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Cardiac Energy Metabolism in Heart Failure

Gary D. Lopaschuk[1], **Qutuba G. Karwi**[1], **Rong Tian**[2], **Adam R. Wende**[3], **E. Dale Abel**[4,5]

[1]Cardiovascular Research Centre, University of Alberta, Edmonton, Alberta, T6G 2S2, Canada

[2]Mitochondria and Metabolism Center, University of Washington, Seattle, WA, 98109, United States

[3]Division of Molecular and Cellular Pathology, Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, 35294, United States

[4]Division of Endocrinology and Metabolism, University of Iowa Carver College of Medicine, Iowa City, IA 52242, United States

[5]Fraternal Order of Eagles Diabetes Research Center, University of Iowa Carver College of Medicine, Iowa City, IA 52242, United States

Abstract

Alterations in cardiac energy metabolism contribute to the severity of heart failure. However, the energy metabolic changes that occur in heart failure are complex, and are dependent not only on the severity and type of heart failure present, but also on the co-existence of common co-morbidities such as obesity and type 2 diabetes. The failing heart faces an energy deficit, primarily due to a decrease in mitochondrial oxidative capacity. This is partly compensated for by an increase in ATP production from glycolysis. The relative contribution of the different fuels for mitochondrial ATP production also changes, including a decrease in glucose and amino acid oxidation, and an increase in ketone oxidation. The oxidation of fatty acids by the heart increases or decreases, depending on the type of heart failure. For instance, in heart failure associated with diabetes and obesity, myocardial fatty acid oxidation increases, while in heart failure associated with hypertension or ischemia, myocardial fatty acid oxidation decreases. Combined, these energy metabolic changes result in the failing heart becoming less efficient (i.e., a decrease in cardiac work/O_2 consumed). The alterations in both glycolysis and mitochondrial oxidative metabolism in the failing heart are due to both transcriptional changes in key enzymes involved in these metabolic pathways, as well as alterations in redox state (NAD^+ and NADH levels) and metabolite signaling that contribute to post-translational epigenetic changes in the control of expression of genes encoding energy metabolic enzymes. Alterations in the fate of glucose, beyond flux through glycolysis or glucose oxidation, also contribute to the pathology of heart failure. Of importance, pharmacological targeting of the energy metabolic pathways has emerged as a novel therapeutic approach to improving cardiac efficiency, decreasing the energy deficit and improving cardiac function in the failing heart.

[*]**Address for Correspondence:** Dr. Gary D. Lopaschuk, 423 Heritage Medical Research Centre, University of Alberta, Edmonton T6G 2S2, Alberta, Canada, gary.lopaschuk@ualberta.ca, Phone: (780)-492-2170, Fax: (780)-492-9753.

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Introduction

The heart has a very high energy demand, and must continuously produce large amounts of ATP to sustain contractile function [1, 2]. For instance, if not replaced, the heart would run out of ATP in 2–10 seconds, resulting in contractile failure. As a result, the continuous production of ATP must occur in order to maintain cardiac function. The heart achieves this by metabolising a variety of fuels (including fatty acids, glucose, lactate, ketones, pyruvate, and amino acids), primarily by mitochondrial oxidative phosphorylation. This process requires large amounts of oxygen, resulting in the heart consuming more oxygen/unit weight than any other organ in the body. Any disruptions in the energy metabolic pathways that produce ATP, or in oxygen supply to the heart, can have catastrophic consequences on cardiac function. As a result, compromised energy production by the heart is an important contributor to most forms of heart disease [1, 3].

Heart failure is a debilitating disease that has a major clinical and economic impact on the world's population [4]. The inability of the heart to adequately pump enough blood to meet the body's needs for nutrients and oxygen results in heart failure patients having significant disabilities and a high mortality rate [5]. Heart failure presents primarily as two major types, heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Both types of heart failure, and their associated co-morbidities and mortality, have a comparable prevalence in our society [6–8]. Heart failure is a heterogenous clinical syndrome, that is caused by multiple different co-morbidities, with ischemic heart disease and hypertension being prominent contributors to heart failure development. It is generally accepted that altered energy metabolism characterizes the failing heart, resulting in an "energy deficit" which contributes to the severity of heart failure (see [3] for review). This compromised energy production results from a number of factors, which includes impaired mitochondrial oxidative metabolism, alterations in energy substrate preference by the heart, and a decrease in cardiac efficiency [9, 10]. More recently, altered flux via diverse metabolic pathways have been shown to generate metabolites or redox alterations that activate pathways that promote myocardial injury and may contribute to ventricular dysfunction [11]. Here we review the current knowledge of the energy metabolic changes that occur in heart failure. This includes distinguishing the cardiac energetic changes that occur in HFrEF, as well as heart failure associated with diabetes (i.e., diabetic cardiomyopathy). Although we briefly address the cardiac metabolic changes that occur in HFpEF the majority of the review will focus on cardiac energy metabolic changes seen in HFrEF, given that to date the majority of studies have examined HFrEF and a consensus on metabolic changes associated with HFpEF has not yet emerged. We also address the underlying mechanisms responsible for these changes in cardiac energy metabolism in heart failure, and how targeting cardiac energy metabolism may be a novel approach to treating heart failure.

Energy metabolism in the normal heart

The adult heart generates enormous quantities of ATP necessary to sustain contractile function from two primary sources: mitochondrial oxidative phosphorylation and glycolysis. Mitochondrial oxidative phosphorylation normally contributes ~95% of myocardial ATP requirements, with glycolysis providing the remaining 5% [12, 13]. The healthy heart is also "metabolically flexible", and can readily shift between different energy substrates to maintain ATP production [2]. The main fuels of the heart are fatty acids, lactate, glucose, ketones, and amino acids, which must be acquired continuously from the blood due to a low ability of the heart to store these energy substrates intracellularly. The majority of mitochondrial ATP production, ~40–60%, is derived from the oxidation of fatty acids and the remainder originating from the oxidation of pyruvate (originating from glucose and lactate), ketone bodies and amino acids (Figure 1). The majority of the oxygen consumed by the heart is used for mitochondrial oxidative phosphorylation by the electron transport chain (ETC), while the synthesis of ATP derived from glycolysis does not require oxygen (Figure 1A).

Fatty acids are delivered to the heart either as fatty acids bound to albumin in the blood, or as fatty acids hydrolysed from triacylglycerols (TGs) contained in chylomicrons and very low-density lipoproteins (VLDL). Following uptake into the cardiomyocyte, fatty acids are esterified forming fatty acyl-CoA. The fatty acid moiety is then transferred to carnitine by carnitine palmitoyl transferase 1 (CPT-1) to form long chain acylcarnitine [14], which is then transported into the mitochondria where the fatty acid group is again transferred to CoA to form fatty acyl-CoA. This fatty acyl-CoA then undergoes β-oxidation to produce acetyl-CoA, that enters the TCA cycle, and flavin adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH) which enter the ETC to generate ATP. The TCA cycle also generates NADH and $FADH_2$ that feed into the ETC, which in the presence of oxygen results in the conversion of ADP to ATP (Figure 1). Fatty acid oxidation in the heart is highly regulated, including via: 1) fatty acid supply to the heart, 2) fatty acid uptake, 3) malonyl CoA induced CPT-1 inhibition [15] (malonyl CoA is produced via acetyl CoA carboxylase [16] and degraded by malonyl CoA decarboxylase [17], 4) the ratios of FAD/$FADH_2$ and NAD^+/NADH (which can influence enzymatic activity of acyl-CoA dehydrogenase and 3-hydroxyacyl-CoA dehydrogenase, respectively), 5) the mitochondrial acetyl-CoA/CoA ratio which can influence the activity of 3-ketoacyl-CoA thiolase, 6) post-translational modification of fatty acid oxidative enzymes, and 7) transcriptional regulation of fatty acid oxidative enzyme expression. This highly coordinated regulation of fatty acid oxidation is central to the ability of the heart to maintain its ability to switch between available substrates. While fatty acids produce the greatest ATP yield per 2 carbon unit of all energy substrates, they also have the highest oxygen requirement to produce this ATP. As a result, fatty acids are the least efficient (ATP produced/O_2 consumed) myocardial energy substrates.

Glucose is an important fuel of the heart that can generate ATP both from cytoplasmic glycolysis, and the mitochondrial oxidation of the pyruvate derived from glycolysis (Figure 1A). It is the most efficient of the energy substrates, due primarily to the anaerobic production of ATP generated by the glycolytic conversion of glucose to pyruvate. Glucose is

taken up by the cardiomyocyte GLUT1 and GLUT4 transporters. Although GLUT4 is responsible for insulin-dependent uptake of glucose, its translocation is also modulated by myocardial contraction. As such, GLUT4 quantitatively remains the major portal for myocardial glucose uptake (Figure 1A). Once glucose is transported into the cell it is phosphorylated by hexokinase, generating glucose 6-phosphate (G6P). G6P can then be utilised in multiple pathways, which include the generation of pyruvate via glycolysis, the synthesis of glycogen, or being shuttled into the hexosamine biosynthetic or pentose phosphate pathways. The pyruvate generated from glycolysis can either be converted to lactate or be transported into the mitochondria via the mitochondrial pyruvate carrier (MPC). The majority of pyruvate is converted to acetyl-CoA by pyruvate dehydrogenase (PDH) and lesser amounts to oxaloacetate via pyruvate carboxylation (mediated by malic enzyme or pyruvate carboxylase) to generate oxaloacetate contributing importantly to anaplerosis that replenishes TCA intermediates. Acetyl-CoA is then further metabolized in the TCA cycle. PDH is activated via dephosphorylation by PDH phosphatase and inhibited by PDH kinase (PDK), the latter of which is activated by increased acetyl-CoA/CoA and NADH/NAD^+ ratios.

Lactate is also an important energy substrate of the heart, especially under conditions in which circulating lactate levels rise [18, 19]. Lactate is taken up by the heart via a monocarboxylic anion transporter (MCT4), and then converted to pyruvate via lactate dehydrogenase. This pyruvate then follows a similar fate as the pyruvate derived from glycolysis. Recent studies have suggested that lactate might represent the major source of pyruvate in the heart [20], may have signaling properties [21] and could under some circumstances provide carbons to the TCA in a pyruvate-independent manner [22, 23].

Ketone bodies are increasingly being recognized as an important energy substrate of the heart [24, 25]. Ketone bodies are produced in the liver from acetyl-CoA (predominately sourced from fatty acid oxidation). β-hydroxybutyrate (βOHB) is the predominant ketone body oxidised in the heart. Its uptake is facilitated by SLC16A1 after which it is transported into the mitochondria for oxidation (Figure 1). β-hydroxybutyrate dehydrogenase 1 (BDH1) catalyses the oxidation of βOHB to acetoacetate (AcAc). AcAc is then activated by the CoA transferase succinyl-CoA:3 oxoacid-CoA transferase (SCOT) to acetoacetyl-CoA (AcAc CoA). AcAc-CoA then undergoes a thiolysis reaction from which acetyl-CoA is produced, that then enters the TCA cycle (Figure 1A). Ketones are readily metabolized by the heart, and if circulating ketone levels are elevated they can become a major fuel of the heart [26]. When considering oxygen consumption for ATP production, ketones are more efficient than fatty acids, but less energy efficient than glucose (discussed in more detail below).

Oxidation of amino acids are also a potential source of ATP production by the heart. Branched chain amino acid (BCAA) oxidation is the best characterized source of amino acid oxidation in the heart [27]. The first step of BCAA metabolism in the heart involves their transamination to their corresponding branched chain α-keto-acid (BCKA) by the mitochondrial branched chain amino-transaminase (BCATm) [28]. This step is reversible and involves the transfer of the α-amino group to α-ketoglutarate producing glutamate. The second step in BCAA metabolism involves the oxidative decarboxylation of the BCKAs by the mitochondrial branched chain α-keto acid dehydrogenase (BCKDH). BCKDH activity is

regulated by phosphorylation of BCKDH by a BCKDH kinase (BDK), which inhibits activity, and dephosphorylation by PPC2m, which activates BCKDH. The products of BCKDH either generates acetyl-CoA for the TCA cycle or succinyl-CoA for anaplerosis (Figure 1). While BCAA oxidation is only a minor source of ATP production in the heart (<2% of ATP production)[19], BCAAs do have an important role in modulating signaling pathways in the heart including insulin and mTOR signaling. In particular, increased systemic BCAAs can promote development of insulin resistance [29]. Two main mechanisms have been proposed for BCAA induced insulin resistance: 1) persistent mTOR signaling (in particular via leucine), that impairs insulin signal transduction via insulin receptor substrates (IRS) and 2) impaired BCAA metabolism, resulting in accumulation of BCAA metabolites that exert toxic effects.

In summary, the healthy adult heart has a high metabolic flexibility, with fatty acids being the predominant substrate used for ATP production, followed lactate, ketone bodies, glucose, and then branched chain amino acids.

Fuel Preference in the Failing Heart

Dramatic changes in energy metabolism can occur in the failing heart. Of importance, the failing heart loses its metabolic flexibility and can become energy deficient due to a decrease in its ability to produce ATP [2, 3]. As a result, the end-stage failing heart can have up to 30% less ATP content than a healthy heart [30, 31]. As mentioned, the majority of ATP produced in a healthy heart occurs as a result of mitochondrial oxidative metabolism, and this energy deficit is likely due to the presence of a reduced mitochondrial oxidative capacity in heart failure (Figure 1B) [32, 33]. Impaired mitochondrial function in the failing heart can occur due to a number of reasons, including: 1) increased reactive oxygen species (ROS) production and dysregulation of mitochondrial Ca^{2+} homeostasis, 2) impairments in mitochondrial dynamics, sustained mitophagy, and increased autophagic cell death of cardiomyocytes and 3) alterations in transcriptional regulation of mitochondrial proteins and increases in post-translational protein modification (see [32, 34–41] for reviews).

Heart failure is characterized by changes in myocardial redox regulation, predominantly characterized by oxidative stress, although reductive stress has also been described [42]. Increased ROS has been described in failing human hearts and in animal models of heart failure [43–46]. Furthermore, circulating ROS levels have been shown to predict cardiovascular outcomes in some patients [47]. Mechanistic studies suggest that ROS increases lipid peroxidation, damages mitochondrial DNA, depletes antioxidants and reduces mitochondrial ATP production [47, 48]. Mitochondrial Ca^{2+} is an important contributor to mitochondrial dysfunction in heart failure [49]. Insufficient Ca^{2+} could reduce the activity of metabolic enzymes in the mitochondria while mitochondrial Ca^{2+} overload may activate cell death pathways [50]. Moreover, the dysregulation of Ca^{2+} homeostasis seen in heart failure, may result in the mitochondria acting as a sink for Ca^{2+}.

Mitochondrial dynamics describes a process by which mitochondrial undergo cycles of fission and fusion, which are essential for maintaining mitochondrial homeostasis [51, 52]. This process is regulated by conserved proteins that include the fusion proteins OPA1 and

mitofusins (Mfn1 and Mfn2) and the fission proteins Drp1 and Fis1. Mitochondrial fusion contributes to the formation of elongated interconnected mitochondrial networks and fission may lead to mitochondrial fragmentation or disruption of the myocardial mitochondrial network [53]. Expression of proteins that regulate mitochondrial dynamics are altered in failing hearts, with altered morphology consistent with increased mitochondrial fission have been described [54]. Excessive or unopposed fission can lead to mitochondrial fragmentation, mitophagy, decreased anti-oxidative capacity and increased production of ROS and cell death [55]. Mitophagy is critical in maintaining mitochondrial quality control by removing damaged mitochondria. Mitophagy is increased in the failing heart, which could represent an adaptive response to limit mitochondrial damage and to maintain ATP production [35]. However, sustained mitophagy in heart failure can induce excessive mitochondrial clearance that reduces the number of mitochondria in the heart. Furthermore, in states in which mitophagy is impaired, dysfunctional mitochondria cannot be adequately degraded. These damaged mitochondria can disrupt energetics in the mitochondrial network or can induce collateral damage by activating cell death pathways such as autophagy [35, 56]. Taken together, altered mitochondrial dynamics may be an important contributor to the overall reduction in mitochondrial oxidative capacity and therefore ATP production in heart failure.

Compromised mitochondrial biogenesis in heart failure contributes to impaired mitochondrial function. An important transcriptional regulator of mitochondrial biogenesis is PPARγ coactivator-1α (PGC1-α). PGC1α activates the transcriptional expression of nuclear respiratory factor-1 NRF-1 and NFR2, whose target genes encode proteins that mediate mitochondrial replication, maintenance and to generate components of the electron transport chain [57]. In heart failure, PGC1α is repressed, which correlates with decreased mitochondrial biogenesis [58]. The transcription factor PPARα, which is the predominant isoform regulating fatty acid oxidation in the heart is also repressed in the failing heart [1]. This leads to decreased expression of many genes involved in fatty acid uptake and oxidation. However, complicating this issue is that PPARα can be activated in some forms of HFpEF, particularly when HFpEF is associated with diabetes and obesity, resulting in an up-regulation of fatty acid oxidation [39, 59]. Post-translational modification of mitochondrial proteins also contributes to a decrease in mitochondrial oxidative capacity in heart failure. These changes, which include altered protein acetylation, will be discussed later in this review.

Glycolytic compensation in heart failure:

A compensatory response to reduced mitochondrial oxidative metabolism and ATP production in heart failure is an induction of glycolysis [60]. Increased myocardial glucose uptake in heart failure has been associated with increased expression of *GLUT1* glucose transporter particularly in animal models in conjunction with increased activity of phosphofructokinase 1 (PFK-1, the first enzyme involved in glycolysis), and glycolytic flux [61, 62]. However, this increase in glycolysis is insufficient to completely compensate for the energy deficit in heart failure or to restore cardiac function. This is in part due to glycolysis producing only two ATP molecules per glucose molecule, compared to 31 ATP molecules that would have been produced if the pyruvate from glycolysis was oxidized. Although increased glycolysis only marginally increases ATP generation, an important consequence of

this is increased flux into metabolic pathways that branch from glycolysis such as the polyol and hexosamine biosynthetic pathways that could independently activate signaling pathways that contribute to myocardial remodelling [11, 63]. Furthermore, increased glycolysis is uncoupled from the oxidation of pyruvate and lactate leading to accumulation of H^+ in the cytoplasm. Increased Na^+/H^+ exchange (NHE) activation coupled with increase Na^+/Ca^{2+} exchange may contribute to cytosolic Ca^{2+} accumulation [64].

Fatty acid oxidation in heart failure:

The energy metabolic changes occurring in heart failure are generally accepted to include reductions in mitochondrial fatty acid oxidation (Figure 1B) [65]. The rate of myocardial fatty acid oxidation decreases with the progression of heart failure severity. However, in studies assessing ^{13}C palmitate uptake and clearance during the stage of compensated hypertrophy (normal systolic function) no differences in fatty acid uptake or oxidation were observed in humans, Dahl salt sensitive rats fed a high salt diet, spontaneously hypertensive rats, or Wistar rats 8 weeks post myocardial infarction [66–68]. However, as the severity of heart failure progresses (EF < 50%), decreased fatty acid oxidation has been reported in humans with idiopathic dilated cardiomyopathy (IDCM).[69–71], Dahl salt sensitive rats fed a high salt diet, spontaneously hypertensive rats, 20-week-Wister rats 6 months post myocardial infarction, and in canine models of cardiac pacing [67, 68, 72–74]. This decrease in fatty acid oxidation, however, is not always a consistent finding. Other studies have observed no differences in fatty acid uptake in patients with IDCM, or an actual increase in fatty acid uptake in patients with congestive heart failure [75–77]. These divergent patterns of fatty acid utilisation are likely attributable to the differences in disease severity e.g., ejection fractions ranging from 16–48% and the presence of co-morbidities such as obesity and the metabolic syndrome in some subjects who participated in human clinical studies. In those studies that reported reduced fatty acid oxidation a parallel decrease in the expression and/or activity of genes and enzymes involved in transcriptional regulation of fatty acid oxidation (PPARα, retinoid X receptor α (a cofactor of PPAR α and PGC-1α, and estrogen related receptors (ERRα and ERRγ) were observed, as well as a number of enzymes involved in fatty acid oxidation, including CPT-1, MCAD, CD36 and FATP1 [67, 68, 72–74, 78, 79]. Similarly, in pressure-overload induced heart failure resulting from transverse aortic constriction (TAC), diminished fatty acid oxidation flux is associated with a lower fraction of ATP generation [80]. These expressional changes are consistent with a reduction in fatty acid oxidation in heart failure. However, although fatty acid oxidation is reduced, fatty acids still account for a greater proportion of mitochondrial ATP generation than glucose in the failing heart [19].

Increases in plasma concentrations of fatty acids have been associated with increased risk for developing heart failure [81]. Myocardial fatty acid oxidation increases in response to conditions such as type 2 diabetes (T2D), obesity and insulin resistance. Obese women with left ventricular hypertrophy and reduced cardiac efficiency show increased myocardial fatty acid uptake and oxidation, with the severity of their insulin resistance correlating with the higher rates of fatty acid oxidation [82]. In addition, type 2 diabetic men with T2D cardiomyopathy also exhibit increased fatty acid uptake and oxidation [83]. These finding are consistent with animal models of obesity and T2D, such as diet induced obese (DIO), *db/db* and *ob/ob* mice. In these animals, hearts predominantly rely on fatty acid oxidation, while

exhibiting left ventricular hypertrophy [84], diastolic dysfunction [85, 86] and in severe cases, systolic dysfunction [87–89]. In a murine model of HFpEF, involving a high fat diet, aging, and deoxycorticosterone treatment, fatty acid oxidation was also increased [90]. Despite the close association, a causal role for increased fatty acid oxidation rates in cardiac dysfunction of obesity or diabetes is less certain. Since cardiac lipid uptake is increased in these models an imbalance between lipid uptake and oxidation likely contributes to lipotoxicity. Increasing mitochondrial fatty acid oxidation in mice with diet induced obesity restores the balance and prevents cardiac dysfunction while it does not affect cardiac function or longevity of normal mice [91, 92]. Furthermore, transgenic models in which fatty acid oxidation is inhibited exhibit cardiac hypertrophy and accelerated impairment in ejection fraction in response to pressure overload [93, 94, 95].

Glucose metabolism in heart failure:

While glucose uptake is commonly reported to be increased in heart failure, this is not always accompanied by an increase in glucose oxidation. More commonly, a decrease in glucose oxidation and an increase in glycolysis is observed (Figure 1B). In patients with IDCM (88–98%) [69–71], in canine models of cardiac pacing (~ 150%) [73] and in Dahl salt sensitive rats fed a high salt diet, an increase in glucose uptake is seen [68]. *GLUT1* expression is also increased, suggesting an increased capacity for glucose uptake that may have a predominant glycolytic fate [67, 72]. In the majority of these models, the oxidation of pyruvate derived from glucose (i.e. glucose oxidation), is decreased in mouse models of heart failure [96–98], in pacing-induced heart failure in pigs and in humans with end-stage heart failure [99]. In support of this decrease in glucose oxidation, myocardial biopsies from patients with heart failure were found to have reduced expression of MCT1, PDH, MPCs and of pyruvate/alanine aminotransferases, suggesting reduced transport and metabolism of pyruvate [100, 101]. However, in a study in pacing-induced heart failure in dogs an increase in glucose oxidation was observed [44]. Increased anaplerosis represents an important adaptation in the failing heart mediated by increased carboxylation of pyruvate by malic enzyme 1 (ME1), which is induced in response to pressure overload and in failing human hearts [102–104]. Increased pyruvate carboxylation reduces the efficiency of glucose oxidation and may contribute to oxidative stress by consuming NADPH [104]. Indeed, lowering ME1 in failing rat hearts increased pyruvate flux into the TCA and restored redox homeostasis by normalizing reduced glutathione (GSH) [104].

The decrease in myocardial glucose oxidation seen in HFrEF is also seen in heart failure associated with obesity and diabetes. Rodent models of T2D and insulin resistance that exhibit left ventricular hypertrophy and diastolic dysfunction [105, 106], also have decreased glucose oxidation rates [107, 108]. Decreases in myocardial glucose oxidation are very prominent in obese and diabetic mice that develop LV hypertrophy and diastolic dysfunction [109–111]. This decrease in glucose oxidation is also seen in angiotensin II induced heart failure in mice, which is accompanied by increased PDK4 expression and reduced PDH activity [107]. This decline in glucose oxidation in angiotensin II treated mice can be blunted in response to PDK4 deletion [108]. Intriguingly, angiotensin II treatment has also been shown to ameliorate diastolic dysfunction in diabetic *db/db* mice [112]. In mice that develop LVH due to aortic constriction, a decrease in myocardial glucose oxidation precedes the development

of diastolic dysfunction [96], which further supports a potential role of reduction in glucose oxidation in the development of heart failure [108]. Notably, in some studies of mouse models of heart failure with reduced rates of FAO, the relative contribution of glucose oxidation to TCA flux might be increased, although net TCA flux is reduced [80]. Transgenic mice with mutations that prevent the uptake of glucose or oxidation of pyruvate also develop LVH, diastolic dysfunction (GLUT4 deletion)[113] and systolic dysfunction (PDH deletion).[114] Upstream of PDH activity, the mitochondrial pyruvate carrier (MPC) provides a new therapeutic point of potential metabolic regulation. Recently, a series of studies, have examined the role of loss-of-function of these proteins in the regulation of cardiac metabolism and function [115]. Mice with cardiac specific deletion of the MPC initially develop age-dependent pathological LVH with preserved ejection fraction that is associated with reduced rates of glucose oxidation in concert with increased rates of fatty acid oxidation [116]. However, as animals age a dilated cardiomyopathy develops. Taken together, reduced mitochondrial oxidation of pyruvate likely plays an important role in the transition from pathological LVH to heart failure.

Ketone body oxidation in heart failure:

Fasting increases circulating concentrations of ketone bodies [117, 118]. Interestingly, in patients with heart failure the fasting-induced increase in circulating ketones is exacerbated. [119]. A number of recent studies have shown that myocardial ketone body oxidation in increased in heart failure [120–122]. One study quantifying substrate utilization in arterio-venous blood samples reported that ketone body oxidation was increased by ~100% in patients with HFrEF [76]. In experimental animals, TAC protocols that induce LVH in mice in the absence of systolic dysfunction, is associated with increased expression of enzymes involved in ketone oxidation, in concert with increased βOHB oxidation [120]. The superimposition of myocardial infarction in these mice induces the progression from LVH to HFrEF. This transition is associated with a further increase in oxidation of βOHB that is accompanied by decreased expression of genes involved in fatty acid oxidation and reduced levels of TCA cycle intermediates (with the exception of succinate). In addition, a prolonged 24 hour fast in these mice induced the expression of *SLC16A1*, which mediates myocardial ketone uptake in the heart. These data suggested that TAC + myocardial infarction-induced HFrEF is associated with an increased capacity for myocardial ketone body uptake and that ketone body oxidation in HFrEF occurs in concert with impaired myocardial fatty acid oxidation and altered anaplerosis [120]. In addition, mice with cardiomyocyte specific knockout of SCOT (preventing them from terminally oxidising βOHB), show increased fatty acid oxidation [123]. Interestingly, these animals are also more susceptible to TAC induced increases in LV mass [123]. These data support the concept that increased ketone body oxidation in heart failure is reciprocally regulated with fatty acid oxidation, which is inhibited. Whether increased ketone metabolism is adaptive or maladaptive in heart failure remains to be established. It is important to consider the efficiency of the substrate and whether ketone body metabolism occurs at the expense of the oxidation of fatty acids or glucose. In regards to efficiency, ketone bodies do indeed produce more energy per 2 carbons than glucose. However, when considering the P/O ratio, ketone bodies are less efficient than glucose. While an increased ketone body metabolism at the expense of fatty acids could represent a desirable shift in substrate preference in the failing heart, it is

important to consider that this may also occur at the expense of glucose oxidation, given that ketone bodies are less efficient in regards to their P/O ratio. Studies to rigorously evaluate this possibility remain to be performed.

Changes in ketone body oxidation in HFpEF remain incompletely understood. A recent study reported a 3-Hit murine model of HFpEF (involving age, long-term high-fat diet and deoxycorticosterone pivalate challenge) [90]. In contrast to findings in HFrEF, myocardial ketone oxidation was not increased in this HFpEF model. Rather, increasing ketone availability, despite decreased ketone oxidation, reduced proinflammatory cytokine-induced mitochondrial dysfunction and fibrosis in HFpEF. Plasma concentration of ketone bodies are also increased in insulin resistance and T2D, two comorbid conditions associated with increased risk for HFpEF. However, it remains unclear if hyperketonemia in these conditions is associated with increased myocardial uptake and oxidation [117, 118]. Serum metabolite analysis detected higher levels of AcAc and β-OHB in patients with HFpEF than in patients with HFrEF, suggesting an increased reliance on ketone bodies as an energy source in HFrEF compared to that in HFpEF [124]. However, a role for ketone bodies in the development of HFpEF remains to be definitively established and future work is required to elucidate the contribution of ketone body metabolism in the development of HFpEF.

Branched chain amino acid (BCAA) oxidation in heart failure:

Increases in plasma BCAA levels are seen in heart failure patients and have been suggested to be an early predictor of the future development of cardiovascular disease [125–129]. These increases in BCAA levels may be due in part to impaired BCAA oxidation in heart failure [130–132]. The accumulation of BCAA's in heart failure may activate cardiac mTOR signaling, thereby promoting cardiac hypertrophy [133, 134]. This is also supported by studies showing that stimulation of BCAA oxidation or inhibition of mTOR (with rapamycin) can improve heart function [132], while BCAA supplementation further increases mTOR signaling and worsens cardiac dysfunction [135].

Modulation of BCKDK activity as an approach to accelerate BCAA metabolism, via dephosphorylation and activation of BCKDH, is shown to lessen contractile dysfunction and cardiac insulin resistance in the settings of HFrEF. For instance, employing the BCKDK inhibitor, BT2, improves BCAA oxidation and reduces BCAA and BCKA accumulation in heart failure [132, 136, 137]. This stimulation of BCAA oxidation is accompanied by enhanced cardiac function and glucose oxidation in the failing heart [132, 136, 137]. The protein phosphatase PPC2m is also important in BCAA oxidation, as it decreases phosphorylation and inhibition of BCKDH, a key enzyme involved in BCAA oxidation. In mice deficient for PPC2m, myocardial BCAA and BCKA levels are elevated. These mice are more susceptible to HFrEF, following TAC, suggesting that decreased BCAA catabolism can contribute to systolic dysfunction in the stressed heart [132]. This same study also reported defects in BCAA metabolism in human heart failure tissue and in mice with TAC induced heart failure [132]. The consequences of the accumulation of BCKA were further investigated *in vitro*, with the authors proposing that products of BCAA oxidation inhibit complex I and increase superoxide production leading to impaired mitochondrial oxidative function [132].

Insulin resistance in the failing heart:

The relationship between insulin resistance and heart failure is complex and involves the cardiac adaptation to the systemic milieu in heart failure that is characterized by generalized insulin resistance in concert with intrinsic changes in insulin signaling within the cardiomyocyte [138]. Whole-body insulin resistance, which occurs in diabetes and obesity, is a risk factor for developing heart failure independent of myocardial infarction, hypertension and serum cholesterol levels [36, 97, 107, 110, 112, 139–142]. Moreover, diabetes also increases the risk of myocardial infarction by ~2–4 fold [143], and the coexistence of ischemic cardiomyopathy with diabetes accelerates the progression of heart failure [144]. Likewise, heart failure itself also aggravates the severity of whole-body insulin resistance[36, 145–148]. Importantly, an early and critical metabolic alteration in the failing heart is that the heart itself becomes insulin resistant in terms of insulin-mediated glucose uptake and the direct insulin stimulation of glucose oxidation, although increased signaling to cytosolic Akt may persist [138, 142, 149–159]. Altered myocardial insulin signaling in heart failure may not only negatively impact cardiac energy metabolism but may also exacerbate the extent of LV remodeling [138138, 142, 149–157]. In addition, cardiac insulin resistance seen in obesity or heart failure is also exacerbated if both co-exist [110, 139–141, 160–163]. Insulin signaling in the heart plays an important role in modulating cardiac preference for the primary oxidative substrates, namely glucose and fatty acids, while myocardial utilization of the minor oxidative substrates ketones and amino acids, are not directly regulated by insulin.

Insulin indirectly stimulates cardiac glucose oxidation by enhancing glucose uptake and, as a result, stimulates glycolysis that converts glucose to pyruvate, where the latter is taken up by the mitochondria to be oxidized to acetyl CoA through glucose oxidation. It has also been shown that insulin can directly stimulate mitochondrial glucose oxidation, independent of enhancing glucose uptake or glycolysis [164]. While the exact mechanism is not fully understood, direct insulin stimulation of glucose oxidation involves activation of mitochondrial PDH, the main regulatory enzyme of mitochondrial glucose oxidation [164–168]. Insulin also directly inhibits cardiac fatty acid oxidation via abrogating the inhibitory effect of 5’AMP-activated protein kinase (AMPK) on acetyl CoA carboxylase (ACC) and increasing malonyl CoA, a potent inhibitor of mitochondrial fatty acid uptake [169]. In addition, insulin-stimulated glucose oxidation can also inhibit fatty acid oxidation based on the Randle Cycle phenomena[170]. While there is still debate about what happens to basal rates of glucose oxidation during the evolution from compensated left ventricular hypertrophy to heart failure, cardiac insulin resistance, which has been generally defined as a marked reduction in cardiac insulin-stimulated glucose oxidation rates, represents one of the early metabolic perturbations that occur in the failing heart [36, 97, 107, 163, 171, 172]. As will be discussed below a fuller understanding of myocardial insulin resistance requires evaluation of proximal insulin signaling pathways, the activity of which could be augmented despite reduced myocardial glucose uptake [173]. Cardiac insulin resistance negatively impacts cardiac function and energy metabolism [36, 97, 107, 163, 171, 172]. In addition, the inhibitory effect of insulin on cardiac fatty acid oxidation becomes less dramatic in the failing heart [36, 163]. This is significant since the failing heart is energy-starved [3, 31], which led to the suggestion that the failing heart is “an engine out of fuel” [3, 31]. Accordingly, the occurrence of insulin resistance in the failing heart may exacerbate the cardiac energy deficit by

reducing cardiac efficiency, thereby contributing to the progression of heart failure [36, 97, 107, 163, 171, 172]. In heart failure associated with obesity, restoring systemic and cardiac insulin sensitivity by caloric restriction-induced weight loss correlated with improved contractile function in the failing obese heart [36]. Together, these data suggest that cardiac insulin resistance could be a marker of contractile dysfunction. Whether these changes mediate contractile dysfunction remain to be established. Depressed glucose oxidation in the failing heart could potentially contribute to contractile dysfunction via reducing glucose-derived ATP production. Moreover, depressed glucose oxidation also exacerbates uncoupling between glycolysis and glucose oxidation and, as a result, accumulation of ATP hydrolysis-derived protons (i.e., acidosis) in the cytosol. Acidosis can further aggravate contractile dysfunction in the failing heart by desensitizing contractile proteins to Ca^{2+}, inhibiting the slow inward Ca^{2+} current and redirecting cardiac ATP toward re-establishing ionic homeostasis instead of the contractile machinery [2].

It is noteworthy that MPC expression is downregulated in chronic HF patients [115]. Consistent with this, genetic impairment of mitochondrial pyruvate oxidation by deleting MPC expression is sufficient to induce LVH, age-dependent cardiomyopathy and increased susceptibility to pressure-overload induced heart failure [101, 115, 116, 174, 175]. Overexpression of MPC enhances coupling between glycolysis and glucose oxidation and reduces cardiac dysfunction and adverse remodeling via increasing glucose oxidation [115]. Thus, reduced glucose oxidation that occurs in conjunction with myocardial insulin resistance may have a detrimental effect on contractile dysfunction. As such, cardiac insulin resistance could potentially not only be a marker of heart failure severity, but also mediate contractile dysfunction in the failing heart. Consistent with this hypothesis, strategies to attenuate adverse remodeling in heart failure have included increasing cardiac energy supply and stimulating glucose cardiac oxidation[1–3], in both, experimental [36, 68, 97, 140, 162, 163, 176] and human heart failure [177].

The mechanisms leading to cardiac insulin resistance in heart failure are not fully understood, but contributing factors could include an impaired overall mitochondrial oxidative capacity and accelerated fatty acid oxidation rates [1]. Moreover, consistent with reduced glucose oxidation in the failing heart, cardiac insulin resistance is also accompanied by changes in cardiac insulin signal transduction, including activation of proximal insulin signaling pathways such as IRS1 and Akt [36, 158, 159, 163, 173]. Recent studies have provided strong evidence for divergent effects of insulin receptor substrates (IRS), namely IRS1 and IRS2, in the failing heart [158, 159, 178, 179]. Hyperactivation of IRS-1/Akt1 in the failing heart and genetic deletion of IRS-1 is protective in a mouse model of heart failure [159], suggesting a detrimental effect of IRS-1 in the failing heart. Moreover, deletion of IRS-2 further aggravated LV dysfunction in failing mouse hearts, suggesting a protective role of IRS-2/Akt2 in the heart [159]. However, it is still not clear how the signaling of IRS-1/Akt1 or IRS-2/Akt2 influences glucose uptake, glycolysis or glucose oxidation in the failing heart. Despite these alterations in cardiac insulin signaling, it has been shown that glycolysis is up-regulated in the failing heart [60, 180, 181], possibly compensating for reducing mitochondrial oxidative metabolism. Therefore, it seems plausible that the reduction in insulin-stimulated glucose oxidation in the failing heart occurs, at least in part, due to decreased direct stimulation of mitochondrial glucose oxidation by insulin [122, 182]. However, how insulin

signaling is transduced to the mitochondria to stimulate PDH and glucose oxidation is not known [165–168].

The insulin signaling pathway in the mitochondria is not well characterized. Insulin has been shown to increase mitochondrial fusion in concert with increased mitochondrial oxidation by a mechanism involving induction of OPA1 expression. [183] Another component of the insulin signaling pathway, namely protein kinase B (Akt), can translocate to the mitochondria following insulin stimulation [165–168]. Interestingly, mitochondrial translocation of Akt has also been implicated in modulating mitochondrial oxidative phosphorylation [165–168]. Therefore, it seems plausible to suggest that Akt could be a potential candidate that mediates the direct insulin stimulation of glucose oxidation. Insulin stimulation results in a marked increase in glucose oxidation rates in the normal mouse heart [182, 184]. Of importance is that insulin stimulation in these hearts did not cause significant changes in glycolysis, likely due to the high glycolysis rates seen in the mouse heart, confirming that insulin can directly stimulate glucose oxidation, independent of stimulating glycolysis. Interestingly, direct insulin stimulation of glucose oxidation is associated with a stimulation of mitochondrial Akt, an effect that is also accompanied by the activation of PDH [182]. Furthermore, we also demonstrated that inhibiting mitochondrial Akt completely abolishes the direct insulin stimulation of glucose oxidation [182]. These findings indicate that insulin-stimulated mitochondrial Akt is a *sine qua non* for mediating the direct insulin stimulation of cardiac glucose oxidation.

NAD(H) alterations in heart failure

Reduction of nicotinamide adenine dinucleotide (NAD) levels or NAD^+/NADH redox state has been observed in many chronic diseases including heart failure [185–189]. Recent studies demonstrated benefits of supplying NAD precursors in preclinical models and in patients with heart failure [186, 187, 190]. These findings have stimulated the investigation of NAD metabolism in heart failure and raise hope for a new therapeutic approach[191]. However, mechanisms leading to the altered NAD(H) levels in heart failure are not fully understood. Furthermore, despite the remarkable benefits observed in animal models of heart failure, the molecular targets of increasing NAD levels are less clear. Elucidation of these mechanisms are necessary for a better understanding of metabolic regulation of heart failure, and importantly, to translate the findings into therapy.

NAD exists in the oxidized (NAD^+) and reduced form (NADH); they serve as the major electron carrier coenzyme in substrate metabolism, e.g. glycolysis and TCA cycle, and in oxidative phosphorylation [192]. NAD^+ is also a required substrate by poly (ADP-ribose) polymerases (PARPs), sirtuins and CD38, thus playing an important role in post-translational modification, DNA damage repair, gene transcription and other signaling mechanisms[188, 193, 194]. Biosynthesis of NAD in mammalian cells occurs through several routes [195]. The *de novo* biosynthesis pathway starts with tryptophan whereas the Preiss Handler pathway utilizes nicotinic acids. Both converge on nicotinic acid mononucleotide (NaMN) to produce NAD^+ through a nicotinamide mononucleotide adenyltransferase (NMNAT) reaction (Figure 2). Important for the maintenance of the NAD pool, nicotinamide (NAM), the product of NAD^+ consumption by sirtuins, PARPs or CD38, is

converted to nicotinamide mononucleotide (NMN) by nicotinamide phosphoribosyl transferase (NAMPT) for resynthesis of NAD^+ (Figure 2).

Increased consumption, as occurs during increased DNA repair in aging or following activation of CD38 by inflammation, could contribute to the depletion of intracellular NAD levels. Specific mechanisms leading to changes of NAD consumption in heart failure are, however, poorly defined. On the other hand, there is evidence of impaired NAD salvage in heart failure. NAMPT expression is downregulated in human and mouse failing hearts while the expression of NRK2, an enzyme converting nicotinamide riboside (NR) to NMN, is upregulated suggesting a metabolic shift in the salvage pathway (Figure 2) [187, 196, 197]. Furthermore, reduced NADH oxidation, due to impaired mitochondrial respiratory function, leads to sequestration of NAD in the NADH form, resulting in a decrease of NAD^+ availability and reduced NAD^+/NADH ratio [186, 198]. Supplementation of NAD precursors NMN or NR are effective in raising NAD levels in mouse failing hearts. Increasing NAD levels in this way has been reported to improve the outcome of heart failure in a variety of mouse models[186, 187, 199, 200]. The effect of overexpressing NAMPT, however, appears to be model dependent. Cardiac-specific overexpression of NAMPT protects against ischemia-reperfusion injury and isoproterenol induced cardiomyopathy, but worsens the outcome of pressure overload induced heart failure [186, 197, 201].

How does a lower cardiac NAD level contribute to the pathogenesis of heart failure, and why does boosting NAD exert benefit on heart failure? Initial studies focused on the role of NAD^+ as a co-substrate for sirtuin deacetylases. Increased protein acetylation has been observed in heart failure or mitochondrial dysfunction induced cardiomyopathy, where decreases in NAD and sirtuins are also found [185, 186]. Several studies linked activation of Sirt3, a mitochondrion localized sirtuin, to the cardioprotective effects of increasing NAD levels [186, 199, 200]. Sirt3 is involved in deacetylation of a large number of mitochondrial proteins, it remains largely unknown which specific targets downstream of Sirt3 mediate the benefit of increasing NAD in heart failure [32]. Moreover, a recent study showed that extreme mitochondrial protein hyperacetylation did not exacerbate heart failure induced by pressure overload in mice [202], calling for the investigation to go beyond Sirt3 and mitochondrial protein acetylation.

NAD levels and NAD^+/NADH redox are critical for energy metabolism (Figure 3). Increasing NAD or restoring NAD^+/NADH redox improves cardiac energy metabolism in mouse models of heart failure [186, 187]. A recent study suggests that hyperacetylation of the muscle form of creatine kinase (CKM) accounts for the long-observed downregulation of CK activity in heart failure [203]. The study also showed that acetylation of CKM, cytosolic protein, was NAD^+-dependent and mediated by Sirt2. Whether increasing NAD^+-dependent deacetylation of CKM improves high energy phosphoryl transfer in the failing heart warrants future study. In addition, supplementation of NAD precursors has recently been found to protect mitochondria of peripheral blood mononucleated cells (PBMC) resulting in reduced inflammatory response in heart failure patients [190]. Thus, both cardiac and systemic responses could also contribute to the NAD-dependent salutary effects in heart failure.

Epigenetic and transcriptional changes in the failing heart

One long held hypothesis surrounding the changes in cardiac metabolic utilization and loss of substrate flexibility is that of transcriptional reprogramming. This was initially described as a return to the foetal gene program,[204] to reflect the increased reliance on glucose utilization in heart failure resulting from ischemic injury or pressure-overload. Although this may differ in the context of diabetes where fatty acid utilization is increased but uncoupled, [205] the conclusion has remained the same in that many of the changes in cardiac energy metabolism in heart failure described within this review are a result of changes in gene expression. Although decades of research have gone into this area, especially as it relates to the aforementioned PGC-1α and PPARα, over the last 10 years regulation of gene expression in heart failure via the metabolites themselves through epigenetic mechanisms has emerged.[206] Epigenetics as a field encompasses long-lasting changes in gene expression without changing the underlying genetic code. Mechanisms of epigenetic regulation include post-translational regulation of histone proteins, DNA modifications, and post-transcriptional regulation via non-coding RNAs. What is particularly enticing is the ability of epigenetic regulation to synthesize changes in intermediary metabolism into changes in gene expression.[207]

Of the histone modifications explored, protein acetylation has received the most attention for its potential as a therapeutic target in treating heart failure. This in part relates to the fact that a number of the enzymes that control histone acetylation are regulated by NAD(H), as well as the acetyl-CoA used as the substrate generated by enzymes such as PDH, linking the pathways described in previous sections to regulation of transcriptional control (Figure 3). One specific family of enzymes in this role are the sirtuins, a class of protein deacetylases, which are NAD-dependent and have been widely studied for their potential role in cardiovascular disease.[208–210] Some of the sirtuins may work through epigenetic regulation while others may directly regulate mitochondrial enzyme function.[209] Additionally, a number of histone deacetylase (HDAC) inhibitors have been developed as therapeutics for various cancers, and have been suggested as potential candidates for treatment of heart failure.[211] In fact, very recent evidence supports that HDAC inhibition improves cardiopulmonary function in a feline model of HFpEF.[212] Although it is important to note that despite the name HDAC, some of the improvements are from non-epigenetic mechanisms of regulation including altered myofibril relaxation,[213] while others clearly are mediated by changes in gene expression.[214, 215] However, it is clear that additional studies distinguishing direct epigenetic effects of these inhibitors versus indirect changes in enzymatic activity of non-histone targets are required. In addition to remaining questions surrounding HDAC inhibitors, it is important to note that many other metabolites will signal to, or directly modulate, histone post-translational regulation (Figure 3). These mechanisms include ketone body regulation of histone deacetylases,[216] TCA metabolic intermediates such as citrate signaling to histone acetyltransferases,[217] α-ketoglutarate to histone methyltransferases,[218] as well as auxiliary glucose signaling pathways like the hexosamine biosynthesis pathway via direct O-GlcNAcylation of histones[219] or indirect O-GlcNAcylation of HDAC4.[220] Many of these pathways have not been fully defined in the heart.

In addition to epigenetic regulation of gene expression by histones, direct modification of DNA may also occur via modification of cytosine nucleotides that are followed by a guanine nucleotide (CpG) by methylation (5mC) or hydroxymethylation (5hmC) (Figure 3B). In general, 5mC occurring at the promoter of a gene is inversely related to gene expression, while 5hmC which is relatively understudied occurs in the gene body, the binding of which is directly proportional to changes in gene expression. Early studies in this area found that DNA 5mC was associated with changes in expression of angiogenesis-related genes related to the progression of human heart failure,[221] and regulation of heart failure genes in a mouse model of TAC.[222] Inhibition of DNA methylation may attenuate cardiac hypertrophy associated gene expression changes in norepinephrine-treated rats.[223] More recently it was shown in human heart failure that some of these changes in DNA methylation are highly correlated with coordinate changes in enzymes responsible for the fatty acid to glucose utilization switch, likely through a mechanism involving DNA methyltransferase 3A (DNMT3A).[224] Interestingly, this mechanism was further defined in human ischemic heart failure to include parallel and inverse epigenetic regulation via the histone methyltransferase and its interaction with DNMT to supress expression of oxidative phosphorylation genes while concurrently interacting with the transcription factor FOXM1 to upregulate cellular remodeling genes.[225] Comparatively much less is known about the role of 5hmC in the regulation of cardiac gene expression with a number of papers emerging the last few years.[226–229] However, some evidence for a disparate relationship between DNA methylation and changes in cardiac gene expression in the context of diabetes has recently emerged.[230] Therefore, additional studies surrounding the contribution, regulation, and reversal of these pathways remains warranted.

The final area of epigenetic regulation is that of non-coding RNAs (Figure 3C). This, like histone modifications, includes a large number of different pathways encompassing microRNA (miR) to long non-coding RNA (lncRNA). However, given the relative ease of measuring non-coding RNAs in the circulation even though this pathway was one of the last to be studied, there is now a large literature surrounding its role in the regulation of gene expression in heart failure as recently reviewed,[231–233] and therefore not described in detail in this review.

Glucose metabolic changes in heart failure: Beyond ATP Production

Fatty acids represent the major substrate for normal hearts. Although in heart failure fatty acid oxidation is reduced relative to non-failing hearts, it remains the predominant metabolic substrate even for the failing heart. A recent study in humans, achieved by measuring arteriovenous differences in multiple metabolites [19] revealed that in the fasting state the healthy human heart generates 85% of its ATP from fatty acid sources, 6.4% from ketones, 4.6% from amino acids and 2.8% from lactate. Whereas in patients with HFrEF substrate contributions to ATP generation is 71% from fatty acids, 16.4% from ketones, 5% from lactate and 6.4% from amino acids. Importantly, both normal or failing hearts under these conditions utilized minimal amounts of glucose. Interestingly there was a significant rate of amino acid turnover of ~ 2% per day. In studies from independent groups in which myocardial biopsies were obtained in patients from end-stage heart failure and analyzed by metabolomics, a common theme was accumulation of pyruvate and other glycolytic

intermediates [61, 78, 115, 174]. In all of these studies, expression levels of the mitochondrial pyruvate carrier were reduced and in one study the phosphorylation of PDH was increased. Two recent independent reports confirmed the repression of MPC expression in human heart failure and also in animal models [101, 175]. Thus impaired mitochondrial pyruvate utilization has emerged as a reproducible signature of the failing heart. The reduction in pyruvate utilization is not likely to contribute to "energy starvation" in the heart failure, but rather may contribute to adverse LV remodeling by non-oxidative metabolism of glycolytic metabolites into pathways such as the polyol pathway, the hexosamine biosynthetic pathway (HBP), the pentose phosphate pathway (PPP) and one carbon cycle pathways (Figure 4) [101, 116, 174, 175]. Unloading of failing hearts following LVAD implantation was associated with reduced flux through the HBP and polyol pathway, but increased PPP flux leading to generation of reduced NADPH that improves redox homeostasis and ribitol, which would mediate changes in alpha-dystroglycan, which would lead to improved extracellular matrix homeostasis [174]. Although flux through these pathways might be small under physiological conditions, a persistent increase over time could lead to the accumulation of metabolic intermediates that could impact cellular function. For example, the cellular consequence of altered flux through the hexosamine biosynthetic pathway is accumulation of O-GlcNAc modifications, which have been described in multiple models of heart failure and which might be sufficient to induce LV remodeling [234, 235].

Additional mechanistic insights have been obtained from animal models and studies of cultured myocytes in which MPC expression or function are altered [101, 115, 116, 175]. These studies all reveal that inhibiting mitochondrial pyruvate utilization by genetically deleting expression of MPC subunits (Mpc1 or Mpc2) or by pharmacologic inhibitors is sufficient to induce pathologic cardiac hypertrophy and heart failure [101, 115, 116, 175]. Metabolomics analysis reveals increased flux into non-oxidative pathways such as the HBP, glycogen synthesis, the PPP and amino acid biosynthetic pathways (Figure 5). Overexpression of MPC in hearts subjected to TAC, or treating isoproterenol-treated mice with an inhibitor of the lactate transporter MCT4, which increased the generation of pyruvate and flux through the MPC limited adverse LV remodeling and reversed these metabolomics changes [101, 115]. In this regard, lactate itself was also shown to exhibit a potent anti-hypertrophic effect after TAC via a mechanism that involves NDRG3 and ERK [21].

Treatment of mice with myocardial Mpc deficiency with a ketogenic or high-fat diet completely reversed the pathological LV remodeling and heart failure [116, 175]. Mechanistically, these hearts at baseline exhibited increased rates of fatty acid oxidation and the ketogenic diet suppressed glycolysis, lactate and pyruvate accumulation and flux of glucose carbons into non-oxidative metabolic pathways such as the HBP and glycogen [116]. MPC deficient hearts fail more rapidly when they are subjected to TAC. Introducing a ketogenic diet at the onset of TAC does not rescue this phenotype suggesting that simply switching substrates will not substitute for the acute increase in hemodynamic requirements [116]. Intriguingly, pre-treating these animals with a ketogenic diet prior to TAC prevents accelerated heart failure. This suggests a temporal relationship between reducing the accumulation of glycolytic intermediates and reversing the negative consequences of accumulation of these intermediates of non-oxidative glucose metabolism, on ventricular remodeling (Figure 4)

Accumulation of pyruvate and amino acid derived acyl carnitines are noted in hearts of spontaneously hypertensive rats early in their development of pathological LVH and treatment with metformin reverses these metabolic abnormalities in concert with LVH regression despite persistent hypertension [236, 237]. Taken together, these findings reveal a strong relationship between non-oxidative metabolism of glucose and glycolytic intermediates and the development of pathological LV remodeling.

Observations in other animal models support a role for non-oxidative glucose metabolism in pathological cardiomyocyte hypertrophy and have provided additional mechanistic insights. Studies in cultured cardiomyocytes reveal that glucose-derived metabolites provide building blocks for increasing cardiomyocyte hypertrophy via the generation of aspartate through the TCA cycle, which supplies nitrogen for nucleotide biosynthesis [238]. Interestingly, MPC deletion which reduces pyruvate import into mitochondria also causes hypertrophy. However, glucose-derived carbon could enter the mitochondria via alternative metabolic pathways, such as alanine, in the absence of MPC [116], the contribution to aspartate or nucleotide synthesis remains to be determined. Moreover, studies of the MPC mutants raise the possibility that glucose-derived carbons could be mediating ventricular remodeling by activating signaling pathways that promote hypertrophy. Glucose suppresses BCAA catabolism by inhibiting CREB-mediated KLF transcription that suppresses expression of genes that encode BCAA catabolic genes. BCAA accumulation promotes cardiac hypertrophy by activating mTOR signaling [239]. Glucose 6 phosphate (G6P) has also been shown to a potent activator of mTOR signaling [240]. Accumulation of G6P has been noted in animal models and humans with heart failure and levels fall when hearts are unloaded [241]. Other regulators of glycolysis have been shown to play regulatory roles in hypertrophic adaptations in the heart. Glycolytic regulation at the level of phosphofructokinase 2 (PFK2) has been suggested to be part of a transcriptional pathway that regulate signal transduction nodes that mediate physiological versus pathological LVH (Figure 5). Specifically, repression of PFK2, as occurs following exercise leads to activation of transcription factors associated with physiological cardiac hypertrophy, whereas activation of PFK2 is associated with signaling pathways that promote pathological LV remodeling [242]. Heart failure in animals and humans is associated with increased expression of the fetal isoform of pyruvate kinase (PKM2), which in contrast to the adult isoform PKM1 is less efficient in converting phosphoenolpyruvate (PEP) to pyruvate + ADP [243]. The consequence of increased PKM2 expression would be accumulation of glycolytic intermediates, which would increase flux into non-oxidative pathways of glucose metabolism (Figure 4).

Mice with cardiomyocyte KO of the GLUT4 glucose transporter develop a compensatory increase in GLUT1 and a two-fold increase in basal myocardial glucose uptake [113]. These animals develop pathologic LVH that is associated with evidence of increased non-oxidative glucose metabolism such as glycogen accumulation [244]. One potential mechanism for LVH in these animals is oxidative stress arising in the cytosol and not the mitochondria, supporting the concept that increased availability of glycolytic intermediates could be maladaptive [245]. Similar mechanism may contribute to metabolic maladaptation in the context of heart failure and diabetes. As previously discussed, heart failure is associated with increased myocardial utilization of ketones. However in heart samples obtained from humans with heart failure and diabetes, genes encoding proteins responsible for ketone body

catabolism are repressed [246]. Moreover in a transgenic model of inducible GLUT4 expression in which diabetes could be superimposed, one of the most significantly repressed pathway are those encoding ketone catabolism [246, 247]. In addition, increased glucose entry leads to O-GlcNAc modifications of transcriptional regulators of mitochondrial electron transport genes leading to reduced expression. Furthermore, mitochondrial proteins are also subjected to increased O-GlcNAc modifications, which could independently reduce their activity[247]. Together, these findings suggest that heart failure in combination with diabetes limits the ability of the failing heart to utilize ketones that in concert with exacerbated mitochondrial dysfunction increases toxicity from glycolytic intermediates while aggravating energy deficiency.

Given the relatively low utilization of glucose by the heart in the fasting state the question arises as to what are the major physiological roles for glucose utilization in the heart. Studies in GLUT4 deficient hearts have revealed that the ability of the heart to increase glucose utilization via GLUT4 is essential for myocardial adaptations following diverse stressors such as acute ischemia, swim training to induce physiological hypertrophy or TAC-induced pathological hypertrophy [244, 248]. Similar conclusions can be drawn from mice with high-level transgenic overexpression of GLUT1 which are more resilient to I/R injury and pressure overload hypertrophy [249, 250]. Also, reducing glucose availability in hearts of mice with BCAA accumulation arising from impaired BCAA catabolism leads to impaired recovery from I/R injury [251]. Inducible GLUT1 expression at the time of TAC, preserves mitochondrial function and attenuates early remodeling, but does not ultimately prevent heart failure [252]. Importantly, GLUT1 is dispensable for response to TAC, suggesting that the maladaptation resulting from pressure overload is not primarily driven by defects in glucose entry, but rather from the fate of glycolytic intermediates, which is regulated at the level of pyruvate utilization by mitochondria [253]. It is important to note though, that the ability to increase fatty acid oxidation during post-ischemic reperfusion is critically important for myocardial recovery post-ischemia even when glucose supply is adequate [254–257].

Lipotoxicity in heart failure: Role of fatty acid oxidation

Lipotoxicity describes the consequences of accumulation of lipid moieties in the heart that activate signaling pathways that impair myocardial function. It is important to note that increasing fatty acid oxidation *per se* does not inexorably lead to lipotoxicity. This has been elegantly demonstrated in many studies performed in $Acc^{-/-}$ hearts that have high rates of fatty acid oxidation on the basis of reduced levels of malonyl CoA [91, 92]. Lipotoxicity represents an important mechanism that augments heart failure risk in diabetes, as extensively reviewed [258, 259]. Lipotoxicity occurs when mitochondrial oxidative capacity is unable to adapt to myocardial lipid overload as occurs in obesity or diabetes, or in animal models with overexpression of fatty acid transporters or transcriptional activators that regulate fatty acid oxidative pathways such as PPARα or PPARγ [260]. Lipid accumulation has been long described in end-stage failing hearts and is exacerbated when heart failure is superimposed on diabetes [261, 262]. The mechanisms responsible for lipotoxicity, particularly in the context of diabetes have been extensively reviewed [258–260]. Mechanisms linking lipotoxicity and heart failure include oxidative stress [53, 263, 264], suppressed autophagy [265],

mitochondrial uncoupling [266–268] altered mitochondrial dynamics [53, 189], accumulation of toxic lipid intermediates such as ceramide or diacylglycerol [265, 269] ER stress [270, 271] and inflammation [272, 273].

Therapeutic strategies targeting cardiac metabolism to treat heart failure

Given the close relationship between altered myocardial metabolism and heart failure, metabolic modulation remains a promising approach to treating heart failure or reducing ventricular remodelling. Pathways, which have been subjected to therapeutic manipulation in animal and human studies are summarized in Figure 5 and detailed in the following sections.

Stimulating ketone oxidation:

Recent studies have suggested that increasing cardiac ketone oxidation is adaptive in the failing heart and can improve heart function (see [25, 274, 275] for reviews) (Figure 5). This can be achieved by increasing circulating ketone body levels, primarily by one of four approaches: 1) ketone infusions, 2) ketone ester administration, 3) SGLT2 inhibitors, and 4) administration of a ketogenic diet. A study by Nielsen R *et al* [276] showed that acute infusions of ß-hydroxybutyrate (ßOHB) into patients with HFrEF improves contractile performance. Chronic administration of ßOHB in dogs with pacing-induced heart failure also decreased adverse remodelling [277]. Acute administration of a ketone ester (KE, (R-3-hydroxybutyral(R)-3-hydroxybutyrate) to HFrEF patients, resulted in an increase in circulating ßOHB by 12.9-fold and an improvement in contractile function [278]. Ketone ester administration was also shown to improve cardiac function and to reduce cardiac remodeling in mouse and rat models of heart failure [279]. Unfortunately, it is difficult to chronically maintain elevated circulating ketone levels with either ketone or ketone ester infusions. SGLT2 inhibitors are one approach to overcoming this problem. Although originally developed as anti-hyperglycaemic agents to treat diabetes, SGLT2 inhibitors have recently been shown to have dramatic cardioprotective effects in heart failure patients [280–282]. One of the proposed methods by which SGLT2 inhibitors may improve cardiac function in heart failure is by increasing circulating ketone bodies and increasing energy supply to the failing heart [283]. Alternatively, increased circulating ketones following SGLT2 inhibitor administration have been proposed to decrease inflammation in the failing heart by modulating the NLRP3 inflammasome [284]. Ketogenic diets are another approach to raising circulating ketones. However, feeding mice with heart failure a ketogenic diet results in very modest improvements in end-diastolic volume and end-systolic volume in a pressure-overload mouse model of heart failure [277].

Stimulating glucose oxidation and improving insulin sensitivity:

Recognising the negative impact of cardiac insulin resistance on glucose oxidation rates and cardiac function in the failing heart, several studies have shown that stimulating cardiac glucose oxidation enhances cardiac function and limits the impact of cardiac insulin resistance in the failing heart. Employing dichloroacetate (DCA), a direct inhibitor of pyruvate dehydrogenase kinase, to stimulate PDH complex activity has been an effective approach to stimulate glucose oxidation in different settings of heart failure. DCA improves post-ischemic recovery and cardiac efficiency following ischemia and reperfusion via

stimulating glucose oxidation and enhancing the coupling between glycolysis and glucose oxidation [285]. Similar improvement in the coupling between glycolysis and glucose oxidation by DCA treatment is also observed in hypertrophied rat hearts [286]. In the Dahl-salt sensitive rats, DCA supplementation attenuates the transition from compensated heart failure to heart failure, and improves survival by limiting oxidative stress and improving cardiac reserve [68]. Using magnetic resonance spectroscopy with hyperpolarized [^{13}C]pyruvate and magnetic resonance imaging, a recent study showed that PDH flux is decreased by ~50% in a porcine model of heart failure [287]. However, DCA treatment improved the contractile reserve and abrogated hypertrophy by enhancing PDH flux in this large animal heart failure model [287]. Although not all clinical data are consistent [288], these promising experimental data were recapitulated in small clinical trials. For instance, DCA administration in patients with angina and coronary artery disease augments left ventricle stroke volume and enhances myocardial efficiency (cardiac work/myocardial oxygen consumption) [289], consistent with glucose being an oxygen-efficient substrate for the heart compared to fatty acid [2, 182]. In line with that, DCA stimulates glucose oxidation and improved left ventricle mechanical efficiency by reducing myocardial oxygen consumption and enhancing cardiac work in patients with New York Heart Association class III and IV congestive heart failure [177]. Another effective approach to enhance insulin sensitivity and glucose oxidation in the failing heart involves enhancing cardiac insulin signaling. For instance, antagonizing glucagon action, using a human monoclonal antibody (mAb A) against glucagon receptor (GCGR), a G-protein coupled receptor, can improve cardiac insulin sensitivity, glucose oxidation and cardiac function post-myocardial infarction [163]. Cardiac insulin sensitivity is further impaired when heart failure is associated with diabetes and obesity; both are accompanied by cardiac insulin resistance. Recent studies have shown that weight loss due to different dietary interventions improves cardiac function by enhancing insulin signaling and insulin-stimulated glucose oxidation rates in heart failure associated with obesity [36, 110].

Altering fatty acid oxidation:

As discussed, alterations in fatty acid oxidation in the failing heart are complex, with decreases, no changes and increases in fatty acid oxidation all being reported in the literature (see [1] for review). Despite this, inhibition of fatty acid oxidation has been shown to improve heart function in the failing heart. Inhibitors of fatty acid oxidation such as trimetazidine, etomoxir, and perhexiline have been shown to be cardioprotective in humans with heart failure [290–295]. These beneficial effects are thought to be due to an increase in glucose oxidation, secondary to fatty acid oxidation inhibition, resulting in an increase in cardiac efficiency [1].

Malonyl CoA is an endogenous inhibitor of fatty acid oxidation in the heart that acts by inhibiting mitochondrial fatty acid uptake. Malonyl CoA levels are regulated in the heart by malonyl CoA decarboxylase (MCD), which degrades malonyl CoA, and by acetyl CoA carboxylase (ACC), which synthesizes malonyl CoA [17]. Inhibition of MCD in a rat model of heart failure results in an increase in myocardial malonyl CoA levels, a decrease in cardiac fatty acid oxidation rates and the prevention of heart failure development [296]. In contrast, inhibition of ACC and stimulation of fatty acid oxidation has also been shown to be cardioprotective the failing mouse heart [91, 92]. While these beneficial effects of MCD

inhibition and ACC inhibition may seem contradictory, interestingly both approaches result in an improved coupling of glycolysis to glucose oxidation, suggesting a decrease in proton production from uncoupled glucose metabolism [91, 296]. Inhibition of ACC is also associated with an improved mitochondrial function [92]. Additional mechanisms linking altered malonyl CoA levels with amelioration of heart failure could include changes in metabolic intermediates such as acetyl CoA, which could mediate post translational modifications such as protein acetylation, which could independently modulate myocardial metabolism and activity of other regulatory proteins. However recent studies have not found a correlation between mitochondrial protein acetylation and susceptibility of mouse hearts to pressure overload induced heart failure [185, 202].

Stimulating branched-chain amino acid (BCAA) oxidation:

High levels of circulating BCAA and its metabolites, namely branched-chain keto acids (BCKAs) (α-ketovalerate (produced from valine), α-keto-ß-methylvalerate (produced from isoleucine), and α-ketoisocaproate (produced from leucine), have also been positivity correlated with increased cardiovascular disease risk [127, 297, 298]. Of interest is that plasma as well as cardiac levels of BCAA and BCKAs increase in the rodent models of myocardial ischemia/reperfusion injury [135, 163, 251] and heart failure [132, 299]. Disruption of cardiac BCAA oxidation aggravates cardiac insulin resistance and contractile dysfunction in murine models of myocardial ischemia/reperfusion [251] and aortic constriction [132], while BCAA supplementation further deteriorates cardiac dysfunction and increases infarct size in a mouse model of coronary artery ligation-induced myocardial infarction[135]. Restriction of BCAA availability also enhances, through an unknown mechanism, fatty acid contribution to ATP production and reduced triglyceride accumulation in hearts of Zucker fatty rats [300]. In contrast, pharmacological interventions to enhance BCAA oxidation and/or decrease circulating BCAA levels are cardioprotective in the ischemic and the failing heart [132, 135, 251, 299]. Taken together, these studies show that alterations in BCAA oxidation are strongly linked to the development cardiac insulin resistance and contractile dysfunction in different forms of heart failure.

Direct measurement of the BCAA oxidation rates in the heart showed only 1–2% of the total cardiac ATP is produced from BCAA [299, 301]. This suggests that it is highly unlikely that interventions to increase BCAA catabolism would materially impact its contribution to cardiac ATP generation or alter the relative utilisation of fatty acids or glucose [302]. However, accumulation of BCAA[163, 299] and/or BCKA[303–305] as a result of impaired BCAA oxidation may increase mTOR activity and impair insulin signaling in the failing heart. Furthermore, high levels of BCAA [251] and/or BCKA[306] will impair cardiac PDH activity, to further reduce glucose oxidation in the failing heart[163]. Impaired protein expression of BCAA catabolic enzymes is evident in the human heart with dilated cardiomyopathy, which is also associated with increased levels of myocardial BCAAs [136]. In line with this, treatment with the BCKDK inhibitor, BT2, increases BCAA oxidation in conjunction with reducing BCAA accumulation[136] and BCKAs[132, 137] in failing murine hearts. However, the exact mechanism through which impaired BCAA oxidation contributes to the development and/or severity of decreased oxidative metabolism of glucose remains to be elucidated. Whether there are divergent roles of BCAA and BCKA in triggering mTOR signaling and mediating

myocardial insulin resistance is also yet to be characterized. Recent studies by our group suggested that BCAA, not BCKA, have a dominant role in aggravating cardiac hypertrophy in the failing heart via activating mTOR, while BCKA, not BCAA, induces cardiac insulin resistance via inhibiting cardiac insulin signaling [307, 308].

Conclusions

The failing heart is energy deficient, primarily due to a decrease in mitochondrial oxidative capacity, increased glycolysis uncoupled from glucose oxidation, and either a decrease or no change in fatty acid oxidation. In contrast, in times of increased fatty acid availability, as occurs in obesity, an increase in cardiac fatty acid oxidation may occur. These energy metabolic changes result in the failing heart becoming less efficient. Alterations in mitochondrial oxidative metabolism in the failing heart are due to both transcriptional changes in key enzymes involved in these metabolic pathways, as well as alterations in redox state and metabolite signaling that contribute to post-translational epigenetic changes in the control of expression of genes encoding energy metabolic enzymes. Alterations in the fate of glucose also contribute to the pathology of heart failure. Of importance, pharmacological targeting of mitochondrial oxidative metabolism has emerged as a novel therapeutic approach to improving cardiac efficiency, decreasing the energy deficit and improving cardiac function in the failing heart.

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Abbreviations:

ATP	Adenosine triphosphate
ADP	adenosine diphosphate
AcAc	acetoacetate
ACC	acetyl CoA carboxylase
Akt	protein kinase B
AMPK	5’ AMP-activated protein kinase
βOHβ	β-hydroxybutyrate

BDH1	β-hydroxybutyrate dehydrogenase
BCAA	branched chain amino acid
BCAT	branched chain aminotransferase
BCATm	mitochondrial branched chain
BCKA	branched chain α-keto-acids
BCKDH	branched chain α-keto acid
BT2	BCKDH inhibitor
BDK	BCKDH kinase
CPT-1	carnitine palmitoyl transferase
CoA	coenzyme
CD36	cluster of differentiation 36
CD38	cluster of differentiation 38
CK	creatine kinase
CKM	muscle form of CK
DCA	dichloroacetate
DNMT3A	DNA methyltransferase 3A
Drp1	dynamin-related protein 1
ETC	electron transport chain
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinase
ERRα	estrogen related receptors α
ERRγ	estrogen related receptors γ
FAO	fatty acid oxidation
FATP-1	fatty acid transport protein-1
FADH2	flavin adenine dinucleotide
Fis1	mitochondrial fission 1 protein
FOXM1	forkhead box protein M1
GCGR	glucagon receptor
G6P	glucose 6-phosphate

GLUT1	glucose transporter 1
GLUT4	glucose transporter 4
GSH	reduced glutathione
CpG	guanine nucleotide
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HBP	hexosamine biosynthetic pathway
H2A, H2B, H3 and H4	histones 2A, 2B, 3 and 4
HAT	histone acetyltransferase
HDAC	histone deacetylase
HDM	histone demethylase
5hmC	hydroxymethylation
IDCM	idiopathic dilated cardiomyopathy
IRS	insulin receptor substrate
KO	knock out
LDH	lactate dehydrogenase
LIVCS	branched chain amino acid\cation symporter family
LV	left ventricle
LVH	LV hypertrophy
LVAD	LV assist device
lncRNA	long non-coding RNA
ME1	malic enzyme 1
MCD	malonyl CoA decarboxylase
mTOR	mammalian target of rapamycin
MCAD	medium chain acyl CoA dehydrogenase
5mc	methylation
miR	microRNA
MPC	mitochondrial pyruvate carrier

Mfn1	mitofusin 1
Mfn2	mitofusin 2
MCT1	monocarboxylate transporter 1
SLC16A1	monocarboxylate ketone transporter
NAD	nicotinamide adenine dinucleotide oxidized
NADH	nicotinamide adenine dinucleotide reduced
NADPH	nicotinamide adenine dinucleotide phosphate
NADS	NAD synthase
NAM	nicotinamide
NDRG3	N-myc downstream-regulated gene 3
NHE	sodium/hydrogen exchanger
NMN	nicotinamide mononucleotide
NMNAT	nicotinic acid mononucleotide adenyltransferase
NR	nicotinamide riboside
NRF-1	nuclear respiratory factor-1
NRF-2	nuclear respiratory factor-2
NRK	nicotinamide riboside kinase
OPA1	mitochondrial dynamin like GTPase
OXPHOS	oxidative phosphorylation
PARPs	poly (ADP-ribose) polymerases
PDK1	3-phoshoinositide-dependent protein kinase 1
PEP	phosphoenolpyruvate
PFK-1	phosphofructokinase 1
PFK-2	phosphofructokinase 2
PPARα	peroxisome proliferator activator receptor α
PPARγ	peroxisomal proliferator activator receptor γ
PGC1-α	PPARγ coactivator 1-α
PPC2m	protein phosphatase C2m
PDH	pyruvate dehydrogenase

PDK4	PDH kinase 4
PKM	pyruvate kinase
PP2Cm	mitochondrial-target 2C-type ser/thr protein phosphatase
PPP	pentose phosphate pathway
ROS	reactive oxygen species
SAM	S-adenosylmethionine
SCOT	succinyl-CoA:3 oxoacid-CoA transferase
SGLT2	sodium/ glucose co-transporter 2
SGLT2i	SGLT2 inhibitor
Sirt3	sirtuin 3
T2D	type 2 diabetes
TAC	transverse aortic constriction
TET	ten-eleven translocation
TCA	tricarboxylic acid
TG	triacylglycerol
VLDL	very low-density lipoproteins

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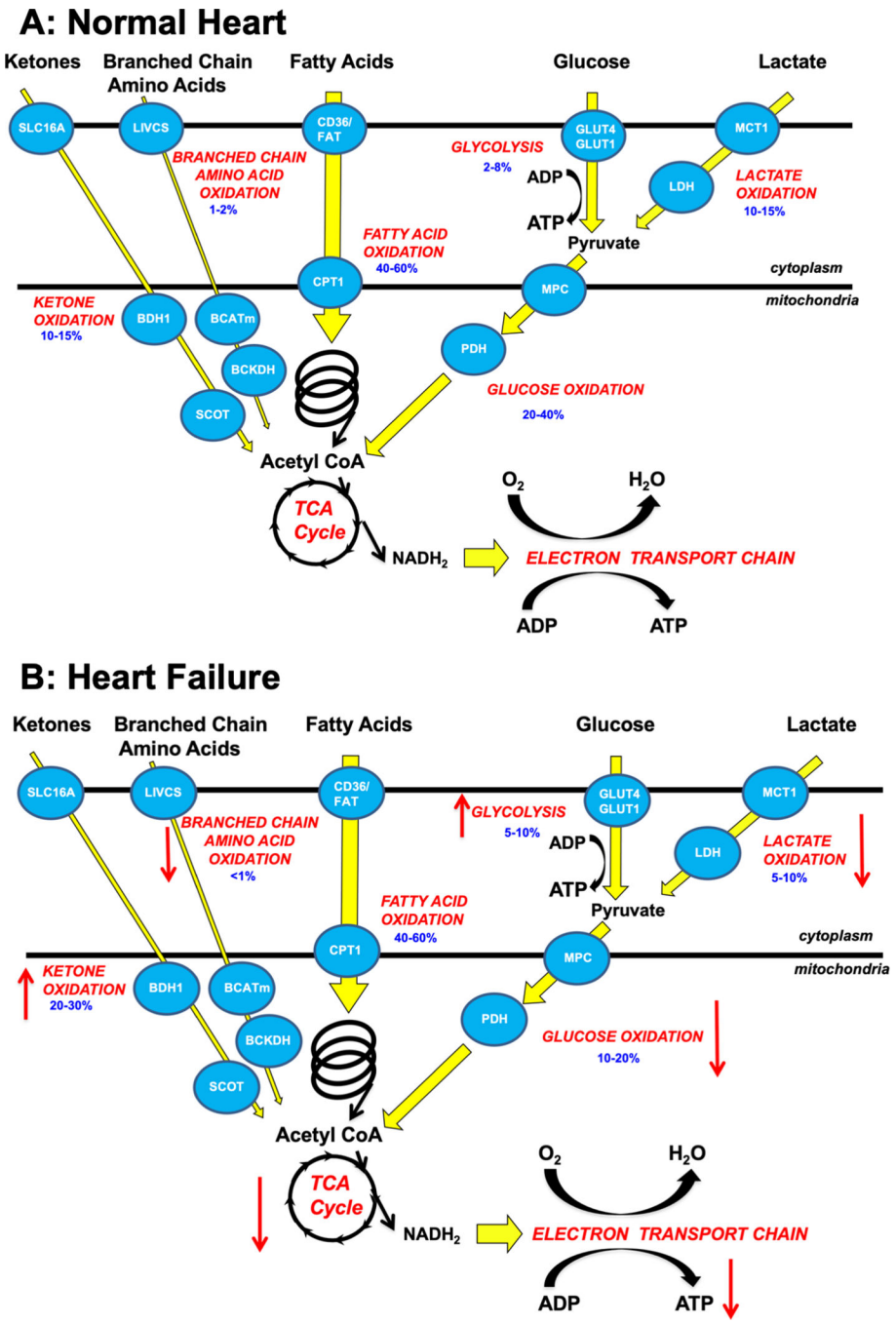

Figure 1: Overview of energy metabolism in the normal heart and failing heart

A: Glucose is transported into the cell via glucose transporter 1 or 4 (GLUT1, GLUT4), it then undergoes glycolysis to produce pyruvate. Lactate is taken up by the cardiomyocytes via monocarboxylic acid transporters (MCT) and converted to pyruvate by lactate dehydrogenase (LDH). The pyruvate from glucose and lactate is transported into the mitochondria via the mitochondrial pyruvate carrier (MPC) and is converted to acetyl CoA by pyruvate dehydrogenase (PDH). Fatty acids are transported into the cardiomyocyte, partly via CD36 and FA transport protein-1 (FATP-1), where they are esterified to fatty acyl-

CoA. The acyl group are transferred to carnitine by carnitine palmitoyl transferase (CPT-1) and transported into the mitochondria where CPT-2 converts it back to fatty acyl CoA which can then undergo β-oxidation producing acetyl CoA. Ketones (i.e., ß-hydroxybutyrate) are transported into the cell via SLC16A1 where βOHB dehydrogenase 1 (BDH1) catalyses the oxidation of βOHB to acetoacetate (AcAc). AcAc is then activated by succinyl-CoA:3 oxoacid-CoA transferase (SCOT) to acetoacetyl-CoA (AcAc-CoA) which undergoes a thiolysis reaction producing acetyl-CoA. Branched chain amino acids (BCAAs) are transported into the cell by the branched chain amino acid:cation symporter family (LIVCS). In the mitochondria, BCAAs are converted to ketoacids by branched chain aminotransferase (BCATm). Acetyl CoA and succinyl CoA are subsequently formed from branch chain acid alpha-keto acid dehydrogenase (BCKDH). The acetyl CoA generated by fatty acid β-oxidation, glucose oxidation, ketone oxidation and BCAA oxidation enter the tricarboxylic acid (TCA) cycle, generating flavin adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH) which then enters the electron transport chain, consuming oxygen (O_2) to generate adenosine triphosphate (ATP). Numbers in blue represent the contribution of the individual pathways to overall ATP production.

B: Alterations in ketone oxidation, amino acid oxidation, fatty acid oxidation, glycolysis, glucose oxidation, and lactate oxidation in the failing heart. An arrow facing up indicates an increase and down indicates a decrease. Numbers in blue represent the contribution of the individual pathways to overall ATP production.

Abbreviations: Glucose transporter 1 and 4 (GLUT1, GLUT4), mitochondrial pyruvate carrier (MPC), pyruvate dehydrogenase (PDH), monocarboxylate transporter (MCT), lactate dehydrogenase (LDH), CD36/fatty acid transporter (CD36/FAT), carnitine palmitoyl transferase (CPT-1), nicotinamide adenine dinucleotide ($NADH_2$), adenosine triphosphate (ATP), adenosine diphosphate (ADP), tricarboxylic acid (TCA), β-hydroxybutyrate (βOHβ), monocarboxylate transporter 1 (SLC16A1), β-hydroxybutyrate dehydrogenase 1 (BDH1), succinyl-CoA:3 oxoacid-CoA transferase (SCOT), branched chain amino acid cation symporter (LIVCS), mitochondrial branched chain amino-transaminase (BCATm), branched chain α-keto acid dehydrogenase (BCKDH).

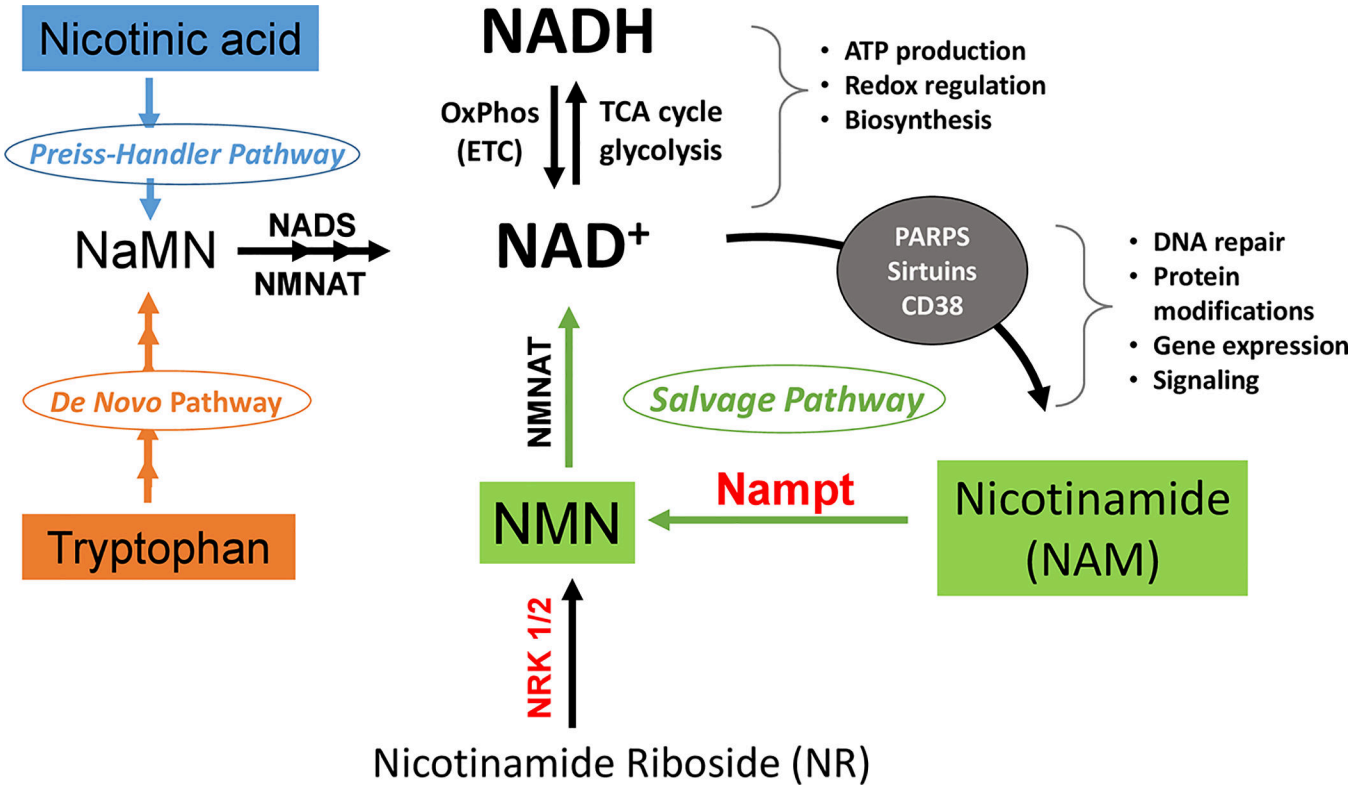

Figure 2: NAD Metabolism and its biological role in mammalian cells.

NAD carries electrons generated from substrate catabolism, e.g. TCA cycle or glycolysis, to oxidative phosphorylation for ATP production. The NAD^+/NADH ratio determines cellular redox and metabolic fluxes. NAD^+ is consumed by multiple enzymes, e.g. Sirtuins and PARPs, for protein and nucleotide modification thus regulating signal transduction. These reactions generate nicotinamide (NAM), which, through the salvage pathway, is converted into nicotinamide mononucleotide (NMN) by nicotinamide phosphoribosyl transferase (NAMPT). The NMN is converted to NAD^+ by nicotinamide mononucleotide adenyltransferase (NMNAT). Alternatively, nicotinamide riboside (NR) can be phosphorylated by nicotinamide riboside kinase (NRK) 1 or 2 to form NMN. NAD^+ can also be synthesized from nicotinic acid (NA) in the Preiss-Handler pathway or from tryptophan in the *de novo* pathway. Both pathways generate nicotinic acid mononucleotide (NaMN). NMNAT then converts NaMN to nicotinic acid adenine dinucleotide (NaAD) which is further metabolized into NAD^+ by NAD synthase (NADS).

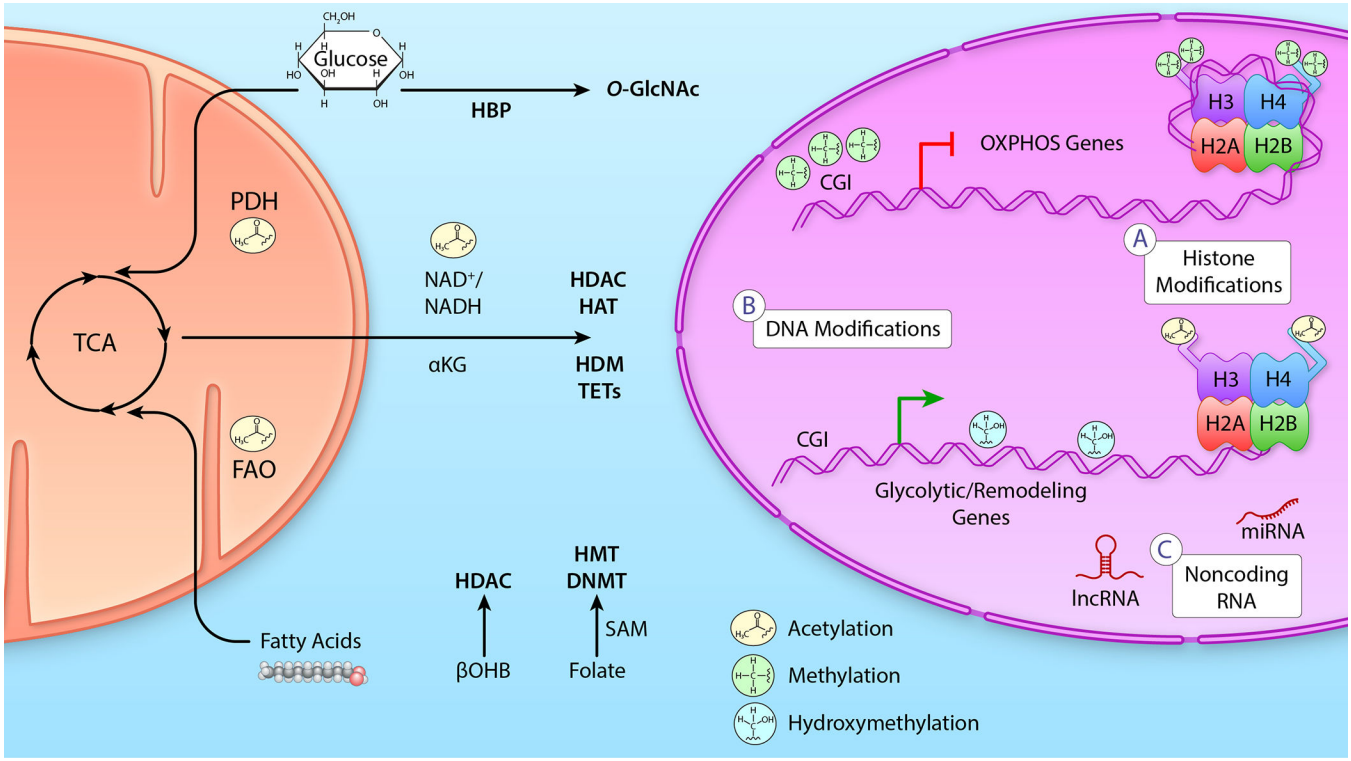

Figure 3: Metabolic signaling to epigenetic transcriptional control in the failing heart.

Left: Mitochondrial metabolic flux of primary cardiac metabolites, glucose and fatty acids, directly alter NAD+/NADH ratios as well as the Acetyl-CoA pool that signal to the nucleus to impact the epigenetic environment. Additionally, glucose that does not enter oxidative metabolism in the mitochondria can signal through the HBP. Additional metabolic intermediates discussed in the text, βOHB, can also regulate activity of epigenetic regulating enzymes as can single carbon metabolism via folate and SAM. *Middle*: Metabolites and metabolic pathways regulate the activity and/or substrate availability of epigenetic modifiers of histones (e.g., HDAC, HAT, HDM, HMT) and DNA (e.g., DNMT and TET). *Right*: A) Histone modifications include inhibitory tri-methylation as well as activating acetylation. B) DNA modifications such as DNA methylation (5mC) at CGI in promoters are associated with gene silencing while CGI demethylation and gene body DNA hydroxymethylation (5hmC) modifications are associated with gene activation. C) Although metabolites are not known to be directly regulated by metabolic intermediates, a number of metabolic genes are regulated by miR and lncRNA expression. Please see references included in the main text for additional details. (Illustration credit: Ben Smith).

Abbreviations: α-ketoglutarate (αKG), β-hydroxybutyrate (βOHB), CpG island (CGI), DNA methyltransferase (DNMT), fatty acid oxidation (FAO), hexosamine biosynthetic pathway (HBP), histones (H2A, H2B, H3, H4), histone acetyltransferase (HAT), histone deacetylase (HDAC), histone demethylase (HDM), histone methyltransferase (HMT), long noncoding RNA (lncRNA), microRNA (miR), oxidative phosphorylation (OXPHOS), pyruvate dehydrogenase (PDH) complex, S-adenosylmethionine (SAM), ten-eleven translocation (TET), and tricarboxylic acid (TCA) cycle.

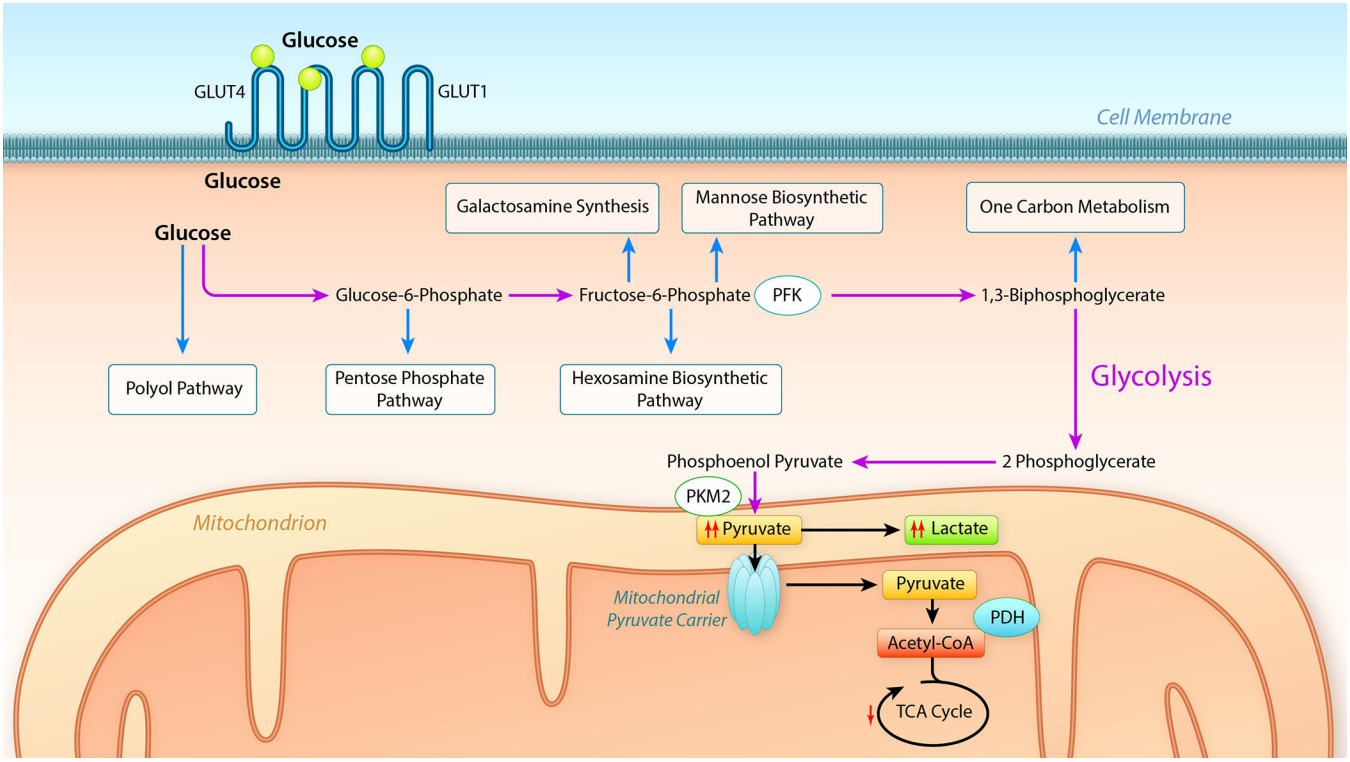

Figure 4: Pathways of non-oxidative glucose metabolism whose by-products contribute to cardiac remodeling

Schematic summary of glucose uptake via GLUT1 and GLUT4 transporters and entry of glucose into the glycolytic pathway (purple arrows) leading to the generation of pyruvate. In heart failure, impaired entry of pyruvate into mitochondria or decreased mitochondrial pyruvate metabolism leads to accumulation of glycolytic intermediates and increased flux into accessory pathways (blue arrows) such as the polyol pathway, pentose phosphate pathway, hexosamine biosynthetic pathway, mannose and galactosamine synthetic pathways and one carbon metabolism pathways, products of which have been linked to the activation of signaling pathways that may contribute to left ventricular modelling. Regulatory steps in glycolysis that have been implicated in heart failure include phosphofructokinase (PFK), pyruvate kinase (PKM1), the mitochondrial pyruvate carrier (MPC) and pyruvate dehydrogenase (PDH). (Illustration credit: Ben Smith).

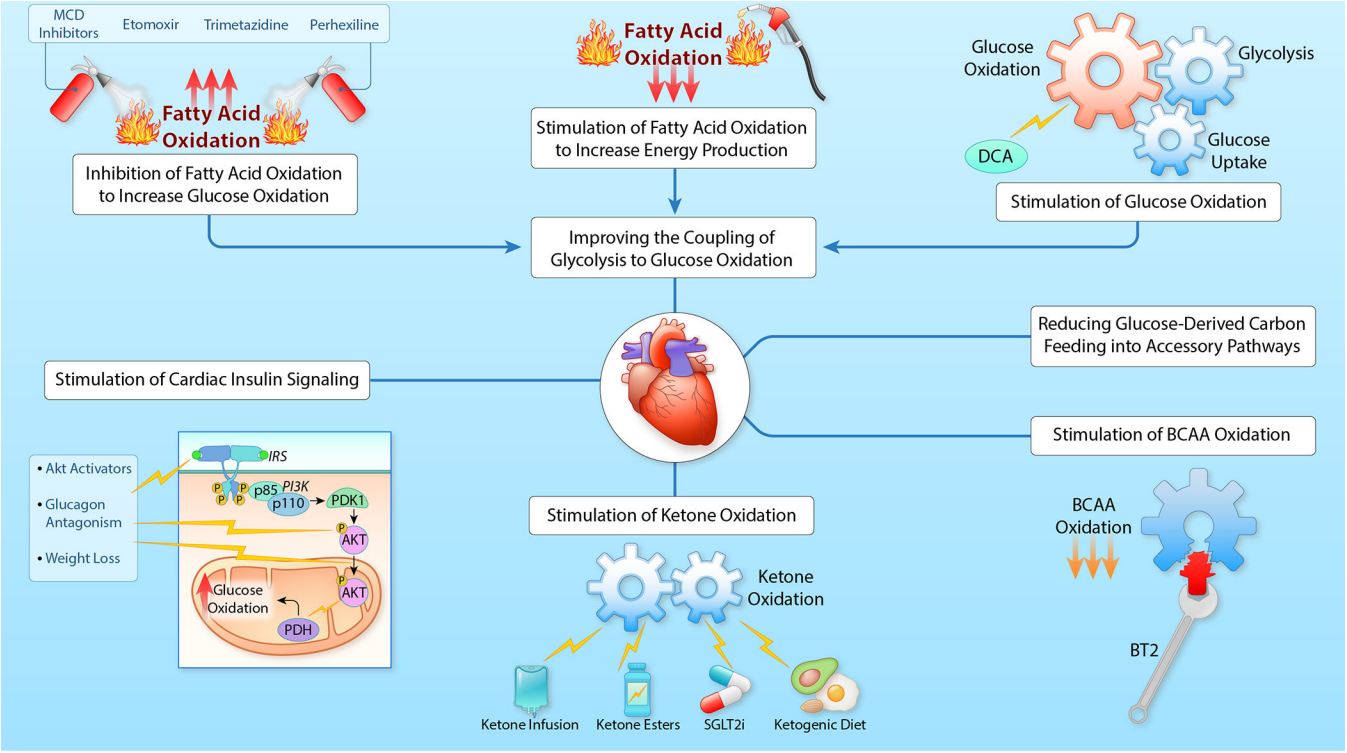

Figure 5: Targeting cardiac metabolism to protect the failing heart.

MCD, malonyl CoA decarboxylase; DCA, dichloroacetate; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3-kinase; PDK1, 3-phosphoinositide-dependent protein kinase-1; Akt, protein kinase B; PDH, pyruvate dehydrogenase; BCAA, branched chain amino acids; BT2, branched chain keto acid dehydrogenase kinase inhibitor; SGLT2i, sodium/glucose cotransporter-2 inhibitors. (Illustration credit: Ben Smith).