The effect of hypertension and left ventricular hypertrophy on the lower range of coronary autoregulation

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ABSTRACT These studies were performed to test the hypothesis that left ventricular hypertrophy arising as a complication of chronic hypertension is associated with impaired coronary autoregulation. Twelve dogs with hypertension and left ventricular hypertrophy (one-kidney, one-clip model) and 11 normal dogs were instrumented and subsequently studied while conscious. Circumflex pressure, measured with an intracoronary catheter, was adjusted to 100, 75, and 40 mm Hg with a hydraulic occluder that was placed proximally. At each circumflex pressure, myocardial perfusion was measured with radioactive microspheres. Reduction of circumflex pressure over this range did not significantly alter heart rate, left atrial pressure, or arterial pressure. In normal dogs, reduction of circumflex pressure did not alter total myocardial perfusion or the transmural distribution of perfusion. In contrast, in dogs with hypertension and left ventricular hypertrophy, circumflex subendocardial perfusion decreased 46% when pressure was decreased from 100 to 40 mm Hg (p < .05 compared with normal). Autoregulation was quantified for each third of myocardium with the use of autoregulatory gain values (1 = perfect autoregulation; 0 = the absence of autoregulation). For pressure changes of 100 to 75 mm Hg, values for autoregulatory gain were near unity for all layers of myocardium in both groups of animals. When pressure was decreased from 75 to 40 mm Hg, values for autoregulatory gain among the normal and hypertensive groups were, respectively: for subepicardium 1 ± 0.2 (mean ± SE) vs 0.9 ± 0.2 (p = NS), for the midwall 0.8 ± 0.2 vs 0.5 ± 0.2 (p = NS), and for the subendocardium 0.8 ± 0.1 vs 0.1 ± 0.2 (p < .05). We conclude that hypertension and left ventricular hypertrophy are associated with a profound impairment of the lower range of autoregulation in the subendocardial myocardium. This abnormality of local control of myocardial perfusion may predispose the hypertrophied myocardium to ischemia or infarction in the setting of either coronary stenoses or systemic hypertension.


AUTOREGULATION is defined as the propensity for blood flow to an organ to be maintained at a constant level over a wide range of perfusion pressures.1, 2 In the coronary circulation of anesthetized animals, myocardial perfusion remains reasonably constant between pressures of 40 and 150 mm Hg.3–6 Below this range of pressures (the autoregulatory range), myocardial perfusion decreases in a linear fashion.3–6 Above this range myocardial perfusion progressively increases as coronary perfusion pressure is increased.6, 7 This autoregulatory range is substantially narrower in the subendocardium than in the subepicardium.7 The factors responsible for coronary autoregulation are unknown but likely include both metabolic and myogenic influences.1

In the cerebral circulation, chronic hypertension results in a shift of both the lower and upper limits of autoregulation.8–10 Although the effect of hypertension and concomitant left ventricular hypertrophy on coronary autoregulation have not been examined previously, there are several reasons to suspect that coronary autoregulation may be altered by this condition, especially the response to lowering perfusion pressure. First, almost all manifestations of coronary artery disease are exaggerated in patients with hypertension and left ventricular hypertrophy. It is conceivable that alterations of coronary autoregulation may contribute to the poor outcome in these patients. Second, hypertrophy of either ventricle is associated with blunted coronary...
vasodilatation in response to either transient ischemia or pharmacologic stimuli. Thus, one might assume that autoregulatory vasodilatation in response to decreased perfusion pressure may also be abnormal in hypertension and left ventricular hypertrophy. This assumption may not be true because it has recently been found that vasodilator reserve to pharmacologic stimuli persists when coronary perfusion is reduced by a decrease in the perfusion pressure below the autoregulatory range.

Several technical limitations have made it difficult to study the effect of hypertension and left ventricular hypertrophy on coronary autoregulation. First, coronary autoregulation is difficult to demonstrate consistently in the anesthetized, open-chest animal. Even under optimal conditions, autoregulatory gain values (when 1 is perfect autoregulation and 0 is absence of autoregulation) are less than 0.7 in these preparations. Second, in conscious animals, when a coronary artery is constricted to reduce perfusion pressure, it is difficult to measure intracoronary perfusion pressure distal to the stenosis. Finally, abnormalities of coronary autoregulation may result in regional rather than global alterations in myocardial perfusion. Thus, measurements of flow through epicardial coronary arteries with either electromagnetic or Doppler techniques may be insensitive to changes in autoregulation in myocardial hypertrophy.

In the present study we sought to determine the effect of chronic hypertension and left ventricular hypertrophy on the lower limit of autoregulation. We studied conscious, previously instrumented dogs 3 to 6 months after the onset of renal hypertension. Regional myocardial perfusion was assessed distal to an imposed coronary stenosis sufficient to decrease coronary pressure to desired levels. Our findings suggest that hypertension and left ventricular hypertrophy are associated with an impairment of the lower limit of coronary autoregulation in the subendocardial myocardium.

**Methods**

**Production of hypertension and left ventricular hypertrophy.** Hypertension and left ventricular hypertrophy were produced in 12 dogs (weight 19 to 30 kg), in a manner similar to that previously described. Briefly, the animals were anesthetized with sodium pentobarbital (30 mg/kg iv) and respiration was maintained with a mechanical ventilator. Through bilateral flank incisions the right kidney was removed and an adjustable metal clamp was placed on the left renal artery. This clamp was tightened until either a thrill or a marked decrease in the pulse was felt distal to the clamp.

Eleven adult conditioned dogs of similar weight were studied as controls.

**Long-term instrumentation.** Both control and hypertensive animals were instrumented so that myocardial perfusion could be measured with radioactive microspheres at varying circumflex coronary perfusion pressures in the conscious state. In the dogs with hypertension and left ventricular hypertrophy this second surgical procedure was performed 3 to 6 months after the initial surgery to induce hypertension and left ventricular hypertrophy.

The animals were anesthetized with a combination of 0.8 mg of fentanyl, 40 mg of droperidol, and sodium pentobarbital (10 mg/kg iv). By a sterile technique, the heart was exposed through a left thoracotomy. Catheters for radioactive microsphere injection and withdrawal of reference samples for determining myocardial blood flow were placed in the left atrium and left internal mammary artery, respectively. A hydraulic occluder was placed around the proximal circumflex coronary artery. An intracoronary catheter, fashioned from silicone rubber tubing (0.012 inch inside diameter, 0.025 inch outside diameter), was inserted into the circumflex coronary artery approximately 2 cm distal to the hydraulic occluder. All catheters and the tubing leading to the hydraulic occluder were tunneled subcutaneously and exteriorized between the scapulae. The catheters were filled with heparin and flushed every other day until the day of the study.

**Measurement of regional myocardial perfusion.** Regional myocardial perfusion was estimated with 15 μm radioactive microspheres labeled with either 46Sc, 99mTc, 82Sr, 123I, 51Cr, 57Co, 111In, 103Ru, 144Ce, or 153Co. For each flow measurement the quantity of radioactive microspheres injected was selected to approximate 20 mCi (approximately 5 to 8 × 10^8 microspheres). Before each microsphere injection the vial containing the microspheres was agitated for 5 min with a vortex mixer. Beginning 30 sec before, and continuing for 1.5 min after the microsphere injection, a reference blood sample was withdrawn at a rate of 3.2 ml/min from the catheter in the internal mammary artery. The radioactive microspheres were injected into the left atrial catheter and flushed with 5 to 10 ml of saline over a 30 sec period.

**Protocol.** Studies were performed at least 7 days after the animals were instrumented. The animals were brought to the laboratory on two to three occasions on separate days before the study to acquaint them with the laboratory environment. On the day of the study the animals were sedated with 0.04 mg of fentanyl and 2 mg of droperidol injected into the left atrium. This was repeated as needed to maintain adequate sedation. Five thousand units of heparin were administered intravenously. Although sedated, the animals remained conscious and either sat or lay quietly throughout the study.

We monitored arterial pressure, circumflex coronary arterial pressure, left atrial pressure, and heart rate throughout the study. All pressure transducers were maintained at the level of the mid thorax.

The general experiment protocol involved measuring myocardial blood flow with radioactive microspheres during stepwise decreases in circumflex pressure. We arbitrarily chose to estimate myocardial blood flow at circumflex mean pressures of approximately 100, 75, and 40 mm Hg for assessment of autoregulation during declining coronary perfusion pressures. In the control animals, the higher of these pressures was usually near mean arterial pressure and thus the hydraulic occluder was not used to attain a circumflex pressure of 100 mm Hg in these instances. In the animals with hypertension and left ventricular hypertrophy the mean arterial pressure was always higher than 100 mm Hg and the hydraulic occluder was partially distended to lower circumflex pressure to this level. In both groups of animals, the hydraulic occluder was always partially distended to attain circumflex pressures approximating 75 and 40 mm Hg.

Before each measurement of myocardial blood flow the hydraulic occluder was partially distended (except at the highest circumflex pressures in the control animals) to reduce circumflex...
pressure to a desired level for at least 1 min before radioactive microspheres were injected. During the microsphere injection we monitored heart rate and circumflex pressure. Immediately before and after microsphere injection we monitored mean and phasic left atrial and systemic arterial pressure. If hemodynamics did not remain stable during the period of microsphere injection or reference sample withdrawal, measurement of myocardial blood flow at that level of circumflex pressure was repeated. We considered changes in circumflex pressure greater than 10% as an indication to repeat the measurement of myocardial blood flow at that level of circumflex pressure. Neither left atrial pressure, heart rate, nor mean arterial pressure changed during the periods of microsphere injection or reference sample withdrawal.

**Identification of the circumflex and left anterior descending perfusion boundaries.** At the end of the experimental protocol, the dogs were killed with an overdose of sodium pentobarbital. Through a left thoracotomy, the heart of each was removed. Catheters were placed in either the left main coronary artery, or in the cases of separate left coronary ostia, in the origins of the circumflex and left anterior descending coronary arteries. The coronary vessels were subsequently perfused with a barium gelatin for 10 min at a pressure of 80 mm Hg.

The hearts were allowed to fix in a 9% formaldehyde mixture for 2 days. Subsequently, the atria and right ventricle were dissected from the left ventricle. The left ventricle was sliced into 1 cm sections parallel to the atrioventricular ring from base to apex. Radiographs of each of these sections were subsequently obtained at 20 keV, 2 mA, for 5 min. By following the distribution of each vessel and its branches from one slice’s x-ray to the next it was possible to define the perfusion field of both the circumflex and left anterior descending coronary arteries. Sections of tissue from the center of each perfusion field were obtained and cut into subendocardial, midwall, and subepicardial thirds weighing at least 0.25 g. These were subsequently weighed, placed in scintillation vials, and counted in a well-type gamma counter with use of a germanium crystal. Radioactive counts from the tissue samples and reference blood samples were used to determine myocardial perfusion by standard techniques.

**Interpretation of data and statistical analysis.** Under basal conditions, although there is temporal and spatial heterogeneity of perfusion to small myocardial segments, the average flow to larger areas, such as the circumflex-perfused myocardium and the left anterior descending–perfused myocardium, are similar. We therefore normalized circumflex perfusion as a percent of left anterior descending perfusion for each transmural third of the myocardium. Changes in this normalized circumflex perfusion resulting as a consequence of decreasing circumflex perfusion pressure were compared between control and hypertensive animals. Changes in the endocardial/subepicardial perfusion ratio in normal and hypertensive animals were also compared. The normalized circumflex flow was used to calculate autoregulation gain values for each layer of the myocardium based on the formula:

\[
\text{Autoregulation gain} = \frac{1}{(\text{change in flow/initial flow})/(\text{change in pressure/initial pressure})}
\]

With the use of this approach to quantify the adequacy of autoregulation, a value of 1 indicates perfect autoregulation, while a gain value of 0 indicates the absence of autoregulation. We used analysis of variance with a repeated-measures design to compare regional changes in myocardial perfusion, endocardial/epicardial flow ratios at varying circumflex pressures, and autoregulation gain values for changes in circumflex pressure between 100 and 75, 75 and 40, and 100 and 40 mm Hg. Within-group differences were tested after a Bonferroni correction. Unpaired t tests were used to compare differences in baseline hemodynamics and left ventricular/body weight ratios in the normal and hypertensive dogs. The data are presented as the mean ± SEM. A p value less than .05 was considered indicative of a significant difference.

**Criteria for acceptable experiment.** We accepted experiments in which transmural perfusion to the left anterior descending region was less than 225 ml/min/100 g. If left anterior descending perfusion exceeded this value we assumed the degree of autoregulation observed may not reflect that present under basal conditions. Five dogs with hypertension and LVH and two control dogs were eliminated for this reason. One other control dog was eliminated because after the first microsphere injection, the hydraulic occluder ruptured and could not be used to decrease circumflex perfusion pressure.

**Results**

**Baseline characteristics.** The average mean aortic pressure among the control animals was 106 ± 6 mm Hg in the control animals and about 20% higher in the animals with hypertension and left ventricular hypertrophy (table 1). The left ventricular weight averaged 103 g in the normal dogs and was increased by approximately 40% in the hypertensive group (table 1). The left ventricular/body weight ratio was 4.5 ± 0.04 in the control group and was also substantially increased in the animals with hypertension (table 1). Thus, hypertension resulted in significant left ventricular hypertrophy.

The baseline heart rate, transmural myocardial perfusion, and regional distribution of perfusion was not different in the control and hypertensive animals (table 1). Left atrial pressure was higher in the animals with hypertension and left ventricular hypertrophy than in the control group, but was not abnormally high in either group (table 1).

**Responses to decreasing circumflex perfusion pressure.** Lowering circumflex pressure from 100 to 75 or from 75 to 40 mm Hg did not alter aortic pressure, left atrial pressure, or heart rate in either group of animals (table 1).

**Myocardial perfusion.** Lowering circumflex perfusion pressure from 100 to 75 did not significantly alter circumflex transmural perfusion in either group of animals (table 1). Similarly, the circumflex transmural distribution of perfusion was not altered by this change in perfusion pressure in either group of animals (table 1, figure 1).

Lowering the circumflex perfusion pressure from 75 to 40 mm Hg did not alter either transmural or regional perfusion to the circumflex region in the normal animals (table 1, figure 1). In contrast, subendocardial perfusion significantly declined as a result of this pressure change in the animals with hypertension and left ventricular hypertrophy. Thus, the subendocardial to subepicardial ratio of perfusion markedly declined in the hypertensive animals, while not changing in the
TABLE 1
Hemodynamics and myocardial perfusion during CX occlusion of animals with HT-LVH vs controls

<table>
<thead>
<tr>
<th></th>
<th>LV weight (g)</th>
<th>LV/body weight ratio</th>
<th>AO pressure (mm Hg)</th>
<th>LA pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>CX flow (ml/min/100 g)</th>
<th>LAD flow (ml/min/100 g)</th>
<th>CX/LAD flow ratio</th>
<th>CX endo/epi ratio</th>
<th>LAD endo/epi ratio</th>
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<tr>
<td>Controls</td>
<td>8</td>
<td>103±5</td>
<td>4.5±0.4</td>
<td>106±6</td>
<td>2±2</td>
<td>110±11</td>
<td>132±16</td>
<td>128±14</td>
<td>1.02±0.04</td>
<td>1.3±0.1</td>
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<tr>
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<td>140±9</td>
<td>6.2±0.2</td>
<td>126±5</td>
<td>8±5</td>
<td>108±11</td>
<td>142±15</td>
<td>134±12</td>
<td>1.06±0.06</td>
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<td>HT-LVH at 100 mm Hg</td>
<td>7</td>
<td>—</td>
<td>—</td>
<td>125±8</td>
<td>7±5</td>
<td>104±5</td>
<td>151±14</td>
<td>145±11</td>
<td>1.03±0.05</td>
<td>1.4±0.1</td>
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Percent changes during CX pressure changes

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<td>1±3</td>
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<td>Mid to low</td>
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<td>High to low</td>
<td>7</td>
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Values are mean ± SEM.
HT-LVH = hypertension and left ventricular hypertrophy; LV = left ventricular; AO = aortic; LA = left atrial; CX = circumflex; LAD = left anterior descending; endo = endocardial; epi = epicardial.

*p < .05 controls vs HT-LVH.

normal group as a result of this decrease in circumflex perfusion pressure (table 1).

Over the entire range of pressure changes from 100 to 40 mm Hg, total transmural perfusion decreased in both the normal and hypertensive animals (table 1), although the degree of decline in transmural perfusion was greatest in the hypertensive animals. The transmural distribution of perfusion was not altered by this large change in circumflex perfusion pressure in the normal group, but it was markedly altered in the hypertensive animals, resulting in a decrease in the subendocardial/subepicardial flow ratio of 43% (table 1).

Autoregulation gain values were similar in the subepicardium and midmyocardium for pressure changes from 100 to 75 and from 75 to 40 mm Hg, and over the entire pressure range of 100 to 40 mm Hg, in the hypertensive and control animals. Likewise, subendocardial autoregulation gain values were similar in the hypertensive and control animals when circumflex pressure was decreased from 100 to 75 mm Hg. However, circumflex autoregulation gain values were significantly lower in the subendocardium for pressure changes of 75 to 40 and 100 to 40 mm Hg in the hypertensive animals (figure 2).

Discussion
In the present experiments, we found that autoregulation was excellent as pressure was changed from 100 to 75 mm Hg in hypertensive animals, but was virtually absent in the subendocardium of these animals when pressure was decreased from 75 to 40 mm Hg. This observation suggests that the lower limit of autoregulation is shifted toward higher pressures as a result of sustained hypertension and left ventricular hypertrophy. This effect of chronic hypertension on the coronary circulation is similar to that observed in the cerebral circulation in several preparations of hypertension in which both the upper and lower limits of autoregulation are shifted toward higher pressures.8–10

Advantages of the experimental design. In these experiments, we measured myocardial perfusion at varying perfusion pressures in conscious previously instrumented dogs. The advantage of this approach is that the effects of anesthesia and thoracotomy are avoided. Although autoregulation may be observed in anesthetized, open-chest animals, the gain values observed in this state are usually substantially less than unity, and often no greater than 0.5,21 suggesting impairment of autoregulation associated with the effects of surgery and anesthesia. The adequacy of autoregulation may be dependent on the anesthetic used or the depth and duration of anesthesia. In contrast to studies in anesthetized animals, in the present experiments in conscious animals, excellent autoregulation was observed in all layers of the myocardium for the entire range of
circumflex pressures in the control animals and in the epicardium and midwall among the hypertensive animals.

Disadvantages of the experimental approach. There are three disadvantages to studies of autoregulation in conscious animals. These will be discussed briefly.

First, the maintenance of myocardial perfusion in the setting of changing coronary perfusion pressure may be the result of several interacting factors. These include neural and reflex influences, alterations of extravascular forces (due to changes in intracardiac pressure or aortic pressure), and changes in heart rate. These factors are more difficult to control in the conscious animal than in the open-chest preparation. In our opinion, these factors probably did not contribute to the differences observed in the normal and hypertensive animals. While neural influences may importantly alter myocardial perfusion, particularly in the setting of a coronary stenosis, this modulation is minimal under basal conditions. Important changes in heart rate, aortic pressure, or left ventricular filling pressure did not occur in either group of animals during partial circumflex occlusion. Left atrial pressure was slightly higher in the hypertensive animals, but was not abnormally high in either group.

A second disadvantage of studies in conscious animals is that the upper range of autoregulation cannot be studied because it is not possible to selectively raise coronary perfusion pressure. The mean arterial pressure encountered in our hypertensive dog preparation is often at the upper limit of the autoregulatory range reported for normal animals in other studies. Despite this, resting myocardial perfusion is generally normal in this preparation of hypertension. This suggests that the upper limit of autoregulation may be shifted toward higher pressures in the setting of chronic hypertension.

A final potential disadvantage of studies of autoregulation in conscious animals is that only regional changes in perfusion pressure can be accomplished. In the present study we used partial circumflex occlusion to alter circumflex perfusion pressure. Because aortic pressure remained essentially unchanged by this maneuver, the potential existed for collateral flow to the myocardium perfused by the circumflex to occur from either the left anterior descending or the right coronary artery. There are several reasons why this likely did not influence our results. The majority of native collaterals interconnect large coronary arteries and thus arise and insert proximal to major sites of resistance in the coronary circulation. Thus, the driving pressure for any flow reaching the circumflex via collaterals is similar to circumflex pressure measured by the catheter distal to the hydraulic occluder. Under this circumstance, analysis of pressure/flow relationships calculated with pressure measured through this catheter would be valid whether or not collateral perfusion contributed to total myocardial perfusion of the circumflex. Additionally, we have shown that collateral perfusion is minimal in the absence of complete coronary occlusion, i.e., in the presence of continued...
antegrade perfusion through a partially stenosed vessel. Others have shown that flow through epicardial coronary vessels is not significantly altered by even large intracoronary arterial pressure differences. Finally, native collateral resistance is not altered by the development of hypertension and left ventricular hypertrophy. Because aortic pressure was higher in the group with hypertension and left ventricular hypertrophy, collateral driving pressure and total collateral flow would be expected to be higher in animals with hypertension than in controls. Therefore, the difference between circumflex perfusion in the normal and hypertensive dogs at the lower pressure might have actually been attenuated in the hypertensive group by the presence of collateral perfusion. In view of these several lines of reasoning, we conclude that collateral perfusion was likely insignificant in this study and if present would not have altered the interpretation of the results.

**Importance of the Gregg phenomenon in studies of autoregulation.** In some experimental preparations, altering coronary perfusion pressure may influence cardiac contractility and myocardial oxygen consumption. This phenomenon, termed the Gregg phenomenon or the garden hose effect, has most often been observed in isolated heart preparations and in open-chest anesthetized animals. If the Gregg phenomenon were exaggerated in hypertensive animals, decrements in coronary perfusion pressure would result in greater indirect decreases in myocardial perfusion related to exaggerated decreases in myocardial contractility and myocardial oxygen demand. While this hypothesis was not directly tested in the present studies, Pandian et al. have previously shown that decreasing coronary perfusion pressure has similar effects on myocardial thickening in normal and hypertensive animals. Canty has shown that the Gregg phenomenon does not occur in conscious animals with coronary perfusion pressure above 40 mm Hg. In this study, we sought to examine autoregulation in animals with stable systemic hemodynamics (suggesting minimal alterations of global left ventricular function during changes in coronary perfusion pressure). Thus, the Gregg phenomenon likely had little effect on the results of this experiment. However, if the Gregg phenomenon were augmented in the presence of hypertension and left ventricular hypertrophy, the effect of decreasing contractility would nonetheless be deleterious, resulting in decreased myocardial function and perfusion as a consequence of decreased coronary perfusion pressure.

**Rejected studies.** In these studies we eliminated five dogs with hypertension and left ventricular hypertrophy and two control dogs in which flow to the left anterior descending (normally perfused) myocardium was inordinately high. This was done to permit comparisons of autoregulation under conditions of basal myocardial perfusion and intact vasomotor tone. We assumed that if perfusion to the left anterior descending region was inordinately high, vasomotor tone was not at basal levels. Under these circumstances, abnormalities of autoregulation may reflect abnormally high basal levels of perfusion rather than an inability to maintain basal perfusion while coronary driving pressure is decreased. There are at least two possible explanations for why coronary perfusion may have been high in these several animals. First, the initial heart rate was higher in these dogs than in those included in the study (average = 123 beats/min for the hypertensive animals, and 140 beats/min for the normal animals vs 90 to 100 beats/min in the study animals). Second, compensatory hyperfunction of the myocardium perfused by the left anterior descending may have occurred in some studies as the perfusion pressure to the circumflex region was altered. Typically, when the hydraulic occluder was initially partially inflated, circumflex pressure would initially fluctuate by 10 to 20 mm Hg around a mean value and within approximately 1 min stabilize, at which time we performed the microscope injection. It is conceivable that episodes of transient ischemia may have produced regional dysfunction of the circumflex perfused myocardium, and concomitant hyperfunction of the left anterior descending perfused myocardium, increasing perfusion to this region. Although regional myocardial function was not measured in these experiments, global indexes of myocardial function suggest that left ventricular dysfunction may have occurred in the hypertensive dogs as circumflex pressure was decreased. The heart rate increased substantially (from an average of 123 to 137 beats/min) in these animals as circumflex pressure was decreased from 100 to 40 mm Hg. In the two normal dogs, the heart rate remained constant (although high) during alterations of circumflex pressure. As a result of these and likely other factors, left anterior descending perfusion during the three successive microsphere injections averaged 282, 292, and 275 ml/min/100 g in the rejected hypertensive dogs and 191, 267, and 453 ml/min/100 g at the respective microsphere injections in the rejected control dogs. Despite these confounding factors, autoregulation seemed superior in the rejected normal animals compared with that in the rejected hypertensive animals. Over the entire range of pressure changes, the autoregulation gain values were 0.4, 0.4, and 0.5 for the epicardium, midwall, and subendocardium, respectively, for the rejected normal animals.
Similar values for the hypertensive rejected animals were 0.4, -0.08, and -0.29. These comparisons are difficult to interpret because of the unstable hemodynamics and the small number of animals. However, they tend to support impaired subendocardial autoregulation in the setting of chronic hypertension.

Explanations for altered autoregulation in the presence of hypertension and left ventricular hypertrophy. These experiments suggest the lower range of autoregulation is shifted toward higher pressures in the setting of hypertension and left ventricular hypertrophy. There are several potential explanations for this finding. Myocardial hypertrophy is often associated with abnormal coronary vasodilator reserve in response to pharmacologic stimuli.11–15 Impaired vasodilator reserve may be an explanation for altered coronary autoregulation in the presence of hypertension and left ventricular hypertrophy. However, impaired vasodilator reserve in response to pharmacologic stimuli is not synonymous with altered vasodilatation in response to lowered perfusion pressure (altered autoregulation). Several groups have shown that when myocardial perfusion is decreased as the result of lowered coronary perfusion pressure, pharmacologic vasodilatation with adenosine or dipyridamole can markedly increase coronary flow.16–19

If coronary autoregulation is at least in part modulated by myogenic mechanisms, it is conceivable that long-term exposure to high perfusion pressures may reset the critical pressures that prompt myogenic vasodilatation in response to lowered pressure. Thus, coronary arterioles chronically constricted in response to sustained elevations of perfusion pressure may not vasodilate appropriately when pressure is lowered.

The left atrial pressure was significantly higher in the hypertensive animals than in the normal animals. While not abnormally high in either group, it is possible that higher left ventricular diastolic pressures may have impaired autoregulation in the hypertensive animals.

Finally, it has recently become apparent that segmental responses of the coronary circulation to neural, pharmacologic, and metabolic stimuli are heterogeneous.33–35 Hypertension may produce sustained myogenic constriction of segments of the coronary circulation proximal to segments of the vasculature responsive to metabolic demands. This would serve to protect the smaller coronary vessels from injury due to chronic exposure to elevated pressures. Thus, lowering perfusion may produce appropriate dilatation of resistance vessels that are reactive to metabolic stimuli, but not of more proximal vessels constricted in response to elevated pressures. This may serve to alter the lower range of autoregulation in the setting of hypertension and left ventricular hypertrophy.

Clinical implications. Impaired coronary autoregulation as a result of chronic hypertension may have important consequences both when blood pressure is abruptly lowered during antihypertensive therapy,36 and in the setting of coronary atherosclerosis. Hypertension predisposes to the development of coronary atherosclerosis.37 The incidence of sudden death and malignant arrhythmias is increased in patients with coexisting coronary artery disease, hypertension, and left ventricular hypertrophy.38 Hypertension and left ventricular hypertrophy are associated with increased size of myocardial infarction,39 suggesting that hypertension and left ventricular hypertrophy may predispose to subendocardial ischemia and infarction in the presence of coexisting coronary narrowing. In the presence of left ventricular hypertrophy, resting blood flow through the epicardial vessels is increased as a result of the enlarged perfusion territory of individual vessels. In at least some preparations of myocardial hypertrophy, the epicardial vessels do not enlarge to accommodate this increase in resting perfusion,40 and thus flow velocity is increased at rest and may be proportionally increased as coronary flow increases in response to metabolic demands. Since the pressure losses across a coronary stenosis are logarithmically related to flow velocity, the increase in coronary flow concomitant with myocardial hypertrophy may result in exaggerated pressure losses any coexisting coronary stenosis. Because left ventricular hypertrophy is associated with an impaired capacity for autoregulation, any pressure loss results in even greater decreases in myocardial perfusion than observed in normal hearts and predisposes the hypertrophied ventricle to the development of subendocardial ischemia and infarction.

References
8. Barry DI, Strandgaard S, Graham DI, Braendstrup O, Svendsen


40. Stack RS, Rembert JC, Schirmer B, Greenfield JC Jr: Relation of left ventricular mass to geometry of the proximal coronary arteries in the dog. Am J Cardiol 51: 1728, 1983
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