The effect of cardiac hypertrophy on the coronary collateral circulation

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ABSTRACT We have previously shown that dogs with renal hypertension and left ventricular hypertrophy have larger infarcts (per risk area size) than do control animals. A potential explanation for this is that collateral resistance is higher in these dogs. Paradoxically, previous postmortem studies in human hearts with left ventricular hypertrophy have suggested that coronary collaterals are actually increased in this condition. To test the hypothesis that left ventricular hypertrophy is associated with alterations in coronary collateral resistance, studies were performed in dogs with renal hypertension and left ventricular hypertrophy and in patients with aortic valvular disease at the time of cardiac surgery. With an isolated, adenosine-vasodilated, blood-perfused cardiac preparation, collateral and normal zone pressure-flow relationships were established by means of radioactive microspheres in nine dogs with renal hypertension and left ventricular hypertrophy and in 17 controls. Collateral resistance calculated from these pressure-flow relationships were similar in both groups (4.0 ± 0.7 in dogs with renal hypertension and left ventricular hypertrophy and 3.9 ± 0.4 mm Hg/ml/min/100 g in controls). In addition, normal zone resistance was not different between groups (transmural resistances 0.17 ± 0.01 in controls and 0.18 ± 0.02 in dogs with renal hypertension and left ventricular hypertrophy. In five patients with aortic valve disease, left ventricular hypertrophy, and normal coronary arteries and in six patients without left ventricular hypertrophy who had normal left anterior descending coronary arteries, a 7 MHz suction-mounted echo transducer was used to monitor systolic wall thickening during transient occlusions of the left anterior descending artery at the time of cardiac surgery. Because noncollateralized myocardium ceases to contract promptly after coronary occlusion, this approach provides an indirect index of collateral perfusion. Twenty seconds after the onset of coronary occlusion, systolic thickening had markedly decreased in both groups (15 ± 10% of control values in nonhypertrophied hearts and 10 ± 10% in hearts with left ventricular hypertrophy; p = NS between groups). Thus the severity of contraction abnormality induced during transient coronary occlusion in these two groups of patients was similar, suggesting that the degree of severity of ischemia was comparable between the two groups. We conclude that collateral resistance is not altered by hypertension and left ventricular hypertrophy and that left ventricular hypertrophy in patients is not associated with functional evidence of an enhanced collateral circulation. Taken together, these results support the concept that the functional capacity of the coronary collateral circulation is not augmented by left ventricular hypertrophy.


CARDIAC HYPERTROPHY is associated with numerous alterations of the coronary circulation. Minimal coronary resistance assessed by a variety of techniques is abnormally elevated in several animal preparations of cardiac hypertrophy.1-5 Capillary den-
mortality injections, confirmed these observations. Fulton, using a postmortem angiographic technique, showed that collaterals in hypertrophied hearts are increased in caliber. Thus anatomic studies suggest that coronary collaterals are increased in left ventricular hypertrophy.

Physiologic studies by Goldstein et al. demonstrated that peripheral coronary pressure was low (<20 mm Hg) in patients with aortic stenosis and normal coronary arteries. These results implied that the functional significance of collateral vessels in these patients was minimal. Recently published studies from this laboratory have shown that dogs with hypertension and left ventricular hypertrophy have larger infarcts (per risk zone size) than do controls. Collateral flow measured with radioactive microspheres was similar between the two groups, although aortic pressure was significantly higher in the animals with left ventricular hypertrophy. Conclusions regarding collateral resistance could not be made from this work because peripheral coronary pressure (pressure distal to the site of circumflex occlusion) was not measured and thus the transcollateral pressure gradient was not known. In addition, overlap flow was not eliminated and extravascular compressive forces were not controlled. Nonetheless, the results implied that collateral resistance may be increased in animals with left ventricular hypertrophy and hypertension. Very recently, Scheel et al. have shown in an isolated, blood-perfused cardiac preparation that collateral resistance in control and hypertrophied hearts is similar. In that study, measurements of perfusion in various regions of the myocardium were not obtained. Thus previous physiologic and anatomic studies have provided conflicting notions regarding the effect of left ventricular hypertrophy on the collateral circulation.

The present studies were performed to test the hypothesis that left ventricular hypertrophy alters native coronary collateral resistance. Two groups of studies were performed. In a canine model of hypertension and left ventricular hypertrophy, we examined collateral resistance by means of an isolated, blood-perfused cardiac preparation. This allowed measurement of collateral flow over a wide range of aortic pressures so that pressure-flow relationships could be established in both the ischemic region of the myocardium and the normally perfused region. In this preparation, extravascular compressive forces were minimized and equalized between groups. In addition, clinically relevant studies were performed in patients with and without left ventricular hypertrophy at the time of open heart surgery to assess the ability of native collaterals to prevent the development of a wall motion abnormality during brief coronary occlusions.

Methods

Animal studies

Production of hypertension and left ventricular hypertrophy. In nine dogs (weight 19 to 30 kg), hypertension and left ventricular hypertrophy were produced in a manner similar to that described previously. Briefly, after sodium pentobarbital anesthesia (30 mg/kg iv), a midline abdominal incision was performed under sterile conditions. The right kidney was removed. An adjustable clamp was placed on the left renal artery and tightened until either a thrill or a marked diminution in pulse was present distal to the clamp.

Hypertension was documented by measuring the animal’s arterial pressure with an intra-arterial catheter 6 to 8 weeks after renal surgery. This involved isolating the omocervical artery under sterile conditions with the animal lightly anesthetized with intravenous thiopental sodium (375 to 625 mg). This vessel was cannulated and the cannula was exteriorized at the back of the neck. The dogs were returned 2 days later and arterial pressure was measured while the animal was sitting quietly in the laboratory.

Seventeen adult mongrel dogs (weight 17 to 31 kg) were used as controls.

Isolated beating heart preparation. On the day of the study the animals were anesthetized with sodium pentobarbital (30 mg/kg iv). The chest was opened by a sternal split and the left brachiocephalic artery was ligated. A specially designed metal cannula that permitted measurement of pressure at its tip was inserted into the right brachiocephalic artery and advanced to the aorta. The animal was given 5000 U of heparin intravenously. Approximately 1 liter of blood used to prime the perfusion system was obtained from the brachiocephalic cannula. During this exsanguination procedure, aortic pressure was maintained above 50 mm Hg by cross-clamping the aorta distal to the left brachiocephalic artery.

After exsanguination the heart was rapidly excised and the aortic cannula was attached to the perfusion apparatus (figure 1). The coronary arteries were then perfused from the aorta with the animal’s own blood. The left ventricle was vented by a cannula passed from an incision in the left atrium through the mitral valve. Blood from the coronary sinus was drained by the inferior vena cava through a specially constructed reservoir to a rotating disk oxygenator. Here the blood was oxygenated with a gas mixture of 95% oxygen and 5% carbon dioxide. This mixture maintained the PaO2 in excess of 350 mm Hg, the PacO2 from 25 to 35 mm Hg, and the pH from 7.32 to 7.45. Blood was pumped from the rotating disk oxygenator through a heat exchanger and subsequently to a pressure reservoir. Temperature was maintained at 38°C. From there the blood returned to the heart and coronary arteries. The reservoir was constructed so that pressure could be controlled with compressed air and an adjustable air gauge. The perfusion tubing to the aorta contained a mixing chamber in which a small magnetic stir bar was present to ensure adequate mixing of blood elements and dispersion of injected microspheres into the blood stream. Beyond the mixing chamber was a Lucite loop that had two withdrawal ports on either side. During microsphere injections constant withdrawal of reference samples were obtained from these ports. Since two reference samples were obtained, the adequacy of microsphere mixing could be examined. The perfusion line contained an electromagnetic flow meter that allowed assessment of the adequacy of the coronary vasodilation. Throughout the experiments the heart contracted in sinus rhythm at a rate of 90 to 110 beats/min.

After establishing aortic perfusion, the proximal circumflex
coronary artery was dissected free and ligated, and a metal cannula was inserted distal to the occlusion and secured in place. This cannula was constructed so that pressure could be monitored at its tip. The cannula was attached to a second length of perfusion tubing leading from the pressure reservoir so that the circumflex artery could be perfused independently from the remainder of the circulation. After occlusion of this cannula tubing, peripheral circumflex pressure could be monitored and estimates of collateral driving pressure (aortic pressure minus peripheral circumflex pressure) were obtained.

Before measurement of blood flow, maximal coronary vaso-dilation was obtained by administration of adenosine (6 mg/min) into the perfusion reservoir.

Measurement of regional myocardial blood flow. Regional myocardial perfusion was measured with 9 μm radioactive microspheres labeled with 46Sc, 99Nb, 89Sr, 141Ce, 113Sn, 153Gd. For each flow measurement, the dose of microspheres was selected to approximate 2 mCi (approximately 500,000 to 800,000 microspheres). These were injected directly into the aortic perfusion cannula (figure 1). Paired reference samples were obtained at a withdrawal rate of 4.94 ml/min beginning 10 sec before and continuing for 1 min after microsphere injection.

A "shadow technique" similar to that described by Hirzel et al. 16 and Cohen 17 was used to identify the region of myocardium normally perfused by the circumflex coronary artery. This involved an injection of radioactive microspheres into the aortic line while the circumflex coronary artery was perfused with radioactive microsphere–free blood at a pressure identical to aortic pressure. Because aortic and circumflex pressure were equal during this injection, there was no impetus for collateral flow to occur.

After this microsphere injection, the circumflex perfusion cannula was occluded. Four to five additional measurements of regional myocardial blood flow were obtained with aortic pressure adjusted to create transcollateral pressure gradients (aortic pressure–peripheral coronary pressure) ranging from 40 to 120 mm Hg.

Determination of the size of the collateral-dependent zone. Because the size of the collateral-dependent zone can be a major determinant of absolute collateral flow per gram of myocardium, 18 we measured the sizes of the collateral-dependent zones in both groups of animals. To estimate the size of the collateral-dependent zone, an autoradiographic technique was used. This was accomplished by reopening the circumflex perfusion line at the end of the study and adjusting circumflex pressure to be equal to aortic pressure. Approximately 600,000 albumin 30 to 80 μm microsphere (3M Co., Minneapolis) labeled with 1 mCi of 99mTc were injected into the circumflex perfusion line. The heart was then perfused with 6% formaldehyde to provide immediate fixation.

Subsequently, the right ventricle and both atria were trimmed from the left ventricle and the left ventricle was sliced in 1 cm rings from the base to the apex parallel to the atrioventricular groove. These were arranged on a sheet of x-ray film that had been covered with cellophane wrap. The x-ray film and the heart slices were placed between two sheets of Plexiglas for 4 to 6 hr. This exposure resulted in an image of the 99mTc-labeled microspheres that had been injected into the circumflex perfusion line. The energy emitted by these microspheres was approximately 500 times greater than that emitted by the microspheres used to determine regional myocardial blood flow and thus produced the only image recorded on the x-ray film. Each ring was subsequently weighed and the image produced was planimetered. Size of the risk zone was determined with the formula for a truncated cone.

Calculation of regional myocardial blood flow. Three to 4 days after the study (when the 99mTc had decayed to negligible levels), the hearts were sectioned for determination of regional myocardial perfusion. The base and apex pieces were discard- ed. Each ring was cut into approximately 14 to 25 pieces and each of these pieces was further divided into endocardial, mid-wall, and epicardial segments of approximately equal size. Each segment was weighed to the nearest 0.01 g, placed in a scintillation tube, and counted in a well-type gamma counter for 5 min.
Separation of the energy spectrum for the various microsphere labels was accomplished with standard techniques. Regional myocardial perfusion for each segment of myocardium was determined by the formula:

\[
\text{myocardial blood flow} = \frac{\text{Cm} \times \text{RBF}}{C_t} \times 100
\]

where Cm represents counts per gram of myocardial tissue in each sample, RBF represents reference blood flow (ml/min) (rate of reference sample withdrawal), and C_t represents counts in reference blood samples.

The flows from the first microsphere injection (when the circumflex artery was perfused with microsphere-free blood at aortic pressure) in each ring of the left ventricle were plotted against each segment number (figure 2). Those segments of tissue that revealed microsphere-measured flows of less than 1 ml/min/100 g of myocardium were identified as being in the collateral-dependent zone. Because these studies were performed during infusion of adenosine, flow to the myocardium not served by the occluded circumflex were in excess of 200 ml/min/100 g. Usually, at least one segment of tissue immediately adjacent to the collateral dependent zone was identified in which this initial microsphere injection revealed an intermediate level of flow. These segments were considered to contain an admixture of tissue from both the truly ischemic zone and from the normally perfused myocardium. Such segments were not included in the analysis of flow in either the normal zone or the ischemic zone. Segments from both the normal and the ischemic zone were combined for determination of both collateral and normal zone flows upon analysis of subsequent microsphere injections.

**Calculation of normal zone resistance.** Because these studies were performed during adenosine vasodilation, the pressure-flow relationships in the normally perfused myocardium could be described reasonably well as a linear relationship. Although pressure-flow relationships in normally perfused myocardium may be curvilinear at lower pressures, the aortic pressures used in this study generally were above those reported to deviate from a straight line by several other investigators. Thus we expressed normal zone conductance (change in flow for an imposed change in pressure) as the slope of this relationship and normal zone resistance (change in pressure needed to accomplish a measured change in flow) as the inverse of this slope.

**Determination of collateral resistance.** The pressure-flow relationship across native canine coronary collaterals has been previously shown to be linear. We therefore used linear regression to analyze the relationship between the transcollateral gradient (aortic pressure minus peripheral coronary pressure) and collateral dependent zone flow per 100 g of myocardium. Collateral conductance (change in collateral-dependent zone flow for an imposed change in driving pressure across the collateral vasculature) was described by the slope of this relationship. Collateral pressure (pressure change needed to accomplish a measured change in flow) was described by the inverse of this slope.

**Patient studies**

**Patient selection.** Five patients with left ventricular hypertrophy secondary to aortic valve disease were studied. Three of these patients had predominant aortic insufficiency, one predominant aortic stenosis, and one mixed aortic stenosis and aortic insufficiency. All had angiographically normal coronary arteries. The electrocardiogram demonstrated left ventricular hypertrophy in each patient. In four, a technically satisfactory preoperative echocardiogram could be obtained demonstrating an increase in interventricular septal and posterior left ventricular wall thickness, left ventricular end-diastolic diameter, or both. Left ventricular hypertrophy was also obvious by visual inspection at the time of surgery in each patient.

Six patients without left ventricular hypertrophy served as controls. In four of these six patients, surgery was performed to place bypass grafts for coronary atherosclerosis. In each of these patients the left anterior descending artery was angiographically normal and none had angiographically demonstrable collaterals. The other two patients had angiographically normal coronary arteries. In one of these surgery was performed for mitral stenosis and in the other for removal of a right atrial mass.

All patients underwent cardiac catheterization and coronary arteriography before cardiac surgery except the patient with a right atrial mass. This patient was a 31-year-old woman without a history suggestive of coronary artery disease. In each of the other patients, catheterization was performed with the Seldinger technique from the femoral artery. In all except the patient with a right atrial mass, the left ventricular ejection fraction was measured from either a right anterior oblique left ventriculogram or a preoperative gated radionuclide ventriculogram.

The studies were approved by the Human Use Committee at the University of Iowa and informed consent was obtained from each patient.

**Reactive hyperemic studies and measurements of systolic thickening at cardiac surgery**

**Patient preparation.** All patients were anesthetized, intubated with an endotracheal tube, and ventilated with a mechanical respirator. The primary anesthetic used was halothane. Blood
gases were maintained in the physiologic range by varying the depth and rate of respiration and the oxygen concentration of the inspired gas. The studies were performed during the operation via a midsternal incision for cardiac exposure and after appropriate preparations for the use of cardiopulmonary bypass. Arterial pressure, measured with a radial arterial catheter, and the electrocardiogram were monitored continuously. A catheter placed in the left atrium via a pulmonary vein was used to monitor left atrial pressure. Just before measurements of coronary blood flow velocity, heparin was administered intravenously to raise the activated clotting time to 480 sec. All measurements of coronary reactive hyperemia were obtained before the onset of cardiopulmonary bypass when the patient’s hemodynamic status was stable.

Mean and phasic coronary blood flow velocity was obtained with a pulsed ultrasonic Doppler probe that has been previously described in detail. This probe consists of a 20 MHz piezoelectric crystal placed at a 45 degree angle in a silicone suction pad. Continuous contact of the crystal to the epicardial surface overlying the left anterior descending coronary artery was accomplished by low-level suction supplied to the silicone pad through a separate vacuum line.

After the Doppler probe was placed on the left anterior descending coronary artery, the position of the probe was adjusted until a coronary blood flow velocity recording of excellent quality was obtained. Simultaneous measurements of mean and phasic coronary velocity, phasic arterial pressure, and electrocardiograms were recorded. A 20 sec coronary occlusion was accomplished by applying gentle pressure with vascular forceps or a soft-tipped Kittner dissector just proximal to the Doppler probe. The time of occlusion was determined by measuring the time during which coronary blood flow velocity was zero. Upon release of the occlusion the reactive hyperemic response was recorded. Each reactive hyperemic response was quantified by measuring peak coronary velocity and dividing this by resting velocity before the onset of transient coronary occlusion. Previous work in this laboratory has shown that the peak-to-resting velocity ratio correlates well with the debt-to-repayment ratio of the hyperemic response.

Measurement of left ventricular systolic wall thickening by intraoperative echocardiography. Intraoperative echocardiographic recordings were obtained with a 7 MHz M mode transducer and a Smith-Kline Ekoline M mode ultrasonoscope with an ultraviolet light-developed hard copy write-out. The transducer was mounted in a small suction cup and held on the left ventricular epicardial surface by suction so that variable pressure from a hand-held device was avoided. The suction-mounted echo probe was positioned on the surface of the myocardium immediately adjacent to the left anterior descending artery, usually between a diagonal branch and the left anterior descending artery. The site of the occlusion was proximal to the origin of the diagonal branch so that the echocardiographic probe was in the center of the presumed area of ischemia. Minor adjustments were made in probe position until a recording of optimal quality was obtained. An example of such a recording is shown in figure 3. Subsequently, measurements were made of left ventricular anterior wall end-diastolic thickness, end-systolic thickness, and systolic change in thickening (end-systolic thickness—end-diastolic thickness). We measured the decrease in systolic thickening (expressed as a percent of control) that occurred at 10 and 20 sec after the onset of coronary occlusion.

Statistical analysis

**Animal studies.** Linear regression was used to describe the relationship between flow and driving pressure into normally perfused myocardium and across the collateral vasculature as described above. Unpaired Student t tests were used to compare left ventricular/body weight and left/right ventricular weight ratios between the control animals and animals with hypertension and left ventricular hypertrophy. In addition, analysis of variance was used to compare the collateral and normal zone resistances between these two groups of animals.

**Patient studies.** Unpaired Student t tests and analysis of variance were used to compare baseline characteristics and hemodynamic parameters between patients studied with and without left ventricular hypertrophy. In addition, unpaired Student t tests were used to compare the percent reduction in systolic thickening after coronary occlusion in these two groups of patients.

**All data** are expressed as the mean ± SE.

**Results**

**Animal studies**

**Baseline characteristics.** The average mean aortic pressure among the nine dogs with left ventricular hypertrophy and hypertension was 131 ± 5.8 mm Hg. The left ventricular/body weight ratio in these animals was 5.6 ± 0.9 g/kg body weight compared with 4.3 ± 0.2

![FIGURE 3. Intraoperative echocardiographic recording obtained before and during coronary occlusion. A prompt decrease in wall thickening occurs during coronary occlusion. The Doppler signal is denoted by the arrows and indicates complete coronary occlusion in the right panel.](http://circ.ahajournals.org/attachment/3.png)
TABLE 1
Normal zone pressure/flow relationships (mean ± SE)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Region</th>
<th>Slope (ml/min/100 g/mm Hg)</th>
<th>Resistance (1/slope)</th>
<th>x intercept (mm Hg)</th>
<th>r</th>
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<tbody>
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<td>Transmural</td>
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<tr>
<td>Controls</td>
<td>6.5 ± 0.5</td>
<td>0.17 ± 0.01</td>
<td>17.7 ± 3.0</td>
<td>.97 ± .01</td>
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<tr>
<td>HT-LVH</td>
<td>6.2 ± 0.7</td>
<td>0.18 ± 0.02</td>
<td>18.2 ± 3.9</td>
<td>.98 ± .01</td>
</tr>
<tr>
<td>Endocardium</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>6.9 ± 0.6</td>
<td>0.16 ± 0.01</td>
<td>16.8 ± 2.8</td>
<td>.97 ± .01</td>
</tr>
<tr>
<td>HT-LVH</td>
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<td>0.15 ± 0.01</td>
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<td>.99 ± .01</td>
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<td>Midwall</td>
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<tr>
<td>Controls</td>
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<td>0.17 ± 0.01</td>
<td>19.0 ± 3.0</td>
<td>.97 ± .01</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>6.5 ± 0.7</td>
<td>0.17 ± 0.02</td>
<td>18.3 ± 4.0</td>
<td>.98 ± .01</td>
</tr>
<tr>
<td>Epicardium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>5.8 ± 0.5</td>
<td>0.19 ± 0.02</td>
<td>17.4 ± 11.6</td>
<td>.97 ± .01</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>5.6 ± 0.6</td>
<td>0.20 ± 0.02</td>
<td>18.8 ± 3.6</td>
<td>.98 ± .01</td>
</tr>
</tbody>
</table>

HT-LVH = renal hypertension and left ventricular hypertrophy.

\textsuperscript{a}Data from regression analysis of aortic pressure/normal zone flow relationships in animals with renal hypertension and left ventricular hypertrophy and in controls.

for controls (p < .01). The left/right ventricular weight ratios were 3.2 ± 0.1 for the animals with hypertension and left ventricular hypertrophy and 2.1 ± 0.1 for the controls (p < .05). Thus the animals with hypertension and left ventricular hypertrophy had approximately a 20% to 30% increase in left ventricular mass as assessed by these parameters. The size of the risk area determined by \textsuperscript{99m}Tc microsphere autoradiographs averaged 29.6 ± 1.7% of the left ventricular mass for control animals vs 30.6 ± 2.4% of left ventricular mass for animals with hypertension and left ventricular hypertrophy (p = NS).

Comparison of resistances to normally perfused (nonoccluded myocardium) in dogs with renal hypertension and left ventricular hypertrophy and in controls. The mean values for the slopes, intercepts, and correlation coefficient of the normal zone pressure-flow relationships are shown in table 1. These values and the calculated minimal vascular resistances were not different between controls and animals with renal hypertension and left ventricular hypertrophy (figure 4).

Comparison of collateral resistances between animals with hypertension and left ventricular hypertrophy and controls. The correlation between collateral flow and collateral driving pressure (aortic pressure − peripheral coronary pressure) was high in both controls and animals with hypertension and left ventricular hypertrophy (r = .98 ± .005 and .97 ± .01, respectively). The mean slopes, x intercepts, calculated resistances (1/slope) and correlation coefficients are shown in table 2. The mean collateral resistance values, 3.9 ± 0.6 mm Hg/ml/min/100 g for animals with hypertension and left ventricular hypertrophy and 3.7 ± 0.7 mm Hg/ml/min/100 g for controls, were similar (figure 4). We also determined resistance to flow to ischemic endocardium, midzone, and epicardium with a similar regression analysis (x = aortic pressure, y = regional myocardial flow) (table 3). The slopes, x intercepts, and calculated resistances were not different between groups of animals.

Thus, in the control group, an aortic pressure of 100 mm Hg would produce ischemic zone flows of 17.8 ± 2.5 ml/min/100 g in the endocardium and 19.2 ± 1.9 ml/min/100 g in the epicardium. In the group with renal hypertension and left ventricular hypertrophy this pressure would produce ischemic zone flows of 16 ± 2.5 and 21 ± 2.8 ml/min/100 g to the endocardium.
and epicardium, respectively. These differences were not significantly different between these two groups of animals.

**Patient studies**

*Baseline characteristics.* Table 4 shows the baseline characteristics for patients with and without left ventricular hypertrophy who were studied in the operating room. There were no differences in age or left ventricular ejection fraction between groups. Blood hemoglobin was slightly higher among patients with hypertrophy.

Hemodynamic values at the time of the reactive hyperemia study are also shown in table 4. There was no difference in heart rate, aortic pressure, or left atrial pressure between the groups of patients.

**Comparison of systolic wall thickening responses to coronary occlusion in patients with and without left ventricular hypertrophy.** Table 5 and figure 5 show the responses to coronary occlusion in patients with left ventricular hypertrophy and in control subjects. The reactive hyperemic response was significantly reduced in the patients with left ventricular hypertrophy. The diastolic wall thickness was significantly increased in the group of patients with left ventricular hypertrophy. Compared with the control patients, the percent thickening before coronary occlusion was markedly reduced in the patients with left ventricular hypertrophy. The percent change from baseline thickening with coronary occlusion was similar between groups. Furthermore, the time course of the loss of systolic thickening was similar between the two groups of patients.

**Discussion**

The principle findings of these studies are: (1) native collateral resistance in dogs with left ventricular hypertrophy secondary to renal hypertension was not different from that in controls and (2) the ability of native collaterals to prevent myocardial contraction abnormalities induced by acute coronary occlusion was not different in patients with left ventricular hypertrophy than in patients with normal left ventricles. These experimental and clinical observations support the concept that the native collateral circulation is not functionally different in hypertrophied left ventricles.

These results are somewhat different than would be expected from previous anatomic studies of hypertrophied human hearts. In 1940 Blumgart et al. published results of angiographic studies in postmortem specimens. These investigators observed that normal hearts from patients without coronary atherosclerosis did not have intra-arterial anastomosis. They noted, however, that hearts with diseases other than coronary arteriosclerosis, including hypertrophied hearts, had such anastomoses. These observations were extended by

**TABLE 3**

Collateral zone pressure/flow relationships (mean ± SE)

<table>
<thead>
<tr>
<th>Slope (ml/min/100 g/mm Hg)</th>
<th>Resistance (1/slope)</th>
<th>x intercept (mm Hg)</th>
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<tr>
<td><strong>Endocardium</strong></td>
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<tr>
<td>Controls</td>
<td>.29 ±.05</td>
<td>5.4 ±.8</td>
<td>26.9 ±3.4</td>
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<tr>
<td>HT-LVH</td>
<td>.21 ±.03</td>
<td>6.3 ±1.4</td>
<td>21.0 ±4.2</td>
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<td><strong>Midwall</strong></td>
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<tr>
<td>Controls</td>
<td>.34 ±.06</td>
<td>4.7 ±0.7</td>
<td>26.1 ±3.1</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>.31 ±.04</td>
<td>4.0 ±0.6</td>
<td>25.9 ±2.4</td>
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<td><strong>Epicardium</strong></td>
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<tr>
<td>Controls</td>
<td>.33 ±.05</td>
<td>4.3 ±0.5</td>
<td>21.7 ±2.6</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>.30 ±.04</td>
<td>4.1 ±0.6</td>
<td>24.4 ±3.5</td>
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</table>

*Data from regression analysis of aortic pressure/collateral zone flow relationships in animals with renal hypertension and left ventricular hypertrophy and in controls.*
TABLE 4
Baseline data (mean ± SE)a

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Hgb (g/dl)</th>
<th>LVEF</th>
<th>HR (bpm)</th>
<th>AoP</th>
<th>LAP</th>
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<tr>
<td>Controls</td>
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<td>13.1</td>
<td>0.58</td>
<td>84</td>
<td>80</td>
<td>11</td>
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<td>±6</td>
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<td>±0.06</td>
<td>±5</td>
<td>±4</td>
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<td>LVH</td>
<td>49</td>
<td>15.0b</td>
<td>0.52</td>
<td>88</td>
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<td>±6</td>
<td>±0.6</td>
<td>±0.08</td>
<td>±6</td>
<td>±7</td>
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</table>

Hgb = blood hemoglobin concentration; LVEF = left ventricular ejection fraction; HR = heart rate; AoP = mean aortic pressure; LAP = mean left atrial pressure; LVH = left ventricular hypertrophy.

aBaseline data and hemodynamics at the time of the study in patients with left ventricular hypertrophy and in control subjects.
bp < .05 vs controls.

Zoll et al.10 in 1951. Using a similar technique, these investigators found that nonhypertrophied hearts from patients without anemia or left ventricular hypertrophy had only a 6% incidence of collaterals. In contrast, 28% of hearts hypertrophied secondary to valvular disease had intra-arterial collaterals. Fulton14 also used a postmortem angiographic technique to examine the quantity and size of collaterals in normal and hypertrophied hearts. These studies suggested that collaterals in hypertrophied hearts were larger in caliber than those observed in normal hearts. Fulton did not observe an increase in the number of collaterals in hypertrophied hearts. The functional significance of these vessels was not addressed by any of these postmortem studies.

Previous estimates of collateral function in vivo in patients with left ventricular hypertrophy were made by Goldstein et al.12 These investigators measured peripheral coronary pressure and retrograde flow from the cannulated right and left coronary arteries in patients with aortic valve disease after instituting cardio-pulmonary bypass. These investigators found retrograde flow to be low, averaging 2.4 and 1.7 ml/min from the left and right coronary arteries, respectively. Collateral resistance was high, averaging 48 and 64 mm Hg/ml/min for flow to the left and right coronary arteries, respectively. These measurements were compared with those in patients who had occlusive coronary artery disease but not with those in a group of patients without either ventricular hypertrophy or coronary artery disease. Recently, Scheel et al.15 examined coronary and collateral resistances using an isolated, blood-perfused beating heart preparation in dogs with left ventricular hypertrophy 4 weeks after banding the ascending aorta. With the retrograde flow technique, collateral resistances were not different from those in control animals.

Thus, Goldstein’s data in patients and Scheel’s data in dogs with left ventricular hypertrophy would suggest that collaterals are not functionally increased in this condition. These studies did not provide information regarding transmural perfusion in the ischemic region. Additionally, the retrograde flow technique provides only an index of collateral perfusion and has recently been shown to underestimate true collateral flow.25

**Practical implications of these observations.** There are several important implications of these observations. We have previously shown that dogs with renal hypertension and left ventricular hypertrophy have increased

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**TABLE 5**

Wall motion and reactive hyperemic responses

<table>
<thead>
<tr>
<th>PRVR</th>
<th>Diastolic wall thickness (cm)</th>
<th>Control % systolic wall thickening</th>
<th>Reduction in thickening (% of control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>3.9 ± 0.6</td>
<td>0.6 ± 0.1</td>
<td>60 ± 9</td>
</tr>
<tr>
<td>LVH</td>
<td>2.3 ± 0.4</td>
<td>1.2 ± 0.1</td>
<td>18 ± 4</td>
</tr>
</tbody>
</table>

PRVR = peak-to-resting velocity ratio of the reactive hyperemic response; LVH = left ventricular hypertrophy.

aComparison of wall motion and reactive hyperemic responses to coronary occlusion in patients with left ventricular hypertrophy and in control subjects.
bAfter onset of occlusion.

*p < .05 LVH vs controls.
infarct size (per unit risk zone size). Patients with left ventricular hypertrophy have an increased incidence of sudden death and heart failure after myocardial infarction, suggesting that these infarcts are larger. A potential explanation for these observations is that during the development of hypertrophy, the collateral circulation does not grow to compensate for the increased myocardial mass. If this were the case, collateral function might be diminished in the presence of left ventricular hypertrophy. Ischemic zone flow, when measured in our studies in vivo, was not different between the two groups of animals. However, microsphere measurements of flow provide information about the quantity of collateral flow reaching ischemic myocardium at one point in time. It is possible that during the several hours after coronary occlusion, subtle decreases in collateral flow may have substantially altered the quantity of myocardial necrosis that occurred. These decreases in collateral perfusion may not have been reflected by our measurements of collateral flow made shortly after coronary occlusion. In light of the present results, however, it would seem that the intrinsic capacity for collaterals to deliver blood to ischemic myocardium is not altered in dogs with renal hypertension and left ventricular hypertrophy. We therefore conclude that factors other than collateral perfusion play the predominant role in the increase in infarct size observed after coronary occlusion in animals with hypertension and left ventricular hypertrophy.

Recently, Marcus et al. have shown that the reactive hyperemic response is reduced in patients with left ventricular hypertrophy secondary to aortic stenosis. This abnormality was attributed to an impairment in coronary reserve related to some intrinsic abnormality of the coronary circulation in aortic stenosis. However, if collateral perfusion were increased in patients with left ventricular hypertrophy, the degree of regional myocardial ischemia might be substantially less during coronary occlusion, resulting in a diminished stimulus for reactive hyperemia. The fact that the changes in systolic wall thickening that occurred with coronary occlusion were equally severe in patients with left ventricular hypertrophy and control subjects suggests that equal degrees of ischemia occurred in the two groups. Thus the reduced reactive hyperemic response observed in patients with aortic stenosis cannot be attributed to a diminished ischemic stimulus but is likely caused by some intrinsic abnormality of the coronary circulation in patients with left ventricular hypertrophy secondary to aortic stenosis.

In the isolated heart studies, coronary vascular resistance in the normally perfused zone, assessed by pressure-flow relationships during adenosine vasodilation, was not increased in dogs with hypertension and left ventricular hypertrophy. These results provide indirect evidence that coronary vascular growth occurred during developing hypertrophy. This finding is in contrast with the results of Mueller et al., who found that minimal coronary vascular resistance in conscious dogs with renal hypertension and left ventricular hypertension was significantly elevated. They also found that minimal vascular resistance remained elevated after correction of renal arterial stenosis and hypertension. Several other workers have found that other preparation of left ventricular hypertrophy are associated with elevations of minimal vascular resistance. These studies were all performed in vivo. The contribution of extravascular compressive forces and neurohumoral influences to these elevations of minimal coronary resistance is unknown. Furthermore, except for the studies of Mueller et al., the preparations of ventricular hypertrophy were quite different than that used in the present study.

In the study of Scheel et al., minimal vascular resistance assessed by pressure-flow relationships in the isolated heart were significantly elevated 4 weeks after aortic banding. Again, the preparation of left ventricular hypertrophy used by these investigators differed significantly from that used in these studies. Furthermore, Scheel et al. imposed a short-term left ventricular pressure increase resulting in an abrupt elevation in end-diastolic pressure. Bishop and Melsen have shown that short-term afterloading of the right ventricle can produce myocardial fibrosis and necrosis. It is conceivable that the abrupt elevation of left ventricular afterload in the study of Scheel et al. was associated with a similar process contributing to the elevated minimal vascular resistance.

Hallback-Nordlander et al. used an isolated cardiac preparation perfused with Krebs-Henseleit buffer to examine coronary pressure-flow relationships during vasodilation in spontaneously hypertensive rats. In this study in vitro, minimal vascular resistance was found to be elevated. The preparation in spontaneously hypertensive rats is significantly different than that used in the present study. In particular, coronary vascular medial hypertrophy and vessel wall thickening has been shown to be an important feature seen in this preparation of hypertension and left ventricular hypertrophy. Vessel wall thickening does not seem to be present 6 weeks after the onset of hypertension in the Goldblatt canine preparation used in the present study.
Advantages and limitations of our experimental design

Animal studies. There are several advantages to the methods we used in the animal studies. The most direct experimental approach to determining coronary collateral resistance is to define the relationship between collateral flow and the pressure gradient across the collateral vessels (aortic pressure — peripheral coronary pressure). Because these relationships exhibit significant x intercepts, it is more accurate to estimate resistance by measuring coronary collateral flow at several perfusion pressures and to construct pressure-flow relationships. The isolated blood perfused heart preparation was selected for this purpose. With this preparation it is possible to vary aortic pressure over a wide range without altering left ventricular pressure or heart rate. This would be difficult using a preparation in vivo. In addition, collateral flow can be influenced by a variety of factors extraneous to the resistance of the collateral vasculature. These “extravascular forces” are in large part related to both systolic and diastolic ventricular pressure and coronary venous pressure, and to a lesser extent to heart rate. Differences in these factors between groups are minimized in the isolated heart preparation.

Our method also allowed us to use strict criteria to eliminate overlap flow from estimates of collateral flow. This is particularly important because failure to eliminate overlap flow can lead to serious overestimation of collateral flow. Recent work in our laboratory has shown that collateral resistance is also altered by the size of the collateral-dependent zone and that small risk zones receive more collateral flow per gram of myocardium than larger risk zones. To ensure that this variable did not influence our results, we demonstrated that risk zone sizes were equal between groups of animals by means of an autoradiographic technique.

The degree of left ventricular hypertrophy in our animal preparation was modest (approximately a 30% increase). However, this degree of left ventricular hypertrophy is similar to that encountered in patients with chronic hypertension. Furthermore, prior work from this laboratory has shown that this preparation of left ventricular hypertrophy is associated with several important abnormalities of the coronary circulation, including diminished vasodilator reserve in vivo, increased intercapillary distance, an increase in the infarct-risk region ratio after coronary occlusion, and a threefold increase in sudden death after coronary occlusion. We therefore believe that this preparation of left ventricular hypertrophy is particularly relevant to the coronary circulation in patients with hypertension. It is conceivable that more pronounced hypertrophy would have provided different results.

In this study, although we documented hypertension in the study group, we did not measure arterial pressure in the control group while the animals were conscious. Measurement of arterial pressure in conscious control animals has been performed in our laboratory in several previous studies and found to be in the range of 90 to 100 mm Hg. This value is significantly lower than that observed in our animals with renal hypertension and left ventricular hypertrophy. Furthermore, the left ventricular/body weight ratio observed in our control group is similar to that encountered in the control groups of our prior studies.

Patient studies. The development of a regional contraction abnormality after acute coronary occlusion in patients provides an indirect index of collateral function. Although subtle differences in collateral flow may not be detectable by analyzing the severity or time course of development of a regional contraction abnormality after coronary occlusion, major differences in the adequacy of collateral perfusion should be evident. Recent work by Tomoike et al. has shown that changes in regional contractility with coronary occlusion in the dog closely reflect the degree of collateral development after placement of ameroid constrictors. Dunn et al. have shown that a 20 sec coronary occlusion in the dog is associated with a 50% decrease in myocardial creatine phosphate concentration and a marked increase in tissue lactate concentration, indicating severe regional ischemia. Other factors that influence the development of a wall motion abnormality relate to myocardial oxygen consumption. Preliminary work in our laboratory suggests that large changes in oxygen consumption produced by atrial pacing or infusion of catecholamines do not alter the time course or severity of the regional contraction abnormality that develops after coronary occlusion in dogs. These considerations support the notion that the major determinant of the time course and severity of a systolic contraction abnormality is residual collateral perfusion.

Summary. The two studies presented in this work are complementary. The patients studied had severe left ventricular hypertrophy present for many years. However, our measurements of systolic thickening after coronary occlusion provide only an indirect index of collateral perfusion. In contrast, the Goldblatt preparation of hypertension had only modest left ventricular hypertrophy, which developed only 6 weeks before the study. Yet the methods used in our animal studies provide an extremely accurate measurement of collateral resistance while allowing control of the numerous

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extravascular factors that influence collateral perfusion. Because evidence of an enhanced native collateral circulation was not observed in our animal model of renal hypertension and left ventricular hypertrophy or in patients with left ventricular hypertrophy, our results strongly support the concept that left ventricular hypertrophy does not augment the functional capacity of the coronary collateral circulation.

We gratefully acknowledge the technical assistance of Steven M. Cooper and Shirley B. Thompson and the secretarial assistance of Mary E. McDermott.

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Circulation. 1985;71:1135-1145
doi: 10.1161/01.CIR.71.6.1135

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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