SACOMERIC MYOSIN AS A PHARMACOLOGICAL TARGET IN CARDIOLOGY

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Division of Clinical Physiology, Department of Cardiology,
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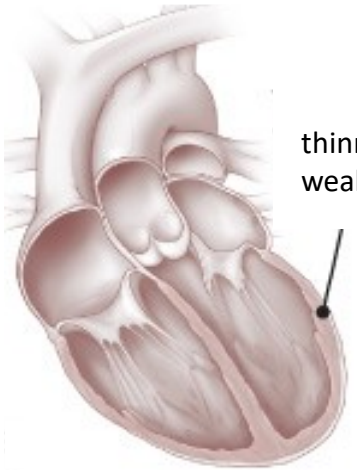
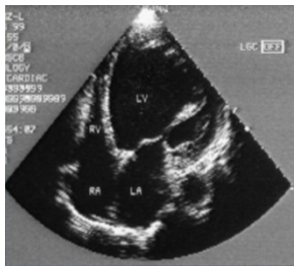
Czech Cardiovascular Research and Innovation Days 2024
Heart failure research network – from basic science to clinical evidence I
Monday 04/11/2024 9:00 - 10:30

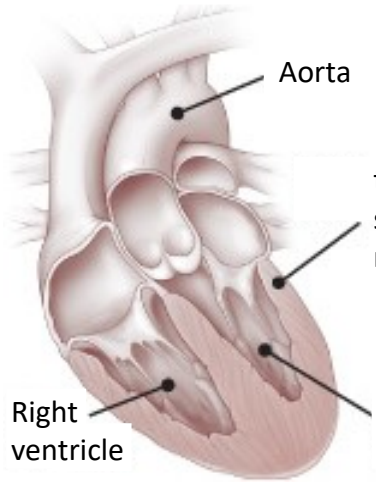
Cardiomyocyte contractility is altered during Heart Failure

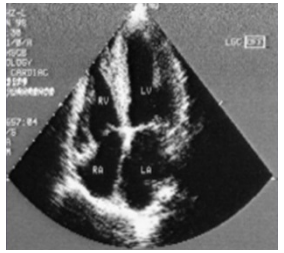
Systolic Heart Failure (HFrEF)



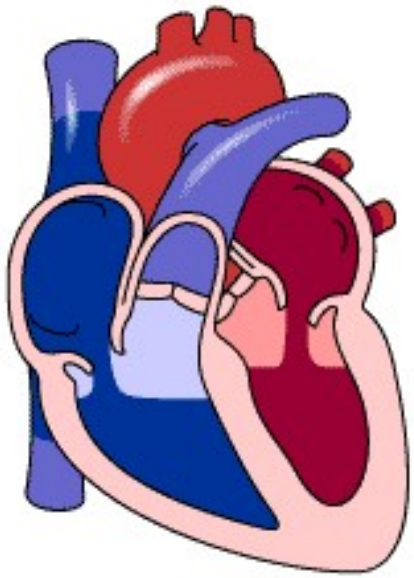


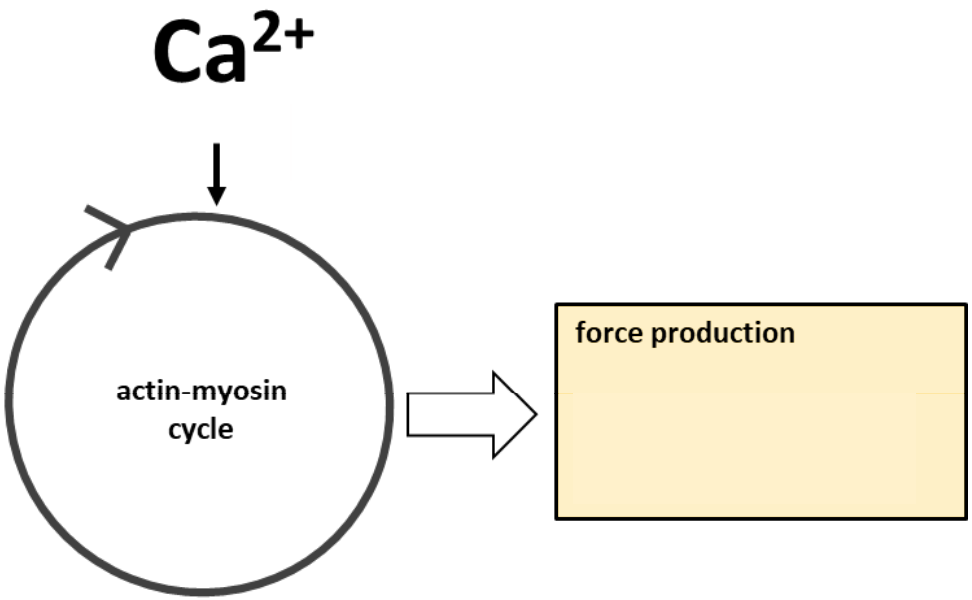
Diastolic Heart Failure (HFpEF)





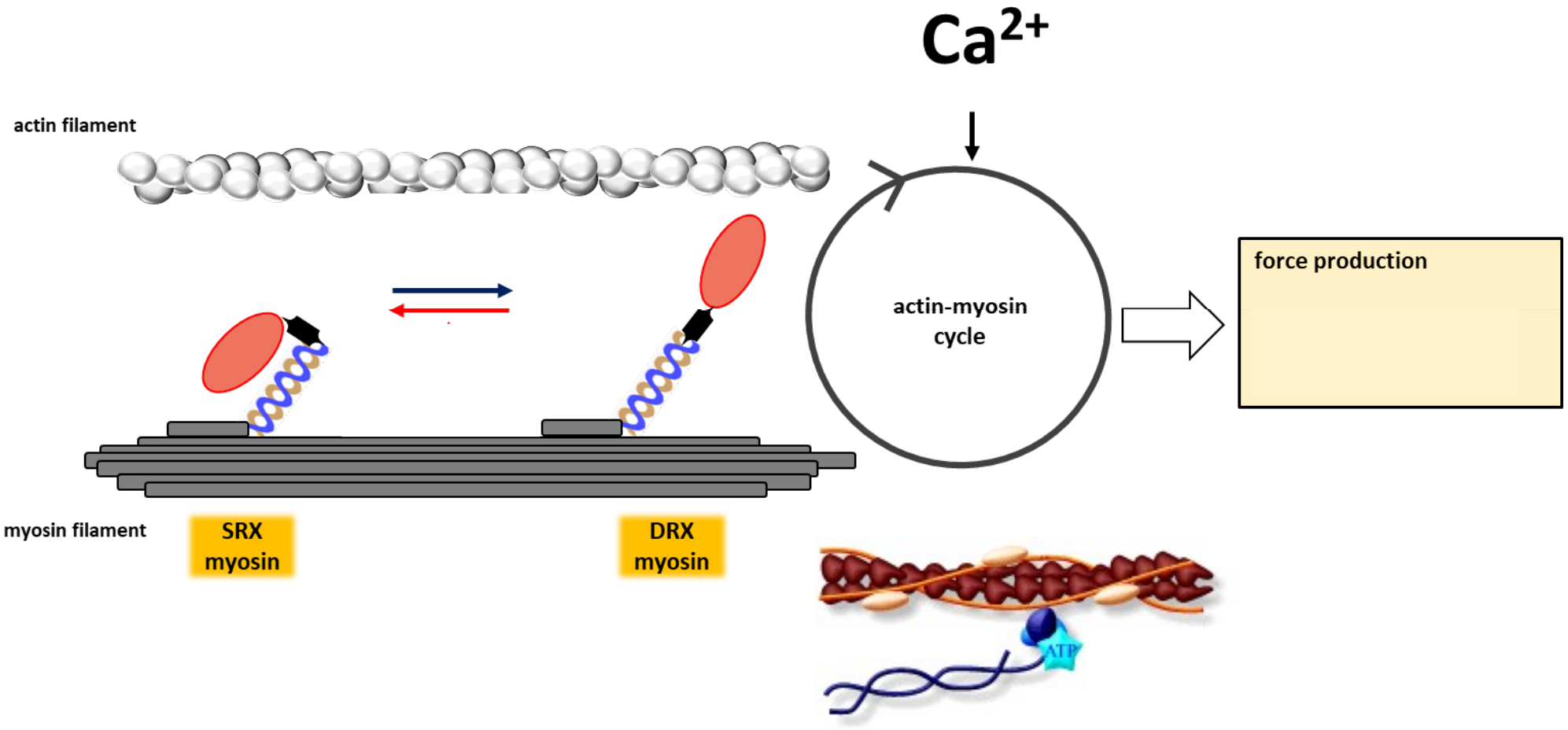
Myocardial force depends on the number and function of actin-myosin cross-bridges





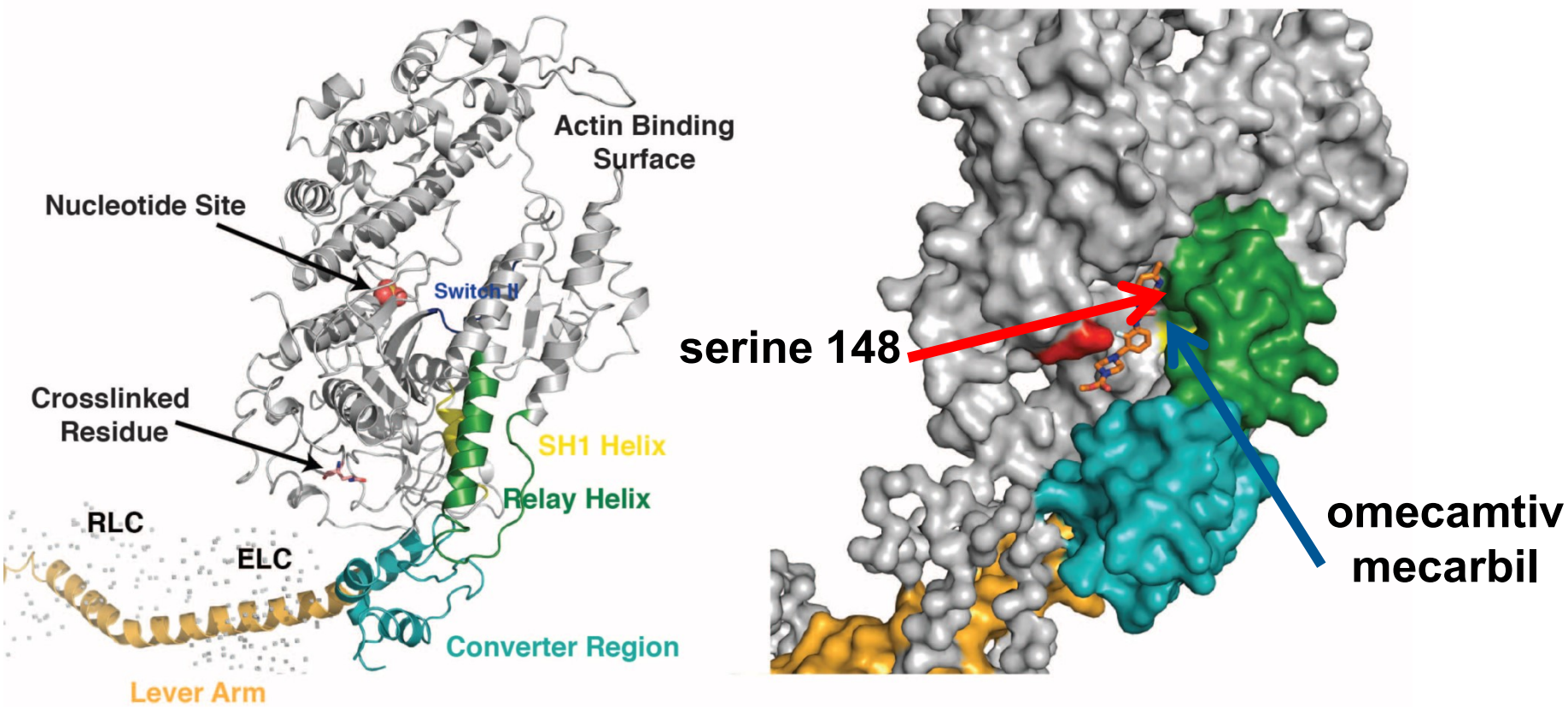
Papp et al., unpublished

Myocardial force depends on the number and function of actin-myosin cross-bridges



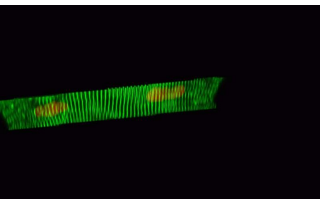
Papp et al., unpublished

Direct myosin activators bind to myosin heavy chain



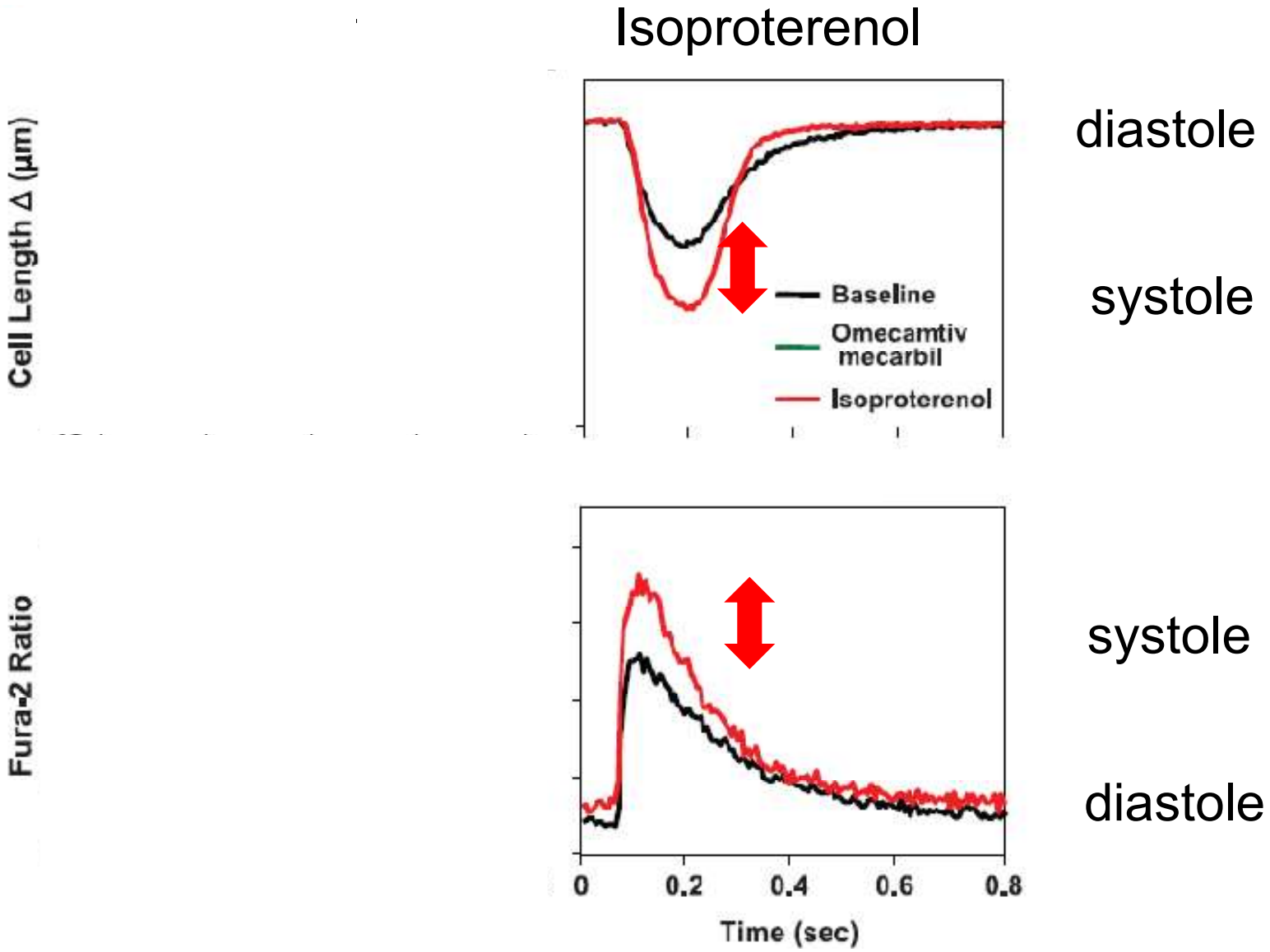
Malik et al., Science 2011;331:1439–1443

Isoproterenol increases the amplitude of the Ca^{2+} transient



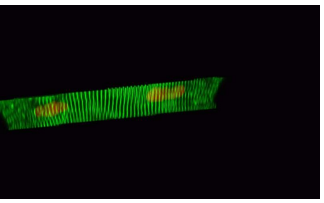
Contractility transient

Ca^{2+} transient



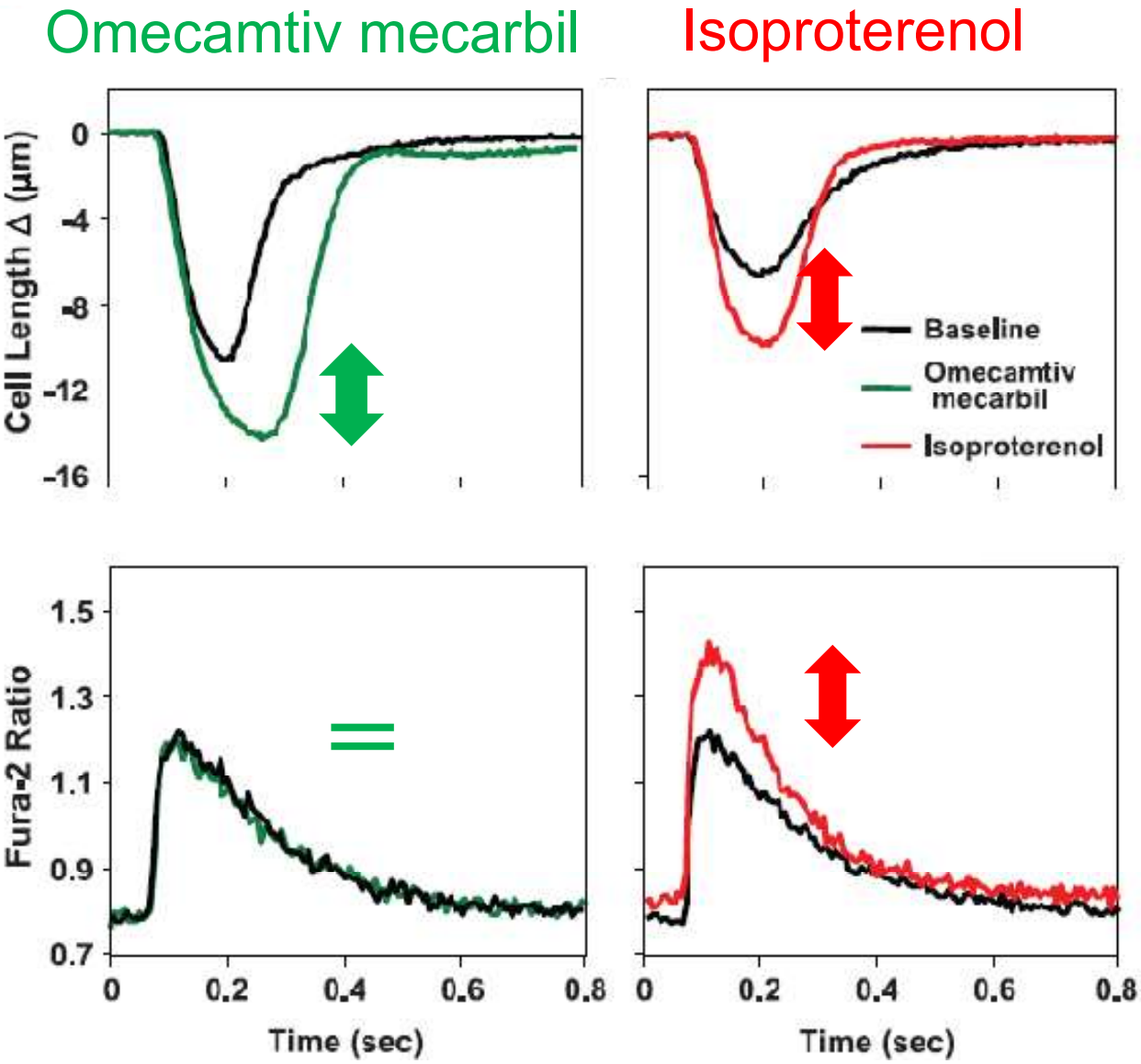
Malik et al., Science 2011;331:143

Omecamtiv mecarbil does not affect the Ca^{2+} transient



Contractility transient

Ca^{2+} transient



diastole

systole

systole

diastole

Malik et al., Science 2011;331:143

Clinical trials with omecamtiv mecarbil

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ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.01.031

MIC-AHF

Acute Treatment With Omecamtiv Mecarbil to Increase ntractility in Acute Heart Failure

COSMIC-HF

Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial

GALACTIC-HF

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

J.R. Teerlir[illegible] A. Arias-Mendoza U. Dahlström, L. D.E. Lanfear, J. Li, F.J.A. Ramires A.A. Voors, M.

METEORIC-HF

JAMA | Original Investigation

Effect of Omecamtiv Mecarbil on Exercise Capacity in Chronic Heart Failure With Reduced Ejection Fraction
The METEORIC-HF Randomized Clinical Trial

Gregory D. Lewis, MD; Adriaan A. Voors, MD, PhD; Alain Cohen-Solal, MD, PhD; Marco Metra, MD; David J. Whellan, MD, MHS; Justin A. Ezekowitz, MBBCh, MSc; Michael Böhm, MD; John R. Teerlink, MD; Kieran F. Docherty, BSc, MB, ChB; Renato D. Lopes, MD, PhD; Punag H. Divanji, MD; Stephen B. Heitner, MD; Stuart Kupfer, MD; Fady I. Malik, MD, PhD; Lisa Meng, PhD; Amy Wohltman, ME; G. Michael Felker, MD, MHS

Direct myosin activators are not yet available

News > Medscape Medical News > News Alerts

FDA Declines Approval for Omecamtiv Mecarbil in HFrEF

Megan Brooks

March 01, 2023

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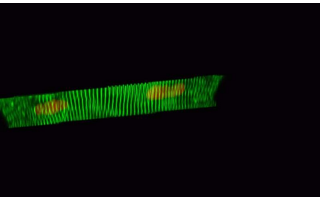
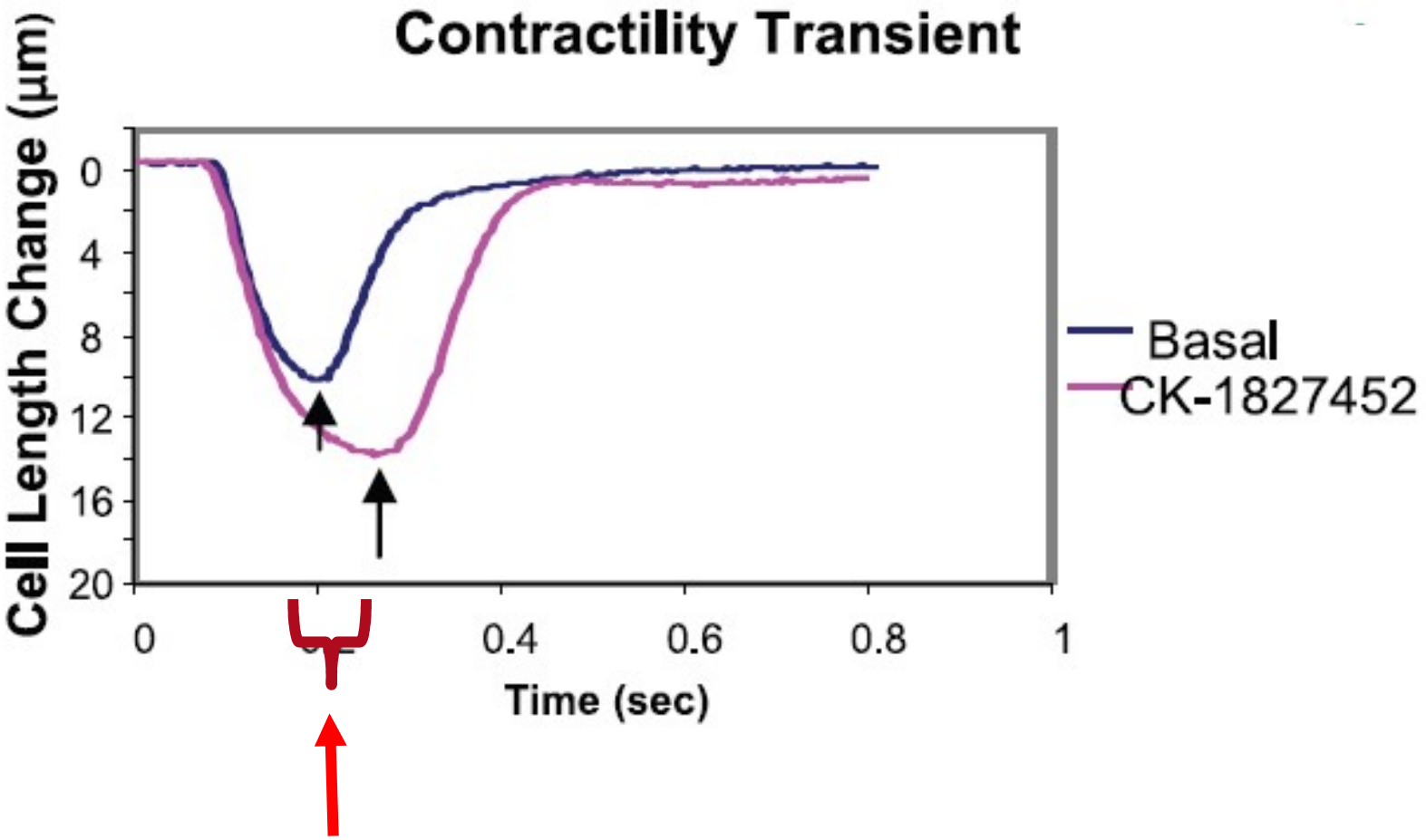
The US Food and Drug Administration (FDA) has declined to approve omecamtiv mecarbil (Cytokinetics) for treatment of adults with chronic heart failure with reduced ejection fraction (HFrEF), citing a lack of evidence on efficacy.

Omecamtiv mecarbil is a first-in-class, selective cardiac myosin activator designed to improve cardiac performance.

Myosin activators increase systolic ejection time



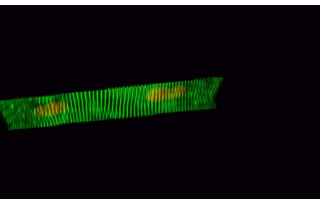


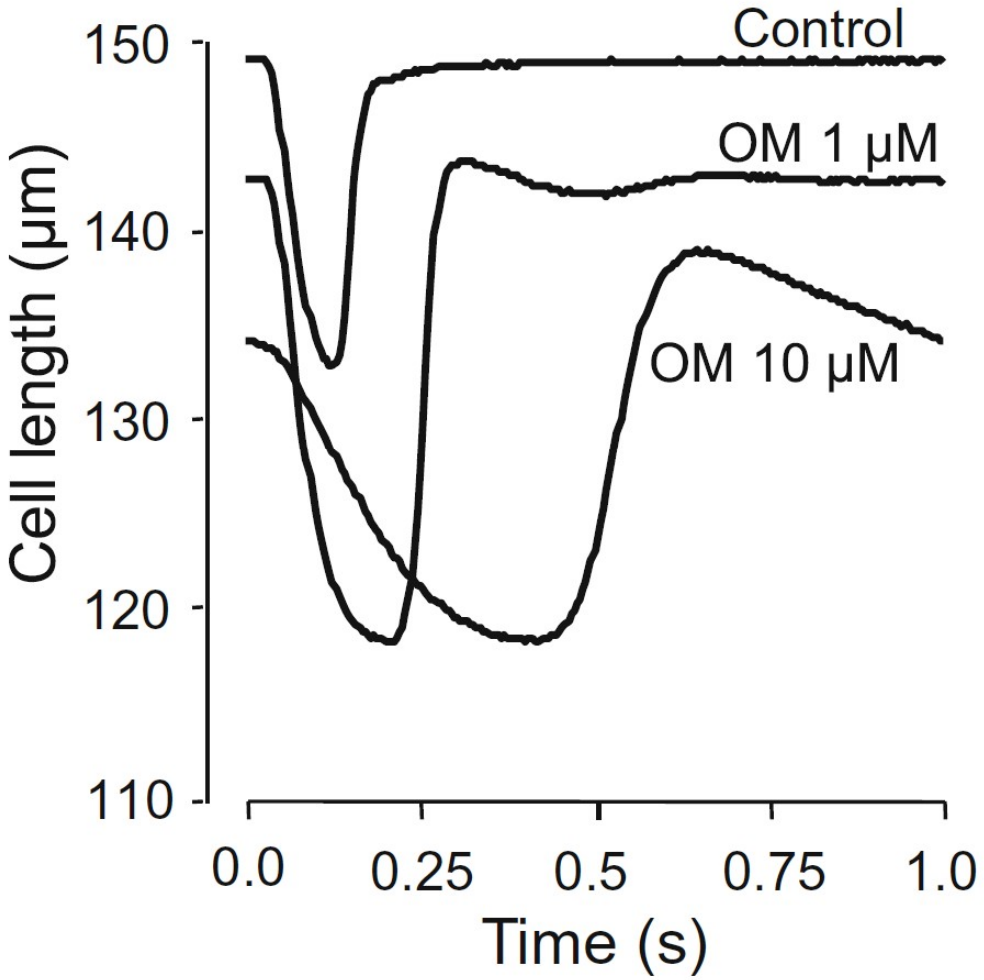
Increased duration of systole

Malik et al., Science 2011;331:1439–1443

Anderson et al., Biophys. Soc. Meeting, 2007, Poster

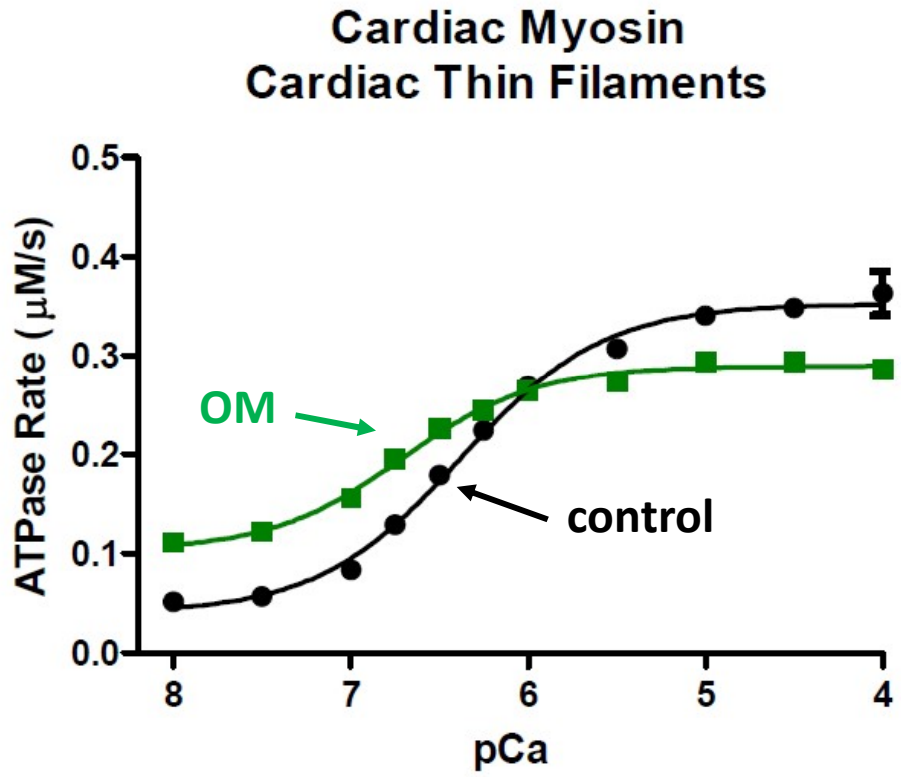
Omecamtiv mecarbil decreases diastolic cell length





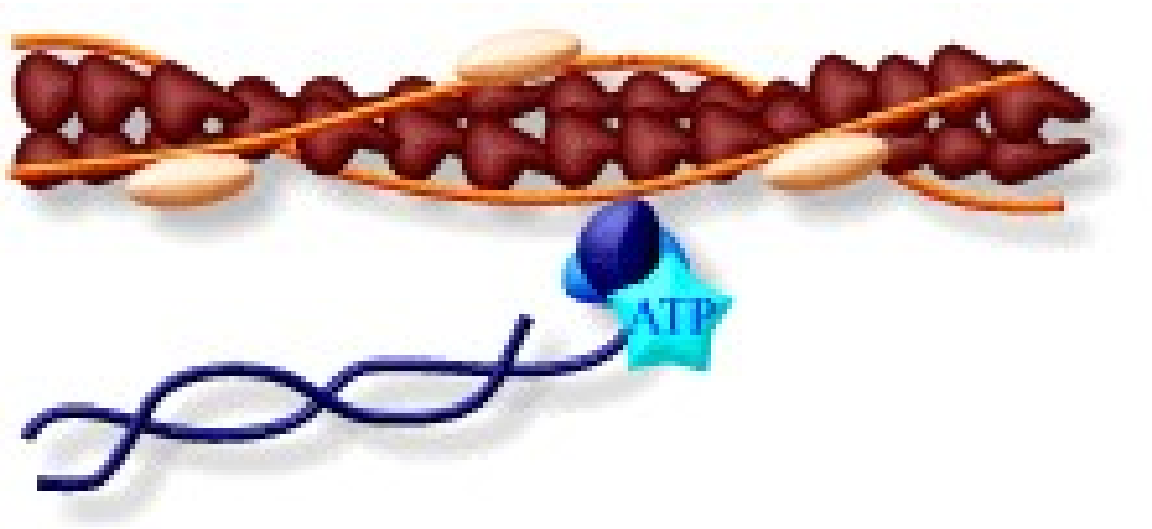
Horvath B…Papp Z. et al. Naunyn Schmiedebergs Arch Pharmacol. (2017),390(12):1239-1

necamtiv mecarbil (OM) increases the ATPase activity of myosin at low [Ca



Malik et al., Science 2011;331:1439–1443

What is the problem here?



Direct myosin activation: everything comes with a price

The two sides of the coin for direct myosin activators

positive inotropy
increase in systolic duration
slower contraction

Direct myosin activation: everything comes with a price

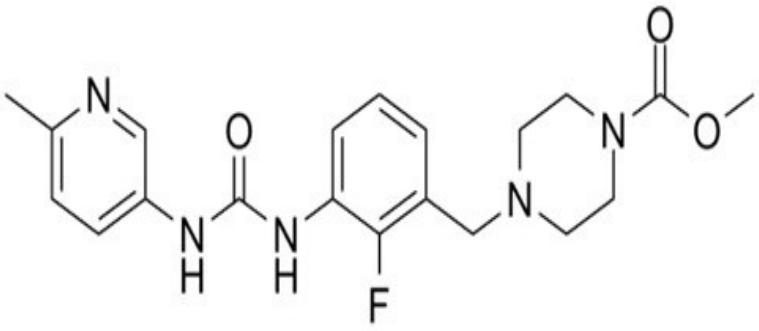
The two sides of the coin for direct myosin activators

positive inotropy
increase in systolic duration
slower contraction

incomplete relaxation
decrease in diastolic duration
slower relaxation
limited tissue selectivity

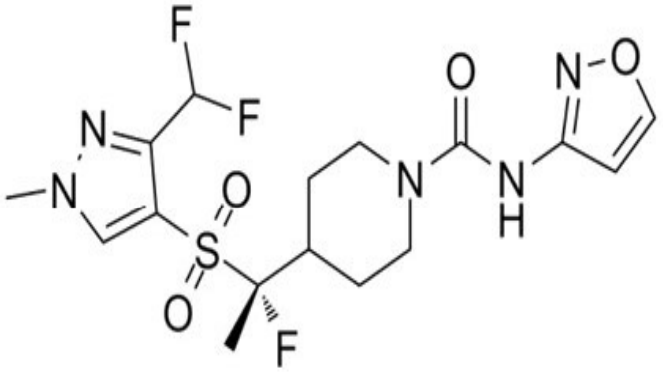
Myosin activators: 1st and 2nd generation

omecamtiv mecarbil



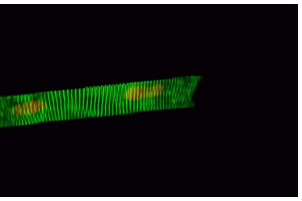
methyl 4-[[2-fluoro-3-[(6-methylpyridin-3-yl)carbamoylamino]phenyl]methyl]piperazine-1-carboxylate

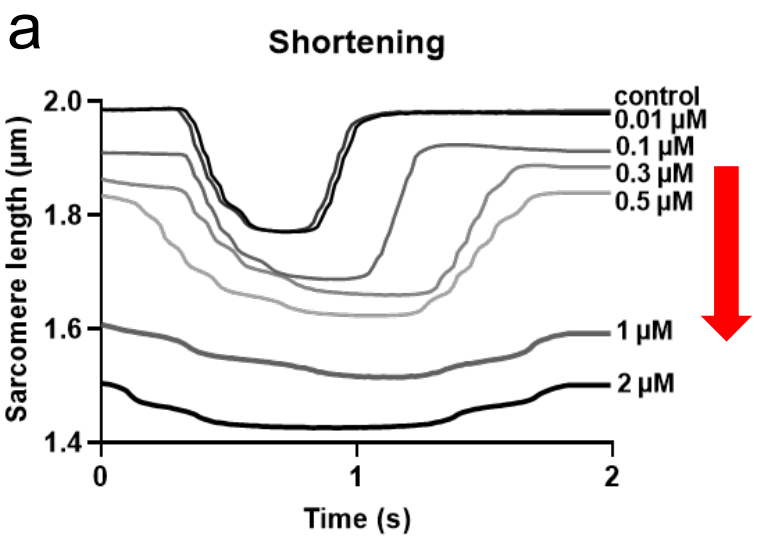
danicamtiv

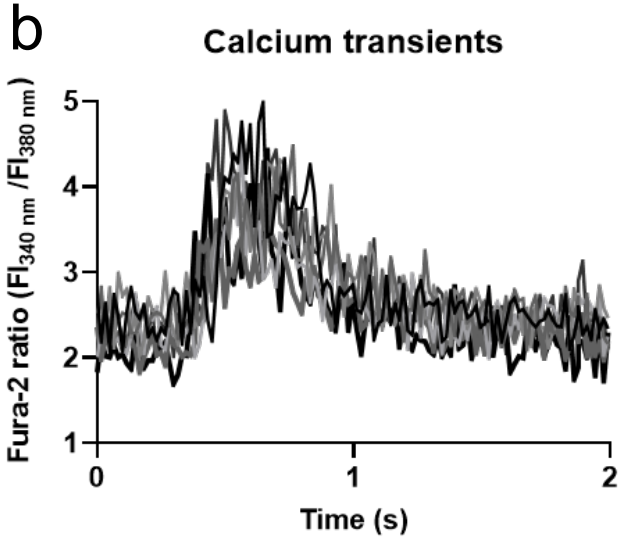


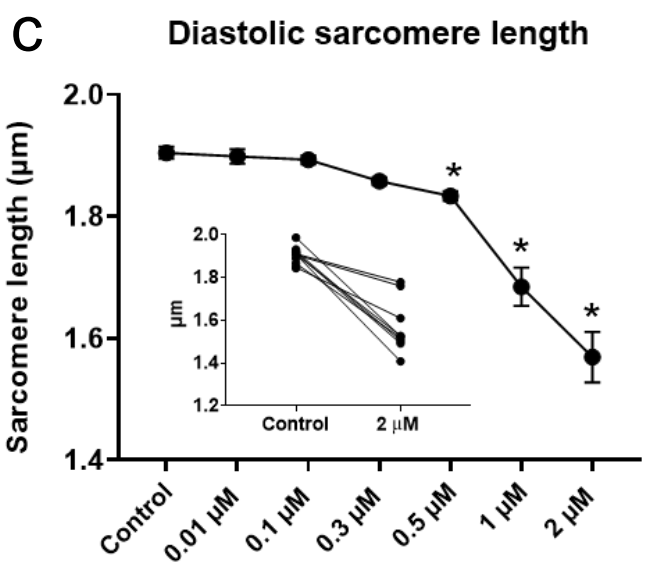
4-[(1*R*)-1-[3-(difluoromethyl)-1-methylpyrazol-4-yl]sulfonyl-1-fluoroethyl]-*N*-(1,2-oxazol-3-yl)piperidine-1-carboxamide

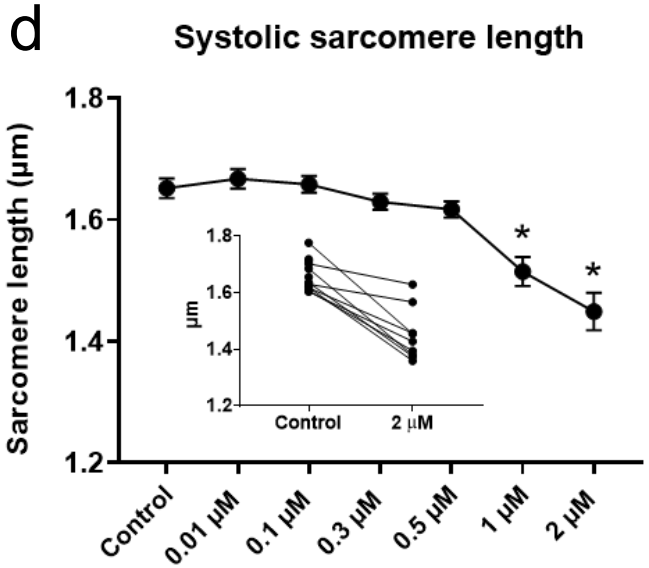
Danicamtiv decreases both systolic and diastolic SLs







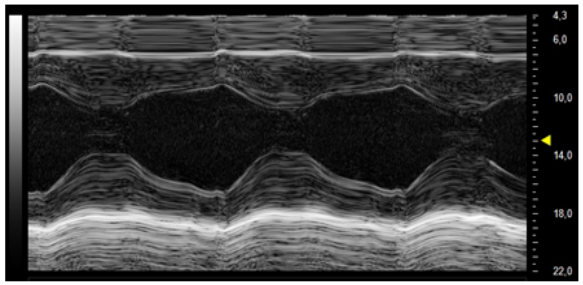




Ráduly A…Papp Z. et al. Int J Mol Sci. 2022 Dec 27;24

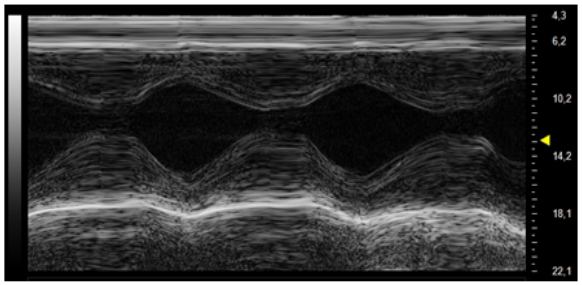
Danicamtiv did not decrease end-diastolic diameter (EDD)

a



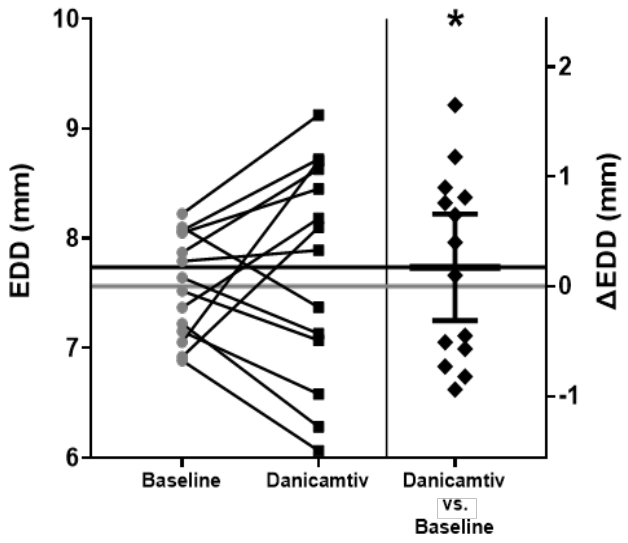
Before danicamtiv

b

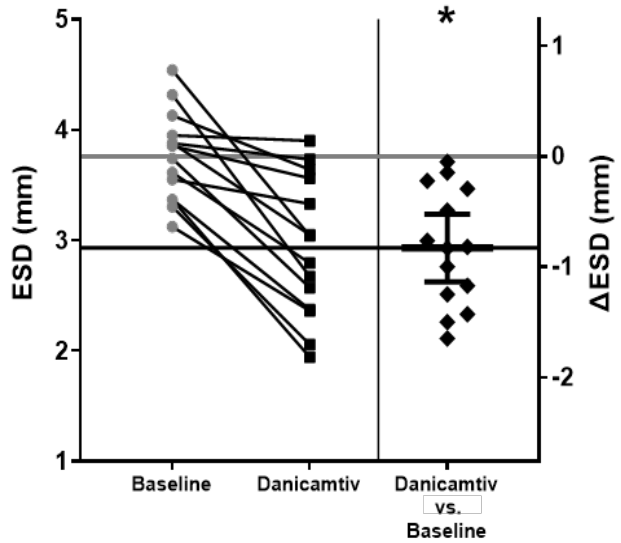


After danicamtiv

c



d



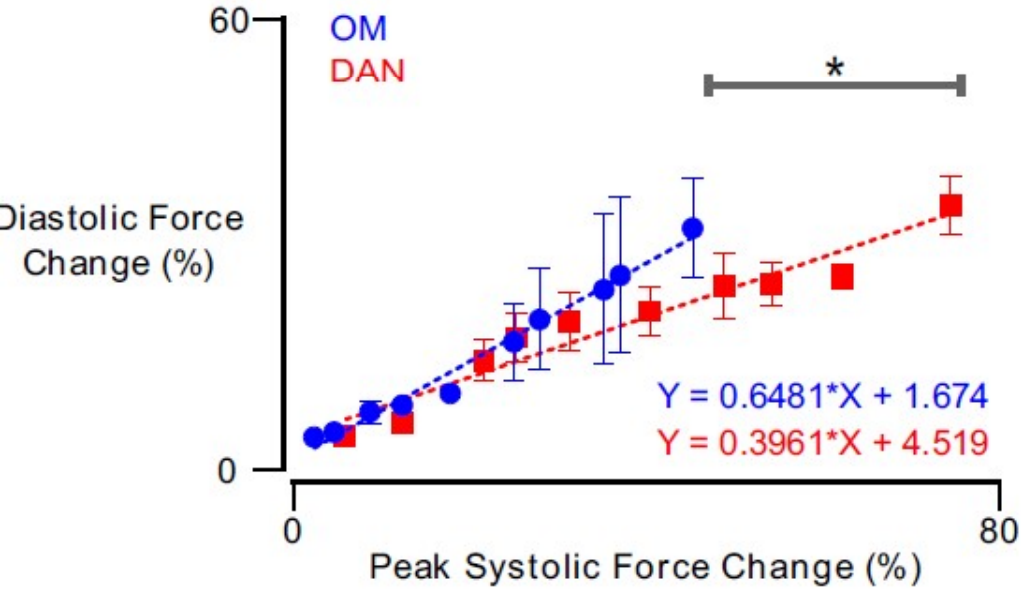
Ráduly A…Papp Z. et al. Int J Mol Sci. 2022 Dec 27;24

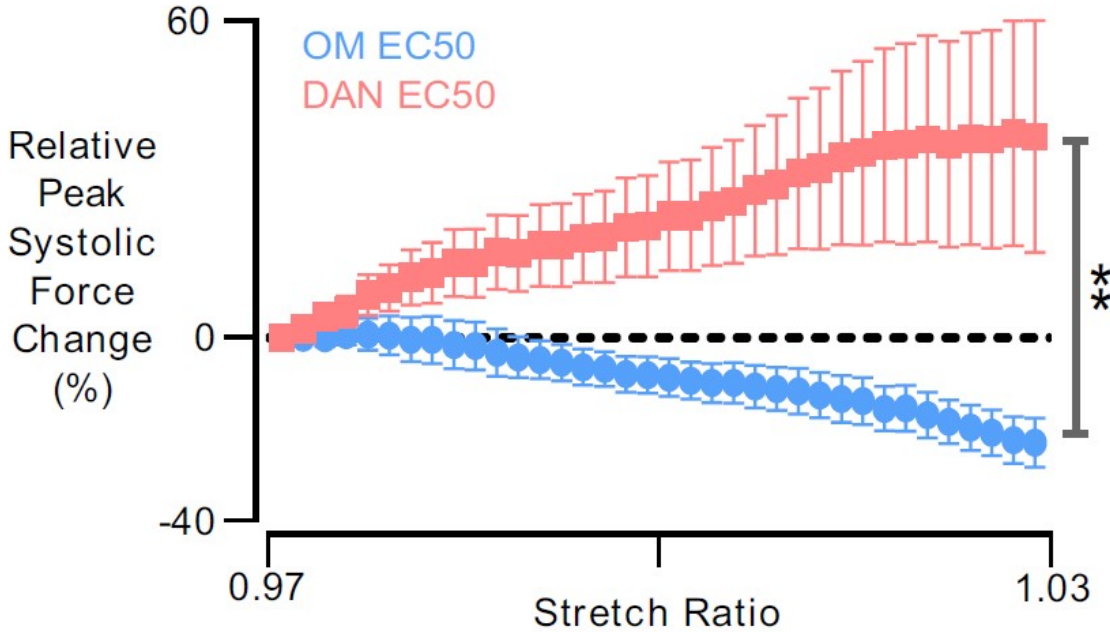
Journal of the American Heart Association

RESEARCH LETTER

Danicamtiv Enhances Systolic Function and Frank-Starling Behavior at Minimal Diastolic Cost in Engineered Human Myocardium

Shi Shen, MS*; Lorenzo R. Sewanan, PhD*; Daniel L. Jacoby, MD; Stuart G. Campbell, PhD





Shen et al., Am Heart Assoc. 2021 Jun 15;10(12):e020860.

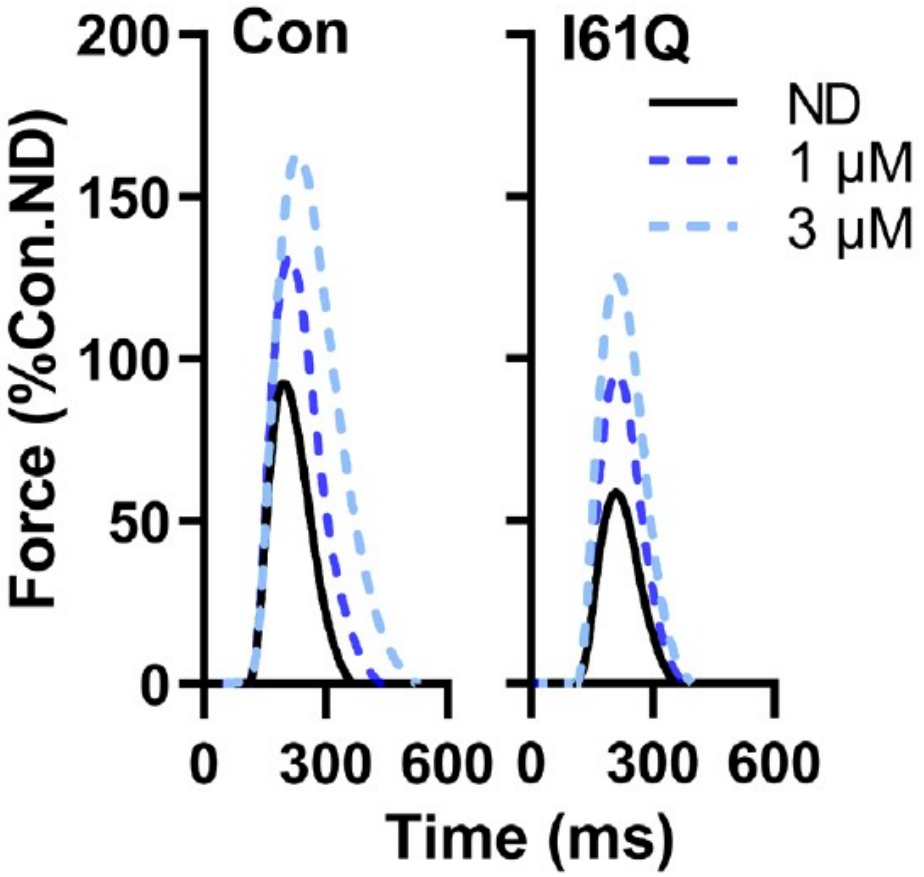
culation Research

Check for updates

GINAL RESEARCH

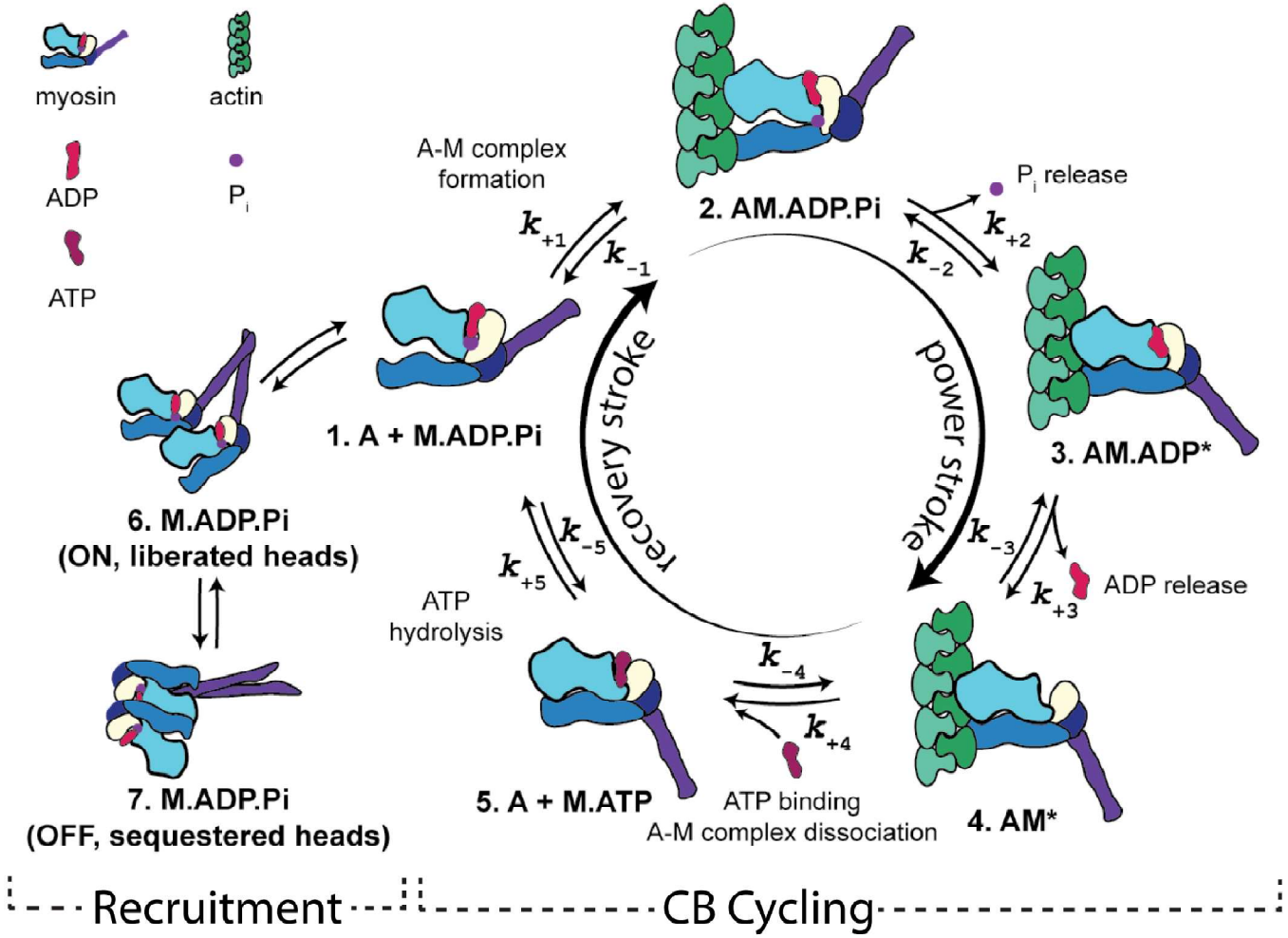
nicamtiv Increases Myosin Recruitment and ers Cross-Bridge Cycling in Cardiac Muscle

B. Kooiker, Saffie Mohran, Kyrah L. Turner, Weikang Ma, Amy Martinson, Galina Flint, Lin Qi, Chengqian Gao, Zheng, Timothy S. McMillen, Christian Mandrycky, Max Mahoney-Schaefer, Jeremy C. Freeman, Gabriela Costales Arenas, An-Yu Tu, Thomas C. Irving, Michael A. Geeves, Bertrand C.W. Tanner, Michael Regnier, r Davis, Farid Moussavi-Harami



Kooiker et al., Circulation Research. 2023;133:430

Danicamtiv recruits myosin motors to aid the failing hea



Kooiker et al., Circulation Research. 2023;133:430

Maicon Landim-Vieira , Bjorn C. Knollmann Circulation Research. **2023;133:4**

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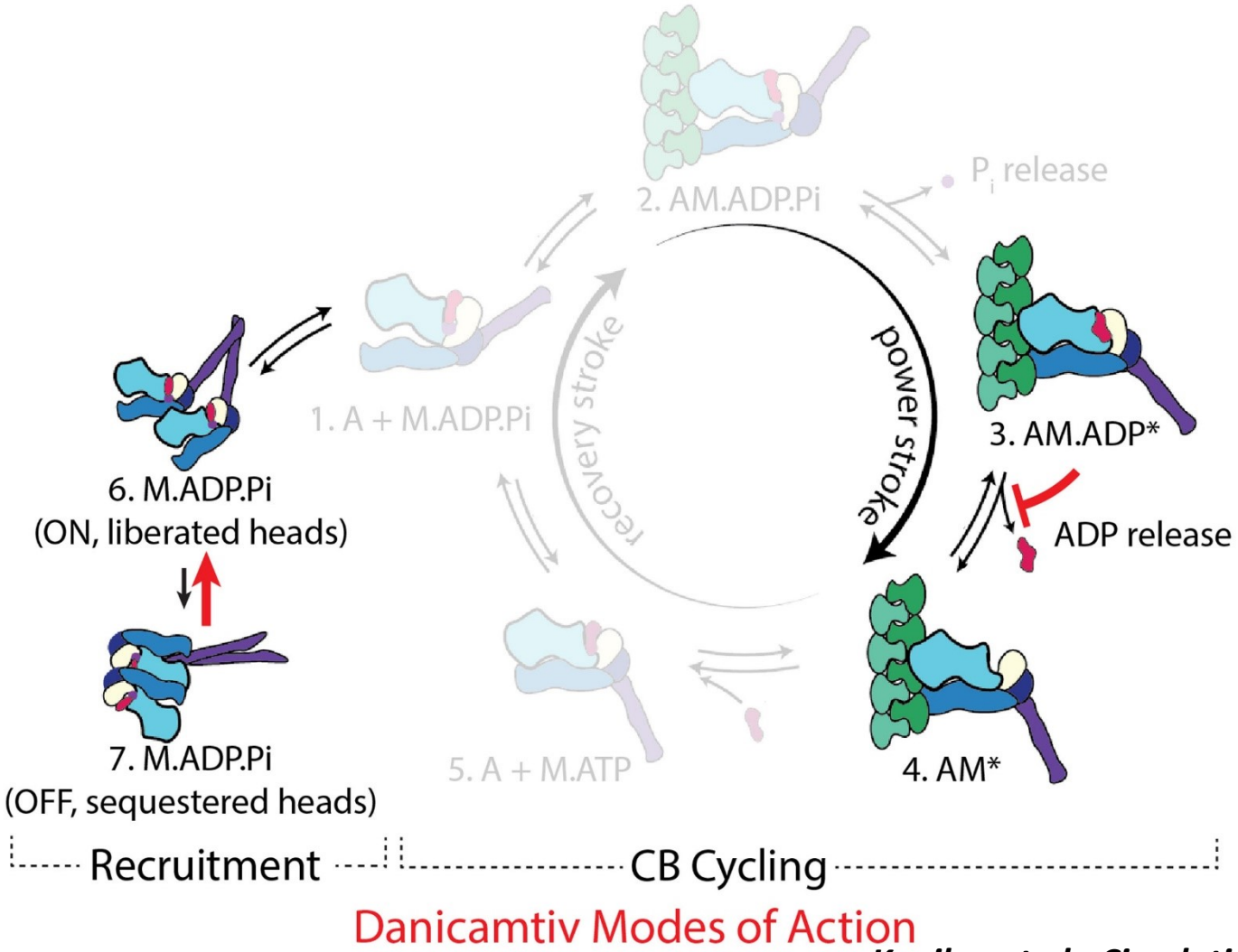
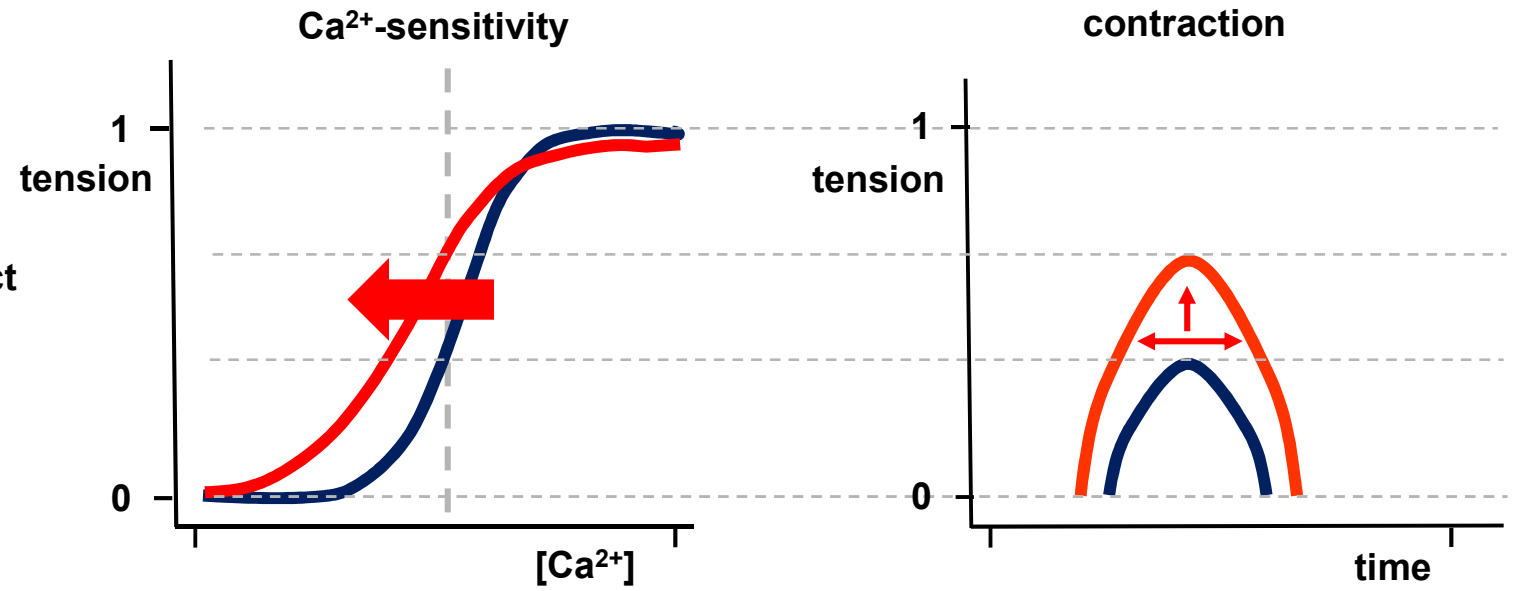


Kooiker et al., Circulation Research. 2023;133:430

Maicon Landim-Vieira , Bjorn C. Knollmann Circulation Research. **2023;133:4**

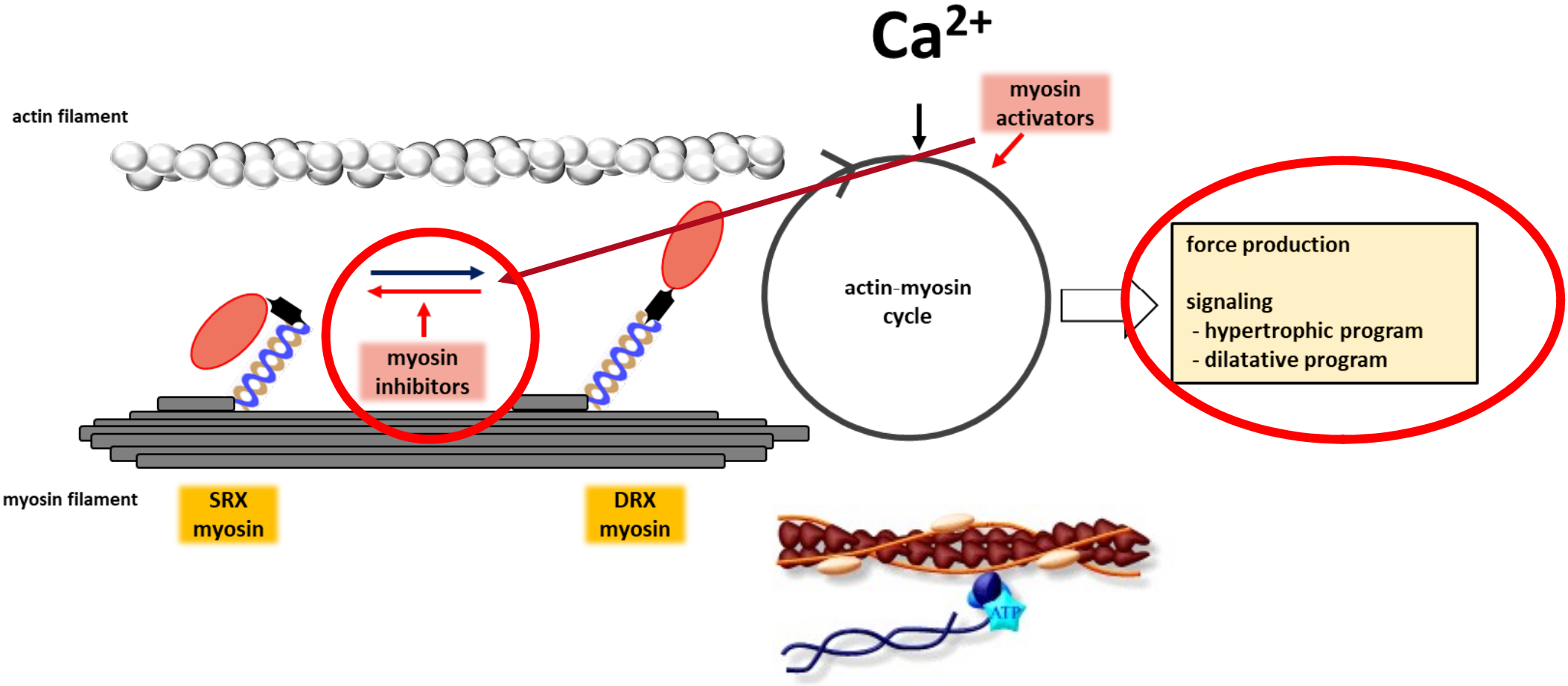
Potential explanation for direct myosin activation effects

myosin activator effect



Papp et al., unpublished

Myosin activators may normalize hypocontractility brought about by genetic alterations



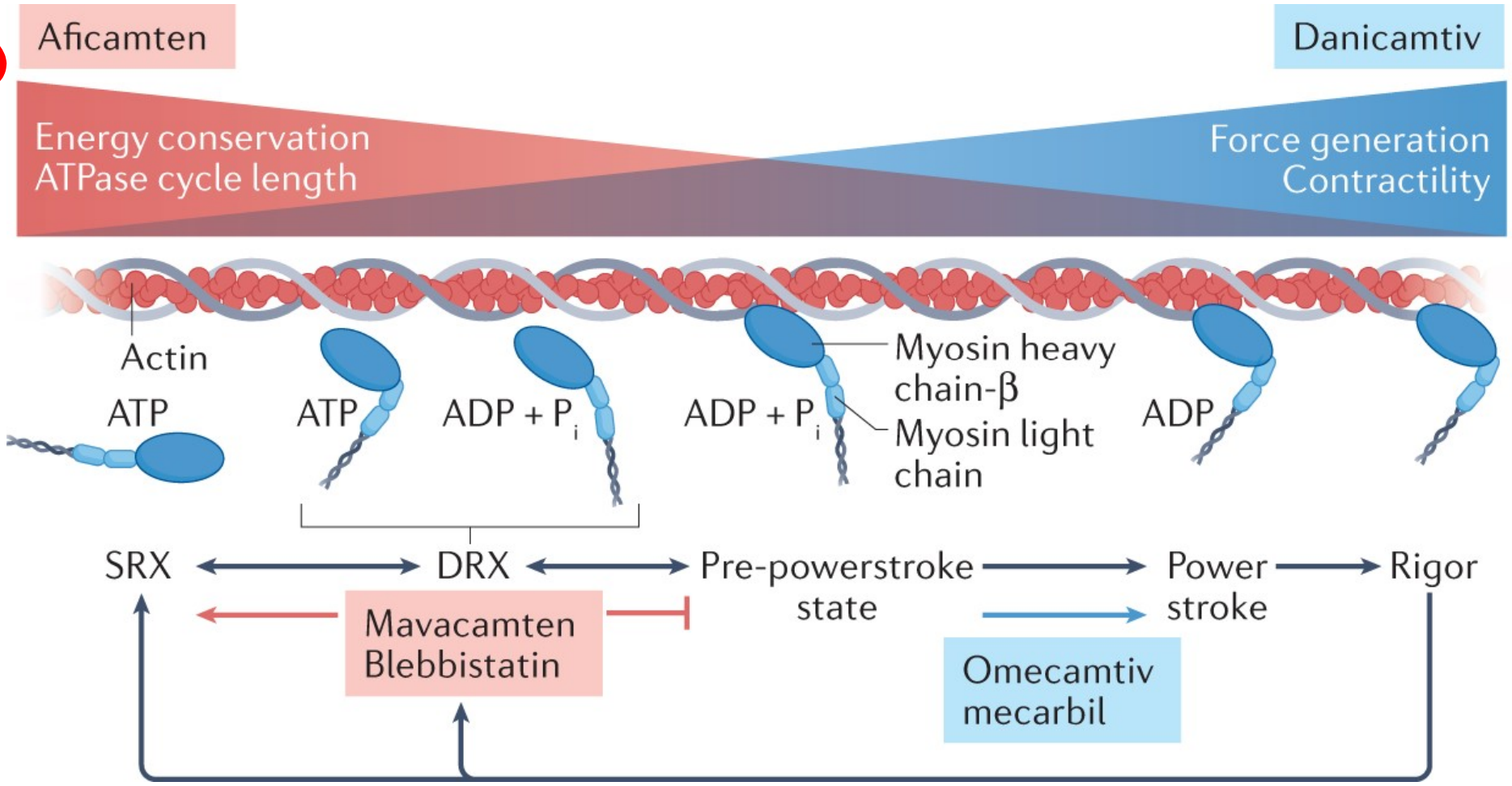
Papp et al., unpublished

NCT trials with danicamtiv

NCT Number	Condition	Start Date	Phase
NCT04572893	Primary Familial Dilated Cardiomyopathy	August 4, 2020	Phase 2
NCT03447990	Heart Failure With Reduced Ejection Fraction|Dilated Cardiomyopathy	February 6, 2018	Phase 1|Phase 2
NCT05162222	Healthy Participants	December 15, 2021	Phase 1
NCT05806359	Healthy Volunteers	March 31, 2023	Phase 1
NCT03062956	Dilated Cardiomyopathy	January 16, 2017	Phase 1
NCT05952089	Heart Failure With Reduced Ejection Fraction	July 17, 2023	Phase 1

https://www.medchemexpress.com

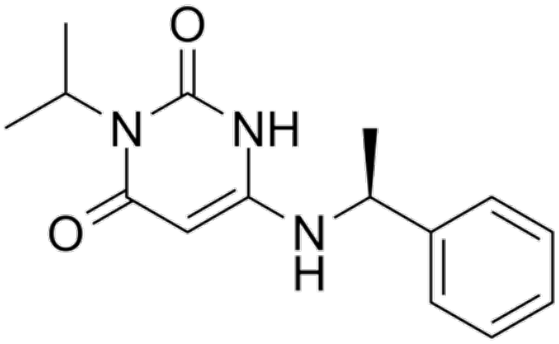
From myosin activation to myosin inhibition



Lehman et al.,
Nature Reviews Cardiology 19, 353–363, 2022

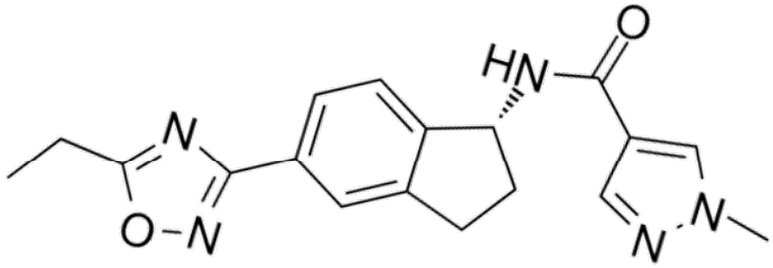
First and second generation of myosin inhibitors

mavacamten



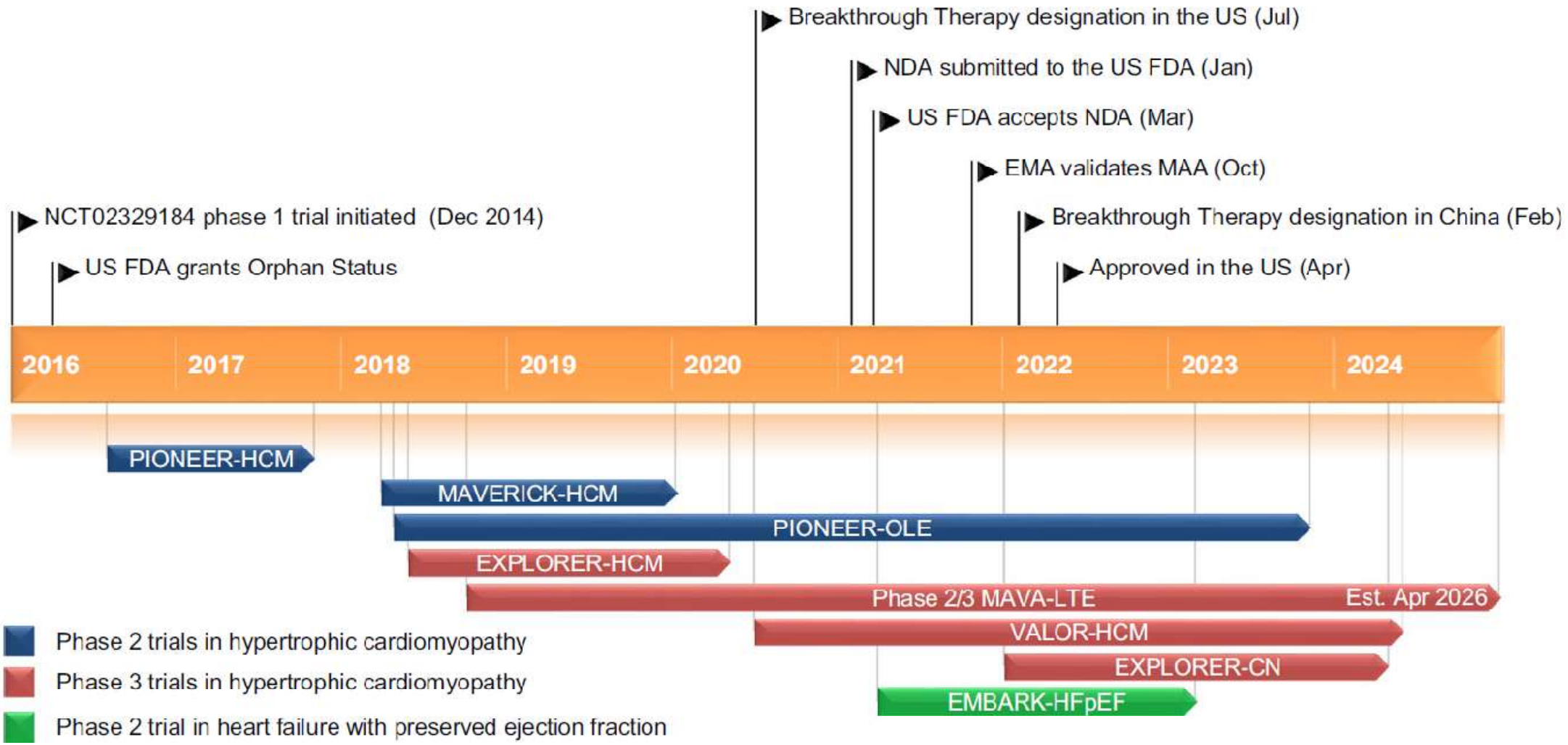
6-[[(1*S*)-1-phenylethyl]amino]-3-propan-2-yl-1*H*-pyrimidine-2,4-dione

aficamten



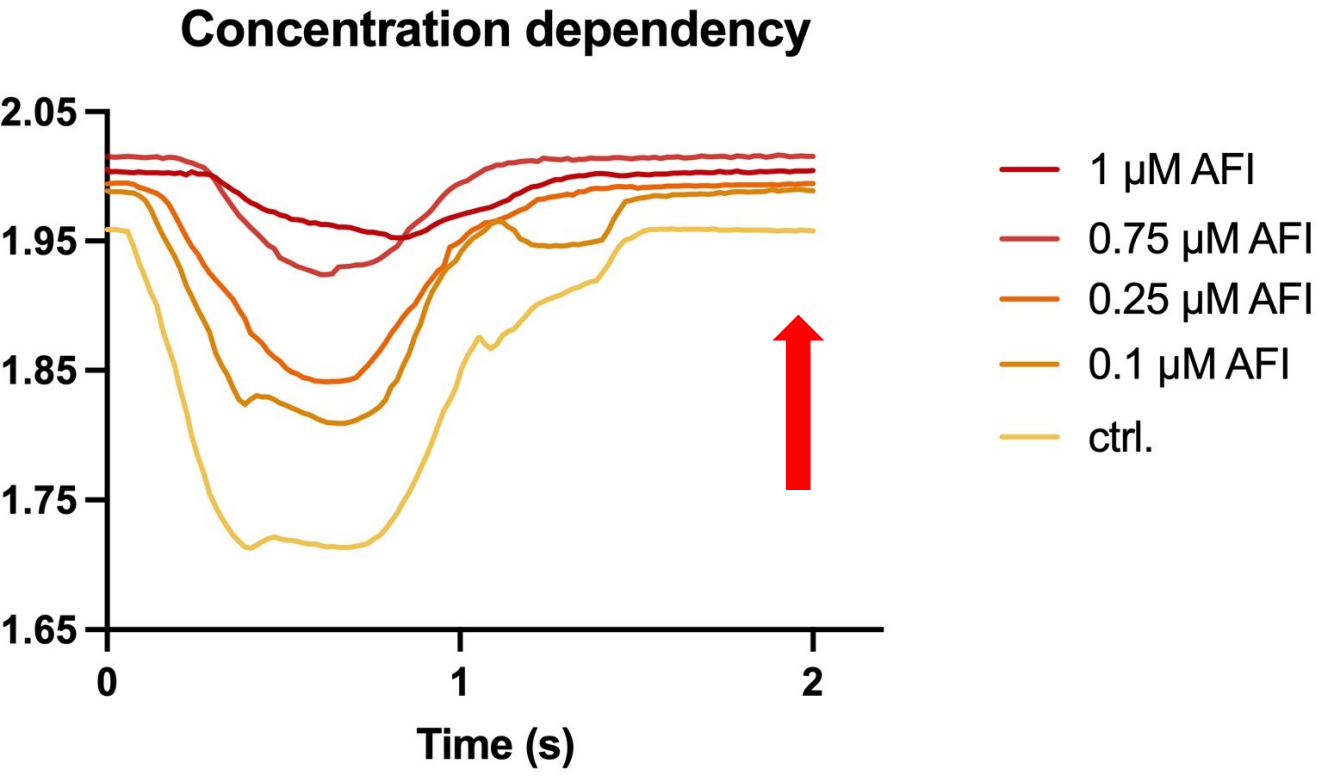
N-[(1*R*)-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1*H*-inden-1-yl]-1-methylpyrazole-4-carboxamide

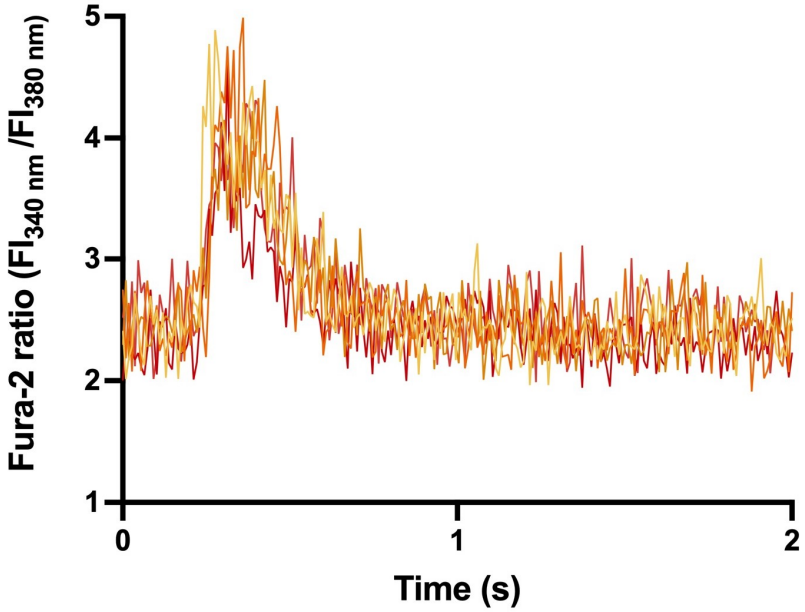
Milestones in the development of mavacamten



Keam S.J. (2022) 82:1127–1135

Effects of aficamten on SL and Ca^{2+} transients



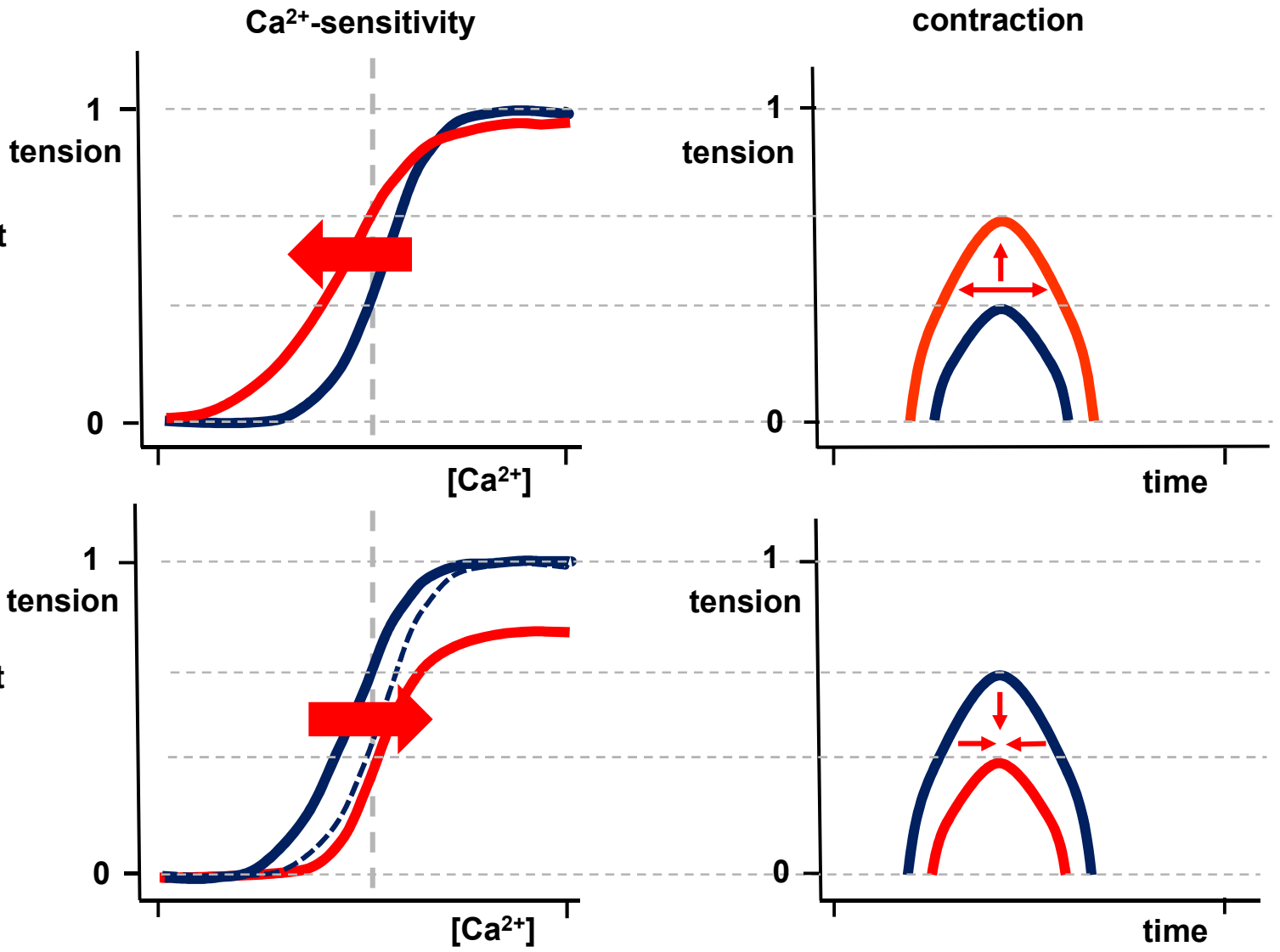


Sárkány et al., unpublished

Potential explanation for direct myosin acivator and inhibitor effects

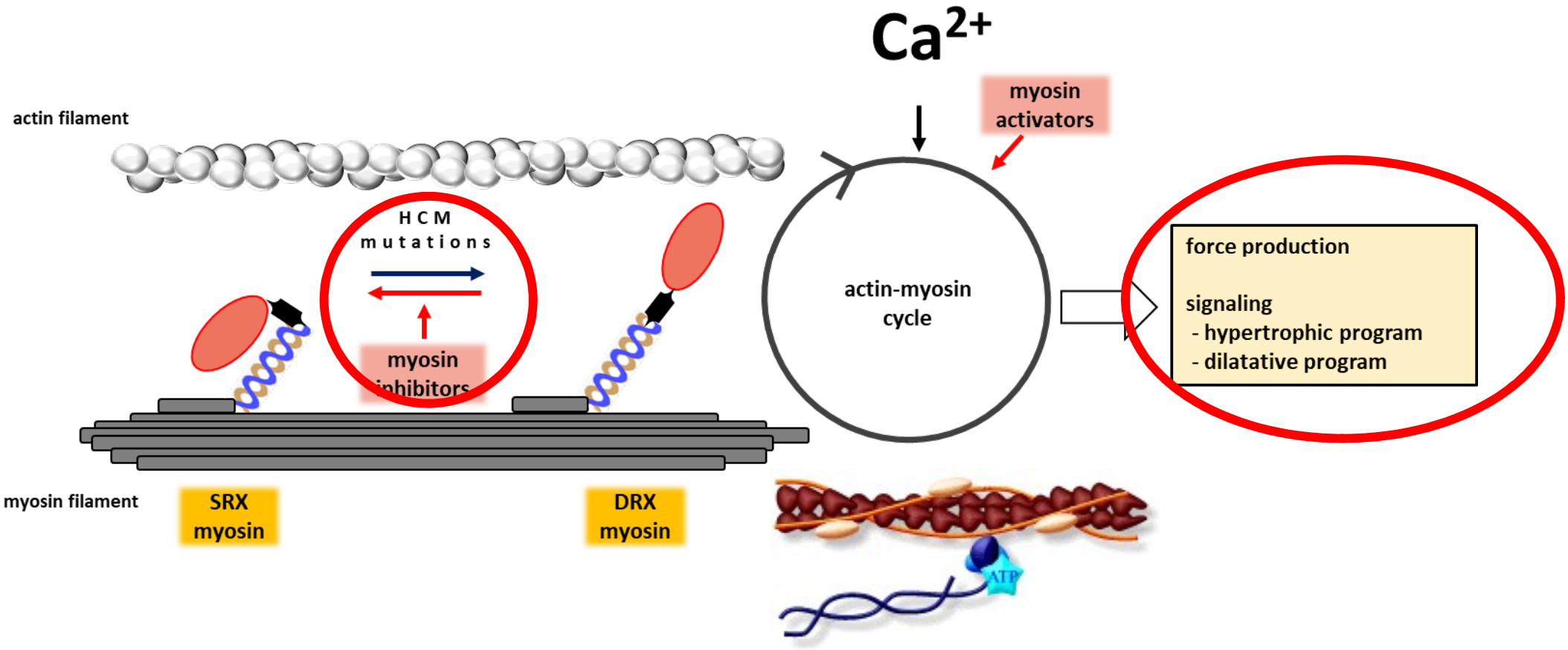
myosin activator effect

myosin inhibitor effect



Papp et al., unpublished

Myosin inhibitors might better compensate for genetic alterations than myosin activators



Papp et al., unpublished

Conclusions

Omecamtiv mecarbil evokes positive inotropic effects in murine, canine and huma cardiac preparations *in vitro* and *in vivo*, consistently with its myosin activating an Ca^{2+}-sensitizing effects.

The myosin activator evoked increase in systolic performance is tightly coupled t increased ejection time and slow contraction-relaxation kinetics.

Bypassing the Ca^{2+}-activation step in cardiomyocytes limits physiological contracti regulation.

Direct myosin inhibitors hold promises for the treatment of hypertroph cardiomyopathy.

Acknowledgements

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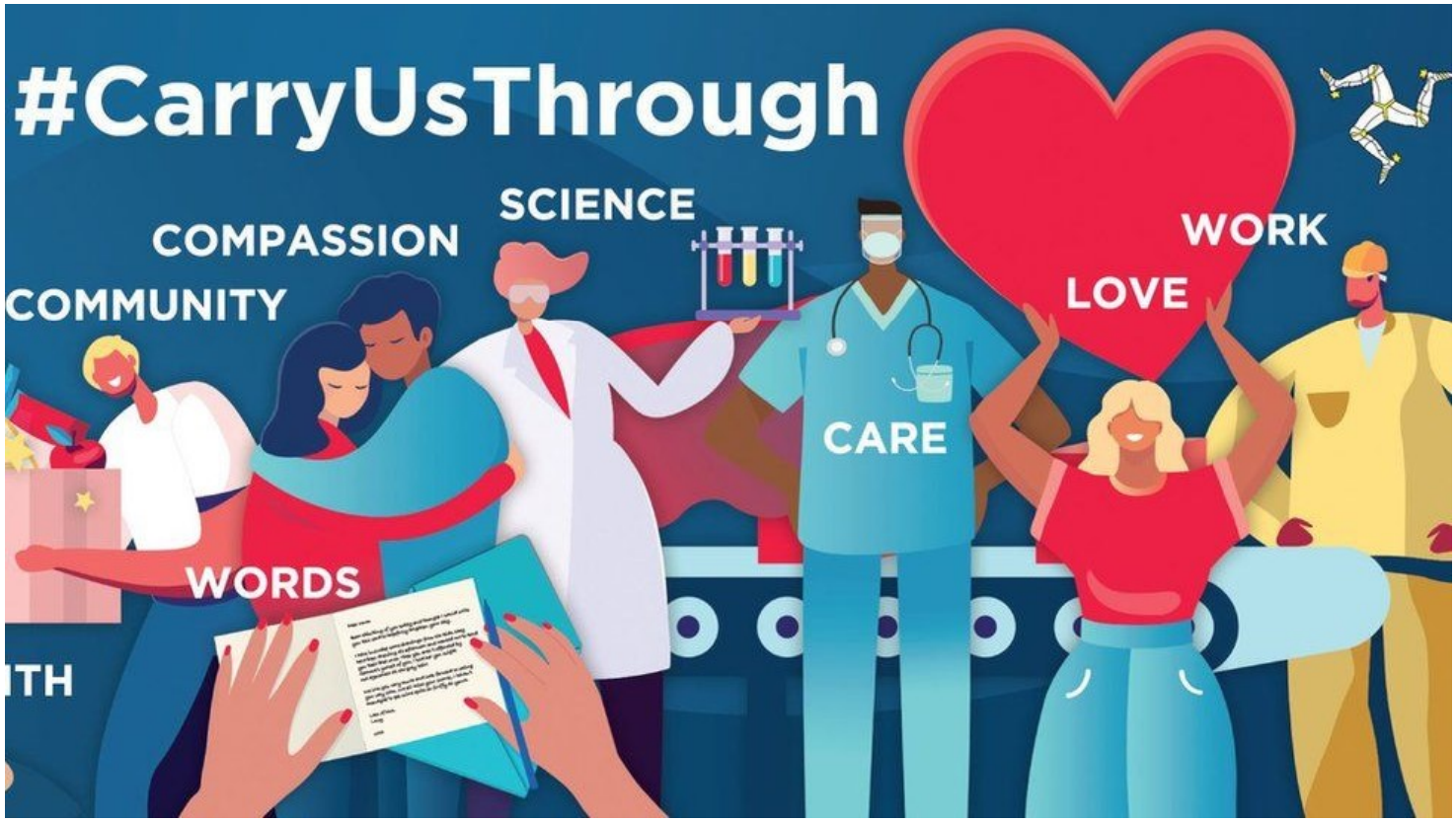
Thank you for your attention!

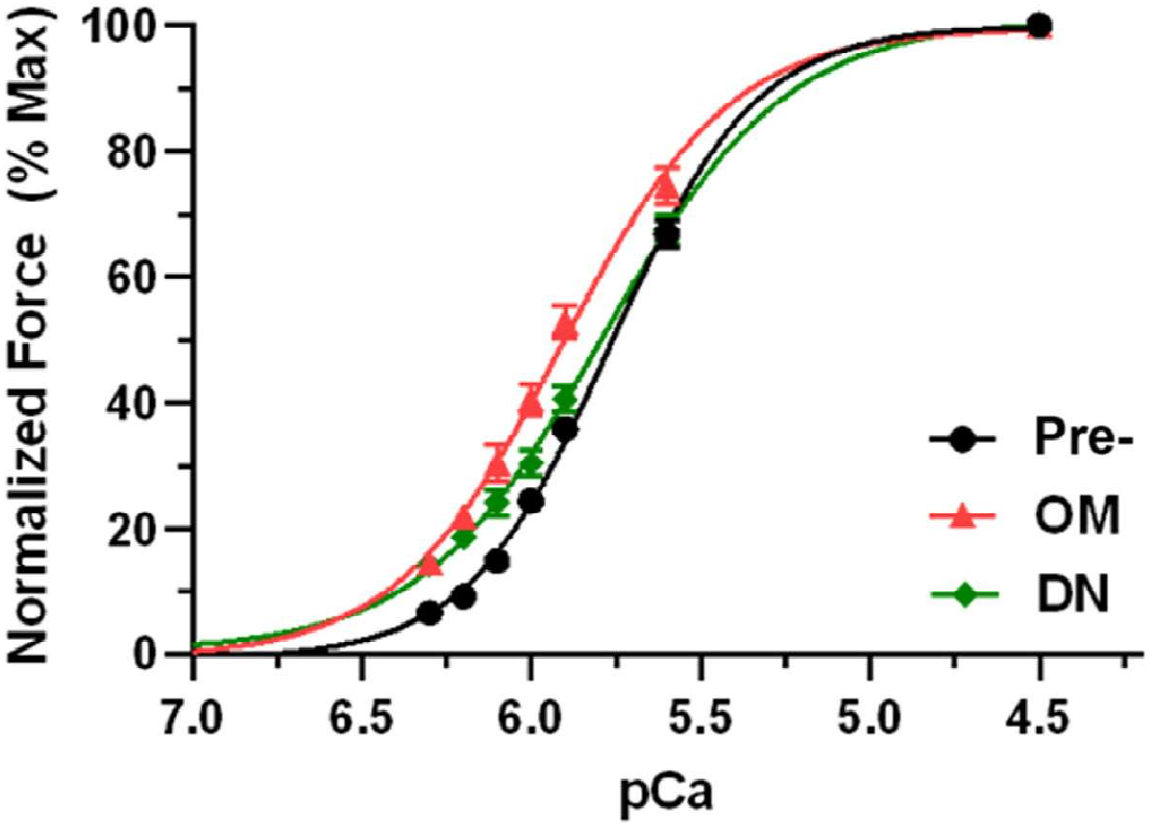


ournal of the American Heart Association

RIGINAL RESEARCH

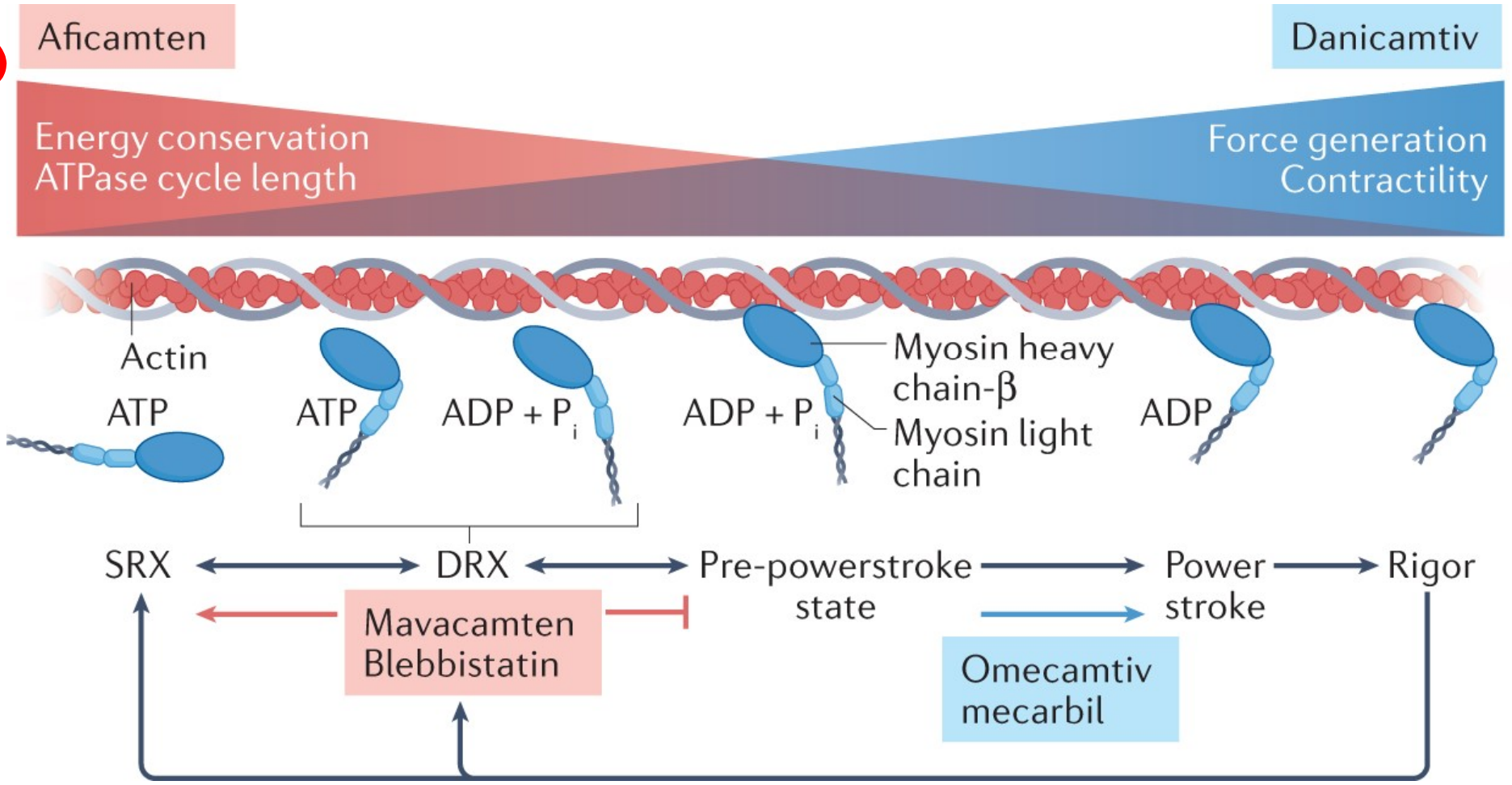
Effect of the Novel Myotrope Danicamtiv on Cross-Bridge Behavior in Human Myocardium

ohee Choi, PhD; Joshua B. Holmes, BS; Kenneth S. Campbell, PhD; Julian E. Stelzer, PhD



Choi et al., J Am Heart Assoc. 2023;12:e030682.

From myosin activation to myosin inhibition



Lehman et al., Nature Reviews Cardiology 19, 353–363,

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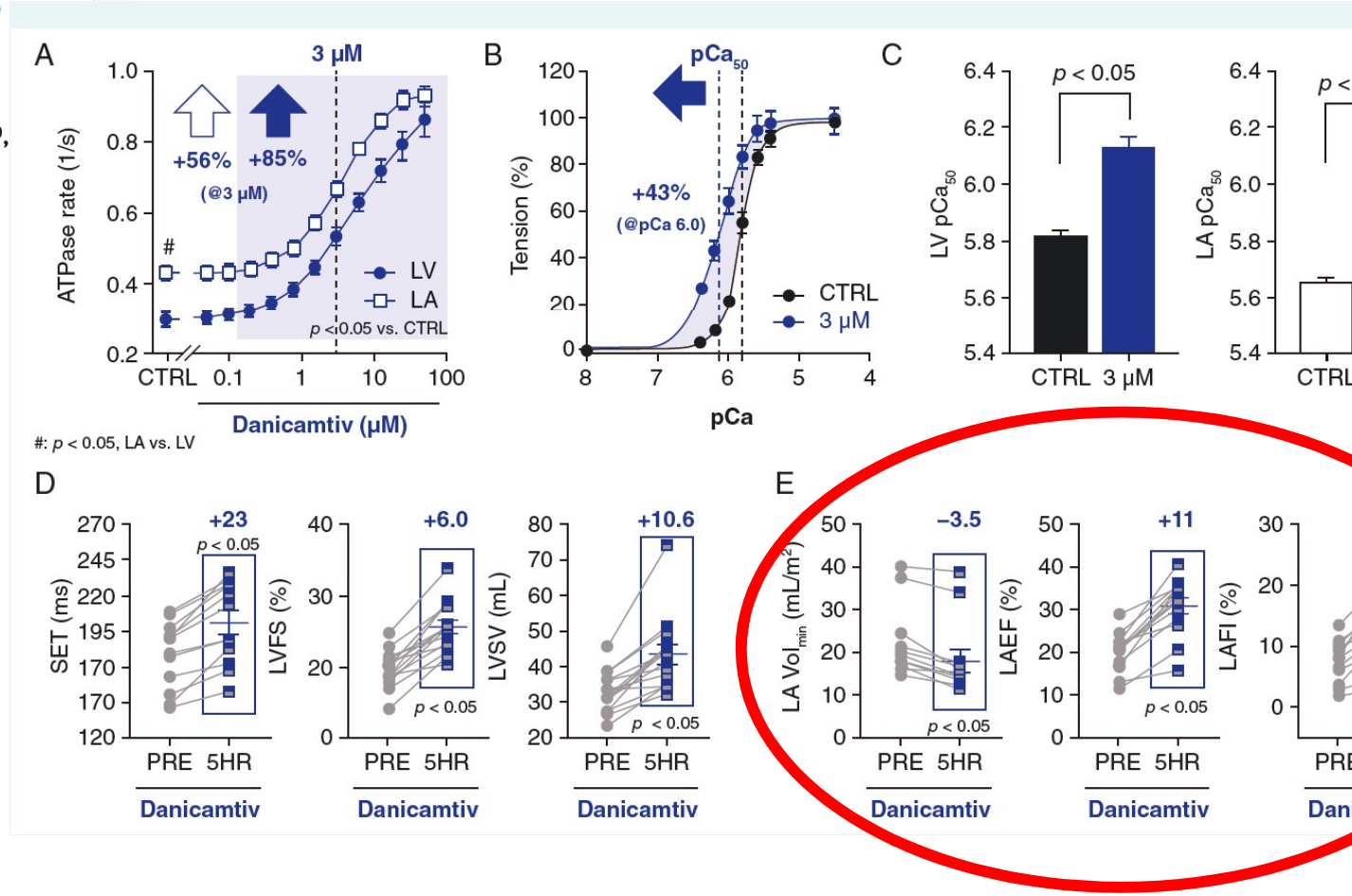
European Journal of Heart Failure (2020) 22, 1649–1658
doi:10.1002/ejhf.1933

RESEARCH ARTICLE

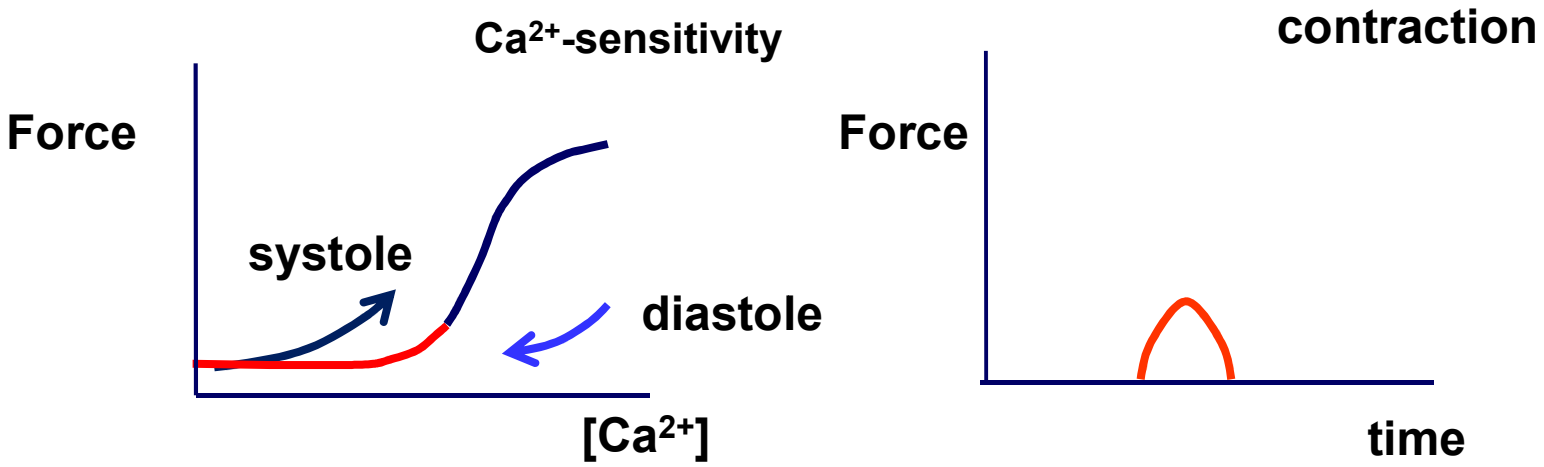
ts of danicamtiv, a novel cardiac myosin ator, in heart failure with reduced ejection ion: experimental data and clinical results a phase 2a trial

A. Voors[1]*, Jean-François Tamby[2], John G. Cleland[3], Michael Koren[4], Forgosh[5], Dinesh Gupta[6], Lars H. Lund[7,8], Albert Camacho[9], Ravi Karra[10], Swart[11], Pierpaolo Pellicori[3], Frank Wagner[12], Ray E. Hershberger[13], a Prasad[14], Robert Anderson[2], Anu Anto[2], Kaylyn Bell[2], Jay M. Edelberg[2], ng[2], Marcus Henze[2], Cynthia Kelly[2], Gregory Kurio[2], Wanying Li[2], lls[2], Chun Yang[2], Sam L. Teichman[15], Carlos L. del Rio[2], t D. Solomon[16]

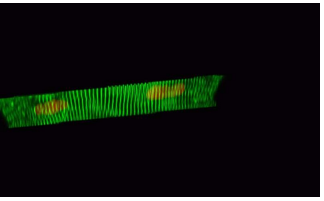


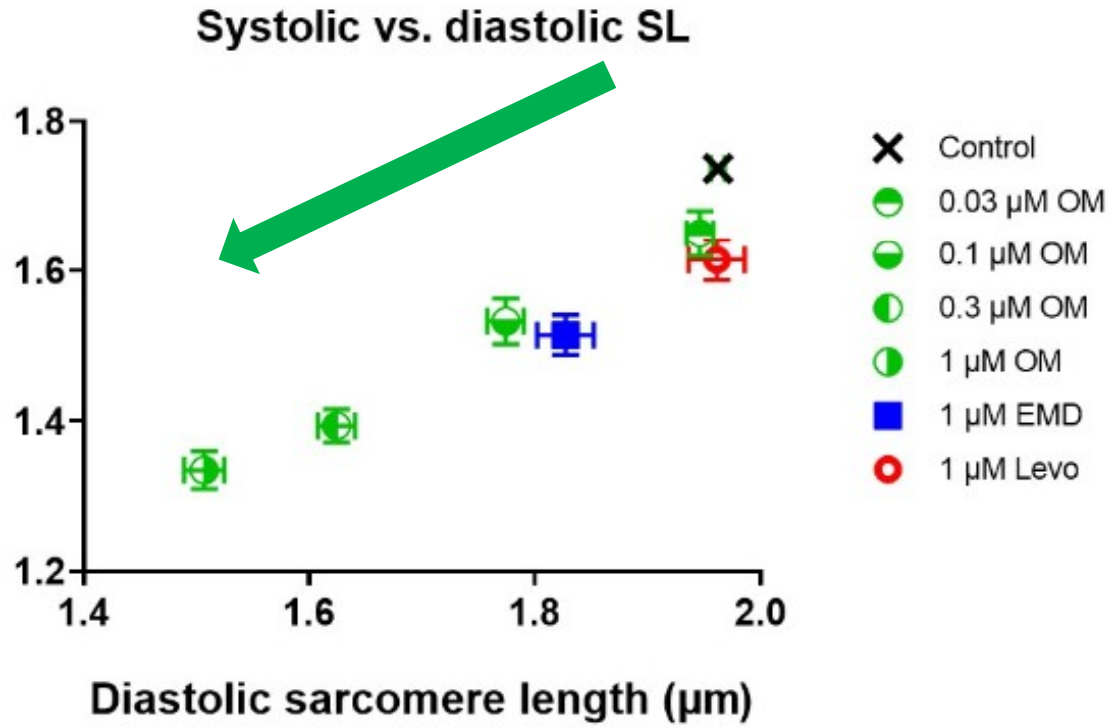
Voors et al., Eur J Heart Fail. 2020 Sep;22(9):1649-165

Ca^{2+}-sensitivity and contractile force under steady-state conditions



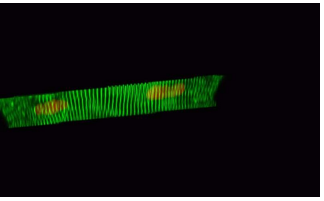
Changes in diastolic sarcomere length are associated with those in systolic sarcomere length/contraction duration

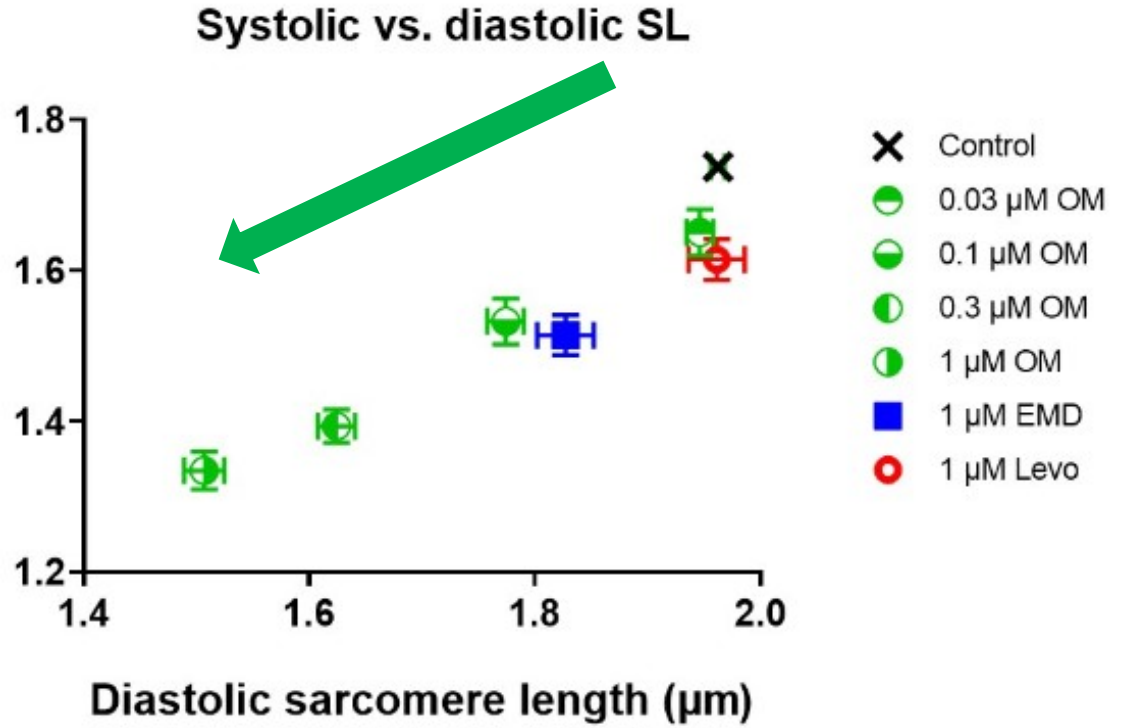


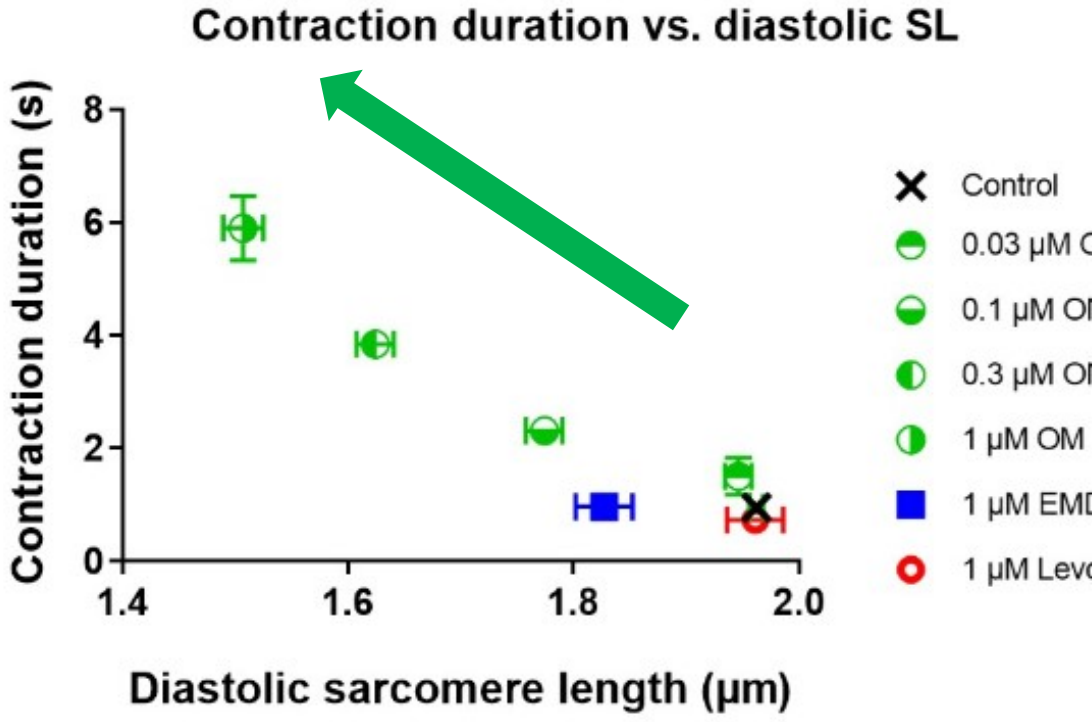


Ráduly A…Papp Z. et al. ESC Heart Fail. 2023 Apr;10(2):1326-

Changes in diastolic sarcomere length are associated with those in systolic sarcomere length/contraction duration







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