

# Impact of fatty acid oxidation on cardiac efficiency

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## Abstract

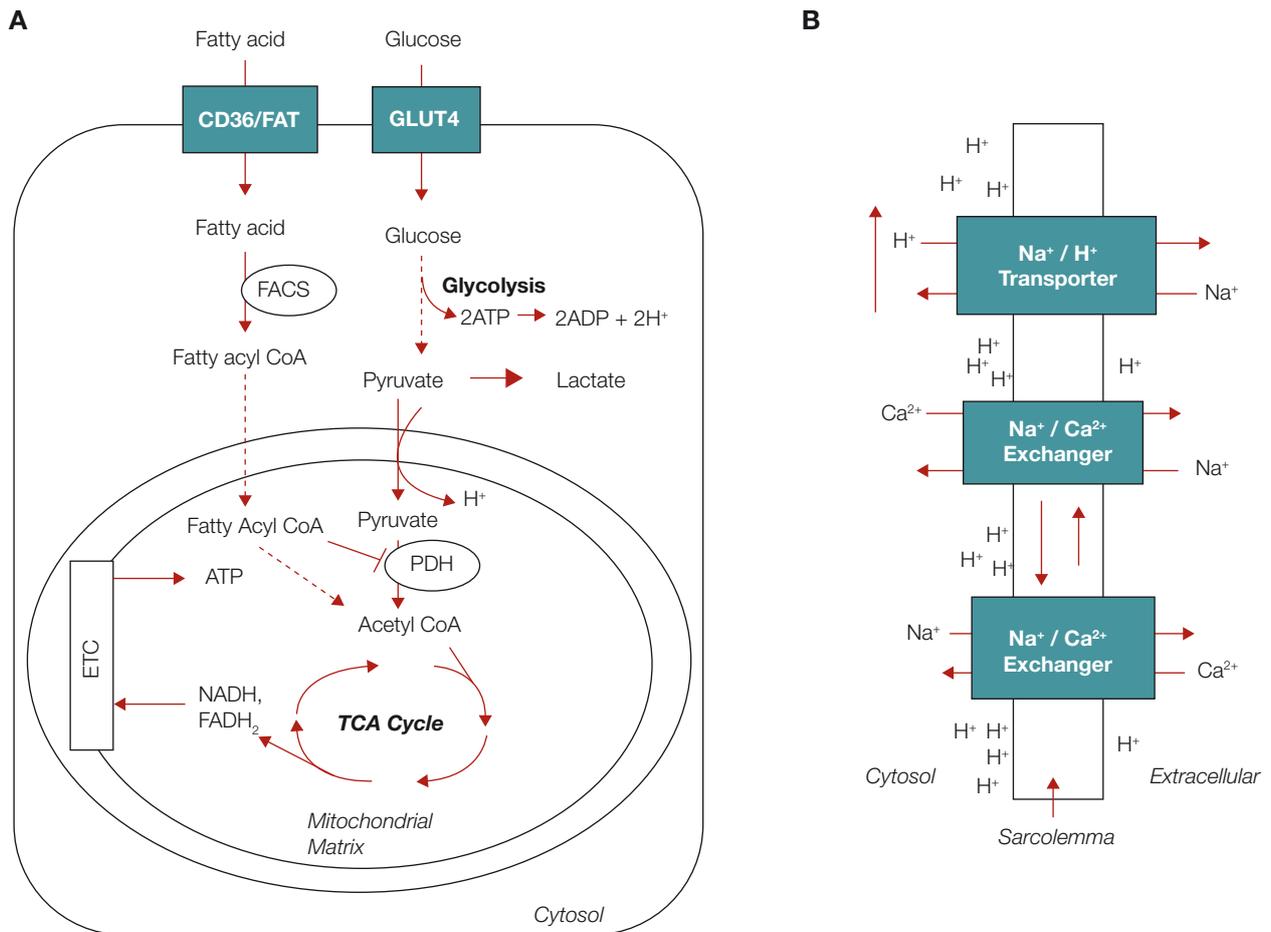
Alterations in energy substrate preference by the heart can lead to significant changes in cardiac efficiency. Cardiac efficiency, which is the amount of work produced by the heart per energy ( $O_2$ ) consumed, is dependent not only on the efficiency of producing energy (ATP), but also on the efficiency of using energy to produce contractile work. Using fatty acids as a source of fuel has the potential to alter both of these pathways. The mitochondrial oxidation of fatty acids utilizes more  $O_2$  per molecule of ATP produced than most other sources of fuel. High rates of fatty acid oxidation also inhibit glucose oxidation in the heart, which can result in alterations in ionic homeostasis, such that more of the ATP produced in the heart is used for non-contractile purposes. Combined, the excessive use of fatty acids by the heart can result in a significant decrease in cardiac efficiency. In certain heart pathologies, such as during and following ischemia or in the failing heart, cardiac efficiency is also decreased. Alterations in the balance between fatty acid and carbohydrate use contribute to these alterations in cardiac efficiency. In this review we will focus on how alterations in cardiac energy metabolism alter cardiac efficiency, as well as on how alterations in energy metabolism that occur in heart failure and ischemia result in decreased cardiac efficiency.

**Keywords:** fatty acid  $\beta$ -oxidation; uncoupling proteins; mitochondrial thioesterase; glucose oxidation; glycolysis

■ Heart Metab. (2011) 53:33–37

## Introduction

The heart has a very high energy demand, while essentially having no energy reserves. For example, consumption of the main energy currency of the heart, adenosine triphosphate (ATP), is so high that in the contracting heart the entire pool of ATP turns over approximately 6 to 8 times a minute [1]. In order to produce this large amount of ATP, the heart consumes a number of different energy substrates, including fatty acids (FAs), glucose, lactate, ketones, pyruvate, and amino acids. Most of the ATP produced requires the consumption of  $O_2$  for mitochondrial oxidative metabolism (Fig. 1) [1]. However, the efficiency of producing ATP can vary dramatically depending on the type of energy substrate used. An example of this is the utilization of FAs, which while being a plentiful source of energy, is also a particularly inefficient source of energy [1]. Different cardiac pathologies can also alter cardiac efficiency, both as a result of a decreased efficiency of producing ATP or alterations in the efficiency of using ATP to produce contractile work [1].



**Fig. 1** Cardiac efficiency is decreased by elevated glycolysis and fatty acid oxidation. **A.** Elevated fatty acid oxidation can reduce cardiac efficiency through a number of mechanisms including inhibition of glucose oxidation and increasing glycolysis. Fatty acyl CoA inhibits PDH, thereby inhibiting glucose oxidation. Under certain conditions glycolysis can become elevated to make up for reduced oxidative metabolism. Protons accumulate because the co-transport of protons with pyruvate into the mitochondria is decreased and cause acidosis. Acidosis can decrease contractile force by decreasing the responsiveness of myofilaments to calcium. The use of ATP for ionic homeostasis can reduce cardiac efficiency. **B.** Return of intracellular pH (low pH caused by uncoupled elevated glycolysis) to normal upon reperfusion decreases cardiac efficiency by affecting ionic homeostasis. A large trans-sarcolemmal proton gradient forms that increases the exchange of the  $\text{Na}^+/\text{H}^+$  transporter resulting in further elevation of intracellular  $\text{Na}^+$ . In response, the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger works in reverse mode, moving calcium into the cell. This results in an overload of intracellular calcium. More energy is expended maintaining calcium homeostasis. PDH pyruvate dehydrogenase

Cardiac efficiency is often expressed as a measure of the amount of cardiac work produced per amount of energy ( $\text{O}_2$ ) consumed by the heart (cardiac work/ $\text{MVO}_2$  ratio) [2]. It is not surprising that alterations in energy metabolism can alter cardiac efficiency, since cardiac work requires ATP and production of ATP via mitochondrial oxidative metabolism requires  $\text{O}_2$ . The type of substrate utilized in the production of ATP via oxidative metabolism affects cardiac efficiency. In addition, metabolic by-products produced during ATP production also have the potential to alter cardiac efficiency.

### Energy metabolism and cardiac efficiency

#### Efficiency of ATP production

A major determinant of cardiac efficiency is the type of fuel being utilized for ATP production. The efficiency with which FAs and glucose are utilized to produce ATP differs [1]. The production of 31 ATP by one glucose molecule going through glycolysis and glucose oxidation (GO) requires 6  $\text{O}_2$ . For the production of 105 ATP by palmitate oxidation, 23  $\text{O}_2$  are required. Therefore, more oxygen is used per ATP produced during fatty acid oxidation (FAO) compared to coupled GO, making FAs a

less efficient substrate than glucose for energy production. In addition, FAO inhibits GO [1]. When the FA supply to the heart rises, assuming  $O_2$  availability, the rate of FAO increases and GO decreases. This explains why under conditions in which circulating free FAs are elevated (such as heart failure [HF], ischemia, and type II diabetes) cardiac efficiency is decreased.

### Futile cycling

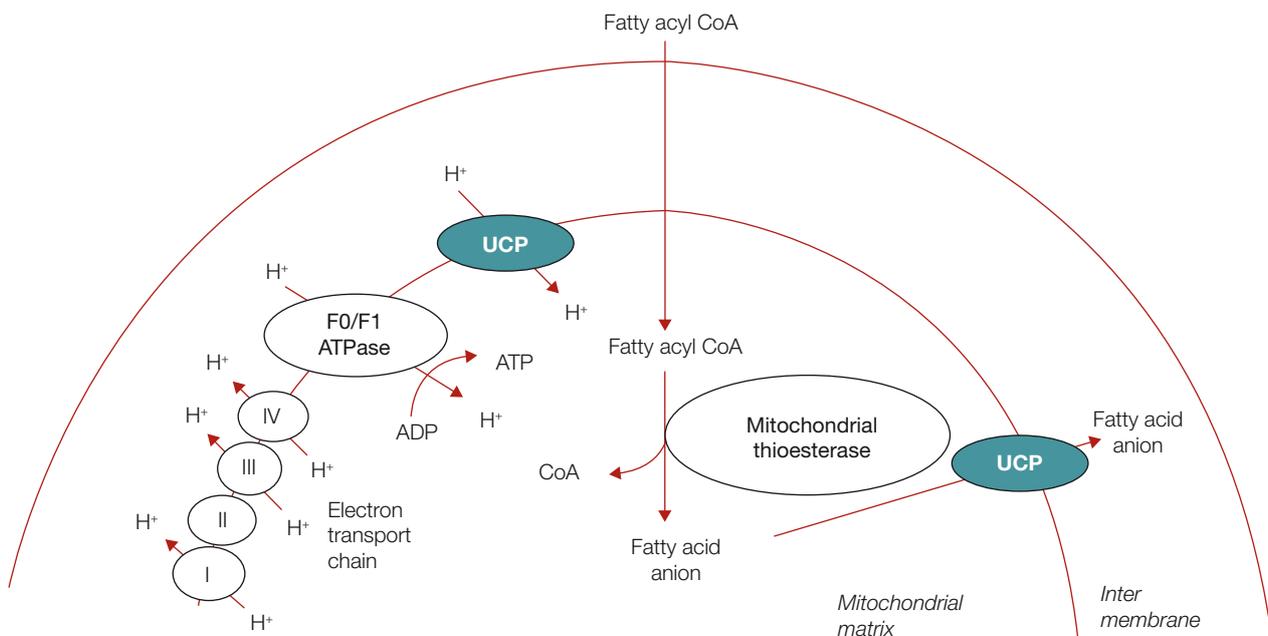
In addition to being less efficient at ATP production per  $O_2$  consumed, FAs can also decrease cardiac efficiency through a number of other mechanisms. This is evident from the fact that there is a large discrepancy between the degree of inefficiency observed in ATP production/ $O_2$  consumed, and actual measurements of cardiac efficiency in the heart (cardiac work/ $MVO_2$ ) [1]. At most, elevated FAO should decrease efficiency by 10 to 12% [1]. In reality, cardiac efficiency has been shown to be decreased by as much as 30% [3]. One possible mechanism to explain this is long-chain FA activation of  $Ca^{2+}$  channels in the sarcolemma [4]. A rise in cytosolic  $Ca^{2+}$  results in more energy being expended to keep cytosolic  $Ca^{2+}$  levels normal. Another mechanism that has been proposed involves FA inhibition of ATP removal from the mitochondria by inhibition of adenine nucleotide transferase [1]. Yet another potential mechanism involved in FA-induced inefficiency is the presence of futile cycles.

One such futile cycle involves the uncoupling proteins. The uncoupling proteins UCP2 and UCP3 are present in ventricular muscle [2]. These proteins are classically believed to work by dissipating the intermembrane proton gradient (Fig. 2). FAs are believed to work through UCP2 and UCP3 to mediate the uncoupling of oxidative phosphorylation [2,5]. Further, UCP2 and UCP3 expression correlate positively with circulating FA levels in the failing human heart [6]. UCP3 may also contribute to cardiac efficiency by transporting FA anions out of the mitochondrial matrix [2,7].

FAs in the cytoplasm can also cycle between their acyl-coenzyme A (CoA) moieties and intracellular triacylglycerol pools [1]. Two high energy phosphates are required to esterify FA to CoA, which can then either be directed to mitochondrial FA  $\beta$ -oxidation or complex lipid synthesis in the heart (such as triacylglycerols). FAs liberated from the triacylglycerol pool prior to subsequent  $\beta$ -oxidation create a futile cycle, potentially contributing to a decreased cardiac efficiency.

### Fatty acid inhibition of glucose oxidation

Another pathway by which FAs may decrease cardiac efficiency is secondary to GO inhibition [1]. FAO products can inhibit GO (i.e., the Randle Cycle) (Fig. 1). This FA inhibition of GO is more dramatic than the effects of FAs on glycolysis [1]. This can result in a scenario where glycolysis is uncoupled from GO, which



**Fig. 2** Mechanisms of uncoupling protein reduction of cardiac inefficiency. Uncoupling proteins dissipate the high proton concentration in the mitochondrial intermembrane space by transferring the hydrogen back into the mitochondrial matrix. UCP3 may also reduce cardiac efficiency by transferring fatty acid anions out of the mitochondrial matrix. CoA coenzyme A, UCP uncoupling protein

can result in elevated lactate and proton levels causing intracellular acidosis [2,8]. The co-transport of protons with pyruvate into the mitochondria is decreased because pyruvate is not taken into the mitochondria when glycolysis is uncoupled from GO. Although glycolysis produces ATP without consuming  $O_2$ , an increase in glycolysis in the presence of low GO rates can result in the accumulation of metabolic byproducts in the heart, that include both lactate and protons [1] (Fig. 1). The clearance of these protons can result in  $Na^+$  and  $Ca^{2+}$  accumulation in the heart (Fig. 1), requiring ATP to remove these ions [1]. This can lead to a decrease in cardiac efficiency, as ATP is redirected away from contractile function and towards ionic homeostasis [1].

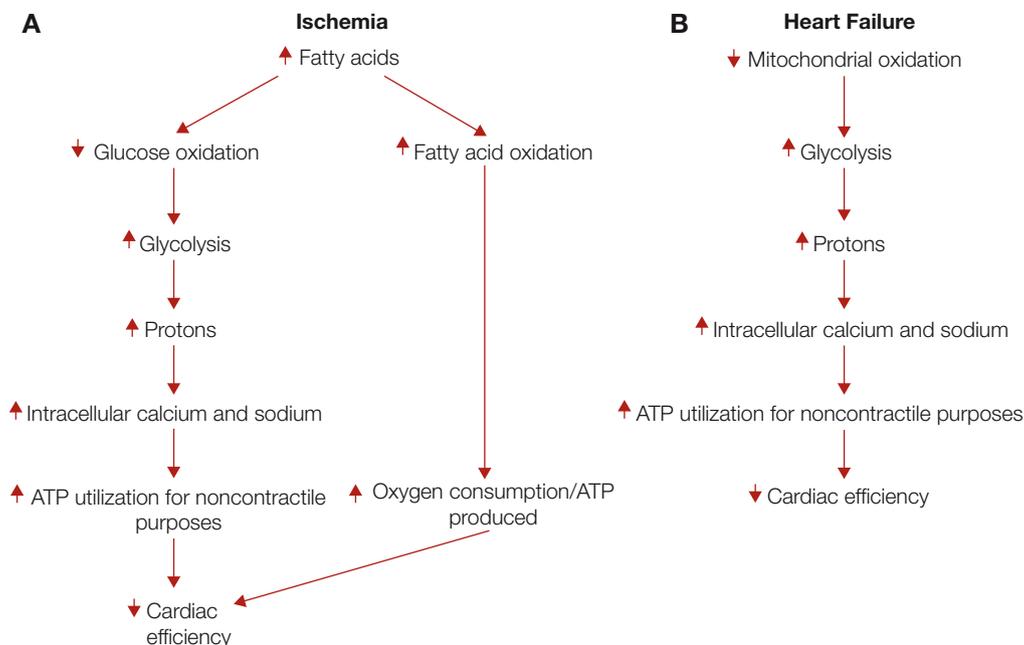
### Altered energy metabolism in ischemic heart disease

Prominent alterations in energy metabolism occur in the setting of myocardial ischemia and reperfusion that result in reduced cardiac efficiency (Fig. 3a) [1]. In the ischemic heart, energy metabolic rates are dependent upon the degree of ischemia. Because of the reduced oxygen availability both GO and FAO are reduced in the ischemic heart [2,9,10]. Interestingly, during mild ischemia FAO predominates as the source

of oxidative metabolism in the heart [2,11,12]. This is likely explained by the exposure of ischemic hearts to high plasma FAs and to direct changes in the intracellular control of FAO, which combine to inhibit GO [1,11]. It is important to note that unlike the normal heart, exposure of the ischemic heart to FAs does not inhibit glycolysis, and that glycolytic rates are increased in the ischemic heart [11].

Increased glycolysis and impaired GO in the ischemic heart result in lactate and proton accumulation in the ischemic myocardium. Indeed, uncoupling of glycolysis from GO can largely explain the acidosis observed in the severely ischemic heart. As described above, accumulation of protons can lead to  $Na^+$  and  $Ca^{2+}$  overload in the heart, resulting in decreased cardiac efficiency as ATP is used to attempt to restore ionic homeostasis [1].

Lack of recovery of cardiac function and efficiency upon reperfusion is also explained by the alterations in metabolism during ischemia and reperfusion [2,13,14]. Return of intracellular pH to normal upon reperfusion can be deleterious. This is because, by modulating the  $Na^+/H^+$  transporter and the  $Na^+/Ca^{2+}$  exchanger, changes in intracellular ion concentrations occur that contribute to impaired cardiac function and efficiency



**Fig. 3** Cardiac inefficiency in the ischemic heart and the failing heart. **A.** During ischemia and reperfusion fatty acid levels rise resulting in elevated fatty acid oxidation. This results in decreased glucose oxidation and elevated glycolysis. As a result of glycolysis and glucose oxidation being uncoupled, proton levels rise causing an overload of sodium and calcium. More energy is expended to maintain ionic homeostasis resulting in a decrease in cardiac efficiency. Through other mechanisms, fatty acids also reduce cardiac efficiency. **B.** In heart failure, a reduction in overall oxidative metabolism results in elevated uncoupled glycolysis resulting in decreased cardiac efficiency through similar mechanisms as described for ischemia

[2]. The large trans-sarcolemmal proton gradient that forms increases the exchange of the  $\text{Na}^+/\text{H}^+$  transporter resulting in further elevation of intracellular  $\text{Na}^+$ . In response, the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger reverse mode is activated. The movement of calcium into the cell via the  $\text{Na}^+/\text{Ca}^{2+}$  exchanger results in an overload of intracellular calcium and thus more energy being expended to maintain calcium homeostasis.

As would be expected, cardiac efficiency and function is reduced in mildly ischemic hearts exposed to high levels of FAs [11]. If a heart is subjected to global ischemia, FA  $\beta$  oxidation decreases secondary to a lack of  $\text{O}_2$  availability for mitochondrial oxidative phosphorylation [15]. During reperfusion FAO recovers, resulting in GO remaining low [2,8,13,14]. Therefore, while glycolysis can remain high during reperfusion, it can still be uncoupled from GO resulting in elevated lactate and proton production [2,13]. Changes in FA supply, the type of oxidative metabolism, and increased glycolysis are responsible for the cardiac inefficiency observed during ischemia and reperfusion.

### Energy metabolism and cardiac efficiency in heart failure

Alterations in energy substrate metabolism accompanying HF are extremely complex, in part due to the heterogeneous nature of HF [1]. In general, however, as HF progresses, what is observed is a decrease in overall mitochondrial oxidative capacity and an increase in glucose uptake and glycolysis [1]. FAO rates have been shown to be elevated, unchanged or decreased in HF (see [1] for review). The increase in glycolysis in HF is an adaptive response to compensate for decreased mitochondrial oxidative capacity. This increase in glycolysis with a low mitochondrial capacity to oxidize glucose can exacerbate lactate and proton production, in a manner similar to that seen in the ischemic heart (Fig. 3b). Since FAO competes with GO, FAs can further exacerbate this uncoupling. Support for this concept comes from a number of clinical studies in which FAO inhibition in HF improved both cardiac efficiency and function.

### Conclusions

Alterations in cardiac energy metabolism can profoundly affect cardiac efficiency. Excessive use of FAs has been shown to be especially important, either by decreasing the efficiency of producing ATP, or by decreasing ATP availability for contractile function. Strategies aimed at

optimizing cardiac energy metabolism have the ability to improve cardiac efficiency and function. For example, the Randle cycle is being targeted in order to increase GO and decrease FAO [1]. Therefore, understanding how energy metabolism affects cardiac efficiency is important for improving the treatment of heart disease. •

**Acknowledgements** Gary D. Lopaschuk is a Scientist of the Alberta Heritage Foundation for Medical Research.

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