Energy metabolism in patients with diabetes and heart failure

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Abstract: The heart has a very high energy demand, which is mostly met by mitochondrial oxidative phosphorylation and, to a lesser extent, by glycolysis. In heart failure, there are substantial alterations in myocardial energy metabolism that lead to an "energy-deficient" state. This includes a marked reduction in overall mitochondrial oxidative phosphorylation and an uncoupling between high glycolysis rates and low glucose oxidation, which together contributes to the energy deficit and deteriorates contractile dysfunction. Cardiac ketone oxidation is also increased in heart failure, although it has yet to be determined whether this is an adaptive or maladaptive alteration. Diabetes is a major risk factor for heart failure development. It induces alterations in myocardial energy metabolism and is often associated with ventricular dysfunction. Similar to heart failure, a major change in myocardial energy metabolism in diabetic patients is a reduction in glucose oxidation, which negatively influences cardiac function. In both heart failure and diabetes, a growing body of evidence suggests that targeting myocardial energy metabolism by optimizing cardiac energy substrate preference could be a potential therapeutic approach to improve patient outcomes. ■ *Heart Metab*. 2019;80:32-36

Keywords: diabetes; fatty acid oxidation; glucose oxidation; heart failure

Introduction

Heart failure is a major cause of death and disability, and represents a huge economic and social burden worldwide.[1] Despite recent improvement in the clinical outcomes of heart failure patients due to new therapies, the mortality and morbidity rates are still high, which emphasizes the need for a new treatment to prevent and/or treat heart failure. Significant metabolic remodeling occurs in heart failure, which includes a marked reduction in mitochondrial oxidative metabolism. These perturbations in cardiac energy metabolism in the failing heart can precede the occurrence of cardiac dysfunction and can influence the progress, as well as the severity, of heart failure.[2,3]

Diabetes is a major metabolic disorder that is associated with either insulin insufficiency (as in type 1 diabetes, T1D) or insulin resistance (as in type 2 diabetes, T2D). Diabetes is a major risk factor for heart failure development, and has been shown to negatively influence contractile function and energy metabolism of the heart. These metabolic changes include the development of cardiac insulin resistance in diabetics, which negatively influences insulin-stimulated cardiac glucose oxidation. High levels of circulating fatty acid in diabetics can further aggravate cardiac insulin resistance, and result in the heart being excessively reliant on fatty acid oxidation as a source of fuel.

The aims of this refresher article are to highlight what the major changes are in myocardial energy

metabolism in heart failure and diabetes, as well as to highlight the similarity between these pathologies. Some controversial issues with regard to energy metabolism on the failing heart and the heart of diabetics will also be discussed.
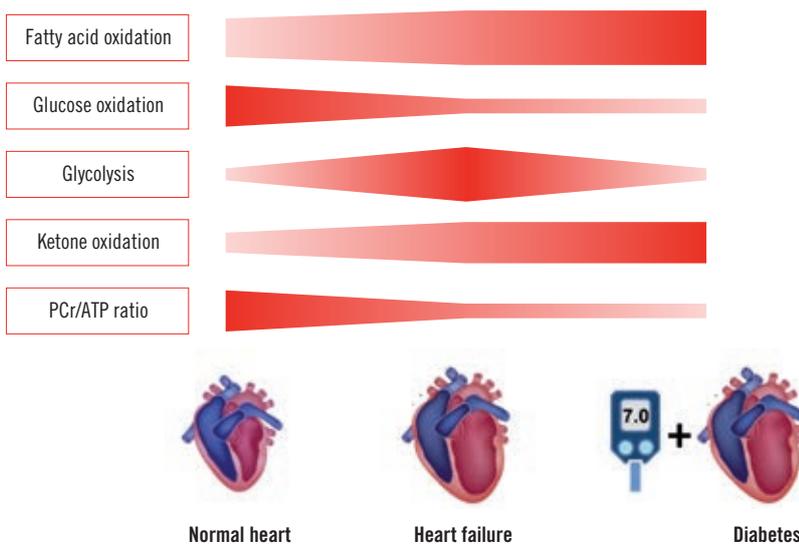
Energy metabolism in the normal heart

The heart represents less than 1% of the whole body mass, but consumes over 5% of the body's oxygen supply.[4] With essentially no energy reserves, the heart relies on the continuous metabolism of different circulating energy substrates by its highly efficient and complex metabolic machinery to produce its energy (in the form of adenosine triphosphate, ATP). The majority of cardiac ATP production (~95%) occurs in the mitochondria through oxidative phosphorylation, with cytosolic glycolytic ATP production only contributing about 5% of the heart's ATP supply.[1,4] Cardiac energy substrates include fatty acids, carbohydrates (lactate and glucose), ketones, and amino acids.[1,4] The normal healthy heart is metabolically flexible, and can switch its preference between these different energy substrates based on contractility demand, hormonal status, and carbon substrate availability.[1,4] Fatty acids are usually the biggest contributor to cardiac ATP production (40% to 60%), followed by carbohydrates (20% to 30%) and ketone (10% to 20%).[1,4]

Figure 1 *Perturbations in cardiac energy metabolism in heart failure and diabetes. There is an increase in glycolysis rates in the failing heart which is uncoupled from depressed glucose oxidation rates. In the diabetic heart, there are high rates of fatty acid oxidation which are driven by insulin resistance-induced high levels of circulating fatty acid.*

Cardiac energy metabolism in the failing heart

One of the main characteristics of the failing heart is that it is generally considered as an "energy-starved" heart *(Figure 1).*[5] This is mainly due to a compromised mitochondrial function, which leads to a considerable reduction in tricarboxylic acid (TCA) cycle activity, mitochondrial oxidative phosphorylation, and cardiac ATP production.[5,6] Mitochondrial dysfunction in the failing heart can be due to reactive oxygen species damage, increased mitophagy and mitochondrial fission, and impaired mitochondrial dynamics/recycling and/or biogenesis.[1,7-9] Another important characteristic of the failing heart is the development of cardiac insulin resistance.[1,4,10-12] Together, these changes impair the metabolic flexibility of the heart and its ability to adapt to different workloads.[1,4] Decreased mitochondrial ATP production results in an upregulation in glycolysis-derived cardiac ATP production in the failing heart in an attempt to compensate for the reduction in oxidative metabolism.[13] However, glycolysis produces a limited amount of ATP (two ATP molecules per molecule of glucose passing through glycolysis) compared with mitochondrial oxidative metabolism (for instance, 31 ATP molecules per molecule of glucose oxidized and 105 ATP molecules per molecule of palmitate oxidized). Accordingly, high glycolytic rates in the failing heart do not compensate for the overall reduction in cardiac ATP production and the heart remains "an engine out of fuel."[5] In addition, the high rates of glycolysis become uncoupled from glucose oxidation, which is impaired in heart failure due in part to a decrease in insulin-stimulation of glucose oxidation.[1,10,11] The increased reliance on glycolysis-derived ATP production leads to the production of lactate and H^+ as metabolic by-products arising from glycolysis uncoupled to glucose oxidation. This compromises cardiac efficiency as ATP is redirecting ATP away from supporting contractile function and towards restoring ionic homeostasis.[14] This decrease in cardiac efficiency[1,4,12,15-17] compounds the energy deficiency problem in the failing heart.

While cardiac preference for mitochondria oxidative metabolism is still a controversial topic, it is generally accepted that the cardiac preference for fatty acid, glucose, and ketone varies according to the etiology, stage, and severity of heart failure.[1,4] Data from human and animal studies suggest that insulin-stimulated mitochondrial glucose oxidation is decreased, and that this decrease in glucose oxidation is uncoupled from high cytosolic glycolytic rates in the failing heart *(Figure 1)*.[10,11,18] In fact, decreased cardiac glucose oxidation rates is a feature of early metabolic remodeling in heart failure and precedes cardiac dysfunction.[2,3,19] Of note, some studies suggested that glucose oxidation is increased in heart failure, but this could be driven by increased glucose uptake and subsequent high glycolytic rates in the failing heart.[20,21]

There is less consensus on the contribution of fatty acid to oxidative metabolism in the failing heart. In 1956, Richard Bing[22] was the first to insert a catheter into the coronary artery in heart failure patients to directly measure the contribution of each cardiac energy substrate to overall energy production. This seminal study showed that fatty acid oxidation is, in fact, increased in heart failure patients compared with healthy volunteers.[22] Using different approaches such as arteriovenous blood sampling and positron-emission tomography (PET), a number of subsequent studies in failing human hearts supported these findings and showed that indeed myocardial fatty acid uptake and oxidation are also increased in heart failure patients.[23-25] It is also worth mentioning that there has been an assumption that fatty acid oxidation is impaired in heart failure due to a decreased expression of fatty acid oxidative enzymes,[5,26] although this is not supported by the majority of experimental and clinical studies where fatty acid uptake and oxidation are directly examined. Measuring myocardial fatty acid oxidation in different murine models of heart failure has not been conclusive, where it has been shown that fatty acid oxidation rates are increased,[10] unchanged,[2,3,12,19] or decreased.[13,21] However, it is not clear whether this reduction in myocardial fatty acid oxidation is secondary to the reduction in cardiac work (which is a major determinant of fatty acid oxidation rates in the heart) in the failing heart.[1,4]

Ketone bodies are another important cardiac energy substrate, the circulating levels of which increase during metabolic stress and starvation.[27,28] Cardiac ketone metabolism has attracted a tremendous interest since it is shown to be increased in the failing heart *(Figure 1)*.[12,29,30] In heart failure patients, an increase in circulating ketone levels along with the upregulation of cardiac ketone oxidative enzymes, namely β-hydroxybutyrate dehydrogenase 1 (BDH1), BDH2, and succinyl-coenzyme A (CoA):3-ketoacid CoA transferase (SCOT), have been reported.[30] These increases in ketone oxidation enzymes have also been seen in a mouse model of pressure-overload induced compensated and decompensated heart failure.[12,29] Recently, by directing measuring cardiac ketone oxidation rates, we showed that ketone oxidation rates are increased in the ex vivo isolated failing mouse heart,[12] although this increase in cardiac ketone oxidation is not accompanied by improved cardiac function. Nevertheless, Horton et al[31] demonstrated that augmented level of circulating ß-hydroxybutyrate alleviates cardiac dysfunction and hypertrophy in a canine model of pacing-induced heart failure. Taken together, this may suggest the role that ketone as a signaling molecule could play in mediating its cardioprotection in the setting of heart failure. However, this hypothesis has yet to be directly addressed.

Cardiac energy metabolism in patients with type 1 diabetes

In type 1 diabetes (T1D), there is an insulin deficiency that results in attenuation in the metabolic effects of insulin in the heart. One of the main metabolic effects of insulin in the heart is its stimulatory effect on glucose uptake and subsequent stimulation of glycolysis and glucose oxidation.[4] Through stimulating glucose oxidation, insulin indirectly inhibits cardiac fatty acid oxidation through what is known as the "Randle Cycle."[32] Moreover, insulin indirectly limits cardiac fatty acid oxidation via inhibiting adipose tissue lipolysis and circulating fatty acid levels. In addition to these indirect effects, insulin directly inhibits cardiac fatty acid oxidation via triggering the activity of acetyl CoA carboxylase which increases the level of malonyl CoA, a potent endogenous inhibitor of carnitine palmitoyl-transferase-1 (CPT-1), a key regulator of mitochondrial fatty acid uptake.[33] All these metabolic effects of insulin are significantly impaired in T1D patients. In support of that, examining cardiac metabolic profile in patients with T1D, using positron emission tomography (PET) imaging technique, showed high rates of cardiac fatty acid oxidation along with a reduction in

cardiac glucose utilization *(Figure 1).*[34] Similar results have been recapitulated in different animal models of T1D. For instance, cardiac ATP production is almost completely reliant on fatty acid oxidation in ex vivo isolated streptozocin-induced T1D rat hearts.[35] In line with this, high rates of fatty acid oxidation are also observed in the Akita mouse, which is a T1D model due to the mutation in insulin 2 gene, isolated working heart perfusion, while glucose oxidation remains unchanged.[36]

Cardiac energy metabolism in patients with type 2 diabetes and obesity

Despite having different etiology, metabolic perturbations in cardiac energy metabolism which occur in type 2 diabetes (T2D) and obesity are similar to those that occur in heart failure and T1D. Importantly, the occurrence of cardiac insulin resistance (ie, impaired insulin signaling) in obesity and T2D patients leads to the reduction of cardiac glucose oxidation rates along with excessive reliance on fatty acid as a source of cardiac energy *(Figure 1).*[10,37,38] In obese women, Peterson et al[39] reported that high rates of cardiac fatty acid oxidation are positively correlated with glucose intolerance. In addition, high rates of cardiac fatty acid oxidation are negatively correlated with cardiac efficiency in obese subjects.[39] Moreover, it has also been shown that increased cardiac fatty acid oxidation and decreased glucose oxidation in the heart is associated with the development of ventricular dysfunction in patients with T2D.[40,41] These alterations in cardiac metabolism in obese/T2D cause a significant drop in overall cardiac ATP production, as is evident by a reduction in cardiac phosphocreatine/:adenosine triphosphate (PCr:ATP) ratio.[41-43] This suggests that the diabetic heart is energy deficient, similar to what is seen with the failing heart. Of importance, is that weight loss improves myocardial function and energetics in obese/T2DM patients [44] and in obese mice with heart failure.[10] Improvement in cardiac function and energy metabolism following weight loss is associated with improved cardiac insulin-stimulated glucose oxidation and its contribution to overall cardiac ATP production.[10] Emerging evidence suggests that myocardial uptake of both β-hydroxybutyrate and acetoacetate are increased in T2D patients.[45] This may suggest an increase in cardiac ketone oxidation, although it is yet to be directly examined.

Conclusion

A growing body of evidence suggests that the failing heart loses its metabolic flexibility to adapt to different work demands and nutritional/hormonal alterations. This is mainly due to impaired mitochondrial oxidative phosphorylation and cardiac insulin resistance in heart failure. The failing heart becomes highly glycolytic in an attempt to compensate for the energy deficit. While there is still some confusion about what happens to fatty acid oxidation in heart failure, there is a marked reduction in glucose oxidation, due to insulin resistance, which is uncoupled from high rates of glycolysis in the failing heart. Emerging evidence suggesting that ketone metabolism may be upregulated in the failing heart and that augmented levels of circulating ketone elicit cardioprotection in experimental models of heart failure. Myocardial energy metabolism is also altered in T1D and obese/T2D patients. Perturbations in cardiac energy metabolism are positively correlated with glucose intolerance and negatively correlated with cardiac efficiency. This is mainly due to a marked reduction in glucose oxidation and excessive reliance on fatty acid oxidation as a main source of energy in the diabetic heart. Therefore, optimizing cardiac energy metabolism potentially through improving cardiac glucose oxidation rates could be a unifying target to limit left ventricular dysplasia and improve cardiac efficiency and energetics in patients with diabetes and heart failure. ■

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