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EDITORIAL COMMENT

Empagliflozin-Induced Changes in Epicardial Fat

The Centerpiece for Myocardial Protection?*

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In patients with type 2 diabetes, sodium-glucose linked cotransporter-2 inhibitors (SGLT2-Is) reduce the risk for heart failure by 30% to 35%. Furthermore, SGLT2-Is have emerged as a dedicated disease-modifying therapy for patients with heart failure with reduced ejection (HFrEF) even in the absence of diabetes, based on the DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) and EMPEROR-Reduced (EMPagliflozin outcome tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) trial results. Numerous, not mutually exclusive, mechanisms have been put forward to explain the beneficial effects seen on heart failure status. Many of these mechanisms were explored in preclinical animal studies. More recently, 2 smaller mechanistic studies using cardiac magnetic resonance (CMR) imaging in patients with HFrEF have shown the capability of SGLT2-Is to induces cardiac reverse remodeling (1,2). The SUGAR-DM-HF (Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure) trial indicated a reduction in left ventricular (LV) end-systolic and end-diastolic volume indexes (LVESVi and LVEDVi) without increase in LV ejection fraction (LVEF) or reduction in LV mass (2). The EMPA-TROPISM (Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity? (ATRU-4)) trial demonstrated a reduction in LVEDV, LVESV, and LV mass and an improvement in LVEF (1). A different CMR study (EMPA-HEART [Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes]) in type 2 diabetes patients with coronary artery disease (but not HFrEF) also illustrated a reduction in LV mass with SGLT2-I treatment (3). In an invasive hemodynamic study, empagliflozin reduced pulmonary capillary wedge pressure at rest and during different stages of exercise, but it did not result in a higher cardiac index during rest or exercise. However, empagliflozin did shift the LV end-diastolic pressure-volume relation relationship (EDPVR) rightward (**Figure 1**), suggesting a decrease in intrinsic LV chamber stiffness (4).

SEE PAGE 578

Building on this pre-existing knowledge of beneficial myocardial changes in patients with HFrEF, the predefined subanalysis of the EMPA-TROPISM trial in this issue of *JACC: Heart Failure* offers further insights into the effect of empagliflozin on epicardial adipose tissue (EAT), extracellular volume (ECV), and aortic stiffness (5). Alterations in EAT, ECV, and aortic stiffness all are associated with adverse clinical outcomes in the field of cardiology. Furthermore, these factors aggravate hemodynamic alterations in heart failure, as excessive EAT enhances pericardial restrain, excessive ECV increases LV chamber stiffness, and aortic stiffness worsens ventriculo-arterial coupling. The current analysis makes a case on how changes in EAT could potentially result in myocardial protection.

The EAT is a visceral fat deposit that surrounds the arcus aorta, coronary arteries, ventricles, and the

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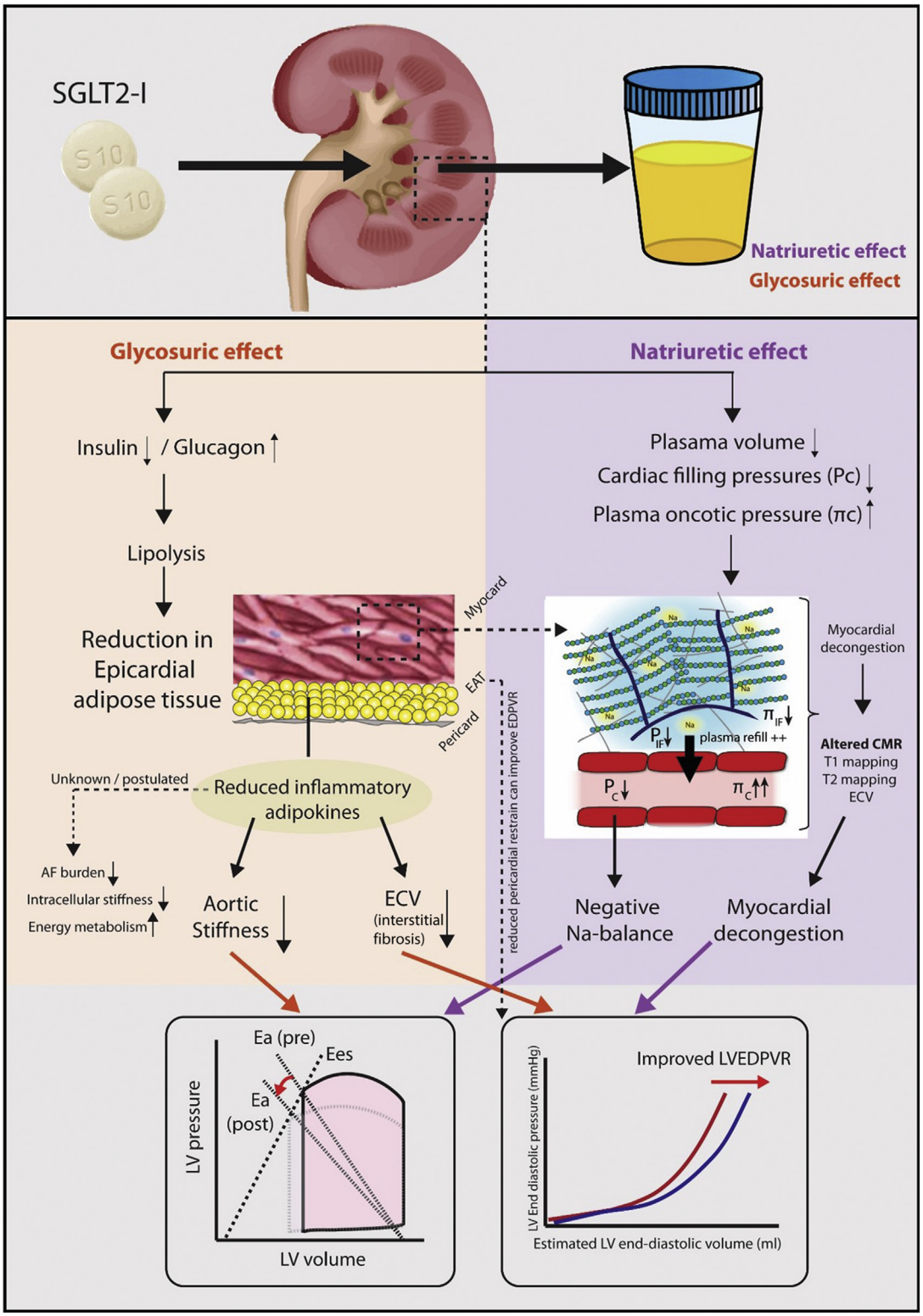
FIGURE 1 Potential Interplay Between Study Findings and Natriuretic and Glycosuric Effects



CMR = cardiac magnetic resonance; EAT = epicardial adipose tissue; ECV = extracellular volume; EDPVR = end-diastolic pressure-volume relation relationship; LV = left ventricular; SGLT2-I = sodium-glucose cotransporter-2 inhibitor.

apex of the heart. The EAT shares a common blood supply with the myocardium, and no structures such as fascia separate the EAT from the myocardium. As a consequence, EAT-derived proinflammatory adipokines have a direct paracrine effect on the myocardium and have been shown to negatively influence cardiomyocyte function. In addition, increased EAT enhances the cardiomechanical pericardial restrain, thereby aggravating diastolic dysfunction through enhanced diastolic ventricular interaction.

Based on the authors' (and other authors') previous preclinical and clinical work, it can be postulated that the glycosuric effects of SGLT2-Is, in addition to inducing a negative caloric balance, alter the ratio of glucagon and insulin, leading to enhanced lipolysis (**Figure 1**). This results in a reduction of EAT, which is probably paralleled by a reduction in proinflammatory adipokines. For example, a reduction in tissue growth factor beta might result in less diffuse interstitial fibroses, potentially explaining the reduced ECV on CMR, and thereby reduce extracellular stiffness. Furthermore, inflammation-mediated modulation of the NO/cGMP/PKG pathway results in enhanced titin phosphorylation, resulting in reduced intracellular stiffness. This reduced intra- and extracellular stiffness might explain the observed rightward shift in LV EDPVR in patients with HFrEF (4). Similarly, reduction in proinflammatory adipokines might also explain the reduced aortic stiffness. This reduced aortic stiffness reduces the pulsatile load and wall stress on the LV, thereby improving ventricular-vascular coupling (**Figure 1**). In addition, reduction in EAT might potentially reduce AF burden. Indeed, dapagliflozin resulted in a lower risk to develop AF in the DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) trial and ongoing trials are evaluating whether SGLT2-Is have a rhythm-control effect. Finally, lipolysis of EAT might shuttle energetic substrate (free fatty acids and ketone bodies) to the myocardium and might beneficially alter myocardial energy metabolism, a topic being further studied in the EMPA-VISION (A Randomised, Double-blind, Placebo-controlled, Mechanistic Cardiac Magnetic Resonance Study to Investigate the Effects of Empagliflozin Treatment on Cardiac Physiology and Metabolism in Patients With Heart Failure) trial.

While the aforementioned mechanisms related to the glycosuric effect of SGLT2-Is and the subsequent reduction in EAT are often put forward to explain their cardioprotective effects, one cannot forget about the natriuretic/diuretic effects of these agents (**Figure 1**). Mediation analysis of cardiovascular outcomes trials with SGLT2-Is hint toward an important contribution of reduction in plasma volume/congestion to explain the beneficial treatment effect. The natriuretic and osmotic diuretic effect of SGLT2-Is lead to about a 7% reduction in plasma volume, translating to long-term lower filling pressures in patients with HFrEF, which can be assessed by means of continuous pulmonary artery pressure monitoring (6). Lowering filling pressures also have a direct effect on cardiac structure and function. For example, selectively inflating an occlusive balloon in the coronary sinus of dogs results in the development of myocardial edema, which is paralleled by enhanced myocardial stiffness (Tau) on pressure/volume analysis. The long-term reduction in filling pressure with the use of an SGLT2-I would likely result in decongestion of the interstitium of the myocardium. The latter in particular occurs with the use of an SGLT2-I because of the increase in plasma oncotic pressures, which further stimulate plasma refill from the interstitium through enhanced Starling forces (7). As such, one needs to recognize the limitations of the present study. Myocardial edema is also associated with higher native T1 values or higher post-contrast T1 values, which are used to calculate ECV. T2 mapping could have provided valuable information, because of changes in myocardial water content, about whether the observed changes in myocardial mass are related (8). Indeed, the effect of SGLT2-Is on myocardial mass occur as early as 3 months in different studies, which is strikingly fast compared with the effect of classic antihypertensive agents (eg, Losartan) on myocardial mass regression (occurring 1-2 years after treatment initiation). This potentially suggests a fast hemodynamic effect rather than a reduction in fibrosis. Reductions in myocardial water content are associated with rightward shifts in EDPVR (8). Furthermore, long-term negative sodium balances have been shown to reduce aortic stiffness. As such, many of the myocardial protective effects of SGLT2-Is can also be explained through the sodium pathway.

In addition to the missed opportunity in terms of T2 mapping, other limitations of the study include the post hoc design of the analysis and thus the lack of an adequately powered sample size for the end points. In addition, the authors mention that this was an intention-to-treat analysis, but the data set is more aligned with a full analysis set, because the numerous patients randomized with missing data for EAT or ECV were not analyzed when using analysis of covariance. It is therefore unclear how sensitive the study findings are for missing data. Nevertheless,

the current analysis by Requena-Ibáñez et al (5) provide interesting data that keeps us wondering about the drivers behind the observed myocardial protection with the use of SGLT2-Is. This analysis suggests a potential central role of changes in EAT which further generates the promise of beneficial effects of SGLT2-Is on other cardiac conditions, such as heart failure with preserved ejection fraction or atrial fibrillation.

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