

Letters

Tolerating Large Preclinical Models of HFpEF But Without the Intolerance?



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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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](#).

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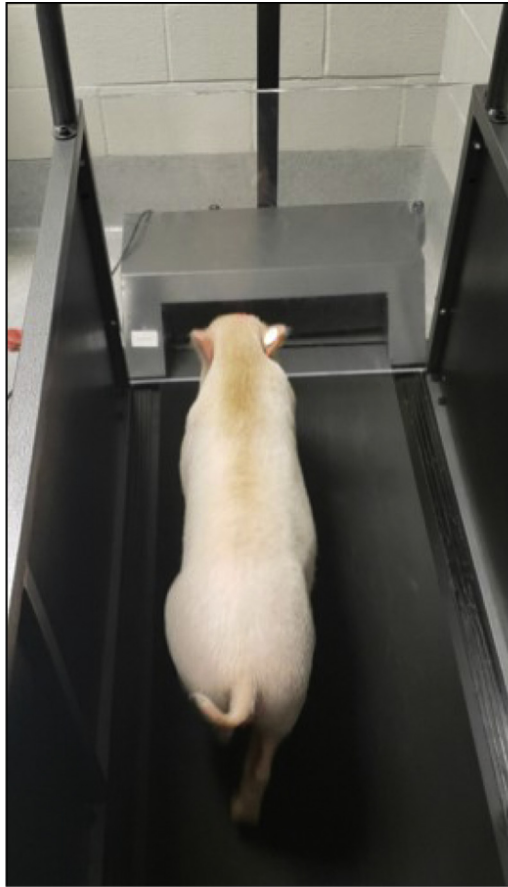
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REPLY: Tolerating Large Preclinical Models of HFpEF But Without the Intolerance?



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

FIGURE 1 Göttingen Minipig Undergoing Treadmill Acclimation and Training



Current studies using our HFpEF Göttingen minipig model have incorporated additional key endpoints, including exercise tolerance testing. HFpEF = heart failure with preserved ejection fraction.

study. We acknowledged that limitation in the text by stating the need for further “physiological functional stress exercise capacity testing” in this model. Additional exercise tolerance testing is currently under way in our laboratory (Figure 1).

Drs. da Silva and Bowen go on to state that the lack of exercise intolerance data preclude the use of the model for HFpEF in that it does not reflect the patient with HFpEF but only key aspects of the disease. Although exercise intolerance is a key feature of human HFpEF and is a very useful functional endpoint for intervention studies, it is not one of the requisite clinical endpoints for diagnosis of HFpEF. As stated, in the presence of normal ejection fraction, elevated left ventricle (LV) filling pressures at rest (LV end-diastolic pressure

>15 mm Hg) and elevated resting pulmonary capillary wedge pressure (>15 mm Hg) confirm definite evidence of HFpEF (1-4), all of which were observed in our model. Drs. da Silva and Bowen appear to have mistaken the use of additional diagnostic criteria for suspected HFpEF with the required diagnostic criteria for confirmed HFpEF. When LV pressures are high and congestion is present at rest, HFpEF is readily diagnosed (1-4).

Filling pressures are elevated at rest in patients with more advanced HFpEF and become elevated during exercise in patients with early stage HFpEF. As was stated, the large animal model presented is one of severe HFpEF; performing exercise testing earlier in disease progression to show “early” HFpEF was beyond the scope of the study. In a recent review by Ho et al. (4), the authors state that cardiopulmonary exercise testing or 6-minute walk testing can help to define limitations in functional capacity among individuals with suspected HFpEF, although the tests do not provide definitive diagnostic information.

Resting hemodynamics is the gold standard for confirming the diagnosis of HFpEF (1-4). However, the invasiveness of left and right heart catheterization does not support use of hemodynamic measurements during initial screening of HFpEF patients, placing a greater emphasis on noninvasive assessments. Various HFpEF algorithms and classifications based on noninvasive blood biomarkers, echocardiography, and exercise testing have been proposed; however, the substantial variations in which noninvasive diagnostic criteria are used have further complicated an already heterogeneous disease. We agree that the burden of proof should be higher in a descriptive animal model of human disease. Our study not only provides physiologic parameters that meet widely accepted clinical diagnostic criteria (including left- and right-sided hemodynamic testing) but also describes systemic phenotypic comorbidities (eg, obesity, insulin resistance, vascular dysfunction, and systemic inflammation), which are contributors to development and progression of HFpEF in a substantial proportion of humans with HFpEF. Therefore, we propose that, in addition to using our new large animal model of HFpEF as a platform for evaluating potential HFpEF treatments, this model has the ability to assist with current validation efforts for noninvasive diagnostic approaches against direct invasive hemodynamic criteria (4).

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