# Cardiac-Specific PAD2 Deletion Causes Diastolic Dysfunction in the Female Heart

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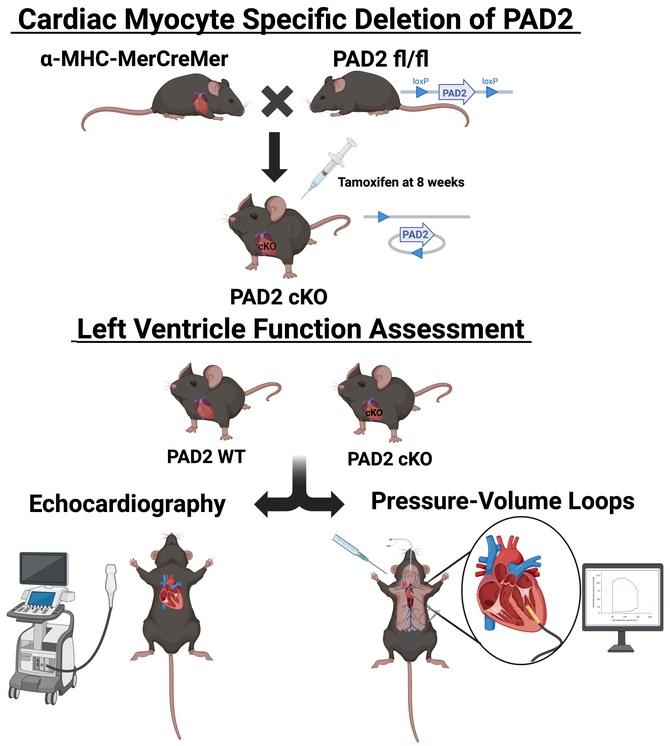
## BACKGROUND

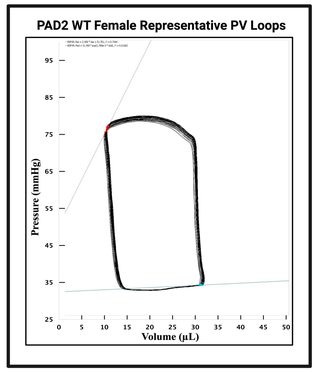
Heart failure (HF) is a leading cause of death in both sexes. While heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) occur in both sexes, HFpEF is twice as prevalent in women. Effective therapies exist for HFrEF, but HFpEF lacks disease-modifying treatments, leaving management largely limited to symptom control. Myocardial protein post-translational modifications (PTMs) are key regulators of systolic and diastolic function. Citrullination, mediated by peptidyl arginine deiminase isozyme 2 (PAD2), critically modulates protein structure and function. Prior studies demonstrate PAD2 expression robustly declines with age in the female heart and global PAD2 deletion induces diastolic dysfunction in middle-aged female mice. **Understanding how PAD2 loss contributes to left ventricular (LV) dysfunction may reveal sex-specific mechanisms underlying HFpEF.**

## METHODS




## RESULTS

**A. PAD2 WT**




**B. PAD2 cKO**

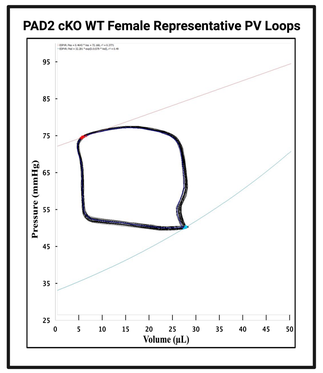



**Figure 1.** LV Pressure Volume Loops in **(A)** PAD2 WT and **(B)** PAD2 cKO.

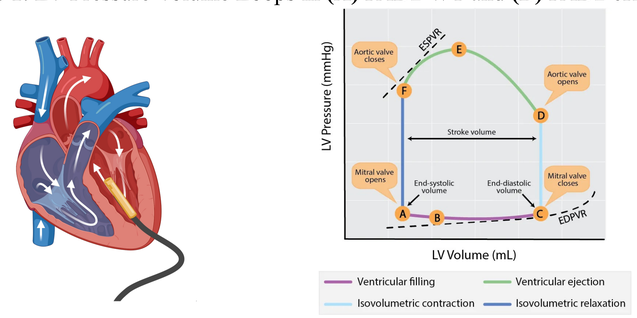



**Figure 2.** ADI Instruments Points on the PV Loop

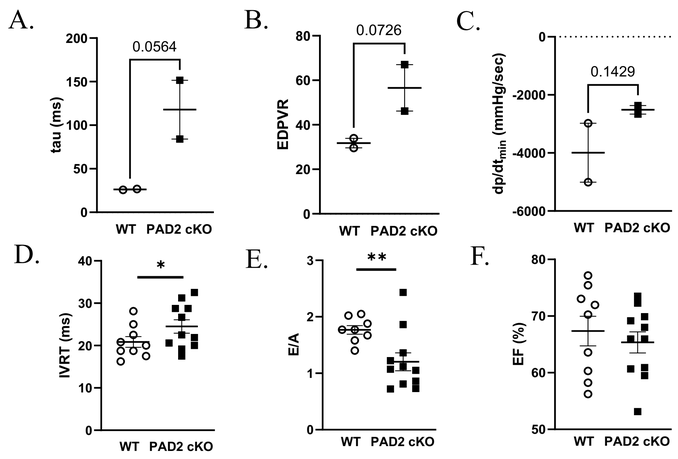



**Figure 3. (A) Tau** (time constant of isovolumic relaxation). **(B) EDPVR (**end-diastolic pressure–volume relationship). **(C) dP/dt min** (peak rate of pressure decline). **(D) IVRT** (isovolumic relaxation time). **(E) E/A** (early-to-late ventricular filling ratio). **(F) EF** (ejection fraction).

## DISCUSSION

**PAD2 cKO mice exhibited LV diastolic dysfunction compared to WT controls.**

- **EF remained normal for WT and PAD2 cKO**
- **Slower LV relaxation time**
  - Elevated Tau
  - Less negative dP/dt min
- **Stiffer LV with impaired filling**
  - Steeper slope EDPVR
  - Reduced End-Diastolic Volume, Stroke Volume, and Stroke Work
  - Increased End-Diastolic Pressure
  - Reduced E/A Ratio
  - Prolonged IVRT

LV area was similar between groups suggesting diastolic dysfunction arises from subcellular PAD2 alterations rather than overt structural remodeling. Diastolic function was normal in male PAD2 cKO, further suggesting a sex-specific role of PAD2 in the heart.

## CONCLUSIONS

**The enzyme PAD2 is critical for maintaining diastolic function in the female heart**. Future studies will identify the specific mechanisms by which loss of PAD2 causes diastolic dysfunction, providing insights into potential targets for HFpEF disease modifying therapies.

## ACKNOWLEDGEMENTS

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