The Effect of LCZ696 on Cardiac Function and Structure in a Novel, Shortened Cardio-Metabolic Mouse Model of HFpEF

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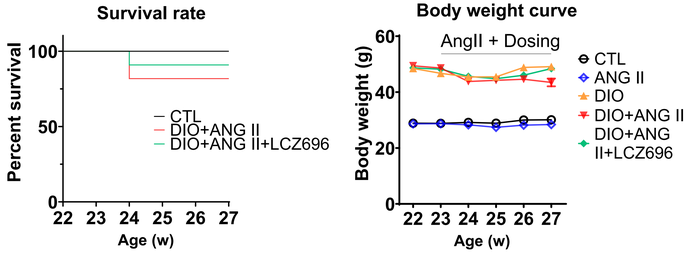
Introduction

Current preclinical murine models for heart failure with preserved ejection fraction (HFpEF) require prolonged modeling periods, pose significant challenges to fast screening in drug development. In response, our study sought to develop a novel, shortened, multifactorial HFpEF mouse model that coupled obesity, hyperglycemia, hypertension and cardiac hypertrophy to closely mirrors the cardio-metabolic phenotypes observed in human patients.

With infusion of Ang II, diet-induced obesity (DIO) mice manifested typical phenotypes as observed in human HFpEF patients, for example, unchanged LVEF, elevated IVRT and increased heart weight and LVPWTs/d, indicating that the diastolic dysfunction and cardiac hypertrophy happened in the model mice. Post-life analysis, heart tissue collection and histopathological staining revealed an increased level of cardiac fibrosis with infiltration of inflammatory cells. Blood chemistry analysis also revealed an upregulation in cardiac biomarker NT-proBNP and GDF15. Administration of LCZ696 significantly attenuated the cardiometabolic abnormalities with restored diastolic function, reduced cardiac hypertrophy and myocardial fibrosis.

Experimental Design

C57/BL6J (CTL) and diet-induced obesity (DIO) mice were fed with normal chow and HFD, respectively. CTL or DIO mice were administered with angiotensin II (Ang II or DIO + Ang II) for 4 weeks via osmotic mini pumps. LCZ696 (60 mg/kg) was administrated (P.O., QD) one day after angiotensin II infusion for 4 weeks. DIO mice at 21W old with 16W-HFD were purchased.



Results

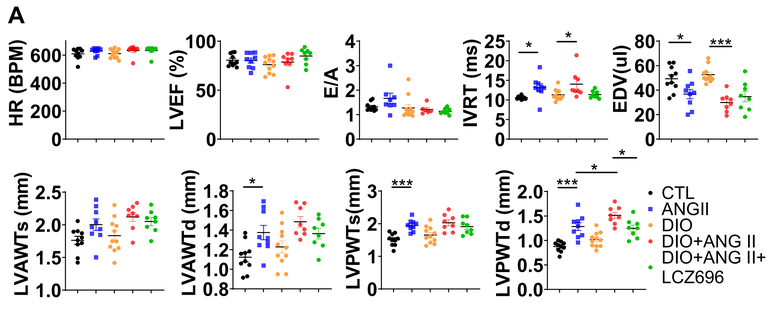


Figure 1. LCZ696 improved cardiac function and structure alternations, blood GDF-15 and NT-proBNP levels in the DIO-Ang II model. **(A)** Cardiac function and structure were analyzed by Echocardiogram and **(B)** blood GDF-15 and NT-proBNP levels were measured by ELISA.

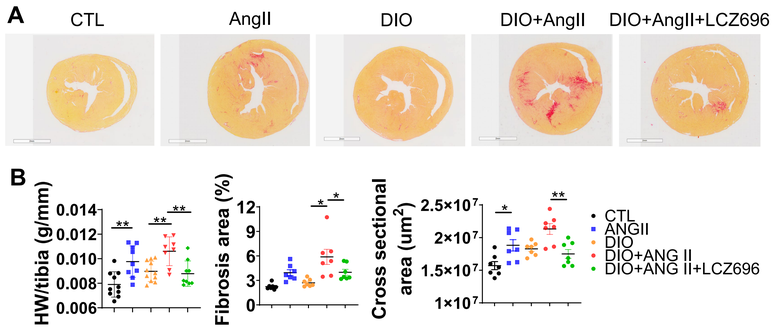


Figure 2. LCZ696 improved heart hypertrophy and fibrosis in the DIO-AngII model. **(A)** Representative images of PSR staining of hearts. **(B)** Cardiac hypertrophy was evidenced by heart weight versus tibia length ratio. Cardiac fibrosis was analyzed by PSR staining and cross-sectional area was used to indicate the heart size.

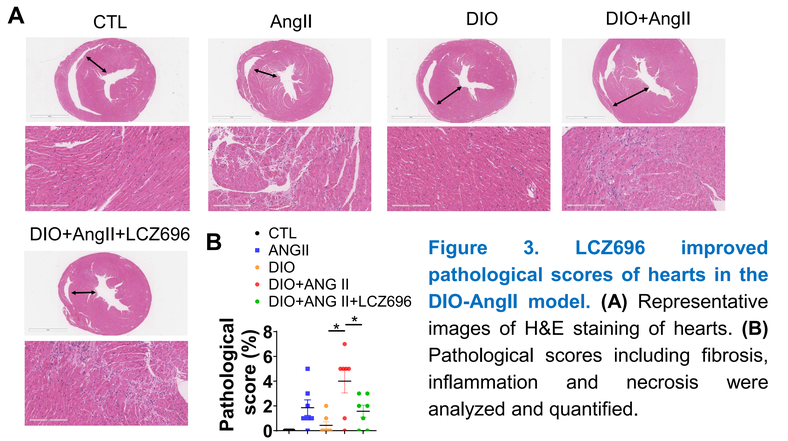


Figure 3. LCZ696 improved pathological scores of hearts in the DIO-AngII model. **(A)** Representative images of H&E staining of hearts. **(B)** Pathological scores including fibrosis, inflammation and necrosis were analyzed and quantified.

Conclusions

We have successfully developed a rapid mouse model that closely mimics human HFpEF, with modeling time around 4 weeks and a robust validation using LCZ696, offering a fast, valuable new platform for advancing therapeutic development of HFpEF treatment.

References

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