Potentiation of Reperfusion-Associated Ventricular Fibrillation by Left Ventricular Hypertrophy

Anne L. Taylor, Robert Winter, Francis Thandroyen, Sidney Murphree, L. Maximilian Buja, Robin Eckels, Patricia Pastor, and Mark Kremers

Important electrophysiological alterations that may predispose hearts to arrhythmias have been described for hypertrophied myocytes, and hypertrophy coupled with ischemia has been associated with an increased incidence of sudden death; however, an influence of hypertrophy on reperfusion arrhythmias has not been previously described. We hypothesized that reperfusion-associated arrhythmias would be potentiated by left ventricular hypertrophy. After induction of renovascular hypertension, 37 awake, unseated dogs (17 with left ventricular hypertrophy and 20 without hypertrophy) underwent 15 minutes of coronary artery occlusion and reperfusion. All dogs were pretreated with lidocaine bolus injections and with lidocaine by continuous infusion during coronary occlusion and reperfusion. Reperfusion-associated ventricular fibrillation occurred in seven of 17 dogs with left ventricular hypertrophy versus one of 18 dogs without hypertrophy \( (p \leq 0.05) \). The presence of hypertension was not significantly associated with an increased incidence of reflow ventricular arrhythmias. Neither QT interval nor area-at-risk was different between the dogs with and without reperfusion ventricular fibrillation; however, increased heart rate just before reperfusion did correlate with an increased incidence of ventricular fibrillation at reperfusion. Thus, 1) left ventricular hypertrophy was associated with a significantly increased incidence of reperfusion-induced ventricular fibrillation after 15 minutes of ischemia, 2) this increased incidence was independent of the presence of hypertension, and 3) lidocaine protected control and hypertrophied hearts against ventricular fibrillation during ischemia but was ineffective in protecting hypertrophied hearts against reperfusion-induced ventricular fibrillation. \( \text{(Circulation Research} 1990;67:501-509) \)

In response to a sustained increase in work load, ventricular myocardium hypertrophies; this process is marked by cellular enlargement, by biochemical,\(^1,2\) electrophysiological,\(^3-5\) and mechanical\(^6,7\) changes in myocytes, as well as by alterations in the coronary circulation.\(^8,9\) While hypertrophy is an adaptive process that permits maintenance of physiological function in the face of increased work load, left ventricular hypertrophy resulting from pressure overload has been shown to interact in a negative synergistic fashion with myocardial ischemia.\(^10,11\) One important mechanism by which left ventricular hypertrophy potentiates the mortality of myocardial ischemia may be an enhanced susceptibility to arrhythmias. Clinically, abnormalities of cardiac rhythm have been noted to be associated with ventricular hypertrophy even in the absence of ischemia.\(^12,13\) Left ventricular hypertrophy has been coupled with an increased likelihood of sudden death\(^14,15\) in excess of the risk of sudden death associated with the presence of hypertension alone. Moreover, in patients with hypertension but without hypertrophy, the incidence of ventricular ectopic activity was no different from normal control subjects; however, if hypertrophy was present in addition to hypertension, ventricular ectopic activity was significantly increased. Coronary artery disease was excluded in this cohort, so that ischemia was not a necessary precondition for the presence of ventricular ectopy in hypertrophic myocardium.\(^12\) It has

\( \text{NIH} \)
therefore been postulated that the hypertrophied myocyte represents an independent risk for sudden death. Important electrophysiological alterations that might predispose hearts to arrhythmias have been described for hypertrophied myocytes. These include increased transmembrane inward calcium current\(^\text{16}\) in isolated myocytes and decreased cesium-sensitive early outward currents resulting in a net increase in slow inward calcium current,\(^\text{17}\) as well as early and delayed afterpotentials resulting in triggered activity.\(^\text{18}\) Significant and selective prolongation of the repolarization phase of the action potential that is nonuniformly distributed among various myocardial layers\(^\text{19}\) has also been described. Thus, electrophysiological alterations providing the substrate for reentrant arrhythmias (prolongation and dispersal of refactoriness) as well as for triggered automaticity (calcium-dependent afterpotentials) may be present in nonischemic, hypertrophied myocardium. In this setting, the arrhythmogenic effects of ischemia and reperfusion may be amplified.

Although incidence of sudden death during coronary artery occlusion has been noted to be increased by the presence of left ventricular hypertrophy and hypertension,\(^\text{11,20}\) an effect of left ventricular hypertrophy on reperfusion-associated arrhythmias has not been previously noted. We present data in the present study suggesting that left ventricular hypertrophy is associated with an enhanced susceptibility to reperfusion-associated ventricular fibrillation. Moreover, we find this enhanced susceptibility of hypertrophied myocardium to reperfusion-associated ventricular fibrillation to be independent of the presence of hypertension.

**Materials and Methods**

This study was approved by the Institutional Review Board for Animal Experimentation. Care of the animals conformed to guidelines defined by the National Institutes of Health and the Food and Drug Administration.

**Surgical Preparation**

Conditioned mongrel dogs of either sex weighing 25–35 kg were anesthetized with sodium pentobarbital (25 mg/kg) and mechanically ventilated with room air. Renovascular hypertension was induced by creating renal artery stenosis in one renal artery with removal of the second kidney. Renovascular hypertension was thereby induced in 2–4 days, with significant increases in left ventricular mass after 6–8 weeks of hypertension. Blood pressure was measured before surgery and at weekly intervals after surgery. When hypertension had been present for 6–8 weeks, the animals were anesthetized and mechanically ventilated; a thoracotomy was performed in the fifth left intercostal space. A Konigsberg catheter was inserted into the left ventricle by an apical stab wound for measurement of left ventricular pressure and the first derivative of left ventricular pressure. A catheter was placed in the left atrium for microsphere injection as well as measurement of left atrial pressure, and a balloon occluder was placed around a segment of the left anterior descending coronary artery distal to the first diagonal branch. Five pairs of 5-MHz pulse transit piezoelectric crystals were implanted oriented endocardium to epicardium in the myocardium in the ischemic and nonischemic portions of the left ventricle for measurement of regional function as part of a separate protocol. Nonhypertrophied control animals did not have a renal artery clip but had identical hemodynamic catheters and a coronary artery occluder placed. A small group of hypertrophied-hypertensive dogs underwent reversal of hypertension by means of renal artery reanastomosis shortly before the time of cardiac instrumentation, so that hypertrophy was present but blood pressure was normal at the time of the experimental protocol.

**Measurement of Regional Myocardial Blood Flow, Ischemic Area-at-Risk, Heart Weight-to-Body Weight Ratio, and Tissue Necrosis**

Regional myocardial blood flow was measured with radiolabeled 15-μm-diameter carbonized microspheres. Microspheres were suspended in a solution containing 10% dextran and 0.01% Tween 80, mechanically agitated, and then injected into the left atrium. A simultaneous reference central arterial blood sample was withdrawn at a constant rate by pump from the aortic catheter.

At the conclusion of the experimental protocol, the surviving dogs were heparinized intravenously with 10,000 units of heparin and deeply anesthetized with sodium pentobarbital (25 mg/kg). A second large dose of sodium pentobarbital (75 mg/kg) was given to cause cessation of cardiac contraction. The hearts were excised and washed, and the left main coronary artery was cannulated. Dogs that had ventricular fibrillation at reperfusion were given a large dose of sodium pentobarbital (75 mg/kg by left atrial catheter) to rapidly cause asystole, and the hearts were quickly excised without heparin administration; otherwise, these hearts were processed identically to hearts from survivors. The left anterior descending coronary artery was cannulated distal to the occluder and then tied off with a 4-0 silk suture at the level of the coronary artery occluder. The two arteries were then simultaneously perfused, the left main coronary artery with monastral blue solution and the left anterior descending artery with a solution of triphenyltetrazolium chloride so that myocardial area-at-risk was delineated by differential staining. Perfusion pressure was equal to the mean arterial pressure of the animal during the experiment; thus, hearts from hypertensive animals were perfused at higher mean arterial pressures than those from normotensive dogs. Hearts were then fixed in buffered Formalin. After fixation, the hearts were sliced into seven to eight equal-thickness slices parallel to the atrioventricular groove, the right ventricle was removed, and the left ventricular slices were weighed and photographed so that areas of differential staining could be
were pretreated. Because some subgroups had more surgical procedures than others, left ventricular weight-to-body weight ratios were calculated using body weights obtained before any surgical procedure, thus avoiding artifactual increase in this ratio due to surgery-related weight loss. Transmural tissue samples between crystal pairs and from a remote control region in the circumflex coronary artery distribution were divided into endocardial, midmyocardial, and epicardial segments, weighed, placed in Formalin, and then placed into a scintillation counter for determination of regional myocardial blood flow. Regional myocardial blood flow was calculated by a computer-assisted program in which flow is determined by the general formula $Q_m = Q_r \times C_m/C_r$, where $Q_m$ is myocardial flow (ml/min), $Q_r$ is the reference blood flow (ml/min), $C_m$ is the counts per minute in myocardium, and $C_r$ is the counts per minute in the reference blood sample. The tissue samples were then reassembled, embedded in paraffin, sectioned, and stained with hemotoxylin and eosin. After this, sections were carefully examined histologically to determine the presence of acute necrosis. If acute necrosis was present, the area of necrosis was measured and expressed as a percentage of the total segment area.

**Experimental Protocol**

When the dogs had recovered from surgery for at least 7 days, they were brought to the laboratory and placed in a standing sling in the awake, unseated state. Care was taken to ensure that the dogs were comfortable and unstressed. Each dog underwent 15 minutes of coronary artery occlusion followed by 24 hours of reperfusion if the dog survived. Before coronary artery occlusion, all dogs were pretreated with lidocaine in the following dosage schedule: 1.5, 1.0, 0.8, and 0.8 mg/kg as intravenous bolus injections at 15-minute intervals, followed by intravenous infusions at a rate of 2 mg/min during coronary artery occlusion and for the initial 15 minutes of reperfusion.

During the experimental period, the following hemodynamic measurements were recorded using a Hewlett-Packard four-channel recorder (Hewlett-Packard Co., Richardson, Tex.): heart rates, left ventricular pressure, the first derivatives of left ventricular pressures, aortic pressures, and phasic and mean left atrial pressures. With an eight-channel Hewlett-Packard recorder, continuous electrocardiogram, left ventricular pressures, the first derivatives of left ventricular pressures, and regional wall thickening from the four or five pairs of ultrasonic crystals were simultaneously recorded. These were analyzed as part of a separate study. Regional myocardial blood flow was measured at control, at 10 minutes of coronary artery occlusion, and at 30 minutes of reperfusion in survivors.

**Statistical Analysis**

Comparisons of reperfusion-associated ventricular fibrillation among the four groups were done by means of a logarithmic likelihood ratio rather than the Pearsonion $\chi^2$ test because of the small numbers in some groups. This test is preferable to the $\chi^2$ test when the observed frequency of an event minus the expected frequency of an event is less than the expected frequency of an event. This condition is true for the control group. Comparisons were done by partitioning according to the presence or absence of hypertrophy and then by the presence or absence of hypertension.

Analyses of hemodynamics and regional myocardial blood flow over time within groups were done by repeated measures analysis of variance for unbalanced data. Student-Newman-Keuls tests were used to make individual comparisons.

Intergroup comparisons at given time points were done by unpaired $t$ tests with a Bonferroni correction based on numbers of comparisons performed. Comparison of differences in areas-at-risk and QT intervals was done by Student's $t$ test.

**Results**

**Mortality**

Thirty-nine dogs underwent coronary artery occlusion, and 37 dogs survived the 15-minute occlusive period. Of these 37 dogs, eight died of ventricular fibrillation immediately after reperfusion. Reperfusion...
ventricular fibrillation always occurred within 15 seconds of reperfusion and was preceded by a short burst of ventricular tachycardia (Figure 1).

The 37 dogs were divided into four groups as follows (Table 1): 1) hypertrophy-hypertension: dogs with hypertension and left ventricular hypertrophy; 2) hypertrophy-normotension: dogs with left ventricular hypertrophy that had undergone renal artery reanastomosis and thus had normal blood pressure but residual hypertension at the time of study; 3) no hypertrophy–hypertension: dogs that had undergone renal artery constriction, that became hypertensive, but in which heart weight-to-body weight ratios were not different from control dogs; and 4) no hypertrophy–normotension control dogs that had undergone no renal artery surgery and thus had neither hypertension nor hypertrophy.

Figure 2 shows heart weight-to-body weight ratios and mean arterial and mean left atrial pressures at the beginning of the experimental protocol for each group. Analysis of variance for each parameter showed highly significant differences among the four groups for each parameter. Figure 2 shows which pairs of these parameters were not different from one another. Thus, among the four heart weight-to-body weight ratios, groups 1 versus 2 were not different nor were groups 3 versus 4. Significant differences in heart weight-to-body weight ratios are attributable to differences between all animals with hypertrophy (groups 1 plus 2) and those without hypertrophy (groups 3 plus 4). Similarly, mean arterial pressures were not significantly different in groups 1 versus 3 and in groups 2 versus 4. Significance is therefore attributable to differences in mean arterial pressure between all hypertensive dogs (groups 1 plus 3) and all normotensive dogs (groups 2 plus 4).

Changes in blood pressures over time in groups undergoing renal artery surgery can be seen in Table 2. Renal artery constriction produced significant increases in mean arterial blood pressure in all three groups. In those animals undergoing successful renal artery reanastomosis (group 2), blood pressure significantly declined to values no different from preoperative baseline.

Ventricular fibrillation during ischemia occurred in two of the 39 dogs entered into the study (one dog with hypertrophy and hypertension, one dog with hypertension but no hypertrophy). Of the 37 dogs surviving coronary artery occlusion, the incidence of reperfusion ventricular fibrillation is cross-classified by the presence or absence of hypertrophy (Table 3) and then by the presence or absence of hypertension (Table 4). Table 3 shows a significant association between hypertrophy and reperfusion ventricular fibrillation measured by the logarithmic likelihood ratio. Table 4 does not show a significant association between reperfusion ventricular fibrillation and the presence of hypertension.

Heart Rate

The relation between heart rate and the occurrence of ventricular fibrillation at reperfusion is shown in Table 5. Survivors had lower heart rates than dogs with reperfusion ventricular fibrillation at all time periods; however, this difference was statistically significant only at the end of the coronary artery occlusion (15 minutes occlusion), the time just before reperfusion (Table 5). When dogs were further subdivided into hypertrophied or nonhypertrophied dogs (Table 5), the same trends were observed. Statistical analysis was omitted for this section of
TABLE 2. Mean Arterial Blood Pressure (mm Hg) Changes in Groups Undergoing Renal Artery Surgery

<table>
<thead>
<tr>
<th>Group</th>
<th>Preoperative baseline</th>
<th>Post–renal artery constriction</th>
<th>Post–renal artery reanastomosis</th>
<th>Experimental control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypertrophy-hypertension (n=10)</td>
<td>106±10</td>
<td>144±8*</td>
<td>...</td>
<td>139±15*</td>
</tr>
<tr>
<td>2. Hypertrophy-normotension (n=6)</td>
<td>108±4</td>
<td>156±18*</td>
<td>115±4†</td>
<td>115±4‡</td>
</tr>
<tr>
<td>3. No hypertrophy–hypertension (n=8)</td>
<td>106±5</td>
<td>141±6*</td>
<td>...</td>
<td>132±9*</td>
</tr>
</tbody>
</table>

Values are mean±SD.
*<0.05 vs. preoperative baseline.
†<0.05 post–renal artery constriction vs. post–renal artery reanastomosis.
‡<0.05 group 2 vs. groups 1 and 3 at Experimental Control time point (the beginning of the experiment).

Table 5 because one group (No hypertrophy, Reflow ventricular fibrillation) had only one subject. Thus, heart rate was the only hemodynamic variable that was different between survivors and those with reperfusion-associated ventricular fibrillation.

**QT Interval**

QT intervals at baseline before coronary artery occlusion were not different between survivors and dogs with reflow ventricular fibrillation (0.22±0.02 versus 0.22±0.02 seconds) nor was there a difference in this parameter at 15 minutes of occlusion just before reperfusion between the two groups (0.20±0.2 versus 0.20±0.03 seconds). Because of the rapidity of arrhythmia onset, QT interval could not be accurately determined in dogs with reperfusion-associated ventricular fibrillation.

**Regional Myocardial Blood Flow**

Regional myocardial blood flow in survivors and in dogs dying of reperfusion ventricular fibrillation is shown in Table 6. Segments were separated according to the function of a particular segment during ischemia as measured by sonomicrometers. Thus, blood flow was compared between the two groups in segments with function unchanged from control during coronary occlusion, in segments becoming hypokineticon, and in those becoming dyskinetic during ischemia. Regional blood flow was significantly lower during ischemia in dyskinetic segments in those animals with reperfusion-associated ventricular fibrillation.

**Area-at-Risk**

Area-at-risk (as percent of left ventricular mass) was measured in 14 dogs (four controls, seven hypertrophied survivors, three hypertrophied with reflow ventricular fibrillation). There was no difference in area-at-risk among these three groups (23±2% versus 26±3% versus 24±4%, p=NS).

**Histology**

Sections stained with hemotoxylin and eosin were examined for neutrophilic infiltrates, altered myocyte morphology and staining, or other evidence of acute coagulative necrosis. While many sections showed scattered contraction bands, tiny microscopic foci of acute coagulative necrosis were found in sections from only eight hearts (five with hypertrophy and three with hypertension but without hypotrophy). These eight sections had only microscopic areas of acute subendocardial necrosis and accounted for at most only 1–2% of total myocardial area in a given transmural section. Occasional sections also showed focal effects of chronic instrumentation such as epicardial chronic inflammation or focal fibrosis.

**Discussion**

In response to sustained increase in work load, ventricular myocardial hypertrophies; this is process during which biochemical, mechanical, coronary vascular, and electrophysiological changes occur.1–19 Despite the clear mechanical adaptive advantage of left ventricular hypertrophy,67 the concomitant qualitative changes induced by hypertrophy may have significant negative synergistic effects with ischemia.10,11,20 The findings of our study strongly suggest that left ventricular hypertrophy is associated with an increased incidence of reperfusion ventricular fibrillation after 15 minutes of coronary artery occlusion, an ischemic interval that in normal hearts results in fully reversible injury. Moreover, the increased susceptibility to reperfusion ventricular fibrillation was independent of the presence of hypertension. Lidocaine, a sodium channel blocker, was administered to prevent ventricular fibrillation during ischemia so that mechanical and electrical activity could be recorded at reperfusion. Lidocaine protected control and hypertrophied hearts against ventricular fibrillation during ischemia but was ineffective in protecting hypertrophied hearts from reperfusion-induced ventricular

**Table 3. Comparison of Reperfusion Ventricular Fibrillation in Hypertrophied Versus Nonhypertrophied Myocardium**

<table>
<thead>
<tr>
<th>Group</th>
<th>Log likelihood $\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+2 7/17 vs. 3+4 1/20</td>
<td>7.658</td>
<td>0.006</td>
</tr>
<tr>
<td>1 3/11 vs. 2 4/6</td>
<td>2.506</td>
<td>NS</td>
</tr>
<tr>
<td>3 1/8 vs. 4 0/12</td>
<td>1.912</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 4. Comparison of Reperfusion Ventricular Fibrillation in Hypertensive Versus Normotensive Dogs**

<table>
<thead>
<tr>
<th>Group</th>
<th>Log likelihood $\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+3 4/19 vs. 2+4 4/18</td>
<td>0.007</td>
<td>NS</td>
</tr>
<tr>
<td>1 3/11 vs. 3 1/8</td>
<td>0.638</td>
<td>NS</td>
</tr>
<tr>
<td>2 4/6 vs. 4 0/12</td>
<td>11.431</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
fibrillation. One may infer from this that the mechanisms of ischemic and reperfusion ventricular fibrillation in hypertrophied hearts may differ, which has been shown to be the case in nonhypertrophied hearts.22 Neither QT interval nor area-at-risk was different between survivors and those dogs with reperfusion-associated ventricular fibrillation. Heart rate, however, was significantly increased just before reperfusion in those dogs with reperfusion ventricular fibrillation.

Arrhythmic mechanisms that have been postulated to be responsible for reperfusion-associated arrhythmias include reentry as well as altered automaticity.23-27 The specific factors contributing to either reentrant or automatic arrhythmias include heterogeneity of injury and recovery, the presence of viable but injured cells, the severity of the injury, the rate of reperfusion, the reintroduction of oxygen, and reperfusion-associated calcium ion shifts, as well as modified adrenergic responsiveness.20,21

### Table 5. Heart Rate Responses in Survivors Versus Dogs With Reperfusion Ventricular Fibrillation (beats/min)

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Time</th>
<th>Preocclusion baseline</th>
<th>Immediate occlusion</th>
<th>15-minute occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>All survivors vs. all reperfusion ventricular fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors (29)</td>
<td></td>
<td>100±18</td>
<td>119±20</td>
<td>118±22</td>
</tr>
<tr>
<td>Reflow ventricular fibrillation (8)</td>
<td></td>
<td>112±16</td>
<td>129±14</td>
<td>145±21*</td>
</tr>
<tr>
<td>Subdivided by presence or absence of hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive (17)</td>
<td></td>
<td>98±17</td>
<td>116±17</td>
<td>116±20</td>
</tr>
<tr>
<td>Reflow ventricular fibrillation (1)</td>
<td></td>
<td>125</td>
<td>141</td>
<td>180</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive (10)</td>
<td></td>
<td>103±23</td>
<td>126±25</td>
<td>123±26</td>
</tr>
<tr>
<td>Reflow ventricular fibrillation (7)</td>
<td></td>
<td>107±16</td>
<td>123±11</td>
<td>140±18</td>
</tr>
</tbody>
</table>

Values are mean±SD. *p=0.01, alive vs. ventricular fibrillation at reperfusion.

### Table 6. Regional Myocardial Blood Flow Classified According to Segmental Systolic Function During Coronary Artery Occlusion

<table>
<thead>
<tr>
<th>Function</th>
<th>Level</th>
<th>Group</th>
<th>n</th>
<th>Baseline</th>
<th>Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>End</td>
<td>Alive</td>
<td>23</td>
<td>1.1±0.4</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>1</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>Alive</td>
<td>23</td>
<td>1.1±0.4</td>
<td>1.3±0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>1</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Epi</td>
<td>Alive</td>
<td>23</td>
<td>0.8±0.3</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>1</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Hypokinetic</td>
<td>End</td>
<td>Alive</td>
<td>28</td>
<td>1.1±0.3</td>
<td>0.3±0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>4</td>
<td>0.9±0.4*</td>
<td>0.2±0.3</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>Alive</td>
<td>28</td>
<td>1.1±0.4</td>
<td>0.4±0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>4</td>
<td>0.9±0.3*</td>
<td>0.3±0.3</td>
</tr>
<tr>
<td></td>
<td>Epi</td>
<td>Alive</td>
<td>28</td>
<td>0.9±0.3</td>
<td>0.4±0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>4</td>
<td>0.7±0.4*</td>
<td>0.3±0.3</td>
</tr>
<tr>
<td>Dyskinetic</td>
<td>End</td>
<td>Alive</td>
<td>15</td>
<td>1.0±0.3</td>
<td>0.3±0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>3</td>
<td>0.7±0.2</td>
<td>0.07±0.1</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>Alive</td>
<td>15</td>
<td>1.1±0.3</td>
<td>0.3±0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>3</td>
<td>0.7±0.2*</td>
<td>0.02±0.02*</td>
</tr>
<tr>
<td></td>
<td>Epi</td>
<td>Alive</td>
<td>15</td>
<td>0.8±0.3</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
<td>3</td>
<td>0.5±0.2*</td>
<td>0.04±0.02*</td>
</tr>
</tbody>
</table>

Values are mean±SD. Blood flow measured in milliliters per gram of myocardium per minute. End, endocardial segment; Mid, midmyocardial segment; Epi, epicardial segment. *p<0.05, alive vs. ventricular fibrillation.
consequence of prolongation of the refractory period, and Keung and Aronson4 noted that the prolongation of the action potential was distributed in a nonuniform fashion across endocardial, epicardial, and papillary muscle segments; thus, action potential duration was heterogeneous in the nonischemic hypertrophied rat heart. White et al28 have described an increase in ventricular excitability threshold in nonischemic hypertrophied feline right ventricle. It has also been reported that the amount of electrically effective membrane area is reduced in hypertrophied myocardium despite the increase in total membrane area29 resulting from cellular enlargement. Cameron et al,5 using a model of aortic constriction with resultant left ventricular hypertrophy, found abnormalities in action potential duration, conduction velocity, and upstroke velocity of the action potential to be heterogeneous within the same heart. These findings may imply an impairment in the generation and spread of electrical depolarization in hypertrophied myocardium, which may result in regional conduction delays, a necessary precondition for reentrant arrhythmias. Spach et al30 have proposed that the inhomogeneous and multidimensional spread of electrical activation related to cellular geometry as well as to connective tissue distribution could alter action potential spread. Osaka et al31 have shown that cellular anisotropy in nonhypertrophied myocytes can affect action potential duration and contribute to spatial inhomogeneity of refractoriness, and Dillon et al32 have presented data showing that electrical activation transverse to myocardial fibers in the epicardial border of 5-day-old infarcts is sufficiently slowed so that reentry could occur. Thus, changes in cellular geometry as well as the extent and distribution of connective tissue during the hypertrophic process may further contribute to electrophysiological inhomogeneity.

In hypertrophied myocardium, because of the larger heart size, the interface region of electrical heterogeneity during ischemia and reperfusion may be larger. In our experiment, the areas-at-risk expressed as percent of left ventricular mass were not different in survivors and those dying of reflow ventricular fibrillation; however, the actual geographic interface area will, nonetheless, be larger in larger hearts, thereby increasing the potential for electrophysiological heterogeneity. Thus, electrophysiological heterogeneity, the substrate of reentry, may exist in hypertrophied myocardium from the cellular to the whole organ level.

Reperfusion and Altered Automaticity

Derangement in calcium homeostasis occurring at the time of reperfusion may contribute to alterations in automaticity.33,34 Thandroyen et al27 have shown that calcium loading of isolated myocytes is associated with the onset of fibrillatory activity. It has also been shown that ryanodine and caffeine, agents blocking release of calcium from the sarcoplasmic reticulum, can prevent reperfusion ventricular fibrillation.35 Kimura et al22 have shown that perfusion of isolated myocardium with calcium-free Tyrode’s solution during reperfusion attenuated or prevented reperfusion-induced ventricular arrhythmias.

In nonischemic, hypertrophied myocardium, calcium handling is altered in such a way that mechanical demands are met.2,26 Keung16 has found that the transmembrane inward calcium current is increased in the isolated hypertrophied myocyte. Calcium-dependent afterdepolarizations resulting in triggered activity have been noted in a similar preparation.18 Additionally, spontaneous oscillatory activity leading to action potentials in hypertrophied myocytes has also been noted.19 Of interest, this spontaneous oscillatory activity could be blocked by caffeine, a substance that blocks both uptake and release of calcium from the sarcoplasmic reticulum.19 It is possible that increases in cellular calcium occurring after brief ischemia may therefore be exaggerated and consequently more proarrhythmic in effect in the hypertrophied myocardium.

Heart Rate and Reperfusion Arrhythmias

A significant increase in heart rate was the only hemodynamic variable differentiating dogs with reflow ventricular fibrillation from survivors (Table 5); however, it is unclear whether the increase in heart rate was simply another consequence of a proarrhythmic process or whether it directly contributed to the onset of ventricular fibrillation. One consideration is that the tachycardia may be a consequence of heightened adrenergic tone, a state thought to be proarrhythmic. Corr et al25,37 have shown enhanced a-adrenergic responsiveness with a correlative increase of a-adrenergic receptor number in ischemic feline myocardium and an accelerated idioventricular rate consistent with altered automaticity at reperfusion. An influence of the adrenergic system in reperfusion arrhythmias is suggested by the experiments of Thandroyen et al,27 who have shown that a-adrenergic blocking agents at concentrations that slow heart rate afford protection against reperfusion ventricular fibrillation in isolated rat hearts. A consequence of heightened adrenergic tone may also be an augmentation of transmembrane calcium currents48 with the consequences previously discussed.

The density of cardiac a- and b-adrenergic receptors is reduced in the heart39,40 of animals with renovascular hypertension, whereas levels of extraneural catecholamine metabolites41 are increased, suggesting that localized increases in adrenergic activity may contribute to the maintenance of hypertension in this model. Ischemia in hypertrophied hypertensive myocardium may further modulate adrenergic response and receptor number and promote reperfusion arrhythmias.

Alternatively, increases in beating rate in isolated ventricular myocytes have been shown to further increase intracellular calcium42; this may particularly predispose the hypertrophied myocyte to calcium-
mediated oscillatory potentials and arrhythmias. James et al have noted that increased heart rate lowers the ventricular fibrillation threshold in isch- 
emic myocardium. Finally, increases in heart rate may result in areas of regional conduction block that contribute to electrophysiological inhomogeneity and thereby to reentrant arrhythmias. 

In summary, the results of our study demonstrate that hypertrophy independent of hypertension is highly associated with an increased incidence of reperfusion ventricular fibrillation. These data would suggest that qualitative differences in the hypertrophied myocyte may contribute to an enhanced sus-
ceptibility to arrhythmias even in the absence of myocardial ischemia. In such a setting, addition of the electrophysiological abnormalities associated with ischemia and reperfusion may greatly enhance the arrhythmic diathesis of hypertension and import-
antly contribute to the increased mortality associated with left ventricular hypertrophy. 

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