Tolerance of the Hypertrophic Heart to Ischemia
Studies in Compensated and Failing Dog Hearts With Pressure Overload Hypertrophy

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Tolerance of the canine heart to prolonged ischemic arrest was studied in 10 hearts from normal control dogs and 15 hearts from dogs with left ventricular hypertrophy (LVH); experiments were performed 1 year after banding the aorta in 8-week-old puppies. At 1 year, hemodynamic studies revealed decreased left ventricular (LV) fiber shortening and elevated end-diastolic pressure (EDP) in five dogs (group with LVH failure); 10 dogs exhibited normal shortening and normal EDP (group with LVH compensation). The left ventricle-to-body weight ratio (g/kg) was 4.4±0.8 in the control group of dogs, 7.7±1.0 in the group with LVH compensation, and 10±2.5 in the group with LVH failure. The tolerance to 60 minutes of global ischemia (37°C) followed by 90 minutes of reperfusion was studied in an isolated blood-perfused heart apparatus (isovolumic left ventricle, coronary perfusion pressure of 100 mm Hg). In the baseline (preischemic) state, coronary blood flow, myocardial oxygen consumption, lactate extraction, and myocardial high-energy phosphate content were essentially equal in the three groups; with LV volume adjusted to produce a systolic pressure of 100 mm Hg, there were no significant differences in LVEDP among the three groups. During ischemia, the diastolic (asystolic) pressure increased from 11±3 to 28±16 mm Hg (p<0.05) in the group with LVH failure; however, it did not increase in the control or the LVH compensation groups. Myocardial ATP levels declined equally in all three groups. During early reperfusion, lactate washout was lowest in the group with LVH failure. By 90 minutes of reperfusion, there were no significant differences in coronary blood flow, myocardial oxygen consumption, lactate extraction, or high-energy phosphate levels. High diastolic pressure persisted at 90 minutes of reperfusion in the LVH failure group (EDP was 34±19 mm Hg); however, there was no significant change in EDP during reperfusion in the control or with LVH compensation groups. After 90 minutes of reperfusion, developed pressures in the control (54±9 mm Hg), the LVH compensation (49±18 mm Hg), and the LVH failure (67±17 mm Hg) groups were not significantly different. These data indicate that hearts with compensated LVH do not exhibit an impaired tolerance to ischemia. By contrast, hypertrophic hearts with pump failure exhibit a mechanical (diastolic) dysfunction during ischemia and reperfusion. The association of impaired tolerance to ischemia and subnormal lactate production suggests that the hypertrophic hearts with failure have a reduced capacity to recruit anaerobic glycolysis, which might contribute to diastolic dysfunction during ischemia and reperfusion. (Circulation 1990;81:1644–1653)
without hypertrophy; this is presumably related to increased ventricular ectopic activity. Second, infarct size (expressed as a function of the myocardial area at risk) and mortality due to myocardial infarction are greater in experimental dogs with hypertension and LVH than those without hypertension and LVH. Third, hypertrophic hearts exhibit a limited coronary vasodilator reserve capacity (even in the absence of coronary artery disease); the stress of exercise or pacing tachycardia can produce a maldistribution of transmural blood flow, subendocardial ischemia, or both, and this can contribute to systolic or diastolic dysfunction of the left ventricle. An additional deleterious consequence of LVH is its tendency to exhibit an increased susceptibility to ischemic injury; this can be particularly important to patients undergoing ischemic cardiac arrest and reperfusion during cardiac surgery as well as to those receiving thrombolytic therapy or angioplasty for acute myocardial infarction.

There is no obvious reason why hypertrophied hearts should be intrinsically more sensitive to ischemic injury than normal hearts. Indeed, some data indicate that pressure-overload hypertrophy results in an efficient biochemical and contractile adaptation that is well suited to pressure work. There are, however, clinical and experimental data that indicate an impaired tolerance to ischemia in hypertrophied hearts. This could be related to abnormalities in the coronary vasculature and ischemic injury before the ischemic arrest, to the effects of ventricular fibrillation at the onset or during ischemia, or to biochemical or other metabolic alterations in hypertrophic myocardium. These and other published data indicate considerable variation in the susceptibility of hypertrophic hearts to ischemic injury.

To date, there have been no attempts to assess the functional state of the left ventricle as an independent factor affecting the tolerance of hypertrophic hearts to ischemic arrest. Therefore, we used the hearts from a previously reported group of dogs with LVH; ventricular function and myocardial blood flow was well characterized (in vivo) in these dogs. Thus, in the present study, we tested the hypothesis that hypertrophied hearts with evidence of pump failure exhibit an impaired tolerance to ischemic arrest, whereas hypertrophied hearts without failure do not.

Methods

LVH was produced by banding the aorta of 8-week-old puppies. One year later, when substantial LVH was present, LV function was described with echocardiographic and catheterization techniques, and tolerance to ischemic arrest was assessed in an isolated heart apparatus. Fifteen hypertrophied hearts and 10 normal control hearts were studied.

Model of LVH

Eight-week-old puppies were anesthetized with sodium pentobarbital (25 mg/kg i.v.) and ventilated with a mechanical respirator. A right thoracotomy was performed through the third right intercostal space, the pericardium was opened, and the aorta was dissected free from the periaortic fat and connective tissue. A 5-mm-wide polyethylene nonconstricting band was placed around the aorta approximately 2 cm above the aortic valve. After the banding procedure, the pericardium was loosely approximated, the thoracotomy was closed, and the pleural space was evacuated of air with a chest tube and suction. The dogs recovered and were then allowed to "grow into" supravalvular aortic stenosis.

Hemodynamic Studies

At 12 months, the dogs underwent cardiac catheterization and echocardiography to define the functional state of the left ventricle. Each dog was lightly sedated with acepromazine and morphine sulfate; using local lidocaine anesthesia, an incision was made over a carotid artery. A 7F micromanometer-tipped catheter (Millar Instruments, Houston, Texas) was introduced and advanced into the left ventricle using fluoroscopic and hemodynamic guidance. Pressures in the aorta (above and below the band) and left ventricle were recorded with a photographic recorder (Honeywell, Electronics for Medicine). The catheter was secured, and the dog was placed in a nylon sling for simultaneous recording of the LV pressure and echocardiographic data.

Two-dimensional and M-mode echocardiographic LV studies (model SSH-1-A, Toshiba and model V3280B, Honeywell, Electronics for Medicine) were obtained from the right parasternal area; the standard short-axis view that includes the minor-axis dimension and wall thickness was readily visualized in all dogs. Measurements of LV chamber dimension at end diastole (Ded) were made at the onset of the Q wave of the electrocardiogram; end-systolic dimension (Des) was measured at the time of the smallest systolic dimension, near the instant of maximum anterior motion of the LV posterior wall. Circumferential fiber shortening at the endocardium, fractional shortening (FS, %), was calculated using the following standard method: FS = (Ded − Des)100/Ded. In our laboratory, normal FS exceeds 34%. Ten dogs exhibited normal fiber shortening; this group was designated "LVH-compensated" (LVH-C). Five dogs had reduced shortening; this group was called "LVH-failure" (LVH-F). The LV end-diastolic pressure was less than 19 mm Hg in all 10 LVH-C dogs, whereas four of the five dogs in the LVH-F group exhibited an end-diastolic pressure exceeding 19 mm Hg. In a similar manner, Wisenbaugh et al used shortening measurements and Parrish et al used end-diastolic pressure to describe LV failure in pigs and dogs with pressure-overload hypertrophy. Although these simple measures of shortening and end-diastolic pressure do not separate the effects of depressed contractility from the effects of afterload excess, they do provide a definition of "pump failure" that is consonant with a substantial clinical and experimental experience.
Measurements

Blood pressures were measured with a Statham P23Db pressure transducer (Gould Inc., Glen Burnie, Maryland). LV systolic function and diastolic pressure-volume relations were evaluated by measuring systolic and diastolic pressure after incremental additions of saline to the ventricular balloon. The volume associated with a peak systolic pressure of 100 mm Hg was assigned a value of 100% \( V_{100} \), and all other volumes were related to the 100% volume. This volume served as a maximum value for comparing subsequent pressure-volume data in the same heart, and it provides a normalization of the volume from the hearts of dogs of differing size. \(^{40-42} \) Thus, systolic function was assessed over a range of volumes \( V_{20}-V_{100} \); likewise, changes in diastolic pressure-volume relations were assessed by measuring LV diastolic pressure over the same range of volumes. With the exception of the time required to measure systolic function and diastolic pressure, the LV balloon was nearly empty \( V_{20} \) throughout the entire protocol. All metabolite, biochemical, and coronary blood flow (CBF) measurements were made at \( V_{20} \). CBF was measured with an in-line flowmeter. Blood was sampled from the arterial (perfusion) and coronary venous catheters; pH and Po2 were determined with a blood gas analyzer (Instrumentation Laboratory, Watertown, Massachusetts). Arterial and venous oxygen contents were calculated from the blood oxygen saturation by using a standard nomogram. \(^{43} \) Arterial and venous lactates were measured by using previously published techniques. \(^{44} \) Transmural LV biopsies were obtained for tissue ATP and creatine phosphate; the samples were immediately frozen on dry ice. After freezing, they were divided into subendocardial and subepicardial halves, immersed in liquid nitrogen, and stored for later analysis. \(^{45} \) Myocardial water content was determined by weighing biopsy samples before and after heat-drying to constant weight. Because myocardial water content was not constant in these experiments, myocardial oxygen consumption (\( MV_{O_2} \)), lactate production, ATP, creatine phosphate, and CBF are all expressed in terms of dry tissue weight. \(^{40-42} \)

Beginning at the onset of ischemia and every 15 minutes throughout ischemic arrest, 100 ml of a neutral crystalloid (washout) solution were infused into the proximal aorta at 100 mm Hg infusion pressure; each infusion required 10–15 seconds. The solution consisted of normal saline with dextran (40,000–80,000 g/MW), osmolality was 290–300 osm, partial pressure of oxygen was equal to that of room air, partial pressure of carbon dioxide was 0, pH was 7.5, and temperature was 37°C. Lactate concentration of the washout solution (collected from the coronary venous line) was measured. Thus, lactate production during ischemic arrest could be assessed.

Experimental Protocol

All hearts were subjected to 60 minutes of normothermic (37°C) global ischemic arrest. After baseline measurements were made, ischemic arrest was initiated by cross-clamping the coronary arterial perfusion line. Measurements of pressure-volume relations and lactate production (washout) were made every 15 minutes during ischemic arrest; at the end of the arrest period (55–60 minutes), a biopsy for tissue high-energy phosphates was obtained. The hearts were then reperfused, and serial measurements of CBF, lactate production (or extraction), and mechanics were made during a 90-minute reperfusion period. At the end of the reperfusion period, additional biopsies were obtained and the LV weight was measured.

Data in the tables and text are presented as the mean±SD; the mean±SEM is used in the figures. The time and group effects were analyzed with analysis of variance and a Dunnett test or a Newman-Keuls multiple-sample comparison test to localize significant differences. Differences were considered significant if the \( p \) value was less than 0.05. These statistical analyses were performed using the PROPHET system, a national computer resource sponsored by the Division of Research Resources.

All dogs received humane care in compliance with the “Principles of Laboratory Animal Care” formu-
TABLE 1. Left Ventricular Echocardiographic, Catheterization, and Mass Data in Normal and Hypertrophied Dog Hearts

<table>
<thead>
<tr>
<th></th>
<th>Control (n=5)</th>
<th>LVH compensation (n=10)</th>
<th>LVH failure (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic (mm Hg)</td>
<td>116±13</td>
<td>227±18*</td>
<td>257±73*</td>
</tr>
<tr>
<td>End diastolic (mm Hg)</td>
<td>7±3</td>
<td>8±5</td>
<td>26±15*†</td>
</tr>
<tr>
<td>Aortic pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>116±13</td>
<td>117±12</td>
<td>99±19</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>79±19</td>
<td>82±13</td>
<td>73±20</td>
</tr>
<tr>
<td>Left ventricular echogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic dimension (mm)</td>
<td>39±4</td>
<td>35±2*</td>
<td>43±4†</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>38±3</td>
<td>43±4*</td>
<td>29±4*†</td>
</tr>
<tr>
<td>Left ventricular mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular weight (g)</td>
<td>98±27</td>
<td>144±33*</td>
<td>178±22†</td>
</tr>
<tr>
<td>Left ventricular/body weight (g/kg)</td>
<td>4.4±0.8</td>
<td>7.7±1.0*</td>
<td>10±2.5†</td>
</tr>
</tbody>
</table>

Values are mean±SD. LVH, left ventricular hypertrophy. *p<0.05 vs. control; †p<0.05 vs. LVH compensation.

Results

The LV echocardiographic, catheterization, and mass data from the normal control and hypertrophied hearts are summarized in Table 1; an extensive analysis of LV function in these hearts has been published previously.37 Substantial LVH was present in all banded dogs. The results of our global ischemia-reperfusion studies in these normal and hypertrophied hearts are shown in Tables 2 and 3 and Figures 1–4. In the baseline (preischemic) state with LV systolic pressure adjusted to 100 mm Hg (V100), there were no significant differences in LV diastolic pressures among the three groups of hearts. The energetic and biochemical data were obtained with the LV nearly empty (V20); at this chamber volume, there were no significant differences in CBF or MVO2 among the three groups of hearts during the baseline state. All hearts exhibited lactate extraction in the baseline state.

LV Mechanical Function

The time course of change in LV pressure during the baseline, ischemic arrest, and reperfusion periods is shown in Figure 1; these measurements were made at V100 in beating, asystolic, and beating hearts, respectively. In the control and the LVH-C hearts, there were no significant changes in LV diastolic (i.e., asystolic) pressure during the 60-minute period of ischemic arrest. By contrast, the LVH-F hearts developed a progressive increase in LV pressure; at 45 and 60 minutes of ischemia, the LV pressure was significantly higher than in the baseline state. At the end of the ischemic arrest period (60 minutes), the LV pressure in the LVH-F hearts (28±16 mm Hg) was significantly (p<0.05) higher than in the control (12±4 mm Hg) and the LVH-C hearts (11±2 mm Hg).

LV diastolic pressure-volume relations were obtained at baseline and every 15 minutes during ischemic arrest; the baseline and 60-minute curves

TABLE 2. Left Ventricular Pressure, Energetic, and Lactate Data During the Baseline Period and After 90 Minutes of Reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Control Baseline</th>
<th>Control Reperfusion</th>
<th>LVH compensation Baseline</th>
<th>LVH compensation Reperfusion</th>
<th>LVH failure Baseline</th>
<th>LVH failure Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed pressure (mm Hg)</td>
<td>97±8</td>
<td>54±9*</td>
<td>104±12</td>
<td>49±18*</td>
<td>95±12</td>
<td>67±17*</td>
</tr>
<tr>
<td>End-diastolic pressure (mm Hg)</td>
<td>10±2</td>
<td>13±5</td>
<td>10±3</td>
<td>10±3</td>
<td>11±3</td>
<td>34±19*</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min/g dry wt)</td>
<td>5.5±3.1</td>
<td>5.6±2.0</td>
<td>5.0±1.1</td>
<td>4.7±1.9</td>
<td>4.8±0.5</td>
<td>5.8±1.1</td>
</tr>
<tr>
<td>Coronary A-V O2 (ml/100 ml)</td>
<td>5.3±1.5</td>
<td>4.5±1.4</td>
<td>5.9±2.2</td>
<td>5.0±2.7</td>
<td>5.9±1.0</td>
<td>4.1±1.0</td>
</tr>
<tr>
<td>MVO2 (ml/min/g dry wt)</td>
<td>0.25±0.1</td>
<td>0.23±0.08</td>
<td>0.29±0.1</td>
<td>0.20±0.06</td>
<td>0.28±0.07</td>
<td>0.24±0.08</td>
</tr>
<tr>
<td>Net lactate production (μm/min/g dry wt)</td>
<td>-2.4±0.9</td>
<td>-2.3±1.3</td>
<td>-2.5±2.0</td>
<td>-2.0±2.3</td>
<td>-1.9±1.1</td>
<td>-1.6±0.9</td>
</tr>
</tbody>
</table>

Values are mean±SD. LVH, left ventricular hypertrophy; A-V, arterio-venous; MVO2, myocardial oxygen consumption. *p<0.05 vs. baseline value.
TABLE 3. Myocardial High-Energy Phosphate Data During Baseline, Ischemia, and Reperfusion Periods in Normal and Hypertrophied Dog Hearts

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Ischemia</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>LVH-C</td>
<td>LVH-F</td>
</tr>
<tr>
<td>ATP (μM/g dry wt)</td>
<td>Endocardial</td>
<td>18.8±3.5</td>
<td>16.6±3.6</td>
</tr>
<tr>
<td></td>
<td>Epicardial</td>
<td>17.3±2.4</td>
<td>17.8±2.7</td>
</tr>
<tr>
<td>CP (μM/g dry wt)</td>
<td>Endocardial</td>
<td>19.6±9.4</td>
<td>19.5±8.1</td>
</tr>
<tr>
<td></td>
<td>Epicardial</td>
<td>17.7±9.9</td>
<td>19.1±4.8</td>
</tr>
</tbody>
</table>

Values are mean±SD. LVH-C, left ventricular hypertrophy compensation; LVH-F, left ventricular hypertrophy failure; CP, creatine phosphate; Endocardial, inner half of left ventricular wall; Epicardial, outer half of left ventricular wall.

*p<0.05 vs. corresponding baseline value.

are shown in Figure 2. In the LVH-F hearts, there was a substantial upward shift of the pressure-volume relation; this decrease in LV chamber distensibility was not seen in the control or the LVH-C hearts.

After reperfusion, the hearts were defibrillated, and systolic function gradually returned in all three groups. By the end of the reperfusion period (90 minutes), there was a tendency for developed pressure to be highest in the LVH-F hearts (67±17 mm Hg) and lowest in the LVH-C hearts (49±18 mm Hg); neither of these values was significantly different from the value in the control hearts (54±9 mm Hg). LV diastolic pressure remained stable in the control and the LVH-C hearts. There was a tendency for the LV diastolic pressure to increase further (during reperfusion) in the LVH-F hearts (34±19 mm Hg at 90 minutes); however, this trend did not achieve statistical significance.

Coronary Blood Flow

In the baseline state, there were no significant differences in CBF among the three groups of hearts (Table 2 and Figure 3). On reperfusion, we observed a significant reactive hyperemia in all three groups of hearts (Figure 3); at 5–15 minutes, CBF was significantly greater than in the baseline state in all three groups of hearts (all, p<0.05). This hyperemia was most pronounced in the control hearts and least pronounced in the LVH-F hearts; at 5 minutes, CBF in the LVH-C hearts was significantly less than in the control hearts (p<0.05) and significantly greater than in the LVH-F hearts (p<0.05). Although CBF in the control hearts remained significantly higher than in the LVH hearts throughout the first 30 minutes of reperfusion, the difference between the two LVH groups of hearts was no longer present at 15 minutes or thereafter. At 60 and 90 minutes of reperfusion, CBF had returned to baseline in all three groups of hearts.
Myocardial Energetic and Biochemical Data

In the baseline state, there were no significant differences in MVO₂ among the three groups of hearts (Table 2). At the end of the reperfusion period, there was a tendency for MVO₂ (in all three groups) to be less than in the baseline state; however, this trend did not achieve statistical significance.

Transmyocardial blood lactate measurements indicate lactate use during the baseline state in all hearts (Table 2 and Figure 4); the net lactate production was $-2.4 \pm 0.9$, $-2.5 \pm 2.0$, and $-1.9 \pm 1.1$ μM/min/g dry wt in the control, the LVH-C, and the LVH-F hearts, respectively. The coronary venous effluent (washout) during ischemic arrest was analyzed for lactate; at 15, 30, and 45 minutes of ischemia, the lactate washout was significantly higher in the control hearts than in the LVH groups of hearts (both, p<0.05). On reperfusion (5 minutes), the lactate production in the LVH-F hearts (2.7±1.7 μM/min/g dry wt) was substantially less than in the control (8.7±5.5 μM/min/g dry wt) and the LVH-C hearts (8.8±6.5 μM/min/g dry wt); both differences were statistically significant. Within 15 minutes, lactate use returned in all hearts; at 15 minutes and thereafter, there were no significant differences among the three groups of hearts.

Myocardial high-energy phosphate data are shown in Table 3. There was no significant difference in tissue creatine phosphate or ATP among the three groups of hearts in the baseline state. During ischemia, creatine phosphate and ATP declined significantly in all three groups of hearts; at the end of 60 minutes of ischemic arrest, there were no significant differences among the three groups of hearts. During reperfusion, there was significant recovery of creatine phosphate in all three groups of hearts. In the normal control hearts, there was a tendency for creatine phosphate to exceed that in the baseline state; this excess was not present in the hypertrophied hearts (endocardial creatine phosphate was significantly higher in the control hearts than in the LVH-F hearts). There was essentially no recovery of ATP in any of the three groups of hearts. There was a tendency for tissue high-energy phosphates to be lowest in the subendocardial layers of the LVH-F hearts; however, this did not achieve statistical significance.

**Discussion**

The notion that hypertrophic hearts exhibit an increased sensitivity to ischemic injury emerged in the clinical literature during the 1960s and 1970s. During this period before the use of hypothermic potassium cardioplegia became widespread, the mortality rate for cardiac surgery was by present standards excessive. Some reports indicate that perioperative death in patients with valvular heart disease and LVH was most commonly due to a low cardiac output syndrome.²⁰ Other reports emphasized the develop-
ment of ischemic contracture ("stone heart") in patients with aortic valve disease and severe LVH. These problems were uncommon in patients without significant hypertrophy, and this clinical experience led to the conclusion that the presence of LVH caused an increased sensitivity to ischemic injury. The experimental data in support of this conclusion, however, are inconclusive.

There are relatively few published experimental studies that were designed to test the hypothesis that hypertrophic hearts are more sensitive than normal hearts to ischemic injury. Most investigators have studied cardioprotective techniques in normal and hypertrophic hearts; although clinically important, such studies were not designed to assess the tolerance of unproected hypertrophic hearts to prolonged ischemia. Other studies lack appropriate control data, and some report only qualitative results. Experiments that were specifically designed to compare normal and hypertrophic hearts exhibit variable results; some indicate moderate differences in systolic recovery after normothermic (unprotected) ischemic arrest, whereas others indicate no difference. Likewise, isolated muscle studies (during a hypoxia-reoxygenation sequence) indicate that recovery of developed tension is essentially equal in normal and hypertrophic myocardium. Based on these published data and our results (indicating no significant difference in systolic recovery among the three groups of hearts), it seems that hypertrophic hearts do not uniformly exhibit an impaired tolerance to ischemia.

Diastolic function (during ischemia-reperfusion) is likewise reported to be impaired more in hypertrophic hearts than in normal hearts; however, again, the published results show substantial variability. Several reports indicate that the time to onset of ischemic contracture is shorter or contracture is more severe in the presence of hypertrophy; others have emphasized differences in diastolic pressure during reperfusion. Some investigators have not observed an increased tendency to develop ischemic contracture in hypertrophic hearts. Others, using a hypoxia-reoxygenation sequence in isolated muscle studies, have concluded that the differences in contracture tension due to age far exceed those due to hypertension. Under the conditions of our ischemia-reperfusion experiments, we did not observe a decrease in diastolic distensibility in the hearts with compensated LVH. By contrast, the presence of pump failure seemed to predispose the hypertrophic heart to ischemic contracture and diastolic dysfunction during reperfusion. It therefore appears that the tolerance to ischemia is related to baseline (in vivo) ventricular function.

Our observation that LV pump failure (in vivo) is associated with an ischemic contracture can help unravel some of the disparate results in the literature. No previous study has included an analysis of subgroups according to the functional state of the left ventricle. Therefore, it is quite possible that the published clinical and experimental data were obtained in groups that consisted of some combination of compensated and failing hypertrophic hearts. Other reasons for the varying published results probably relate to species and methodological differences and to differences in the preischemic (baseline) state of the myocardium. For example, if hypertrophic hearts are marginally perfused, intermittently ischemic, or both in the baseline state, the high-energy phosphate content would likely become depleted and, as a consequence, a decreased tolerance to ischemia might exist. This hypothesis is supported by reports of reduced ATP and a tendency to develop ischemic contracture in hypertrophic hearts and dog hearts where myocardial blood flow is low in the baseline state. Menasche et al also found an impaired tolerance to ischemia in hypertrophic rat hearts when myocardial perfusion was subnormal during the baseline (preischemic) state; however, when similar studies were performed with comparable baseline perfusion in the normal and hypertrophic hearts, the recovery of systolic function was similar in the two groups. These latter results are consonant with our observations.

CBF in the baseline state was essentially equal in the three groups of hearts (Table 2); average values in the range of 5.0–5.5 ml/min/g dry wt correspond to approximately 100 ml/min/100 g wet wt. During reperfusion, reactive hyperemia was blunted in the LVH-C hearts and markedly attenuated in the LVH-F hearts. These data are consonant with those of Marcus et al and others who have emphasized a decreased coronary reserve in hypertrophic hearts. Likewise, there were no significant differences in MVO2 among the three groups of hearts; average values in the range of 0.25–0.30 ml/min/g dry wt correspond to approximately 5 ml/min/100 g wet wt. These coronary flow and oxygen consumption data were obtained in nearly empty (V20) hearts; for this reason, it remains possible that energetic differences are present in working or heavily loaded hearts. It is apparent, however, that normal myocardial energetics and normal high-energy phosphate content (Table 3) in the baseline state were associated with essentially equal systolic recovery among the three groups of hearts. These deliberations, unfortunately, do not identify the defect or defects leading to ischemic contracture and diastolic dysfunction in the hypertrophied hearts with pump failure.

Previous ischemic injury and high-energy phosphate depletions can be responsible for an impaired myocardial tolerance to prolonged ischemic arrest; therefore our finding of equivalent ATP content among the three groups is of considerable importance. This finding, however, does not exclude differences in the turnover rate or transfer of high-energy phosphates; such a condition has recently been reported in spontaneously hypertensive rats with LVH and functional decompensation. Wexler et al described "exaggerated hypoxia-induced diastolic dysfunction" in pressure-overload hypertrophy
that was not related to high-energy phosphate depletion per se. Thus, by limiting energy-dependent processes (i.e., membrane-ion pumps), an abnormality of high-energy phosphate turnover could have contributed to the ischemic contracture in the LVH-F hearts. Such a hypothesis is consonant with our findings of markedly reduced lactate production in this group of hearts.

Less lactate production in the LVH hearts relative to the control hearts (Figure 4) undoubtedly represents less anaerobic glycolysis during ischemia. Similar observations have been made in hypertrophied pig hearts during ischemia and in hypertrophied rat hearts during hypoxia. The mechanism responsible for this decreased glycolysis by hypertrophied hearts during ischemia or hypoxia is not well understood; however, it does not simply represent a lower glycogen content in the hearts with LVH.

Inhibition of the glycolytic pathway during hypoxia or ischemia has consistently accelerated the development of contracture and decreased the recovery of function; by contrast, exaggerated hypoxic dysfunction in LVH can be reversed by perfusion with high levels of glucose and insulin. These observations indicate that impaired glycolytic flux underlies ischemic or hypoxic diastolic dysfunction. Thus, it is tempting to speculate that the greater mechanical dysfunction observed in our LVH-F group was related to a reduced or inefficient glycolysis.

The predicted functional consequences of reduced glycolysis during ischemia are controversial. Neely and Grotyohann reported an inverse correlation between ischemic tissue lactate accumulation and postischemic functional recovery, and they suggested that myocardial tissue lactate accumulation during ischemia is deleterious. Similarly, Hearse et al reported that the addition of glucose to a cardioplegic solution resulted in diminished postischemic recovery of isolated rat hearts; in these experiments, the glucose was added before a sustained period of zero-flow ischemia without intermittent washout, so tissue lactate accumulation was maximized. By contrast, other studies indicate that tolerance to hypoxia or low-flow ischemia is improved by increasing myocardial glycogen levels or increasing perfusate levels of glucose and insulin. In such studies, continued perfusion during hypoxia or low-flow ischemia prevents or attenuates lactate accumulation. As with these low-flow ischemia and hypoxia protocols, our multiple coronary washout protocol might have prevented or attenuated lactate accumulation and, in this manner, blunted the potentially toxic effects of lactate. Therefore, if lactate accumulation is prevented, glycolysis leads to better functional recovery.

The precise mechanisms by which anaerobic glycolysis protects hypoxic or ischemic myocardium is not known; however, at least two possibilities have been suggested. First, the acidosis resulting from glycolysis might confer an element of protection, perhaps by desensitizing the myofilaments to calcium thereby decreasing the degree of ischemic contracture tension. Bing et al have demonstrated that acidosis protects hypoxic papillary muscles during hypoxia, and Kitakaze et al have reported that acidosis during reperfusion improves postischemic functional recovery. Thus, reduced lactate production in LVH could contribute to impaired recovery as a result of less "protective" acidosis. Second, glycolysis results in the production of ATP, which can be used to maintain ionic homeostasis and structural integrity during ischemia or hypoxia. Our observation that myocardial creatine phosphate and ATP levels were comparable among the three groups of hearts during the ischemic arrest period is not inconsistent with less glycolytic flux in the LVH-F group of hearts. The relatively greater glycolysis in the control and the LVH-C hearts might have resulted in greater ATP synthesis during ischemia; however, this ATP might have been used to maintain structural integrity and ionic homeostasis. Such an ATP turnover would not necessarily be reflected in the overall tissue concentration of ATP. Indeed, the recent studies of Bittl and Ingwall indicate that high-energy phosphate turnover and transfer rates during hypoxia can be quite different among experimental groups despite comparable steady-state levels of high-energy phosphates. If, as Weiss has suggested, ATP derived from anaerobic glycolysis is preferentially used by membrane-ion pumps, a decrease in glycolysis might lead to an ischemic contracture that is secondary to a failure to maintain cytosolic calcium levels at a sufficiently low level. Although speculative, this argument provides an explanation for the observed ischemic contracture in the LVH-F group.

We conclude that hypertrophic hearts with pump failure exhibit a potential to develop mechanical dysfunction during an ischemia-reperfusion sequence. Our data and those of others indicate that differences in diastolic function during reperfusion seem to be substantially more prominent than differences in systolic function; impaired anaerobic glycolysis might underly these mechanical abnormalities. In distinct contrast to these findings in failing hearts, hypertrophic hearts with normal pump function do not exhibit an impaired tolerance to ischemia. Therefore, future experimental work as well as clinical studies of myocardial protection should include a definition of the functional state of the left ventricle and consider baseline energy stores and sources.

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