

EDITORIAL COMMENT

Metabolic Reprogramming After Left Ventricular Assist Device

Remodeling Without Recovery of Cardiac Energetics*

J. Eduardo Rame, MD, MPHIL,^a Emma J. Birks, MD, PhD^b



Despite impressive changes at the organ, tissue and cellular level in myocardial reverse remodeling with left ventricular assist device support, reprogramming the presumed “end-stage” human heart toward the nonfailing phenotype has not been convincingly demonstrated (1-5). Many have questioned the possibility of achieving sustained myocardial “recovery” using our current technology, leading to a call for further investigation by a recently gathered National Heart, Lung, and Blood Institute task force (6). Metabolic adaptations have been reported in the calorie-restricted, exercising, ischemic, and failing myocardium—and recently, the lipidomic signature of the end-stage failing, nondiabetic human heart has revealed rarefied lipid stores and evidence for a newly discovered shift to ketones as an alternative energy fuel (7-10).

SEE PAGE 432

Enter the highly anticipated work by Diakos et al. (11) to fill in the translational knowledge gaps between myocardial recovery and metabolic adaptation after left ventricular assist device (LVAD) support. The authors performed targeted and untargeted quantitation of metabolites with mass spectroscopy to characterize the metabolic phenotype of myocardial reverse remodeling with mechanical unloading in nonfailing donor hearts, as well as paired myocardial

samples obtained before LVAD and before transplantation after LVAD support. Their analyses revealed the following signatures: 1) increased glycolytic flux without a commensurate increase in glucose oxidation resulting in increased myocardial pyruvate and shuttled lactate levels; 2) a persistent disruption in the tricarboxylic acid (TCA) cycle characterized by splitting between first-span and second-span levels of intermediates; 3) a deficit in mitochondrial oxidative capacity with decreased State III and State IV respiration in the chronically failing heart not improved with mechanical unloading; and 4) decreased density and altered structure of mitochondria in failing hearts pre- and post-mechanical unloading. The authors (11) reason that the decoupling of the utilization of glucose in the failing myocardium—glycolysis from oxidation—is linked with deficits in mitochondrial function, both in the cycling of intermediary metabolites and oxidative phosphorylation. In order to interpret the significance of these findings, we first need to step back and understand the current work in the context of recent advances in our understanding of the metabolic adaptation of the failing heart. Second, we need to ask exactly what are the mechanisms behind this remodeling in the adaptive metabolism of the failing heart that fall well short of recovering the cardiac energetics with mechanical assist device support?

Muscle, both cardiac and skeletal, has a high degree of plasticity to the changing conditions challenging its environment. In response to a change in loading conditions and loss of contracting mass and function, metabolic adaptations have been demonstrated in the failing mammalian heart including decreased utilization of fatty acids with a shift to the more oxygen-sparing energetic substrate of glucose (12-14). The work by Diakos et al. (11) convincingly

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From the ^aCardiovascular Division, University of Pennsylvania, Philadelphia, Pennsylvania; and the ^bCardiovascular Division, University of Louisville, Louisville, Kentucky. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

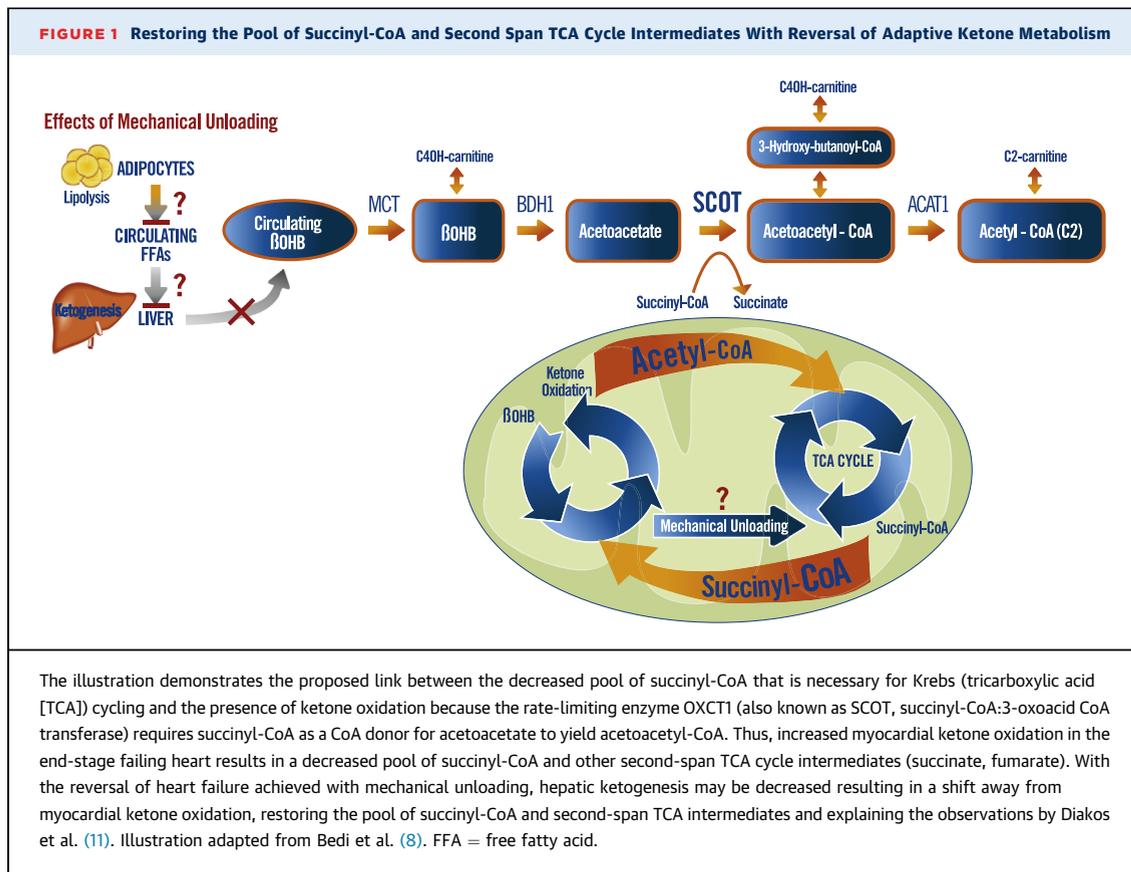
demonstrates decreased levels of glucose-1-phosphate and glucose-6-phosphate in the end-stage failing myocardium, which is indicative of a decreased utilization of glucose, and is consistent with decreased glycolysis in advanced heart failure. The importance of this finding, coupled with the demonstration that with mechanical unloading there is an increase in the levels of glycolytic metabolites is extremely important, insofar as it shows that there is not a uniform shift to increased glucose metabolism across the broad spectrum of heart failure. Instead, these data support the dynamic model of metabolic adaptation across the different stages of heart failure, with specific metabolic signatures apparent in responders versus non-responders. Indeed, although not large enough for analysis, the subgroup of patients with significant myocardial functional improvement after mechanical unloading did show greater mitochondrial functional and structural improvement than the “nonresponders.” A study investigating the metabolic phenotype of nonselective adrenergic receptor blockade in chronic human heart failure with 18-fluoro-deoxyglucose positron emission tomography demonstrated an increased uptake of glucose in the patients with the most significant degree of myocardial reverse remodeling and improved left ventricular ejection fraction (15). Thus, an improved myocardial phenotype may shift more towards increased reliance on glucose metabolism. The work by Diakos et al. (11) extends the observation of myocardial plasticity in metabolic adaptation to the end-stage failing heart transitioning to mechanical support and provides evidence of increased glucose utilization through glycolysis but without the capacity to couple this with the oxidation of pyruvate and increased oxidative metabolism.

When considering the impact of these results on future investigation, an important question concerns the mechanism of how glycolytic flux becomes uncoupled from glucose oxidation. This uncoupling results in a bottleneck increasing the myocardial levels of pyruvate and lactate above the nonfailing levels after a period of mechanical unloading. Could the increase in glycolysis be the result of improving myocardial insulin resistance that has been reported after LVAD therapy (16,17), with the bottleneck at pyruvate representing a failure to release the brake on pyruvate dehydrogenase (PDH) caused by the excess circulating fatty acids? In essence, the effects of the Randle Cycle (18)—inhibition of glucose oxidation by fatty acid uptake and utilization—may persist until the complete reversal of the heart failure syndrome with subsequent normalization of the peripheral metabolic milieu. Alternatively, is the

increased concentration of glycolytic metabolites the result of a “shift back to glucose” and away from ketone metabolism (7,8), as peripheral insulin signaling improves, effectively decreasing or halting hepatic ketogenesis? If so, there may be a novel link switching cardiac substrate utilization on/off under failing conditions which accompanies the metabolic reprogramming to an earlier stage of heart failure marked by a preferential metabolism of glucose.

Diakos et al. (11) have correctly identified abnormalities in mitochondrial structure and function in the failing heart that persist after a period of mechanical unloading, invoking this broader mechanism as the reason for the impaired oxidation of glucose and the decoupling from glycolysis. They present very convincing data that the TCA cycle, which was recently demonstrated to be disrupted in advanced heart failure with a decreased ratio of succinyl-CoA (an early second-span intermediate) to acetyl-CoA (the proximal metabolic point of entry), remains abnormal despite effective mechanical unloading with LVAD therapy (8). A proposal is made by the authors that mechanisms involving anaplerosis and cataplerosis interacting with amino acid metabolism can explain the changes in the intermediate metabolites of the Krebs cycle. However, what remains unexplained is the difference in post-LVAD levels between first-span (remain decreased) and second-span (restored to non-failing levels) intermediates. Precisely why are the metabolites after succinyl-CoA restored as the end-stage failing heart remodels with mechanical unloading? This may again represent a “switch away from ketones” because succinyl-CoA is no longer shuttled from the TCA cycle to serve as the CoA donor in the rate-limiting step of ketone oxidation through the enzyme SCOT (succinyl-CoA:3-oxoacid CoA transferase) that was demonstrated to be significantly up-regulated in the end-stage failing human heart (8) (Figure 1). Thus, the active oxidation of ketones results in a depletion of succinyl-CoA while reversing this state through a decrease or halting of ketogenesis restores the myocardial pool of succinyl-CoA and second-span TCA cycle intermediates. Given the importance of succinylation and acetylation in the transcriptional and enzymatic control of important metabolic pathways, the myocardial concentration of succinyl-CoA may play a key role in the regulation of metabolic adaptations across the various stages of heart failure.

What are the therapeutic implications of this work in the field of myocardial recovery with LVAD therapy? It should be noted that the present study by Diakos et al. (11) focused on the effects of mechanical unloading rather than the metabolic signature of



recovery because these were paired samples from patients bridged to transplantation. We are approaching the final follow-up phase of the prospective, multicenter study of myocardial reverse remodeling with LVAD and standard optimized heart failure therapies (ReSTAGE HF [Remission from Stage D Heart Failure]). The ReSTAGE-HF study was designed to evaluate the rate of recovery when centers optimize pump speed for unloading and use optimal heart failure therapy. By including intermittent testing of underlying function at set time points in a common protocol the rate of recovery under “best standard” conditions will be determined. Once this has been established the next phase will be to consider adjunctive therapies, that is, drugs and strategies that can be added, to firstly further promote reverse remodeling and enhance the rate and degree of myocardial reverse remodeling, and secondly and importantly, to enhance its durability. Previously, the Harefield, United Kingdom, group successfully added clenbuterol as an adjunctive second stage of the therapy, which was done to enhance the durability of recovery (1). Adding a period of cardiac reloading before explantation is

also likely to be beneficial, and the work by these authors suggests this might have beneficial effects on mitochondrial structure and function. Like exercise, which has been shown to improve mitochondrial function, cardiac reloading may prove to be an important addition to recovery protocols. The current study also suggests that novel drugs targeting mitochondrial function and enhancement of metabolic adaptation might serve as important additions to recovery protocols to improve the myocardial function and durability of the therapeutic approach. Starting with this important contribution by Diakos et al. (11), further understanding of the metabolic phenotypes resulting from the reversal of heart failure is likely to enhance, not only our rate of myocardial recovery, but the durability after explantation that may be the real target in our efforts to reprogram the failing human heart.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. J. Eduardo Rame, Cardiovascular Institute, University of Pennsylvania, 11th Floor South Tower, 3400 Civic Center Boulevard, Philadelphia, Pennsylvania 19104. E-mail: Eduardo.rame@uphs.upenn.edu.

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