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EDITORIAL COMMENT

Cardiometabolic Heart Failure and HFpEF

Still Chasing Unicorns*

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Heart failure (HF) is a complex and heterogenous syndrome that is projected to affect more than 8 million adults by 2030 (1). The HF patient population can be separated into 2 general groups, those with HF with reduced ejection fraction and those with HF with preserved ejection fraction (HFpEF). HFpEF has been estimated to affect approximately one-half of the HF patient population, and this population is predicted to increase over the next decade (2). The pathophysiological drivers that cause or exacerbate HFpEF are under investigation because the precise cardiac and extracardiac pathologies that cause or exacerbate the HFpEF phenotype remain largely unknown. There are no Food and Drug Administration–approved therapeutic agents to treat patients that have HFpEF, in part because the pathobiology is still not clearly defined, and there is a lack of suitable preclinical models that can be used to define causes and test therapies (3). Complicating matters further, current clinical research suggests that HFpEF is not caused by a single pathology but is a result of multiple, distinct, and unique diseases with different primary driving factors. This was eloquently presented by Shah et al. (4), where 3 primary phenotypes were observed in patients: 1) young patients with moderate diastolic dysfunction and normal B-type natriuretic peptide (BNP) levels; 2) obese, diabetic patients with sleep apnea and worsened left ventricular (LV) relaxation; and 3) older patients with chronic kidney disease, myocardial dysfunction, and pulmonary hypertension. This characterization of distinct phenotypes may aid in better clinical trial design and outcomes but leaves the basic research community in a conundrum regarding the development of suitable translational animal models which reliably recapitulate each of these different HFpEF phenotypes. Although rodent models of HFpEF have emerged (5), the physiological differences between rodents and humans are well established and suggests that large animal models might be more predictive of therapies that could be effective in humans (6). It is imperative, that these newly developed large animal models of HFpEF recapitulate essential pathophysiological features of HFpEF and its progression to allow for translation to the clinic. In this issue of *JACC: Basic to Translational Science*, Olver et al. (7) have characterized a swine HFpEF model that includes several of the key comorbidities (obesity, early metabolic derangement, and pressure overload) observed in patients.(8,9).

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The study was performed in Ossabaw swine, which are well characterized to have a “thrifty phenotype,” becoming obese and pre-diabetic when fed a western diet (WD) (10). The authors fed 2-month-old, female Ossabaw swine a control or WD for 10 months to induce obesity with metabolic derangements. They then placed an aortic band (AB) at 6 months of age to induce pressure overload in an attempt to induce HFpEF. Functional, morphological, and molecular endpoints were measured to assess the degree of

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cardiac and systemic dysfunction at 12 months of age in 4 to 5 control and WD-AB swine. The authors describe the cardiac structural and functional changes observed at 10-months' post-diet and 6-months' post-aortic banding (7). The expected hypertrophic response due to aortic banding was demonstrated by increased heart weight and LV wall thickness. Furthermore, they conclude LV systolic function remained normal, whereas diastolic function was impaired based solely on the end-diastolic pressure volume relationship and isolated single cardiomyocyte T-tubule structure and function. They attribute impaired relaxation to LV mitochondrial dysfunction as previously reported in the Ossabaw swine (11). Furthermore, the investigators also explore the molecular signature through transcriptomic analysis of LV tissue, reporting alterations of a myriad of genes that are consistent with cardiovascular diseases and their related comorbidities. The authors conclude that their model recapitulates features of HFpEF.

In our view, the model in the study by Olver et al. (7) represents an early-stage of HFpEF, and as such may not faithfully mimic HFpEF in humans. Although Ossabaw swine on a WD develop dyslipidemia, immature vascular plaque formation, and hyperinsulinemia, the investigators acknowledge they do not spontaneously develop HF (12). HFpEF is recognized to also be an age-related disease, because age is a primary predictor of HFpEF's initial diagnosis (13), whereas the investigators used very young animals (2 months of age for 10 months). To induce HF in the WD-fed animals, the investigators implanted a surgical band on the aorta to produce acute pressure overload. This technique is widely used in both large and small animal models (14–17) but has caveats. More rapid pressure overload usually causes compensatory states (hypertrophic response) (18,19) or decompensation (LV dilation with reduced ejection fraction) such as in mouse transverse aortic constriction models of acute pressure overload (15). By contrast, slow, progressive pressure overload models more closely parallel the type of structural heart disease induced by aortic stenosis in humans (14). There are several alternatives to aortic banding that are more physiologically relevant, including an increase in dietary salt consumption or introduction of agonists that activate the renin-angiotensin-aldosterone system to develop a global hypertensive phenotype. The gene ontology data herein is generalized and could conceivably be altered by HF-independent cardiovascular disease (7).

Although systolic function was preserved (no change in LVEF) in the model, there was a leftward shift in the EDPVR, consistent with diastolic dysfunction, many traditional measures of LV diastolic dysfunction were not measured (i.e., E/A, E/e′, Doppler flow velocities). Moreover there was no physiological measurement of pulmonary hypertension (elevated pulmonary artery pressure or pulmonary capillary wedge pressure). Most importantly, LV end-diastolic pressure was not elevated (LVEDP), which is an essential feature of HFpEF involving pressure overload. Lastly, there was no traditional HFpEF biomarkers (i.e., cardiac troponin I, BNP, atrial natriuretic peptide) studies.

The authors also studied the cellular mechanisms that may contribute to impaired relaxation by investigating isolated single cardiomyocyte physiology in the basal state and after exposure to adrenergic agonists. Myocytes isolated from the WD-AB animals did not have significant alterations in Ca^{2+} regulation, either in the basal state or after treatment with an adrenergic agonist. This suggests the presence of the very earliest stages of adaptation to persistent disease stress. These findings are at odds with previous studies of myocytes with hypertrophy from slow progressive pressure overload, where myocyte contractile derangements are present even though global pump performance parameters (LVEF) are maintained (18). In these studies, persistent disease caused derangements of cardiac functional reserve (20,21). The absence of these changes suggests that the model fails to show any systolic defects that are present in patients with HFpEF. The absence of any significant changes in Ca^{2+} transient dynamics is also a bit surprising, given the T-tubules are disrupted in the WD-AB myocytes (7).

In conclusion, HFpEF is a complex and heterogenous clinical syndrome for which there are no effective therapies. Developing novel HPpEF therapies will require developing large animal models that faithfully mimic the HFpEF phenotype. The model developed by Olver et al. (7) combines metabolic derangements together with mechanical pressure overload in young, female swine. Although these animals develop cardiac hypertrophy and some metabolic disturbances, as noted above many of the phenotypic features characteristic of human HFpEF are not observed in this model, which raise important questions about the overall clinical utility of the model. In our view, the critical features of a large animal HFpEF model should include adverse LV structural and functional remodeling, abnormal

diastolic function, decreased systolic functional reserve, increased LV filling pressures, and pulmonary hypertension. Models with several comorbidities such as increased body mass index, dyslipidemia, moderately resistant hypertension, and metabolic derangements are also critical for the development of HFpEF models. In this regard, the study by Olver et al. (7) represents an important first step in developing an appropriate large animal model that mimics the cardiometabolic phenotype of HFPEF in humans.

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