Coronary Pressure–Flow Relation in Left Ventricular Hypertrophy

Importance of Changes in Back Pressure Versus Changes in Minimum Resistance

Dirk J. Duncker, Jianyi Zhang, and Robert J. Bache

Perfusion abnormalities in the pressure-overloaded hypertrophied left ventricle could result from an increase in minimum coronary resistance or an increase in effective back pressure due to increased extravascular compressive forces. Since the pressure–flow relation of the maximally vasodilated coronary bed allows dissociation of minimum resistance (inverse slope [1/αPF]) and back pressure (pressure at zero flow [Pzero]), the present study was undertaken to examine the coronary pressure–flow relation in left ventricular hypertrophy (LVH). Ascending aortic banding in eight dogs at 6–8 weeks of age (LVH group) increased the left ventricular to body weight ratio to 8.7±0.6 g/kg as compared with 4.8±0.2 g/kg in nine normal dogs (p<0.05). Maximum coronary vasodilation was produced by infusion of adenosine (1 mg/kg per minute i.v.). The slope of the coronary pressure–flow relation (αPF) was 5.8±0.5 10⁻² (ml/min per gram)/mm Hg in the LVH group and 9.3±0.6 10⁻² (ml/min per gram)/mm Hg in the normal group (p<0.05). αPF was significantly correlated with the left ventricular to body weight ratio but not with coronary pressure, suggesting that the degree of hypertrophy and not exposure to high coronary pressure was responsible for the observed decrease in αPF. Pzero was 24.1±2.6 mm Hg in the LVH group and 11.7±1.2 mm Hg in the normal group (p<0.05). To determine the contribution of the higher left ventricular late-diastolic pressure in the LVH group (13.9±2.2 mm Hg) compared with that in the normal group (6.1±0.7 mm Hg, p<0.01), we infused blood into seven normal dogs until left ventricular diastolic pressure (16.3±1.2 mm Hg) was similar to that in the LVH group. With the higher left ventricular diastolic pressure, Pzero increased (22.6±1.8 mm Hg) to levels not significantly different from those in the LVH dogs, suggesting that increased extravascular compressive forces are primarily due to elevated left ventricular intracavitary pressure. Stepwise regression analysis revealed that both left ventricular late-diastolic pressure and the degree of hypertrophy exerts significant independent effects on Pzero. These findings demonstrate both an increase in minimum coronary resistance and an increase in effective back pressure in the pressure-overloaded severely hypertrophied left ventricle. The increase in minimum coronary vascular resistance is related to the degree of hypertrophy, whereas the increase in effective back pressure results principally from the elevated left ventricular diastolic pressure. (Circulation Research 1993;72:579–587)

Key Words • coronary vasodilator reserve • coronary vasodilation • adenosine • supravalvular aortic stenosis

Left ventricular hypertrophy (LVH) secondary to chronic pressure overload is associated with increased susceptibility to myocardial hypoperfusion and ischemia during periods of increased cardiac work.1–3 Increased vulnerability to abnormal perfusion in the hypertrophied heart has been ascribed to 1) vascular rarefaction, which occurs as the myocardium hypertrophies but the coronary vessels fail to grow, 2) hypertensive vascular changes due to exposure of the coronary vessels to high perfusion pressure, or 3) increased extravascular forces acting on the intramural coronary vessels.4

Previous reports have described abnormally elevated values for minimum coronary vascular resistance per unit myocardial mass in the pressure-overloaded hypertrophied left ventricle. However, these values were derived from single measurements of coronary pressure divided by maximum coronary blood flow. Such calculated values do not distinguish between a true increase in minimum resistance (defined by the inverse slope of the pressure–flow relation during maximum vasodilation [1/αPF]) and an increase in the effective back pressure, which opposes coronary flow (zero-flow pressure [Pzero]).5,6 A decrease in the cross-sectional area of the coronary bed would be expected to cause a decrease of the slope of the pressure–flow line (αPF), whereas

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increased extravascular forces acting on the intramural coronary vasculature can result in elevations of $P_{aP}\text{F}$ without an effect on $aP\text{F}$.

This study was designed to examine the effect of LVH on $aP\text{F}$ and $P_{aP}\text{F}$ in the maximally vasodilated coronary circulation. Coronary pressure-flow studies were performed in dogs with LVH secondary to chronic pressure overload produced by aortic banding and in normal control dogs. Since an increase in $P_{aP}\text{F}$ could be due to the elevated diastolic intracavitary pressure that occurs in the hypertrophied ventricle, we also examined the effect of increasing left ventricular diastolic pressure in normal animals to the level observed in dogs with LVH.

Materials and Methods

Studies were performed in 19 mongrel dogs, eight animals with LVH and 11 normal control dogs. Nine normal dogs served as controls with a normal left ventricular diastolic pressure, whereas in seven normal dogs (five of which were also studied with a normal preload), data were obtained after left ventricular diastolic pressure had been elevated to levels comparable to those in the dogs with LVH. All experiments were performed in accordance with the guiding principles for the care and use of animals as approved by the Council of the American Physiological Society.

Production of Supravalvular Aortic Stenosis

At 6–9 weeks of age, seven dogs were sedated with fentanyl (0.4 mg i.m.), anesthetized with sodium thiopental (20–25 mg/kg i.v.), intubated, and ventilated with oxygen-enriched room air. A thoracotomy was performed through the third intercostal space. The ascending aorta was dissected from the surrounding tissue approximately 1.5 cm above the aortic valve and encircled with a polyethylene band 2.5 mm in width. While measuring left ventricular and distal aortic pressure simultaneously, the band was tightened until a 20–25 mm Hg peak systolic pressure gradient across the aortic constriction was achieved. The chest was then closed, air was evacuated from the thorax, and the animals were allowed to recover. Thereafter, the animals were maintained in enclosed runs on a standard laboratory diet until 10–14 months of age, at which time they were returned to the laboratory for study.

Surgical Preparation

After an overnight fast, the animals were weighed, sedated with fentanyl (0.4 mg i.m.), anesthetized with $\alpha$-chloralose (120 mg/kg i.v., followed by a continuous intravenous infusion of 10 mg/kg per hour), intubated, and ventilated with a mixture of oxygen (20%) and room air (80%). Respiratory rate and tidal volume were adjusted to keep arterial blood gases within physiological limits. A 7F NIH catheter filled with heparinized saline was introduced via the femoral veins and positioned in the inferior vena cava for fluid and drug administration. A similar catheter was introduced via the right femoral artery and advanced into the ascending aorta for measurement of central aortic blood pressure and for withdrawal of blood samples. A left thoracotomy was performed through the fifth intercostal space, and the heart was suspended in a pericardial cradle. Polyvinyl chloride 7F catheters filled with heparinized saline were inserted into the left ventricular cavity via the apical dimple and the left atrium for measurement of left ventricular blood pressure and injection of radiolabeled microspheres, respectively. Approximately 1.5 cm of the proximal left circumflex coronary artery was dissected free, and a Doppler flow probe (Craig Hartley, Houston, Tex.) and a variable hydraulic occluder were positioned on the artery. The occluder was positioned at least 5 mm distal to the flow probe to prevent inflation of the occluder from altering the diameter of the coronary artery within the flow probe. The hydraulic occluder was connected to a micrometer-driven syringe to secure controlled partial inflation during the experiments. Finally, a silastic catheter (0.3 mm i.d.) was inserted into the artery just distal to the occluder for measurement of coronary perfusion pressure.

Myocardial Blood Flow

To allow comparisons between normal and hypertrophied myocardium, data obtained with the Doppler flowmeter were normalized per gram myocardial tissue. For this purpose, microspheres that were 15 $\mu$m in diameter and labeled with either $^{125}$I, $^{14}$Ce, $^{35}$Cr, $^{85}$Sr, $^{90}$Nb, or $^{99}$Sc (3M Co., St. Paul, Minn.) were injected into the left atrium at the end of each experimental protocol. Before injection, the microspheres were agitated for 15 minutes in an ultrasonic bath. An arterial blood reference sample was withdrawn at a constant rate of 15 ml/min starting 10 seconds before the injection of microspheres and continuing for 90 seconds.

At the end of the experiment, the area perfused by the left circumflex coronary artery was identified by injection of 5 ml Evans blue dye into the coronary artery catheter. Immediately thereafter, the hearts were arrested with potassium chloride, excised, weighed, and fixed in 10% buffered formalin. The atria, aorta, right ventricular free wall, and large epicardial blood vessels were dissected from the left ventricle and discarded. The blue-stained region of the left ventricle perfused by the left circumflex coronary artery was excised, weighed, and placed in vials for counting. Myocardial and blood reference samples were counted in a gamma spectrometer (model 5912, Packard Instrument Co., Inc., Downers Grove, Ill.). The counts per minute and the corresponding sample weights were entered into a digital computer programmed to correct for background activity and to calculate the corrected counts per minute per gram myocardial tissue. Blood flow to the myocardial specimen ($Q_m$, in milliliters per minute per gram myocardium) was computed as

$$Q_m = Q_t \cdot C_m / C_t$$

where $Q_t$ is rate of withdrawal of reference blood sample (in milliliters per minute), $C_m$ is counts per minute per gram of the myocardial specimen, and $C_t$ is counts per minute of the reference blood sample. The mean coronary velocity signal, measured with the coronary artery Doppler probe, was calibrated with the simultaneous microsphere measurement.

Experimental Protocol

Recordings were made on an eight-channel direct-writing recorder at a chart speed of 50 mm/sec. Left ventricular, aortic, and coronary arterial pressures were...
measured with Statham P23XL pressure transducers. Left ventricular pressure, mean and phasic aortic and coronary pressures, and mean and phasic coronary blood flow were recorded continuously. Left ventricular pressure was recorded at both normal and high gain for measurement of left ventricular late-diastolic pressure.

After a 30-minute stabilization period, baseline measurements were made of left ventricular, aortic, and coronary pressures and coronary blood flow velocity. Subsequently, an intravenous infusion of adenosine (1 mg/kg per minute) was started and continued throughout the remainder of the protocol. This dose of adenosine produced maximum coronary vasodilatation, as evidenced by the absence of reactive hyperemia after a 15-second coronary artery occlusion. Adenosine was dissolved in warm saline so that the desired dosage was infused at a rate of 1.3 ml/min. Ten minutes later, when systemic and coronary hemodynamics had reached a new steady state, recordings were repeated. Then the hydraulically occluder was partially inflated to provide 15–30 separate pressure–flow measurements. The level of inflation was applied in random order and varied from no inflation to total coronary artery occlusion. At each level of inflation, 15 seconds was allowed for stabilization before measurements were made, after which the occluder was completely deflated. A minimum of 2 minutes was allowed before the occluder was again inflated. Continuous monitoring of systemic and coronary hemodynamics ensured the stability of the preparation during the coronary pressure–flow measurements.

To study the influence of an elevated left ventricular diastolic pressure on the pressure–flow relation, an intravenous infusion of blood was administered to seven normal dogs until levels of late-diastolic pressure (measured immediately before atrial contraction) were comparable to those observed in the dogs with LVH. Subsequently, coronary pressure–flow measurements were made as described above.

Data Analysis

Hemodynamic data were measured from the strip-chart recordings. Left ventricular late-diastolic pressure was measured just before the A wave. Pressure–flow relations were generated by plotting mean coronary pressure (millimeters of mercury) and blood flow normalized per gram myocardium (milliliters per minute per gram); regressions were determined by first-order curve fitting. The slope (αPF [milliliters per minute per millimeters of mercury]) and the x intercept (Pf=0 [millimeters of mercury]) of the regression line were used to describe the pressure–flow relation. Stepwise regression analysis was performed to assess the influence of hemodynamic variables and the degree of hypertrophy on αPF and Pf=0.

All data are presented as mean±SEM. Comparisons of data between the three groups was performed with one-way analysis of variance testing. When a significant effect was observed, group comparisons were made using Scheffe’s test. Statistical significance was accepted at p<0.05 (two-tailed test).

Results

Anatomic Data

Left ventricular weight of the animals with supravalvular aortic stenosis was significantly greater than nor-

<table>
<thead>
<tr>
<th>TABLE 1. Anatomic Characteristics of Control Dogs With Normal and Elevated Preload and Dogs With Left Ventricular Hypertrophy Secondary to Supravalvular Aortic Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control dogs</strong></td>
</tr>
<tr>
<td><strong>n=9</strong></td>
</tr>
<tr>
<td>LVW (g)</td>
</tr>
<tr>
<td>BW (kg)</td>
</tr>
<tr>
<td>LVW/BW (g/kg)</td>
</tr>
</tbody>
</table>

LVH, left ventricular hypertrophy; LVW, left ventricular weight; BW, body weight. Values are mean±SEM.

*p<0.05 vs. control dogs with normal preload.
†p<0.05 vs. control dogs with elevated preload.

mal despite the lower body weights (Table 1). The left ventricular to body weight ratio was 8.7±0.6 g/kg in the eight dogs with aortic banding (LVH group) versus 4.8±0.2 g/kg in the 11 control dogs (p<0.05).

Systemic Hemodynamics

In the normal animals under basal conditions, heart rate and mean arterial pressure were 139±4 beats per minute and 88±5 mm Hg, respectively. These values were not significantly different from those in LVH dogs or in normal dogs with elevated preload (Table 2). Left ventricular systolic (175±11 mm Hg) and late-diastolic pressure were higher in LVH than in control dogs (p<0.05).

<table>
<thead>
<tr>
<th>TABLE 2. Systemic Hemodynamics Under Basal Conditions and During Adenosine Infusion in Control Dogs With Normal and Elevated Preload and in Dogs With Left Ventricular Hypertrophy Secondary to Supravalvular Aortic Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control dogs</strong></td>
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<tr>
<td><strong>n=9</strong></td>
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<tr>
<td>HR (bpm)</td>
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<tr>
<td>Basal</td>
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<tr>
<td>Adenosine</td>
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<tr>
<td>LVSP (mm Hg)</td>
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<tr>
<td>Basal</td>
</tr>
<tr>
<td>Adenosine</td>
</tr>
<tr>
<td>AoSP (mm Hg)</td>
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<tr>
<td>Basal</td>
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<tr>
<td>Adenosine</td>
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<tr>
<td>AoDP (mm Hg)</td>
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<td>Basal</td>
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<td>Adenosine</td>
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<td>AoP (mm Hg)</td>
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<td>Basal</td>
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<tr>
<td>Adenosine</td>
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<tr>
<td>LVLDP (mm Hg)</td>
</tr>
<tr>
<td>Basal</td>
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<tr>
<td>Adenosine</td>
</tr>
</tbody>
</table>

LVH, left ventricular hypertrophy; HR, heart rate; bpm, beats per minute; LVSP, left ventricular systolic pressure; AoSP, aortic systolic pressure; AoDP, aortic diastolic pressure; AoP, mean aortic pressure; LVLDP, left ventricular late-diastolic pressure. Values are mean±SEM.

*p<0.05 vs. corresponding basal value.
†p<0.05 vs. control dogs with normal preload.
‡p<0.05 vs. control dogs with elevated preload.
(12.0±1.8 mm Hg) pressures were higher in the LVH hearts compared with the normal hearts. In response to blood transfusions in seven normal animals, left ventricular late-diastolic pressure increased to levels comparable to those in the LVH group (14.8±2.3 mm Hg). Regression analysis revealed that the left ventricular to body weight ratio was significantly correlated with the left ventricular pressure gradient (r=0.87, p<0.001). During infusion of adenosine, mean arterial pressure decreased significantly in both the control group with normal preload and the LVH group (each p<0.05). Left ventricular systolic and late-diastolic pressures were unchanged in all three groups.

**Coronary Hemodynamics**

As shown in Table 3, under basal conditions there were no statistically significant differences between myocardial blood flows in the LVH and normal hearts. In the normal dogs in which preload was acutely elevated, myocardial blood flow tended to be higher than in control dogs with a normal preload, but this did not reach statistical significance. During adenosine infusion, coronary blood flows were not significantly different between groups, despite the higher coronary pressure in the LVH dogs and the normal dogs with elevated preload (Table 3).

Figure 1 depicts pressure–flow points from all dogs in the three experimental groups. αPF during maximal vasodilation in the LVH group was significantly lower than in the normal animals with either normal or elevated preload (Figure 1, Table 3). Stepwise regression analysis of αPF against coronary pressure and left ventricular to body weight ratio revealed a significant correlation between αPF and the left ventricular to body weight ratio (Figure 2) but not between the αPF and coronary pressure. In the LVH group, Pₚ₀ was considerably higher than in control dogs with a normal preload. In the normal dogs with an elevated preload, Pₚ₀ increased to levels that were not significantly different from those found in LVH dogs. Stepwise regres-

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**Table 3. Coronary Hemodynamics Under Basal Conditions and During Adenosine Infusion and Pressure–Flow Relations Reported for Control Dogs With Normal and Elevated Preload and Dogs With Left Ventricular Hypertrophy Secondary to Supravalvular Aortic Stenosis**

<table>
<thead>
<tr>
<th>Coronary hemodynamics</th>
<th>Control dogs (n=9)</th>
<th>Elevated preload (n=7)</th>
<th>LVH dogs (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP (mm Hg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Basal</td>
<td>81±6</td>
<td>92±5</td>
<td>101±7</td>
</tr>
<tr>
<td>Adenosine</td>
<td>54±4*</td>
<td>81±5†</td>
<td>82±9*†</td>
</tr>
<tr>
<td>CBF (ml/min per gram)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>1.16±0.12</td>
<td>1.71±0.19</td>
<td>1.46±0.15</td>
</tr>
<tr>
<td>Adenosine</td>
<td>3.96±0.35*</td>
<td>5.13±0.72*</td>
<td>3.45±0.54*</td>
</tr>
<tr>
<td>Coronary pressure–flow relation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope [(10⁻² ml/min per gram)/mm Hg]</td>
<td>9.3±0.6</td>
<td>9.0±0.8</td>
<td>5.8±0.6†</td>
</tr>
<tr>
<td>Pₚ₀ experimental (mm Hg)</td>
<td>11.7±1.2</td>
<td>21.3±2.3†</td>
<td>24.1±2.6†</td>
</tr>
<tr>
<td>Pₚ₀ regression (mm Hg)</td>
<td>12.3±0.8</td>
<td>22.6±1.8†</td>
<td>26.5±2.6†</td>
</tr>
</tbody>
</table>

LVH, left ventricular hypertrophy; CP, coronary pressure; CBF, coronary blood flow; Pₚ₀, experimental coronary pressure at zero flow measured during total coronary artery occlusion; Pₚ₀, regression coronary perfusion pressure at zero flow obtained by linear regression. Values are mean±SEM.

* p<0.05 vs. corresponding basal value.
† p<0.05 vs. control dogs with normal preload.
‡ p<0.05 vs. control dogs with elevated preload.
sion analysis of Pf against left ventricular late-diastolic and systolic pressure, heart rate, and left ventricular to body weight ratio revealed a significant correlation between left ventricular late-diastolic pressure and Pf (Figure 3) but not between Pf and the other variables. Furthermore, this relation was significantly shifted upward in the LVH group as compared with the normal group (p<0.05) (Figure 3).

Although the experimentally determined Pf tended to be slightly lower than Pf determined by linear regression analysis, this difference was not significant, indicating good linearity of the pressure–flow relation with only mild curvilinearity in the lower part of the curve (Table 3). Furthermore, this trend was not different between groups.

**Discussion**

The present study describes the coronary pressure–flow relation during maximum vasodilation in the chronically pressure-overeloaded hypertrophied left ventricle studied in vivo. The most important findings were that aPF was decreased in the LVH hearts whereas Pf was increased. The implications of these findings will be discussed in detail.

**Previous Studies of Minimum Coronary Vascular Resistance in LVH: Single Pressure–Flow Measurements**

Table 4 lists currently available studies in canine models of pressure-overload hypertrophy in which minimum coronary vascular resistance, derived from single measurements of pressure and flow during pharmacological coronary vasodilatation, have been reported. Most of these studies reported an increase in computed minimum resistance. In dogs with supravalvular aortic stenosis and LVH similar in magnitude to those in the present study, Holtz et al reported a 50–60% increase in computed minimum vascular resistance. Similarly, in adult dogs in which 6 weeks of supravalvular aortic stenosis had resulted in a modest degree of LVH (left ventricular to body weight ratio, 5.1 g/kg), O'Keefe et al reported a 60% increase in computed minimum coronary resistance. Minimum coronary vascular resistances were not different whether aortic banding was performed in young or adult dogs, suggesting little effect of age at the onset of pressure overload on the response of the coronary vasculature. To dissociate the effects of hypertension from coronary vascular abnormalities induced by hypertensive perfusion, Alyono et al studied the effects of hypertension produced by valvular aortic stenosis. The increase in computed minimum coronary vascular resistance was similar in valvular and supravalvular stenosis, suggesting that hypertension per se, and not increased coronary perfusion pressure, was responsible for the higher computed minimum resistance in the LVH hearts.

In adult dogs with LVH secondary to 6 weeks of renovascular hypertension, Mueller et al, Marcus et al, and Tomanek et al reported increased computed minimum coronary vascular resistance during maximal vasodilatation with intravenous adenosine (Table 4). After 6–7 months of renovascular hypertension, Marcus et al reported that minimum coronary resistance remained elevated, whereas Tomanek et al observed normalization of minimum coronary resistance. The latter authors suggested that this finding corresponded to growth of coronary vasculature within the hypertrophied myocardium with prolonged pressure overload.

**Previous Studies of Minimum Coronary Vascular Resistance in LVH: Pressure–Flow Relation**

Examining the pressure–flow relation over a wide range of perfusion pressures represents a fundamentally different approach for characterizing the resistive properties of the coronary vascular bed. During maximal vasodilatation, the pressure–flow relation is linear throughout most of its length, often with slight convexity toward the flow axis at very low perfusion pressures. aPF represents maximum conductance (inverse of minimum resistance), whereas Pf represents the effective back pressure opposing antegrade coronary blood flow. In the reports in Table 4, minimum coronary vascular resistance was computed from single measurements of coronary pressure divided by maximum coronary blood flow.
flow. This computation assumes a linear pressure–flow relation with a $P_{e-o}$ of 0 mm Hg. Only O'Keefe et al.\(^8\) attempted to correct for back pressure by computing coronary driving pressure as perfusion pressure minus left ventricular end-diastolic pressure. Importantly, impairment of maximum flow rates in LVH hearts ascribed to alterations in minimum resistance cannot be distinguished from changes due to an increase in $P_{e-o}$. Examining the entire coronary pressure–flow relation differentiates between true changes in resistance and alterations in the back pressure opposing flow. This allows better understanding of the behavior of the vasculature in myocardial hypertrophy, since failure of adequate growth of the coronary vasculature during hypertrophy or impaired vasodilator capacity would cause a decrease of $aPF$, whereas increased extravascular compressive forces would result in elevation of $P_{e-o}$.\(^7\)

Three previous studies examined coronary pressure–flow relations during maximal vasodilation with adenosine in canine models of pressure-overload hypertrophy (Table 5). Scheel et al.\(^9\) studied the late-diastolic pressure–flow relation using blood-perfused empty beating hearts of dogs with moderate LVH produced by 4 weeks of supravalvular aortic stenosis. They observed both a decrease in $aPF$ and a slight but significant increase in $P_{e-o}$, correlating well with the present findings. In contrast, Harrison et al.\(^20\) also using empty beating blood-perfused hearts from dogs with mild hypertrophy

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Hypertrophy stimulus</th>
<th>LVW/BW (g/kg)</th>
<th>Experimental conditions</th>
<th>Slope [(ml/min per gram)/mm Hg]</th>
<th>$P_{e-o}$ (mm Hg)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td>LVH</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td>LVH</td>
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<tr>
<td>Aortic stenosis</td>
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<td></td>
<td></td>
<td>12.4</td>
<td>7.7*</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>17.2</td>
<td>19.1*</td>
</tr>
<tr>
<td>Scheel et al.(^9)</td>
<td>SVAS Adult</td>
<td>4 Weeks</td>
<td>Diastolic measurements, empty beating hearts</td>
<td>8.7</td>
<td>5.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.7</td>
<td>24.1*</td>
</tr>
<tr>
<td>Duncker et al. (present study)</td>
<td>SVAS Puppy</td>
<td>10–14 Months</td>
<td>Transmural measurements, in vivo hearts</td>
<td>6.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Renovascular hypertention</td>
<td></td>
<td></td>
<td></td>
<td>17.7</td>
<td>18.2</td>
</tr>
<tr>
<td>Harrison et al.(^20)</td>
<td>1KIC Adult</td>
<td>6–8 Weeks</td>
<td>Transmural measurements, empty beating hearts</td>
<td>13.5</td>
<td>8.5*</td>
</tr>
<tr>
<td>Jeremy et al.(^21)</td>
<td>1KIC</td>
<td>Adult 6–12 Weeks</td>
<td>17.8</td>
<td>15.2</td>
<td></td>
</tr>
</tbody>
</table>

LVW/BW, left ventricular to body weight ratio; $P_{e-o}$, coronary pressure at zero flow; SVAS, supravalvular aortic stenosis; 1KIC, one-kidney, one-clip model.

\(^*\)p<0.05 vs. normal dogs.
secondary to renovascular hypertension, found no differences in either the slope or \( P_{c,o} \) of the coronary pressure–flow relation when flow was averaged over the cardiac cycle by using microspheres. Jeremy et al\(^1\) studied the late-diastolic pressure–flow relation in extracorporeally perfused hearts of dogs with LVH produced by renovascular hypertension. \( \alpha PF \) was lower in LVH than in normal hearts, but \( P_{c,o} \) was not altered. The disparities between these studies are likely related to methodological differences.

The late-diastolic coronary pressure–flow relations reported by Scheel et al\(^9\) and Jeremy et al\(^\)\(^1\) are susceptible to capacitance effects, since flowmeter measurements do not take into account capacitive discharge of blood from the distal arterial vasculature during diastole. Capacitance effects were minimized by Scheel et al\(^9\) by using a constant coronary perfusion pressure and empty left ventricles vented to atmospheric pressure. Jeremy et al\(^\)\(^1\) studied in situ hearts with supravalvular aortic stenosis, in which the capacitive discharge may be amplified by the increased coronary arterial pulse pressure. Since the capacitance effect leads to underestimation of actual late-diastolic flow in the microcirculation, the decreased \( \alpha PF \) in the LVH hearts could have been due to greater capacitive discharge from the epicardial vessels during diastole. Full cycle measurements as used by Harrison et al\(^\)\(^2\) average pressure and flow over the cardiac cycle and consequently are not influenced by capacitance effects. The failure of Harrison et al to find a difference in \( P_{c,o} \) between normal and LVH hearts might be related to venting of the left ventricle to atmospheric pressure, which eliminates differences resulting from the increased left ventricular intracavitary pressure. The effect of venting seems to be mediated primarily by eliminating differences in diastolic pressure between groups, since Van Winkle et al\(^\)\(^3\) reported that venting of normal left ventricles had no effect on systolic impediment to blood flow in the maximally dilated coronary circulation of isolated hearts. In the vented ventricle, systolic stresses are minimal, but systolic strains, which can impede systolic myocardial perfusion, are increased.\(^9\) Scheel et al\(^9\) also vented the left ventricle, but they minimized the influence of systolic strains on their measurements by recording late-diastolic flow measurements at constant perfusion pressure. Venting the left ventricle to atmospheric pressure excluded increased diastolic intracavitary pressure as a cause for the increase in \( P_{c,o} \) in LVH hearts.

**Mechanism of Increased Coronary Back Pressure in LVH**

In the present study we observed an increase in \( P_{c,o} \) in LVH dogs, which is likely the result of greater extravascular compressive forces in the hypertrophied hearts. Extravascular compressive forces can be increased because of altered hemodynamic conditions, such as an elevated preload, or altered material properties of the hypertrophied myocardium. Alternatively, coronary collateral blood flow could be responsible for the observed elevations of coronary \( P_{c,o} \).

**Left ventricular diastolic pressure.** Pressure-overload LVH is associated with increased left ventricular diastolic pressure.\(^1\)\(^\)\(^0\)\(^\)\(^\)\(^\)\(^\)\(^\) Ellis and Klocke\(^7\) observed in normal dogs that an increase in left atrial pressure from 6 to 20 mm Hg caused an elevation of \( P_{c,o} \) from 12 to 19 mm Hg with no effect on \( \alpha PF \). In the present study, increasing left ventricular late-diastolic pressure in normal hearts to values equal to those in LVH hearts increased \( P_{c,o} \) were not significantly different from those in LVH hearts. The positive correlation between preload and \( P_{c,o} \) (Figure 3) suggests that the increases in back pressure were caused primarily by elevated diastolic ventricular pressures. However, the relation between left ventricular late-diastolic pressure and \( P_{c,o} \) was shifted upward in the LVH animals (Figure 3). The experiments of Scheel et al\(^9\) in empty ventricles vented to atmospheric pressures also suggest that in supravalvular aortic stenosis extravascular compressive forces are increased independent of hemodynamic factors.

**Myocardial material properties.** Severe pressure-overload hypertrophy is associated with decreased intrinsic compliance of the myocardium.\(^4\) Apstein et al\(^1\) reported that ischemia-induced decreases of myocardial compliance are associated with parallel increases in coronary vascular resistance computed from single measurements of coronary perfusion pressure and blood flow. It is unclear from their report whether the impairment of maximum flow rates secondary to decreased myocardial compliance is the result of a decreased \( \alpha PF \) or increased \( P_{c,o} \). However, it is likely that abnormally increased compliance would result in increased extravascular compression of the intramural coronary vessels. Such extravascular effects are generally expressed as an increase in \( P_{c,o} \). Thus, it is possible that \( P_{c,o} \) in the LVH hearts that was greater than predicted from the increased filling pressure (Figure 3) could be ascribed to increased extravascular forces secondary to abnormal material properties of the hypertrophied myocardium.

**Coronary collateral blood flow.** The lower part of the coronary pressure–flow relation can be influenced by collateral blood flow. \( P_{c,o} \) values of 8.1, 12.8, and 15.8 mm Hg were reported in normal dog hearts when perfusion pressures in the adjacent coronary vascular beds were 0, 80, and 100 mm Hg, respectively.\(^26\) In our experiments, mean arterial pressures during adenosine infusion were 54±4 and 81±8 mm Hg in the control animals with normal and elevated preload, respectively, and 82±9 mm Hg in the LVH animals. The increase in \( P_{c,o} \) of the pressure–flow relation of the animals with aortic stenosis and the control animals with elevated preload may thus have been overestimated because of a higher collateral driving pressure. Harrison et al\(^\)\(^2\) showed that the collateral pressure–flow relation in LVH hearts per gram myocardium is identical to that of normal hearts. Therefore, we can predict, based on the observations by Messina et al,\(^\)\(^2\)\(^6\) that the measured \( P_{c,o} \) would have been 3–5 mm Hg higher in the LVH group and control group with an elevated preload compared with the control group with a normal preload. However, we observed increments in \( P_{c,o} \) of 10–15 mm Hg that cannot be explained by differences in collateral flow. More importantly, the differences of the pressure–flow relations in these three groups occurred at all levels of perfusion pressure, whereas collateral flow affects only the lower part of the pressure–flow relation.\(^2\)
Mechanism of Increased Minimum Coronary Resistance in LVH

In the present study, aPF was decreased in the hypertrophied left ventricle, implying an increase in minimum coronary vascular resistance. This increase could result from vascular rarefaction as the coronary vessels fail to grow in proportion to the degree of hypertrophy. Normal arteriolar densities have been reported in hypertrophied myocardium of renovascular hypertensive rats,17 dogs,18 and swine subjected to aortic banding.28 However, the degree of hypertrophy in each of these studies was considerably less (left ventricular to body weight ratios of 50%,27 46%,17 and 45%28) than in the present study (80%). In view of the significant correlation between aPF and the left ventricular to body weight ratio (Figure 2), which suggests that the degree of hypertrophy exerts an important influence on the flow capacity of the coronary bed, it is possible that the greater degree of hypertrophy in the present study could be associated with abnormalities of coronary arteriolar density. Perfusion abnormalities could also occur from chronic exposure of the coronary vasculature to high perfusion pressures, independent of the degree of hypertrophy.29,30 Vascular medial hypertrophy has been described in coronary arterioles of hypertensive rats,27,31–33 whereas normal vessel wall to lumen ratios were observed in hypertensive dogs.16,17 Furthermore, an increase in wall to lumen ratio does not necessarily imply narrowing of the lumen.16,34 In the present study, we observed a significant correlation between aPF and the degree of hypertrophy (Figure 2) but not between the aPF and coronary pressure, suggesting that hypertrophy and not exposure to high perfusion pressures was responsible for the decreased aPF. This conclusion is supported by the study of Alyono et al.,10 in which perfusion abnormalities were observed despite normal coronary pressures.

Conclusions

Several previous reports have ascribed perfusion abnormalities in the pressure-overloaded hypertrophied left ventricle to increased minimum coronary vascular resistance. The present study demonstrates that impairment of blood flow rates during maximum coronary vasodilation in pressure-overloaded hypertrophied left ventricles can result from elevated effective back pressure opposing flow as well as increased minimum vascular resistance. The increase in back pressure is due to the elevated left ventricular diastolic pressure, as well as to altered material properties of the hypertrophied myocardium. The decrease of aPF was related to the degree of hypertrophy, suggesting that hypertrophy and not hypertensive vascular changes are responsible for the increase in minimum coronary vascular resistance in the pressure-overloaded hypertrophied left ventricle.

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Coronary pressure-flow relation in left ventricular hypertrophy. Importance of changes in back pressure versus changes in minimum resistance.

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