Effects of Hyperthermic Stress on Myocardial Function during Experimental Coronary Ischemia

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SUMMARY We evaluated hyperthermic influences on ischemic hearts by comparing two groups of intact working swine hearts (n = 20) made globally ischemic. Heart muscle temperature was selectively increased from 37.5 ± 0.3°C to 39.7 ± 0.3°C in one group (n = 11) by warming the coronary perfusate. Ischemia in normothermic hearts significantly (P < 0.05) decreased mechanical function (as reflected by increases in left ventricular end-diastolic pressure [LVEDP]), myocardial oxygen consumption (MVO₂), glucose uptake, glycolytic flux, free fatty acid (FFA) uptake and oxidation, and tissue stores of high energy phosphates. Heating in ischemic hearts further depressed mechanical function at similar reductions in coronary flow and MVO₂. Glucose uptake was terminally increased over normothermic values (329 vs. 221 μmol/hr per g), as was glycolytic metabolism, FFA uptake (21 vs. 17 μmol/hr per g), and FFA oxidation (21 vs. 11 μmol/hr per g). However, these changes were not translated into increased energy stores of tissue creatine phosphate and ATP. Thus, in ischemic hearts, hyperthermia neither prevented the development of mechanical deterioration nor improved oxidative phosphorylation despite increases in metabolic substrate utilization. These data suggest that in experimental global ischemia heat is an added energy drain in already burdened myocardium.

HEAT HAS WELL documented effects on the heart. Although opinion differs on selected aspects of these changes [no doubt explained by the many differences in experimental design, technique, and ranges of temperature studied (38-46°C)], most workers agree that mild to moderate hyperthermia promotes a general rise in cardiac output and heart rate together with a fall in peripheral vasomotor tone. These are associated biochemically with a transient increase in myocardial oxygen consumption, an enhanced rate of fatty acid oxidation, and a rise in glycolysis and glucose uptake, most of which ends in lactate accumulation rather than glucose oxidation. Despite the overall acceleration in metabolism, myocardial concentrations of high energy phosphates decline, probably from the demands of increased left ventricular work.

During malignant hyperthermia, severe mechanical and metabolic deteriorations occur. Cardiac output and arterial pressures may fall drastically and are linked biochemically with significant declines in myocardial oxygen consumption and cardiac ATP stores together with increases in tissue adenosine nucleotide intermediate levels and lactate. Histologically, there are areas of subendocardial hemorrhage, myocardial necrosis, and rupture of muscle fibers which in other studies have been shown to cause release of intracellular contents of creatine (derived from breakdown of myocardial creatine phosphate), lactic acid dehydrogenase (LDH), and ammonia (also presumably as a result of altered adenine nucleotide metabolism).

Such findings are akin to those of myocardial ischemia and raise questions as to the consequences of pyrexia per se on the function of heart muscle independently rendered ischemic by critically restricting coronary flow. Clinically, fever is a well recognized complication of myocardial infarction. The extent to which the action of hyperthermia alters the mechanical and metabolic functions of ischemic heart muscle therefore requires further documentation and was the goal of this study. Mild to moderate levels of heat stress were evaluated experimentally in a previously described globally ischemic, intact working swine heart preparation.

Methods

Twenty-seven swine of either sex, weighing 29.5-59.6 kg (average wt, 45.7 kg), were studied following anesthesia with pentobarbital (35 mg/kg) and the establishment of controlled positive-pressure ventilation using 100% 0₂. Frequent determinations of the swine's arterial pH, P0₂, Pco₂, and co₂ combining power were obtained throughout each study to ensure adequacy of ventilation and acid-base balance.

EXPERIMENTAL PREPARATION

Whole heart ischemia in the intact working swine heart preparation has been described previously. Following bilateral thoracotomy with transthoratomy, right heart bypass from venae cavae to pulmonary artery was constructed with antegrade control of systemic cardiac output maintained by a high flow Sarns roller pump. The circuit was primed with 1-2 liters of heparinized, fresh whole blood from a donor pig. Total coronary perfusion was established using a recirculation closed loop from the right ventricular drainage sump to the cannulated left and right coronary arteries. Blood flows to the left and right coronary arteries were controlled and regulated by two separate low flow
Sarns perfusion pumps. Proximal to the pumps the coronary perfusate was reoxygenated by a Bentley blood oxygenator (Q-130) with a 97.3% gas mixture of O₂:CO₂. Distal to the pumps, the perfusate was passed through Travenol low prime, minimal impedance heat exchangers with capabilities of rapidly changing perfusate temperatures. Rectal, coronary perfusate, and myocardial temperatures were monitored with a probe and needle thermistors (Yellow Springs Instrument Co.) and a telethermometer. The central aorta and left ventricle were cannulated with short, fluid-filled catheters inserted retrograde from the femoral and left carotid arteries, respectively, and connected to Statham P23Db pressure transducers for monitoring arterial and ventricular pressures. All hearts were paced from the right atrium using Medtronic 5880 A pacemakers on the demand mode at a frequency slightly above the intrinsic heart rate (mean heart rates over the course of perfusion were 103 ± 4 beats/min in normothermic hearts, 103 ± 5 beats/min for hyperthermic hearts). All signals including an electrocardiogram were displayed on a Brush Mark 200 recorder.

**CORONARY PERFUSATE**

Central coronary loop volume in each study averaged 1,500 ml. The perfusate consisted of the swine’s own whole blood obtained by previous exchange transfusion with dextran. Coronary loop hemoglobin concentration averaged 10.1 g/100 ml. To the perfusate were added extra levels of substrate and hormone including: (1) palmitic acid (Fisher Scientific) with tracer quantities (70 μCi) of [U-14C]palmitate (New England Nuclear) complexed to bovine albumin, fraction V (4 g/100 ml), to give an initial average free fatty acid (FFA) concentration of 0.60 mM, (2) regular zinc insulin (25 mU/ml), and (3) excess glucose to provide an initial loop concentration of 29.1 mM (resultant osmolarity, 328 mOsmol/liter). Labeled palmitate was used to estimate FFA consumption and oxidation, insulin to ensure rapid transport of glucose into the cell, and extra glucose to avoid substrate depletion during the course of perfusion. Samples of perfusate were obtained during the studies from side ports just distal to the right ventricular stump and proximal to the coronary cannulas for sampling arteriovenous differences of oxygen and metabolites across the myocardium.

**HEMODYNAMIC AND METABOLIC MEASUREMENTS**

Heart rate, coronary flow (summed from the flows of the two coronary perfusion pumps), cardiac index (determined from the flow rate of the right heart bypass perfusion pump normalized by swine weight in kilograms), aortic and ventricular pressures, and peripheral vascular resistance (aortic pressure/cardioc index) were determined during both normal and ischemic perfusions. From coronary arterial and venous blood, myocardial oxygen consumption was calculated both for hemoglobin and plasma transport by formulas previously described.14, 15 Hemoglobin, arterial and venous O₂ tensions (PₐO₂), and hemoglobin O₂ saturations were obtained with an Instrumentation Laboratories blood gas analyzer and co-oximeter, respectively. Results were normalized per dry weight of ventricular myocardium.

Myocardial uptake of fatty acids were estimated from the clearance of [U-14C]palmitate from the labeled coronary perfusate. Samples of coronary arterial and venous blood were centrifuged and a sample of serum was used for determining radioactivity due to [14C]palmitate. After removal of [14CO₂ more than 90% of the serum radioactivity was extractable by chloroform or Dole's reagent and therefore was present as long chain fatty acids. The radioactivity present in the aqueous phase after fatty acid extraction represented no more than 8% of the remaining radioactivity, even after 1 hour of perfusion, and no more than 2% of the radioactivity added initially as [U-14C]palmitate. A change in the amount of aqueous soluble radioactivity between arterial and venous samples could not be detected. The total fatty acid content of serum was determined colorimetrically.16 Fatty acid uptake (μmol FFA/hr per g dry) was calculated as previously described,16 using the ratio of the difference in labeled fatty acid counts between coronary arterial and venous samples x total coronary flow/average coronary arterial and venous specific activities of labeled fatty acid normalized by the dry weight of ventricular myocardium.

The rate of fatty acid oxidation in myocardium was estimated by measuring 14CO₂ production from [U-14C]palmitate. Coronary blood samples for CO₂ analysis were collected under heptane. One milliliter of whole blood was transferred to a 25-ml Erlenmeyer flask containing 1.0 ml of 12 N H₂SO₄ in the bottom of the flask and 0.4 ml of Hyamine hydroxide in a plastic central bucket suspended from the stopper. After mixing the blood and acid, the samples were allowed to stand for 2 hours before the buckets were removed, placed in 10 ml of toluene scintillator, and counted in a Beckman 150 liquid scintillation counter. Corrections for quenching were made by the channels-ratio method. Fatty acid oxidation was calculated as the ratio of the difference in 14CO₂ counts between coronary venous and arterial counts x total coronary blood flow/average coronary arterial and venous specific activity of labeled fatty acid normalized by the dry weight of ventricular myocardium.

The rate of glucose utilization was estimated by measuring the disappearance of glucose from the coronary loop blood over the course of the perfusion run. Serum glucose was measured on a Technicon Auto-Analyzer. Comparative estimations by the glucose oxidase method in preliminary studies were in near perfect agreement with measurements from the Auto-Analyzer, excluding the presence of significant levels of other reducing substances. The difference in perfusate glucose levels between consecutive sampling times was obtained and multiplied by the coronary loop blood volume at that time to calculate the glucose consumption, expressed as μmol of glucose/hr per dry weight of ventricular myocardium.

At the conclusion of each perfusion study transmural sections of ventricular myocardium were immediately removed and frozen between blocks of aluminum which had been cooled in liquid nitrogen. From this tissue several intermediates of glycolysis and adenine nucleotide metabolism were measured by techniques previously described and referenced.19 Measurements were determined for tissue glycogen, creatine phosphate, ATP, ADP, AMP, lactate, pyruvate, glucose 6-phosphate, fructose 1,6-diphosphate, triosephosphates, and α-glycerol phosphate.
EXPERIMENTAL PROTOCOL

In all studies, total coronary blood flow was maintained for 20 minutes at control levels, determined initially in each swine by measuring right ventricular drainage prior to closure of the coronary loop perfusion circuit. From previous experience it was determined that this initial 20-minute period permitted adequate mixing of the various added substrates and hormone into the coronary perfusate and allowed for incorporation of intracellular and extracellular \([1^4C]palmitate\) together with achievement of steady state production rates of \(1^4CO_2\) from the oxidation of \([1^4C]palmitate\). Following this equilibration period in 20 hearts, coronary flow was reduced over a period of 10 minutes to a critically restricted perfusion level (calculated as \(2.5 \times \text{dry weight of ventricular myocardium}\)). Projected heart weights were predicted from a normogram relating swine body weight to ventricular dry weight by linear regression \((r = 0.962;\) unpublished data from 218 previously studied swine). The constant 2.5 was an empirical derivation which, when multiplied by the value of myocardial dry weight, yielded a calculated coronary flow rate in ml/min which reproducibly effected advanced levels of global ischemia. Incremental rather than precipitous reductions in coronary flows were necessitated since in this preparation sudden drops in flow of such large magnitude almost invariably resulted in the development of ventricular fibrillation. Over the same period of incremental reductions in coronary flow (between 20 and 30 minutes of perfusion) in 11 of the 20 ischemic hearts, coronary perfusate temperatures were increased by adjusting the heat exchangers so that myocardial tissue temperature was brought to a new state level of 39.7 ± 0.3°C (as measured by a needle thermistor inserted into the middle third of left ventricular myocardium). Mechanical data and metabolic measurements from the perfusate were obtained at identical 10-minute intervals in each of the normothermic and hyperthermic ischemic hearts over a maximum possible perfusion time of 60 minutes. Experiments were terminated either at the end of the 60-minute perfusion time or with the onset of ventricular fibrillation which sometimes occurred in hearts following progressive left ventricular failure. Transmural tissue samples were immediately taken from all hearts for later study. Concentrations of tissue metabolites from these terminal samplings were grouped for both normothermic and hyperthermic ischemic hearts and compared with data from seven normothermic hearts perfused for 60 minutes at normal coronary blood flows. Comparisons were made using paired and unpaired Student's \(t\)-tests with statistical significance defined for probability values less than 5%.

Results

HEMODYNAMICS

In ischemic hearts perfused normothermically, mean myocardial tissue temperature was 37.5 ± 0.3°C (SEM) while heated hearts averaged 2.2°C higher. Core body temperatures were no different in either group (range, 36.4-38.6°C). Their respective indices of mechanical performance are compared in Figure 1 and Table 1. In the normothermic group, total coronary blood flow was reduced from 5.06 ± 0.2 to 2.41 ± 0.07 ml/min per g (ventricular weights averaged 32.6 ± 2.5 g). Heart rate averaged 103 ± 4 beats/min over the course of perfusion. To maintain aortic and left ventricular pressures at near-constant levels, and thereby maintain an important determinant of myocardial oxygen consumption throughout the period of restricted oxygen availability, cardiac index was increased in small increments from 44.3 ± 3.2 ml/min per kg at 20 minutes of

![Figure 1](http://circres.ahajournals.org/)

**Figure 1.** Hemodynamic responses in two groups of swine hearts rendered globally ischemic, beginning at 20 minutes of myocardial perfusion. Normothermic hearts are represented by filled circles; hyperthermic hearts by open circles. Arrows in each panel indicate the beginning of warming to the coronary perfusate and myocardium which occurred concomitantly with the onset of coronary flow restriction. Steady state, hyperthermic myocardial temperatures were accomplished by the onset of absolute global ischemia, beginning at 30 minutes of perfusion. There were significant differences in aortic pressure between groups during the course of ischemic perfusions (see Experimental Protocol, under Methods; and Hemodynamics, under Results, for further discussion).
TABLE I  Changes in Peripheral Vascular Resistances from Swine with in Situ, Globally Perfused, Temperature-Controlled Hearts

<table>
<thead>
<tr>
<th>Myocardial perfusion times</th>
<th>t0</th>
<th>t10</th>
<th>t20</th>
<th>t30</th>
<th>t60</th>
<th>tfinal</th>
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<tr>
<td>Swine with normothermic hearts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.09</td>
<td>2.06</td>
<td>2.08</td>
<td>1.87</td>
<td>1.99</td>
<td>1.65</td>
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<tr>
<td>SEM</td>
<td>±0.17</td>
<td>±0.11</td>
<td>±0.17</td>
<td>±0.17</td>
<td>±0.26</td>
<td>±0.20</td>
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<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Swine with hyperthermic hearts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.20</td>
<td>2.18</td>
<td>2.22</td>
<td>1.97</td>
<td>1.57</td>
<td>1.34</td>
</tr>
<tr>
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<td>±0.14</td>
<td>±0.28</td>
<td>±0.18</td>
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<td>±0.13</td>
</tr>
<tr>
<td>P</td>
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<td>NS</td>
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<td>&lt;0.005</td>
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<tr>
<td>P1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Resistance data are expressed in mm Hg/ml per min per kg. Perfusion times (t) are expressed in minutes and listed numerically as subscripts of t. P compares intragroup resistance data with the values of t0. P1 compares the normothermic with hyperthermic data at identical perfusion times. NS = not statistically significant.

perfusion to 46.8 ± 3.2 ml/min per kg terminally. Only two hearts tolerated global ischemia for the entire 60-minute perfusion period and group mean survival was reduced to 44.4 ± 3.5 minutes (14.4 minutes of global ischemia). Peripheral vascular resistance (Table I) fell over the course of restricted coronary flow (but not significantly by paired Student's t-test) while left ventricular end-diastolic pressure rose precipitously to levels suggesting advanced mechanical failure.

In heated hearts (ventricular dry weight = 28.9 ± 1.3 g) rendered similarly ischemic to those in the normothermic group (Fig. 1), heart rates were comparable at similar times of perfusion.

Despite continued adjustments in cardiac index during ischemia (39.2 ± 4.1 ml/min per kg at 20 minutes of perfusion to 44.0 ± 2.9 ml/min per kg terminally), aortic and left ventricular pressures could not be maintained at preischemic levels (unlike normothermic hearts) and fell significantly and progressively throughout ischemic exposures, as did peripheral vascular resistance (Table I). As defined by left ventricular systolic developed pressure, i.e., aortic mean pressure-left ventricular end-diastolic pressure, this reflected a further decline in mechanical performance in heated hearts as compared to the normothermic ischemic group. Group mean survival time (51.2 ± 3.5 minutes of perfusion or 21.2 minutes of global ischemia) and rates of increase in left ventricular end-diastolic pressure were statistically comparable to the normothermic group.

METABOLISM

The profile of biochemical responses resulting from critical restrictions in total coronary blood flow are shown for normothermic and hyperthermic hearts in Figures 2-4. Following 20 minutes of normal perfusion in normothermic hearts, a progressive reduction in myocardial oxygen consumption, glucose uptake, and fatty acid consumption and oxidation occurred with increasing exposures to global ischemia (Fig. 2). By the final determinations at 44.4 minutes of perfusion all parameters of oxygen and substrate utilization were significantly (P < 0.005) reduced from preischemic data at 20 minutes of perfusion. In hyperthermic hearts oxygen availability was comparably restricted by limiting total coronary blood flow, and myocardial oxygen consumption was similarly reduced to levels observed in normothermic ischemic hearts. Ischemic inhibition of glucose uptake by the myocardium was also generally comparable between groups except for a higher terminal value in heated hearts (329 vs. 221 μmol/hr per g dry, P < 0.05). In contrast, however, hyperthermia per se in ischemic hearts induced significant increases in both fatty

![Figure 2](http://circres.ahajournals.org/)

Figure 2. Metabolic changes in oxygen and substrate utilizations in the same two groups of swine hearts. While myocardial oxygen consumptions were comparably reduced during global ischemia in both groups, there were significant increases in substrate metabolism both for carbohydrate and fatty acid in hyperthermic hearts (open circles) as compared with normothermic hearts (filled circles). Arrows signify the onset of warming, which occurred simultaneously with restrictions in coronary flow (see Experimental Protocol, under Methods; and Metabolism, under Results, for further discussion).
HEAT STRESS ON ISCHEMIC HEARTS/Liedtke and Hughes

Figure 3 Estimate of glycolysis derived from comparisons of glycolytic intermediates in the two groups of ischemic hearts (to the right in each panel) with a third group of normothermic hearts perfused for 60 minutes at normal coronary flows (to the left in each panel) (see Metabolism, under Results, for further discussion). Ischemia stimulated glycojenolysis, but glycolysis was impaired, chiefly at the step mediated by glyceraldehyde-3-phosphate dehydrogenase. This resulted in an accumulation of intermediates preceding this reaction (glucose 6-phosphate, fructose 1,6-diphosphate, α-glycerol phosphate, and triosephosphates) and a drop in product (pyruvate) following it. The majority of pyruvate present was anaerobically converted to lactate. In hyperthermic ischemic hearts, accumulation of preceding intermediates was less and pyruvate stores were greater, suggesting improved enzymatic performance and accelerated anaerobic glycolysis. All tissue data are from terminal samplings, at 44.4 ± 3.2 minutes of perfusion in normothermic ischemic hearts and 51.2 ± 3.2 minutes of perfusion in hyperthermic ischemic hearts. (Survival times between ischemic groups were statistically comparable.)

Acid consumption and oxidation over normothermic ischemic hearts and terminal values were closer to the preischemic values at 20 minutes of perfusion.

A more detailed description of intracellular glycolysis was attempted through comparisons of tissue concentrations of glycogen and glycolytic intermediates (Fig. 3) in the normothermic and hyperthermic hearts. As compared to seven normothermic hearts perfused for 60 minutes at normal coronary flows, ischemia per se stimulated glycojenolysis (glycogen levels were 226.3 ± 16.9 μmol/g in control hearts vs. 186.0 ± 14.0 μmol/g in ischemic hearts, P < 0.05) but impaired glycolysis at the expected enzymatic step of glyceraldehyde-3-phosphate dehydrogenase. This was evidenced by a buildup of glucose 6-phosphate (1,192.1 ± 114.9 μmol/g in ischemic hearts vs. 1,008.3 ± 138.9 μmol/g in control hearts), fructose 1,6-diphosphate (202.9 ± 19.9 vs. 59.9 ± 12.8 μmol/g, P < 0.001), triosephosphates (373.5 ± 47.2 vs. 52.4 ± 6.6 μmol/g, P < 0.001), and α-glycerol phosphate (6,505.2 ± 1,076.2 vs. 427.1 ± 81.2 μmol/g, P < 0.001) preceding the rate-inhibited step and a reduction in pyruvate following it (199.7 ± 19.9 μmol/g in ischemic hearts vs. 310.3 ± 40.3 μmol/g in control hearts, P < 0.025). A significant accumulation of tissue lactate also was documented.

Hyperthermia in myocardial ischemia was associated with increased levels of glycogen (222.8 ± 12.7 μmol/g; statistically no different from normothermic control hearts; P < 0.05 compared with normothermic ischemic hearts), suggesting either an inhibition of glycojenolysis or an acceleration of glycogenesis. There was also a trend toward buildup of glycolytic intermediates before the enzymatic step of a glyceraldehyde-3-phosphate dehydrogenase, as in normothermic ischemic hearts, but with notable exceptions. In general the accumulations were less than in unheated hearts: glucose 6-phosphate, 1,093.0 ± 58.3 μmol/g; fructose 1,6-diphosphate, 126.5 ± 18.7 μmol/g, P < 0.05; triosephosphates, 158.9 ± 22.6 μmol/g, P < 0.001. Pyruvate levels were higher, 359.4 ± 38.8 μmol/g, P < 0.005. This suggested an increased flux rate through the critically inhibited enzymatic step of anaerobic glycolysis.

Comparisons of myocardial high energy phosphate stores and adenine nucleotide intermediate levels are shown in Figure 4. Ischemia, as compared to control hearts, resulted in significant reductions in creatine phosphate (−53.5%; P < 0.001) and ATP (−21.4%; P < 0.001) and was associated with increased ADP (+20.6%; P < 0.005) and AMP (+115.4%; P < 0.01) levels. Hyperthermic ischemic hearts had concentrations comparable to normothermic ischemic hearts. Specifically, there was no net accumulation of energy production from enhanced fatty acid oxidation or anaerobic glycolysis, or from both, suggesting that hyperthermia per se was an energy-draining process.

Discussion

Past conclusions concerning the influence of hyperthermia on cardiovascular performance have been varied, and at times contradictory, explained no doubt by the wide varieties of experimental protocols, types of model systems or
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energy production. Unfortunately, from reported rates of central areas of ischemia) which must rely almost exclusively on anaerobic conversion of glycogen to lactate for possible in less well perfused areas (endocardial tissue and increase in the oxidative rates of glucose relative to that of hearts, fatty acid is the preferred substrate, with energy consumption, and a weak coronary vasodilator property which could improve coronary flow. In fact, however, the present data indicate that exact opposite is true; that is, heating is a detriment metabolically to ischemic heart muscle and indeed may place unacceptable burdens on already compromised metabolic functions in a setting of restricted oxygen supply.

Cardiac muscle is capable of utilizing a variety of metabolic fuels, with the two most preferred substrates being fatty acids and glucose. In well oxygenated hearts, fatty acid is the preferred substrate, with energy production resulting from both β-oxidation and the tri-carboxylic acid cycle. This is prevented in myocardial ischemia, and the heart is forced to rely more on glucose for residual oxidative metabolism in ischemic tissue. While an increase in the oxidative rates of glucose relative to that of free fatty acids does occur in the peripheral and better perfused compartments of ischemic heart muscle, such is not possible in less well perfused areas (endocardial tissue and central areas of ischemia) which must rely almost exclusively on anaerobic conversion of glycogen to lactate for energy production. Unfortunately, from reported rates of glycogen breakdown and glucose uptake during sustained oxygen deprivation, only 10–15% of the energy needs of mammalian hearts can be met through this pathway. It has long been hoped that this source of energy production might in some way be metabolically improved by accelerating glycolytic flux rates. Early efforts included the infusions of “polarizing” solutions containing excess glucose, insulin, and potassium, but these were unsuccessful in increasing glycolysis because of the overriding effects of ischemia on inhibiting key glycolytic enzymes, particularly glyceraldehyde-3-phosphate dehydrogenase. Hyperthermia did appear to increase anaerobic glycolysis in ischemic hearts but unfortunately was not associated with any long term advantages.

The metabolic effects of heat on ischemic heart muscle have not been tested previously but observations in aerobic hearts suggested a general increase in substrate utilization, possibly by thermodynamic influences on critical enzyme systems. Opie et al. documented a working, perfused rat heart preparation that hyperthermia, over a comparable range of temperatures studied in this report, effected several changes including: an increase in glucose uptake, which unfortunately did not participate in oxidative phosphorylation through the Krebs cycle but rather appeared ultimately as lactate; a 60% decrease in glycogen synthesis; an increase in fatty acid oxidation (26.7% increase in 14CO2 production from labeled palmitate); no net change in incorporation of labeled fatty acids into neutral lipids; a biphasic effect on myocardial oxygen consumption consisting of an early increase in consumption over the first 20 minutes of hyperthermic exposure followed thereafter by a decrease in utilization; and a decline in high energy phosphate stores measured both directly (ATP levels) and indirectly (creatinine phosphate stores). The authors interpreted this paradoxical decrease in high energy phosphate levels to result from nonspecified thermic injuries to cellular metabolic function which superseded any benefits in energy production from accelerations in substrate consumption.

Present results in ischemic hearts bear closely on these findings in that hyperthermic influences also produced an acceleration in anaerobic glycolysis and fatty acid oxidation, even despite limited availability of oxygen supplies through critical restrictions in coronary flow. This latter observation suggested a return to a more normal preference of metabolic fuel utilization and represents a unique modification of substrate consumptions for ischemic heart muscle. However, the increased energy production that must have resulted from these utilisations was not demonstrated in the terminal tissue levels of ATP and creatine phosphate from heated hearts, and thus may reflect an energy-draining process in already jeopardized ischemic tissue. The exact cause of the energy drain postulated in these studies was not defined but may relate in some fashion to the combined effects of heat on the peripheral circulation and heart. Hyperpyrexia has been shown to affect left ventricular mechanical function adversely in settings of heat stroke by promoting marked peripheral vasodilatation. This results in increased pooling of blood peripherally leading to decreased venous return and reduced cardiac output. Ischemia per se can also elicit peripheral vasodilatation independently by vagal reflex mechanisms which operate through mechanoreceptors in the ventricular wall or coronary
arteries, or through both. Together, these two determinants (heat and ischemia) may so alter peripheral vasomotor tone as to prevent the heart from operating satisfactorily as a pump. Our present data indicate that indeed a greater reduction in peripheral vascular resistance was observed in swine with hyperthermic ischemic hearts than in those with normothermic ischemic hearts, even when the heat was applied selectively to the coronary perfusate and myocardium. An added factor which may relate to this energy drain is the recent observation that hyperthermia in nonischemic hearts impairs mechanical function by decreasing contractile force through alterations in viscous and elastic properties leading to reduced stiffness. It seems reasonable to postulate that such an influence might be greater in globally ischemic myocardium and thereby cause accelerations in metabolic demands to no positive advantage.

These findings as described indicate that heat is an added burden to ischemic heart muscle, and its consequences, if extrapolated clinically, seem clear. Swine hearts were chosen for use in these studies because of their close similarities to man in cardiovascular function, size and anatomy of cardiac structures, and perfusion distributions and collateral flows of the coronary arteries. The model system is blood-perfused, working, in an in situ setting and, when rendered globally ischemic (done principally to maximize the homogeneity of metabolic samplings from ischemic tissue and improve the quantitative estimates of metabolic performance), is somewhat analogous to ischemic hearts with multivessel coronary artery disease. The present results suggest that hyperthermia induced further functional impairment of the contractile machinery and was linked metabolically with wasteful energy expenditure in ischemic hearts. Even under the implicit restrictions of extending animal data from globally ischemic swine hearts to a clinical context, the above results may prove helpful. The biochemical and circulatory alterations observed experimentally with heat may be reasoned clinically to further reduce the already-impaired reserve of patients with diseased hearts, produce profound changes in the functional cardiac capacity and reserve, and evenuate in advanced cardiac decompensation. Such conclusions from studies with swine may emphasize the need for early and aggressive measures to treat fever in all patients with either acute or chronic ischemic heart disease.

References

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