EXPERIMENTAL STUDIES

Dichloroacetate Improves Postischemic Function of Hypertrophied Rat Hearts

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OBJECTIVES We sought to determine whether improving coupling between glucose oxidation and glycolysis by stimulating glucose oxidation during reperfusion enhances postischemic recovery of hypertrophied hearts.

BACKGROUND Low rates of glucose oxidation and high glycolytic rates are associated with greater postischemic dysfunction of hypertrophied as compared with nonhypertrophied hearts.

METHODS Heart function, glycolysis and glucose oxidation were measured in isolated working control and hypertrophied rat hearts for 30 min before 20 min of global, no-flow ischemia and during 60 min of reperfusion. Selected control and hypertrophied hearts received 1.0 mmol/liter dichloroacetate (DCA), an activator of pyruvate dehydrogenase, at the time of reperfusion to stimulate glucose oxidation.

RESULTS In the absence of DCA, glycolysis was higher and glucose oxidation and recovery of function were lower in hypertrophied hearts than in control hearts during reperfusion. Dichloroacetate stimulated glucose oxidation during reperfusion approximately twofold in both groups, while significantly reducing glycolysis in hypertrophied hearts. It also improved function of both hypertrophied and control hearts. In the presence of DCA, recovery of function of hypertrophied hearts was comparable to or better than that of untreated control hearts.

CONCLUSIONS Dichloroacetate, given at the time of reperfusion, normalizes postischemic function of hypertrophied rat hearts and improves coupling between glucose oxidation and glycolysis by increasing glucose oxidation and decreasing glycolysis. These findings support the hypothesis that low glucose oxidation rates and high glycolytic rates contribute to the exaggerated postischemic dysfunction of hypertrophied hearts. ([Am Coll Cardiol 2000;36:1378–85] © 2000 by the American College of Cardiology)

Postischemic left ventricular dysfunction is greater in hypertrophied hearts than in nonhypertrophied hearts (1–6). Alterations in myocardial energy metabolism, particularly glucose metabolism, are thought to contribute to the increased susceptibility of hypertrophied hearts to injury after ischemia and reperfusion (1–6). During reperfusion of the hypertrophied heart, glycolysis and oxidation of glucose, fatty acid and lactate recover to preischemic values (3). This finding indicates that impairments in glycolysis and oxidative metabolism are not responsible for the greater postischemic left ventricular dysfunction of hypertrophied as compared with nonhypertrophied hearts.

Although overall energy metabolism is not impaired, the pattern of energy substrate use is altered and may influence postischemic left ventricular function in the hypertrophied heart (3,4). Rates of glycolysis are accelerated in hypertrophied as compared with nonhypertrophied hearts during postischemic reperfusion (3,4). However, rates of glucose oxidation during reperfusion are not correspondingly increased in hypertrophied hearts (3,4). Under normal circumstances, the increased production of pyruvate accompanying accelerated rates of glycolysis should lead to higher rates of glucose oxidation by way of pyruvate-induced activation of pyruvate dehydrogenase (PDH), a key enzyme involved in glucose oxidation in mammalian tissues (7,8). Thus, relative to glycolysis, glucose oxidation is substantially lower than normal in the hypertrophied heart during reperfusion.

These low rates of glucose oxidation result in a dramatic imbalance (or uncoupling) between glycolysis and glucose oxidation in the hypertrophied heart that is much greater than that seen in the nonhypertrophied heart (9,10). In nonhypertrophied hearts, low rates of glucose oxidation and increased uncoupling between glycolysis and glucose oxidation are detrimental during reperfusion after ischemia (9,10). Stimulation of glucose oxidation, which improves coupling between glycolysis and glucose oxidation, is clearly beneficial to the nonhypertrophied heart during reperfusion.

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after ischemia (9–14). Taken together, these data suggest that low rates of glucose oxidation, high glycolytic rates and the accompanying accentuated uncoupling between glycolysis and glucose oxidation are responsible for the increased postischemic dysfunction of hypertrophied as compared with nonhypertrophied hearts.

Therefore, we undertook this study to test the hypothesis that improving coupling between glucose oxidation and glycolysis by stimulating glucose oxidation enhances postischemic function of the hypertrophied heart.

**EXPERIMENTAL METHODS**

**Animal model.** As previously described (3,4,15), a mild pressure overload cardiac hypertrophy was induced in male Sprague-Dawley rats by constriction of the suprarenal abdominal aorta. In control rats, the aorta was isolated but not constricted. Food and water were available as desired. These experiments were approved by the University of British Columbia’s Committee on Animal Care in accordance with guidelines set by the Canadian Council on Animal Care.

**Isolated heart preparation.** As described (3,4,15), hearts from halothane-anesthetized rats were perfused as isolated working preparations at a preload of 11.5 mm Hg and an afterload of 80 mm Hg with 100 ml of Krebs-Henseleit solution eight weeks after the operation. The solution, which contained 1.2 mmol/liter palmitate prebound to 3% albumin, 5.5 mmol/liter (5-3H)-glucose (31,838 ± 1,132 disintegrations per minute [dpm]/μmol glucose), (U-14C)-glucose (40,611 ± 1,381 dpm/μmol glucose), 0.5 mmol/liter lactate, 2.5 mmol/liter calcium and 100 mU/liter insulin, continuously circulated through the closed perfusion system. The solution was oxygenated with 95% oxygen and 5% carbon dioxide and maintained at 37°C throughout the perfusion. A high concentration of palmitate was used to recapitulate the levels of fatty acids observed in vivo during ischemia and reperfusion (16).

A pressure transducer (Viggo-Spectramed, Oxnard, California) inserted in the preload line was used to measure heart rate and peak systolic pressure. Cardiac output and aortic flow were measured by means of external flow probes (Transonic Systems Inc., Ithaca, New York) on the preload and aortic outflow lines, respectively. Coronary flow was calculated as the difference between cardiac output and aortic flow. The external work performed by the heart was expressed as the rate–pressure product (calculated as the product of heart rate and peak systolic pressure) and hydraulic work (calculated as the product of cardiac output and peak systolic pressure) (11,15).

**Perfusion protocol.** Spontaneously beating hearts were subjected to 30 min of normoxic, nonischemic perfusion followed by 20 min of global (no-flow) normothermic ischemia and 60 min of normoxic reperfusion. This severity of ischemia was chosen because it maximizes the number of hearts that recover (approximately two-thirds) and reliably causes significant postischemic myocardial dysfunction (30% to 60% of preischemic function). Reperfusion was initiated by unclamping the preload and afterload lines. Perfusate in these lines was replenished throughout the ischemic period. As such, hearts received warm, oxygenated perfusate (with or without dichloroacetate [DCA]) immediately at the onset of reperfusion. When administered, DCA (1.0 mmol/liter) was introduced into the recirculating perfusate 5 min before the end of ischemia to achieve complete mixing before reperfusion. We exclusively determined the effect of DCA on postischemic function when administered only at reperfusion, because not only is this the most clinically relevant situation, but it also has been shown that DCA and insulin are detrimental to postischemic recovery when given together before ischemia (9). The exaggerated dysfunction under these circumstances is likely a consequence of increased proton and lactate accumulation during ischemia (9,12). A subset of this series was perfused nonischemically for 30 min in the presence or absence of 1.0 mmol/liter DCA.

A separate series of control and hypertrophied hearts was also studied in which the hearts were paced electrically (300 beats/min) during reperfusion to account for differences in heart rate. The paced hearts were perfused exactly as the first series, except that glycolysis and glucose oxidation were not measured.

Left ventricular function was measured every 10 min of nonischemic perfusion and at intervals of 5, 10, 15, 20, 40 and 60 min during reperfusion. At the end of the nonischemic and reperfusion periods, the hearts were quickly frozen using tongs cooled to the temperature of liquid nitrogen. The frozen tissue was weighed to determine ventricular weight, powdered and stored at −70°C. The atrial tissue remaining was dried, weighed and used in the calculation of the total heart weight. A portion of the ventricular tissue was dried to determine the dry/wet ratio used in the calculation of the total dry weight of the heart. Glycogen content was determined in representative samples of frozen myocardium by standard techniques.

**Measurement of glucose oxidation and glycolysis.** Glycolysis and glucose oxidation rates were determined as previously described (3,4,15). Glycolysis was determined by measuring the rate at which 3H2O was released from (5-3H)-glucose at the triose phosphate isomerase and enolase steps of glycolysis. Glucose oxidation was measured by quantitative collection of 14CO2 liberated from (U-14C)-
of preischemic perfusion (Before Ischemia) or at the end of 60 min reperfusion (Reperfusion).

There were no differences in heart weight or body weight between treated and untreated control groups or between treated and untreated aortic-banded groups (data not shown). The heart weight of the aortic-banded rats (2.1 ± 0.1 g, n = 39) was greater than that of the control rats (1.9 ± 0.1 g, n = 34, p < 0.05). Body weight was not different between aortic-banded (488 ± 11 g) and control rats (479 ± 7 g, p = NS).

Mechanical function of control and hypertrophied hearts. Before ischemia, significant differences were not observed in either series—that is, between control hearts with and without DCA during reperfusion or between hypertrophied hearts with and without DCA during reperfusion (data not shown). In spontaneously beating hearts, all variables of function, except peak systolic pressure, were lower in hypertrophied hearts than in control hearts before ischemia (Table 1, Fig. 1). During reperfusion, all functional variables were lower in untreated, spontaneously beating control and hypertrophied hearts, as compared with corresponding preischemic values (Table 1, Fig. 1). With the exception of hydraulic work and peak systolic pressure, left ventricular functional indexes were lower in untreated hypertrophied hearts than in untreated control hearts during reperfusion (Table 1, Fig. 1).

Treatment of spontaneously beating control and hypertrophied hearts with DCA during reperfusion improved most functional variables in both groups, as compared with corresponding values in untreated hearts (Table 1, Fig. 1). Heart function and coronary flow increased in DCA-treated hypertrophied hearts to values that were significantly greater than or comparable to those in untreated control hearts (Table 1, Fig. 1). However, hydraulic work and coronary flow were significantly lower in DCA-treated hypertrophied hearts than in DCA-treated control hearts. Exposure of nonischemic hearts to DCA also significantly improved function in both groups (Table 2).

Mechanical function of control and hypertrophied rat hearts that were paced during reperfusion is summarized in Table 3. The results of this series were very similar to those of the spontaneously beating control and hypertrophied hearts during reperfusion (Table 1). Dichloroacetate improved functional recovery during reperfusion of both control and hypertrophied hearts, as compared with corresponding values in untreated hearts. In the presence of DCA, contractile function during reperfusion of paced hypertrophied hearts was comparable to that seen in untreated, paced control hearts. Except for peak systolic pressure, contractile function of DCA-treated, paced control hearts was significantly greater than that of DCA-treated, paced hypertrophied hearts during reperfusion.

Myocardial glucose metabolism. GLYCOLYSIS. Rates of glycolysis were accelerated in hypertrophied hearts as compared with control hearts during the preischemic period.

**Table 1.** Mechanical Function of Spontaneously Beating Control and Hypertrophied Working Rat Heart Reperfused After Ischemia

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 13)</th>
<th>Hypertrophy (n = 13)</th>
<th>Control + DCA (n = 6)</th>
<th>Hypertrophy + DCA (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>247 ± 5.0</td>
<td>228 ± 6.8*</td>
<td>229 ± 19.5*</td>
<td>252 ± 6.4§</td>
</tr>
<tr>
<td>Peak systolic pressure (mm Hg)</td>
<td>135 ± 2.4</td>
<td>133 ± 2.4</td>
<td>109 ± 4.8*†</td>
<td>117 ± 3.4†</td>
</tr>
<tr>
<td>Rate–pressure product (mm Hg × min⁻¹ × 10⁻⁴)</td>
<td>33.2 ± 0.6</td>
<td>30.0 ± 0.6*</td>
<td>24.7 ± 1.9*†</td>
<td>29.4 ± 0.3§$</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>60.4 ± 1.0</td>
<td>50.3 ± 1.0*</td>
<td>38.8 ± 1.6*†</td>
<td>52.6 ± 1.7$$</td>
</tr>
<tr>
<td>Hydraulic work (mm Hg × ml × min⁻¹ × 10⁻⁴)</td>
<td>81.4 ± 2.2</td>
<td>66.6 ± 1.5*</td>
<td>42.3 ± 3.1‡‡</td>
<td>65.3 ± 3.9$$</td>
</tr>
<tr>
<td>Coronary flow (ml/min per g wet weight)</td>
<td>16.4 ± 0.9</td>
<td>11.4 ± 0.6*</td>
<td>12.4 ± 1.0*</td>
<td>11.7 ± 0.5§$</td>
</tr>
</tbody>
</table>

Significant differences (p < 0.05) are indicated as *versus preischemic control hearts; †versus preischemic hypertrophy hearts; ‡versus reperfused untreated control hearts; §versus reperfused DCA-treated control hearts. Data are presented as mean value ± SEM. Values were obtained at the end of 30 min of preischemic perfusion (Before Ischemia) or at the end of 60 min reperfusion (Reperfusion).

DCA = dichloroacetate.
During reperfusion, rates of glycolysis in untreated control and hypertrophied hearts did not differ from corresponding preischemic values. Glycolytic rates were not significantly altered by DCA in control hearts during reperfusion (Fig. 2). However, rates of glycolysis were significantly reduced by DCA during reperfusion in hypertrophied hearts, as compared with values in untreated hypertrophied hearts and in hypertrophied hearts before ischemia (Fig. 2). As during reperfusion, glycolysis was decreased by DCA in nonischemic hypertrophied hearts, but not in nonischemic control hearts (Table 2).

**Table 2.** Mechanical Function and Glucose Metabolism in Spontaneously Beating Nonischemic Control and Hypertrophied Working Rat Hearts

<table>
<thead>
<tr>
<th></th>
<th>No DCA Control (n = 4)</th>
<th>Hypertrophy (n = 4)</th>
<th>No DCA Control (n = 4)</th>
<th>Hypertrophy (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>258 ± 6</td>
<td>229 ± 13*</td>
<td>250 ± 14</td>
<td>217 ± 14*</td>
</tr>
<tr>
<td>Peak systolic pressure (mm Hg)</td>
<td>124 ± 3</td>
<td>117 ± 3</td>
<td>134 ± 2*†</td>
<td>135 ± 4*†</td>
</tr>
<tr>
<td>Rate-pressure product (mm Hg × min⁻¹ × 10⁻³)</td>
<td>31.9 ± 1.1</td>
<td>26.7 ± 1.0*</td>
<td>33.5 ± 2.4†</td>
<td>29.2 ± 1.3‡</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>71.5 ± 0.3</td>
<td>57.0 ± 1.8*</td>
<td>73.8 ± 1.4†</td>
<td>64.0 ± 1.8*‡</td>
</tr>
<tr>
<td>Hydraulic work (mm Hg × ml × min⁻¹ × 10⁻³)</td>
<td>88.3 ± 2.7</td>
<td>66.8 ± 2.2*</td>
<td>98.9 ± 3.2†</td>
<td>86.5 ± 2.2‡</td>
</tr>
<tr>
<td>Coronary flow (ml/min per g wet weight)</td>
<td>21.8 ± 1.0</td>
<td>11.2 ± 1.4*</td>
<td>20.3 ± 1.0†</td>
<td>15.4 ± 0.3*‡</td>
</tr>
<tr>
<td>Glycolysis (nmol/min per g dry weight)</td>
<td>2,352 ± 102</td>
<td>3,243 ± 205*</td>
<td>1,923 ± 149†</td>
<td>2,077 ± 160†</td>
</tr>
<tr>
<td>Glucose oxidation (nmol/min per g dry weight)</td>
<td>235 ± 24</td>
<td>200 ± 22</td>
<td>402 ± 24†</td>
<td>366 ± 16†</td>
</tr>
<tr>
<td>H⁺ production (nmol/min per g dry weight)</td>
<td>4,234 ± 220</td>
<td>6,086 ± 176*</td>
<td>3,042 ± 453†</td>
<td>3,421 ± 375†</td>
</tr>
</tbody>
</table>

Significant differences (p < 0.05) are indicated as *versus untreated control hearts; †versus untreated hypertrophy hearts; ‡versus DCA-treated control hearts. Data are presented as mean value ± SEM. Functional variables were obtained at the end of the 30 min of nonischemic perfusion.

DCA = dichloroacetate.

**GLUCOSE OXIDATION.** During the preischemic period, rates of glucose oxidation tended to be lower in hypertrophied hearts than in control hearts, but the difference was not significant (Fig. 3). As with glycolytic rates, glucose oxidation rates in untreated control and hypertrophied hearts during reperfusion were not different from corresponding preischemic values (Fig. 3). However, glucose oxidation during reperfusion was significantly depressed in untreated hypertrophied hearts as compared with untreated control hearts (Fig. 3). Glucose oxidation during reperfusion was significantly increased by DCA in both control and hypertrophied hearts.
hypertrophied hearts, as compared with preischemic values or with values in untreated control and hypertrophied hearts during reperfusion. Glucose oxidation rates during reperfusion in DCA-treated hypertrophied hearts were lower, but not significantly, than rates in DCA-treated control hearts (Fig. 3). Dichloroacetate treatment also increased glucose oxidation nearly twofold in nonischemic control and hypertrophied hearts (Table 2).

**Myocardial glycogen.** Glycogen did not differ significantly between control and hypertrophied hearts before ischemia (control 95 ± 4 vs. hypertrophy 101 ± 2 μmol/g dry weight, p = NS). During ischemia, glycogen decreased to comparable values in control and hypertrophied hearts (control 63 ± 5 vs. hypertrophy 64 ± 6 μmol/g dry weight, p = NS). Glycogen was resynthesized to similar but slightly different degrees in all groups during reperfusion (control 100 ± 2 vs. control + DCA 109 ± 2 μmol/g dry weight, p < 0.05; hypertrophy 107 ± 3 vs. hypertrophy + DCA 115 ± 4 μmol/g dry weight, p < 0.05).

**DISCUSSION**

**Dichloroacetate, contractile function and glucose oxidation.** The beneficial effects of DCA on functional recovery of nonhypertrophied hearts after ischemia are well described (9–14). The improved postischemic function of nonhypertrophied hearts produced by DCA has been associated with and attributed to a stimulation of glucose (and pyruvate) oxidation (9–14). The current study demonstrates that this association also occurs in the reperfused ischemic hypertrophied heart (Tables 1 and 3, Fig. 1 and 3). Dichloroacetate stimulates glucose oxidation because it activates PDH, a mitochondrial multienzyme complex that oxidatively decarboxylates pyruvate to form carbon dioxide, reduced nicotin-
amide adenine dinucleotide (NADH) and acetyl coenzyme A (7,8). The activity of PDH is a major determinant of the extent of myocardial glucose oxidation (7,8). Activity of PDH is regulated by reversible phosphorylation of PDH and by end-product inhibition by acetyl coenzyme A and NADH (7,8). Phosphorylation by pyruvate dehydrogenase kinase (PDK) inactivates the PDH complex, whereas dephosphorylation by pyruvate dehydrogenase phosphatase leads to reactivation (7,8). Dichloroacetate activates PDH by inhibiting PDK (18,19), thereby stimulating glucose oxidation.

Dichloroacetate and glycolysis. In the absence of DCA, rates of glycolysis before and after ischemia were accelerated in hypertrophied as compared with nonhypertrophied hearts (Fig. 2, Table 2)—a finding in keeping with previous observations (3,4,15,20–22). This observation is also consistent with findings in hearts exposed to a pressure overload where the in vitro activity of a number of glycolytic enzymes is increased, as compared with nonhypertrophied hearts (23), and isoenzymes of lactate dehydrogenase (24), enolase (25) and creatine kinase (26) shift toward more anaerobic, fetal forms.

Activation of glucose (and pyruvate) oxidation is expected to lead to a corresponding decrease in glycolytic flux (Pasteur effect) in the presence of a constant or lowered energy demand. Experimentally, however, the effect of DCA on glycolysis in nonischemic and reperfused nonhypertrophied hearts has been variable—sometimes inhibiting glycolysis (9) and sometimes having no effect (11). In the studies reported here, DCA inhibited glycolysis during nonischemic perfusion and reperfusion, but only in hypertrophied hearts (Fig. 2, Table 2). It has been proposed that DCA may directly inhibit glycolysis by reducing the activities of hexokinase and pyruvate kinase (27)—two enzymes in the glycolytic pathway. This possibility was not assessed in the current study. The explanation for the difference between the effect of DCA on glycolysis in control and hypertrophied hearts remains to be determined.

Contractile function and myocardial H+ production. Despite an acceleration of glycolytic rates in untreated hypertrophied hearts, there was no corresponding increase in the rates of glucose oxidation (Fig. 2 and 3, Table 2). In fact, the rates of glucose oxidation during reperfusion in untreated hypertrophied hearts were lower than those in untreated control hearts. The mechanism(s) responsible for depressed rates of glucose oxidation in untreated hypertrophied hearts are not yet known. Of interest, our very recent experiments suggest that alterations in PDH cannot account entirely for the low rates of glucose oxidation in hypertrophied hearts (28). Regardless of the mechanism, a dramatic uncoupling between glycolysis and glucose oxidation was observed in hypertrophied hearts that was substantially greater than that seen in control hearts. A glucose molecule passing through glycolysis leads to the production of 2 H+ by way of adenosine triphosphate (ATP) hydrolysis, and a molecule of glucose oxidized to carbon dioxide results in no net H+ production (9). As such, H+ production, calculated from rates of glycolysis and glucose oxidation (9), was accelerated in untreated hypertrophied hearts as compared with untreated control hearts before and after ischemia (Fig.
4). Importantly, the absence of differences in glycogen degradation between control and hypertrophied hearts during ischemia indicates that the proton burden arising from glycogen catabolism during no-flow ischemia did not differ between the two groups.

We hypothesize that excess \( H^+ \) production, arising from alterations in glucose metabolism, is responsible for greater dysfunction of hypertrophied hearts as compared with nonhypertrophied hearts during reperfusion. Accumulation of \( H^+ \) in the myocardium can interfere with contractile function directly (29). It can also cause influx and intracellular accumulation of \( Na^+ \) and \( Ca^{2+} \) by means of \( Na^+ /H^+ \) and \( Na^+ /Ca^{2+} \) exchange (6,9,10,30). The influx of \( Na^+ \) and \( Ca^{2+} \) that occurs secondary to clearance of \( H^+ \) may reduce contractile function and cardiac efficiency (cardiac work/oxygen consumed) by redirecting ATP toward processes involved in cellular ion transport and away from those involved in contractile function or by leading to myocardial damage, or both (6,9,10,31). Importantly, hypertrophied hearts have alterations in transport processes responsible for \( Na^+ \) and \( Ca^{2+} \) homeostasis (6). Many of these alterations potentiate the detrimental effects of \( Na^+ \) and \( Ca^{2+} \) influx and accumulation, especially during reperfusion. In keeping with this scenario, impaired recovery of hypertrophied hearts during reperfusion has been shown to be associated with exaggerated \( Ca^{2+} \) and \( Na^+ \) overload (2,32).

**Dichloroacetate and myocardial \( H^+ \) production.** In the current study, \( H^+ \) production in the hypertrophied heart was dramatically reduced by DCA, because glucose oxidation was stimulated and glycolysis was inhibited (Fig. 2 through 4, Table 2). This reduction in \( H^+ \) production, and its resultant effects on myocardial ion concentrations, was likely a key factor in the functional improvements observed in DCA-treated hypertrophied hearts, particularly during reperfusion. In support of this view, we have shown that a \( Na^+ /H^+ \) exchange inhibitor can mimic the effects of DCA in nonhypertrophied hearts perfused under identical conditions (11). Furthermore, we have recently shown that DCA, given at reperfusion, stimulates glucose oxidation, decreases \( H^+ \) production, increases the rate of recovery of intracellular \( H^+ \) concentration (pHi) and enhances postischemic recovery of nonhypertrophied hearts (33). However, direct measurement of changes in pHi and \( Na^+ \) and \( Ca^{2+} \) concentration during reperfusion of hypertrophied hearts, as well as demonstration that inhibitors of \( Na^+ /H^+ \) exchange provide similar benefit, will be required to prove that this view is correct. That some variables of contractile function were lower in hypertrophied hearts than in nonhypertrophied hearts in the presence of DCA (Tables 1 through 3) may have resulted from several factors, including lower rates of coronary flow and glucose oxidation as well as alterations in ion pumps and channels (6) in hypertrophied hearts.

**Other potential effects of dichloroacetate.** Dichloroacetate may have also improved postischemic function by alternative, but not necessarily mutually exclusive, mechanisms. The beneficial effect of enhanced glucose oxidation may also be due to increases in the intramitochondrial NADH\( _2 \)/oxidized nicotinamide adenine dinucleotide (NAD) ratio, which would thereby increase the mitochondrial oxidative phosphorylation potential (13). The DCA-
induced improvement in coronary flow during reperfusion may also have been a contributing factor (Tables 1 through 3).

Conclusions. We show for the first time, to our knowledge, that DCA normalizes postischemic function of hypertrophied rat hearts in association with stimulation of glucose oxidation and inhibition of glycolysis. These findings support the hypothesis that excess H⁺ production, arising from high glycolytic rates and low glucose oxidation rates, is responsible for the greater dysfunction of hypertrophied hearts as compared with nonhypertrophied hearts during reperfusion. Furthermore, the data also indicate that pharmacologic modulation of the activity of pyruvate dehydrogenase in hypertrophied hearts may be a therapeutically useful approach to improve function of the hypertrophied heart in the setting of ischemia and reperfusion.

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REFERENCES

9. Lopaschuk GD, Wambolt RB, Barr RL. An imbalance between glycolysis and glucose oxidation is a possible explanation for the detrimental effects of high levels of fatty acid during aerobic perfusion of ischemic hearts. J Pharmacol Exp Ther 1993;264:135–44.