On substrate selection for ATP synthesis in the failing human myocardium

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In regulating entire metabolic pathways for fatty acid uptake and oxidation and glucose uptake and utilization in the hypertrophied and failing heart have been identified. These include “low on fuel” sensor AMP-dependent protein kinase, nuclear transcriptional factors such as peroxisome proliferator-activated receptor (PPAR)-α (5, 10), and transcriptional coactivators such as PPAR-γ coactivator (PGC)-1α (1, 11). The consequences of these important regulators on ATP production and contractile performance are being defined in both the normal and failing myocardium (see Ref. 3 for more discussion). Despite all this new knowledge, many questions remain: Is molecular remodeling of the metabolic network common to all forms of heart failure? At all stages? Is it progressive? Can it be manipulated? Is it adaptive or maladaptive? Most important, what is the human phenotype?

The report entitled “Impaired myocardial metabolic reserve and substrate selection flexibility during stress in patients with idiopathic dilated cardiomyopathy” by Neglia et al. (8), published in this issue, makes an important contribution to this field. Using a group of primarily class I and II patients with dilated cardiomyopathy (DCM) and age- and gender-matched normal subjects as controls, the authors tested whether the normal increase in glucose utilization that occurs with acute increases in work, in this case caused by pacing, occurs in the failing heart. Arteriovenous differences in metabolite concentrations of glucose, lactate ([13C]lactate), and free fatty acid ([3H]oleate) were used to estimate glucose uptake (glucose oxidation was not measured), lactate uptake and efflux, and fatty acid uptake and oxidation. They found that the approximately twofold increase in glucose uptake observed for the DCM myocardium at baseline did not increase further with pacing, whereas it doubled in control subjects. In terms of absolute values, glucose uptake was as high at baseline for the DCM myocardium as it was for the control myocardium with pacing, suggesting that there is an upper limit for glucose uptake in the myocardium. Fatty acid uptake and oxidation, lower in DCM hearts, remained low. The authors suggest that the decrease in fatty acid oxidation in the failing heart, while possibly compensatory at baseline, may be detrimental during stress, and that this metabolic rigidity likely contributes to the progression to failure.

The notion that the reduced energy reserve characteristic of the failing heart contributes to reduced contractile reserve is not new (4, 9). What is new is the direct demonstration that metabolic remodeling in a relatively homogenous group of class I and II heart failure patients results is rigid. This is the antithesis of the way integrated metabolism works in the normal myocyte: substrate metabolism in the normal myocyte is flexible enough to produce sufficient ATP to meet acute increases in demand. Demonstrating that substrate metabolism in class I and II DCM patients is not flexible is important for several reasons. First, although ATP content was not measured here (the experiments are very challenging as it is), there is little doubt based on basic
METABOLIC RIGIDITY OF THE FAILING MYOCARDIUM

Fig. 1. Left: diagram showing that fatty acids are the primary substrate used by the normal myocardium for ATP synthesis. Right: diagram showing that in the failing heart, fat utilization decreases while glucose utilization for ATP synthesis increases.

Tenets of biochemistry that this metabolic rigidity would contribute both to decreased ATP supply and, likely, contractile dysfunction.

Second, these clinical results provide strong support for conclusions drawn from animal studies in which genetic strategies were used to test whether the metabolic reserve of the failing heart was sufficient to support increased contractile demand. Tian and colleagues (7) showed that PPAR-α-null mouse hearts, with threefold decrease in fatty acid oxidation and threefold increase in carbohydrate utilization characteristic of the failing heart, could sustain baseline function but were not able to sustain high workloads. PPAR-α-null mouse hearts had higher than normal oxygen consumption, yet produced less ATP, and ATP concentration fell with inotropic challenge. Importantly, increasing glucose uptake and utilization further by crossing the PPAR-α-null mouse with the glucose transporter 1 overexpresser rescued the PPAR-α phenotype. Hearts were now able to sustain increased work without losing ATP concentration, and oxygen consumption and ATP synthesis rates returned to near normal. This animal study suggested that glucose utilization, if sufficiently high, can support and sustain high workload in the failing heart.

Both the mouse and clinical studies under comment here lend strong support for the concept that metabolic remodeling designed to increase ATP production is an effective strategy for treating the failing heart. It remains to be tested whether increasing fatty acid utilization or increasing glucose utilization in the failing heart would be more efficacious. Much more research needs to be done to test whether the metabolic rigidity of the failing heart persists or worsens with advanced heart failure, whether the increase in glucose utilization (or insufficient increase in glucose utilization) or decrease in fatty acid utilization is the primary defect, whether metabolic rigidity is a fundamental property of all types of heart failure, and whether novel strategies based on informed knowledge of metabolic remodeling can rescue the failing human myocardium. Overcoming metabolic rigidity in the failing heart would have significant clinical impact.

REFERENCES