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Targeting Myocardial Substrate Metabolism in the Failing Heart: Ready for Prime Time?

Salva R. Yurista[1,2], **Shi Chen**[1,2], **Aidan Welsh**[1,2], **W. H. Wilson Tang**[3,5], **Christopher T. Nguyen**[1,2,3,4,5,6]

[1]Cardiovascular Research Center, Corrigan Minehan Heart Center, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Boston, MA 02129, USA

[2]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA

[3]Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH, USA

[4]Division of Health Science Technology, Harvard-Massachusetts Institute of Technology, Cambridge, MA, USA

[5]Cardiovascular Innovation Research Center, Cleveland Clinic, Cleveland, OH, USA

[6]Imaging Institute, Cleveland Clinic, Cleveland, OH, USA

Abstract

Purpose of Review—We review the clinical benefits of altering myocardial substrate metabolism in heart failure.

Recent Findings—Modulation of cardiac substrates (fatty acid, glucose, or ketone metabolism) offers a wide range of therapeutic possibilities which may be applicable to heart failure. Augmenting ketone oxidation seems to offer great promise as a new therapeutic modality in heart failure.

Summary—The heart has long been recognized as metabolic omnivore, meaning it can utilize a variety of energy substrates to maintain adequate ATP production. The adult heart uses fatty acid as a major fuel source, but it can also derive energy from other substrates including glucose and ketone, and to some extent pyruvate, lactate, and amino acids. However, cardiomyocytes of the failing heart endure remarkable metabolic remodeling including a shift in substrate utilization and reduced ATP production, which account for cardiac remodeling and dysfunction. Research to understand the implication of myocardial metabolic perturbation in heart failure has grown in recent years, and this has raised interest in targeting myocardial substrate metabolism for heart failure therapy. Due to the interdependency between different pathways, the main therapeutic metabolic approaches include inhibiting fatty acid uptake/fatty acid oxidation, reducing circulating fatty acid levels, increasing glucose oxidation, and augmenting ketone oxidation.

✉Salva R. Yurista, syurista@mgh.harvard.edu.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Keywords

Cardiac metabolism; Heart failure; Fatty acid; Glucose; Ketone bodies

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by structural and/or functional impairments in the myocardium. Despite significant prevention and therapeutic advances, the prevalence of HF in the USA is still expected to increase from 2.4% in 2012 to 3.0% in 2030 [1]. Moreover, patients with HF have a higher risk of death than those with some of the most common types of cancer [2]. Thus, new therapeutic approaches are urgently needed. The heart has high energy demand and is capable to utilize a variety of substrates to maintain its proper function. It is generally accepted that many aspects of myocardial energetics are altered in HF. These include a shift in substrate preference from fatty acid towards increased glucose utilization and decreased ATP production [3–6]. As HF becomes more advanced, glucose oxidation is also reduced, which is concomitant with increased reliance on ketone bodies as fuel source. [7••, 8••, 9] Since accumulating evidence has linked metabolism with HF development, these altered pathways represent attractive therapeutic targets in HF.

This review will focus on myocardial substrate metabolism in heart failure with reduced ejection fraction (HFrEF), given that to date deranged cardiac metabolism in HFrEF has been extensively characterized, while metabolic derangements in heart failure with preserved ejection fraction (HFpEF) remain poorly understood.

Myocardial Substrate Utilization in Adult Heart: Fatty Acid, Glucose, and Ketone

The heart produces and consumes ~ 6 kg of ATP per day and requires a large amount of oxygen to maintain its function. It is equipped with a highly complex machinery to efficiently produce sufficient ATP using various substrates, including fatty acid (FA), carbohydrate, ketone bodies, and, to a lesser extent, pyruvate, lactate, and amino acids. For more detailed descriptions of the cardiac metabolic pathways, we refer the reader to the various reviews on this topic. [10••, 11, 12, 13••, 14]

Fatty Acid

Fatty acid is the main fuel source for the heart. [15••, 16] FA that is used by the heart either comes as free FA bound to albumin or is derived from triacylglycerol (TAG). FA primarily enters the cardiomyocytes via a protein carrier-mediated pathway, including fatty acid translocase (FAT)/CD36, the plasma membrane isoform of fatty acid binding protein (FABPpm), and fatty acid transport protein (FATP). Of these, CD36 plays the most dominant role. [17, 18] FA is then converted to long-chain fatty acyl-CoA via the action of fatty acyl-CoA synthase. To enter the mitochondria, the long-chain fatty acyl CoA must undergo a series of steps, includes the conversion to long-chain acylcarnitine by carnitine palmitoyl transferase 1 (CPT1), carnitine acylcarnitine translocase (CAT) transport across the inner

mitochondrial membrane, and subsequently the acylcarnitine is converted back to acyl-CoA by CPT2, following which the long-chain acyl CoA can enter FA β-oxidation (FAO). [19, 20] Of note, FAO requires 11–12% more oxygen for a given amount of ATP produced as compared to glucose, making it a less efficient substrate.

Glucose

Glucose is supplied to the heart either comes from uptake of exogenous glucose or is released from glycogen stores. Glucose uptake in cardiomyocytes is mediated by insulin-independent glucose transporters (GLUT1) or insulin-sensitive glucose transporters (GLUT4), with GLUT4 as the predominant glucose transporter in the adult heart and accounts for the majority of glucose transport. [21, 22] Glucose is phosphorylated to glucose-6-phosphate (G-6-P) by hexokinase, and subsequently goes through different metabolic pathways including glycolysis which eventually yields pyruvate for TCA cycle, as well as precursor for the pentose phosphate pathway and the hexosamine biosynthetic pathway. The oxidation of pyruvate is controlled by pyruvate dehydrogenase (PDH) activity. If glycolysis is coupled to glucose oxidation, the net energy production is 30–32 ATP per molecule of glucose metabolized. Although only 2 ATP are produced from each glucose through glycolysis, a previous study showed its critical role in sustaining cardiac contractile function. [23] Intriguingly, a recent study showed that healthy heart consumes only a small amount of glucose, lower than previously reported. [15••]

Ketone

Under normal physiological conditions, the levels of circulating ketone bodies (KB) are low. However, fasting, ketogenic diet, and extreme exercise can drive up ketone levels (i.e., ketosis, βOHB level > 0.5 mmol/l). [24•] Ketone body metabolism includes both ketogenesis and ketolysis. Ketogenesis is the process by which ketone bodies (KB, which include acetoacetate [AcAc], beta-hydroxybutyrate [βOHB], acetone) are produced mainly in hepatocytes as well as kidney epithelial, astrocytes, and enterocytes though to a lesser extent. FA transport from the cytosol to the mitochondrial matrix is triggered by carnitine palmitoyl transferase 1 (CPT1), and after a series of steps necessary for ketogenesis, ketone bodies are synthesized from acetyl-CoA that is derived via β-oxidation. AcAc and βOHB are then released into circulation by monocarboxylate transporter (MCT). The process of redeeming energy from ketone oxidation is called ketolysis, which can occur in almost all cells except hepatocytes. After internalization in extra-hepatic tissues, β-OHB is converted back to AcAc by beta-hydroxybutyrate dehydrogenase (BDH), and succinyl-CoA-dependent transferase (succinyl-CoA:3-ketoacid-CoA transferase, OXCT/SCOT) converts AcAc back to acetoacetyl-CoA, following which is cleaved into acetyl CoA and subsequently metabolized in the TCA cycle to generate ATP. Acetone is not converted back to acetyl-CoA and metabolically inactive; thus, it is either exhaled or excreted through urine. [10••, 25–28] Interestingly, KB produce more energy per 2 carbons than glucose, making it an efficient substrate. However, when calculating the P/O ratio, KB are less efficient than glucose. Unlike FA and glucose, ketone is readily oxidized by the heart and recent comprehensive mapping of human cardiac fuel uptake revealed that the healthy heart also uses a substantial amount of KB. [15••]

Metabolic Derangements in the Failing Heart

Altered energy metabolism has long been characterized in HF. Clinical studies demonstrated that the failing myocardium had ~ 30% reduction in ATP concentration compared to healthy myocardium, alongside with reduction in its flux through creatine kinase. [13••, 29•, 30•, 31•] Furthermore, the depletion of ATP production has been linked with changes in substrate preferences in the myocardium. [12] The following sections will review FA, glucose, and ketone metabolic alterations in the failing heart.

Fatty Acid Oxidation in Heart Failure

Healthy myocardium preferentially utilizes fatty acid as a means of ATP supply as the vast majority of ATP is generated from FAO (approximately 70–90%). [16] However, reduction in mitochondrial FAO was observed in patients with heart failure (HF). Specifically, the rate of myocardial FAO decreases with the progression of HF. [6, 32–34] Detailed mechanisms are still unclear, but one main hypothesis is that the reversal to a fetal metabolic phenotype serves a protective role to the failing heart and prevents it from further impairment. [35] Since the fetal heart lacks mature mitochondria compared to the adult heart, it has limited ability to efficiently oxidize long-chain FA. As a result, glucose utilization predominates in the fetal heart as a source of ATP production, which also happens in the failing heart. [35] On the other hand, there were conflicting results showing no decrease in FAO in patients with HF. [36•] These divergent observations were likely due to the severity, the type of heart failure, and presence of comorbidities in study subjects. In a previous study that reported significant reduction in FAO, transcriptional activation of genes regulated by PPARα/RXRα/PGC-1α was also decreased. [37] Also, PPARα protein levels were significantly decreased in the hearts of subjects with end-stage HF [38]. Moreover, down-regulation of the FAO gene in the failing human hearts was consistent with reduced levels of PGC-1α [39].

Glycolysis and Glucose Oxidation in Heart Failure

Cardiac failure results in inadequate supply of oxygen and washout of metabolic wastes, which deteriorate cardiomyocytes' ability to utilize FAs as energy sources. As a result, this change indirectly activates glycolysis and decreases rate of glucose oxidation in the heart. Upregulation of fructose 2,6-BP, an activator of phosphofructose-1, which is an enzyme that catalyzes an irreversible reaction in glycolysis was observed in rats with pressure-overload LV hypertrophy [40]. However, an increase in glycolysis is likely to be accompanied by a reduction in glucose oxidation. Reduced glucose oxidation was observed in mouse models with HF, pacing-induced HF in pigs, and human subjects with end-stage HF [41•, 42]. A previous study measuring substrate oxidation at various time points in rat after TAC surgery revealed that myocardial glucose oxidation inclined to increase firstly, but was comparable relative to controls in the stage of compensated hypertrophy and eventually lessened when systolic dysfunction happened [43]. Under severe ischemia, the lack of washout after glycolysis may lead to the buildup of protons and disruption of ionic homeostasis, which can cause deleterious effects in contractile function [44]. Taken together, increased rate of glycolysis is likely to be concomitant with decreased glucose oxidation, which contributes to severe myocardial injury. The uncoupling between glycolysis and

glucose oxidation has also been discovered in small animal models and human failing hearts. [45•, 46•] Although there was mounting evidence towards FAO reduction and uncoupling between glycolysis and glucose oxidation in the failing heart, conflicting conclusions were also discovered. An increase in glucose oxidation was found in pacing-induced HF in dogs[47] and higher glucose oxidation rates were observed in patients with idiopathic dilated cardiomyopathy [6]. Therefore, the difference metabolic derangements in the heart may vary depending on the experimental methods (in experimental studies), type and severity of cardiac dysfunction, and different pathological stimuli.

Switch to Ketone Use in Heart Failure

As the heart loses its ability to oxidize FA and glucose, ketone bodies (KB) were suggested to serve as an alternative fuel option for the failing heart. Increased circulating KB levels and myocardial ketone oxidation were found in HFrEF and HFpEF. [9, 48••, 49] Furthermore, plasma βOHB and myocardial KB utilization were also elevated in diabetic hearts and arrhythmogenic cardiomyopathy [50•, 51], which suggests that ketogenic shift is a universal cardiac response to stress. [52•] Ketone body oxidation accounts for approximately ~ 20% of total cardiac energy production in small animal models of HFrEF. [53•] This finding is similar to what has been observed in patients with HFrEF. [15••] Although limited studies have directly studied KB metabolism in myocardium, a strong correlation between circulating ketone concentration and myocardial ketone oxidation has been reported. [15••] Furthermore, mice with cardiomyocyte-specific knockout of the ketolytic enzyme SCOT or BDH1 exhibited worsened cardiac hypertrophy and accelerated pathologic cardiac remodeling following myocardial injury, highlighting the importance of KB in the failing heart. [8••, 54] Collectively, the existing evidence supported the hypothesis that KB oxidation is greatly increased in the failing myocardium as an energy source.

Pharmacologic Modulators of Myocardial Substrate Metabolism

Accumulating evidence from experimental and clinical studies suggests that targeting metabolic substrate metabolism by reducing FAO, increasing glucose oxidation, or augmenting ketone oxidation may be beneficial in HF. Several pharmacological agents that modulate myocardial substrate metabolism, direct and indirectly, have been developed and tested in patients with HF (Fig. 1). The overall goal is to exploit “fuel efficiency” thereby allowing better inotropy and lusitropy without increasing energy expenditure.

Inhibiting FA Uptake

CPT1 is the rate-limiting enzyme for FAO, and thus a potential drug target for regulating FA uptake. Treatment with etomoxir and perhexiline, the inhibitors of CPT1, reduces the activity of this enzyme and hence limits FA oxidation along with increased glucose oxidation. A small pilot study has shown that etomoxir, initially developed to treat diabetes, can improve cardiac function in patients with HF. [55•] A preclinical study indicates that etomoxir improves cardiac function, [56] and slows the progression of HF in pressure-overload cardiac hypertrophy by augmenting sarcoplasmic reticulum uptake [57]. Perhexiline is a specific cardiac isoform of CPT1 inhibitor and was initially developed to treat angina pectoris. An earlier study with perhexiline was associated with improvement

of VO_2 max, left ventricular ejection fraction (LVEF), and myocardial energetics in chronic HF patients [58]. Improvement of exercise capacity and myocardial energetics were also observed in patients with hypertrophic cardiomyopathy treated with perhexiline. In patients with dilated cardiomyopathy, perhexiline increased PCr/ATP ratio and New York Heart Association functional class, without changing LVEF or altering cardiac substrate utilization [59]. Conversely, in hypertrophic heart secondary to aortic stenosis, perhexiline had no benefit in improving hemodynamic performance or decreasing myocardial injury [60]. Of note, some concerns have been raised regarding the use of CPT1 inhibitors related to its neurotoxicity and hepatotoxicity, making the clinical use of perhexiline limited and even strictly prohibited for etomoxir.

Inhibiting FAO

The mitochondrial enzymes involved in FA β-oxidation can also be targeted for HF therapy. Trimetazidine is a competitive inhibitor of 3 ketoacyl-CoA thiolase, the final enzyme in FA oxidation, and has been used clinically for stable angina. Trimetazidine was shown to reduce the frequency of angina attack and improve exercise tolerance and use of SAN [61]. Treatment with trimetazidine was reported to improve functional class [62•] and LVEF [62•, 63•, 64–66] in HF patients. A similar beneficial effect on LVEF has also been reported in patients with idiopathic dilated cardiomyopathy [67] and diabetic cardiomyopathy [68•]. Improvement of LVEF was more prominent when trimetazidine was used together with β-adrenoreceptor antagonist, suggesting a synergistic effect [67]. Furthermore, improvement in exercise performance and reduction of brain natriuretic peptide (BNP) and cardiac troponin T (cTnT) was also observed in patient with ischemic cardiomyopathy treated with trimetazidine [69]. Contrariwise, trimetazidine administration showed no benefit on cardiac function and exercise capacity in patients with stable nonischemic HF [70].

Reducing Circulating FA Levels

Reducing the circulating levels of FA may indirectly serve as a therapeutic approach to modulate FA oxidation in HF. Among others, β-adrenergic receptor antagonists (metoprolol and carvedilol) can improve cardiac performance and survival in patients with HF. [71, 72•, 73, 74] β-Adrenergic receptor antagonists have energy-sparing effects, by decreasing myocardial FA use [72•] and increasing carbohydrate oxidation [73]. However, metoprolol provides the same benefit as carvedilol without reducing free FA [73]. Niacin, the broad-spectrum lipid drug, can decrease circulating FA levels and therefore decreases myocardial FA oxidation. Though, studies with nicotinic acid derivatives acipimox in dilated cardiomyopathy [75] and ischemic HF [76] were associated with a significant reduction in cardiac work and efficiency, despite a significant reduction in circulating FA. Reducing FA delivery to the heart with peroxisome proliferator–activated receptor (PPAR)α and PPARγ agonists (fibrates and thiazolidinediones) also did not prevent the development of HF. Thiazolidinedione use was also associated with risk of new or worsened heart failure [77].

Increasing Glucose Oxidation

Treatment with pyruvate dehydrogenase kinase (PDK) inhibitor dichloroacetate (DCA) demonstrated benefit in preclinical models of HF [78••, 79•]. As an analog of pyruvate, DCA increases PDH activity and therefore promotes glucose oxidation. However, DCA did

not improve LV function or exercise performance in patients with HF. [80, 81] Also, human study with DCA is limited due to its chronic neurotoxicity [82, 83].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recommended treatment option for glycemic control in patients with type 2 diabetes. Recent guidelines recommend the use of GLP1-RAs in all patients with T2DM with high risk for or with prevalent atherosclerotic cardiovascular disease (ASCVD) [84–87]. GLP-1RAs have consistently shown safety and reduction in cardiovascular events in patients with established CVD. It has been hypothesized that GLP-1RAs may prevent heart failure through augmenting glucose uptake and utilization. Preclinical studies showed that GLP-1 promoted increased myocardial glucose uptake [88, 89•, 90]. However, the results in humans are not convincing enough to support the hypothesis that increased myocardial glucose uptake mediates cardioprotection following GLP-1 therapy. Forty-eight hours subcutaneous infusion of GLP-1 did not change metabolic parameters in non-diabetic patients with congestive HF. [91•] Furthermore, GLP1 increased myocardial blood flow without changing myocardial glucose uptake in diabetic patients without coronary artery disease [92].

Increasing Ketone Oxidation

Increasing ketone oxidation is an effective way to supply the heart with more energy-efficient substrate that may be beneficial in HF. [24•] It is believed that ketone may exert extra pleiotropic effects beyond cardiac energetics. Ketone oxidation rate is directly proportional to its arterial concentration; thus, increasing delivery of ketone to the heart results in increased cardiac ketone oxidation and/or utilization. [10••, 93••] Elevated ketone levels can be achieved by fasting, ketogenic diet, medium-chain triglyceride (MCT), 1,3-butanediol, ketone salts (KSs), or ketone ester (KE) supplementation. Interestingly, sodium-glucose co-transporter 2 inhibitors (SGLT2i) have also been reported to increase circulating ketone levels and cardiac energetics that may contribute to clinical benefits in HF. [94••, 95••, 96••, 97•] In addition, increased circulating ketones following SGLT2 inhibitor administration may modulate the NLRP3 inflammasome thereby reducing inflammation in the failing heart. [97•] Significant positive effects of fasting, ketogenic diet, medium-chain triglyceride (MCT), ketone supplementation, or increased ketone levels mediated by SGLT2i treatment were previously shown in preclinical models of HF. [93••, 96••, 98–101] For instance, supplementation of KE attenuated LV dysfunction and remodeling in two preclinical models of HFrEF. [93••] Moreover, increased expression of MCT1, Bdh1, and SCOT were observed in rats with HFrEF, indicative of increased myocardial ketone update and utilization. [93••] The benefits of ketone supplementation in HFpEF are not fully understood. In a mice model with HFpEF (combining the age, long-term high-fat diet, and deoxycorticosterone pivalate challenge), increasing circulating ketones provided benefits by suppressing proinflammatory cytokines, improving mitochondrial dysfunction, and attenuating cardiac fibrosis, despite reduced ketone oxidation [99]. However, the opposite results were reported in non-HF animals. Long-term ketogenic diet promoted cardiac fibrosis and reduced cardiac function in healthy adult rats [102]. Increased cardiac fibrosis and remodeling were also demonstrated in spontaneous hypertensive rats following 4 weeks of ketogenic diet [103]. To date, only ketone salts and ketone ester have been tested clinically for HF. [104•, 105••] In general, KSs are less expensive and taste better but less

ketogenic than KE (1–3 mmol/l for KSs vs. 2–6 mmol/l for KE). Infusion of KSs Na-βOHB for 3 h improved cardiac output and reduced systemic vascular resistance in HFrEF patients [105••], whereas acute oral supplementation of KE induced ketosis and increased cardiac ketone utilization, and it was associated with degree of cardiac function and remodeling in patients with HFrEF. [104•]

Assessing Myocardial Metabolism in HF In Vivo

A major challenge in metabolism research is understanding which metabolic pathways operate in HF in a native microenvironment. Thus, the assessment of cellular energy metabolism in vivo is essential for understanding the HF pathophysiology, developing new targeted therapy, and evaluation of benefits of metabolic modulation in HF. During the past decade, several approaches have been developed and introduced that measures a few aspects of metabolism in the human heart.

Arterio-venous (Transcardiac) Gradient

While the cardiac venous system can be variable, drainage is predominantly via the coronary sinus (CS). In addition to electrophysiological mapping and pacing, the CS can be cannulated and used to draw blood samples to measure biomarkers and metabolites. In this respect, simultaneous arterial and coronary sinus blood sample can give access to quantify transcardiac gradient of myocardial substrate metabolism [106]. For instance, a recent study utilized this method to perform comprehensive mapping of human cardiac fuel use in HFrEF and HFpEF. [15••]

Biomarkers

While biomarkers such as natriuretic peptides have been widely used to facilitate diagnosis, prognostication, and management of patients with HF and are included into HF practical guidelines [77], there are no standardized specific biomarkers for cardiac metabolism. However, to date, metabolomic biomarkers and profiling of myocardium, serum, or breath have been studied to create metabolic profiles in patients with HF. [9, 107] Although all this is as yet a relatively new field, metabolomics is poised to have a broad range of potential clinical applications for clinical diagnostic (e.g., develops new biomarkers), therapeutic evaluations, or prognostic purposes in HF.

Metabolic Imaging

A better understanding of the different aspects of cardiac metabolism and alterations in cardiac metabolism in health and disease in vivo might lead to better characterization, prevention, and treatment of HF. To date, metabolic imaging modalities in humans include a range of noninvasive imaging techniques such as chemical exchange saturation transfer (CEST) for creatine mapping [108]; magnetic resonance spectroscopy techniques for quantification of metabolites, e.g., triglycerides, ATP, creatine, phosphocreatine, and metabolic flux [109–111]; and single-photon emission computed tomography (SPECT) and positron emission tomography (PET) for assessment of myocardial substrate uptake [112•]. Despite its great potential, most of metabolic imaging studies have only been performed ex vivo and in animal models, and largely limited to research settings in humans. Yet,

consistency and reproducibility remain a challenge, and more study will be required before any certainty can be attained in the design of expanding its application in the clinical arena.

Concluding Remarks and Future Perspectives: an Opinion

Our understanding of myocardial metabolism and its role in HF, mostly HFrEF, has grown in recent years with the importance of cardiac metabolism being highlighted in the 2016 Scientific Statement from the American Heart Association [113]. HF is linked with profound alterations in cardiac metabolism. It is characterized by a shift in substrate preference away from FAO to an increased glucose utilization. When heart failure progresses to an advanced stage, the failing heart reprograms to overall reduction in glucose oxidation and increased reliance on ketones. Alterations in myocardial substrate metabolism result in impaired cardiac ATP production and may contribute to the severity of HF. Therefore, it has been proposed that myocardial substrate metabolism may be potential new therapeutic targets in HF.

Accumulating evidence suggests that perturbations in myocardial energy metabolism and mitochondrial function contribute to the pathological remodeling that leads to HF. One common adaptation in the failing heart is that the heart undergoes fetal reprogramming, where the fetal heart and the failing heart show similar fuel preference, shifting from fatty acids to glucose for energy provision due to more readily available ATP despite less produced per oxygen unit than from FAO. Alterations in myocardial substrate metabolism result in impaired cardiac ATP production and may contribute to the severity of HF. [12, 35, 114, 115] Depletion of high energy phosphate levels is reduced in both animals and humans. [29•, 116••, 117, 118] Previous observation showed human inborn errors in mitochondrial fuel metabolism and ATP production cause cardiomyopathy, supporting the concept that derangements in myocardial metabolic contribute to HF development and/or progression. [119–121] We believe that these observations are profound enough to be considered “adaptive” response to cardiac stress.

At certain point, this fetal-like reprogramming no longer suffices to support cardiac structure and function. When heart failure progresses to an advanced stage, the failing heart reprograms to overall reduction in glucose oxidation and increased reliance on ketones. So far, previous studies have reported that the failing rodent and human heart increases ketone body utilization. [7••, 8••, 9, 93••, 122] In addition, a ketogenic diet, which increases circulating levels of the ketone body βOHB, retarded the development of HF in mice, and infusion of βOHB markedly enhanced cardiac function and reduced elevated ventricular filling pressures in a canine tachypacing model of progressive HF. [8••] In clinical setting, acute infusion of βOHB to humans with HF resulted in impressive hemodynamic improvement. Recently, ketone ester–enriched diets that induce sustained ketonemia reduce pathological cardiac remodeling and enhance ventricular function in multiple heart failure models across both mice and rats using both prevention and treatment strategies. [105••] Importantly, ketones do not influence the oxidation rates of other substrates. Indeed, when ketone delivery to the heart is increased, cardiac ATP production increases in a dose-dependent fashion without compromising glucose and fatty acid oxidation. As such, ketones provide an additional fuel source. However, while ketones increased ATP production, they

do not affect cardiac efficiency. [53•, 123] These collective results suggest that the increase in myocardial ketone oxidation observed in heart failure is an adaptive response to overcome bioenergetic insufficiency, and increasing delivery of easily processed fuels in the form of ketone bodies provides beneficial effects in HF. Therefore, it has been proposed that myocardial substrate metabolism may be potential new therapeutic targets in HF.

Recent advances in metabolomics and transcriptomic analysis also revealed the role of other substrates, such as short-chain fatty acids (SCFAs) and branched-chain amino acids (BCAAs) in HF. Previous studies highlighted the potential role of SCFAs as an alternative fuel for HF [124] and that BCAA catabolic deficiency promotes the progression of cardiac pathological remodeling and dysfunction [125]. However, the evidence is very limited and fairly well defined; more studies are needed to validate the proposed hypothesis.

Multidisciplinary approaches in both experimental and clinical research have provided valuable mechanistic insight regarding myocardial substrate metabolism and some metabolic agents have been developed and tested in HF. Now, the next question that may come in mind is: “is it ready for prime time?” Unfortunately, the answer is “not yet.” Despite some positive results observed by targeting myocardial substrate metabolism in HF, their clinical applications are still in their infancy. Currently, there are several major questions that need to be addressed to determine whether targeting myocardial metabolism is a viable strategy for HF therapy.

First, to date, the available data from preclinical studies and (a few of) clinical trials have produced inconsistent results. This partly could be explained by the exact mechanisms linking metabolic changes to HF development are still poorly understood. Moreover, the need for consistency and reproducibility remains a main challenge. Also, most of these mechanistic data were only derived from studies in HFrEF, and direct evidence in HFpEF is limited.

Second, the toxic effects of inhibiting metabolic enzymes responsible for myocardial substrate uptake/utilization need to be deciphered. For example, there has been a growing concern about the hepatotoxicity of (nonselective) CPT1 inhibitors and neurotoxicity of PDK inhibitors.

Third, ketone therapy may hold a greater promise as it may treat and restore cardiac function of the failing heart through its pleiotropic effects in addition to providing ancillary fuel for the energy-starved heart. Yet, there are only limited data available; hence, long-term studies are needed to understand the implications of these findings.

Despite these challenges, links between myocardial metabolism and HF are recently being uncovered. More work and studies are needed to examine the safety, feasibility, and efficacy of “metabolic” therapy, including the exact mechanism of benefits in HF in rigorous large population clinical studies.

Conflict of Interest

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• Of importance

•• Of major importance

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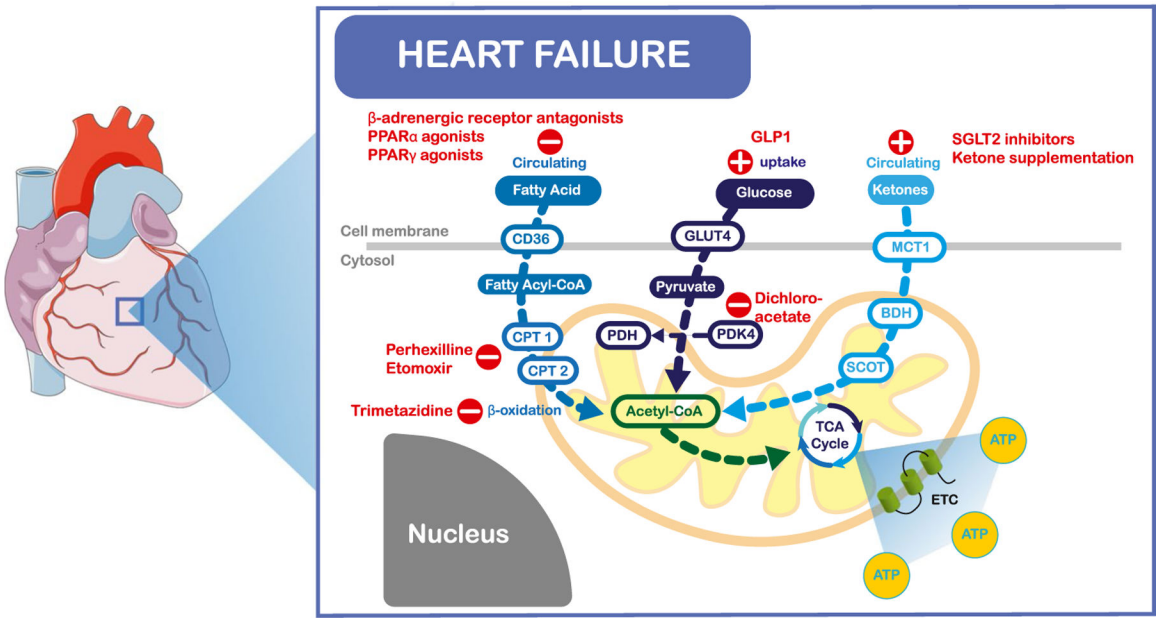

Fig. 1.

Metabolic modulation in heart failure. Reduction of fatty acid oxidation (FAO) can be achieved by decreasing circulating fatty acid levels (with the use peroxisome proliferator–activated receptor (PPAR) agonists and β-adrenoceptor antagonists), decreasing mitochondrial uptake of fatty acid (with the use of carnitine palmitoyl transferase 1 (CPT1) inhibitors etomoxir and perhexiline), or inhibiting FAO directly (with the use of trimetazidine). Stimulating glucose uptake and/or oxidation can be done by increasing glucose uptake (with the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) or increasing glucose oxidation (with the use of dichloroacetate that increases pyruvate dehydrogenase (PDH) complex activity by inhibiting PDK4). Ketone oxidation can be augmented by increasing ketone availability with the use of sodium-glucose co-transporter 2 (SGLT2 inhibitors) and ketone supplementation (e.g., ketone salts, ketone ester). CD36, fatty acid translocase (FAT); GLUT4, glucose transporters 4; MCT1, monocarboxylate transporter 1; BDH, beta-hydroxybutyrate dehydrogenase; SCOT, succinyl-CoA:3-ketoacid-CoA transferase; ATP, adenosine triphosphate; TCA, tricarboxylic acid; ETC, electron transport chain. Part of the illustrations elements courtesy of Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0