Acceleration of the Wavefront of Myocardial Necrosis By Chronic Hypertension and Left Ventricular Hypertrophy in Dogs

Kevin C. Dellsperger, Jennifer L. Clothier, Jane A. Hartnett, Linda M. Haun, and Melvin L. Marcus

Previous studies have shown that hypertension and left ventricular hypertrophy (HT-LVH) increase completed infarct size. Myocardial infarction progresses in a wavefront of myocardial necrosis from the subendocardium to the subepicardium. We tested two hypotheses: First, HT-LVH accelerates the wavefront of myocardial necrosis when compared with normotensive animals; and second, lowering of arterial pressure by infusing nitroprusside 1 hour after coronary artery occlusion exerts a salutary effect on infarct size. To test these hypotheses, systemic hypertension (mean aortic pressure = 141 ± 3 mm Hg) and left ventricular hypertrophy (18% increase in left ventricular mass) were induced in dogs using a single-kidney, single-clip model. Seventeen adult mongrel dogs were used as controls. We measured mean aortic pressure, heart rate, left atrial pressure, and myocardial perfusion (microspheres) in several groups of normal and HT-LVH awake dogs. In two groups (normal and HT-LVH), 1 hour of circumflex coronary artery occlusion was followed by 4 hours of reperfusion. In two additional groups (normal and HT-LVH), 3 hours of circumflex coronary artery occlusion was followed by 90 minutes of reperfusion. In another group with HT-LVH, nitroprusside was infused to reduce mean arterial pressure to 100 mm Hg beginning 1 hour after occlusion and was continued for the duration of reperfusion period (HT-LVH + N). Infarct size was assessed using triphenyltetrazolium chloride stain and risk area was determined using postmortem barium angiography. Fifteen of 17 (88%) control animals survived coronary artery occlusion, whereas only 17 of 42 (40%) dogs with HT-LVH survived coronary occlusion (p<0.05). Infarct-to-risk ratios in the various layers of the left ventricular wall were determined for survivors in all groups. After 1 hour of coronary occlusion more than twice as much mid-wall and epicardium was infarcted in the HT-LVH group compared with the control group. After 3 hours of coronary occlusion significantly more endocardium, mid-wall, and epicardium was infarcted in the dogs with HT-LVH. In the nitroprusside-treated HT-LVH dogs, the infarct sizes were similar to control animals. From these data we conclude: 1) the rate of infarction is accelerated in animals with HT-LVH; 2) nitroprusside infused 1 hour after coronary artery occlusion and continued throughout the reperfusion period exerts beneficial effect on infarct size when compared with control animals; and 3) acute coronary artery occlusion in animals with HT-LVH is associated with significantly greater mortality when compared with control animals. (Circulation Research 1988;63:87-96)

C hronic arterial hypertension increases the morbidity and mortality of myocardial infarction in patients.1,2 The high morbidity and mortality from acute coronary occlusion could be related to the presence of more extensive coronary artery disease in hypertensive patients since it is known that the atherosclerotic process is accelerated by hypertension.3 Several recent studies in our laboratory have shown that, in dogs with chronic hypertension and left ventricular hypertrophy (HT-LVH), there is an increase in the size of completed myocardial infarction4,5 due to the occlusion of a single vessel. These experiments suggest that accel-
Other factors in addition to accelerated atherosclerosis may contribute to the deleterious effects of coronary occlusion in a model of HT-LVH. Left ventricular hypertrophy (LVH) is associated with an increase in diameter of myocardial cells without a proportional proliferation of the capillary vasculature. As a consequence of this, the diffusion distance is increased. Vascular permeability may be adversely affected in hypertrophied hearts, and vasodilator reserve appears to be compromised in LVH in both patients and animals. Recently, Inou et al demonstrated a return of infarct size to control values in dogs with HT-LVH when the hypertension was reversed before coronary artery occlusion with either nitroprusside or renal artery reanastomosis. This study suggested that hypertension rather than LVH may be the predominant factor that augments the adverse effects of infarction in animals with HT-LVH.

Several investigators have described a wavefront phenomenon of ischemic cell death that begins with subendocardial necrosis and proceeds in a time-dependent manner toward the subepicardium. Several studies have shown that infarction progresses at a much more rapid pace in swine and rats than in dogs. A study by Müller and colleagues found that the relation of mass of infarcted tissue to arterial HT-LVH will result in a slower wavefront across the risk area.

We have undertaken the present investigation to test the hypothesis that the wavefront of ischemic cell necrosis is accelerated in dogs with chronic arterial HT-LVH when compared with controls. Furthermore, we also tested the hypothesis that normalization of arterial pressure at some point into the coronary artery occlusion in dogs with chronic arterial HT-LVH will result in a slower wavefront of myocardial necrosis when compared with untreated dogs with HT-LVH.

Materials and Methods

The care of all animals complied with the principles of the American Physiological Society on animal experimentations. These studies were approved by the University of Iowa Animal Care and Use Review Committee.

Surgical Preparation of Dogs

Systemic hypertension was induced in 42 adult mongrel dogs of either sex (18–31 kg). The method of producing hypertension has been described previously in detail and will be summarized briefly. Dogs were anesthetized with sodium pentobarbital (30 mg/kg body wt i.v.). Ventilation was maintained with a Harvard respirator (South Natick, Massachusetts). Under sterile conditions, bilateral flank incisions and unilateral nephrectomy were done and a clamp, described by Ferrario et al, was implanted on the contralateral renal artery. The clamp was tightened to a point at which the control level of blood flow produced a thrill in the distal renal artery.

A second surgical procedure was performed 8–9 weeks after the renal surgery. The dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and ventilated with a Harvard respirator, and a left thoracotomy was performed. Catheters were placed into the thoracic aorta and into the left atrium. A hydraulic coronary arterial occluder was placed around the proximal circumflex coronary artery. The occluder and catheters were exteriorized in the back between the scapulae. The catheters were filled with heparin (1,000 units/ml) and flushed daily.

Seventeen adult mongrel dogs of either sex (20–28 kg) were used as controls. These dogs underwent placement of catheters and the hydraulic coronary arterial occluder as described above.

Measurement of Infarct Size and Area at Risk

Following the reperfusion period, the dogs were killed with an overdose of barbiturate and potassium chloride. After the animals were killed, a left thoracotomy was performed. The proximal thoracic aorta and left and right brachiocephalic arteries were tied and ligated. The heart was rapidly excised and placed in normal saline at 40°C. A perfusion cannula was inserted into the ascending aorta and secured into place. A 10% solution of triphenyltetrazolium chloride (TTC) in phosphate-buffered saline was perfused into the coronary arteries through the aortic perfusion cannula at systemic pressures for 4.5 minutes. Thereafter, to stop the TTC reaction a 10% solution of formalin was infused into the coronary arteries through the perfusion cannula for at least 2 minutes.

Following TTC staining, cannulas (o.d. = 2–3 mm) were secured into the left main coronary artery or separately into the left anterior descending and the left circumflex coronary arteries when they arose from separate orifices. The cannulas were flushed with saline to remove air and formalin from the coronary vessels. A barium-gelatin mixture was then perfused into the left coronary cannula (or simultaneously into the left anterior descending and left circumflex cannula) at a perfusion pressure.
The various regions were summed, including risk and infarct areas within each myocardial region. The area at risk in grams was expressed as a percent of the total left ventricular mass. The infarct size in grams was expressed as a percent of the total left ventricular mass and as a ratio of the infarcted mass to risk mass in percentage. In addition, the regional infarcted area was expressed as a percentage of regional area at risk for the endocardium, midwall, and epicardium.

**Measurement of Regional Myocardial Perfusion**

Regional myocardial perfusion was measured using radioactive microspheres 15 μm in diameter labeled with 42Sc, 85Sr, 99mTc, 113Sn, 141Ce, or 153Gd. For each flow measurement approximately 20 x 106 microspheres were injected through the left atrial catheter, which was subsequently flushed with 10 ml of saline over 10 seconds. Prior to injection, the microspheres were mechanically agitated for 5 minutes. A reference arterial blood sample was withdrawn from the catheter in the thoracic aorta at a constant rate of 3.84 ml/min with a Harvard pump, starting 20 seconds before microsphere injection and continuing at least 90 seconds after injection. Left atrial and arterial pressure did not change significantly before or after microsphere injection.

Myocardial perfusion was measured from samples obtained from the following regions: normal perfused region (nonrisk region perfused by the left anterior descending coronary artery), normally appearing tissue within the area of risk, and infarcted region. Each region was divided into subepicardial, midwall, subendocardial, and papillary muscle layers of about equal thickness. The individual myocardial segments were weighed, placed in a plastic scintillation tube, and counted for 5 minutes in a 3-inch well counter with a sodium iodide or Germanium crystal.19 Myocardial blood flow in each sample was calculated by the formula

\[
MBF = \frac{(Cm \times 100 \times RBF)}{Cr}
\]

where MBF = myocardial blood flow (ml/min/100 g), Cm = counts per gram of myocardium, RBF = reference blood flow (the rate of withdrawal from the reference artery), and Cr = total counts in the reference blood.20

**Experimental Groups**

**General protocol.** Studies were performed 6–10 days after thoracotomy when all dogs appeared healthy. Approximately 20 minutes before the experiment, morphine sulfate (0.5 mg/kg) was given intravenously. The arterial and left atrial catheters were connected to Statham P23dB strain gauges (Gould, Cleveland, Ohio) placed at the mid-chest level. Aortic and left atrial pressures and a V-lead of the electrocardiogram were recorded continuously.

When the dogs were lying quietly and hemodynamics were stable, myocardial blood flow was measured with microspheres. Lidocaine (2 mg/kg
i.v.) was then administered, and the circumflex coronary artery occlusion was accomplished with the hydraulic occluder. Ventricular fibrillation occurred in one control dog (6%) and 23 hypertensive dogs (55%) within 1 hour of coronary artery occlusion. Cardio-pulmonary resuscitation and electrical defibrillation was performed but none of these dogs recovered. All animals with ventricular fibrillation were excluded from infarct size analysis. In nonsurvivors, risk area was determined as previously described. In surviving dogs, measurements of hemodynamics and myocardial blood flows were obtained 5 minutes after coronary artery occlusion, 5 minutes before reperfusion, 5 minutes after reperfusion, and 1 hour after reperfusion was established. Protocol 1: Determination of the wavefront of myocardial necrosis. To test the hypothesis that the wavefront of myocardial necrosis was accelerated in the presence of HT-LVH, time points during the progression of myocardial infarction were chosen. One- and 3-hour occlusions were selected. One hour of circumflex coronary artery occlusion and 4 hours of reperfusion was successful in seven dogs with HT-LVH and nine controls. Three hours of circumflex coronary artery occlusion and 90 minutes of reperfusion was successful in five dogs with HT-LVH and six controls. Fibrillation occurred with reperfusion in one dog with HT-LVH and one control dog.

Protocol 2: Nitroprusside-treated group. Prior studies in our laboratory have shown that correction of hypertension by two methods at the beginning of coronary artery occlusion had a beneficial effect on infarct size and mortality rate. To determine the clinical applicability of this observation, we sought to determine if, after sudden coronary artery occlusion, decreasing arterial pressure with intravenous nitroprusside would decrease infarct size and the incidence of sudden cardiac death. We used 3 hours of circumflex coronary artery occlusion and 90 minutes of reperfusion in this protocol. One hour into the coronary artery occlusion nitroprusside was infused and titrated to decrease mean arterial blood pressure to control values (range 2-23 μg/min). The nitroprusside infusion was maintained throughout the remainder of the 3-hour coronary artery occlusion and 90 minutes of reperfusion. Five successful studies using this protocol were performed. One dog fibrillated 2 hours after coronary artery occlusion.

Criteria for an Acceptable Experiment
Animals that completed the entire protocol were included in analysis. These animals had to appear

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>HT-LVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>17</td>
<td>42</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>23 ± 1</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>LV weight (g)</td>
<td>115 ± 6</td>
<td>138 ± 4*</td>
</tr>
<tr>
<td>LV weight/body weight (g/kg)</td>
<td>4.9 ± 0.2</td>
<td>5.8 ± 0.1*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>95 ± 5</td>
<td>116 ± 4*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>100 ± 3</td>
<td>141 ± 3*</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>5 ± 1</td>
<td>6 ± 1</td>
</tr>
</tbody>
</table>

HT-LVH, hypertension and left ventricular hypertrophy; LV, left ventricular. *p<0.05 vs. control. Values are mean ± SEM.

### Table 2. Hemodynamic Effects of Sudden Coronary Occlusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Before occlusion</th>
<th>5 minutes after CAO</th>
<th>5 minutes before release of CAO</th>
<th>5 minutes after release of CAO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1 hour</td>
<td>86 ± 4</td>
<td>108 ± 9*</td>
<td>110 ± 7</td>
<td>113 ± 12</td>
</tr>
<tr>
<td>HT-LVH 1 hour</td>
<td>117 ± 4†</td>
<td>141 ± 10†</td>
<td>122 ± 10</td>
<td>133 ± 14</td>
</tr>
<tr>
<td>Control 3 hours</td>
<td>104 ± 9</td>
<td>129 ± 4†</td>
<td>98 ± 5‡</td>
<td>111 ± 8</td>
</tr>
<tr>
<td>HT-LVH 3 hours</td>
<td>116 ± 8‡</td>
<td>123 ± 12</td>
<td>106 ± 17</td>
<td>112 ± 12</td>
</tr>
<tr>
<td>HT-LVH + N 3 hours</td>
<td>127 ± 11†</td>
<td>126 ± 10</td>
<td>143 ± 22</td>
<td>128 ± 15</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1 hour</td>
<td>96 ± 3</td>
<td>90 ± 4</td>
<td>92 ± 3</td>
<td>89 ± 5</td>
</tr>
<tr>
<td>HT-LVH 1 hour</td>
<td>142 ± 5§</td>
<td>129 ± 10§</td>
<td>142 ± 10§</td>
<td>128 ± 11†</td>
</tr>
<tr>
<td>Control 3 hours</td>
<td>104 ± 5</td>
<td>107 ± 4</td>
<td>112 ± 6</td>
<td>115 ± 6</td>
</tr>
<tr>
<td>HT-LVH 3 hours</td>
<td>142 ± 5§</td>
<td>134 ± 5§</td>
<td>142 ± 9§</td>
<td>138 ± 8§</td>
</tr>
<tr>
<td>HT-LVH + N 3 hours</td>
<td>143 ± 8§</td>
<td>135 ± 7§</td>
<td>99 ± 1*‡</td>
<td>96 ± 7*‡</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control 1 hour</td>
<td>6 ± 1</td>
<td>8 ± 1</td>
<td>8 ± 2</td>
<td>7 ± 2</td>
</tr>
<tr>
<td>HT-LVH 1 hour</td>
<td>8 ± 1</td>
<td>14 ± 28</td>
<td>12 ± 28</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Control 3 hours</td>
<td>4 ± 1</td>
<td>9 ± 2</td>
<td>9 ± 2</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>HT-LVH 3 hours</td>
<td>5 ± 1</td>
<td>9 ± 2</td>
<td>8 ± 1</td>
<td>9 ± 2</td>
</tr>
<tr>
<td>HT-LVH + N 3 hours</td>
<td>4 ± 1</td>
<td>7 ± 2</td>
<td>1 ± 1*‡</td>
<td>1 ± 1*‡</td>
</tr>
</tbody>
</table>

CAO, coronary artery occlusion; HT-LVH, hypertension and left ventricular hypertrophy; N, nitroprusside. Values are mean ± SEM. *p<0.05 5 minutes after CAO vs. before occlusion, †p<0.05 vs. control 1 hour, ‡p<0.05 vs. 5 minutes after CAO, §p<0.05 vs. control 1 hour or control 3 hours, ||p<0.05 vs. HT-LVH 1 hour and 3 hours, ¶p<0.05 vs. all other groups.
healthy, survive the entire period of coronary artery occlusion and reperfusion, have adequate TTC staining for infarct size, and an interpretable barium angiogram for risk area analysis. In addition, animals who underwent renal surgery had to have mean arterial pressures greater than 115 mm Hg and left ventricular mass greater than 5 g/kg body wt. Coronary artery occlusion was verified using myocardial perfusion as measured with microspheres.

We encountered a great deal of difficulty in obtaining complete coronary artery occlusion for the duration of intended occlusion using commercially available hydraulic occluders. Fifteen dogs with HT-LVH and nine controls were excluded from analysis because partial occlusion or complete occlusion did not last the entire period of intended occlusion. Five dogs with presumed chronic arterial HT-LVH did not meet the inclusion criteria and were excluded from analysis. A poor-quality TTC stain was defined as one that had diffuse areas of nonstaining clearly outside the area at risk. This occurred in three dogs with chronic arterial HT-LVH and seven controls. These animals were excluded from further analysis. Most of these experiments occurred early in our experience with the TTC technique. In one dog with chronic arterial HT-LVH and two controls the barium angiogram was not of suitable quality to clearly delineate the area at risk and therefore these animals were excluded from analysis.

In total, 24 animals with chronic arterial HT-LVH and 18 control animals were excluded from analysis. All exclusions were made according to previously defined criteria and before the infarct/risk measurements were made. Twenty-four of the 42 animals were excluded from analysis because of incomplete coronary artery occlusion. This finding emphasizes the importance of measuring coronary blood flow after abrupt occlusion of a coronary vessel and before reperfusion in studies that analyze effects of occlusion time on infarct size.

**Data Analysis**

The data are presented as mean ± SEM, and the level of statistical significance was p < 0.05. Hemodynamic and myocardial blood flow data were analyzed by analysis of variance or paired t test with Bonferroni correction. Comparison of left ventricular weight between groups was made by unpaired t test. χ² tests were used to analyze the difference in mortality rate. The infarct-to-risk relations were compared using unpaired t test.

**Results**

**Anatomical Size and Hemodynamics**

Left ventricular mass was 115 ± 6 g in control dogs and 138 ± 4 g in dogs with HT-LVH (p < 0.05). The left ventricular mass-to-body weight ratio was 4.9 ± 0.2 g/kg in controls and 5.8 ± 0.1 g/kg in dogs with HT-LVH (p < 0.05). Thus, left ventricular mass was increased by approximately 18% in hypertensive dogs.

Mean aortic pressure was substantially elevated and heart rate modestly increased in the dogs with HT-LVH. Left atrial pressure was similar in the experimental and control groups (Table 1). Following coronary artery occlusion the heart rate and left atrial pressure increased (Table 2). After 1 hour of coronary occlusion, nitroprusside sufficient to decrease mean aortic pressure to 100 mm Hg, which was similar to aortic pressure in the control animals, was administered intravenously to the nitroprusside-treated group. Concomitant with the decrease in aortic pressure in this group was an increase in heart rate. Nitroprusside decreased the left atrial pressure when compared with the other groups (p < 0.05).

**Mortality**

During coronary occlusion and reperfusion two of 17 control dogs (12%) died, whereas 25 of 42 dogs (60%) with HT-LVH died (p < 0.05). The risk areas

---

**TABLE 2. Baseline Characteristics of Animals Surviving and Not Surviving Coronary Artery Occlusion**

<table>
<thead>
<tr>
<th>Group</th>
<th>Area at risk of total LV (%)</th>
<th>LV weight/body weight (g/kg)</th>
<th>Mean arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control survivors (n=15)</td>
<td>36 ± 3</td>
<td>5.0 ± 0.2</td>
<td>99 ± 3</td>
</tr>
<tr>
<td>Control nonsurvivors (n=2)</td>
<td>37 ± 6</td>
<td>4.6 ± 0.1</td>
<td>106 ± 9</td>
</tr>
<tr>
<td>HT-LVH survivors (n=17)</td>
<td>38 ± 2</td>
<td>6.1 ± 0.2</td>
<td>143 ± 5</td>
</tr>
<tr>
<td>HT-LVH nonsurvivors (n=25)</td>
<td>37 ± 1</td>
<td>5.5 ± 0.1*</td>
<td>141 ± 3</td>
</tr>
</tbody>
</table>

LV, left ventricle; n, number; HT-LVH, hypertension and left ventricular hypertrophy. Values are mean ± SEM. *p < 0.05 nonsurvivor vs. survivor.
### Table 4. 1-Hour Regional Myocardial Perfusion in Normal Regions (Nonrisk), Normal-Appearing Risk Regions, and Infarcted Regions

<table>
<thead>
<tr>
<th>Group</th>
<th>Before coronary artery occlusion</th>
<th>5 Minutes after coronary artery occlusion</th>
<th>5 Minutes before reperfusion</th>
<th>5 Minutes after reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPI</td>
<td>MID</td>
<td>ENDO</td>
<td>PAPM</td>
</tr>
<tr>
<td>Control (n = 9)</td>
<td>88 ± 6</td>
<td>101 ± 8</td>
<td>111 ± 8</td>
<td>...</td>
</tr>
<tr>
<td>HT-LVH (n = 7)</td>
<td>98 ± 14</td>
<td>116 ± 15</td>
<td>113 ± 15</td>
<td>...</td>
</tr>
</tbody>
</table>

EPI, epicardium; MID, midmyocardium; ENDO, endocardium; PAPM, papillary muscle; PPM, posterior papillary muscle; HT-LVH, hypertension and left ventricular hypertrophy.

*p<0.05 vs. control 1 hour, tp<0.05 vs. normal-appearing risk.

Values in milliliters per minute per 100 grams wet weight.

### Table 5. 3-Hour Regional Myocardial Perfusion in Normal Regions (Nonrisk), Normal-Appearing Risk Regions, and Infarcted Regions

<table>
<thead>
<tr>
<th>Group</th>
<th>Before coronary artery occlusion</th>
<th>5 minutes after coronary artery occlusion</th>
<th>5 minutes before reperfusion</th>
<th>5 minutes after reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPI</td>
<td>MID</td>
<td>ENDO</td>
<td>PAPM</td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>121 ± 14*</td>
<td>130 ± 18*</td>
<td>139 ± 17*</td>
<td>...</td>
</tr>
<tr>
<td>HT-LVH (n = 5)</td>
<td>89 ± 20</td>
<td>106 ± 21</td>
<td>96 ± 16</td>
<td>...</td>
</tr>
<tr>
<td>HT-LVH + N (n = 5)</td>
<td>134 ± 20*</td>
<td>163 ± 2*</td>
<td>165 ± 23*</td>
<td>...</td>
</tr>
</tbody>
</table>

EPI, epicardium; MID, midmyocardium; ENDO, endocardium; PAPM, papillary muscle; PPM, posterior papillary muscle; HT-LVH, hypertension and left ventricular hypertrophy; n, number; N, nitroprusside.

*p<0.05 vs. HT-LVH 3 hour, tp<0.05 vs. before coronary occlusion, tp<0.05 vs. normal-appearing risk, §p<0.05 vs. HT-LVH + N 3 hour, ||p<0.05 vs. 5 minutes after coronary artery occlusion.

Values in milliliters per minute per 100 grams wet weight.
Dellsperger et al Wavefront of Infarction in Hypertension and LVH 93

TABLE 6. Risk and Infarct Sizes

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk mass (g)</th>
<th>Risk % of total LV mass</th>
<th>Infarct mass (g)</th>
<th>Infarct % of total LV mass</th>
<th>Infarct (g) × 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1 hour (n = 9)</td>
<td>37 ± 6</td>
<td>34 ± 5</td>
<td>11 ± 2</td>
<td>10 ± 3</td>
<td>27 ± 3</td>
</tr>
<tr>
<td>HT-LVH 1 hour (n = 7)</td>
<td>50 ± 4*</td>
<td>35 ± 2</td>
<td>17 ± 3*</td>
<td>12 ± 2</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>Control 3 hours (n = 6)</td>
<td>49 ± 3</td>
<td>40 ± 3</td>
<td>22 ± 4</td>
<td>17 ± 3</td>
<td>44 ± 6</td>
</tr>
<tr>
<td>HT-LVH 3 hours (n = 5)</td>
<td>66 ± 10†</td>
<td>44 ± 3</td>
<td>44 ± 9†</td>
<td>29 ± 4†</td>
<td>64 ± 6†</td>
</tr>
<tr>
<td>HT-LVH + N 3 hours (n = 5)</td>
<td>50 ± 3</td>
<td>36 ± 2†</td>
<td>20 ± 2†</td>
<td>15 ± 3†</td>
<td>40 ± 6†</td>
</tr>
</tbody>
</table>

LV, left ventricle; HT-LVH, hypertension and left ventricular hypertrophy; N, nitroprusside. Values are mean ± SEM.

*p<0.05 vs. control 1 hour, †p<0.05 vs. control 3 hours, ‡p<0.05 vs. HT-LVH 3 hours.

of dogs that died prematurely were not significantly different than those in surviving dogs (Figure 2). Furthermore, the degree of hypertension was similar between the dogs that died prematurely and those that survived within each group. The increase in left ventricular mass was slightly less in the dogs that died prematurely compared with survivors (Table 3).

Myocardial Perfusion

Protocol I groups. Myocardial perfusion was similar in the normally perfused areas, normal-appearing risk areas, and infarcted areas within each group at baseline states (Tables 4 and 5). There were no significant intergroup differences.

Following coronary artery occlusion, there was a tendency for perfusion to increase in the normally perfused area. The normal-appearing risk tissue had slightly greater flow than the infarcted tissue in each region. The infarcted tissue tended to have myocardial blood flow of <20 ml/min/100 g tissue. There was no significant difference between the myocardial blood flow in the control groups or the groups of animals with HT-LVH. Specifically, 5 minutes after coronary artery occlusion the acute collateral flow was similar between the control groups and the animals with HT-LVH.

During coronary occlusion, the flow within the normal-appearing risk and infarcted areas increased compared with 5 minutes after coronary artery occlusion. In addition, there was a slight increase in the collateral flow within the control groups during this time period. Following reperfusion, there was a slightly greater flow to the normally perfused areas compared with the baseline state. In the risk and infarcted areas there was a marked increase in flow compared with the baseline state occasionally reaching threefold to fourfold increases.

Protocol 2: Nitroprusside-treated group. Myocardial perfusion in this group of dogs during baseline conditions was similar to the other groups studied. Five minutes after coronary artery occlusion the blood flow decreased within the normal-appearing risk area and more so within the infarcted area but was not significantly different from other dogs studied. Five minutes before reperfusion myocardial blood flow to the normal area was twice as high as that observed in the other groups. Perfusion within the risk area, however, was not different from other dogs with HT-LVH.

Relation of Infarct Size to Risk Area

Protocol 1. The absolute size of the risk area and infarct area in grams was greater in dogs with HT-LVH than in control dogs (Table 6). However, when normalized for left ventricular mass the risk area expressed as a percent of left ventricular mass was similar between the groups. The infarct area as a percent of left ventricular mass was least in control dogs with 1-hour coronary occlusion and greatest in hypertensive dogs with a 3-hour coronary occlusion. The overall infarct mass-to-risk mass ratio was greatest in hypertensive dogs when compared with control dogs with similar coronary occlusion times (Figure 3).

FIGURE 3. Effects of nitroprusside (N) on relation between transmural infarct-to-risk ratio versus treatment group. Treatment groups are control, 1 hour; hypertension and left ventricular hypertrophy (HT-LVH), 1 hour; control, 3 hours; HT-LVH, 3 hours; and HT-LVH+N, 3 hours (N infused 1 hour after coronary artery occlusion). The infarct-to-risk ratio in animals treated with N was similar to that in controls.
After 1 hour of coronary artery occlusion significantly more midmyocardium and epicardium was infarcted in hypertensive dogs with LVH when compared with controls (Figure 4).

After 3 hours of coronary artery occlusion, there is significantly more infarcted endocardium, midmyocardium, and epicardium in hypertensive animals with LVH when compared with control animals. The percent of infarcted myocardium in the midmyocardium and epicardial regions in animals with HT-LVH was substantially increased when compared with controls (Table 7).

Protocol 2: Nitroprusside-treated animals. Overall, nitroprusside-treated groups had similar risk area, infarct area, and infarct-to-risk ratio as a 3-hour coronary occlusion in the control group. The regional infarct-to-risk ratio was similar to that observed in the control group.

Discussion

There are two major new findings in this study. First, the wavefront of myocardial necrosis is accelerated in dogs with chronic HT-LVH at 1 and 3 hours of coronary artery occlusion. Second, infusion of nitroprusside to reduce mean arterial pressure to control levels at 1 hour after coronary artery occlusion is associated with a retardation of this accelerated wavefront of myocardial necrosis as evidenced by return of the infarct-to-risk relation back to control levels (Figures 3 and 4).

Previous work by Koyanagi et al. has shown that the size of infarction at 48 hours in HT-LVH dogs is larger than in normal dogs. These investigators have also shown mortality associated with coronary occlusion is greater in dogs with HT-LVH. These studies did not evaluate the wavefront of myocardial infarction. Inou et al. studied the effects of either nitroprusside or renal artery reanastomosis to normalize arterial pressure in HT-LVH dogs prior to coronary occlusion. They found that these interventions reduced infarct size and mortality from ventricular fibrillation to control levels. In these studies, the rate of myocardial necrosis was not determined.

Our data interpretations and conclusions depend on several factors, including 1) methodology, 2) the similarity of collateral flow among the groups during coronary artery occlusion, and 3) the effects of nitroprusside on coronary blood flow.

Methodology. The protocol that we employed had many strengths to its design. First, coronary artery occlusion was performed in awake animals, negating the possible deleterious effects of anesthetic agents and surgical trauma. Second, myocardial perfusion was measured at important selected times during the protocol. Measurement of myocardial perfusion allowed us to verify that complete coronary occlusion was maintained for the desired period and to determine the effects of HT-LVH and nitroprusside on collateral flow. Third, our model of HT-LVH is similar in many ways to that occurring in humans. Fourth, risk area and infarct size were measured directly.

We measured infarct size with TTC. This method is widely employed. There is a good relation between electron microscopic evidence of necrosis.
and TTC staining. Results obtained with the TTC stain in this study and others confirmed concepts about infarction that have been established using histological techniques for infarct sizing.

Collateral flow. Following coronary artery occlusion, the myocardial blood flow reaches the ischemic myocardium via coronary collaterals. Collateral flow affects the size of myocardial infarction. Collateral flow during coronary artery occlusion was similar in all groups of animals studied. If collateral flow was significantly altered by HT-LVH or nitroprusside, this might provide an explanation for the findings on the wavefront of myocardial necrosis found in these studies. If the collateral flow was less in dogs with HT-LVH, one might expect the wavefront to be accelerated. Several other studies in dogs and humans have indicated that the perfusion delivered by native coronary collateral vessels is not different in hypertrophied left ventricles compared with normal left ventricles. However, it should be noted that measured resistance in native collaterals in hypertrophied hypertensive hearts is greater than that in controls.

Effects of nitroprusside on coronary circulation. Infusion of nitroprusside 1 hour after coronary artery occlusion, which reduced mean arterial pressure to control levels, resulted in a decrease in infarct size in the present study. Although it is possible that the effect of nitroprusside was related solely to its ability to decrease arterial pressure, we cannot exclude other contributing mechanisms. Nitroprusside directly dilates coronary vessels, activates various reflexes and humoral events, and alters myocardial oxygen consumption and extracellular compressive forces on coronary vessels. One potential mechanism involved in the reduction of the infarct size is due to a reduced myocardial oxygen consumption related to decreasing wall tension. In addition, there are neurohumoral reflexes activated from the administration of nitroprusside. Inou et al have demonstrated that reversal of hypertension in renal hypertensive dogs with LVH by either renal anastomosis or nitroprusside infusion reduced infarct size. They found no difference in the groups treated with renal artery reanastomosis (nonpharmacological) versus the group treated with infusion of nitroprusside. These results support the concept that hypertension is the detrimental determinant in producing a larger infarct size and that nitroprusside reduces infarct size primarily by its hypotensive effect.

Mechanisms for marked increase in mortality. Previous studies in our laboratory have shown an increased incidence of ventricular fibrillation in animals with chronic HT-LVH. In addition, Inou and colleagues have shown that, by normalizing arterial pressure in dogs with HT-LVH with either infusion of nitroprusside at the time of coronary occlusion or renal artery reanastomosis prior to coronary artery occlusion, the incidence of sudden death returns to that of control levels. We found a fourfold increase in the incidence of lethal ventricular fibrillation in dogs with chronic arterial HT-LVH during 1 hour of coronary artery occlusion.

There are several electrophysiological effects that are specifically related to hypertrophied or ischemic hypertrophied cardiac muscle. These electrophysiological observations could play a role in the mechanism of the augmented lethal arrhythmias that occur in this model. Aronson and others have shown a prolongation of the action potential in isolated strips of hypertrophied rat cardiac muscle. Studies by Martins and colleagues have shown a distinct increase in the incidence of inducible monomorphic ventricular tachycardia in a similar animal model of chronic HT-LVH when exposed to a 3-hour coronary artery occlusion. They also noted that animals with chronic arterial HT-LVH had an excessive conduction delay in the ischemic zones. These electrophysiological abnormalities may explain, in part, the higher prevalence of sudden cardiac death following coronary artery occlusion in hypertensive dogs with LVH.

Clinical Implications

Our findings may have important clinical implications when treating patients with chronic arterial HT-LVH in the setting of acute myocardial infarction. With the increasing use of thrombolytic therapy and mechanical reperfusion, it is especially important to retard the wavefront of myocardial necrosis. These data suggest that the infusion of nitroprusside as late as 1 hour after coronary artery occlusion in an animal model of chronic arterial HT-LVH may retard the wavefront of infarction. This would permit more myocardial salvage using reperfusion techniques. Therefore, the time window for reperfusion therapy appears to be shortened by chronic HT-LVH. This time window may be shifted back to control levels with the infusion of nitroprusside 1 hour into a 3-hour coronary artery occlusion.

Acknowledgments

The authors wish to thank Dina Janzen and Van DeBruyn for their expert technical assistance. The authors wish to acknowledge Drs. Allyn Mark, Donald Heistad, David Harrison, and Kathryn Lamping for their thoughtful and critical review of this manuscript. In addition, the authors wish to recognize the expert secretarial assistance of Maureen Kent and Ruth Hurlburt in the preparation of this manuscript.

References


12. Reimer KA, Jennings RB: The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979;40:633-644


**Key Words**: dogs · hypertrophy · nitroprusside · myocardial infarction · hypertension
Acceleration of the wavefront of myocardial necrosis by chronic hypertension and left ventricular hypertrophy in dogs.
K C Dellsperger, J L Clothier, J A Hartnett, L M Haun and M L Marcus

Circ Res. 1988;63:87-96
doi: 10.1161/01.RES.63.1.87

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/63/1/87

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/