#AHA23

EDG-7500, A CARDIAC SARCOMERE REGULATOR THAT PRESERVES INTRINSIC MYOSIN-MOTOR FUNCTION, IMPROVES CARDIAC FUNCTION AND RESERVE IN A MINIPIG MODEL OF HCM

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Edgewise THERAPEUTICS

American Heart Association.

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This presentation concerns product candidates that are under clinical investigation, and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). It is currently limited by federal law to investigational use, and no representation is made as to its safety or effectiveness for the purposes for which it is being investigated.

EDG-7500 is an investigational agent and is not approved in any territory

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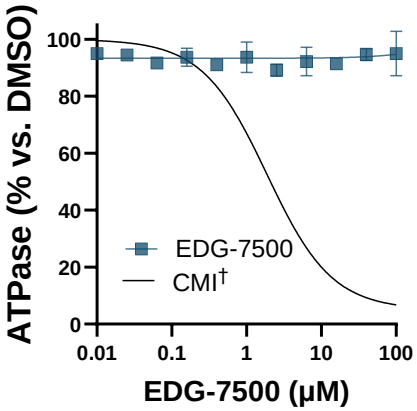
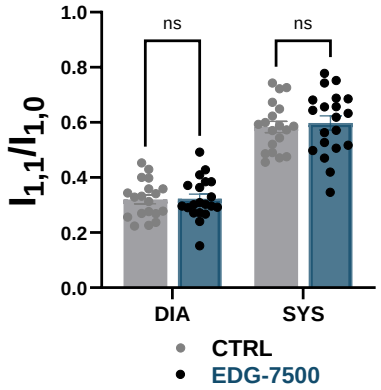
EDG-7500 PRESERVES MYOSIN MOTORS AND PARTIALLY REDUCES ATP USE

Myosin motor-head ‘S1-subfragment’



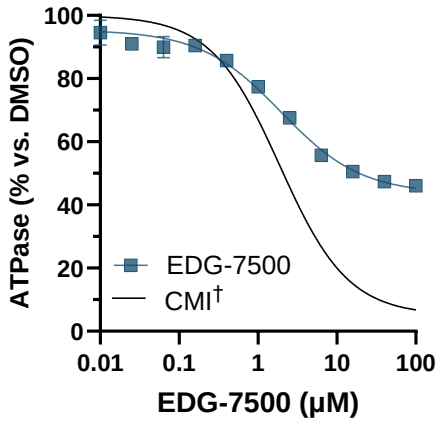
Does not directly inhibit myosin motor activity

X-ray patterns showing ON/OFF populations at low and high calcium



Myosin ‘ON/OFF’ populations unchanged

Myofibrils containing the full compliment of contractile proteins

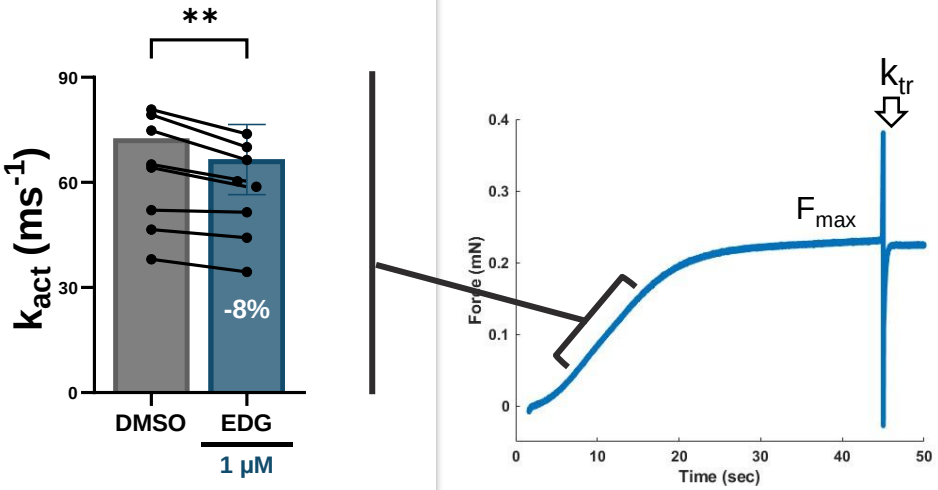


Partial reduction of ATP use

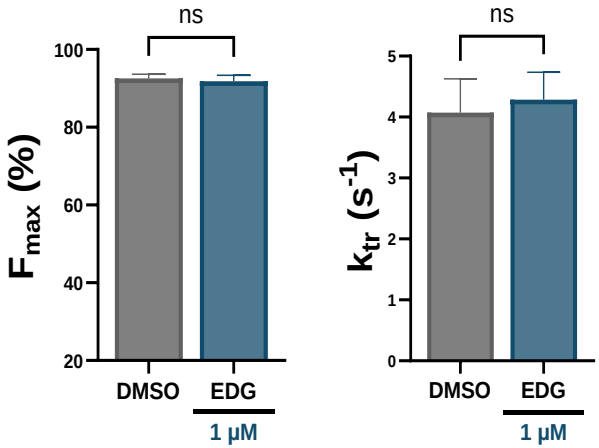
** P < 0.05, ** P < 0.01, *** P < 0.001, ns = not significant*
$I_{1,1}/I_{1,0}$ = indicator of myosin head location relative to actin
DIA = Diastole
SYS = Systole

CMI = cardiac myosin inhibitor
† = data is simulated

EDG-7500 SLOWS FORCE DEVELOPMENT WITHOUT LOSS OF PEAK FORCE



Slows force development at low calcium

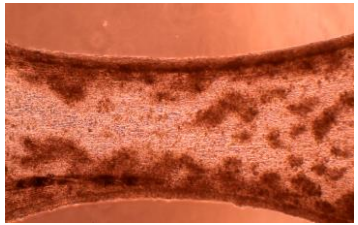


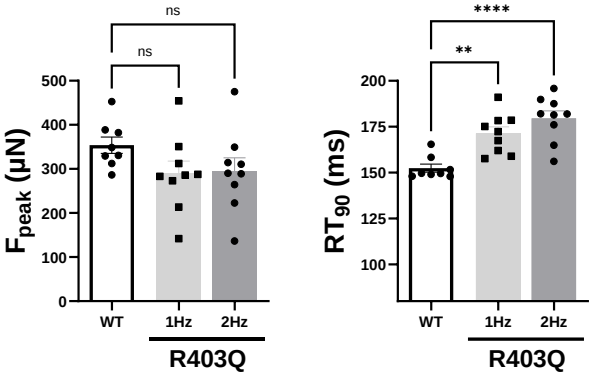
Max force and re-attachment rate (k_{tr}) of Xbridges maintained

** P < 0.05, ** P < 0.01, *** P < 0.001, n.s. = not significant*
Kact = rate of activation
Fmax = Maximum force
Ktr = rate or tension re-development

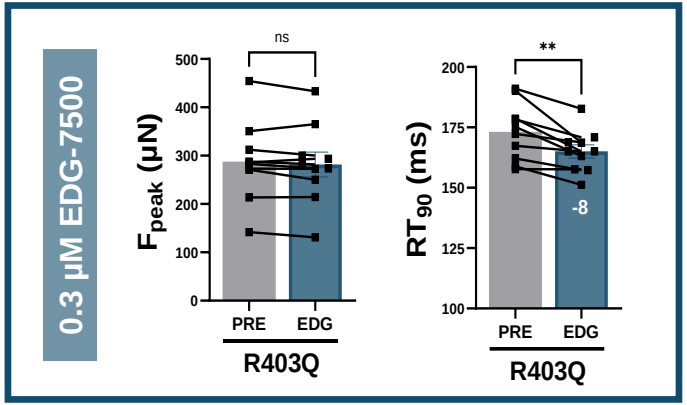
EDG-7500 INCREASES THE RATE OF RELAXATION IN MYH7 R403Q ENGINEERED HEART TISSUE (EHT)

Impaired relaxation in R403Q EHTs relative to WT



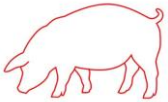


EDG-7500 shortens the relaxation time in R403Q EHTs



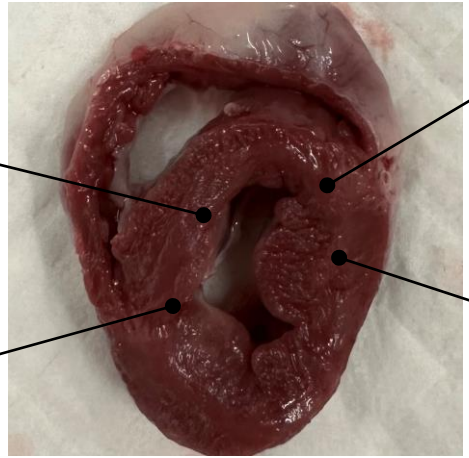
CAN THE EDG-7500 MECHANISM ALTER THE DISEASE PHENOTYPE IN A MODEL OF HCM?

MYH7 R403Q genetic model of nHCM‡



Increased myosin ON-state

Sensitized myofilaments (lower pCa50), particularly at diastolic calcium (increased diastolic tension)



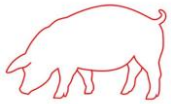
Hyperdynamic
Elevated LVEF
Impaired diastole
Elevated filling pressures
Reduced cardiac reserve

Fibrosis and disarray

LVEF = left ventricular ejection fraction
‡Del Rio et al. Circulation. 2017;136:A20770

MYH7 R403Q MINIPIG MODEL OF nHCM ‡

Hyperdynamic, impaired relaxation, and elevated filling pressures



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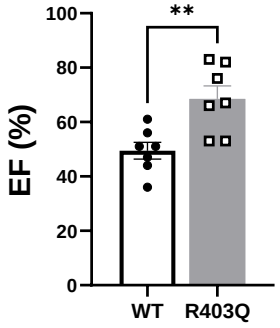
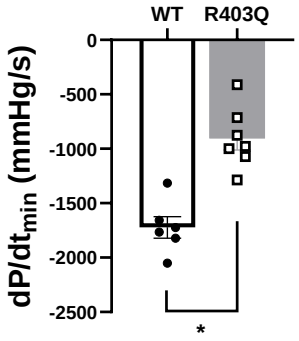
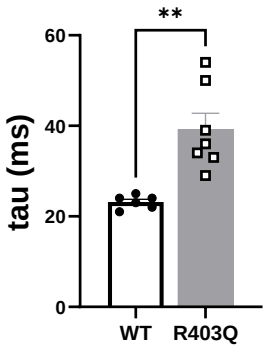
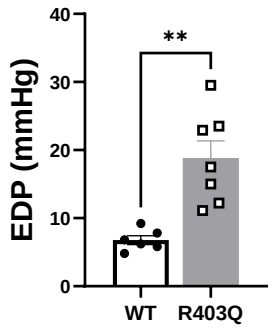
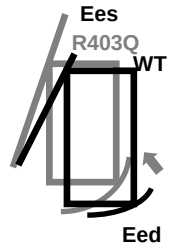
R403Q



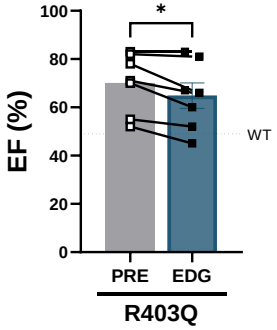


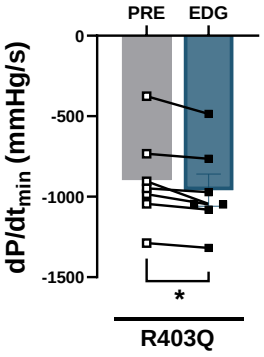


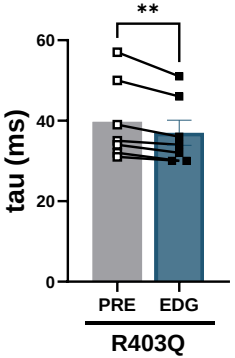


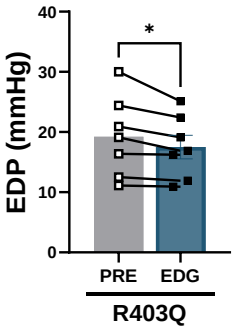


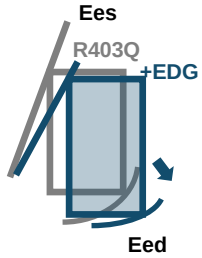
+EDG-7500











** P < 0.05, ** P < 0.01, *** P < 0.001*
EF = ejection fraction
dP/dtmin = rate of pressure development change
EDP = end diastolic pressure
‡Del Rio et al. Circulation. 2017;136:A20770

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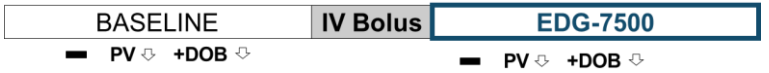
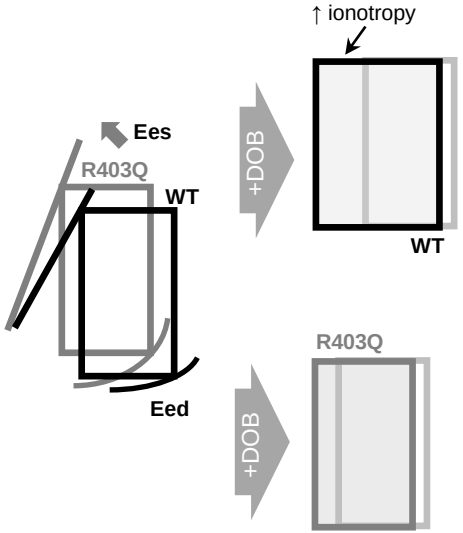
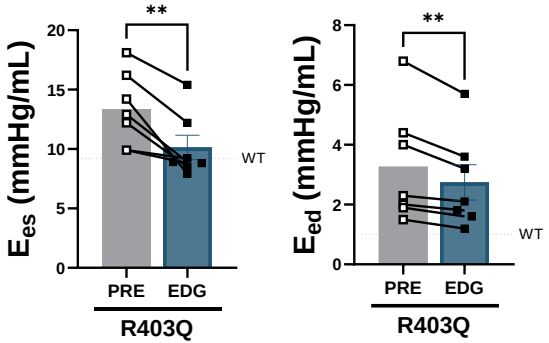
RESTORATION OF CARDIAC RESERVE WITH EDG-7500 IN A MODEL OF HCM

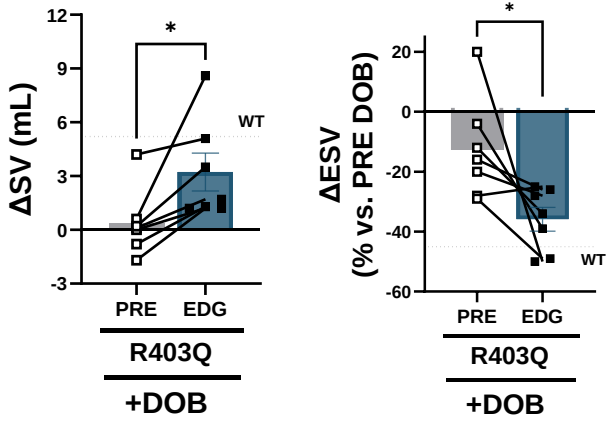
MYH7 R403Q genetic model of nHCM







EDG-7500 moves elastance toward normal



EDG-7500 increases cardiac reserve w/dobutamine

** P < 0.05, ** P < 0.01, *** P < 0.001*
ΔSV = change in stroke volume
Δ ESV = change in end systolic volume
Ees = End systolic elastance
Eed = End diastolic elastance
DOB = dobutamine
PRE = predose

SUMMARY

1. In vitro studies show EDG-7500 slows force development and maintains maximal force.
2. In minipings with the HCM-pathogenic MYH7 R403Q mutation, EDG-7500 improved both diastolic function and cardiac reserve in response to β-AR stimulation.
3. EDG-7500 is currently in a phase 1 study (NCT06011317) to evaluate safety, tolerability, and PK.

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THANK YOU

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