Is chronic heart failure a reversible metabolic syndrome?

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Abstract

Heart failure is a progressive syndrome marked by systemic and pulmonary venous congestion, and maladaptive neuroendocrine activation in the setting of structural heart disease. Another facet of this syndrome has recently emerged, involving metabolic dysregulation, which implicates adipose tissue, skeletal muscle and the endocrine systems (insulin, leptin, adiponectin) in interacting with the failing heart. Chronic heart failure is associated with increased systemic and myocardial insulin resistance, impaired cardiac energetics, and a spectrum of weight loss (including cachexia) in the more advanced stage. This review will focus on the metabolic adaptations that have been associated with heart failure and focus on the reversible components that have been identified with therapeutic interventions known to achieve a significant degree of reverse myocardial remodeling – β-adrenergic receptor blockade and mechanical unloading with left ventricular assist device support. ■ Heart Metab; 2013;61:8–14

Keywords: Cachexia; cardiac metabolism; chronic heart failure; insulin resistance.

Introduction

In order to sustain function, cardiac and skeletal muscle have evolved with endogenous adaptive mechanisms to respond to physiologic and pathologic stress. Central in this adaptation is the maintenance of a flexible metabolic phenotype, which optimizes function with varying caloric intake, substrate availability and thermogenic response to environmental change. Thus, an essential component to adaptation in muscle is the metabolic circuitry that is flexible – capable of switching preferred energy substrates and regulating pathways of oxidative and nonoxidative energy transduction to optimize the organ to the physiologic challenge.

In a current synthesis of chronic heart failure – a progressive syndrome of cardiac dysfunction marked by systemic and pulmonary venous congestion – the myocardial response to an acute or chronic injury that challenges cardiac mechanical efficiency includes: (1)

The activation of a genetic program of fetal genes accompanied by a downregulation of the adult gene program regulating cardiac structure and function; (2) A switch from α to β myosin heavy chain subtypes; (3) A metabolic shift from a predominant bio-energetic source of lipid substrate utilization (β-oxidation of free fatty acids; FFAs) to carbohydrate use.

Both hemodynamic-mechanical and neurohormonal stressors have been implicated in the chronic progression of this syndrome – driving left ventricular dilatation, left and right ventricular dysfunction due to cardiomyocyte apoptosis and myocardial fibrosis.

More recently, a metabolic signature of chronic heart failure is emerging with phenotypic components that involve the myocardium and other organs – such as skeletal muscle and adipose tissue, which are undergoing changes affecting their mass and function. In the current synthesis of the metabolic phenotype in human heart failure, the components that

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Abbreviations

DAG: diacylglycerol; **FFA:** free fatty acid; **GLUT:** glucose transporter; **HOMA-IR:** homeostatic model assessment of insulin resistance; **ICDM:** idiopathic dilated cardiomyopathy; **LpL:** lipoprotein lipase; **LVAD:** left ventricular assist device; **NRF-1:** nuclear respiratory factor 1; **PET:** positron emission tomography; **PPARα:** peroxisome proliferator activated receptor; **RXRα:** retinoid X receptor α; **TAG:** triacylglycerol

have been implicated thus far include: (1) systemic and myocardial insulin resistance; (2) mitochondrial dysfunction; (3) progressive weight loss leading to "cardiac cachexia" in the more advanced stages; and (4) myocardial energetic failure associated with a downregulation of lipid metabolism, resulting in a shift from fatty acid to glucose as the primary energy substrate, decreased oxidative phosphorylation, and dysregulated systems of ATP transfer [1].

In this paper we will review the reversibility of this chronically and potentially maladaptive metabolic response with the current medical and device therapy being applied in the management of human heart failure. We will focus on the therapeutic interventions that are most commonly used in the management of early to moderate and advanced heart failure – respectively, β-adrenergic receptor blockade and mechanical assist device support. Furthermore, our focus will be on the programs of cardiac metabolic adaptation, cachexia, and insulin resistance, which have been linked to pathologic myocardial hypertrophy and failure, summarizing the changes and reversal of the metabolic phenotypes with these clinically relevant therapeutic interventions.

Metabolic adaptation in heart failure: losing flexibility

Glucose uptake and utilization increase and fatty acid uptake and oxidation decrease in the failing myocardium. This is often referred to as a shift to the "fetal pattern", and has been interpreted to be a favorable adaptation given the favorable bio-energetic yield (increased ATP equivalents) under hypoxic conditions [2, 3]. This preferential dependence on carbohydrate metabolism has been attributed to the efficiency of glucose oxidation in the generation of high-energy phosphates; however, other mechanisms such as non selective downregulation of genes governing myocardial FFA metabolism induced by epigenetic factors such as the endoplasmic reticulum stress response could also be present. For instance, one study identified that a downregulation of adult gene transcripts (such as the glucose transporter GLUT-4) rather than an increase in the transcripts constituting the fetal program could explain the switch to a "fetal pattern" [3]. Several studies have identified the downregulation of enzymatic gene products involved in fatty acid oxidation in explanted myocardium from patients with advanced heart failure at the time of cardiac transplantation. A study in the canine pacing-induced heart failure model identified a decrease in myocardial uptake and oxidation of FFAs associated with a decrease in the transcriptional control of the FFA oxidation program via the nuclear receptor retinoid X receptor α (RXRα) [4]. These and other studies have identified an association between heart failure and suppressed myocardial FFA oxidation – whether this is the result of a demand for higher fuel efficiency from glucose metabolism (adaptive response) or the result of cellular remodeling that disrupts lipid metabolism is not known.

The impaired FFA uptake and oxidation and increased reliance on glucose oxidation requires that glucose transport and oxidation be highly regulated to meet the demands of the myocardium in heart failure. Thus, the presence of myocardial insulin resistance, which has been described along with systemic insulin resistance in the more advanced phase of chronic heart failure, limits both glucose uptake and oxidation and impairs the heart's ability to generate much needed ATP. In a canine model of pacing-induced heart failure, one study provided the first evidence of myocardial and whole body insulin resistance associated with progressive left ventricular dysfunction and identified impaired myocardial insulin signaling with decreased activation of Akt-1 and translocation of GLUT-4 [5]. This animal model demonstrated the metabolic phenotype of disease progression in heart failure, identifying increased serum FFAs and whole body insulin resistance in the more advanced stage of this syndrome, confirming the importance of preserved insulin sensitivity as a prognostic factor in human heart failure [6, 7]. Independent of diabetes, chronic heart failure patients identified to have decreased insulin sensitivity have a worse prognosis. Given these findings, it is not surprising that patients with chronic heart failure demonstrate impaired myo-

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cardial "metabolic reserve" in response to physiologic stress. Another important study in human dilated cardiomyopathy identified preferential utilization of carbohydrates, but a markedly impaired ability to increase glucose uptake during the physiologic stress of atrial pacing (no change in glucose uptake over a 15 minute period) compared to control subjects who exhibited the expected increase in glucose uptake (2-fold increases from baseline) during stress [8]. That study clearly demonstrates a concept that has been repeatedly observed in animal models – that the loss of the flexible metabolic phenotype that is characteristic of the normal myocardium to a more rigid program of substrate utilization is physiologically limited and most likely detrimental.

In the case of diabetes and diet-induced obesity – and more recently in the syndrome of chronic heart failure – lipotoxicity has been implicated in the pathogenesis of impaired glucose utilization. The end-organ toxicity that results from the dysregulated lipid metabolism in obesity includes nonalcoholic fatty liver disease, cardiomyopathy, increased intramyocellular lipid accumulation in skeletal muscle with impaired insulin signaling, and pancreatic β-cell dysfunction and apoptosis progressing to diabetes mellitus. Animal models that manipulate a specific metabolic target, such as lipoprotein lipase (LpL), have demonstrated that both cardiac-specific knockout of LpL and transgenic overexpression of cardiomyocyte anchored LpL result in myocardial dysfunction via different mechanisms: in the case of the former [9, 10] a loss of FFA substrate utilization that cannot be compensated by transport of nonesterified fatty acids or increased glucose metabolism and in the latter case the finding of cardiac lipotoxicity [11, 12].

In translational studies in humans, advanced heart failure patients with diet-induced obesity or diabetes mellitus were found to have increased intramyocardial triacylglycerol (TAG) levels at the time of cardiac transplantation, a phenotype that has been recapitulated in several animal models of obesity and diabetes, including the Zucker diabetic fatty rodent model [13]. It was postulated that the combination of impaired myocardial FFA oxidation, which had been implicated in chronic heart failure, along with the increased delivery of FFAs in patients with diabetes and obesity would result in intramyocardial lipid overload associated with myocardial dysfunction. By distinguishing neutral lipid species such as TAGs

from toxic lipid intermediates such as diacylglycerols (DAGs) and ceramides in the myocardium of patients with end-stage heart failure, a more recent study was able to demonstrate a decrease in TAGs and an increase in the lipotoxic DAGs and ceramide species in comparison to non failing controls [14]. This finding that lipotoxic stress may play a role in the progression of human heart failure provides yet another mechanism that may be targeted in the advanced, refractory stage of the syndrome. Furthermore, the study identified decreased activation of insulin signaling in the myocardium of end-stage human heart failure and postulated that the accumulation of these toxic lipid intermediates could be playing a role, via increased activation of protein kinase C, in the development of impaired insulin signaling, which has been associated with chronic heart failure. This mechanism of insulin resistance induced by lipid overload and specifically driven by the accumulation of fatty acid metabolites (fatty acyl coenzyme A, DAGs, ceramides) in skeletal muscle has been proposed for obese patients with increased circulating fatty acids [15]. The study linked the lipotoxicity hypothesis, namely that intracellular lipid accumulation will render the heart and other organs susceptible to various forms of injury, including cellular apoptosis and end-organ failure, as an underlying mechanism of a cardinal feature in the metabolic syndrome associated with chronic heart failure – myocardial insulin resistance.

A major challenge to the "lipotoxicity hypothesis" is the body of evidence pointing to chronic heart failure as an energy-starved state and the failing heart as an "engine out of fuel" [16]. The clinical observations that disease progression in heart failure is associated with weight loss not only affecting muscle protein but also fat tissue have been reproduced in single-center studies as well as substudies performed within large multicenter trials. The presence of cachexia, defined by the nonedematous weight loss of more than 6% of total body weight over a period of at least 6 months, has been identified as a robust predictor of increased mortality in heart failure and associated with decreased functional capacity and a more advanced stage. Furthermore, recent data generated from an untargeted lipidomic survey in myocardium from lean, nonischemic, and non diabetic end-stage heart failure patients undergoing orthotopic heart transplantation has demonstrated that the vast majority of differentially present lipid

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species, including DAGs and ceramides, are significantly decreased in comparison to lean, non diabetic non failing control subjects [17].

By introducing variability in the substrate available for cardiac bioenergetic maintenance, the dynamic variable of weight and body composition in cachectic and non cachectic heart failure may partly explain the conflicting data that exist regarding the preferential switch to glucose from FFAs as the metabolic substrate in failing myocardium [18–20]. The discrepancy in the translational body of work generated with positron emission tomography (PET) studies is most likely explained by several variables that are known to impact FFA metabolism, including gender, the presence of diabetes mellitus, and the degree of insulin resistance, all of which in turn impact substrate availability in the normal and failing heart. An important study measuring FFA oxidation with PET in idiopathic dilated cardiomyopathy (IDCM) identified a decrease in FFA uptake but no difference in the FFA oxidation constant in chronic heart failure patients compared to non failing control subjects [21]. Within the cohort of IDCM, the patients with the most systolic dysfunction and worst state of insulin resistance were identified to have increased FFA uptake and oxidation, respectively – an observation that is consistent with the hypothesis that the availability of substrate is intricately linked with metabolic shift and cardiac performance.

In line with the "engine out of fuel" paradigm, clinical studies of high-energy phosphate metabolism by 31-P magnetic resonance spectroscopy all very consistently demonstrate impaired ATP transfer and utilization implicating very significant deficits in the creatine kinase system in human heart failure [22–26]. Those studies have identified a decreased ratio of phosphocreatine to ATP, a powerful index of energetic status in the heart, in chronic cardiomyopathy patients, and this index has been correlated with left ventricular ejection fraction, New York Heart Association class, and has been shown to be a strong predictor of mortality in patients with dilated cardiomyopathy [24].

Reversing heart failure with β-adrenergic receptor blockade

β-Adrenergic blockade has not only achieved confirmed efficacy in terms of short and long-term survival in chronic heart failure, but is the medical therapy that has been most strongly linked to the regression of pa-

thologic hypertrophy associated with improved myocardial function – a process known as reverse myocardial remodeling. The positive effects on survival may partly be explained by the beneficial effects on weight changes and body composition in a syndrome of chronic heart failure in which survival has been repeatedly associated with increased body mass index (obesity or "lipid" paradox). In a substudy of a large randomized clinical trial (Carvedilol Prospective Randomized Cumulative Survival; COPERNICUS), patients treated with carvedilol had a significant increase in weight (1.1 kg at 12 months) compared to placebo-treated patients (0.2 kg at 12 months) [27]. This clinical finding was confirmed in the Cardiac Insufficiency Bisoprolol Study (CIBIS-II), with increased weight at 12 (0.8 kg) and 24 months (1.2 kg) in the bisoprolol-treated compared to the placebo-treated patient [28]. A small study identified that the positive effect on weight of β-blockers in chronic heart failure patients was predominantly due to an increase in fat mass [29]. Another study in heart failure patients before and after 6 months of β-adrenergic receptor blocker therapy identified that patients with cachexia, defined as unintentional and nonedematous weight loss of more than 7.5% of body weight over a period of at least 6 months, demonstrated increased weight gain and concordantly increased plasma leptin levels in response to β-blocker therapy [30]. These observations on the reversibility of weight loss (predominantly fat mass in cachectic patients) with β-adrenergic receptor blockade suggest that heart failure may be a state of sustained lipolysis driven by the chronic activation of adrenergic and natriuretic peptide systems, which have both been implicated in the increased hydrolysis of glycerolipids by adipocyte triglyceride lipase and hormone-sensitive lipase in adipocytes. Sustained and dysregulated lipolysis may result in increasing circulating fatty acids (analogous to what is observed in diet-induced obesity and noninsulin-dependent diabetes mellitus) leading to the accumulation of toxic and neutral lipid species in the myocardium, especially when fatty acid oxidation is decreased. This process, known as lipotoxicity, would lead to the development of systemic and myocardial insulin resistance. Chronic lipolysis may be further sustained by the development of insulin resistance, as insulin is known to mediate antilipolytic effects, and thus a vicious metabolic cycle may be present. Although not yet proved in chronic heart failure, invoking sustained lipolysis could explain

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two cardinal features of the metabolic phenotype – weight loss in fat mass and insulin resistance. An improvement in insulin sensitivity with β-adrenergic blockade has not been conclusively reported and further investigation into the effects of β-blockade on glucose metabolism is warranted.

A large body of literature supports the beneficial effects of β-adrenergic receptor blockade on cardiac efficiency [31] and myocardial function. The mechanisms behind the favorable cardiac efficiency have not been elucidated, but the observation of increasing stroke work without increasing oxygen consumption may be explained by the suppression of fatty acid oxidation by β-blockade through the restriction of substrate in the setting of high catecholamine levels driving lipolysis, allowing for a more efficient use of oxygen with a shift to glucose metabolism. In a well-characterized animal model of dilated cardiomyopathy, administering the β-blocker carteolol led to a normalization of myofibrillar ATPase activities, along with creatine kinase and ATP synthase activities [32]. That study suggests broader effects on metabolic remodeling achieved by β-adrenergic receptor blockade in failing myocardium and calls for the study of myocardial high-energy phosphate metabolism in responders and non responders to β-blocker therapy. Evidence for changes in metabolic circuitry that may constitute active metabolic remodeling of the failing heart in response to β-adrenergic blockade is clearly lacking. However, a study of serial gene expression profiling of myocardium sampled from heart failure patients who variably responded to β-blocker therapy identified a significant proportion of metabolic genes to be differentially expressed, and improved myocardial function was associated with a differential increase in metabolic category gene expression [33].

Reversing heart failure with mechanical ventricular unloading

Although not consistently seen in the heterogeneous population of advanced heart failure patients requiring mechanical assist device support, mechanical unloading with a left ventricular assist device (LVAD) has resulted in some dramatic cases of reverse myocardial remodeling. LVADs were originally designed for patients who needed short-term circulatory support as a bridge to recovery after open heart surgery. With the possibility of longer term circulatory support, it became clinically apparent that the chronically dila-

ted heart could improve with mechanical unloading of the left ventricle [34, 35].

Hemodynamic unloading achieved with a ventricular assist device implies a reduction in left ventricular pressure of sufficient magnitude to impact favorably on mechanical stress. Changes in mechanical stress are known to cause a cellular and molecular response in cardiomyocytes to this biomechanical stimulus. In the context of mechanical unloading, reverse remodeling implies that this myocardial response at the cellular and molecular level is sustained to achieve a more favorable elasticity of the heart. It is clear from several studies that mechanical unloading over a sustained period of time will improve left ventricular function and geometry, reverting the properties of the left ventricle towards, but not quite back to, normal [36,37]. This has been a recurring theme in the majority of studies that have been performed and that document changes pre/post LVAD at the cellular/molecular level – that mechanical unloading provides a marked improvement in failing human myocardium but does not revert this phenotype back to normal. The changes in the myocardial biology of metabolic adaptation in response to mechanical unloading are incompletely understood, and therefore great potential exists in identifying novel therapies that may enhance the reversal of heart failure by targeting metabolism in mechanically assisted or unassisted heart failure.

Every component of cardiac metabolism – substrate utilization, oxidative phosphorylation and ATP transfer – has been demonstrated to be altered in heart failure. Chronic heart failure is marked by decreased fatty acid utilization with increased reliance on glucose metabolism, increased myocardial and systemic insulin resistance, decreased activity of the electron transport chain and ATP synthase, and a significant decrease in ATP transfer capacity with a reduction in the activity of both mitochondrial and myofibrillar creatine kinase. There are insufficient data to support the theory that the metabolic signature of heart failure is reversed with mechanical unloading and further studies are needed in this area. Cardiomyocyte mitochondrial respiratory function has been demonstrated to be improved with long-term LVAD support, with primarily improvement in the control of state 2 and state 4 respiration [38]. Another study identified an improvement in nitric oxide-mediated regulation of mitochondrial respiration measured in myocardial preparations taken from end-stage heart

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failure patients who were bridged to cardiac transplantation with a LVAD compared to patients without LVAD-induced mechanical unloading [39]. Taken together, both of those studies suggest that mitochondrial function may not be irreversibly impaired in end-stage human heart failure and that the mechanisms for the recovery of mitochondrial function in cardiomyopathy should be investigated further.

The metabolic signature in end-stage heart failure reveals both transcriptional and post-translational changes, which are consistent with a preferential utilization of glucose and a downregulation of lipid metabolism. More recently, analysis of paired samples pre and post-LVAD in patients without diabetes demonstrated a significantly increased expression of genes implicated in β-oxidation of FFAs (peroxisome proliferator activated receptor; PPARα), mitochondrial biogenesis (nuclear respiratory factor 1; NRF-1), and glucose metabolism (GLUT-4), suggesting an improvement in myocardial energetics with mechanical unloading. In contrast, another study, which also analyzed paired myocardial samples pre and post-LVAD support found that the potentially maladaptive changes in key metabolic genes associated with heart failure persist after mechanical assist device support, including the glucose transporters GLUT-1 and GLUT-4, as well as the key regulatory enzyme in glucose metabolism pyruvate dehydrogenase kinase 2 [40]. This finding of a persistent fetal pattern of gene expression, including the metabolic subset of genes, was also reported by another investigation comparing gene expression profiling before and after LVAD support [3, 41].

In a recent, landmark study [14], which linked lipotoxicity to myocardial insulin resistance, the authors provide proof that these metabolic derangements may be specifically associated with myocardial failure by demonstrating that both impaired insulin signaling and the accumulation of lipotoxic species in the heart are reversible components after a period of mechanical unloading with a long-term LVAD. After a period of mechanical circulatory support, the study identified improved myocardial insulin signaling as confirmed by increased phosphorylation of Akt and Foxo, decreased cardiac lipotoxicity, increased expression of genes implicated in lipid metabolism (CD36, CPT1, ACO), and a decrease in systemic insulin resistance as measured by the homeostatic model assessment of insulin resistance (HOMA-IR) [14].

Conclusions

A growing body of evidence has elucidated the presence of an energy starved state in chronic heart failure and the failing heart as an "engine out of fuel". The failing heart has been characterized as a glucose-dependent organ with loss of the plasticity to switch energy substrates (lipids, glucose, lactate, etc.) in response to the physiologic demand of increased workload. Several studies, including in-vivo PET metabolic protocols have confirmed the increased dependence of the failing human heart on glucose utilization for fuel. β-Adrenergic receptor blockade continues to play a central role in the reversal of the heart failure syndrome, but the specific mechanisms of cellular and molecular remodeling, including the relevant changes in cardiac metabolism that may explain the increased cardiac efficiency, improved functional capacity and increased survival, remain elusive. The potential for reversibility of these metabolic derangements with mechanical unloading in patients on long-term LVAD support also requires further study, especially with the advances in molecular imaging and PET metabolism *in vivo*. We have identified in this review that the adaptive and potentially maladaptive metabolic response in chronic heart failure may not be reversed with these current, powerful therapeutic strategies. Thus, great promise exists in future studies that may elucidate the unified, common metabolic signature in chronic heart failure, and through the introduction of therapies that modulate the metabolic response, such as glucagon-like peptide 1 [42], may further enhance the outcomes of patients living with heart failure. ■

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