

# Acute Administration of The Novel Cardiac Sarcomere Modulator EDG-7500 Improves Ventricular Filling While Preserving LVEF In Dogs with Pacing Induced Left-Ventricular Systolic Dysfunction

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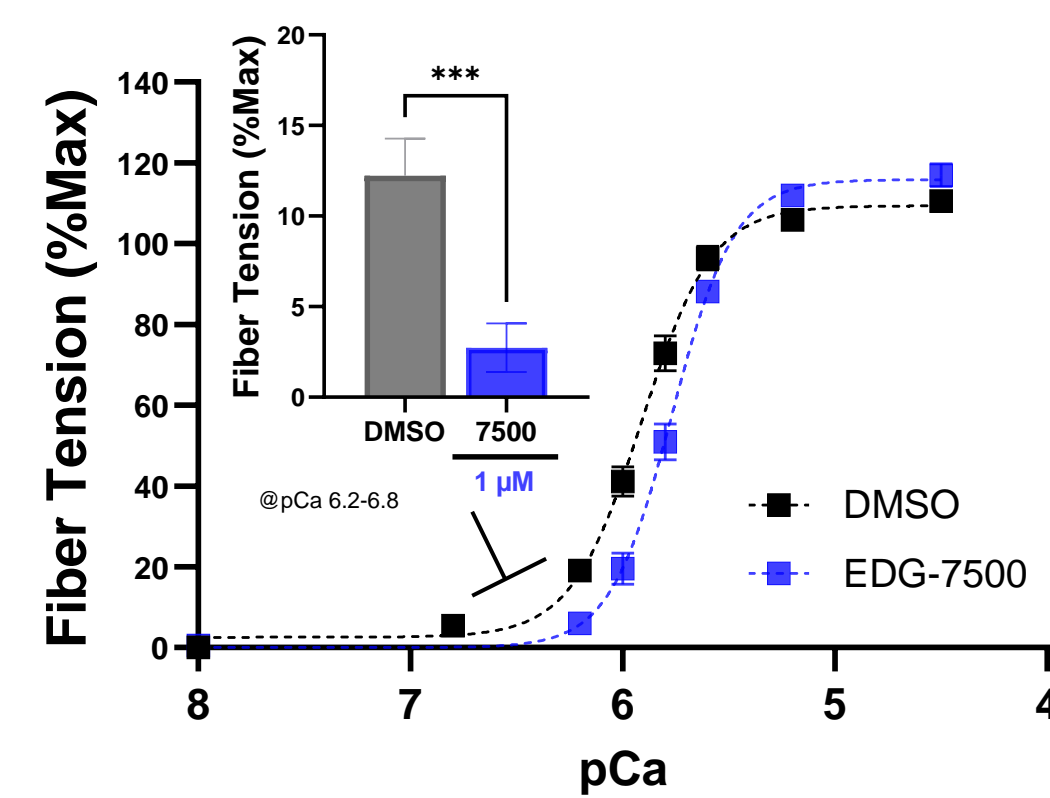
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## Background

EDG-7500 is a cardiac sarcomere modulator that has been shown in preclinical models to slow the rate of early LV contraction and improve diastolic filling, without directly inhibiting the cardiac myosin motor head<sup>1</sup>. EDG-7500 is being developed as a potential treatment for HCM and other diseases of diastolic dysfunction. An ongoing Phase 2 study (NCT06347159) is evaluating EDG-7500 in both oHCM and nHCM patients.

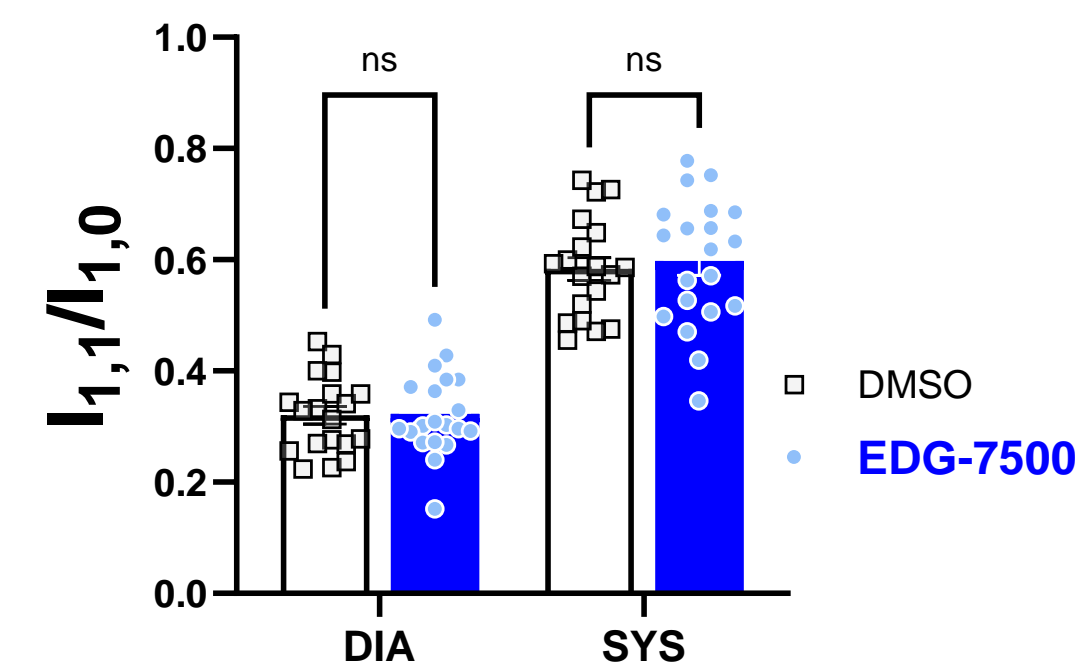
<sup>1</sup><https://doi.org/10.1161/circ.148.suppl.1.15822>

EDG-7500 preferentially **decreases tension** during early activation and relaxation



*In vitro*: EDG-7500 desensitizes tension generation preferentially at low calcium levels, pig fiber SL = 2.3mm. Inset is the average of pCa 6.2 and 6.8 EDG-7500 and DMSO control. \*\*\* = p value < 0.001.

ON/OFF state of acto-myosin is unchanged with EDG-7500



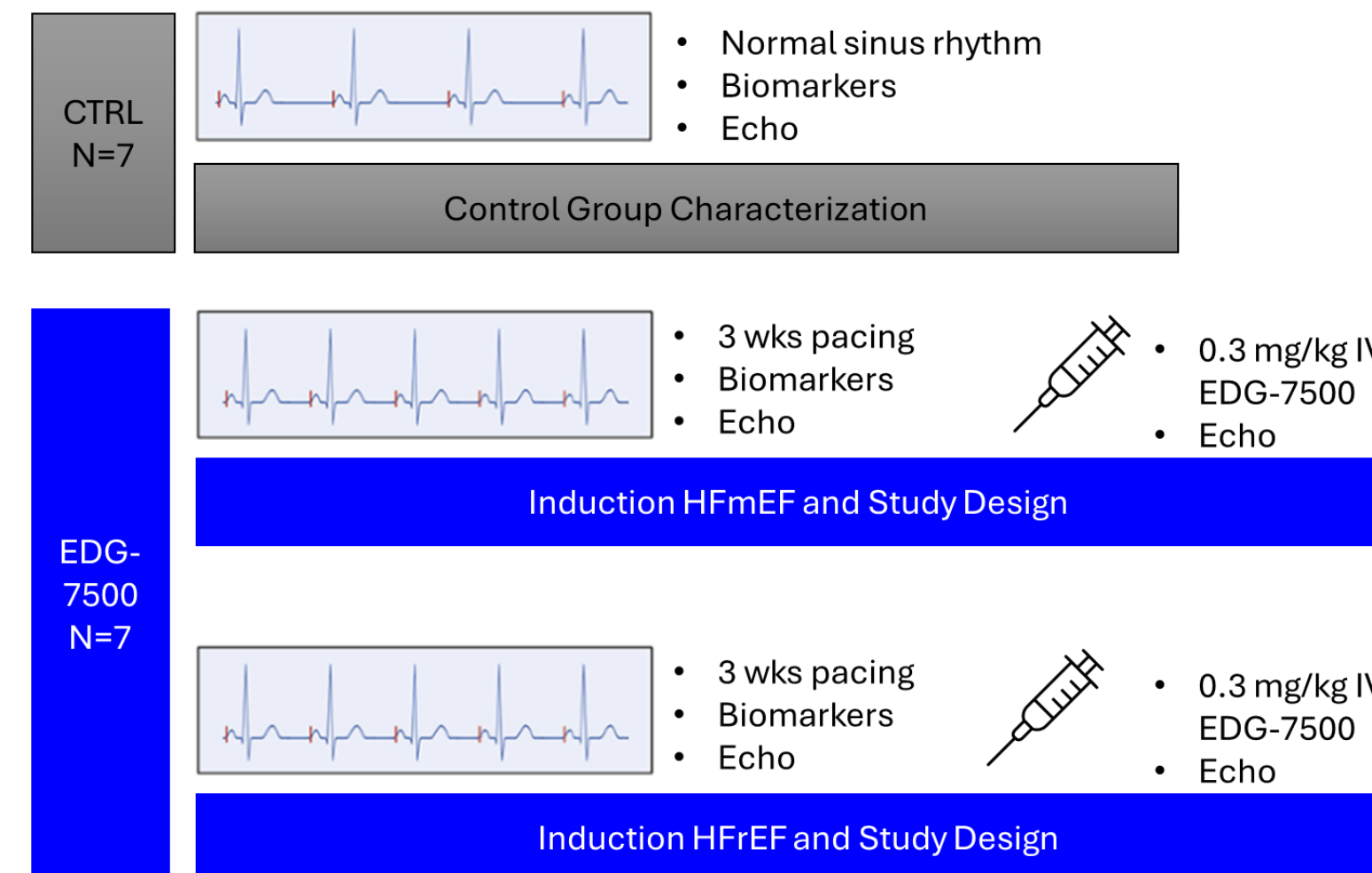
*In vitro*: Equatorial X-ray diffraction patterns of EDG-7500 or DMSO treated pig left ventricular tissue. DIA = diastolic calcium; SYS = systolic calcium; ns = not significant; I<sub>1,1</sub>/I<sub>1,0</sub> is an indicator of the proximity of myosin to actin in relaxed muscle and an indicator of the number of acto-myosin cross-bridges during contraction.

## Study Aims

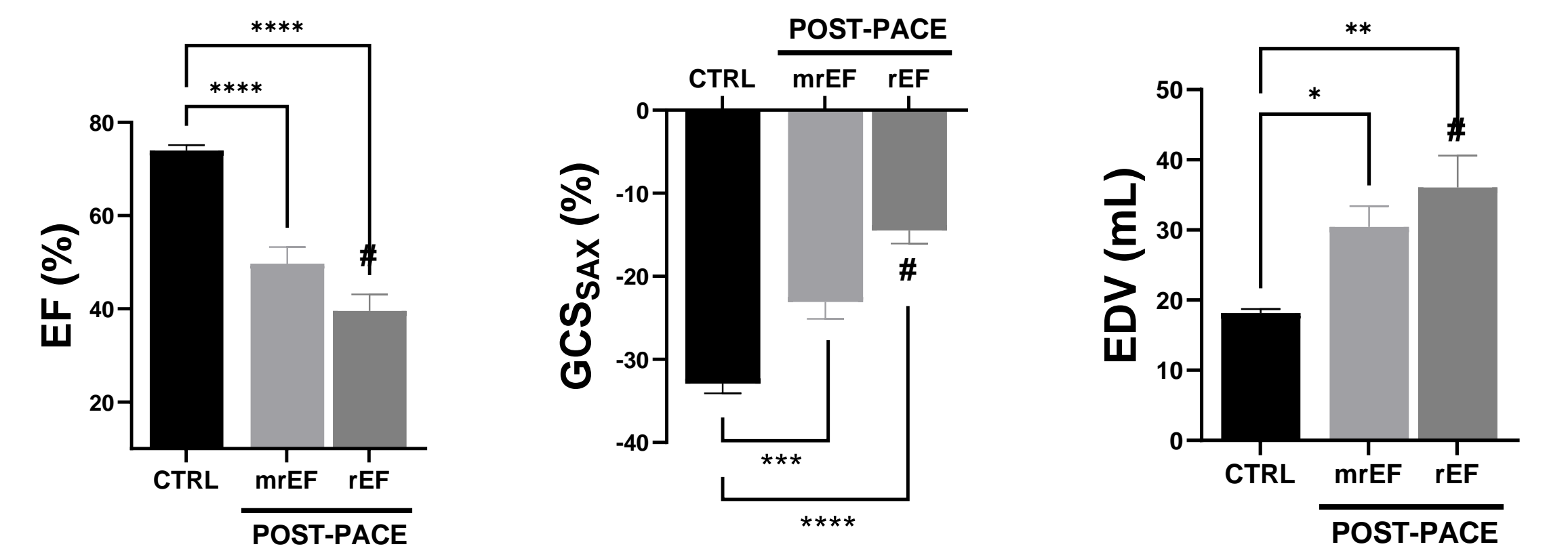
The goal of the current study was to assess the acute hemodynamic effects of EDG-7500 in a model of depressed systolic and diastolic LV function. Echocardiography assessment in dogs with pacing-induced LV dysfunction before and after EDG-7500 administration was evaluated.

## Study Design and Model Characterization

Beagle dogs (n = 7) underwent chronic RV pacing (180 to 240 ppm), and were studied, in sinus rhythm, at two levels of induced-dysfunction: first at mid-range EF (mrEF, targeting ~50%), and later at reduced EF (rEF, targeting ~40%). At each %EF level, animals were evaluated by echocardiography before and after administration of 0.3 mg/kg IV EDG-7500. Healthy beagle dogs served as disease controls (n = 7).

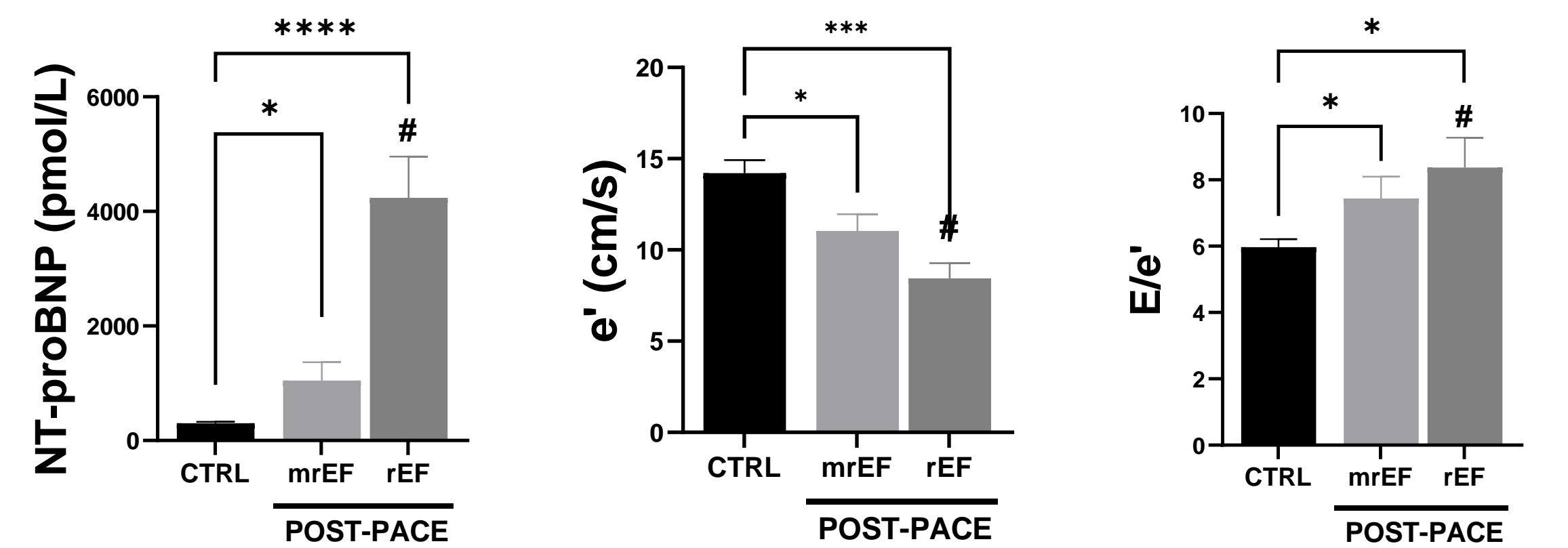


HFmrEF and HFrEF: Evidence of induced **diastolic disease** with graded impaired systolic function



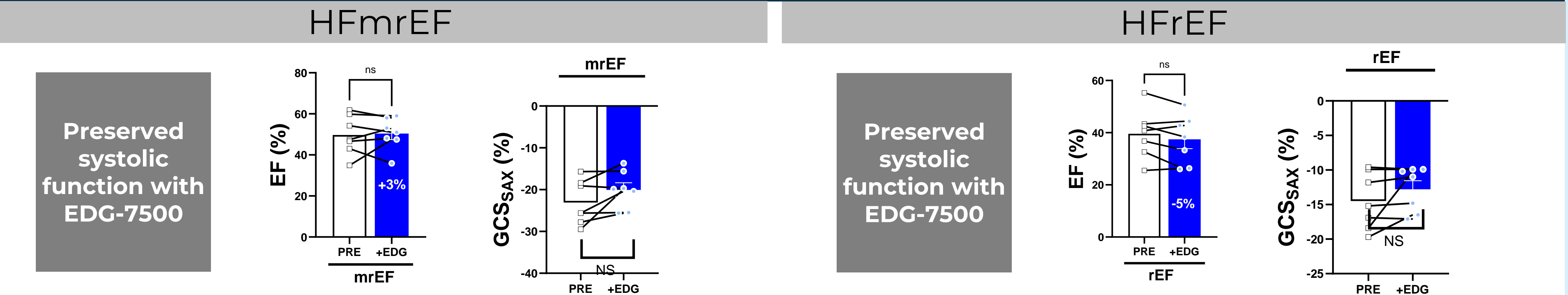
EF = ejection fraction; mrEF = mid-range EF; rEF = reduced EF; GCS<sub>sax</sub> = global circumferential strain measured in short axis; EDV = end diastolic volume; \*\*\*\* = p value < 0.0001; \*\*\* = p value < 0.001; \*\* p value < 0.01; \* p value < 0.05; # indicates statistical significance between mrEF and rEF groups.

HFmrEF and HFrEF: **wall stress increased**, impaired relaxation, and **elevated filling pressure**



NT-proBNP = terminal pro b-type natriuretic peptide; e' = mitral annular early diastolic velocity; E/e' = ratio of early mitral inflow velocity and mitral annular early diastolic velocity; \*\*\*\* = p value < 0.0001; \*\*\* = p value < 0.001; \* p value < 0.05; # indicates statistical significance between mrEF and rEF groups.

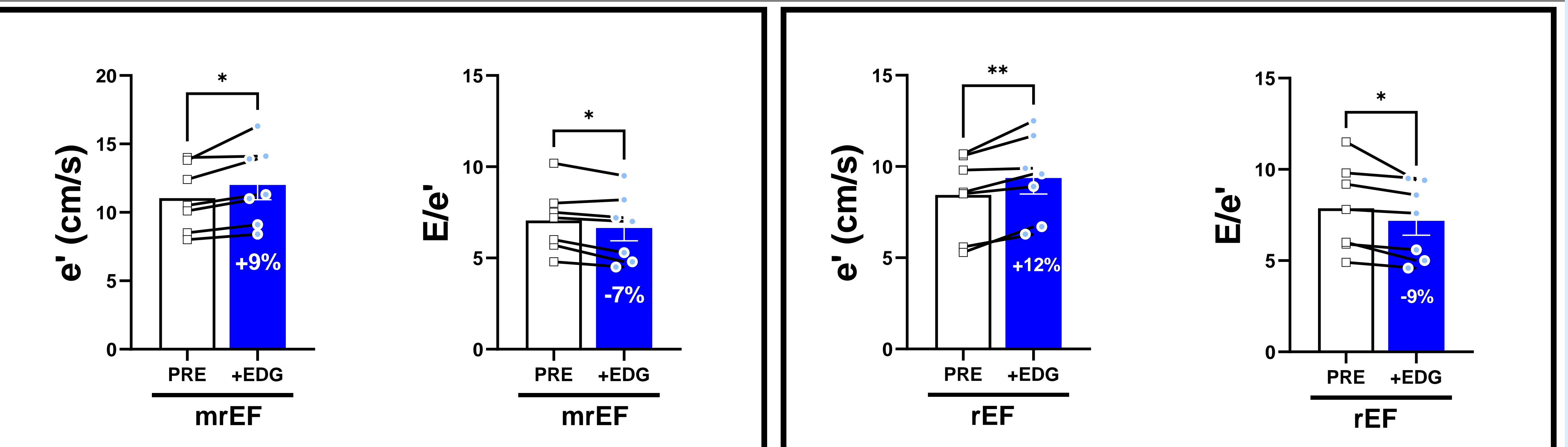
## Results



Preserved systolic function with EDG-7500

Preserved systolic function with EDG-7500

Improved early filling velocity and reduced filling pressures in both HFmrEF and HFrEF



## Summary and Conclusions

- At mid-range EF, EDG-7500 improved echocardiographic indices of early LV ventricular filling and filling pressures without significant effect on systolic performance.
- At reduced EF, EDG-7500 improved echocardiographic indices of LV early ventricular filling and filling pressures without significant effect on systolic performance.
- This data suggests **directly targeting the sarcomere with EDG-7500 improves diastolic performance** in animal models of reduced systolic function.
- The safety and potential therapeutic effects of EDG-7500 administration to patients with diseases of diastolic dysfunction across a broad range of systolic function should be considered.**

