise</td>
<td>197±10</td>
<td>192±13</td>
<td>154±12</td>
<td>284±15*</td>
</tr>
<tr>
<td>Exercise, CP55</td>
<td>200±4</td>
<td>193±10</td>
<td>145±8</td>
<td>230±12‡</td>
</tr>
<tr>
<td>Exercise, CP42</td>
<td>205±4</td>
<td>189±13</td>
<td>139±7†</td>
<td>213±13‡</td>
</tr>
</tbody>
</table>

LV, left ventricular; CP55, stenosis that decreased coronary pressure to 55 mm Hg; CP42, stenosis that decreased coronary pressure to 42 mm Hg. Values are mean±SEM. *p<0.05 in comparison with normal; †p<0.05 in comparison with control exercise.
The most important finding of this study is that, for similar levels of coronary hypotension produced by a proximal coronary artery stenosis, the resultant myocardial perfusion deficit was more severe in hypertrophied than in normal hearts. Previous studies in normal hearts have demonstrated that when an arterial stenosis limits the increase in blood flow that can occur during exercise, the resultant perfusion abnormality is most severe in the subendocardium.\(^7\) Several factors may contribute to the redistribution of blood flow away from the subendocardium that occurs when arterial inflow fails to meet myocardial demands. First, generalized vasodilation of the coronary resistance vessels compromises the transmural gradient of vascular resistance, which normally favors blood flow to the subendocardium during diastole, to compensate for the lack of systolic perfusion in this area.\(^1\) Second, because of the low intravascular pressure distal to the stenosis, extravascular forces assume an increased role in determining the distribution of blood flow. Since intramyocardial pressure increases from epicardium to endocardium, the greatest impedence to blood flow occurs in the subendocardium.\(^1,2,13\)

No previous studies have examined the coronary pressures at which redistribution of flow away from the subendocardium occurs during exercise. Studies in open-chest animal preparations have demonstrated that, during basal conditions, subendocardial
blood flow is maintained until coronary pressure falls to approximately 50 mm Hg. In chronically instrumented awake dogs, Harrison et al. found that, during resting conditions, total myocardial blood flow and the transmural distribution of perfusion remained normal even at a coronary pressure of 40 mm Hg. In contrast, in the present study, blood flow to the subendocardium of normal hearts was significantly reduced even at a coronary pressure of 55 mm Hg, while at a coronary pressure of 42 mm Hg, total blood flow was decreased by one half, with prominent underperfusion of the inner half of the left ventricular wall. It is likely that the greater perfusion abnormality in the normal hearts in the present study occurred because the increased myocardial oxygen consumption during exercise required a greater degree of vasodilation of the coronary resistance vessels during control conditions. Gould and Lipscomb and Gould et al. demonstrated that, in response to a proximal arterial stenosis, the distal coronary vasculature undergoes progressive vasodilation to compensate for the resistance offered by the stenosis. The ability of the microvasculature to dilate in response to a proximal arterial stenosis is dependent on the baseline level of vasomotor tone of the resistance vessels before the stenosis is applied.

During exercise, the increased myocardial oxygen consumption requires vasodilation of the coronary resistance vessels. This basal level of vasodilation would encroach on the vasodilator reserve of the coronary resistance vessels, thereby limiting their capacity for further vasodilation to compensate for the resistance offered by the stenosis. In addition, the increased heart rate during exercise results in a decreased interval of diastole, during which the subendocardium is perfused, thereby further decreasing blood flow to deeper myocardial layers. These factors would result in impairment of blood flow with a less-severe degree of coronary hypotension during exercise than previously reported in either chronically instrumented, resting, awake animals or in open-chest animal preparations during basal conditions.

Harrison and associates examined coronary auto-regulation in normal dogs and in chronically instrumented dogs in which LVH had been produced by renovascular hypertension. Blood flow was measured by the microsphere method in three transmural layers across the left ventricular wall during normal conditions and during reductions of coronary artery pressure produced by a hydraulic occluder that resulted in coronary artery pressures of 100, 75, and 40 mm Hg. These investigators found that during quiet resting conditions, perfusion of the hypertrophied left ventricle was normal at coronary pressures of 100 and 75 mm Hg. Increasing the severity of the stenosis (to decrease coronary pressure from 75 to 40 mm Hg) resulted in a significant decrease in blood flow to the subendocardium. However, even at 40 mm Hg, subepicardial and midwall blood flows were well maintained. In contrast, in the present study, blood flow was significantly decreased in all transmural layers of the hypertrophied hearts at a coronary pressure of 42 mm Hg although the perfusion deficit was most severe in the subendocardium. These findings indicate that the abnormal response of myocardial perfusion to coronary hypotension in the hypertrophied heart is considerably more pronounced during exercise than at rest.

The finding of more-severe hypoperfusion in hypertrophied than in normal hearts at equivalent degrees of coronary hypotension could be the result of both structural and functional abnormalities of the coronary vascular system in the hypertrophied heart. Anatomic studies have demonstrated a decreased vascular density in the pressure-overloaded left ventricle that is most noticeable in the endomyocardium. Minimum coronary vascular resistance achieved during maximal pharmacological vasodilation of the coronary vascular system is abnormally increased in animals with LVH secondary to supravalvular aortic stenosis or arterial hypertension. This abnormality of minimum coronary vascular resistance is not the result of hypertensive vascular changes: animals in which LVH was produced by creating valvular aortic stenosis, in which the coronary arteries were not exposed to increased perfusion pressure, also demonstrate impairment of minimum coronary vascular resistance. To maintain normal blood flow rates per gram of myocardium in the presence of decreased vascular density would require a greater degree of vasodilation during baseline conditions. Use of a portion of the vasodilator reserve capacity to maintain adequate flow rates during basal conditions would encroach on the ability for further vasodilation.

In addition to structural abnormalities of the coronary vasculature, functional alterations may amplify the hypoperfusion produced by a coronary artery stenosis in the hypertrophied heart. Left ventricular end-diastolic pressure was significantly increased in animals with LVH. The effect of the increased left ventricular cavitary pressure during diastole would be expected to be especially prominent in the deeper myocardial layers. In addition, the systolic ejection period has been demonstrated to be prolonged in dogs with hypertrophy secondary to ascending aortic banding. The resultant decrease in diastolic interval, when perfusion of the subendocardium occurs, would also decrease blood flow to the deeper myocardial layers. Buckberg et al. have suggested that the adequacy of coronary blood flow relative to myocardial oxygen demands can be assessed from the ratio of the diastolic pressure-time index–systolic pressure-time index. This ratio indicates that subendocardial blood flow is a function of mean coronary perfusion pressure and the time spent in diastole, while integrated left ventricular pressure during systole reflects myocardial oxygen demands. Reduction of this ratio to a value less than 0.7 predicts inadequate oxygen delivery in the normal heart. However, values obtained in the hypertrophied heart are not comparable with normal values. As the result of
myocardial hypertrophy, the increased systolic load is distributed across a greater myocardial cross-sectional area. Thus, in compensated hypertrophy, systolic wall stress (and oxygen consumption per unit of myocardial mass) returns to normal or near-normal levels despite persistently elevated systolic intracavitary pressure. Hoffman and Buckberg suggested the term systolic pressure-time index, rather than the more-traditional term tension-time index, to indicate that left ventricular cavity pressure is not representative of systolic wall stress (and oxygen demands) if abnormalities of wall thickness or cavity diameter exist. In the present study, the lack of wall thickness measurements and cavity size prevented comparison of this ratio between normal and hypertrophied hearts.

The occurrence of subendocardial ischemia would be expected to cause abnormalities in myocardial mechanical function that might further aggravate the perfusion deficit. Ischemia causes an increase in myocardial stiffness as the result of impaired relaxation or increased diastolic tone. Apstein et al have shown that ischemia-induced decreases in myocardial compliance cause parallel increases in coronary resistance. Thus, ischemia-induced abnormalities in diastolic relaxation could contribute to further impairment of blood flow in the ischemic area.

Even in normally perfused areas, the transmural distribution of myocardial blood flow was abnormal during exercise in the hypertrophied hearts. In the normal heart, exercise results in increases in coronary blood flow in response to the increased myocardial oxygen demands, while the transmural gradient of perfusion favoring flow to the deeper myocardial layers is maintained. In contrast to normal, in the pressure-overloaded hypertrophied left ventricle, exercise produces a redistribution of blood flow away from the subendocardium. This phenomenon was observed in the present study, in which the ratio of subendocardial to subepicardial blood flow in the normally perfused area was significantly lower in hypertrophied than in normal hearts. It is likely that this abnormal transmural distribution of blood flow in normally perfused areas during exercise is the result of the previously discussed structural and functional abnormalities of the coronary vascular system of the hypertrophied left ventricle.

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References


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