Metabolic changes in the acutely ischemic heart

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Abstract

The onset of ischemia is associated with dramatic alterations in cardiac energy metabolism. A mismatch between oxygen demand and oxygen supply to the heart muscle results in a decrease in mitochondrial oxidative metabolism, leading to an energy deficient state in the heart muscle. Glycolysis (which does not require oxygen) accelerates during ischemia in an attempt to increase adenosine triphosphate (ATP) production, although this is associated with the accumulation of by-products of glycolysis, including lactate and hydrogen ions (H^+'s). During ischemia, there are also changes in the source of energy substrate used to support residual mitochondrial oxidative metabolism. These metabolic changes include an increase in the contribution of cardiac fatty acid oxidation to residual mitochondrial oxidative metabolism and a decrease in glucose oxidation. Low glucose oxidation accompanied by increased glycolysis results in an uncoupling of glycolysis from glucose oxidation, and the accumulation of lactate and H^+'s. Reperfusion after ischemia lessens the mismatch between oxygen demand and oxygen supply to the heart muscle. However, fatty acid oxidation as a source of energy increases at the expense of glucose oxidation. This continues to uncouple glycolysis from glucose oxidation, resulting in a continued decrease in cardiac efficiency, which can contribute to myocardial injury. Therapeutic strategies that inhibit fatty acid oxidation and increase glucose oxidation can decrease the severity of ischemic injury. ■ *Heart Metab*. 2016;70:32-35

Keywords: glycolysis; ischemia; reperfusion

Introduction

The heart has a very high energy demand, due to the need to continuously produce energy (in the form of adenosine triphosphate [ATP]) to sustain contractile function. The majority of this energy is obtained from mitochondrial oxidative phosphorylation, a process requiring a considerable amount of oxygen.[1] Indeed, although the heart normally makes up less than 0.5% of the body weight, it uses more than 5% of the oxygen consumed by the body. Mitochondrial oxidative phosphorylation in the heart utilizes various energy substrates—which include fatty acids, glucose, lactate, amino acids, and ketone bodies—to generate ATP. The contributions of each energy substrate to ATP generation are tightly regulated, and there is a significant degree of plasticity and interdependence between energy substrates. Under normal physiological conditions, fatty acids and carbohydrates (ie, glucose and lactate) represent the primary metabolic fuels that sustain cardiac function, and upwards of 95% of ATP production is attributable

to mitochondrial oxidative phosphorylation (*Figure 1*).[1] The remainder of this ATP production (approximately 5%) originates from glycolysis, which can produce ATP without the consumption of oxygen.

Myocardial ischemia in the heart arises as a result of a decreased oxygen supply to the heart (eg, such as by a blockage of a coronary artery) and/or an increased demand of oxygen to the heart (ie, increased workload) that outstrips the oxygen supply to the heart. Both during and after ischemia there are dramatic alterations in energy metabolism in the heart.

Energy metabolism in the ischemic heart

In the ischemic myocardium, mitochondrial oxidative phosphorylation decreases, and because there are essentially no reserves of energy in the heart, there is a depletion of high energy phosphates.[2,3] Although there is an initial transfer of phosphates from phosphocreatine to ATP (via creatine kinase) in an attempt to preserve ATP levels, this is not enough to maintain ATP levels, and in severely ischemic hearts, a depletion of myocardial ATP occurs.[2]

During ischemia, glycolysis accelerates and becomes a very important source of energy, owing to its ability to generate ATP in the absence of oxygen (O_2) (*Figure 1B*). Glucose from intracellular intramyocardial stores of glycogen is also mobilized during ischemia.[2] Although this additional ATP production from glycolysis may be sufficient to maintain/correct ionic homeostasis during mild to moderate ischemia, the hydrolysis of glycolytically derived ATP uncoupled from subsequent pyruvate oxidation leads to the increased generation of hydrogen ions (H^+'s), which can result in a decrease in intracellular pH within the ischemic myocardium.[4] Because pyruvate cannot be oxidized by the mitochondria, it is converted to lactate, resulting in an increased lactate production by the heart. In the presence of severe ischemia, the H^+'s and lac-

A) Aerobic heart

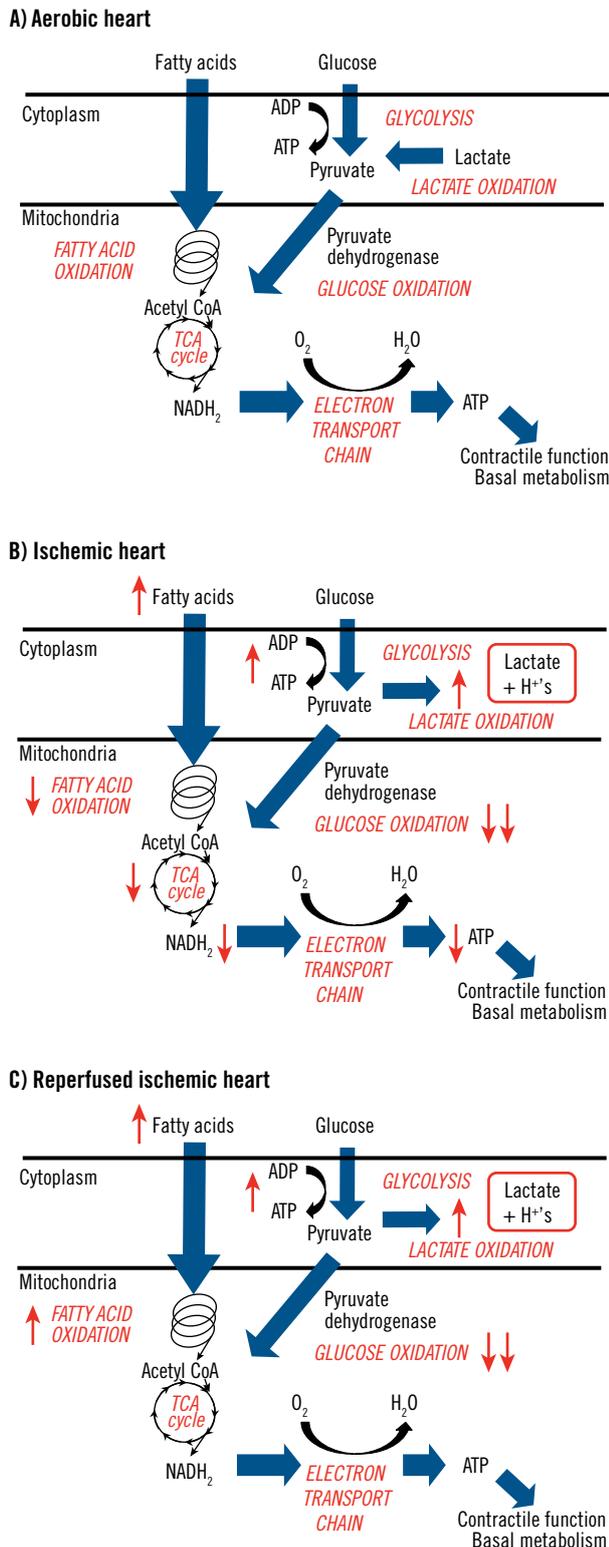**B) Ischemic heart**

C) Reperfused ischemic heart

Fig. 1 *Alterations in myocardial energy metabolism during and after ischemia.*
(A) In the aerobic heart, mitochondrial fatty acid oxidation and glucose oxidation are the major sources of energy production. In contrast, glycolysis provides less than 5% of ATP production. (B) During ischemia, mitochondrial oxidative metabolism decreases and glycolysis becomes a more important source of energy production. Fatty acids dominate as the substrate for residual oxidative metabolism. The increase in glycolysis and decrease in glucose oxidation results in the production of both lactate and H^+'s. (C) During reperfusion, mitochondrial oxidative metabolism recovers, but fatty acid oxidation dominates as the source of ATP production, due to increased plasma levels of fatty acids and decreased control of mitochondrial fatty acid uptake. Glucose oxidation rates remain low in reperfusion. Since glycolysis remains elevated, the uncoupling of glycolysis from glucose oxidation persists during reperfusion, leading to an increase in H^+ and lactate production, which can decrease cardiac efficiency and cardiac function.
Abbreviations: *ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoA, Coenzyme A; H^+, hydrogen ion; H_2O, water; $NADH_2$, NADH dehydrogenase subunit 2; O_2, oxygen; TCA, tricarboxylic acid.*

tate produced from glycolysis are not removed, which eventually leads to an inhibition of glycolysis in order to prevent further accumulation of these glycolytic by-products.[1,2] These effects can further aggravate disturbances in ionic homeostasis. As glycolysis only provides a small fraction of ATP compared with that provided by the oxidation of carbohydrates and fatty acids, its ability to maintain ionic homeostasis during ischemia is finite.

Mitochondrial ATP production during ischemia decreases in proportion to the decrease in oxygen supply to the heart. However, the source of energy substrate for any residual mitochondrial oxidative metabolism can dramatically change. Due to increased fatty acid supply to the heart and alterations in the control of mitochondrial fatty acid uptake, the oxidation of fatty acid dominates as the main residual source of ATP production, and glucose oxidation decreases.[5] This decrease in glucose oxidation, coupled with the increase in glycolysis, results in a further uncoupling of glycolysis from glucose oxidation, which increases the production of both lactate and H+'s.[6,7] This contributes to a decrease in cardiac efficiency, as ATP is directed away from contractile processes to deal with the intracellular H+ accumulation.[7] As a result, myocardial ischemia not only compromises cardiac ATP production, but also decreases the efficiency of using ATP for muscle contraction.

Energy metabolism during reperfusion after ischemia

If previously ischemic myocardium is reperfused in a timely manner (such as by mechanical revascularization or by use of thrombolytic agents), the increased delivery of oxygen to the heart results in a recovery of mitochondrial oxidative phosphorylation. However, during this period, rates of fatty acid oxidation recover to a greater extent than rates of glucose oxidation.[7,8] This occurs because the heart is exposed to elevated circulating levels of fatty acids (a consequence of ischemic stress) and due to alterations in the subcellular control of fatty acid oxidation.[1] These high levels of fatty acid oxidation decrease the rate of recovery of glucose oxidation, due to a phenomenon called the "Randle Cycle" (*Figure 1C*).[9] At the same time, glycolysis rates remain high in the early period of postischemic reperfusion.[7] This results in a continued uncoupling of the rates of glycolysis and glucose oxidation, despite the restoration of coronary flow and hence O$_2$ delivery. This results in a continued production of both H+'s and lactate in the reperfusion period (*Figure 1C*). The continued production of H+'s during reperfusion[7] contributes to the altered ionic homeostasis and decreased cardiac efficiency that occurs after ischemia.[6,7,10,11] In addition to high fatty acid oxidation rates during reperfusion contributing to an uncoupling of glucose oxidation from glycolysis, high rates of fatty acid oxidation are less efficient as an energy substrate (in terms of O$_2$ consumed/ATP produced),[12] which also contributes to a decrease in cardiac efficiency seen during reperfusion.[1,6,7] This decrease in cardiac efficiency contributes to a decreased contractile function during the reperfusion period.

Switching from fatty acid to glucose oxidation during and after ischemia

Optimizing energy substrate metabolism both during ischemia and during reperfusion after ischemia is a novel strategy to preserve mechanical function and efficiency and to enhance the recovery of postischemic function. This includes pharmacological approaches that shift the balance from the oxidative utilization of fatty acid toward carbohydrate oxidation. In particular, inhibition of fatty acid oxidation and direct stimulation of glucose oxidation are potentially promising anti-ischemic interventions. Inhibition of fatty acid oxidation during ischemia can switch any residual oxidative metabolism from fatty acid oxidation to glucose oxidation, and inhibition of fatty acid oxidation during reperfusion after ischemia decreases the high rates of fatty acid oxidation seen after ischemia.[5-7,13] During both ischemia and reperfusion after ischemia, inhibition of fatty acid oxidation results in a stimulation of glucose oxidation, which can improve the coupling between glycolysis and glucose oxidation.[7] This decreases both H+ and lactate production, leading to an increase in cardiac efficiency, a decrease in tissue injury, and an increase in contractile function.

Presently, there is only one clinically available drug that uses a direct metabolic approach to inhibit fatty acid oxidation and stimulate glucose oxidation in the heart. Trimetazidine inhibits the fatty acid oxidation enzyme 3-ketoacyl CoA thiolase, resulting in an inhibition of fatty acid oxidation.[13,14] Inhibition of fatty acid oxidation by trimetazidine has been observed in both

experimental[13,14] and clinical studies.[15] This results in an increase in glucose oxidation both during and after ischemia,[13,14] which decreases the severity of pH changes during ischemia[16] and improves contractile function. This metabolic action can explain the beneficial effects of trimetazidine in the clinical setting of ischemia.[17-19]

Conclusions

Dramatic alterations in energy metabolism occur in the heart during and after ischemia. High glycolysis rates accompanied by low mitochondrial glucose oxidation rates result in a decrease in cardiac efficiency and depressed contractile function. Stimulating glucose oxidation by inhibiting fatty acid oxidation can improve both cardiac efficiency and function, and therefore protect the ischemic heart. ■

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