Energetics in heart disease

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Editorial

Even subtle variations in the efficiency of energy generation or utilization may have a profound impact on cellular energy levels. Different cardiac pathologies can alter cardiac efficiency, both as a result of a decrease efficiency of producing ATP or alterations in the efficiency of using ATP to produce contractile work. Given that the requirement for ATP for all metabolic processes and for cell viability is absolute, a renewed interest in metabolism has led to identification of the molecular links between physiological and metabolic stimuli and the regulation of gene expression in the heart. Metabolism remodels in the failing heart leading to the inability to increase ATP supply. Ultimately, this may lead to a fall in ATP. The likely time line is decreased energy production via the phosphotransferase reactions (creatine kinase and adenylate kinase) leading to increases in ADP and AMP. As heart failure evolves, ATP synthesis from oxidation of metabolic substrates by mitochondria, the major source of ATP in the heart, falls. Remodeling of the failing myocardium is controlled by energy sensors, such as AMP-activated protein kinase (AMPK) that regulates energy substrate metabolism and regulates transcription of metabolic genes. This issue of *Heart and Metabolism* addresses the important topic of energetics in heart disease.

In the Basic Article, Dr. Aasum offers a concise review of myocardial energetic mechanisms, focusing on alterations in processes related to energy production and energy utilization in the failing heart. The Main Clinical Article by Dr. Ashrafian gives a clear and elegant overview of successful metabolic therapies presently available, especially for chronic ischemic heart disease. While considering the likely future directions for metabolic therapy, Dr. Ashrafian also points out the need for greater experience with the existing metabolic therapies, which could benefit most to those patients with concomitant metabolic disease, such as metabolic syndrome or diabetes mellitus.

In this context the Refresher Corner article by Drs. Fillmore and Lopaschuk provides a didactic summary of the state of the art, showing notably how metabolic substrates compete at myocardial cell level for energy production and how they may affect cardiac efficiency. Alterations in the balance between fatty acid and glucose use are known to occur in certain heart pathologies such as during ischemia and in the failing heart. This leads to decreased cardiac efficiency through a number of mechanisms that are reviewed and discussed herein, among which are intracellular ionic (H^+, Na^+, Ca^{2+}) disturbances and their deleterious consequences. Measuring metabolic substrate utilization in humans has been difficult. The Metabolic Imaging article by Dr. Camici underlines that although the quantification of glucose utilization rates in patients encounters many difficulties, positron emission tomography with the glucose

analogue 18F-fluorodeoxyglucose (FDG) may help to establish values of the metabolic rates of glucose utilization in normal and pathologic conditions.

Furthermore, Drs. Baskin and Taegtmeyer provide an authoritative New Therapeutic Approaches article that broadens the role of energy substrate metabolism from a provider of ATP to a regulator of self-renewal of cardiac myocytes. They highlight the exciting new concept of how heart muscle cells can renew themselves from within by the identification of certain metabolic signals as a root cause for altered rates of intracellular protein turnover and, hence, self-renewal of cardiac myocytes. Metabolic remodeling precedes, triggers and sustains structural and functional remodeling of the heart. As mentioned before, AMPK supports energy provision in the cell by sensing changes in the ratio [ATP]/[AMP]. In addition, decrease in [ATP]/[AMP] and the subsequent activation of AMPK regulate protein degradation. Since individual proteins are degraded through the ubiquitin proteasome system Drs. Baskin and Taegtmeyer investigated the role of AMPK in proteasome-mediated protein degradation. They found that proteasome-mediated protein degradation in the heart is indeed increased with AMPK activation. They therefore speculate that the activation of AMPK results in enhanced availability of intracellular amino acids for either ATP production or the synthesis of new proteins as the heart adapts to a new physiological state. These most recent data advance a new understanding of cardiac metabolism. They should also set us on the path to develop novel strategies aimed at optimizing metabolic therapy in heart disease. •