Lost in Translation
Modulation of the Metabolic-Functional Relation in the Diabetic Human Heart

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In the United States, the prevalence of diabetes mellitus has increased dramatically over the past 30 years, with most cases being attributed to type 2 diabetes mellitus (T2DM). Cardiovascular disease is the leading cause of death in these patients, with atherosclerosis accounting for ≈80% of the cases. The cluster of insulin resistance, hyperglycemia, dyslipidemia, hypercoagulability, obesity, and hypertension that typically track with T2DM is largely responsible for the increase in coronary atherosclerosis. However, the presence of T2DM also increases the manifestations of coronary atherosclerosis, with larger infarct size and greater postinfarction remodeling in T2DM patients compared with their nondiabetic counterparts being prime examples. Even in the absence of coronary atherosclerosis, the presence of T2DM potentiates the manifestations of a variety of cardiovascular disease processes such as left ventricular (LV) hypertrophy and heart failure secondary to dilated cardiomyopathy.

Indeed, evidence is increasing for a true diabetic cardiomyopathy: the presence of LV systolic and diastolic dysfunction that occurs in the absence of concomitant coronary artery disease and hypertension. The mechanisms by which these cardiovascular complications become manifest in T2DM are multifactorial and include an increased prevalence of hyperlipidemia and hypertension, impaired fibrinolysis, abnormal myocardial endothelial function, and reduced sympathetic neuronal function.

However, it is clear that abnormalities in myocardial substrate metabolism underlie many of the cardiovascular abnormalities observed in T2DM. Under normal conditions, the heart is an omnivore capable of oxidizing different classes of substrates, such as fatty acids and carbohydrates, for energy production. This plasticity in substrate use is fundamental to cardiac health because it permits efficient response to various stimuli such as the pattern of substrate availability, the hormonal milieu, the level of tissue perfusion, and the amount of workload by the heart. In T2DM, this plasticity is lost, with the heart becoming almost solely dependent on the metabolism of fatty acids.

Multiple mechanisms are responsible for this metabolic pattern. The most notable and likely earliest contributor is the increase in delivery of plasma fatty acids to the heart because of peripheral insulin resistance. An increase in the myocardial uptake of fatty acids results in an increase in myocardial fatty acid oxidation and a reduction in glucose oxidation. This occurs initially through the Randle phenomenon and then later through activation of peroxisome proliferator–activated receptor α, a nuclear receptor that regulates the transcription of an array of genes responsible for multiple components of cellular fatty acid metabolism. In addition, fatty acids reduce insulin action by inhibiting insulin signaling pathways, leading to a decrease in glucose transporter function and further reductions in glucose oxidation. Thus, a sustained increase in myocardial fatty acid uptake and oxidation occurs, along with a decrease in glucose oxidation. However, it should be noted that myocardial glucose uptake is frequently normal because of the presence of hyperglycemia.

Numerous detrimental effects on the myocardium ensue from this loss in metabolic flexibility and can lead to impaired LV function. For example, a decrease in adenosine triphosphate production per mole of oxygen used for fatty acid oxidation compared with glucose oxidation and an increase in mitochondrial uncoupling leads to an unfavorable energetic state. Moreover, the presence of increased fatty acid oxidation and of hyperglycemia leads to an overproduction of reactive oxygen species and their attendant pathological effects on ion channels, calcium homeostasis, mitochondrial function, and cell survival. Ultimately, myocardial fatty acid and glucose uptake exceeds oxidative capacity, leading to the accumulation of lipid and glucose intermediates, so-called lipotoxicity and glucotoxicity. These intermediates can further impair cell survival and LV function.

Further supporting this metabolic-functional relation are studies in experimental models of type 1 diabetes mellitus and T2DM, which demonstrate that reversing these metabolic alterations results in improved contractile function. The metabolic improvements are paralleled by a more favorable energetic profile, reduced lipid accumulation, increased cell survival, and improved LV function. The success of these studies has led to the investigation of myocardial metabolic manipulation in patients with T2DM. Initial studies using the insulin sensitizer rosiglitazone and the biguanide metformin demonstrated that insulin-stimulated glucose uptake, measured with positron emission tomography, was improved with rosiglitazone but not with metformin. This metabolic response appeared to be related to a reduction in plasma fatty acids.
levels and was independent of the level of glycemic control. The metabolic improvement was not associated with a change in LV systolic function. From these studies numerous questions remained unanswered, particularly on the impact of these therapies on myocardial fatty acid metabolism and whether, with more sensitive measurements of LV function, a correlation between the metabolic changes and an improvement in LV function could be demonstrated.

In the current issue of Circulation, Van der Meer et al describe a very elegant study designed to help address these questions. They assessed the effects of pioglitazone (an insulin sensitizer) and metformin on various LV myocardial parameters, including structure and function, perfusion and substrate metabolism, and high-energy phosphate (HEP) metabolism and lipid accumulation. These measurements were performed in relation to changes in whole-body insulin sensitivity, plasma substrate delivery, and hepatic lipid accumulation. Key aspects of the study population were that only men were included, the T2DM was of short duration (≈3 to 4 years) and fairly well controlled, and the men were in relatively good health and lacked structural heart disease or inducible ischemia according to appropriate clinical evaluation and testing. Indeed, the extent of LV dysfunction was limited to subtle abnormalities in diastolic function and compliance demonstrated by fairly sensitive magnetic resonance imaging techniques consistent with T2DM. Subjects then underwent a 10-week run-in period during which previous diabetic therapies were discontinued and the sulfonylurea glimepiride was instituted. Then, patients underwent measurements of myocardial fatty acid and glucose metabolism with positron emission tomography, LV systolic and diastolic function with magnetic resonance imaging, HEP metabolism using phosphorous-31 magnetic resonance spectroscopy, myocardial and hepatic lipid content with proton magnetic resonance spectroscopy, and whole-body insulin sensitivity. Of note, the measurements of myocardial fatty acid metabolism, lipid accumulation, HEP metabolism, and LV function were performed under fasting conditions whereas the measurements of myocardial glucose uptake were performed during insulin clamp. After these studies, subjects were randomized to either the addition of pioglitazone or metformin. They were treated for 6 months, after which the studies were repeated.

As anticipated, both therapies improved whole-body insulin sensitivity. From a cardiac function perspective, improvement occurred in LV diastolic function and compliance with pioglitazone that was not observed with metformin. In contrast, cardiac work decreased with metformin. From a metabolic perspective, pioglitazone had a minimal effect on fatty acid metabolism with only a slight increase in esterification being observed. However, it did increase insulin-stimulated myocardial glucose uptake. In contrast, metformin reduced both myocardial fatty acid oxidation and insulin-stimulated glucose uptake. As anticipated, it appears that most of the metabolic changes could be explained by the actions of these drugs on the plasma substrate environment. Of note, no correlation was found between the metabolic changes induced with pioglitazone and the improvement in LV diastolic function and compliance. In addition, neither therapy impacted myocardial HEP metabolism or lipid content.

So, what conclusion can be drawn from this study? At first blush, the reader might conclude that the robust link between improvement in myocardial substrate metabolism and LV function in various animal models of diabetes mellitus is not relevant to the human condition. However, this is not necessarily correct. As mentioned previously, the subjects studied were healthy, under reasonable glycemic control, and without significant complications from their diabetes mellitus. Moreover, they exhibited minimal cardiac involvement except for mild abnormalities in LV diastolic function and LV compliance. Thus, the likelihood was low that associations between metabolic changes and functional improvement would be identified. In a similar vein, HEP metabolism in this cohort was similar to that observed in normal controls, thus making it unlikely that improvement would occur with the therapeutic regimens. In contrast, studies in animals are typically performed with the diabetes mellitus uncontrolled and associated with significant abnormalities in LV function. Clearly, studying patients with poorly controlled T2DM and LV dysfunction might provide results more closely resembling what is obtained in experimental animals. However, given the standard of care for T2DM and the likely multiple confounding variables (eg, matching for disease severity) this approach is neither realistic nor desirable. More likely, meaningful comparisons of therapeutic responses between animal models of T2DM and humans with the disease will require that the animal studies incorporate treatment protocols more reflective of the clinical research environment. That being said, extending considerably the duration of human studies should be considered to evaluate whether metabolic therapies slow the progression of LV dysfunction or other pathological processes, such as cardiac hypertrophy, known to be potentiated in T2DM.

Where do we go from here? Beyond the suggestions mentioned above, a logical first step is to determine if the metabolic and functional responses to different diabetic therapies observed in this study occur in women with T2DM. Gender impacts the myocardial metabolic phenotype under both normal conditions and in obesity, a well known precursor for T2DM. Moreover, cardiovascular morbidity and mortality in T2DM is significantly greater in women than in men. Thus, it is likely that there will be a sexually dimorphic response in myocardial metabolism and perhaps LV function to various diabetic therapies. Given the importance of plasticity in substrate metabolism to cardiac health, future studies of this type should be geared toward determining which antidiabetic regimens restore this capability. Addressing this question will require fairly complex metabolic studies in which the relative contributions of fatty acid and glucose metabolism are assessed in response to known determinants of myocardial metabolism such as fasting versus insulin clamp or resting conditions versus increased cardiac work. Then, it can be determined if restoration in metabolic flexibility is paralleled by improved LV functional capacity or preservation of myocardium under ischemic conditions, which in turn conveys a survival or lifestyle benefit. For all of these questions, performing equivalent protocols in animal...
models of disease and patients should stop key information on the myocardial metabolic-functional relation in T2DM from getting lost in translation.

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References

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