Effect of Hypertension and Hypertrophy on Coronary Microvascular Pressure

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We tested the hypothesis that transmural differences in coronary microvascular pressures may be greater in the setting of hypertension and left ventricular hypertrophy. Epicardial and endocardial microvascular pressures were measured in isolated lidocaine-arrested hearts during adenosine vasodilation. In both normotensive (n=19) and hypertensive (one clip, one kidney, n=10) dogs, microvascular pressures in epicardial arterioles at 60, 70, 80, 90, and 100 mm Hg of left main coronary perfusion pressures were lower than in epicardial arterioles (p<0.05 at all perfusion pressures). The pressures in epicardial arterioles as a percentage of the left main coronary perfusion pressure were similar in normotensive versus hypertensive hearts at all perfusion pressures. In contrast, the pressures in endocardium at 90 and 100 mm Hg of perfusion pressure were significantly (p<0.05) lower in dogs with hypertension and hypertrophy than in the controls (41±4 versus 50±2 and 40±4 versus 50±3 mm Hg at 90 and 100 mm Hg of perfusion pressure, respectively). Thus, there is a greater transmural resistance to microvascular perfusion in hearts with myocardial hypertrophy secondary to hypertension. This is likely due to differences in the vascular anatomy, secondary to hypertension and hypertrophy, and may contribute to vulnerabilities in subendocardial ischemia encountered in this condition. (Circulation Research 1992;71:120–126)

KEY WORDS • microvascular pressure • microcirculation • renal hypertension

Coronary flow autoregulation varies substantially between subendocardial and subepicardial layers of the myocardium.1–5 Subendocardial flow autoregulation in anesthetized animals is lost when mean coronary pressure falls below about 60–70 mm Hg, while subepicardial autoregulation persists until perfusion pressure is decreased to below 40 mm Hg.1,2 This transmural variation of coronary autoregulation may explain the mechanism by which the subendocardium is more vulnerable to ischemic injury.3,5–7 Moreover, reports in dogs with hypertension and hypertrophy have demonstrated that the limitation in subendocardial coronary flow and the depression in subendocardial wall thickening become prominent during physiological stresses such as pacing or exercise compared with normotensive dogs.8–10 These data suggest that the subendocardial muscle of the hypertrophied left ventricle may be at increased risk for ischemia compared with normal.

Recently, Harrison et al11 have suggested that the lower limit of autoregulation in subendocardium is shifted toward higher pressures as a result of sustained hypertension and hypertrophy. Studies by Chilian12 have demonstrated in normal hearts that arteriolar pressure was lower in the subendocardium than in the subepicardium. One explanation for the decreased ability of subendocardium to autoregulate in hypertension may be that the pressure dissipation across arteries that course through the ventricular wall is greater than in normal hearts. This would result in a reduction of endocardial microvascular pressure at any given aortic perfusion pressure, thus limiting the ability of the subendocardium of hypertensive hearts to autoregulate. We hypothesized that this inherent transmural gradient in microvascular pressure is greater in dogs with hypertension and left ventricular hypertrophy compared with normal. To test this hypothesis, we measured epicardial and endocardial microvascular pressures in normal dogs and dogs with hypertension and hypertrophy by using a servo-null technique. To minimize extravascular compressive forces that might vary between normal and hypertensive hearts, the studies were performed while the hearts were arrested and the coronary vasculature was maximally dilated.

Materials and Methods

Surgical Preparation

The care of all animals used in these experiments complied with the guiding principles of the American Physiological Society on animal experiments. Left ventricular hypertrophy and hypertension were pro-
duced in adult mongrel dogs of either sex (18–28 kg). The method of inducing hypertension has been described previously. Briefly, anesthesia was induced with sodium thiopental (25 mg/kg i.v.) and maintained with halothane anesthesia (1–2%). The trachea was intubated, and the animals were mechanically ventilated. A bilateral flank incision was performed using a sterile surgical technique. A unilateral nephrectomy was performed, and a stainless steel screw clamp, similar to that described by Ferrario et al., was implanted on the contralateral renal artery. The clamp was tightened until renal blood flow produced a thrill in the artery distal to the clamp. The incision was closed, and each dog received ampicillin (500 mg i.m.) and bicillin (900,000 units i.m).

To measure arterial pressure in awake normotensive and hypertensive dogs, a catheter was placed into the omocervical artery 8–9 weeks after the renal surgery. To accomplish this, the dogs were anesthetized with sodium thiopental (25 mg/kg i.v.) and ventilated. The omocervical artery was isolated via a supraclavicular incision and cannulated with a heparin-filled catheter. The catheter was tunneled subcutaneously to a position between the scapulae and the incision closed.

One day after placement of the omocervical catheter, awake arterial pressure was measured with a Statham transducer placed at the mid-chest level while the animals were conscious.

Isolated Heart Preparation

On the day of the study the dogs (controls, n=23; hypertensive, n=13) were anesthetized with sodium thiopental (25 mg/kg i.v.) and α-chloralose (50 mg/kg plus sodium borate 50 mg/kg i.v.), intubated, and ventilated with a respirator (Harvard Apparatus, South Natick, Mass.). A catheter was inserted into the femoral vein for drug administration, and a left thoracotomy was performed at the fourth intercostal space. A stainless steel catheter (4 mm o.d.) was inserted into the ascending aorta via the innominate artery for collection of blood for the perfusion system. The left main coronary artery was isolated for later cannulation and perfusion. After administration of heparin (750 units/kg i.v.) approximately 800 ml blood was collected via the aortic catheter. The heart was rapidly isolated, and a stainless steel catheter (3.5 mm o.d.) was advanced into the left main coronary artery via the coronary ostium and secured. The left main coronary artery was perfused from a pressurized reservoir initially at 80 mm Hg. The left ventricle was arrested in diastole with intracoronary lidocaine in the perfusate (10 ml of 2% lidocaine). Supplemental lidocaine was injected into the perfusion line as required. Adenosine (6 mg/min) was continuously infused into the perfusion line to produce maximal coronary vasodilation. The posterior left ventricle at the junction of the interventricular septum and the free walls of the left and right ventricles were incised to expose the subendocardium. The edges of the incision were hemostatically clamped or tied so that all visible sources of arterial bleeding were eliminated. Venous blood was collected by gravity drainage in a rotating disk oxygenator, and the blood gases and pH were maintained within physiological ranges by varying the inflow rate of gas (95% O2–5% CO2). The oxygenated blood was pumped through a filter to the pressure reservoir. The pressure perfusing the heart was measured at the tip of the coronary catheter. Temperature of the blood was kept at 37°C.

The left main coronary perfusion pressure was measured with a Statham transducer connected to a side port at the tip of the catheter. The coronary flow was measured with an in-line electromagnetic flow probe in the left main coronary perfusion circuit. After each experiment 5 ml of 2.5% Evans blue solution in saline was injected through the left main coronary catheter to delineate the perfused area and the flow transducer was calibrated by timed collection of blood into a cylinder. The weight of the left ventricle was measured.

Microvascular Preparation

An intravital microscope (Plemopak, E. Leitz, Rockleigh, N.J.) was used to visualize coronary microvessels. The epicardial or endocardial surface of the left ventricle was illuminated with a xenon light source. The microscope objective was Leitz A6 (numerical aperture, 0.18) and the eyepiece was ×10. Differentiation of microvascular arteries and veins was performed by viewing the sequence of illumination of vessels with a Leitz fluorescent filter after injection of fluorescein isothiocyanate dextran (MW, 149,000; Sigma Chemical Co., St. Louis, Mo.) injected as a bolus of 0.1 ml (20 mg/ml in 0.9% saline) into the perfusion circuit. The arterial circulation fluoresced first and the venous circulation later.

Microvascular pressures were measured in coronary microvessels by using a servo-null technique (Instrumentation for Physiology & Medicine, Inc., San Diego, Calif.). The micropipette with the tip diameter of 2–5 μm was filled with a 1.5 M NaCl solution and beveled at an angle of 15–25° to achieve a final probe impedance of 2.8–3.5 MΩ. The micropipette was mounted in an electromechanical micromanipulator that could move in three dimensions. Under microscopy, the micropipette was inserted into a target vessel for pressure measurements. To test the validity of the recorded pressure, several criteria were used. If the micropipette was in the lumen of the microvessel and was patent, increasing the gain of the servo-null system would induce high-frequency oscillations superimposed on the pressure tracing but would not change the mean pressure. If the micropipette was in the lumen of the microvessel and was not plugged, the recorded pressure would not change when the balance point for the servo-null system was varied. Furthermore, the microvascular pressure was expected to follow changes over a range of 5 mm Hg in left main coronary perfusion pressure. Microvascular pressures were accepted only if all of these criteria were fulfilled.

To measure microvascular diameters, a silicon-intensified tube video camera (General Electric, Owensborough, Ky.) was optically coupled to the intravital microscope. After each experiment, images of the vessels and a micrometer grid projected in the microscopic field were recorded on videotape and digitized with a video digitizer (Imaging Technology, Woburn, Mass.). The digitized images were displayed on a high-resolution monitor (National Japan), and the edges of the vessels and the micrometer were aligned with cursors on a digitizing tablet (Summa Graphics, Seymour, Conn.).
computer program was used to calculate vessel diameter.

**Measurement of Myocardial Perfusion**

Regional myocardial blood flow was measured with the radioactive microsphere technique. A mixing chamber was inserted in the perfusion line between the left main coronary catheter and the pressurized reservoir. A donor dog was used to collect supplemental blood (1,200 ml) for withdrawal of reference blood flows. Microspheres (approximately 3x10^-3, 15-μm diameter) labeled with ^58^Sr, ^85^Sr, ^14^Ce, ^51^Cr, or ^51^Co were vortexed for 5 minutes and injected upstream from the mixing chamber. Two reference flow samples were withdrawn from the perfusion line at a constant rate of 2.47 ml/min, beginning 10 seconds before the microsphere injection and continuing for 30 seconds. During microsphere injection, the venous outflow from the heart was collected and removed and supplemental blood was infused into the perfusion system. Tissue and reference samples were counted in a germanium crystal gamma counter (Canberra Industries Inc., Meriden, Conn.), and myocardial blood flow (MBF) was calculated using the equation

\[
MBF (ml/min/100 g) = CM (counts/time/g) \times W (ml/min)/CR (counts/time)
\]

where CM is sample counts, W is withdrawal rate of the pump, and CR is reference blood-flow counts. Myocardial blood flow was expressed as the mean of all samples in each study.

**Experimental Protocols**

In the present study, two different experimental protocols were used. In the first protocol (normotensive dogs, n=19; hypertensive dogs, n=10), we measured microvascular pressures in the endocardium and epicardium. The order in which these measurements were obtained was randomized. Initially, microvascular pressure was measured at 80 mm Hg of left main coronary pressure, and the perfusion pressure was gradually increased or decreased. In some vessels, the measurements were repeated at all perfusion pressures (60, 70, 80, 90, and 100 mm Hg). However, microvascular pressures were not obtained at all perfusion pressures in all microvessels because of displacement of the pipette from the microvessel during changes in perfusion pressure. The duration of recording for the measurement of microvascular pressure at each perfusion pressure was 30–40 seconds. The duration of the experiment was approximately 2 hours after the incision of the ventricle. In a few vessels, the perfusion pressure was increased up to 140 mm Hg.

In the second protocol (normotensive dogs, n=4; hypertensive dogs, n=3), myocardial blood flow was measured at a perfusion pressure of 80 mm Hg before and 30 minutes after the incision of the ventricle with the radioactive microsphere technique.

**Experimental Calculations**

All measurements of coronary microvascular pressures were performed in maximally dilated arterioles and venules approximately 100 μm in diameter. To compare the pressure losses between the left main coronary perfusion pressure and the arteriolar and venular pressures in hypertensive hearts with those in normotensive hearts, the microvascular pressure was expressed as a percentage of the perfusion pressure.

**Data Analysis**

Microvascular pressure and diameter were compared by analysis of variance in conjunction with Scheffe’s multiple comparison test. Comparisons of arterial pressure, coronary blood flow, and left ventricular size between and within the normal and hypertensive dogs were made by unpaired t test and paired t test, respectively. The data were presented as mean±SEM, and the level of statistical significance was p<0.05.

**Results**

**Baseline Characteristics**

As shown in Table 1, the average mean arterial blood pressure in the dogs subjected to renal surgery was 130±3 mm Hg or about 30% higher than that of the control animals (102±4 mm Hg). The left ventricular wet weight averaged 162±4 g in the hypertensive group and 137±4 g in the control group, respectively, resulting in the significantly greater left ventricular/body weight ratio in the hypertensive dogs (Table 1). Thus, renovascular hypertension produced significant left ventricular hypertrophy.

Maximal left main coronary blood flow induced by adenosine infusion was 418±15 ml/min (at 80 mm Hg of perfusion pressure) in the control group versus 393±26 ml/min in the hypertensive group (p=NS). When normalized for left ventricular mass, however, coronary flow during adenosine infusion was significantly less in dogs with hypertension and hypertrophy (243±18 versus 308±13 ml/min/100 g in the control group, Table 1). Over the course of the experiment, coronary flow remained stable at any given perfusion pressure. For example, maximal coronary flow per left ventricular mass in the control group (at 80 mm Hg of perfusion pressure) was 308±13 and 280±13 ml/min/100 g (p=NS) before the incision and at the end of the experiment, respectively.

**Myocardial Blood Flow**

Maximal regional myocardial blood flow before and after the incision of the left ventricle is shown for each

**Table 1. General Observation in Control Dogs and Dogs With Hypertension and Left Ventricular Hypertrophy**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=23)</th>
<th>HT-LVH (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>23±1</td>
<td>24±1</td>
</tr>
<tr>
<td>LV weight (g)</td>
<td>137±±4</td>
<td>162±±6*</td>
</tr>
<tr>
<td>LV weight/body wt (g/kg)</td>
<td>6.1±0.1</td>
<td>6.8±0.2*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>102±4</td>
<td>130±±4*</td>
</tr>
<tr>
<td>Maximum LMCBF at 80 mm Hg of perfusion (ml/min)</td>
<td>418±15</td>
<td>393±±26</td>
</tr>
<tr>
<td>Maximum LMCBF/100 g at 80 mm Hg of perfusion pressure (ml/min/100 g)</td>
<td>308±±13</td>
<td>243±±18*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Maximum LMCBF at 80 mm Hg of perfusion pressure was measured before the incision of the ventricle. HT-LVH, hypertension and left ventricular hypertrophy; LV, left ventricular; LMCBF, left main coronary blood flow.

*p<0.01, control vs. HT-LVH.
region in Table 2. In both normotensive and hypertensive dogs, there was no significant difference in myocardial flows after incision of the left ventricle.

**Microvascular Pressures in Normotensive and Hypertensive Hearts**

Maximally dilated coronary diameters at the site of micropuncture were measured at 80 mm Hg of perfusion pressure. In control dogs, diameters in epicardial and endocardial arterioles were 114±7 (n=19) and 100±12 μm (n=13), respectively, and those in epicardial and endocardial venules were 128±11 (n=8) and 127±10 μm (n=11), respectively. In dogs with hypertension and hypertrophy, diameters in epicardial arterioles, endocardial arterioles, epicardial venules, and endocardial venules averaged 114±10 (n=10), 106±14 (n=7), 136±8 (n=8), and 124±9 μm (n=10), respectively. There were no significant differences in vessel diameters within each or between groups.

Arteriolar and venular pressures in epicardium and endocardium were increased in a linear fashion as the aortic perfusion pressures were progressively increased both in dogs with hypertension and hypertrophy and in control dogs (Figure 1). In a few instances in which aortic pressure was increased to 140 mm Hg of perfusion pressure, there was a linear relation between perfusion pressure and microvascular pressure in both groups. In both groups, microvascular pressures in endocardial arterioles were significantly lower at all coronary perfusion pressures than those in epicardial arterioles (Figure 1). Microvascular pressures in endocardial venules tended to be higher than those in epicardial venules at any perfusion pressure, but these differences were not statistically significant in either group (Figure 1).

**Comparison Between Normotensive Dogs and Dogs With Hypertension and Hypertrophy**

In the epicardium, the microvascular pressures in both arterioles and venules were similar in control and hypertensive dogs at all perfusion pressures (Figure 2). In contrast, the microvascular pressures in endocardial arterioles were lower in dogs with hypertension and hypertrophy than in controls (p<0.05 at 90 and 100 mm Hg of perfusion pressure; Figure 3, left panel). Pressures in the endocardial venules at any perfusion pressure tended to be higher in hypertensive dogs than in controls, but significance was not attained (Figure 3, right panel).

**Discussion**

This study of isolated arrested hearts demonstrated that both in dogs with hypertension and hypertrophy and in control dogs, endocardial arteriolar pressure during maximal vasodilation was significantly lower than epicardial microvascular pressure. The greater decrement in microvascular pressures in the subendocardium in normotensive dogs is similar to the findings in pigs by Chilian.12 Furthermore, this transmural microvascular pressure loss was increased in dogs with hypertension and left ventricular hypertrophy. These observations

![Figure 1. Graphs showing epicardial (Epi) and endocardial (Endo) microvascular pressures in maximally dilated vessels of dogs with hypertension and hypertrophy and the controls at 60, 70, 80, 90, and 100 mm Hg of left main coronary (LMC) perfusion pressure. Values are mean±SEM. The data of epicardial arterioles in normotensive dogs at 60, 70, 80, 90, and 100 mm Hg of LMC pressure represent 14, 15, 19, 14, and 14 vessels, respectively. Endocardial arterioles, 12, 12, 13, 11, and 9 vessels. Epicardial venules, 7, 7, 8, 8, and 8 vessels. Endocardial venules, 10, 9, 11, 10, and 10 vessels, respectively. The data of epicardial arterioles in hypertensive dogs represent 9, 8, 10, 9, and 10 vessels, respectively. Endocardial arterioles, 7 vessels at all perfusion pressures. Epicardial vein, 8 vessels at all perfusion pressures. Endocardial vein, 9, 8, 10, 9, and 10 vessels, respectively. *p<0.05, epicardial arteriole vs. endocardial arteriole. Although significance symbols are not represented, in both the hypertensive and control groups, microvascular pressures of arterioles are significantly higher than those of venules at all LMC pressures (p<0.05).
were obtained in the absence of myocardial contraction, suggesting that inherent differences in the vasculature are important factors in the transmural gradient of microvascular pressures.

In the present study the left ventricular weight-to-body weight ratios in the normotensive control group were greater than previously reported from our laboratory. Two factors may have contributed to this result. First, there may have been an increased blood volume in these hearts with maximal vasodilation, and second, the animals used in the control group were nonconditioned dogs with slightly leaner builds than the conditioned dogs with left ventricular hypertrophy and hypertension. Both factors could have contributed to the higher than normal left ventricular weight-to-body weight ratios.

An important implication of these results is that the proximal coronary pressure is not transmitted uniformly across the left ventricular wall and that penetrating vessels traversing from subepicardium to subendocardium are altered in hypertrophied hearts. The transmural pressure loss may be attributed to differences in the physical characteristics of the microcirculation such as vascular lumen diameter, length and branching pattern in vessels, and wall stress independent of cardiac motion between subendocardium and subepicardium. However, in this study it is unlikely that a change in lumen diameter contributes to the greater pressure loss across the myocardium in hypertension and hypertrophy. Although coronary arteries in spontaneously hypertensive rats have an increased wall/lumen ratio, Tomanek and coworkers have not demonstrated medial hypertrophy in either subepicardial or subendocardial arterioles during the first 6 weeks to 7 months of renal hypertension in canines. The left ventricle has two types of intramyocardial blood vessels. One is an artery that ramifications within the first third of the myocardial thickness by shallow branching from epicardial vessels, and the second perforates the myocardial wall until it connects with the subendocardial plexus to supply the inner or deep portions of the myocardium. Thus, a difference in the branching pattern of vessels exists between subepicardium and subendocardium. The development of left ventricular hypertrophy may elongate the pathway as well as increase the muscle mass to be perfused by the perforating vessel. Hittinger et al have demonstrated that in dogs with left ventricular hypertrophy and failure induced by aortic banding, myocardial fibrosis is greater in the subendocardium and there is a trend toward increased connective tissue in subendocardial and mid-wall. The results of the present study would suggest that the lower feed pressure into the subendocardial microcirculation in animals with left ventricular hypertrophy

Figure 2. Bar graphs showing microvascular pressures expressed as a percent of perfusion pressure in epicardial arterioles and venules approximately 100 μm in diameter in hearts from normotensive and hypertensive dogs. Values are mean ± SEM. See legend to Figure 1 for numbers of vessels. LMC, left main coronary.

Figure 3. Bar graphs showing microvascular pressures expressed as a percent of perfusion pressure in endocardial arterioles and venules approximately 100 μm in diameter in hearts from normotensive and hypertensive dogs. Values are mean ± SEM. See legend to Figure 1 for numbers of vessels. LMC, left main coronary.
secondary to hypertension may be one of the factors involved in the vulnerability of the subendocardium to ischemia.

Numerous in vivo studies have reported that total coronary vascular resistance is similar between normotensive and hypertensive dogs during maximal vasodilation.\(^8,20,23,24\) Minimum coronary vascular resistance per unit mass of left ventricle, which is an indicator of the cross-sectional area of the vascular bed, is higher in dogs with hypertension and hypertrophy than in normotensive dogs. This increased minimal coronary vascular resistance can be due to the greater extracellular compression. Mueller et al.\(^6\) however, demonstrated that increased minimal coronary vascular resistance was observed in dogs with hypertrophy without hypertension. Furthermore, our study, which totally eliminated extracellular compression, indicated that maximal coronary blood flow expressed per mass of left ventricle in hypertrophied hearts was decreased. Thus, an anatomic or architectural alteration may be more important in the decreased coronary flow reserve although one cannot exclude the additional effects of compressive forces under in vivo conditions. This increase in minimal coronary vascular resistance can occur as a result of rarefaction, or a limited growth of resistance vessels, and a reduction in luminal radii of resistance vessels. Tomanek et al.\(^19\) have suggested that at the early stage (6–8 weeks) of hypertension with one kidney and one clip, inadequate arteriolar growth was responsible for the elevated minimal vascular resistance per mass of left ventricle. Because we investigated the early stage of hypertension in the present study in a similar way as Tomanek et al, impaired flow reserve observed in our study may be attributed to the insufficient coronary angiogenesis rather than the reduction in wall/lumen ratio of coronary arterioles. At the later stages (7 months) of renovascular hypertension, flow reserve and arteriolar density are normalized, suggesting that angiogenesis of left ventricular arterioles occurred.\(^20\) Evidence that arteriolar growth keeps pace with left ventricular hypertrophy in pigs given triiodothyronine has also been provided by Breisch et al.\(^25\)

Arteriolar segments approximately 100 \(\mu\)m in diameter in which we performed pressure measurements under maximally dilated conditions can be considered to be important components of coronary vascular resistance and vascular responses during autoregulation. Recent measurements of coronary microvascular pressure have indicated that approximately 50% of coronary vascular resistance is observed in arteriolar vessels greater than 100 \(\mu\)m in diameter under control conditions.\(^26\) Kanatsuka et al.\(^27\) and Chilian et al.\(^28\) have also demonstrated that vascular responses during autoregulation are predominantly found in microvessels less than 150 \(\mu\)m. Therefore, changes in the vascular anatomy secondary to hypertension and hypertrophy may partially explain the transmural difference in autoregulation and the impairment in autoregulation in the subendocardium of hypertrophied hearts reported by Harrison et al.\(^11\)

Previous studies in animals with experimental left ventricular hypertrophy have demonstrated that exercise- or pacing-induced perfusion abnormalities are most severe in the subendocardium.\(^5–10\) Hypertension and left ventricular hypertrophy are associated with increased size of myocardial infarction,\(^29,30\) suggesting that hypertension and left ventricular hypertrophy may predispose to subendocardial ischemia and infarction in the presence of coexisting coronary narrowing. Clinical observations have also indicated that the incidence of sudden death and malignant arrhythmias is increased in patients with coexisting coronary artery disease, hypertension, and left ventricular hypertrophy.\(^31\) The increased transmural pressure loss within the microvasculature of hypertensive hearts may in part contribute to these abnormalities in subendocardial perfusion and vulnerability to ischemic injury.

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**References**

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