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EDITORIAL COMMENT

Refueling the Failing Heart

A Case for Sodium-Glucose Cotransporter 2 Inhibition in Cardiac Energy Homeostasis*

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The EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial) and CANVAS (Canagliflozin Cardiovascular Assessment Study) trials revealed that the antihyperglycemic sodium-glucose cotransporter 2 inhibitors (SGLT2i) empagliflozin and canagliflozin, developed to treat diabetes, confer a striking cardiovascular mortality benefit that cannot be attributed to glycemic control (1,2). Although these trials were not originated and designed to demonstrate primary benefit for heart failure, both trials revealed that these agents were associated with significant reduction in overall mortality, cardiovascular mortality, and heart failure hospitalization. These benefits did not appear to proceed through protection from myocardial ischemic insults (1,3). Moreover, a preclinical model of pressure overload-induced heart failure revealed that pathological ventricular remodeling was ameliorated by empagliflozin (4). However, the mechanisms underlying these benefits remain elusive. In this issue of *JACC Basic to Translational Science*, Verma et al. (5) present studies in *db/db* diabetic mice indicating that myocardial energetics and hemodynamics may be favorably improved by empagliflozin.

SEE PAGE 575

SGLT2 is specifically expressed in the renal proximal tubule and is responsible for ~90% of glucose reabsorption, and its selective inhibition causes significant glucosuria and natriuresis. The clinical success of SGLT2 antagonism has triggered diverse hypotheses designed to reveal potential underlying mechanism(s) driving the salutary effects on cardiac function. Indeed, although the molecular targets of SGLT2i are limited, these agents provoke pleiotropic systemic consequences, improving hemodynamics through plasma volume contraction through natriuresis and osmotic diuresis; controlling neurohumoral activation, with no compensatory activation of the sympathetic nervous system; and altering metabolism: 1) as volume contraction increases hematocrit, oxygen delivery is improved; and 2) a shift away from carbohydrate, toward fatty acid utilization (6–8). As a reflection of increased systemic fat oxidation, SGLT2i increases hepatic ketogenesis, even causing diabetic ketoacidosis at low incidence, but nonetheless high enough to modestly dissipate enthusiasm for their use. This concern has been countered by the notion that the benefit of SGLT2i may proceed in part by furnishing a greater supply of an alternative fuel, ketone bodies, to the failing heart. Indeed, rodent and human studies indicate that both the diabetic and the nondiabetic failing heart adapt by increasing ketone oxidation to offset metabolic abnormalities which restrict myocyte access to fatty acid and/or glucose substrate fuels (9–11).

Verma et al. (4) treated *db/db* mice, a model of type 2 diabetes, for 4 weeks with empagliflozin, 10 mg/kg per day, mixed in with their standard chow, and compared responses between vehicle-fed control and vehicle-fed *db/db* mice. No empagliflozin-treated control group was tested. Body weight in *db/db* mice

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was not significantly altered by empagliflozin, but as expected, blood glucose was decreased, and circulating ketones were modestly increased. The most striking observation was hemodynamic: under the isolated working heart perfusion conditions tested, cardiac work and ATP production were markedly impaired in hearts from vehicle-fed *db/db* mice, but these indices were completely reversed by empagliflozin. Particularly in the presence of high-dose insulin, empagliflozin increased ATP production by 30% in isolated working hearts from *db/db* mice, which was driven by modest increases in both fat and glucose oxidation. Unlike prior observations, intrinsic capacity for ketone (specifically β-hydroxybutyrate [β-OHB]) oxidation was decreased in hearts from *db/db* mice, and SGLT2i had no effect on this rate. Overall, cardiac efficiency (work per unit of oxygen consumed) was not significantly improved by either empagliflozin or β-OHB.

In the absence of empagliflozin, the isolated working diabetic heart in these studies exhibited features of the classic "engine out of fuel," that is, low energy turnover and low cardiac output (12). However, the ex vivo perfusion studies used only 5 mM glucose (with 0.8 mM palmitate), a glucose concentration less than one-half that in the circulation of vehicle-treated *db/db* animals and 30% less than that in empagliflozin-treated *db/db* animals. Thus, ex vivo failure in hearts of *db/db* mice might have resulted from a mismatch of substrate delivery to tuning of the "myocardial engine." Indeed, in vivo echocardiographic assessment revealed increased left ventricular ejection fraction in vehicle-treated *db/db* mice, compared to vehicle-treated lean control mice, and ejection fraction was not altered by empagliflozin treatment in *db/db* mice. Doppler assessments of left ventricular filling and relaxation were also not altered by empagliflozin, although left ventricular mass was mildly diminished in the *db/db* empagliflozin group compared to *db/db* mice receiving vehicle. Taken together, it is striking that, under consistent conditions of preload, afterload, and substrate and insulin concentrations, empagliflozin improved cardiac work and energy turnover in the insulin-resistant diabetic heart. Future experiments will examine the cardiac responses of both control and diabetic animals to SGLT2i to a matrix of hemodynamic and metabolic conditions (absence of a lean control group treated with empagliflozin is another modest limitation). Moreover, although preliminary findings suggest hemodynamic improvement in response to empagliflozin-treatment in the context of pressure overload (4), it will be important to determine whether this is similarly correlated with metabolic and energetic responses.

A key elusive question is the role of ketone bodies in the failing heart. Indeed, the pleiotropic effects of SGLT2i and whether myocardial ketone metabolism is necessary and sufficient to extend those benefits to myocardium still need to be carefully scrutinized. Much evidence suggests the failing human heart relies on ketone oxidation to a greater extent. Circulating ketone concentrations are increased in nondiabetic patients with heart failure (13). Studies in nonfailing human type 2 diabetes (11), nondiabetic human heart failure (10,14), and compensated pathological hypertrophy in mice (9) all indicate increased myocardial ketone oxidation. However, the studies presented by Verma et al. (5) suggest that the insulin-resistant diabetic mouse heart does not exhibit increased ketone oxidation and that SGLT2i has no effect on ketone oxidation in this context. Furthermore, whereas most studies indicate that ketone oxidation is increased in the failing heart, whether such an increase is salutary, deleterious, or a bystander is unknown. One hint may derive from mice in which succinyl-CoA oxotransferase (SCOT), the enzyme required for ketone oxidation, is genetically deleted specifically in cardiomyocytes. These animals exhibit accelerated pathological remodeling in response to pressure overload (15).

Many questions remain in failing and diabetic hearts with regard to SGLT2i and ketone metabolism. Although questions of myocardial ketone oxidation directly relate to the effects of SGLT2 inhibition, they should not be conflated. SGLT2i-derived hemodynamic and clinical benefit may correlate with increased ketosis, and ketones may exert benefits to an energetically challenged heart, but this correlation does not prove causation extending from SGLT2i through ketone bodies to the heart. Alternative mechanisms contributing to SGLT2i benefit still require exploration, for example: inhibition of the Na^+/H^+ exchanger and consequent reduction of cytosolic Na^+ with coronary vasodilation (16). Thus, ongoing experiments need to test for combinatorial effects of SGLT2 inhibition and also account for variations posed by the model studied, including the nature of the metabolic and hemodynamic insult as well as species- and sex-dependent differences.

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