Letters

Tolerating Large Preclinical Models of HFpEF But Without the Intolerance?

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https://doi.org/10.1016/j.jacbts.2021.02.011

Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Sharp et al. (1) report a novel large animal model of heart failure with preserved ejection fraction (HFpEF) induced through long-term dietary and mineralocorticoid administration, using a well-established minipig breed with known susceptibilities to obesity, metabolic syndrome, and atherosclerosis. We would like to congratulate the authors on attempting to make the complex transition from smaller to larger pre-clinical experimental models, an important step that is urgently required to progress therapeutic treatments in HFpEF. The authors concluded that their model accurately and appropriately recapitulated all the comorbidity complexities characteristic of the human HFpEF condition. Curiously, however, as stated by the authors in the introduction, all patients typically demonstrate elevated left ventricular (LV) filling rates, despite preserved LVEF alongside exercise intolerance. However, it appears no data were provided as to whether the minipigs developed signs of exercise intolerance compared to healthy controls. Given the sine qua non of patients with HFpEF is exercise intolerance, one begs the question of whether this current minipig model addresses this important point. Exercise intolerance, characterized by impairments to both cardiac and noncardiac physiological reserves, is a cardinal feature of HFpEF, as shown in the American College of Cardiology Foundation/American Heart Association clinical guidelines. Moreover, exercise intolerance is closely linked to peripheral alterations in HFpEF that includes skeletal muscle, peripheral blood flow, and vascular abnormalities (2–5). Without data corroborating the presence and severity of exercise limitation, as well as secondary development of peripheral limitations, we should pause to carefully reflect whether this model does in fact closely reflect the patient with HFpEF or simply reflect an almost but not quite.

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REPLY: Tolerating Large Preclinical Models of HFpEF But Without the Intolerance?

We thank Drs. da Silva and Bowen for their comments regarding our recent paper describing a new miniswine translational animal model of heart failure with preserved ejection fraction (HFpEF). This model exhibits the spectrum of multiorgan pathophysiology characteristics of human HFpEF. We are excited that other researchers are critically evaluating our paper and welcome further discussions, as this can only aid in moving the field forward in finding effective treatments for HFpEF patients. Drs. da Silva and Bowen are correct in their observations that our study did not incorporate exercise tolerance, and we wholeheartedly agree that this was a limitation of the