Left atrial dysfunction is an early and transitional driver in the development of heart failure with preserved ejection fraction

Jasmine Matsuda[1] , Parnia Mobasheran[1 2], Scott Jennings[1 2], Qinglin Yang[1 2]

[1]Cardiovascular Center of Excellence, Louisiana State university Health Sciences Center, New Orleans, LA 70112, USA [2]Department of Pharmacology and Experimental Therapeutics, Louisiana State university Health Sciences Center, New Orleans, LA 70112, USA 3Department of Genetics, University of Alabama at Birmingham, Birmingham, Alabama 35294, USA

Background

- Heart failure with preserved ejection fraction (HFpEF) accounts for over 50% of heart failure cases in the U.S., particularly among aging and metabolically burdened populations. Despite its prevalence, HFpEF remains poorly understood, and effective treatments are lacking.
- Recent clinical studies increasingly implicate left atrial (LA) dysfunction as a key early driver of HFpEF pathogenesis. LA plays a crucial role by acting as a reservoir during ventricular contraction.
- Impaired LA function leads to reduced LV filling or elevated filling pressures, the latter has recently proposed as a hallmark of HFpEF progression
- It is impossible to establish the definitive LA's roles in the development and progression of HFpEF in patients. To address this, we developed a novel pre-clinical mouse model to investigate how LA plays a critical role in initiating and sustaining HFpEF.

Method

Using a fine-tip cautery pen, we applied controlled epicardial burns to the left atrial (LA) surface of 5–6-month-old male C57BL/6J mice to induce localized atrial dysfunction (AD). Burns were distributed across multiple non-overlapping regions to achieve widespread injury (Fig. 1)

Mice were assigned to three groups, including sham (no injury), mild AD (3 burns), and moderate AD (5 burns). Over the following 4 weeks, we evaluated cardiac function (transthoracic echocardiography), pulmonary function (whole-body plethysmography), and exercise capacity (treadmill test) to monitor disease progression.

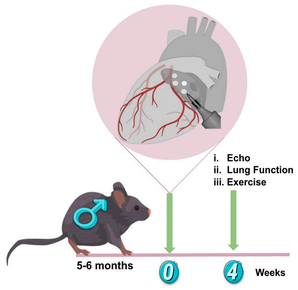

Figure 1. Experimental plan

AD causes systolic and diastolic heart function impairment

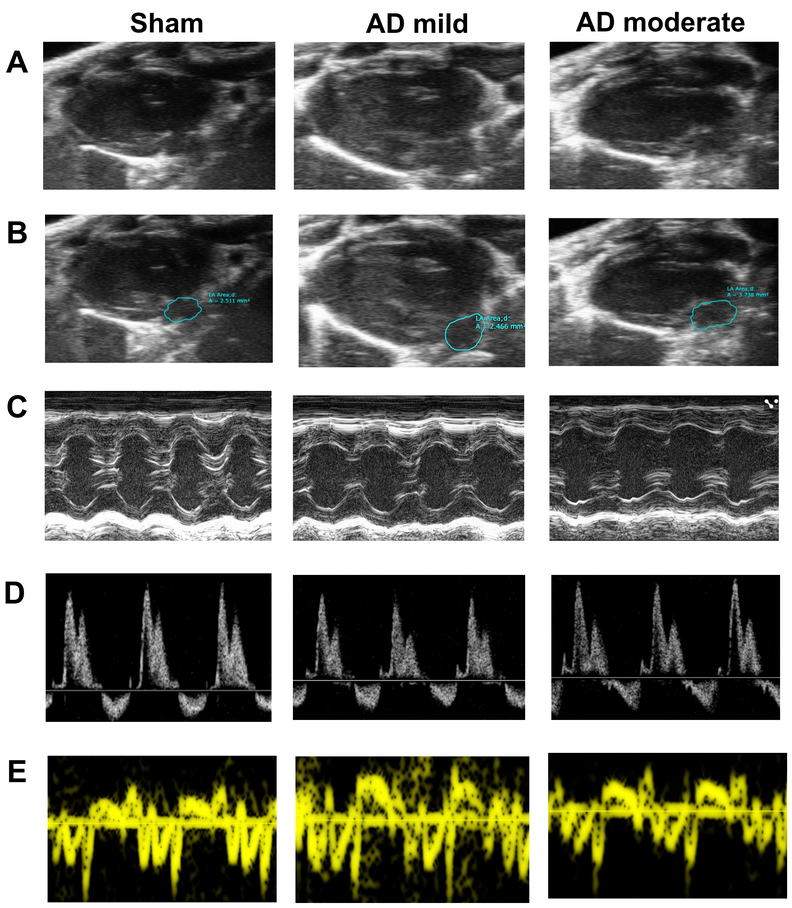

Figure 2. Echocardiogram – Vevo F2 System echocardiographic images comparing Sham and AD mice. (**A**) B-mode image showing LV structure, (**B**) B-mode image with LA area trace (d = diastole), (**C**) M-mode image assessing LV contraction, (**D**) PW Doppler, (**E**) Tissue Doppler

Left atrial injury leads to severity-dependent ventricular functional impairment

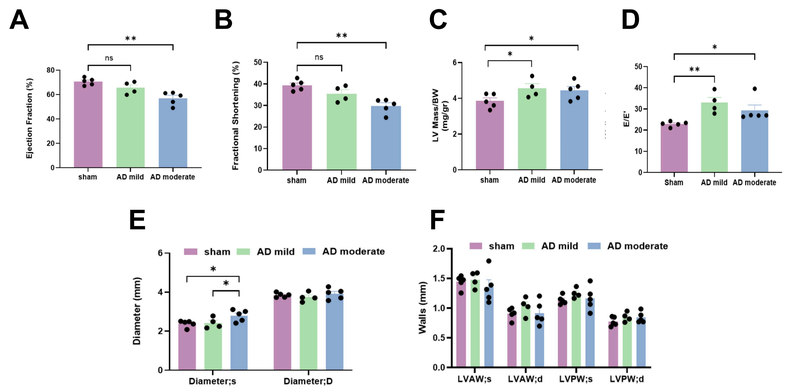

Figure 3. Echocardiography measurement of sham, mild and moderate AD. (**A-C**) LV ejection fraction (EF) and fractional shortening (FS) LV mass normalized to body weight. **(D)** E to E' ratio (**E**) LV chamber diameter, systolic(s), diastolic (d) **(F)** LV wall thickness.

Regional and directional LV strain analysis using Speckle tracking echocardiography

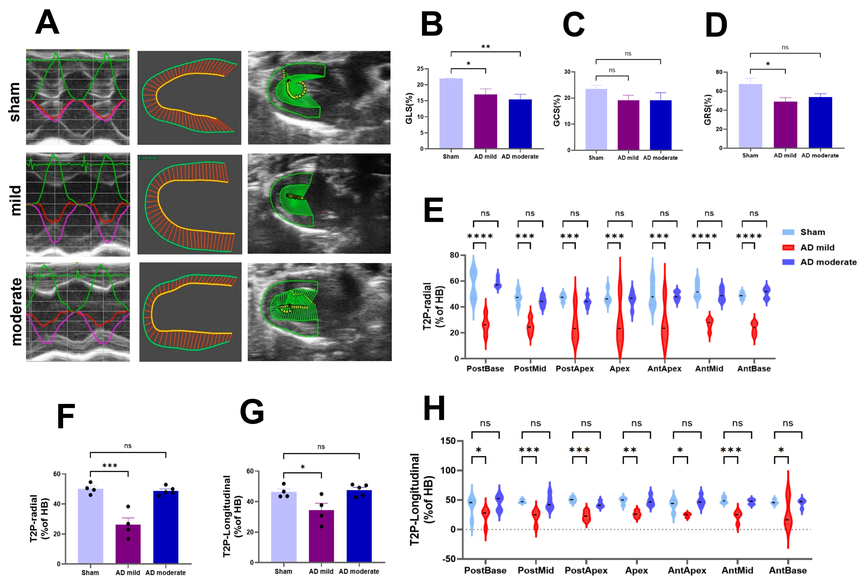

Figure 4. LV Speckle tracking echocardiography of sham, mild and moderate AD. (**A**) Schematic images of strain analysis. **(B-D**) Global longitudinal, circumferential, and radial strain. **(E)** Regional time-to-peak (T2P) of LV radial strain normalized to heart rate. **(F)** Average T2P-radial across segments. **(H)** Regional T2P of LV longitudinal strain normalized to heart rate.

Left atrial structural and functional changes following graded atrial injury

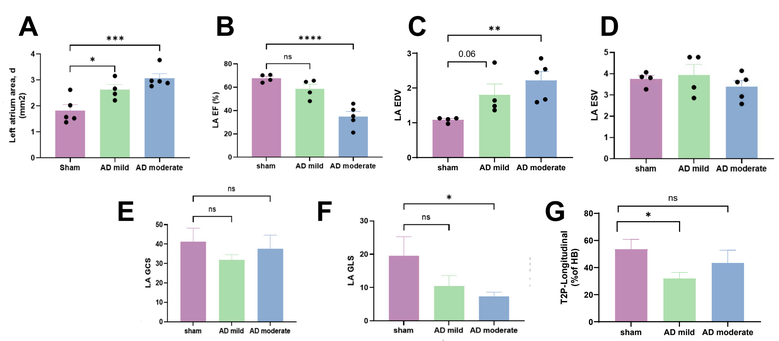

Figure 5. LA function analysis (**A**) LA area in diastole, (**B**) LA ejection fraction, (**C**) LA end-diastolic volume (EDV), (**D**) LA end-systolic volume (ESV), (**E–F**) LA circumferential (GCS) and longitudinal (GLS) strain, (**G**) time to peak of LA maximal contraction

Exercise capacity is reduced in both mild and moderate AD

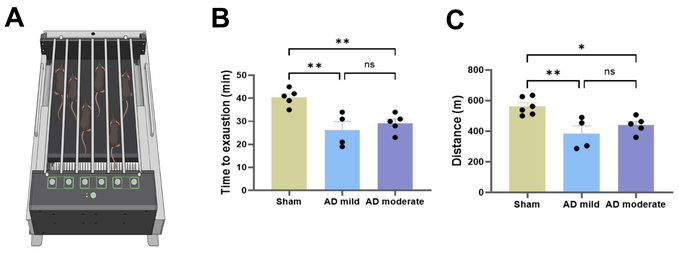

Figure 6. Treadmill test to evaluate exercise tolerance. (**A**) Image of the multi-lane treadmill system used in experiment. **(B)** Time to exhaustion and (**C**) Distance run.

Pulmonary dysfunction emerges in mild AD but not in moderate AD

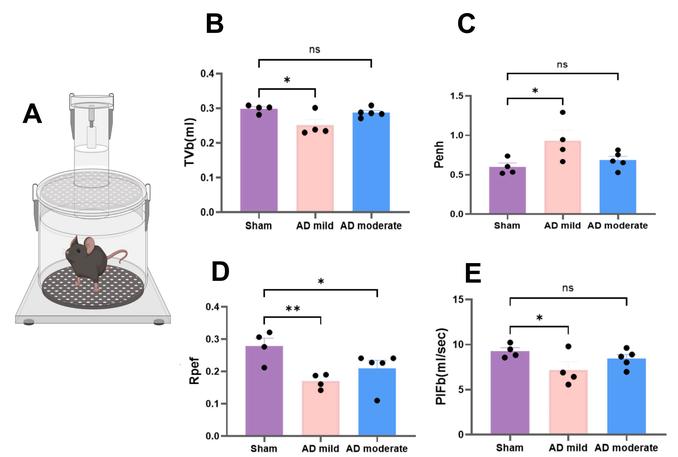

Figure 7. Lung function analysis on experimental groups. (**A**) Image of the whole-body plethysmography chamber used to assess lung function in conscious, unrestrained mice. **(B)**Tidal volume (TVb) and (**C**) Enhanced pause (Penh) (**D**) Rpef, a measure of expiratory flow, (**E**) Peak inspiratory flow (PIFb).

Conclusion and future direction

Conclusion

- Mild AD findings closely resemble the HFpEF phenotype, emphasizing LA dysfunction as a critical early and transitional driver.
- Above results provide strong evidence supporting the hypothesis that LA is a crucial hallmark in the development and progression of HFpEF.
- This highly innovative preclinical model provides a valuable platform to study the pathogenesis and pathological mechanisms of HFpEF, explore therapeutic targets, and identify biomarkers for early detection.

Future direction

- Measuring histological changes (e.g., collagen deposition, inflammation) to quantify the extent of LA dysfunction and its impact on diastolic function.
- Measuring molecular markers of heart failure, such as brain natriuretic protein (BNP).
- Using catheterization to measure end systolic and end diastolic pressure to validate cardiac function changes.

References

- **Khan, Muhammad Shahzeb, et al. "Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis." European Journal of Heart Failure 22.3 (2020): 472-485**
- **Fang, Fang, Alex Pui-Wai Lee, and Cheuk-Man Yu. "Left atrial function in heart failure with impaired and preserved ejection fraction." Current opinion in cardiology 29.5 (2014): 430-436.**

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