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

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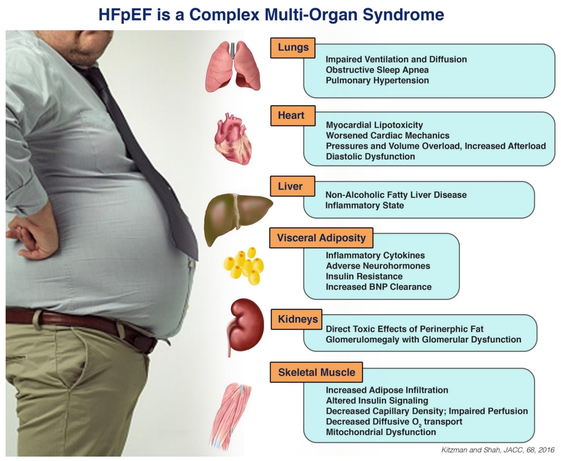
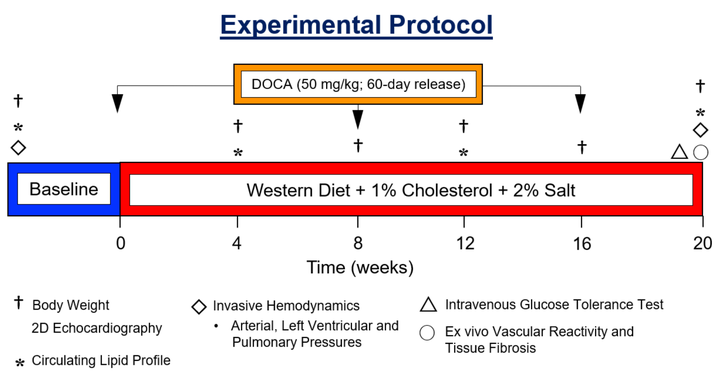
Background



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.[1] While studies have used a variety of techniques to induce hypertension and other pathologies (hypertension, diabetes, age, obesity, inflammation) of HFpEF, they ultimately fail to mimic heart failure clinical guidelines.[2] 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



Results

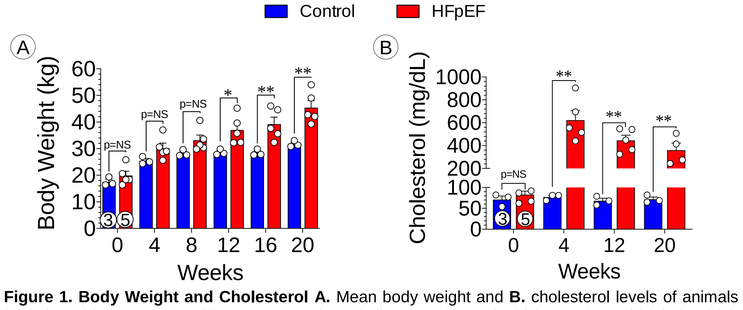


Figure 1. Body Weight and Cholesterol A. Mean body weight and **B.** cholesterol levels of animals following either a regular diet or Western-based diet, the latter of which consists of high fat, high sucrose, and high sodium. Obesity and hypercholesterolemia help drive a systemic change in energy sources and inflammation.

Results

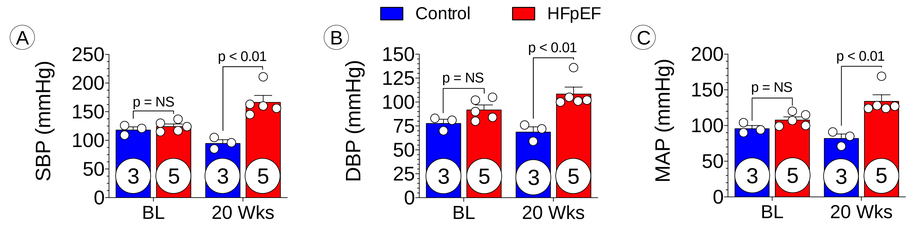


Figure 2. Increased Systemic Blood Pressure in HFpEF Measurements of the systolic **A**, diastolic **B**, and mean arterial **C** blood pressures recorded over the 20-week period. Elevated blood pressures allow for a hypertensive state conducive to cardiac dysfunction and remodeling as seen in the clinical HFpEF model.

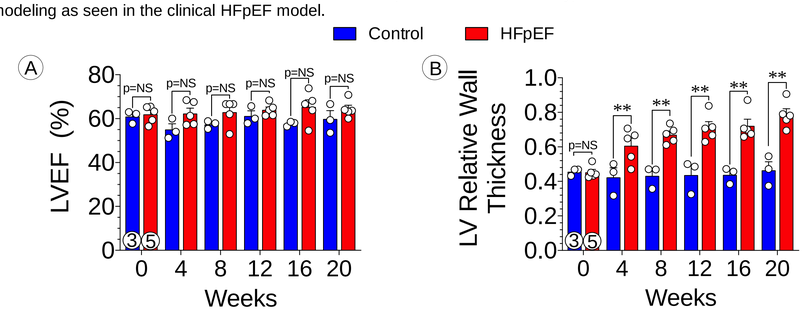


Figure 3. Preserved Left Ventricular Ejection Fraction and Progressive Increase in Relative Wall Thickness Measurements of left ventricular ejection fraction **A** and left ventricular relative wall thickness **B** obtained via echocardiographic assessment. An LVEF ≥ 50% represents a preserved ejection fraction and, considering other comorbidities, can denote normal to mildly abnormal LV systolic function. Increases in LV relative wall thickness depict the response of cardiac remodeling to elevated filling pressures.[3]

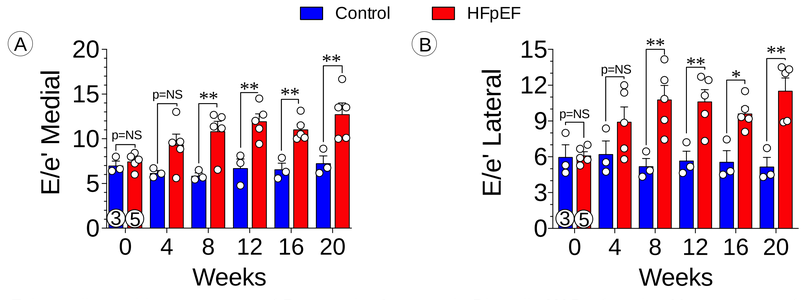


Figure 4. Echocardiographic assessment of Progressive Increase in Diastolic LV Dysfunction Measurements of the ratio of early mitral valve flow velocity (E) to early diastolic lengthening velocities (e') in the medial wall **A** and lateral wall **B** of the left ventricle. A high ratio of E/e' indicates a high gradient of blood flow into the left ventricle with little change in volume, indicating diastolic dysfunction.[4]

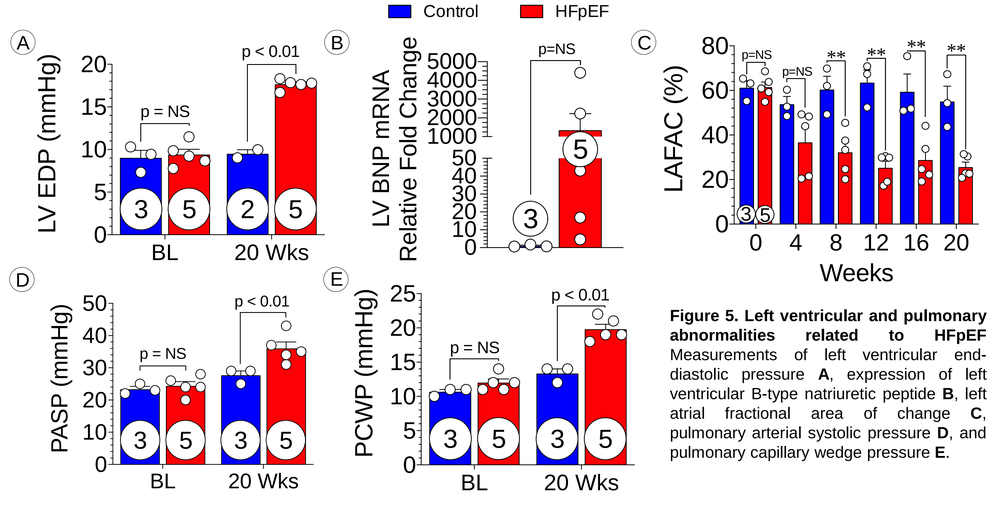


Figure 5. Left ventricular and pulmonary abnormalities related to HFpEF Measurements of left ventricular end-diastolic pressure **A**, expression of left ventricular B-type natriuretic peptide **B**, left atrial fractional area of change **C**, pulmonary arterial systolic pressure **D**, and pulmonary capillary wedge pressure **E**.

Results

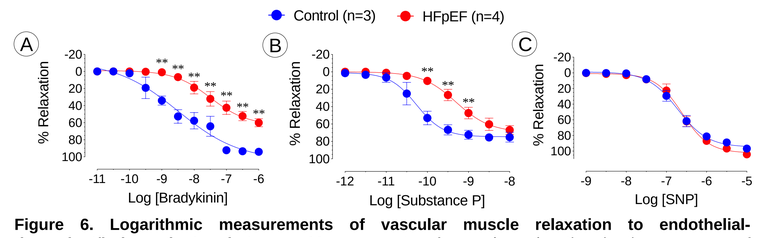


Figure 6. Logarithmic measurements of vascular muscle relaxation to endothelial-dependent/independent substances Measurements of vascular relaxation in the presence of endothelial-dependent **A** bradykinin **B** substance P, and endothelial-independent **C** sodium nitroprusside. Decreases in percentage muscle relaxation indicate endothelial dysfunction, pertinent to HFpEF development.

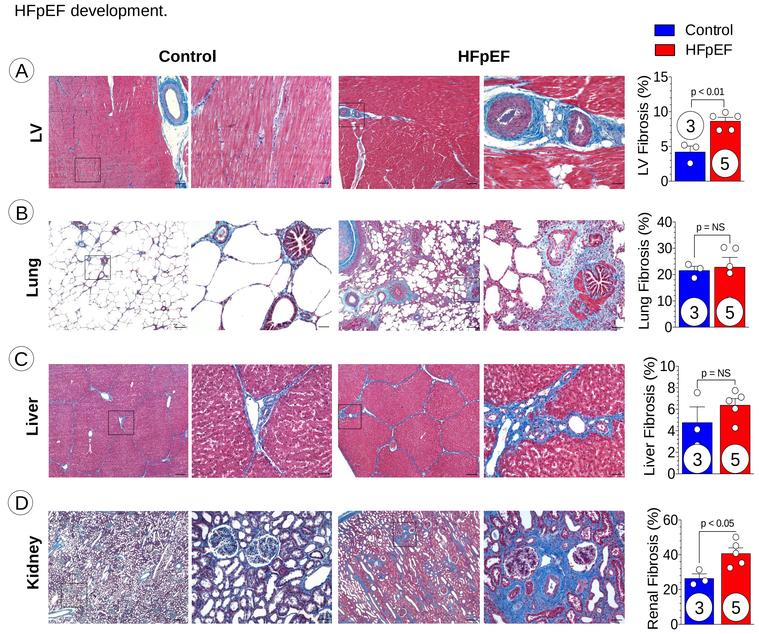


Figure 7. Histopathologic Assessment of Fibrosis HFpEF Left ventricle **A**, lung **B**, liver **C**, and kidney **D** tissue was obtained in both animal groups. Inflammation and fibrosis present in the HFpEF group represents the multi-systems effect that can be seen in the clinical HFpEF model.

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. The successful characterization of the large animal HFpEF model can help forward advancements in therapeutic interventions to be used in the clinical setting. Future studies should focus on therapeutic interventions in the large animal model.

References

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5. Background image from: Kitzman, D. W. & Shah, S. J. The HFpEF Obesity Phenotype: The Elephant in the Room. *Journal of the American College of Cardiology* (2016). doi:10.1016/j.jacc.2016.05.019