EDITORIAL

Is it time to reassess the role of myocardial metabolic modulation for the treatment of heart failure?

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Under normal conditions, the heart utilizes a variety of substrates (primarily fatty acids, glucose, and lactate) to support overall oxidative metabolism which is the primary engine for energy production. The biochemical reactions that control the metabolism of these various substrates provide dynamic and uniquely reciprocal control of substrate flux through myocardial fatty acid (FA) β-oxidation and glycolytic pathways as dictated by ever-changing physiologic conditions such as the plasma substrate environment, neurohumoral milieu, and level of cardiac work. These acute adaptations in substrate selection and metabolism are central to cardiac myocyte health.

However, in the progression of cardiac hypertrophy to left ventricular (LV) dysfunction this flexibility in substrate use is lost. Nearly 50 years ago, Wittels and Spann made the seminal observation in pig heart that systolic dysfunction, in response to aortic constriction, was associated with a decrease in the oxidation of palmitate, a long-chain fatty acid.[1] This observation was confirmed by numerous subsequent studies that led to the general paradigm that the expression of genes encoding for enzymes regulating β-oxidation are coordinately decreased, resulting in a shift in myocardial substrate metabolism to primarily glucose use, similar to that seen in the fetal heart.[2] These metabolic changes are paralleled by re-expression of fetal isoforms of a variety of contractile and calcium regulatory proteins. It should be noted that this metabolic adaptation becomes more complex when there is concomitant insulin resistance.[3] This loss of flexibility in myocardial substrate utilization can lead to a host of downstream effects detrimental to myocyte health including impaired energetics and increased oxidative stress and apoptosis.[4] Metabolic imaging studies in humans with heart failure with reduced ejection fraction (HFrEF) have generally confirmed these metabolic patterns.[5] Because oxidation of glucose is viewed as more efficient from an oxygen usage perspective compared with FA β-oxidation, and the presence of concomitant insulin resistance, there has been tremendous interest in developing pharmacologic therapies that stimulate myocardial glucose oxidation, with the insulin sensitizer glucagon-like peptide-1 being a prime example.

GLP-1 agonists are endogenous hormones with insulinotropic and insulinomimetic effects.[6] They have been promoted for the treatment of Type-2 Diabetes Mellitus (DM).[6] However, the discovery of GLP-1 receptor mRNA in myocardial tissue as well as coronary endothelial cells[7] prompted interest in its potential utilization in the HFrEF population. Specifically, it has been postulated that in HFrEF the reduction in myocardial insulin sensitivity in the setting of increased dependence upon glucose as a substrate for metabolism leads to energy depletion and impaired systolic function. Consequently, restoring myocardial glucose metabolism by GLP-1 could potentially improve myocardial contractility.

Initial animal models for the use of GLP-1 to treat heart failure were promising. For example, canine experiments demonstrated augmented overall

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myocardial glucose utilization (MGU) and improvement in left ventricular function after infusion of GLP-1.[8] Furthermore, GLP-1 infusion was also associated with vasodilation and increased myocardial blood flow (MBF) with an accompanying improvement in survival.[9] The mechanism behind the increased MBF was attributed to GLP-1-induced increase in myocardial nitric oxide production. These promising animal studies prompted investigations of the potential therapeutic effects of GLP-1 in humans.

Unfortunately, the use of GLP-1 in initial human trials has not been definitive in demonstrating benefit. For example, GLP-1 agonism augmented MGU [measured by PET with ^{18}F-fluorodeoxyglucose (FDG)] in lean patients but not in obese or diabetic subjects.[10] Similarly in DM patients, GLP-1 agonism has been shown to either increase resting MBF or have no effect.[11] In non-DM patients with HFrEF (AHA class II/III) of either ischemic or non-ischemic etiology, the GLP-1 agonist, albiglutide, failed to increase PET-derived measurements of MGU or oxygen consumption (using ^{11}C-acetate) but did increase peak oxygen consumption.[12]

Three randomized controlled trials have continued the debate regarding the efficacy of GLP-1 agonists and have introduced concern regarding their safety. The LEADER trial assessed the efficacy of the GLP-1 agonist, liraglutide, in DM patients with at least one cardiovascular risk factor.[13] Compared to placebo, the liraglutide group demonstrated a lower rate of mortality with a trend towards less non-fatal myocardial infarction, stroke, or hospitalization for heart failure. Conversely, the LIVE trial assessed clinically stable HFrEF patients with and without DM and found no improvement in LV ejection fraction (LVEF) as well as a higher rate of adverse events including death, ventricular tachycardia, and heart failure exacerbation in the liraglutide cohort.[14] Similar to the LIVE trial, the FIGHT trial examined the efficacy of liraglutide in the HFrEF population but unlike LIVE focused on those patients with recent heart failure exacerbations.[15] A non-significant trend of worse cardiovascular outcomes was witnessed in patients receiving liraglutide. Consequently, concern has risen regarding the safety of the use of liraglutide in the heart failure population and the need for fundamental studies to better understand the biologic actions of these drugs in normal and diseased human myocardium.

It is within this context that Nielsen et al. investigated the ''effect of liraglutide on myocardial glucose uptake and blood flow in stable chronic heart failure.'' As a substudy of LIVE, this investigation randomized 36 stable HFrEF patients (LVEF < 45%, New York Heart Association I to III) without DM to 24 weeks of either liraglutide 1.8 mg daily or placebo. MGU was assessed by PET with FDG after administration of an oral glucose load. MBF was measured by $^{15}OH_2O$ PET both at rest and during vasodilator stress induced with adenosine. The patients were nearly all male, lean, and predominantly had HFrEF due an ischemic origin. It should be noted that both insulin resistance as measured by the homeostatic model assessment (HOMA-IR) and the level of plasma glucose control as measured by glycosylated hemoglobin A1c (HbA1c) were at the upper ranges of normal. MGU, MBF and myocardial flow reserve (stress MBF/rest MBF) remained unchanged after treatment with liraglutide therapy. This was despite a greater decline in HbA1c and the 2-hour post-oral glucose [measured during an oral glucose tolerance test (OGTT)] in the liraglutide group indicating an improvement in systemic glucose control. Of note, heart rate increased in the liraglutide group.

The results of Nielsen and colleagues' study, in concert with the recent trials conducted with GLP-1 agonists encourage reflection upon our current understanding of the myocardial metabolic shift to an overdependence on glucose metabolism in the HFrEF patient and how this might impact targets for therapeutic intervention. As mentioned above, one of the most important determinants of myocardial substrate use is the level of plasma substrates delivered to the heart, particularly FAs. In the current study, the impact of liraglutide on baseline plasma FAs was not reported. We only know that the 2-hour post-OGTT FA levels did not change with therapy. Assuming the baseline plasma FA levels mirrored these levels, it would not be surprising that MGU did not change.

It is also critical to examine the specific demographics and clinical variables of patient population being investigated and how this might have influenced the study results. First, an overwhelming majority (94%) of the study population was male. Previous animal and human studies have demonstrated a sexual dimorphism with regard to myocardial metabolic substrate utilization and MBF with women exhibiting a greater dependence on FA metabolism and men on glucose use.[16] Indeed, this sexual dimorphism persists, at least for myocardial FA metabolism in patients with HFrEF due to non-ischemic origin.[17] Age is also a critical determinant in myocardial substrate utilization with an increasing dependence on MGU with advancing age.[18] Obesity is another patient attribute that needs to be considered when assessing cardiac metabolic activity. The mean body mass index in the current study (26 to 27 kg/m^2) suggested an overweight but not obese population. PET imaging studies in humans have noted that overweight to obese females have increased MBF, oxygen consumption, and FA metabolism,[19] whereas obese males

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demonstrated both increased FA metabolism (but to a lesser extent than females) and a decline in MGU and glucose oxidation.[20,21] The specific etiology of HFrEF in Nielsen et al.'s patient population may have potentially influenced the findings as well. Three quarters of the patients in this study were deemed to have ischemic HFrEF. Prior work has demonstrated that even under mild–moderate ischemic conditions myocardial FA utilization declines and is replaced by glucose as the primary substrate for metabolism.[22] Even after resolution of ischemia, abnormalities in myocardial substrate metabolism may persist (e.g., ischemic memory). While non-ischemic dilated cardiomyopathy patients exhibit a similar metabolic pattern, it is unclear whether they will be consistent with the extent and magnitude of changes seen in the ischemic HFrEF population.

Finally, it should be noted that the increase in MGU observed in the progression from myocardial hypertrophy to LV dysfunction is not the result of an increase in GLUT-1 or GLUT-4 upregulation but rather from a shift of glucose oxidation via anaplerotic flux.[23] This may explain why in Nielsen et al.'s study population decreased serum glucose and HbA1c (i.e., stimulation of glucose uptake by non-cardiac tissue) which are GLUT-1- and GLUT-4-derived processes were noted but increased MGU was not.

As mentioned above, in Nielsen et al.'s study, heart rate was increased with liraglutide therapy. This finding is consistent with the main LIVE trial as well as several others.[13] Both prior[24] and contemporary[25] studies have demonstrated the importance of optimizing heart rate control in the HFrEF population. Therefore, an increase in heart rate without a corresponding improvement in MGU and MBF may have been one etiology for the worse outcomes seen in the LIVE and FIGHT trial patients receiving liraglutide.

Contemporary knowledge of metabolic changes in heart failure is continuing to evolve as is our understanding of potential therapeutic agents. Indeed, the contribution of ketone bodies and branched chain amino acids to the pathogenesis of heart failure is just one example.[26] Among the other areas to be explored include the assessment of MGU in the acute HFrEF population as well as assessing whether the use of recombinant GLP-1 agents might be more beneficial given that its metabolites, including GLP-1 (9 to 26) amide, may have beneficial effects that are independent of the GLP-1 receptor agonist.[27] Furthermore, given the expanding literature that supports unique myocardial substrate utilization based upon specific patient demographics such as sex and age as well as clinical situations, including body habitus, it remains to be seen how the results of Nielsen et al.'s study may have differed if an alternative patient population had been

assessed. Ultimately, the current literature regarding the benefits of GLP-1 agonist therapy in the HFrEF patient is proving disappointing and parallels the negative outcomes with the use of other insulin-secreting or insulin-sensitizing agents such as dipeptidyl peptidase 4 inhibitors or thiazolidinediones.[28] Therefore, further investigations of alternative patient populations need to be conducted to determine if the results of Nielsen et al. can be applied broadly. If similar findings are discovered, then a shift in the current approach to therapeutic interventions in these patients may be necessary.

Disclosures

The authors have nothing to disclose.

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