Heart Failure and Loss of Metabolic Control

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Abstract: Heart failure is a leading cause of morbidity and mortality worldwide, currently affecting 5 million Americans. A syndrome defined on clinical terms, heart failure is the end result of events occurring in multiple heart diseases, including hypertension, myocardial infarction, genetic mutations and diabetes, and metabolic dysregulation, is a hallmark feature. Mounting evidence from clinical and preclinical studies suggests strongly that fatty acid uptake and oxidation are adversely affected, especially in end-stage heart failure. Moreover, metabolic flexibility, the heart's ability to move freely among diverse energy substrates, is impaired in heart failure. Indeed, impairment of the heart's ability to adapt to its metabolic milieu and associated metabolic derangement are important contributing factors in the heart failure pathogenesis. Elucidation of molecular mechanisms governing metabolic control in heart failure will provide critical insights into disease initiation and progression, raising the prospect of advances with clinical relevance.

Key Words: heart failure, metabolism

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INTRODUCTION

Cardiovascular disease is the leading cause of mortality worldwide, posing an enormous burden to individuals and society.[1] Heart failure, a syndrome defined by clinical criteria, is the point of convergence of numerous cardiovascular diseases—the final common pathway of an injured heart. Thanks to tremendous advances in modern diagnostic and therapeutic technologies, the survival of acute myocardial infarction (AMI) has increased markedly in recent years. This, combined with an aging population, the epidemic of obesity and diabetes, and successes in other realms of medicine, such as oncology, has culminated in an ever-rising prevalence of heart failure.

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Heart failure affects approximately 5 million Americans and is especially prevalent among the elderly, where it is the leading cause of hospitalization.[1] Heart failure prevalence, already rampant, is expected to increase 25% by 2030, with total annual costs slated to reach $70 billion. Despite new therapies and considerably improved survival in recent years, 50% of patients still die within 5 years of diagnosis. Current therapeutic strategies emphasize the suppression of neurohumoral activation and normalization of hemodynamics. However, despite significant improvements in clinical symptoms and attenuated pace of clinical decline, the progression of heart failure remains all-too-often unremitting. Novel therapeutic approaches are urgently needed.

Over the past years, numerous studies have firmly established metabolic derangement as a cardinal feature of the pathophysiology of heart failure.[2–4] Heart failure–related changes in uptake and utilization of metabolic substrates, combined with alterations in cardiomyocyte energetics, have been described in numerous preclinical and clinical studies.[5,6] Availability of new technologies to detect alterations in metabolic events, coupled with major advances in our understanding of metabolic regulation, has raised the prospect of targeting cardiac metabolism to treat heart failure. Here, we provide an overview of normal cardiac metabolism and a description of the metabolic derangements in heart failure, followed by the discussion of potential therapies targeting cardiac metabolism. Because of the complexity of these events, all aspects of cardiac metabolism are not included. Several recent reviews are therefore recommended for further reading.[7–9]

MYOCARDIAL METABOLISM IN NORMAL HEART

The heart is the most avid adenosine triphosphate (ATP)–consuming organ in the body. The adult human heart weighs approximately 300 g, yet it uses 6 kg of ATP to pump 10 tons of blood daily. Cardiac ATP reserve is quite low, representing enough stored energy for fewer than 10 contractions.[2] Thus, to maintain uninterrupted contraction and relaxation, the myocardium requires constant and robust ATP synthesis. To accomplish this, the heart functions as an omnivore, extracting energy from a wide range of metabolic substances, including free fatty acids (FFAs), glucose, lactate, and ketones. At generally prevailing concentrations of circulating substrates, the heart derives 50% to 70% of its newly generated ATP from the oxidation of FFA.

Triglyceride Metabolism

Plasma triglycerides (TGs) are largely associated with lipoproteins and chylomicrons. Triacylglycerol-enriched

lipoproteins are catabolized by lipoprotein lipase, whose localization at the luminal surface of coronary blood vessels may serve to increase local levels of FFAs.[10]

Cardiomyocyte uptake of FFAs is driven mainly by a transmembrane concentration gradient and mediated by either passive diffusion or transporter-facilitated transport (Fig. 1). CD36 is a fatty acid translocase that is abundant in the cardiomyocyte. Deficiency of CD36 in cardiomyocytes leads to reduced FFA oxidation and TG storage.[11] Conversely, overexpression of CD36 in muscle enhances FFA oxidation in myocytes and TG clearance from the circulation.[12] Together, these data highlight the fact that CD36 is the major translocase facilitating FFA uptake in heart.

Once inside the cardiomyocyte, FFA is esterified by fatty acyl CoA synthase (FACS). The resulting fatty acyl CoA is then either reesterified to TG for storage or transported to mitochondria for beta-oxidation. In addition, intramyocyte TG may be synthesized de novo from glycerol-3-phosphate. Myocardial TG is a dynamic FFA pool, subjected to stringent hormonal regulation, and recent studies suggest that metabolism and turnover of myocardial TG play critical roles in cardiac physiology.[13] Banke et al[14] found that the turnover of palmitoyl units of endogenous TG is 3.75-fold faster than the oxidation of palmitate in a normal heart, suggesting preferred oxidation of TG-derived FFA. Overexpression of peroxisome proliferator-activated receptor (PPAR)-α in cardiomyocytes further enhances TG turnover, which is associated with the upregulation of several key enzymes involved in TG synthesis and lipolysis.

Derangements in TG dynamics contribute to the pathophysiology of various heart diseases. Indeed, myocardial steatosis has been implicated in the initiation and progression of diabetic cardiomyopathy, a prominent disorder associated with metabolic syndrome.[15] Intramyocyte accumulation of TG is also associated with pressure overload-induced cardiac hypertrophy and myopathy.[16] Collectively, intramyocyte TG serves as a dynamic FFA reserve, and its metabolism participates in the various aspects of cardiac health and disease.

FFA Metabolism

Circulating FFA levels are subject to stringent metabolic control. During starvation, declines in insulin levels lead to enhanced lipolysis in adipocytes through activation of hormone-sensitive lipase, which liberates FFAs from TG stores, releasing them into the circulation. Lipolysis is also enhanced under various pathological conditions, such as AMI, obesity, and diabetes.

TG-derived FFAs and albumin-bound FFA from lipolysis are activated by FACS to fatty acyl CoA, which is readily fueled into the mitochondrial beta-oxidation pathway. In addition, FFA may be released from the intramyocyte pool of TG and channeled into catabolism. Although short- and medium-chain FFAs diffuse passively into mitochondria where they are catabolized, long-chain fatty acyl CoA requires the carnitine shuttle for transport. Long-chain fatty acyl CoA is first converted to long-chain acylcarnitine in the outer mitochondrial membrane by carnitine palmitoyltransferase I (CPT-I), followed by transport across the inner mitochondrial membrane mediated by carnitine translocase. Finally, long-chain fatty acylcarnitine is reverted to long-chain fatty acyl CoA by CPT-II, and carnitine is recycled back to the cytosol for the next round of fatty acid shuttling.

In this process, CPT-I is the rate-limiting enzyme and subject itself to metabolic regulation. Malonyl CoA is a potent allosteric inhibitor of CPT-I and hence fatty acid metabolism. Malonyl CoA is synthesized by acetyl CoA carboxylase (ACC), a direct target of AMP kinase.[17] Phosphorylation of ACC by AMPK strongly suppresses ACC enzymatic activity and inhibits the production of malonyl CoA, a process deemed to be the most important mechanism of AMPK-stimulated fatty

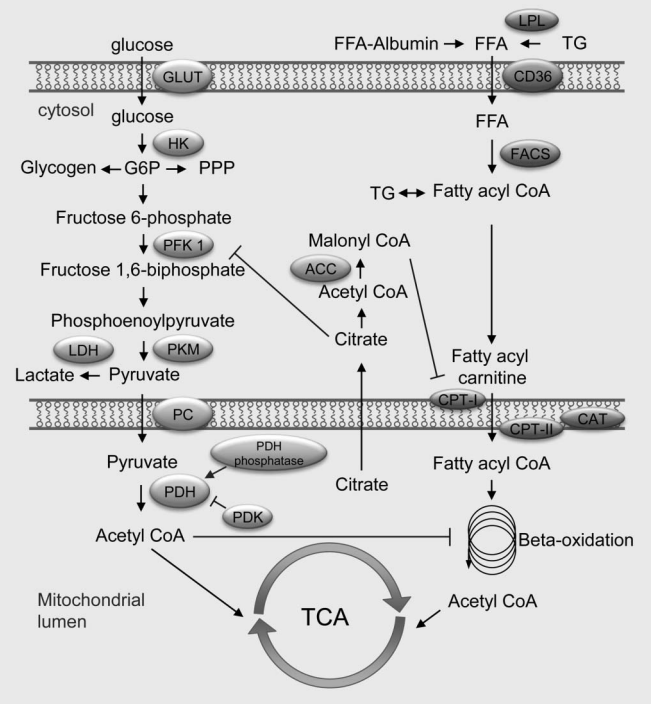

FIGURE 1. Glucose and fatty acid metabolic pathways in the cardiomyocyte. Glucose is transported into the cardiomyocyte by GLUT. After phosphorylation by HK, G6P is fed into the glycogen synthetic pathway, glycolysis, or the pentose phosphate pathway. PFK-1 is the first commitment enzyme of glycolysis. The glycolytic product pyruvate is transported into mitochondria or converted to lactate by lactate dehydrogenase. PDH is a pivotal enzyme to catabolize pyruvate to acetyl CoA, which ultimately enters the citrate acid cycle. PDH enzymatic activity is inhibited by PDK4-dependent phosphorylation and stimulated by dephosphorylation through PDH phosphatase. FFAs are transported into cardiomyocytes by diffusion or through a fatty acid translocase, such as CD36. Once inside the cell, FFAs are esterified to fatty acyl CoA by FACS. The carnitine shuttle, composed of CPT-I, CPT-II, and CAT, is responsible for the transport of FFA from the cytosol to mitochondria for beta-oxidation, which generates acetyl CoA for the citric acid cycle. Glucose and FFA metabolic pathways are subject to complex reciprocal regulation. Citrate can be transported to the cytosol, where it undergoes lysis to acetyl CoA. Cytosolic acetyl CoA is converted to malonyl CoA by ACC. Malonyl CoA is a potent inhibitor of CPT-1 and FFA metabolism.

acid catabolism and ATP generation.[18] CPT-I is also an established pharmacological target to suppress fatty acid utilization (see below).

Within the mitochondrial lumen, fatty acyl CoA is broken down by beta-oxidation to acetyl CoA. There are 4 enzymes involved in beta-oxidation, each regulated at distinct levels. Although acetyl CoA is fed into the citric acid cycle, the other products of beta-oxidation, NADH and FADH2, are used by the electron transfer chain to generate a transmembrane proton gradient and synthesize ATP.

Glucose Metabolism

Glucose uptake into cells is mediated by glucose transporters (GLUT) (Fig. 1). In cardiomyocytes, 2 GLUT isoforms are abundant, GLUT1 and GLUT4.[19] The translocation of GLUT4 from intracellular compartments to the sarcolemmal membrane is stimulated by insulin.[20] AMPK can similarly trigger GLUT4 translocation to enhance glucose uptake.[18] Once inside the cell, glucose is immediately phosphorylated by hexokinase, generating glucose-6-phosphate (G6P). G6P, in turn, serves as the starting point for various metabolic processes, such as glycolysis, glycogen synthesis, and the pentose phosphate pathway.

Phosphofructokinase-1 (PFK-1) is a critical enzyme in glycolysis, catalyzing the first commitment step from fructose 6-phosphate to fructose 1,6-biphosphate. PFK-1 is subjected to complex allosteric regulation.[2] PFK-1 enzymatic activity is inhibited by ATP and citrate and stimulated by AMP and fructose 2,6-biphosphate. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) catalyzes the first ATP-generating step in glycolysis. The product of GAPDH, NADH, functions as a potent inhibitor of GAPDH. Under anaerobic conditions, glycolytic flux is facilitated by the removal of NADH through lactate dehydrogenase and generation of lactate. Finally, pyruvate kinase stimulates the second ATP-generating step in glycolysis, conversion of phosphoenoylpyruvate to pyruvate. There are 2 pyruvate kinase isoforms in muscle, PKM1 and PKM2, deriving from a single gene that undergoes alternative splicing.[21] Recent studies suggest that levels and activities of PKM2 are critical for cellular coordination of ATP generation and growth.[22] However, the role of these pyruvate kinases in heart failure remains largely unknown. Pyruvate is translocated to mitochondria by recently identified pyruvate carriers.[23,24]

Pyruvate dehydrogenase (PDH) complex is a pivotal multiprotein regulatory nexus in glucose metabolism. PDH is subjected to elegant regulation by allosteric metabolites and posttranslational modifications. The products of PDH, acetyl CoA, and NADH inhibit PDH enzymatic activity, whereas NAD^+ and CoA stimulate it. PDH kinase (PDK) and phosphatase are associated within the PDH complex. Phosphorylation by PDK (mainly PDK4 in heart) suppresses PDH enzymatic activity, and dephosphorylation enhances it.[25] Thus, PDK may be another important target for pharmacological intervention to stimulate glucose metabolism.

Glycogen Metabolism

One branch of glucose metabolism results in the synthesis of glycogen. G6P is first converted to G1P by phosphoglucomutase. G1P is then activated to UDP-glucose, which can be readily incorporated into the growing chain of glycogen by glycogen synthase. Glycogen is an important energy repository in heart, which can be quickly mobilized when needed.[26] During energy shortage or increased workload, the rise of AMP activates PKA, which in turn phosphorylates and activates phosphorylase kinase, leading to glycogen breakdown and glycogenolysis.

Glycogen occupies as much as 2% of cardiomyocyte cell volume, and this component is significantly greater during fetal stages, suggesting an important role of glycogen homeostasis during development.[26] Indeed, depletion of cardiac glycogen by disrupting glycogen synthase 1 leads to early defects in cardiac development and increases in mortality.[27] This result is consistent with the finding that glycogen synthase 1 is the major synthase isoform in heart.[28]

Glycogen metabolism contributes significantly to the aerobic myocardial glucose use. Early studies showed that glycogen oxidation may provide >40% of total ATP from glucose.[29] Importantly, >50% of glycogen-derived glucose is oxidized instead of generating lactate. Contemporaneously, Taegtmeyer et al[30] used dual labeling techniques to simultaneously measure glucose and glycogen metabolism. They found that epinephrine stimulation leads to almost complete oxidation of glycogen, while about 50% of exogenous glucose passes through a nonoxidative pathway. Furthermore, glycogenolysis responds rapidly to epinephrine, during the lag phase seen in glucose utilization. Glycogen is therefore a critical reservoir to accommodate rapid changes in cardiac demand, but not at the expense of creating more lactate or inefficient utilization of substrates.[31]

Preferential oxidation of glycogen-derived glucose, as opposed to lactate generation, has also been observed under disease conditions. Allard et al[32] found that myocardial hypertrophy is associated with increases in glycolysis. However, a greater proportion of glycogen is oxidized compared with exogenous glucose, suggesting hypertrophied heart maintains the ability to efficiently metabolize glycogen.

In ischemic conditions, however, the metabolism and functional role of glycogen is more complicated. Cross et al found that high glycogen content protects heart from brief ischemia and consequent contracture probably due to enhanced nutrient reserves. However, prolonged ischemia provoked exacerbated injury in the presence of higher levels of glycogen, which may result from lower ischemic pH and increased sodium–proton exchange during reperfusion.[33]

Interplay Between FFA and Glucose Metabolism

Fifty years ago, Randle et al[34] first described a glucose/fatty acid cycle to explain the reciprocal relationship between these 2 substances in metabolism. Acetyl CoA generated from FFA beta-oxidation stimulates PDK, which in turn, phosphorylates PDH and suppresses PDH activity (Fig. 1). On the other hand, acetyl CoA derived from glycolysis and PDH imposes direct inhibition on beta-oxidation reactions. Moreover, citrate from the citric acid cycle can be transported back to the cytosol, where it is lysed to acetyl CoA.[35] Acetyl CoA

in the cytosol, then, is subjected to carboxylation to malonyl CoA by ACC. Malonyl CoA strongly inhibits CPT-I and FFA uptake. This "Randle hypothesis" seems to hold true under controlled experimental conditions. However, accumulating findings point to more complex metabolic interactions with insulin signaling in chronic situations such as insulin resistance.[36]

As a consequence of these interlacing events involving enzymatic substrates and products, gene expression, and posttranslational protein modifications, metabolism of both FFA and glucose is maintained in a delicate balance.[37] Indeed, the metabolic flexibility of the myocardium, the ability to move rapidly among energy sources and coordinate a wide range of intracellular metabolic processes, is pivotal to mechanical contraction and relaxation in the setting of cardiac stress.[38] Disruption of this flexibility is held to be a significant contributor to cardiomyocyte dysfunction and heart failure.

Amino Acid Metabolism

Amino acids are also important substrates for energy production in heart. Through transamination and deamination reactions, various amino acids generate metabolic intermediates and feed into the citric acid cycle. Early studies have shown that alanine is effectively secreted from the myocardium during pacing stress, whereas glutamate manifests net uptake.[39] These differences are significantly larger in patients with ischemic heart disease, suggesting pathological implications. Moreover, the increase in alanine production is largely because of de novo synthesis, which occurs proportionate to intracellular pyruvate levels.[40] The ischemic heart may also adapt to the hypoxic situation by selectively reducing lactate concentrations through conversion of pyruvate to alanine. Because lactate accumulation during ischemia severely inhibits anaerobic metabolism, secretion of pyruvate through transamination may relieve this inhibition and maximize energy production. In addition, glutamate uptake and metabolism under ischemic conditions may lead to significant increases in succinate, which can contribute to substrate phosphorylation and energy production.[41]

Recently, catabolism of branched-chain amino acids has garnered attention because of connections to cardiac hypertrophy and heart failure.[42] Through a series of reactions, branched-chain amino acids can be converted to metabolic intermediates for the citric acid cycle metabolism. The rate-limiting enzyme is the branched-chain α-keto acids dehydrogenase complex, whose activity is inhibited by phosphorylation. The mitochondrial phosphatase PP2C is capable of dephosphorylating and activating the dehydrogenase complex. PP2C expression is significantly reduced in failing heart, which raises the possibility that accumulation of branched-chain amino acids may participate in the pathogenesis of heart failure.[43] Moreover, silencing the gene coding for the enzyme and catalyzing the first step in peripheral branched-chain amino acid metabolism leads to remarkable improvements in glucose tolerance and insulin sensitivity, which involves an active futile cycle of increased protein synthesis and degradation.[44]

Nucleotide Metabolism

Degradation of nucleic acids may be another important substrate for energy production in heart. Riboses derived from nucleotide catabolism may feed into glycolysis and the citric acid cycle through the nonoxidative phase of the pentose phosphate pathway. Recent studies identified a specific form of autophagy, ribophagy (targeting mature ribosomes) under nutrient deprivation in yeast.[45] Considering the rich content of nucleic acids in ribosomes, it is tempting to speculate that the pentose phosphate pathway is involved. Purine catabolism in cardiomyocytes, however, involves xanthine oxidase, which is also an important source of reactive oxygen species.[46] Indeed, accumulating evidence suggests that inhibition of xanthine oxidase leads to improvements in cardiac function in patients with heart failure. Future work is therefore warranted to examine the role of ribophagy and nucleotide metabolism in cardiac energy homeostasis and function.

Considering the massive amounts of energy required by the heart to maintain unremitting mechanical contraction, it is not surprising that the modulation of cardiac metabolism may influence whole body energy homeostasis. A recent study by Grueter et al[47] reported that cardiomyocyte-specific overexpression of MED13, a subunit of the Mediator complex, protects mice from diet-induced obesity and improves glucose tolerance. Mechanistically, MED13 induction in heart increases whole body energy expenditure by selectively inhibiting nuclear receptor-responsive genes and enhancing energy homeostasis.

Metabolic Derangements in the Progression of Heart Failure

As noted, heart failure is a complex and highly prevalent clinical syndrome that results from a wide range of diseases including hypertension, ischemic disease, diabetes, and many more.[48] However, despite the diverse etiologies that trigger heart failure, altered cardiac metabolism is a common theme.[4,49] Generally, it is agreed that in mild-to-moderate heart failure, phosphocreatine and total creatine stores begin to decline; simultaneously, there is a shift in metabolic substrate utilization from FFA oxidation to glucose oxidation. Recently, however, an essential role for creatine in heart has been challenged.[50] In end-stage heart failure, FFA uptake and oxidation are impaired, and the heart becomes highly reliant on glycolysis for energy production (Fig. 2).

Early-Stage Heart Failure

Early stages of heart failure are marked by a wide range of compensatory processes, occurring at both molecular and functional levels. Clinical studies have revealed variable findings. For example, measurements of arteriocoronary sinus metabolite concentrations or fractional extractions among numerous substrates were not altered in a study of patients with moderate heart failure (NYHA II-III).[51] Furthermore, absolute FFA uptake was similar in patients with heart failure and controls. On the other hand, significant increases in FFA oxidation were detected in similar patients (NYHA II-III) relative to healthy controls.[52]

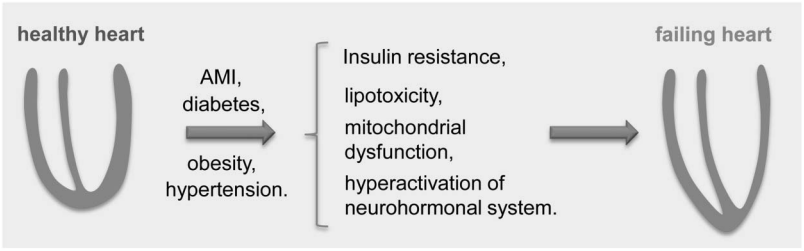

FIGURE 2. Heart failure progression and metabolic derangements. The healthy heart is a metabolic omnivore, capable of using virtually any available nutrient. Progression of heart failure correlates with progressive metabolic derangements, which include insulin resistance, elevations in intracellular TG levels, and mitochondrial dysfunction. Moreover, hyperactivation of the neurohumonal system leads to alterations in substrate availability in heart. In the early stages of heart failure, FFA uptake and oxidation remain either unchanged or moderately increased, whereas glucose oxidation is increased. When faced with persistent stress, advanced-stage heart failure emerges, and oxidation of both glucose and FFA are severely diminished.

Experimental studies have not revealed major alterations in substrate metabolism in early-stage heart failure. Using isotope tracer technology, Stanley et al[53] did not detect abnormalities in metabolic substrate utilization in a dog model of moderate heart failure. Total PDH activity was not altered. However, malonyl CoA levels were significantly reduced in the heart failure group compared with controls.[53] Similarly, relatively normal rates of FFAs and glucose metabolism have been described during the early stages of pacing-induced heart failure.[54] In a comprehensive study using Dahl salt-sensitive rats, Kato et al[55] showed that FFA uptake was not changed during the compensated stage of heart failure. Overall, these clinical and animal model studies support the notion that FFA utilization and global substrate metabolism are not negatively affected at early stages of heart failure.

Advanced Heart Failure

In contrast to the subtle metabolic changes occurring in early-stage heart failure, substrate extraction and oxidation are significantly altered at advanced stages of the syndrome. Metabolic labeling in patients of idiopathic dilated cardiomyopathy (DCM) uncovered correlations between reductions in FFA uptake and heart failure severity.[56] Similarly, FFA uptake and oxidation were significantly impaired in patients with DCM; however, during pacing stress, the increase in glucose uptake seen in controls was severely diminished in DCM patients.[57] In aggregate, these data highlight that the loss of metabolic flexibility in response to stress is a consistent feature of heart failure.

These clinical observations have been validated and extended in animal studies. FFA uptake is severely reduced and glucose uptake significantly increased in end-stage heart failure (left ventricular end diastolic pressure $\geq$25 mm Hg).[54] Likewise, in a rapid pacing canine model, glucose uptake was significantly reduced in advanced heart failure under both basal and insulin-stimulated conditions.[58] Prolonged exposure to a high-salt diet in Dahl salt-sensitive rats led to a gradual increase in glucose uptake and sudden declines in FFA extraction at the onset of severe dysfunction.[55] Thus, there is wide consensus that FFA uptake and utilization are significantly diminished in advanced heart failure. The discrepancies observed in glucose uptake may derive from differences in experimental model and/or experimental approaches used. Thus, alterations in cardiac metabolism in heart failure derive from a combination of alterations in coronary flow and nutrient availability plus shifts in intrinsic myocardial substrate metabolism.

Metabolic Derangements in Nonischemic Heart Failure

Metabolic alterations are considered among the most important contributors to the pathophysiology of nonischemic heart failure. Various mechanisms have been proposed to participate in syndrome initiation and progression.

Lipotoxicity

Fat accumulation in heart, or fatty heart, has long been recognized by clinicians.[59] Numerous experimental and clinical studies have established the correlation between TG accumulation and cardiomyopathy. Lipotoxicity is therefore held to be an important mechanism linking obesity and cardiac dysfunction.

Intramyocyte TG pools are maintained within a dynamic balance, determined by the rate of FFA uptake, TG synthesis, and TG catabolism. In Zucker diabetic rats, cardiac dilation and reduced contractility are associated with TG accumulation in cardiomyocytes as measured chemically and morphologically.[60] The aberrant deposition of TG within the myocyte is because of the reduced expression of fatty acid oxidative enzymes. More importantly, treatment of Zucker rats with troglitazone significantly lowered myocardial TG levels and improved cardiac function.

On the other hand, cardiomyocyte-restricted overexpression of enzymes involved in TG synthesis leads to TG accumulation and cardiac dysfunction. In 2 studies, Chiu et al[61,62] overexpressed long-chain FACS and fatty acid transport protein 1 in mouse heart and observed similar phenotypes of lipid accumulation and lipotoxicity. Likewise, cardiomyocyte-specific overexpression of lipoprotein lipase or PPAR-α provoke increases in lipid uptake and cardiac dysfunction.[63,64] Collectively, these results indicate that the breakdown of the finely tuned balance of TG homeostasis in cardiomyocytes leads to abnormal accumulation of lipid and cardiomyopathy.

Glucolipotoxicity

Although it is generally accepted that long-term consumption of high caloric foods modifies cardiac metabolism and impairs heart performance, the interplay between glucose and FFA in the progression of heart disease may be

complicated in diabetes. The levels of both glucose and FFA are elevated in diabetic conditions. Excessive uptake and metabolism of FFA may provoke accumulation of intermediate metabolites, such as ceramides, which can promote cell death.[60] Moreover, when oxidation of FFA falls below uptake, FFA may be esterified to intramyocyte TG and this lipid deposition may deteriorate cardiac contractile function. On the other hand, increases in glucose levels in diabetes cause insulin resistance in cardiomyocytes, which may be mediated by upregulation of the hexosamine biosynthetic pathway.[65] Furthermore, chronic hyperglycemia is also accompanied by increases in ROS, which may interfere with calcium handling, mitochondrial function, and cardiac contractility.[9,66] In addition, elevations in glucose metabolism also inhibit FFA oxidation, contributing to the severity of lipid accumulation in cardiomyocytes. Collectively, the coexistence of hyperlipidemia and hyperglycemia in diabetes may result in excessive lipid deposition within cardiomyocytes, insulin resistance, and ROS overproduction, a combination of events that has been termed glucolipotoxicity.[67]

Metabolic Hypertrophy

Recent clinical studies have suggested that defects in glycogen metabolism may predispose to hypertrophic cardiomyopathy. Arad et al[68] identified mutations in LAMP2 and PRAKG2 in patients with hypertrophic cardiomyopathy and electrophysiological abnormalities. Indeed, gain-of-function mutations of PRKAG2 trigger enhanced glycogen synthesis and enlargement of cardiomyocytes harboring glycogen-laden vacuoles.[69]

Mitochondrial Dysfunction

Mitochondria are the energy powerhouses of the cardiomyocyte, and loss of normal mitochondrial function has long been implicated in the pathogenesis of heart failure.[70,71] Early studies using guinea pigs and cats, however, revealed that mitochondrial oxidative phosphorylation, oxygen consumption, and ATPase activity do not differ between normal and diseased hearts.[72] It was therefore proposed that the decrease in myocardial contractility in heart failure may stem from metabolic control instead of intrinsic mitochondrial defects. On the other hand, studies in a canine chronic heart failure model identified severe abnormalities of mitochondrial size and integrity.[73] These morphological alterations are translated into deterioration of mitochondrial respiratory activity after addition of substrates.[74] For example, stage 3 respiratory rate is reduced 50% in chronic heart failure. Additionally, a detailed time course analysis showed that mitochondrial dysfunction develops in parallel with the onset of systolic dysfunction.[75] Inconsistencies among these studies may be because of different subpopulations of cardiomyocyte mitochondria evaluated. Indeed, recent studies suggest that the 2 mitochondrial subpopulations in cardiomyocytes, subsarcolemmal and interfibrillar, exhibit distinct properties in terms of respiration capacity, protein synthesis, and sensitivity to increased calcium.[76]

Accumulating evidence supports a model in which decreases in FFA oxidation and mitochondrial biogenesis may account for reductions in mitochondrial activity.[77] Enzymes of the first and third steps of FFA oxidation are severely reduced in patients with heart failure, findings that have been confirmed in preclinical models.[78] In another study based on canine heart failure models, Osorio et al[79] found the activity of 2 key enzymes of FFA oxidation, CPT-I and medium-chain acyl CoA dehydrogenase, was significantly reduced, which may be because of diminished expression of retinoid X receptor α. At a molecular level, an extensive literature points to significant reductions in master regulators of FFA oxidation and mitochondrial biogenesis, including PPAR-α and PGC1α.[77]

In addition, defects in mitochondrial respiration during heart failure may lead to overproduction of ROS, which in turn fosters further deteriorations in mitochondrial function, disruptions in mitochondrial membrane integrity, and cell death. Significant accumulations of cytochrome c have been described in the cardiomyocyte cytosol of myocardial samples from patients with cardiomyopathy, which were associated with activation of caspase 3 and cell death.[80]

Interplay Between Systemic Hemodynamics and Cardiac Metabolism

Clinical heart failure is, of course, associated with profound alterations in systemic hemodynamics. As a compensatory mechanism to counteract the insufficiency of circulatory supply, a complex set of neurohormonal reflexes is activated.[81] Whereas the acute response may be adaptive in the short term, chronic overdrive of the sympathetic system promotes deterioration of cardiac performance. Indeed, countering these reflexes is bedrock therapy in heart failure management currently. Now, accumulating evidence suggests that metabolic derangements elicited by hyperactivation of the sympathetic system play important roles in disease initiation and progression.

Substrate Availability

Activation of neurohormonal systems serves to maintain cardiac output to support systemic demand. Part of this response, however, is accompanied by increases in circulating norepinephrine (NE), elevations in sympathetic outflow, and NE spillover. The augmentation of plasma NE levels activates beta 3-adrenergic receptors in adipose tissues and enhances TG lipolysis,[82] triggering increases in FFA levels that provide substrate necessary for the maintenance of cardiac performance. With time, however, elevations in plasma FFA can adversely impact cardiac metabolism.

Increases in plasma FFA levels promote FFA uptake and metabolism in cardiomyocytes, which may interfere with glucose utilization. Excessive reliance on FFA metabolism can also promote ROS formation, which may further impair mitochondrial function and cardiac function. Indeed, elevated plasma FFA levels are an independent risk factor of sudden cardiac death in patients referred for coronary angiography.[83] Conversely, clinical therapy for neurohormonal hyperactivation is associated with significant declines in circulating FFA levels in healthy men because of suppression of lipolysis in adipose tissues.[84] Furthermore, blockage of beta-adrenoreceptors using carvedilol leads to 57% decreases in FFA utilization in the

myocardium in patients with heart failure, which is associated with significant improvements in cardiac performance.[85]

Overdrive of the sympathetic nervous system also participates in the pathogenesis of whole body insulin resistance. Elevations in circulating FFA levels can cause profound insulin desensitization in various tissues, such as liver, skeletal muscle, and heart. Underlying mechanisms may include ROS overproduction, interference with the insulin signaling pathway, or lipid accumulation, which can further impair left ventricular function. A 20-year follow-up study identified insulin resistance and associated factors as independent risk factors for systolic dysfunction.[86] Genetic modulation to enhance cardiac insulin sensitivity leads to dramatic improvements in cardiac function, highlighting the fact that insulin resistance plays an important role in the pathogenesis of heart failure.[87]

Ischemia in Advanced Heart Failure

Myocardial metabolic situations in advanced heart failure are distinct relative to earlier phases of the disorder. As discussed above, there is a consistent reduction in FFA oxidation in late stages of the syndrome. Although some discrepancies exist in the literature regarding glucose utilization, it is generally agreed that glucose oxidation is impaired, promoting reductions in metabolic substrates and ATP production. Diastolic ventricular pressure is elevated and diastolic wall tension is increased. As a consequence, coronary perfusion can be compromised, which creates a circumstance of myocardial ischemia in the absence of obstructive coronary artery disease. This is consistent with the findings that glucose uptake and glycolysis are enhanced while glucose oxidation is suppressed in advanced heart failure, which phenocopies the metabolic presentation of ischemic heart disease.[88] Collectively, heart failure is associated with prominent metabolic dysregulation, which may likely emerge as a major underlying mechanism of cardiomyopathy.

METABOLIC THERAPY FOR THE FAILING HEART

The failing heart has been likened to "an engine out of fuel"[4] and targeting cardiac metabolism has been proposed as a novel means of enhancing cardiac energetics and function. However, caution is warranted in efforts to translate preclinical observations to patients. First, responses to metabolic manipulations may vary significantly depending on metabolic state and cardiac insulin sensitivity. Second, there are well-established differences in cardiac metabolism across species, such that observations made in animals may not pertain, at least not completely so, to humans. Similarly, drugs that manifest beneficial effects in small clinical trials may later prove neutral or even harmful in large well-controlled clinical trials. Despite these concerns and issues, accumulating evidence from animal studies and small clinical trials strongly suggests that cardiac metabolism is a promising target for novel heart failure therapy.

Of the potential therapeutic strategies targeting cardiac metabolism, modulating substrate utilization has garnered considerable attention. Glucose oxidation generates less ATP per molecule than does FFA oxidation. However, for each oxygen molecule consumed, glucose oxidation provides 12% more ATP, a difference that may be significantly greater in reality because of adverse effects of FFA metabolism on ATP generation. Glucose is therefore an energetically more efficient substrate.[49] Furthermore, the shift from FFA oxidation to glucose utilization can protect cardiomyocytes from ROS accumulation and damage, which may result from buildup of FFA metabolic intermediates.[89] Thus, the preferential use of glucose as metabolic substrate could potentially ease the burden of the failing heart. In concert with this, a number of studies in animals and humans suggest that boosting glucose oxidation improves cardiac function in heart failure.[26]

Promoting Glucose Utilization

Glucose–Insulin–Potassium Infusion

Glucose–Insulin–Potassium (GIK) was first proposed as a therapy for AMI, seeking to increase glucose utilization and suppress FFA oxidation.[90] A meta-analysis of clinical trials was suggestive of potential benefit in reducing in-hospital mortality.[91] However, 2 more recent, large, randomized clinical trials have shown that GIK infusion does not affect mortality or development of heart failure after AMI.[92,93]

Clinical studies of GIK as a potential treatment for chronic heart failure are less robust but have revealed some beneficial effects. In one study of patients with ischemic cardiomyopathy, a single dose of GIK infusion elicited improvements in ventricular wall motion and ejection fraction.[94] Furthermore, intermittent and long-term GIK infusion in patients with systolic heart failure led to improvements in cardiac function at 1 week and 1 month.[95] It is not clear, however, whether the beneficial effects are because of enhancement of glucose utilization or suppression of FFA availability or both. Additional large-scale randomized trials are therefore warranted to test for efficacy and assess potential side effects, such as hyperkalemia, hyper/hypoglycemia, etc.

Glucagon-Like Peptide-1

Clinical studies have revealed a robust correlation between heart failure and insulin resistance.[96] That said, glucose intolerance is exceedingly common in patients with heart failure. A positive correlation has been reported between blood glucose levels and the severity of heart failure.[97] Mechanistically, insulin resistance leads to impaired insulin signaling in cardiomyocytes and reduced glucose utilization. Furthermore, systemic insulin resistance provokes dyslipidemia and increases in circulating FFA levels, which worsen cardiomyocyte metabolic imbalance. Therefore, improving insulin sensitivity represents a potential means to enhance glucose utilization and inhibit lipotoxicity.[49]

Glucagon-like peptide-1 (GLP-1), an incretin peptide released from intestinal cells, potently stimulates insulin production from pancreatic islet β cells. Recombinant GLP-1 infusion has been shown to improve cardiac function in multiple preclinical models, including a canine heart failure model induced by right ventricular pacing,[98] hypertensive heart failure-prone rats,[99] and a postischemic rat model.[100] However, only a few clinical trials, with limited numbers of patients,

have been performed to evaluate the effects of GLP-1 in human heart failure.[101] In NYHA class III–IV patients, both short term (3 days)[102,103] and long term (5 weeks),[104] GLP-1 infusions improved cardiac function and exercise tolerance, independent of diabetes mellitus. In contrast, the GLP-1 effect in patients with NYHA class II/III heart failure in other studies was either not observed or without statistical significance.[105] This raises the intriguing question of whether GLP-1 efficacy exists only in end-stage heart failure, when energy production is severely perturbed and insulin sensitivity is greatly suppressed. Overall, only modest increases in ejection fraction (4.4%) in GLP-1–treated patients have been noted. Additional studies with larger numbers of patients with diverse etiologies and heart failure stages are required to conclusively assess the clinical value of GLP-1 in heart failure. Recently, however, 2 large clinical trials evaluating saxagliptin and alogliptin, inhibiting DPP4 and increasing GLP-1 levels, failed to uncover beneficial cardiovascular effects in patients with type 2 diabetes.[106,107]

At a mechanistic level, GLP-1 is generally considered to enhance insulin sensitivity and therefore promote glucose utilization. Infusion of recombinant GLP-1 in dogs with DCM leads to significant increases in insulin sensitivity measured by hyperinsulinemic-euglycemic clamp.[98] Both basal and insulin-stimulated glucose uptake in myocardium are augmented by GLP-1 infusion, which is associated with upregulation of oxygen consumption and coronary blood flow.

Other findings suggest that GLP-1 may improve cardiac function beyond the incretin effect and target-cell insulin sensitization. GLP-1 induces dose-dependent relaxation of preconstricted arteries.[108] This endothelium-modulating effect was later extended in a clinical study, where infusion of recombinant GLP-1 elicited relative changes in brachial artery diameter from baseline without affecting plasma levels of glucose or insulin.[109] Moreover, Elmquist et al[110] showed that both central and peripheral administration of a GLP-1 receptor agonist leads to increases in blood pressure and heart rate, highlighting a central regulatory role of GLP-1. Silencing the GLP-1 receptor in mice elicits profound cardiac phenotypes including increased left ventricle thickness, reduced resting heart rate, and impaired contractility after insulin administration.[111] Collectively, these findings suggest that the cardiac actions of GLP-1 stem from hemodynamic effects beyond incretin action.

Inhibiting FFA Oxidation

As noted, metabolic alterations in heart failure are complex, partially because of the various disease etiologies of the syndrome.[112] In addition, the stage and severity of heart failure also play important roles in determining the oxidative capacity of the heart. Overdrive of the sympathetic nervous system and insulin resistance contribute significantly to rises in circulating FFA levels and consequent increases in FFA oxidation. As a result, glucose uptake and utilization may be suppressed. Numerous studies have examined the approach of inhibiting FFA utilization in heart failure with some promising insights emerging.[71] However, efficacy may vary, depending on the stage of syndrome progression. In advanced stage heart failure, mitochondrial oxidative capacity is already depressed. At that point, the inhibition of FFA oxidation by pharmacological means may prove deleterious because FFA is an important substrate of ATP production. Caution is warranted before this biology is moved forward toward the clinic.

Long-Chain 3-Ketoacyl Coenzyme A Thiolase Inhibitors

Trimetazidine suppresses FFA oxidation by inhibiting long-chain 3-ketoacyl coenzyme A thiolase, a key enzyme in the beta-oxidation pathway.[113] Accumulating evidence suggests that trimetazidine confers protection in heart failure, especially of ischemic etiology. For example, in an ex vivo working heart model, trimetazidine infusion significantly improved functional recovery after 30 minutes of ischemia, which was associated with stimulation of glucose oxidation and decreases in lipid utilization.[114] Additionally, long-term treatment of patients with heart failure with trimetazidine improved left ventricular function and increased the ratio of phosphocreatine to ATP.[115] Other work exploring different models suggests that additional mechanisms may be involved in trimetazidine-mediated cardioprotection, including suppression of fibrosis[116] and enhancement of antioxidant capacity.[117]

More recently, an international multicenter retrospective cohort study of 669 heart failure patients from 2002 to 2010 reported that addition of trimetazidine on top of optimized standard therapy improved clinical outcomes and cardiovascular mortality.[118] These results are promising, especially as the duration of observation was relatively long compared with other studies (38–40 months). However, this was not a prospective clinical trial and therefore causal relationships cannot be established. Additionally, 2 meta-analyses summarizing multiple randomized clinical trials of trimetazidine noted that most trials reported benefit.[119,120] Also, although trimetazidine is generally well tolerated, significant Parkinsonism-like side effects have been reported in multiple cases.[121]

CPT-I Inhibitors

CPT-I is the rate-limiting enzyme in mitochondrial uptake and oxidation of long-chain FFAs. It has been hypothesized that pharmacological suppression of CPT-I could suppress FFA uptake and oxidation, decrease futile oxygen use, reduce lipotoxicity, and potentially promote more efficient glucose oxidation.

Originally developed in the 1970s as an antianginal agent, perhexiline has emerged with promise in the treatment of heart failure. Mechanistically, perhexiline suppresses CPT-I enzymatic activity and therefore inhibits FFA oxidation and enhances glucose utilization and myocardial efficiency.[122] A randomized double-blind clinical trial was carried out in 2 medical centers evaluating perhexiline's effect in 56 patients with heart failure.[123] At 3 months, the perhexiline-treated group manifested improvements in symptoms, peak exercise oxygen consumption, left ventricular ejection fraction, and resting and peak stress myocardial function.[123]

Etomoxir was originally developed to treat diabetes by suppressing FFA uptake and utilization. However, long-term administration (12 weeks) was reported to improve cardiac

function in a rat model of pressure overload.[124] Additionally, in FFA-perfused rat heart, etomoxir elicited improvements in functional recovery associated with enhancement of glucose utilization.[125] The first clinical trial of etomoxir in patients with heart failure was conducted in 2000 with 10 patients (NYHA II-III). Three-month treatment with etomoxir led to significant benefits in cardiac stroke volume and maximum cardiac output during exercise.[126] However, a larger clinical trial (Etomoxir for the Recovery of Glucose Oxidation) was terminated because of detection of a liver injury signal.[127]

Oxfenicine, another CPT-I inhibitor, has been shown to prevent cardiac remodeling and delay decompensation in a canine model of pacing-induced heart failure.[128] However, evidence of toxicity in heart, liver, and kidney and inhibition of membrane ion channels highlights the need for thorough evaluation before consideration of clinical use.[129]

PPAR Agonists

PPARs are a class of nuclear receptors that regulate lipid metabolism by governing expression of multiple enzymes in the pathway. Of the 3 PPAR family members, PPAR-α is a major regulator of genes responsible for fatty acid uptake and oxidation. Cardiomyocyte-restricted overexpression of PPAR-α leads to upregulation of FFA uptake and oxidation, which mimics the metabolic phenotype of diabetic cardiomyopathy.[64] Also, PPAR-α levels are significantly repressed in cardiac hypertrophy elicited by pressure overload. A study by Young et al[130] suggests that reactivation of PPAR-α may actually deteriorate cardiac contractile performance in hypertrophied rat heart. That said, systemic activation of PPAR-α pharmacologically triggers robust induction of mitochondrial FFA oxidation in liver, which may contribute to beneficial effects in heart.[131] Increased hepatic extraction of circulating FFA can effectively reduce myocardial FFA uptake and utilization, especially under the conditions of heart failure. Previous studies showed that activation of PPAR-α protects heart from ischemia/reperfusion injury by metabolic modulation and suppression of inflammation.[132] However, preclinical studies of the PPAR-α agonist fenofibrate in heart failure yielded variable results, ranging from beneficial to neutral, possibly because of differences in severity of disease, treatment duration, or dosage.[133,134] To date, no human studies on PPAR-α agonists in heart failure have been conducted.

PPAR-γ is the target of the thiazolidinedione (TZD) class of antidiabetic drugs. PPAR-γ activation enhances lipid uptake and storage in adipose tissue. In doing so, circulating levels of FFA and TG can be significantly reduced, which may benefit cardiac function in heart failure. TZD administration in Zucker fatty rats can protect from ischemic injury through enhancing insulin sensitivity and glucose uptake.[135] However, whether the improvement in cardiac metabolism contributes to the protection by TZD remains to be defined using loss-of-function approaches. A similar beneficial effect in cardiac function was reported in an ischemia/reperfusion model.[136] Moreover, additional animal studies have demonstrated that PPAR-γ agonist administration improves left ventricular function and remodeling in ischemia-induced heart failure.[137] More recently, TZD administration was reported to increase GLUT4 expression, improve insulin sensitivity, and enhance cardiac function in dogs.[138] However, clinical use of PPAR-γ agonists to treat heart failure, cardiac ischemia/reperfusion, and even diabetes has been hindered because of potential cardiac toxicity manifested as fluid retention.[139]

Beta-Adrenoreceptor Antagonists

Patients with heart failure and ischemic heart disease are usually treated with medications targeting beta-adrenoreceptors. These pharmacological approaches improve cardiac function by decreasing workload and oxygen demand. Accumulating evidence, however, indicates that beta-receptor antagonists elicit profound metabolic changes in heart and body. Metoprolol treatment for 12 weeks led to significant reductions in CPT-I activity in a canine model of heart failure.[140] Furthermore, 6-month treatment with beta-adrenoreceptor antagonists reduces resting energy production in patients with moderate heart failure, which is accompanied by reductions in lipid oxidation and enhancement of glucose oxidation.[141] These results suggest that beta-adrenoreceptor antagonism modulates cardiac metabolism, which may contribute to their pharmacological efficacy in presently unknown ways.

Collectively, multiple potential targets governing FFA and glucose utilization have been evaluated for therapeutic efficacy. CPT-I inhibitor-dependent suppression of FFA oxidation, and GLP-1–dependent enhancement of glucose oxidation hold the greatest promise to stimulate myocardial efficiency and enhance cardiac recovery in heart failure. However, a number of questions must be answered in comprehensive clinical trials before consideration of clinical use. At what stage of heart failure should patients be treated? Do different etiologies of heart failure affect drug efficacy and usage? Can metabolic drugs improve heart failure with preserved ejection fraction, a syndrome presently without effective therapy?

CONCLUSIONS AND PERSPECTIVES

Despite the longstanding, pervasive, and rapidly expanding prevalence of heart failure, optimal therapy has evolved little in recent years beyond the widespread use of mechanical devices. Novel targets and therapeutic strategies are therefore urgently needed. Among these, disease-associated metabolic derangements have long been the focus of great interest. Yet, it is only recently that appreciation of the importance of metabolic events, and metabolic flexibility, in cardiac stress has emerged. Concomitantly, several drugs targeting substrate metabolism have been developed.

Because of the intrinsic complexities of cardiac metabolism and the profound interplay among various substrates during disease progression, additional work is warranted to advance our understanding of fuel utilization, signal transduction, mitochondrial functionality, and cardiac contractility. Together, these events will converge on a rapidly evolving biology, where promise is heightened for novel means of targeting the devastating clinical syndrome of heart failure.

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