STANDARDIZATION OF A FEMALE MURINE MODEL OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

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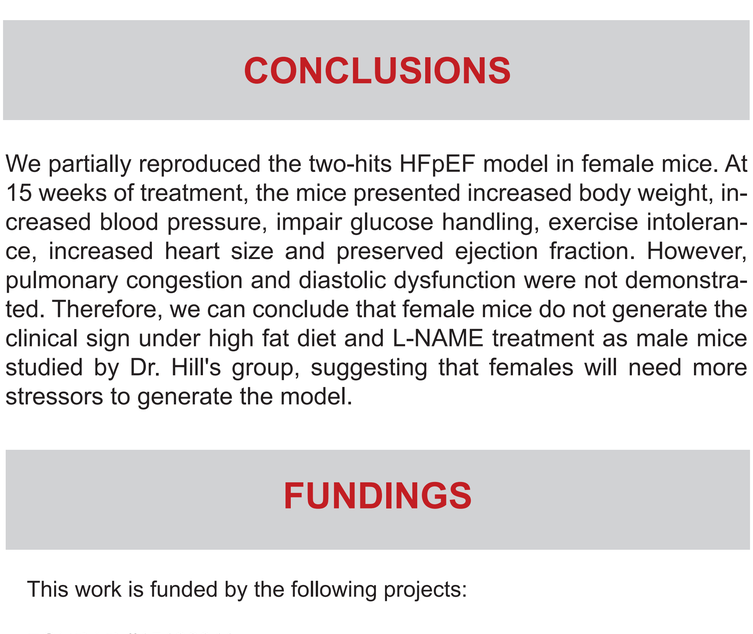
INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a disease highly prevalent in older women and people with metabolic syndrome. Unfortunately, the pharmacological management of HFpEF has shown to be ineffective, so there is a need to understand the multifactorial physiopathology to improve the efficacy of treatments. The standardization of an animal model has become an imperative to study the molecular processes. As described by Valero-Muñoz (Valero-Muñoz et al., 2017) the murine model of HFpEF must fulfill certain parameters to simulate accurately the human pathology, within these we find the preserved systolic function or ejection fraction, exercise intolerance as a clinical sign, pulmonary edema and cardiac hypertrophy.
Dr. Hill's group (Schiattarella et al., 2019) developed a murine model based on the Two-Hit which consists of generating metabolic syndrome (obesity and glucose mismanagement) and hypertension in male. However, given the high prevalence in females, it is necessary to standardize the model to determine possible gender-related differences in the development of the disease and contribute to the understanding and development of future therapies.

METHODS

Twelve-week-old C57BL/6N mice (n=12) were fed a high-fat diet (60% kilocal fat) and L-NAME (a NOS inhibitor, 0.5 g/L in water) for 15 weeks.
Body weight measurements were performed weekly and contrasted with control group (n=12).
We determined, in each group, the glucose tolerance, blood pressure, exercise tolerance through the treadmill walking test, and finally the systolic and diastolic function through echocardiography.
Once the animals were euthanized, the heart and lungs were removed and weighed.
Statistical analysis. GraphPad Prism 7 was used for statistical analysis. The shapiro-wilk test was used as a normality test. Statistical difference was determined by mann-whitney test or t-test as appropriate. A $p<0.05$ was considered statistically significant.



CONCLUSIONS

We partially reproduced the two-hits HFpEF model in female mice. At 15 weeks of treatment, the mice presented increased body weight, increased blood pressure, impair glucose handling, exercise intolerance, increased heart size and preserved ejection fraction. However, pulmonary congestion and diastolic dysfunction were not demonstrated. Therefore, we can conclude that female mice do not generate the clinical sign under high fat diet and L-NAME treatment as male mice studied by Dr. Hill's group, suggesting that females will need more stressors to generate the model.

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RESULTS

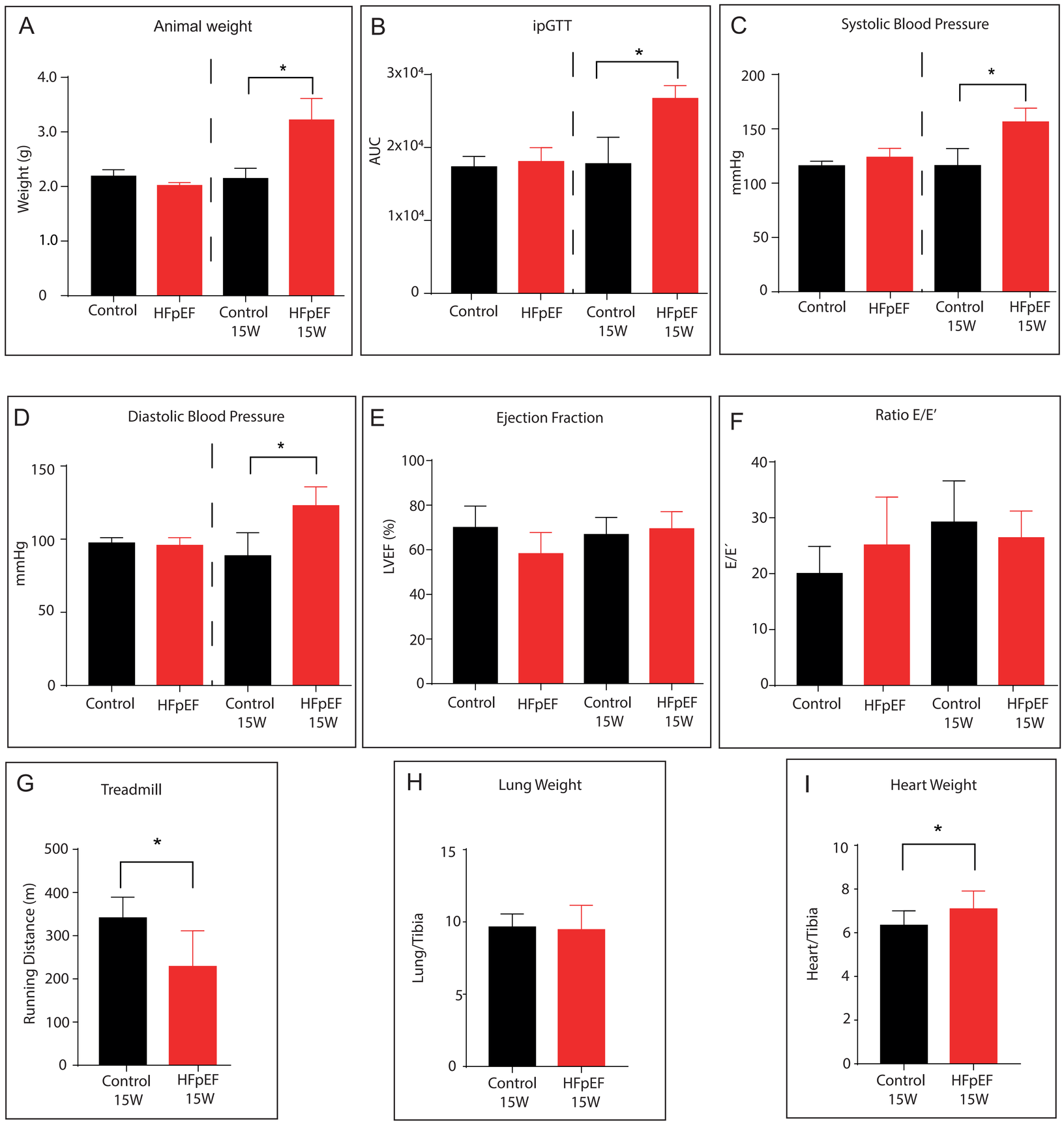

Figure 1. Systemic and cardiac phenotype of mice after 15 weeks of different diets.
A) Body weight of female mice from initial week and after 15w of HFpEF diet. B) Area under the curve of the intraperitoneal glucose tolerance test (ipGTT) in basal conditions and after 15w of HFpEF diet. C) Systolic blood pressure and D) Diastolic blood pressure basal and after 15w of treatment. E) Percentage of left ventricular ejection fraction in control and HFpEF groups. F) Ratio between E wave and mitral E' wave. diet at 15w. G) Running distance of mice after 15 weeks feed with HFpEF diet in treadmill fatigue test. H) Ratio between lung weight and tibia length. I) Ratio between heart weight and tibia length. n= 12 mice per group. Data are mean ± SD. *$p<0.05$ vs control