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and Metabolism

Heart failure and metabolic disease

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The metabolic contribution to heart failure

Gary D. Lopaschuk
Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, AB, Canada

Correspondence: Dr Gary D. Lopaschuk, A423 HMRC, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, AB, Canada T6G 2S2
Tel: +1 780 492 2170, e-mail: gary.lopaschuk@ualberta.ca

Obesity and diabetes are widely recognized as major risk factors for the development of heart failure [1, 2]. Heart failure in obese individuals and those with diabetes is characterized by the early development of left ventricular diastolic dysfunction, increased left ventricular mass, increased left ventricular wall thickness, and the eventual development of left ventricular systolic dysfunction [3–7]. This increased risk of developing heart failure in obese individuals and those with diabetes persists even after adjusting for independent factors including coronary artery disease and hypertension [3–7]. As a result, a considerable research effort has focused on the mechanisms responsible for the increased prevalence of heart failure in obesity and diabetes. Potential contributing factors identified include increased oxidative stress, development of cardiac autonomic neuropathies, accelerated apoptosis, accelerated inflammatory responses, accelerated fibrosis, altered cardiac Ca^{2+} and Na^+ handling, production of advanced glycation end products and receptors for advanced glycation end product activation, increased polyol pathway activity, activation of NADPH oxidase, and increased O-linked β-N-acetylglucosamine. Alterations in cardiac energetics also occur in the failing heart, especially in the setting of obesity and diabetes, and are thought to contribute to the severity of heart failure. This issue of *Heart and Metabolism* focuses on the energy metabolic changes that occur in the setting of obesity and diabetes, and how these changes may contribute to the severity of heart failure.

In the article entitled "Is chronic heart failure a reversible metabolic syndrome?", J. Eduardo Rame describes what metabolic adaptations are associated with heart failure and summarizes the reversible components that are amenable to therapeutic interventions that may reverse myocardial remodelling. One major pathway that is altered in obesity, diabetes and heart failure is cardiac energy metabolism [8]. Obesity results in dramatic changes in cardiac energy metabolism, which include an increase in fatty acid oxidation and a decrease in glucose oxidation. In the Refresher Corner article Lionel Opie discusses the energy metabolic changes that occur in the diabetic heart. He nicely describes the adverse metabolic effects of hyperglycemia, the metabolic syndrome, and the diabetic heart. In the article entitled "Inhibition of fatty acid oxidation as an approach to treat diastolic heart failure", John Ussher and Jagdip Jaswal describe the changes in diastolic function that can occur in heart failure in obesity and diabetes, as well as the metabolic abnormalities in the myocardium that appear to be associated with the progression of diastolic dysfunction. They also describe how optimizing cardiac energetics, potentially through inhibiting myocardial fatty acid oxidation, may represent a novel target for improving diastolic function. This can be achieved with the fatty acid oxidation inhibitor, trimetazidine. In the article entitled "Use of trimetazidine to treat diabetes patients with heart failure", Rui Yan and Dengfeng Gao discuss the use of trimetazidine to treat diabetes patients with heart failure. They provide evidence showing that trimetazidine can improve cardiac function and prognosis, as well as improve left ventricular dysfunction and heart failure.

Understanding what alterations in energy metabolism occur in heart failure in obese and/or diabetes patients requires sophisticated imaging techniques.

In the article entitled "Imaging metabolism and perfusion in patients with diabetes and heart failure", Patricia Iozzo and Maria Angela Guzzardi discuss some of the new approaches for imaging metabolism and perfusion in patients with diabetes and heart failure. The authors demonstrate that myocardial insulin resistance is a modifiable marker of fatty acid overload in the heart, and may contribute to cardiac dysfunction in cardiovascular disease. They also highlight how reducing fatty acid oxidation may be beneficial in this setting.

While studies have shown that obesity increases the incidence of heart failure, it is now becoming clear that obese patients with heart failure have better outcomes; known as the "obesity paradox" [9–12]. The clinical literature thus offers conflicting results with regard to the relationship between obesity and heart failure. In the article entitled "The metabolic basis for the obesity paradox in heart failure", Stephan von Haehling addresses the metabolic basis for the obesity paradox, and the potential reasons for differences in heart failure outcomes between obese and nonobese individuals. Interestingly, in the Case Report article by Vitantonio Di Bello and colleagues a clinical case is discussed as to how dramatic weight loss in an obese patient with heart failure can lessen the severity of diabetic cardiomyopathy.

While the heart can be impacted by a number of hormones, it is now becoming clear that the heart itself may actually also function as an endocrine organ. In the Hot Topics article, Andrew Swick discusses irisin, a novel myokine, and its potential role in obesity and diabetes. The author discusses how irisin may play a role in the regulation of energy expenditure and metabolism secondary to "browning" of subcutaneous white fat, resulting in increased energy expenditure and resistance to diet-induced obesity and diabetes.

Combined, the articles in this issue of *Heart and Metabolism* highlight the importance of considering the contribution of energy metabolic changes that occur in obesity and diabetes to the development of heart failure. These articles also emphasize that optimizing energy metabolism may be a promising approach to treating heart failure in this patient population. ■

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The metabolic basis for the obesity paradox in heart failure

Stephan von Haehling
Applied Cachexia Research, Department of Cardiology, Charité Medical School,
Campus Virchow-Klinikum, Berlin, Germany

Correspondence: Dr Stephan von Haehling, MD, PhD, Applied Cachexia Research, Department of Cardiology,
Charité Medical School, Campus Virchow-Klinikum, Augustenburger Platz 1, D – 13353 Berlin, Germany
Tel: +49 30 450 553 506, fax: +49 30 450 7 553 506, e-mail: stephan.von.haehling@web.de

Abstract

A higher body mass index (BMI) carries a survival benefit in patients with heart failure. Data from more than 28 000 patients with heart failure support the view that the optimal BMI ranges between 30 and 35 kg/m^2 as opposed to the common belief that weight loss and being slim is generally good. In chronic diseases such as heart failure, chronic kidney disease, or chronic obstructive pulmonary disease, this assumption no longer holds true, a phenomenon called the "obesity paradox", and weight loss is no longer advisable. The origin of this clinical observation is not entirely clear, but some factors may have an influence: obese patients with heart failure are on average younger, have better nutritional status and appetite, present at an earlier stage of the disease, are less catabolic, have lower levels of natriuretic peptides and have higher muscle mass. An optimal BMI has not been defined, and it is not clear if fat mass is as beneficial as muscle mass when looking at absolute BMI values. ■ Heart Metab; 2013;61:4–7

Keywords: Heart failure; muscle; obesity; obesity paradox.

Introduction

The first description of the obesity paradox dates back to 1999. However, many physicians have still never heard of the obesity paradox at present. The reason may be that the time frame is simply not long enough to allow for paradigm shifts, and it seems that nothing less is necessary with regard to our perception of obesity in patients who are chronically ill. Therefore, it is not surprising that current guidelines for heart failure issued by the large European and American societies do not mention the existence of an obesity paradox [1, 2]. Clinicians involved in the everyday care of patients may thus not be aware that the advice to lose weight commonly advocated for overweight or obese individuals with cardiovascular disease may not make sense for all of them.

We should, however, approach the obesity paradox in an orderly manner. The term describes a common phenomenon seen in many chronic illnesses, including coronary artery disease, arterial hypertension, heart failure, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease and several others. Among patients with these illnesses, overweight and mild obesity are counterintuitively but commonly associated with better survival than underweight or what is usually called normal weight, ie, a body mass index (BMI) up to 25 kg/m^2. In terms of survival, heart failure patients seem to fare best with a BMI between 30 and 35 kg/m^2.

Survival benefit with higher BMI

The first description of the phenomenon stems from data of more than 1300 patients with chronic kidney

Abbreviations
BMI: body mass index; **CI:** confidence interval; **RR:** relative risk

disease undergoing hemodialysis [3]. The authors' conclusion was that "nutrition aimed to achieve the high end of normal body mass index may help to reduce the high mortality and morbidity in hemodialysis patients". This notion is of particular interest, because the authors of that study did not even analyze nutritional intake and thus extrapolated far beyond their data using proxies such as serum albumin or prealbumin. However, the study paved the way for an avalanche of publications dealing with the subject. Indeed, only one year later, Davos et al [4] described the existence of an obesity paradox in an abstract at the annual meeting of the American Heart Association, only to be published in 2003 as a full report. In the meantime, other groups had taken up the issue, leading to a larger publication using data from 1203 patients with advanced heart failure to show that cardiopulmonary exercise testing, pulmonary capillary wedge pressure and serum sodium were strong predictors of survival in this group of patients. Importantly, the authors concluded "higher body mass index was not a risk factor for increased mortality, but was associated with a trend toward improved survival" [5]. Several independent groups have confirmed these results using large databases mainly from prospective trials now involving more than 28 000 patients. A meta-analysis of those patients [6] with a mean follow-up of 2.7 years has shown that individuals with a BMI between 25.0 and 29.9 kg/m^2 (relative risk [RR] 0.84, 95% confidence interval [CI] 0.79–0.90) and those with a BMI of 30 kg/m^2 or greater (RR 0.67, 95% CI 0.62–0.73) had lower all-cause mortality than individuals with a normal BMI. This finding could be confirmed for cardiovascular mortality, and it remained true after adjusting for several risk factors. However, it has to be taken into account that the available data do not permit an upper threshold to be given for the beneficial effects of obesity, simply because the number of individuals with a BMI greater than 40 kg/m^2 remains small, both in real life and in clinical studies.

Metabolic differences in obesity
A matter of ongoing debate is whether the obesity paradox really does exist and if it does, what is the meta-

bolic basis for its existence? Indeed, a number of factors need to be considered when looking at the data. On average, obese patients with heart failure are younger, have better nutritional status and appetite, present at an earlier stage of the disease, are less catabolic, have lower levels of natriuretic peptides, have higher muscle mass and potentially higher left ventricular ejection fraction (*Figure 1*) [7, 8]. Our group has recent-
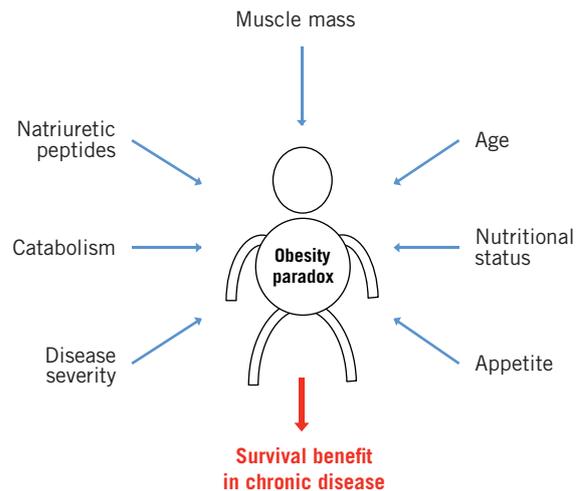
Fig. 1 *Factors influencing survival benefits in obese patients with heart failure.*

ly shown that patients with heart failure and appendicular skeletal muscle mass 2 SD below the mean of a healthy young population are significantly older and have significantly less body weight than patients with normal skeletal muscle mass [9]. Indeed, obesity leads to unavoidable exercise simply by carrying one's own weight, and such exercise – as recommended by the guidelines – may help to maintain skeletal muscle [8]. Obesity may thus primarily be a marker of a different status [8]. On the other hand, the guidelines state that the presence of obesity is a risk factor for the development of heart failure, because obesity is in many cases associated with the clustering of cardiovascular risk factors, ie, the metabolic syndrome, and because obesity leads to an increase in circulating blood volume and consequently to higher cardiac output, cardiac work and systemic blood pressure [1]. Other changes in obese individuals include an enhanced turnover of free fatty acids, increased sympathetic tone, the activation of inflammatory mediators, and a hypercoagulable state [10]. In addition, obesity itself may be involved in the chief complaint of heart failure patients, shortness of breath, thus creating an overlap of symptoms derived from the obese status and from the failing heart.

Body composition issues in heart failure

Taking these data together it seems that both is true – obesity is a risk factor for developing heart failure, but obesity also carries a survival benefit when heart failure has become manifest. A low BMI or the development of cachexia are certainly detrimental in patients with heart failure [6, 10, 11]; mild or even moderate obesity, on the other hand, may well be acceptable. There is no need to ask heart failure patients to gain weight, but there is good reason to make them stop losing it. Having said this, the discussion needs to be extended to matters of body composition, as it is not clear if there is such a thing as an optimal body composition [12], ie, content of lean mass versus fat mass, in patients with heart failure. The BMI, originally described by Adolphe Quetelet in 1832 (Quetelet index) and renamed "body mass index" in 1972, was originally used as an estimation tool of body fat content [13]. Critics of the BMI have argued that it fails to distinguish between fat mass and lean mass, and that for that reason muscular people are frequently misclassified as overweight or obese. Factors such as the course of body composition changes over the lifespan need to be considered. Indeed, after the age of 30 years, lean mass decreases at the expense of increases in fat mass [14]. Despite the loss in muscle mass, this usually leads to a net increase in body weight. Some 5 or 10 years before death, BMI usually starts to decline as a consequence of inactivity, anorexia and poor nutritional intake [7]. The term "sarcopenia" describes loss of muscle mass and strength with advancing age. On average, 5–13% of elderly people between 60 and 70 years are affected by sarcopenia, and the numbers rise to 11–50% for those aged 80 years and above [15, 16]. It was therefore surprising to see that the criterion of sarcopenia or muscle wasting, ie, muscle mass 2 SD below the mean of a healthy young cohort, was present in almost 20% of stable heart failure outpatients with a mean age of 67 years [9]. The mean BMI of patients affected by muscle wasting was significantly lower than that of those not presenting with muscle wasting. It is clear now that a higher BMI is beneficial in heart failure, but it is tempting to speculate that higher muscle mass is even better than fat mass, even though fat mass as an energy depot may also help in decreasing mortality rates.

Conclusions

We are only starting to understand the obesity paradox in heart failure as many questions still remain unanswered. However, the obesity paradox is there – as the data are more than convincing – and it is there to stay. The optimal BMI in heart failure seems to be somewhere between 30 and 35 kg/m^2 and certainly not in the region commonly considered as normal BMI. It cannot be stressed too often that patients with chronic disease and healthy individuals are different. The influence of age, nutritional status, appetite, disease severity, catabolic status and muscle mass all need to be considered as they all contribute to the obesity paradox. In particular, muscle mass and strength require more research, as we do not yet know whether only a higher BMI is beneficial or whether higher muscle mass is also required. An upper threshold for the BMI needs to be defined. In the meantime, clinicians' advice to their patients should be to stop losing weight once heart failure is present. ■

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Is chronic heart failure a reversible metabolic syndrome?

J. Eduardo Rame
Cardiovascular Research Institute, University of Pennsylvania, Philadelphia, USA

Correspondence: Dr J. Eduardo Rame, MD, MPhil, Cardiovascular Research Institute, University of Pennsylvania,
3400 Civic Center Boulevard, Philadelphia, PA 19104, USA
E-mail: eduardo.rame@uphs.upenn.edu

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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Imaging metabolism and perfusion in patients with diabetes and heart failure

Patricia Iozzo and Maria Angela Guzzardi
Institute of Clinical Physiology, National Research Council (CNR), Pisa, Italy
Turku PET Centre, University of Turku, Turku, Finland

Correspondence: Dr Patricia Iozzo, MD, PhD, Institute of Clinical Physiology, National Research Council (CNR),
Via Moruzzi 1, 56124 Pisa, Italy
E-mail: patricia.iozzo@ifc.cnr.it

Abstract

Recent advances in imaging technologies have made it possible to quantify myocardial substrate handling and perfusion in humans. This review examines results obtained in patients with type 2 diabetes and/or heart failure. To establish how this knowledge can be profitable for patient management, we summarize a series of targeted intervention studies addressing the causal relationship between cardiac metabolism and cardiac function or perfusion. ■ Heart Metab; 2013;61:15–19

Keywords: Cardiac fat; intervention; fatty acid oxidation; magnetic resonance spectroscopy; myocardial insulin resistance; positron emission tomography.

Introduction

Fatty acids (FAs) are the main fuel of the heart. After a meal, hyperinsulinemia stimulates myocardial glucose utilization and suppresses the use of endogenous FAs, while chylomicron-bound FAs become available through gut absorption. A metabolic shift in favor of glucose consumption also occurs when the oxygen supply does not meet the demands of the heart. Glucose is a more efficient and oxygen-sparing energy source than FAs. Most FAs entering the myocardium are oxidized, but a significant 15% (fasting state) to 33% (hyperinsulinemia) of them are channeled into triglycerides, representing a local depot of mobile energy [1]. Heart metabolism responds to the cardiac workload, and is finely tuned to the surrounding hormonal and substrate milieu, and to the delivery of oxygen through myocardial perfusion.

Recent advances in imaging technologies have made it possible to quantify myocardial substrate handling and perfusion in humans (*Figure 1*).

Myocardial metabolism and perfusion in type 2 diabetes and heart failure

Uncomplicated type 2 diabetes mellitus (T2DM), cardiovascular disease, heart failure and their combination are characterized by myocardial insulin resistance [2–4], which is related to a lower ejection fraction [2] and worse prognosis after revascularization [5]. Myocardial FA uptake and oxidation are high in patients with T2DM [3], and can be either elevated or reduced in individuals with heart failure [6–8]. Imaging of the absorption and distribution of a labeled FA meal has revealed that the myocardial uptake of dietary (chylomicron-derived) FA was also greater in patients with impaired glucose tolerance compared to controls [9]. It was correlated with myocardial oxidative metabolism and lower systolic and diastolic function. The content of triglycerides is increased in the hearts of individuals with diabetes, compared to those without diabetes, irrespective of body mass index, and in patients with ischemic, but not with other kinds of cardiomyopathy [10, 11].

Abbreviations

FA: fatty acid; **GLUT-4:** glucose transporter 4; **LVEF:** left ventricular ejection fraction; **T2DM:** type 2 diabetes mellitus

Myocardial glucose and FA metabolism are reciprocally regulated, and both are highly dependent on the circulating levels of FAs.

In the healthy heart, perfusion responds to the energy and oxygen requirements of the organ. Both T2DM and heart failure, even in the absence of significant macrovascular disease, are frequently characterized by an impaired coronary flow reserve, which is a negative prognostic indicator [12, 13]. Within the myocardium, segments with a lower perfusion reserve show greater glucose uptake in individuals with T2DM and heart disease [4], which may reduce the consumption of oxygen in the poorly perfused myocardium.

In synthesis, the metabolic features observed in the myocardium of patients with T2DM or heart disease represent the expected, physiological response to variations in the lipolytic FA load and coronary vasodilator capacity, both of which are commonly abnormal in these patients. To profit from these observations and apply them to patient management, fundamental questions need to be answered:

1. Do these physiological adaptations contribute to cardiac disease?
2. Is it safe to intervene against these adaptive responses?
3. If so, which one(s) should be counteracted to improve cardiac health?

Cause–effect relationships between cardiac metabolism and function

The manipulation of substrate delivery to the heart or the direct modulation of myocardial metabolism (*Figure 2*) may indicate therapeutic strategies to improve cardiac function and/or perfusion.
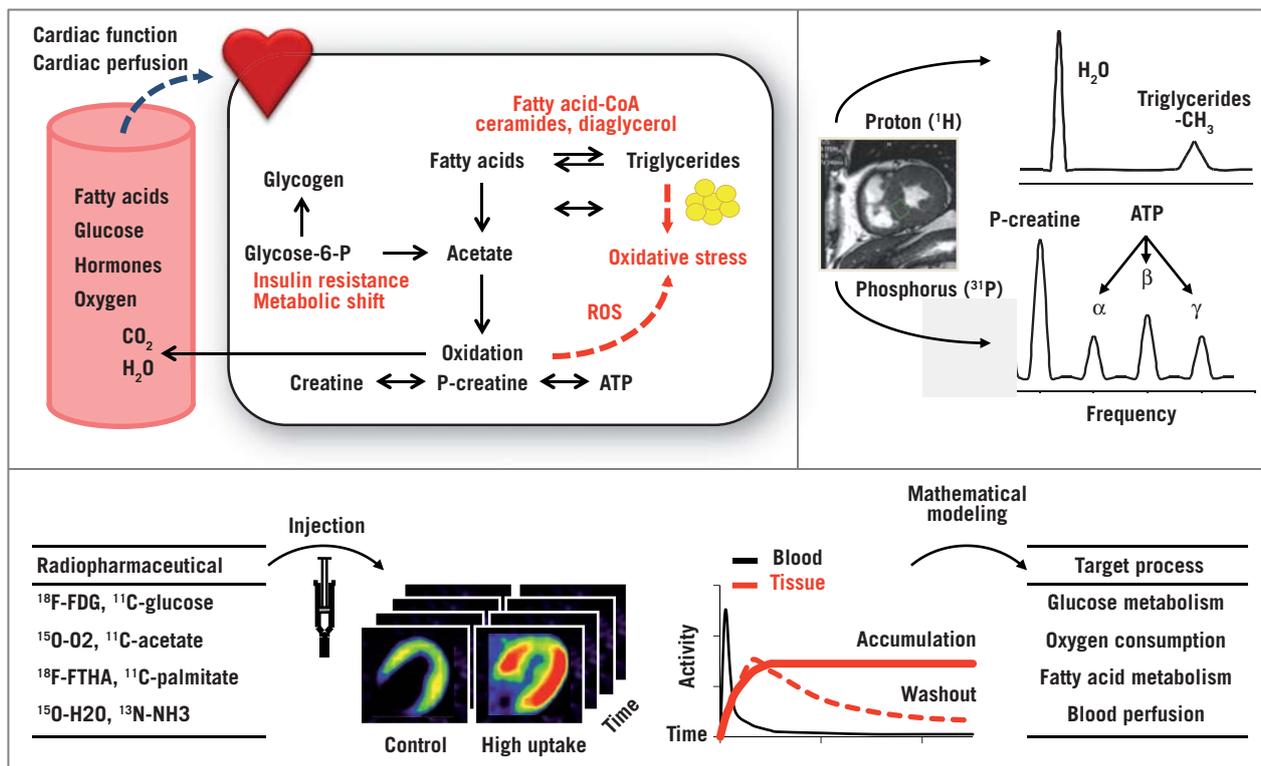
Fig. 1 *Positron emission tomography (bottom panel) allows the kinetics of labeled molecules in the heart to be followed over time. Depending on the radiopharmaceutical used, metabolic rates or perfusion can be computed. Magnetic resonance proton spectroscopy (top right panel) enables molecules to be distinguished based on chemical shift properties and has been validated to quantify the pools of triglycerides and high-energy phosphate compounds in the heart. The top left panel shows the processes of interest, including: myocardial insulin resistance, which may indicate an inability of the heart to shift from FAs to glucose use under the appropriate conditions, including ischemia; FA oxidation, which is paralleled by the formation of ROS, leading to oxidative damage and to the inefficient formation of high-energy phosphate compounds; and triglyceride storage, which may protect the heart by buffering the FA in excess, but is also a substrate of peroxidation. The saturation of this depot may promote the formation of toxic lipid intermediates. Fatty acid CoA, fatty acid co-enzyme A; ROS, reactive oxygen species*

Improving myocardial insulin resistance

Glitazones enhance myocardial insulin sensitivity in patients with T2DM with and without ischemic heart disease or diastolic dysfunction, in parallel with the decline in circulating FA levels [14, 15]. Fasting myocardial FA metabolism, cardiac lipids and myocardial perfusion were unaffected. Those studies included subjects with normal systolic left ventricular function and diastolic dysfunction [15], which makes it difficult to establish the relationship between myocardial insulin sensitivity and clinically significant cardiac dysfunction. They suggest that myocardial insulin resistance can be partly reversed by reducing the FA supply to the heart, and that the improvement in diastolic function is not a direct outcome of the change in myocardial glucose uptake.

Suppressing fasting myocardial FA uptake

The acute administration of the antilipolytic agent acipimox in healthy controls and patients with heart failure resulted in a massive suppression of myocardial FA uptake [16]. Myocardial perfusion was unaffected. The metabolic change was associated with a reduction in cardiac work in patients and controls, and a reduction in oxygen consumption in healthy controls. Therefore, the efficiency of forward work declined in
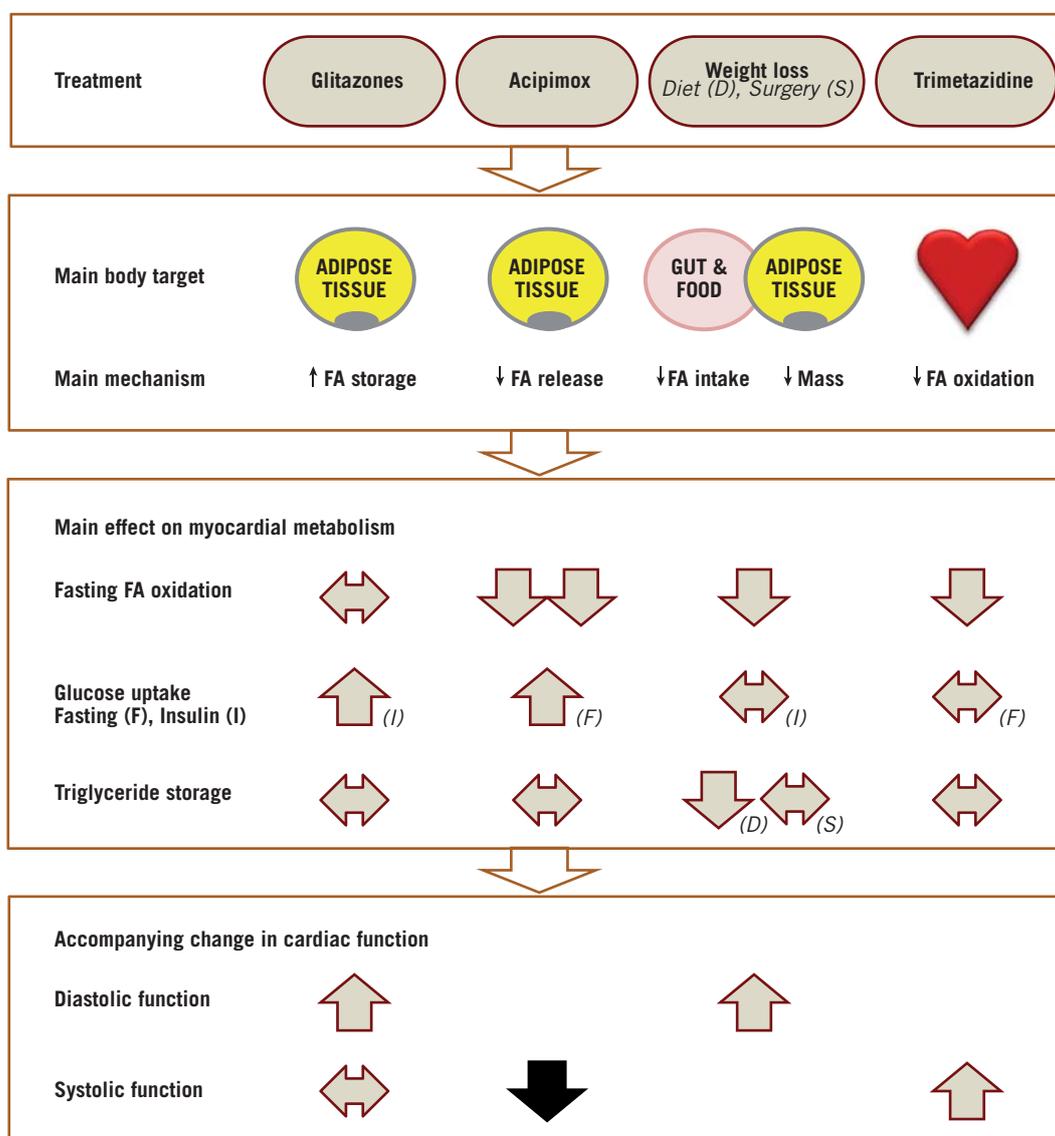
Fig. 2 The figure exemplifies the main outcomes of intervention studies evaluating the relationship between myocardial metabolic modulation and cardiac function. In a majority of cases, peripheral tissues are the primary targets of treatment, consistent with the adaptive nature of cardiac metabolism in response to the systemic supply of substrates. Indirect and/or direct mechanisms may link cardiac metabolism and function, because their changes are not always statistically correlated, as described in the text. The black arrow indicates an unequivocally negative outcome. (D), effect of low-calorie diet; FA, fatty acid; (F), fasting; (I), insulin; (S), effect of bariatric surgery

patients with heart failure, especially in those with insulin resistance, who may have been less responsive to FA suppression. A subsequent study attempted to target myocardial triglycerides [17]. We postulated that a sustained 1-week suppression of FA by acipimox would reduce cardiac fat, allowing its effects on cardiac function to be examined, but no change in cardiac fat was observed. The intervention resulted in a significant impairment in left ventricular work and function, and in left ventricular ejection fraction (LVEF). Under conditions of very low FA levels, all body tissues become glucose avid and insulin levels tend to decline, which may limit any compensatory rise in myocardial glucose uptake. We therefore concluded that the depletion of FA beyond a certain threshold cannot be compensated by glucose in the heart. Consistently, we interpreted the lack in myocardial triglyceride changes to indicate that, once the heart senses conditions of fuel depletion it prioritizes the replenishment of lipid stores by using dietary lipids at meal times. A reduction in FA intake may thus be required to abate the triglyceride stores of the heart as illustrated in the next section.

Reducing post-prandial myocardial FA uptake

Low or very low-calorie diets reduce cardiac triglycerides [18–20] in obese individuals with and without T2DM, independent of dietary composition [19], but bariatric surgery does not [21]. Changes in lipid-lowering or insulin treatments may have impacted triglyceride hydrolysis in opposite ways. The important observation was that both dietary and surgically induced weight losses led to a similar decrease in left ventricular mass, heart rate and cardiac output, and a similar improvement in diastolic function, independent of whether cardiac triglycerides were reduced or unchanged. Instead, the reduction in fasting myocardial oxidative metabolism was directly correlated with the improvement in diastolic function after weight loss [21]. These findings suggest that a selective and moderate suppression of myocardial FA oxidation can improve cardiac function in obese and T2DM individuals.

Direct inhibition of myocardial FA oxidation

A partial inhibition of β-oxidation can be achieved by using the metabolic modulator trimetazidine [22]. Placebo controlled studies conducted in patients with heart failure have documented that this drug improves cardiac function, with no change in myocardial perfu-

sion [23, 24]. In addition, the drug alleviated systemic insulin resistance and increased the phosphocreatine to ATP ratio, as an index of preservation of myocardial high-energy phosphates in these patients [24]. The drug showed a significant, but limited effect on the fractional oxidation of plasma-derived FAs [23]. In a subsequent study addressing the mechanism of action of trimetazidine in slightly overweight individuals with normal cardiac function, we observed a marked reduction in the oxidation of intramyocardial rather than plasma-derived FAs [25]. This change was accompanied by a significant increase in LVEF and stroke volume, in the absence of changes in cardiac fat and fasting myocardial glucose uptake or circulating FA levels. These studies in humans lend support to the concept that in conditions of FA overload and in heart failure, a selective and modest reduction in oxidative metabolism results in an improvement in cardiac function.

Effects of metabolic modulation on myocardial perfusion

Acutely, insulin increases myocardial blood flow and this response does not seem to be compromised in T2DM and/or heart disease [4]. Chronic insulin therapy did not change perfusion in individuals with T2DM and left ventricular dysfunction, but the achievement of a better glucose control was a significant predictor of positive changes in hyperemic myocardial perfusion and coronary flow reserve [26]. Pooled data from glyburide alone or in combination with metformin showed a stimulatory effect in relation to the degree of systemic glucose lowering [27].

Conclusions

Myocardial insulin resistance is a consequence of FA overload and is at least partly reversible. It parallels the decline in LVEF and may contribute to cardiac dysfunction in cardiovascular patients. FA oxidation correlates positively with the cardiac workload, and negatively with the efficiency of work and with post-prandial systolic and diastolic function. A moderate reduction in FA oxidation is beneficial, but interventions aimed at reducing FA oxidation need to guarantee an adequate energy supply to the heart, and may require caution in patients in whom FA oxidation is already depressed. Cardiac triglycerides correlate, but do not change consensually with diastolic dysfunction. They are resistant to a reduction, and may exert a protective role in situations of FA overload

or extreme depletion. The coronary vasodilator response is a negative prognostic marker and responds to hypoglycemic agents. Consistent with the adaptive nature of cardiac metabolism, imaging studies addressing its relationship with adipose tissue dysregulation in patients with heart disease would focus attention on primary rather than secondary causes of cardiac dysfunction. ■

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Inhibition of fatty acid oxidation as an approach to treat diastolic heart failure

John R. Ussher[1] and Jagdip S. Jaswal[2]

[1]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada;
[2]Cardiovascular Research Centre, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada

Correspondence: Dr. John Ussher, Lunenfeld-Tanenbaum Research Institute, 5-1001-DD, 25 Orde Street, Toronto, Ontario, Canada M5T 3H7
Tel: +1 (416) 586 4800 ext. 2308, fax: +1 (416) 586 5186, e-mail: ussher@lunenfeld.ca

Abstract

Heart failure (HF) is characterized by an impaired ability of the ventricle to fill with and eject blood commensurate with the metabolic demands and requirements of the body, and has emerged as a major cause of morbidity and mortality in the developed world. It is now becoming clear that a significant portion of the world's HF population does not exhibit defects in systolic function, but rather presents with significant declines in diastolic function. Unfortunately, there are no approved therapies for the management/treatment of diastolic HF, with current therapies aimed at improving patient symptoms. Recent evidence illustrates that similar to systolic HF, a number of metabolic abnormalities in the myocardium appear to be associated with the progression of diastolic dysfunction/HF. As ventricular relaxation during diastole is an energy-consuming process dependent on ATP hydrolysis, the optimization of cardiac energetics, potentially through inhibiting myocardial fatty acid oxidation rates, may represent a novel target for improving diastolic function. ■ Heart Metab; 2013;61:20–24

Keywords: Cardiac energetics; diastolic heart failure; diastolic dysfunction; fatty acid oxidation.

Introduction

Cardiovascular disease is currently a primary cause of death and disability. With recent advances in evidence-based medicine, the overall management of patients with cardiovascular diseases has greatly improved, although there has been a concomitant rise in the prevalence of heart failure (HF). HF is not a disease, but rather a complex clinical syndrome, defined by an impaired ability of the ventricle to fill with (diastolic HF) and/or eject (systolic HF) blood corresponding to the metabolic demands and requirements of the body [1]. HF has emerged as a leading cause of morbidity and mortality in the developed world. The etiology of HF is generally attributed to pre-existing ischemic heart disease, but it can also be of nonischemic/idiopathic origin. Epidemiological studies have identified that approximately 50–60% of HF patients have a dilated left ventricular chamber and reduced ejection fraction (systolic HF), while the remainder have a normal left ventricular chamber, and preserved ejection fraction (diastolic HF) [2, 3]. As such, systolic HF and diastolic HF are often considered to be two separate entities that contribute to clinically recognized HF. While there are a number of approved therapies for the management of systolic HF, there are currently no approved therapies for those with diastolic HF, with treatment

Abbreviations

Ang II: angiotensin II; **CoA:** coenzyme A; **CPT:** carnitine palmitoyl-transferase; **GLUT:** glucose transporter; **HF:** heart failure; **PDH:** pyruvate dehydrogenase; **PET:** positron emission tomography; **SR:** sarcoplasmic reticulum; **TDGA:** 2-tetradecylglycidic acid

primarily aimed at improving patient symptoms. However, recent work has demonstrated that targeting cardiac energetics, in particular reducing myocardial fatty acid oxidation rates, may be a novel approach to treat diastolic HF. Whereas we have previously described the characteristics that differentiate diastolic from systolic HF [3], the aims of this article are to describe the etiology of diastolic HF, the metabolic aspects of ventricular relaxation that contribute to diastolic function, the alterations in cardiac metabolism that accompany the development of diastolic HF, and the potential for optimizing myocardial energetics as an approach to treating diastolic HF.

Etiology and characteristics of diastolic HF

Although ejection fraction is preserved, diastolic HF is characterized by the classic symptoms of HF in addition to abnormalities of diastolic function. In particular, an increase in ventricular chamber stiffness/decreased distensibility impairs ventricular relaxation and thus filling at normal diastolic pressures. Interestingly, approximately half of all HF patients have preserved ejection fraction. As such, the prevalence of diastolic HF is similar to that of HF in general [2]. Predominant risk factors predisposing to the development of diastolic HF include increasing age, hypertension, obesity, dyslipidemia, diabetes and gender (ie, female sex) [4, 5]. At the gross morphological level, hallmark alterations in left ventricular structure and geometry (ie, left ventricular remodeling) also characterize diastolic HF. Concentric left ventricular hypertrophy, exemplified by increased left ventricular wall thickness, increased left ventricular mass, and an increase in the mass to cavity ratio, is a prominent change observed in diastolic HF [6]. The increase in left ventricular wall thickness also contributes to decreased ventricular compliance/increased stiffness. Alterations in the expression of titin isoforms (ie, decreased titin 2A expression) and increased fibrosis further decrease ventricular compliance in the setting of diastolic HF, and contribute to impaired ventricular relaxation [7].

Despite differences in etiology and left ventricular remodeling, diastolic HF is treated with many of the same therapeutic agents as systolic HF. Current therapeutic strategies focus on resolving the symptoms of diastolic HF by means of optimal blood pressure and heart rate control [8]. However, there is limited evidence from randomized clinical trials demonstrating that these therapies possess equivalent efficacies with respect to decreasing morbidity and mortality in the setting of diastolic HF relative to systolic HF. As such, there exists a need to identify novel therapeutic interventions to decrease the burden of diastolic HF. Of interest, one of the consequences of increased left ventricular wall thickness may provide such a novel target. Although the increase in left ventricular wall thickness may initially serve a compensatory function by normalizing wall stress in the presence of chronic pressure overload (ie hypertension) that can predispose to diastolic HF, the change does become maladaptive, and correlates with increased myocardial oxygen consumption [9]. As cardiac muscle predominantly relies on oxidative metabolism to meet its energetic requirements, optimizing energy substrate metabolism such that ATP is generated in an oxygen-efficient manner (ie by inhibiting fatty acid oxidation/stimulating glucose oxidation) may represent a novel strategy that may have therapeutic utility in the treatment of diastolic HF (see below).

Active ventricular relaxation and diastolic function

Ventricular diastole is the period during which the ventricles relax and fill with blood. Blood flow into the ventricle is governed by two key phases, first an early (E) diastolic phase arises due to the flow of blood from the atria down its pressure gradient into the ventricle, while the second phase occurs later as a result of atrial contraction (A). Therefore, the E/A ratio is often used as a diagnostic measure, because it is reduced during diastolic dysfunction as a greater fraction of the left ventricular end diastolic volume becomes dependent on the A phase.

Ventricular relaxation itself is the process by which the myocardium returns to its original length and tension, and takes place once the aortic valve closes and the mitral valve is still closed. Furthermore, it is an energy-consuming process as ATP hydrolysis is required for myosin detachment from actin filaments, Ca^{2+} dissociation from troponin C, and sarcoplasmic reticulum (SR) Ca^{2+} reuptake (*Figure 1*) [3]. Optimal

ATP supply and tight regulation of the metabolic pathways that generate ATP is thus essential for the maintenance of normal diastolic function. Support for this concept is provided by demonstrations that diastolic function is impaired in pathologies including pressure overload hypertrophy (secondary to syste-

Fig. 1 *ATP-dependency of ventricular relaxation. Ventricular relaxation is an energy-consuming process, with ATP hydrolysis essential for (a) sarco/endoplasmic reticulum Ca²⁺-ATPase reuptake into the SR, and during the process of (b) cross-bridge cycling (once power stroke induces the sliding of myofilaments, ATP binds to the myosin head releasing it from actin, which is followed by ATP hydrolysis, allowing the cross-bridge to return to its original orientation in the resting state). SR, sarcoplasmic reticulum*
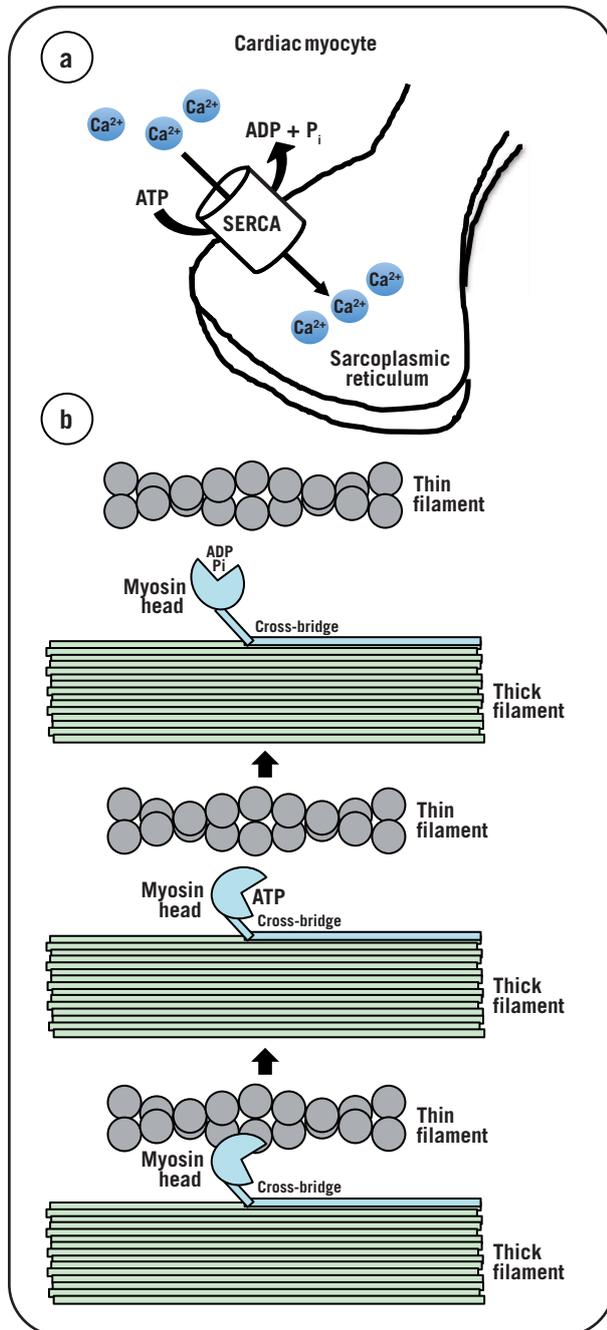
mic hypertension), obesity, and diabetes, all of which can significantly impact myocardial metabolism [10, 11]. Whether myocardial metabolism can be targeted to improve diastolic HF will be discussed below.

Cardiac glucose oxidation

Glucose and lactate are the primary carbohydrates metabolized by the heart (for an in-depth review of the regulation of cardiac carbohydrate oxidation, please refer to Jaswal et al [10]). Glucose transporters (ie, GLUT-1/4) are responsible for glucose uptake into the cardiac myocyte whereby glucose catabolism for ATP production can be separated into two major components: glycolysis and glucose oxidation. Glycolysis generates pyruvate and accounts for less than 10% of the total ATP produced by the aerobic adult heart [12]. If glycolysis is coupled to glucose oxidation, the pyruvate generated from glycolysis will be converted into acetyl coenzyme A (CoA) by the enzymatic action of pyruvate dehydrogenase (PDH).

Cardiac fatty acid oxidation

Before oxidation in cardiac mitochondria, fatty acids must first be activated into fatty acyl CoA by fatty acyl CoA synthase, which converts a fatty acid into a fatty acyl CoA moiety in an ATP-dependent manner (for an in-depth review of the regulation of cardiac fatty acid oxidation, please refer to Lopaschuk et al [11]). Mitochondrial uptake of fatty acyl CoA requires a complex of proteins that relies on a carnitine-dependent shuttle system [13]. Carnitine palmitoyl-transferase I (CPT-I), which is the rate-limiting enzyme for mitochondrial fatty acid uptake and subsequent oxidation converts fatty acyl CoA esters into their respective fatty acylcarnitine moieties [14, 15]. The acylcarnitine is subsequently transported into the mitochondrial matrix by carnitine translocase, and converted back into its respective fatty acyl CoA moiety by CPT-II [11]. Fatty acyl CoA esters are sequentially oxidized inside the mitochondrial matrix by the successive enzymatic activities of acyl CoA dehydrogenase, enoyl CoA hydratase, 3-ʟ-hydroxyacyl CoA dehydrogenase, and 3-ketoacyl CoA thiolase. Fatty acid β-oxidation progressively shortens fatty acyl CoA esters by two carbon units via the liberation of acetyl CoA, while also generating reducing equivalents (NADH and reduced flavine adenine dinucleotide), which act as electron donors for the electron transport chain, in order to drive ATP synthesis by the process of oxidative phosphorylation [16].

Glucose–fatty acid cycle

In its simplest form, the glucose–fatty acid cycle refers to the inverse relationship between glucose and fatty acid oxidation, whereby increases in the oxidation of one energy substrate (ie, fatty acids) decrease the oxidation of the competing substrate (ie, glucose), a phenomenon originally described by the work of Dr Philip Randle and colleagues in the 1960s [17]. In addition to being the more oxygen-efficient fuel, increasing glucose oxidation also improves efficiency by reducing the amount of ATP required to remove excess protons arising from the hydrolysis of glycolytically derived ATP uncoupled from the subsequent mitochondrial oxidation of pyruvate (ie, glucose oxidation) [18]. Therefore, one could postulate that by inhibiting fatty acid oxidation rates in the heart, the corresponding increase in glucose oxidation would conserve ATP and possibly improve left ventricular relaxation in diastolic HF.

Energy metabolism in diastolic HF

It is now becoming clear that similar to systolic HF, diastolic HF is also accompanied by significant changes in cardiac energy metabolism. In type 1 diabetic Akita mice, diastolic function is selectively impaired, and is associated with increased myocardial fatty acid oxidation rates, which coincides with a substantial accumulation of intramyocardial ceramide and diacylglycerol levels [19]. Such a metabolic signature has been shown to negatively impact cardiac function and cardiac insulin sensitivity [10, 20]. Of interest is the fact that these metabolic abnormalities and diastolic dysfunction were reversed following insulin therapy [19], suggesting that energy metabolism represents a potential target to alleviate diastolic dysfunction/HF. Type 2 diabetes-associated diastolic dysfunction in Zucker diabetic fatty rats demonstrated similar metabolic derangements, as an assessment of myocardial metabolism by positron emission tomography (PET) revealed elevations in myocardial fatty acid oxidation rates and reduced myocardial glucose uptake [21]. Patients with nonischemic diastolic dysfunction present with a similar metabolic profile, as PET imaging studies demonstrated elevations in both myocardial fatty acid uptake and oxidation, while myocardial glucose uptake was reduced [22]. Furthermore, recent studies utilizing either a 2-week angiotensin II (Ang II) or phenylephrine infusion in mice to induce diastolic dysfunction demonstrate that both models selectively reduce myocardial glucose oxidation rates due to an inhibition of

PDH activity [23]. Intriguingly, treatment with the Ang II type 1 receptor blocker, irbesartan, improved diastolic function and was associated with a restoration of myocardial PDH activity and subsequent glucose oxidation rates [23]. Collectively, these findings suggest that the metabolic alterations associated with diastolic dysfunction/HF may contribute to disease pathology.

Inhibition of fatty acid oxidation to improve diastolic function in diastolic HF

In striking contrast to the overall premise of this article, studies performed in the 1990s demonstrated that inhibition of CPT-1 with 2-tetradecylglycidic acid (TDGA) induces left ventricular hypertrophy and diastolic dysfunction [24, 25]. However, neither of these studies actually measured the effect of TDGA treatment on myocardial fatty acid oxidation rates. On the contrary, treatment with the fatty acid oxidation inhibitor, trimetazidine, prevents the increase in diastolic $[Ca^{2+}]i$ and the decrease in SR Ca^{2+} content in rats subjected to acute myocardial injury following a 2-day isoprenaline administration [26]. These improvements in diastolic Ca^{2+} handling may account for the improvements in diastolic function observed in type 2 diabetic *db/db* mice treated with trimetazidine [27]. Ranolazine, a US Food and Drug Administration approved agent for treating angina pectoris by inhibition of the late inward sodium current, has also been shown to inhibit fatty acid oxidation at similar concentrations [10], and has been reported to improve diastolic function in deoxycorticosterone acetate salt-induced hypertensive mice, as well as in humans [28, 29]. Furthermore, weight loss as a result of gastic bypass surgery reduced myocardial oxygen consumption and fatty acid oxidation rates, which was associated with a 28% improvement in left ventricular relaxation [30]. Finally, reducing fatty acid oxidation rates by inhibition of CPT-1 with perhexiline corrects diastolic dysfunction and improves exercise capacity in patients with hypertrophic cardiomyopathy [31]. Despite these promising findings, the exact role myocardial fatty acid metabolism plays in contributing to diastolic function and its potential contribution towards the overall pathology of diastolic dysfunction/HF is a relatively understudied area deserving of further attention.

Conclusions

As there are currently no approved therapies for the treatment of diastolic HF, there is a growing need to

improve our understanding of the physiology/patho-physiology of diastolic function/dysfunction. As ventricular relaxation is an active, energy-requiring process, and recent studies have demonstrated alterations in cardiac energy metabolism in the setting of diastolic dysfunction/HF, the optimization of cardiac energetics may represent a novel therapeutic approach to improve this condition. However, whether this can be achieved by inhibiting fatty acid oxidation in the heart remains to be determined. ■

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Use of trimetazidine to treat diabetes patients with heart failure

Rui Yan and Dengfeng Gao
Department of Cardiology, The Second Affiliated Hospital,
Xi'an Jiaotong University School of Medicine Xi'an, Shaanxi 710004, PR China

Correspondence: Dengfeng Gao, PhD, Department of Cardiology, The Second Affiliated Hospital,
Xi'an Jiaotong University School of Medicine, Xi'an, Shaanxi 710004, PR China
Tel: +86 29 87679770, fax:+86 29 87679775, e-mail: gaomedic@163.com

Abstract

Heart failure (HF) occurs commonly in modern society and is a major cause of morbidity and mortality all over the world. Cardiac energy metabolism is altered in HF and has been demonstrated to be an important factor in the development of HF in clinical and animal research. Trimetazidine is a metabolism modulator, which shifts energy production from free fatty acid to glucose oxidation. There is evidence demonstrating that trimetazidine can improve cardiac function and prognosis, even affecting cardiac electrophysiology. In this paper, recent literature on the beneficial therapeutic effects of trimetazidine on left ventricular dysfunction and HF is reviewed and discussed, especially in diabetes patients with HF. ■ Heart Metab; 2013;61:25–28

Keywords: Energy metabolism; heart failure; trimetazidine.

Introduction

Heart failure (HF) is a clinical syndrome characterized by the abnormality of cardiac structure and/or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues [1]. Approximately 1–2% of the adult population in developed countries has HF [1]. In the USA, the total number of HF-related hospitalizations increased from 3 891 737 in 2001 to 4 244 865 in 2009 [2]. The incidence of HF has brought about an enormous financial burden, estimated to be US$39.2 billion each year in the USA [3]. The causes of HF commomly are cardiac ischemia, cardiac hypertrophy, myocarditis, diabetic cardiomyopathy (DCM) and other secondary cardiomyopathies. According to the European Society of Cardiology guidelines on HF in 2012, coronary artery disease (CAD) is the cause of approximately two-thirds of cases of systolic HF [1]. Meanwhile, in the last Heart Failure Pilot Survey, it was reported that 64% of patients with acute HF and 85% with chronic HF had an ischemic etiology [4].

Energetic modulation during HF

In order to preserve normal cardiac ejection, the myocardium requires more energy than any other tissues. Herrmann [5] reported that HF was a state of energy starvation in 1939. Ever since then, evidence has demonstrated that altered energetic modulation may play an important role in the mechanisms of HF [6]. The energy that the heart uses (ATP) is produced in myocardium mainly by oxidizing fatty acids (60–90%), carbohydrates (10–40%) and some amino acids. Metabolism insufficiency in HF has been described in detail by Neubauer [6]. In brief, the metabolic machinery of the heart has three main components: substrate utilization, oxidative phosphorylation and ATP

Abbreviations

CAD: coronary artery disease; **DCM:** diabetic cardio-myopathy; **HF:** heart failure

transfer and utilization. When HF occurs, all three components change. Despite some inconsistent results, there is consensus that the failing heart relies more on glucose as its preferential substrate for ATP synthesis [7, 8], that is, there is a shift of metabolism away from a preference for fatty acids to more carbohydrate oxidation, which may be a compensatory or protective mechanism for HF [9]. In advanced HF, both fatty acids and glucose metabolism decline. In earlier HF, the phosphocreatine and total creatine levels are reduced, although ATP levels remain normal. The eventual outcome of the loss of high-energy phosphates and creatine kinase activity is contractile dysfunction and particularly the loss of inotropic reserve of myocardium. At the same time, the free ADP levels rise when HF occurs, which can inhibit

the function of many intracellular enzymes, causing contractile dysfunction.

Effects of trimetazidine in HF

According to experimental and clinical data, targeting cardiac energy metabolism can be beneficial in HF [10]. One of strategies is due to an improvement of substrate utilization. Furthermore, trimetazidine may improve cardiac function by other mechanisms such as preservation of intracellular levels of phosphocreatine and ATP [11], reduction of calcium overload and free radical-induced injury, inhibition of cell apoptosis, improvement of endothelial function, and inhibition of cardiac fibrosis [12] (see *Figure 1*). There is controversy about the beneficial and adverse effects of a reduction in fatty acid oxidation for HF. However, multiple results have suggested that partial inhibition of fatty acid oxidation is promising. Trimetazidine is the first competitive inhibitor of long chain 3-ketoacyl-coenzyme A thiolase on the market, and can decrease the oxidation of fatty acids and pro-
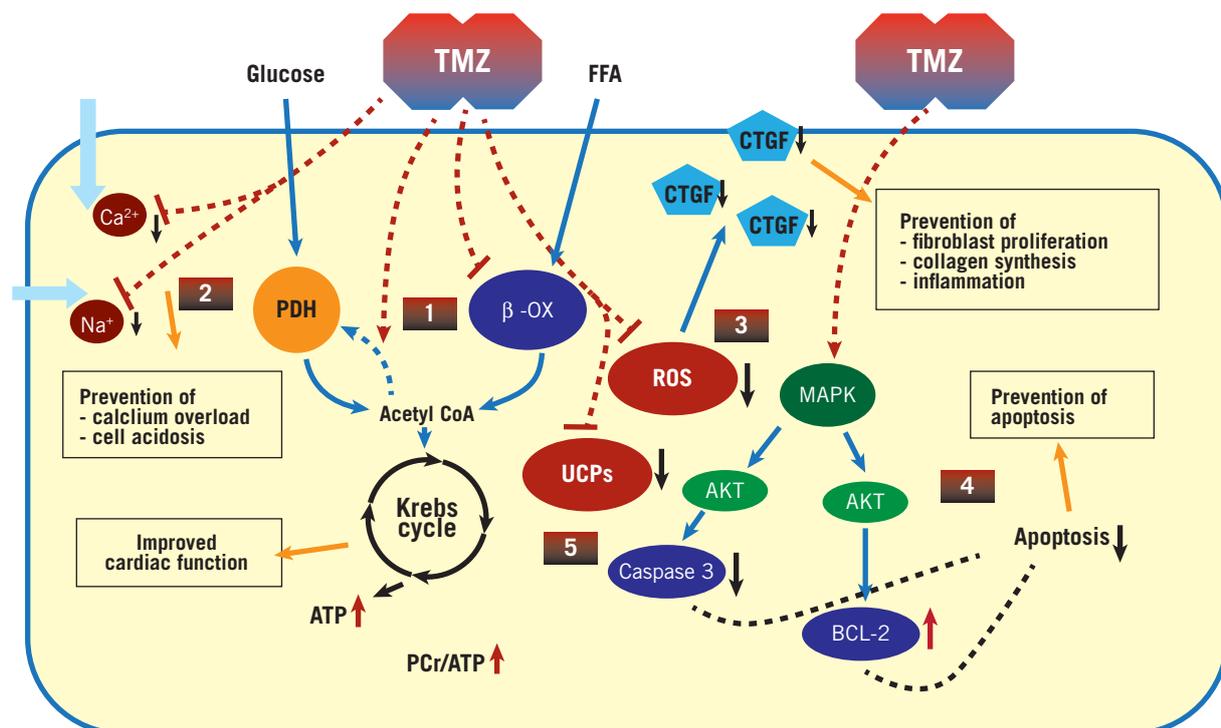
Fig. 1 *Possible mechanisms for the beneficial effects of trimetazidine in heart failure: from metabolism to myocardial protection. Administration of trimetazidine induces the partial inhibition of fatty acid β-oxidation and increases pyruvate dehydrogenase (1), and determines the increase in glucose oxidation, energetically useful in heart failure. (2) Limitation of the accumulation of sodium and calcium and intracellular acidosis. (3) Reduction of reactive oxygen species-induced cell damage, and inhibition of cardiac fibrosis and inflammation through the reactive oxygen species/connective tissue growth factor pathway. (4) Prevention of cell apoptosis through the mitogen-activated protein kinase/AKT pathway. (5) Reduction of uncoupling proteins and increase in creatine phosphate/ATP ratio. The final effect is a reduction in cellular damage and an improvement in heart failure. Adapted with permission from Gao et al [12]. β-OX, β-oxidation; CTGF, connective tissue growth factor; FFA, free fatty acid; HF, heart failure; MAPK, mitogen-activated protein kinase; PCr, creatine phosphate; PDH, pyruvate dehydrogenase; ROS, reactive oxygen species; TMZ, trimetazidine; UCP, uncoupling protein*

mote the metabolism of glucose in HF [13], thereby decreasing oxygen utilization, especially in ischemia. Some studies have shown that trimetazidine brings about beneficial effects in patients with HF, including ischemic and nonischemic etiologies. However, other studies have shown limited benefits, because the small sample sizes produced underpowered results and metabolic therapy was just indicated by the guidelines [1]. We therefore performed a meta-analysis to explore the potential therapeutic effects of trimetazidine in the management of chronic HF in 2011 [12]. In the meta-analysis we found that trimetazidine could improve left ventricular ejection fraction, subjective and objective measures of functional status in HF, and perhaps most intriguingly reduced all-cause mortality. At the same time, the addition of trimetazidine to current optimal HF treatment does not increase the incidence of cardiovascular events and hospitalization. These data confirm that trimetazidine might be an effective strategy for treating HF. Ashrafian and Neubauer [14] commented that the study may present a credible argument that trimetazidine might be effective across almost all measures of cardiac function and provide the strongest statistical rationale to date that metabolic modulation may be successful in HF.

Effects of trimetazidine in diabetes patients with HF

DCM has become a more significant cause of HF, along with the increase in newly diagnosed cases of diabetes mellitus throughout the world. The utilization of substrate in myocardium presents a preference that varies in physiologic or pathologic demands, in order to produce enough energy for preserved cardiac function. However, in diabetes, the high levels of blood glucose and fatty acids cause this preference to be constrained [15]. The diabetic heart thus relies on fatty acid β-oxidation with increased oxygen consumption for ATP synthesis even in HF or myocardial ischemia. Trimetazidine might then improve the detrimental consequences. Evidence has suggested that trimetazidine could reduce silent and symptomatic episodes of transient myocardial ischemia in diabetes patients with CAD [16]. Another clinical trial that included diabetes patients with idiopathic dilated cardiomyopathy proved that trimetazidine could improve the left ventricular ejection fraction, improve left ventricular end-systolic volume, reduce C-reactive protein concentrations, reduce plasma N-terminal pro brain natriuretic peptide levels, and increase the 6-minute walking distance after 6 months' follow-up [17]. These results indicated that trimetazidine might be an effective therapeutic strategy.

Electrophysiological effect of trimetazidine in HF

In recent years, some studies have been carried out on the electrophysiological effect of trimetazidine in HF. A clinical trial, which included 36 patients with HF treated by trimetazidine added to optimal treatment for HF, suggested that trimetazidine may improve the maximum P-wave duration and P-wave dispersion in association with improved left ventricular function. This suggests that trimetazidine may decrease the risk of atrial fibrillation in HF [18]. Another study showed that the addition of trimetazidine can effectively reduce QTc, $T_{peak}-T_{end}$ and $T_{peak}-T_{end}$ dispersion [19]. However, this effect appears mainly confined to patients with post-ischemic HF. These effects of electrophysiology indicate that trimetazidine could be used for reducing the risk of major arrhythmias, which may be by means of an undiscovered mechanism.

Conclusion

Energy metabolism treatment is a more recent theory in HF. Some energy metabolism modulators including trimetazidine, coenzyme Q [10], and phosphocreatine, which regulate the cell metabolism by means of different mechanisms, have been proved effective in HF. However, despite our recent meta-analysis showing that these benefits also translate into improved survival, larger and long-term follow-up clinical studies are required to confirm the efficacy in HF. ■

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Dramatic loss of weight in an obese patient with heart failure: a mighty heart in a big man

[1]Vitantonio Di Bello, [1]Lorenzo Conte, [1]Iacopo Fabiani, [1]Valentina Barletta,
[2]Letizia Pieruzzi, [2]Giovanna Scartabelli, [2]Ferruccio Santini
[1]Department of Surgery, Medical, Molecular and Critical Area Pathology, University of Pisa, Pisa, Italy;
[2]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Correspondence: Prof. Vitantonio Di Bello, Department of Surgery, Medical, Molecular and Critical Area Pathology,
University of Pisa, Via Paradisa 2, Cisanello, 56100 Pisa, Italy,
e-mail: vitantonio.dibello@med.unipi.it

Abstract

Obesity has reached global epidemic proportions and has been associated with numerous comorbidities, including major cardiovascular diseases and heart failure. It has many adverse effects on hemodynamics and cardiovascular structure and function; it increases total blood volume and cardiac output, and also activates several neurohumoral systems that play an important role in causing cardiac dysfunction. Typically, obese patients have a higher cardiac output but a lower level of total peripheral resistance at any given level of arterial pressure. Over the past few years, experimental evidence has unraveled some important pathogenetic mechanisms that may underlie a specific form of "obesity cardiomyopathy". However, many unanswered questions remain regarding the pathophysiological interactions between obesity and the heart. ■ Heart Metab; 2013;61:29–31

Keywords: Echocardiography; heart failure; natriuretic peptides; obesity.

Clinical case

We present the case of P.M., a 50-year-old man with a history of progressive weight gain from the age of 18 years, up to the weight of 188 kg (body mass index [BMI] 61 kg/m^2; obesity stage VI).

This patient attended the emergency department for worsening dyspnea. He presented with severe anasarca, with elephantiasis and trophic lesions of the lower limbs, tachycardia, tachypnea, and blood pressure within normal limits (120/70 mm Hg).

Blood gas analysis revealed respiratory failure type 2 (pH 7.38, PO_2 49.6 mm Hg, PCO_2 44.7 mm Hg). Blood tests showed advanced renal insufficiency (serum creatinine 4.4 mg/dL, estimated glomerular filtration rate 40 mL/min), liver dysfunction (severe coagulation deficiency, cholinesterase 2900 U/l) and severe anemia (hemoglobin 9 g/dL). At recovery B-type natriuretic peptide [BNP] was 663 pg/mL and pro-BNP was 2317 pg/mL. Urgent chest X-ray showed severe cardiomegaly and severe pulmonary congestion (*Figure 1*). The echocardiogram displayed left ventricular dilation with end-diastolic volume (EDV) 280 mL, with diffuse parietal hypokinesis and reduction of global ejection fraction (EF) 32%. ECG recordings revealed tachycardial atrial fibrillation with right bundle branch block and low voltages of QRS in the peripheral derivations. The diagnosis was congestive heart failure (CHF) complicated by respiratory, renal and hepatic failure.

The patient was therefore hospitalized and treated with furosemide, first intravenously (mean 500 mg/

Abbreviations

BMI: body mass index; **BNP:** B-type natriuretic peptide; **CHF:** congestive heart failure; **EDV:** end-diastolic volume; **EF:** ejection fraction
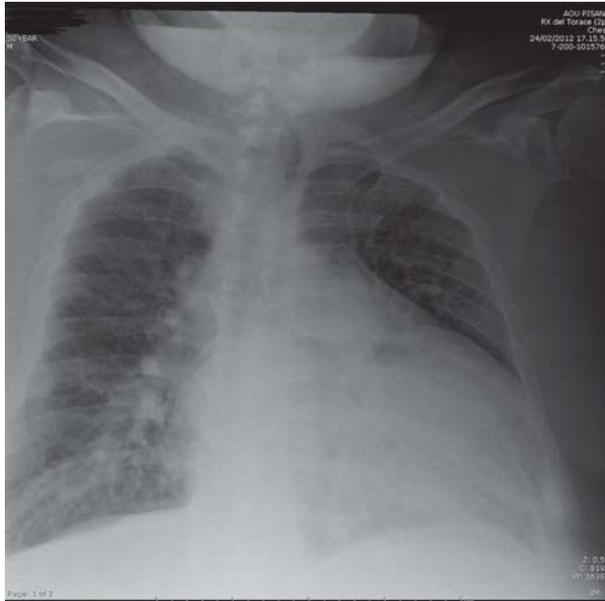
Fig. 1 Chest X-ray

day) and then oral therapy (125 mg/day), angiotensin-converting enzyme inhibitor therapy (ramipril 5 mg/day), potassium canrenoate 50 mg twice a day, digitalis (0.250 mg/day), intravenous albumin, adequate water restriction and the introduction of a low-calorie diet.

On observing polyclonal hypergammaglobulinemia with an increase in kappa and lambda light chains, leading to a suspicion of cardiac amyloidosis, the patient underwent biopsy of the periumbilical fat (which was negative for amyloidosis) and angiocardiac magnetic resonance imaging, which confirmed the echocardiographic findings and excluded the presence of subendocardial or diffuse hyperenhancement (typical of cardiac amyloidosis).

In the days after hospitalization, we observed a dramatic progressive weight loss (78 kg in 45 days), with a marked improvement in renal function (serum creatinine 0.82 mg/dL), gas exchange, liver function (cholinesterase 4300 U/L) and progressive resolution of trophic lesions in the inferior limbs.

One month after discharge the patient underwent a complete check-up. Blood sample tests showed normalization of hepatorenal function, a marked re-

duction in BNP levels (217 pg/mL) and reduced left ventricular volumes (EDV 200 mL) with improvement of left ventricular function (EF 42%). Cardioactive therapy was modified with the introduction of a β-blocker (carvedilol) and dose reduction of the diuretic and anti-aldosterone drug (*Figure 2*).
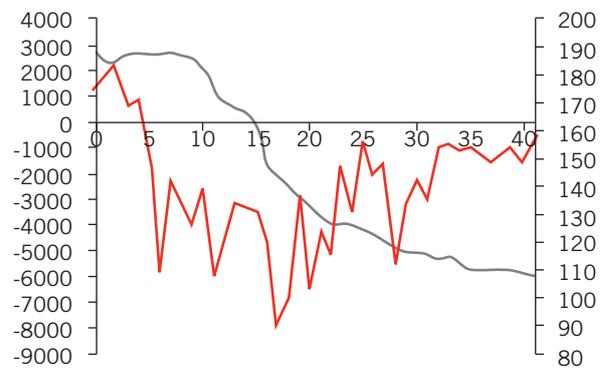
Fig. 2 Body weight trend in relation to water balance

In order to complete the diagnosis and rule out the suspicion of secondary cardiomyopathy, the patient underwent myocardial perfusion scintigraphy, which showed reversible perfusion defects in the mid-distal anterior area and inferior area. Coronary angiography did not reveal the presence of significant coronary artery disease.

After 1 year, successive cardiologic controls confirmed the stability of the patient's clinical status (BNP 73 pg/mL) and further improvement of systolic left ventricular function (EF 46%, EDV 175 mL). The patient has currently reported significant improvement in symptoms and quality of life.

Discussion

Obesity is one of the most prevalent diseases of our time. Severe obesity (BMI >40 kg/m^2) is estimated to affect 5–10 million individuals in the USA [1,2]. Obesity induces several modifications in cardiac structure and function as a result of hemodynamic overload, and represents a risk factor for heart failure [3–6]. Adipose tissue is a metabolically active compartment, which requires 2–3 mL/min per 100 g of blood and constitutes an important blood reserve. With the accumulation of adipose tissue, blood flow at that level also increases (in patients with severe obesity it can reach half the cardiac output at rest) and blood volume expands in order to compensate for the increased oxygen demand. The expansion of

blood volume results in left ventricular dilation and is accompanied by eccentric hypertrophy of the myocardium even in normotensive individuals (ventricular cavity/ventricular diameter ratio remains almost unchanged). Moreover, the complex structural and functional alterations found in severely obese patients such as increased left ventricular mass, increased interstitial collagen content, left ventricular and left atrial dilatation, systolic and diastolic intramyocardial dysfunction (confirmed by different studies) would suggest the presence of a distinct typical form of "obese cardiomyopathy" that may be linked to insulin resistance, leptin and lipotoxicity [7–9].

The heart can tolerate this work overload for a very long period. However, over time cardiac function (both systolic and diastolic) deterioration is observed. During this phase reduced systolic function triggers a vicious circle, which leads to further dilatation of the heart chambers and activation of the noradrenergic system and renin angiotensin aldosterone system. These changes, together with the volume overload, further depresses cardiac function. Eventually, signs and symptoms of CHF appear.

A recent epidemiological study demonstrated that insulin resistance could represent a link between obesity and CHF. Insulin resistance, by an increase in circulating insulin, is capable of stimulating insulin-like growth factor 1 receptors, which are probably also implicated in the pathogenesis of myocardial hypertrophy observed in obese patients.

Hyperinsulinemia may lead to sodium retention that could cause subclinical myocardial dysfunction as a result of volume expansion. Furthermore, hyperinsulinemia may lead to sympathetic nervous system activation. Insulin resistance is related to an increased pressure response to angiotensin II, which stimulates left ventricular hypertrophy and interstitial fibrosis through its interaction with aldosterone.

Secretion of locally active molecules from fat cells like leptin (increased adiposity causes higher serum leptin concentrations) has been linked to ventricular hypertrophy in both animals and humans, independently from ventricular dilatation due to overload in obesity. Lipid accumulation in "non fat" cells results in cellular dysfunction with consequent lipotoxicity (low mitochondrial oxidative capacity, increased lipolysis) [9]. Over the past few years, experimental investigations have unraveled some important pathogenetic mechanisms, such as cardiac steatosis, lipoapoptosis, and the activation of specific cardiac genes that may underlie a specific form of "obesity cardiomyopathy". The integration between hemodynamic and metabolic models partly explains some differences observed in this particular patient population.

This case is pathognomonic of how obesity could be a determinant of myocardial dysfunction and could cause, when it is not rapidly recognized, severe CHF with secondary multiple organ failure. The rapid resolution of CHF is fundamental for this type of patient and can avoid severe complications; on the other hand, it allows recognition of the real obesity status clear of the volume overload induced by CHF itself. Once the problem of CHF is resolved, overweight treatment still remains, which we try to address by modifying the patient's lifestyle nutritionally and with increased physical activity and, if necessary, when this approach fails, we resort to bariatric surgery. ■

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Energy metabolic changes in the diabetic heart

Lionel H. Opie
**Hatter Research Institute for Cardiovascular Research in Africa,
Department of Medicine, University of Cape Town, South Africa**

Correspondence: Lionel H. Opie, Hatter Research Institute for Cardiovascular Research in Africa,
Department of Medicine, University of Cape Town, South Africa
E-mail: lionel.opie@uct.ac.za

Abstract

The progression of the metabolic syndrome to diabetes is accompanied by dramatic changes in cardiac energy metabolism. This includes an increased reliance of the heart on fatty acids as a source of energy, and a decrease in glucose metabolism. These metabolic alterations can contribute to the development of diabetic cardiomyopathies. Therapeutic strategies that inhibit fatty acid oxidation or stimulate glucose metabolism are potential approaches that can prevent the development of cardiac dysfunction during the development of diabetes. This paper discusses the metabolic changes that occur in diabetes, and the potential approaches that can be used to treat diabetic cardiomyopathies.
■ Heart Metab; 2013;61:32–38

Keywords: Fatty acid oxidation; hyperglycemia; insulin resistance; metabolic syndrome.

Introduction

The heart relies almost exclusively on aerobic oxidation of substrates in order to generate ATP, which is required to maintain its cellular and contractile functions. A keen interest in the substrate supply in human heart failure (HF) dates back more than 50 years to the pioneering work of Bing and colleagues [1]. Both glucose and free fatty acids (FFAs) are major physiological fuels for the normal myocardium; glucose in the fed state and FFAs in the fasted state. Glucose uptake is promoted by insulin and inhibited by high concentrations of FFAs [2, 3], both of which occur in type 2 diabetes mellitus (T2DM). Such diabetes commonly occurs against a background of the metabolic syndrome, which in turn predisposes to cardiovascular abnormalities. The key to understanding the metabolism of T2DM lies in the 2-fold aspects of insulin resistance, which has metabolic consequences by promoting hyperglyce-mia and has pro-inflammatory effects. This paper will concentrate on the adverse metabolic effects of hyperglycemia, the metabolic syndrome, and the diabetic heart. Similar principles apply to the ischemic and failing heart [4], showing how robust these metabolic principles are.

Metabolic syndrome and progression to diabetes

The metabolic syndrome

When this state is fully developed, there are five features: an increased waistline, fasting hyperglycemia, blood pressure (BP) elevation, increased circulating triglycerides and decreased circulating high-density lipoprotein (HDL) cholesterol [5]. Three of these are required for the diagnosis of the metabolic syndrome [6] (*Figure 1*). The metabolic syndrome comprises a group of cardiovascular risk factors each of which individually may only be only of borderline

Abbreviations

AMPK: AMP-activated protein kinase; **BP:** blood pressure; **CoA:** coenzyme A; **DKA:** diabetic ketoacidosis; **FFA:** free fatty acid; **GLUT:** glucose transporter; **HDL:** high-density lipoprotein; **HF:** heart failure; **IL:** interleukin; **MCD:** malonyl CoA decarboxylase; **MR:** magnetic resonance; **NFκB:** nuclear factor kappa B; **PPAR:** peroxisome proliferator-activated receptor; **TMZ:** trimetazidine; **T2DM:** type 2 diabetes mellitus; **UCP:** uncoupling protein

Fig. 1 *The metabolic syndrome potentially consists of five clinical components, namely abdominal obesity, high blood TGs, low HDL-cholesterol levels, prehypertension (BP equal to or above 130/85 mm Hg) or higher, and hyperglycemia. A proposed sequence of events that could lead to this syndrome is as follows. Excess calories and too little exercise give rise to abdominal adiposity. From there, increased FFAs are released into the circulation, thereby inhibiting the uptake of glucose by muscle. Plasma glucose rises and elicits an insulin response. Adipose tissue also releases cytokines such as tumor necrosis factor alpha, which alter the insulin receptor substrate 1 so that insulin signaling is deficient. Increased release of angiotensin II from the abdominal fat causes vasoconstriction and increases the BP. The net overall effect is insulin resistance with increased fasting plasma glucose despite the increased circulating insulin. Increased plasma FFAs and glucose predispose to increased hepatic synthesis of TGs and increased blood levels of TGs, which in turn decrease levels of HDL-cholesterol. Note that an increased total cholesterol level is not part of the syndrome. BP, blood pressure; CoA, coenzyme A; FFA, free fatty acid; HDL, high-density lipoprotein; TG, triglyceride*

significance, but when taken together indicate an enhanced risk of developing overt diabetes or cardiovascular disease. The risk of developing future cardiovascular problems is proportional to the number of features of the metabolic syndrome [7]. The basic metabolic abnormality in the metabolic syndrome is excess abdominal adipose tissue, which is a metabolically active organ [7] and liberates excess circulating FFAs [6]. The inhibitory effect of plasma

FFAs on insulin signaling follows a rather modest increase in plasma FFAs, developing at concentrations that are well within the physiological range at plasma FFA levels observed in obesity and T2DM [8], and hence found in the metabolic syndrome.

Molecular steps leading from increases in blood FFAs to insulin resistance

Excess FFAs entering the muscle cell is activated to long-chain acyl coenzyme A (CoA), which inhibits the insulin signaling pathway so that there is less translocation of glucose transporter vesicles (GLUT-4 and GLUT-1) to the cell surface to increase glucose uptake. Glucose uptake is decreased and hyperglycemia promoted. The increased uptake of FFAs promotes lipid metabolite accumulation in various organs including the heart and pancreas. Exercise and the antidiabetic drug metformin, by stimulating the enzyme AMP-activated protein kinase (AMPK), both promote the translocation of glucose transport vesicles to the cell surface to promote glucose entry and to oppose insulin resistance [9].

Role of hyperglycemia

The choice of diet could help to control hyperglycemia. The higher intake of vegetables, fruits, nuts, whole grains, and a lower intake of red meat could reduce the risk of T2DM as shown in a review of 48 studies [10]. Furthermore, in T2DM adherence to the Mediterranean diet can help to control hyperglycemia [11]. Olive oil in liberal amounts is a crucial component of the Mediterranean diet, because in T2DM it delays gastric emptying and attenuates the postprandial increases in glucose, insulin, and the glucose-dependent insulinotropic polypeptide, while increasing glucagon-like peptide 1 [12].

Cardiovascular risks of metabolic syndrome

First, it should be emphasized that the metabolic syndrome comprises a group of cardiovascular risk factors, namely abdominal obesity, high blood triglycerides, low HDL-cholesterol levels, high normal BP hypertension and hyperglycemia, which when taken together indicate enhanced risks of the development of overt diabetes or cardiovascular disease. There is doubt as to whether every one of the five components of the metabolic syndrome could singly predict the development of diabetes [13]. Others have emphasized the predictive value of two components

of the metabolic syndrome, modest elevations of glucose and BP, which were mostly responsible for increasing the cardiovascular risk by 71% [14]. For cardiologists, becoming alert to the clustering of these risk factors is an important widening of clinical vision [15]. The risk of the metabolic syndrome developing into future cardiovascular events is proportional to the number of metabolic syndrome features [16]. With four or five features, the risk of diabetes was 25-fold greater than with no features and still much more than with only one feature [17]. In an important definitive analysis of 172 573 persons in 37 studies, the metabolic syndrome had a relative risk of 1.78 for future cardiovascular events, significant even after adjusting for more traditional cardiovascular risk factors (relative risk 1.54) [18].

Insulin resistance

Insulin resistance leads to the metabolic syndrome [19] and increased circulating FFAs and glycemia, plus elevated glucose production in the liver, which are precursors of T2DM [20]. There is a dose–response effect of elevated plasma FFAs on insulin signaling [21]. Experimentally, cardiac insulin resistance with decreased production of ATP is found in pressure overload hypertrophy, preceding the development of systolic HF [22].

Where does obesity enter the picture? Obese persons have high blood FFA levels, which even at modest elevations inhibit insulin signaling and stimulate nuclear factor kappa B (NFκB) to promote insulin resistance (see Figure 1 in Kim) [23]. NFκB in turn stimulates macrophages to provoke the chronic low-grade inflammatory response (see Figure 2 in Kim) [23] with increased plasma levels of C-reactive protein, and inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL)-6, monocyte chemoattractant protein 1 and IL-8. Macrophages in human adipose tissue are the main but not the only source of these inflammatory mediators that stimulate insulin resistance in multiple organs [23]. The "western" type high-fat diet experimentally enhances such cytokine production, whereas exercise diminishes it [24].

Obesity: → high FFAs → molecular signaling (NFκB, others) → macrophages → inflammatory cytokines → insulin resistance → risk of diabetes

Molecular steps in diabetes leading from increased FFAs to insulin resistance

Excess FFAs entering the muscle cell are activated to long-chain acyl CoA, which inhibits the insulin signaling pathway so that there is less translocation of glucose transporter vesicles (GLUT-4 and GLUT-1) to the cell surface (see Figure 1). Glucose uptake is decreased and hyperglycemia promoted. The increased uptake of FFAs promotes lipid metabolite accumulation in various organs including the heart and pancreas. Metformin and exercise, by stimulating AMPK, promote the translocation of transport vesicles to the cell surface to promote glucose entry and to oppose insulin resistance. Protein kinase B, also called Akt, plays a key role. These changes are reviewed elsewhere [25]. When compared with glucose as myocardial fuels, excess FFAs as in the metabolic syndrome are ATP-wasting (see next section).

## Changes in fatty acid and glucose metabolism that occur in diabetes

In a genetic animal model of T2DM, the db/db mouse, there was a major decrease in the cardiac efficiency of work, with an 86% increase in unloaded myocardial oxygen consumption [26]. Furthermore, the angle of the pressure–volume area/oxygen consumption measured during work had a steeper slope, suggesting reduced efficiency of cardiac work. This implies a negative inotropic effect (see Figure 3.8 in Opie) [27] and decreased efficiency of work. These changes reflect the adverse effects of the high blood FFAs, about double normal [26], which imply decreased glucose utilization and increased fatty acid oxidation. Acute elevation of the FFA supply in both normal and db/db mouse hearts increased myocardial oxygen consumption due to the increased oxygen cost for basal metabolism and for excitation–contraction coupling. Beta-adrenergic stimulation, on top of a high fatty acid supply, led to a further increase in the unloaded myocardial oxygen consumption [28]. There is thus a firm link in this model between FFA levels and adverse effects on the heart.

Likewise, In patients with T2DM the increased plasma FFA levels have adverse effects on ATP, as will be discussed in the next section [29]. The onset of diabetes and its progression can be delayed by lifestyle interventions including weight loss and exer-

cise [30]. In particular, robust weight loss in response to bariatric surgery not only ameliorates circulating glucose, insulin, and FFA levels, but also normalizes cardiac diastolic function [31].

Possible metabolic therapies

There are a number of interventions including glucose–insulin–potassium [32] and trimetazidine (TMZ) that can reduce the abnormalities of excess FFA metabolic breakdown (*Figure 2*). TMZ is a metabolically
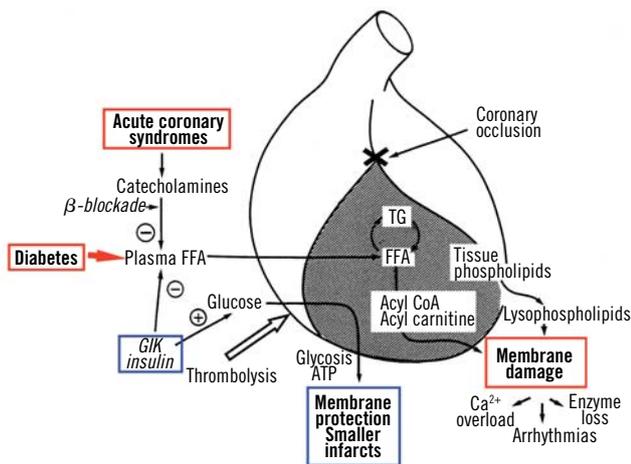
Fig. 2 *In diabetes, increased levels of circulating FFAs indirectly lead to metabolic inefficiency (see text) and membrane damage, whereas the promotion of glycolysis by providing glycolytic ATP and increasing metabolic efficiency gives membrane protection. Note that in acute coronary syndromes similar principles of metabolic cardioprotection apply [32]. Circulating FFAs may be reduced both by β-blockade and by infusion of glucose–insulin–potassium with therapeutic benefit. BP, blood pressure; CoA, coenzyme A; FFA, free fatty acid; GIK, glucose-insulin-potassium; HDL, high-density lipoprotein; TG, triglyceride*

active antianginal agent widely used in Europe but not licensed in the USA. TMZ has multiple potentially cardioprotective mechanisms besides partial inhibition of FFA oxidation, together with increased glucose oxidation as found in isolated rat hearts [33, 34]. In patients with T2DM and HF, TMZ induced an increase in peripheral muscle glucose oxidation and decreased fatty acid oxidation (as measured by citrate release) [35].

ATP wastage with FFA use in diabetic states

Experimental data

ATP wastage implies uncoupling of oxygen consumption by the respiratory chain from ATP synthesis. Mitochondria are regarded as the major source of reactive oxygen species [36]. Excess circulating FFAs, as in uncontrolled diabetes, may

inhibit ATP transfer from mitochondria to cytosol [37]. Furthermore, excess uptake of FFAs by cardiac myocytes leads to an increase in long chain acyl CoAs in the mitochondrial matrix [37]. Uncoupling proteins (UCPs) are anion carriers expressed in the mitochondrial inner membrane that uncouple oxygen consumption by the respiratory chain from ATP synthesis. Their net effect is proton leakage [37]. At any given level of cardiac work, primary use of FFA rather than glucose can decrease the efficiency of work by 10–25% [37] and oxygen wastage by over 40% [38]. FFAs also inhibit pyruvate oxidation, thereby further promoting the switch away from glucose metabolism. Overall, predominant and excessive use of FFAs as myocardial fuel can cause ATP wastage by multiple mechanisms.

ATP wastage may also be generated by UCPs. Mitochondria from genetically diabetic db/db mice have fatty acid-induced mitochondrial uncoupling that may be mediated by UCPs with the isoform subtype not specified [39]. Furthermore, and controversially, UCPs may play a role in the pathogenesis of diabetes mellitus, as recently reviewed [40]. UCP-1 is considered to be a candidate gene for diabetes because of its role in thermogenesis and energy expenditure. UCP-2 is expressed in several tissues and acts in the negative regulation of insulin secretion by β cells and in fatty acid metabolism. UCP-3 plays a role in fatty acid metabolism and energy homeostasis and modulates insulin sensitivity. Of these, UCP-3 is proposed as playing an essential role in the mitochondrial adaptation to fasting in that mitochondria of ucp3$^{-/-}$ mice exhibited impaired fatty acid oxidation with consequential matrix accumulation of palmitate [41].

In the diabetic state, potentially cardioprotective glucose metabolism is regulated not only by FFA–glucose interaction, but also by malonyl decarboxylase (MCD). This key enzyme is highly regulated by peroxisome proliferator-activated receptor (PPAR)-α and its activity and expression is increased in diabetes [37]. Conversely, selective MCD inhibitors increase myocardial malonyl CoA content and stimulate glucose metabolism, which is turn will reduce FFA-induced ATP wasting [37].

Lipotoxicity and diabetic cardiomyopathy

High circulating fatty acids predispose to lipotoxicity and contribute to insulin resistance. Cytoplasmic ac-

cumulation of lipid metabolites results in contractile dysfunction and thus may contribute to the cardiomyopathies found in obesity and diabetes [37]. How does this apply to myocardial ATP wastage? The underlying etiology of diabetic cardiomyopathy can be related to cardiac lipotoxicity [42] thus indirectly contributing to myocardial ATP wastage. Furthermore, in patients with diabetes and/or obese patients with severe end-stage idiopathic dilated cardiomyopathy and a mean ejection fraction of19%, referred for cardiac transplantation, intramyocardial lipid overload was found in about one-third of the hearts, especially in patients with diabetes and obesity (body mass index >30) [43].

Skeletal muscle also suffers [44]. In patients with T2DM proton nuclear magnetic resonance (MR) could detect intramyocellular fat as long chain fatty acyl CoA in biopsies. Treatment of such patients to reduce insulin resistance by the PPAR-γ agonist, pioglitazone, reduced both intramyocellular triglyceride content and skeletal muscle long chain fatty acyl CoA. The latter decrease strongly correlated with enhanced insulin sensitivity. The term lipotoxicity thus has widespread implications with links to many metabolic abnormalities in T2DM, metabolic syndrome and advanced HF.

Myocardial lipid abnormalities in patients with aortic stenosis

Myocardial steatosis, the condition of abnormal lipoid deposits in myocardial cells, has been associated with obesity, impaired glucose tolerance, and T2DM. Those studies showed that myocardial triglyceride content was an independent correlate of both systolic and diastolic dysfunction, implying a causal relationship between steatosis and such functional changes [45]. In this novel observation, 39 patients with severe aortic stenosis but with normal left ventricular ejection fraction and similar blood levels of FFAs, glucose, triglycerides, and lipoproteins, but without significant coronary artery disease and 20 matched healthy controls were studied. They underwent cardiac 1H-MR spectroscopy and imaging for the determination of steatosis (myocardial triglyceride content). Left ventricular function tests included circumferential strain (measured by MR tagging). Strain was decreased in both symptomatic and asymptomatic patients but more so in those with symptoms (−16.4 ± 2.5% and −18.1 ± 2.9%, respectively,

versus controls −20.7 ± 2.0%, both $P < 0.05$). Myocardial steatosis was found in both symptomatic and asymptomatic patients (0.89 ± 0.42% in symptomatic; 0.75 ± 0.36% in asymptomatic versus controls 0.45 ± 0.17, both $P < 0.05$). Importantly, multivariable analysis indicated that steatosis was independently correlated to impaired left ventricular strain. Pronounced myocardial steatosis was thus present in severe aortic stenosis, regardless of symptoms, and was independently associated with the degree of left ventricular strain impairment.

Lipotoxicity has been implicated in the development of muscle insulin resistance and T2DM [44], which implies that this lipid abnormality can further be linked to defective ATP metabolism as an early abnormality in these apparently asymptomatic patients. The further hypothesis would be that abnormal myocardial mechanical strain from other chronic valve abnormalities could also suffer from superadded lipid abnormalities that could potentially contribute to increasingly abnormal left ventricular function.

Hypothesis: Mechanical defect → increased left ventricular strain → unknown signaling → lipid deposits in left ventricle → metabolic ATP wastage

ATP wastage in patients with T2DM

Although a specific biochemical-based diabetic cardiomyopathy has long been suspected [46], with experimental proof in 1997 [47], the clinical problem in defining a pure diabetic metabolic heart disease has been frequent concurrent diabetic coronary artery disease [48]. Focusing on the diabetic myocardium, Taegtmeyer et al [48] introduced the concept of glucolipotoxicity, reflecting the adverse myocardial effects of excess circulating FFAs and the consequent block in cardiac metabolism at the level of inhibited glucose uptake and glycolysis at the level of pyruvate dehydrogenase, with insulin giving rise to high circulating glucose levels. In combination, these are the metabolic changes that lead to myocardial ATP wastage.

To prove that ATP wastage occurs in human diabetic cardiomyopathy, Scheuermann-Freestone et al [29] studied patients with diabetes but without coronary heart disease or evidence of clinical HF. They found a complex metabolic disequilibrium associated with insulin resistance and accompanied by

decreased cardiac phosphocreatine to ATP ratios. Furthermore, there was impaired post exercise recovery of skeletal high-energy phosphate. Cardiac high-energy phosphate metabolites were measured at rest using 31P nuclear MR spectroscopy. Although their cardiac morphology, mass, and function appeared to be normal, the patients with diabetes had lower phosphocreatine/ATP ratios than the healthy volunteers. Of interest is the fact that the cardiac phosphocreatine/ATP ratios correlated negatively with the fasting plasma FFA concentrations. Furthermore, there was impaired post exercise recovery of skeletal high-energy phosphate compounds. Proof of metabolic ATP wastage was decreased cardiac levels of phosphocreatine and ATP.

Proposal: Metabolic defect in T2DM → increased FFA and less glucose usage → less ATP synthesis → metabolic ATP wastage

Diabetic coma

There is no exact replica of this complex human condition, yet relevant to the human condition of type 1 diabetes with coma is the study by How et al [49] on genetically diabetic db/+ mice given streptozotocin in a model with reduced body and heart weights, without elevations in plasma FFA levels. Plasma glucose concentrations were very high (mean 31.8 mmol/L) with ketosis. Stage 3 respiration decreased in mitochondria incubated with either palmitoyl-carnitine or pyruvate. Diabetic hearts showed decreased cardiac efficiency, with an 86% increase in unloaded myocardial oxygen uptake. The corresponding human condition seen in type 1 diabetes is pure diabetic ketoacidosis (DKA) without significant hyperosmolarity, which typically indicates the total or relative absence of insulin [50].

Although the pathogenesis of the hyperosmolar hyperglycemic diabetic comatose state is less well understood than that of DKA, the basic underlying mechanism for both disorders is a reduction in the net effective action of circulating insulin, ie, insulin resistance [50]. This state, but without ketoacidosis, typically occurs with lesser degrees of insulin deficiency, as seen in T2DM. However, there is usually a mixed clinical presentation depending on the duration of symptoms, coexisting medical illnesses, or underlying precipitating cause. Diabetic coma is thus a complex and varying metabolic illness that results from a combination of major insulin resistance and increased activity of the counterregulatory hormones, including catecholamines.

Conclusion

The adverse myocardial metabolic effects of hyperglycemia, the metabolic syndrome, and the diabetic state are analyzed with special reference to: the metabolic syndrome, obesity, and insulin resistance as precursors to T2DM; the inhibitory effects on glucose metabolism of high blood FFA levels leading to insulin resistance; the changes in fatty acid and glucose metabolism that occur in diabetes; and the significance of these changes of wastage of energy in the form of ATP depletion. ■

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Irisin, a novel myokine: potential role in obesity and diabetes

Andrew G. Swick
Metagenics, Gig Harbor, WA, USA

Correspondence: Andrew G. Swick, PhD, Metagenics, 9770 44th Ave NW, #100, Gig Harbor, WA 98332, USA
E-mail: andrewswick@metagenetics.com

Abstract
Obesity is a worldwide health problem that results in a significant increased risk of morbidity and mortality. While we know that obesity is the consequence of a chronic imbalance between energy intake and energy expenditure, how energy expenditure is regulated in humans is not clearly understood. Recent publications suggest that specific depots of white adipose tissue can be converted to thermogenically active beige adipose tissue and that the myokine, irisin may be a key regulator of this conversion. ■ Heart Metab; 2013;61:39–40

Keywords: Brown adipose tissue; energy expenditure; irisin; myokine.

According to the World Health Organization, worldwide obesity has doubled since 1980, with more than 1.4 billion adults now considered to be overweight or obese. In the USA more than 60% of the adult population is now considered to be overweight or obese [1]. Obesity is associated with a number of comorbidities including type 2 diabetes, cerebrovascular and coronary heart disease, sleep apnea, pulmonary dysfunction, knee osteoarthritis, nonalcoholic steatosis, and certain types of cancer.

In simple mathematical terms, obesity is caused by chronic excess energy intake relative to energy expenditure (EE). In practice, however, the equation is not that simple. We know that there is considerable individual variation in the susceptibility to weight gain, and the ability to lose weight. This individual variability is highlighted by studies demonstrating significant heterogeneity in response to sustained caloric excess or deficit. In both acute [2] and chronic [3] over-feeding studies, for example, variability in weight gain was evident despite tight compliance with supervised mealtimes, indicating that differences in EE may be

driving this variability [4]. Although the mechanisms underpinning this are uncertain, it is likely that a wide variation exists in physiological controls governing energy balance, helping to maintain an individual's body weight within a given range [5].

While fat free mass can explain approximately 80% of the variance in 24-hour EE [6], there is still considerable variability in energy requirements between individuals. The 20% variation in EE has a potentially tremendous impact on the prevalence and severity of obesity in the general population. One potential biological source of variable EE is adipose (fat) tissue, in particular brown adipose tissue (BAT), which clearly contributes to EE in some animals including mice and rats. Although BAT is present in newborn humans, its existence and function in adult humans has been debated [7]. Recent reports using positron emission tomography suggest the presence of active BAT in some, but not all, adults [8]. Furthermore, there appears to be a correlation between the presence of active BAT and increased EE in response to stimuli such as cold exposure and

Abbreviations

BAT: brown adipose tissue; **EE:** energy expenditure; **PGC-1α:** proliferator-activated receptor-gamma coactivator-1α

the consumption of capsaicin [9, 10]. The regulation of BAT in humans is poorly understood; however, a recently discovered peptide, irisin, may play a role in the regulation of EE and metabolism. Irisin is a proliferator-activated receptor-gamma coactivator-1α (PGC-1α)-dependent myokine shown to induce "browning" of white adipose tissue, resulting in increased thermogenesis in mice [11]. Muscle-specific overexpression of PGC-1α in mice induced the expression of the *Fndc5* gene in muscle, which encodes a type 1 membrane protein that is proteolytically cleaved to produce a secreted plasma hormone named irisin [11]. Adenoviral expression of *Fndc5* in mice increased *Ucp1* and *Cidea* gene expression in subcutaneous white fat, resulting in increased EE and resistance to diet-induced obesity and diabetes. Exercise increases plasma irisin levels in both mice and humans. It is unclear why exercise would stimulate irisin synthesis when conservation of calories to fuel exercise would seem paramount. One hypothesis suggests that irisin is released from shivering muscle to induce thermogenesis and prevent hypothermia [11]. Furthermore, an additional contribution of fat to EE could be attributed to the adipokines leptin and adiponectin [12]. Irisin may play a role alongside leptin and adiponectin in the maintenance of lean and fat mass, and may well predict the efficacy of sustainable weight loss.

In addition to irisin's proposed role in energy balance it may also be involved in insulin resistance and type 2 diabetes [13]. Irisin levels have been reported to increase with exercise and to be lower in patients with type 2 diabetes [14]. A role for irisin in insulin action is supported by the report that two single nucleotide polymorphisms in the *FNDC5* gene have been associated with insulin sensitivity, as measured *in vivo* [15]. Furthermore, irisin levels have been reported to correlate inversely with intrahepatic fat content in obese adults [16]. At this point there are many unanswered questions, but it is important to determine whether irisin plays a role in mediating the beneficial effects of exercise on metabolism and EE.

It is clear that obesity results in an increased risk of diabetes and metabolic diseases and that exercise increases insulin sensitivity and metabolic health. However, the exact mechanisms and physiological pathways responsible are not clearly understood. The recently discovered myokine, irisin, may be an important link between exercise and its benefits on body weight, diabetes and metabolic health. ■

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Adiponectin

Adiponectin is an adipokine that is released from adipose tissue. It is an important signaling molecule that acts centrally at the level of the hypothalamus to decrease food intake, and peripherally to modify fatty acid and glucose metabolism. Low levels of adiponectin are associated with obesity and insulin resistance.

Akt-1

Akt, which is sometimes called protein kinase B (PKB), is an intracellular kinase that is important in a number of cellular functions, including regulation of glucose metabolism and cell growth. It is a kinase in the insulin signaling pathway, and insulin activation of Akt results in glucose transporter-4 (GLUT-4) translocation to the cell membrane, thereby stimulating glucose uptake. Overexpression of Akt in the heart can cause a marked hypertrophy of the muscle.

GLUT-4

Glucose transporter- 4 (GLUT-4) is a protein that transports glucose across cell membranes. In insulin-responsive tissues (such as the heart), insulin will cause GLUT-4 to be translocated from inside the cell to the plasma membrane, thereby stimulating glucose uptake.

HOMA-IR

Homeostasis model assessment of insulin resistance (HOMA-IR) is a clinically utilized index of insulin resistance calculated as the product of fasting plasma glucose concentration (expressed in mmol/L) and fasting plasma insulin concentration (expressed in µU/mL) normalized to a constant, 22.5. The constant, itself, reflects the product of normal fasting plasma glucose (ie, 4.5 mmol/L) and normal fasting plasma insulin (ie, 5 µU/mL).

Insulin

Insulin is a pancreatic peptide hormone secreted from β cells of the islets of Langerhans in the postabsorptive state. Its major metabolic effects are anabolic in nature, exemplified by the ability of insulin to: increase glucose and amino acid uptake as well as glycogen and protein synthesis in muscle; increase glucose uptake and triacylglycerol synthesis in adipose tissue; and increase glucose uptake, glycogen and triacylglycerol synthesis in the liver.

Leptin

Leptin is a peptide hormone synthesized by adipocytes that plays a key role in the regulation of appetite and energy expenditure. This can occur through direct actions of leptin on the hypothalamus or via direct actions of leptin on peripheral lipid and glucose metabolism.

Triacylglycerol

Triacylglycerol (TAG) is the major storage form of fatty acids in the body and consists of three fatty acids attached to a glycerol backbone. Fatty acid storage in adipocytes primarily occurs in the form of TAG. The heart also contains sizable TAG stores as a source of fatty acids for energy production.

Diacylglycerol

Diacylglycerol (DAG) consists of two fatty acids attached to a glycerol backbone and is the preceding intermediate in the biosynthesis of TAG. The accumulation of DAG in skeletal muscle and the liver has been linked to the development of muscle and hepatic insulin resistance.

Ceramide

Ceramides are specialized lipids that are derived from sphingomyelin and glycosphingolipids present in plasma membrane of cells. Various cytokines can release ceramides, which then act as important intracellular signaling molecules. Considerable interest has focused on ceramide as a signaling molecule in apoptosis (programmed cell death) and in the development of muscle insulin resistance.

Lipoprotein lipase

Lipoprotein lipase (LPL) is an enzyme that cleaves fatty acids from TAG contained within lipoproteins.

Pyruvate dehydrogenase kinase 2

Pyruvate dehydrogenase kinase 2 (PDK2) is an intramitochondrial kinase that phosphorylates and inhibits pyruvate dehydrogenase (PDH). As PDH is the rate-limiting enzyme for the mitochondrial metabolism of carbohydrates, activation of PDK2 will result in a decrease in the mitochondrial metabolism of carbohydrates. Maintaining mitochondrial glucose metabolism is an important therapeutic strategy to protect the ischemic heart. Therefore, inhibition of PDK2 (which is expressed in the heart) is a potential therapeutic approach to treating ischemic heart disease.

Peroxisome proliferator activated receptor alpha

Peroxisome proliferator activated receptor alpha (PPARα) is a nuclear receptor involved in the transcriptional regulation of proteins. PPARα has many functions, including regulating the expression of many enzymes involved in the control of fatty acid oxidation in muscle, heart and liver.

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