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EDITORIAL COMMENT

The *Bslc2*$^{-/-}$ Mouse

Adding a Missing Phenotype to the Repertoire of HFpEF Animal Models*

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The quest to find a treatment for heart failure with preserved ejection fraction (HFpEF) remains 1 of the biggest challenges in modern medicine. This is mainly due to the poor understanding of the disease pathophysiology and the lack of comprehensive animal models, as well as the absence of a general consensus on the characteristics of the disease itself. Over the past few years, however, a shared belief has emerged in the scientific community: HFpEF, just like heart failure in general, may not be a singular disease but rather a syndrome with its own subtypes and phenotypes (1). HFpEF is associated with several co-morbidities such as hypertension, coronary artery disease, arrhythmias, chronic kidney disease, aging, obesity, and diabetes, which are believed to be the substrates for the development of HFpEF. Therefore, patients with HFpEF have different phenotypes, leading to a vast heterogeneity that has largely affected the outcomes of clinical trials aimed at testing therapies to effectively treat this clinical syndrome (1,2). The recognition of this heterogeneity has led the research community to identify major phenotypes in which patients present a reduced heterogeneity, with the aim of developing more targeted therapies that are better suited for the selected phenotype (2).

The use of animal models is a pivotal part of the quest to discover a new treatment because it provides an opportunity to test original hypotheses and find new and/or more effective therapies to combat clinical challenges (3). The basic research field of HFpEF has suffered considerably from the lack of adequate models that could recapitulate the complexity of this syndrome in humans. Although the development of a model that reproduces the broad spectrum of phenotypes seen in HFpEF remains the ultimate goal, adoption of simpler models of disease that develop diastolic dysfunction and signs of HFpEF seems like a closer reach for translational research. Animal models of obesity or hypertension, based on genetic, hormonal, or dietary interventions, have been developed and adopted to recapitulate some of the HFpEF phenotypes.

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Recent epidemiological studies have shown that patients with HFpEF and diabetes in Asia are more likely to be lean compared with North European white patients with diabetes and HFpEF, who are prevalently obese (4,5). This patient population seems different from other patients usually seen in the clinics in the Western countries. The study by Bai et al. (5) in this issue of *JACC: Basic to Translational Science* explored the effect of *Bslc2* (seipin) deletion in mice to reproduce the diabetic lean phenotype while aiming to recapitulate some of the characteristics of the Asian diabetic patient population with HFpEF. The Berardinelli-Seip congenital lipodystrophy-2 (*Bslc2*)/seipin mutation in human patients induces a lipodystrophic phenotype (leanness, diabetes) with left ventricular hypertrophy and normal ejection fraction. The *Bslc2*$^{-/-}$ mice had a

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growth curve similar to that of the wild-type (*Bslc2*$^{+/+}$) mice, with a similar amount of lean mass and systolic blood pressure, but they developed severe hyperglycemia and cardiac hypertrophy compared with the *Bslc2*$^{+/+}$ mice. The *Bslc2*$^{-/-}$ mice also displayed an increased end-diastolic pressure/volume relationship, increased end-diastolic pressure, and enlargement of the left atrium. It is interesting to note that cardiac hypertrophy developed at 23 weeks of age, after the appearance of diastolic dysfunction (i.e., increase in isovolumetric relaxation time) and exercise intolerance, which were significantly impaired earlier in the rodent life (15 weeks). At 15 weeks, myocardial collagen deposition and neutrophil infiltration were already significantly increased in the *Bslc2*$^{-/-}$ mice. Together with the histological and physiological changes, titin phosphorylation and increased protein kinase C-α expression accompanied the development of HFpEF in the *Bslc2*$^{-/-}$ mice.

Intriguingly, all the reported changes were independent from direct effects due to the BSLC2 deletion in cardiomyocytes (5). In fact, Bscl2 messenger ribonucleic acid was barely expressed in the muscle tissue and in the heart of *Bslc2*$^{+/+}$ mice, whereas it was mostly expressed in the white and brown adipose tissues. In addition, the selective deletion of *Bslc2* in cardiomyocytes did not affect cardiac mass and function, and therefore Bai et al. suggested that systemic effects secondary to *Bslc2* deletion, such as hyperglycemia, were the culprit for the development of the HFpEF phenotype in *Bslc2*$^{-/-}$ mice. The authors also proposed, based on their findings, that neutrophil extracellular traps, cellular alterations in titin, and interstitial fibrosis may represent promising therapeutic targets in Asian patients with HFpEF.

Overall, the *Bslc2*$^{-/-}$ mouse displayed features of diastolic dysfunction and failure and recapitulated several characteristics of the lean diabetic patient with HFpEF (5). However, it is noteworthy that the glycemic levels of the *Bslc2*$^{-/-}$ mice were extremely high (>20 mM or >360 mg/dl) in the absence of any type of glycemic control, which is expected to be better managed in patients undergoing clinical assessment, treatment, and follow-up. Moreover, the relevance of the deletion/mutation of *Bslc2* for the lean diabetic patients with HFpEF in Asia or elsewhere remains unclear. Despite this lack of evidence, the *Bslc2* deletion seems to affect the heart through an extracardiac mechanism, and thus this model may prove to be useful for testing new hypotheses in this HFpEF category. The *Bslc2*$^{-/-}$ mouse, therefore, represents a new tool to be added to the existing animal models of HFpEF that can be particularly useful for studying more closely the lean diabetic phenotype of HFpEF.

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