THE FAILING HEART: ENERGY SUPPLY, PROCESSING, AND TRANSFER

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The failing human heart is energy depleted regardless of the underlying etiology. Noninvasive ^{31}P -MR spectroscopy studies document this in human hearts. These same studies reveal a progressive decline in energy or phosphocreatine-to-ATP ratio as the severity of heart failure increases.¹ Furthermore, the degree of depletion predicts all-cause and cardiovascular mortality.

To understand cardiac energy depletion, one must have a general understanding of the cardiac metabolic process. The free energy released from the terminal phosphate bond of ATP during conversion to ADP fuels contraction. These high-energy bonds originate by and large from the intramitochondrial process of oxidative phosphorylation. The energy contained in carbon bonds of glucose, fatty acids, amino acids, glutamate, and lactic acid supplies the power chain; it is transferred to ATP and stored as phosphocreatine. ATP itself is short lived, and its availability depends on the phosphocreatine reservoir. Cardiac energy depletion can result from several mechanisms. For example, mitochondrial dysfunction or impaired energy transfer of phosphocreatine from mitochondria to cytoplasm can affect substrate supply and/or processing and result in a decreased phosphocreatine-to-ATP ratio. In individual cases, a question remains as to the cause of the decline—whether from substrate supply, substrate metabolism, or energy transfer. If the specific mechanism could be identified in an individual patient, then personalized therapeutic interventions could be designed.

In this issue of the *Methodist DeBakey Cardiovascular Journal*, investigators from the Houston Methodist Research Institute's Center for Bioenergetic and Metabolic Research and a guest author from the University of Alabama School of Medicine review their research in the field of cardiac metabolism with a special focus on the failing human heart. The objective of these laboratory efforts is to provide insight into metabolic mechanisms in a variety of heart failure etiologies.

The article by Shumin Li, Ph.D., and Anisha Gupte, Ph.D., presents evidence on the link between estrogen and heart failure with preserved ejection fraction (HFpEF), while another article by Deokhwa Nam, Ph.D., and Erin Reineke, Ph.D., discusses the mechanism of pressure overload-induced metabolic preconditioning in the left ventricular wall that precedes anatomic hypertrophy. In the estrogen paper, Drs. Li and Gupte describe a preclinical model developed at the Houston Methodist Research Institute to investigate the role of estrogen deficiency in HFpEF and discuss the mechanisms that could lead to novel therapeutic interventions. In their article on pressure overload, Drs. Nam and Reineke review current findings on the control of gene expression and metabolic adaptations to pressure overload that precede the anatomic changes leading to left ventricular hypertrophy. The authors provide an interesting perspective that increases awareness of the need for early diagnostics and novel interventions to prevent subsequent anatomical changes.

Another article, this one by Dr. Yang Wu, visiting cardiovascular surgeon, Dr. Aijun Zhang, center research scientist, and Tuo Deng, Ph.D., senior author, discusses the impact of epicardial fat on cardiovascular health. The impact of epicardial fat on myocardial function is not well understood. Distinct from pericardial fat, epicardial fat is more than just a cushion for the coronary arteries; this depot of inflammatory epicardial adipose tissue has a negative impact on cardiac energy metabolism. The elucidation of pathophysiologic mechanisms of this depot and its role in cardiovascular disease is emerging. Awareness and understanding of the mechanistic impact on myocardial function and its blood supply may help determine how new therapeutic interventions can be developed.

The special article by Martin Young, D.Phil., relates circadian rhythm to cardiovascular disease, a link that at first glance might not be on the top of our minds. However, one need consider the possibility of achieving better outcomes if interventional procedures were completed at a certain time of day, or if metabolism and cardiac function were assessed later in the day rather than earlier. The review by Dr. Young highlights the roles of cardiac metabolism rhythms, including clock effects at the cardiomyocyte level, and discusses the potential pathological consequences of their impairment.

A final article by Zhang Li and colleagues presents the emerging role of metabolic imaging using positron emission tomography (PET) and how it could redirect and individualize our therapeutic guidelines. The use of specific positron-emitting isotopes, some with very short half-lives such as carbon-11 radiotracers, must be generated by an on-site cyclotron. Myocardial [^{11}C]palmitate and [^{18}F]fluoro-D-glucose PET studies, such as those that have been completed using the Research Institute cyclotron and the small-animal PET facility, could be used to identify substrate changes in the stressed myocardium, ascertain a diagnosis, and guide clinical decision making.²

Our goal for this issue of the *Methodist DeBakey Cardiovascular Journal* is to increase awareness of contemporary metabolic research efforts that may lead to future diagnostic modalities and therapeutic interventions in clinical cardiology. We emphasize the development of personalized metabolic and diabetic therapy based on mechanistic evaluations for individuals with heart failure. The next issue of this journal will expand on this by reviewing the impact of the endocrine system on cardiovascular disease.

References

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