

STATE-OF-THE-ART REVIEW

Metabolic Origins of Heart Failure



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SUMMARY

For more than half a century, metabolic perturbations have been explored in the failing myocardium, highlighting a reversion to a more fetal-like metabolic profile (characterized by depressed fatty acid oxidation and concomitant increased reliance on use of glucose). More recently, alterations in ketone body and amino acid/protein metabolism have been described during heart failure, as well as mitochondrial dysfunction and perturbed metabolic signaling (e.g., acetylation, O-GlcNAcylation). Although numerous mechanisms are likely involved, the current review provides recent advances regarding the metabolic origins of heart failure, and their potential contribution toward contractile dysfunction of the heart. (J Am Coll Cardiol Basic Trans Science 2017;2:297-310) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

In order to meet the exceptionally high metabolic demands of continuous contractility, the heart catabolizes an array of substrates. Indeed, the heart has been termed a “metabolic omnivore,” capable of consuming fatty acids (FAs), glucose, ketone bodies, and amino acids (AA) for the replenishment of ATP. Central to achievement of this goal is metabolic flexibility, wherein the heart shifts reliance from one substrate to another, in response to acute perturbations in workload and/or substrate availability (including feeding-fasting and sleep-wake cycles, which occur on a daily basis). The importance of metabolic flexibility is underscored by appreciation for the fact that various substrates are more than just a fuel for the heart, serving also as building blocks for numerous cellular components (e.g., membranes, proteins), cofactors, and signaling molecules. During various disease states, particularly heart failure (HF), cardiac metabolism is perturbed in a chronic manner, resulting in metabolic inflexibility. Thus, HF is characterized by relatively permanent and

predictable shifts in metabolism, associated with impaired signaling (e.g., Ca²⁺, reactive oxygen species [ROS]), energy insufficiency, and contractile dysfunction. This review highlights recent insights regarding the metabolic basis of HF; for the contribution of perturbed Ca²⁺ homeostasis and ROS signaling, the reader is directed to the papers by Brown and Griendling (1) and Bers (2).

CONTRIBUTIONS OF INDIVIDUAL SUBSTRATES

FATTY ACID METABOLISM. Fatty acid oxidation (FAO) represents a significant fuel source for the myocardium, providing an estimated 50% to 70% of the ATP consumed during contraction (3). In comparison with carbohydrate use, rates of cardiac FAO are relatively unaffected by acute changes in workload or energy demand (4,5). Cardiac FAO typically exhibits greater flexibility following changes in substrate availability (6). Such observations could

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ABBREVIATIONS AND ACRONYMS

AA	= amino acid
BCAA	= branched-chain amino acids
FA	= fatty acid
FAO	= fatty acid oxidation
GCN2	= general control nonderepressible 2
GLOX	= glucose oxidation
HBP	= hexosamine biosynthesis pathway
HF	= heart failure
IR	= insulin resistance
LV	= left ventricle
MI	= myocardial infarction
PTM	= post-translational modification
ROS	= reactive oxygen species
TauT	= taurine transporter

indicate that FAO maintains baseline energy needs of the heart while matching rates of FA uptake with oxidation. If true, then cardiac FAO deficits could potentially precipitate contractile dysfunction through energy impairment and/or diversion of excess FAs into signaling and/or “lipotoxic” pathways. This section reviews evidence supporting these concepts.

One of the most consistent metabolic perturbations during HF is decreased use of FA, which has been observed in both animal and human studies (7-11). In doing so, the failing heart reverts to a fetal-like metabolic program, reflected by a repression of various genes encoding core FAO pathway proteins (e.g., medium chain acyl-coenzyme A [CoA] dehydrogenase, beta-hydroxyacyl-CoA dehydrogenase) and their upstream regulators (e.g., PPAR- α , RXR- α , PGC-1 α) (12,13). It has been proposed that, acutely, this metabolic

perturbation serves as an adaptation by promoting increased reliance on more energy-efficient fuels (in terms of ATP per oxygen molecule consumed), which may be particularly important in the setting of ischemic heart disease (14). Consistent with this concept, attenuation of FAO is observed prior to the onset of contractile dysfunction (e.g., induced by pressure overload) (15). However, this metabolic reprogramming causes chronic dyssynchrony between energy demand (which is increased), substrate availability (circulating FAs are typically increased), and use (i.e., FAO is decreased) during HF. In other words, a decrease in FAO rates could reduce ATP availability for contraction (if below the capacity of alternative compensating pathways) concomitant with increased diversion of FA species into signaling/lipotoxic pathways, culminating in impairment of contractility. Evidence in support of this concept includes reports of modest perturbations in markers of energy status in the failing myocardium, as well as accumulation of lipotoxic markers (16-18). The latter, when elevated, can contribute to cell death and cardiac remodeling.

Energy deficiency versus lipotoxicity. Both genetic and pharmacologic approaches have been used to address causal relationships between FAO impairment and HF. Genetic studies revealed that inborn errors of FAO, such as inherited deficiencies in acyl-CoA dehydrogenases, can be associated with cardiomyopathy in humans; similar pathologies are often recapitulated through targeted genetic manipulation in mouse models (19). One example includes very-long-chain acyl-CoA dehydrogenase (VLCAD); germline deletion results in energy impairment and a

cardiomyopathic phenotype (20). Importantly, cardiac-restricted VLCAD deletion also results in contractile dysfunction, illustrating the importance of normal cardiac FA metabolism (21). Similarly, genetic deletion of lipoprotein lipase (LPL) (liberates FAs from circulating lipoproteins), long chain acyl-CoA synthetase-1 (ACSL1) (activates long-chain FAs for metabolism), and adipose triglyceride lipase (ATGL) (liberates FAs from intracellular triglyceride stores) result in concomitant decreases in cardiac FAO and contractile function (22-24). It is noteworthy, however, that genetic mutations resulting in decreased cardiac FAO do not always result in contractile dysfunction. For example, knockout of CD36 (FA transporter) or PPAR- α /PGC-1 α (transcription factors promoting FAO/mitochondrial metabolism) results in decreased FAO without effects on basal contractility (25-27). Possible explanations for the latter discrepancies are that FAO is only modestly impaired; sufficient compensation from alternative substrate use occurs; diversion of FAs species into lipotoxic pathways is limited; and/or a secondary stress is required to elicit dysfunction (e.g., pressure overload, high-fat diet, and so forth).

If acquired deficiencies in cardiac FAO were to contribute significantly to contractile dysfunction of the failing myocardium, then normalization of the FAO deficit would be predicted to improve contractility. Both genetic and dietary strategies have been used to address this concept. An important example includes the study by Kolwicz et al. (28), wherein selective deletion of acetyl-CoA carboxylase 2, an enzyme that generates malonyl-CoA (a potent inhibitor of β -oxidation), prevents pressure overload-induced depression of FAO and concomitantly maintains contractile function. Interestingly, feeding rodents calorie-dense high-fat diets has been shown to preserve and even improve contractility in distinct models of HF (including pressure overload, myocardial infarction, and hypertension), although not all studies report this benefit (perhaps due to differences in dietary composition, duration of feeding, and other factors) (29-33). Observations such as these raise the question of whether cardiac FAO impairment primarily leads to energy deficiency as opposed to lipotoxicity and signaling imbalance. However, strategies designed to cause a mismatch between FA uptake and FAO (e.g., overexpression of FATP-1 or ACSL-1) invariably result in cardiomyopathy associated with markers of lipotoxicity (34,35). In addition, the failing heart is considered to be in a pro-lipotoxic environment (36). Furthermore, haploinsufficiency of mCPT1 increases susceptibility to pressure overload-induced cardiac dysfunction through lipotoxic

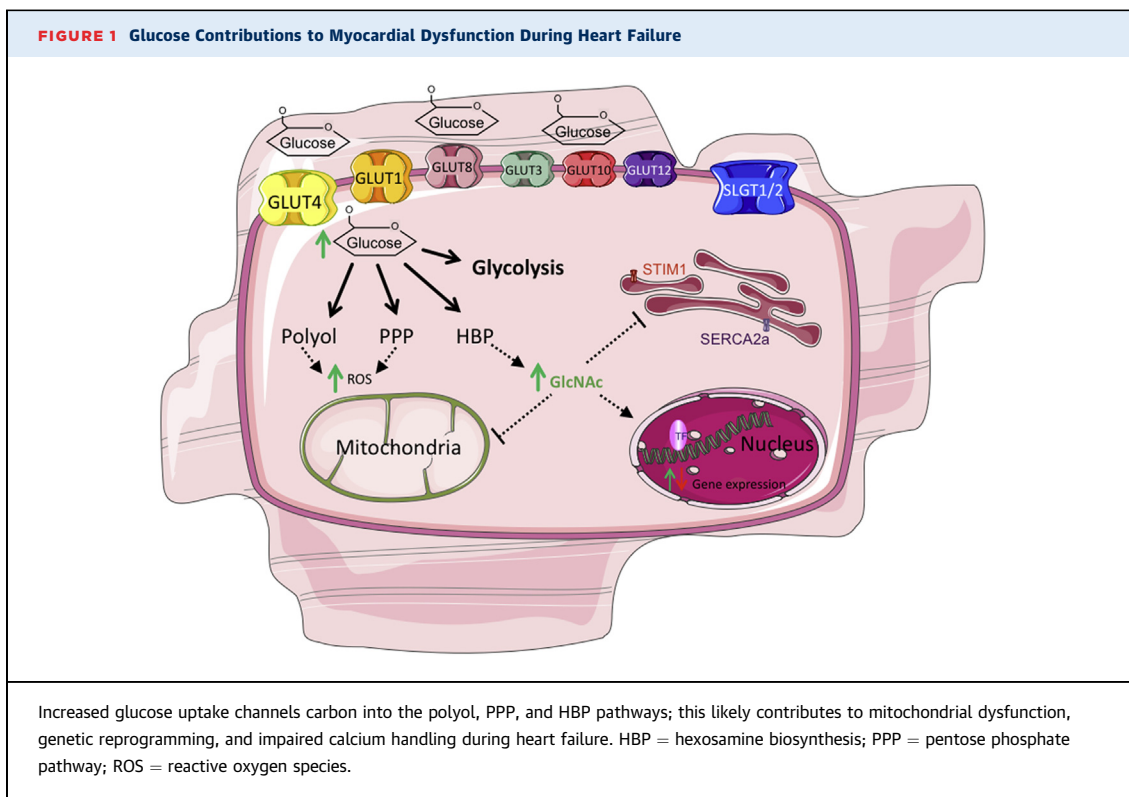
pathways (37). Similarly, germline VLCAD deletion increases cardiac lipotoxicity during high-fat feeding (38). Collectively, these studies suggest that impaired cardiac FAO could lead to cardiac dysfunction not only through energy deficiency but also through lipotoxicity.

Mediators of depressed FAO during HF. Various mechanisms have been proposed as mediators of cardiac FAO impairment during HF. These include transcription-based mechanisms, post-translational modifications (PTMs), mitochondrial dysfunction, cofactor availability, and substrate competition. With regard to transcription-based mechanisms, particular attention has been given to multiple PPAR isoforms (particularly PPAR- α); upon complex formation with RXR- α , FAs (ligand), and coactivators (e.g., PGC-1 α), PPAR- α induces a number of genes encoding known FA transporters and core β -oxidation enzymes (13). Importantly, during HF, cardiac levels of PPAR- α , RXR- α , and PGC-1 α have been shown to decrease, to varying degrees, associated with decreased expression of target genes (8,12). Furthermore, PPAR- α activity may be repressed even more through PTMs (39). The enzymes involved in FA metabolism also undergo PTMs during HF, such as acetylation; this PTM potentially promotes FAO in the heart both directly (i.e., acetylation and activation of β -oxidation enzymes) and indirectly (i.e., acetylation and inhibition of pyruvate dehydrogenase, and therefore impairment of glucose oxidation) (40,41). It is noteworthy that cardiac FAO capacity is extremely high, such that enzymes involved in β -oxidation must be inhibited markedly in order to impact FAO flux. This is exemplified by VLCAD and CPT1b heterozygous knockout mouse hearts, which exhibit no baseline phenotype despite a 50% loss in enzymatic activity (21,37); homozygous cardiomyocyte-specific knockout of VLCAD also has no significant effects on cardiac FAO rates, likely due to compensation by other acyl-CoA dehydrogenase isoforms (e.g., LCAD) (21). In contrast, cardiac FAO is affected by cofactor availability (e.g., carnitine, CoA) and/or mitochondrial function, which is decreased in the failing myocardium (42-44); decreased carnitine would attenuate mitochondrial FA uptake, and decreased CoA would attenuate β -oxidation, whereas limited mitochondrial electron transfer would attenuate dehydrogenases in the β -oxidation spiral. Furthermore, increased reliance on alternative substrates (e.g., glucose and ketone bodies, as discussed below) during HF would attenuate FAO through established allosteric and cofactor limitation mechanisms. In the failing myocardium, all the above-referenced mechanisms likely contribute to attenuated FAO.

GLUCOSE METABOLISM. Use of cardiac glucose (i.e., glycolysis and glucose oxidation [GLOX]), is important for the developing (fetal) heart, during which time glucose delivery is high, and oxygen availability is relatively low (45). Soon after birth, use of glucose decreases concomitant with increased dietary FA and oxygen delivery. However, the healthy adult heart has the capacity to increase reliance on use of glucose in response to both physiologic (e.g., exercise) and pathologic (e.g., ischemia) stresses. During HF, metabolic flexibility is lost, which may be due in part to cardiac insulin resistance (IR); complex alterations in insulin signaling within cardiomyocytes during HF have been reviewed recently (46). It has been suggested that, under some conditions (e.g., hemodynamic stress), IR may actually protect the heart by reducing fuel toxicity (47). However, as HF progresses, an uncoupling between glycolysis and GLOX ensues, potentially contributing to cellular dysfunction (48). Interestingly, circulating glucose levels tend to be elevated during both acute and chronic HF. For example, elevated serum glucose levels at the time of hospital admission for acute HF syndromes, independent of diabetes status, are associated with higher mortality (49,50). Chronically, HF is also associated with peripheral IR. Whether these perturbations in cardiac and/or whole-body glucose homeostasis contribute to the pathogenesis of HF is still under debate (46). The purpose of this subsection (Figure 1) is to review current knowledge regarding the use of glucose during HF; we will focus primarily on this independent of diabetes status, as the latter has been reviewed extensively elsewhere (51-53).

Whether perturbations in use of cardiac glucose are adaptive or maladaptive during HF appears to depend on the underlying stress (i.e., ischemic versus non-ischemic), as well as duration (i.e., acute versus chronic). In the context of hypertension-induced dilated cardiomyopathy, glucose use is increased, with a predominate augmentation of glucose uptake and glycolysis, and a concomitant uncoupling of glycolytic flux from GLOX (48,54). There is mounting evidence that the remodeling of glucose metabolism is one of the initial changes driving the heart to hypertrophy and could act as an early marker of disease progression (55). Acutely enhancing glucose metabolism in the setting of ischemic injury and ventricular fibrillation may be protective (56,57).

Glucose transport during HF. Regulation of glucose uptake into the cardiomyocyte is regulated by members of the solute carrier family 2A (SLC2A), which encode the GLUT proteins (54,58). Of the 12 SLC2A genes expressed in human and rodent cardiac tissue, three are predominantly expressed in the



myocardium: GLUT1, GLUT4, and GLUT8 (59). Of these, GLUT1 and GLUT4 have received extensive attention, in part due to observations that both proteins are decreased in failing human hearts (60). Such observations are consistent with repressed insulin-mediated glucose uptake (primarily through GLUT4) during HF, potentially secondary to chronic activation of GRK2 and IR (61). However, during HF, basal rates of glucose uptake and glycolysis are elevated (and even exceed rates of glucose oxidation) (62). One possible explanation for this apparent disconnect is increased GLUT translocation or activity in an insulin-independent manner. A number of cardiomyocyte-specific gain- and loss-of-function models have been used in an attempt to address this question, as well as the importance of glucose use during HF.

A number of studies have interrogated the importance of various GLUT isoforms in the maintenance of cardiac function. Lifelong GLUT1 overexpression protects against pressure overload-induced contractile dysfunction (63), whereas acute GLUT1 augmentation partially rescues disease progression (64), suggesting that enhanced glucose uptake is protective in this setting. However, cardiomyocyte-specific ablation of GLUT1 did not exacerbate pressure-overload-induced dysfunction (perhaps due to sufficient glucose uptake by other GLUT isoforms) (65).

Conversely, cardiomyocyte-specific GLUT4 ablation decreased functional recovery in response to ischemic injury (66). Although loss of GLUT8 has been explored in the context of diet-induced obesity (67), a direct role during HF remains to be explored. Studies of these transporters, as well as those of the other cardiac-enriched GLUTs (GLUT3, GLUT10, and GLUT12) will continue to provide crucial insight into the contribution of glucose uptake and metabolism during the progression of HF.

An emerging area has focused on non-GLUT-mediated glucose transport through the sodium-glucose cotransporters (SGLT), especially given that empagliflozin (an SGLT2 inhibitor) decreased HF incidence in diabetic patients (68). The mechanism of this protection is likely multifaceted, including lowering of both glucose and sodium, as well as influences on glomerular filtration and the cardiorenal axis (69). Interestingly, SGLT1 is induced in the heart during both diabetic and ischemic cardiomyopathy (70), and phlorizin (another SGLT inhibitor) decreased cardiac glucose uptake and directly affected tolerance of the heart to ischemia (71). Future studies will undoubtedly reveal important insights regarding the effects of SGLT inhibitors on cardiac metabolism and protection.

Polyol pathway. Augmented glucose uptake and glycolytic flux, particularly when in excess of GLOX,

enhances diverting of glucose moieties into signaling pathways. This includes the polyol pathway. Although primarily implicated in diabetic complications, overexpression of aldose reductase, the first step in this pathway, results in an age-related decline in heart function and exacerbated ischemic injury (72). Further studies are warranted in order to elucidate fully the importance of the polyol pathway in the pathogenesis of HF.

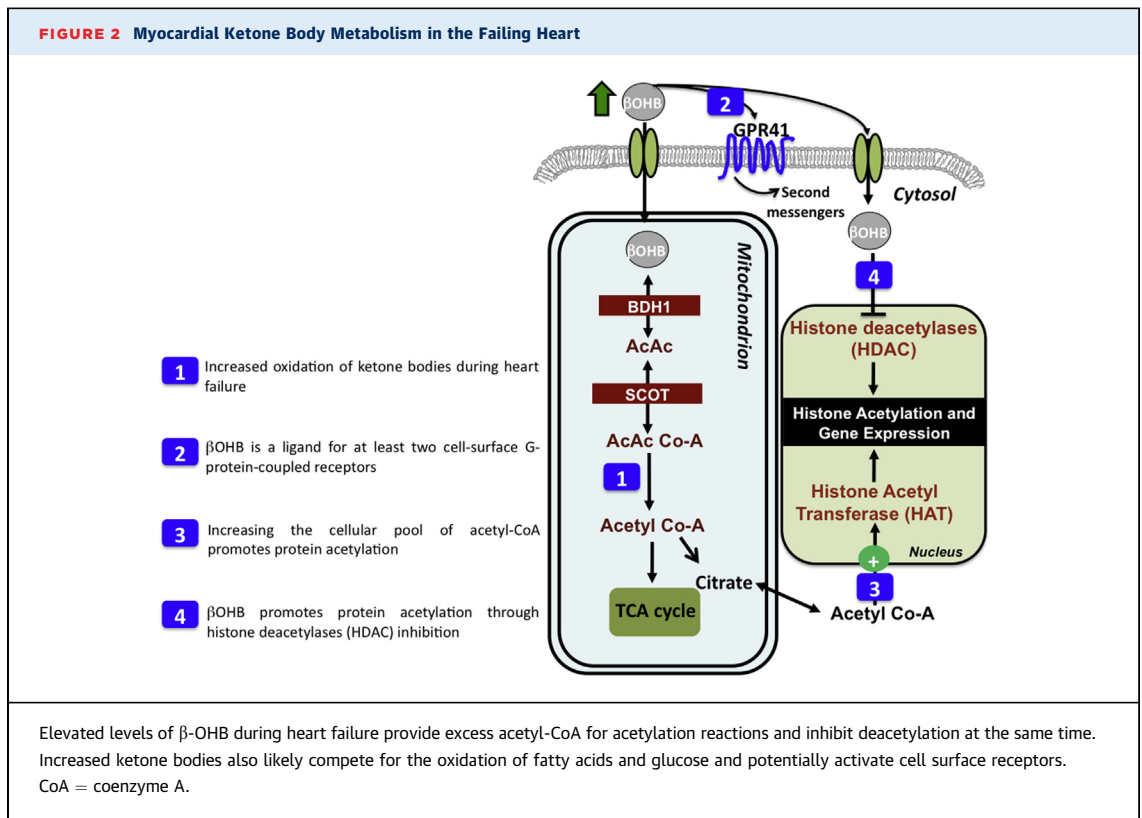
Pentose phosphate pathway. The pentose phosphate pathway (PPP) is important for NADPH and ribose-5-phosphate generation. In a canine model of congestive HF, post-prandial glycemic levels were sufficient to increase PPP flux. When this was prevented, cardiac GLOX and stroke work were normalized (73). Furthermore, in a genetic mouse model of dilated cardiomyopathy that progressed to HF, non-oxidative glucose pathways such as the PPP and glycogen synthesis were increased (74). The PPP affects ROS balance not only through NADPH but also through regulation by pyridine nucleotides (75). Interestingly, glucose-6-phosphate dehydrogenase (G6PD) (first enzyme of the PPP) deficiency is associated with cardiac disease progression; however, mice with G6PD deletion have shown both protective and deleterious effects on cardiac function (76), suggesting the need for further study.

Hexosamine biosynthesis pathway. The hexosamine biosynthesis pathway (HBP) requires input from glucose, AAs, FAs, and nucleotides, resulting in the end product uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc). This molecule in turn is used to regulate nearly all aspects of cell physiology through the PTM of serine and threonine residues by the addition of an *O*-linked *N*-acetylglucosamine (*O*-GlcNAc) (77). This *O*-GlcNAc modification is elevated in both hypertrophy and HF (78) and has both adaptive and maladaptive contributions to cardiac function (79,80). Specifically, increased *O*-GlcNAc is protective following acute ischemic injury; whereas, during HF, elevated *O*-GlcNAc may contribute to contractile and mitochondrial dysfunction. *O*-GlcNAc likely impacts a number of cardiac processes, including transcription, epigenetics, metabolism, and Ca²⁺ handling. In the last case, *O*-GlcNAc can regulate SERC2A, CaMKII, and STIM1 (81-84), either increasing or decreasing calcium sensitivity, depending on the duration and disease state (e.g., ischemic or nonischemic).

KETONE BODY METABOLISM. Compared with FA and glucose metabolism, current knowledge of the role of altered ketone body metabolism during HF is relatively limited. However, a growing body of evidence from pharmacological (85,86), dietary (86-89), and

genetic (90) manipulation studies suggest that perturbations in the use of ketone bodies can play a role in cardiac health and disease. The heart readily uses ketone bodies such that their oxidation is typically increased in proportion to their delivery (91). Acetoacetate (AcAc) and β -hydroxybutyrate (OHB) are the primary ketone bodies that can be metabolized, which are synthesized by the liver during periods of elevated FA availability, including fasting, prolonged exercise, ketogenic diets, uncontrolled type 1 diabetes, and HF (92). In the last case, multiple studies have consistently shown that HF patients with no history of diabetes present with elevated levels of systemic ketone bodies (93,94). During HF, elevated norepinephrine levels secondary to increased sympathetic outflow likely promote ketogenesis by increasing FA supply through lipolysis in adipose tissue (95). The strength of these associations is such that exhaled acetone (indication of ketoacidosis) is a predictive biomarker for severity of HF (96-98). It is noteworthy, however, that a recent study reported reduced circulating ketone body levels in HF patients with reduced ejection fraction relative to that in HF patients with preserved ejection fraction and non-HF controls (99). Severity of HF and other comorbidities associated with the patients recruited in these studies could potentially account for these discrepancies.

Whether altered myocardial ketone body metabolism contributes to the pathogenesis of HF was recently investigated in rodents and humans (100,101). These studies reported increased expression of ketone body metabolism enzymes (α - β -hydroxybutyrate dehydrogenase (BDH1) and succinyl-CoA:3-oxoacid CoA transferase (SCOT), reduced intermediary metabolites of ketone body catabolism, as well as increased ketone body oxidation (stable isotope measurements) in the failing heart. An important question relates to whether increased use of ketone body during HF is adaptive or maladaptive. In support of an adaptive role, cardiomyocyte-specific deletion of SCOT led to adverse cardiac remodeling following pressure overload (90). However, these studies do not address whether normalization of ketone body use, particularly in the setting of HF, is beneficial or detrimental (as opposed to ablation during compensated hypertrophy). Interestingly, elevated ketone body availability would be anticipated to repress both FAO and GLOX in the heart through substrate competition, thus resulting in a metabolic signature reminiscent of advanced HF. Furthermore, ketone bodies serve as signaling molecules, acting through both extracellular receptors (e.g., GPR41) and intracellular inhibitors of histone deacetylases (HDACs) (85,102), which in turn

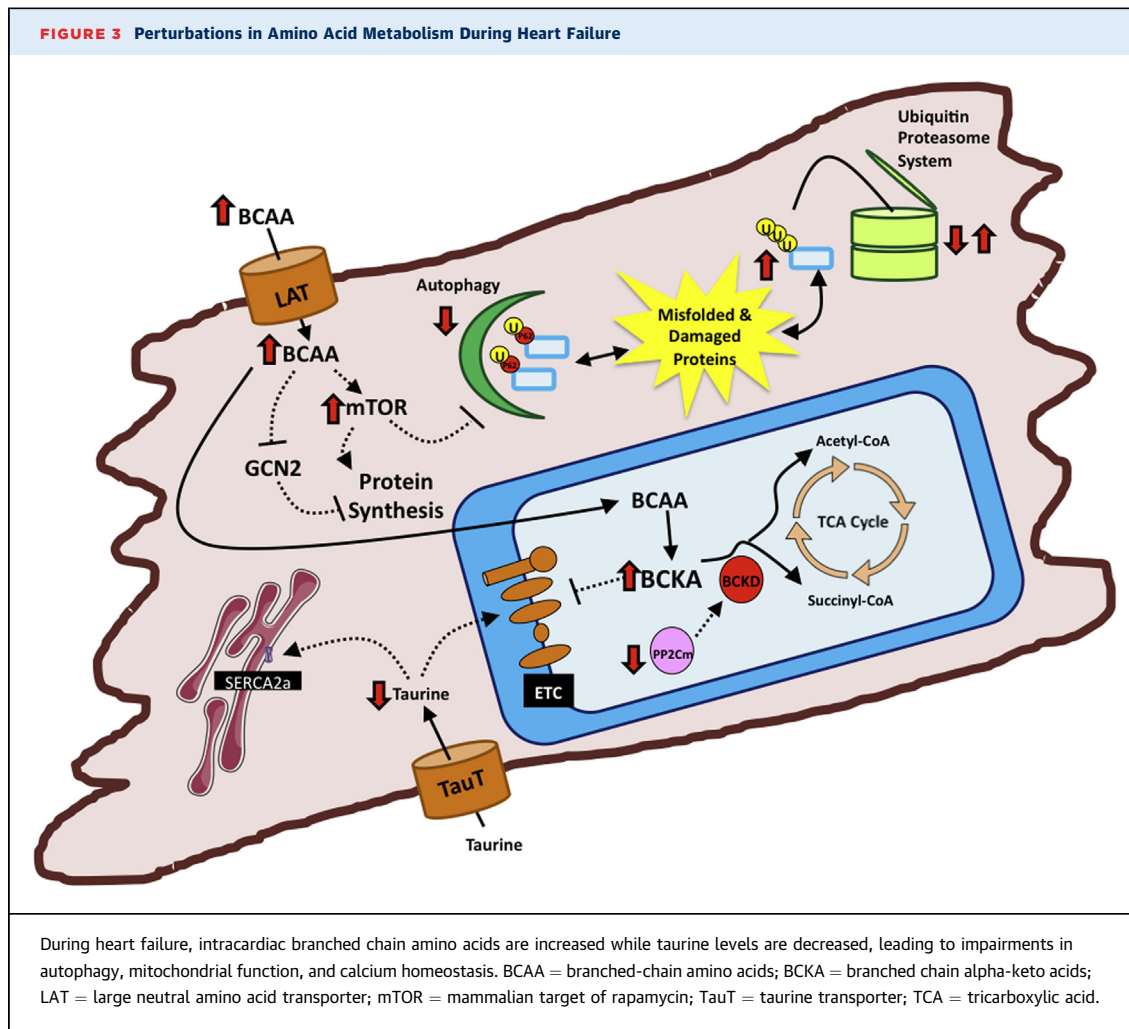


could influence cardiac processes (Figure 2). The mechanisms by which ketone body uses enzymes are induced during HF also remain unanswered. Future studies interrogating these questions are warranted, which will aid in understanding the role of ketone body metabolism in the pathogenesis of HF.

AMINO ACID METABOLISM. Compared with FAs and glucose, AAs quantitatively contribute to a lesser degree to ATP generation in the heart. However, AAs play essential roles in myocardial function that extend beyond energy, such as synthesis of protein, metabolic and signaling intermediates, and cofactors. In the last case, notable AA derivatives include L-carnitine (from lysine and methionine), CoQ10 (from tyrosine and mevalonate), and taurine (from methionine or cysteine), which play important roles in cardiac processes (e.g., metabolism, redox biology, and calcium homeostasis). Furthermore, it has been estimated that the mammalian heart renews all cellular components within a 30-day period (50), illustrating a significant demand on AA availability for protein and cofactor synthesis. Moreover, protein turnover is accelerated in the heart during periods of remodeling, such as hypertrophic growth. Significant efforts have been made to increase our understanding of AA metabolism perturbations during HF and have

yielded novel insights. This subsection (Figure 3) highlights the contribution that AA metabolism perturbations potentially play in the cause of HF.

Amino acids during HF. Both AA availability and use are influenced by HF. For example, profiling plasma AAs (and their derivatives) from HF patients using high-performance liquid chromatography revealed that the circulating levels of almost one-half of the species assessed (17 of 41) were altered in HF, the majority of which were increased (15 of 17) (103). Furthermore, a subset of these AAs, including glutamate and monoethanolamine (a serine derivative), negatively correlated with ejection fraction in HF patients (with trends for phenylalanine and tyrosine as well), suggesting higher circulating AAs were indicative of worsening cardiac function. This is likely due to accelerated protein breakdown in skeletal muscle, which serves as an AA reservoir during HF (104). Despite increased demand for AAs in the heart, there is evidence of AA accumulation in the failing myocardium, as shown by metabolomic analysis of failing mouse myocardium accumulation of AAs, consistent with the notion that AA catabolism was compromised (105). Transcriptomic analysis in mice shows that genes associated with AA catabolism are down-regulated during compensated hypertrophy and overt failure (105).



Considerable interest has been placed on branched-chain AA (BCAA; leucine, isoleucine, valine) metabolism during HF. Branched chain alpha-keto acids (BCKA; product after initial step of BCAA catabolism) are elevated within the myocardium in HF patients (106). Furthermore, subunits of the branched chain alpha-keto acid dehydrogenase (BCKD) complex, which is responsible for subsequent catabolism of BCKAs, are transcriptionally repressed. These findings have been replicated in mice during transaortic constriction-induced HF, where pharmacologic activation of BCKD normalized BCAA catabolism, prevented BCKA accumulation, and protected against cardiac dysfunction (106). These findings suggest that an imbalance between BCAA availability and use during HF may contribute to contractile dysfunction and that normalization of this balance may be a novel, efficacious therapeutic strategy.

Consistent with impairment of appropriate AA use and metabolism by the failing myocardium, various

cofactors are often found to be depleted, including taurine. The importance of taurine in the heart is supported by studies using taurine-deficient mice (induced by genetic ablation of the taurine transporter [TauT]) and rats (TauT inhibition with β -alanine), resulting in cardiomyopathy (107). Taurine deficiency is characterized by reduced glucose and FAO in isolated perfused rat hearts (108), reduced mitochondrial complex I and III activity, and increased ROS production in cardiomyocytes (109). Taurine deficiency is also associated with aberrant Ca^{2+} homeostasis and signaling, involving alterations in phospholamban and SERCA2 (110). Taurine supplementation has been shown to be efficacious during HF, eliciting improvements in left ventricular (LV) function (111) and exercise capacity (112).

Various studies suggest that AA supplementation increases functional capacity and quality of life in patients with chronic, stable HF (113). For example, mixed AA supplementation increased functional

exercise capacity (Vo_2 peak, exercise time during exercise test, 6-min walk test) in humans with chronic HF (114,115). Similarly, BCAA supplementation preserved cardiac function during high-salt-induced HF in Dahl salt-sensitive rats (a physiological model of hypertension leading to HF) (116). These somewhat counterintuitive observations (i.e., beneficial effects of AA supplementation during HF, when AA availability appears to exceed capacity of the myocardium to metabolize them) may be explained by extracardiac effects. For instance, BCAA supplementation represses skeletal muscle cachexia (i.e., muscle wasting), and previous studies suggest that the degree of cachexia is a strong independent risk factor for mortality during HF and significantly reduces survival (117).

Amino acids regulate signaling during HF. Various AAs (and their derivatives) function as signaling molecules. This is particularly true for BCAAs, which activate the mammalian target of rapamycin (mTOR), a modulator of various anabolic (i.e., protein synthesis) and catabolic (i.e., autophagy [discussed in the next section]) pathways. Aberrant mTOR signaling has been implicated in the progression of HF (118,119). In mice, mTOR is activated by pressure overload and pharmacologic inhibition (with rapamycin) improves contractile function of the decompensated myocardium (120). However, ablation of mTOR complex-1 signaling (through genetic deletion of Raptor) prevents compensated hypertrophy following pressure overload (121), resulting in a rapid transition to HF and increased mortality. These findings suggest mTOR activation may be adaptive during the initial compensated phase but maladaptive during overt failure. It is noteworthy that BCAAs also appear to affect cellular processes in an mTOR-independent manner, potentially through eukaryotic initiation factor-2- α (eIF2- α) kinase general control nonderepressible-2 (GCN2). GCN2 is activated by noncharged tRNA during AA starvation (particularly BCAA depletion), which leads to eIF2 α phosphorylation and repression of translation. Interestingly, when exposed to pressure overload, GCN2 null mice are protected against contractile dysfunction (122), raising the possibility that BCAA supplementation may afford some protection during HF through GCN2 inhibition.

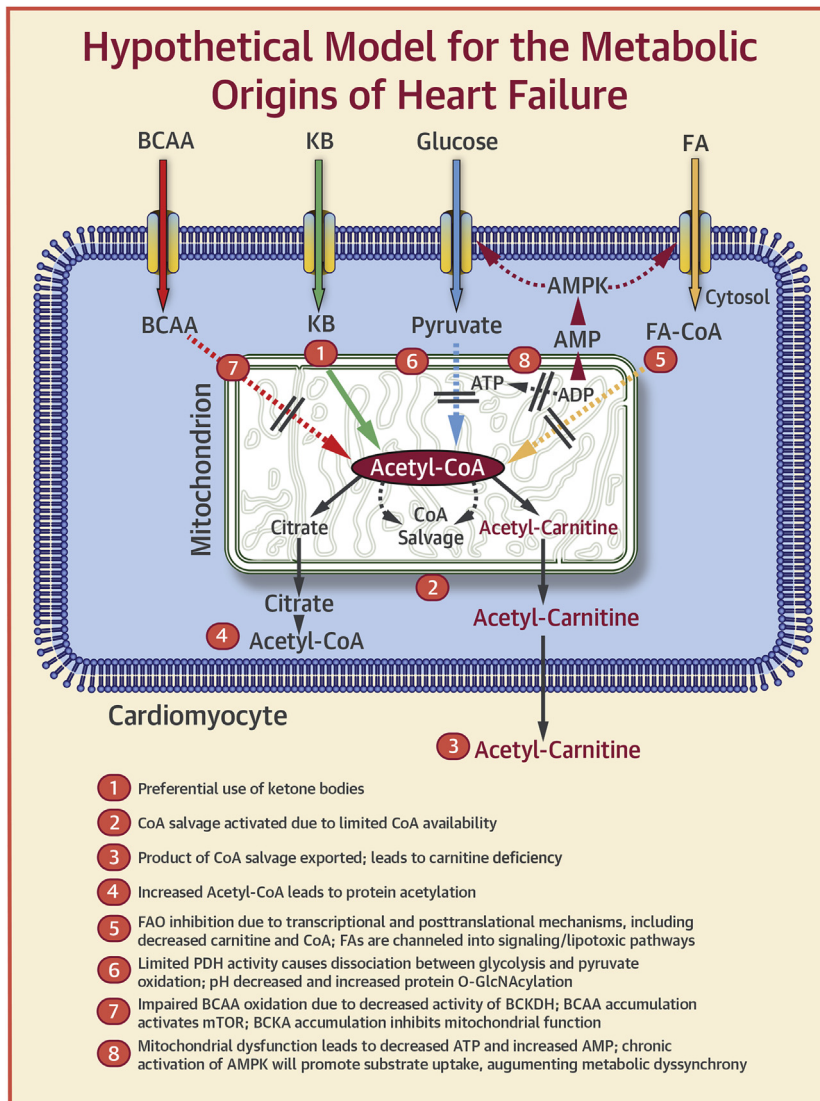
Autophagy and the ubiquitin proteasome system during HF. Turnover of cellular components (such as proteins) is essential for maintenance of function, especially in terminally differentiated cells with limited capacity for renewal, such as cardiomyocytes. Several cellular processes, including autophagy and the ubiquitin proteasome system, are critical for the turnover or degradation of proteins

and organelles and, therefore, myocardial quality control. While target-specific forms of autophagy exist, including mitophagy (mitochondria), glyco-phagy (glycogen), and lipophagy (lipids), this subsection focuses on macroautophagy (hereafter referred to as autophagy).

Observational evidence (e.g., electron microscopy) in humans with ischemic and dilated cardiomyopathy, as well as congestive HF, suggests that autophagy might be induced in the stressed myocardium (123,124). Paired sampling of cardiac tissue during LV assist device (LVAD) implantation or explantation indicates autophagy markers are increased during HF and are reduced following mechanical unloading (125). However, difficulties with measuring autophagic flux in static samples can hinder interpretation of observational results in clinical human studies, necessitating the use of animal models. Experimental evidence in mice subjected to pressure overload indicated transient activation of autophagy, which is elevated within hours of transaortic constriction in mice, returning to subbasal levels within days (126,127). Interestingly, diminishing myocardial autophagy in cardiomyocyte-specific Beclin-1^{+/-} mice partially rescued myocardial function following pressure overload. Conversely, inducing autophagy in cardiomyocytes (through overexpression of Beclin-1) significantly increased mortality and cardiac remodeling following pressure overload (126), suggesting autophagy is maladaptive during cardiac stress. However, genetic disruption of myocardial autophagy through cardiomyocyte-specific deletion of the autophagy-related gene-5 (ATG5) exacerbated hypertrophy and remodeling during pressure overload (128). One possible explanation for these seemingly opposing observations is related to the manner in which autophagy is disrupted: if inhibited later in the process (as opposed to initiated), autophagosomes will accumulate within the myocardium, thus impairing cellular function. Consistent with this concept, doxorubicin-induced cardiomyopathy is characterized by an imbalance in autophagy initiation versus completion, resulting in accumulation of autophagosomes and dysfunction of cardiomyocytes (129).

The ubiquitin proteasome system also plays a critical role in protein turnover. Accumulation of ubiquitinated proteins has been consistently observed across studies investigating human HF samples (123,125,130,131). This accumulation could result from an imbalance between the activity of ubiquitin ligases, de-ubiquitinating enzymes, and the proteasome. In the last case, studies assessing proteasome activity have produced inconsistent results.

CENTRAL ILLUSTRATION Hypothetical Model for the Metabolic Origins of Heart Failure



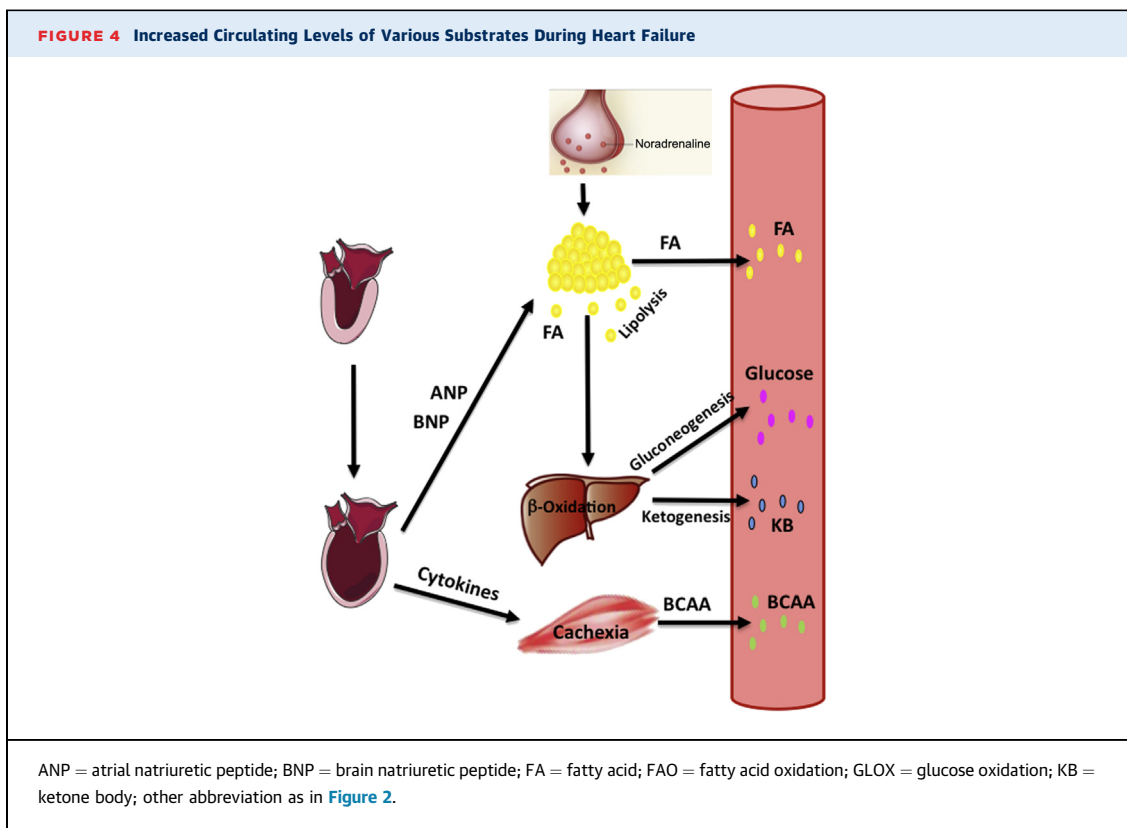
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ADP = adenosine diphosphate; AMP = adenosine monophosphate; AMPK = adenosine monophosphate kinase; ATP = adenosine triphosphate; BCAA = branched-chain amino acids; BCKA = branched chain keto acid; BCKDH = branched chain keto acid dehydrogenase; CoA = coenzyme A; FA = fatty acid; FAO = fatty acid oxidation; KB = ketone body; mTOR = mammalian target of rapamycin.

For example, Birks et al. (131) reported increased 20S proteasome chymotrypsin-like activity, whereas Day et al. (132) showed chymotrypsin-like and caspase-like proteasome activities were reduced. Interestingly, proteasome activity increases in patients after LVAD implantation (130). Additional studies are required to elucidate fully the contribution of perturbed ubiquitin proteasome system function in the cause of HF.

METABOLIC DYS-SYNCHRONY DURING HF: AN ENGINE FLOODED WITH FUEL?

Previous sections have outlined macronutrient metabolic perturbations during HF, the potential mechanisms leading to their occurrence, and their potential contribution to contractile dysfunction of the heart. Here, we propose a unifying hypothesis for the metabolic origins of HF, based on the concept



that the failing heart is oversupplied with macronutrients, leading to an imbalance in fuel availability and use and subsequent accumulation of key metabolic intermediates that worsen contractile function of the heart (**Central Illustration**). The rationale for this model will be discussed.

During HF, the myocardium is undoubtedly in a state of dys-synchrony with regard to energy demand and ATP generation. Accordingly, compensatory mechanisms attempt to regain synchrony through decreasing workload and increasing metabolism. For example, increased atrial natriuretic peptide/brain natriuretic peptide secretions promote natriuresis, thus reducing workload (133). Elevation of these cardiokines, as well as various cytokines (e.g., tumor necrosis factor [TNF]- α) and sympathetic tone, also serve to signal fuel mobilization during HF, enhancing adipocyte lipolysis (releasing FAs), hepatic gluconeogenesis (releasing glucose), and skeletal muscle proteolysis (releasing AAs, including BCAAs) (104,134,135). These fuels become available not only to the heart (for ATP generation) but also to extracardiac tissues, including the liver; increased FA availability promotes ketogenesis, thereby elevating circulating ketone bodies in HF subjects (95-98).

Collectively, the failing myocardium is in an environment rich in fuels (**Figure 4**).

The myocardium has a high capacity and preference for use of ketone body, which attenuates use of other substrates; elevated use of ketone body concomitant with decreased total CoA in the failing myocardium (42) will limit mitochondria-free CoA for FAO, pyruvate oxidation, and BCAA metabolism. One strategy to liberate CoA for continued oxidative metabolism involves exchanging the CoA with carnitine, and subsequent generation of acetyl-carnitine (as observed during HF) (100,101,136). However, diminished carnitine levels in the failing heart (137) will attenuate FAO capacity further. Impairment of FAO in the face of elevated circulating FAs would promote diversion of FA species into signaling and lipotoxic pathways. Elevated use of ketone body would also limit the activity status of pyruvate dehydrogenase; in the face of elevated glucose uptake, an uncoupling between glycolysis and glucose oxidation ensues. Similarly, impairment of the BCKD due to cofactor perturbations and/or PTM, coupled with increased circulating BCAAs, will lead to accumulation of BCKA and mitochondrial dysfunction. The latter amplifies metabolic dyssynchrony further due to activation of

mechanisms designed to promote cardiomyocyte substrate uptake in the face of energy deficit (e.g., AMPK activation promoting GLUT1/4 and CD36 translocation for glucose and FA uptake, respectively). Importantly, during diabetes, dyssynchrony between fuel availability and use will be amplified further, due to greater levels of circulating FAs, ketone bodies, glucose, and BCAAs. In other words, the failing myocardium can be considered an engine flooded with fuel.

CONCLUSIONS

According to the model described above (**Central Illustration**), strategies designed to regain synchrony among energy demand, substrate availability, and substrate use would be beneficial during HF. Established and emerging HF therapeutics include β -blockers and valsartan-sacubitril. Both treatments focus primarily on reduction of workload, which in turn would help regain synchrony due to attenuation of energy demand. In addition, β -blockers help regain synchrony further through inhibition of lipolysis, thus decreasing substrate supply (FAs, and likely ketone bodies). In contrast, through promotion of lipolysis, valsartan-sacubitril therapy has the potential to negatively affect metabolic synchrony, augmenting substrate supply further. Although no pharmacological strategy has been taken to specifically attenuate ketogenesis in the setting of HF, some strategies may influence this indirectly. For

example, nicotinic acid, an antilipolytic agent, has been proposed to be beneficial during ischemic heart disease (138); attenuation of lipolysis would reduce FAs available for ketogenesis and lipotoxicity. Similarly, inhibition of hepatic FAO would attenuate ketogenesis; this may contribute to the benefit of FAO inhibitors, such as trimetazidine, in the setting of HF (139-141). However, some FAO inhibitors, such as etomoxir, appear to have detrimental effects due to hepatic toxicity (142). According to our model, limited availability of specific cofactors (e.g., carnitine and CoA) during HF would exacerbate metabolic dyssynchrony. Interestingly, several studies suggest that carnitine supplementation has benefits during HF (143); whether pantothenate (precursor for CoA biosynthesis) supplementation has benefit during HF is currently unknown. Promotion of oxidation of individual substrates, such as pyruvate and BCKA, also appears to be beneficial in animal models (106); whether this translates to the clinical setting is currently unknown. However, caution should be taken to promote the use of a single substrate in the presence of excess FA availability, as this in turn could result in further inhibition of FAO, and potentially lipotoxicity.

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