Incidence of Sudden Cardiac Death Associated With Coronary Artery Occlusion in Dogs With Hypertension and Left Ventricular Hypertrophy Is Reduced by Chronic $\beta$-Adrenergic Blockade

Kevin C. Dellsperger, MD, PhD, James B. Martins, MD, Jennifer L. Clothier, BA, and Melvin L. Marcus, MD†

Because $\beta$-adrenergic blockade has as one of its many effects altered electrophysiological abnormalities after dogs with left ventricular hypertrophy have been subjected to coronary occlusion, we tested the hypothesis that metoprolol (200–400 mg/day) would reduce mortality rates in dogs with one-kidney, one clip left ventricular hypertrophy while a similar reduction in arterial pressure with enalapril (20–40 mg/day) would not. Dogs with left ventricular hypertrophy were given metoprolol or enalapril for 5–7 days before a 3-hour coronary occlusion. Infarct size and risk area were measured with triphenyltetrazolium chloride stain and barium angiography, respectively. For control ($n=15$), left ventricular hypertrophy ($n=17$), left ventricular hypertrophy plus metoprolol ($n=12$), and left ventricular hypertrophy plus enalapril ($n=15$) groups, mean arterial pressure, ratio of infarct size to risk area, and dogs experiencing sudden death were 110±4, 142±4, 121±7, and 120±3 mm Hg; 44±5%, 65±5%, 44±7%, and 30±4%; and 27%, 65%, 17%, and 53%, respectively. Thus, the excessive increase in early mortality occurring when dogs with hypertension and left ventricular hypertrophy undergo coronary occlusion is interrupted with $\beta$-blockade, possibly via electrophysiological effects rather than by changes in arterial pressure or infarct size. (Circulation 1990;82:941–950)

Chronic arterial hypertension (HT) is correlated with an increased incidence of acute myocardial infarction and sudden cardiac death. The pathogenesis of this increase must be multifactorial. The atherosclerotic process in patients is accelerated by HT, suggesting the possibility of more extensive coronary artery disease. Several studies in our laboratory have shown that there is a threefold increase in mortality in dogs with chronic HT and left ventricular hypertrophy (HT-LVH) when they are subjected to acute coronary artery occlusion compared with dogs without HT-LVH. In addition, after coronary artery occlusion, there was a 35% increase in the size of the resulting infarct in animals with HT-LVH. Also, the wave front of infarction is accelerated in animals with HT-LVH. These experiments suggested to us that accelerated atherosclerosis was not the sole explanation for an increased infarct size and the high incidence of lethal arrhythmias with coronary occlusion in the presence of HT-LVH.

The Framingham Study reported that the electrocardiographic features that predicted an increased incidence of sudden death were previous myocardial infarction, prolonged QRS, and LVH. There were several electrophysiological abnormalities that are specifically related to the normal or ischemic hypertrophied cardiac muscle, including a prolongation of action potential, inducible sustained ventricular tachycardia in the setting of infarction, and the modulation of conduction abnormalities and the rate of tachycardia with changes in arterial pressure that were altered with $\beta$-blockade. These electro-
physiological abnormalities may in part explain the higher prevalence of sudden cardiac death after coronary artery occlusion in hypertensive patients.

There was evidence of an antiarrhythmic effect of $\beta$-adrenergic blockers that may not be limited to hypertrophied myocardium because they prevented not only recurrent myocardial infarction but also sudden cardiac death after acute myocardial infarction in large populations. These data were somewhat contradictory to the Beta-Blocker Heart Attack study data, which showed a decrease in reinfarction and sudden death rates but also showed that the decrease in sudden death rates was not proportionately greater than the decrease in total mortality rates. However, compared with a group of men treated with a thiazide diuretic, a primary prevention trial of metoprolol treatment of men with mild-to-moderate HT demonstrated lower total and cardiovascular mortality rates in the metoprolol-treated group. Other effects of $\beta$-adrenergic blockade include the blockade of the metabolic effects of sympathetic stimulation and nonspecific drug effects.

In summary, during ischemia, the pressure hypertrophy of left ventricle has specific electrophysiologically abnormal abnormalities that may predispose it to the development of lethal ventricular arrhythmias. These effects are ameliorated by either normalization of arterial pressure or $\beta$-adrenergic blockade. Previous studies suggest that this beneficial effect may relate to a reduction of infarct size and to a direct antiarrhythmic effect of $\beta$-adrenergic blockade.

Therefore, the present study was undertaken to determine 1) whether chronic $\beta$-adrenergic blockade would decrease the incidence of sudden cardiac death when conscious dogs with HT and LVH are subjected to sudden coronary artery occlusion and 2) whether the salutary effects of $\beta$-adrenergic blockade are simply related to their influence on arterial pressure and reduction of infarct size or whether they are related to other effects of $\beta$-adrenergic blockade. To accomplish this, we studied animals with HT-LVH that were treated with the angiotensin converting enzyme inhibitor enalapril. Enalapril was administered to reduce mean arterial pressure to a level similar to that of the metoprolol-treated animals.

Methods

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

Surgical Preparation

Systemic HT was induced in 44 adult mongrel dogs of either sex (weight, 15–29 kg). The method of producing HT has been described in detail and will be summarized briefly. Under general anesthesia and sterile conditions, bilateral flank incisions and unilateral nephrectomy were done, and a clamp (described by Ferrario et al) was implanted on the contratral renal artery, which produced a thrill in the renal artery.

A second surgical procedure was performed 8–9 weeks after the renal surgery. Under anesthesia with sterile techniques, catheters were placed into the thoracic aorta and 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.

Measurement of Infarct Size and Area at Risk

Detailed methodology for measuring infarct size and risk area size has been published. Briefly, a 10% solution of triphenyltetrazolium chloride (TTC) in phosphate-buffered saline was perfused into the coronary arteries through an 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. After TTC staining, a barium mixture was perfused into the coronary arteries at a perfusion pressure equal to the mean arterial pressure of that dog. The atria and right ventricle were removed, and the left ventricle was sectioned into six to eight transmural slices of approximately 1-cm thickness parallel to the atrioventricular groove and weighed (left ventricular mass). Stereoscopic radiographs (20 keV and 2 mA for 5 minutes) of the ventricular slices were obtained without magnification. The perfusion area of the occluded artery, that is, the area at risk, was determined by carefully following the course of the occluded and nonoccluded vessels with stereoscopic radiographs of the transverse slices and the whole left ventricle. The infarct area was determined by visual inspection of the TTC-stained slices. Noninfarcted tissue was stained red by TTC, whereas infarcted tissue was not stained by TTC. With planimetric techniques, the risk and infarct areas (% of total left ventricular mass) were calculated. In addition, total and regional (endocardial, midwall, and epicardial) infarct-to-risk ratios (%) were calculated.

Measurement of Regional Myocardial Perfusion

Regional myocardial perfusion was measured before and during coronary occlusion with 15-$\mu$m diameter radioactive microspheres labeled with scandium-46, strontium-85, niobium-95, tin-113, cerium-141, or gadolinium-153. For each flow measurement, approximately $20 \times 10^6$ microspheres were injected through the left atrial catheter, which was subsequently flushed with 10 ml saline for 10 seconds. Before 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 for at least 90 seconds after injection. Left atrial and arterial pressures.
did not change significantly before or after microsphere injection.

Myocardial perfusion was measured from the samples obtained from the normal perfusion region (nonrisk region perfused by the left anterior descending coronary artery) and the normal-appearing tissue within the area at risk and infarct regions. Each region was divided into subepicardial, midwall, subendocardial, and papillary muscle layers of approximately equal thicknesses. The individual myocardial segments were weighed, placed into plastic scintillation tubes, and counted for 5 minutes in a 3-in. well counter with a sodium iodide or germanium crystal.21 Myocardial blood flow in each sample was calculated by the following formula:

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

where MBF is myocardial blood flow (ml/min/100 g), Cm is counts per gram of myocardium, RBF is reference blood flow (rate of the withdrawal from the reference artery), and Cr is total counts in the reference blood.22

**General Protocol**

Studies were performed 6–10 days after thoracotomy and 5 days after institution of drug therapy, when all dogs appeared to be healthy. Electrolytes, blood urea nitrogen, serum creatinine, and arterial blood gases were measured and were within the normal limits. 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 midchest level. Aortic and left atrial pressures and a precordial electrocardiographic lead were continuously recorded at paper speeds of 5–25 mm/sec.

When the dogs were lying quietly and the hemodynamics were stable, myocardial blood flow was measured with microspheres. Lidocaine (3 mg/kg i.v.) was then administered, and the circumflex coronary artery was occluded with the hydraulic occluder. If ventricular tachycardia ensued (three or more wide complexes at a rate >100 beats/min, which generated arterial pressure pulses), treatment with additional boluses of lidocaine at 1–2 mg/kg was attempted. If ventricular fibrillation (disorganized electrical activity without generation of arterial pulse pressure13) occurred, cardiopulmonary resuscitation and electrical defibrillation with as much as 200 J was performed, but none of these dogs survived. Because the electrocardiogram was recorded at slow paper speeds, the evidence for ventricular fibrillation as the mechanism of sudden death was a sudden change in electrocardiographic height to fibrillatory levels with concomitant pulseless arterial pressure. The evidence for ventricular tachycardia was a sudden increase in the QRS height associated with pulsatile arterial pressure. All animals with sudden cardiac death were excluded from infarct size analysis. In nonsurvivors, risk area was determined as previously described.7 In surviving dogs, measurements of hemodynamics and myocardial blood flows were obtained 5 minutes after coronary artery occlusion, 5 minutes before and after reperfusion, and 1 hour after reperfusion. All animals were subjected to a 3-hour coronary artery occlusion and a 90-minute period of reperfusion.

**Control (group 1).** Fifteen mongrel dogs without HT and LVH served as controls; these dogs had undergone thoracotomy for placement of catheters.

**HT-LVH (group 2):** Seventeen animals with HT-LVH were not treated with additional drug therapy.

Eight control animals and 12 animals with HT-LVH have been reported.7 Seven and five additional dogs in the control and HT-LVH groups, respectively, were studied for the HT-LVH+β and HT-LVH+E animals.

**HT-LVH+β (group 3):** Twelve animals with HT-LVH received chronic β-adrenergic blockade. Two days after surgery for placement of catheters and the coronary artery occluder, these animals underwent an isoproterenol challenge. Heart rate and blood pressure were monitored before and after boluses of 0.125 and 0.25 μg i.v. isoproterenol. After this, metoprolol (100–200 mg p.o. b.i.d.) was begun. On the day of study, a second isoproterenol challenge was performed to evaluate the adequacy of β-adrenergic blockade. A blunting of the heart rate response to isoproterenol was interpreted as adequate β-adrenergic blockade. If the heart rate response was not blunted, the metoprolol dose was doubled, and a repeat isoproterenol challenge was attempted in 2–3 days. In addition, blood was drawn at the time of coronary occlusion to determine metoprolol levels.

**HT-LVH+E (group 4):** Fifteen animals were treated with enalapril (5–20 mg p.o. b.i.d.), beginning on the second postoperative day and continuing until coronary artery occlusion. This was done because metoprolol lowered mean arterial pressure in animals with HT and LVH. If the blood pressure response to enalapril was not midway between the control value (100 mm Hg) and the value before enalapril, the enalapril dose was doubled before coronary artery occlusion. Two to 3 days later, if the blood pressure was lowered to the target level, coronary artery occlusion was performed. To validate adequacy of drug intake, plasma renin activity and angiotensin converting enzyme levels were obtained before and after enalapril treatment.

**Criteria for an Acceptable Experiment**

Animals that completed the entire protocol were included in the analysis of infarct size. These animals had to survive the entire period of occlusion and reperfusion and have adequate TTC stains and barium angiography. In addition, animals with renal surgery had to have mean arterial pressures of more than 115 mm Hg before drug therapy and a left
ventricular mass of more than 5 g/kg. Coronary artery occlusion was verified with myocardial perfusion as measured with microspheres. Animals with ventricular fibrillation were included in baseline characteristics and mortality evaluation but were excluded from infarct analysis. In addition, dogs treated with metoprolol or enalapril had to have verifiable proof of drug intake. With these criteria (isoproterenol for metoprolol and blood pressure for enalapril), all dogs satisfying the other criteria were included in the study.

**Data Analysis**

Values are given as mean±SEM, and a p value of less than 0.05 was considered statistically significant. Hemodynamics, baseline characteristics, myocardial blood flow data, and infarct sizes were analyzed by analysis of variance. Intergroup differences were determined with Scheffe’s F test. A χ² test was used to analyze the difference in mortality rates. Within-group comparisons of hemodynamics before and after drug treatment were made with a paired or unpaired Student’s t test where appropriate.

**Results**

**Left Ventricular Mass and Hemodynamics**

Left ventricular mass was 112±5 g in control dogs and 129±5 g in dogs with HT-LVH (p<0.05). The ratio of left ventricular mass to body weight was 4.8±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 21% in hypertensive dogs. In addition, there were no differences between group 2, 3, and 4 animals with HT and LVT in ratios of left ventricular mass to body weight (Table 1).

Compared with control animals, mean aortic pressure was substantially elevated in dogs with HT-LVH (141±3 compared with 110±5 mm Hg, p<0.05).

There were no significant differences between groups 2, 3, and 4 dogs in HT before drug therapy. After drug treatment with metoprolol or enalapril, mean arterial pressures were 121±7 and 120±3 mm Hg, respectively.

After coronary artery occlusion, heart rate increased in groups 1 and 4 and left atrial pressure (Table 2) increased in groups 1, 2, and 3 animals, whereas mean arterial pressure did not change significantly. Heart rate was lowest in group 3 (HT-LVH+β) animals. After coronary artery occlusion, blood pressure was similar in groups 1, 3, and 4 and statistically different from that in group 2 (HT-LVH).

**Effect of Metoprolol and Enalapril Treatment in Animals With Hypertension and Left Ventricular Hypertrophy**

Group 3 animals achieved a metoprolol level of 261±82 μg/l (n=10). Effectiveness of β-adrenergic blockade was documented in all animals by response to isoproterenol (0.125 and 0.25 μg i.v. boluses). Before metoprolol treatment, a 0.25 μg i.v. bolus of isoproterenol increased heart rate by 69% (213±8 compared with 126±7 beats/min, p<0.05). After treatment with metoprolol, heart rate increased by only 35% (131±7 compared with 97±6 beats/min, p<0.05). After metoprolol, arterial pressure was significantly reduced (122±7 compared with 135±5 mm Hg, p<0.05).

In group 4, the enalapril dose was targeted to lower the blood pressure to a level similar to that of group 3 animals treated with metoprolol (Table 1). After enalapril (31±2 mg/day), the plasma renin activity levels were significantly increased (3.6±0.5 compared with 1.2±0.4 ng/ml/hr, p<0.05), and the angiotensin converting enzyme levels were significantly decreased (22±3 compared with 41±2 units/l, p<0.05).

---

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (control)</th>
<th>Group 2 (HT-LVH)</th>
<th>Group 3 (HT-LVH+β)</th>
<th>Group 4 (HT-LVH+E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>17</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>23±1</td>
<td>23±1</td>
<td>22±1</td>
<td>21±1</td>
</tr>
<tr>
<td>LV weight (g)</td>
<td>112±5</td>
<td>133±8*</td>
<td>132±7*</td>
<td>117±6</td>
</tr>
<tr>
<td>LV weight/body weight (g/kg)</td>
<td>4.8±0.2</td>
<td>5.9±0.2*</td>
<td>6.0±0.2*</td>
<td>5.6±0.2*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>108±5</td>
<td>123±7†</td>
<td>92±8</td>
<td>115±7†</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>110±4</td>
<td>142±4‡</td>
<td>121±7*</td>
<td>120±3*</td>
</tr>
<tr>
<td>Mean arterial pressure before treatment (mm Hg)</td>
<td>...</td>
<td>...</td>
<td>135±5</td>
<td>143±4</td>
</tr>
<tr>
<td>Left atrial pressure</td>
<td>5±1</td>
<td>7±1</td>
<td>7±2</td>
<td>2±‡</td>
</tr>
<tr>
<td>Risk area (% of left ventricle)</td>
<td>41±2</td>
<td>40±2</td>
<td>37±3</td>
<td>36±2</td>
</tr>
<tr>
<td>pH</td>
<td>7.45±0.03</td>
<td>7.43±0.01</td>
<td>7.40±0.02</td>
<td>7.42±0.02</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>29±2</td>
<td>34±1</td>
<td>32±1</td>
<td>30±3</td>
</tr>
<tr>
<td>PO₂ (mm Hg)</td>
<td>87±4</td>
<td>84±5</td>
<td>85±4</td>
<td>84±4</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>44±2</td>
<td>46±2</td>
<td>44±2</td>
<td>41±6</td>
</tr>
<tr>
<td>Creatinine (g/dl)</td>
<td>1.0±0.1</td>
<td>1.1±0.1</td>
<td>1.2±0.1</td>
<td>1.0±0.2</td>
</tr>
</tbody>
</table>

HT, hypertension; LVH, left ventricular hypertrophy; β, metoprolol; E, enalapril; LV, left ventricular.

*p<0.05 compared with group 1; †p<0.05 compared with group 3; ‡p<0.05 compared with all groups.
Myocardial Perfusion

Myocardial perfusion was similar in the normally perfused areas, normal-appearing risk areas, and infarcted areas within each group at baseline (Table 3).

After coronary artery occlusion, there was a tendency for perfusion to increase in the normally perfused area compared with the control state. The normal-appearing risk tissue had slightly greater flow than the infarcted tissue in each region within each group. Tissue without TTC staining had endocardial blood flows equal to or less than 18 ml/min/100 g tissue. There were no significant intergroup differences after coronary artery occlusion. Specifically,

TABLE 2. Hemodynamic Effects of Sudden Coronary Artery Occlusion

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart rate (beats/min)</th>
<th>Before occlusion</th>
<th>5 minutes after occlusion</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>
<td></td>
</tr>
<tr>
<td>1 (n=11)</td>
<td>103±6</td>
<td>136±4*†</td>
<td>110±5</td>
<td>116±6</td>
<td></td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>117±16†</td>
<td>128±9</td>
<td>123±12</td>
<td>120±10</td>
<td></td>
</tr>
<tr>
<td>3 (n=10)</td>
<td>96±8</td>
<td>108±7</td>
<td>103±7</td>
<td>105±5</td>
<td></td>
</tr>
<tr>
<td>4 (n=7)</td>
<td>115±7†</td>
<td>145±6*†</td>
<td>119±9</td>
<td>118±5</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=11)</td>
<td>110±5</td>
<td>107±4</td>
<td>112±6</td>
<td>117±4</td>
<td></td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>141±8‡</td>
<td>134±5‡</td>
<td>142±9‡</td>
<td>127±9‡</td>
<td></td>
</tr>
<tr>
<td>3 (n=10)</td>
<td>121±7§</td>
<td>111±7</td>
<td>116±7</td>
<td>106±9</td>
<td></td>
</tr>
<tr>
<td>4 (n=7)</td>
<td>113±2</td>
<td>115±11</td>
<td>111±7</td>
<td>108±6</td>
<td></td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=11)</td>
<td>5±1</td>
<td>10±2*</td>
<td>9±2</td>
<td>9±2</td>
<td></td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>4±1</td>
<td>12±2*</td>
<td>8±1</td>
<td>9±1</td>
<td></td>
</tr>
<tr>
<td>3 (n=10)</td>
<td>6±2</td>
<td>12±2*</td>
<td>9±3</td>
<td>8±2</td>
<td></td>
</tr>
<tr>
<td>4 (n=7)</td>
<td>2±1§</td>
<td>3±1§</td>
<td>2±1§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAO, coronary artery occlusion. *p<0.05 compared with previous condition, †p<0.05 compared with group 1.

Myocardial Perfusion

Myocardial perfusion was similar in the normally perfused areas, normal-appearing risk areas, and infarcted areas within each group at baseline (Table 3).

After coronary artery occlusion, there was a tendency for perfusion to increase in the normally perfused area compared with the control state. The normal-appearing risk tissue had slightly greater flow than the infarcted tissue in each region within each group. Tissue without TTC staining had endocardial blood flows equal to or less than 18 ml/min/100 g tissue. There were no significant intergroup differences after coronary artery occlusion. Specifically,

TABLE 3. Normal Regions (Nonrisk), Normal- Appearing Risk Regions, and Infarct Regions

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal regions</th>
<th>Normal-appearing risk regions</th>
<th>Infarct regions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EPI</td>
<td>MID</td>
<td>ENDO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before CAO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=11)</td>
<td>116±11</td>
<td>135±13</td>
<td>142±14</td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>104±18</td>
<td>117±23</td>
<td>96±16</td>
</tr>
<tr>
<td>3 (n=10)</td>
<td>127±16</td>
<td>145±19</td>
<td>146±18*</td>
</tr>
<tr>
<td>4 (n=7)</td>
<td>142±24</td>
<td>147±22</td>
<td>140±20</td>
</tr>
<tr>
<td>5 minutes after CAO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=11)</td>
<td>162±10</td>
<td>186±15</td>
<td>179±12</td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>161±29</td>
<td>204±27</td>
<td>182±32</td>
</tr>
<tr>
<td>3 (n=10)</td>
<td>148±22</td>
<td>169±27</td>
<td>165±22</td>
</tr>
<tr>
<td>4 (n=7)</td>
<td>214±11†</td>
<td>237±14†</td>
<td>227±10</td>
</tr>
<tr>
<td>5 minutes before reperfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=11)</td>
<td>112±10</td>
<td>123±14</td>
<td>133±14</td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>106±30</td>
<td>120±28</td>
<td>128±40</td>
</tr>
<tr>
<td>3 (n=10)</td>
<td>165±25</td>
<td>188±30</td>
<td>185±26</td>
</tr>
<tr>
<td>4 (n=7)</td>
<td>143±44</td>
<td>187±36</td>
<td>182±33</td>
</tr>
<tr>
<td>5 minutes after reperfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=11)</td>
<td>134±21</td>
<td>133±27</td>
<td>164±32</td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>142±43</td>
<td>187±45</td>
<td>192±48</td>
</tr>
<tr>
<td>3 (n=10)</td>
<td>148±31</td>
<td>169±33</td>
<td>175±31</td>
</tr>
<tr>
<td>4 (n=5)</td>
<td>121±20</td>
<td>132±18</td>
<td>122±10</td>
</tr>
</tbody>
</table>

CAO, coronary artery occlusion; ENDO, endocardium; EPI, epicardium; MID, midmyocardium.

Values are given in ml/min/100 g wet wt±SEM.

*p<0.05 compared with group 2; †p<0.05 compared with before CAO; ‡p<0.05 compared with normal-appearing risk.
5 minutes after coronary artery occlusion, the collateral flow was similar among all four groups of animals.

Just before reperfusion, the flow within the normal-appearing risk and infarcted areas tended to increase compared with the flow at 5 minutes after coronary artery occlusion measurement. After reperfusion, there was a slightly greater flow to the normally perfused areas as well as the areas at risk. In addition, there tended to be an increase in the flows to the risk regions compared with that to the nonrisk regions.

Mortality

During coronary artery occlusion and reperfusion, four of 15 control dogs died [confidence interval (CI), 27%; range, 11–43%] (Figure 1). Eleven of 17 animals (CI, 65%; range, 43–87%) with HT-LVH had sudden cardiac death after coronary artery occlusion. Ten of 11 HT-LVH animals had sudden cardiac death within 15 minutes after coronary occlusion. One animal had sudden cardiac death on reperfusion. Treatment with metoprolol (HT-LVH+β) lowered the mortality rate to 17% (CI, −9% to 42%; \( p < 0.05 \) compared with HT-LVH and HT-LVH+E groups). Although enalapril lowered the mean arterial pressure before coronary artery occlusion to a level similar to that of the group 3 animals (Table 2), eight of 15 animals had sudden cardiac death within 15 minutes after coronary artery occlusion (CI, 53%; range, 43–63%) (see Figure 1). The electrocardiographic tracings were of satisfactory quality to define the mechanism of sudden death in 68% of the animals that died after coronary artery occlusion. In all cases, the terminal rhythm was a tachyarrhythmia (either ventricular fibrillation or ventricular tachycardia). In addition, there were no instances of bradyarrhythmias or electromechanical dissociation. The risk areas of dogs that died prematurely were not significantly different from those of the survivors. Furthermore, the degree of HT, heart rate, and left atrial pressures were similar in the surviving and nonsurviving dogs of each group (Table 4).

Relation of Infarct Size to Risk Area

The risk areas as percentages of total left ventricle were similar among the four groups (see Table 5). Group 2 animals had significantly greater infarct sizes, both as percentages of total left ventricle and as percentages of risk areas, compared with the other three groups (Figure 2). There were no statistically significant differences in infarct-to-risk ratios among group 1, 3, and 4 animals.

The regional infarct-to-risk relations are shown in Figure 3. Animals treated with enalapril had the smallest endocardial infarct-to-risk ratios. The
were no statistically significant differences among control, HT-LVH+β, and HT-LVH+E animals in midwall and epicardium in infarct sizes.

**Discussion**

The present study resulted in three findings. First, the mortality rates associated with acute coronary artery occlusion in animals with HT and LVT can be significantly reduced by pretreatment with the β-adrenergic blocker metoprolol (Figure 1). Second, the decrease in sudden cardiac death observed after pretreatment with metoprolol was not solely related to its antihypertensive effect because a similar decrease in arterial pressure produced with enalapril had no effect on the incidence of sudden cardiac death after coronary artery occlusion. Third, a moderate decrease in mean arterial pressure produced by treatment with either metoprolol or enalapril was associated with a complete return to control levels of infarct size (Figures 2 and 3 and Table 5).

Our data analyses and conclusions depend on several factors, including methodology, similarity of collateral flow among the groups during coronary artery occlusion, and effects of metoprolol and enalapril on coronary blood flow.

**Methodology**

The protocol used in these studies has many strengths. First, coronary artery occlusion was performed in awake animals, negating the possible confounding effects of anesthetic agents and surgical trauma. Second, myocardial perfusion was measured at critical times during the protocol. Measurement of myocardial perfusion 5 minutes after coronary artery occlusion and 5 minutes before reperfusion allowed us to verify that coronary artery occlusion was maintained for the desired period and to determine the effects of HT, LVH, and drug treatment with metoprolol and enalapril on coronary collateral flow. Third, our model of HT and LVH was similar in many ways to that occurring in humans; an increase in left ventricular mass of 20% is frequently observed in patients with HT-LVH. Fourth, risk area and infarct size were directly measured. Fifth, the efficacy of drug effects were carefully documented. β-Adrenergic blockade was demonstrated by a reduction in heart rate response to an intravenous dose of isoproterenol. In addition, metoprolol levels were measured. Measurements of plasma renin activity and angiotensin converting enzyme levels demonstrated enalapril effectiveness.

Some animals in groups 1 (n=8) and 2 (n=12) have been previously reported. Although use of "historical controls" is not ideal, data presented recently are confirmatory of two previous studies of mortality rates and infarct sizes in animals with HT-LVH in our laboratory. The seven control animals and five animals with HT-LVH not previously reported were studied with the same methodology used with group 3 and 4 animals. There was no significant difference in mortality rates between historical controls and recently studied animals (group 1, 25% compared with 29%, respectively; group 2, 58% compared with 80%, respectively). In addition, there was no difference in mean arterial pressure.

**Table 5. Risk and Infarct Sizes**

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk (% total LV)</th>
<th>Infarct (% total LV)</th>
<th>Infarct risk x 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=11)</td>
<td>41±2</td>
<td>18±2</td>
<td>44±5</td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>40±2</td>
<td>29±4*</td>
<td>65±5*</td>
</tr>
<tr>
<td>3 (n=10)</td>
<td>37±3</td>
<td>18±4</td>
<td>44±7</td>
</tr>
<tr>
<td>4 (n=7)</td>
<td>36±2</td>
<td>12±2</td>
<td>30±4</td>
</tr>
</tbody>
</table>

LV, left ventricle.
*p<0.05 compared with groups 2, 3, and 4.

untreated animals with HT-LVH had the largest infarctions in the midwalls and epicardiums. There were no statistically significant differences among control, HT-LVH+β, and HT-LVH+E animals in midwall and epicardium in infarct sizes.

**Figure 2.** Bar graph of effects of a 3-hour acute coronary artery occlusion on regional infarct-to-risk ratios in four groups of dogs: control, (group 1, n=11), hypertension (HT) and left ventricular hypertrophy (LVH) (group 2, n=6), HT-LVH plus metoprolol (β) (group 3, n=10), and HT-LVH plus enalapril (E) (group 4, n=7). HT-LVH infarct-to-risk ratio was significantly larger than that in the other three groups.

**Figure 3.** Bar graph of effects of a 3-hour acute coronary artery occlusion on regional infarct-to-risk ratios in four groups of dogs: control, (group 1, n=11), hypertension (HT) and left ventricular hypertrophy (LVH) (group 2, n=6), HT-LVH plus metoprolol (β) (group 3, n=10), and HT-LVH plus enalapril (E) (group 4, n=7).
(group 1, 104±5 compared with 115±5 mm Hg; group 2, 142±5 compared with 140±5 mm Hg) and ratio of left ventricular mass to body weight (group 1, 5.0±0.2 compared with 4.6±0.2 g/kg; group 2, 5.8±0.3 compared with 6.1±0.5 g/kg) in the historical controls and new animals, respectively.

In our model, we used lidocaine before coronary occlusion. In previous studies,6–7 lidocaine was used before infarction to evaluate the relation of infarct size to risk area in animals with HT-LVH. Although this is not clinically possible in most circumstances, all treatment groups had the same antiarrhythmic treatment.

**Effects on Coronary Flow**

Treatment with metoprolol or enalapril resulted in only relatively small changes in perfusion of normal myocardium. Our protocol, however, was not optimized to examine such effects by comparatively measuring myocardial perfusion before and after drug treatment.

After coronary artery occlusion, myocardial blood flow reaches the ischemic myocardium via coronary collateral channels. Collateral flow affects the size of myocardial infarction.27–29 Collateral flow during coronary artery occlusion was similar in all groups of animals studied; therefore, we can conclude that metoprolol or enalapril did not decrease infarct size in group 3 and 4 animals by improving collateral flow. Other studies have shown that the perfusion delivered by native coronary collaterals in hypertrophied left ventricles does not differ from that in normal left ventricles.4,27 However, it should be noted that measured resistance in native collaterals of hypertrophied hypertensive hearts is greater than in controls.

**Potential Mechanisms for Marked Increase in Mortality**

Patients with LVH have an increased incidence of sudden cardiac death.8–10 Previous studies in our laboratory4–7 have shown increased incidence of sudden cardiac death and ventricular fibrillation in animals with chronic HT-LVH after coronary occlusion. Inou and colleagues6 have shown that by using renal reanastomosis to normalize arterial pressure in dogs before coronary occlusion, the increase in mortality rates can be reduced to that of control levels. Nitroprusside infusion, which also normalized arterial pressure, reduced mortality in HT-LVH animals but not to the same extent as renal artery reanastomosis. It seemed prudent to expect that any antihypertensive agent may also exert antiarrhythmic effects; we were impressed to find that this was not the case. It is important to point out that in contrast to previous work,6 we did not normalize arterial pressure with metoprolol or enalapril. While infarct size was similarly decreased in metoprolol- and enalapril-treated animals, the occurrence of sudden death was not. This suggests that the β-adrenergic receptors, which are inhibited with metoprolol treatment, may play a role in the arrhythmogenesis in this model that is independent from infarct size and modulation of collateral flow.

There are several electrophysiological effects specifically related to the normal or ischemic hypertrophied myocardium that may result in a greater prevalence of lethal arrhythmias. Aronson11 has shown that a prolongation of the action potential in isolated strips of hypertrophied rat cardiac muscle exists. Because ischemia shortens the action potential, a greater dispersion of refractoriness may occur. Trittardt et al12 showed that moderate hypertrophy may cause conduction delay that could be critically worsened by ischemia. Martins et al13 have evaluated this possibility in a model showing a dramatic increase (compared with normotensives) in the prevalence of inducible monomorphic ventricular tachycardia in dogs with chronic HT and LVH after a 3-hour coronary artery occlusion. The rates of ventricular tachycardia varied from 240 to 460 min⁻¹, which could lead to hemodynamic collapse and ventricular fibrillation. These investigators found no evidence of refractory period dispersion, but they did find that excessive endocardial-to-epicardial conduction delay occurred in ischemic zones. Recently, Hopson and Martins14 identified another marker of the arrhythmogenic state in ischemic hypertrophied myocardium. They showed that a reduction of the blood pressure by nitroprusside 3–6 hours after coronary artery occlusion potentiated conduction delay and slowed the rate of inducible ventricular tachycardia. Metoprolol administration prevented this exacerbation of conduction delay and also prevents induction of ventricular tachycardia.15 The antiarrhythmic effect of metoprolol may have been due to the antagonism of sympathetic influences that potentiate conduction delay in the ischemic zone.

Another possible effect of metoprolol was heart rate slowing (group 3 dogs). Because heart rate may be an important mechanism controlling spontaneous ventricular arrhythmias, it is possible that bradycardia alone, although not significantly different from group 2 after coronary artery occlusion, may have prevented the occurrence of sudden death in group 3. However, because metoprolol prevents ventricular tachycardia induction at the same pacing rates,15 we cannot attribute the salutary effect of metoprolol to heart rate slowing alone.

**Effect on Antihypertensive Therapy in Patients**

Ideal antihypertensive therapy includes an agent that reduces blood pressure to desired levels with minimal adverse effects. Results of the present study indicate there may be other important factors that guide the selection of antihypertensive therapy. Other nonhypertensive effects of antihypertensive agents may be quite diverse.30,31 Results also indicate that treatment of hypertensive patients with metoprolol may exert a beneficial effect on the incidence of lethal arrhythmias in addition to a blood pressure–lowering effect. Because patients with HT often have accelerated atherosclerosis, which predisposes them
to acute myocardial infarction, it is not unreasonable to choose metoprolol as a primary line of antihypertensive therapy in patients with HT and LVH who are at risk for acute myocardial infarction.

**Study Limitations**

Although the cardiac rhythm was constantly monitored, recordings of the terminal arrhythmia were not always interpretable due to the slow paper speed, although we can exclude electromechanical dissociation because the rhythms at death were always rapid. Because multichannel electrocardiograms were not recorded at rapid paper speeds, the precise identification of the terminal tachycardia was not possible. Several possibilities include monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, and primary ventricular fibrillation.

In the present study, all dogs received lidocaine before occlusion. This limitation must also be considered in extrapolating our results to patients who do not. While lidocaine may be arrhythmogenic as well as antiarrhythmic, its use still allowed us to demonstrate a consistent risk of sudden death. In addition, rapid and hypotensive ventricular tachycardia was inducible without a lidocaine intervention in dogs with LVH. Nevertheless, we cannot exclude a potential interaction between metoprolol and lidocaine in this study that may be theoretically additive in antiarrhythmic effect. We doubt such an interaction exists because we have previously shown that metoprolol alone prolongs conduction in the ischemic zone of dogs with LVH and prevents induction of rapid hypotensive ventricular tachycardia.

The lack of response to defibrillation is unusual. However, the maximum output of our defibrillation unit was 200 J, and it is possible that the transthoracic impedance in closed-chest animals coupled with the low output of the unit did not deliver sufficient energy for cardioversion.

**Conclusions**

The mortality rates associated with acute coronary artery occlusion in animals with HT and LVH can be significantly reduced by pretreatment with metoprolol. This decrease in mortality rates is not due solely to its antihypertensive effect or effect on infarct size. Results from this study may have serious ramifications on the treatment of hypertensive patients.

**Acknowledgments**

We wish to acknowledge the expert technical assistance of Linda Haun and James Lundy in the conduct of these studies. The authors wish to thank Drs. David Harrison, Kathryn Lamping, and Allyn Mark for their critical review of this manuscript. We also acknowledge the expert secretarial assistance of Maureen Kent and Cindy Evans in the preparation of this manuscript.

**References**

21. Eastham CE, Marcus ML, Chilian WM: Validation of Ge detector-base gamma counting system for multiple micro-

Downloaded from http://circ.ahajournals.org/ by guest on November 10, 2017

KEY WORDS  • hypertension  • left ventricular hypertrophy  • occlusions  • β-adrenergic blockers  • metoprolol  • enalapril
Incidence of sudden cardiac death associated with coronary artery occlusion in dogs with hypertension and left ventricular hypertrophy is reduced by chronic beta-adrenergic blockade.

K C Dellsperger, J B Martins, J L Clothier and M L Marcus

*Circulation*. 1990;82:941-950
doi: 10.1161/01.CIR.82.3.941

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/82/3/941

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* 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* is online at:
http://circ.ahajournals.org//subscriptions/