Increased Size of Myocardial Infarction in Dogs with Chronic Hypertension and Left Ventricular Hypertrophy

SAMON KOYANAGI, CHARLES L. EASTHAM, DAVID G. HARRISON, AND MELVIN L. MARCUS

SUMMARY Impaired coronary reserve in animals and patients with left ventricular hypertrophy (LVH) might be expected to augment infarct size following coronary occlusion (CO). To test this hypothesis, the circumflex coronary artery was acutely occluded in 30 control dogs and in 28 renal hypertensive (HT)-LVH dogs during the conscious state. Hemodynamics and regional myocardial flow (microspheres) were measured. After 48 hours of CO, we assessed infarct size pathologically and area at risk by postmortem coronary angiography. Mean arterial pressure (130 ± 5 mm Hg) and LV:body weight ratio (6.1 ± 0.1 g/kg) in HT-LVH dogs were about 35% greater than in control dogs (P < 0.05). During the 48 hours following CO, mortality rate was markedly increased in HT-LVH (54%) compared to control (17%) (P < 0.01). We performed a linear regression analysis of the relationship between area at risk (AR; % of LV mass) and infarct size (IS; % of LV mass); control, IS = 1.20AR - 25.6 (r = 0.96); HT-LVH, IS = 1.19AR - 16.3* (r = 0.95) (*P < 0.05 vs. control). Although the slopes of these relationships were similar, the intercepts were different. Consequently, the minimal AR associated with infarction was 35% smaller in HT-LVH (15 ± 2% of LV mass) than in control (22 ± 1%), and over the entire range of AR, the IS was increased in HT-LVH. The distance between the lateral extent of infarct size and area at risk in different layers of LV was measured. The increase in infarct size in the HT-LVH group reflected primarily an increase in midwall layer infarction. Increase in collateral flow to the risk area was attenuated in HT-LVH. In conclusion, infarct size relative to the area at risk is increased significantly in HT-LVH. This interaction between LVH and myocardial ischemia may significantly influence the outcome of myocardial infarction in patients with hypertension and LVH. Circ Res 50: 55-62, 1982

PATIENTS with systemic arterial hypertension are particularly susceptible to coronary artery disease (Robertson and Strong, 1968). Furthermore, once myocardial infarction occurs, it is much more likely to be fatal in patients with hypertension and left ventricular hypertrophy (LVH) than in normotensive patients (Kannel et al., 1969; Kannel, 1974; Kannel et al., 1975; Rabkin et al., 1977). The high morbidity and mortality from myocardial infarction have been attributed generally to accelerated occlusive atherosclerotic coronary lesions secondary to hypertension (Perper et al., 1973; Pick et al., 1974; Hollander et al., 1977). However, other factors could also contribute to the deleterious effects of coronary occlusion in hypertensive patients. Prolonged hypertension induces LVH. Ventricular hypertrophy increases the diameter of myocardial cells without a proportional proliferation of capillary vessels (To-

manek, 1979; Murray et al., 1979; Breisch et al., 1980). Also, many recent studies suggest that coronary vasodilator reserve is compromised in LVH both in humans and animals (Mueller et al., 1978; O'Keefe et al., 1978; Rembert et al., 1978; Marcus et al., 1980).

These fundamental abnormalities in the coronary circulation may potentiate the adverse effects of ischemic injury in LVH. Therefore, we hypothesized that the extent of myocardial infarction following sudden coronary occlusion may be greater in pressure-induced LVH. The experiments described in this manuscript support this hypothesis.

Methods

Preparation of the Dogs

Systemic hypertension was induced in 28 adult mongrel dogs (weight: 14-27 kg). The method of producing hypertension has been described previously in detail (Mueller et al., 1978) and will be summarized briefly.

Under sodium pentobarbital anesthesia (30 mg/kg, iv), a bilateral flank incision was performed under sterile conditions. An externally adjustable clamp, described by Ferrario et al. (1971), was implanted around a renal artery and tightened until a thrill could be felt at the distal renal artery. Then
the kidney on the contralateral side was removed. A second surgical procedure was performed 6-8 weeks after the renal surgery. The dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv), ventilated with a respirator, and a left thoracotomy was performed through the 4th intercostal space. Catheters were placed in the ascending aorta through the left internal mammary artery and in the left atrium through its appendage. A 1-0 silk snare was placed around the circumflex coronary artery distal to the first or second marginal branch (1-3 cm from the origin of the circumflex artery) in 19 dogs. In the other nine dogs, snare was placed distal to the second marginal branch (3-5 cm from the origin of the circumflex artery). The snare and the catheters were tunnelled subcutaneously and attached to skin buttons at the back. The catheters were filled with heparin (1000 U/ml) and flushed every other day.

Thirty adult mongrel dogs (weight: 17-29 kg) were used as controls. These dogs also underwent thoracotomy for placement of catheters and a coronary arterial snare. The snare was placed around the circumflex coronary artery distal to the first marginal branch (n = 20) or the second marginal branch (n = 10).

Experimental Protocol

Studies were performed 7-12 days after the thoracotomy when all dogs appeared healthy and were free from severe infection, anemia (hematocrit was 38-45%) or chronic renal failure (serum creatinine was <1.8 mg/ml). About 20 minutes before the experiment, morphine sulfate (2-5 mg) was given intramuscularly. The arterial and left atrial catheters were connected to Statham P23dB strain gauges placed at midchest level. Aortic and left atrial pressures and the lead II electrocardiogram were recorded continuously.

When the dogs were lying quietly and hemodynamics were stable, myocardial blood flow was measured with microspheres. Lidocaine (1.5 mg/kg, iv) was then administered, and the circumflex coronary artery was acutely and totally occluded with the exteriorized snare. Some dogs became restless immediately after the occlusion, but that was usually transient. Ventricular fibrillation occurred in three control dogs (10%) and eight hypertensive dogs (29%) within 2 hours. Although cardiopulmonary resuscitation was performed, none of these dogs recovered. In surviving dogs, measurements of hemodynamics and myocardial blood flow were obtained 5 minutes, 2 hours, and 48 hours after coronary occlusion. The dogs then were anesthetized with sodium pentobarbital and killed with potassium chloride.

Measurement of Regional Myocardial Perfusion

Regional myocardial perfusion was measured, using carbonized radioactive microspheres 7-10 μm in diameter labeled with 46Sc, 85Sr, 90Nb, 113Sn or 125I. For each flow measurement, 20-μCi microspheres (11.6 ± 0.7 x 10^6) were injected through the left atrial catheter, which was subsequently flushed with 10 ml of saline over 10 seconds. Prior to the injection, the vial containing the microspheres suspended in 10% dextran and 0.05% of Tween-80 was mechanically agitated for at least 5 minutes. A reference arterial blood sample was withdrawn from the catheter in the aortic arch at a constant rate of 2.06 ml/min with a Harvard pump, starting 20 seconds before microsphere injection and continuing until 2 minutes after injection. During measurements of blood flow with microspheres, a continuous electrocardiogram showed no arrhythmias or significant change in heart rate. Left atrial pressure and arterial pressure did not change significantly before or after microsphere injection.

For analysis of perfusion, myocardial samples were obtained from the following regions: normally perfused region (non-risk region perfused by left anterior descending coronary artery), border region 5 mm lateral to the area at risk, normal appearing region within the area at risk, and infarct region. Each region was subdivided into subepicardial, midwall, and subendocardial layers of about equal thickness. In the infarct area, the posterior papillary muscle was separated from other endocardial segments. A transition zone about 2 mm wide between the normal-appearing risk region and infarct area was excluded from perfusion analysis to avoid cross-contamination. Myocardial segments were weighed, placed in plastic scintillation tubes, and counted for 5 minutes in a 3-inch well counter. Myocardial blood flow in each sample was calculated by the formula:

$$MBF = \frac{(Cm \times 100 \times RBF)/Cr}{MBF = \frac{(Cm \times 100 \times RBF)/Cr}{MBF = \frac{(Cm \times 100 \times RBF)/Cr}{MBF = \frac{(Cm \times 100 \times RBF)/Cr}{MBF = \frac{(Cm \times 100 \times RBF)/Cr}{MBF = \frac{(Cm \times 100 \times RBF)/Cr}}$$

where MBF = myocardial blood flow (ml/min x 100 g), Cm = counts/g of myocardium, RBF = reference blood flow (the rate of withdrawal from the reference artery), and Cr = total counts in the reference blood.

Measurement of Infarct Size and Area at Risk

After the heart was excised, cannulas (o.d. = 2-3 mm) were secured in the left main and right coronary arteries. When the left anterior descending coronary and the left circumflex coronary artery had separate orifices from the aorta, each artery was cannulated at its origin. Cannulas were flushed with saline to remove blood from coronary vessels. A barium-gelatin mixture then was perfused simultaneously into the coronary vessels at a perfusion pressure of 50 mm Hg, and sites of leakage were stopped by ligation. Then, the perfusion pressure was increased to 20 mm Hg higher than the mean aortic pressure in situ (about 120 mm Hg in control dogs and 150 mm Hg in hypertensive dogs) and maintained for 5 minutes. The total volume of
injectate was 5–7 ml. After the hearts were fixed in 10% formaldehyde overnight, stereoscopic radiographs of the whole heart were taken. The atria and the right ventricle were removed, and the left ventricle was sectioned into seven transmural slices of approximately equal thickness (0.8–1.1 cm) parallel to the atrioventricular groove. Stereoscopic radiographs of the ventricular slices were then taken without magnification. Microscopic examination showed that the injectate filled the coronary vessels to the arteriolar level in all hearts. The barium-gelatin mass filled the arterial bed distal to the occlusion in dogs that survived more than 24 hours after occlusion. However, in the dogs that died immediately after coronary occlusion, the distal bed was not filled with injectate because of inadequate collaterals. The perfusion area of the occluded artery, i.e., the area at risk, was determined by carefully following the course of occluded and non-occluded vessels by means of stereoscopic views of the transverse slices and whole left ventricular arteriograms.

Infarct area was determined by gross pathological examination. After 24 hours of coronary occlusion, the infarcted myocardium was clearly delineated from the surrounding normal muscle. Then, the tracings of the area at risk and the infarct area of the top of each slice were superimposed, and the normal area, infarct area, and area at risk of all slices were measured using computerized planimetry. The infarct and risk area for subepicardium, midwall, subendocardium, and papillary muscle were measured independently.

Thereafter, the ventricular slices were trimmed of the right ventricle, connective tissue, and epicardial large vessels, and weighed. The mass of each risk and infarct region was calculated by multiplying the average area of the top and the bottom of a slice expressed as a percentage of total area times the weight of the slice. For each heart, these various regions were summated. Area at risk and infarct area were determined by two observers, independently. The interobserver difference was minimal: 0.3% of left ventricular weight for mass of risk region and 0.2% for infarct mass.

Histology

Myocardial segments selected from each dog were fixed in a 10% buffered formalin solution for at least 2 weeks. These segments were prepared for histological sections using hematoxylin and eosin stain and examined by two observers. Histological criteria for myocardial infarction include pyknosis, karyorrhexis, karyolysis, fiber fragmentation, polymorphonuclear cell infiltration, loss of cross-striations of myocardial fibers, and deep eosinophilic appearance of fibers (Maroko et al., 1971). A tissue area was not classified as infarcted unless at least two of the above criteria were fulfilled. The estimated extent of infarction was expressed as a percentage of total area in each specimen.

Data Analysis

The data are presented as mean values ± se, and the level of statistical significance was P < 0.05. Hemodynamic and myocardial blood flow data were analyzed by analysis of covariance with multiple comparisons performed using Duncan’s multiple range test. Comparison of left ventricular weight between groups was made by unpaired t-test. Chi-square test was used to analyze the difference in mortality rate and lateral border width between groups. Regression lines were fitted to the grouped data using the least-squares method. The slopes and the intercepts of the regression lines of the relationships between infarct size and area at risk were compared using an unpaired t-test.

Results

Anatomical Characteristics

Left ventricular weight was 101 ± 4 g in control dogs, and 125 ± 4 g in hypertensive dogs (P < 0.05). The left ventricular weight-to-body weight ratio was 4.5 ± 0.1 g/kg in controls and 6.1 ± 0.1 g/kg in hypertensives (P < 0.01). Thus, left ventricular mass was increased by about 35% in hypertensive dogs.

Mortality Rate

During the 48 hours after coronary occlusion, 5 of 30 control dogs (17%) died, whereas 15 of 28 dogs (54%) with hypertension and left ventricular hypertrophy (HT-LVH) died (P < 0.01). However, the risk area was similar in the control group (31 ± 2% of left ventricular mass) and in the HT-LVH group (30 ± 2%). The risk area in dogs that died prematurely (30 ± 2%) was not significantly different from that in survival dogs (31 ± 2%). Furthermore, increases in left ventricular mass and arterial pressure were almost identical between the dogs that died prematurely and the survival dogs in HT-LVH group. Among these animals, 4 control and 12 HT-LVH died too soon (less than 24 hours) to allow assessment of infarct size. Accordingly, these 16 dogs were excluded from further analysis.

Hemodynamic Changes (Table 1)

During the control state, aortic pressure was about 35% higher (P < 0.05) in the HT-LVH group. Heart rate and left atrial pressure were similar in the control and HT-LVH groups. After coronary occlusion, heart rate and left atrial pressure increased to a similar extent in both groups. Aortic pressure decreased in the HT-LVH group, but aortic pressure remained higher than that of the control group during the 48 hours following occlusion.

Relationship between the Size of Myocardial Infarct and the Area at Risk

Overall, the infarct:risk ratio was higher in the HT-LVH group than in the control group (P < 0.05, Table 2). The relationship of the infarct size and
TABLE 1  Hemodynamic Effects of Sudden Coronary Occlusion in Control Dogs and Hypertensive Dogs with Left Ventricular Hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>Before occlusion</th>
<th>5 min</th>
<th>2 hr</th>
<th>48 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>93 ± 4</td>
<td>109 ± 5</td>
<td>110 ± 5†</td>
<td>112 ± 5†</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>94 ± 5</td>
<td>123 ± 7†</td>
<td>106 ± 5†</td>
<td>111 ± 6†</td>
</tr>
<tr>
<td><strong>Systolic arterial pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>118 ± 3</td>
<td>111 ± 2†</td>
<td>116 ± 3</td>
<td>109 ± 2†</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>166 ± 6*</td>
<td>144 ± 5††</td>
<td>137 ± 5††</td>
<td>133 ± 5††</td>
</tr>
<tr>
<td><strong>Mean arterial pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>94 ± 2</td>
<td>93 ± 1</td>
<td>97 ± 2</td>
<td>89 ± 2†</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>130 ± 5*</td>
<td>123 ± 4*</td>
<td>115 ± 5††</td>
<td>110 ± 5††</td>
</tr>
<tr>
<td><strong>Diastolic arterial pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>81 ± 2</td>
<td>83 ± 1</td>
<td>86 ± 3</td>
<td>77 ± 2</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>112 ± 4*</td>
<td>110 ± 3*</td>
<td>103 ± 5††</td>
<td>96 ± 4††</td>
</tr>
<tr>
<td><strong>Left atrial pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4 ± 1</td>
<td>7 ± 1†</td>
<td>6 ± 1†</td>
<td>6 ± 1†</td>
</tr>
<tr>
<td>HT-LVH</td>
<td>6 ± 1</td>
<td>7 ± 1†</td>
<td>7 ± 1†</td>
<td>7 ± 1†</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. HT-LVH = hypertension with left ventricular hypertrophy.
* P < 0.05 compared to control group.
† P < 0.05 compared to preocclusion value.

The area at risk was plotted for individual dogs (Fig. 1). The linear regression line was estimated using only points with infarction in both groups (n = 21 for controls, n = 15 for HT-LVHs). Although the slope of the relationship was similar in the control and HT-LVH groups, the intercept for zero-infarct was shifted from 22.5% ± 1.1 in controls to 15.5% ± 1.7 (P < 0.05) in HT-LVH dogs. Consequently, overall infarct size in the HT-LVH group was greater than that in the control group over the entire range of risk areas that we examined.

We also determined the infarct-risk relationships in various transmural layers (Koyanagi et al., in press). In the subendocardial and midwall layers, the zero-infarct intercepts of the infarct-risk relationship were significantly decreased in the HT-LVH group (Table 3). Increased size of infarction in the HT-LVH group occurred to a small extent in the subendocardium and to a moderate degree in the midwall layer, but not in the epicardial layer.

Lateral Border Zone

The distance between the lateral margin of the area at risk and the lateral extent of infarct area was narrowest at endocardium and widest at epicardium in both the control and HT-LVH groups. Frequency histograms of the lateral border width (Fig. 2) indicated that, in the endocardial and mid-
TABLE 3  Relationship between Infarct Size and Area at Risk

<table>
<thead>
<tr>
<th>Regression equation</th>
<th>Control group</th>
<th>Hypertensive-LVH group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmural y = 1.20x - 25.6 0.96 22.5 ± 1.1 y = 1.19x - 16.3 0.95 15.5 ± 1.7*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardium y = 1.36x - 6.3 0.91 5.5 ± 0.3 y = 1.28x - 3.9 0.89 3.7 ± 0.5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midwall y = 1.21x - 8.1 0.97 7.1 ± 0.6 y = 1.10x - 4.2 0.95 4.3 ± 0.7*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epicardium y = 0.92x - 7.8 0.92 9.2 ± 0.4 y = 0.72x - 2.7 0.59 9.2 ± 1.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM. x = mass of risk region/left ventricular mass (%); y = mass of infarct region/left ventricular mass (%).

* P < 0.05 compared to control group.

dwall layers, the lateral border width was smaller in the HT-LVH group than in the control group. The endocardial lateral border was less than 1 mm wide in 45% of the ventricular slices for the control group, and in 64% for the HT-LVH group (P < 0.01). The midwall lateral border was less than 3 mm wide in 35% of the ventricular slices for the control, and in 70% for the HT-LVH group (P < 0.01).

Regional Myocardial Blood Flow (Table 4)

Prior to coronary occlusion, myocardial blood flow was similar in the control and HT-LVH groups. The endocardial-to-epicardial flow ratio was also similar: 1.14 ± 0.03 for control and 1.19 ± 0.01 for the HT-LVH group. Prior to occlusion, the ratio of perfusion in the infract area to perfusion in the normal area was not significantly different from unity: 0.99 ± 0.02 in the control group and 0.95 ± 0.02 in the HT-LVH group. This indicates that microsphere loss from the infract region was negligible.

Five minutes after coronary occlusion, myocardial blood flow decreased by 87% (range: 65-95%) in the infract area and by about 36% (range: 0-72%) in the normal-appearing risk area in the control group. These values were almost identical in the HT-LVH group. By 2 hours post-occlusion, the blood flow to the normal appearing risk area increased by about 20% in the control group (P < 0.05). In contrast, there was no change in blood flow to the normal appearing risk area in the HT-LVH group.

During the following 46 hours, the blood flow to the normal-appearing risk zone returned to preocclusion level in both groups. In the infract zone, with the exception of the epicardium, blood flow remained severely depressed, especially in the HT-LVH group. In the normally perfused area, the border area, and the normal appearing risk area, myocardial perfusion for the HT-LVH group tended to be higher than the control group. However, these differences were not statistically significant.

The Histological Extent of Myocardial Necrosis

The myocardial samples from the normally perfused and border areas were completely free of necrosis or significant fibrosis, on histological examination. In the normal-appearing risk area, 13 ± 3% and 12 ± 2% of the tissue demonstrated histological evidence of infarction in the control group and HT-LVH group, respectively. Segments that were infarcted by gross inspection contained 7 ± 3% and 3 ± 2% of the normal tissue in the control group and HT-LVH group, respectively.

![Figure 2](http://circres.ahajournals.org/)

**Figure 2**  Frequency histogram of the distance between lateral margins of risk area and infract area for various transmural layers in control and hypertensive (HT)-LVH groups. Lateral border was narrower in the inner layer of the left ventricle. In the subendocardial and the midwall layers, the lateral border was narrower in the hypertensive-LVH group than in the control group.
layers of the left ventricle (Koyanagi et al., in press).

Between dogs (Lowe et al., 1978; Jugdutt et al., 1979a), and the perfusion field at a given coronary no- tion and LVH augmented infarct size. We estimated the area at risk using postmortem stereoscopic coronary arteriography. The advantage of this method is that the three-dimensional “anatomical” risk zone can be obtained in the heart several days after coronary occlusion (Schaper et al., 1979; Jugdutt et al., 1979a). The infarct area was determined by gross inspection, because the infarct zone was clearly delineated from surrounding normal tissue after 24 hours of coronary occlusion. Reproducibility of the estimation of risk area and infarct area was excellent: the interobserver or intraobserver difference was almost negligible (<1% of LV mass). Thus, the methods we used to estimate infarct size and the area at risk in our study are reasonably precise.

There are several limitations of our study. First, several studies have shown that microspheres injected prior to coronary occlusion are lost from necrotic tissue during the first several days of infarction (Capurro et al., 1979; Jugdutt et al., 1979b; Reimer and Jennings, 1979). However, Murdock and Cobb (1980) recently have indicated that the loss of microspheres does not significantly affect the interpretation of serial measurement of collateral flow. Furthermore, the microsphere loss can be minimized by using large number of microspheres (6–20 × 10⁶) (Koyanagi et al., in press; White et al., 1978). In this study, 2 days after coronary occlusion, the ratio of preocclusion measurement in the normal and infarct area was almost unity. Thus, microsphere loss from infarcted tissue was probably negligible.

Discussion

We have demonstrated that, following acute coronary occlusion, myocardial infarct size is increased substantially in pressure overload LVH. The increase in infarct size was most prominent in the midwall layer. This discussion will focus on methodological considerations and speculation about mechanisms that may increase infarct size in pressure-overload LVH.

Methodological Considerations

There are several advantages of the experimental design and the methods that we employed. First, because the most common cause of LVH in patients is hypertension, we chose as our experimental model dogs with chronic hypertension and LVH. Second, we produced myocardial infarction when the dogs were conscious to avoid the adverse effects of anesthesia and surgical trauma. Third, for the purpose of assessing infarct size, we determined the relationship between infarct size and the perfusion field of occluded artery, or area at risk, in control and hypertensive LVH dogs. This is of critical importance because the perfusion area of the coronary artery at the same anatomical site is highly variable between dogs (Lowe et al., 1978; Jugdutt et al., 1979a), and the perfusion field at a given coronary vessel may be altered with cardiac enlargement. We have demonstrated that the relationship between infarct and risk area varies in different transmural layers of the left ventricle (Koyanagi et al., in press). By using this approach, we could define the specific layers of the left ventricular wall in which hyper-

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th></th>
<th>Hypertensive-LVH group</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
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<td>occlusion</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>Transmural</td>
<td>17</td>
<td>100 ± 8</td>
<td>104 ± 9</td>
<td>105 ± 11</td>
</tr>
<tr>
<td>Endocardium</td>
<td>17</td>
<td>103 ± 8</td>
<td>108 ± 9</td>
<td>110 ± 12</td>
</tr>
<tr>
<td>Epicardium</td>
<td>17</td>
<td>93 ± 7</td>
<td>97 ± 8</td>
<td>100 ± 11</td>
</tr>
<tr>
<td>Border area</td>
<td>17</td>
<td>104 ± 8</td>
<td>106 ± 12</td>
<td>110 ± 12</td>
</tr>
<tr>
<td>Transmural</td>
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<td>95 ± 8</td>
<td>99 ± 12</td>
<td>100 ± 9</td>
</tr>
<tr>
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<td>112 ± 12</td>
<td>121 ± 12</td>
</tr>
<tr>
<td>Epicardium</td>
<td>17</td>
<td>96 ± 7</td>
<td>96 ± 9</td>
<td>105 ± 11</td>
</tr>
<tr>
<td>Normal-appearing area</td>
<td>17</td>
<td>101 ± 7</td>
<td>65 ± 7*</td>
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<tr>
<td>Transmural</td>
<td>17</td>
<td>103 ± 7</td>
<td>58 ± 9*</td>
<td>109 ± 11†</td>
</tr>
<tr>
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<td>96 ± 7</td>
<td>69 ± 5</td>
<td>106 ± 10‡</td>
</tr>
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<td>98 ± 8</td>
<td>67 ± 7*</td>
<td>105 ± 12‡</td>
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<td>14</td>
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<tr>
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<tr>
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<td>10</td>
<td>88 ± 10</td>
<td>9 ± 3*</td>
<td>32 ± 8*</td>
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<tr>
<td>Epicardium</td>
<td>10</td>
<td>107 ± 13</td>
<td>18 ± 8*</td>
<td>32 ± 9*</td>
</tr>
<tr>
<td>PPM</td>
<td>10</td>
<td>137 ± 15</td>
<td>9 ± 3*</td>
<td>18 ± 8*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (ml/min per 100 g). PPM-posterior papillary muscle.

* P < 0.05 compared to value before occlusion.
† P < 0.05 compared to value before occlusion.
‡ P < 0.05 compared to value 5 minutes post occlusion.
§ P < 0.05 compared to value 2 hours post occlusion.
Second, the method used to determine the infarct area and the normal-appearing risk area is not perfect. Histological examination indicated that about 12.5% of tissue was necrotic in myocardial segments from the normal-appearing risk area. Also, about 5% of tissue was not necrotic in myocardial samples from the infarct area. Some contamination seems to be technically unavoidable because the border of infarct and normal tissue is highly irregular (Factor et al., 1978; Jugdutt et al., 1981). Thus, although some contamination was present in our samples, fortunately the degree of contamination was similar in the control and HT-LVH groups.

Third, because over one-half of the hypertensive dogs died prematurely, the survivors may or may not be representative of the entire group. However, the area at risk was almost identical between survivors and non-survivors. Furthermore, in survivors and non-survivors, left ventricular mass and arterial pressure were similarly increased. Thus, it is unlikely that increased mortality in HT-LVH group biased the direction of our conclusion.

Potential Mechanisms of Increased Infarct Size in Pressure-Overload Hypertrophied Ventrices

Epidemiological studies have demonstrated that mortality and morbidity from myocardial infarction is increased in patients with arterial hypertension (Kannel, 1974; Kannel et al., 1975; Rabkin et al., 1977). The usual explanation for this is that hypertension augments the severity of coronary atherosclerosis and consequently the complications of coronary occlusive disease are exaggerated. We have demonstrated that infarct size is larger in pressure-induced hypertrophied heart than in the normal heart when the perfusion field of the occluded artery, or area at risk, is comparable. Thus, factors other than the extent of coronary atherosclerosis must play an important role in augmenting infarct size in the presence of hypertension and LVH.

There are several mechanisms which should be considered.

First, there is considerable evidence that cardiac hypertrophy is associated with fundamental abnormalities in the coronary circulation. When cardiac hypertrophy is produced in adult animals, capillary proliferation does not keep pace with the hypertrophic process of myocardial cells (Rakusan et al., 1969; Murray et al., 1979; Breisch et al., 1980). Consequently, capillary density is decreased and the diffusion distance from capillary to the center of the myocardial cell is increased (Henquell et al., 1977). In the presence of a marked decrease in flow, this increase in diffusion distance may augment the size of myocardial infarction. Furthermore, recent studies have shown that coronary reserve is compromised in hypertrophied ventricles (Mueller et al., 1978; O'Keefe et al., 1978; Rembert et al., 1978; Marcus et al., 1980). These studies strongly suggest that the anatomical and physiological abnormalities in coronary circulation potentiate the adverse effect of coronary occlusion in hypertrophied heart. It is interesting to note that, in hypertrophied hearts, impairment in the coronary circulation is greatest at the subendocardial muscle (Mueller et al., 1978; O'Keefe et al., 1978; Rembert et al., 1978). In this study, the increase in infarct size in the dogs with hypertension and LVH was due primarily to an increase in the extent of infarct in the endocardial and midwall layers of the left ventricle.

Second, differences in development of collateral flow in normal and hypertrophied hearts may be important. In our study, the decrease in blood flow to the normal appearing risk area and the infarct area immediately after coronary occlusion was similar in the control and hypertensive LVH groups. Thus, the degree of reduction in myocardial flow immediately after coronary occlusion could not explain the increased infarct size in the HT-LVH group. However, the increase in collateral flow to these ischemic areas was attenuated in hypertrophied hearts (Table 4). Although this trend did not reach statistical significance, it could augment the infarct size in LVH.

Third, oxygen consumption of the myocardium or wall stress could have been augmented in hypertensive animals, which potentially increases ischemic injury. If so, infarct size may be less extensive when blood pressure is normalized after the development of LVH.

Fourth, the renin-angiotensin system might have affected the infarct size in the hypertensive dogs. However, we think that the renin-angiotensin system had little effect in our experimental model, because in chronic Goldblatt hypertensive animals plasma renin activity is normal and [Sar1, Ala8] angiotensin II, angiotensin II antagonist, does not decrease blood pressure (Bianchi et al., 1970; Ferrario, 1974; Freeman et al., 1977; Stephen et al., 1979; Bing et al., 1981). However, neurohumoral abnormalities associated with hypertension and LVH other than the renin-angiotensin system could contribute to the increase in size of myocardial infarction.

Fortunately, since renal function appeared to be within normal limits in the hypertensive dogs, it is not likely that renal failure affected our study.

In conclusion, we have demonstrated that myocardial infarct size relative to the area at risk is significantly increased in hypertensive dogs with LVH. This increase in infarct size was shown in the endocardial and midwall layers. This interaction between LVH and myocardial ischemia may have significant influence on the outcome of myocardial infarction in patients with hypertension and LVH.

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