Effect of hyperglycemia and fatty acid oxidation inhibition during aerobic conditions and demand-induced ischemia

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Chavez, Pedro N., William C. Stanley, Tracy A. McElfresh, Hazel Huang, Joseph P. Sterk, and Margaret P. Chandler. Effect of hyperglycemia and fatty acid oxidation inhibition during aerobic conditions and demand-induced ischemia. Am J Physiol Heart Circ Physiol 284: H1521–H1527, 2003. First published January 9, 2003; 10.1152/ajpheart.00974.2002.—Metabolic interventions improve performance during demand-induced ischemia by reducing myocardial lactate production and improving regional systolic function. We tested the hypotheses that 1) stimulation of glycolysis would increase lactate production and improve ventricular wall motion, and 2) the addition of fatty acid oxidation inhibition would reduce lactate production and further improve contractile function. Measurements were made in anesthetized open-chest swine hearts. Three groups, hyperglycemia (HG), HG + oxfenicine (HG + Oxf), and control (CTRL), were treated under aerobic conditions and during demand-induced ischemia. During demand-induced ischemia, HG resulted in greater lactate production and tissue lactate content but had no significant effect on glucose oxidation. HG + Oxf significantly lowered lactate production and increased glucose oxidation compared with both the CTRL and HG groups. Myocardial energy efficiency was greater in the HG and HG + Oxf groups under aerobic conditions but did not change during demand-induced ischemia. Thus enhanced glycolysis resulted in increased energy efficiency under aerobic conditions but significantly enhanced lactate production with no further improvement in function during demand-induced ischemia. Partial inhibition of free fatty acid oxidation in the presence of accelerated glycolysis increased energy efficiency under aerobic conditions and significantly reduced lactate production and enhanced glucose oxidation during demand-induced ischemia.

The normal heart obtains approximately two-thirds of its energy from free fatty acid (FFA) oxidation, even during partial reductions in flow that result in lactate production (20, 22, 27, 35, 46). Under aerobic conditions, the mechanical efficiency of the heart is greater when carbohydrate oxidation is enhanced (16), and efficiency is reduced by elevated fatty acid oxidation (28). It is unclear if improved efficiency with enhanced carbohydrate use persists during ischemia. Ischemia stimulates the glycolytic pathway; however, there is continued oxidation of fatty acids and a greater mitochondrial NADH-to-NAD+ ratio, which operate to inhibit flux through pyruvate dehydrogenase (PDH) (39). Thus there is greater pyruvate formation from glycolysis but a decreased ability to oxidize pyruvate and NADH in the mitochondria, which drives pyruvate conversion to lactate, accumulation of lactate and H+, and contractile dysfunction (39).

Patients with coronary artery disease commonly have a decreased coronary blood flow reserve. Thus, in response to stress, there is a failure to increase coronary flow and myocardial oxygen consumption (MV02) sufficiently, resulting in “demand-induced” ischemia (35, 42). We recently developed a model of demand-induced ischemia in pigs, where ischemia is the result of flow restriction and dobutamine stimulation of heart rate and contractility, with no change in MV02 (5). In this model, demand-induced ischemia stimulated non-oxidative glycolysis and lactate production but did not affect fatty acid uptake.

Classic therapy for demand-induced ischemia is aimed at increasing oxygen delivery or reducing the external work of the myocardium. Proposed alternative metabolic therapies are aimed either at increasing ATP production by stimulating glycolysis with exogenous glucose and/or insulin (1, 10, 34) or by partially inhibiting fatty acid oxidation [with agents like ranolazine, oxfenicine (Oxf), or trimetazidine] to relieve inhibition of pyruvate oxidation and decrease lactate production (42). Increasing glycolytic substrates to the myocardium during an ischemic insult improves myocardial systolic and diastolic function in isolated hearts (10, 48). Similarly, pharmacological agents that partially inhibit fatty acid oxidation increase pyruvate oxidation and the uptake and oxidation of glucose and lactate under aerobic conditions in humans and animals (17, 33, 44). Although clinical trials in stable angina patients (e.g., exercise-induced angina) with partial fatty acid oxidation inhibitors (8, 25) and carnitine palmitoyl transferase I (CPT-I) inhibitors (2, 6)
show clear clinical benefits, as reflected in improved exercise duration and time to 1-mm ST segment depression on the ECG, it is important to note that there is no direct evidence that these agents reduce lactate production or improve regional mechanical function in angina patients during demand-induced ischemia. In a swine model of demand-induced ischemia, we recently showed that acute inhibition of myocardial fatty acid oxidation reduced lactate production and improved regional mechanical function; however, the potential benefits of accelerated glycolysis was not investigated (4). Therefore, we used this model to investigate whether, during demand-induced ischemia, 1) stimulation of glycolysis would increase nonoxidative glycolysis and lactate production and improve ventricular wall motion; and 2) the addition of a partial fatty acid oxidation inhibitor would stimulate oxidative glycolysis by increasing pyruvate oxidation, resulting in less lactate production and additional improvements in myocardial contractile function.

METHODS

Study design. This study is a prospective, randomized, investigator-blinded, controlled trial in a porcine model. An independent statistician randomly assigned 27 domestic pigs to one of three study groups: control (CTRL; n = 9, mean weight 37 ± 3 kg), hyperglycemia (HG; n = 9, mean weight 36 ± 2 kg); and HG with Oxf (HG + Oxf; n = 9, mean weight 36 ± 3 kg). The experimental solutions were prepared by an independent laboratory and collected and administered by the blinded investigators. The study was conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 85-23) and the Institutional Animal Care and Use Committee at Case Western Reserve University.

Surgical preparation. Animals were fasted overnight and sedated with intramuscular zolazepam-tiletamine at 6–7 mg/kg, and anesthesia was induced with 5% isoflurane by mask (Vaprostick plus anesthesia machine). The airway was intubated through a midline tracheotomy, and ventilation was controlled by a SAV 2500 anesthesia ventilator to maintain physiological parameters: pH 7.4, arterial PCO2 40 mmHg, and arterial PO2 above 100 mmHg. Anesthesia was maintained with 0.5–2.0% isoflurane and 4 mg·kg⁻¹·h⁻¹ ketamine.

An anterior thoracotomy was performed, and the heart was exposed (37). The animals were heparinized, and a 20% triglyceride emulsion was infused to increase plasma FFA to ~0.6 mmol/l (41). The left anterior descending coronary artery (LAD) was catheterized, and blood flow was controlled for coronary venous saturations of 30–40% by an extracorporeal perfusion circuit via a roller pump with blood supplied from the femoral artery, as previously described in detail (24, 37, 41). Arterial blood samples were obtained from a constant-flow (10 ml/min) withdrawal loop from the LAD perfusion circuit so that blood sampling would not disturb coronary artery blood flow. A second cannula was placed in the anterior interventricular vein to collect venous blood samples from the perfusion zone of the LAD, whereas the right main and circumflex coronary artery blood flows were not restricted (13, 14). A dual-transducer catheter was advanced through the left carotid artery to continuously assess left ventricular (LV) pressure (LVP).

Regional segment length was measured in the LAD bed using sonomicrometry crystals placed in the LAD midwall as previously described (14, 24). This allowed for calculation of anterior wall power from the segment length-LVP loop area times heart rate.

Experimental protocol. After the instrumentation was completed and steady state was reached (20 min of stable hemodynamic parameters), a continuous infusion at a rate of 0.1 ml/min of [U-14C]glucose (0.2 μCi/min) and [9,10-3H]oleate (0.2 μCi/min), plus one of the experimental solutions [mannitol (CTRL group, 9 mmol/l, n = 9); glucose (HG group, 12 mmol/l, n = 9) or glucose (12 mmol/l) plus Oxf (HG + Oxf group, 2 mmol/l, n = 9)], was infused directly into the coronary perfusion circuit. Arterial and interventricular venous samples were collected at baseline, 10 min before infusion, and at 32 and 37 min after tracer and treatment infusions were initiated. Forty minutes after the tracer infusion was initiated, demand-induced ischemia was initiated with dobutamine at 15 μg·kg⁻¹·min⁻¹ to increase myocardial oxygen demand, and the LAD blood flow was reduced by 20%. Arterial and interventricular venous blood samples were then taken at 3, 6, 10, and 15 min of demand-induced ischemia. Blood samples were analyzed for the concentrations of oxygen, lactate, and glucose in blood and plasma FFA. In addition, samples were analyzed for [14C]glucose, [14C]CO2, [3H]oleate, and [3H2O for calculation of the rates of glucose and oleate oxidation, as described in Calculations.

Heart rate, LVP, peak positive and negative first derivative of pressure (dP/dt), and segment length were continuously recorded using a commercial on-line data-acquisition system. Small myocardial biopsies (10–20 mg) were taken from the anterior LV free wall with a 14-gauge biopsy needle 5 min before demand-induced ischemia was initiated and at 8 min of demand-induced ischemia, immediately freeze clamped (3–5 s) on aluminum blocks precooled in liquid nitrogen, and stored at −80°C for subsequent analysis. Tissue lactate and ATP were assayed in these samples. After 15 min of demand-induced ischemia, two large (~3 g) punch biopsies were rapidly obtained from the anterior and posterior LV free wall and freeze clamped in large steel tongs precooled in liquid nitrogen; these samples were assayed for concentrations of tissue glyogen and triglycerides.

Analytic methods. Detailed analytic methods have been previously cited in the literature (5). Blood samples for glucose, lactate, and [14C]glucose were deproteinized and analyzed for glucose and lactate using enzymatic spectrophotometric assays. [14C]Glucose and [14C]Lactate were measured using ion-exchange chromatography. Plasma [3H]oleate concentration was measured by extracting the fatty acids from plasma in heptane-isopropanol and counting the organic phase. [3H2O concentration was measured by distilling plasma in modified Hickman stills. Blood [14C]CO2 concentration was measured by expelling [14C]CO2 with the addition of concentrated lactic acid and trapping it in hyamine hydroxide. Plasma FFA concentration was measured using a commercially available enzymatic spectrophotometric kit. Tissue lactate and triglyceride concentrations were measured using enzymatic spectrophotometric methods. Tissue glyogen was assayed using the amyloglucosidase method.

Actual and total PDH activity was determined using a newly developed radiochemical assay (43). The assay is based on the production of [1-14C]acetetyl CoA from [2-14C]pyruvate, which is converted to [1-14C]acetyl carnitine in the presence of excess L-carnitine and carnitine acetyltransferase. The positively charged product [1-14C]acetyl carnitine is then sep-
Hemodynamics. Hemodynamic variables are listed in Table 1. Demand-induced ischemia resulted in significant increases in heart rate in all groups. LV peak pressure did not change significantly from baseline for any of the groups, but maximum first derivative of pressure (+dP/dt) increased in all groups. Coronary blood flow was not different between the three groups (0.70 ± 0.01, 0.81 ± 0.08, and 0.75 ± 0.01 ml·min⁻¹·g⁻¹ wet wt⁻¹ for CTRL, HG, and HG + Oxf groups respectively, during the aerobic period). There was no increase in MV0₂ in the LAD perfusion bed during demand-induced ischemia for any of the three groups (Table 1).

Substrate metabolism. Lactate production values are presented in Fig. 1 and Table 2. During aerobic conditions, there was net lactate uptake except in the HG group, where there was minor lactate production just before the onset of demand-induced ischemia. However, during demand-induced ischemia, there was a dramatic switch to net lactate production in all groups (Fig. 1). The time course of lactate production indicates that the switch from lactate uptake to lactate production occurred as early as 3 min after the onset of demand-induced ischemia and was significantly greater than aerobic conditions in all three groups. After the initial 3 min of demand-induced ischemia, lactate production in the HG + Oxf group was signifi-
was significantly lower in the CTRL group (at 6 and 10 min of demand-induced ischemia) and HG group (6, 10, and 15 min of demand-induced ischemia). During demand-induced ischemia, myocardial tissue lactate content was also significantly greater in the HG group compared with both the CTRL and HG + Oxf groups (Table 2).

Arterial FFA concentrations were not different under aerobic conditions (0.834 ± 0.073, 0.860 ± 0.063, and 0.835 ± 0.078 μmol/ml) and during demand-induced ischemia (0.856 ± 0.083, 0.886 ± 0.045, and 0.825 ± 0.070 μmol/ml) among the CTRL, HG, and HG + Oxf groups, respectively. Arterial insulin concentrations were also not different under aerobic conditions (20.4 ± 7.7, 16.8 ± 3.9, and 22.5 ± 9.5 pM) and during demand-induced ischemia (20.5 ± 6.5, 18.0 ± 3.0, and 25.7 ± 10.5 pM) between the CTRL, HG, and HG + Oxf groups, respectively. FFA tracer uptake was not different between the groups under aerobic conditions and during demand-induced ischemia (Fig. 2A). However, during aerobic conditions, FFA oxidation was significantly lower in the HG + Oxf group (0.021 ± 0.005 vs 0.119 ± 0.016 and 0.140 ± 0.036 μmol·min⁻¹·g⁻¹ for the CTRL and HG groups, respectively, P < 0.05). FFA oxidation was also significantly reduced during demand ischemia compared with aerobic conditions in all groups (by 67 ± 16%, 55 ± 19%, and 92 ± 33% in the CTRL, HG, and HG + Oxf groups, respectively) with total inhibition of FFA oxidation during demand-induced ischemia in the HG + Oxf group (Fig. 2B). The rates of glucose oxidation were significantly higher in the HG + Oxf group compared with the CTRL group during both aerobic and demand-induced ischemia conditions and were significantly greater than the HG group during demand-induced ischemia conditions only (Fig. 2C).

Table 2. Tissue concentrations for lactate, glycogen, triglycerides, and ATP (in the ischemic LAD bed) and lactate output integrals during aerobic conditions and demand-induced ischemia for the control, hyperglycemia, and hyperglycemia + oxfenicine groups

<table>
<thead>
<tr>
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<th>Control</th>
<th>Hyperglycemia</th>
<th>Hyperglycemia + Oxfenicine</th>
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<tbody>
<tr>
<td>Tissue lactate, μmol/g wet wt</td>
<td>3.77 ± 0.58</td>
<td>6.52 ± 0.53*</td>
<td>4.82 ± 0.42</td>
</tr>
<tr>
<td>Lactate integral, μmol</td>
<td>15.3 ± 2.0</td>
<td>21.4 ± 5.0</td>
<td>14.0 ± 2.8</td>
</tr>
<tr>
<td>Tissue glycogen, μmol/g wet wt</td>
<td>8.8 ± 1.3</td>
<td>12.8 ± 2.7</td>
<td>14.3 ± 1.5†</td>
</tr>
<tr>
<td>Tissue triglycerides, μmol/g wet wt</td>
<td>2.64 ± 0.28</td>
<td>2.04 ± 0.17</td>
<td>3.14 ± 0.37‡†</td>
</tr>
<tr>
<td>Tissue ATP, μmol/g wet wt</td>
<td>7.76 ± 1.01</td>
<td>7.13 ± 1.21</td>
<td>8.30 ± 1.94</td>
</tr>
<tr>
<td>Acrobic</td>
<td>3.75 ± 0.47</td>
<td>4.54 ± 0.60</td>
<td>5.23 ± 0.62</td>
</tr>
<tr>
<td>Demand ischemia</td>
<td>3.75 ± 0.47</td>
<td>4.54 ± 0.60</td>
<td>5.23 ± 0.62</td>
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Values are means ± SE. Tissue concentrations for ATP are reported under aerobic conditions, and lactate, glycogen, triglycerides, and ATP are reported after 15 min of demand-induced ischemia in the ischemic anterior LV free wall [left anterior descending coronary artery (LAD)] beds. Lactate output integral is calculated for the entire 15 min of demand-induced ischemia. *P < 0.05, hyperglycemia vs. control and hyperglycemia + oxfenicine; †P < 0.05, hyperglycemia + oxfenicine vs. control; ‡P < 0.05, hyperglycemia + oxfenicine vs. hyperglycemia.

Fig. 2. The rates of free fatty acid (FFA) uptake (A), FFA oxidation (B), and glucose oxidation (C) under aerobic conditions (27–32 min of treatment) and during demand-induced ischemia, g wet wt⁻¹. *P < 0.05, HG + Oxf vs. HG; †P < 0.05, HG + Oxf vs. CTRL; ‡P < 0.05, aerobic conditions vs. demand-induced ischemia.
During demand-induced ischemia, total PDH activity and the amount of PDH in the active form were not different among the three groups. These results are in agreement with a previous study from our laboratory, where we reported a tripling in the rate of flux through PDH despite no increase in the activity of PDH when the heart was subjected to a twofold increase in power with dobutamine (13). Furthermore, pharmacological inhibition of CPT-I has been reported to increase flux through PDH, even when there was no activation of PDH via dephosphorylation (15).

**Regional LV wall efficiency.** Sonomicrometry was used to assess the anterior wall work and power index as calculated from the LVP-segment length loop area (5). Anterior wall energy efficiency index was calculated as the anterior wall power index divided by the estimated ATP production (calculated from M\(\dot{V}O_2\) and the rate of glycolytic ATP production). Under aerobic conditions, acute treatment with HG or HG + Oxf improved the energy efficiency index compared with the CTRL group (155 ± 13% and 151 ± 9% vs. 117 ± 10%, respectively; Fig. 3). Efficiency during demand-induced ischemia was not different among the three groups (Fig. 3). The anterior wall work and power index were not different among the three groups during aerobic conditions or during demand-induced ischemia.

**DISCUSSION**

Results of this investigation demonstrate that HG, either alone or in combination with partial inhibition of fatty acid oxidation, increased mechanical efficiency under aerobic conditions. However, when the heart was stressed, HG alone increased lactate production with no further improvement in mechanical efficiency. On the other hand, inhibition of fatty acid oxidation in the presence of accelerated glycolysis significantly reduced lactate production and enhanced glucose oxidation during demand-induced ischemia, but also did not cause any further improvement in mechanical efficiency. Thus stimulation of glycolysis under aerobic conditions resulted in improvement in myocardial energy efficiency; however, there was no further increase in mechanical efficiency during demand-induced ischemia even when lactate production was reduced by partial inhibition of fatty acid oxidation.

The results from this study demonstrate that during demand-induced ischemia, HG alone resulted in enhanced lactate production and increased tissue lactate content with no improvement in mechanical function compared with the CTRL group. Despite the protective benefits attributed to increased glycolytic flux, excess glycolysis can be detrimental. Increased nonoxidative glycolysis provides anaerobic ATP regeneration, but it also has the disadvantage of an increase in lactate, H\(^+\), and other metabolic end products and their associated negative effects. In vitro studies show that lactate and H\(^+\) accumulation and efflux during ischemia have negative effects on the ability of cardiac muscle to maintain Ca\(^{2+}\) homeostasis and to use the energy released from the breakdown of ATP to perform contractile work (11, 30). Moreover, stimulation of glucose oxidation has been shown to reduce lactate accumulation and mechanical efficiency in the postischemic-reperfused rat heart (23). Intracellular lactate accumulation has been shown to be deleterious both directly (12) and through inhibition of glyceraldehyde-3-phosphate dehydrogenase after NADH accumulation, thereby inhibiting glycolysis (29, 32). Several human studies provide evidence for the disadvantage of increasing glycolytic flux when not matched with appropriate increases in pyruvate oxidation. Increasing glycolytic substrate availability using glucose-insulin-potassium solutions did not improve exercise tolerance or the time to ST segment depression in patients with stable angina subjected to atrial pacing-induced tachycardia (18) or supine bicycle exercise (47). The results of the present study suggest that stimulation of nonoxidative glycolysis during demand-induced ischemia results in no net benefit, as distinguished by a lack of improvement in regional external power or mechanical efficiency.

**Fig. 3.** Myocardial energy efficiency index in the anterior left ventricular free wall during treatment under aerobic conditions and during demand-induced ischemia expressed as a percentage of the values obtained during the pretreatment period. *P < 0.05, HG + Oxf and HG vs. CTRL.
Traditional therapies for myocardial ischemia improve oxygen delivery to the ischemic cardiac muscle or they reduce the oxygen requirement of the myocardium by decreasing heart rate, blood pressure, or ino-tropy (42). While these therapies effectively lessen the degree of ischemia by better matching the delivery of oxygen to the amount of myocardial external power, they do not improve myocardial mechanical efficiency. Metabolic agents that suppress fatty acid oxidation and increase the oxidation of pyruvate by PDH in the mitochondria will reduce the ischemia-induced disruption in cardiac metabolism by lowering the rate of lactate production and the associated fall in pH, resulting in clinical benefits to the ischemic patient (2, 8, 19, 25, 42). This direct metabolic approach is optimally suited for conditions such as demand-induced ischemia, where there is sufficient residual oxygen delivery to the myocardium to support pyruvate oxidation in the mitochondria. We (4) recently demonstrated in a swine model of demand-induced ischemia that acute inhibition of myocardial fatty acid oxidation reduced lactate production and improved regional mechanical function; however, the potential benefits of accelerated glycolysis were not investigated. In the present investigation, we observed that when enhanced glycolysis was accompanied by partial inhibition of fatty acid oxidation with Oxf, lactate production and tissue lactate accumulation were reduced during demand-induced ischemia but did not result in improved external mechanical power or mechanical efficiency. It is unclear how these results relate to clinical markers of demand-induced ischemia, namely ST segment depression and chest pain. Angina pectoris has been attributed to stimulation of afferent nerve endings by adenosine, H⁺, and K⁺ (7), whereas ST segment changes can be attributed to opening of the ATP-sensitive K⁺ channel (21). It is possible that in the present study, the stimuli for angina and ST segment changes were reduced by Oxf treatment, suggesting a dissociation between contractile function and clinical markers of angina.

It has been suggested that improvements in cardiac function with agents that switch myocardial substrate oxidation from fatty acids to carbohydrates are due to a greater theoretical ATP-to-O₂ ratio and a lower MV₀₂ for glucose and lactate than for long-chain fatty acids (35, 42, 45). In the present investigation, under aerobic conditions, HG alone and HG with Oxf resulted in enhanced glucose oxidation and partial inhibition of fatty acid oxidation (in the HG + Oxf group) at no greater MV₀₂ cost, which translated into greater mechanical efficiency compared with the CTRL group. These changes in the balance of myocardial substrate oxidation might cause a slight change in the ATP-to-O₂ ratio without an increase in MV₀₂, which could partially explain this increase in mechanical efficiency. Previous studies have demonstrated that high levels of FFAs increase oxygen consumption by uncoupling oxidative phosphorylation (3), by a wasting of ATP by mitochondria (38), or by a futile cycling of fatty acids in and out of the triglyceride pool (31, 36). Furthermore, a recent study in pigs demonstrated that increasing the rate of glucose oxidation relative to the rate of fatty acid oxidation resulted in an increase in LV power for a given rate of MV₀₂ (16). Although other studies have demonstrated that insulin increases coronary flow and cardiac efficiency in vivo (26) and that insulin also increases cardiac efficiency in the posts ischemic rat heart in vitro (9), there were no differences in arterial insulin concentrations during the aerobic period that could account for the changes we observed in mechanical efficiency. Our results add support for the concept that switching the myocardial fuel selection toward carbohydrate oxidation improves the efficiency of the transfer of chemical to mechanical energy in the heart; however, the precise mechanism(s) responsible for this phenomenon requires further study.

In conclusion, HG alone, or in the presence of partial inhibition of fatty acid oxidation, led to an increased mechanical efficiency under aerobic conditions. When the heart was stressed, HG alone increased lactate production, with no additional improvement in myocardial efficiency. However, when HG was accompanied by partial fatty acid oxidation inhibition, there was a significant reduction in lactate production and enhanced glucose oxidation during demand-induced ischemia. Thus HG under aerobic conditions resulted in an improvement in myocardial energy efficiency; however, there was no further increase in mechanical efficiency during demand-induced ischemia even when lactate production was reduced by partial inhibition of fatty acid oxidation.

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