Remodeling the failing heart: :
the biology and future treatment options

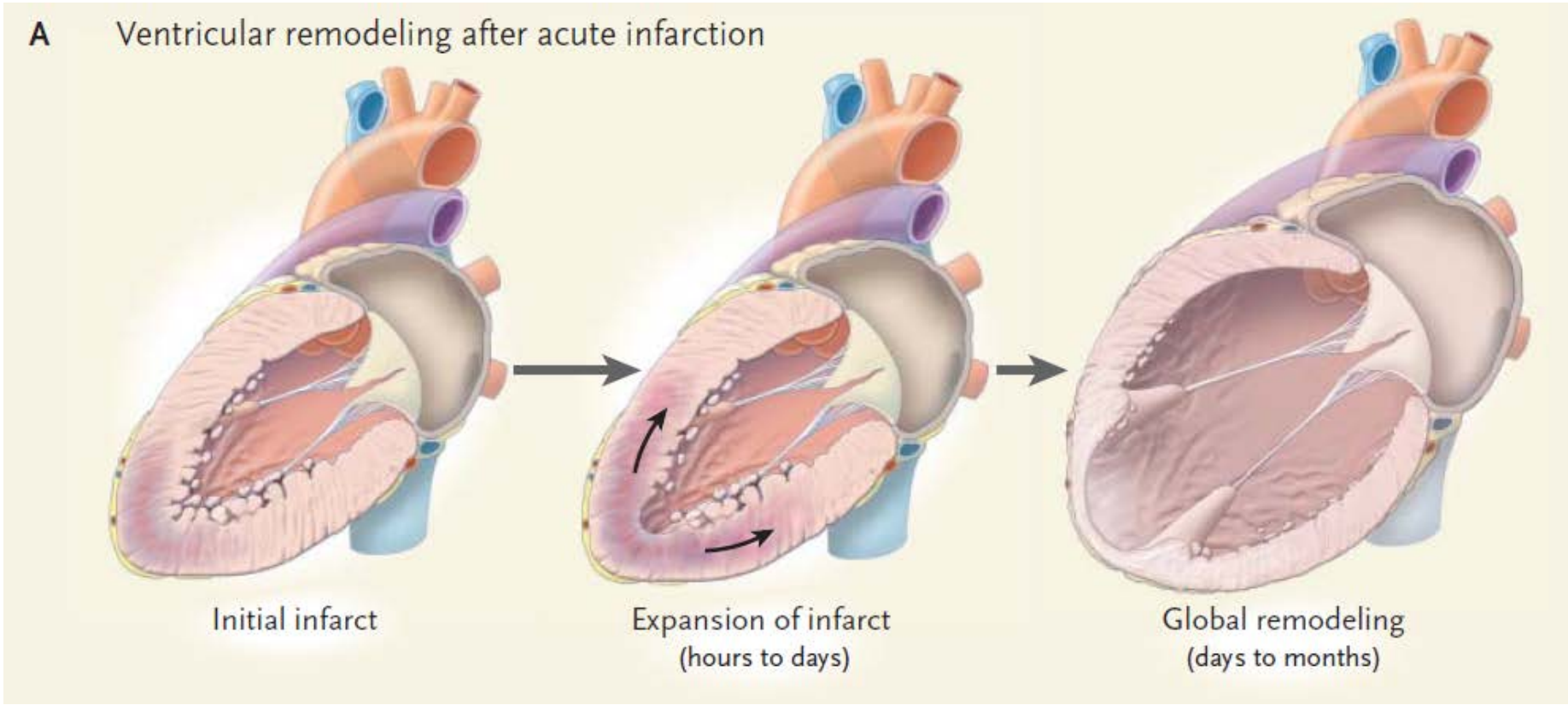
J-L Balligand (UCL-Brussels, BE)

jl.balligand@uclouvain.be

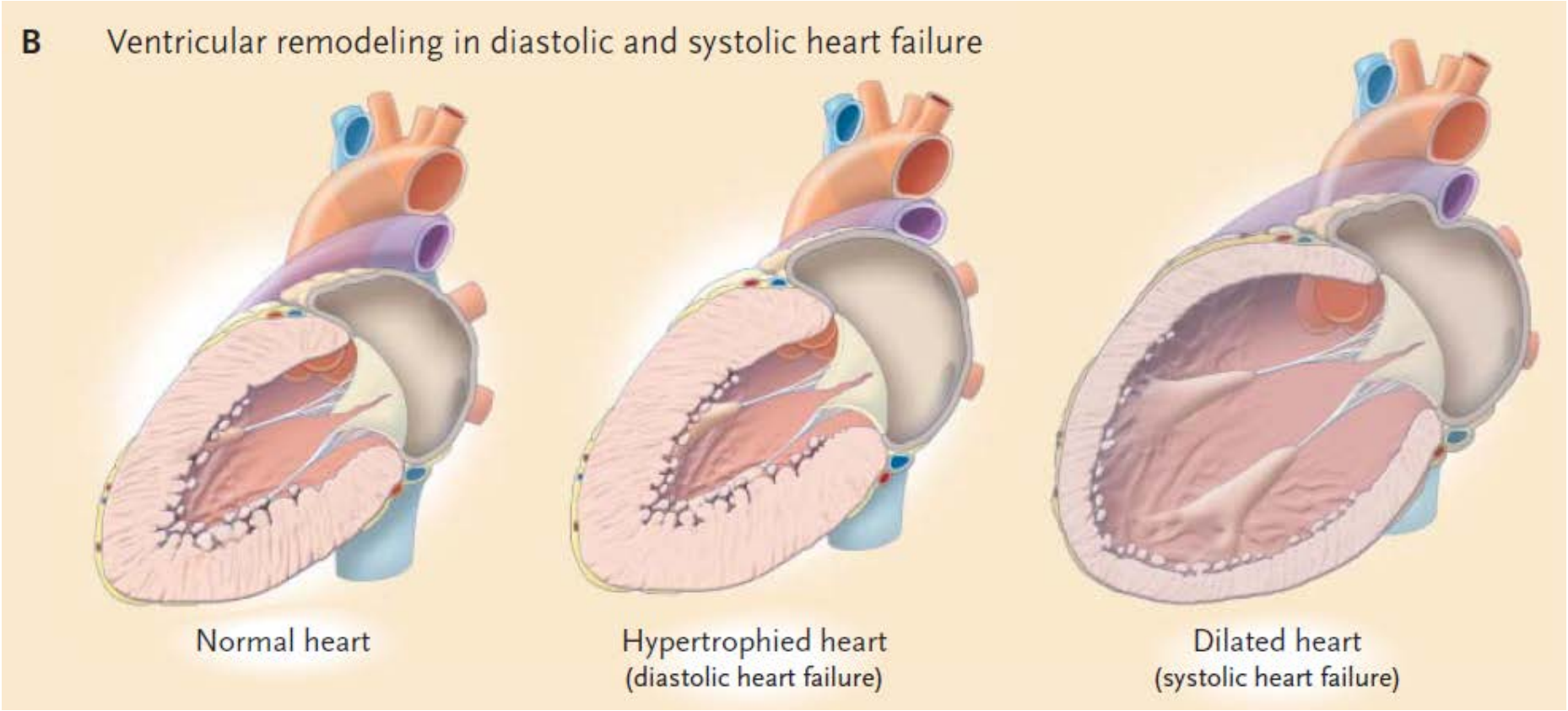
Myocardial remodeling: definitions

- phenotypic **plasticity** : remodeling is characterized by changes in myocardial structure that happen in response to either mechanical overload or a loss of substance such as that occurring after myocardial infarction.

- Myocardial remodeling is an essential mechanism that allows for cardiac output to be maintained in the presence of chronically abnormal loading conditions or depressed contractility.

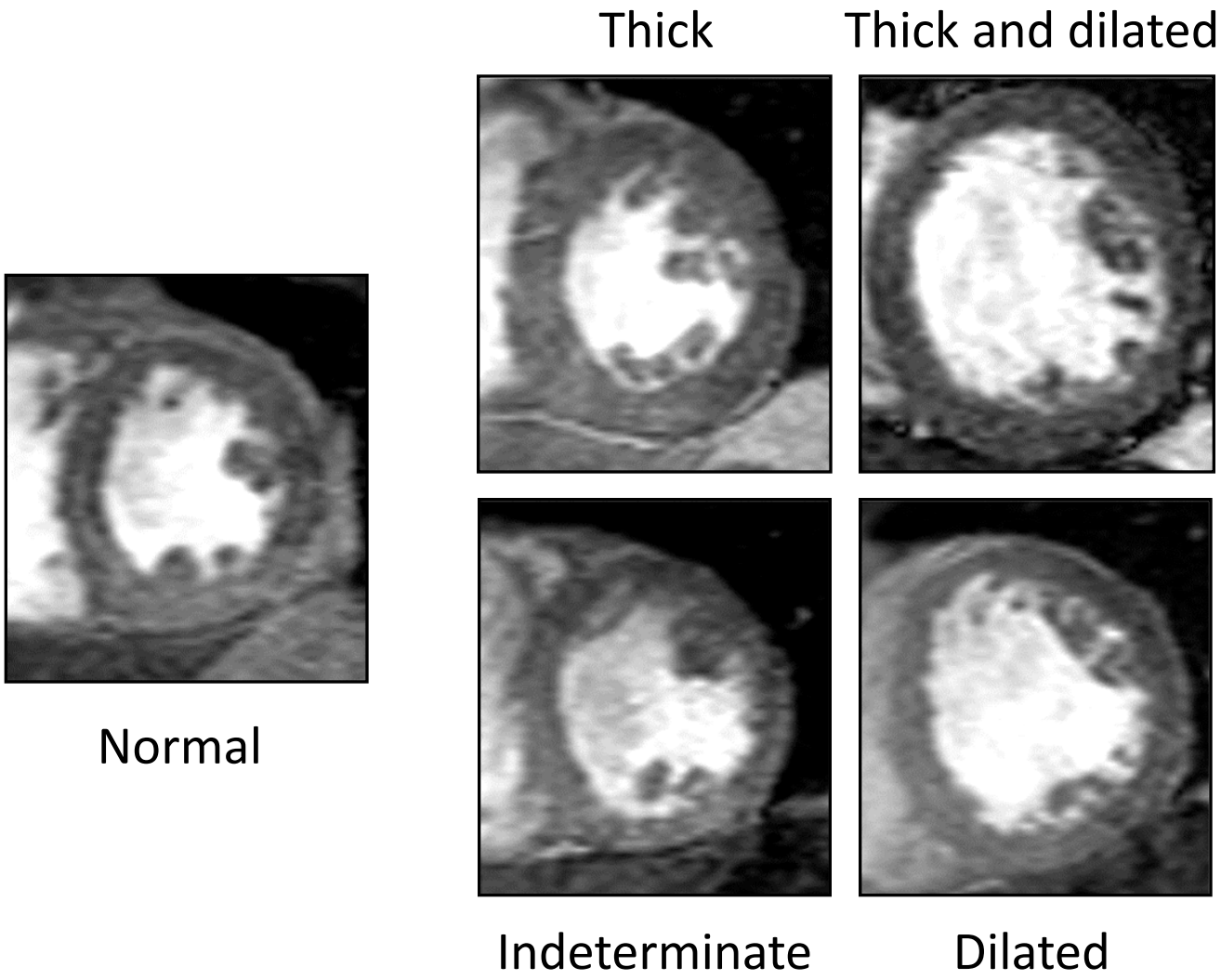


Jessup et al N Engl J Med, 2003 (review)



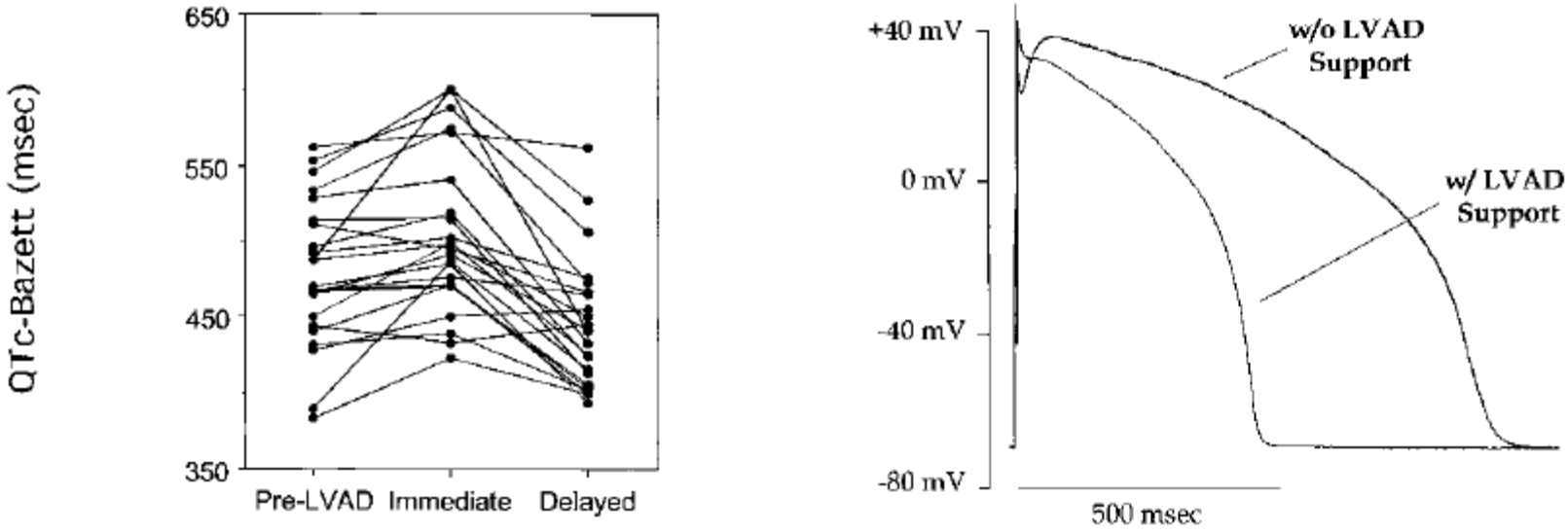
Jessup et al N Engl J Med, 2003 (review)

Patterns of LV remodeling with cardiac magnetic resonance imaging



Khouri MG et al. *Circ Cardiovasc Imaging* (2010) 3;164-171

Reversal of electrical remodeling with LVAD



Harding JD et al ***Circulation*** 2001

Remodeling involves:

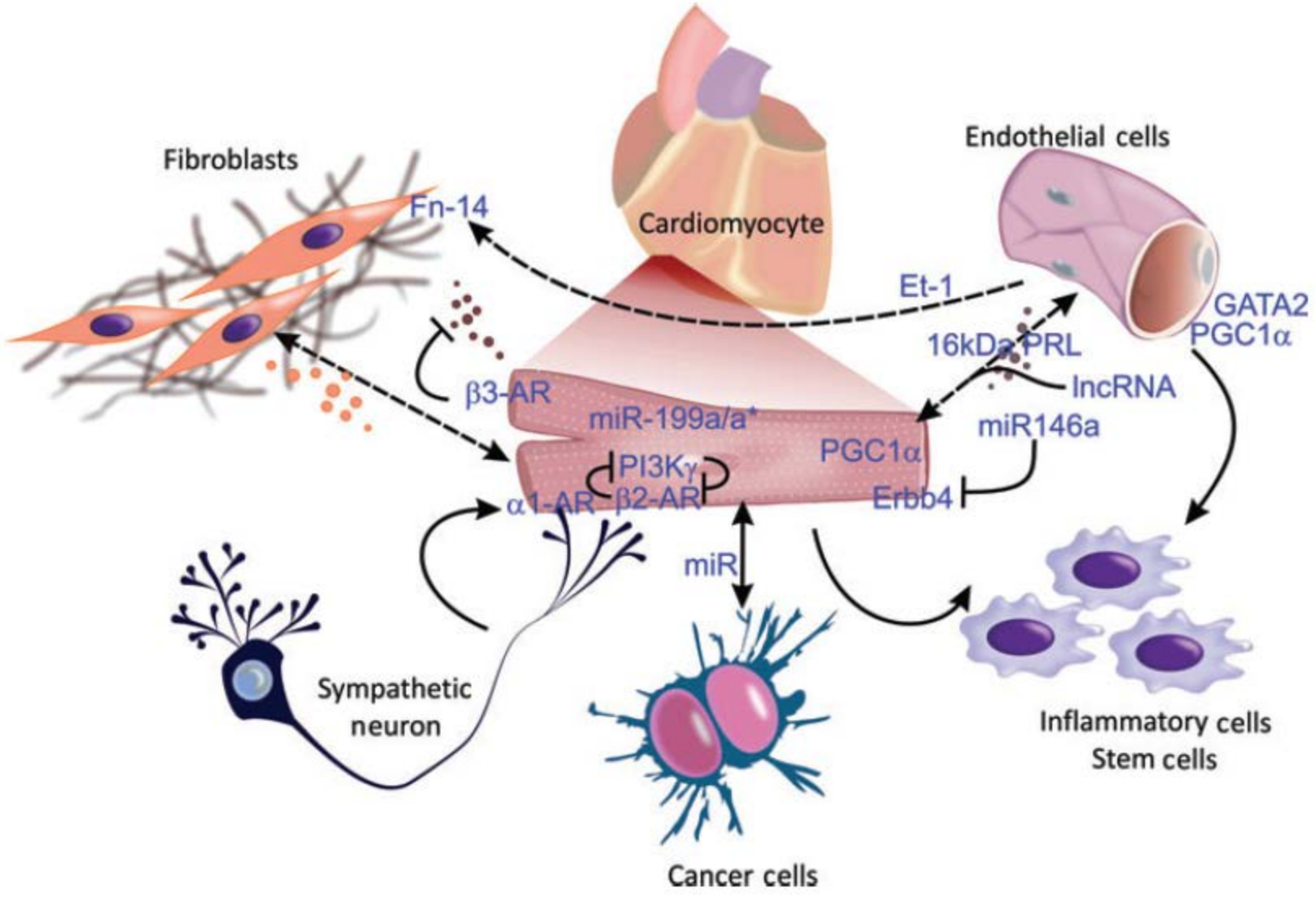
Myocyte changes

Extracellular matrix changes

Microvascular changes

Myocardial regeneration

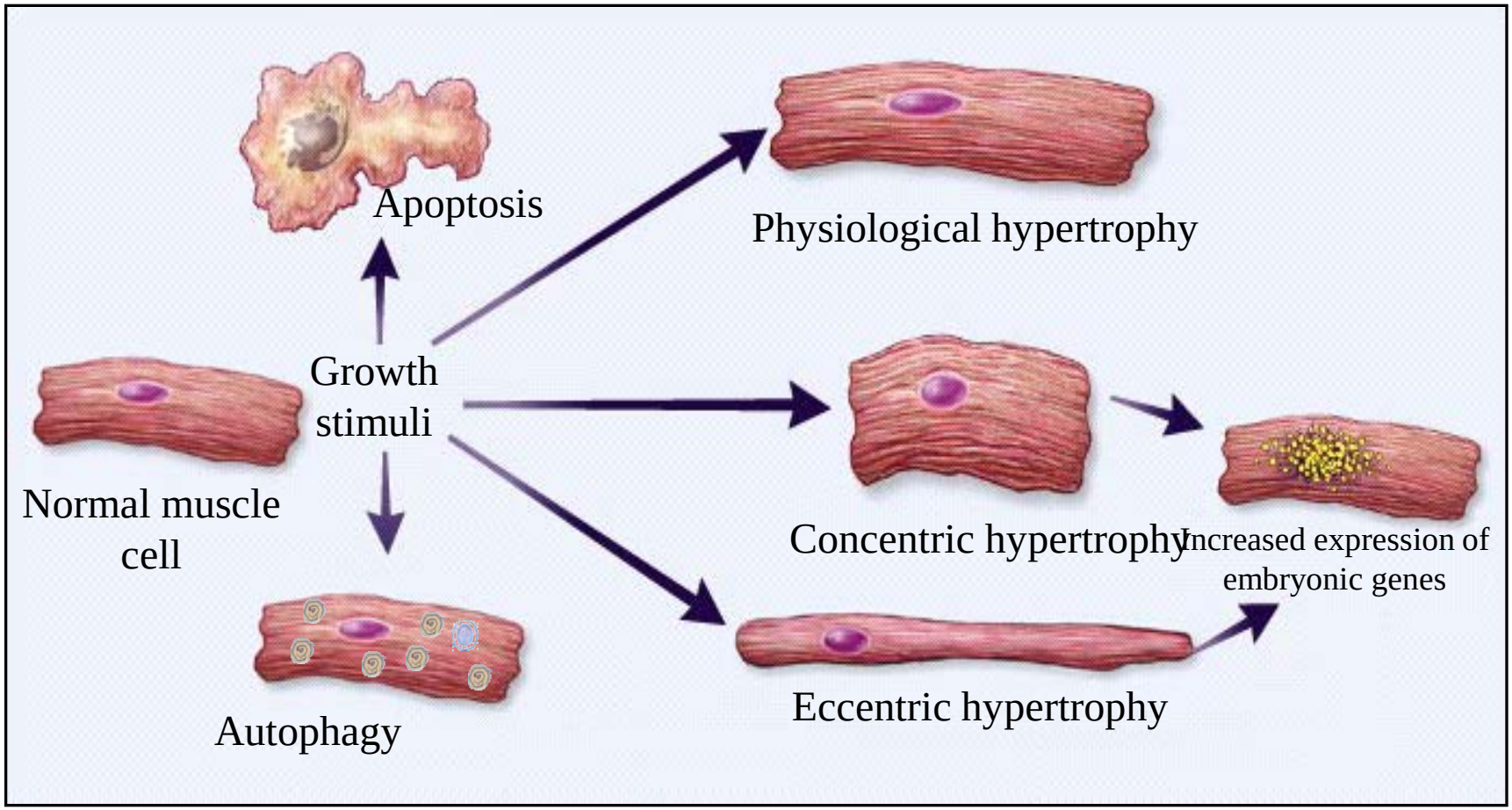
Cell-cell cross-talk

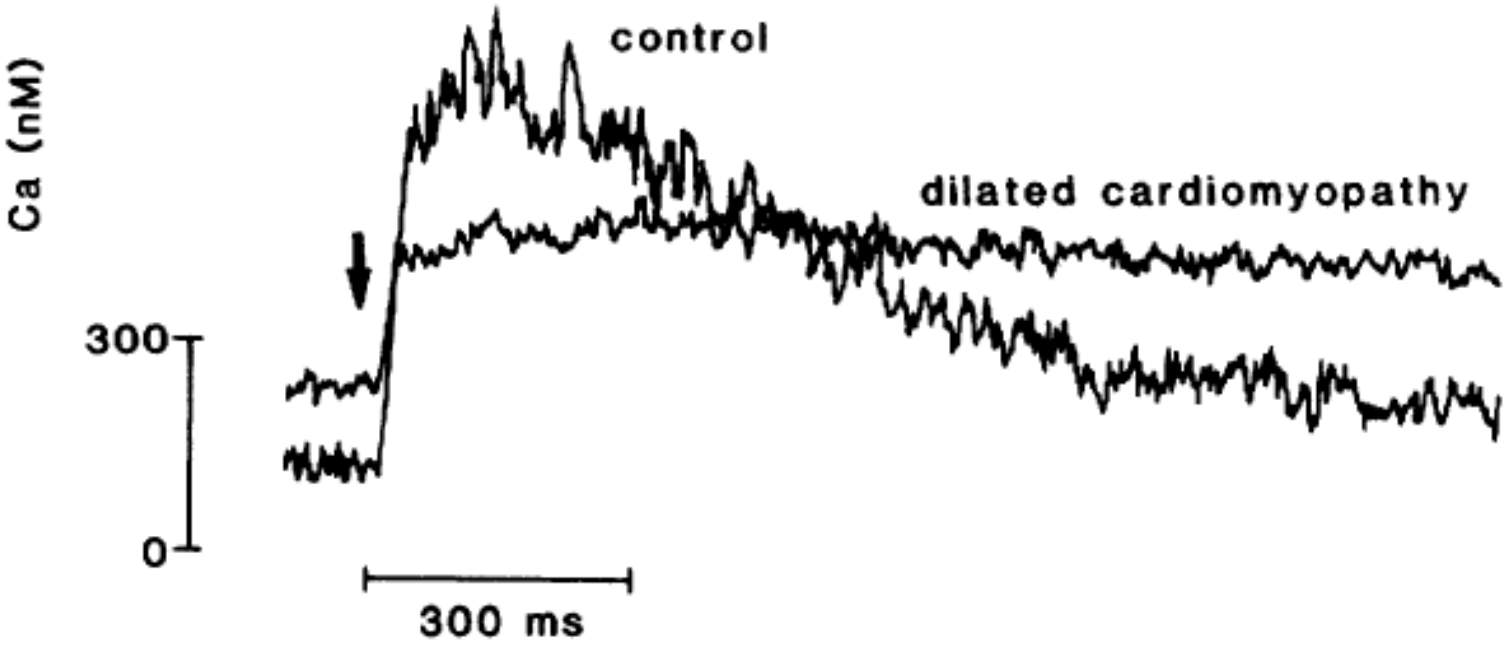


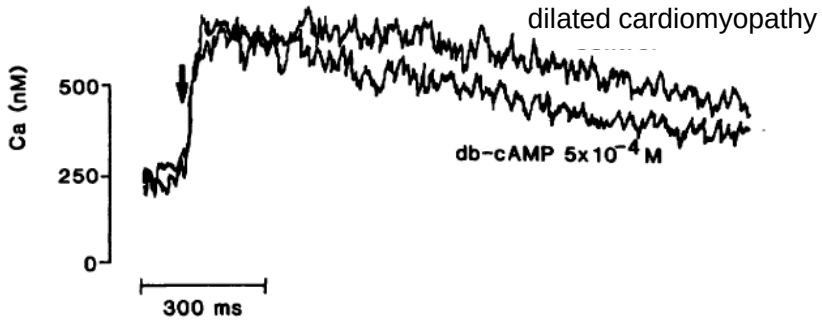
Hirsch E et al on behalf of WG Myocardial Function ESC ***Eur J Heart Fail*** (2013)

Cardiac myocyte

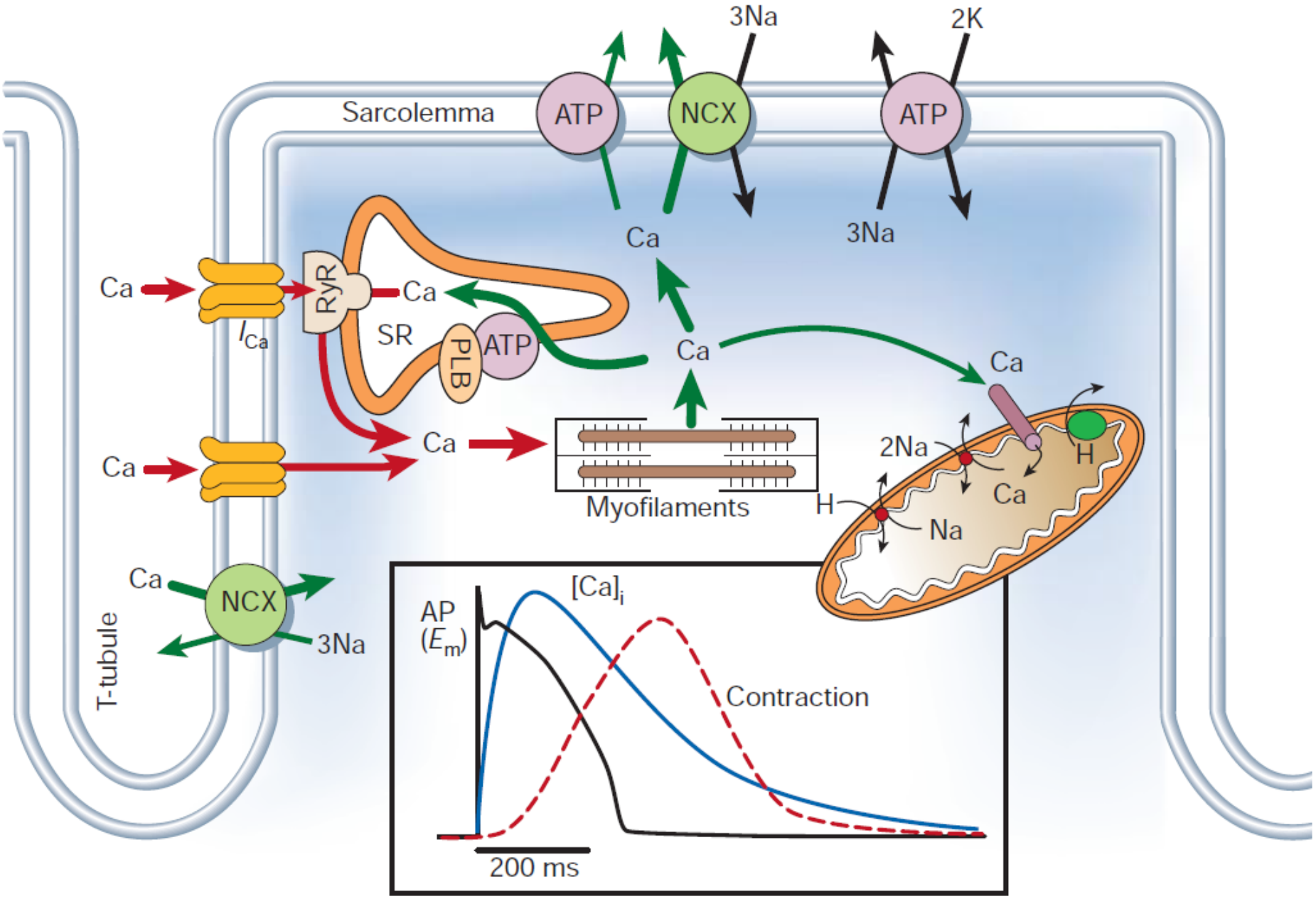
Patterns of myocyte hypertrophy in myocardial remodeling







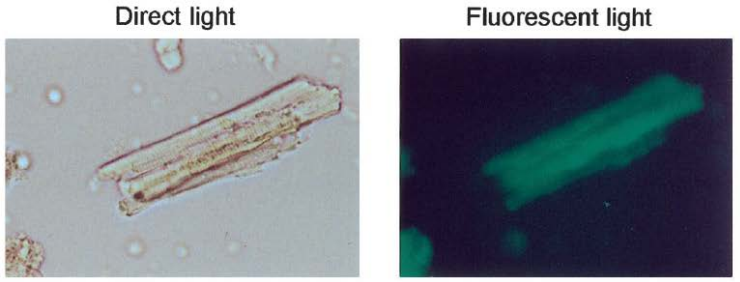
Beuckelmann D et al ***Circulation*** 1992


3Na
2K
Sarcolemma
ATP
NCX
ATP
3Na
Ca
Ca
RyR
Ca
SR
PLB
ATP
Ca
Ca
I_{Ca}
Ca
Ca
Myofilaments
2Na
H
Ca
H
Na
Ca
NCX
3Na
T-tubule
AP
(E_m)
$[Ca]_i$
Contraction
200 ms

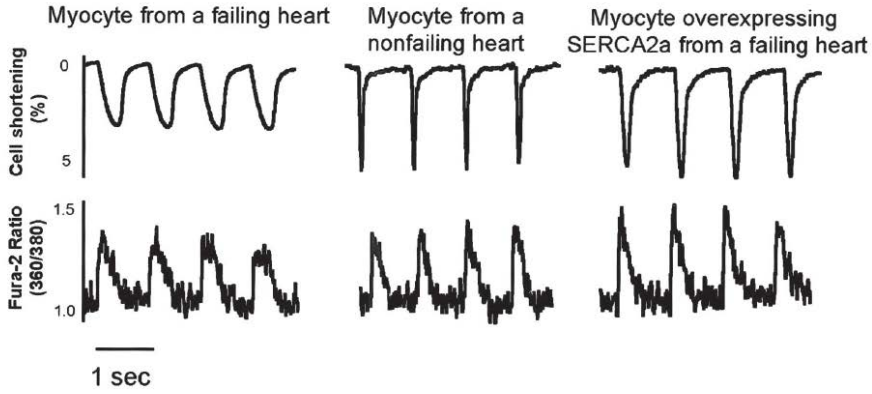
Serca2a

- Gene therapy (AAV1-Serca2a)
- Antagomir (miR-25)
- SUMO-ylation

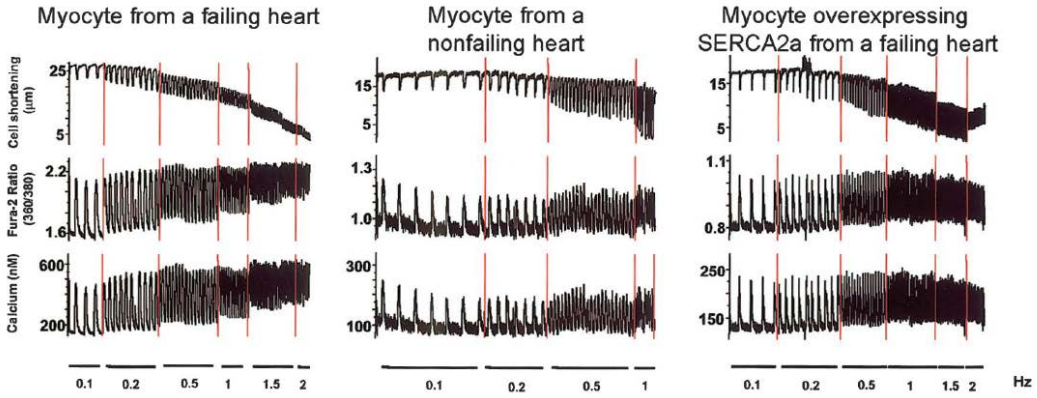
Human myocyte overexpressing SERCA2a



Cell shortening and Ca^{2+} transient



Force-frequency relationship



Del Monte et al ***Circulation*** 1999

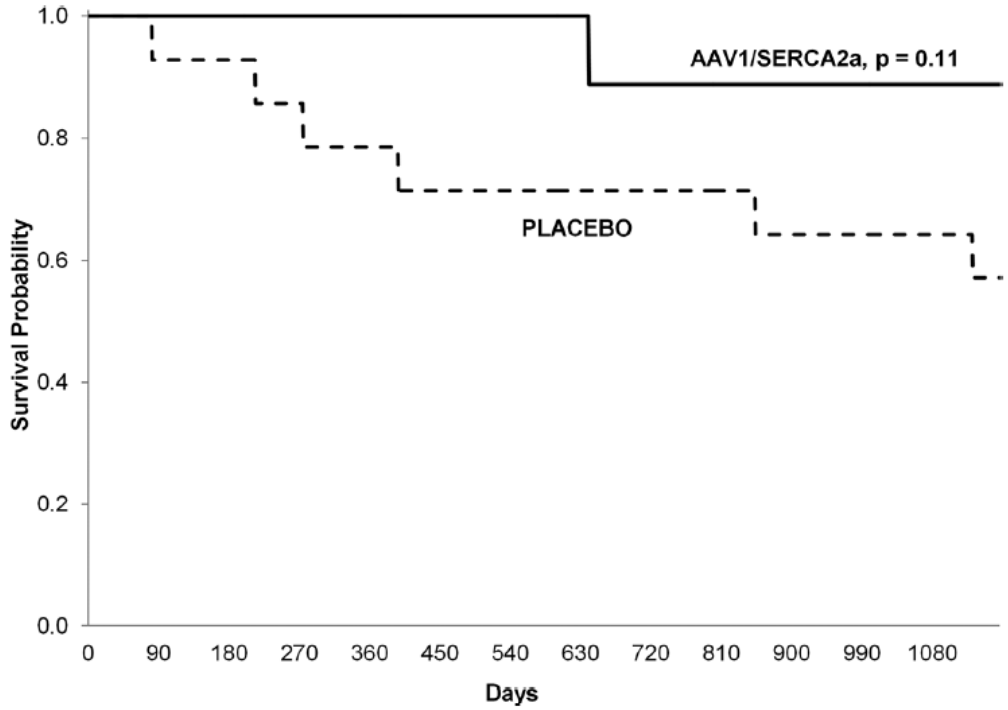


Figure 4. Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease phase 2 survival curve for all-cause mortality in high-dose recombinant adeno-associated viral vector (AAV) containing human sarcoplasmic reticulum Ca^{2+} ATPase2a (SERCA2a) gene (AAV1/SERCA2a) group versus placebo. The survival curve for patients in high-dose AAV1/SERCA2a and the survival curve for the patients in the placebo group demonstrate a much higher survival probability over time for the patients receiving high-dose AAV1/SERCA2a compared with those in the placebo group.

Zsebo K…Hajjar R ***Circ Res*** 2014

Inhibition of *miR-25* improves cardiac contractility in the failing heart

Christine Wahlquist[1]*, Dongtak Jeong[2]*, Agustin Rojas-Muñoz[1], Changwon Kho[2], Ahyoung Lee[2], Shinichi Mitsuyama[2], Alain van Mil[1,3], Woo Jin Park[4], Joost P. G. Sluijter[3], Pieter A. F. Doevendans[3], Roger J. Hajjar[2] & Mark Mercola[1]

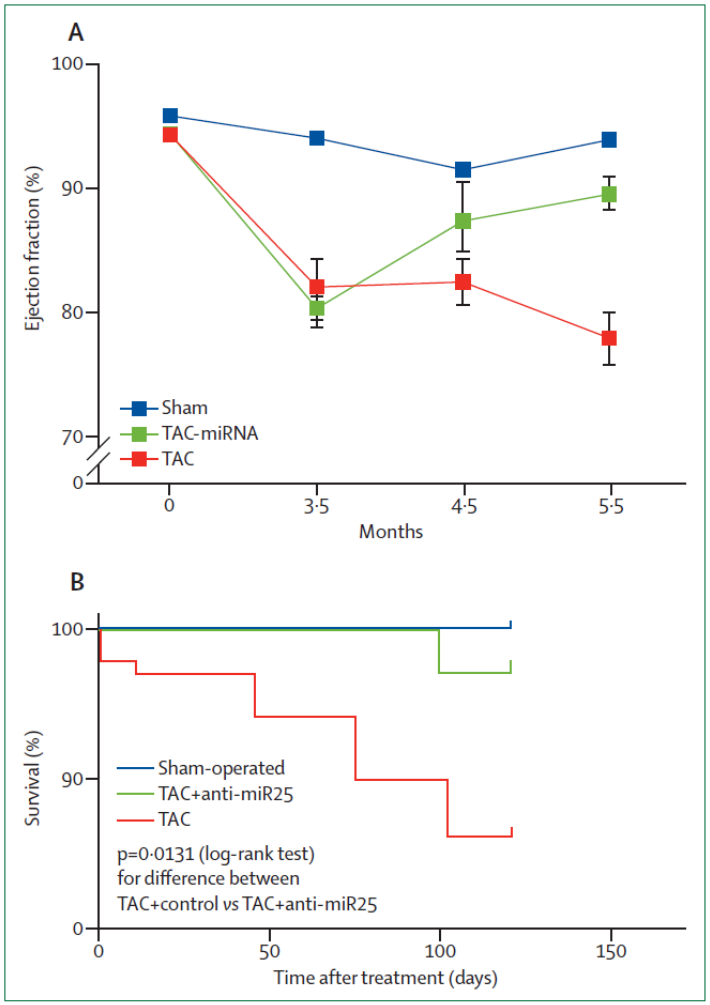


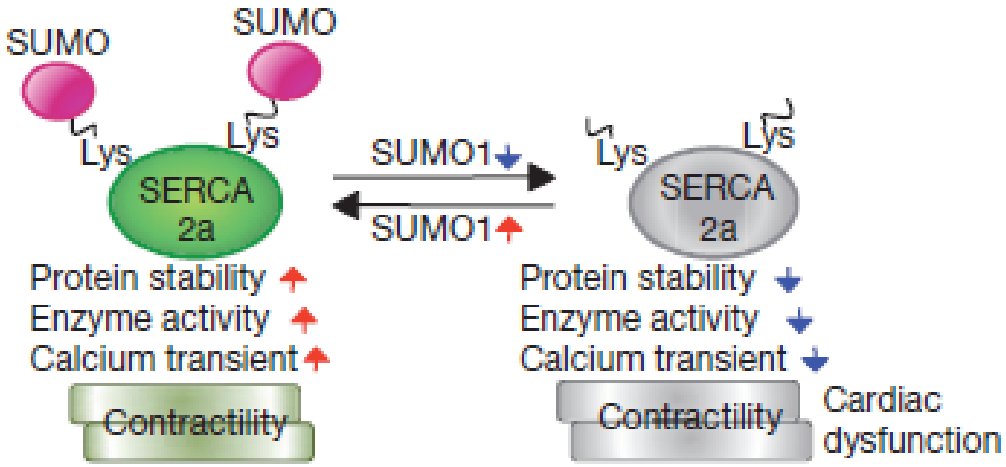
Figure 4: **Effect on the left ventricular ejection fraction (A) and survival (B) in mice**

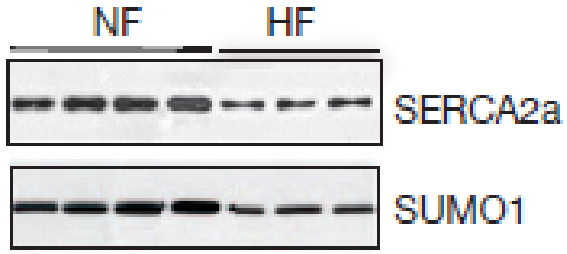
Kaplan-Meier survival curves for sham operated mice, mice with thoracic aortic constriction (TAC) and mice with TAC treated with anti-miR25 (at 3·5 months). Modified from Wahlquist C, Jeong D, Rojas-Muñoz A, et al.[79]

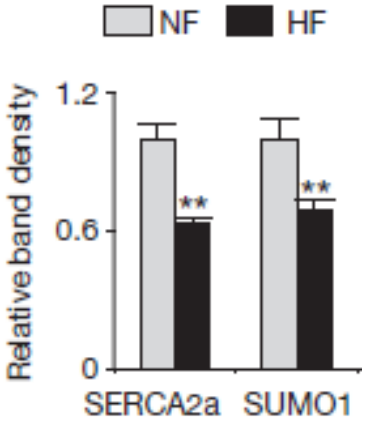
Lancet 2015; 385: 812–24

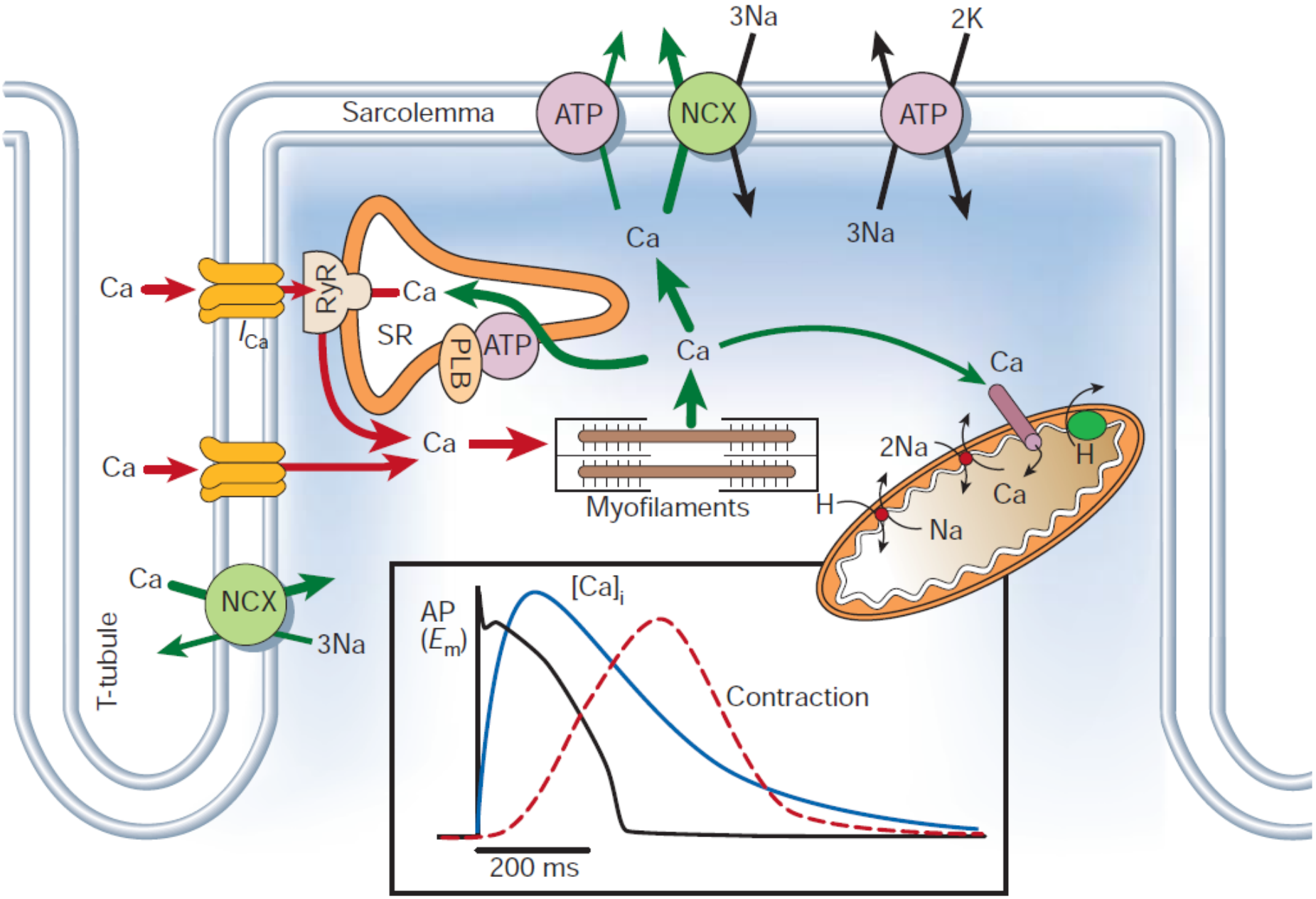
SUMO1–dependent modulation of SERCA2a in heart failure

Changwon Kho[1]*, Ahyoung Lee[1]*, Dongtak Jeong[1], Jae Gyun Oh[2], Antoine H. Chaanine[1], Eddy Kizana[3], Woo Jin Park[2] & Roger J. Hajjar[1]



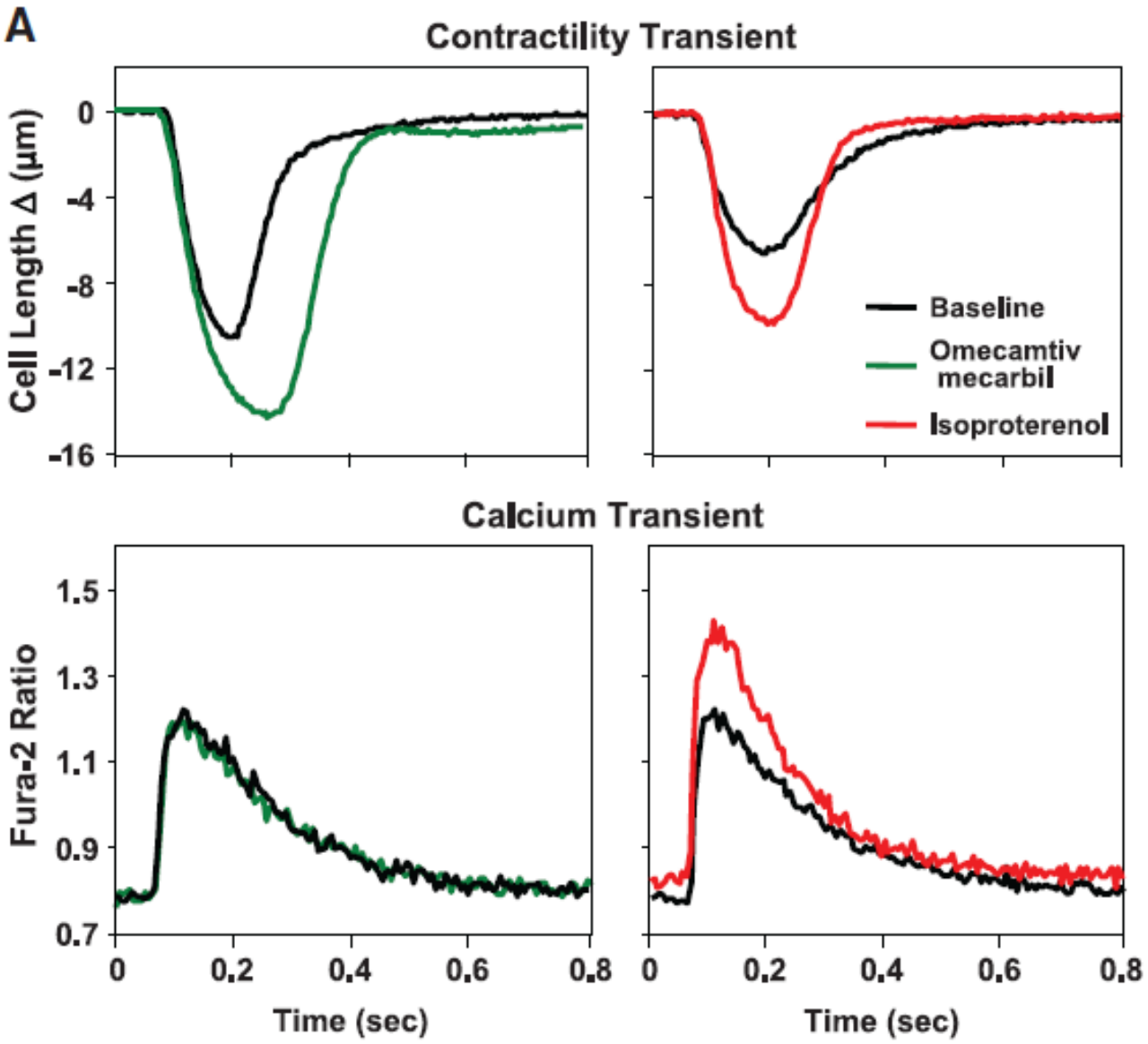




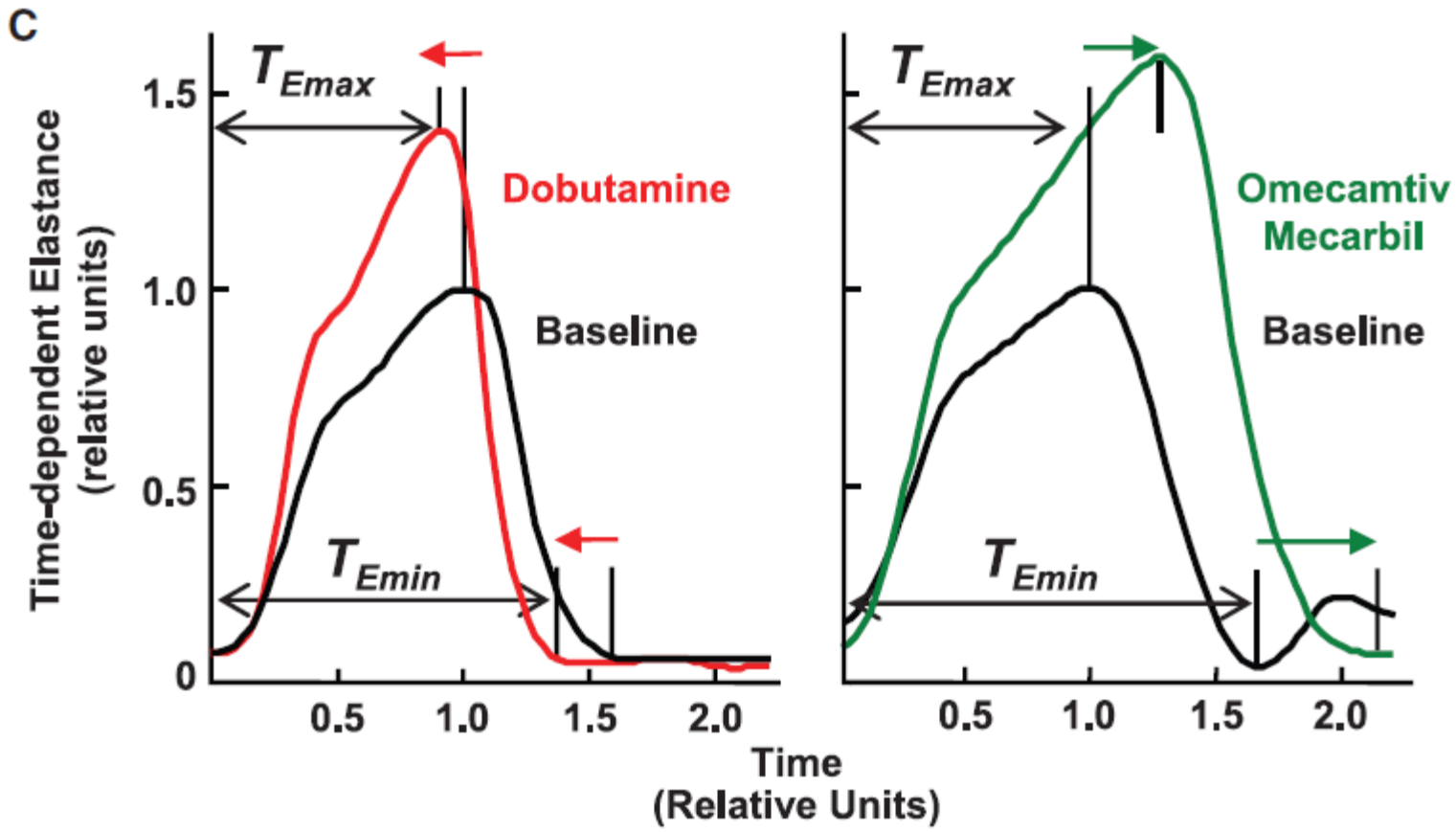

3Na
2K
Sarcolemma
ATP
NCX
ATP
3Na
Ca
Ca
RyR
Ca
SR
PLB
ATP
Ca
Ca
I_{Ca}
Ca
Ca
Myofilaments
2Na
H
Ca
H
Na
Ca
NCX
3Na
T-tubule
AP
(E_m)
$[Ca]_i$
Contraction
200 ms

Myofilaments

- Myosin ATPase: omecantiv mecarbil



Malik F et al ***Science*** 2011



Malik F et al ***Science*** 2011

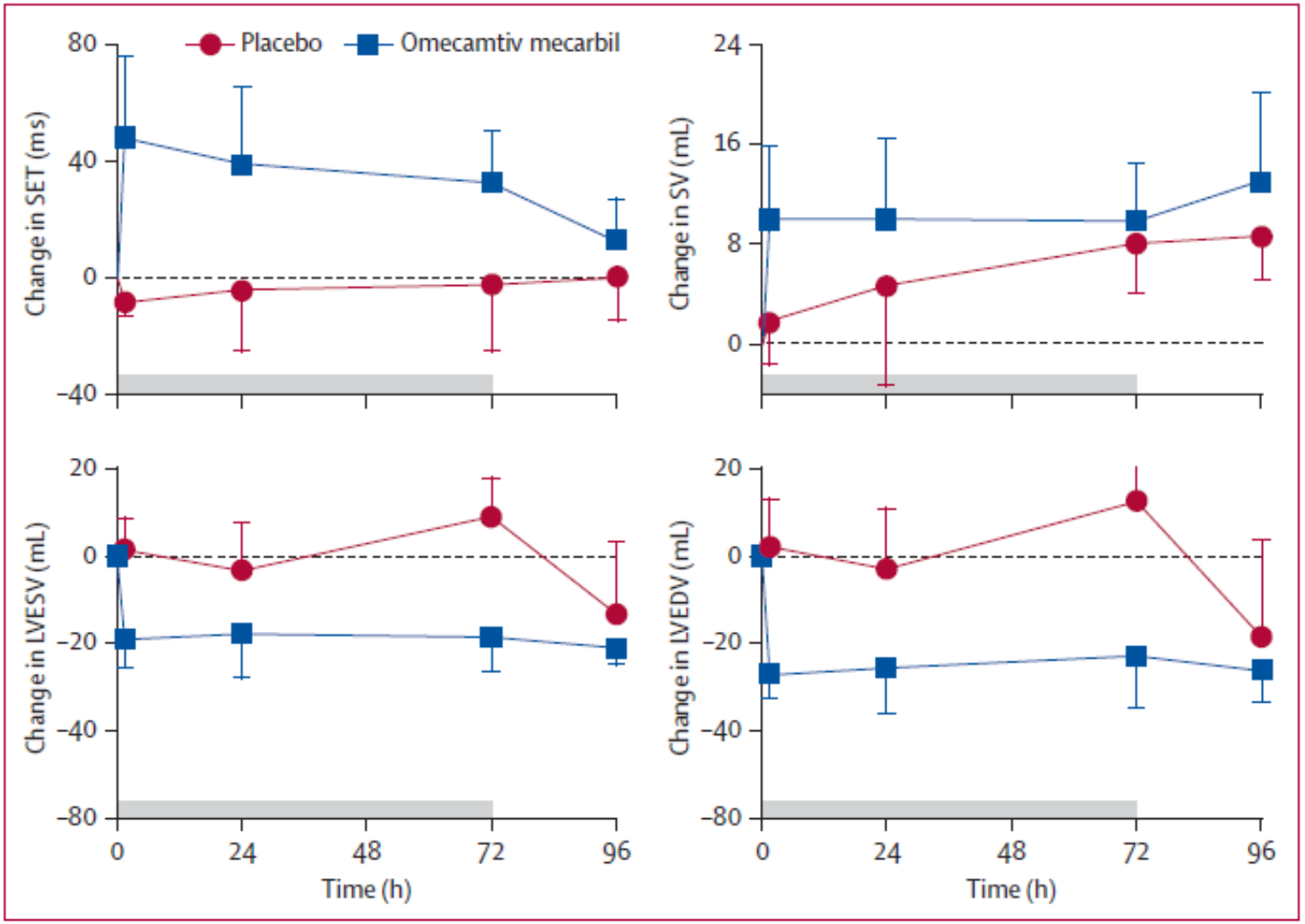


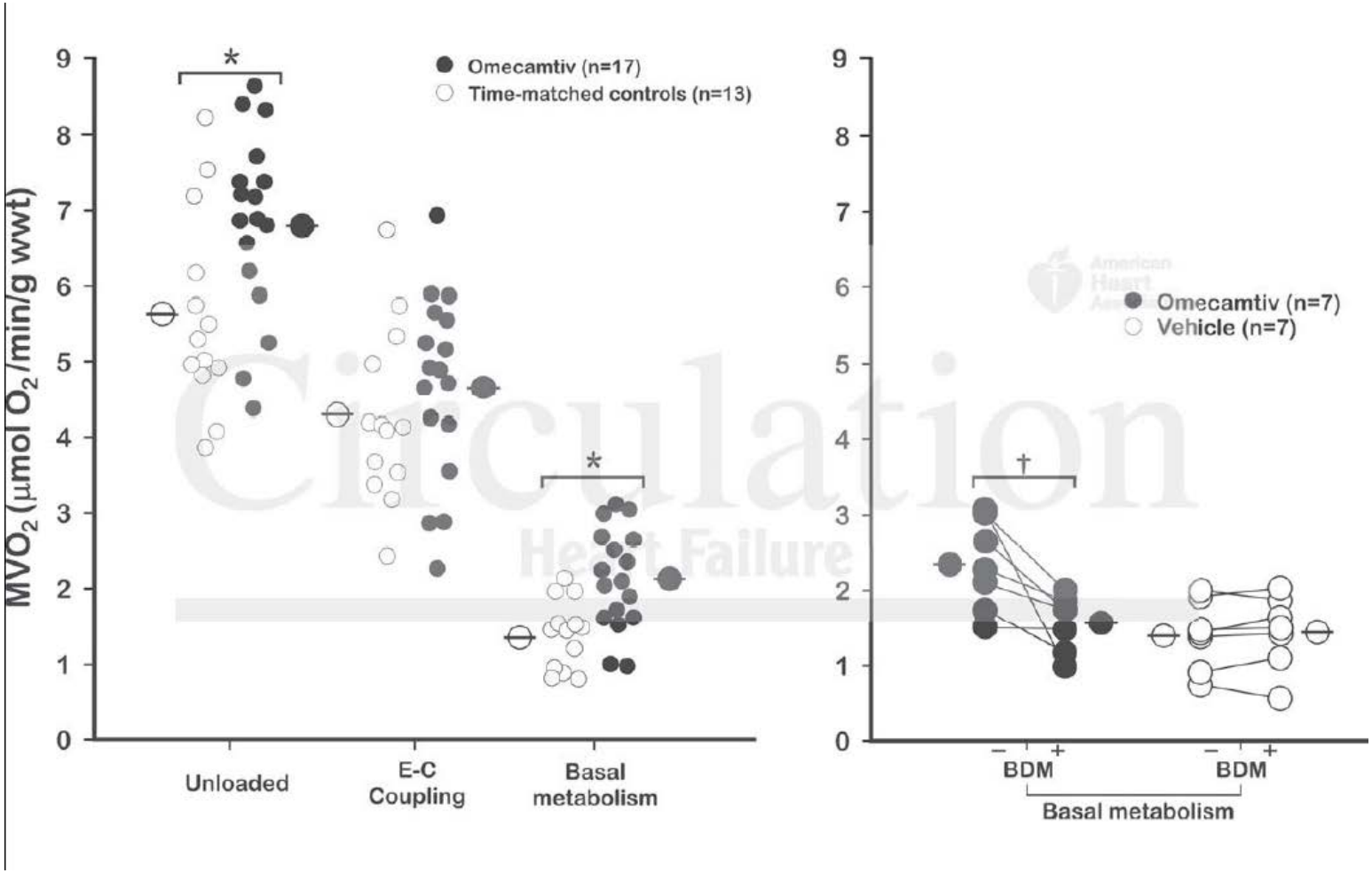
Figure 1: **Time-dependent changes from baseline in key echocardiogram measures for eight patients treated in cohort 5 with 72-h infusions of omecamtiv mecarbil or placebo**

Data are mean; error bars show SEM. Patients received 1·0 mg/kg per h for 1 h, followed by 0·5 mg/kg per h for 1 h, and then 0·1 mg/kg per h for 70 h. SET=systolic ejection time. SV=stroke volume. LVESV=left ventricular end-systolic volume. LVEDV=left ventricular end-diastolic volume.

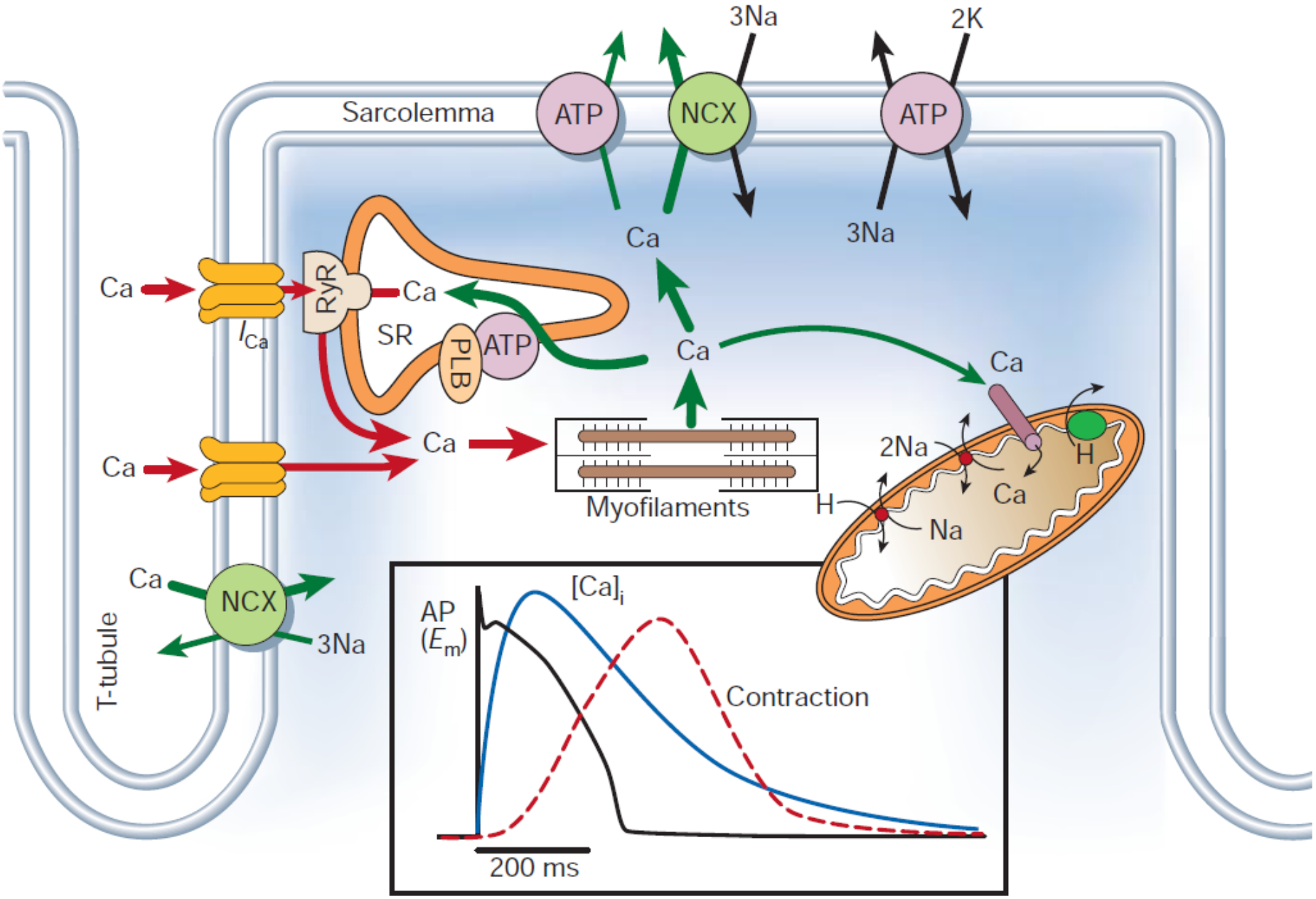
Cleland JGF et al ***Lancet*** 2011

The Myosin Activator Omecamtiv Mecarbil Increases Myocardial Oxygen Consumption and Impairs Cardiac Efficiency Mediated by Resting Myosin ATPase Activity

Jens Petter Bakkehaug, Anders Benjamin Kildal, Erik Torgersen Engstad, Neoma Boardman, Torvind Næsheim, Leif Rønning, Ellen Aasum, Terje S. Larsen, Truls Myrmel and Ole-Jakob How



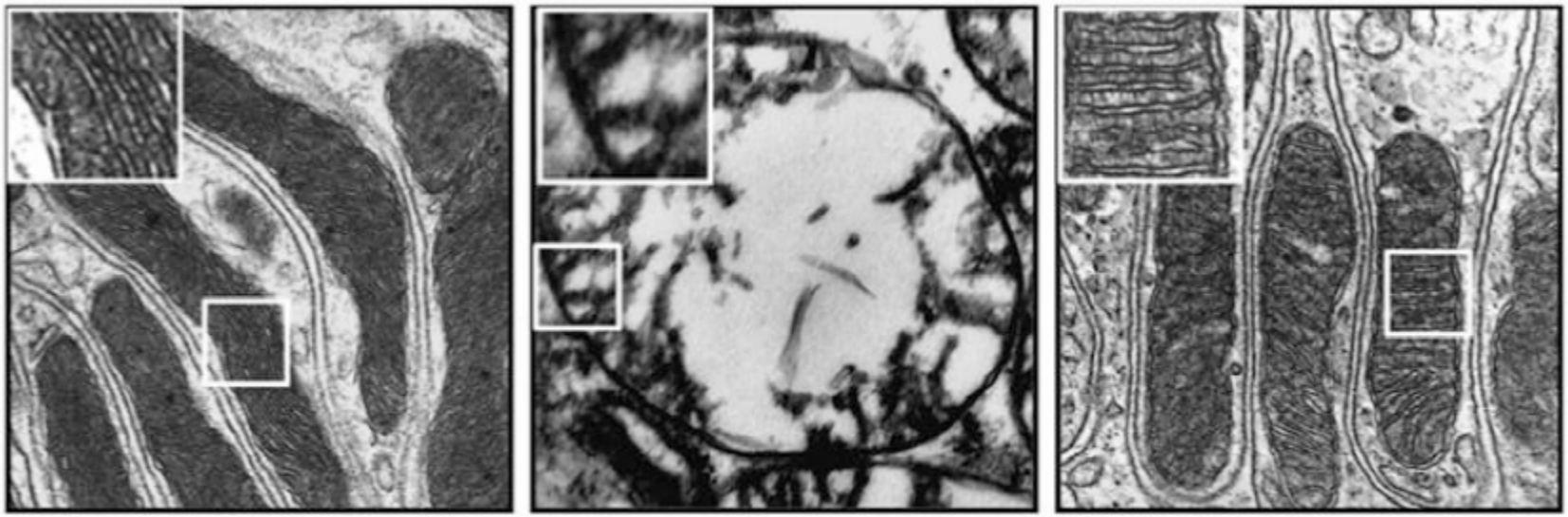
Circ Heart Fail. 2015 May 29. pii: CIRCHEARTFAILURE.114.002152. [Epub ahead of print]

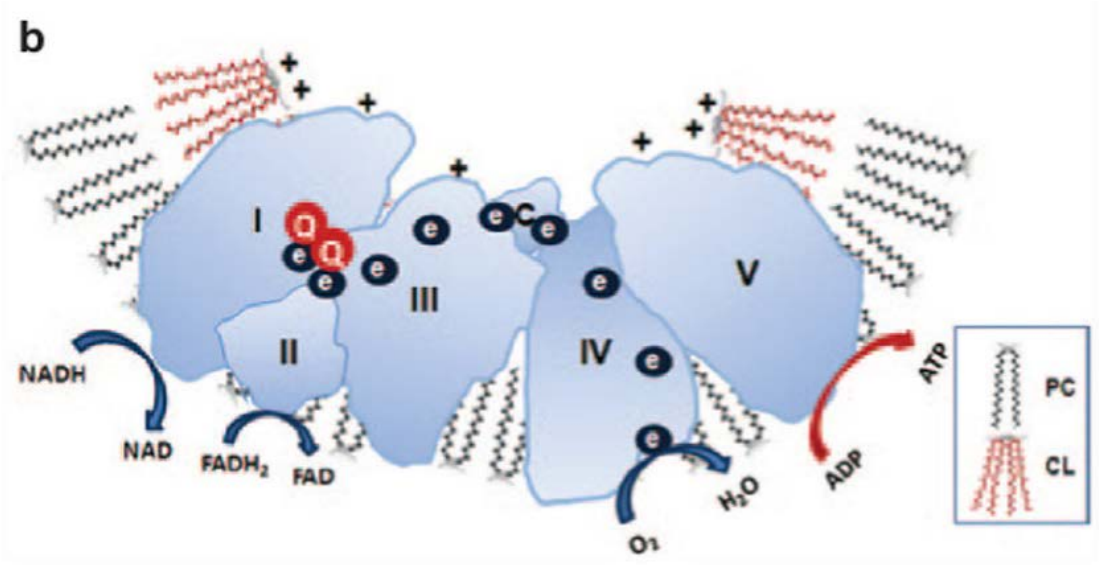

3Na
2K
Sarcolemma
ATP
NCX
ATP
3Na
Ca
Ca
RyR
Ca
SR
PLB
ATP
Ca
Ca
I_{Ca}
Ca
Ca
Myofilaments
2Na
H
Ca
H
Na
Ca
NCX
3Na
T-tubule
AP
(E_m)
$[Ca]_i$
Contraction
200 ms

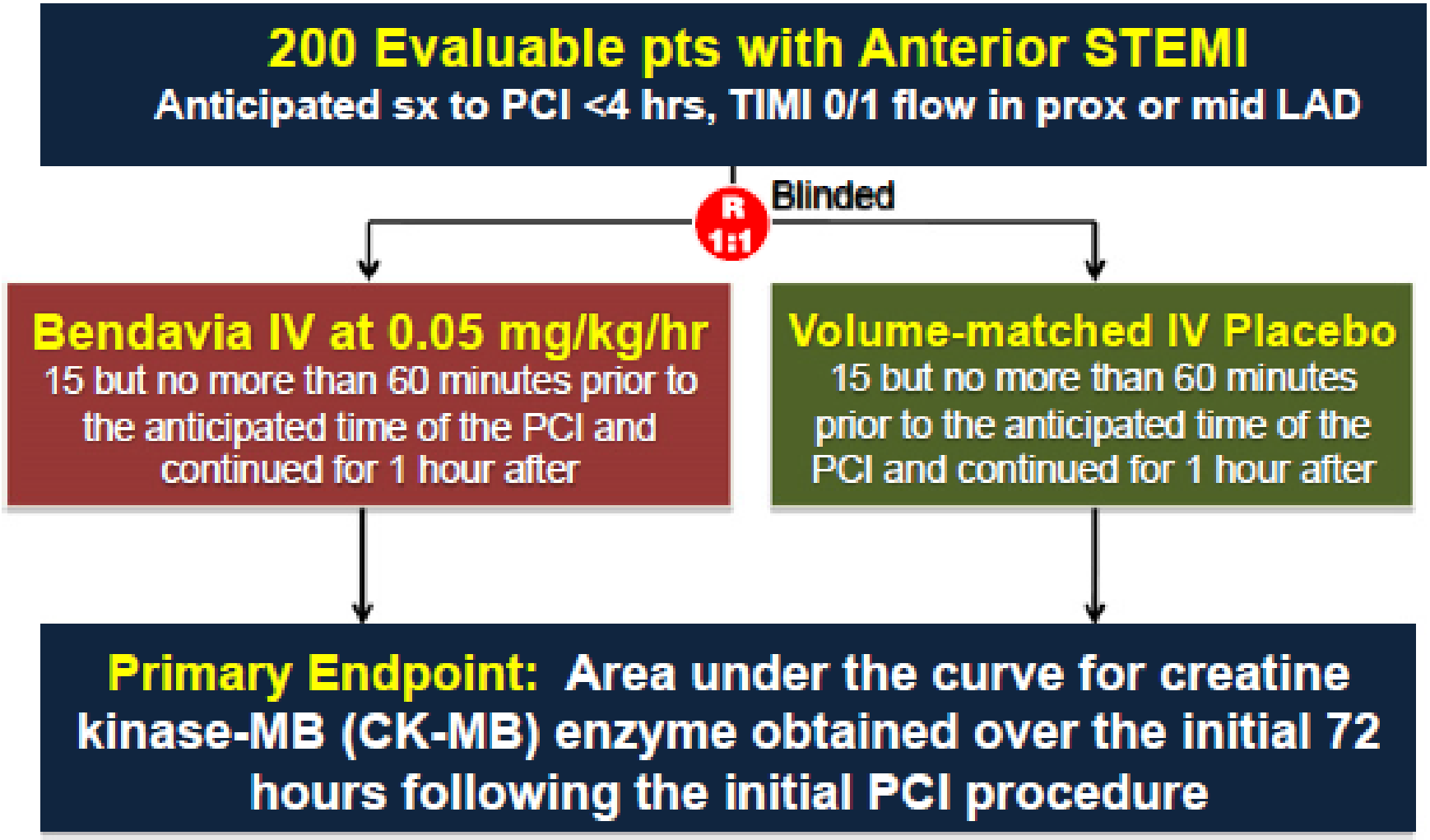
Mitochondria

- Cardiolipin protection by SS peptides

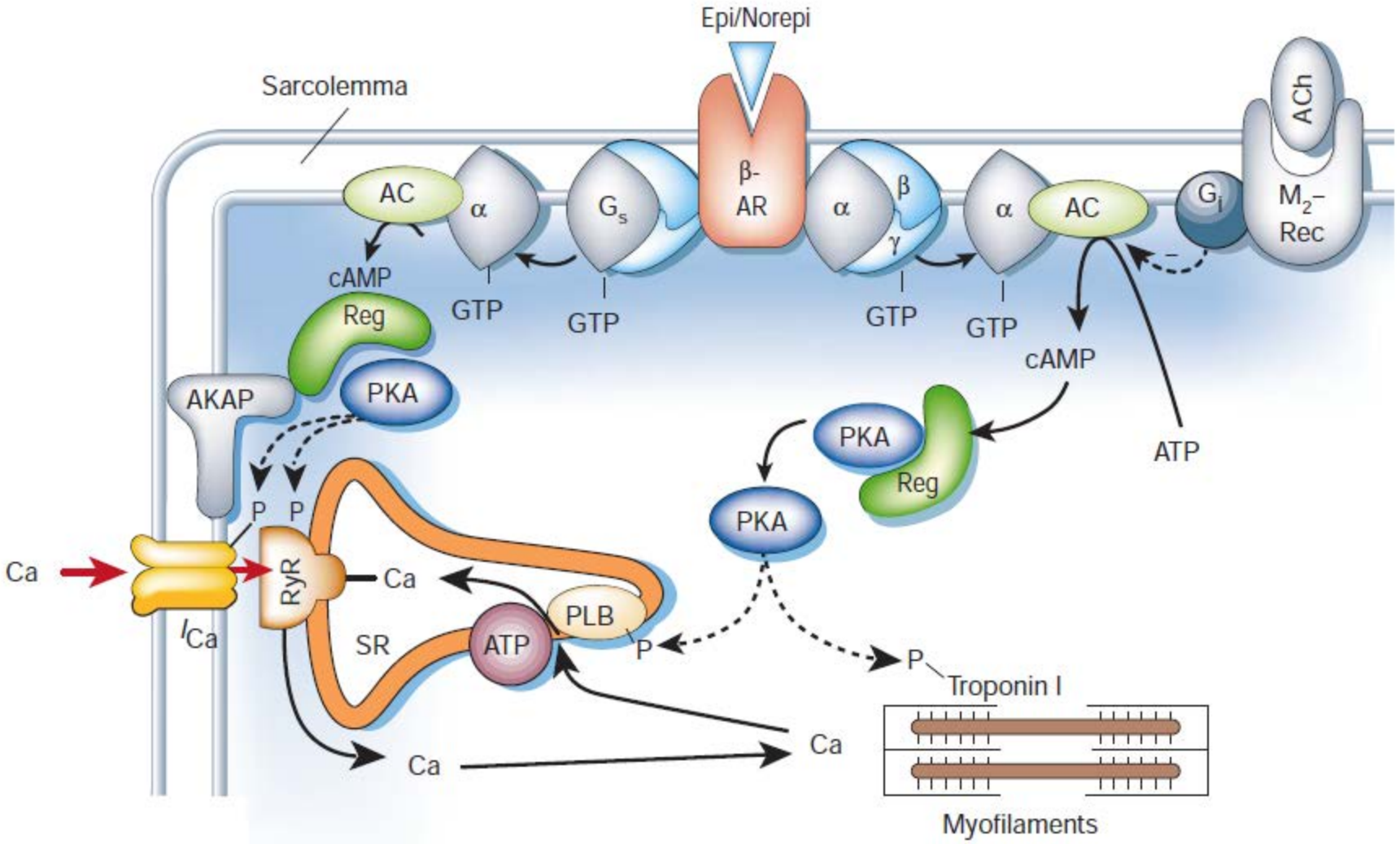
SS peptides protect mitochondria from oxidative damage







EMBRACE-STEMI study design.

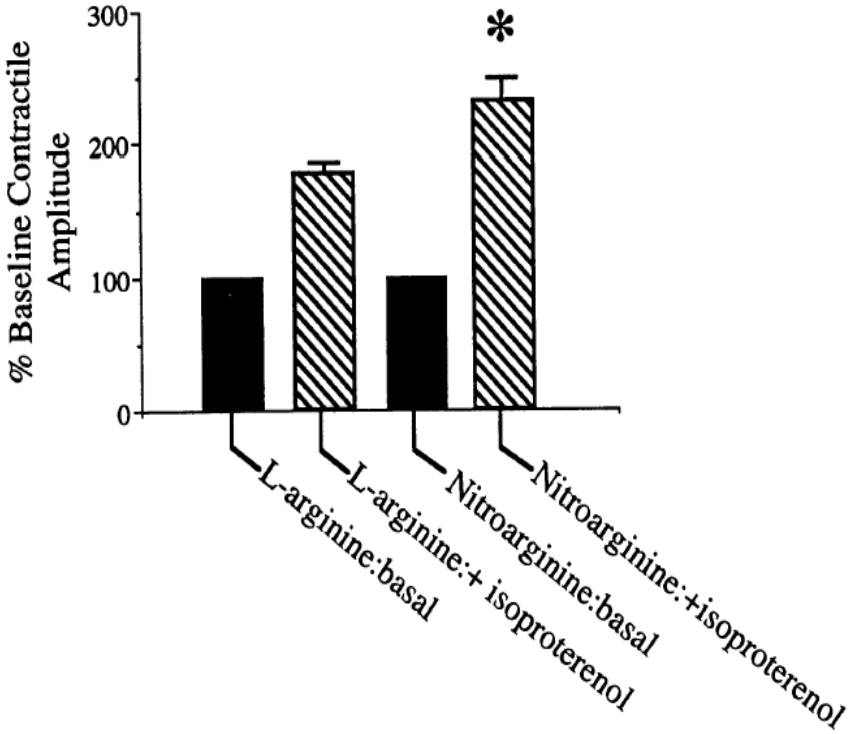

Epi/Norepi
Sarcolemma
ACh
AC
α
G_s
β-
AR
α
β
γ
α
AC
G_i
M_2–
Rec
cAMP
Reg
GTP
GTP
GTP
GTP
cAMP
AKAP
PKA
PKA
Reg
ATP
P
P
PKA
Ca
RyR
Ca
PLB
I_{Ca}
SR
ATP
P
P
Troponin I
Ca
Ca
Myofilaments

Membrane receptors

- The beta3-adrenergic receptor

β-adrenergic stimulation of NO Synthase attenuates the inotropic effect

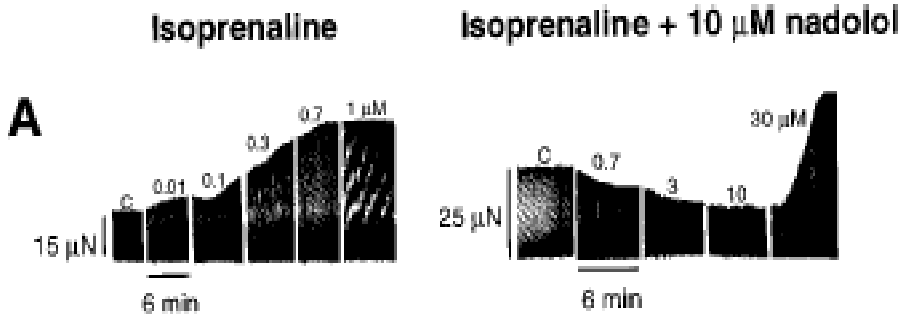
Which β-adrenergic receptor ?



Balligand et al. ***Proc Nat Acad Sci USA***(1993)

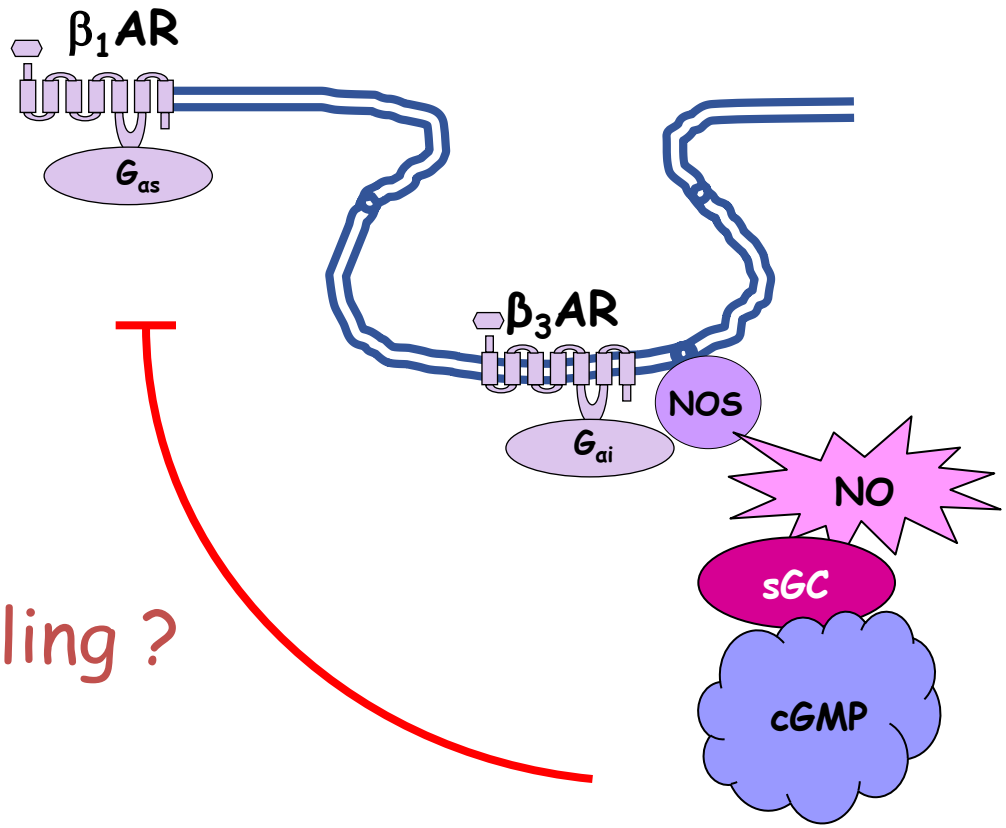
β1+2-adrenergic receptor blockade unveils a negative inotropic effect of isoproterenol, a non-specific β-adrenergic agonist

By what mechanism ?



Gauthier et al. ***J Clin Invest*** (1996)

β3 AR coupling in mammalian heart



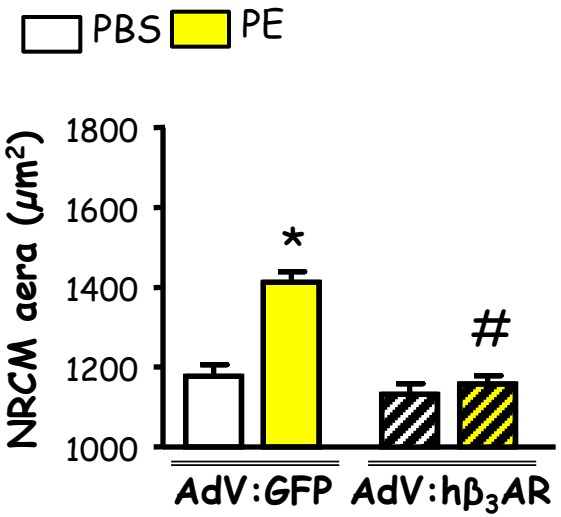
Effect on remodeling ?

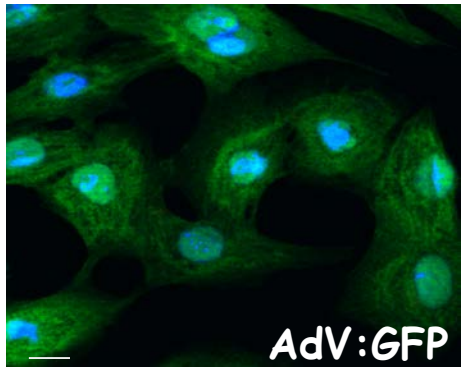
1. hypertrophy
2. coronary vasodilatation
3. fibrosis
4. metabolism ?

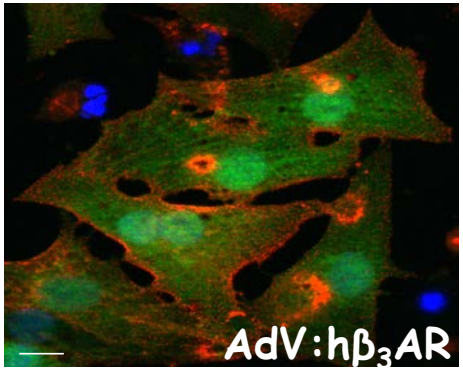
Gauthier *et al J Clin Invest* 1998:102 (7): 1377
Moniotte *et al Circulation* 2001: 103 (12); 1649
Dessy et al *Circulation* 2004;110(8):948
Moniotte *et al Eur J Heart Failure* 2007; 9 (12): 1163
Hammond J, Balligand JL, *JMCC* 2012 ; 52(2): 330-340
Belge C et al. *Circulation* 2014; 129: 451

β3AR protects against cardiac hypertrophy

In vitro

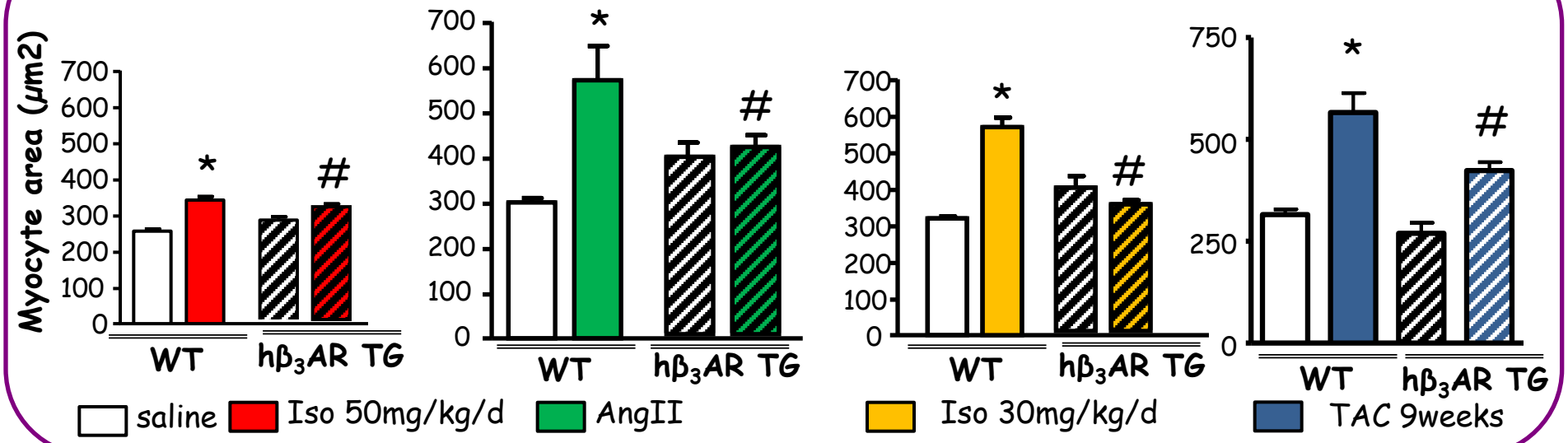






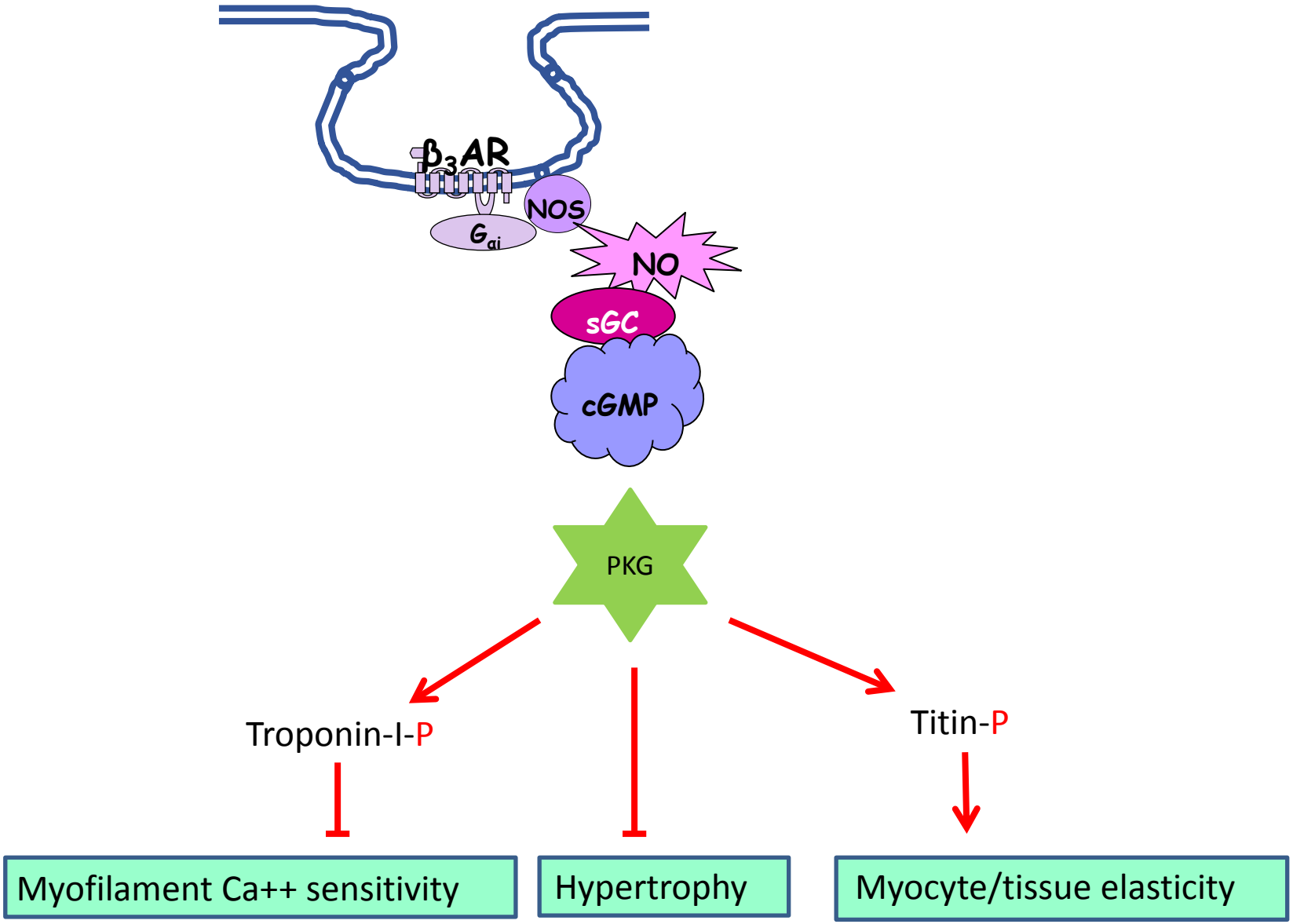
Belge C*, Hammond J*, Dubois-Deruy E* et al, *Circulation* 2014 129, 451-62

In vivo



Belge C et al. ***Circulation*** 2014;129:451-462

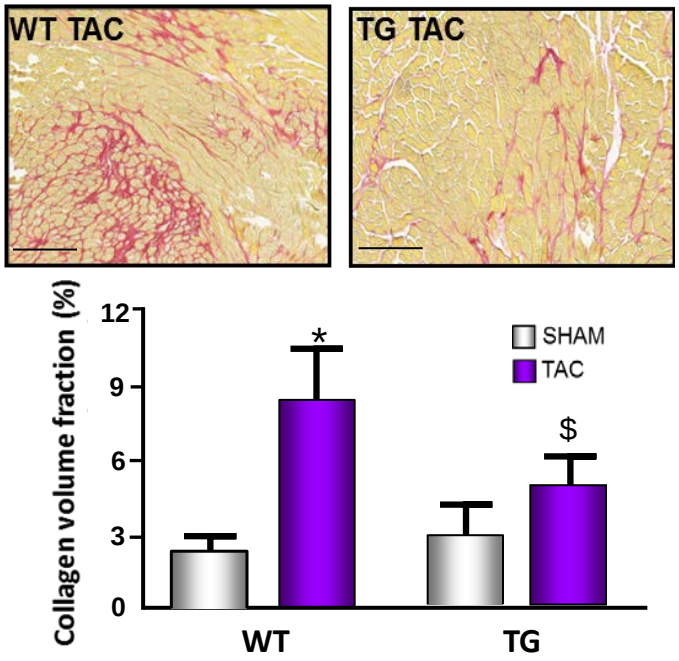
Targets downstream NOS/cGMP



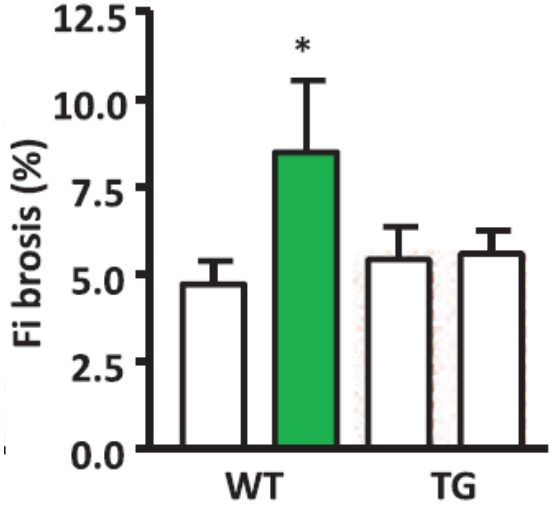
The cardiac fibroblast and myocyte-fibroblast cross-talk

β3AR protects against myocardial fibrosis

Myocardial fibrosis after TAC 9 weeks

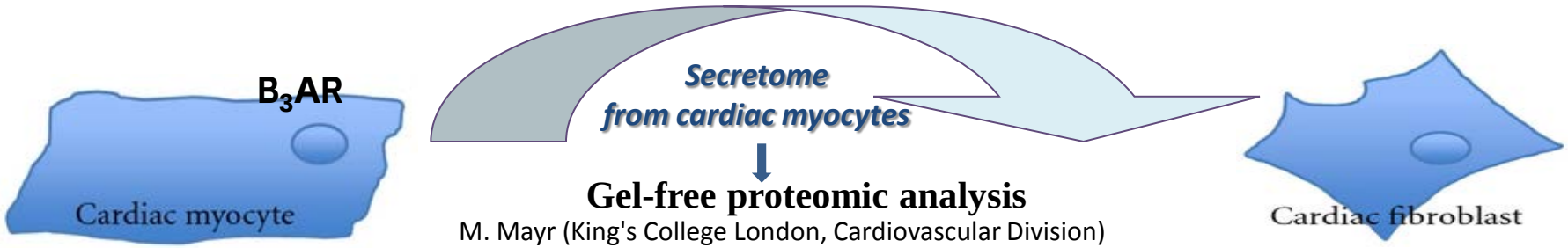


Myocardial fibrosis after Angiotensin II infusion by minipump (14 days)



Belge C et al. ***Circulation*** 2014;129:451-462

POTENTIAL PARACRINE FACTORS INVOLVED IN THE ANTIFIBROTIC EFFECT FROM β3-AR CARDIAC MYOCYTES TO CARDIAC FIBROBLASTS

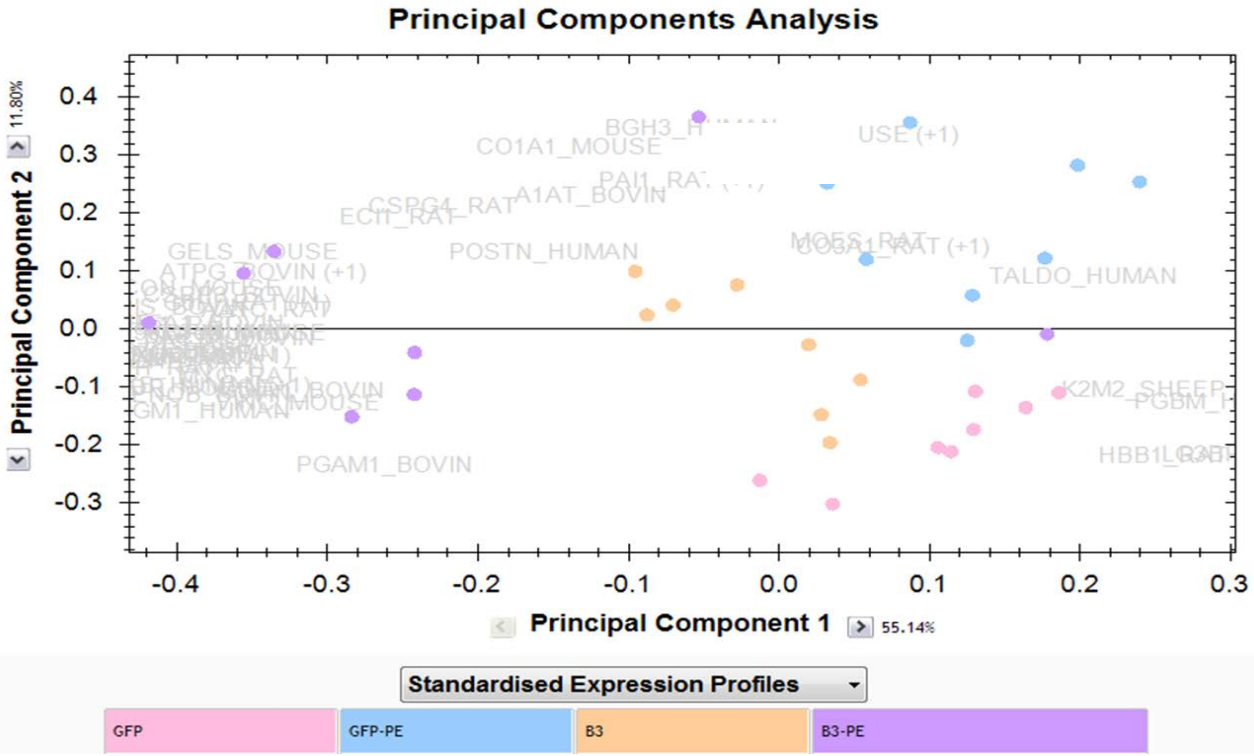


Gel-free proteomic analysis

M. Mayr (King's College London, Cardiovascular Division)

GFP PE +/-

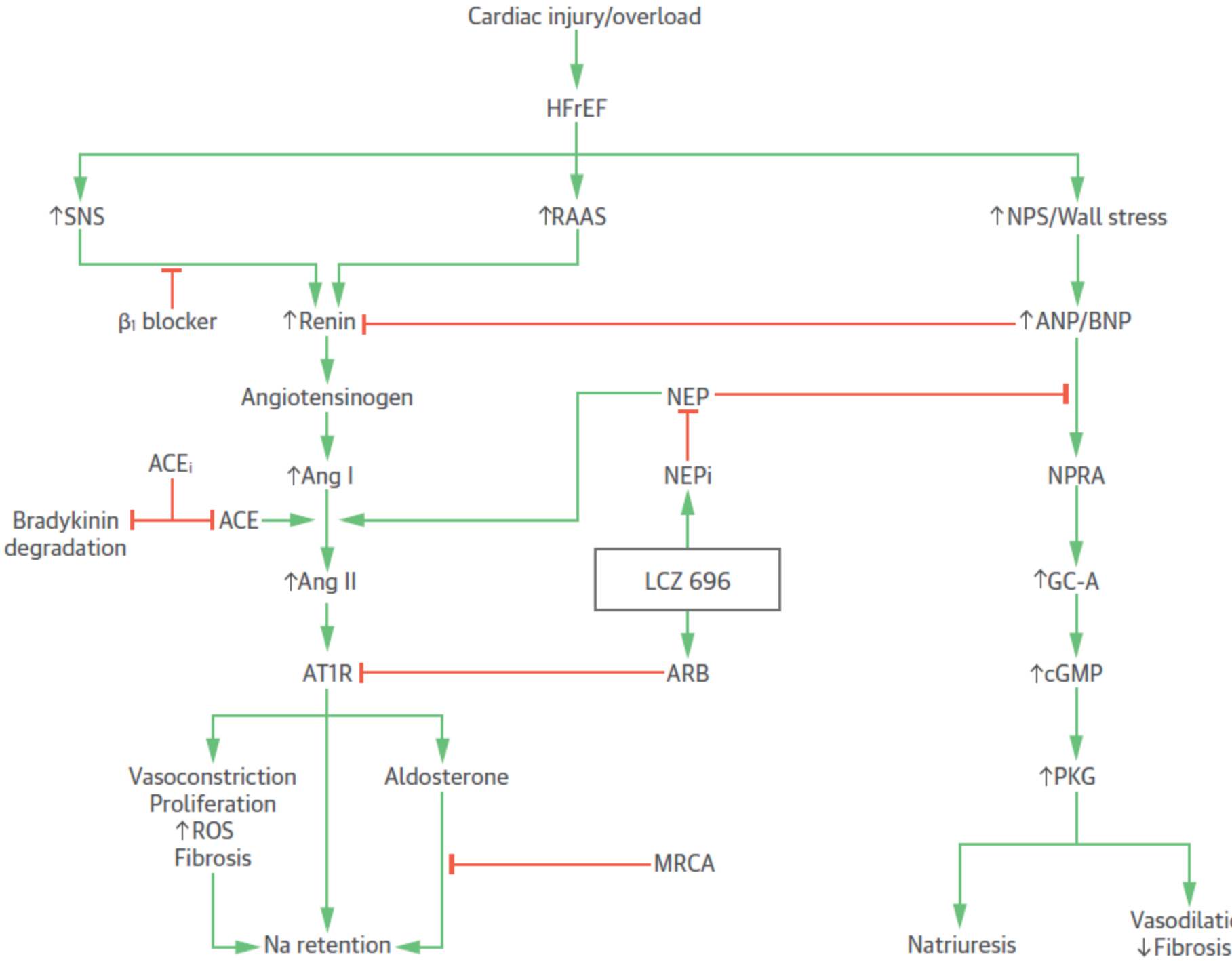
β3 PE +/-



This project has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement N° 634559

Membrane receptors

- Combined AT1-R antagonist and neprilysin inhibitor: LCZ 696


Cardiac injury/overload
HFrEF
↑SNS
↑RAAS
↑NPS/Wall stress
β1 blocker
↑Renin
↑ANP/BNP
Angiotensinogen
NEP
ACEi
↑Ang I
NEPi
NPRA
Bradykinin degradation
ACE
LCZ 696
↑GC-A
↑Ang II
AT1R
ARB
↑cGMP
Vasoconstriction
Proliferation
↑ROS
Fibrosis
Aldosterone
↑PKG
MRCA
Na retention
Natriuresis
Vasodilati
↓Fibrosis

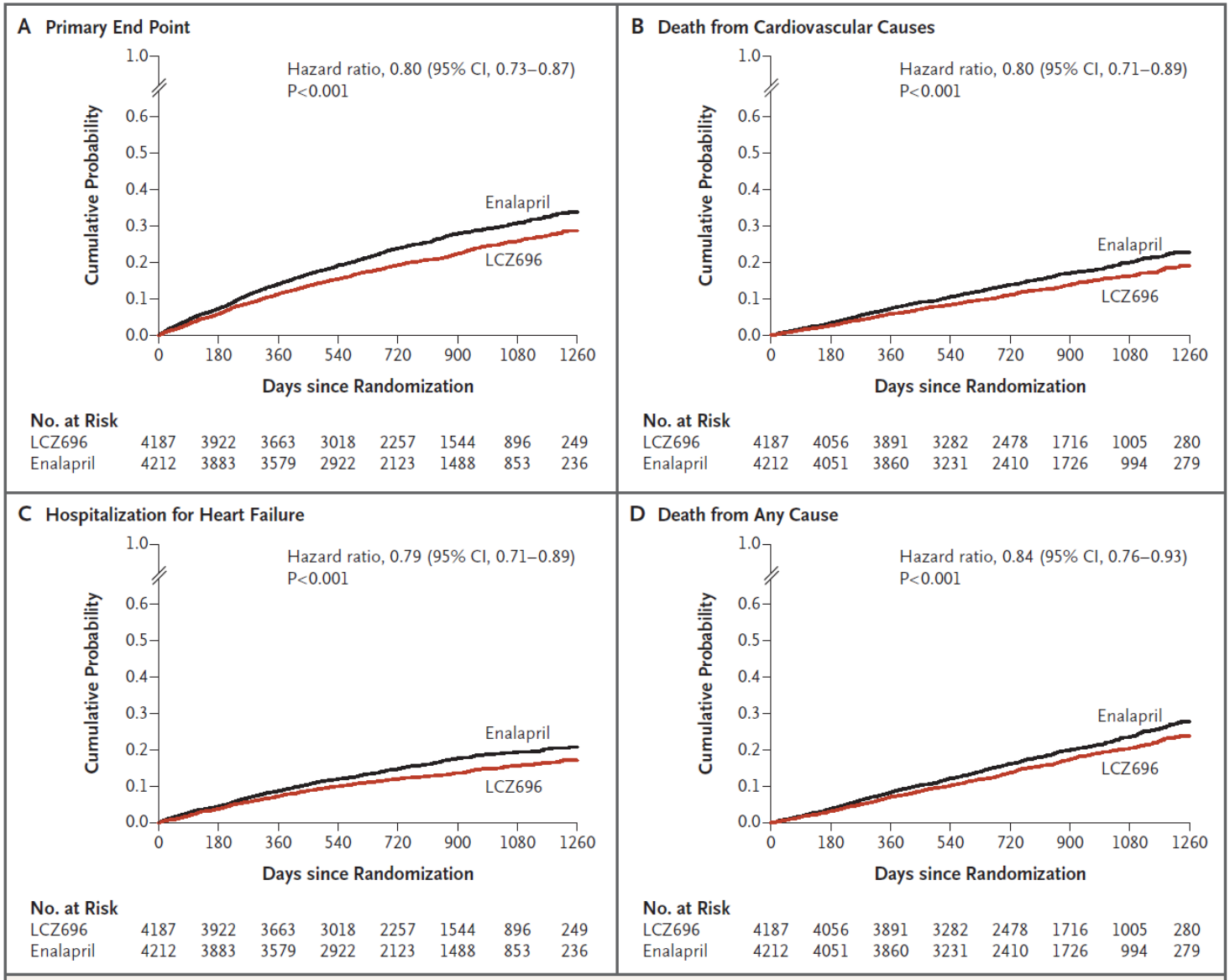


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.

Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial

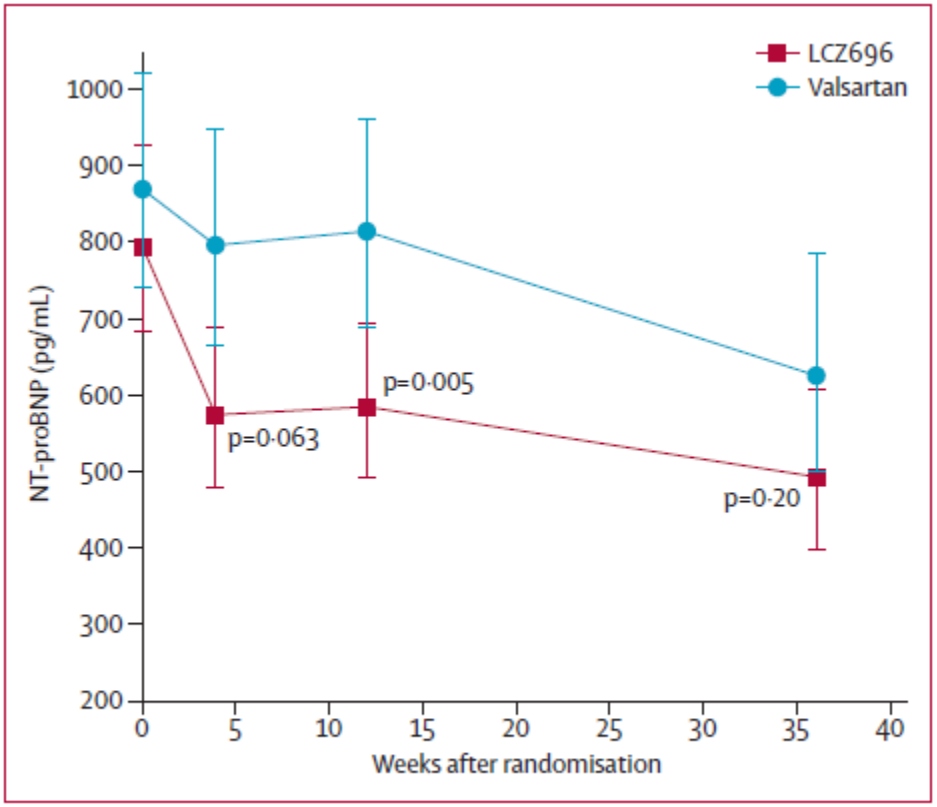
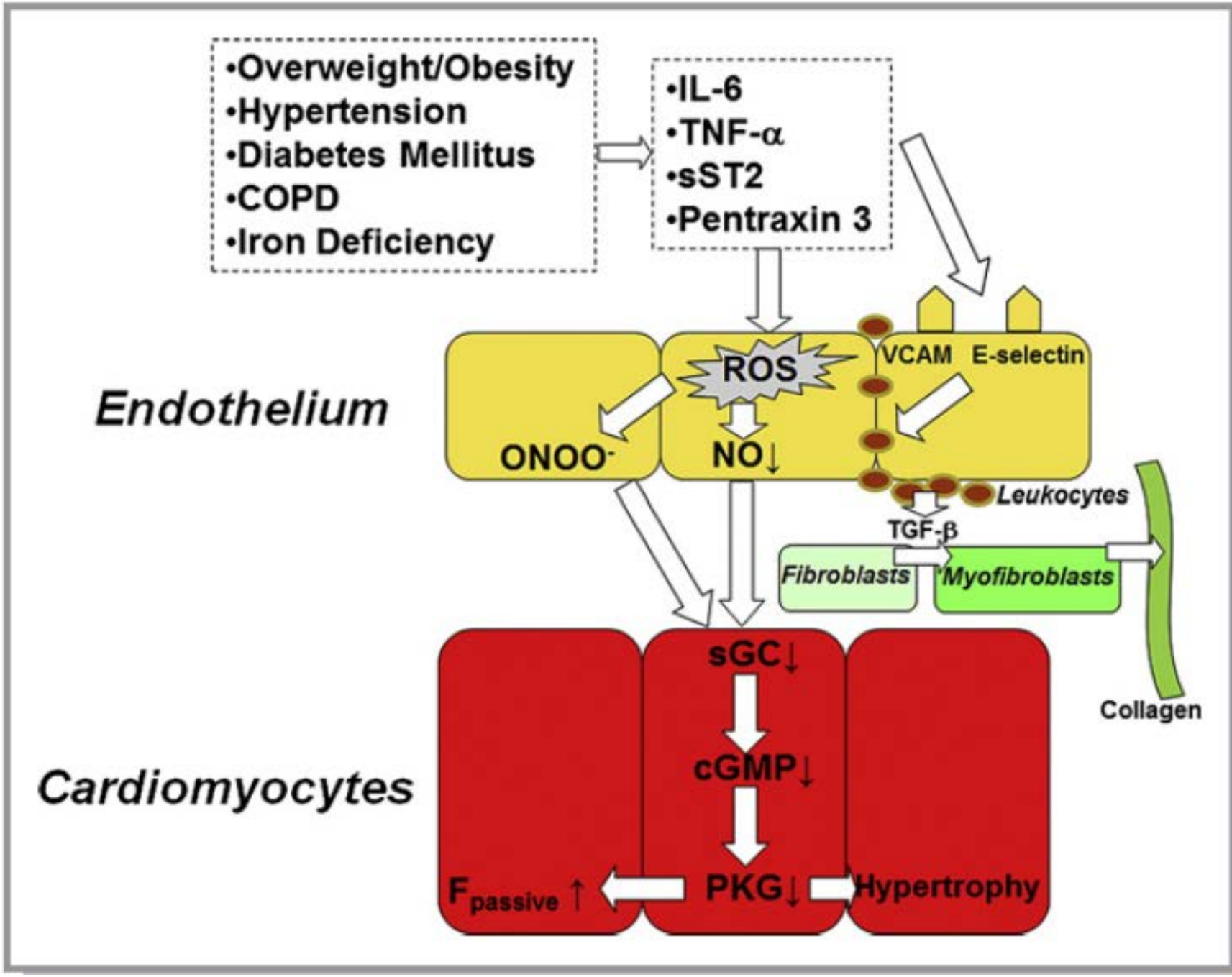


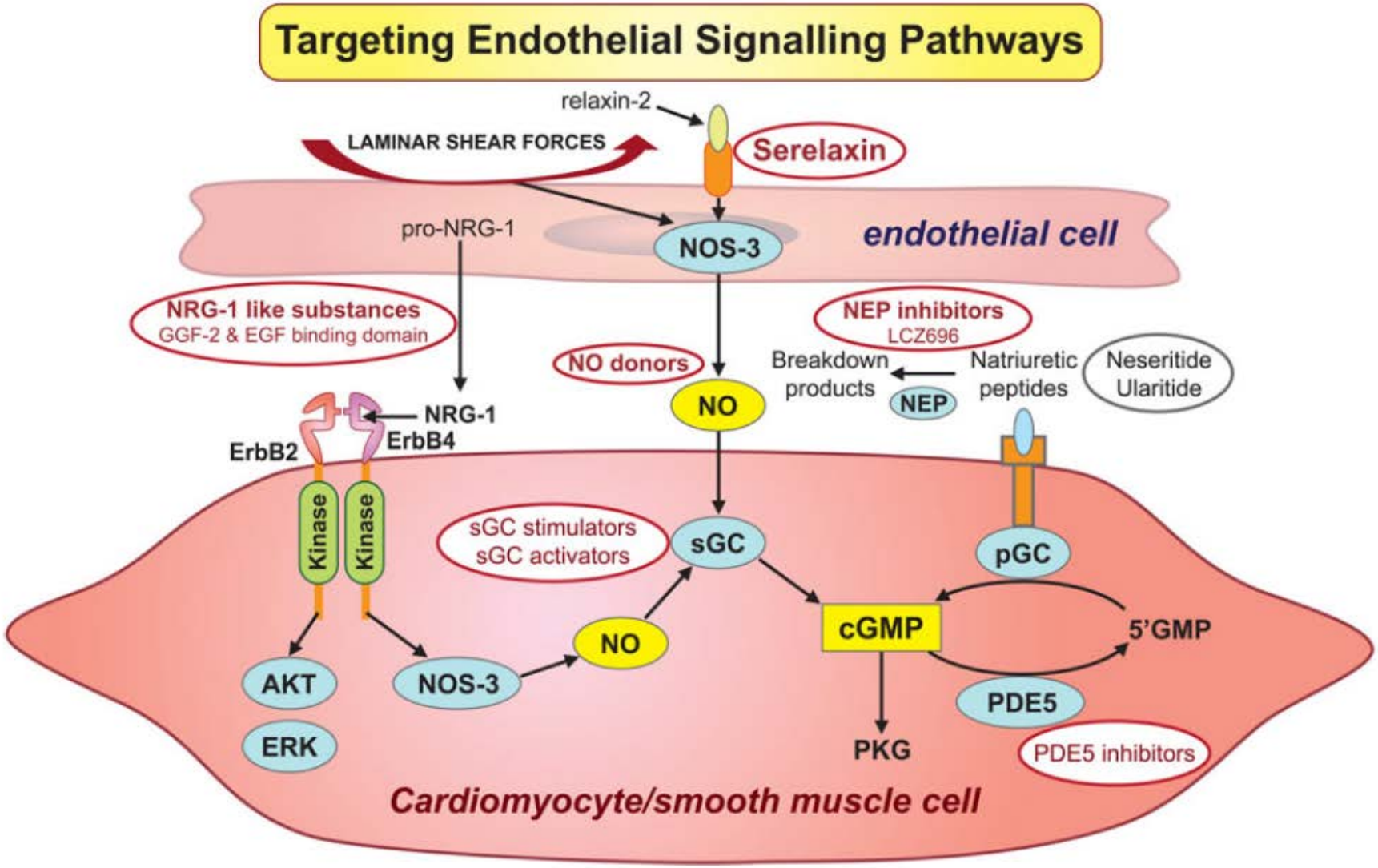
Figure 2: NT-proBNP at 4, 12, and 36 weeks in the LCZ696 and valsartan groups

Lancet 2012; 380: 1387–95

The endothelial cell and endothelial-myocyte cross-talk

Close apposition of cardiac myocytes and capillary endothelial cells


•Overweight/Obesity
•Hypertension
•Diabetes Mellitus
•COPD
•Iron Deficiency
•IL-6
•TNF-α
•sST2
•Pentraxin 3
Endothelium
ROS
VCAM
E-selectin
ONOO-
NO↓
Leukocytes
TGF-β
Fibroblasts
Myofibroblasts
Collagen
Cardiomyocytes
sGC↓
cGMP↓
PKG↓
Fpassive ↑
Hypertrophy

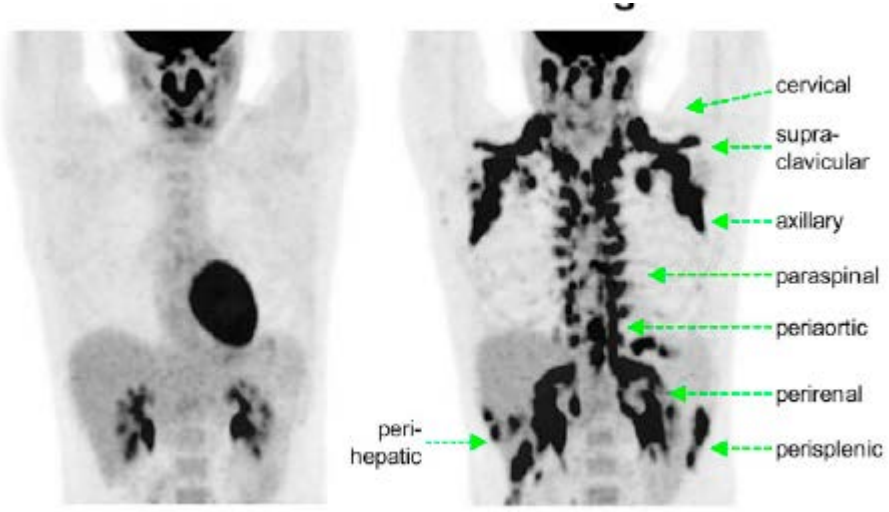


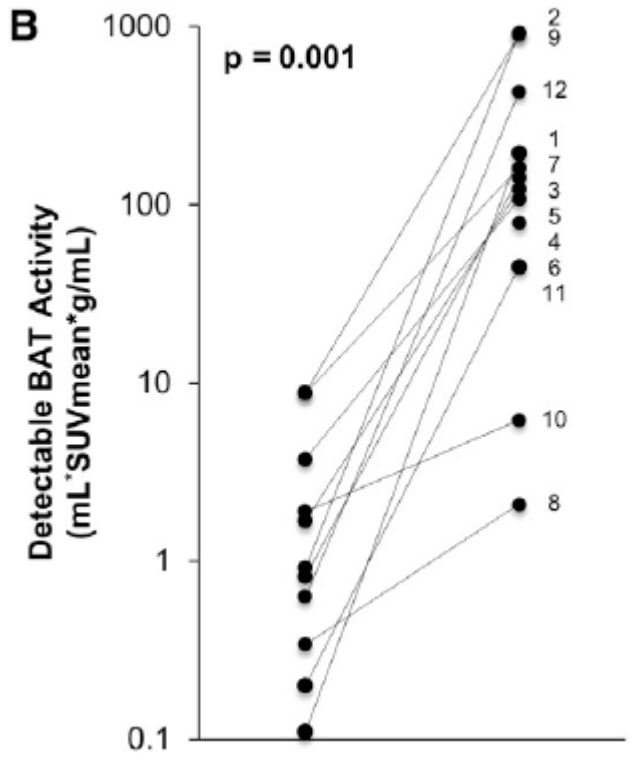
Lim SL et al ***Eur Heart J*** 2015

Cell Metabolism
Article

Activation of Human Brown Adipose Tissue by a β3-Adrenergic Receptor Agonist

Aaron M. Cypess,[1,*] Lauren S. Weiner,[1] Carla Roberts-Toler,[1] Elisa Franquet Elía,[2] Skyler H. Kessler,[1] Peter A. Kahn,[3] Jeffrey English,[2] Kelly Chatman,[4] Sunia A. Trauger,[4] Alessandro Doria,[5] and Gerald M. Kolodny[2]





That’all

- Questions