

# What fuels the failing heart?

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## Abstract

The heart has a very high energy demand that is met by ATP produced mainly from mitochondrial oxidative phosphorylation and, to a lesser extent, from glycolysis. Heart failure is associated with a decline in myocardial ATP production that leads to “energy starvation” that can contribute to contractile dysfunction. The compromised energetics in the failing heart result not only from impairment in mitochondrial function, but also to selective decreases in the type of fuel used by the mitochondria for ATP production. Due to compromised mitochondrial function, the failing heart shifts toward a greater reliance on glycolysis as a source of energy. However, this is accompanied by a decrease in the mitochondrial oxidation of pyruvate from glycolysis (ie, glucose oxidation), resulting in an increased production of lactate and H<sup>+</sup>s from glycolysis uncoupled from glucose oxidation. Although fatty acid oxidation is a major source of ATP production in the heart, the consensus on what happens to fatty acid oxidation in heart failure is lower. While it is generally believed that fatty acid oxidation decreases, a number of clinical and experimental studies suggest that fatty acid oxidation is either not changed or increased in heart failure. Ketones are also an important source of energy for the heart, and recent studies have shown that ketone oxidation is increased in the failing heart. Whether this increase is an adaptive or maladaptive metabolic change remains unclear. However, increasing evidence does suggest that increasing cardiac ATP production and/or modulating cardiac energy substrate preference positively correlates with heart function, which can lead to better outcomes. ■ *Heart Metab.* 2018;77:32-36

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

## Introduction

**H**eat failure is a major cause of death and disability, and presents a tremendous burden on society, the health care system, and the economy. While therapies to treat heart failure have improved substantially in the last decade, morbidity and mortality rates associated with heart failure remain high. This suggests that additional approaches need to be developed to prevent and treat heart failure. One such approach may be to optimize energy metabolism in the failing heart.<sup>1</sup> Substantial adverse alterations

in energy metabolism occur in the failing heart, and these changes can contribute to the severity of heart failure.<sup>1,2</sup> As a result, preventing or reversing these energy metabolic changes has the potential to improve heart failure outcomes. The purpose of this “Refresher Corner” article is to provide an overview of the energy metabolic changes that occur in the failing heart.

## Energy metabolism in the normal heart

The heart is an omnivore that metabolizes a variety of different energy substrates to meet its high energy

### Abbreviations

**BDH:**  $\beta$ -hydroxybutyrate dehydrogenase; **SCOT:** succinyl-CoA:3-ketoacid CoA transferase; **SGLT2:** sodium glucose cotransporter 2; **TCA:** tricarboxylic acid

demands, which include fatty acids, carbohydrates (glucose and lactate), ketones, and amino acids. Normally, fatty acid oxidation is the biggest contributor to ATP production ( $\approx 40\%$  to  $60\%$ ), followed by carbohydrate metabolism ( $\approx 20\%$  to  $30\%$ ) and ketone oxidation ( $\approx 10\%$  to  $20\%$ ) (Figure 1A). The majority of the ATP produced by the heart is generated from mitochondrial oxidation of these carbon substrates, with a small amount of ATP ( $\approx 2\%$  to  $8\%$ ) originating from cytoplasmic glycolysis. The heart has a “metabolic flexibility,” a virtue that allows it to switch between these energy substrates according to workload, availability of the energy substrates, and hormonal status.

### Energy metabolism in the failing heart

The failing heart is generally considered to be in an “energy deficient” state, due to a compromised ATP production,<sup>2</sup> which is primarily due to an impairment in mitochondrial function, including a decrease in mitochondrial tricarboxylic acid (TCA) cycle activity and a decrease in oxidative phosphorylation.<sup>3,4</sup> Impaired mitochondrial function in the failing heart can occur due to a number of reasons, including increased mitochondrial reactive oxygen species production, decreased mitochondrial biogenesis, increased autophagy, and alterations in mitophagy and mitofusion.<sup>5</sup>

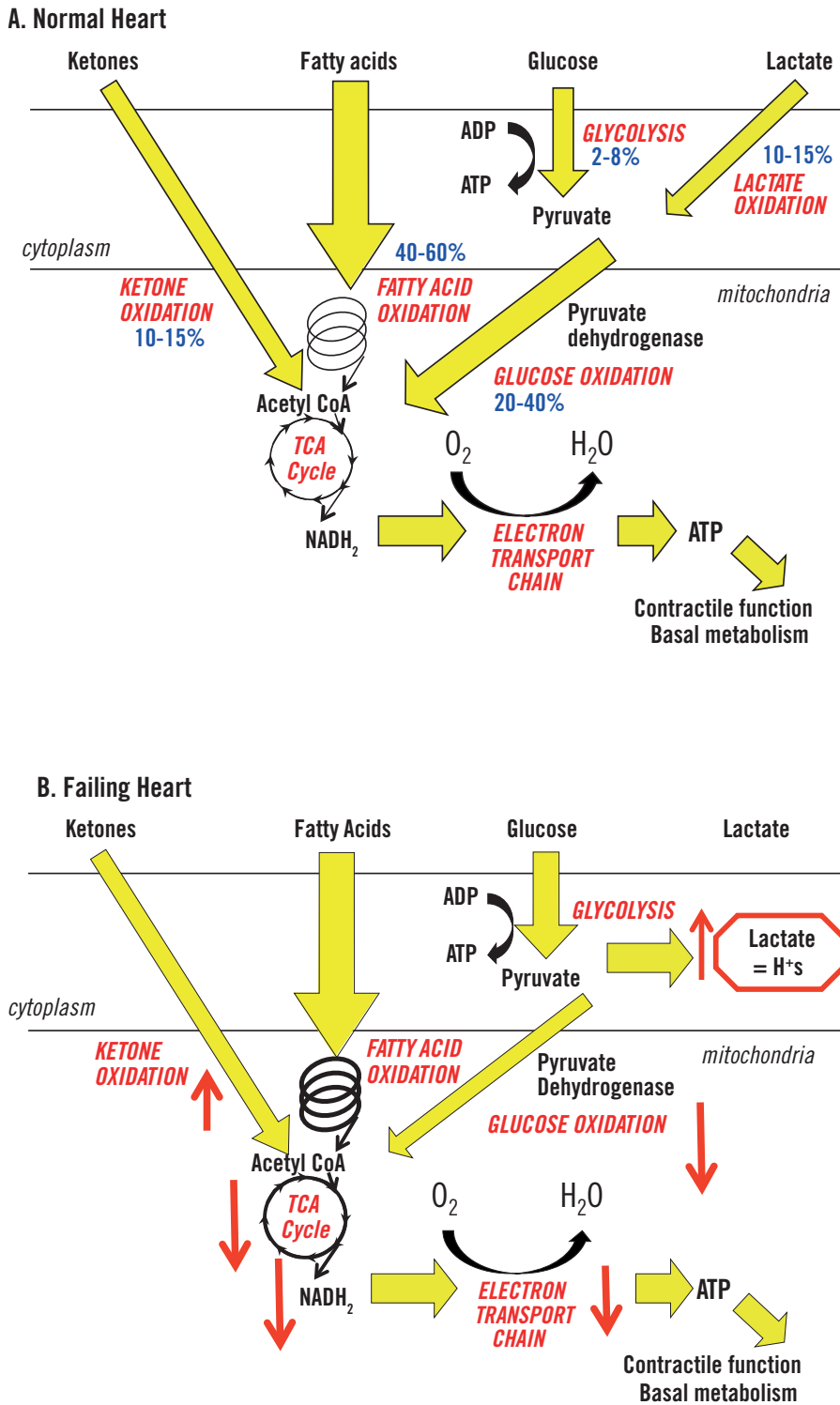
In an attempt to compensate for the decreased mitochondrial ATP production, an increase in ATP production from glycolysis occurs in the failing heart (Figure 1B).<sup>6</sup> In fact, an increase in glucose uptake and glycolysis is one of the earliest energy metabolic changes that occurs in the failing heart.<sup>7</sup> However, the amount of ATP generated from glycolysis (2 ATP molecules per molecule of glucose passing through glycolysis) is small compared with the amount of ATP generated from mitochondrial oxidative metabolism (for example, 31 molecules of ATP produced per molecule of glucose oxidized or 105 molecules of ATP produced per molecule of palmitate oxidized). As a result, the increase in glycolytic ATP production in the failing heart cannot compensate for the loss of mito-

chondrial ATP production, and the heart remains in an “energy deficient” state.

Although overall mitochondrial oxidative metabolism decreases in the failing heart, there are also alterations in the type of energy substrate used by the mitochondria in the failing heart. However, there is controversy as to the exact mitochondrial energy substrate preference in the failing heart. For example, both the oxidation of fatty acids, glucose, and ketones have been shown to vary depending on the heart failure model used and the duration of heart failure.<sup>6–27</sup> Of importance is that, although glycolysis is increased in the failing heart, this increase is not matched by an increase in the subsequent oxidation of glycolytically derived pyruvate (glucose oxidation).<sup>6,8–10</sup> The majority of studies directly examining the failing heart’s glucose oxidation rates in humans and animals show a marked decrease in glucose oxidation in the failing heart and a reduced contribution of glucose oxidation to overall ATP production.<sup>7,8,13,20,22,23,26</sup> The impairment in glucose oxidation precedes the development of cardiac dysfunction in different animal models of heart failure.<sup>7,8,21</sup> Although increases in glucose oxidation have been observed in some models of heart failure,<sup>9,10</sup> these may occur in part due to a marked increase in glucose uptake seen in these failing hearts.

What is consistent in most studies that have examined glucose metabolism in heart failure is that glucose uptake and glycolysis rates are much higher than glucose oxidation rates.<sup>6,7,9,10</sup> The consequences of this is that lactate and H<sup>+</sup>s are metabolic byproducts of this pathway, which contribute to decreasing cardiac efficiency in the failing heart (due to ATP being redirected away from contractile function to reestablishing ionic homeostasis).<sup>28</sup>

Despite being a major fuel for the heart, it is less clear what happens to fatty acid oxidation in the failing heart. It is generally assumed that cardiac fatty acid oxidation is decreased in heart failure,<sup>2,24</sup> although direct measurements of fatty acid oxidation rates in both human and experimental models of heart failure do not always support this assumption. Studies in heart failure patients have shown an increase in myocardial fatty acid uptake and fatty acid oxidation<sup>22,23,25</sup> or a decrease in fatty acid oxidation.<sup>17,24</sup> Animal studies also show differing results as to what happens to fatty acid oxidation in the failing heart. Studies in mice in which heart failure was produced secondary to pressure overload or a myocardial infarction have



**Fig. 1** Alterations in myocardial energy metabolism in the failing heart. **Panel A.** In the normal aerobic heart, mitochondrial fatty acid oxidation, glucose oxidation, lactate oxidation, and ketone oxidation are the major sources of energy production in the heart. The percent of contribution to ATP production is shown in blue. **Panel B.** In the failing heart, both mitochondrial electron transport chain activity and TCA cycle activity are compromised, leading to an impaired production of ATP from oxidative metabolism. The failing heart also becomes “metabolically inflexible” with ketone oxidation increasing and glucose oxidation decreasing. Glycolysis increases in the failing heart in an attempt to increase ATP production, although this increase in glycolytic ATP production cannot compensate for the loss of mitochondrial ATP production, leaving the heart in a potentially “energy starved” situation.

shown that cardiac fatty acid oxidation rates are increased, unchanged,<sup>7,8,13,21</sup> or decreased.<sup>6,10</sup> It is not clear, however, how much the decrease in fatty acid oxidation observed in heart failure is secondary to decreased cardiac work in the failing heart, which is a major determinant of fatty acid oxidation rates. The issue of what happens to fatty acid oxidation in the failing heart becomes more complex in the presence of obesity and/or diabetes. High cardiac fatty acid oxidation rates are seen in both human and animals studies of heart failure in obesity and diabetes.<sup>1</sup>

Ketones are also an important source of fuel for the heart, and recent studies have shown that ketone oxidation rates increase in the failing heart.<sup>11,12</sup> In a mouse model of compensated and decompensated pressure overload cardiac hypertrophy, proteomics data demonstrated that a key enzyme involved in ketone body oxidation, namely β-hydroxybutyrate dehydrogenase (BDH1), was upregulated 2 to 3 fold.<sup>11</sup> Moreover, the myocardial metabolite profile of mice with heart failure was comparable with mice fed a 4-week ketogenic diet. In parallel, Bedi et al<sup>12</sup> also observed an increased ratio of serum to myocardial ketone bodies with upregulated expression of BDH1, BDH2, and succinyl-CoA:3-ketoacid CoA transferase (SCOT) in human heart failure

patients. We have also seen an increase in myocardial ketone body oxidation rates in the ex vivo isolated failing murine heart.<sup>13</sup> Taken together, these studies suggest that the failing heart has an increased reliance on ketone body oxidation.

Recent clinical trials have shown that sodium glucose cotransporter 2 (SGLT2) inhibition can markedly decrease hospitalization for heart failure in diabetic patients who are at risk for cardiovascular disease.<sup>29</sup> Some of this beneficial effect of SGLT2 inhibition has been proposed to be due to an increase in cardiac ketone oxidation due to the increase in circulating ketones that can be seen in patients taking SGLT2 inhibitors. In support of this concept, we recently demonstrated that SGLT2 inhibition can improve overall cardiac energetics and cardiac function in genetically obese leptin receptor-deficient (*db/db*) mice.<sup>30</sup>

## Conclusions

Due to the heart's constant high energy demand, a fine balance between energy substrate utilization is crucial in maintaining metabolic flexibility. The metabolic profile of the failing heart is not simply a shift from "fatty acids to glucose." Rather, the failing heart can be considered to have increased rates of glycolysis, depressed glucose oxidation rates, and increased ketone body oxidation rates. With regard to the controversial nature of fatty acid oxidation, while the genes involved in fatty acid oxidation are downregulated, direct measurements of rates have presented conflicting results. Thus, further studies are needed to have a complete understanding of the way in which fatty acid oxidation is perturbed in heart failure. Finally, definitively characterizing the metabolic profile of the failing heart will help direct future pharmacological therapies that can combine approaches to harmonize and normalize the metabolic flexibility of the failing heart. ■

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