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EDITORIAL COMMENT

Evolving Challenges for Targeting Metabolic Abnormalities in Heart Failure*

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With limited capacity to store adenosine triphosphate (ATP) in the form of glycogen and phosphocreatine, the heart is continuously dependent on ATP synthesis to maintain force generation, myofibrillar relaxation, and ionic homeostasis. The ability of normal myocardium to adapt its substrate use to meet these essential demands has been appreciated for over half a century. Central in this adaptation is the flexible metabolic circuitry that is capable of switching preferred energy substrates and regulating pathways of oxidative and nonoxidative energy transduction to optimally adapt to physiological demands (1). Normally, fatty acids (FAs) are the predominant energetic substrate for the heart; their beta-oxidation provides 60% to 70% of myocardial ATP, with 30% of ATP derived from glucose.

In heart failure with reduced ejection fraction, both animal models and human studies demonstrate alterations in the otherwise versatile capacity of the myocardium to use alternative substrates. Sack et al. (2) reported the down-regulation of genes required for myocardial FA use in human hearts and rats with progressive heart failure. Davila-Roman et al. (3) used in vivo imaging with positron emission tomography (PET) to confirm reduced FA oxidation with increased dependence on glucose metabolism in patients with compensated dilated cardiomyopathy. As heart failure progresses, myocardial insulin resistance develops (4), further compromising the versatility of substrate use and increasing the metabolic stress on the heart. Importantly, chronic heart failure patients with decreased systemic insulin sensitivity have a worse prognosis (5).

Accordingly, therapies designed to increase glucose uptake by overcoming insulin resistance or other mechanisms hold promise for improving myocardial energetics and preventing the progression of contractile abnormalities. In this context, glucagon-like peptide (GLP)-1 is a naturally occurring incretin peptide that enhances glucose uptake by stimulating insulin secretion and by enhancing insulin sensitivity in target tissues (6). Administration of exogenous GLP-1 as a continuous infusion in patients with type 2 diabetes causes an impressive increase in insulin sensitivity in both skeletal muscle and adipose tissue, with substantial improvements in both insulin-mediated glucose uptake (6) and insulin-independent glucose uptake (7). Receptors for GLP-1 have been identified in human myocardium (8), thereby identifying the heart as a potential target for GLP-1 action. Although native GLP-1 is rapidly degraded, degradation resistant GLP-1 analogues, which are widely used for treatment of type 2 diabetes, permit subcutaneous administration at intervals ranging from 12 h to 1 week.

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Relevant to these considerations, a study by LePore et al. (9) in this issue of *JACC: Heart Failure* explores the effects of 12 weeks of treatment with a long-acting GLP-1 agonist (albiglutide) in patients with stable, chronic heart failure with reduced ejection fraction and New York Heart Association functional class II to III symptoms. As a small proof-of-concept investigation, the trial was well-designed and carefully executed. Initial plans for assessing 3 different doses of albiglutide with 25 patients per group were abandoned after an interim analysis

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showed no effects of the lower 2 doses. For the comparisons of high-dose albiglutide treatment (30 mg weekly) with placebo, there was a small increase in peak oxygen consumption (VO_2) (1.5 ± 0.7 ml/kg/min; p = 0.024). Consistent with the known appetite suppressing effects of GLP-1 analogues, there was a small decrease in weight with albiglutide (1.6 ± 0.4 kg; p = 0.003). However, these findings were not accompanied by any significant improvement in cardiac function by echocardiography, changes in 6-min walking distance, quality of life scores, or improvements in myocardial glucose use, oxygen consumption, or efficiency based on PET-based analyses.

Because of the lack of significant improvements in myocardial function or metabolism, the investigators concluded that mild improvements in VO_2 might be due to extra-cardiac GLP-1 effects. Because VO_2 was the only variable that was measured at the peak of exercise, the conclusion that there were no cardiac effects of albiglutide is not definitive. Perhaps if cardiac variables were measured during exercise, an effect of albiglutide on contractile reserve, relaxation reserve, or metabolic reserve might have been revealed. In contrast, although peripheral factors such as improved skeletal muscle metabolism could be at play, there are no data that directly demonstrates any extra-cardiac improvements with albiglutide. The investigators also noted that the relatively short duration of albiglutide treatment could have contributed to the largely negative results.

It is perhaps most important to view this study in the context of recent full and preliminary reports of randomized trials of GLP-1 agonists in patients with various stages of heart failure.

Relevant to American Heart Association/American College of Cardiology stage A and B patients, the LEADER (Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation) trial investigated the cardiovascular safety of liraglutide in >9,000 adults with type 2 diabetes at high risk of major adverse cardiovascular events (10). A preliminary announcement by the sponsor indicated that, compared with placebo, addition of liraglutide reduced the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke during a follow-up period of up to 5 years (11). In >6,000 patients with diabetes and a recent acute coronary event, including 22% with a history of heart failure, the ELIXA (Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 [Lixisenatide]) trial compared lixisenatide with placebo (12). In ELIXA, lixisenatide treatment had no effect on the primary composite endpoint (death, myocardial infarction, stroke, or hospitalization for unstable angina) or the rates of hospitalization for heart failure (12). Finally, in recently hospitalized patients with advanced chronic heart failure with reduced ejection fraction, the FIGHT (Functional Impact of GLP-1 for Heart Failure Treatment) trial randomized 300 patients with and without diabetes to 6 months of treatment with liragluide or placebo (13). In this more advanced heart failure population, liraglutide produced no improvement in the primary composite endpoint, with a trend toward increase adverse outcomes among the diabetic patients treated with liraglutide (14). At least for patients with heart failure and type 2 diabetes, these trials indicate that differences in the stage of heart failure may profoundly affect the therapeutic impact of a single class of drug targeting cardiac and systemic metabolism.

The composite findings that GLP-1 agonists exhibit favorable cardiovascular effects in early stages of heart failure, a lack of efficacy in early symptomatic disease, and potential harm in more advanced degrees of heart failure inspires some general observations. First, these findings suggest the likely need for stage-dependent strategies in treating diabetes among patients with heart failure. Beyond GLP-1 agonists, this concept is supported by the adverse cardiovascular outcomes with other otherwise effective therapies for diabetes when applied to patients with established heart failure. Thiazolidinediones and dual peroxisome proliferator-activated receptor alpha/gamma agonists increase fluid retention and the risk of heart failure in multiple analyses (15). Dipeptidylpeptidase-4 inhibitors have been associated with small but significant signals of increased heart failure hospitalization based on a recent meta-analysis (16). This contrasts with neurohormonal modulators (angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists) that have therapeutic benefits across a broader spectrum of heart failure stages. These stage-dependent distinctions in therapeutic responses underscore the need to more fully elucidate the molecular triggers underpinning the key transitions in myocardial substrate use, as well as the bioenergetics and the biomarkers that reliably identify these transitions.

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