The promise and problems of metabolic-based therapies for heart failure

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Abstract

Despite standard therapies, heart failure patients have high rates of morbidity highlighting the need to develop alternative therapeutic approaches. Heart failure has been described as an energy-starved condition that is hypothesized to drive the pathological remodeling of the heart. Numerous studies have described the metabolic defects that occur when the heart fails and adaptive changes that take place to maintain the energy needed for the heart to function properly. In this minireview we will summarize the metabolic requirements of a normal heart and what happens during failure. We will also summarize the various metabolic therapeutic strategies that have been developed over the years to treat heart failure and their results from clinical trials.

Keywords: Adrenergic receptor • Metabolism • Heart failure • Myocyte

Introduction

The heart requires a high metabolic rate to sustain needed Adenosine Triphosphate (ATP) levels, more so than any other organ besides the kidney [1]. The heart also has tremendous flexibility to metabolize various types of substrates besides normal glucose and Fatty Acids (FA), such as lactate, amino acids, and ketone bodies though these are minor contributors to energy production in a normal heart [2]. During Heart Failure (HF), large energy deficits build up from alterations and defects in the ability to metabolize FAs properly, increasing oxidative stress and contractile dysfunction which ultimately contribute to progression of HF and poor clinical outcomes [3].

Literature Review

Fatty acid and glucose metabolism

Fatty Acid Oxidation (FAO) (Figure 1) supplies the vast majority of the ATP requirements (60%-90%) in the normal heart, followed by glucose oxidation (Figure 2) [4]. FAO provides 105 ATP molecules for every 23 molecules of oxygen while glucose oxidation generates 31 ATP molecules per 6 molecules of oxygen, a more efficient use of oxygen even though less ATP is made [4].

During HF, the ability to metabolically utilize FA decreases [5,6], prompting a switch to greater carbohydrate metabolism. This switch in substrate utilization during HF is due to decreases in the number of mitochondria [7], mitochondrial dysfunction caused by Reactive Oxygen Species (ROS) [7-9], downregulation of FAO genes (i.e. FATP1, CPT-1) (Figure 1) [10] and enzymes involved in β-oxidation and oxidative phosphorylation (i.e. electron transport system), resulting in greater use of oxygen-sparing carbohydrate metabolism. HF also results in the upregulation of genes and activity associated with glucose oxidation or the flux of glucose into the heart, such as Glucose Transport proteins (GLUT), the enzyme Phosphofructokinase (PFK), Pyruvate Dehydrogenase (PDH) (Figures 2 and 3) [11-13]. Eventually, at end-stage HF, there is decreased ability to metabolize any type of substrate [14]. As such, HF is not
merely shifting metabolically from FA to glucose utilization, but is also associated with decreased overall oxidation rates and increased oxidation of alternate substrates (i.e. amino acids, ketone bodies). While these metabolic changes occur during pressure overload and ischemic HF, an exception to this pathological metabolic remodeling occurs during diabetic-induced HF where there is an increase in FA uptake, shifting metabolism to even greater FAO which leads to damaging oxidative stress and dysfunction [15].

**Figure 1:** Fatty Acid Metabolic Pathways. **Abbreviations:** ADP: Adenosine Diphosphate; ATP: Adenosine Triphosphate; CoA: Coenzyme A; CPT: Carnitine Palmitoyltransferase; FAD: Flavin Adenine Dinucleotide; FATP1: Fatty Acid Transport Protein 1; FFA: Free Fatty Acid; IMM: Inner Mitochondrial Membrane; NAD: Nicotinamide Adenine Dinucleotide; OMM: Outer Mitochondrial Membrane; TCA: Tricarboxylic Acid Cycle.

**Figure 2:** Glucose Metabolic Pathways. **Abbreviations:** ADP: Adenosine Diphosphate; ATP: Adenosine Triphosphate; CoA: Coenzyme A; FAD: Flavin Adenine Dinucleotide; GLUT: Glucose transporter; IMM: Inner Mitochondrial Membrane; OMM: Outer Mitochondrial Membrane; PFK: phosphofructokinase; PPP: Pentose Phosphate Pathway; NAD: Nicotinamide Adenine Dinucleotide; NADP: Nicotinamide Adenine Dinucleotide Phosphate; TCA: Tricarboxylic Acid Cycle.
Randle effect

In cellular metabolism, there is a competition of substrates between the oxidation of FA and carbohydrates as described by the Randle cycle, also referred to as the glucose-fatty acid cycle (Figure 3) [16]. Its role is thought to be a signaling mechanism to the cell that it has an excess of one type of fuel and allows for fine-tuning of metabolism without the intervention by hormonal signals. The Randle cycle describes the inverse relationship where the increase in utilization by one type of metabolic substrate will lead to the other’s inhibition. FAO increases acetyl-CoA which inhibits Pyruvate Dehydrogenase (PDH), which is essential to converting pyruvate to acetyl-CoA to feed the TCA cycle from glycolysis [17]. Increased levels of citrate from the TCA cycle inhibits a key glycolytic enzyme, PFK, the rate limiting enzyme for glycolysis and prevents pyruvate from accumulating [18]. The Randle cycle becomes important to understand why HF metabolic therapeutics are predicted to increase glucose oxidation when their main effect is to decrease FAO.

Ketone metabolism

The heart is metabolically flexible due to its high metabolic rate requirements [1] and can adapt to utilizing various substrates for fuel as they are available. Ketone bodies are generated as intermediate products of FAO in the liver and consist of acetoacetic acid, β-hydroxybutyric acid and acetone (Figure 4). During non-fasting conditions, ketone bodies are not utilized for energy but can be a critical part of maintaining energy homeostasis during stress and starvation by conserving glucose [19]. As HF is hypothesized to be in an “energy-starvation” state [20], the failing heart’s utilization of ketone bodies becomes more critical [21,22]. There is also an increase in the enzymes and metabolic intermediates associated with ketone metabolism during end-stage HF in addition to the expected downregulation of FAO associated proteins [21,22]. Ketones are very efficient in its energetic properties but circulating levels, while normally low, can increase quickly during starvation or HF. Ketone bodies can generate more ATP than glucose and with greater efficiency than FAO, but not as efficient as glucose. As HF progresses, later stages have deficits in both FA and glucose oxidation, causing the heart to utilize alternate metabolic substrates. Ketone oxidation increases during HF because it bypasses the normal oxidative pathways that are affected and downregulated during HF [19,21-23]. However, excessive ketone body oxidation could also lead to a depletion of TCA intermediates (Figure 4) [24] and will not provide the long-term energy needed for contractile function [25], so its usefulness as a therapeutic strategy for HF is limited.

Metabolic Therapeutics and Clinical Trial Outcomes

Our knowledge of cardiac metabolism and its alterations during failure as reviewed above has increased greatly during the years making metabolic therapeutic strategies an attractive target to treat HF. Traditional therapies to treat HF include renin-angiotensin inhibitors [26,27], β-blockers [28], mineralocorticoid antagonists [29], and vasodilators [30]. While these traditional therapeutics are the gold-standard and improve contractile function, long-term use has failed to improve outcomes.
β-Adrenergic receptor blockers

β-blockers are still a mainstay in HF treatment. Their primary action is to reduce heart rate which results in a decrease in work load and oxygen consumption. However, β-blockers are also being appreciated more for a secondary effect on cardiac metabolism. The best described β-AR blocker for its treatment for HF is carvedilol. Carvedilol is a β-AR antagonist and an β1/α1 antagonist [31]. While metoprolol and other α1-AR blockers have similar effects on cardiac metabolism, carvedilol has better effects on improving glucose metabolism [32], improve insulin sensitivity [33], and has greater antioxidative properties [34]. Carvedilol can achieve this by decreasing the pool of free fatty acids, which shifts energy substrate availability in the heart to increase glucose oxidation and energy efficiency [35,36]. In clinical trials, carvedilol reduces the mortality risk in HF patients better than metoprolol [37], but has not been assessed for its metabolic benefit in large scale studies. In a small clinical study of 9 patients with class III HF, carvedilol treatment for 3 months decreased myocardial free FA metabolism by 57% [38].

Heart Rate Control

The magnitude of heart rate reduction to the magnitude of survival benefit is strongly correlated in HF, more so than the type or dosage of β-AR blocker [39]. In a different class than β-AR blockers but with similar physiological effects, ivabradine lowers heart rate by inhibiting the inward Na+/K+ current that regulates sinus rhythm generation [40]. Ivabradine has an advantage over β-AR blockers in that it is a pure heart rate reducing drug, eliminating some of the potential side effects of β-AR blockers. During exercise studies, ivabradine caused a similar reduction in heart rate as β-AR blocker atenolol and improved cardiac oxygen consumption but without any negative lusitropic effect [41]. In several clinical studies, ivabradine reduced oxidative stress, improved cardiovascular endpoints, as well as morbidity and mortality in HF [42]. However, more clinical studies are needed directly comparing ivabradine vs. β-AR blockers to determine any significantly different long-term effects on efficacy or outcomes [42].

Sodium-Glucose Co-Transporter 2 inhibitors (SGLT2i)

Inhibitors of the type 2 Sodium Glucose Transporters (SGLT2) were originally approved for treatment of type 2 diabetes. Of the 12 family members, SGLT2 are expressed on the kidney proximal tubules and reabsorbs a large part (90%) of the glucose in the body [43]. Hence, SGLT2 inhibitors (SGLT2i) would increase the urinary excretion of glucose. They are also expressed on pancreatic alpha cells [44] and regulate glucagon release that exert beneficial effects on both glucose and lipid metabolism to improve cardiovascular outcomes [45].

A number of studies have shown that SGLT2i provide profound reductions in the hospitalizations for HF by at least 26% [46-49]. It is postulated that the primary benefit of SGLT2i is to increase circulating ketone levels which increase ketogenesis, but this is not certain [50-52]. The SGLT2i, empagliflozin, improved remodeling and function in the heart by increasing ketogenesis which has better metabolic efficiency than glucose to produce ATP [53]. Empagliflozin also lowered levels of ROS and improved mitochondrial dysfunction in HF, resulting in a reduction of LV mass and fibrosis [54]. SGLT2i have been shown to also prevent and reduce NADPH-mediated oxidative stress and its resulting damage [55-57] that contributes to HF progression [58].

The cardioprotective benefits of SGLT2i have also been ascribed to the activation of sirtuin-1 (SIRT1: Silent Information Regulator 1)
signaling pathways [59]. SIRT1 is a NAD-dependent deacetylase of the histone deacetylase family [60] and transcriptionally-regulates many of the major genes involved in aging, metabolism, oxidative stress, and mitochondrial biogenesis and function in the heart through its downstream signals [61,62]. During starvation or energy-starved states such as HF, SIRT1 stimulation promotes FAO and gluconeogenesis which can drive ketone body production and ketogenesis [63], thus, increasing metabolic efficiency. These results may explain the cardioprotective effects of the red wine chemical, resveratrol and its derivatives, which has a SIRT1 activating effect [64,65]. Clinical trials with synthetic SIRT1 activators have shown cardiovascular benefit [66,67] but have not been tested in HF. Future clinical studies may reveal a potential for the consumption of SIRT1 activators as an attractive target to treat HF.

However, not all cardioprotective effects of SGLT2i may be metabolic [68]. The heart contains some of the highest levels of the enzymes required for ketone oxidation in the body [69] but the receptors for SGLT2 are not expressed in the myocardium [70]. One hypothesis is that HF causes an increase in SGLT1 receptor expression in the heart which undergo non-specific inhibition by SGLT2i [71] or that ketosis is indirect [70]. Other benefits from SGLT2i are 45% reduction in the progression of kidney failure [72]. A large scale meta-analysis of four different SGLT2is also revealed significantly increased risk of diabetic ketoacidosis and genital infection [73].

**Carnitine Shuttle**

L-Carnitine is important in FAO, being utilized as a cofactor in the carnitine shuttle that transports fatty acids into the mitochondria where FA undergo oxidative phosphorylation (Figure 1). L-propionylcarnitine has been previously studied for metabolic enhancement in the heart as carnitine supplementation may improve FAO through substrate availability. However, the actions of l-propionylcarnitine cannot be explained by stimulation of FAO but by increasing glucose oxidation via relief of PDH inhibition. The metabolic premise is that inhibition of FAO shifts cardiac metabolism towards utilizing more of the energy-efficient glucose metabolism via the Randle cycle. Although l-propionylcarnitine showed increased exercise tolerance and improved symptoms in HF patients compared with a placebo control group [74], a large randomized and double-blind clinical trial failed to reach sufficient efficacy [75]. Similar results have been found with meldonium, a FAO inhibitor used illegally by Soviet and Latvian professional athletes to increase performance. Meldonium (i.e. Mildronate®) is biochemically related to l-carnitine and partially inhibits the last enzymatic step in the body’s synthesis of l-carnitine. There are reports of positive outcomes in HF when meldonium is used in combination therapy [76-78]; however, there are no large-scaled controlled clinical trials as the drug is not available in the United States. An alternate way to modulate the carnitine pathway and shuttle is through the enzymes, Carnitine Palmitoyl Transferase (CPT), which has two variants: CPT1 and CPT2 (Figures 1 and 4). Long-chain fatty acyl-CoA is converted to acylcarnitine by CPT1 on the outer membrane of mitochondria. Acylcarnitine is then transported to the inner membrane by a transposase and CPT2 is used to transfer the acyl group on acylcarnitine to long-chain fatty acyl-CoA. Once inside the mitochondria, FAs are oxidatively metabolized. The CPT1 inhibitors, etomoxir or perhexiline, have been shown to improve cardiac energetics, exercise capacity, and diastolic function in hypertrophic cardiomyopathy patients after 4-5 months of dosing [79-82]. However, it has a narrow therapeutic window with possible neurotoxic and hepatoxic side effects [83,84]. A clinical trial is now underway that will test whether prolonged treatment with perhexiline for 12 months will improve left ventricular hypertrophy which is the main driver of systolic dysfunction and HF [85].

**General FAO inhibition**

Trimetazidine or ranolazine are anti-anginal drugs that inhibit FAO to indirectly increase glucose oxidation via the Randle cycle. Once thought to act by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase [86], a subsequent study have kinetically shown that both trimetazidine and ranolazine are not substrates for the thiolase but do inhibit FAO [87]. In general, smaller clinical trials and meta-analysis with either trimetazidine or ranolazine demonstrated efficacy against HF, particularly when the dosing was long-term [88-94] but other studies did not improve exercise capacity or mortality in HF but this was attributed to them being weaker FAO inhibitors than the CPT1 inhibitor perhexiline. Trimetazidine is currently approved for coronary artery disease [94] but not HF due to the lack of large-scale clinical trials. A meta-analysis is currently being undertaken to assess trimetazidine in combination therapy with the β-AR blocker, bisoprolol [99] after a smaller combination therapy clinical study demonstrated efficacy to treat HF [100].

**Directly increasing glucose oxidation**

While several metabolic inhibitors of FOA indirectly increase glucose oxidation via the Randle cycle (Figure 3), potential therapeutics that can directly increase glucose uptake and/or its oxidation is an alternative approach to metabolically treat HF. During glycolysis, pyruvate is transported into the
mitochondria for subsequent oxidation (Figures 2 and 4). Pyruvate Dehydrogenase (PDH) converts pyruvate into acetyl CoA which enters the TCA cycle and fuels oxidative phosphorylation. PDH is tightly regulated by Pyruvate Dehydrogenase Kinases (PDK) and pyruvate dehydrogenase phosphatases [101]. PDKs phosphorylate PDH, which reduces its activity and phosphate is removed by the phosphatase, increasing PDH activity. This highly-regulated control makes PDH a potential therapeutic target. Dichloroacetate (DCA) is an inhibitor of PDKs, increasing PDH activity by promoting the conversion of pyruvate into acetyl-CoA, thereby increasing oxidation through the TCA cycle [102]. In early animal studies, DCA showed promising results [103,104] but human studies are limited and conflicting. A small clinical trial tested DCA (50 mg/kg) in HF patients [105] resulted in increased left ventricular mechanical efficiency and stimulated lactate consumption. However, another study showed that DCA administration did not improve LV function [106]. DCA has side effects of neurotoxicity and carcinogenicity that restricts clinical use and further development [107,108]. However, a more recent clinical study using lower dose of DCA (3-6 mg/kg b.i.d) for 4 months to treat pulmonary arterial hypertension improved lung capacity and was well tolerated [109]. In this study, an increase in right ventricular ejection fraction was detected even with this lower dose which might mitigate potential side effects. DCA treatment may also induce epigenetic remodeling during HF through histone acetylation that may help reverse the cardiac pathophysiology [110].

Discussion

Various modulators of the metabolic pathways have been discussed here with their results from clinical trials. Early clinical trials that used FAO inhibitors to improve oxygen efficiency and increase glucose oxidation did produce some favorable results but could not reach efficacy milestones. While our understanding of the metabolic changes that occur during the progression of HF has increased, targeting these changes with metabolic small molecules have not done particularly well in clinical trials. SGLT2is have shown the most consistent and efficacious results in clinical trials [111]. Several metabolic therapeutics developed undesirable side effects or were variable in outcomes. One explanation for the variable outcomes of metabolic-based clinical trials in HF may be due to comorbidities which also vary upon gender and type of HF [112]. During the SGLT2i clinical trial using empagliflozin which reduced adverse cardiovascular events in HF patients with type 2 diabetes [113], a subsequent post-hoc analysis [46] indicated that the beneficial outcome of SGLT2i did not depend upon a HF diagnosis and variable differences were noted depending upon the type of cardiovascular disease [72] or type of SGLT2i used [114]. The vast majority of clinical trials in HF are performed in patients under the age of 65 [115]. A common comorbidity and potential clinical trial outcome variability that is often overlooked is a sedentary lifestyle brought on by the chronic illness of HF, particularly in the aged population. A randomized and controlled clinical trial on the effects of exercise training in elderly HF patients significantly improved both cardiac and pulmonary function after only 4 weeks of training [116]. Since HF patients often develop multiple and variable comorbidities, a holistic and multidisciplinary approach is needed to manage HF and to include these populations in future clinical trials.

Conclusion

Metabolic therapies have promise as a sole or add-on to currently used treatments, such as β-blockers to treat HF. SGLT2is have the current best potential to become the new standard in HF care but their mechanistic actions are not known if they are truly metabolic. As HF is very complex with variable comorbidities, a patient-specific approach may be more viable and conjoined with metabolomics, could provide information for the better design of future clinical trials and which metabolic therapy may provide the best treatment options.

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