Mitochondrial dysfunction in heart failure. Lessons from a hereditary mitochondrial disease

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Energy is continuously required to sustain myocardial contractile and electrical function, and insufficient energy production has been associated with heart failure.¹ The normal heart requires about 15 times its weight (6 kg) of adenosine triphosphate (ATP) daily to sustain normal function. ATP can be generated from differing substrates via different metabolic pathways, depending on age. The fetal heart relies primarily on aerobic glycolysis and the oxidation of lactate for energy production.² In the early neonatal period, exposure to a higher oxygen tension and LV pressure-volume work is associated with a rapid increase in myocardial mitochondrial mass and oxidative capacity. As the heart matures, lactate oxidation and glycolysis decrease as fatty acid oxidation assumes increasing importance as a source for ATP production. However, the mature heart is an “omnivore” and it can flexibly utilize differing substrates to generate ATP, depending on specific substrate availability, energy demand, and hormonal milieu. Amino acids, ketone bodies, lactate, lipids, and carbohydrates can all be consumed. Normally, more than 95% of the ATP generated by the heart is derived via mitochondrial oxidative phosphorylation. Mitochondria are the key to energy production in the cardiomyocyte, and understanding how their function is impacted in heart failure is crucial for identifying alternative energy-

producing pathways that might potentially be manipulated for therapeutic benefit.

BARTH SYNDROME: A MITOCHONDRIAL DISEASE

In this issue, Cade and colleagues describe the findings on PET imaging, echocardiography, and ³¹P magnetic resonance spectroscopy in 14 patients with Barth Syndrome without overt heart failure.³ Barth Syndrome is an X-linked recessive disorder characterized by skeletal myopathy, neutropenia and cardiomyopathy.⁴ It is believed to affect about 1/300,000 to 1/400,000 live births. The syndrome results from a mutation in a gene on chromosome Xq28 which codes for tafazzin.^{5,6} Tafazzin is a protein (a transacylase) which resides on the inner mitochondrial membrane, where it serves to remodel the phospholipid cardiolipin. Cardiolipins are key participants in mitochondrial ATP production, and alterations in these phospholipids may result in reduced mitochondrial membrane potential, respiratory chain dysfunction (complex V), and ultrastructural muscle damage.

Barth cardiomyopathy usually presents before age 5 as a progressive dilated cardiomyopathy. However, it may spontaneously improve or remain stable. Cardiomyopathy can occur with or without ventricular non-compaction, and with or without endocardial fibroelastosis. Rarely, hypertrophic cardiomyopathy can be identified and it may transition from the hypertrophic type to the dilated type over time and vice versa. Heart failure may not develop until late in some patients, and it may not be manifest at all in others. *Thus, the patients in this study may not be representative of all with Barth Syndrome, as they survived to adulthood (mean age = 26 years) and did not have overt heart failure at the time of imaging.* Whether similar findings would be

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found in younger subjects with more advanced left ventricular dysfunction is uncertain.

FINDINGS IN BARTH SYNDROME

As compared with 11 controls, Barth Syndrome patients had higher myocardial glucose extraction fractions, uptake, and rates of utilization. These findings are concordant with the accelerated rates of glucose uptake and glycolysis previously reported in heart failure, in which reversion to a fetal pattern of metabolism has been proposed.² Plasma glucose levels and insulin levels did not differ between the groups, and the findings are not explicable because of differences in these levels. Moreover, myocardial blood flows and rate-pressure products did not differ between the groups, suggesting comparable ventricular workloads when imaged. Due to radiation safety concerns, C-11 acetate imaging was not performed. Dynamic C-11 acetate imaging could have given information regarding myocardial oxygen consumption, and indicated whether glucose oxidation rates per se were increased or decreased in the patients. Prior studies suggest that increases in glucose uptake and glycolytic rates in heart failure may not be associated with increases in glucose oxidation, possibly reflecting increased activity of 6-phosphofructokinase (a rate-limiting glycolytic enzyme) and unchanged or decreased mitochondrial oxidation of pyruvate. Thus, prior studies indicate that while the relative contribution of glucose to ATP generation in the failing heart increases, the flux of this substrate through oxidative pathways may actually be decreased.

Fatty acid extraction and uptake were lower in the patients, but overall rates of fatty acid oxidation and utilization did not differ from controls. Plasma free fatty acid levels in the patients were about 40% higher than controls and higher substrate delivery rates might, in part, explain why rates of oxidation and utilization were comparable. The findings differ from patients with inherited cardiomyopathies associated with acyl-CoA dehydrogenase and 3-hydroxyacyl-CoA deficiencies, in which both fatty acid uptake and oxidation rates are lower, and in which systemic free fatty acid levels are similar to normals.^{7,8} In contrast to findings in the authors' mouse Barth Syndrome model, rates of leucine turnover in the patients did not differ from the controls, suggesting similar utilization rates of this amino acid.

RELATION TO MYOCARDIAL CONTRACTILE FUNCTION

In previous studies, impairment in glucose and lactate oxidation have preceded an identifiable impairment in fatty acid oxidation and a decline in ventricular

contractile function. Employing a step-wise regression statistical analysis, the authors found that the only predictor of global strain on echocardiography in the patients was the glucose extraction fraction. Similarly, the best predictors of LVEF in the patients were glucose extraction fraction and rates of fatty acid oxidation. While mean phosphocreatine/ATP ratios on ³¹P magnetic resonance spectroscopy (an index of available myocardial energy) were about 18% lower than in controls, the ratios were not predictive for either global LV strain or ejection fraction. Unfortunately, while the disturbances in metabolism in Barth Syndrome appear related to left ventricular function, it was not possible to test for interactions between blood flow, substrate levels, cardiac phosphocreatine/ATP ratios, and glucose and fatty acid metabolism in a multivariate statistical model, due to the limited number of subjects available for study.

CAN METABOLIC INTERVENTION IMPROVE HEART FAILURE?

The study by Cade et al adds to our knowledge of the cellular metabolic disturbances in heart failure. If the failing heart is an "engine out of fuel,"¹ then the hope is that therapeutic manipulation of metabolism might increase energy for ventricular function. However, this concept must be considered further, as the failing myocardium may be incompletely characterized by analysis of substrate metabolic rates alone. For example, energy created by mitochondrial oxidative phosphorylation is transferred from inside the mitochondrion to the cytosol via a phosphocreatine shuttle. Mitochondrial creatine kinase transfers a phosphate group from ATP to creatine, yielding phosphocreatine. Phosphocreatine quickly diffuses into the cytosol, where cytosolic creatine kinase transfers the phosphate group to ADP. This generates cytosolic ATP which can be utilized to fuel contractile function. Prior studies indicate that the rate of cytosolic creatine kinase dependent ATP synthesis is reduced in heart failure and that this reduction is correlated with poorer outcomes.⁹ The reduced rate of ATP synthesis thus appears more important for cellular energetics than the absolute size of the ATP pool or the phosphocreatine/ATP ratio, at least in the early stages of failure.

In addition, altered metabolism affects more than ATP synthesis.¹⁰ Some metabolic intermediates also serve as signal transducers, and interventions which impact the level of these intermediates could affect these signaling processes. For example, acetyl-CoA induces cellular growth and proliferation by promoting the acetylation of histones, while pyruvate stimulates mitochondrial biogenesis. Moreover, in diabetes and obesity, there is a shift in mitochondrial phenotype which

promotes fatty acid oxidation and the blunting of glucose oxidation.¹¹ With higher fatty acid fluxes, there can be an uncoupling of mitochondrial ATP formation and the creation of reactive oxygen species. Reactive oxygen species can in turn influence the activity of multiple enzymes and the redox state of the tissue, inflict structural damage to mitochondria, result in the accumulation of lipids, promote lipotoxicity, incite inflammation, and induce hypertrophy and fibrosis. Thus, heart failure is also associated with structural remodeling which can impact contractile function.

Once remodeling occurs in the failing myocardium, it is unclear if the process can be reversed even if the appropriate intervention can be identified. For example, in patients with Takotsubo cardiomyopathy, persistently abnormal phosphocreatine/ATP ratios can be identified more than a year following the clinical event, despite normal left ventricular ejection fractions and serum biomarkers.¹² “Reverse remodeling” has also been examined in human hearts explanted from transplant recipients who have undergone mechanical circulatory support with left ventricular assist devices.¹³ Although mechanical support improves left ventricular contractile function and may decrease the deposition of collagen in the extracellular matrix (especially when employed with an ACE-inhibitor), mitochondrial oxidative capacity remains reduced and increased rates of glycolysis persist. In addition, persistent abnormalities in gene expression and in protein-coding and non-coding RNAs have been identified in reverse remodeled myocardium.

HOPE FOR METABOLIC TREATMENT OF HEART FAILURE

Despite the complexities, clinical trials have tested or are in the process of assessing metabolic interventions in human heart failure. These therapies differ from those employed in traditional heart failure regimens and thus may provide additional tools for the clinician. For example, resveratrol, a naturally occurring polyphenol with antioxidant properties is currently being tested in several clinical trials of patients with heart failure (NCT01914081, NCT03525379). In the Q-SYMBIO trial, coenzyme Q₁₀ was employed in a study of 420 patients with Class III/IV heart failure¹⁴ (Low myocardial levels of coenzyme Q₁₀, a lipid-soluble electron carrier which is key to mitochondrial electron transport and ATP synthesis, are present in heart failure). In this randomized, double-blind clinical trial, 300 mg of coenzyme Q₁₀ daily resulted in significant reductions in two-year all-cause mortality, cardiovascular mortality and the incidence of hospitalizations for heart failure.

Myocardial utilization of ketone bodies also increases in heart failure, and a recent study by Nielsen

and colleagues¹⁵ examined the acute effects of a three-hour intravenous infusion of 3-hydroxybutyrate on cardiac output, myocardial external energy efficiency and oxygen consumption in 16 patients with chronic heart failure (mean LVEF = 37 ± 3%). The ketone infusion significantly increased LVEF by 8 ± 1% and cardiac output by 2.0 ± 0.2 L/min. Although myocardial oxygen consumption increased, this was in proportion to the increase in cardiac work, resulting in no change in myocardial external energy efficiency.

Elamipretide, a tetrapeptide which associates with cardiolipin on the inner mitochondrial membrane, has been shown in pre-clinical trials to reduce mitochondrial dysfunction and to improve cardiac function. It improves electron flow through the electron transport chain, thereby increasing ATP synthesis and reducing the generation of reactive oxygen species. In 8 patients with heart failure,¹⁶ a four-hour infusion of the drug acutely decreased end-diastolic and end-systolic volumes (by 18 and 14 mL, respectively). Currently, elamipretide is being employed in a clinical trial of patients with Barth Syndrome (MCT03098797), in the hopes of improving the hereditary mitochondrial dysfunction in these patients.

As these clinical trials illustrate, there is growing enthusiasm for metabolic intervention in patients with heart failure. As such, noninvasive imaging techniques such as those employed by Cade and colleagues in the present investigation will likely prove helpful in the future for identifying potential therapeutic targets for metabolic intervention and also provide a means of assessing the efficacy of these treatments.

DISCLOSURES

The author has no disclosures relevant to this editorial.

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