**Coronary Blood Flow After the Regression of Pressure-Overload Left Ventricular Hypertrophy**

Kazuaki Ishihara, Michael R. Zile, Masayoshi Nagatsu, Kiyoharu Nakano, Masaaki Tomita, Shigeo Kanazawa, Linda Clamp, Gilberto DeFreyte, and Blase A. Carabello

Abnormal coronary blood flow (CBF) in long-standing left ventricular (LV) pressure-overload hypertrophy has been associated with ischemia and LV dysfunction. Thus, goals of therapy in pressure overload are not only the relief of the overload itself but also regression in hypertrophy and subsequent improvement in CBF. However, little is known about CBF in humans or in large mammals after the relief of pressure overload, when the hypertrophy has regressed. This study was performed to test the hypothesis that, even 6 months after the relief of pressure overload in the dog, CBF would still be abnormal. Three groups of dogs were studied: 1) normal control dogs (NL group), 2) dogs with LV pressure-overload hypertrophy (LVH group), and 3) dogs that had developed LV pressure-overload hypertrophy but in whom the pressure overload was relieved 6 months before the final study (LVH Reg group). CBF was studied in conscious dogs by use of the radiolabeled microsphere technique at rest, during rapid atrial pacing, and during maximum coronary vasodilation produced by adenosine infusion. The ratio of LV weight (g) to body weight (kg) (LVBW) was 4.2±0.3 in the NL group, 7.1±0.6 in the LVH group, and 7.7±0.5 in the LVH Reg group before pressure-overload relief (p=NS, LVH versus LVH Reg). Six months after removal of the pressure overload, the LVBW in the LVH Reg group had fallen to 5.5±0.3 (p<0.05), but this LVBW was still greater than that in the NL group (p<0.05). During rapid atrial pacing, endocardial and epicardial CBF rose significantly in NL dogs. However, during rapid atrial pacing, endocardial CBF fell from 1.18±0.22 to 0.7±0.20 ml/min per gram in the LVH group (p<0.05) and did not rise in the LVH Reg group. During adenosine infusion, endocardial blood flow increased in NL dogs from 1.63±0.13 to 4.0±0.3 ml/min per gram and increased to a similar level in the LVH Reg group. Although CBF increased during adenosine infusion in the LVH group, the increase was less than that in the NL or LVH Reg group (p<0.05). Minimum coronary vascular resistance was similar in NL dogs (14±2 units) and LVH Reg dogs (18±3 units, p=NS) but was significantly elevated (32±10 units) in LVH dogs (p<0.05). We conclude that after significant but incomplete regression of pressure-overload hypertrophy, maximum CBF and minimum coronary vascular resistance return to normal. However, during rapid atrial pacing, significant abnormalities in CBF still exist. (Circulation Research 1992;71:1472-1481)

**KEY WORDS** • coronary circulation • ventricular hypertrophy • pressure overload

Chronic left ventricular pressure overload results in the development of left ventricular hypertrophy, which is initially considered adaptive because increased muscle mass normalizes wall stress (afterload) at the myofibrillar level, thereby helping to maintain pump function. However, if the pressure overload is long-standing and severe, hypertrophy becomes associated with unwanted sequelae, including congestive heart failure and stress-induced ischemia. With the occurrence of these negative sequelae, hypertrophy is generally considered pathological in nature instead of adaptive. A manifestation of the pathological nature of the hypertrophy is the development of abnormal coronary blood flow. Abnormalities of coronary blood flow in pressure-overload hypertrophy are most marked during stress and most severely affect the endocardium. These abnormalities have been implicated both in the angina and in the stress-induced contractile dysfunction that may occur in this pathological condition.

Ideally, therapy for pressure overload should not only remove the pressure overload itself but should also allow for the regression of the hypertrophy and its pathological manifestations. Although the abnormalities in coronary blood flow associated with pressure-overload hypertrophy have been studied extensively, less is known about coronary blood flow after the relief of the pressure overload, when the hypertrophy has regressed. In recently studied rodent models, correction of the pressure overload by removal of aortic constriction or antihypertensive therapy resulted in total or partial regression of the left ventricular hypertrophy, with a return of coronary blood flow to normal or nearly to normal. Although these models have produced important data regarding coronary blood flow after the regression of hypertrophy, rodent hypertrophy may differ from that present in humans in amount, duration, and extent of regression. In humans, months or years...
are typically required for complete regression of the hypertrophy. The status of coronary blood flow after the regression of hypertrophy in humans or in large mammals is unknown. However, it is known that stress-induced abnormalities in ventricular function may persist even after the regression of hypertrophy. If ventricular dysfunction is linked to abnormal coronary blood flow, it is conceivable that coronary blood flow remains abnormal and continues to play a pathophysiological role.

We have recently developed a model that allows for the study of progression and regression of left ventricular hypertrophy in the dog. This model produces approximately 50–70% regression of hypertrophy 6 months after removal of the pressure overload. The amount of hypertrophy that occurs in this model and the pattern of regression (rapid regression followed by a plateau phase) is similar to that seen in humans. The current study was performed using this model to test the hypothesis that, despite significant regression in hypertrophy, coronary blood flow would still be abnormal 6 months after removal of the pressure overload.

Materials and Methods

Study Design

Coronary blood flow was studied at rest, during rapid atrial pacing, and during maximum coronary vasodilation with adenosine in three groups of dogs: 1) eight normal control dogs (NL group), 2) five dogs with pressure-overload hypertrophy (LVH group), and 3) six different dogs studied 6 months after removal of the pressure overload, a period during which the hypertrophy partially regressed (LVH Reg group). Coronary blood flow was studied with dogs in the closed-chest conscious state by use of the microsphere technique. Left ventricular hypertrophy was produced by aortic banding in puppies, after which subsequent growth produced an increase in gradient and consequent hypertrophy. Removal of the pressure overload in the LVH Reg group was accomplished by surgical removal of the band, followed by balloon aortoplasty of the residual aortic stenosis. The amount of left ventricular hypertrophy was evaluated using the left ventricular weight/body weight ratio at the time of death in all three experimental groups. Left ventricular hypertrophy was assessed echocardiographically in the LVH Reg group at peak hypertrophy before removal of the band. The left ventricular weight/body weight ratio of three of the six LVH Reg dogs was reported previously.

At all times the animals were cared for by trained veterinary personnel according to standards that met or exceeded those of the American Physiological Society and the American Association for Accreditation for Laboratory Animal Care.

Creation of pressure overload. Five mongrel puppies, 10 weeks of age, underwent aortic banding according to previously described methods. Briefly, anesthesia was induced with an intramuscular injection of a combination of droperidol and fentanyl (0.15 ml/kg). Tracheal intubation was performed, and the animals were placed on a mechanical respirator. Anesthesia was then supplemented by inhalation of isoflurane. After a cutdown was performed over the right groin, a 6F sheath was inserted into the right femoral artery. A 5F pigtail catheter was inserted into the sheath and guided to the left ventricle by pressure monitoring. The side arm of the sheath and the pigtail catheters were connected to two previously calibrated and balanced fluid-filled transducers. A left thoracotomy was performed, and the ascending aorta was exposed after a pericardiectomy. A 5-mm-wide Mersilene band was placed around the ascending aorta just above the coronary arteries. The band was tightened until a 30-mm Hg peak gradient was present between the left ventricle and the distal catheter. The catheters were removed, the thoracotomy and cutdown were repaired, and the animals recovered from anesthesia. They grew on a standard diet under close veterinary supervision.

Reversal of the pressure overload and pressure-overload hypertrophy. A second group of six dogs was also banded at 10 weeks of age in a fashion identical to that described above. Three months later, echocardiography was performed, during which measurements were made for the calculation of left ventricular mass. One week later, by use of the anesthetic techniques described above, a right thoracotomy was performed. After adhesions were lysed, the aortic band was located, transected, and removed. The thoracotomy was repaired, and the animals recovered. One month later, after anesthesia was provided with the inhalation of isoflurane, cardiac catheterization was performed. In every case, there was a residual transtentostic gradient that exceeded 50 mm Hg. Therefore, as previously described, a 15-mm balloon catheter was inserted into the left femoral artery and advanced across the residual aortic stenosis, where the balloon was inflated. If dilatation with the 15-mm balloon did not resolve the residual gradient, repeat dilatation was performed with an 18-mm balloon. After dilatation with the 18-mm balloon, five animals had no transtentostic gradient; one had a gradient of 5 mm Hg. The catheters were then removed, and the animals were allowed to recover. The animals were then followed for 6 months. This period of follow-up was chosen because by 6 months the rate of hypertrophy regression reaches a stable plateau phase similar to that seen in humans.

Determination of coronary blood flow. Coronary blood flow was determined with dogs in the closed-chest conscious state by use of the radiolabeled microsphere technique. Light sedation was provided by infusion of sufentanil (0.05–0.1 µg/kg per minute). Coronary blood flow was measured 3 months after banding in the LVH group and 6 months after aortoplasty in the LVH Reg group. Coronary blood flow was determined at rest, during adenosine infusion (1.06 mg/kg per minute), and during rapid atrial pacing. During these interventions, care was taken so that diastolic blood pressure did not fall below 60 mm Hg, where hypotension might itself have been responsible for abnormalities in flow. The maximum dose of adenosine was tolerated by every animal. However, not every animal was able to maintain a diastolic aortic pressure of ≥60 mm Hg at our maximum attempted pacing rate of 250 beats per minute. Thus, maximum pacing rates for the LVH and LVH Reg groups were slightly slower than those for the NL group so that we could maintain an adequate perfusion pressure.

Instrumentation for determination of coronary blood flow was performed after local infiltration of the catheter insertion sites with lidocaine. A 5F pigtail catheter
was advanced from the right carotid artery into the left ventricle and then prolapsed across the mitral valve into the left atrium for the purpose of injecting microspheres and recording left atrial pressure. A second 5F pigtail catheter was inserted into the right femoral artery and advanced into the descending aorta, where it was used to measure systemic pressure and also to withdraw blood to provide the arterial reference sample for coronary blood flow determination. A pacing catheter was inserted from the right femoral vein into the right atrial appendage for rapid atrial pacing.

Three differently labeled 15-μm microspheres (51Cr, 103Ru, and 147Ce) were used to measure coronary blood flow during the three different experimental conditions. Approximately $3 \times 10^5$ microspheres were injected. The microspheres were sonicated for at least 20 minutes before the injection. Beginning 30 seconds before the injection and continuing for 2 minutes after the injection, a reference sample of blood was removed from the aortic catheter at a rate of 7.75 ml/min.

After microsphere injection, anesthesia was induced using droperidol/fentanyl and inhalation of isoflurane. When a deep plane of anesthesia was achieved, the animals were killed. The hearts were removed and placed in formalin for 3 days before sectioning. Sectioning was performed as previously described.5,20 Briefly, the right ventricle and atria were dissected free from the left ventricle, and the left ventricle was then sectioned into three equal slices from base to apex. These slices were then divided into quadrants, and the quadrants were sectioned into epicardial, midwall, and endocardial layers. Tissue sections were weighed and, with the reference samples, were analyzed in a Beckman 800 multichannel scintillation analyzer. Each channel's window was set to match the peak energy of the isotope of interest, and the counts were corrected for background and crossover activity.

Determination of left ventricular mass. In all three groups, the left ventricle was weighed at the time of

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<th>Table 1. Hemodynamic Data</th>
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<th>NL</th>
<th>LVH</th>
<th>LVH reg</th>
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<tr>
<td></td>
<td>S</td>
<td>D</td>
<td>M</td>
</tr>
<tr>
<td>Rest</td>
<td>125±12.2</td>
<td>81±9.4</td>
<td>100±11</td>
</tr>
<tr>
<td>Pacing</td>
<td>119±10.1</td>
<td>90±8</td>
<td>102±12.5</td>
</tr>
<tr>
<td>Adenosine</td>
<td>110±4</td>
<td>62±5.4</td>
<td>76±5.5</td>
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AoP, aortic pressure; HR, heart rate; bpm, beats per minute; LAP, mean left atrial pressure; NL, normal dogs; LVH, dogs with left ventricular hypertrophy; LVH Reg, dogs with partially regressed left ventricular hypertrophy; S, systolic aortic pressure; D, diastolic aortic pressure; M, mean aortic pressure. Values are mean±SEM.

*p<0.05 vs. NL; †p<0.05 vs. LVH; ‡p<0.05 vs. rest; §p<0.05 vs. pacing.
death. Obviously, left ventricular mass before debanding in the LVH Reg group could not be measured directly but was estimated using echocardiographic measurements. In previous studies, we have demonstrated accuracy in our laboratory in the echocardiographic assessment of left ventricular mass compared with the actual measurement of left ventricular mass obtained at autopsy.\textsuperscript{18,21} Echocardiographic measurements were obtained as the animals were supported in a specially designed sling. End-diastolic dimension was measured from two-dimensional directed M-mode echocardiograms of the left ventricular minor axis using the leading-edge technique according to the recommendations of the American Society of Echocardiography. Wall thickness was measured from the posterior wall.

**Calculations**

Left ventricular mass (m) was calculated from echocardiographic measurements using the following formula:

\[
m = CSA \times \text{major axis}
\]

where CSA is the left ventricular cross-sectional area, calculated as

\[
CSA = \pi \left[ \frac{\text{DED} + \text{th}}{2} \right]^2 - \pi \left[ \frac{\text{DED}}{2} \right]^2
\]

where DED is end-diastolic dimension and th is diastolic wall thickness.

Coronary blood flow (Qm) was calculated from the following formula:

\[
Qm = Qr \cdot \frac{Cm}{Cr}
\]

where Qr is the rate of reference sample withdrawal (7.75 ml/min), Cm represents counts per minute in the myocardial samples, and Cr represents reference sample counts per minute. The values obtained were divided by tissue weight and expressed as milliliters per minute per gram.

Coronary vascular resistance (CVR) was calculated as

\[
CVR = \frac{\text{AoP} - \text{LAP}}{\text{CBF}}
\]

where \(\text{AoP}\) is mean aortic pressure, \(\text{LAP}\) is mean left atrial pressure, and \(\text{CBF}\) is mean total coronary blood flow.

**Statistics**

Dispersion from the mean is noted in this study as ±1 SEM. When parameters from the three groups were compared, two-way analysis of variance was used to determine if a difference existed among the groups or among interventions. If differences were detected, a Newman-Keuls test was then used to determine where the differences lay.

**Results**

**Hypertrophy**

Left ventricular mass was 85±4 g in the NL group, 130±3 g in the LVH group (\(p<0.05\) versus NL group), 142±10 g in the LVH Reg group at peak hypertrophy (\(p<0.05\) versus NL group, \(p=\text{NS}\) versus LVH group), and 114±5 g in the LVH Reg group at death (\(p<0.05\) versus the NL group, the LVH group, and the LVH Reg group at peak hypertrophy). Figure 1 demonstrates the left ventricular masses relative to body weight for the three groups of dogs. Left ventricular mass for the LVH group was similar to that of the LVH Reg group at peak hypertrophy. Six months after aortoplasty, however, mass had fallen significantly in the LVH Reg group and was significantly less than that in the LVH group. However, left ventricular mass in the LVH Reg group was still greater than that in the NL group (\(p<0.05\)).

**Hemodynamics**

Table 1 demonstrates the hemodynamics during coronary blood flow determinations. Mean aortic blood pressure during pacing and adenosine infusion in the LVH Reg group was reduced compared with that during resting conditions. Mean left atrial pressure was higher in the LVH Reg group than in the NL group at rest, during pacing, and during adenosine infusion. In the LVH Reg group, left atrial pressure was similar to that in the NL group except during rapid atrial pacing, when it was substantially higher than that in the NL group and similar to that in the LVH group.

**Coronary Blood Flow**

Coronary blood flow is demonstrated in Figure 2. In the NL group, endocardial coronary blood flow rose significantly during rapid atrial pacing and significantly again during adenosine infusion.

In the LVH group, endocardial blood flow fell during rapid atrial pacing. Although endocardial flow increased significantly in the LVH group during adenosine infusion, it was less than that observed for the NL or LVH Reg group.

In the LVH Reg group, during rapid atrial pacing, endocardial blood flow did not increase significantly and was significantly less than that in the NL group. However, during adenosine infusion, endocardial blood flow

**Table 1. Continued**

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>LAP (mm Hg)</th>
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<tr>
<td></td>
<td>NL</td>
</tr>
<tr>
<td>Rest</td>
<td>105±4</td>
</tr>
<tr>
<td>Pacing</td>
<td>244±2‡</td>
</tr>
<tr>
<td>Adenosine</td>
<td>142±9‡§</td>
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FIGURE 2. Top panel: Bar graph showing endocardial coronary blood flow (ENDO CBF) in normal dogs (NL), dogs with left ventricular hypertrophy (LVH), and dogs with partially regressed left ventricular hypertrophy (LVH reg) at rest, during rapid atrial pacing, and during adenosine infusion. The statistical analysis comparing the groups for a given intervention is shown below the bar graphs. *p<0.05 vs. rest; $\ddot{p}$<0.05 vs. pacing. Bottom panel: Bar graph showing epicardial coronary blood flow (EPI CBF) in the same groups during the same experimental conditions as in the top panel. The statistical treatment is the same.

greatly increased over the resting state in the LVH Reg group and was similar to that observed during adenosine infusion in the NL group and higher than that in the LVH group.

Epicardial coronary blood flow also increased significantly in the NL group during rapid atrial pacing and again during adenosine infusion. However, epicardial blood flow did not increase significantly during rapid
atrial pacing in the LVH group. Likewise, during rapid atrial pacing, there was no significant increase in epicardial coronary blood flow in the LVH Reg group. During adenosine infusion, epicardial coronary blood flow increased significantly in all groups. Although epicardial coronary blood flow tended to be lower in the LVH group during adenosine infusion compared with the NL and LVH Reg group, this difference was not statistically significant.

No significant differences between posterior, anterior, or lateral wall flow existed in any group during any intervention (Table 2). The only significant difference among the groups in the endocardial/epicardial flow ratio was a decreased value during pacing and adenosine infusion in the LVH group.

Regional coronary vascular resistance during pacing is demonstrated in Table 3. Whereas epicardial resistance fell normally in the LVH group during pacing, endocardial resistance did not fall at all. In the LVH Reg group, endocardial resistance fell significantly during pacing but not to the normal value. Because mean aortic pressure tended to be elevated in the LVH Reg group, it was possible that increased coronary vascular resistance in this group was due to the hypertension or its causes rather than a property of ventricular muscle itself. To help elucidate this issue,
Table 3. Coronary Vascular Resistance During Pacing

<table>
<thead>
<tr>
<th>Coronary vascular resistance (resistance units)</th>
<th>NL</th>
<th>LVH</th>
<th>LVH Reg</th>
</tr>
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<tbody>
<tr>
<td>Rest</td>
<td>59±6</td>
<td>112±16*</td>
<td>94±18*</td>
</tr>
<tr>
<td>ENDO</td>
<td>74±15</td>
<td>139±27</td>
<td>134±32</td>
</tr>
<tr>
<td>Pacing</td>
<td>37±5†</td>
<td>114±21*</td>
<td>64±9†</td>
</tr>
<tr>
<td>EPI</td>
<td>42±5†</td>
<td>41±6†</td>
<td>62±15†</td>
</tr>
</tbody>
</table>

NL, normal dogs; LVH, dogs with left ventricular hypertrophy; LVH Reg, dogs with partially regressed left ventricular hypertrophy; ENDO, endocardium; EPI, epicardium.

methoxamine was infused in seven additional normal dogs (NL-HT group) to raise and maintain mean arterial pressure to a level (136±2 mm Hg) similar to that in the LVH Reg group. Coronary blood flow was determined in this hypertensive state at rest and during pacing to 209±1 beats per minute—the rate achieved in the LVH Reg group. Figure 3 demonstrates that endocardial coronary vascular resistance was increased in the NL-HT dogs to a level slightly but not statistically higher than that in the LVH Reg group (106±13 units for the NL-HT group versus 94±18 units for the LVH Reg group). During pacing, coronary vascular resistance fell in the NL-HT group so that it was significantly less than in the LVH Reg group (48±2.0 units for the NL-HT group versus 64±9 units for the LVH Reg group, p<0.05). The value in the NL-HT group during pacing was not statistically different from the value in the NL group during pacing, although it tended to be lower in the NL group. This tendency is probably explained by the faster pacing rate (244 beats per minute) in the NL group than in the NL-HT group (209 beats per minute).

Total coronary vascular resistance is demonstrated in Figure 4 at rest and during adenosine infusion. The value obtained during adenosine infusion is considered to represent minimum coronary vascular resistance. At rest, coronary vascular resistance was significantly higher in both the LVH and the LVH Reg groups compared with the NL group. However, during adenosine infusion, minimum vascular resistance was similar in both the NL and LVH Reg groups but was significantly higher in the LVH group than in the NL group.

Discussion

Left ventricular volume overload or pressure overload causes the development of left ventricular hypertrophy, a compensatory response that allows the ventricle to bear the increased hemodynamic load. Eventually, however, the hypertrophied ventricle may exhibit pathology manifested as both systolic or diastolic dysfunction. In pathological pressure-overload hypertrophy, abnormalities in coronary blood flow are well described and may be, in part, the cause of some of the

![Figure 3](http://circres.ahajournals.org/)

**Figure 3.** Left panel: Plot showing endocardial coronary vascular resistance in normal dogs, normal dogs made hypertensive (HT), and dogs with partially regressed left ventricular hypertrophy (LVH reg) at rest and during rapid atrial pacing. Coronary vascular resistance in the normal (HT) group fell to a significantly lower level than that in the LVH reg group. Right panel: Plot showing epicardial vascular resistance in the same groups as in the left panel.
pathological sequelae of the hypertrophy.15-25 Particularly during stress, endocardial coronary blood flow in pressure-overload hypertrophy is abnormal20 and has been associated with stress-induced endocardial dysfunction.9 Because of the pathological nature of the hypertrophy that develops in left ventricular pressure overload, therapeutic interventions should not only relieve the pressure overload but should lead to the regression of the left ventricular hypertrophy as well. Regression of left ventricular hypertrophy does occur after the removal of the pressure overload, but at least in humans, complete regression may not occur for several years after the overload correction.16,22,23 As noted above, although much is known about the abnormalities in coronary blood flow accompanying pressure-overload hypertrophy, less is known about coronary blood flow during the regression of hypertrophy.

The most important findings in the current study are that 1) after regression of more than half the hypertrophy that developed, maximum coronary blood flow produced by maximum coronary vasodilation with adenosine returned to normal, but 2) during rapid atrial pacing, coronary blood flow after the regression of hypertrophy was still clearly abnormal. These findings could have important scientific and clinical implications. Scientifically, the mechanisms proposed to explain the reduction in coronary blood flow in pathological ventricular hypertrophy include the following: 1) the arteriolar or capillary bed size is reduced in comparison to the amount of muscle mass that it must nourish; 2) structural abnormalities in the coronary vessels themselves limit blood flow through them; and 3) functional vascular compressive forces produced by increased left ventricular filling pressure limit coronary blood flow.24,25 Our data suggest that, after partial regression of hypertrophy, maximum coronary blood flow can return to normal, indicating that mechanisms 1 and 2 are no longer operative. That is, if minimum coronary vascular resistance and maximum flow can be normal under any circumstance, then intrinsic abnormalities of the coronary tree can no longer be limiting flow. However, subendocardial blood flow during rapid atrial pacing in the LVH Reg group as well as in the LVH group remained abnormal. These abnormalities in flow were associated with high left ventricular filling pressure. It is possible that reduced coronary flow during pacing resulted in left ventricular ischemia, in turn producing ventricular dysfunction and elevated filling pressure, or diastolic abnormalities intrinsic to the hypertrophy present could have exacerbated increased filling pressure during pacing, thereby limiting coronary blood flow.26,27 Against this premise is recent evidence that intraventricular pressure changes have little effect on coronary blood flow in diastole28 or systole.29 An alternative hypothesis is that tachycardia, which compromises the diastolic coronary filling period, in conjunction with endothelial dysfunction reduced coronary blood flow during pacing because of inadequate vasodilatation.30 Our data support this conclusion, since endocardial coronary resistance (which took increased filling pressure into account) failed to decrease during pacing in the LVH group and did not decrease normally in the LVH Reg group, whereas endocardial resistance did decrease during adenosine infusion. The hypertensive tendency of the LVH Reg group may also have affected coronary vascular resistance; i.e., whatever caused the hypertension may also have increased coronary vascular resistance independent of the residual hypertrophy. However, coronary vascular resistance in normal dogs that were made hypertensive (NL-HT

Figure 4. Bar graph showing coronary vascular resistance (CVR) at rest and during adenosine infusion for normal dogs (NL), dogs with left ventricular hypertrophy (LVH), and dogs with partially regressed left ventricular hypertrophy (LVH reg). CVR fell significantly in each group during adenosine infusion, but it remained higher in the LVH group than in the NL group. The difference between the LVH group and the LVH reg group approached statistical significance. *p<0.05 vs. rest.
group) acted more like that found in NL dogs than in LVH Reg dogs during pacing. This suggests that a property of the residual hypertrophy rather than the hypertension itself was operative in the LVH Reg group in preventing a normal fall of coronary vascular resistance during pacing. Differences in perfusion pressure between subepicardial and endocardial regions could also account for reduced subendocardial flow during pacing.

Another potential cause of reduced coronary blood flow during pacing was a statistically significant fall in mean aortic pressure in the LVH Reg group and a statistically insignificant fall of 26 mm Hg in the LVH group. This fall may have been induced by the development of left ventricular dysfunction during pacing. In turn, the reduced aortic pressure may have been responsible, in part, for the failure of coronary blood flow to increase normally in the LVH and LVH Reg groups, although our observed pressures were well above those required for autoregulation of flow.10

Our study cannot determine which of these mechanisms was operative. However, regardless of the mechanism, if these data are also applicable to humans, they may have clinical significance. The data suggest that, even after relief of pressure overload and after partial regression of hypertrophy, stress might still induce abnormalities in coronary blood flow, which might in turn make such a patient susceptible to stress-induced ischemia and/or ventricular dysfunction.

Relation of this study with previous reports. Our results from the LVH group are consistent with a large body of experimental data that demonstrate abnormal endocardial perfusion during adenosine infusion and/or rapid atrial pacing. In most studies, endocardial flow failed to increase normally during rapid atrial pacing.5–8,11–13 Our actual decline in endocardial flow during pacing is similar to that found by Alyono et al.10 In their study, differences in endocardial flow and the fall in the endocardial/epicardial flow ratio were most marked in the posterior left ventricular wall, a difference we did not find. However, in their study, the most severe difference was in the area of the posterior papillary muscle, an area our sectioning protocol did not allow us to examine specifically.

Previous studies of coronary blood flow and regression of hypertrophy in rats demonstrated that maximum coronary blood flow returned to or toward normal after the reversal of brief pressure overload. Canby and Tomanek12 administered captopril to spontaneously hypertensive rats with established left ventricular hypertrophy. Captopril reduced blood pressure, allowing for the regression of hypertrophy and significant improvement in previously elevated minimal coronary vascular resistance. Anderson and colleagues14 treated spontaneously hypertensive rats with hydralazine, resulting in an 8% decrease in left ventricular mass. This modest decrease in mass, coronary flow reserve improved substantially from 29% to 75%, although it did not attain the magnitude of reserve seen in normal rats (105%). Isoyama and colleagues15 found complete regression in hypertrophy with a return of coronary flow rate to normal after aortic debanding that followed 4 weeks of aortic constriction. Coronary autoregulation examined in a similar model also returned to normal.12 Ito and colleagues13 found similar results for coronary blood flow after debanding the aorta after 4 weeks of pressure overload. However, after 10 weeks of pressure overload followed by four weeks of pressure-overload relief, coronary flow abnormalities were still present in isolated left ventricles, even though the hypertrophy had largely regressed.

The present study is the first to study coronary blood flow in vivo in a large animal model after the regression of hypertrophy. This study is also the first to report the effects of rapid atrial pacing. Our results are similar to those found in rodent models, in which coronary blood flow reserve was improved after the regression of hypertrophy. However, our results of the rapid atrial pacing studies indicate that coronary blood flow can still be markedly abnormal after the regression of hypertrophy, even though maximum flow has returned to normal.

Limitations

One potential limitation of this study is the lack of direct left ventricular mass data in the LVH Reg group at peak hypertrophy. For us to conclude that the differences between the LVH and LVH Reg groups accrued from the regression of hypertrophy, we must be certain that the two groups were similar with respect to hypertension before removal of the pressure overload. Since we obviously could not weigh the hearts of the LVH Reg group at peak hypertrophy, we made our mass assessment echocardiographically. Although this approach could be subject to error, we have previously validated our ability to calculate mass from echocardiographic measurements in our laboratory.16,21

Second, it is fair to point out that our model is a supracoronary model of aortic constriction that exposes the coronaries to systolic hypertension, which may by itself affect coronary flow.25 As such, the model is relevant to hypertrophic disease states such as systemic hypertension and coartation of the aorta. The model does differ from valvular aortic stenosis, in which the coronaries are excluded from the hypertensive circuit. This fact may, in part, be the cause of the increased resting coronary vascular resistance that we observed in the LVH subjects.

Third, hypertrophy regression in this study was not complete. It may be that complete regression may have occurred after a longer observation period. On the other hand, we noted a relatively large although statistically insignificant increase in aortic pressure in the LVH Reg dogs, which may have inhibited complete regression of the pressure-overload hypertrophy. This increase may be similar to that seen after manipulation of the aorta during surgery for coarctation of the aorta. Although complete lack of regression could be viewed as a shortcoming, our model follows the pattern of regression found in humans—a rapid regression phase followed by a long plateau phase. Coronary blood flow was studied in this plateau phase, and it is this phase that is particularly relevant to regression of hypertrophy in humans.

Fourth, the LVH and LVH Reg groups differed in age (5 months and 11 months old, respectively) at the time of study. Although we do not believe that this difference would affect coronary blood flow, we cannot be certain of this fact.
Conclusions

Six months after the removal of left ventricular pressure overload in a large animal model of hypertrophy, the hypertrophy regressed by approximately 70%. At that time, maximum coronary blood flow and minimum vascular resistance had returned to normal. However, during rapid atrial pacing, abnormalities in coronary blood flow persisted. These abnormalities may have functional consequences that could also pertain to human subjects in which only partial regression of hypertrophy has occurred after the removal of a pressure overload.

References

Coronary blood flow after the regression of pressure-overload left ventricular hypertrophy.

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