

# Cardiac energy metabolism in mild and severe ischemia

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## Abstract

The heart must continuously produce large amounts of adenosine triphosphate (ATP) to maintain contractile function. The majority of this cardiac ATP is derived from mitochondrial oxidative phosphorylation, a process that consumes large amounts of oxygen. Ischemia results in a mismatch between oxygen demand and oxygen supply to the heart, which, in turn, results from a decrease in mitochondrial oxidative phosphorylation and an energy deficient state in the heart muscle. The magnitude of the decrease in mitochondrial oxidative phosphorylation during ischemia depends on the severity of ischemia and the degree to which oxygen supply is impaired. Glycolysis (which does not require oxygen) accelerates during ischemia in an attempt to increase ATP production. During ischemia, there are also changes in the source of energy substrate used to support residual mitochondrial oxidative phosphorylation, which includes an increase in the contribution of fatty acid oxidation, a decrease in glucose oxidation, and residual mitochondrial oxidative metabolism. Increased glycolysis accompanied by a decrease in glucose oxidation during ischemia results in an accumulation of H<sup>+</sup> and lactate. Accumulation of these glycolytic byproducts decreases cardiac efficiency and adds to the severity of the oxygen supply-demand mismatch seen during ischemia. Therapeutic strategies that inhibit the contribution of fatty acid oxidation to residual mitochondrial oxidative metabolism will result in an increase in glucose oxidation, an improved coupling between glycolysis and glucose oxidation, a decrease in glycolytic byproduct accumulation, an increase in cardiac efficiency, and a decrease in the severity of ischemic injury. ■ *Heart Metab.* 2018;75:33-36

**Keywords:** fatty acid oxidation; glucose oxidation; glycolysis

## Introduction

The heart must produce large amounts of energy, in the form of adenosine triphosphate (ATP), to maintain contractile function. Under aerobic conditions, approximately 5% of this ATP production originates from glycolysis, with the remaining 95% originating from mitochondrial oxidative phosphorylation.<sup>1</sup> The production of ATP by the mitochondria requires a considerable amount of oxygen to

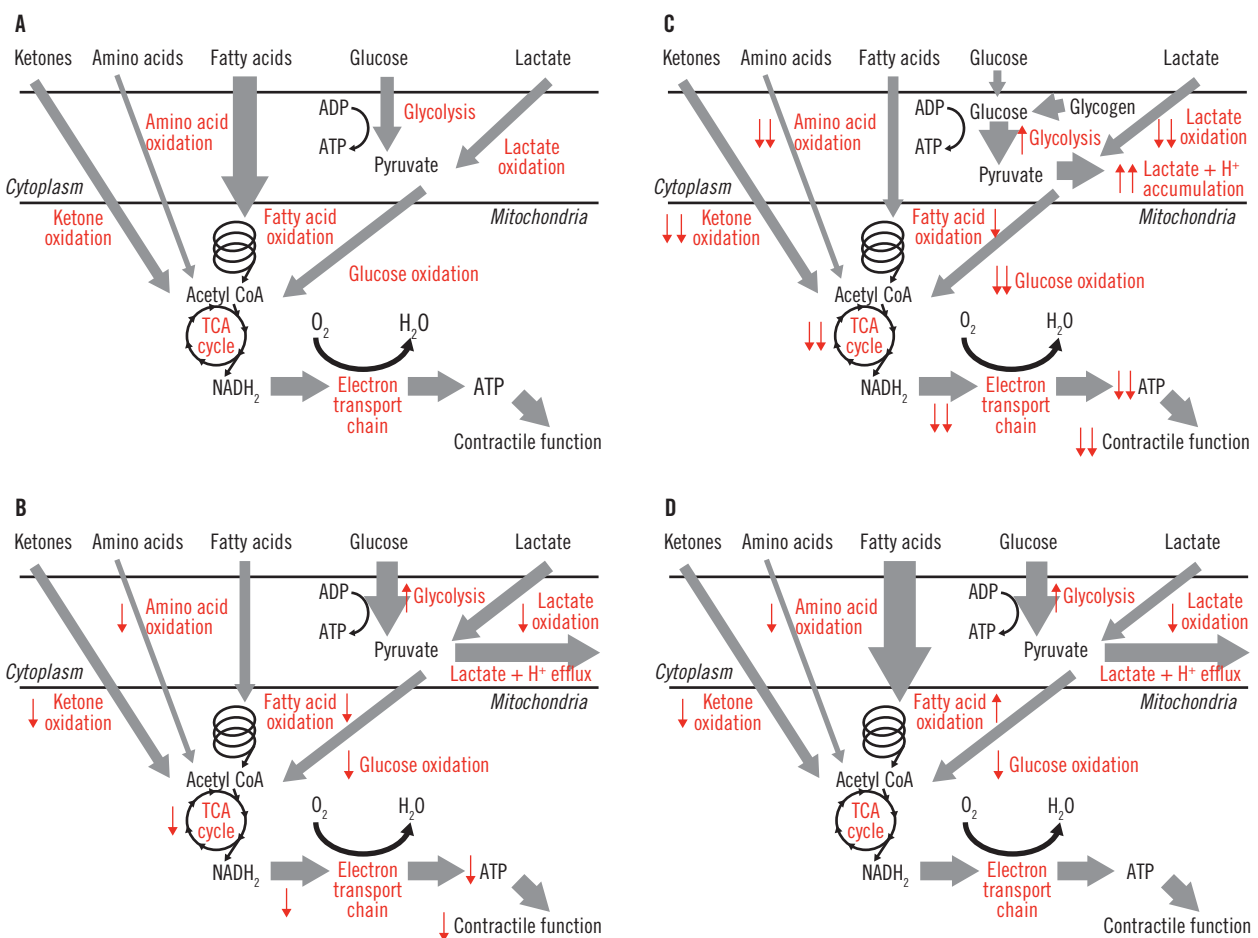
metabolize a number of different energy substrates, including fatty acids, glucose, lactate, amino acids, and ketones (*Figure 1A*). There are no significant energy reserves in the heart, and the demand of the heart muscle for ATP to sustain contractile function must be met primarily by the continuous and rapid synthesis of ATP by the mitochondria.

Myocardial ischemia is a major health problem worldwide and results from a decreased oxygen supply to the heart (such as by a blockage of a coronary

artery) and/or an increased demand of oxygen to the heart (ie, increased workload) that is not met by an increased oxygen supply to the heart (such as seen with angina pectoris). Myocardial ischemia disrupts normal oxygen delivery to the heart, resulting in impaired mitochondrial oxidative phosphorylation, which decreases mitochondrial ATP production, resulting in an energy deficiency in the heart. This decreased energy production compromises cardiac contractile function, and, in the presence of severe ischemia, can lead to myocyte cell death. This “Refresher Corner” article reviews the cardiac energy metabolic changes that occur in the heart during both mild and severe ischemia.

**Cardiac energy metabolic changes during mild ischemia**

Oxygen is consumed by the mitochondria primarily at the level of the electron transport chain, which is coupled to the phosphorylation of adenosine diphosphate to form ATP (hence the term oxidative phosphorylation). In the presence of mild ischemia, a decreased oxygen supply decreases mitochondrial oxidative phosphorylation, resulting in a decrease in ATP synthesis.<sup>2,3</sup> The entry of NADH and FADH<sub>2</sub> into the electron transport chain is decreased, resulting in a build-up of these nucleotides



**Fig. 1** Alterations in myocardial energy metabolism during and following ischemia. **Panel A.** In the aerobic heart, mitochondrial fatty acid oxidation and glucose oxidation are the major sources of energy production in the heart; whereas, glycolysis provides <5% of ATP production. **Panel B.** During mild 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 H<sup>+</sup> and lactate. **Panel C.** In severely ischemic hearts, mitochondrial oxidative phosphorylation is markedly impaired due to a limitation in oxygen supply. Glucose uptake also decreases due to a decrease in glucose supply from the coronary circulation. However, glucose supply for glycolysis is increased due to an increase in glycogenolysis. The uncoupling of glycolysis from glucose oxidation and lack of coronary flow results in an accumulation of H<sup>+</sup> and lactate in the myocardium. **Panel D.** During reperfusion or reversibly injured severely ischemic hearts, 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 into reperfusion, leading to an increase in H<sup>+</sup> and lactate production, which can decrease cardiac efficiency and cardiac function.

in the mitochondria, which feedback and inhibit the pathways involved in their synthesis; ie, the tricarboxylic acid cycle and the metabolic pathways of oxidative metabolism. As a result, the oxidation of the two main carbon substrates, fatty acids and glucose, decreases during mild ischemia (*Figure 1B*).

The decrease in mitochondrial ATP production during mild ischemia is accompanied by an increase in glycolysis, which can generate ATP in the absence of  $O_2$  (*Figure 1B*). The glucose for glycolysis during mild ischemia originates from both extracellular glucose and from an increased mobilization of glucose from intracellular glycogen stores.<sup>2</sup> While the glycolytically derived ATP provides an additional source of energy during ischemia, it cannot completely compensate for the loss of mitochondrial ATP production, since glycolysis only produces 2 ATP molecules per molecule of glucose passing through glycolysis (compared with the 30 ATP molecules produced per molecule of glucose oxidized).

While glycolysis increases during mild ischemia, mitochondrial glucose oxidation is impaired.<sup>1</sup> The consequence of the increased glycolytically derived ATP uncoupled from subsequent glucose oxidation is an increased generation of  $H^+$  and lactate, which can result in a decrease in intracellular pH within the ischemic myocardium.<sup>4</sup> The accumulation of  $H^+$  results in disturbances in ionic homeostasis during ischemia (eg, by increasing  $Na^+$  influx into the cardiomyocytes during ischemia), which can lead to a decrease in cardiac efficiency (ie, cardiac work/ $O_2$  consumed), since ATP is consumed in order to reestablish this ionic imbalance.

During a mild ischemic episode, mitochondrial ATP production decreases in proportion to the decrease in oxygen supply to the heart. However, the proportion of fatty acid and glucose used for residual mitochondrial oxidative metabolism changes. During ischemia, blood levels of fatty acids increase and there are alterations in the control of mitochondrial fatty acid uptake.<sup>1</sup> As a result, fatty acid oxidation dominates as the main residual source of ATP production, which occurs at the expense of a greater decrease in glucose oxidation.<sup>5</sup> This decrease in glucose oxidation contributes to an uncoupling of glycolysis from glucose oxidation, which increases the production of both  $H^+$  and lactate.<sup>6,7</sup> This increase contributes to a decrease in

cardiac efficiency, as ATP is directed away from contractile processes to deal with the intracellular  $H^+$  accumulation.<sup>7</sup> As a result, myocardial ischemia not only compromises cardiac ATP production, it also decreases the efficiency of using ATP for muscle contraction.

### Cardiac energy metabolism during severe ischemia

During a severe decrease in coronary flow, both oxygen supply and energy substrate supply to the myocardium are decreased, which dramatically decreases mitochondrial oxidative phosphorylation and ATP production. A decrease in glucose supply to the heart also results in a dramatic mobilization of glucose from endogenous glycogen stores in an attempt to maintain the myocardial glucose supply for glycolysis (*Figure 1C*). Increased glycolysis and a marked impairment in mitochondrial glucose oxidation result in an increased production of  $H^+$  and lactate in the heart. Since coronary flow is markedly reduced, these glycolytic by-products accumulate in the myocardium, resulting in a drop in cellular pH, which can lead to cell death. The accumulation of  $H^+$  in severely ischemic heart muscle eventually feedbacks and inhibits glycolysis in an attempt to prevent the further accumulation of  $H^+$ .

If previously reversibly injured ischemic myocardium is reperfused (eg, by mechanical revascularization or using thrombolytic agents after a myocardial infarction), mitochondrial oxidative phosphorylation recovers as oxygen is reintroduced. However, mitochondrial fatty acid oxidation recovers to a greater extent than the rates of glucose oxidation (*Figure 1D*),<sup>7,8</sup> which occurs due to hearts being exposed to increased fatty acids in the coronary circulation and to the alterations in the subcellular control of fatty acid oxidation.<sup>1</sup> The high levels of fatty acid oxidation decrease the rate of recovery of glucose oxidation (*Figure 1D*).<sup>9</sup> Glycolysis rates remain high in the early period of reperfusion postischemia, resulting in a continued uncoupling of glycolysis and glucose oxidation,<sup>7</sup> which results in a continued production of both  $H^+$  and lactate in the reperfusion period, contributing to continued alterations in ionic homeostasis and decreased cardiac efficiency following ischemia.<sup>6,7,10,11</sup> This decrease in cardiac efficiency contributes to a decreased contractile function into the reperfusion period.

### Inhibition of fatty acid oxidation and stimulation of glucose oxidation as an approach to treat myocardial ischemia

In mild ischemia, one therapeutic strategy is to increase glucose oxidation to improve coupling of glycolysis to glucose oxidation; this can be achieved by inhibiting residual fatty acid oxidation or directly stimulating with glucose. Inhibition of fatty acid oxidation during mild ischemia switches any residual oxidative metabolism from fatty acid oxidation to glucose oxidation, while inhibition of fatty acid oxidation during reperfusion following severe ischemia decreases the high rates of fatty acid oxidation seen postischemia.<sup>5-7,12</sup> During both ischemia and reperfusion following ischemia, inhibiting fatty acid oxidation will increase glucose oxidation, which can improve the coupling between glycolysis and glucose oxidation,<sup>7</sup> which decreases both H<sup>+</sup> and lactate production, leading to an increase in cardiac efficiency, a decrease in tissue injury, and an increase in contractile function. An example of a clinically available drug that inhibits fatty acid oxidation and stimulates glucose oxidation in the heart is trimetazidine.<sup>13-15</sup> Inhibition of fatty acid oxidation by trimetazidine increases glucose oxidation both during and following ischemia,<sup>13,14</sup> which decreases the severity of pH changes during ischemia<sup>16</sup> and improves contractile function. This metabolic action may explain the beneficial effects of trimetazidine in the clinical setting of ischemia.<sup>17-19</sup>

### Conclusions

Dramatic alterations in energy metabolism occur in mildly and severely ischemic hearts. High glycolysis rates accompanied by low mitochondrial glucose oxidation rates result in a decrease in cardiac efficiency and a 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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