Circulation Research

HEART FAILURE COMPENDIUM

Cardiac Energy Metabolism in Heart Failure

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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 comorbidities such as obesity and type 2 diabetes. The failing heart faces an energy deficit, primarily because of 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 (ie, 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 NAD redox state (NAD^+ and nicotinamide adenine dinucleotide levels) and metabolite signaling that contribute to posttranslational 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.

Key Words: acetylation ■ diabetic cardiomyopathies ■ insulin resistance ■ ketones ■ mitochondria

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 to 10 seconds, resulting in contractile failure. As a result, the continuous production of ATP must occur to maintain cardiac function. The heart achieves this by metabolizing 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 patients with heart failure having significant disabilities and a high mortality rate.[5] Heart failure presents primarily as 2 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 comorbidities and mortality, have a comparable prevalence in our society.[6–8] Heart failure is a heterogenous clinical syndrome, which is caused by multiple different comorbidities, 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

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For Sources of Funding and Disclosures, see page 1505.

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Nonstandard Abbreviations and Acronyms

βOHB	β-hydroxybutyrate
ACC	acetyl CoA carboxylase
Akt	protein kinase B
AMPK	AMP-activated protein kinase
BCAA	branched chain amino acid
BCATm	mitochondrial branched chain aminotransferase
BCKA	branched chain α-keto-acids
BCKDH	branched chain α-keto acid dehydrogenase
BDH1	β-hydroxybutyrate dehydrogenase 1
BDK	BCKDH kinase
CD36	cluster of differentiation 36
CD38	cluster of differentiation 38
CK	creatine kinase
CoA	coenzyme
CPT-1	carnitine palmitoyl transferase-1
DNMT3A	DNA methyltransferase 3A
Drp1	dynamin-related protein 1
ERK	extracellular signal-regulated kinase
$FADH_2$	flavin adenine dinucleotide
FATP-1	fatty acid transport protein-1
Fis1	mitochondrial fission 1 protein
FOXM1	forkhead box protein M1
G6P	glucose 6-phosphate
GCGR	glucagon receptor
GLUT1	glucose transporter 1
GLUT4	glucose transporter 4
HBP	hexosamine biosynthetic pathway
HDAC	histone deacetylase
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
IRS	insulin receptor substrate
LDH	lactate dehydrogenase
LIVCS	branched chain amino acid\cation symporter family
LV	left ventricle
LVAD	LV assist device
LVH	LV hypertrophy
MCAD	medium chain acyl CoA dehydrogenase
MCD	malonyl CoA decarboxylase
MCT1	monocarboxylate transporter 1
ME1	malic enzyme 1
Mfn1	mitofusin 1
Mfn2	mitofusin 2
MPC	mitochondrial pyruvate carrier
mTOR	mammalian target of rapamycin
NAD	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NAMPT	nicotinamide phosphoribosyl transferase
NMNAT	nicotinic acid mononucleotide adenyltransferase
NRF-1	nuclear respiratory factor-1
NRF-2	nuclear respiratory factor-2
NRK	nicotinamide riboside kinase
PARP	poly (ADP-ribose) polymerase
PDH	pyruvate dehydrogenase
PDK4	PDH kinase 4
PFK-1	phosphofructokinase 1
PFK-2	phosphofructokinase 2
PKM	pyruvate kinase
PPARγ	peroxisome proliferator activator receptor γ
PPC2m	protein phosphatase C2m
ROS	reactive oxygen species
SCOT	succinyl-CoA:3 oxoacid-CoA transferase
SGLT2	sodium/glucose co-transporter 2
Sirt3	sirtuin 3
SLC16A1	monocarboxylate ketone transporter
T2D	type 2 diabetes
TAC	transverse aortic constriction
TCA	tricarboxylic acid
VLDL	very low-density lipoprotein

(see Neubauer[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 (ie, 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 2 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% to -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, 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 hydrolyzed from triacylglycerols (TGs) contained in chylomicrons and VLDLs (very low-density lipoproteins). Following uptake into the cardiomyocyte, fatty acids are esterified forming fatty acyl-CoA (coenzymeA). The fatty acid moiety is then transferred to carnitine by CPT-1 (carnitine palmitoyl transferase 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, which enters the tricarboxylic acid (TCA) cycle, and $FADH_2$ (flavin adenine dinucleotide) and nicotinamide adenine dinucleotide (NADH), which enter the electron transport chain to generate ATP. The TCA cycle also generates NADH and $FADH_2$ that feed into the electron transport chain, 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 ACC [acetyl CoA carboxylase][16] and degraded by MCD [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 (glucose transporter 1) and GLUT4 (glucose transporter 4) 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 G6P (glucose 6-phosphate). G6P can then be utilized 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 MPC (mitochondrial pyruvate carrier). The majority of pyruvate is converted to acetyl-CoA by PDH (pyruvate dehydrogenase) 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 PDK (PDH kinase), 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 MCT4 (monocarboxylic anion transporter) and then converted to pyruvate via LDH (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 oxidized in the heart. Its uptake is facilitated by

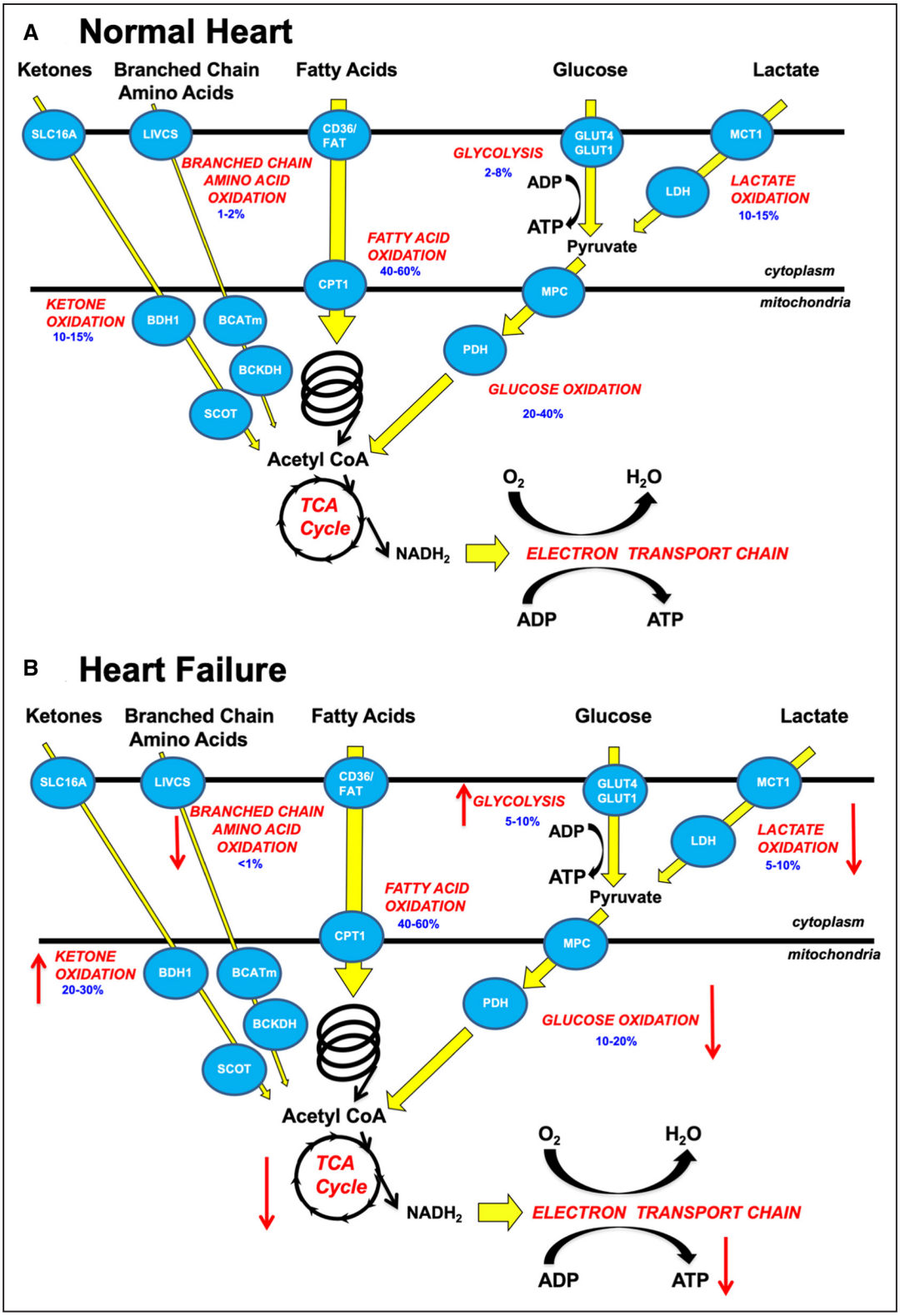

Figure 1. Overview of energy metabolism in the normal heart and failing heart.
A, Glucose is transported into the cell via GLUT1 (glucose transporter 1) or GLUT4 (glucose transporter 4), it then undergoes glycolysis to produce pyruvate. Lactate is taken up by the cardiomyocytes via MCT (monocarboxylic acid transporter) and converted to pyruvate by LDH (lactate dehydrogenase). The pyruvate from glucose and lactate is transported into the mitochondria via the mitochondrial pyruvate carrier (MPC) and is converted to acetyl CoA by PDH (pyruvate dehydrogenase). Fatty acids are transported into the cardiomyocyte, partly via CD36 and FATP-1 (FA transport protein-1), where they are esterified to fatty acyl-CoA. The acyl group is transferred to carnitine by CPT-1 (carnitine palmitoyl transferase) and transported into the mitochondria where CPT-2 converts it back to fatty acyl CoA, (*Continued*)

SLC16A1 after which it is transported into the mitochondria for oxidation (Figure 1). BDH1 (β-hydroxybutyrate dehydrogenase 1) catalyses the oxidation of βOHB to acetoacetate. Acetoacetate is then activated by the CoA transferase SCOT (succinyl-CoA:3 oxoacid-CoA transferase) to acetoacetyl-CoA (Acetoacetate-CoA). Acetoacetate-CoA then undergoes a thiolysis reaction from which acetyl-CoA is produced, which 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 is 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 BCATm (mitochondrial branched chain aminotransaminase).[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 BCKDH (branched chain α-keto acid dehydrogenase). BCKDH activity is regulated by phosphorylation of BCKDH by a BDK (BCKDH kinase), which inhibits activity, and dephosphorylation by PPC2m (protein phosphatase C2m), 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 (mammalian target of rapamycin) 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), which 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 by lactate, ketone bodies, glucose, and then BCAAs.

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 because of 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 because of 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 posttranslational protein modification (see study by Zhou and Tian,[32] Knowlton et al,[34] Song et al,[35] Karwi et al,[36] Smith and Eisner,[37] Tong et al,[38] Kenny and Abel,[39] Tian et al,[40] and Fukushima and Lopaschuk[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]

Figure 1 Continued. which can then undergo β-oxidation producing acetyl CoA. Ketones (ie, β-hydroxybutyrate) are transported into the cell via SLC16A1 (monocarboxylate transporter 1) where BDH1 (β-hydroxybutyrate dehydrogenase 1) catalyses the oxidation of β-hydroxybutyrate (βOHB) to acetoacetate (AcAc). AcAc is then activated by SCOT (succinyl-CoA:3 oxoacid-CoA transferase) 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 mitochondrial branched chain aminotransferase (BCATm). Acetyl CoA and succinyl CoA are subsequently formed from BCKDH (branched chain alpha-keto acid dehydrogenase). 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 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. BDH1 indicates β-hydroxybutyrate dehydrogenase; FAT, fatty acid transporter; and $NADH_2$, nicotinamide adenine dinucleotide.

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 mitochondria 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 mitochondrial dynamin like GTPase (OPA1) and Mfn1 (mitofusin 1) and Mfn2 (mitofusin 2) and the fission proteins Drp1 (dynamin-related protein 1) and Fis1 (mitochondrial fission 1 protein). 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 having been described.[54] Excessive or unopposed fission can lead to mitochondrial fragmentation, mitophagy, decreased antioxidative 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 (peroxisome proliferator activator receptor γ) coactivator-1α (PGC1-α). PGC1α activates the transcriptional expression of NRF-1 (nuclear respiratory factor-1) and NFR2 (nuclear respiratory factor-2), 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.[57] 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 upregulation of fatty acid oxidation.[39,58] Posttranslational 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.[59] Increased myocardial glucose uptake in heart failure has been associated with increased expression of *GLUT1* glucose transporters particularly in animal models in conjunction with increased activity of PFK-1 (phosphofructokinase 1, the first enzyme involved in glycolysis), and glycolytic flux.[60,61] 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 2 ATP molecules per glucose molecule, compared with 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 remodeling.[11,62] Furthermore, increased glycolysis is uncoupled from the oxidation of pyruvate and lactate leading to accumulation of H^+ in the cytoplasm. Increased Na^+/H^+ exchange activation coupled with increase Na^+/Ca^{2+} exchange may contribute to cytosolic Ca^{2+} accumulation.[63]

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).[64] 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.[65–67] However, as the severity of heart failure progresses (EF<50%), decreased fatty acid oxidation has been reported in humans with idiopathic dilated cardiomyopathy.[68–70] 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.[66,67,71–73] 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 idiopathic dilated cardiomyopathy, or an actual increase in fatty acid uptake in patients with congestive heart failure.[74–76] These divergent patterns of fatty acid utilization are likely attributable to the differences in disease severity, for example, ejection fractions ranging from 16% to 48% and the presence of comorbidities 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 (medium chain acyl CoA dehydrogenase), CD36 (cluster of differentiation 36) and FATP1 (fatty acid transport protein-1).[66,67,71–73,77,78] 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.[79] 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.[80] Myocardial fatty acid oxidation increases in response to conditions such as type 2 diabetes (T2D), obesity, and insulin resistance. Obese women with left ventricular (LV) hypertrophy (LVH) 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.[58] In addition, type 2 diabetic men with T2D cardiomyopathy also exhibit increased fatty acid uptake and oxidation.[81] These finding are consistent with animal models of obesity and T2D, such as diet-induced obese, db/db, and ob/ob mice. In these animals, hearts predominantly rely on fatty acid oxidation, while exhibiting LVH,[82] diastolic dysfunction,[83,84] and in severe cases, systolic dysfunction.[85–87] In a murine model of HFpEF, involving a high fat diet, aging, and deoxycorticosterone treatment, fatty acid oxidation was also increased.[88] 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.[89,90] Furthermore, transgenic models in which fatty acid oxidation is inhibited exhibit cardiac hypertrophy and accelerated impairment in ejection fraction in response to pressure overload.[91–93]

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 idiopathic dilated cardiomyopathy (88%–98%),[68–70] in canine models of cardiac pacing (≈150%),[72] and in Dahl salt sensitive rats fed a high salt diet, an increase in glucose uptake is seen.[67] *GLUT1* expression is also increased, suggesting an increased capacity for glucose uptake that may have a predominant glycolytic fate.[66,71] In the majority of these models, the oxidation of pyruvate derived from glucose (ie, glucose oxidation) is decreased in mouse models of heart failure,[94–96] in pacing-induced heart failure in pigs, and in humans with end-stage heart failure.[97] In support of this decrease in glucose oxidation, myocardial biopsies from patients with heart failure were found to have reduced expression of MCT1 (monocarboxylate transporter 1), PDH, MPCs, and of pyruvate/alanine aminotransferases, suggesting reduced transport and metabolism of pyruvate.[98,99] 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 ME1 (malic enzyme 1), which is induced in response to pressure overload and in failing human hearts.[100–102] Increased pyruvate carboxylation reduces the efficiency of glucose oxidation and may contribute to oxidative stress by consuming nicotinamide adenine dinucleotide phosphate.[102] Indeed, lowering ME1 in failing rat hearts increased pyruvate flux into the TCA and restored redox homeostasis by normalizing reduced glutathione.[102]

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 LVH and diastolic dysfunction[103,104] also have decreased glucose oxidation rates.[105,106] Decreases in myocardial glucose oxidation are very prominent in obese and diabetic mice that develop LVH and diastolic dysfunction.[107–109] This decrease in glucose oxidation is also seen in angiotensin II-induced heart failure in mice, which is accompanied by increased PDK4 (PDH kinase 4) expression and reduced PDH activity.[105] This decline in glucose oxidation in angiotensin II-treated mice can be blunted in response to PDK4 deletion.[106] Intriguingly, angiotensin II treatment has also been

shown to ameliorate diastolic dysfunction in diabetic *db/db* mice.[110] In mice that develop LVH due to aortic constriction, a decrease in myocardial glucose oxidation precedes the development of diastolic dysfunction,[94] which further supports a potential role of reduction in glucose oxidation in the development of heart failure.[106] Notably, in some studies of mouse models of heart failure with reduced rates of fatty acid oxidation, the relative contribution of glucose oxidation to TCA flux might be increased, although net TCA flux is reduced.[79] Transgenic mice with mutations that prevent the uptake of glucose or oxidation of pyruvate also develop LVH, diastolic dysfunction (GLUT4 deletion),[111] and systolic dysfunction (PDH deletion).[112] Upstream of PDH activity, the 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.[113] 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.[114] 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.[115,116] Interestingly, in patients with heart failure, the fasting-induced increase in circulating ketones is exacerbated.[117] A number of recent studies have shown that myocardial ketone body oxidation is increased in heart failure.[118–120] One study quantifying substrate utilization in arterio-venous blood samples reported that ketone body oxidation was increased by ≈100% in patients with HFrEF.[75] In experimental animals, TAC protocols that induce LVH in mice in the absence of systolic dysfunction are associated with increased expression of enzymes involved in ketone oxidation, in concert with increased βOHB oxidation.[118] 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.[118] In addition, mice with cardiomyocyte-specific knockout of SCOT (preventing them from terminally oxidizing βOHB) show increased fatty acid oxidation.[121] Interestingly, these animals are also more susceptible to TAC-induced increases in LV mass.[121] 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).[88] 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, 2 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.[115,116] Serum metabolite analysis detected higher levels of acetoacetate 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 with that in HFpEF.[122] 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.

BCAA Oxidation in Heart Failure

Increases in plasma BCAA levels are seen in patients with heart failure and have been suggested to be an early predictor of the future development of cardiovascular disease.[123–127] These increases in BCAA levels may be due in part to impaired BCAA oxidation in heart failure.[128–130] The accumulation of BCAAs in heart failure may activate cardiac mTOR signaling, thereby promoting cardiac hypertrophy.[131,132] This is also supported by studies

showing that stimulation of BCAA oxidation or inhibition of mTOR (with rapamycin) can improve heart function,[130] while BCAA supplementation further increases mTOR signaling and worsens cardiac dysfunction.[133]

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.[130,134,135] This stimulation of BCAA oxidation is accompanied by enhanced cardiac function and glucose oxidation in the failing heart.[130,134,135] 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.[130] This same study also reported defects in BCAA metabolism in human heart failure tissue and in mice with TAC-induced heart failure.[130] 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.[130]

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.[136] 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.[36,95,105,108,110,137–140] Moreover, diabetes also increases the risk of myocardial infarction by ≈2- to 4-fold,[141] and the coexistence of ischemic cardiomyopathy with diabetes accelerates the progression of heart failure.[142] Likewise, heart failure itself also aggravates the severity of whole-body insulin resistance.[36,143–146] 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 (protein kinase B) may persist.[136,140,147–157] Altered myocardial insulin signaling in heart failure may not only negatively impact cardiac energy metabolism but may also exacerbate the extent of LV remodeling.[136,140,147–155] In addition, cardiac insulin resistance seen in obesity or heart failure is also exacerbated if both coexist.[108,137–139,158–161] 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.[161] 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.[162–166] Insulin also directly inhibits cardiac fatty acid oxidation via abrogating the inhibitory effect of 5′ AMPK (AMP-activated protein kinase) on ACC and increasing malonyl CoA, a potent inhibitor of mitochondrial fatty acid uptake.[167] In addition, insulin-stimulated glucose oxidation can also inhibit fatty acid oxidation based on the Randle Cycle phenomena.[168] While there is still debate about what happens to basal rates of glucose oxidation during the evolution from compensated LVH 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.[36,94,95,105,106,161] 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.[169] Cardiac insulin resistance negatively impacts cardiac function and energy metabolism.[36,94,95,105,106,161] In addition, the inhibitory effect of insulin on cardiac fatty acid oxidation becomes less dramatic in the failing heart.[36,161] 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.[36,94,95,105,106,161] 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 (ie, 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 reestablishing ionic homeostasis instead of the contractile machinery.[2]

It is noteworthy that MPC expression is downregulated in patients with chronic heart failure.[113] 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.[99,113,114,170,171] Overexpression of MPC enhances coupling between glycolysis and glucose oxidation and reduces cardiac dysfunction and adverse remodeling via increasing glucose oxidation.[113] 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 cardiac glucose oxidation,[1–3] in both experimental[36,67,95,138,160,161,172] and human heart failure.[173]

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.[36,156,157,161,169] Recent studies have provided strong evidence for divergent effects of IRS, namely IRS1 and IRS2, in the failing heart.[156,157,174,175] Hyperactivation of IRS-1/Akt1 in the failing heart and genetic deletion of IRS-1 is protective in a mouse model of heart failure,[157] 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.[157] 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 upregulated in the failing heart,[59,176,177] 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, because of decreased direct stimulation of mitochondrial glucose oxidation by insulin.[120,178] However, how insulin signaling is transduced to the mitochondria to stimulate PDH and glucose oxidation is not known.[163–166]

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 mitochondrial dynamin like GTPase expression.[179] Another component of the insulin signaling pathway, namely Akt, can translocate to the mitochondria following insulin stimulation.[163–166] Interestingly, mitochondrial translocation of Akt has also been implicated in modulating mitochondrial oxidative phosphorylation.[163–166] 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.[178,180] Of importance is that insulin stimulation in these hearts did not cause significant changes in glycolysis, likely because of 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.[178] Furthermore, we also demonstrated that inhibiting mitochondrial Akt completely abolishes the direct insulin stimulation of glucose oxidation.[178] 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.[181–185] Recent studies demonstrated benefits of supplying NAD precursors in preclinical models and in patients with heart failure.[182,183,186] These findings have stimulated the investigation of NAD metabolism in heart failure and raise hope for a new therapeutic approach.[187] 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, for example, glycolysis and TCA cycle, and in oxidative phosphorylation.[188] NAD^+ is also a required substrate by PARPs (poly [ADP-ribose] polymerases), sirtuins, and CD38 (cluster of differentiation 38), thus playing an important

role in post-translational modification, DNA damage repair, gene transcription and other signaling mechanisms.[184,189,190] Biosynthesis of NAD in mammalian cells occurs through several routes.[191] 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 NMNAT (nicotinamide mononucleotide adenyltransferase) reaction (Figure 2). Important for the maintenance of the NAD pool, nicotinamide, the product of NAD^+ consumption by sirtuins, PARPs or CD38, is converted to nicotinamide mononucleotide by NAMPT (nicotinamide phosphoribosyl transferase) 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 (nicotinamide riboside kinase 2), an enzyme converting nicotinamide riboside to nicotinamide mononucleotide, is upregulated suggesting a metabolic shift in the salvage pathway (Figure 2).[183,192,193] Furthermore, reduced NADH oxidation, because of 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.[182,194] Supplementation of NAD precursors nicotinamide mononucleotide or nicotinamide riboside 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.[182,183,195,196] The effect of overexpressing NAMPT, however, seems 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.[182,193,197]

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

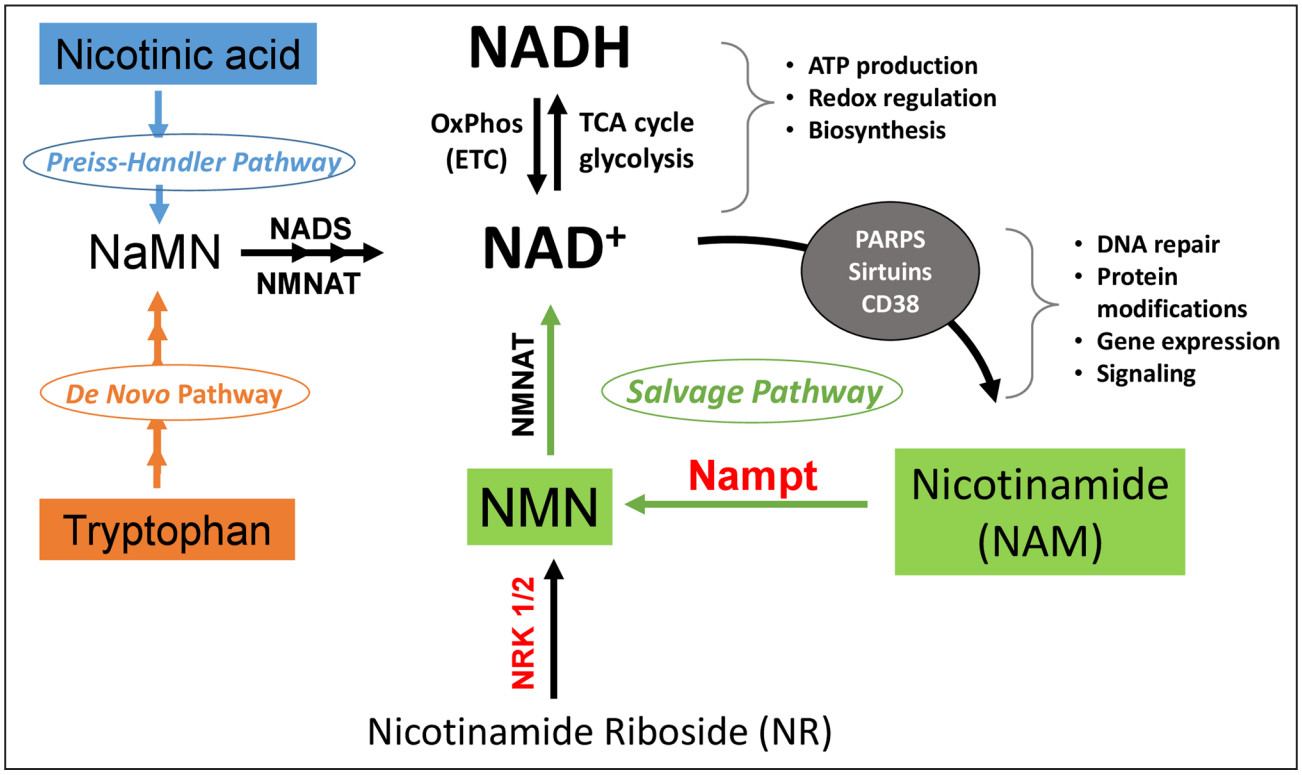

Figure 2. Nicotinamide adenine dinucleotide (NAD) metabolism and its biological role in mammalian cells.
NAD carries electrons generated from substrate catabolism, for example, tricarboxylic acid (TCA) cycle or glycolysis, to oxidative phosphorylation for ATP production. The NAD^+/NADH ratio determines cellular redox and metabolic fluxes. NAD^+ is consumed by multiple enzymes, for example, sirtuins and PARPs (poly (ADP-ribose) polymerases), 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 NAMPT (nicotinamide phosphoribosyl transferase). The NMN is converted to NAD^+ by NMNAT (nicotinamide mononucleotide adenyltransferase). Alternatively, nicotinamide riboside (NR) can be phosphorylated by NRK (nicotinamide riboside kinase) 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 NADS (NAD synthase).

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.[181,182] Several studies linked activation of Sirt3 (sirtuin 3), a mitochondrion localized sirtuin, to the cardioprotective effects of increasing NAD levels.[182,195,196] 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,[198] 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.[182,183] A recent study suggests that hyperacetylation of the muscle form of creatine kinase accounts for the long-observed downregulation of CK (creatine kinase) activity in heart failure.[199] The study also showed that acetylation of muscle form of creatine kinase, cytosolic protein, was NAD^+-dependent and mediated by Sirt2. Whether increasing NAD^+-dependent deacetylation of muscle form of creatine kinase 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 resulting in reduced inflammatory response in patients with heart failure.[186] Thus, both cardiac and systemic responses could also contribute to the NAD-dependent salutary effects in heart failure.

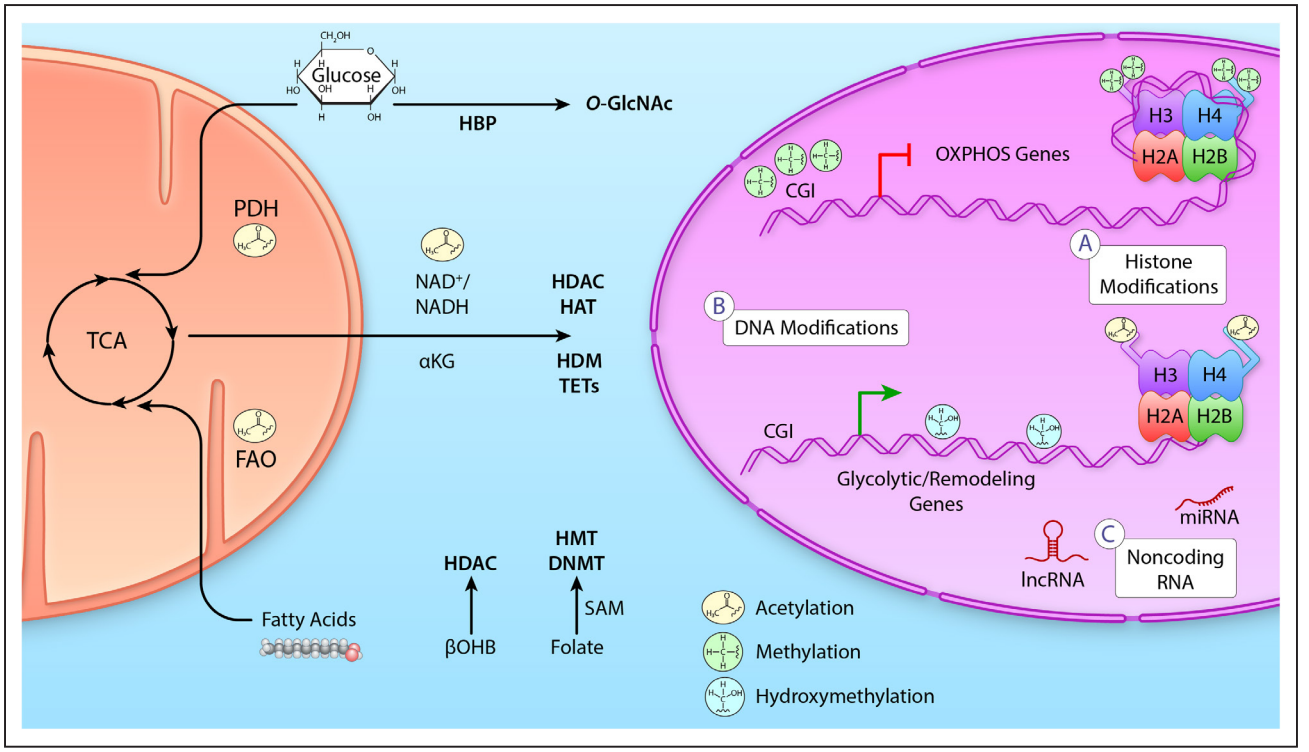

Figure 3. Metabolic signaling to epigenetic transcriptional control in the failing heart.
Left: mitochondrial metabolic flux of primary cardiac metabolites, glucose and fatty acids, directly alter NAD^+/nicotinamide adenine dinucleotide (NADH) ratios as well as the acetyl-CoA pool that signal to the nucleus to impact the epigenetic environment. Additionally, glucose that does not enter oxidative metabolism in the mitochondria can signal through the hexosamine biosynthetic pathway (HBP). Additional metabolic intermediates discussed in the text, β-hydroxybutyrate (βOHB), can also regulate activity of epigenetic regulating enzymes as can single carbon metabolism via folate and S-adenosylmethionine (SAM). Middle: metabolites and metabolic pathways regulate the activity and/or substrate availability of epigenetic modifiers of histones (eg, HDAC [histone deacetylase], HAT [histone acetyltransferase], HDM [histone demethylase], HMT [histone methyltransferase]) and DNA (eg, DNMT [DNA methyltransferase] and ten-eleven translocation [TET]). Right: **A**, Histone modifications include inhibitory tri-methylation as well as activating acetylation. **B**, DNA modifications such as DNA methylation (5mC) in promoters are associated with gene silencing while CGI demethylation and gene body DNA hydroxymethylation (5hmC) CpG island (CGI) modifications are associated with gene activation. **C**, Although non-coding RNA's 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). αKG indicates α-ketoglutarate; FAO, fatty acid oxidation; HBP, hexosamine biosynthetic pathway; lncRNA, long noncoding RNA; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; SAM, S-adenosylmethionine; TCA, tricarboxylic acid; and TET, ten-eleven translocation. (Illustration credit: Ben Smith).

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 fetal gene program,[200] 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,[201] 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.[202] Epigenetics as a field encompasses long-lasting changes in gene expression without changing the underlying genetic code. Mechanisms of epigenetic regulation include posttranslational regulation of histone proteins, DNA modifications, and posttranscriptional regulation via noncoding RNAs. What is particularly enticing is the ability of epigenetic regulation to synthesize changes in intermediary metabolism into changes in gene expression.[203]

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.[204–206] Some of the sirtuins may work through epigenetic regulation, while others may directly regulate mitochondrial enzyme function.[205] Additionally, a number of HDAC (histone deacetylase) inhibitors have been developed as therapeutics for various cancers and have been suggested as potential candidates for treatment of heart failure.[207] In fact, very recent evidence supports that HDAC inhibition improves cardiopulmonary function in a feline model of HFpEF.[208] 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,[209] while others clearly are mediated by changes in gene expression.[210,211] However, it is clear that additional studies distinguishing direct epigenetic effects of these inhibitors versus indirect changes in enzymatic activity of nonhistone 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 posttranslational regulation (Figure 3). These mechanisms include ketone body regulation of histone deacetylases,[212] TCA metabolic intermediates such as citrate signaling to histone acetyltransferases,[213] α-ketoglutarate to histone methyltransferases,[214] as well as auxiliary glucose signaling pathways like the hexosamine biosynthesis pathway via direct O-GlcNAcylation of histones[215] or indirect O-GlcNAcylation of HDAC4.[216] 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 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,[217] and regulation of heart failure genes in a mouse model of TAC.[218] Inhibition of DNA methylation may attenuate cardiac hypertrophy–associated gene expression changes in norepinephrine-treated rats.[219] 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 DNMT3A (DNA methyltransferase 3A).[220] 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 (forkhead box protein M1) to upregulate cellular remodeling genes.[221] Comparatively much less is known about the role of 5hmC in the regulation of cardiac gene expression with a number of articles emerging the last few years.[222–225] However, some evidence for a disparate relationship between DNA methylation and changes in cardiac gene expression in the context of diabetes has recently emerged.[226] Therefore, additional studies surrounding the contribution, regulation, and reversal of these pathways remains warranted.

The final area of epigenetic regulation is that of noncoding RNAs (Figure 3C). This, like histone modifications, includes a large number of different pathways encompassing microRNA to long noncoding RNA. However, given the relative ease of measuring noncoding RNAs in the circulation although 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,[227–229] 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 nonfailing 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.[60,77,113,170] In all of these studies, expression levels of the MPC 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.[99,171] 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 heart failure but rather may contribute to adverse LV remodeling by nonoxidative metabolism of glycolytic metabolites into pathways such as the polyol pathway, the hexosamine biosynthetic pathway, the pentose phosphate pathway, and one carbon cycle pathways (Figure 4).[99,114,170,171] Unloading of failing hearts following LV assist device implantation was associated with reduced flux through the hexosamine biosynthetic pathway and polyol pathway but increased pentose phosphate pathway flux leading to generation of reduced nicotinamide adenine dinucleotide phosphate that improves redox homeostasis

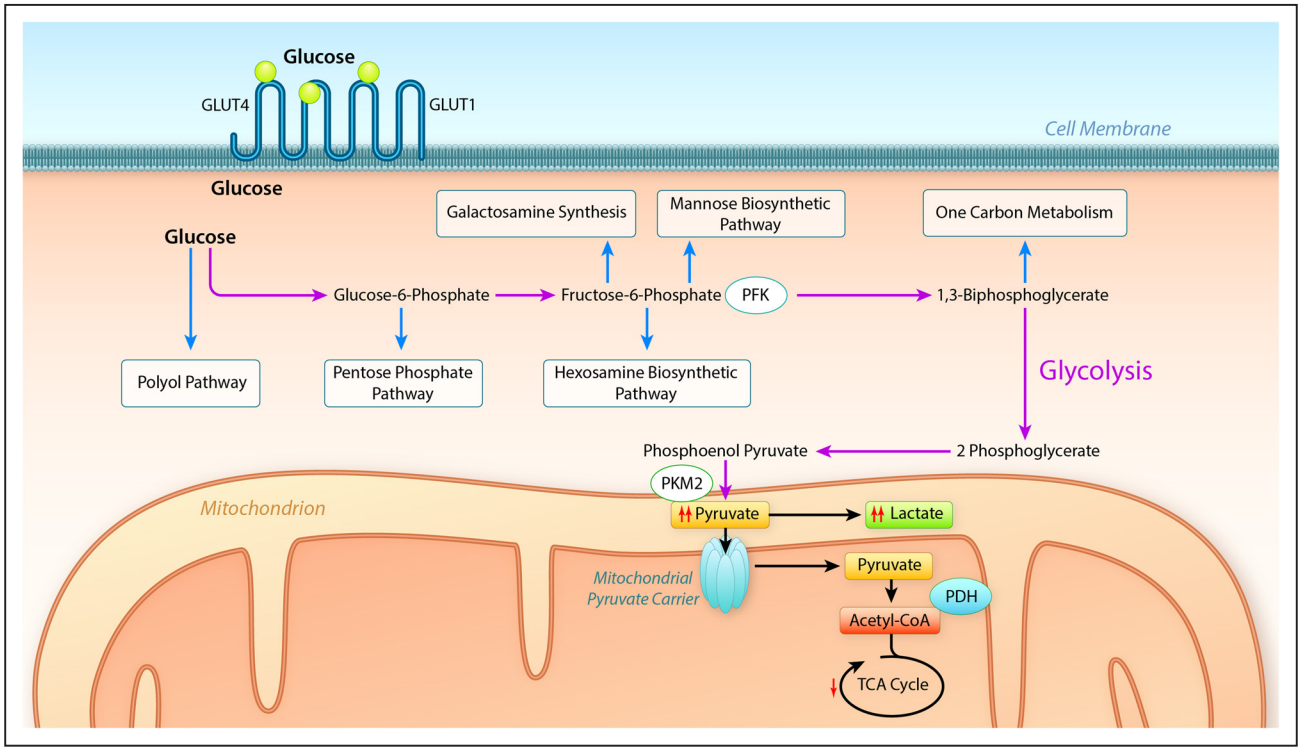

Figure 4. Pathways of nonoxidative glucose metabolism whose by-products contribute to cardiac remodeling.
Schematic summary of glucose uptake via GLUT1 (glucose transporter 1) and GLUT4 (glucose transporter 4) transporters and entry of glucose into the glycolytic pathway (purple arrows) leading to the 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 modeling. Regulatory steps in glycolysis that have been implicated in heart failure include PFK (phosphofructokinase), PKM1 (pyruvate kinase), the MPC (mitochondrial pyruvate carrier), and PDH (pyruvate dehydrogenase; Illustration credit: Ben Smith). PFK indicates phosphofructokinase; and PKM2, pyruvate kinase 2.

and ribitol, which would mediate changes in alpha-dystroglycan, which would lead to improved extracellular matrix homeostasis.[170] 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.[230,231]

Additional mechanistic insights have been obtained from animal models and studies of cultured myocytes in which MPC expression or function are altered.[99,113,114,171] These studies all reveal that inhibiting mitochondrial pyruvate utilization by genetically deleting expression of MPC subunits (Mpc1 or Mpc2) or by pharmacological inhibitors is sufficient to induce pathological cardiac hypertrophy and heart failure.[99,113,114,171] Metabolomics analysis reveals increased flux into nonoxidative pathways such as the hexosamine biosynthetic pathway, glycogen synthesis, the pentose phosphate pathway, and amino acid biosynthetic pathways (Figure 4). 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.[99,113] In this regard, lactate itself was also shown to exhibit a potent antihypertrophic effect after TAC via a mechanism that involves N-myc downstream-regulated gene 3 and ERK (extracellular signal-regulated kinase).[21]

Treatment of mice with myocardial Mpc deficiency with a ketogenic or high-fat diet completely reversed the pathological LV remodeling and heart failure.[114,171] 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 nonoxidative metabolic pathways such as the hexosamine biosynthetic pathway and glycogen.[114] 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.[114] Intriguingly, pretreating these animals with a ketogenic diet before 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 nonoxidative glucose metabolism, on ventricular remodeling (Figure 4)

Accumulation of pyruvate and amino acid–derived acyl carnitines are noted in hearts of spontaneously

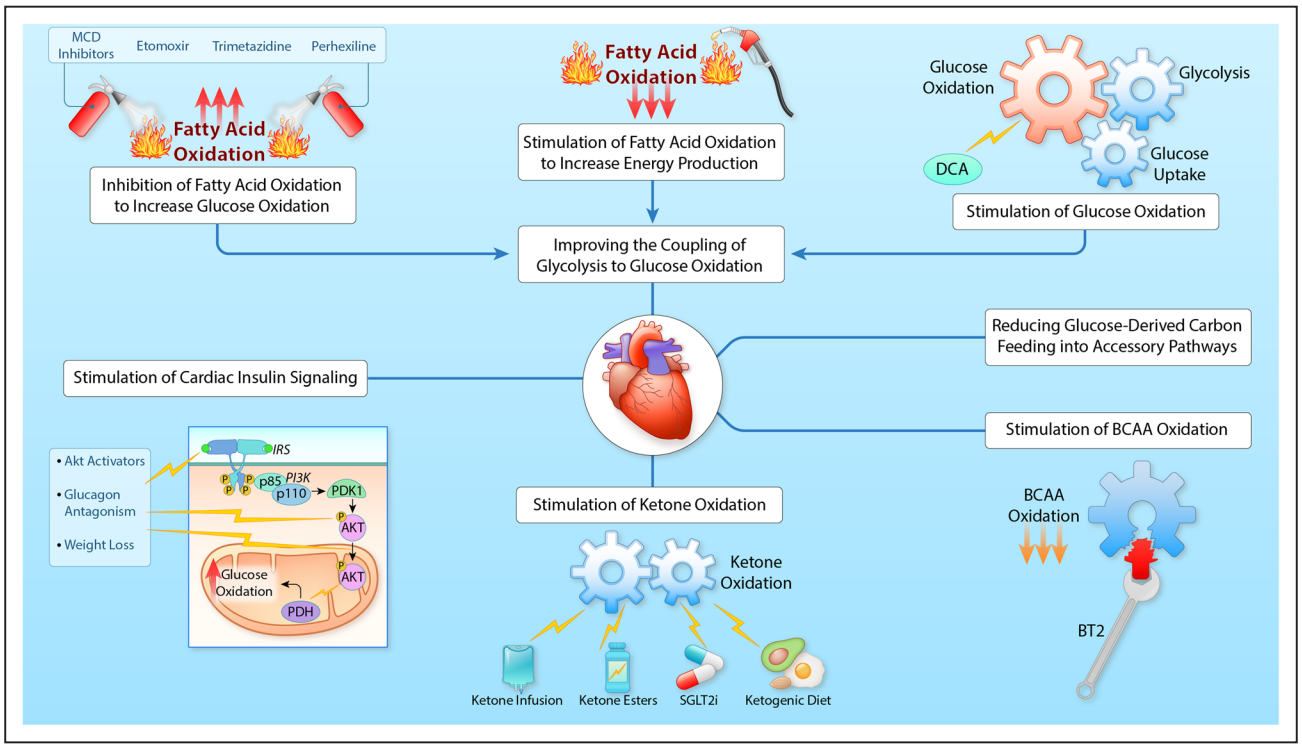

Figure 5. Targeting cardiac metabolism to protect the failing heart.
Akt indicates protein kinase B; BCAA, branched chain amino acid; BT2, branched chain keto acid dehydrogenase kinase inhibitor; DCA, dichloroacetate; IRs, insulin receptor substrate; MCD, malonyl CoA decarboxylase; PDH, pyruvate dehydrogenase; PDK1, 3-phosphoinositide-dependent protein kinase-1; PI3K, phosphatidylinositol 3-kinase; and SGLT2i, sodium/glucose cotransporter-2 inhibitor. (Illustration credit: Ben Smith).

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.[232,233] Taken together, these findings reveal a strong relationship between nonoxidative metabolism of glucose and glycolytic intermediates and the development of pathological LV remodeling.

Observations in other animal models support a role for nonoxidative 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.[234] Interestingly, MPC deletion which reduces pyruvate import into mitochondria also causes hypertrophy. Although, glucose-derived carbon could enter the mitochondria via alternative metabolic pathways, such as alanine, in the absence of MPC,[114] 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.[235] G6P has also been shown to be a potent activator of mTOR signaling.[236] Accumulation of G6P has been noted in animal models and humans with heart failure, and levels fall when hearts are unloaded.[237] Other regulators of glycolysis have been shown to play regulatory roles in hypertrophic adaptations in the heart. Glycolytic regulation at the level of PFK2 (phosphofructokinase 2) 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.[238] Heart failure in animals and humans is associated with increased expression of the fetal isoform of PKM2 (pyruvate kinase), which in contrast to the adult isoform PKM1 is less efficient in converting phosphoenolpyruvate to pyruvate+ADP.[239] The consequence of increased PKM2 expression would be accumulation of glycolytic intermediates, which would increase flux into nonoxidative pathways of glucose metabolism (Figure 4).

Mice with cardiomyocyte knock out of the GLUT4 glucose transporter develop a compensatory increase in GLUT1 and a 2-fold increase in basal myocardial glucose uptake.[111] These animals develop pathological LVH that is associated with evidence of increased nonoxidative glucose metabolism such as glycogen accumulation.[240] 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.[241] 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.[242] Moreover, in a transgenic model of inducible GLUT4 expression in which diabetes could be superimposed, one of the most significantly repressed pathways are those encoding ketone catabolism.[242,243] 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.[243] 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.[240,244] 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.[245,246] Also, reducing glucose availability in hearts of mice with BCAA accumulation arising from impaired BCAA catabolism leads to impaired recovery from I/R injury.[247] Inducible GLUT1 expression at the time of TAC preserves mitochondrial function and attenuates early remodeling but does not ultimately prevent heart failure.[248] 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.[249] It is important to note though that the ability to increase fatty acid oxidation during postischemic reperfusion is critically important for myocardial recovery postischemia even when glucose supply is adequate.[250–253]

LIPOTOXICITY IN HEART FAILURE: ROLE OF FATTY ACID OXIDATION

Lipotoxicity describes the consequences of accumulation of lipid moieties in the heart, which 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.[89,90] Lipotoxicity represents an important mechanism that augments heart failure risk in diabetes, as extensively reviewed.[254,255] 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.[256] Lipid accumulation has been long described in end-stage failing hearts and is exacerbated when heart failure is superimposed on diabetes.[257,258] The mechanisms responsible for lipotoxicity, particularly in the context of diabetes have been extensively reviewed.[254–256] Mechanisms linking lipotoxicity and heart failure include oxidative stress,[53,259,260] suppressed autophagy,[261] mitochondrial uncoupling,[262–264] altered mitochondrial dynamics,[53,185] accumulation of toxic lipid intermediates such as ceramide or diacylglycerol,[261,265] endoplasmic reticulum stress,[266,267] and inflammation.[268,269]

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 remodeling. 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 Karwi et al,[25] Lopaschuk et al,[270] and Selvaraj[271] for reviews; Figure 5). This can be achieved by increasing circulating ketone body levels, primarily by one of the 4 following approaches: (1) ketone infusions, (2) ketone ester administration, (3) SGLT2 (sodium/glucose co-transporter 2) inhibitors, and (4) administration of a ketogenic diet. A study by Nielsen et al[272] 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 remodeling.[273] Acute administration of a ketone ester (KE (R-3-hydroxybutyral(R)-3-hydroxybutyrate) to patients with HFrEF resulted in an increase in circulating ßOHB by 12.9-fold and an improvement in contractile function.[274] Ketone ester administration was also shown to improve cardiac function and to reduce cardiac remodeling in mouse and rat models of heart failure.[275] 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 antihyperglycemic agents to treat diabetes, SGLT2 inhibitors have recently been shown to have dramatic cardioprotective effects in patients with heart failure.[276–278] 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.[279] Alternatively, increased circulating ketones following SGLT2 inhibitor administration have been proposed to decrease inflammation in the failing heart by modulating the NLRP3 inflammasome.[280] 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.[273]

Stimulating Glucose Oxidation and Improving Insulin Sensitivity

Recognizing 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, 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. Dichloroacetate improves postischemic recovery and cardiac efficiency following ischemia and reperfusion via stimulating glucose oxidation and enhancing the coupling between glycolysis and glucose oxidation.[281] Similar improvement in the coupling between glycolysis and glucose oxidation by dichloroacetate treatment is also observed in hypertrophied rat hearts.[282] In the Dahl-salt sensitive rats, dichloroacetate supplementation attenuates the transition from compensated heart failure to heart failure and improves survival by limiting oxidative stress and improving cardiac reserve.[67] 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.[283] However, dichloroacetate

treatment improved the contractile reserve and abrogated hypertrophy by enhancing PDH flux in this large animal heart failure model.[283] Although not all clinical data are consistent,[284] these promising experimental data were recapitulated in small clinical trials. For instance, dichloroacetate administration in patients with angina and coronary artery disease augments left ventricle stroke volume and enhances myocardial efficiency (cardiac work/myocardial oxygen consumption),[285] consistent with glucose being an oxygen-efficient substrate for the heart compared to fatty acid.[2,178] In line with that, dichloroacetate stimulated 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.[173] 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 GCGR (glucagon receptor), a G-protein coupled receptor, can improve cardiac insulin sensitivity, glucose oxidation, and cardiac function post–myocardial infarction.[161] 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.[36,108]

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 Lopaschuk et al[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.[286–291] 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 MCD, which degrades malonyl CoA, and by 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.[292] In contrast, inhibition of ACC and stimulation of fatty acid oxidation has also been shown to be cardioprotective the failing mouse heart.[89,90] 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.[89,292] Inhibition of ACC is also associated with an improved mitochondrial function.[90] 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 posttranslational 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.[181,198]

Stimulating BCAA Oxidation

High levels of circulating BCAA and its metabolites, namely 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.[125,293,294] Of interest is that plasma as well as cardiac levels of BCAA and BCKAs increase in the rodent models of myocardial ischemia/reperfusion injury[133,161,247] and heart failure.[130,134] Disruption of cardiac BCAA oxidation aggravates cardiac insulin resistance and contractile dysfunction in murine models of myocardial ischemia/reperfusion[247] and aortic constriction,[130] while BCAA supplementation further deteriorates cardiac dysfunction and increases infarct size in a mouse model of coronary artery ligation-induced myocardial infarction.[133] 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.[295] In contrast, pharmacological interventions to enhance BCAA oxidation and/or decrease circulating BCAA levels are cardioprotective in the ischemic and the failing heart.[130,133,134,247] 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% to 2% of the total cardiac ATP is produced from BCAA.[27,134] 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 utilization of fatty acids or glucose.[296] However, accumulation of BCAA[134,161] and/or BCKA[297–299] as a result of impaired BCAA oxidation may increase mTOR activity and impair insulin signaling in the failing heart. Furthermore, high levels of BCAA[247] and/or BCKA[300] will impair cardiac PDH activity, to further

reduce glucose oxidation in the failing heart.[161] 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.[134] In line with this, treatment with the BCKDK inhibitor, BT2, increases BCAA oxidation in conjunction with reducing BCAA accumulation[134] and BCKAs[130,135] 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.[301,302]

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 contributes 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.

ARTICLE INFORMATION

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Sources of Funding

G.D. Lopaschuk is funded by a Canadian Institute for Health Research Foundation Grant and a Heart and Stroke Foundation of Canada Grant. Q.G. Karwi is supported by an Alberta Innovates Postgraduate Fellowship in Health Innovation. R. Tian is funded by grants from the National Institute of Health HL129510, HL110349, HL142628, and HL144937. A.R. Wende is funded by National Institutes of Health grants HL133011 and HL152354. E.D. Abel is funded by grants from the National Institutes of Health HL141783, HL127764, and HL112413 and the American Heart Association grants 20SFRN35120123 and 16SFRN31810000.

Disclosures

None.

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