A new porcine model of hypertensive cardiomyopathy: a helpful tool to explore the HFpEF mystique

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HEART FAILURE WITH preserved ejection fraction (HFpEF) is a challenging clinical entity with a lack of clear diagnostic criteria and evidence for therapy (3, 5, 15). Most clinical studies have failed to demonstrate a benefit of drugs in HFpEF (7). Since HFpEF is heterogenous both in aetiology and pathophysiology and notable with multiple cardiac and noncardiac comorbidities (13), the “one size fits all” principle will probably not work. HFpEF may require an individualized, targeted therapy based on age, the underlying aetiology, comorbidities, and so on (4, 14).

The underlying mechanisms of the HFpEF syndrome are not fully understood (3). Research animals may be tools for in-depth understanding of pathophysiology and the development of novel therapies. For HFpEF, only few animal models have been proposed. Doi et al. (2) placed Dahl salt-sensitive rats on 8% NaCl from the age of 6 to 7 wk; these hypertensive rats developed HFpEF after 18–21 wk and left ventricular (LV) hypertrophy, followed by transition to congestive heart failure with maintained LV fractional shortening and increased LV stiffness (2, 11). Regan et al. (9) showed that chronic infusion of low-dose angiotensin II results in a HFpEF phenotype in the mouse, without increasing systemic arterial blood pressure. Reil et al. (10) demonstrated that selective reduction of heart rate by If-inhibition improved vascular stiffness, LV contractility, and diastolic function in male leptin receptor-deficient C57BL/KsJleprdb/leprdb type 2 diabetic HFpEF mice. Repeat biopsies, blood sampling, and access to multiple vessels are not feasible in small animals such as rodents and are advantages of large animal studies. Swine and human subjects have similarities in their cardiovascular system and share many characteristics in excitation-contraction coupling (6). In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Schwarzl and colleagues (12) describe a HFpEF model induced by deoxycorticosterone acetate (DOCA, 100 mg/kg, 90-day release subcutaneous depot) and a Western diet (WD) containing high amounts of salt, fat, cholesterol, and sugar for 12 wk in landrace pigs (12).

In this model, hypertension, hyperlipidemia, LV concentric hypertrophy, and left atrial dilatation were observed in absence of significant changes in LV ejection fraction or symptoms of heart failure at rest. The LV end-diastolic pressure-volume relationship was markedly shifted leftward. Thus this model almost perfectly represents the major features of clinical HFpEF in patients with hypertension, dyslipidemia and physical inactivity: LV hypertrophy, left atrial enlargement, and preserved ejection fraction. HFpEF induced by both hypertension and hyperlipidemia as well as physical inactivity belong to the novel features of this porcine model, and future intervention on blood pressure and hyperlipidemia (alone or in combination) in this model might therefore highlight the impact of blood pressure/hyperlipidemia in the pathogenesis (molecular and pathological mechanisms) of HFpEF.

During simultaneous right atrial pacing and dobutamine infusion, cardiac output reserve and LV peak inflow velocities were reduced and LV end-diastolic pressures were increased in DOCA/WD treated pigs (12). These features are in line with findings in hypertensive HFpEF patients with increased total, collagen-dependent, and titin-dependent stiffness, insoluble collagen, and increased titin phosphorylation (16). Exploring changes on the above parameters post-antihypertensive therapy alone or in combination with lipid-lowering strategies in this model would be helpful in understanding the collagen remodeling in the pathogenesis of HFpEF. It is worthwhile to note that swine expresses more N2BA isoform (N2BA-to-N2B ratio of 1–1.5) than humans (N2BA-to-N2B ratio of 0.4–1.2); this point should be taken into account on interpreting the study results.

Increased systemic and endothelial inflammation status, reduced nitric oxide bioavailability, and protein kinase G activity are important characteristics of HFpEF (8). Accordingly, this model demonstrated a higher baseline superoxide production level, suggesting a potential role of reactive oxygen species in the HFpEF disease course, thus exploring reactive oxygen species changes after various interventions that belong to a “to do” task in this model.

There are some limitations of this model. Plasma NH2-terminal brain natriuretic peptide could not be detected in a meaningful way using commercially available ELISA kits. Nitric oxide bioavailability and protein kinase G activity remained unchanged, and blood glucose level and potential insulin resistance parameters were not determined. Because of anatomical limitations, reliable apical views during echocardiography could not be obtained. Thus classical echocardiographic parameters reflecting LV relaxation and filling like E-to-A ratio, E-to-E’ ratio, or left atrial volumes were not reported. One might consider adding diabetes to this model since diabetes alone represents some kind of HFpEF model. Since pigs grow very fast, the authors restricted the study period to 12 wk; minipigs might be an alternative. HFpEF in humans is primarily a disease of advanced age. Despite the
above limitations, this model may improve our understanding of the mechanisms of HFpEF and provide a valuable tool to test targeted new therapeutic strategies.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

K.H. and G.E. interpreted results of experiments and drafted manuscript. G.E. approved final version of manuscript.

REFERENCES


