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EDITORIAL COMMENT

Metabolic Coupling as a Therapeutic Strategy for Heart Failure*

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The heart is a metabolic omnivore that requires use of a plethora of substrates, not only to meet energetic demands for continual contraction, but also to provide necessary building blocks for turnover of cellular constituents and synthesis of metabolically derived signaling species (1). A key concept for cardiac metabolism centers around the need for homeostasis (i.e., maintenance of processes within a discrete physiological range) in the face of perpetual fluctuations in environmental stimuli and/or stresses. This is achieved through metabolic flexibility, which in essence affords a buffering capacity. A simple example involves perturbations that occur over the course of the day; sleep and/or wake and fasting and/or feeding cycles result in daily fluctuations in energetic demand and nutrient availability, as well as a host of additional neurohumoral factors that are met by reciprocal oscillations in cardiac metabolism (2). During cardiac disease states, the heart is often described as metabolically inflexible, typically being suspended at extremities (i.e., chronic activation or repression, depending upon the pathology and metabolic parameter), coupled with an inability to appropriately respond to physiological challenges (3). This is exemplified by heart failure. The failing human heart has been described as an engine without fuel, due to severe metabolic impairments and an inability to generate sufficient adenosine triphosphate (ATP) for maintenance of contractile performance (4). Dysfunction of mitochondria (the primary site of ATP synthesis via oxidative phosphorylation) appears to be central to this pathology (4). Consistent with this idea, numerous studies suggest that myocardial oxidation of both glucose and fatty acids (major substrates for the heart) are reduced during heart failure. This is despite observations that circulating levels of these substrates are often elevated (5), which potentially leads to an imbalance between carbon availability and use. Glucose serves as a good example. During heart failure, diminished glucose oxidation occurs concomitantly with accelerated glucose uptake and glycolytic flux (4,5). This uncoupling of glycolysis from glucose oxidation is associated with accumulation of lactate and protons; the latter decreases cardiac efficiency, in part, through augmented ATP-dependent ion homeostasis required for proton extrusion from the cardiomyocyte (6). Uncoupling of glycolysis from glucose oxidation has been reported during other pathological states, including diabetes mellitus and acute ischemia and/or reperfusion (7,8).

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Multiple groups have reasoned that targeting metabolic derangements during heart failure has the therapeutic potential to improve cardiac function. The uncoupling of glycolysis and glucose oxidation was targeted in the study by Wang et al. (9) in this issue of *JACC: Basic to Translational Science*. More specifically, these investigators hypothesized that pharmacological inhibition of malonyl-CoA decarboxylase (MCD) would decrease the severity of heart failure in a rat model of myocardial infarction (permanent ligation of the left anterior descending artery). MCD is most commonly known for regulation of fatty acid oxidation; by catabolizing malonyl-CoA (an

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established endogenous inhibitor of the mitochondrial carnitine shuttle, a process critical for fatty acid uptake into the mitochondrial matrix), MCD promotes fatty acid oxidation (FAO) (10). Accordingly, MCD inhibition is predicted to increase malonyl-CoA levels, thus inhibiting FAO. Initially, it may appear counterintuitive to selectively inhibit FAO in the failing myocardium, because this process is apparently diminished already. However, due to the interrelationship between FAO and glucose oxidation [initially described by Randle et al.(11)], inhibition of FAO invariably promotes glucose oxidation (thereby augmenting coupling with glycolysis). As a proof of concept, Wang et al. (9) reported that a pharmacological inhibitor of MCD (CBM-3001106) acutely (<1 h) increased cardiac malonyl-CoA levels, in parallel with attenuated FAO and concomitant glucose oxidation augmentation (in ex vivo perfused working rat hearts). The investigators also observed an improvement in cardiac function in vivo (echocardiographic parameters, such as ejection fraction and fractional shortening) when rats with heart failure were treated with the MCD inhibitor either acutely (2 h) or for the long term (4 weeks). Moreover, improvements in cardiac function following 4 weeks of MCD inhibition persisted in ex vivo working heart perfusions. The latter studies also revealed a dramatic reduction in glycolytic flux in rats with heart failure treated with the MCD inhibitor (translating to a significant reduction in calculated proton production) and improved cardiac efficiency. Adverse remodeling markers were also attenuated in rats with heart failure following long-term MCD inhibitor treatment (in the absence of differences in infarct size). This included normalization of sarcoplasmic/endoplasmic reticulum Ca (2+) ATPase 2a (SERCA2a) levels and lactate dehydrogenase (LDH) isoform switching. Additional parameters were assessed, including forkhead box O3 (FOXO3) nucleo-cytoplasmic distribution and superoxide dismutase 2 (SOD2) acetylation, both of which were normalized in the failing heart by MCD inhibition. Collectively, these observations suggested that MCD (and presumably, FAO) inhibition reversed adverse remodeling of the failing myocardium, potentially through improved coupling of glycolysis with glucose oxidation.

Metabolic modulation as a heart failure therapy is an attractive concept. In addition to extensive evidence that perturbed myocardial metabolism plays a causal role in adverse remodeling during heart failure, various cardiometabolic disease states are significant contributors to the etiology of heart failure. These include obesity and diabetes mellitus. Moreover, heart failure profoundly disrupts systemic metabolism, in a manner similar to cachexic states (e.g., skeletal muscle loss, lipolysis, insulin resistance). Heart failure–induced perturbations in systemic metabolism likely worsen myocardial contractility and outcomes (i.e., a viscous feed-forward cycle develops). Pharmacological inhibition of FAO as a therapeutic for cardiometabolic diseases and/or heart failure has been proposed previously. Both inhibitors of carnitine acyl-transferase I (CPTI) (the carnitine shuttle component inhibited by malonyl-CoA; CPTI inhibitors include oxfenicine, perhexiline, and etomoxir) and β-oxidation enzymes (e.g., trimetazidine inhibits 3-ketoacyl thiolase) have reported beneficial effects in preclinical models of heart failure, as well as in humans (12). For example, oxfenicine attenuated heart failure progression in a dog model (13), whereas perhexiline was shown to improve ejection fraction in patients with heart failure (14). However, some CPT1 inhibitors might have detrimental side effects. For example, although etomoxir initially appeared to confer contractile function improvements in patients with heart failure (15), clinical trials were halted due to hepatotoxicity (16). This led to concerns that CPTI inhibition in the liver may promote nonalcoholic hepatic steatosis (NASH). Wang et al. (9) proposed that one advantage of targeting MCD was that the liver isoform of CPT1 was less sensitive to malonyl-CoA–mediated inhibition, relative to the muscle isoform. However, whether prolonged MCD inhibition, particularly during dyslipidemic states (e.g., obesity, diabetes), leads to NASH is a distinct possibility. Germline MCD knockout mice developed triglyceride accumulation in the liver with age (17).

In addition to an uncoupling between glycolysis and glucose oxidation, heart failure is also characterized by an uncoupling between substrate availability and use. Circulating levels of glucose, fatty acids, ketone bodies, and amino acids (notably branched chain amino acids [BCAAs]) are typically elevated during heart failure, concomitant with decreased myocardial oxidative metabolism (5). This mismatch has the potential of precipitating contractile dysfunction. Putative glucose- and lipid-dependent mechanisms have been studied extensively, including imbalances in signaling metabolites (e.g., ceramide, diacylglycerol), redox status (e.g., NAD(P)+/NAD(P)H ratios), and post-translational modifications (e.g., protein palmitoylation and/or O-GlcNAcylation) (5). Recently, impaired ketone body and BCAA oxidation has been reported in the failing myocardium (18–20); accumulation of metabolites in these catabolic pathways adversely affects cellular signaling, protein acetylation, and mitochondrial function. In light of these findings, the failing

myocardium has been described as a broken engine flooded with fuel (5). How might MCD (and therefore, FAO) inhibition help resolve this mismatch? Two main possibilities exist. First, inhibition of FAO in tissues such as skeletal muscle and the liver would likely lower circulating glucose (through increased skeletal muscle glucose use and reduced hepatic gluconeogenesis; etomoxir was initially developed as a glucose-lowering agent), BCAAs (through increased oxidation in both muscle and liver), and ketone bodies (through decreased hepatic acetyl-CoA availability for ketogenesis) levels. Second, FAO inhibition in the heart would increase myocardial glucose, ketone body, and BCAA oxidation. Together, a balance between availability and oxidation would be reestablished for these substrates. The study by Wang et al. (9) provides indirect evidence of this concept, at the level of protein acetylation. Elevated SOD2 acetylation in the failing heart is normalized by MCD inhibition. Moreover, nuclear translocation of FOXO3 following MCD inhibition is consistent with reduced acetylation [as acetylation sequesters FOXO3 in the cytosol (21)]. These observations raise the possibility that, in addition to improving the coupling between glycolysis and glucose oxidation, MCD inhibition may improve coupling between substrate availability and oxidation, thereby reducing excess acetyl-CoA (and subsequent use for protein acetylation). However, MCD inhibition would not normalize the balance between lipid availability and oxidation, an issue that may become more problematic in dyslipidemic states.

In summary, Wang et al. (9) have revealed MCD inhibition as a promising therapeutic target for heart failure. Improved cardiac function and efficiency following MCD inhibition (in a rat model of myocardial infarction–induced heart failure) was associated with reduced myocardial glycolytic flux (and presumably, proton accumulation). The investigators postulated that benefits of MCD inhibition were primarily through coupling of glycolysis with glucose oxidation. The relative contribution of other metabolism-related mechanisms (e.g., coupling between substrate availability and oxidation) requires further elucidation.

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REFERENCES

1. Taegtmeyer H, Lubrano G. Rethinking cardiac metabolism: metabolic cycles to refuel and rebuild the failing heart. F1000Prime Rep 2014;6:90.

2. Young ME. Temporal partitioning of cardiac metabolism by the cardiomyocyte circadian clock. Exp Physiol 2016;101:1035–9.

3. Taegtmeyer H, Golfman L, Sharma S, Razeghi P, van Arsdall M. Linking gene expression to function: metabolic flexibility in the normal and diseased heart. Ann N Y Acad Sci 2004;1015:202–13.

4. Neubauer S. The failing heart-an engine out of fuel. N Engl J Med 2007;356:1140–51.

5. Wende AR, Brahma MK, McGinnis GR, Young ME. Metabolic origins of heart failure. J Am Coll Cardiol Basic Transl Sci 2017;2:297–310.

6. Liu Q, Docherty JC, Rendell JC, Clanachan AS, Lopaschuk GD. High levels of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. J Am Coll Cardiol 2002;39:718–25.

7. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiol Rev 2010;90:207–58.

8. Fillmore N, Mori J, Lopaschuk GD. Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy. Br J Pharmacol 2014;171:2080–90.

9. Wang W, Zhang L, Battiprolu PK, et al. Malonyl CoA decarboxylase inhibition improves cardiac function post myocardial infarction. J Am Coll Cardiol Basic Transl Sci 2019;4:385–400.

10. Fillmore N, Lopaschuk GD. Malonyl coA: a promising target for the treatment of cardiac disease. IUBMB Life 2014;66:139–46.

11. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785–9.

12. Lionetti V, Stanley WC, Recchia FA. Modulating fatty acid oxidation in heart failure. Cardiovasc Res 2011;90:202–9.

13. Lionetti V, Linke A, Chandler MP, et al. Carnitine palmitoyl transferase-I inhibition prevents ventricular remodeling and delays decompensation in pacing-induced heart failure. Cardiovasc Res 2005;66:454–61.

14. Lee L, Campbell R, Scheuermann-Freestone M, et al. Metabolic modulation with perhexiline in chronic heart failure: a randomized, controlled trial of short-term use of a novel treatment. Circulation 2005;112:3280–8.

15. Bristow M. Etomoxir: a new approach to treatment of chronic heart failure. Lancet 2000;356:1621–2.

16. Holubarsch CJ, Rohrbach M, Karrasch M, et al. A double-blind randomized multicentre clinical trial to evaluate the efficacy and safety of two doses of etomoxir in comparison with placebo in patients with moderate congestive heart failure: the ERGO (Etomoxir for the Recovery of Glucose Oxidation) study. Clin Sci (Lond) 2007;113:205–12.

17. Ussher JR, Fillmore N, Keung W, et al. Genetic and pharmacological inhibition of malonyl CoA decarboxylase does not exacerbate age-related insulin resistance in mice. Diabetes 2016;65:1883–91.

18. Aubert G, Martin OJ, Horton JL, et al. The failing heart relies on ketone bodies as a fuel. Circulation 2016;133:698–705.

19. Bedi KC Jr., Snyder NW, Brandimarto J, et al. Evidence for intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. Circulation 2016;133:706–16.

20. Sun H, Olson KC, Gao C, et al. Catabolic defect of branched-chain amino acids promotes heart failure. Circulation 2016;133:2038–49.

21. Senf SM, Sandesara PB, Reed SA, Judge AR. p300 Acetyltransferase activity differentially regulates the localization and activity of the FOXO homologues in skeletal muscle. Am J Physiol Cell Physiol 2011;300:C1490–501.

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