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Obesity, Hypercholesterolemia and Hypertension Drive Pathophysiological Remodeling in a Novel Minipig Model of Heart Failure with Preserved Ejection Fraction

Background: Heart failure with preserved ejection fraction (HFpEF) presents as a challenging multi-organ syndrome for which there is a lack of effective treatments and very high morbidity and mortality. HFpEF is a distinct form of heart failure in which the primary pathology is left ventricular (LV) diastolic dysfunction with impaired cardiac relaxation resulting in LV stiffness, abnormal filling and exertional intolerance. Previous preclinical studies have investigated various animal models in which LV diastolic dysfunction was the sole pathology. However, HFpEF is now understood to be a highly complex disease state caused by multiple pathologies (hypertension, diabetes, age, obesity, inflammation) involving multiple organ systems besides the heart. In addition, while these studies have used a variety of techniques to induce hypertension and characteristics of HFpEF, they ultimately fail to mimic heart failure clinical guidelines.

Hypothesis: The goal of the present study was to develop a large animal model of HFpEF that very closely mimics HFpEF observed in the clinic.

Methods: Our study utilized a Western-based diet to induce obesity and diabetes coupled with 11-deoxycorticosterone acetate (DOCA) for induction of hypertension in Gottingen miniswine over a 20-week period. Serial echocardiographic assessment was performed over the 20-weeks. Invasive hemodynamics were measured at baseline and 20-weeks.

Results: While LVEF was preserved in the HFpEF group, comorbidities led to a significant ($p<0.01$) increase in LV relative wall thickness (20 week: HFpEF, 0.79 ± 0.03 cm; Control, 0.46 ± 0.05 cm). Progressive diastolic dysfunction as measured by E/e' (20 week: HFpEF, 12.8 ± 1.3; Control, 7.3 ± 0.8; $p<0.01$) and left atrial remodeling. This adverse remodeling lead to significantly elevated filling pressures at 20 weeks in the HFpEF group compared to control (17.7 ± 0.3 mmHg vs. 9.5 ± 0.5 mmHg; $p<0.01$) and pulmonary hypertension as measured by the pulmonary artery systolic pressure (36.0 ± 2.0 vs. 24.4 ± 1.3 mmHg, respectively; $p<0.01$). Endothelial-dependent vascular dysfunction was present in the HFpEF group along with histopathological abnormalities including cardiac fibrosis, adipose infiltrate, pulmonary remodeling, and extensive renal fibrosis.

Conclusions: The combination of a Western-based diet and DOCA-salt induced hypertension in the Gottingen miniswine led to the development of a novel preclinical large animal model of HFpEF exhibiting multi-organ involvement and a full spectrum of comorbidities associated with human HFpEF.