METABOLIC RECOVERY OF THE FAILING HEART: EMERGING THERAPEUTIC OPTIONS

Dale J. Hamilton, M.D.

Houston Methodist Research Institute, Houston Methodist Hospital, Houston, Texas

Abstract

Heart failure has mortality rates that parallel those of breast cancer. Current management strategies include neurohormonal blockade, rate control measures, natriuretic peptide preservation, implantation of mechanical assist devices, and heart transplantation. Despite these strategies, however, the failing myocardium remains energy depleted. New strategies to promote metabolic recovery are being developed to potentially augment current treatment guidelines. For example, an unexpected finding of our own studies showed that mechanical unloading with assist devices in advanced-stage heart failure restored metabolic flux. Unfortunately, at that point it is too late for myocardial recovery.

Traditional metabolic therapies addressing hyperglycemia have had limited long-term outcome benefit. Now, new therapeutic options are emerging based on increased understanding of the molecular mechanisms underlying energy depletion. Metabolic cardiac imaging combined with laboratory diagnostics could guide the design of individual therapeutic strategies. To date, agents that show benefit in select individuals include mimetics that stimulate glucagon-like peptide-1, inhibitors of sodium-glucose cotransporter receptors, drugs that limit fatty acid oxidation, and hormonal therapy in select individuals. This review will summarize mechanisms and investigations related to these metabolic approaches to heart failure.

Introduction

Heart failure (HF) mortality rates parallel those of breast and other common forms of cancer. The unadjusted 5-year fatality rate for HF is 59% compared to 58% for cancer-related deaths.[1] Current therapeutic strategies, including neurohormonal and mineralocorticoid blockade as well as mechanical interventions, have improved HF survival.[2] Recent advances have expanded on this, such as the introduction of natriuretic peptide mimetics and vasopeptidase inhibitors, sinoatrial node inhibitors, and medications for hyperkalemia control. Also, a recombinant form of the hormone relaxin has shown efficacy via vasodilator mechanisms. Despite these developments, metabolic treatments to date have had limited success, and the failing myocardium remains energy deprived. In terms of prevention, intensive glucose control measures have had no demonstrable favorable impact on HF occurrence.[3] Myocardial energy depletion has been demonstrated by a variety of techniques, most notably ^{31}P-magnetic resonance spectroscopy (MRS).[4] Oxidative metabolic flux transfers energy from carbon bonds to high-energy phosphate ATP and phosphocreatine (PCr). As heart failure progresses, the PCr/ATP energy ratio declines.

Our local HF investigations of paired left ventricular (LV) wall samples unexpectedly demonstrated reversal of the stalled metabolic flux related to energy transfer. The sample pairs from the same hearts were procured at the time of left ventricular assist device (LVAD) placement and again during transplantation.[5] These samples of course were from advanced, end-stage heart failure. Metabolic reversal notwithstanding, hemodynamic recovery would be unlikely. However, this provides a rational for earlier interventions to maintain substrate oxidation and high-energy phosphate production with the goal of preventing or even recovering the myocardium. This update offers an overview of the rationale for and identification of emerging therapeutics for HF treatment. The emphasis in this review is on the emerging role of metabolic management with medical decision making based on the stage of heart failure and the presence of comorbidities such as obesity, insulin resistance, and diabetes. These variables impact myocardial substrate selection and utilization and their response to specific therapeutic options. For example, early stage heart failure is characterized by fatty acid oxidation. A shift to enhanced glucose utilization occurs as the stress of heart failure progresses or becomes more severe.[6] However, in individuals with obesity, insulin resistance, and/or type 2 diabetes, this shift is hindered. Relative fatty acid utilization then increases.[7]

Current Therapeutic Practices

There are more than 12 therapeutic classes of drugs for glucose control, and several drugs within each class are approved for use in individuals with diabetes and normal ventricular function. These include both oral and injectable agents. Three of the classes include injectables: insulin, incretin mimetics, and amylin analogues. Oral agents include sulfonylureas, biguanides (metformin), thiazolidinediones (TZD), alpha-glucosidase inhibitors, meglitinides, dipeptidyl peptidase-4 inhibitors (DPP-4), and more recently, the glycosuric sodium-glucose cotransporter 2 (SGLT-2) inhibitors. Bile acid sequestrates and dopamine agonists are less commonly used, especially in this population. The cardiovascular disease benefit of these agents, either alone or in combination, remains incomplete.[8] Several of these drugs have warnings and restrictions with regard to their use in HF patients, the TZDs in particular. Recently there have been seemingly conflicting study results related to the DPP-4 agents,[9] with initial studies to the contrary yielding to more nuanced analyses that indicate cardiovascular safety.[10]

Metabolic Impact of Mechanical Unloading

Continuous-flow LVAD placement has saved and prolonged the lives of those with advanced HF and is progressively replacing heart transplantation as long-term therapy. It has been

Metabolic Agents for the Failing Heart		
Class	**Cardiac Effect**	**Mechanism**
GLP-1 receptor agonist (injectable agents)	Improves myocardial glucose utilization	Stimulates GLP-1 surface receptors cardiac and systemic, reduces glucagon secretion, and improves hyperglycemia
DPP-4 inhibitor (oral medications)	Improves glucose utilization, reduces glucagon levels	Inhibits endogenous GLP-1 and GIP breakdown
Biguanides (metformin)	Improves insulin sensitivity and glucose utilization	Mitochondrial mechanism, mild inhibition of complex I, and AMPK activation
SGLT-2 inhibitors (oral agents)	Reduces CV mortality and HF hospitalization, possible benefit to remodeling	Direct cardiac mechanism unidentified but appears related to improved glucose utilization; secondary benefits include weight reduction, improved blood pressure and blood sugar
Anti-ischemic metabolic agent (trimetazadine, not available in U.S., and ranolazine)	Potentiates glucose by reducing fatty acid oxidation	Inhibits beta-oxidation pathway of fatty acids; ranolazine also a slow sodium current inhibitor
CPT-1 inhibitors (etomoxir, adverse liver effects, perhexiline)	Increases glucose oxidation by reducing fatty acid utilization	Partial inhibition of long-chain FA entry into mitochondrial matrix
Pyruvate dehydrogenase kinase inhibitors (dichloroacetate)	Increases glucose oxidation	Enhances the activity of pyruvate dehydrogenase and pyruvate entry into Krebs cycle
Mitochondria-targeting peptide SS-31 (Bendavia®)	Reduces ischemia-reperfusion injury; may have benefit of enhanced ATP energy production in the failing heart	Reduces ROS injury and cell death; targets cardiolipin and improves electron transport
GLP-1: glucagon-like peptide-1; dpp-4: dipeptidyl peptidase-4; GIP: glucose-dependent insulinotropic polypeptide; AMPK: AMP-activated protein kinase; SGLT-2: sodium-glucose transporter-2; HF: heart failure; CPT-1: carnitine palmitoyltransferase-1; FA: fatty acid; ROS: reactive oxygen species; ATP: adenosine triphosphate		

Table 1. Overview of therapeutic agents for metabolic management of the failing heart.

documented to have hemodynamic and cellular effects on the failing heart.[11] An additional and unanticipated consequence of unloading, which we were able to document in collaboration with the Houston Methodist Hospital HF and cardiothoracic surgery teams, was the LVAD's metabolic impact. We initially reported the presence of a subpopulation of mitochondria capable of coupled oxidative phosphorylation, contrary to convention at the time.[12] We then completed paired pre- and post-LVAD LV wall sample metabolomic, transcriptomic, and protein analyses. The results demonstrated reversal of metabolic alterations and gene expression changes in HF that was unexpected and promising.[5] This and earlier studies such as that by Thohan et al.[11] would indicate possible recovery. Of course, early implantation of the LVAD for recovery alone would not be taken lightly; however, these findings open the door to early medical metabolic interventions for recovery of the failing ventricle.

Identifying the Metabolic Phenotype

As metabolic therapeutic agents become available, there will be an increased need for diagnostic interventions to identify the phenotype of the individual with heart risk or established disease. In addition to identifying traditional demographics, body type, and comorbidities, these diagnostics should be able to assess specific metabolic characteristics—for example, identifying the presence or absence of whole body and organ-specific cardiac insulin resistance—and answer questions such as: Is the myocardium predominately oxidizing fat or is it primarily utilizing glucose? Are amino acids and ketone bodies used as fuels? These features would form the basis for personalized metabolic treatment, and the identification of these parameters with reassessment longitudinally could guide current and upcoming therapeutics. Clinical methods to do this are already partially available, including laboratory and imaging diagnostics. Going forward, the development of cardiac metabolic imaging either with single-photon emission computed tomography (SPECT) or positron emission tomography (PET)/CT could individualize therapeutics to enhance outcomes.[13] A comparative PET study using fluorodeoxyglucose (FDG) to assess glucose uptake and a palmitate isotope for fatty acid oxidation could guide the decision to enhance glucose and limit fatty acid utilization for cardiac energy production.[14] As our understanding of metabolic management therapeutics advances, this concept could be expanded by incorporating positron-emitting isotopes into ketone bodies and/or amino acids.

Emerging and Future Therapeutics

The current classes of medication that show promise for HF include agents that impact various metabolic and energy transfer pathways, such as those that stimulate glucagon-like peptide-1 (GLP-1) or inhibit SGLT-2 receptors (Table 1). Both are FDA approved and have widespread clinical use treating individuals with type 2 diabetes. GLP-1 mimetics have potential benefits that go beyond glucose control alone.[15,16] The positive impact of GLP-1 on myocardial glucose metabolism has recently been reviewed[17] and shown to increase myocardial glucose uptake in a nondiabetic dog model with dilated cardiomyopathy.[18] GLP-1 mimetics improve myocardial glucose utilization and show positive cardiovascular

effects, including improved ejection fraction, endothelial function, and perfusion, although these effects could be indirect. These injectable drugs often promote weight reduction with reduced blood pressure and blood glucose. The GLP-1 agonists would potentially be beneficial to the myocardium that is locked into oxidizing fatty acids, as in obesity and diabetes, although the heart failure is continuing to progress.[19]

Whether by direct, indirect, or combined effects, these agents appear to have positive cardiac metabolic effects. The recently published LEADER trial reports improvement in cardiovascular outcomes including mortality, nonfatal stroke, and myocardial infarction in individuals with type 2 diabetes taking liraglutide. It was not a heart failure trial.[20] If one were to use cardiac metabolic imaging to demonstrate a relative decline in cardiac ^{18}F-FDG uptake by PET/CT relative to fatty acid such as ^{11}C-palmitate, then targeted measures to enhance glucose utilization through use of metformin and GLP-1 mimetics might prove to be beneficial. At this stage of investigation, however, the reports on GLP-1 action on myocardial substrate metabolism are incomplete and need further evaluation.

The SGLT-2 class has had favorable cardiovascular outcomes in individuals with type 2 diabetes. These drugs result in glycosuria by inhibiting glucose reabsorption through SGLT-2 transporters in the proximal renal tubule. The result is urinary loss of glucose and reduction of blood glucose concentrations. SGLT receptors are also expressed in the heart, with SGLT-1 as the dominate isoform. However, SGLT-2 receptors have also been identified. Activation rather than inhibition of the SGLT-1 isoform has been reported to have a role in optimizing cardiac energy metabolism, at least during acute ischemia-reperfusion injury.[21] This would raise concern if SGLT-1 were coinhibited by SGLT-2 agents, but the SGLT-2 inhibitors are isoform specific. Specific agents as reviewed by Kurosaki et al. have varying selectivity for the SGLT-2 and -1 receptors.[22] The recently published Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) reported a 14% reduction in adverse cardiac events, including a 38% relative risk reduction in cardiovascular mortality in subjects taking the inhibitor. They also reported a 35% reduction in hospitalization for HF,[23] although the mechanisms have yet to be identified.[24] A phase-IV randomized, double-blind, placebo-controlled trial was begun in March 2015 and designed to assess the effects of SGLT-2 inhibition on LV remodeling.[25] There are reports of a shift to glucose oxidation in heart and kidney metabolism associated with these agents that might account for the benefits.[26] Additionally, noncardiac treatment effects including improved glycemic control, reduced blood pressure, and weight reduction might be factors. Use with metformin appears to have an additive effect.

The failing myocardium utilizes noncarbohydrate substrates such as fatty acids and ketone bodies. An approach to reduce long-chain fatty acid oxidation in combination with the agents noted above could potentially replenish depleted energy stores. Trimetazidine, while not available in the United States, has been one the most studied fatty acid oxidation inhibitors.[27] Agents that inhibit carnitine palmitoyltransferase-1 (CPT-1) would limit entry of long-chain fatty acid moieties into the mitochondria for beta-oxidation. These agents include etomoxir, which in clinical trials increased liver enzymes in patients with HF, and perhexiline, which was developed as an antianginal agent. Perhexiline inhibits the cardiac CPT-1 isoform and reduces fatty-acid oxidation.[28] Ranolazine, also available as an antianginal agent, has been shown to have mitochondrial effects.[29] Intracellular malonyl-coenzyme-A inhibits and regulates CPT-1; agents that then would inhibit its synthesis are under development. Likewise, inhibiting phosphoinositide-dependent protein kinase, which inhibits pyruvate dehydrogenase activity and pyruvate entry into the Krebs cycle, would enhance glucose oxidation and help reenergize the failing myocardium. Finally, mitochondrial-targeted agents such as SS-31 (Bendavia®) that may stabilize cardiolipin structure and reduce oxidative damage are under investigation and in clinical trials.[30,31]

Conclusions and Clinical Implications

Heart failure progresses even in the setting of current evidenced-based therapies, with many patients ultimately requiring mechanical support and/or heart transplantation for survival. Therapies that complement current treatments and promote metabolic recovery are desperately needed. As our awareness and understanding of the molecular mechanisms underlying energy depletion increases, so too does the opportunity for metabolic therapy. Noninvasive cardiac imaging modalities such as SPECT and PET/CT offer the opportunity to identify the mechanisms that are unique to a specific etiology or stage of disease. Treatments targeted to specific metabolic phenotypes at different stages of heart failure are emerging. Agents that have so far shown benefit in select patients include mimetics that stimulate glucagon-like peptide-1, inhibitors of sodium-glucose cotransporter receptors, drugs that limit fatty acid oxidation, and hormonal therapy. In addition, new classes of medications that impact various metabolic and energy transfer pathways are being evaluated. The above review offers a rationale for earlier interventions to maintain substrate oxidation and high-energy phosphate production with the goal of reversing the outcomes associated with heart failure.

Key Points:

- The failing myocardium is energy depleted.
- Adaptive and possible maladaptive metabolic changes in substrate selection characterize different etiologies and stages of heart failure.
- The emerging technological advances in cardiac metabolic imaging allow identification of patterns of substrate utilization.
- With knowledge of the metabolic phenotype, therapeutic interventions could be individualized using established and emerging agents.

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Keywords: metabolic management, heart failure, energy recovery

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