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REPLY: Diet-Induced Obesity HFpEF Murine Models

We thank Dr. Carbone and colleagues for their suggestion to add the diet-induced model of obesity to our recent review of murine models of heart failure with preserved ejection fraction (HFpEF) (1). The diet-induced obesity model (including high-fat diets, Western diet, and others) is an important model in the context of cardiac remodeling and cardiac dysfunction. It is known that mice and rats that are fed these types of diets become obese; frequently, but not always, develop a cardiac phenotype characterized by cardiac hypertrophy, fibrosis, and diastolic dysfunction (2–6); and may also develop systolic dysfunction with a depressed left ventricular ejection fraction (7). These features depend on several parameters, such as study duration, caloric intake, and, as mentioned by the authors, the specific composition of nutrients in the diet (% saturated and unsaturated fat, as well as carbohydrates). Carbone and colleagues, as well as others, showed that obese mice fed a Western or high-fat diet had higher left ventricular end-diastolic pressure by invasive hemodynamics than nonobese mice on a control diet (6,8). It has also been shown that Western diet-induced obesity caused impairment in exercise capacity (9). Conversely, others have found no cardiac phenotype with a high-fat diet (10). We, therefore, agree with the authors that with some *select* diets, the diet-induced obesity model *may be* representative of HFpEF. However, not all diet-induced obesity models mirror HFpEF in humans (9,10). Finally, to our knowledge, we are unaware of any other studies of diet-induced obesity, in either mice or rats, where post-mortem pulmonary congestion was assessed.

We would also like to again re-emphasize that diastolic dysfunction is not a surrogate for HFpEF in preclinical studies, nor is it enough to establish it, as diastolic dysfunction occurs in *heart failure with reduced ejection fraction* (HFrEF) (1).

Recently, the quest for the perfect animal model to phenocopy human HFpEF has overtaken the heart failure field (11). This is likely because of alarm over why clinical trials in HFpEF have been negative/neutral, and this concern has extended to scrutinizing preclinical studies. This intense dissection did not occur in animal models of HFrEF where, for example, left anterior descending artery ligation was simply a model of ischemic cardiomyopathy/HFrEF due to coronary artery disease. There was no cause for concern that these animal models did not include hypertension, obesity, type 2 diabetes mellitus, or tobacco exposure, despite these being very strong risk factors for coronary artery disease. That being said, both clinical and experimental HFpEF are dissimilar to HFrEF, and the challenges that are outlined in the review persist (1). Murine models of HFpEF that represent HFpEF in humans are important tools to study HFpEF, as they provide mechanistic insights into this challenging disease/syndrome (12–15).

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