

Danicamtiv (MYK-491) A Novel Small-Molecule Cardiac Activator: in vitro/in vivo Evidence for Overall Myocardial Inotropy

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(IL, USA) and 3: QTest Labs (OH, USA)

Declaration of Interest (DOI) - Disclosures

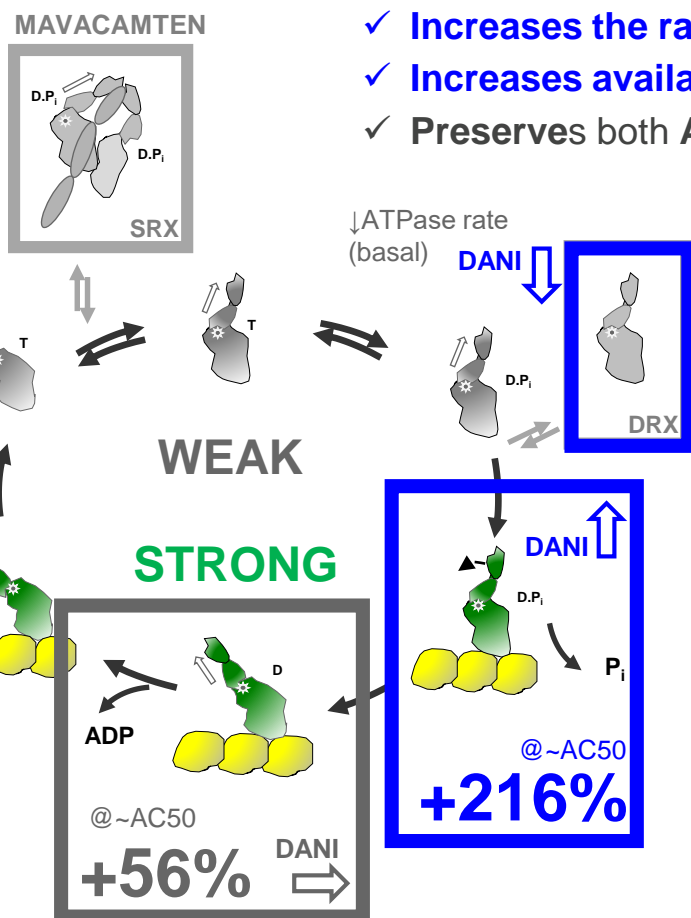
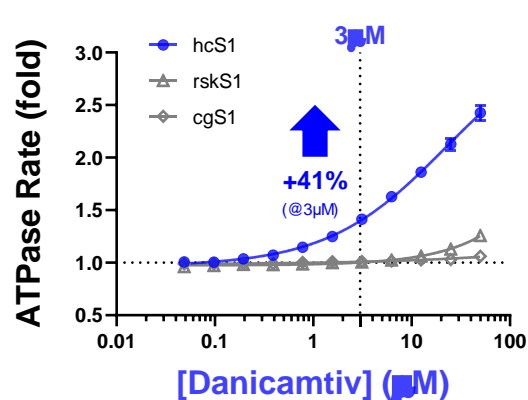
Presenting author: Employment/Ownership (MyoKardia, CA, USA) and Research Support (MyoKardia, CA, USA)

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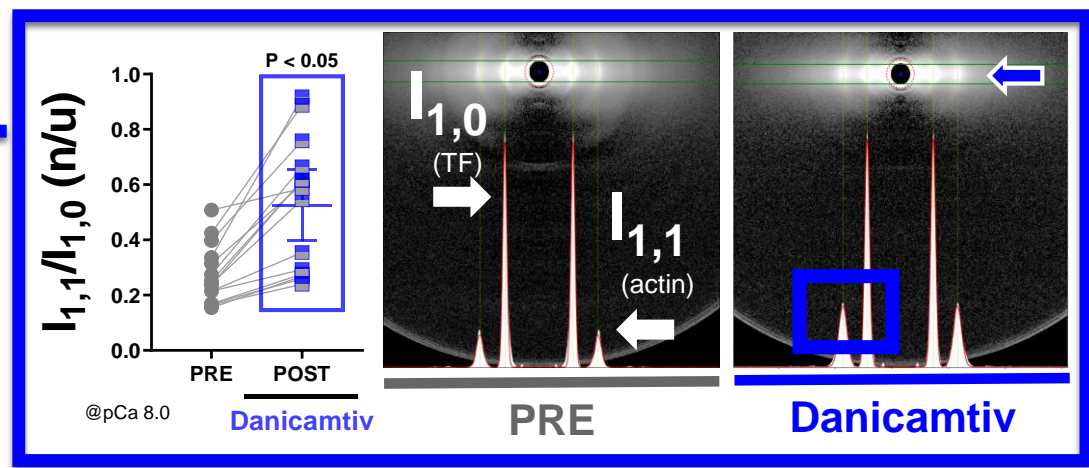
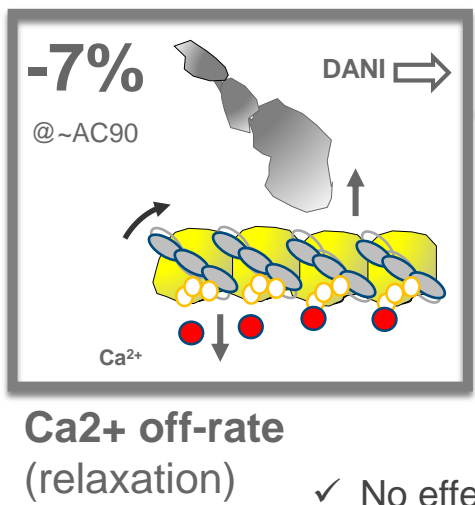
Danicamtiv (formerly MYK-491) is an investigational drug

Background: What is Danicamtiv (MYK-491)?

Danicamtiv is a novel, selective small-molecule direct activator of cardiac acto-myosin, that enhances the force-producing chemo-mechanical cycle



- ✓ **Increases the rate of phosphate (Pi) release** of cardiac myosin (acto-myosin)
- ✓ **Increases availability of myosin-heads** that can form cross-bridges (closer to actin)
- ✓ **Preserves both ADP release** (increased) and **power-stroke rates** (+2% @ ~AC90)

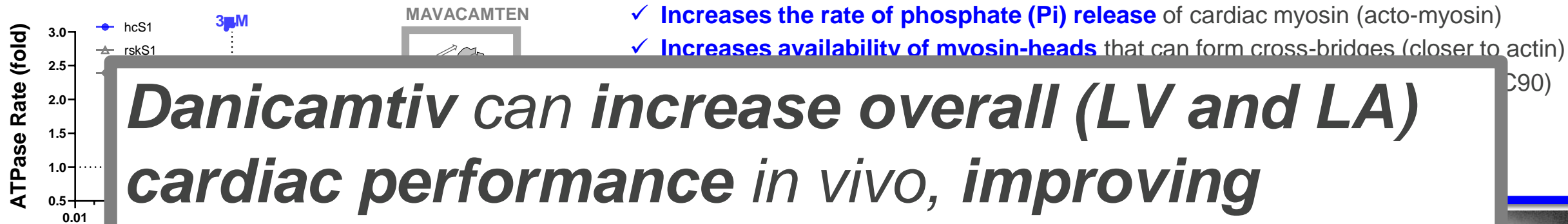


✓ No effects on Ca²⁺ homeostasis/transients

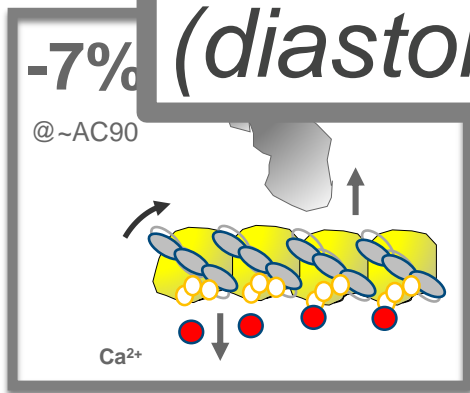
hrS1: human (recombinant) cardiac sub-fragment 1 myosin
 rskS1: rabbit (fast) skeletal sub-fragment 1 myosin
 cgS1: chicken gizzard (smooth muscle) sub-fragment 1 myosin

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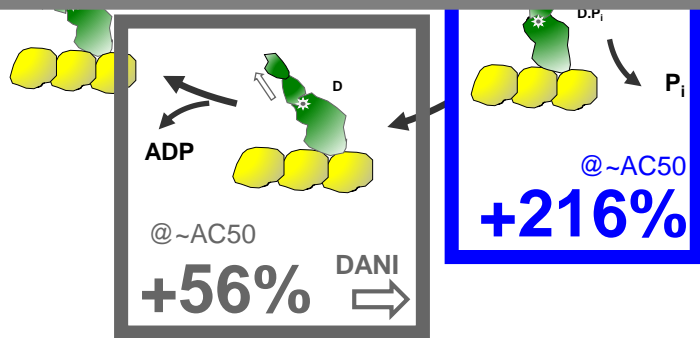
Danicamtiv is a novel, selective small-molecule direct activator of cardiac acto-myosin, that enhances the force-producing chemo-mechanical cycle



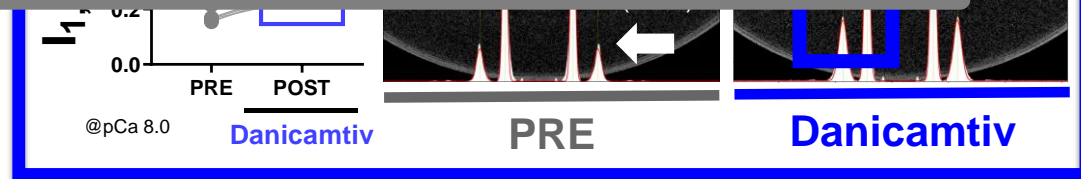
Danicamtiv can increase overall (LV and LA) cardiac performance in vivo, improving mechanical efficiency while preserving resting (diastolic) tension and filling



Ca²⁺ off-rate (relaxation)



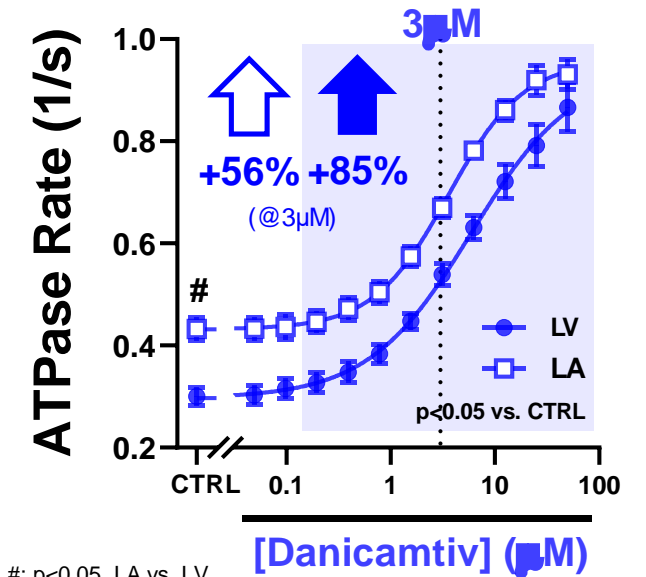
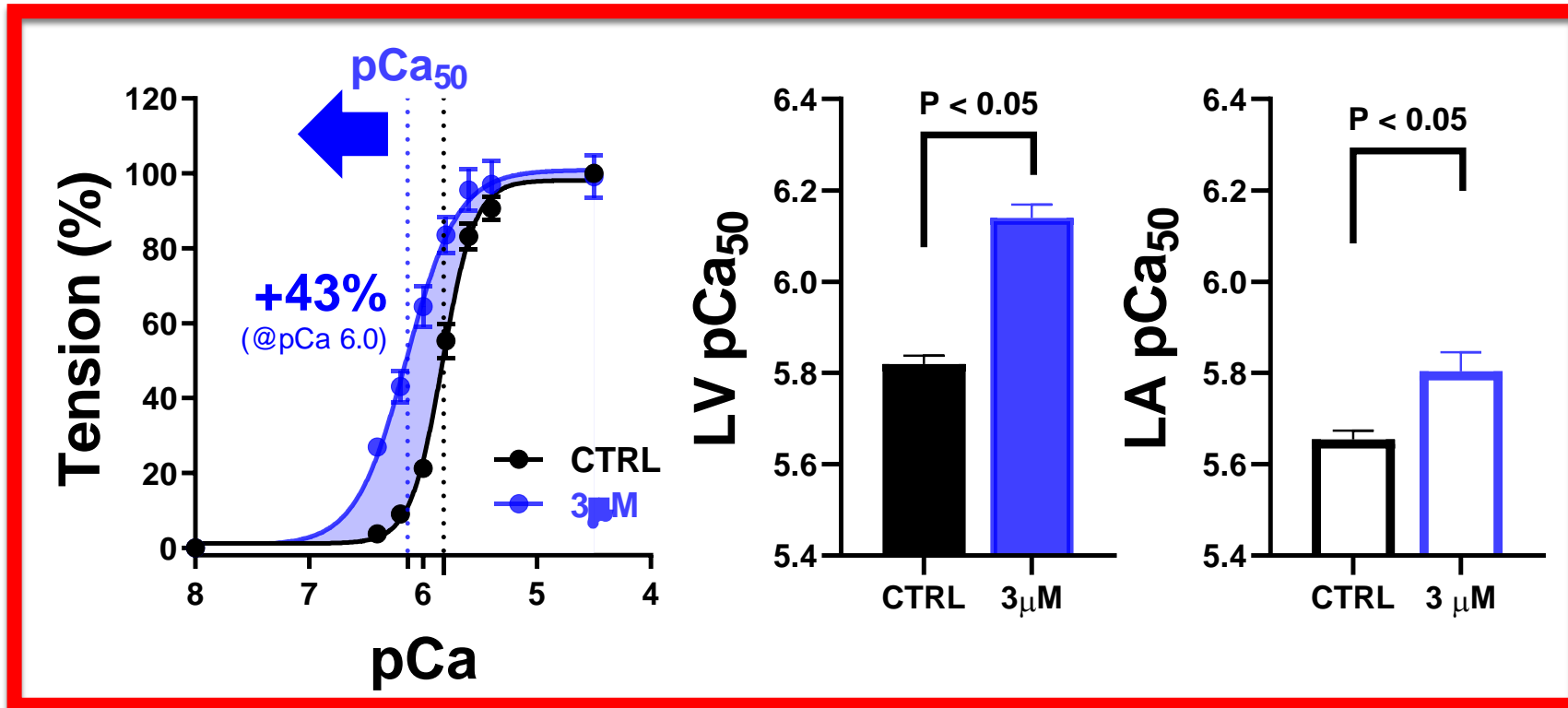
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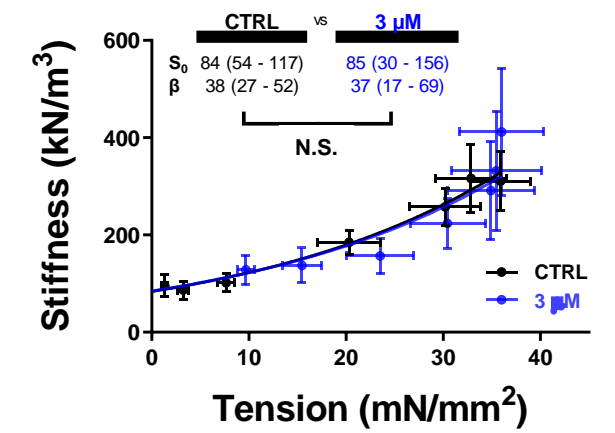
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RESULTS: Direct LV and LA systolic activation (*ex vivo*)

- ✓ Increases myofibrilar (ATPase) activity...
...and tension generation in **both LA and LV**

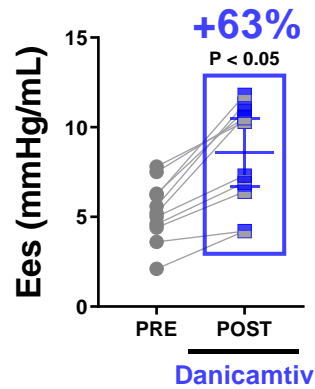


✓ Preserving stiffness

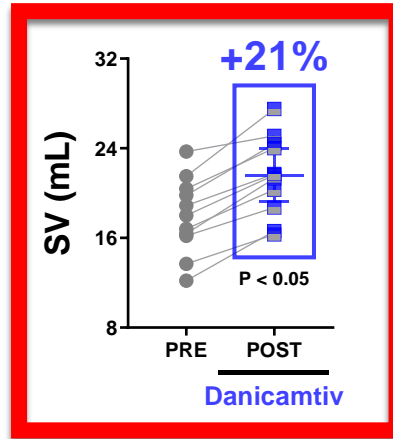
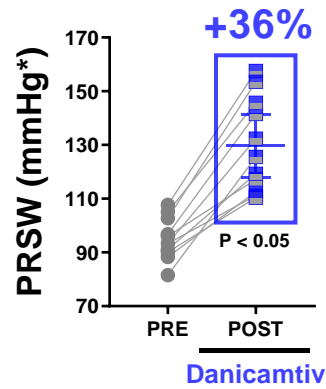


RESULTS: Efficient Improvement in Myocardial Function (1)

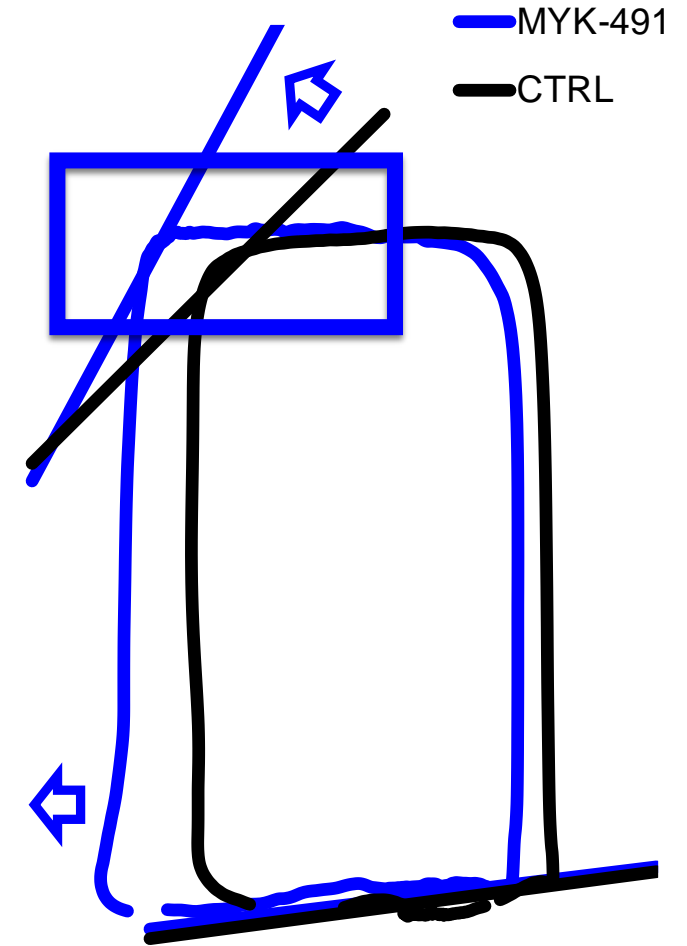
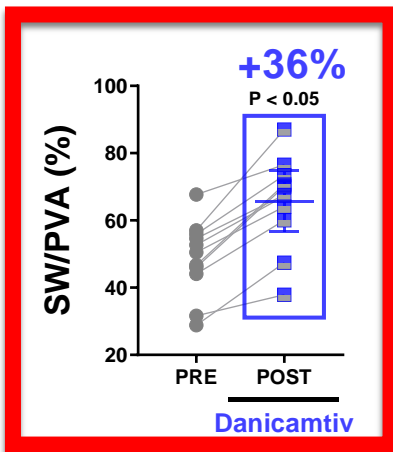
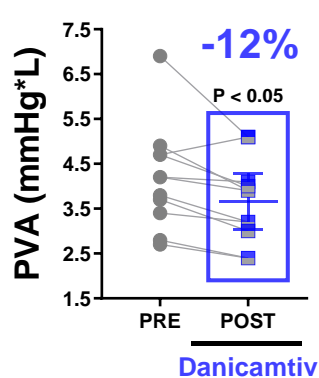
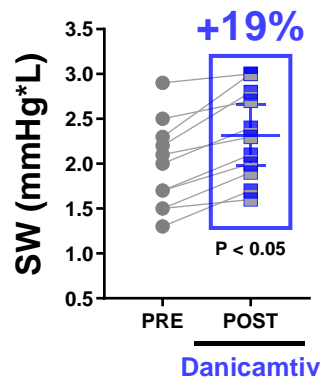
✓ Increases contractility and stroke-volume (SV)



@ 1366 ± 222 ng/mL



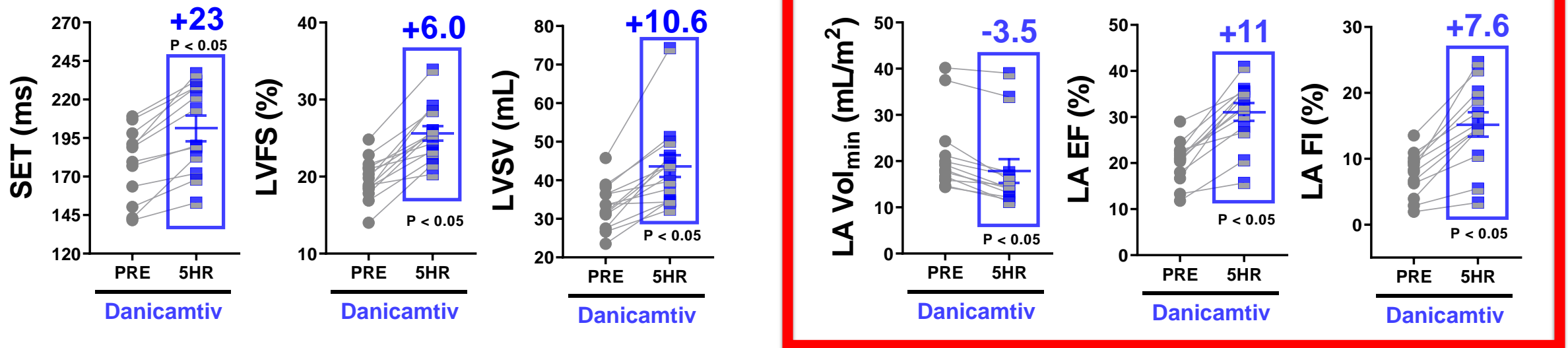
...as well as stroke-work, enhancing mechanical efficiency (SW/PVA)



SYSTEM: conscious healthy beagle dogs (chronically instrumented for left-ventricular pressure-volume relationships). Danicamtiv (3 mg/kg PO); data at baseline (PRE) and +5hr post-dose

RESULTS: Efficient Improvement in Myocardial Function (2)

- ✓ Increases contractility and stroke-volume (SV)
...as well as stroke-work, enhancing mechanical efficiency (SW/PVA)
- ✓ Prolongs systole (SET), but preserves compliance
- ✓ Improves LV and LA performance, decreasing LA size (chronic HF)



CONCLUSIONS

*Direct actomyosin activation with **danicamtiv** has a unique cardiovascular profile characterized by **direct atrial and ventricular systolic activation**, as well as by both preserved efficiency and diastolic properties.*

Data provides mechanistic support for the (preliminary) observations in healthy volunteers and DCM patients