Effects of Chronic Hypertension and Left Ventricular Hypertrophy on the Incidence of Sudden Cardiac Death After Coronary Artery Occlusion in Conscious Dogs

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SUMMARY When acute myocardial infarction occurs in patients with hypertension and left ventricular hypertrophy (LVH), the incidence of sudden cardiac death increases markedly. Possible explanations include increased size of the occluded vascular bed secondary to more extensive atherosclerotic coronary vascular disease in the presence of hypertension, decreased coronary reserve secondary to LVH, and intrinsically electrophysiologic abnormalities in hypertrophied cardiac muscle. To explore these possibilities, we produced acute circumflex coronary occlusion during the resting, conscious state in 32 control dogs and in 28 dogs with hypertensive LVH. Before coronary occlusion, mean arterial pressure was 96 ± 0.1 mm Hg in control dogs and 125 ± 5 mm Hg in dogs with hypertensive LVH (p < 0.01). The control left ventricular/body weight ratio was 4.5 ± 0.1 g/kg, compared with 6.1 ± 0.4 g/kg in hypertensive LVH (p < 0.01). Cumulative mortality at 6, 24 and 48 hours was 9%, 13% and 16% in control dogs and 32%, 43% and 54%, respectively, in dogs with hypertensive LVH (all p < 0.01 vs control).

The perfusion fields of the occluded vessel defined by postmortem coronary angiography were similar in the two groups (31 ± 2% of left ventricular mass for control vs 29 ± 2% for hypertensive LVH). Thus, the increased incidence of sudden cardiac death after coronary artery occlusion in hypertensive LVH dogs cannot be explained by increased size of the occluded vascular bed and is probably related to the decreased coronary reserve or intrinsic electrophysiologic abnormalities that characterize pressure-induced hypertrophied cardiac muscle.

SUDDEN CARDIAC DEATH IS a major cause of death in patients with coronary artery disease. Epidemiologic studies have shown that the incidence of sudden cardiac death is markedly increased in patients with systemic arterial hypertension and left ventricular hypertrophy (LVH).1-4 Animal studies and clinical observations suggest that hypertension potentiates atherosclerosis.5-8 Therefore, the high incidence of sudden cardiac death in the patient with hypertension is generally attributed to unusually severe coronary atherosclerosis. However, other factors could contribute to the deleterious effects of coronary occlusion in patients with hypertension and LVH.

Recent studies have shown that coronary reserve is decreased in pressure-induced LVH,9-12 and intrinsic electrophysiologic abnormalities have been observed in hypertrophied myocardial cells.13-16 These abnormal physiologic changes may contribute to the high incidence of sudden cardiac death after myocardial infarction in patients with hypertension and LVH.

The present study was undertaken to test the hypothesis that the incidence of death after acute coronary occlusion in the presence of hypertension and LVH may be related to factors other than the size of the potentially ischemic zone. To avoid the effects of anesthesia, the study was conducted in conscious dogs.

Methods

Preparation of the Dogs

Hypertension was induced in 28 adult mongrel dogs that weighed 14–27 kg, as described previously.17 In brief, the dogs were anesthetized with i.v. sodium pen-
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Toobarbital, 30 mg/kg, and a bilateral flank incision was performed. A clamp, described by Ferrario et al., \( ^{18} \) was placed around one renal artery, and a nephrectomy was done on the contralateral side. Six to 8 weeks after this operation, the dogs were anesthetized with i.v. sodium pentobarbital, 30 mg/kg, and a left thoracotomy was performed through the fourth intercostal space. Cannulas were placed in the aorta through the left internal mammary artery and in the left atrium through its appendage. A 1-0 silk snare was placed around the circumflex coronary artery distal to the first or second marginal branch. The catheters were filled with heparin (1000 U/ml), tunneled subcutaneously and attached to skin buttons at the back.

Thirty-two adult mongrel dogs that weighed 17–29 kg served as a control group and underwent thoracotomy as described above. At the time of the study, 7–12 days after thoracotomy, all dogs appeared healthy and did not have anemia (hematocrit 40–48%) or renal failure (serum creatinine < 1.8 mg/dl).

Experimental Protocol

The study was conducted when the dogs were conscious and quiet. Cannulas were attached to Statham P23Db strain gauges, and arterial pressure, left atrial pressure and standard ECG lead II were continuously recorded.

When the hemodynamics were stable, i.v. lidocaine, 1.5 mg/kg, was injected. One minute later, the snare was pulled, and the coronary artery was permanently occluded. All dogs that had ventricular fibrillation died despite attempted defibrillation. The dogs that did not have ventricular fibrillation were returned to the kennel 3 hours after coronary occlusion. Forty-eight hours after coronary occlusion, the hemodynamics were measured and the dogs killed by i.v. injection of sodium pentobarbital and potassium chloride. The hearts of these dogs and those that died during the first 48 hours after coronary occlusion were excised to determine the risk zone.

Measurement of Risk Zone

To determine the risk zone, large PE cannulas were advanced to the origins of the circumflex, left anterior descending and right coronary arteries and secured. A barium-gelatin mixture was injected into the cannulas simultaneously at a perfusion pressure 20 mm Hg higher than the mean aortic pressure in situ (about 120 mm Hg in control dogs and 150 mm Hg in hypertensive dogs). The heart was fixed in formalin overnight and stereoscopic radiographs of the whole heart were taken. The atria and the right ventricle were removed, and the left ventricle was sectioned into seven transmural slices of approximately equal thickness parallel to the atroventricular groove. Stereoscopic radiographs of the sectioned ventricle were also taken without magnification.

In the dogs that died within 6 hours after coronary occlusion, the barium-gelatin mass did not fill the arterial bed distal to the obstruction. In dogs that lived 24 hours or longer after occlusion, the distal arteries were filled with injectate through collateral vessels in both control and hypertrophied hearts. The area at risk was determined by carefully following the course of occluded and unoccluded vessels from slice to slice (fig. 1). The stereoscopic angiogram of the whole heart was helpful in identifying the vessels in each slice. The risk area and left ventricular area of each slice were measured using the computerized planimeter. From these values and the weight of each cardiac slice, the risk region was computed as a percentage of total left ventricular mass. The area at risk was determined by two independent observers. The interobserver difference was minimal (0.3% of LV mass).

Statistical Analysis

Data are expressed as mean ± SEM. The level of statistical significance was \( p < 0.05 \). The chi-square test was used to assess the difference in mortality rate between the control group and the group with hypertension and LVH. The intergroup differences in heart weight, hemodynamics and area at risk were assessed by unpaired \( t \) tests.

Results

Baseline Characteristics

LV weight and the ratio of LV weight to body weight were significantly increased in hypertensive LVH dogs (table 1). Resting aortic pressure was 32% higher in hypertensive LVH dogs, but heart rate and left atrial pressure were similar in the two groups.

Mortality Data

The cumulative mortality rate (fig. 2) for the first 48 hours after occlusion was higher in hypertensive dogs (54%) than in control dogs (16%), although the difference in mortality for the first 2 hours after coronary occlusion was not statistically significant.

Risk Area

Figure 3 shows the mass of risk area normalized by LV mass. The average mass of the area at risk was similar in control dogs (32 ± 3 g, or 31 ± 2% of LV mass) and in hypertensive LVH dogs (38 ± 3 g, or 29 ± 2%). The mass of the area at risk in the control dogs that died prematurely (40 ± 9 g, or 34 ± 3% of LV mass) was not significantly different from that of hypertensive LVH dogs that died during the first 48 hours after coronary occlusion (39 ± 3 g, or 30 ± 2%).

If the area at risk was less than 26% of LV mass in control dogs or 20% in hypertensive LVH dogs the dog did not die. Fifty percent of the hypertensive LVH dogs died when the risk area was 20–25% of LV mass. When the risk area was larger than 26% of LV mass, 27% of the control dogs died and 53% of the hypertensive LVH dogs died (\( p < 0.05 \)).

In dogs that died less than 24 hours after coronary occlusion, myocardial infarct size could not be determined accurately with standard pathologic techniques. Although infarct size could be determined pathologically in dogs that died 24 hours or longer
after coronary occlusion, the number was too small (one control and three LVH dogs) for statistical analysis.

Effects of Coronary Occlusion on Hemodynamics

Hemodynamic and anatomic data were compared in dogs that survived 48 hours after occlusion and those that died prematurely (table 2). In the control group there was no difference in hemodynamics between dogs that survived 48 hours after occlusion and those that died earlier. In the hypertensive LVH group, however, the heart rate of dogs that died early tended to be higher during control conditions and was significantly higher 2 hours after coronary occlusion than that of the dogs that survived 48 hours. Left ventricular mass, left atrial pressure and mean aortic pressure were similar in these two subgroups.

Discussion

The principal new observation in the present study was that the mortality rate after acute coronary occlusion is markedly higher in dogs with chronic hypertension and LVH than in control dogs, even though the perfusion field of the occluded coronary artery or area at risk was similar in the two groups.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control dogs (n = 32)</th>
<th>Hypertensive LVH dogs (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV weight (g)</td>
<td>101 ± 4</td>
<td>129 ± 4*</td>
</tr>
<tr>
<td>LV/body weight ratio (g/kg)</td>
<td>4.5 ± 0.1</td>
<td>6.1 ± 0.1*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>96 ± 3</td>
<td>99 ± 6</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>94 ± 2</td>
<td>126 ± 3*</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>4.6 ± 0.6</td>
<td>4.5 ± 0.6</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
*p < 0.01 vs control.
Abbreviations: LV = left ventricular; LVH = LV hypertrophy.

Methodologic Considerations

Our experimental design has several advantages. First, the experimental model, dogs with LVH secondary to renal hypertension, is somewhat similar to patients with moderate hypertension and cardiac hypertrophy. Second, the study was performed in conscious dogs to avoid the effects of anesthesia, which may influence the vulnerability of the heart to ventricular fibrillation by altering autonomic nervous activity. Third, we define the three-dimensional perfusion field of the occluded vessel by postmortem angiography. This is critically important because the perfusion field of a coronary vessel is highly variable even if the anatomic site of obstruction is fixed and because one might expect that the three-dimensional perfusion field of any surface coronary vessel would increase with cardiac enlargement.

Our experimental design also had several limitations. First, the hemodynamics were not continuously monitored during the 2 days after coronary occlusion, so the cause of death in each dog was not precisely documented. The eight dogs that died within 2 hours after coronary occlusion died of ventricular fibrillation. The mechanism of death in the dogs that died more than 2 hours after coronary occlusion was probably ventricular fibrillation. The other probable causes of death after coronary occlusion — shock or heart failure — are much less likely. There were no signs of heart failure at postmortem examination and the left atrial pressure 2 hours after coronary occlusion was similar in dogs that survived and in those who died early. Also, none of the dogs had significant hypotension within 2 hours after coronary occlusion. A second limitation was that a bolus of lidocaine was injected in every dog before the coronary occlusion. The lidocaine should have little effect on the difference in mortality between control and hypertensive LVH groups because the doses of lidocaine in the two groups were identical (1.5 mg/kg), the effect of this
dose of lidocaine is transient, and differences in mortality between the groups persisted long after the drug effects had presumably disappeared. Finally, our experimental model is far from perfect. Patients with sudden coronary death usually have multivessel coronary disease and impaired LV function, whereas our dogs had one-vessel occlusion and minimal impairment in global LV function.

Possible Explanations for the High Incidence of Sudden Death in Animals and Man with Hypertension and LVH After Infarction

The Framingham studies showed that the incidence of sudden cardiac death after acute myocardial infarction is markedly increased in patients with systemic arterial hypertension and patients with electrocardiographic evidence of LVH. The pathogenesis of the high incidence of sudden death in such patients is uncertain. Potential explanations include increased size of the occluded vascular bed secondary to extensive atherosclerotic coronary vascular disease, decreased coronary reserve secondary to LVH, intrinsic electrophysiologic abnormalities in hypertrophied cardiac muscle, and alterations in autonomic tone related to hypertension.

Severe atherosclerotic coronary lesions are common in patients with sudden cardiac death. Evidence from clinical and experimental studies indicates that hypertension accelerates the development of coronary atherosclerosis. Hypertension produced by constriction of renal arteries or coarctation of aorta significantly accelerated the atherosclerotic narrowing of the coronary arteries in monkeys fed an atherogenic diet compared with normotensive monkeys fed the same diet. In monkeys with coarctation of the aorta fed an atherogenic diet, electrocardiographic evidence of ischemic heart disease and sudden cardiac death occurred more frequently than in monkeys exposed to the diet alone. Pathologic studies of human coronary arteries have also shown that atherosclerotic lesions are more extensive and more severe in hypertensive than in normotensive subjects. There is clinical evidence that myocardial infarct size is a major determinant of mortality and incidence of ventricular dysrhythmia early after infarction. These observations indicate that extensive coronary atherosclerosis secondary to hypertension may increase the size of vascular bed involved, and consequently increase the infarct size and the incidence of sudden cardiac death after myocardial infarction.

This explanation, however, cannot explain our results. The incidence of sudden death after coronary occlusion was significantly higher in dogs with hypertension and LVH, even though the perfusion field of
the occluded coronary artery (area at risk) was similar to that of the control dogs. The cause of the increased incidence in sudden death after myocardial infarction in hypertensive patients cannot be attributed solely to increased perfusion area of occluded coronary vessels. Factors other than the size of the occluded vascular bed may contribute to the pathogenesis of sudden death when patients with hypertension and LVH sustain myocardial infarction.

The high incidence of sudden cardiac death in patients with hypertension and LVH might also relate to the coronary microcirculation and coronary vasodilatory reserve. Cardiac hypertrophy due to pressure overload decreases capillary density. Consequently, diffusion distance from capillaries to the center of the myocardial cells is increased, which could impair the delivery of nutrients to myocardial cells and potentiate the adverse effects of myocardial ischemia. Studies in our laboratory have shown that coronary vascular dilatatory reserve is compromised in dogs with hypertension and LVH. Many other studies have also shown limited coronary vasodilatory reserve and abnormal transmural distribution of myocardial blood flow in LVH, especially under physiologic stresses. These observations suggest that fundamental abnormalities in the coronary circulation of the hypertrophied left ventricle may adversely affect responses to ischemic injury and thereby potentiate the mortality after myocardial infarction.

Another possible explanation is electrophysiologic abnormalities in hypertrophied myocardial cells. Aronson investigated the effects of cardiac hypertrophy on transmembrane action potentials recorded from the papillary muscle in renal hypertensive rats. He showed that the action potential duration was significantly longer for hypertensive rats than for normal rats. Prolongation of action potential duration has also been observed in hypertrophied right ventricle with chronic pulmonary artery constriction. Because myocardial ischemia shortens action potential duration after coronary occlusion, the dispersion of action potential durations in normal and ischemic tissue could be larger in hypertrophied than in normal ventricles, and might contribute to the high incidence of sudden cardiac death in animals with hypertrophy.

Acknowledgment

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References

Left Ventricular Diastolic Capacity in Man

ATHAN P. FLESSAS, M.D., AND THOMAS J. RYAN, M.D.

SUMMARY Plasma volume expansion with 500 ml of low-molecular-weight dextran was used in 27 patients (nine normal subjects, 13 patients with ischemic heart disease, four with aortic stenosis and one with cardiomyopathy) to increase left ventricular end-diastolic pressure (LVEDP) from a control value of 12.4 ± 7.0 mm Hg (mean ± SD) to 23.3 ± 7.0 mm Hg and end-diastolic volume (EDV) from 84.0 ± 23.8 ml/m² to 97.6 ± 22.9 ml/m². EDV-LVEDP curves constructed for 12 patients from multiple angiograms at progressively increasing LVEDP during plasma volume expansion showed an initial part where EDV increased in parallel with LVEDP and a final steep or perpendicular part where EDV increased minimally or not at all as LVEDP exceeded 20 mm Hg. Exponential equations were used to fit diastolic volume-pressure data obtained with catheter-tip manometers in seven patients: the exponential constant, k, was 0.012-0.044 ml⁻¹ and was inversely related to EDV (Spearman’s rank correlation coefficient = −1). For comparable EDV, there were no differences in k values between normal subjects and patients with a variety of heart diseases.

STUDIES of the hemodynamic responses in acutely induced hypervolemia have shown the ability of the human heart to augment its stroke volume. The ventricles, even during normovolemia and in the supine position, maintain some capacity to enlarge beyond their normal operative end-diastolic volume (EDV) and thus augment stroke output by the Frank-Starling mechanism. In the present study, we quantified this left ventricular (LV) diastolic reserve by measuring ventricular volumes during plasma volume expansion induced by infusion of low-molecular-weight dextran. We also investigated LV systolic function and diastolic volume-pressure relationships over a wide range of diastolic pressures.

Methods

Twenty-seven patients undergoing diagnostic cardiac catheterization participated in this study. Thirteen patients had ischemic heart disease, four aortic stenosis and one congestive cardiomyopathy; nine patients with atypical chest pain had no discernible heart disease and were considered normal. Five of the ischemic heart disease patients had ECG evidence of old myocardial infarction. All patients gave informed consent.

Cardiac catheterization was performed in the fasting state, after premedication with 10 mg of oral diazepam. After coronary arteriography by the Sones technique, a #8 angiographic catheter (Gensini in 20 patients and Millar microtip catheter pressure transducer PC-481 in seven) was advanced into the left ventricle, and a #8 Cournand catheter was positioned in

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