Cardiac Effects of EDG-7500, A Novel Cardiac Sarcomere Regulator: In Vitro and In Vivo Evidence For Slowing Isovolumic Contraction And Improved Ventricular Compliance

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Background and Methods

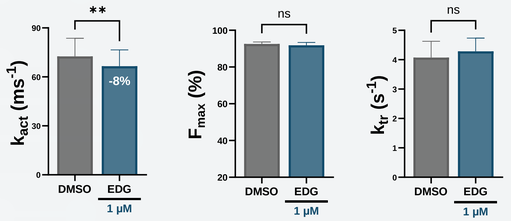
Background: Hypertrophic Cardiomyopathy (HCM) is a disease where excess acto-myosin crossbridge formation results in hyperdynamic contraction, LV hypertrophy, and diastolic dysfunction due to increased myocardial stiffness. Conventional negative inotropes can alleviate the systolic alteration in HCM, but do not improve LV filling or compliance. EDG-7500 is a small molecule that preferentially decreases diastolic tension and slows the velocity of myocardial force. This study assessed pharmacodynamic responses to EDG-7500 under the hypothesis that EDG-7500 can improve myocardial stiffness and distensibility.

Methods: In vitro: Myofilament biomechanics and sarcomere structure were evaluated in LV permeabilized pig fiber by assessing tension vs. pCa relationships and x-ray diffraction patterns.

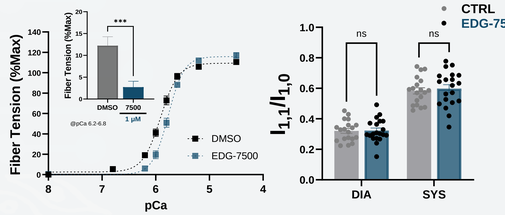
In vivo: dogs were acutely instrumented for arterial pressure and LV pressure-volume recordings. Measurements were obtained at baseline (PRE), and after administration of EDG-7500 (EDG: 0.3 mg/kg IV, n = 10), or metoprolol (METO: 1-4 mg/kg IV, n = 7). METO was confirmed to block β-adrenergic receptor (β-AR) stimulation (+DOB, 2μg/kg IV) and reached plasma concentrations of 289 ± 69 ng/mL. A subset of EDG-7500 animals were studied after the additional administration of METO (n = 5). *P<0.05, ** P<0.01, ***P<.001 for EDG-7500 or METO vs. vehicle.

EDG-7500 Targets Early Systolic and Diastolic Myofilament Force Generation and Relaxation

EDG-7500 slows force generation (Kact) without affecting peak force (Fmax) or *rate of* cross-bridge re-attachment (Ktr)



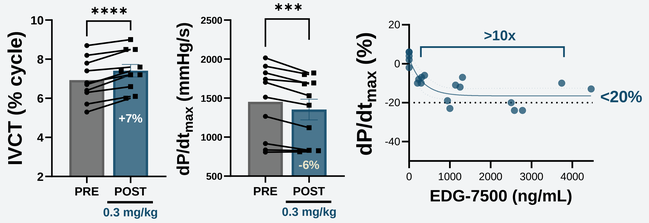
EDG-7500 decreases low-Ca^{++} tension at early activation and relaxation. $I_{1,1}/I_{1,0}$ ratio indicates the ON/OFF state of myosin, which is unchanged with EDG-7500



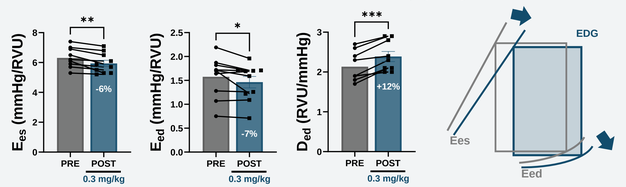
JT, MD, NH, AR, MS, and ME are employees of Edgewise and may own shares of Edgewise Therapeutics
CDR, WM, and TI are consultants for Edgewise

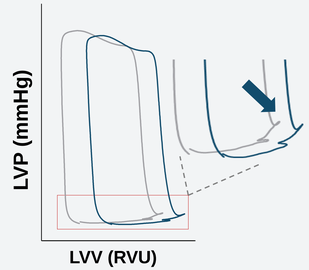
EDG-7500 Slows Early Contraction and Increases Ventricular Compliance in Healthy Dogs

EDG-7500 prolongs Isovolumic contraction time (IVCT) and reduces the peak rate of left ventricular pressure development (dP/dt_{max}). dP/dt_{max} reduction was limited to <20% at all tested EDG-7500 exposures

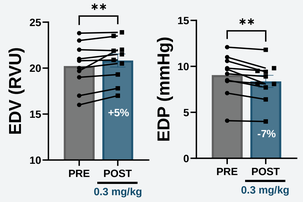


EDG-7500 reduces both end-systolic (Ees) and end-diastolic (Eed) elastances, resulting in a right-downward shift of the LV pressure-volume relationships. LV distensibility (Ded) increased

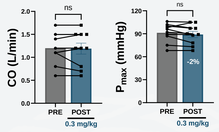




EDG-7500 Facilitates LV filling

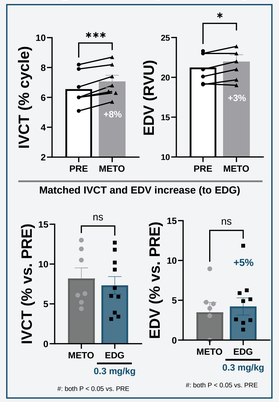


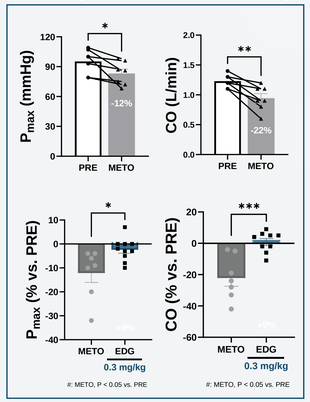
EDG-7500 preserved cardiac output (CO) and systemic pressures (Pmax).

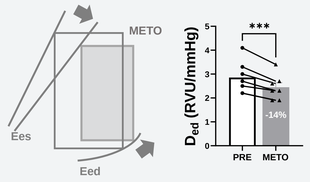


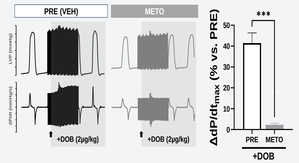
Unlike β-AR Blockade (METO), EDG-7500 Preserved Systemic Hemodynamics and Improved Compliance

METO blocked β-AR challenge, prolonging IVCT (matched to EDG-7500) although at the expense of systemic hemodynamics and distensibility



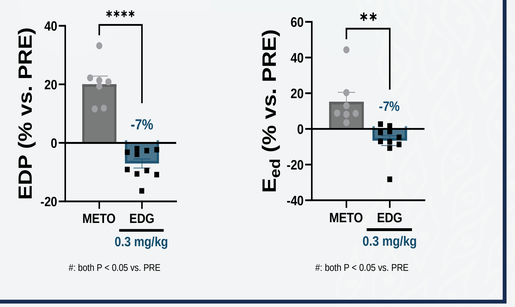






EDG-7500 improved compliance, permitting EDV increase without EDP elevations

METO did not change the end-diastolic pressure-volume relationship resulting in higher filling pressures (EDP) and decreased distensibility.



CONCLUSIONS

Cardiac sarcomere modulation with EDG-7500 demonstrates unique cardiovascular profile characterized by:

- *in vitro:* unchanged myosin-actin proximity and cross-bridge re-attachment rates, reduction in myofilament tension at low Ca2+, and the slowing of force development with preserved peak force.
- *in vivo*: slowing of early cardiac contraction and improved LV distensibility with preserved systemic hemodynamics. This profile differentiates EDG-7500 from β-AR blockade with metoprolol.

EDG-7500 in currently being evaluated in a Ph1 study (NCT06011317).

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