Effective Metabolic Approaches for the Energy Starved Failing Heart

Bioenergetic Resiliency via Redundancy or Something Else?

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One of the major unresolved questions in cardiovascular physiology is which steps in the cascade of carbon substrate preference, mitochondrial ATP production, conduction, and utilization ultimately limit maximal performance of a normal heart or contribute to the dysfunction of a failing heart.[1–4] For the past 3 decades or more, scientists have been trying to modulate carbon substrate utilization by increasing or decreasing glucose or free fatty acid utilization and more recently by modulating ketone body metabolism, as a metabolic therapeutic approach to treat heart failure.[5] Approaches have included modulating carbon substrate utilization and flux by altering the expression of substrate transporters, key metabolic enzymes, allosteric regulators of these pathways, or mitochondrial oxidative capacity as metabolic approaches to examine the old hypothesis that a failing heart is energy starved. Some of these studies have supported the hypothesis although others have not. There is no question that myocardial energy flux and mitochondrial capacity is reduced in the failing heart.[3,4,6] The question is whether these changes are causal or a secondary adaptation of the failing heart. For example, increasing substrate flux capacity before the insult has in some instances decreased the susceptibility to heart failure,[7,8] however, the modulation of metabolism at the time of the hemodynamic insult might not prevent contractile dysfunction.[9] Moreover, increasing mitochondrial biogenesis might not prevent left ventricular (LV) dysfunction despite maintaining mitochondrial capacity.[10] Examination of myocardial substrate intermediates before and after LV assist device implantation suggest the existence of mitochondrial plasticity, and examination of mitochondrial respirometry in isolated mitochondria from failing hearts in vitro have not revealed overt defects in oxidative capacity.[11]

Two concepts that warrant further consideration is the notion that the heart has multiple redundant mechanisms that increases its resiliency. The interaction and integration of these pathways might be perturbed in the failing heart and for metabolic modulation to work, these nodes of integration need to be completely understood and will be the major focus of this perspective. The second concept might be that changes in the metabolic fluxes that characterize the failing heart lead to the accumulation of metabolic intermediates that alter signal transduction pathways that promote LV remodeling.[12,13] Our laboratory and others have contributed to the notion of increased myocardial resilience. For example, after inhibition of free fatty acid utilization by blocking CPT1 (carnitine palmitoyl transferase) using oxfenicine, or inhibiting glucose utilization using 2 deoxyglucose, the heart can quickly switch to the other available carbon substrates, to maintain mitochondrial oxidative phosphorylation and LV chamber function. Further, we have done experiments in the extreme to examine whether mitochondrial oxidative capacity (proximal to ATP synthase) was exhausted in hypertrophied and failing hearts during catecholamine stimulation and concomitant exposure to the mitochondrial uncoupling agent 2,4-dinitrophenol,[1] or after inhibition of creatine kinases by iodoacetamide.[2] The heart continues pumping despite these extreme interventions after blockade of one key bioenergetic pathway. These extreme experiments demonstrate that in the heart in vivo, when one of the important pathways in the bioenergetics networks is removed (in this case the ATPase or CK [creatine kinase] system), the other supporting systems such as AK (adenylate kinase), glycolytic, and other phosphotransfer pathways can be activated to support the energy demand at the contractile apparatus to maintain cardiac output. We speculate that in the energy machinery system of the in vivo failing heart, the redundant ATP production/transportation systems, such as CK, mitochondrial electron transport system, AK, glycolytic, and guanine nucleotide phosphotransfer pathways, may all be impaired, thus reserve is exhausted. Consequently, the severity of each of the alterations of these systems may synergistically act to increase the severity of LV dysfunction of failing hearts. This resiliency of the heart to the blockade of one, or even multiple, metabolic pathways and the redundancy of chemical energy production systems may explain why other regulators of mitochondrial metabolism such as calcium may contribute to the maintenance of cellular energy homeostasis in the failing heart.

Cardiac muscle can increase ATP turnover rates from resting to heavy exercise, by 10-fold; whereas, the skeletal muscle manifests an energy reserve range of up to 100-fold.[14] These underscore the very wide dynamic range in the cellular balance of ATP production and utilization. The apparent

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narrower range in the heart relative to skeletal muscle may reflect fundamental differences in the physiological roles of the heart versus skeletal muscle, in which the heart maintains consistently high levels of contractile function, whereas the need for large increases in skeletal muscle performance is intermittent. With such an extreme capacity of energy reserve in the muscle, it is almost inconceivable that energy starvation can occur in any muscular organ in vivo, which in principle, disputes the age-old hypothesis that dysfunction of the failing heart is caused by the energy insufficiency. With such a fast turnover rate in myocardial cellular bioenergetics, many investigators have wondered how chemical energy produced in the mitochondrial inner membrane is rapidly delivered to the contractile apparatus in the cytosol. Using advanced imaging technology, Balaban's group recently demonstrated that in skeletal muscle this bioenergetics of ATP turnover may occur through a conduction system, but not diffusion.[15] Recently, the Zhang group[6] used a novel double magnetization saturation transfer to measure ATP hydrolysis rate in the in vivo normal porcine heart and demonstrated an ATP utilization rate of ≈0.9 μmol/g per second, which is similar to the baseline of a normal human heart. This translates to ≈8 kg of ATP/day in an adult human heart, which matches rates that scientists have speculated for decades. Healthy hearts can respond to exercise by increasing the rate of ATP production and utilization 5-fold within a few seconds, but the myocardial concentration of ATP remains constant, which illustrates how extraordinarily fine-tuned this system is, with a very high reserve in production capacity, but very low storage of energy. In addition, this bioenergetic system is extremely efficient in that ATP produced from the mitochondrial inner membrane, is almost immediately available at the cytosolic contractile apparatus. This extreme efficiency may reflect conduction in the mitochondrial reticulum, rather than facilitated diffusion.[15] In muscle, the concentration of mitochondrial oxidative phosphorylation complexes is finely tuned and regulated to match the requirements of the contractile apparatus for chemical energy. Importantly, mitochondrial ATPase activity was shown to be modulated by changes in the metabolic need of the heart in vivo, and protein phosphorylation of mitochondrial ATPase is linearly correlated with the energy demand suggesting that protein phosphorylation may contribute to activity modulation of cellular energy homeostasis. These data are consistent with the notion that metabolic stress modulates mitochondrial oxidative phosphorylation complexes activity in the heart.

The complexity of life sciences is enormous. It may be reasonable to concede that our understanding of the mechanisms and signaling pathways of myocardial bioenergetics remains a work in progress. As such, although we might be inching closer to novel metabolic interventions for treating heart failure patients with energy starvation in the failing heart, it is important to acknowledge that the solution might transcend repairing carbon flux. Specifically, it will be important to restore compensatory mechanisms that increase myocardial resiliency and to address changes in signaling pathways that develop on the basis of nonmetabolic effects of signaling intermediates that may accumulate in the failing heart. Life sciences have completed 2 revolutions since 1950s. We are now in the third revolution of convergence of sciences across multiple disciplines. The molecular and cellular revolution (1953) and genomic revolution (2001–2009), and systems integration of rapidly accumulating knowledge in the past half-century usher in the third revolution: Convergence Revolution. With the integration of sciences in physics, computer engineering, and large data insights, which are increasingly guiding life sciences discoveries, we should get closer to delivering metabolic approaches to prevent or treat heart failure that address the complex pathophysiological interactions that exist in this clinically challenging condition. Having said that, it is important to convey that the management of patients with heart failure must also address hemodynamics of the muscle chamber and not only the expression of selected genes or proteins, or activity levels of signaling or metabolic pathways in cardiomyocytes.

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Disclosures

None.

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