Coronary Angiogenesis During Long-term Hypertension and Left Ventricular Hypertrophy in Dogs

Robert J. Tomanek, Kimberly A. Schalk, Melvin L. Marcus, and David G. Harrison

Many studies have documented that during the development of left ventricular hypertrophy (LVH) coronary vascular growth lags behind that of cardiac muscle. To ascertain whether significant growth of coronary resistance vessels occurs with long-standing hypertension and LVH, we studied dogs with Goldblatt (one-kidney, one-clip) hypertension seven months after surgery. Left ventricular minimal coronary vascular resistance (LV MCVR) was derived from adenosine-induced maximal flow measured with 15 μm microspheres. Morphometric data were based on perfuse-fixed hearts arrested in diastole. Hypertension and LVH were associated with a 46% increase in left ventricular weight/body weight ratio (LVH, 6.73 ±0.31; control, 4.62±0.30), no significant change in LV MCVR/100 g, and a reduction in total LV MCVR (LVH, 0.11±0.02 mm Hg/ml/min; control, 0.15±0.02 mm Hg/ml/min). Arterial and arteriolar wall/lumen ratios were virtually identical in the two groups. Arteriolar (lumen diameter <200 μm) numerical densities (arteriolar profiles/mm²) were also similar for the two groups even when analyzed according to lumen diameter size class and by ventricular location (epimyocardium, midmyocardium, and endomyocardium). Moreover, the relative frequency distribution of any arteriolar size class was similar for both groups. Because MCVR and arteriolar density were normal, this study provides new evidence that angiogenesis during long-term LVH in this model is of sufficient magnitude to enable the cross-sectional area of the coronary resistance vessels to increase in proportion to the increase in left ventricular mass. (Circulation Research 1989;65:352-359)

Left ventricular (LV) enlargement associated with hypertension is usually characterized by decrements in coronary reserve, as well as an increase in minimal coronary resistance per unit ventricular weight. The latter is thought to be a consequence of a smaller cross-sectional area of the vascular bed per unit mass of myocardium. Two structural variables can explain this phenomenon: 1) an inadequate growth of the vascular bed while ventricular mass is increasing or 2) a reduction in the luminal radii of major resistance vessels.

In a recent study on dogs with renal hypertension of 6 weeks duration, we found that minimal coronary vascular resistance was elevated but that the wall/lumen ratios of arterioles and arteries were not increased. Thus, we concluded that vessel narrowing due to remodeling or hypertrophy of the media does not occur during the first 6 weeks of renal hypertension in the dog. There is, however, some evidence for increased wall/lumen ratios in coronary arterioles of spontaneously hypertensive rats with longer periods of elevated blood pressure.

The present study was designed to address the effects of long-term hypertension and left ventricular hypertrophy (LVH) in dogs. Specifically, we raised three questions regarding long-term renovascular hypertension. First, do coronary arteries and arterioles eventually undergo medial thickening that leads to an increase in wall/lumen ratio and a decrease in luminal diameter? Second, to what extent do arterioles grow as cardiac hypertrophy progresses? Finally, do vascular responses and the magnitude of cardiocyte enlargement differ transmurally in the left ventricle during long-term hypertension?

Materials and Methods

Induction of Renal Hypertension

In 13 adult mongrel dogs, we induced renal (Goldblatt, one-kidney, one-clip) hypertension as previously described in detail. Briefly, a midline abdominal incision was made in dogs anesthetized with...
sodium pentobarbital (30 mg/kg i.v.) and mechanically ventilated with room air. A clamp was placed around the left renal artery and tightened to the point that a thrill could be detected distal to the clamp. Then, a right nephrectomy was performed. Seven months later, the 10 dogs that survived the surgery and 11 control dogs were prepared for study. Each dog was anesthetized with pentobarbital (30 mg/kg i.v.) and maintained by mechanical respiration; under sterile conditions, an incision was made in the fourth intercostal space. The dog was then instrumented by the placement of cannulas in the descending aorta and the left atrium; the cannulas were tunneled subcutaneously and exteriorized dorsally. We studied the dogs after a 1-week recovery period. All variables were not successfully measured in each dog. Of the 21 dogs studied, hemodynamic and perfusion data were obtained for 16–19 dogs. This occurred because of technical difficulties in measuring myocardial perfusion or hemodynamics. Of the 15 hearts used to obtain histological data, four control hearts were not used for arteriolar densities because sufficiently large samples were not obtained.

**Experimental Protocol**

Before the time of study, the dogs were brought into the laboratory on two or three occasions to familiarize them with the surroundings. At the time of study, the dog was lightly sedated intravenously with 0.04 mg fentanyl and 2 mg droperidol and given 5,000 units sodium heparin (i.v.). All hemodynamic and perfusion measurements were obtained in conscious dogs that were either standing or sitting. Arterial pressure and heart rate were continuously monitored and recorded on a direct-writing oscillographic recorder. Resting (baseline) myocardial perfusion was obtained by injecting microspheres into the left atrium after hemodynamic parameters were stable. Subsequently, maximal vasodilation was induced by a constant infusion of intravenous adenosine (1 mg/kg/min). This dose has been shown to maximally vasodilate the coronary vasculature of dogs. Ten minutes after the onset of adenosine infusion, microspheres were injected, the adenosine infusion was continued, and once blood pressure and heart rate stabilized, another batch of differently labeled microspheres was injected. We continued the adenosine infusion for an additional 4 minutes. After these procedures were completed, the dog was anesthetized with pentobarbital (30 mg/kg i.v.), a thoracotomy was performed, and the heart was arrested by injecting procaine (10 ml) into the left ventricle. The heart was then rapidly excised and prepared for perfusion fixation as described below. After the heart was fixed, we obtained multiple specimens for histological analysis and for the determination of radioactivity (regional myocardial perfusion).

**Measurement of Regional Myocardial Perfusion**

We used 15-μm diameter carbonized radioactive microspheres labeled with Sr, Nb, Ce, Sc, Sn, Cr, Co, Ru, or Cd. Before injection, the vial of microspheres was vigorously agitated with a mechanical mixer for at least 3 minutes. To obtain a reference sample, blood was withdrawn at a rate of 2.06 ml/min beginning 20 seconds before microsphere injection and continuing for 90 seconds after flushing the atrial cannula with 10 ml saline. Approximately 6.3±0.3×10⁶ microspheres were injected during a 10-second period. These procedures do not cause alterations in heart rate or arterial pressure.

During postmortem dissection, tissue samples were obtained at midlevel of the left ventricular free wall at three transmural locations: epimyocardium, midmyocardium, and endomyocardium. The samples were placed in a counting vial, and their radioactivity was determined in a sodium iodide gamma scintillation counter. Myocardial perfusion (MP, ml/min/100 g) was calculated from the formula: 

\[
MP = \frac{C_m \times 100 \times RWR/C}{Q}
\]

where \(C_m\) is counts per gram of myocardial tissue, RWR is reference artery withdrawal rate, and \(C\) is total counts in the reference blood samples.

Coronary vascular resistance was calculated and expressed in two ways: 1) resistance/100 g equals mean aortic pressure divided by coronary perfusion/100 g left ventricle and 2) total resistance (whole ventricle) equals mean aortic pressure divided by total coronary perfusion.

**Microscopy**

Fixation was accomplished by vascular perfusion performed in vitro immediately after removing the heart from the dog. A cannula was placed through the brachiocephalic artery into the aorta and secured with umbilical tape. The heart, which had been arrested in diastole with procaine (200 mg), was then flushed with 1 l Locke’s solution, containing 300 mg procaine (37°C) followed by 2 l fixative (room temperature). The fixative consisted of 1.5% glutaraldehyde, 0.1 M cacodylate, 0.2% paraformaldehyde, and 0.01 M CaCl₂ (pH 7.4). Details concerning this fixative were previously published. Perfusion flow was adjusted to maintain a pressure of approximately 100 mm Hg.

After fixation, the ventricles were dissected and weighed separately. Multiple tissue samples were obtained as previously described. They included samples from epimyocardial, midmyocardial, and endomyocardial layers (taken from similar sites in each dog) as well as individual epicardial arteries (left anterior descending and its branches and a branch of the circumflex). Samples from all of these sites were processed and embedded in Spurr’s plastic; 1-μm sections were cut and stained with Richardson’s solution. These sections were used for wall/lumen ratio measurements. We also excised
multiple samples about 1 cm in width from each of the three layers noted above. After processing, these specimens were embedded in JB-4 (methacrylate) and sectioned at 2 μm. Sections that were stained with Jones' methanamine silver⁸ were used in the determination of regional cross-sectional cardiocyte areas; those stained with hematoxylin and eosin were used in assessment of arteriolar densities. The use of silver stain makes it possible to accurately demarcate cardiocyte cell borders. All tissue specimens, except those that were limited to a specific large epicardial cardiocyte, were dissected with reference to cardiocyte orientation and sectioned so that cardiocytes were cut at a right angle to their long axis.

After measurements were obtained with light microscopy, representative arteries and arterioles were selected, the blocks were trimmed to isolate the particular vessel, and thin sections for electron microscopy were obtained with a Reichert Ultratome (Vienna, Austria). These sections, stained with uranyl acetate and lead citrate, were photographed on a Hitachi 7000 electron microscope (Tokyo, Japan).

**Morphometry**

Cardiocyte cross-sectional areas were determined by projecting images of the silver-stained sections onto drawing paper and tracing outlines of cells in which a nucleus could be seen. Thirty to 40 cells from several fields were included and subsequently digitized for cross-sectional area. The mean value for each specimen was considered as representative of cell size for a particular ventricular region for a given dog.

Wall/lumen ratios of arteries and arterioles were also based on images of slides (Spurr's embedded specimens cut at 1 μm). As previously described,² the smallest diameter of the vessel, which was considered representative of luminal diameter, was used in order to minimize the effects of obliquely sectioned vessels. Wall thickness was determined at the same two points corresponding to lumen diameter. We measured the length of a line extending from the endothelium to the outer limit of the tunica media. The mean of the two measures was recorded. Wall thickness was always determined at ×1,440; lumen diameter was obtained at the highest magnification (up to ×1,440) that would accommodate the entire diameter. All measures were subsequently entered into a computer, which was programmed to convert the values from millimeters to microns in accordance to the specific magnification.

Arteriolar numerical densities (profile densities) were based on the 2-μm-thick sections of JB-4 (methacrylate)-embedded tissues stained with hematoxylin and eosin. Tissue sections were systematically scanned, and all arterioles photographed. For each ventricular region, slides from all (from five to seven) blocks were analyzed. The total tissue area for each region, determined by digitization of the projected images from the glass slides, ranged from about 130–250 mm². We calculated a “progressive mean” in preliminary work to test the adequacy of this sample size. The mean based on this size range was consistently within 0–10% of a mean based on a larger sample (360 mm²). Care was taken to exclude areas with artifactual tissue separation. We measured the lumens of all arterioles from the negatives, which were projected to enlarge the images (×17). Each vessel was then classified into one of four size classes (μm): <30, 30–49, 50–99, and 100–200. We also checked the negatives to see if any arterioles were photographed more than once. Arteriolar densities were then expressed as number of profiles per square millimeter of tissue.

**Statistical Analyses**

Comparisons of group means are based on a one-tailed Student's t test with a p<0.05 denoting statistical significance. The data are present as mean±SEM.

**Results**

**Magnitude of LVH, Hemodynamics, and Regional Myocardial Perfusion**

Compared with the controls, left ventricular weight/body weight and right ventricular weight/body weight ratios were 46% and 64% greater, respectively, in the hypertensive group (Table 1). LV cardiocyte cross-sectional areas were measured to determine the magnitude of hypertrophy in three different layers of the LV free wall. Since these are absolute values, they are not representative of the precise magnitude of hypertrophy for each region. However, the means do indicate that all three regions underwent substantial hypertrophy, that is, 45–55% in absolute terms (Table 1). The LV weight difference between the hypertensive and control dogs was 67%, a finding that suggests that cardiocyte length may have increased modestly.

Table 2 includes the hemodynamic and myocardial perfusion data obtained at rest and during

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**Table 1. Anatomical Data on the Magnitude of Ventricular Hypertrophy in Hypertensive Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypertension</th>
<th>Intergroup difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td>21±1</td>
<td>24±1</td>
<td>...</td>
</tr>
<tr>
<td>RVW (g)</td>
<td>30±4</td>
<td>59±4*</td>
<td>98%</td>
</tr>
<tr>
<td>RVW/BW (g/kg)</td>
<td>1.48±0.15</td>
<td>2.43±0.13*</td>
<td>64%</td>
</tr>
<tr>
<td>LVW (g)</td>
<td>98±10</td>
<td>164±10*</td>
<td>67%</td>
</tr>
<tr>
<td>LVW/BW (g/kg)</td>
<td>4.62±0.30</td>
<td>6.73±0.31*</td>
<td>46%</td>
</tr>
<tr>
<td>LV Cross-sectional cell area (μm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epimyocardium</td>
<td>327±25</td>
<td>473±37*</td>
<td>45%</td>
</tr>
<tr>
<td>Midmyocardium</td>
<td>337±29</td>
<td>524±32*</td>
<td>55%</td>
</tr>
<tr>
<td>Endomyocardium</td>
<td>356±34</td>
<td>531±38*</td>
<td>49%</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Left ventricular (LV) cross-sectional area data are based on seven control and eight hypertensive dogs. All other data were obtained from 11 control and 10 hypertensive dogs. BW, body weight, RVW, right ventricular weight; LVW, LV weight. *Statistically significant differences (p<0.05).
maximal vasodilation induced by adenosine infusion. At rest, mean aortic pressure was elevated by 37% in the hypertensive dogs compared with the controls, but myocardial perfusion per unit mass and endomyocardial/epimyocardial perfusion ratios were similar for the two groups. During maximal vasodilation, the two groups of dogs had similar values for LV and right ventricular perfusion and LV endomyocardial/epimyocardial perfusion ratio.

Minimal coronary vascular resistance (MCVR) data (Figure 1) indicate two important findings. First, MCVR per unit mass of left ventricle in the hypertensive group was not significantly different from the controls; this finding indicated that the total cross-sectional area of the vascular bed per unit mass was similar for the two groups. Six of eight control and five of eight experimental dogs had resistances (per 100 g) that were 0.16 or less. Second, total MCVR was lower in the hypertensive dogs than in the controls. This finding demonstrates a vascular growth commensurate with the magnitude of LVH.

**Arteriolar Morphometry**

The wall/lumen ratios of more than 1,500 arteries and arterioles (Figure 2) were obtained in order to determine whether long-term hypertension led to medial thickening that narrowed the vessel's lumen. Values for this parameter were nearly identical for all size classes of arteries and arterioles measured. It is also clear that there is no evidence for even a subtle trend for higher wall/lumen ratios in any size class of vessels in the hypertensive dogs.

Consistent with our goal of establishing whether growth of resistance vessels occurs during long-term hypertension and LVH, arteriolar profile numerical densities were determined transmurally in the LV free wall. In Figure 3, it can be seen that the numerical densities of arterioles (precapillary vessels <200 μm in diameter) for any region are nearly identical for the two groups of dogs. Even when the numerical densities are subdivided into four size classes (Figure 4), no differences between groups are seen. Arteriolar frequency distributions for the various size classes, illustrated in Figure 5, show that the percent of the arterioles for any given size class is virtually identical for the two groups. It can also be appreciated that the arterioles with diameters <100 μm account for 94% and 95% of the arteriolar populations in the control and LVH groups, respectively, and that about 50% of the arteriolar population consists of vessels with diameters <30 μm.

**Electron Microscopy**

We examined and photographed representative arteries and arterioles with the electron microscope. The only consistent difference noted in these vessels between the two groups was the medial fibrosis in the large coronary arteries (left anterior descending and its primary branches) from the hypertensive dogs. This change was, however, limited only to these large arteries and was not observed in arteries smaller than 500 μm or in arterioles. In a few cases we noted with the light microscope non-uniform wall thickenings in arterioles from hyper-

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**TABLE 2.** Hemodynamics and Myocardial Perfusion at Rest and During Maximal Vasodilation Induced by Adenosine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Hypertensive group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Max</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>111±6 (8)</td>
<td>131±10 (9)</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>93±5 (8)</td>
<td>78±9 (9)</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV myocardial perfusion</td>
<td>123±15 (8)</td>
<td>588±52 (8)</td>
</tr>
<tr>
<td>(ml/min/100 g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo/epi ratio</td>
<td>1.28±0.05 (8)</td>
<td>0.82±0.09 (8)</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Max, maximal vasodilation; LV, left ventricular; Endo, endomyocardium; epi, epimyocardium. The number of animals for each variable is indicated in parentheses.

*Statistically significant difference (p<0.05).
tensive dogs, which at the electron microscopic level proved to be focal disruptions of the media. Such sites showed subendothelial infiltration of phagocytic and smooth muscle cells and some disorientation of medial cells. A second alteration that was noted occasionally in arterioles was vacuolization. On occasion, the vacuoles were spaces between smooth muscle cells and endothelial cells, but usually they were intracellular components of smooth muscle cells (Figure 6). We emphasize that although such changes were observed in most of the hypertensive dogs, their occurrence was inconsistent. Accordingly, they were not widespread.

Discussion

The data obtained in this study provide new evidence that angiogenesis of major resistance vessels can parallel the left ventricular hypertrophy associated with long-term hypertension. Our conclusion is based on three complementary findings. Compared with the controls, total minimal coronary vascular resistance was lower whereas MCVR per gram was similar in dogs with LVH. These two findings show, respectively, that 1) the total cross-sectional area of the coronary vasculature was greater in the LVH dogs and 2) that the magnitude of the growth approximated the magnitude of the LVH. The third finding, essential to our conclusion, was that arteriolar profile densities were normal in dogs with LVH; this finding suggested that the growth of these resistance vessels approximated the increase in LV mass. Finally we have demonstrated that medial wall/lumen ratios were not increased in any size arteriole or artery in dogs with long-term hypertension. The absence of such a change also enabled the cross-sectional area of the resistance vessels per unit LV mass to be normal.

Factors Contributing to Resistance

An increase in MCVR during hypertension can occur as a result of: 1) rarefaction or a limited growth of resistance vessels, 2) reduction in luminal radii of resistance vessels, 3) decrease in vasodilatory capacity, and 4) extravascular compression. In a previous study on dogs with 6 weeks of one-kidney, one-clip hypertension, we found a mild degree of LVH (27%), a marked increase in MCVR per unit mass (67%) and no change in wall/lumen ratio of coronary arteries and arterioles. These data suggested that inadequate arteriolar growth and/or increased extravascular forces were responsible for the observed elevated MCVR per unit mass. In consideration of our current and previous findings, it is evident that significant angiogenesis occurred after the first 6 weeks of hypertension as LVH continued to progress. If extravascular compression was a factor during the early stage of LVH, its role was no longer significant with the persistence of hypertension and the further development of LVH. The finding that MCVR per unit mass is initially elevated in dogs has been documented by previous investigators who studied dogs 6–8 weeks after evoking pressure overload by
means of aortic stenosis or one-kidney, one-clip renovascular hypertension.  

**Duration of Hypertension: Models and Species**

Three groups of investigators have produced pressure overload in puppies by constricting the aorta and then evaluating myocardial perfusion when the dogs were approximately 1 year old. Both Holtz et al\(^{11}\) and Bache et al\(^{10}\) showed that MCVR was elevated in dogs with LVH although the magnitude of the increment was less than the increase in left ventricular mass. The third group of investigators\(^{12}\) demonstrated that the major coronary abnormality is an underperfusion of the endocardial layer in situations requiring high flow.

Marcus et al\(^{13}\) compared short-term (6-week) and long-term (6-month) hypertension using the two-kidney, one-clip model of renovascular hypertension. The magnitude of LVH was identical in both groups (27%), and MCVR increased by about 50%.

There are, however, substantial differences between the present study and the previous investigation. It is evident that in the two-kidney, one-clip model, LVH was completed during the first 6 weeks since no further increase in LV weight occurred after that time. In contrast, in this study, which used the one-kidney, one-clip model, nearly half of the LVH occurred after the first 6 weeks. A second possible explanation of the disparate results is that there are intrinsic differences between these two models of hypertension. In most species, plasma renin is increased in the two-kidney, one-clip model but remains normal in one-kidney, one-clip hypertension. Thus, the vasculature is not under identical influences in the two models, a factor that cannot be minimized when considering vascular growth. For example, it has been shown that coronary arteries of two-kidney, one-clip hypertensive rats undergo extensive pathological alterations that are believed to be related to the actions of angiotensin II.\(^{14}\)
Unlike resistance vessels of other vascular beds, coronary arteries do not show predictable increases in wall/lumen ratio during hypertension. Although such increases have been noted in spontaneously hypertensive rats,2,3 we have provided evidence that wall/lumen ratios throughout the hierarchy of precapillary vessels of dogs are unaltered after 6 weeks2 or 7 months of renovascular hypertension and LVH. It is also recognized that medial thickening of coronary vessels, as seen in patients with aortic coarctation, does not necessarily result in a decreased lumen diameter.15

Our earlier work with spontaneously hypertensive rats lends some support to the idea that angiogenesis, over time, may restore the myocardial perfusion deficit characteristic of hypertension-associated hypertrophy. After LVH stabilizes in this model of genetic hypertension, LV MCVR drops to the levels observed in the normotensive Wistar-Kyoto strain.16 This finding suggests that the resistance vessels in the genetically hypertensive rat may grow sufficiently over time to allow for a normalization of MCVR per unit mass.

In contrast to experimental animal studies, there is no evidence for a significant angiogenesis in humans with LVH. Strauer,17 who measured flow with the argon clearance method, noted a significant reduction in coronary reserve in patients with essential hypertension. Moreover, a reduction in coronary reserve has been noted in LVH secondary to volume overload.18

**Coronary Angiogenesis**

Although MCVR is an indicator of the cross-sectional area of the vascular bed, two separate parameters, that is, vessel diameter and density, need to be considered when evaluating the growth of the major resistance vessels. Rakusan and colleagues19 could not find a significant difference in arteriolar densities between rats with renovascular hypertension and their normotensive controls, despite the fact that MCVR during carbochrome-induced dilation was 80% higher in the hypertensive group. Since wall/lumen ratio of arterioles was higher in the hypertensive rats, it was concluded that the impaired coronary reserve in hypertensive cardiac hypertrophy is related to arteriolar structural alterations rather than a decrement in density. Breisch and associates20 found that arteriolar densities in pigs with LVH secondary to aortic banding 30 days earlier tended to be lower, but not significantly, than in the controls. Thus, data from these two models of pressure overload in two different species suggest that even during shorter periods of time some arteriolar growth occurs. Although we have demonstrated that wall/lumen ratios of arterioles and arteries spanning the entire size range of the coronary vasculature are not increased in our model of canine hypertension, we caution that such findings should not be generalized to other models and species. Our own findings on spontaneously hypertensive rats suggest that coronary arterioles may have enhanced wall/lumen ratios.4

In most vascular beds (e.g., cremaster muscle,21 mesentery,22 and skin23), systemic hypertension is associated with a decrease in arteriolar density. Such a decline in density occurs as a consequence of rarefaction and may be considered as a "long-term autoregulatory adjustment" of blood flow24; that is, normal flow is maintained. Similarly, arteriolar number has been shown to increase after ligation of an artery to the rat cremaster muscle.24 However, unlike other organs, heart mass increases with hypertension, and therefore, total myocardial perfusion requirements also increase. Thus, the coronary vasculature must adapt differently than that of other organs. Although our knowledge regarding coronary angiogenesis is limited, there is evidence that mechanical factors related to increased flow (rather than decreased flow) through a vessel may trigger its growth.25 Most of the supporting data are based on capillary growth. The transformation of capillaries with high flow rates into arterioles was first demonstrated in rabbit ear chambers nearly 50 years ago.26 By observing the same vessels over periods of months, these investigators noted that capillaries with increased flows undergo a metamorphosis into arterioles within a 6-day period. During cardiac hypertrophy, one might expect that capillary flow would increase as diffusion distance becomes greater and, therefore, serve as a stimulus for arteriolar angiogenesis and consequently the maintenance of a normal arteriolar density.

Further support for the hypothesis that increased myocardial perfusion may provide the milieu for angiogenesis comes from two other models of LVH. In rats with LVH secondary to 3 months of thyrotoxicosis, total MCVR was less, and peak/resting coronary flow velocity, an index of coronary reserve, was greater than the controls.27 This study is supported by more recent work demonstrating that arteriolar growth keeps pace with LVH in pigs given triiodothyronine.28 Evidence that arteriolar angiogenesis may exceed myocardial growth was also provided by Breisch et al,29 who induced LVH in pigs by exercise training over a 3 month period. They found that arteriolar density actually increased in the pigs with hypertrophy, a factor that maintained MCVR/g at control values. An increased diastolic time interval, a characteristic of the trained pigs, might have contributed to the vascular growth during hypertrophy, as suggested by Hudlicka and Tyler25 for capillaries.

In conclusion, our data demonstrate that angiogenesis during long-term hypertension and LVH normalizes MCVR per unit mass and that at least part of the underlying anatomical adaptation involves growth of arterioles. Although we have demonstrated myocardial angiogenesis in a model of pressure-overload, the responsible mechanisms are not evident at this time. We anticipate that future investigations will focus on factors that regulate...
coronary vascular growth. In addition to mechanical factors, such studies need to consider growth-promoting molecules, cell-to-cell interactions, and the extracellular matrix.

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