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Energy Metabolism in Reperfused Heart Muscle: Metabolic Correlates to Return of Function

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An important question in energy metabolism of the reperfused, previously ischemic myocardium is whether the return of a normal tissue adenosine triphosphate (ATP) content is a prerequisite for normal rates of oxygen consumption (that is, ATP turnover) and cardiac function. To study this problem, isolated working rat hearts were perfused with bicarbonate saline solution containing glucose (10 m*M*) at near physiologic work load. After 20 minutes, hearts were made totally ischemic by clamping the aortic and atrial lines for 5, 10 or 20 minutes and then were reperfused for another 10 minutes. Heart rate, aortic pressure, cardiac output and myocardial oxygen consumption were measured continuously. Adenine nucleotides, phosphocreatine, glycogen and the products of glycolysis were determined in freeze-clamped tissue extracts.

Functional recovery was assessed by return of aortic pressure and oxygen consumption to preischemic values. Time required for return of function after reperfusion was 90 seconds after 5 minutes and 124 seconds after 10 minutes of ischemia. No recovery was observed after 20 minutes of ischemia. Tissue ATP content decreased significantly at the end of 5 (−38%) and 10 (−56%) minutes of ischemia and did not increase significantly at return of aortic pressure and oxygen consumption to preischemic values. Glycogen stores decreased by more than 50% at the end of 10 minutes of ischemia and did not normalize on recovery. In contrast to ATP or glycogen, the phosphocreatine content decreased to even lower levels at the end of ischemia, but returned to levels higher than the control level after recovery from 5 to 10 minutes of ischemia in association with return of function. These results indicate that transfer of energy-rich phosphate from ATP to creatine during and immediately after reversible ischemia was probably unimpaired. With 5 and 10 minutes of ischemia, lactate and alanine increased significantly and both metabolites were normal on reperfusion. Irreversible impairment of function ensued after 20 minutes of total ischemia in association with an 80% decrease in ATP content and no resynthesis of phosphocreatine or oxidation of lactate.

The results demonstrate that 1) rapid resynthesis of phosphocreatine and oxidation of lactate characterizes reversibly damaged ischemic tissue, 2) there is no direct relation between tissue content of ATP and cardiac function, and 3) restoration of oxidative metabolism determines functional recovery of the reperfused ischemic myocardium despite the presence of low ATP levels.

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The function of heart muscle depends on the availability of adenosine triphosphate (ATP). Since the tissue content of ATP is relatively low, steady state concentrations of the triphosphate are maintained by the balance of synthesis (mainly through oxidative phosphorylation) and degradation (mainly during the contractile process). This cycle is disrupted in ischemia when ATP synthesis cannot meet ATP requirements. Consequently, a decrease in ATP or the "free energy charge" of the heart has been hypothesized as the mechanism for contractile failure in the reperfused ischemic heart (1,2) and correlated with irreversible cell damage (3). Some investigators (4) reported that contractile dysfunction occurs despite relatively small changes in the tissue ATP content and concluded that loss of ATP is not a causative factor in contractile failure. Thus, there are conflicting data on whether "normal" ATP levels are a prerequisite for normal cardiac function.

Our present work was undertaken to resolve whether restoration of energy-rich phosphate compounds to preisch-

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emic levels is a prerequisite for normal cardiac function after reperfusion of previously ischemic heart muscle. If this were the case, manipulations that increase adenine nucleotides during reperfusion (5) might be beneficial for restoring contractile function. An additional aim of this study was to assess variables that indicate irreversible tissue damage. In particular, we investigated the relation between glycogen content (as the major endogenous substrate in ischemic heart muscle) and the removal of glycolytic end products with functional recovery of reperfused heart muscle.

Methods

Perfused heart preparation. The heart was removed from fed male COBS Wistar rats (animal weight 250 to 350 g) and perfused with oxygenated Krebs Henseleit bicarbonate saline solution, containing 10 m*M* glucose, in the perfusion apparatus previously described (6). Each heart was kept in a temperature-controlled (37°C) perfusion chamber throughout the experiment.

Perfusion protocol. Perfusion was initiated through the aortic cannula at a hydrostatic pressure of 80 cm H_2O and continued for 3 minutes after all blood had been washed from the heart. During this time the left atrium was cannulated. Perfusion as a "working" heart was then begun at a left atrial pressure of 8 cm H_2O and an aortic afterload of 100 cm H_2O and continued for 20 minutes before the heart was made globally ischemic by clamping the tubing leading to the left atrium and from the aorta. The heart was allowed to beat spontaneously throughout the experiment and ceased to beat within 40 seconds after induction of ischemia. For the purpose of reperfusion, medium was readmitted to the heart by opening both the aortic and the atrial lines at the same time. Heart rate and aortic systolic, diastolic and mean pressures were recorded continuously through a sidearm in the aortic cannula using a fluid-filled catheter system with a Statham 23 Db transducer attached to a Hewlett-Packard 7782A physiologic recorder (6). Cardiac output was measured on line using calibrated glass tubes for the measurement of aortic and coronary flow (6). The same medium was recirculated throughout the experiment.

The heart was made ischemic for 5, 10 or 20 minutes and then reperfused for another 10 minutes after return of aortic pressure to preischemic levels (5 and 10 minutes of ischemia) or for another 20 minutes when there was no recovery of aortic pressure (20 minutes of ischemia). We freeze-clamped the heart between aluminum blocks cooled to the temperature of liquid nitrogen at the following time points: 1) immediately on opening the chest wall (in situ, n = 4); 2) after 20 minutes of perfusion under control conditions (n = 6); 3) at the end of the ischemic period (n = 7 for 5 minutes, n = 4 for 10 and 20 minutes); 4) during reperfusion on return of aortic pressure to its preischemic value (n = 6 for each group); and 5) at the end of the reperfusion period (n = 4 for each group).

Oxygen consumption. In selected experiments oxygen consumption was measured with a Clark type oxygen electrode by analysis of the "arterial" and "coronary venous" perfusate in a separate, temperature-controlled chamber connected to the perfusion apparatus (6).

Preparation of tissue extracts and analytical procedures. Tissue extracts of the heart freeze-clamped between aluminum blocks cooled in liquid nitrogen were prepared as described elsewhere (7). Enzymatic methods for the analysis of ATP, adenosine diphosphate (ADP), adenosine monophosphate (AMP), phosphocreatine, lactate, alanine and pyruvate were the same as those used in previous studies (7). Glycogen was determined as glucose after treatment of the tissue homogenate with amyloglucosidase using the method of Bartley and Dean (8).

Presentation and statistical analysis of data. The power output of the heart was calculated as kg · m/hour per g dry weight and is presented as percent of control value. Oxygen consumption is presented as μmol/min per g dry weight and tissue metabolite content as μmol/g dry weight. The measurement for glycogen is μmol glucose/g dry weight (after subtraction of any glucose present before amyloglucosidase treatment). Data are shown as mean values ± SD. Student's *t* test was used for statistical analysis and only probability (p) values of less than 0.01 are recorded.

Results

Effect of ischemia on return of cardiac function. The number of hearts returning to preischemic function after ischemia and their recovery times are presented in Table 1. After 5 and 10 minutes of ischemia, seven (88%) of the eight hearts recovered function, as defined by a return of the aortic mean pressure to its preischemic level of 100 cm H_2O. Recovery times increased with the duration of ischemia. After 20 minutes of ischemia, reperfusion did not result in functional recovery of any heart. The time required for recovery of function after reperfusion was 90 seconds after 5 minutes and 124 seconds after 10 minutes of ischemia.

Tissue content of metabolites and return of oxidative metabolism. The tissue contents of adenine nucleotides, phosphocreatine, glycogen, glucose-6-phosphate, lactate, alanine and pyruvate before ischemia, at the end of ischemia and during reperfusion are shown in Figures 1 to 3.

Table 1. Cardiac Performance and Recovery Time to Preischemic Aortic Pressure

Duration of Ischemia (min)	Number of Hearts Recovering	Recovery Time (s)
5	6 of 8	90 ± 22
10	6 of 8	124 ± 64
20	0 of 6	—

Data are mean values ± SD for the number of hearts recovering.

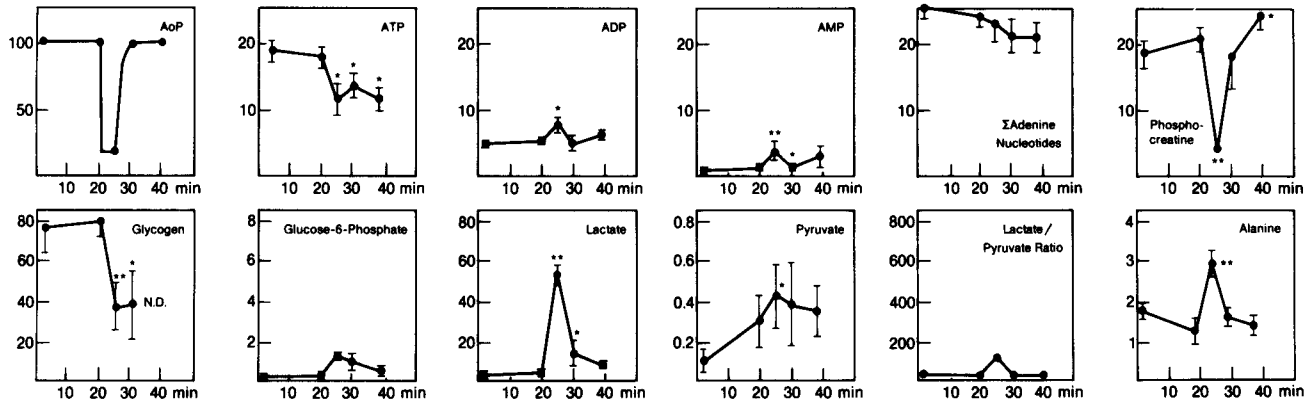


Figure 1. Effects of total global ischemia (5 minutes) on aortic pressure (AoP), adenine nucleotides, phosphocreatine and glycolytic metabolites. The decrease in adenosine triphosphate (ATP) content with ischemia was not reversed at return of aortic pressure to preischemic level. By contrast, the phosphocreatine content returned to its preischemic values. Glycogen stores were not replenished on reperfusion, while the products of glycolysis decreased markedly. *$p < 0.01$ and **$p < 0.001$ when compared with preischemic control. ADP = adenosine diphosphate; AMP = adenosine monophosphate; N.D. = not determined.

It should be noted that absolute values for energy-rich phosphate compounds differ among different strains of rats. Values of COBS Wistar rats used in the present experiments are about 20% lower than values of the same metabolites in Sprague-Dawley rats (H. Taegtmeyer, unpublished observations), a fact that has to be taken into account when reported data from different strains are compared.

Five minutes of ischemia. After 5 minutes of ischemia, ATP had decreased from 19.8 to 12.3 μmol/g dry weight (−38%) and did not increase to more than 14.2 μmol/g dry weight (−28% compared with control values) at recovery of preischemic aortic pressure (Fig. 1). Both ADP and AMP peaked at the end of ischemia and returned to preischemic values on reperfusion. There was a loss of total adenine nucleotides with reperfusion, presumably due to their degradation to nucleosides, which on balance accounts for the loss of ATP.

Phosphocreatine decreased substantially from 18.5 to 3.2 μmol/g dry weight (−83%) and increased, in contrast to ATP, to its preischemic value on reperfusion (18.5 μmol/g dry weight) immediately after recovery and to a value higher than the preischemic value after 10 minutes of reperfusion (22.3 μmol/g dry weight). As already observed, this "overshoot" of phosphocreatine was accompanied by a slight decrease in ATP and a slight increase in ADP (both p = NS).

Glycogen in the tissue decreased from 94.9 to 41.1 μmol glucose equivalents/g dry weight and did not increase to more than 43.7 μmol glucose equivalents/g dry weight on reperfusion at the time of recovery to preischemic aortic pressure. The data show that glycogen stores are not replenished immediately on reperfusion.

The glycolytic intermediate, glucose-6-phosphate, became measurable with our assay system during activation of glycolysis. Lactate, the main product of glycolysis, increased 30-fold from 2.1 to 64.9 μmol/g dry weight and decreased to 16.2 on reperfusion, indicating oxidation or washout of lactate, or both, by previously ischemic heart muscle. We have shown previously (9) that the amino acid alanine is, like lactate, an end product of glycolysis. As expected, alanine increased twofold with ischemia and normalized with reperfusion. The pyruvate content did not change significantly with ischemia and reperfusion. Thus, glycogen was converted to lactate and alanine. The lack of accumulation of pyruvate with ischemia indicates quantitative conversion of pyruvate to lactate and alanine. Accumulation of lactate was probably responsible for the inhibition of glycolysis (10), which is reflected by the amount of glycogen still present in the tissue.

The lactate/pyruvate ratio has been used as an indicator of the cytosolic redox state (11). As expected, it increased with ischemia and returned to preischemic values with return of oxidative metabolism and functional recovery.

Ten minutes of ischemia. After 10 minutes of ischemia, ATP had decreased to 8.7 μmol/g dry weight (−56%). ATP did not increase to more than 12.5 (−37% compared with control level) at the return of preischemic aortic pressure and to no more than 13.3 (−33% compared with control) at the time of full functional recovery when cardiac output had also returned to preischemic levels (Fig. 2). As was the case with the shorter period of ischemia, both ADP and AMP increased at the end of ischemia and returned to normal with reperfusion. Thus, the net loss of adenine nucleotides could be accounted for by a net loss of ATP.

Phosphocreatine decreased even more markedly (from 18.5 to 2.2 μmol/g dry weight, −88%) after 10 minutes than after 5 minutes of ischemia. Phosphocreatine increased immediately on recovery to its preischemic value and continued to increase in the next 10 minutes. This again indicates rapid rephosphorylation of creatine by energy-depleted postischemic myocardium, as previously described in the

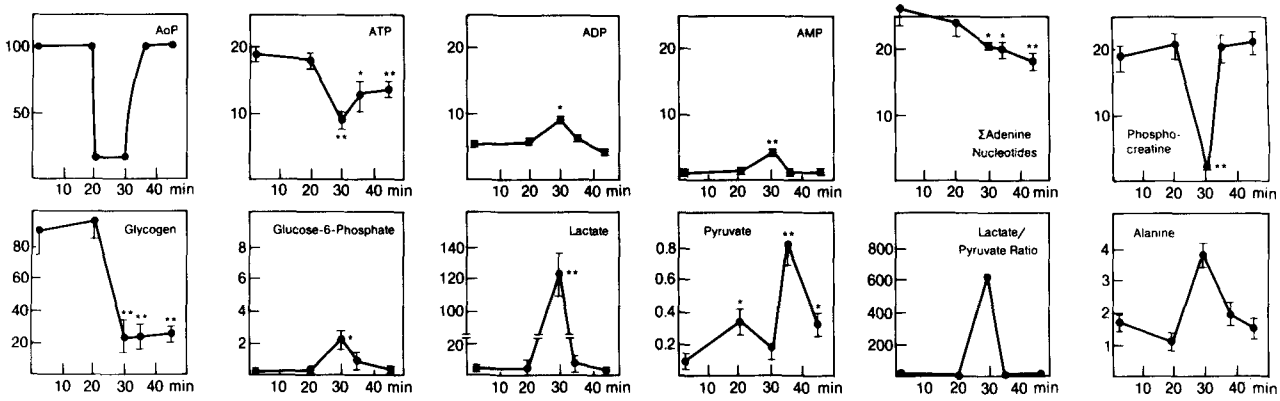


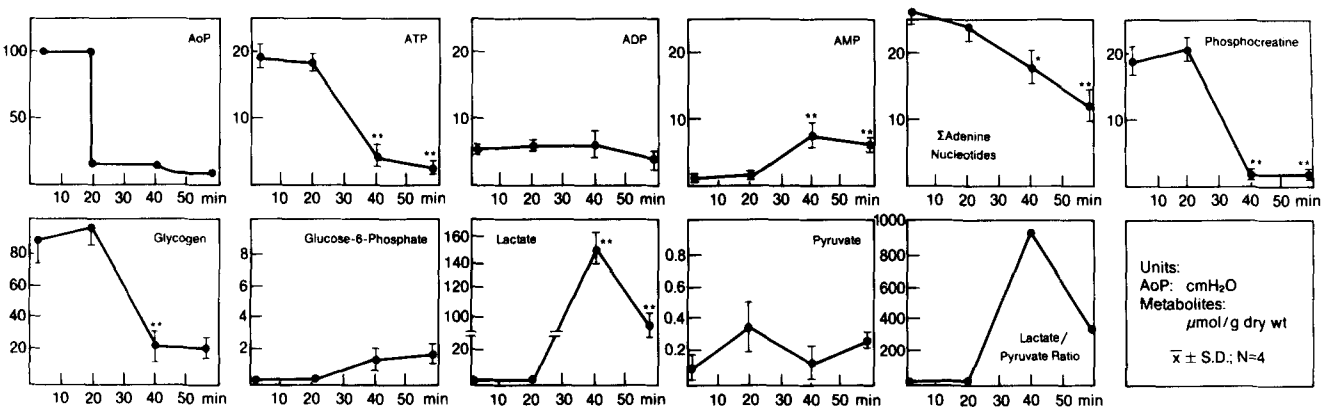
Figure 2. Effects of total global ischemia (10 minutes) on aortic pressure (AoP), adenine nucleotides, phosphocreatine and glycolytic metabolites. The ATP content decreased by 56% at the end of ischemia and remained significantly lower than control values at return of aortic pressure and 10 minutes later. Adenosine diphosphate (ADP) and adenosine monophosphate (AMP) contents increased with ischemia and returned to preischemic values on reperfusion. There was a loss of adenine nucleotides that continued during reperfusion. Glycogen stores were nearly depleted at the end of ischemia and were not replenished on reperfusion. Lactate increased to very high values that returned to normal values on reperfusion. *$p < 0.01$ and **$p < 0.001$ when compared with preischemic control values.

reperfused dog heart (3,12) and in the isolated rat heart (13), examined by nuclear magnetic resonance spectroscopy but without correlation to functional recovery.

Tissue glycogen stores were reduced to a greater extent (from 94.9 to 23.6 μmol glucose equivalent/g dry weight, −75%) after 10 than after 5 minutes of ischemia. Glycogen stores remained depleted at full recovery of aortic pressure and cardiac output on reperfusion. There was an increase in glucose-6-phosphate from less than 0.3 to 2.1 μmol/g dry weight, and the glycolytic end product lactate increased 57-fold from 2.1 to 122.7 μmol/g dry weight. At the same time, pyruvate decreased from the control level of 0.40 to 0.19 μmol/g dry weight at the end of ischemia, while alanine increased from 1.14 to 3.92 μmol/g dry weight. The increase in lactate and the decrease in pyruvate resulted in a marked increase in the lactate/pyruvate ratio, which returned to normal immediately on reperfusion, suggesting either lactate washout or, more likely, oxidation of lactate, or a combination of both on reperfusion. Thus, when cardiac function returns to normal on reperfusion after 5 or 10 minutes of global ischemia, oxidative metabolism also returns to normal.

Twenty minutes of ischemia. After 20 minutes of ischemia, there was no return of contractile function to preischemic levels (Fig. 3), although the heart resumed beating

Figure 3. Effects of total global ischemia (20 minutes) on aortic pressure (AoP), adenine nucleotides, phosphocreatine and glycolytic metabolites. There was no recovery of aortic pressure when the adenosine triphosphate (ATP) content had decreased to 21% of the preischemic control, and ATP decreased further on reperfusion. Total adenine nucleotides decreased linearly with ischemia and subsequent reperfusion, indicating their irreversible loss from tissue. The phosphocreatine content remained decreased on reperfusion. Ischemia and reperfusion also depleted glycogen stores. Lactate increased to very high values and remained elevated with reperfusion. *$p < 0.01$ and **$p < 0.001$. Abbreviations as in Figure 2.



at a slow rate. ATP had decreased markedly from 19.8 to 4.2 μmol/g dry weight (−79%) and after 20 minutes of reperfusion decreased further to 2.5 μmol/g dry weight (−88%). In contrast to the shorter periods of ischemia, ADP did not increase after 20 minutes of ischemia, while AMP increased 17-fold. The increase in AMP probably resulted from an attempt to maintain ATP by the adenylate kinase reaction:

$$ADP + ADP = ATP + AMP, K_{eq} = 0.41,$$

where K_{eq} = equilibrium constant. Because of further metabolism or loss of all adenine nucleotides, or both, the adenylase kinase reaction does not readily reach a new equilibrium.

In further contrast to the observations made with the shorter periods of ischemia, there was no recovery of phosphocreatine with reperfusion after 20 minutes of ischemia. This result indicates that oxidative energy metabolism was insufficient to rephosphorylate both ADP and creatine. Thus, the recovery of phosphocreatine correlates with the return of cardiac function after reperfusion. However, there is no correlation between ATP content and functional recovery, except for severe, prolonged ischemia, when the ATP content has become very low in association with permanent, irreversible loss of function.

Glycogen stores did not decrease more after 20 minutes than after 10 minutes of ischemia (to 22.5 μmol glucose equivalents/g dry weight, −76%), and there was no further decrease on reperfusion. Just as observed with shorter periods of ischemia, the glycolytic intermediate, glucose-6-phosphate, increased to measurable quantities with ischemia. The glycolytic end product, lactate, increased 66-fold from 2.1 ± 1.0 to 142.0 ± 28.8 μmol/g dry weight and remained increased at 95.7 ± 17.3 on reperfusion. The lactate/pyruvate ratio increased from 5 to 922 at the end of ischemia; it decreased but remained elevated with reperfusion. The data suggest that the tissue damaged by ischemia had lost its ability to oxidize lactate and reducing equivalents that accumulated in the cytosol.

Return of oxidative metabolism on reperfusion is demonstrated in the experiments shown in Table 2, in which the reperfusion period was extended to 20 minutes. Although oxygen consumption and cardiac function were the same before and after reperfusion and associated with normalized phosphocreatine levels, ATP levels were only about half those found in the nonischemic control hearts. Table 2 provides direct evidence for the dissociation between cardiac output and oxygen consumption, which rapidly returned to control values, and ATP content of the tissue, which remained decreased.

Discussion

Myocardial ischemia leads to a number of well documented disturbances in energy metabolism including a decrease in energy-rich phosphate compounds, a loss of adenine nucleotides and glycogen, as well as the accumulation of breakdown products of energy-providing substrates (14). Many previous investigators (2–5,12,15) have used complex models to assess the metabolic and functional responses to reperfusion after myocardial ischemia. Our globally ischemic isolated working rat heart offers the advantage that biochemical variables can be studied without influences from hormones, changes in substrate supply, collateral circulation or regional wall motion abnormalities. In addition, the pump function of the heart can be evaluated, and oxygen con-

Table 2. Effects of Global Ischemia and Reperfusion on Cardiac Output, Oxygen Consumption, Adenosine Triphosphate (ATP) and Phosphocreatine

Duration of Ischemia (min)	Variable	Time Before Ischemia (min)			Time After Ischemia (min)			ATP	Phosphocreatine
		1	10	20	1	10	20	(μmol/g dry wt.)	
5 (n = 3)	Cardiac output (ml/min per g dry wt.)	442 ±38	418 ±41	389 ±68	468 ±112	451 ±40	438 ±28		
								10.4* ±1.0	24.2 ±3.9
	Oxygen consumption (μmol/min per g dry wt.)	64.8 ±6.0	56.7 ±2.6	51.9 ±7.0	58.9 ±3.5	62.7 ±10.2	59.5 ±3.9		
10 (n = 4)	Cardiac output (ml/min per g dry wt.)	423 ±35	445 ±29	602 ±68	413 ±95	427 ±68	412 ±56		
								9.1* ±3.5	19.4 ±4.7
	Oxygen consumption (μmol/min per g dry wt.)	60.4 ±7.0	58.0 ±7.4	61.9 ±3.8	57.9 ±2.9	59.6 ±7.8	60.8 ±6.3		

*Significant difference ($p < 0.01$) from values obtained at 45 minutes of normoxic perfusion (19.2 ± 0.9 and 20.8 ± 3.8 μmol/g dry weight for ATP and phosphocreatine, respectively). Cardiac output and oxygen consumption were measured 1, 10 and 20 minutes before and after 5 and 10 minutes of total global ischemia. ATP and phosphocreatine were measured at the end of 20 minutes of reperfusion. Values are mean ± SD.

sumption can be measured under controlled conditions of afterload and preload. Hence, we could assess reversibility of the ischemic injury with good control of all variables. It is characteristic of this model that recovery of function and oxidative metabolism were limited to a time period of less than 20 minutes of ischemia. Longer periods of tolerance to ischemia have been reported during cardioplegic arrest (2) and in regional ischemia of the dog heart in situ (15). The increased tolerance to ischemia under those conditions is probably the result of hypothermia.

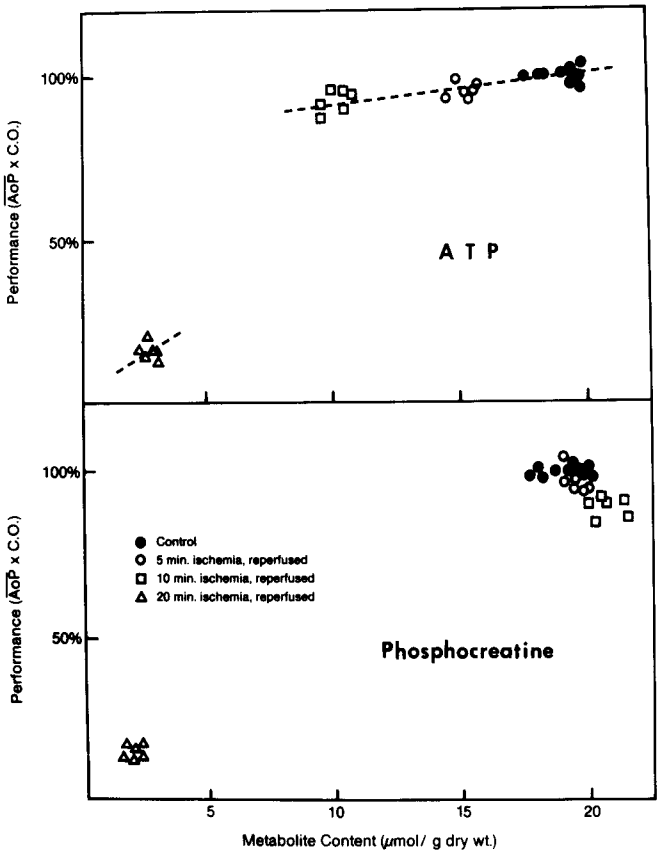
ATP content versus cardiac contractile function. The most striking finding of our results is the lack of correlation between tissue ATP content and cardiac function as assessed by left ventricular pressure development, cardiac output and oxygen consumption. This point becomes even clearer when data on ATP and phosphocreatine of individual experiments are plotted against cardiac performance (Fig. 4). For both ATP and phosphocreatine there are two clusters of data points. The computed correlation coefficient for ATP values greater than 9.8 μmol/g dry weight was 0.110 (p = NS), whereas the same coefficient for ATP values of less than 2.6 μmol/g dry weight was 0.899 ($p < 0.001$). This statistical analysis shows that in normothermic reperfused ischemic heart muscle over a wide range, no direct relation exists between ATP content and myocardial contractile function. In contrast to the ATP values, which showed a wide spread on functional recovery, phosphocreatine values were clustered in one area. No statistical analysis of these data was attempted.

Our results differ from those of Reibel and Rovetto (1) and DeWitt et al. (2), who found a direct linear relation between tissue ATP content and cardiac performance on reperfusion. Both groups of investigators used models of long-term ischemia in which ATP was allowed to decrease to levels lower than 40% of control level. This low level of ATP and loss of adenine nucleotides over a prolonged experimental period may be the reason for poor functional recovery of the severely damaged tissue. By contrast, relatively brief periods of complete normothermic ischemia used in our work resulted in either restoration of function or complete failure to restore function on reperfusion. The shorter experimental period and less severe depression of ATP levels permitted us to observe changes in function without comparable profound changes in ATP levels associated with cell death.

Our data are in agreement with those of Vary et al. (16), who found no correlation between tissue ATP content and performance after ischemia in rat hearts perfused with glucose and acetate as substrates. However, in contrast to all previous studies, we observed return of function and normal rates of oxygen consumption when tissue ATP had decreased to below 50% of control values (see data for reperfusion after 10 minutes of ischemia). The lack of correlation between ATP content on the one hand and rates of ATP hydrolysis as well as resynthesis (that is, "turnover") on the other might be expected because of the low Michaelis constant (K_m) for ATP required for activation of ATP hydrolysis by the enzymes of contractile proteins (17).

Total adenine nucleotides in ischemia. Loss of total adenine nucleotides follows their irreversible degradation during ischemia, as previously observed in ischemic and reperfused myocardium both of the dog (3,15,18) and the rat (1,16). In our present study we observed that the ischemic heart tolerates a modest (approximately 20%) loss of total adenine nucleotides, while a greater loss (approximately 50%) is no longer compatible with recovery. As a result of the action of adenylate kinase, the loss of adenine nucleotides can be directly translated into a loss of ATP. Our data are roughly in agreement with data obtained in the ischemic dog heart (15), where irreversible tissue damage

Figure 4. Lack of correlation between cardiac performance and tissue content of adenosine triphosphate (ATP) **(top panel)** and phosphocreatine **(bottom panel)**. "Control" refers to hearts perfused for 45 minutes at an aortic afterload of 100 mm H_2O; ischemic hearts were subjected to 5, 10 or 20 minutes of global ischemia and then reperfused for 10 minutes. Each data point represents an individual experiment. Note that the ATP content varied over a wide range for a given level of functional recovery. Linear regression analysis was performed for each cluster of ATP values. See text for details. $\overline{AoP} \times C.O.$ = mean aortic pressure × cardiac output.



seems to coincide with ATP content of less than 40% of normal values.

Phosphocreatine content in ischemia. In contrast to the low tissue content of ATP and alanine nucleotides, a low tissue content of phosphocreatine has no predictive value for recovery of mechanical function and restoration of oxidative metabolism. A return of function was associated with a rapid restoration of phosphocreatine levels. The resynthesis of phosphocreatine by oxidative metabolism is in agreement with observations by others (1,3,13,18,19) and probably relates to preservation of the inner mitochondrial membrane during reperfusion of mildly ischemic heart muscle (3). The inner mitochondrial membrane also exerts a regulatory function on the transport of long-chain fatty acids into the mitochondrial matrix through the carnitine-acyltransferase system (20). In an ischemic heart most of the coenzyme A and carnitine are converted to their long-chain acyl derivatives. High levels of acyl-carnitine, as they occur with severe ischemia, may have a detergent effect on the inner mitochondrial membrane and lead to its functional disintegration.

Lactate levels. The inner mitochondrial membrane is also the site of citric acid cycle and respiratory chain enzymes. Not surprisingly, the functional integrity of the enzymes of oxidative metabolism in reversibly ischemic myocardium is reflected by the disappearance of lactate through washout and oxidation on reperfusion. In viable myocardium most of the lactate produced during ischemia is reoxidized in situ on reperfusion, as demonstrated by the observation that lactate levels decrease in hearts during functional recovery. However, lactate remains high in hearts that do not resume function on reperfusion after 20 minutes of ischemia and is not readily washed out by the reestablished coronary flow. Furthermore, the lactate/pyruvate ratio, which reflects the redox state of the cytosol (11), returned to normal in hearts that recovered from ischemia, indicating oxidation of reducing equivalents by the respiratory chain.

Conclusions. Ischemia leads to a decrease in the energy-rich phosphate compounds, phosphocreatine and ATP, while functional recovery on reperfusion is associated with a return of oxidative metabolism, but not with a normalization of the steady state ATP content in the tissue. In contrast to ATP, phosphocreatine increases to normal and even above control values on reperfusion of reversibly ischemic myocardium in association with return of function. Failure to recover function is associated with a severe loss of all adenine nucleotides and lack of phosphocreatine resynthesis and lactate oxidation. It appears that integrity of the pathways of oxidative metabolism, but not steady state ATP levels, determines the return of function after ischemia.

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