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Metabolic Therapy for Heart Failure

By RONG TIAN, MD, PhD

Heart failure affects approximately 5 million Americans and more than a half million new cases are diagnosed each year.¹ The steady rise in the prevalence of congestive heart failure (CHF) in recent years can be attributed to multi-factorial causes. Improved survival after acute ischemic episodes has paradoxically resulted in the increased diagnosis of CHF in post-myocardial infarction (MI) patients. Furthermore, a worldwide increase in diabetes, a major risk factor, and the aging of the population, have also contributed to the escalation in the number of CHF cases. While the incidence of CHF continues to rise, the efficacy of CHF therapy is somewhat stagnant. After nearly 2 decades of success with neurohormonal inhibition, which significantly improves survival in the CHF population, many patients still experience progression of their disease and CHF remains the number one killer in the United States (US).¹ The recent failure of treatment trials with endothelin-1 receptor blockers and cytokine antibodies^{2,3} has fueled the search for alternative options in chronic therapy to further improve the limited prognosis of CHF patients. This issue of *Cardiology Rounds* examines one of these options, myocardial substrate metabolism in CHF.

Energy metabolism of the heart – An opportunity for heart failure

There are several reasons for considering energy metabolism as a novel target for CHF therapy. First, the heart requires a huge amount of energy to function. An adult human heart has the highest oxygen uptake rate in the body (~0.1 ml O₂/g/min at basal conditions) and consumes about 6 kg of adenosine triphosphate (ATP) daily – 15-20 times its own weight – to maintain the daily activities of an individual.^{4,5} Since the cardiac ATP content is <1 gram,⁵ cardiac myocytes have to work diligently to match the energy supply to the tremendous demand and, thereby, maintain normal energetics and cardiac function. Because of its high energy-dependent nature, the heart has developed an extraordinary capacity for energy production. Indeed, the heart features the highest mitochondrial density among all organs; approximately one-third of the cell volume in cardiac myocytes is occupied by mitochondria, in which oxidative metabolism for ATP synthesis occurs. Moreover, the heart is able to utilize a variety of substrates for energy generation, including carbohydrates (glucose and lactate), lipids (free fatty acids and triglycerides), and ketones (Figure 1). These mechanisms allow a normal heart to maintain its functional performance in a wide range of physiological conditions without experiencing an energy debt.

Despite the extraordinary capacity for energy production, failing hearts become energy deprived. This is evident by a significant decrease in the myocardial content of the energy reserve compound, phosphocreatine (PCr), which rapidly regenerates ATP when there is an abrupt increase in energy demand.⁶⁻⁹ The decrease in PCr is followed by the eventual depletion of myocardial ATP content during end-stage heart failure.^{9,10} Long-term follow-up studies in patients with idiopathic dilated cardiomyopathy demonstrate that decreased PCr is an independent predictor of mortality,⁸ suggesting that impaired myocardial energetics play an active role in the progression of heart failure. This notion is further supported by consistent observations in clinical CHF trials revealing that energy-costly treatments, such as positive inotropic agents (beta-receptor mimetic drugs, phosphodiesterase inhibitors), increase mortality, while energy-sparing treatments (eg, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II blockers, or beta-receptor blockers) reduce mortality.

Taken together, cardiac function is highly dependent on myocardial energy supply and the heart has developed an elaborate system for ATP synthesis. However, an energy deficit has been observed during the development of CHF that directly relates to patient prognosis. Indeed, it has been proposed



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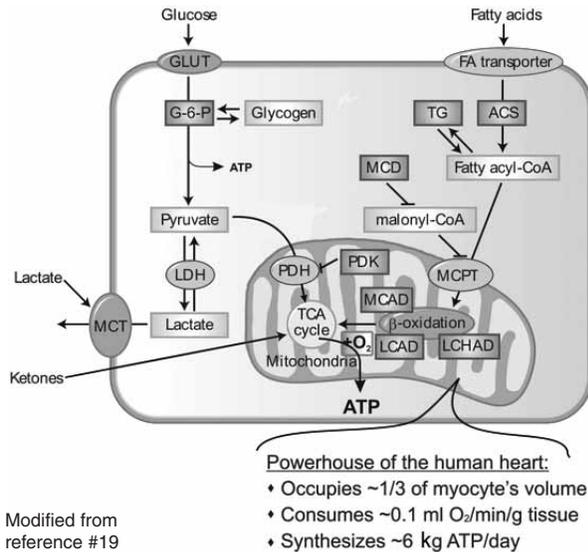
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Figure 1: Pathways for substrate metabolism in the heart.

Multiple metabolic pathways have been established in the heart so that a variety of carbon substrates (eg, fatty acids, glucose, lactate, and ketones) can be utilized for ATP synthesis. Glucose utilization involves glycolysis and glucose oxidation, and the latter is the oxidation of pyruvate in the mitochondria. Under normal conditions, >95% of ATP is synthesized by oxidative metabolism in the mitochondria, and <5% of ATP is generated by glycolysis in the cytosol. Mitochondrial density is highest in cardiac myocytes in order to meet the high-energy demands of the heart.



Modified from reference #19

ACS = acyl-CoA synthase; GLUT = glucose transporter; LCAD = long-chain acyl-CoA dehydrogenase; LCHAD = 3-OH long-chain acyl-CoA dehydrogenase; LDH = lactate dehydrogenase; MCAD = medium-chain acyl-CoA dehydrogenase; MCD = malonyl-CoA decarboxylase; MCT = monocarboxylate transporter; mCPT-1 = carnitine palmitoyl transferase-1, muscle isoform; PDH = pyruvate dehydrogenase; PDK = pyruvate dehydrogenase kinase; TCA = tricarboxylic acid; TG = endogenous triacylglycerols

that this “power plant” failure contributes to mechanical dysfunction in the case of CHF.^{9,11,12} However, this knowledge presents an opportunity to mend a failing heart by optimizing the “power supply.”

The following sections review recent advances in our understanding of myocardial substrate metabolism in heart failure and provides a basis for identifying the “parts” that need to be mended in order to restore “power” to an exhausted heart. These advances in the clinical care of CHF patients will be evaluated from 2 perspectives:

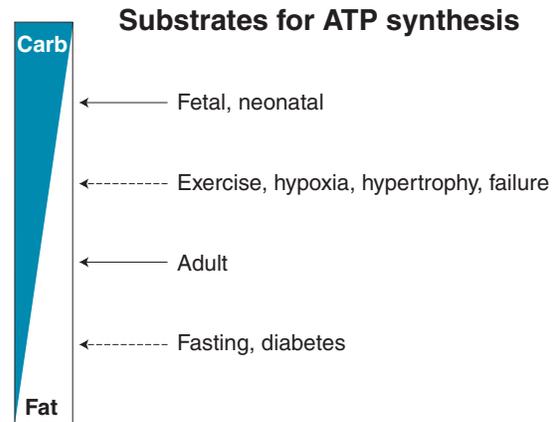
- Has this knowledge led to new opportunities for intervening in cardiac metabolism in addition to the current treatment regimens?
- What are the new directions in both basic and clinical areas for further development of metabolic therapy for heart failure?

Targeting energy metabolism: concepts derived from animal models

An important change in energy metabolism observed in hypertrophied and failing hearts is the shift in the preference of substrates for energy generation. Although the heart is able to utilize a variety of substrates, preference in substrate utilization has been documented and it can change in response to

Figure 2: Substrate preference of the heart

Fatty acids are the predominant fuel for the adult hearts, while carbohydrates are the preferred substrates for fetal hearts. However, the adult heart can shift its substrate utilization profile due to altered substrate availability and certain pathological conditions.



altered substrate availability or altered regulation of metabolic pathways. As illustrated in Figure 2, substrate preference in the heart changes under multiple physiological and pathological situations. For example, glucose and lactate (collectively referred to as carbohydrates) are the primary carbon substrates for fetal hearts, while fatty acids become the predominant fuel in adult hearts, supporting more than two-thirds of the total ATP synthesized.¹³⁻¹⁶ In contrast, hypertrophied and failing hearts demonstrate increased reliance on glucose as a fuel, while decreasing fatty acid utilization; this is an apparent reoccurrence of the fetal metabolic profile.¹⁷⁻¹⁹ Studies using animal models of heart failure reveal that this shift of substrate preference is associated with the downregulation of peroxisome proliferator-activated receptor α (PPAR α), a transcription factor controlling the expression of key enzymes for fatty acid oxidation.^{20,21} Subsequent studies using transgenic mouse hearts deficient in PPAR α demonstrate a similar shift in substrate selection that supports a causal role for PPAR α in altered substrate utilization with cardiac hypertrophy and failure.^{22,23}

Is this shift in substrate preference beneficial, detrimental, or of no functional significance for the heart? To address this question, substrate preference needs to be altered by a mechanism independent of heart failure. This was made possible by studying transgenic mouse hearts, in which substrate preference has been altered by genetic manipulation. In mouse hearts deficient in PPAR α , increased glucose utilization was observed and was sufficient to compensate for the decrease in fatty acid oxidation at baseline workload.²²⁻²⁴ However, these hearts showed energetic and contractile failure when they were challenged to increase contractile performance, ie, mimicking the response to high workloads.²⁴ Interestingly, these defects could be corrected by further increasing the capacity for glucose utilization by over-expressing an insulin-independent glucose transporter GLUT1 (Figure 3a-b).²⁴ Analysis of the substrate oxidation profile by the carbon ion nuclear magnetic resonance (¹³C NMR) technique demonstrated that the compensatory increases in glucose oxidation in PPAR α -deficient hearts at baseline exhausted the reserves

Figure 3: Relationship of energy metabolism and cardiac function

A. Contractile function assessed by rate pressure product in isolated perfused hearts

B. Dynamic changes in the myocardial ATP concentration, assessed by ^{31}P NMR spectroscopy in mouse hearts deficient in PPAR α (PPAR $\alpha^{-/-}$) or in PPAR $\alpha^{-/-}$ hearts with the overexpression of GLUT1 (PPAR $\alpha^{-/-}$ TG). In PPAR $\alpha^{-/-}$ hearts, the inability to sustain their contractile performance at high workload is accompanied by a loss of myocardial ATP. These defects are rescued by overexpressing an insulin-independent glucose transporter GLUT1.

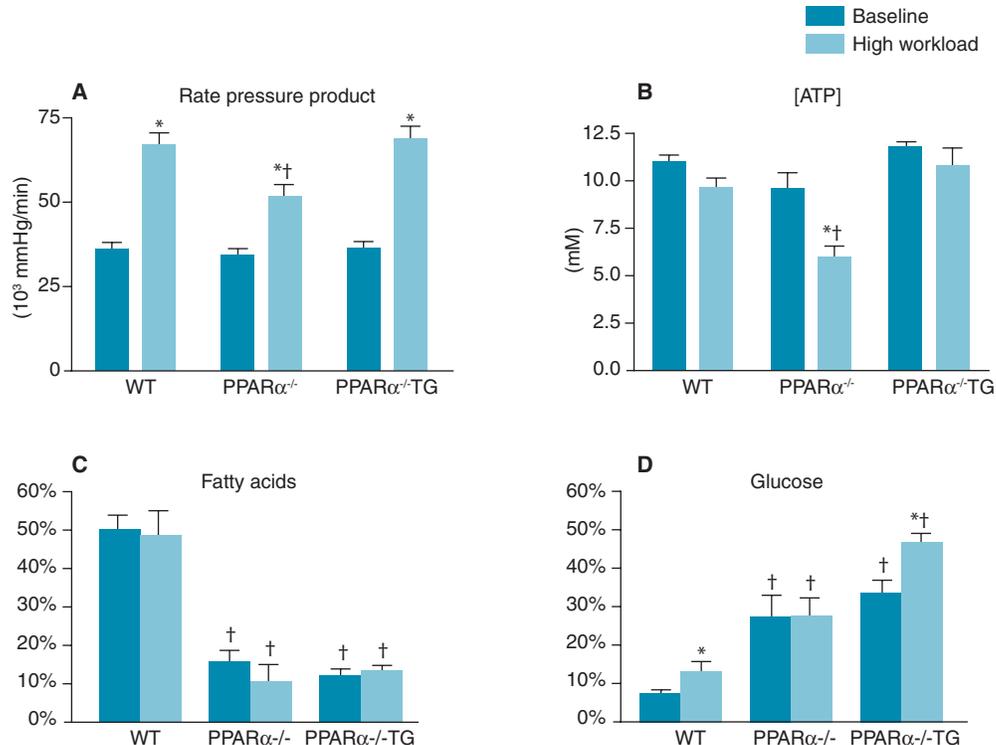
C. and D. ^{13}C NMR isotopomer analysis of the extracts from these hearts determines the relative contribution of fatty acids (C) and glucose (D) to the oxidative metabolism at baseline workload (shown in dark blue) and at high workload (shown in light blue). For wild-type (WT) hearts, fatty acids contribute to ~50% of oxidative metabolism, while glucose contributes <10% at baseline.

At high workload, the contribution of fatty acid is unchanged, but there is a doubling in the contribution of glucose in WT hearts.

The PPAR $\alpha^{-/-}$ hearts show a marked decrease in fatty acid utilization and a substantial increase in glucose utilization at baseline.

However, the substrate utilization profile remains the same at high workload with no further increase in the contribution of glucose.

In PPAR $\alpha^{-/-}$ hearts with the overexpression of GLUT1 (PPAR $\alpha^{-/-}$ TG), although fatty acid utilization is still depressed, the contribution of glucose is higher, and importantly, it increases further during the high workload suggesting a restored metabolic flexibility.



*: $p < 0.05$ vs. baseline; †: $p < 0.05$ vs. WT.

Modified from reference #24

needed for a further increase at high workload. Thus, the metabolic reserve was depleted and, consequently, the contractile reserve of the heart, as well. By overexpressing GLUT1, the ability to further increase the contribution of glucose to oxidative metabolism is restored (Figure 3c-d).²⁴

An important lesson learned from these studies is that increased reliance on glucose *per se* is not harmful for the heart. However, the intrinsic adaptation to impaired fatty acid oxidation by increasing glucose utilization is limited in an adult heart and comes with the cost of depleting its functional reserve. Such a scenario is clearly unfavorable for a failing heart that is constantly struggling to accomplish its workload. This is even more problematic considering that heart failure is often associated with insulin insensitivity,^{25,26} which further compromises glucose utilization by the heart. As a result, the altered substrate metabolism that is a part of the myocardial remodeling process following an initial pathological event (eg, MI, pressure or volume overload of the heart), may ultimately fail to satisfy the high energy demands of a heart coping

with mechanical overload caused by underlying disease. This mismatch between energy supply and demand drives a vicious cycle that contributes to the ultimate failure of the heart.

Based on this hypothesis, several targets can be considered for metabolic manipulation with the ultimate goal of restoring energy supply to an overloaded heart. One obvious site is altered regulatory mechanisms due to molecular remodeling. Since downregulation of PPAR α is likely responsible for reduced fatty acid oxidation in failing hearts, one possibility is to re-activate PPAR α using pharmacological compounds such as fibrates. Although the benefits of PPAR α -agonists in lipid-lowering and their potentially anti-inflammatory effects have been noted in several studies,^{27,28} increased myocardial fatty acid oxidation due to reactivation of PPAR α is apparently detrimental to hypertrophied hearts.^{29,30} Thus, it is possible that downregulation of PPAR α is a necessary adaptation during cardiac remodeling. A recent study revealed that decreased PPAR α activity in ischemic cardiomyopathy protected the heart from lipotoxicity by shifting the fuel

preference away from fatty acids.³⁰ This is consistent with prior observations that partial inhibition of fatty acid utilization is cardioprotective.^{31,32}

The demonstration that decreased myocardial use of fatty acids brought about by downregulation of PPAR α plays a protective role in cardiac hypertrophy and failure suggests that strategies for improving the supply of energy to the failing heart without increasing fatty acid use should be sought. The rescue of PPAR α -deficient hearts by overexpression of GLUT1 indicates that improving myocardial glucose use can be an effective approach. In support of this concept, mouse hearts overexpressing GLUT1 showed an increased tolerance to chronic pressure overload with a delayed progression to CHF and reduced mortality.³³ Similarly, in a large animal model of CHF due to dilated cardiomyopathy, enhancement of myocardial glucose uptake and use by recombinant glucagon-like peptide-1 (GLP-1) improved left ventricular performance.³⁴ These studies serve as “proof of principle” and clearly demonstrate the therapeutic potential of manipulating cardiac metabolism in CHF.

Metabolic therapy for CHF: from mice to men

Although animal studies have generated compelling evidence, translating the principle of metabolic therapy to clinical practice is not as straightforward. Experimental results have been obtained with minimal confounding factors, but many more factors need to be taken into consideration when it comes to human hearts. What then are the major challenges when considering metabolic therapy for CHF?

First, changes in the molecular mechanisms regulating substrate preference in human hearts have not been documented during the development of CHF, largely due to difficulties in obtaining myocardial biopsy samples at earlier stages of CHF. The expression of PPAR α is decreased in explanted human hearts with end-stage heart failure,^{20,35} but it is unknown whether such a decrease occurred at a less-severe stage when there might have been an opportunity for intervention. Then, is there an alternative approach for investigating the optimal fuel for an overloaded heart at high risk of failure? Clinically, myocardial substrate metabolism is indirectly assessed by positron emission tomography (PET) imaging using ¹⁸Fluoro- or ¹¹Carbon-labeled substrates. However, PET studies of various patient populations yield inconsistent pictures regarding the substrate preference of a failing heart.³⁶⁻⁴⁰ It is important to recognize that, except for a very few highly specialized centers, PET scans measure cardiac substrate uptake rather than oxidation. Cardiac substrate uptake is highly influenced by substrate availability and varies greatly in patients with different underlying diseases or dietary habits. For example, increased fatty acid uptake may occur because of elevated plasma fatty acid levels in obesity, diabetes, or during a high sympathetic state. Increased myocardial fatty acid uptake under these conditions does not necessarily reflect a preference for fatty acids by the heart, *per se*. Indeed, excessive influx that overwhelms the capacity of the heart to handle fatty acids is a likely cause of lipotoxicity. Thus, comparing observations made in animal models with

those in human heart failure cannot be made until more vigorous diagnostic tools are available. In this regard, advances in the development of novel tracers and probes for molecular imaging hold a promise for the future.

Pharmacological treatments

Despite our limited knowledge of myocardial biology in failing human hearts, pharmacological treatments that effectively alter cardiac substrate metabolism have added to our understanding of the metabolic needs in CHF. The partial inhibitors of fatty acid oxidation (eg, trimetazidine, ranolazine, perhexiline, and etomoxir) constitute one class of drugs.^{31,32} These compounds act by inhibiting entry of fatty acids into the mitochondria or beta-oxidation within the mitochondria.^{31,32,41,42} Because of the reciprocal inhibition of fatty acid oxidation and the increase in glucose oxidation, treatment with these compounds results in enhanced glucose oxidation, leading to a switch in substrate utilization towards glucose. Although there is no evidence that these compounds change the myocardial capacity for glucose utilization, increasing the relative contribution of glucose to ATP synthesis may improve oxygen efficiency, which is desirable in an ischemic myocardium. Multiple clinical studies have demonstrated the anti-angina effect of these compounds^{43,44} and recent studies in a small patient population reveal that long-term treatment with partial fatty acid oxidation inhibitors improves LV function and slows the deleterious remodeling of ischemic hearts.^{43,45,46} This suggests the therapeutic potential of these compounds for heart failure due to ischemic heart disease.

Such observations are consistent with animal studies showing that decreased fatty acid use associated with downregulation of PPAR α is necessary and beneficial for ischemic cardiomyopathy, thus implying that switching the fuel preference to glucose is a welcome adaptation in human hearts under similar conditions. It remains to be tested whether this class of agents also benefits patients with non-ischemic cardiomyopathy.

Another class of compounds acts on the other side of the balance, ie, by enhancing myocardial glucose utilization through improved insulin sensitivity. The “insulin sensitizers,” including the thiazolidinediones (TZDs) and metformin, are commonly used to improve glucose homeostasis in diabetics. Experimental studies reveal that these compounds improve myocardial glucose uptake by upregulating myocardial glucose transporters and/or improving whole body insulin sensitivity.⁴⁷⁻⁵⁰ Treatment with rosiglitazone in patients with type 2 diabetes improves myocardial glucose uptake during insulin stimulation.⁵ Based on concepts developed in animal models, the effects of this class of drugs in enhancing glucose utilization should be beneficial for failing human hearts. However, because of concerns about fluid retention with the TZDs and lactic acidosis with metformin, the US Food and Drug Administration (FDA) and professional societies have warned against using these drugs in patients with heart failure.⁵²

Despite the warnings, TZDs and metformin are increasingly prescribed to diabetic patients with heart failure.⁵³ A recent observational study in >16,000 patients

concluded that TZDs and metformin did not increase mortality, but rather, improved outcomes in older patients with diabetes and heart failure.⁵⁴ This study obviously raised many questions, for example:

- Is the overall benefit observed due to direct metabolic effects on the heart or to the reduction in cardiovascular risk factors secondary to better glycemic control and lower plasma fatty acid levels, or both?

- Can the use of these compounds be extended to non-diabetic patients with heart failure, since advanced heart failure is often accompanied by insulin resistance?^{25,26}

A prospective, randomized, clinical trial is clearly warranted to further establish the optimal use of insulin-sensitizers in heart failure patients. Furthermore, due to the noted side effects of TZDs and metformin, new generations of insulin-sensitizers with cardiac-specificity and fewer side effects are highly desirable and could broaden the spectrum of target patients.

Summary

We have come a long way toward recognizing the potential of metabolic therapy in heart failure. “Proof-of-concept” studies at the bench have generated strong evidence to drive future translational research. Initial clinical observations, obtained by using existing pharmacological compounds that effectively alter cardiac metabolism, reveal favorable evidence for metabolic intervention in heart failure. The outstanding challenge is to demonstrate in a large-scale clinical trial that metabolic modulation can delay the progression of heart failure and improve survival in otherwise fully-treated patients. At the same time, development of novel compounds with high efficacy in myocardial metabolism and low side effects are urgently needed to advance the practice of metabolic therapy.

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