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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., Ca^{2+}, 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 Ca^{2+} 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 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

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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

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-1α) (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 inborne 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-1α (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