



Basic concepts of remodeling

Heiner Post

Clinical dept. of cardiology

Medical University of Graz, Austria



remodeling:

- cavity dilation after myocardial infarction (1975)
- increase in mass

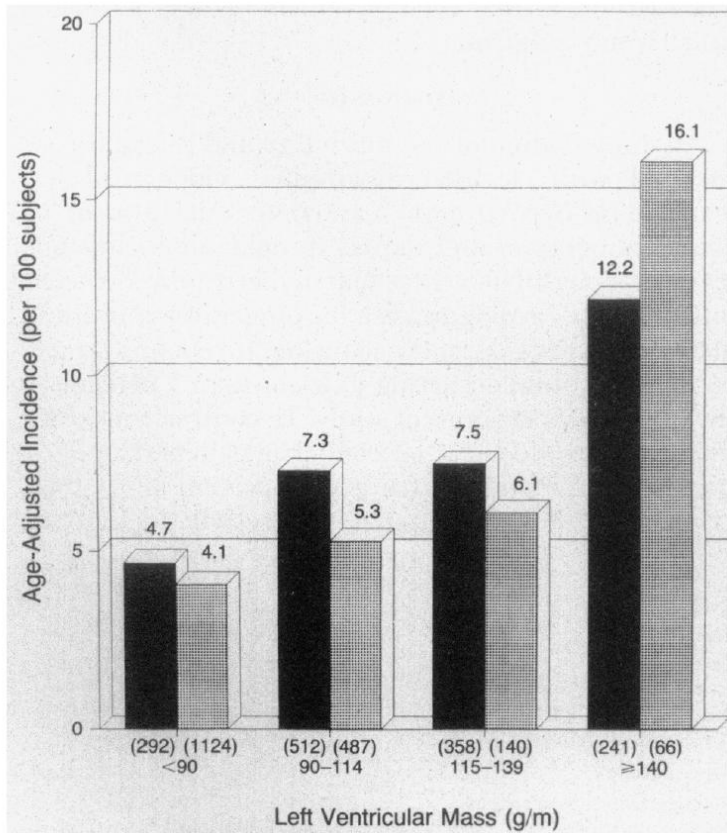
- structural changes in response to physiological and pathological stimuli

LV mass – 4y risk

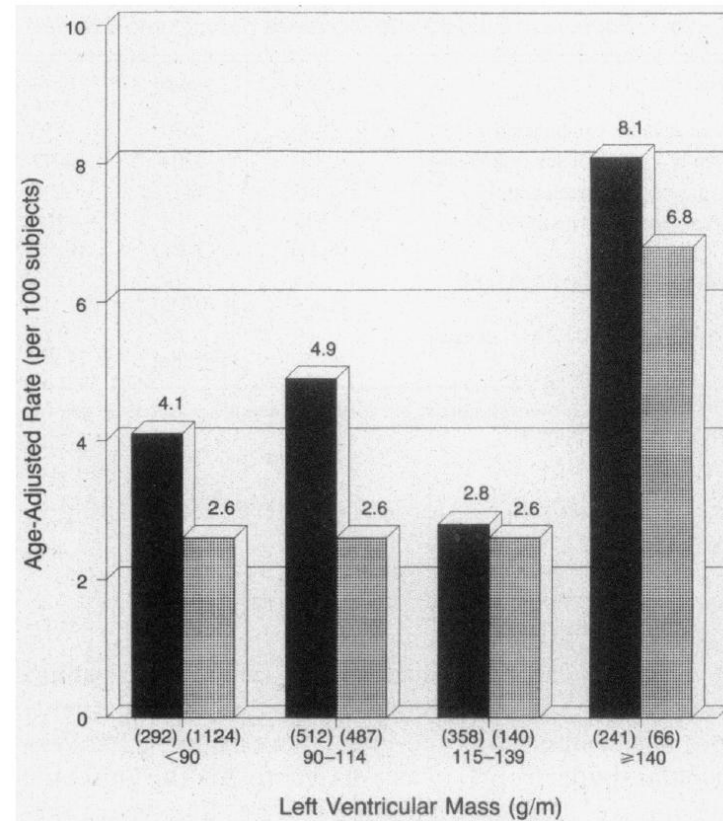


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CV disease

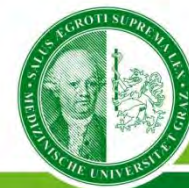


mortality



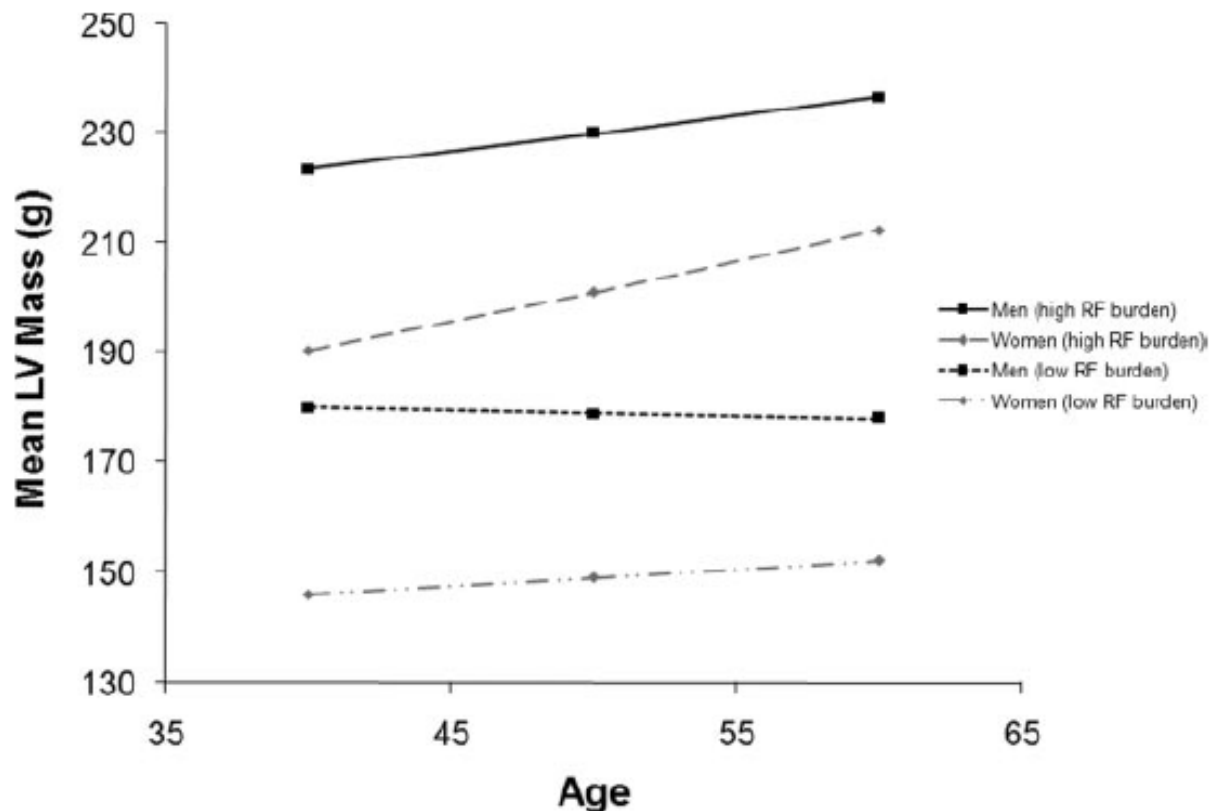
Levy, NEJM, 1990

LV mass and risk factors



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Framingham study



risk factors:

- hypertension
- obesity
- diabetes
- smoking

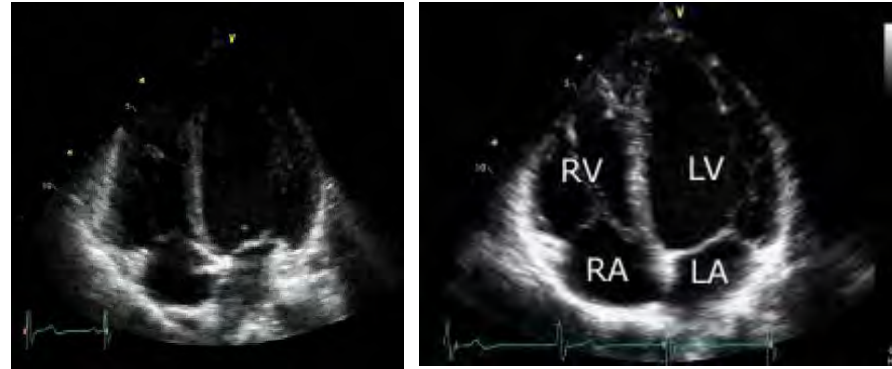
Vasan, Circulation, 2009

Pathologic remodeling

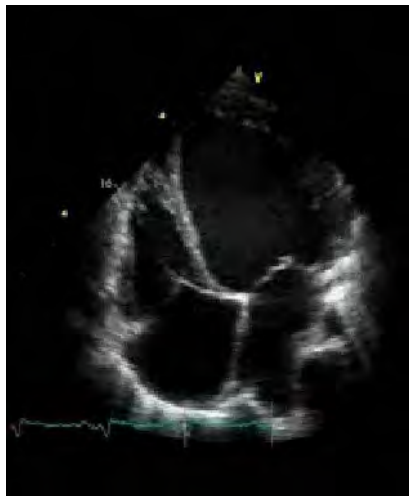


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healthy

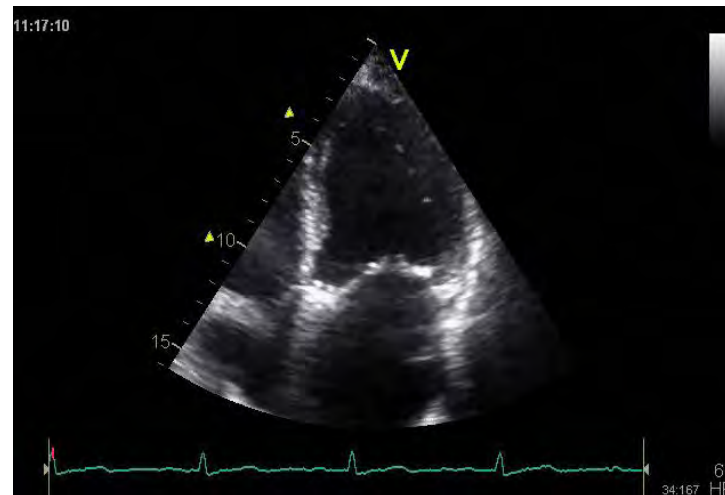


eccentric



LV volume \uparrow
LV wall \approx , \downarrow

concentric



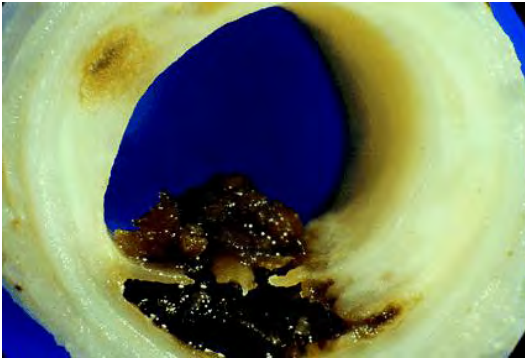
LV volume \approx , \downarrow
LV wall \uparrow

Myocardial infarction

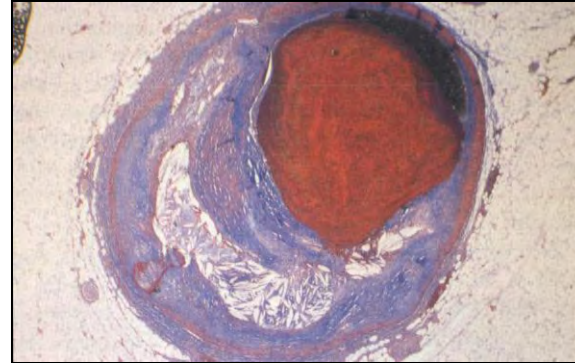


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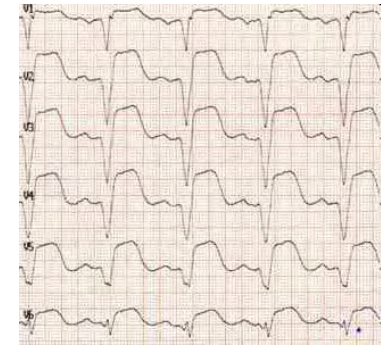
plaque rupture



thrombotic occlusion



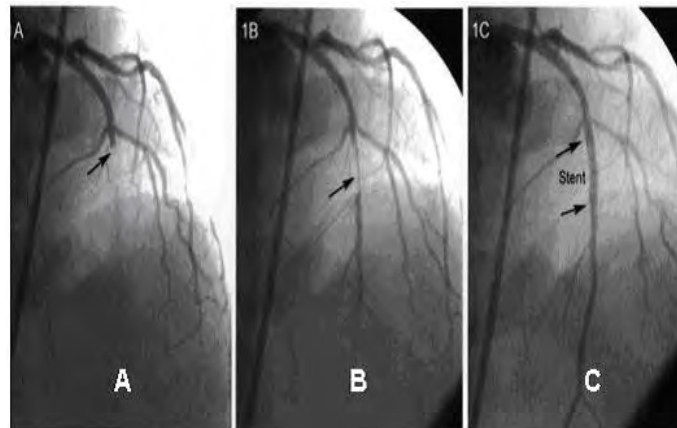
STEMI



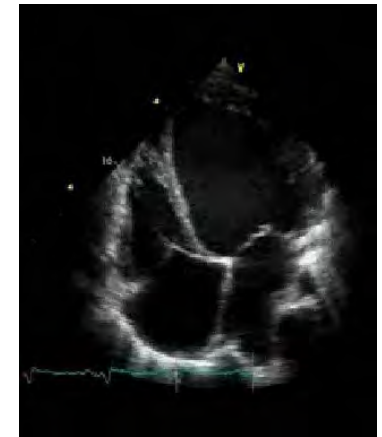
regional dysfunction



reperfusion



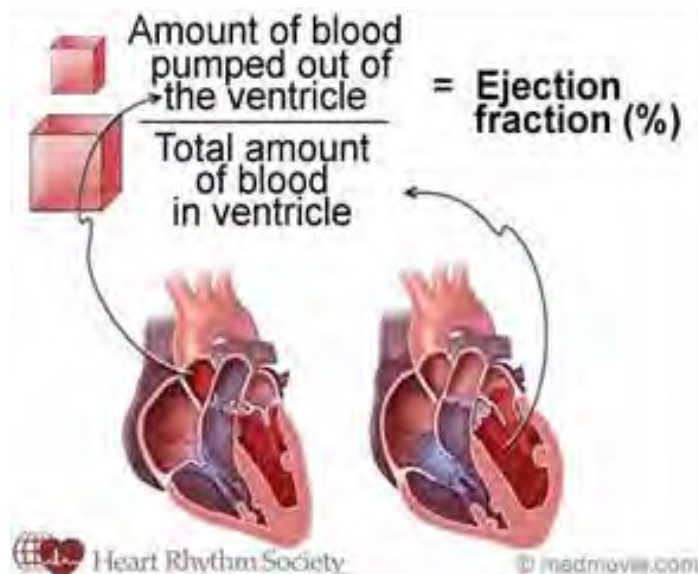
global dysfunction



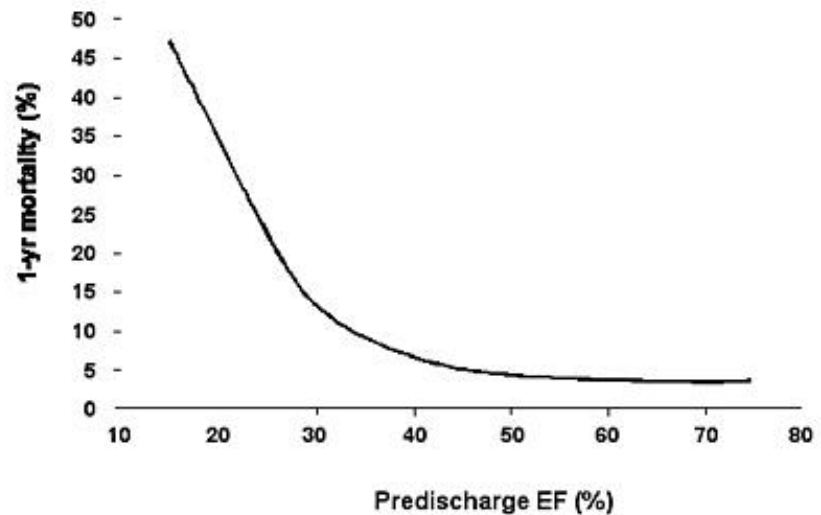
remodeling



Ejection fraction



patients after myocardial infarction
- mortality -



EF = stroke volume/end-diastolic volume

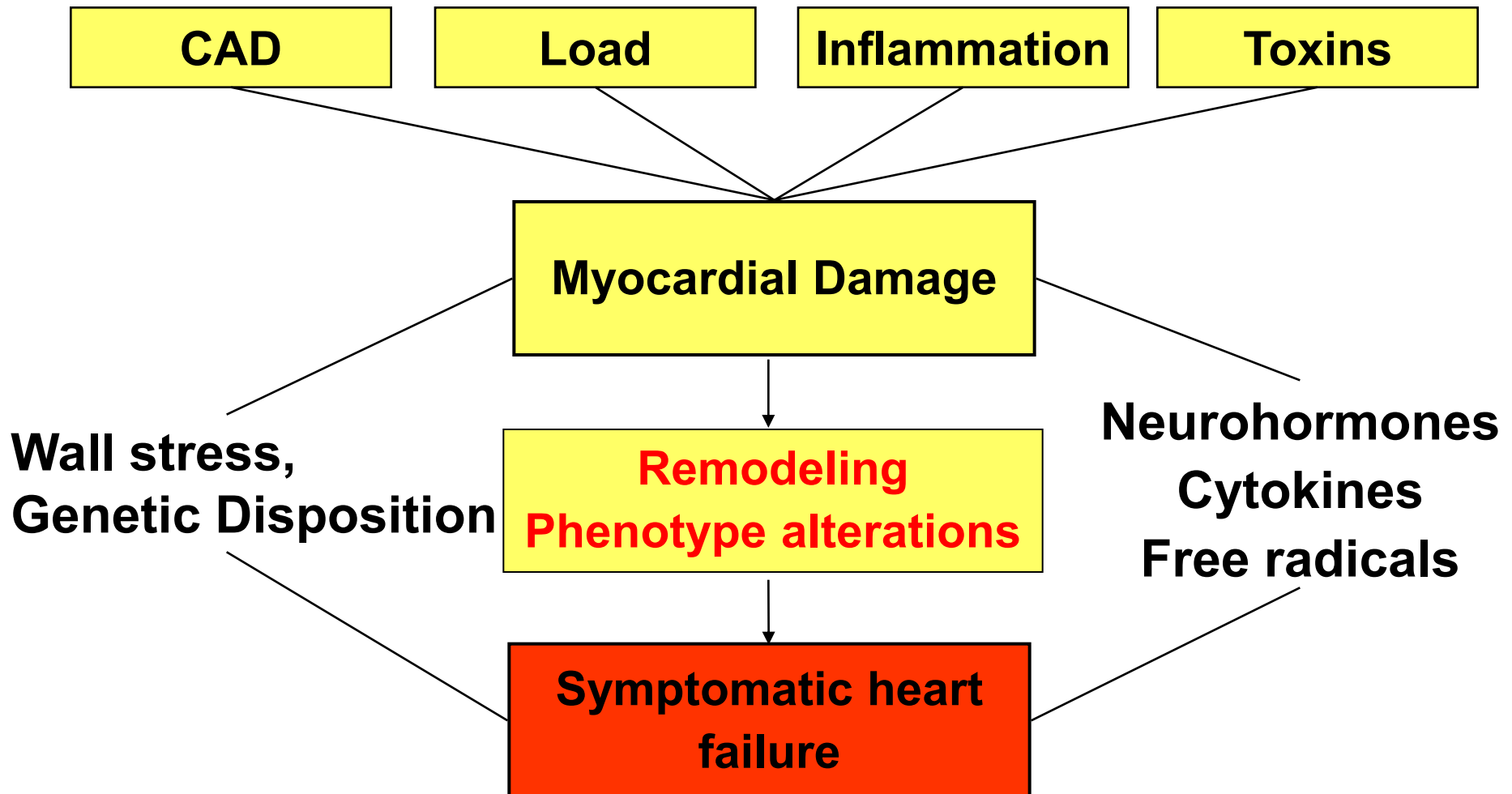
Systolic heart failure = HFREF



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- art. hypertension
- CAD, myocardial ischemia and infarction
 - RF: smoking, hyperlipidemia, HTN, diabetes, obesity
- DCM (genetic)
- valve diseases
- myocarditis: coxsackie, influenza,...
- toxic: alcohol, chemotherapeutics (anthrazyklines, herceptin)

Many reasons, but a uniform response



Sympathetic activation

- tachycardia
- arrhythmia
- „catecholamine poisoning“, β -receptors $\downarrow\downarrow$

RAAS activation (angiotensin II, aldosteron)

- AT II: peripheral resistance $\uparrow\uparrow$
- AT II: potentiates noradrenaline effects
- AT II: volume- and sodium-retention
- AT II: promotes aldosterone release
- aldosteron: volume- and sodium-retention

- AT II: oxidative stress (NADPH-Ox.) $\uparrow\uparrow$
- AT II: fibrosis (Herz, Niere)
- aldosteron: fibrosis

Inflammatory activation (TNF α , IL6,...)

- cachexia



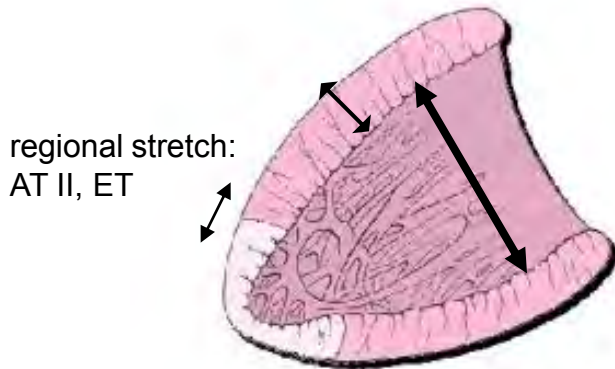
cardiac output \downarrow

Remodeling in HFREF



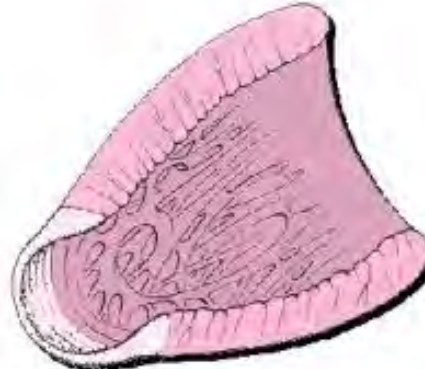
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Acute MI

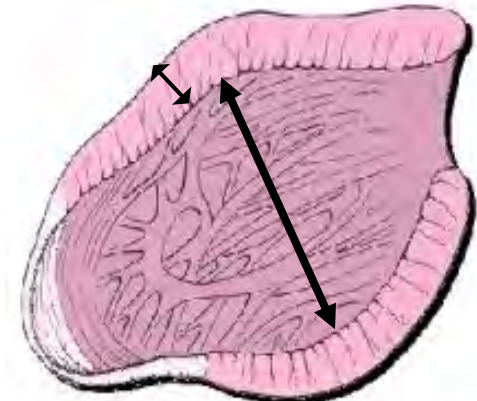


regional stretch:
AT II, ET

Extension



Dilatation



wall tension:
LaPlace

$$\frac{\text{pressure} * \text{radius}}{2 * \text{wall thickness}}$$

- diameter ↑
- wall thickness ↓
- ejection fraction ↓
- wall tension ↑↑

increased wall tension: - increased energy demand
- permanent maladaptive stimulus

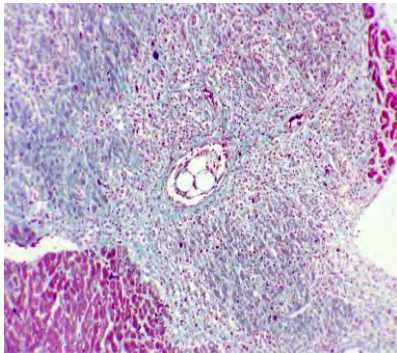
Remodeling in HFREF



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↓ scar



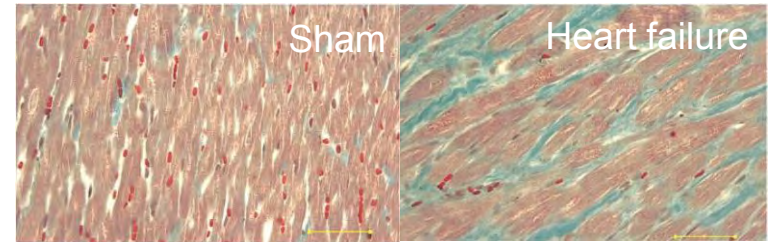
contractile
tissue



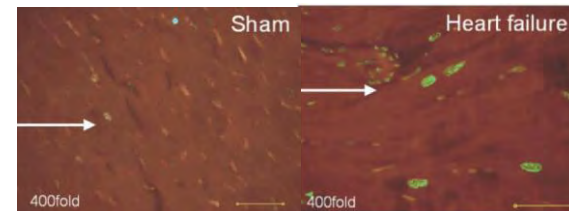
**noradrenaline
angiotensin II
aldosteron**

remodeling

fibrosis, CM hypertrophy



apoptosis



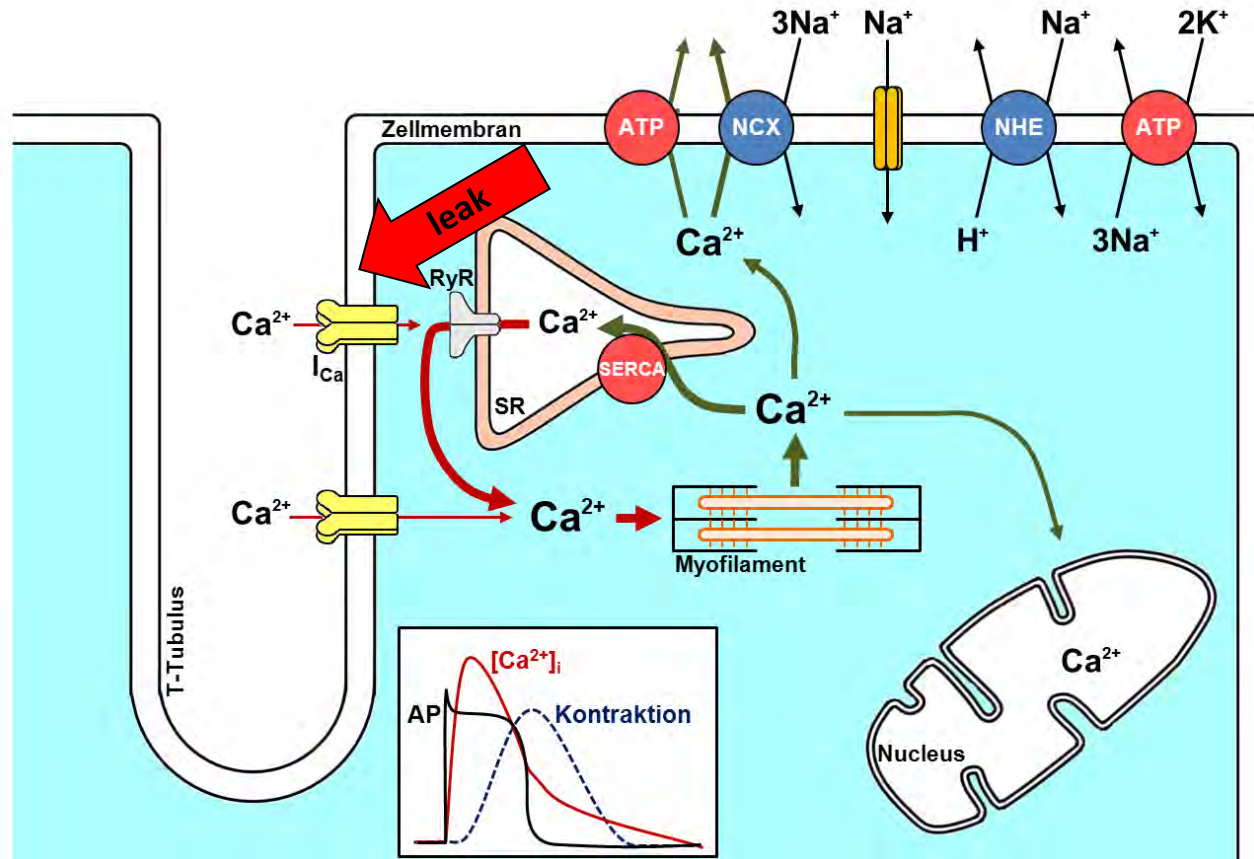
vital CMs during remodeling
decreased contractility

stem cells?

Excitation-contraction coupling in HFREF

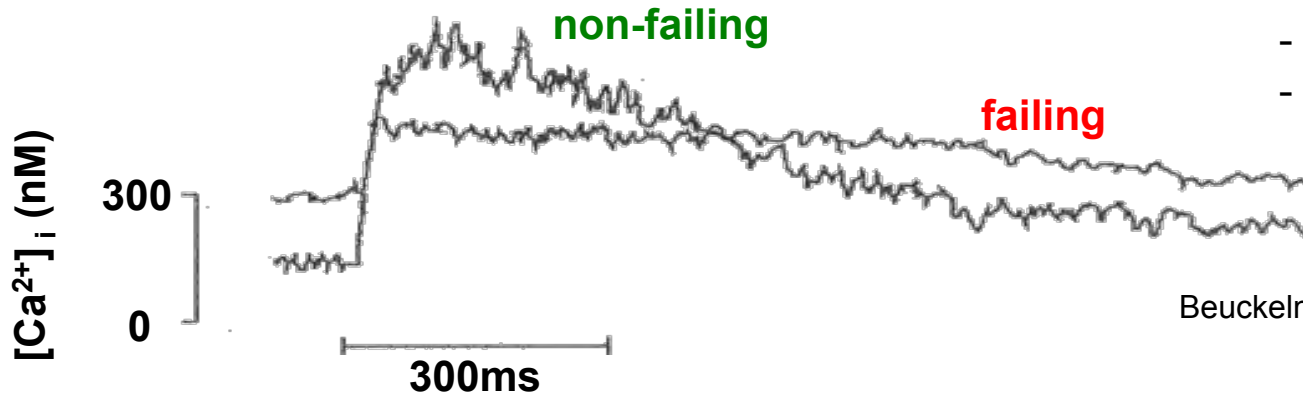


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modified from Hasenfuss & Pieske 2002 & Bers 2009

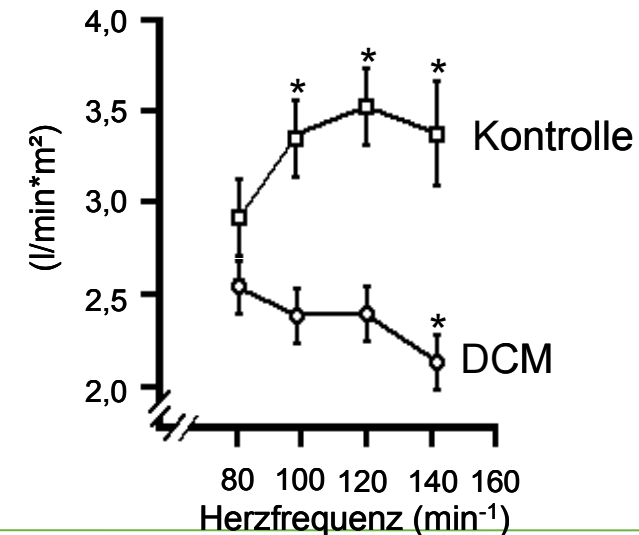
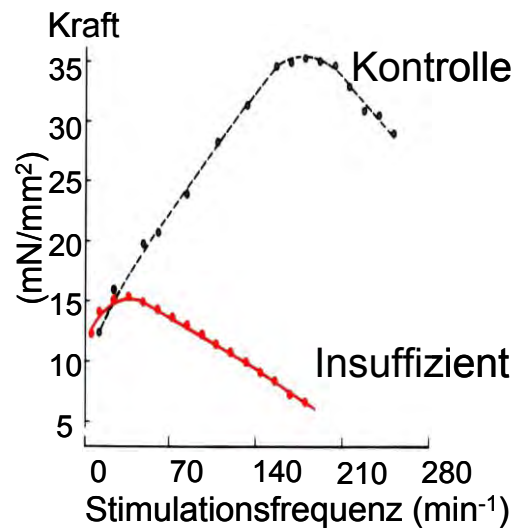
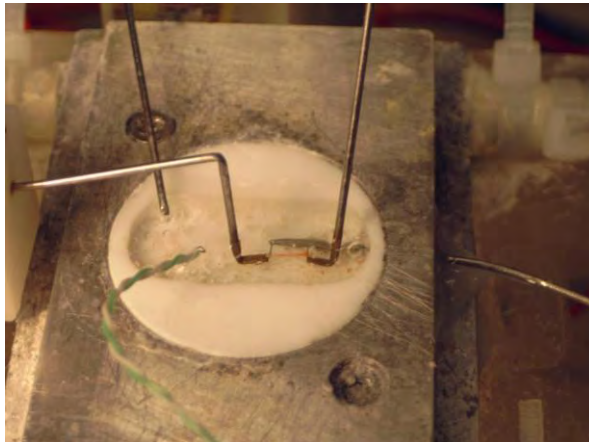
CM: contractile dysfunction in HFREF



- decreased Ca-transient
- increased diastolic Ca

Beuckelmann 1992

heart rate



Force-frequency-relationship



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non-failing

Calcium

300 mV



force

5 mN



failing

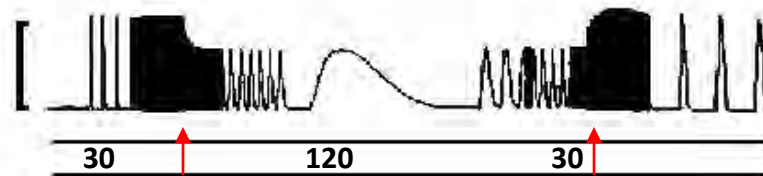
Calcium

300 mV



force

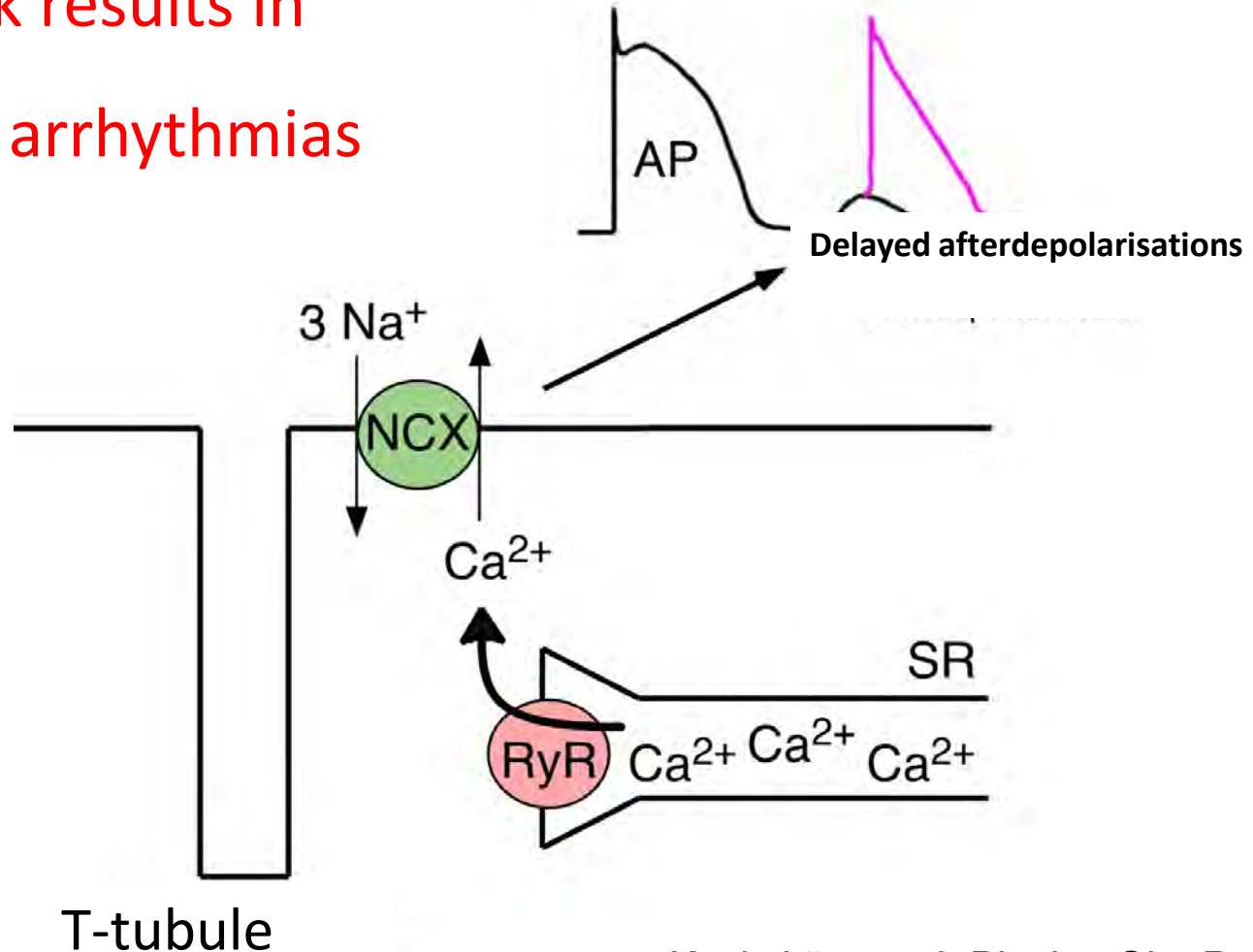
5 mN



min⁻¹

*Pieske et al.,
Circulation 1995*

SR Ca leak results in
triggered arrhythmias



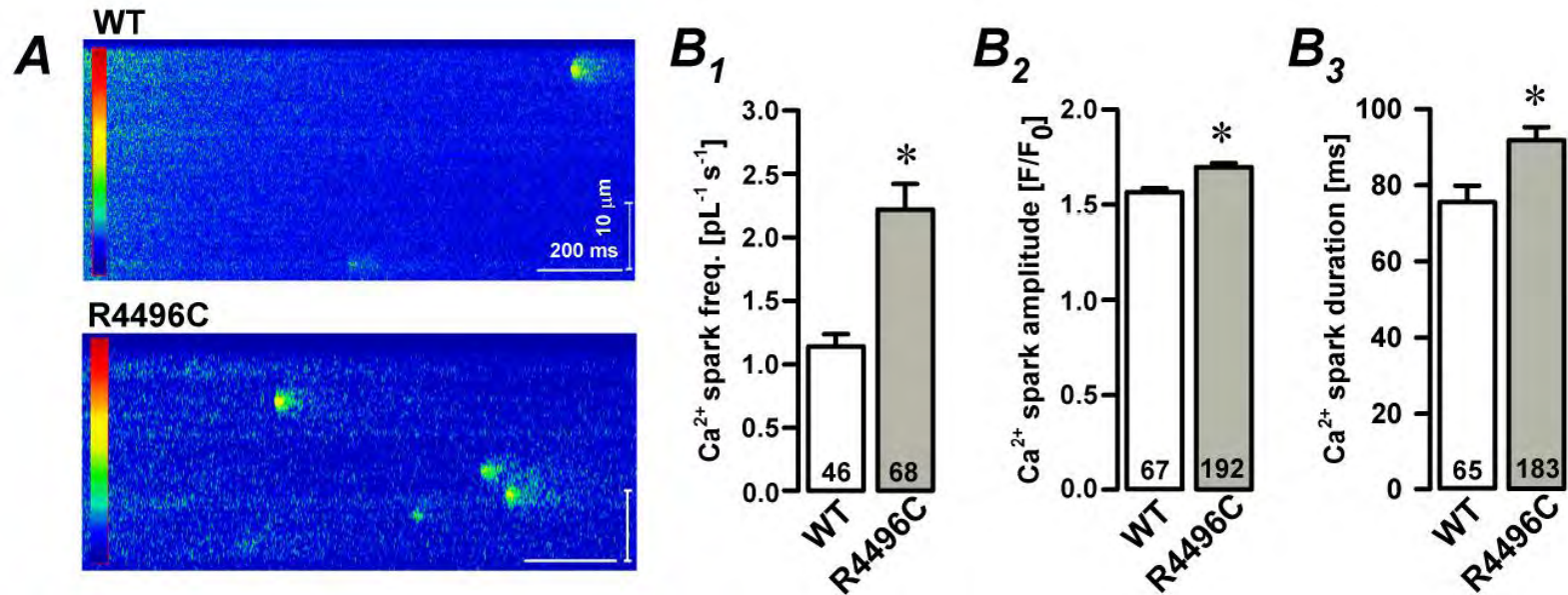
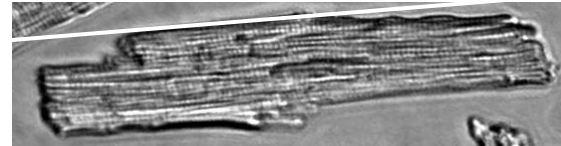
Kockskämper & Pieske, Circ Res 2009

Ca spark frequency in WT and TG mice



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Line-scan confocal microscopy

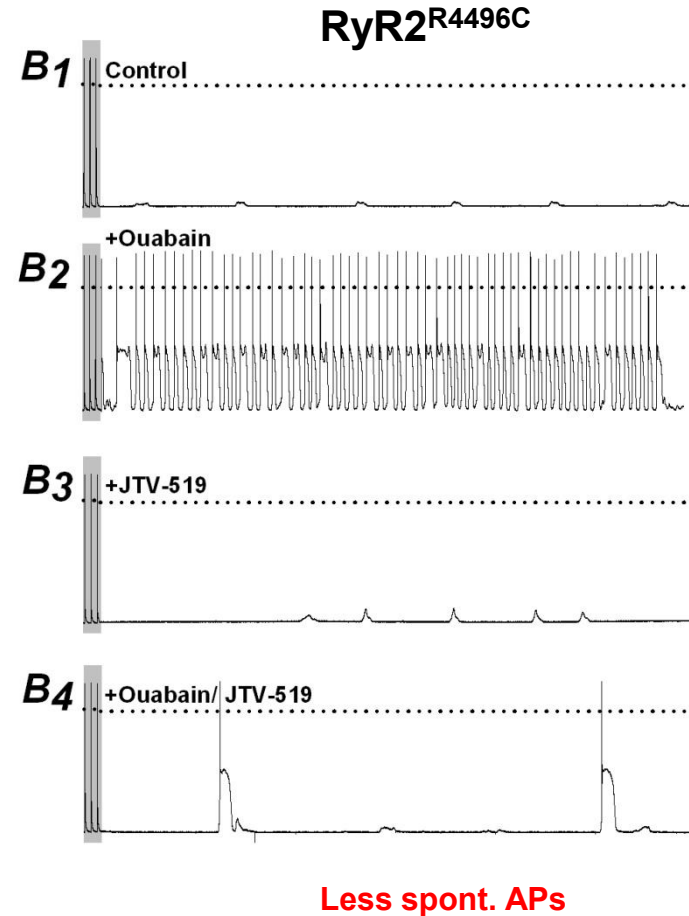
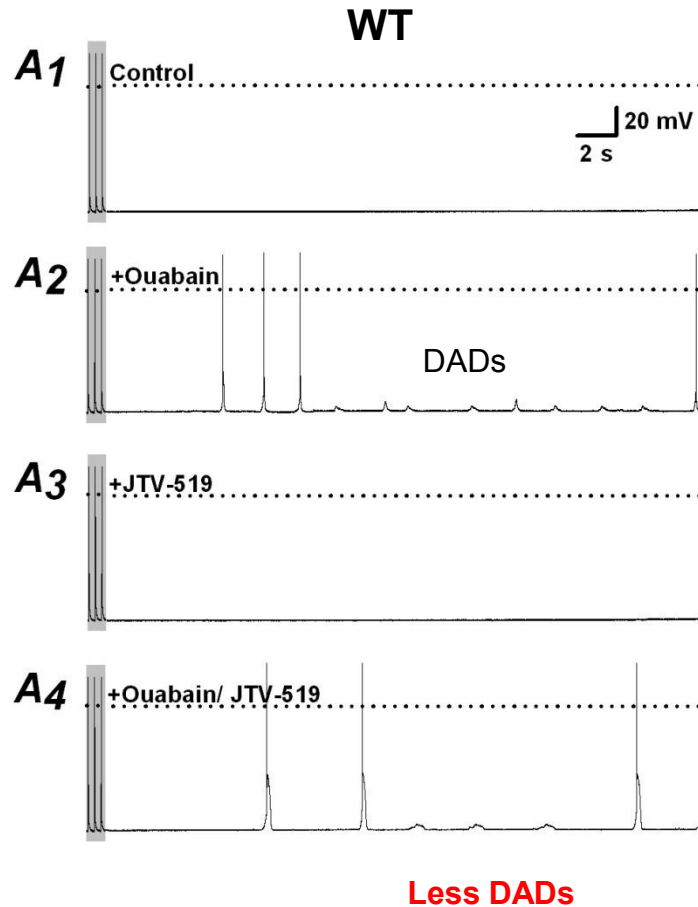


Sedej et al., Cardiovasc Res, 2010

Quabain triggers arrhythmias/DAD in TG mice



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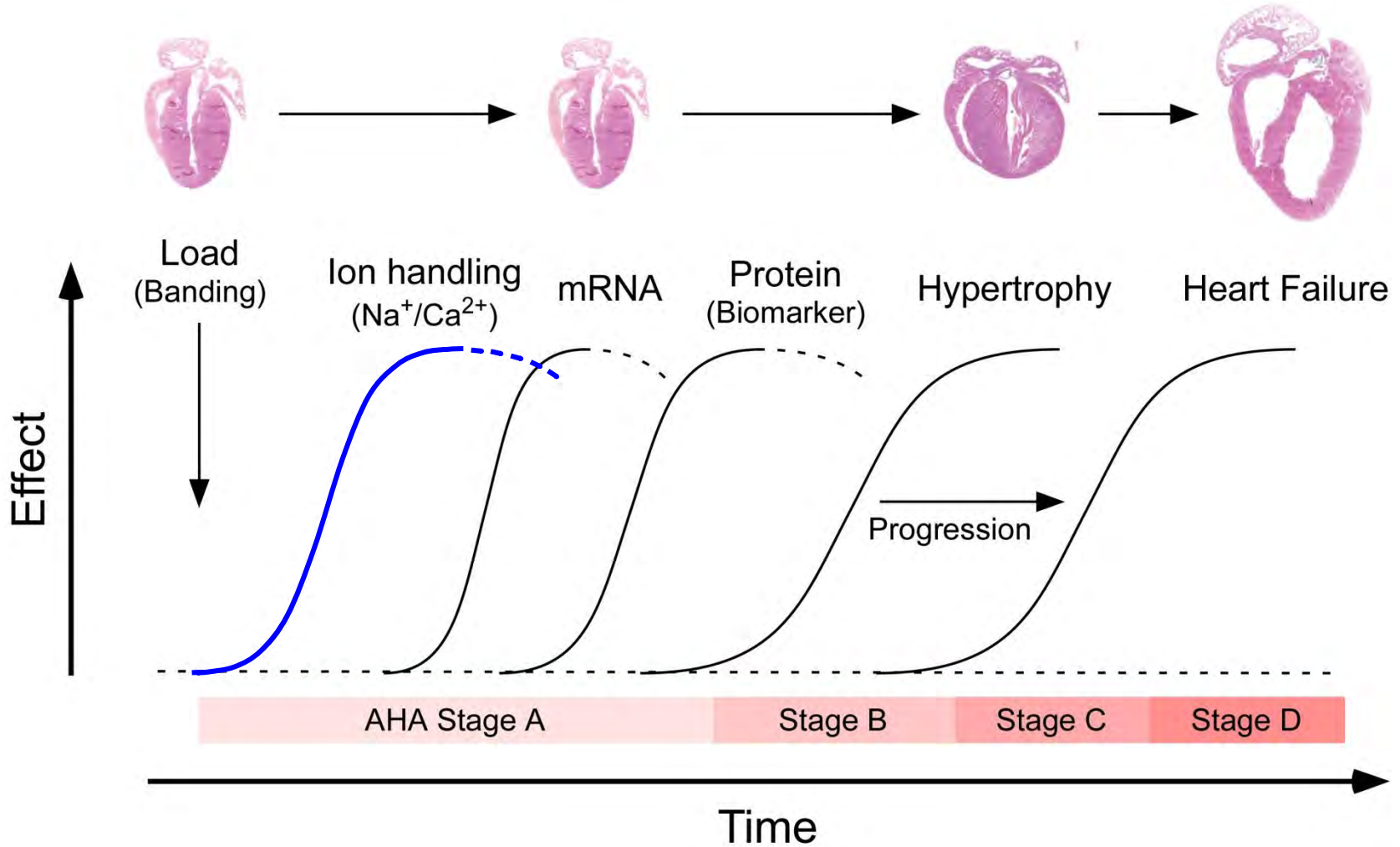


Sedej et al., Cardiovasc Res, 2010

Current hypothesis: ions and remodeling



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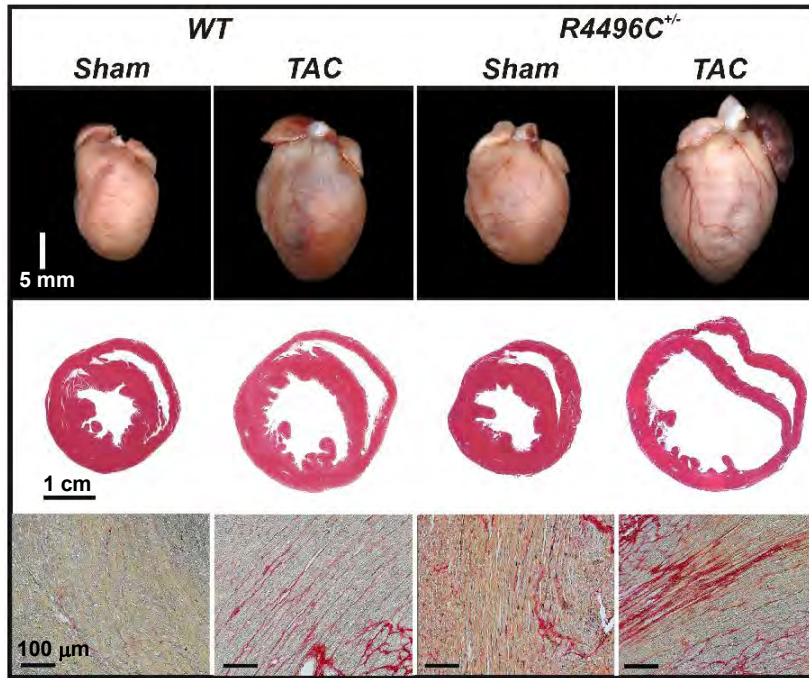


TAC-induced remodeling in TG mice

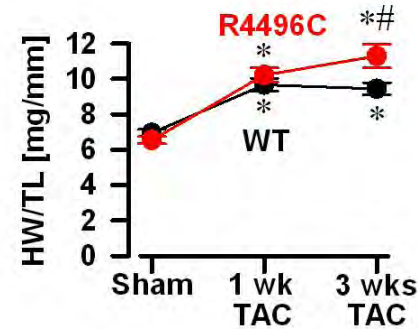


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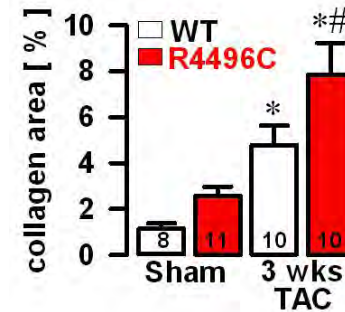
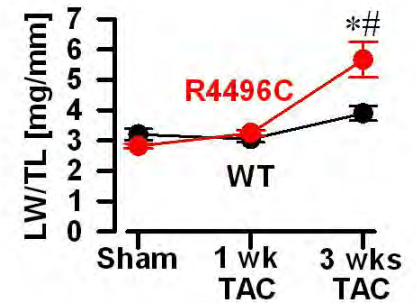
3 weeks TAC



hypertrophy



pulm. edema



fibrosis

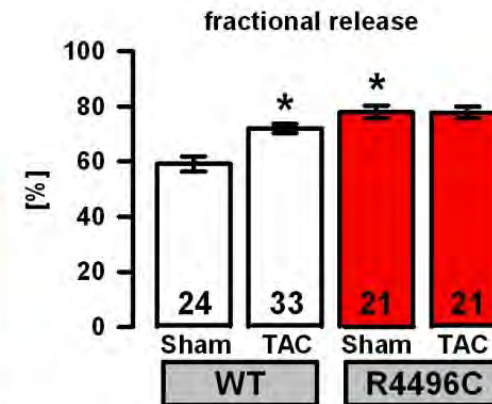
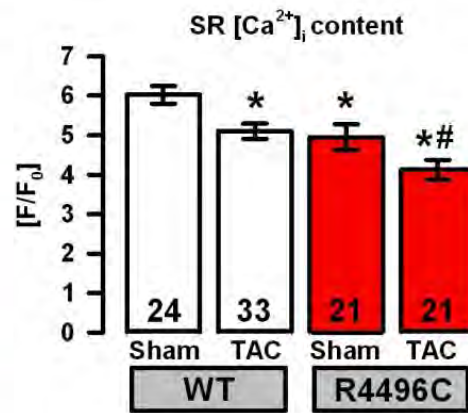
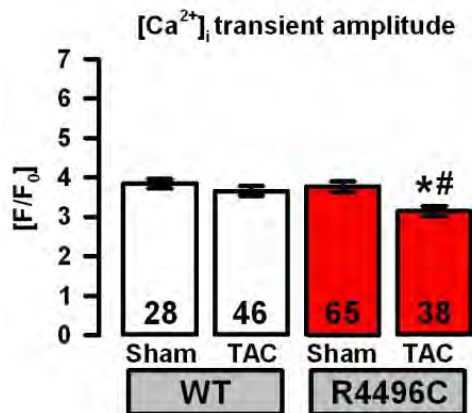
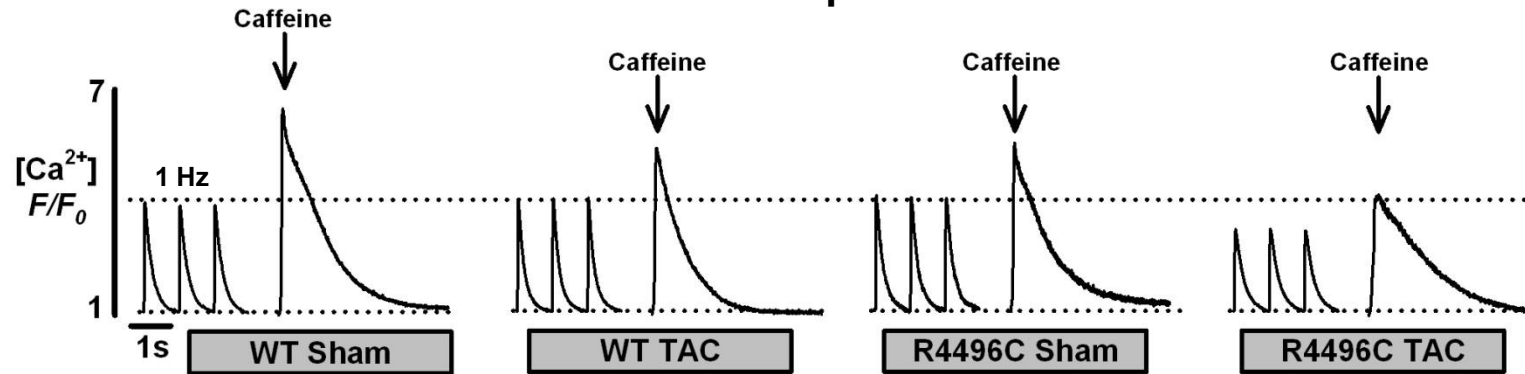
* $P < 0.05$ vs. Sham
$P < 0.05$ vs. WT TAC

Reduced Ca-transients and SR content



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1 week post TAC

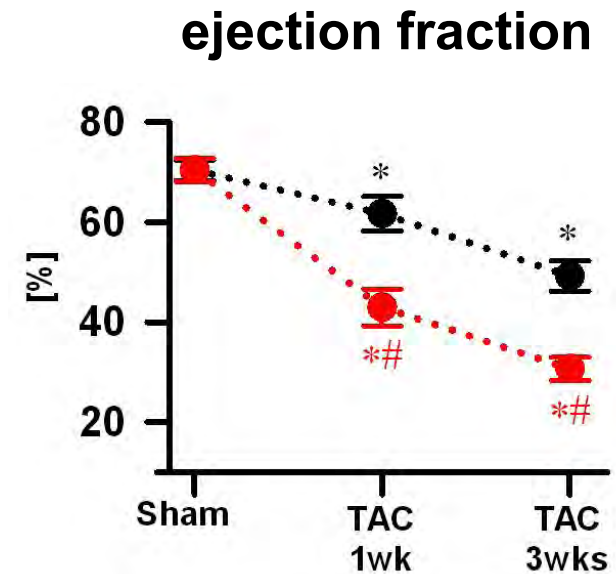
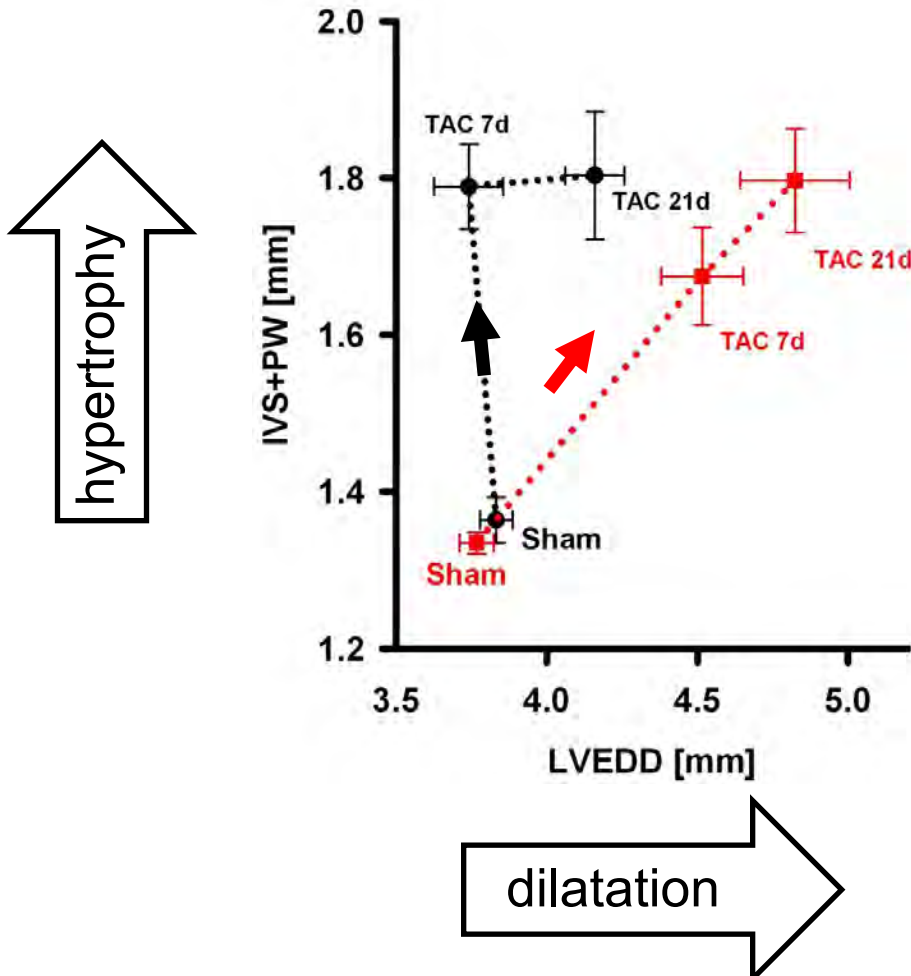


* $P < 0.05$ vs. Sham
$P < 0.05$ vs. WT TAC

TG: accelerated dilatation during TAC



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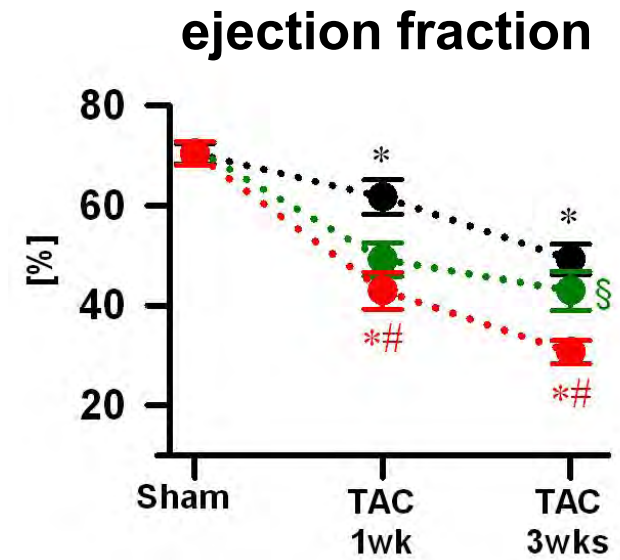
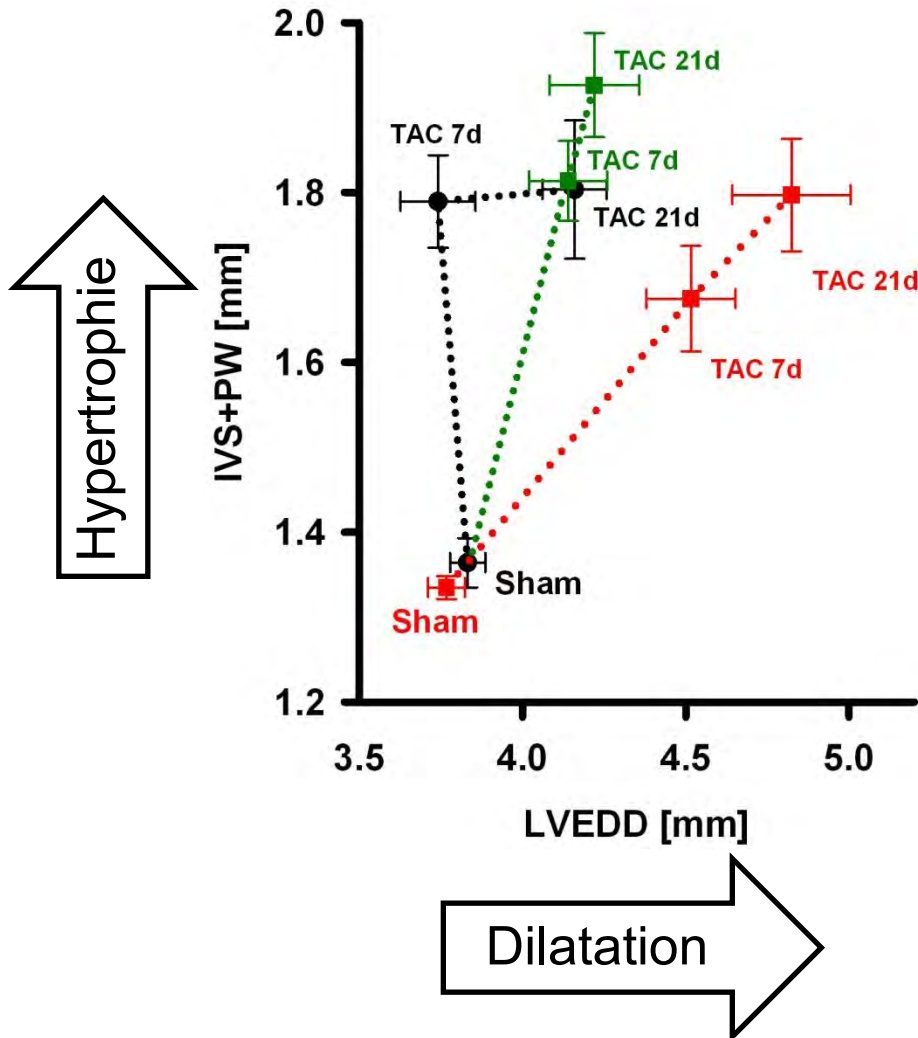


* $P < 0.05$ vs. Sham
$P < 0.05$ vs. WT TAC

JTV-519: sealing the RYR prevents dilatation



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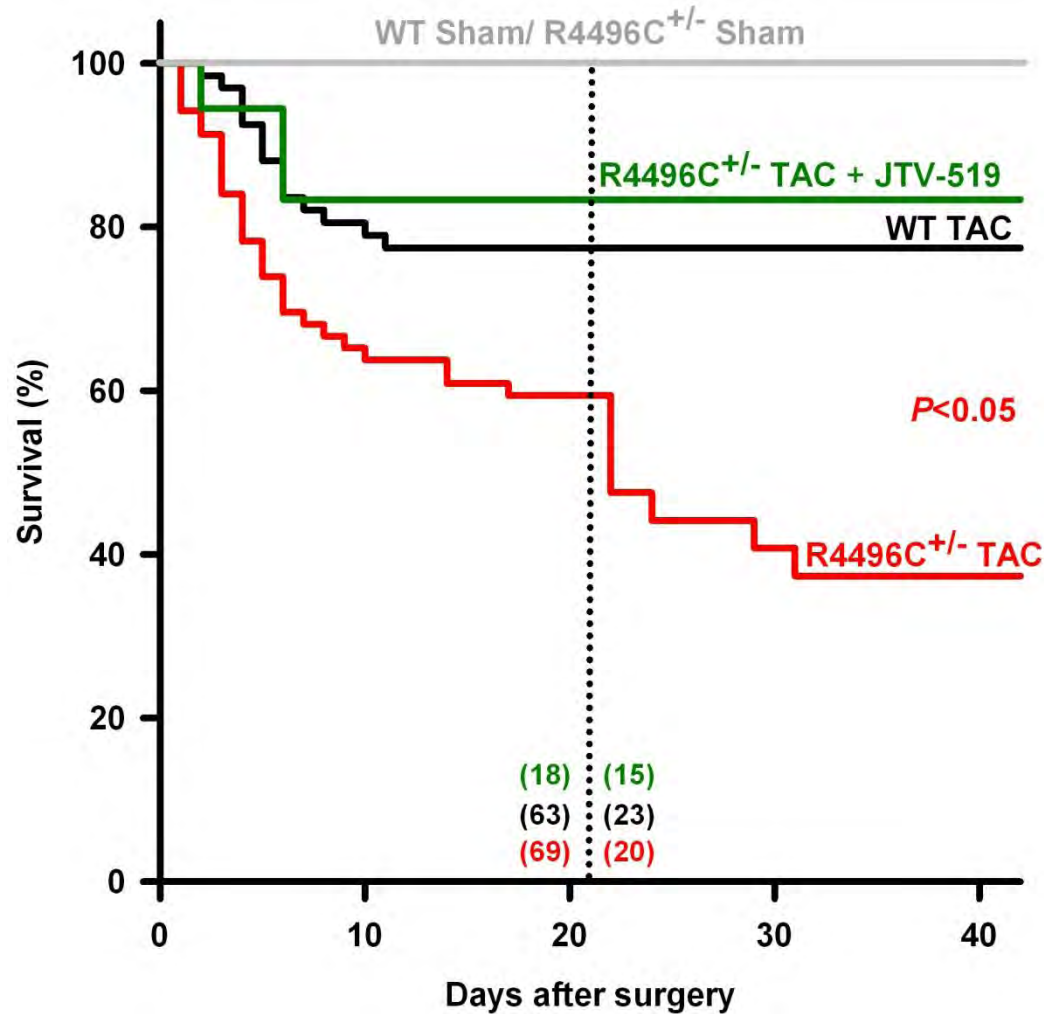


* $P < 0.05$ vs. Sham
 # $P < 0.05$ vs. WT TAC

JTV-519: sealing the RYR leak increases survival



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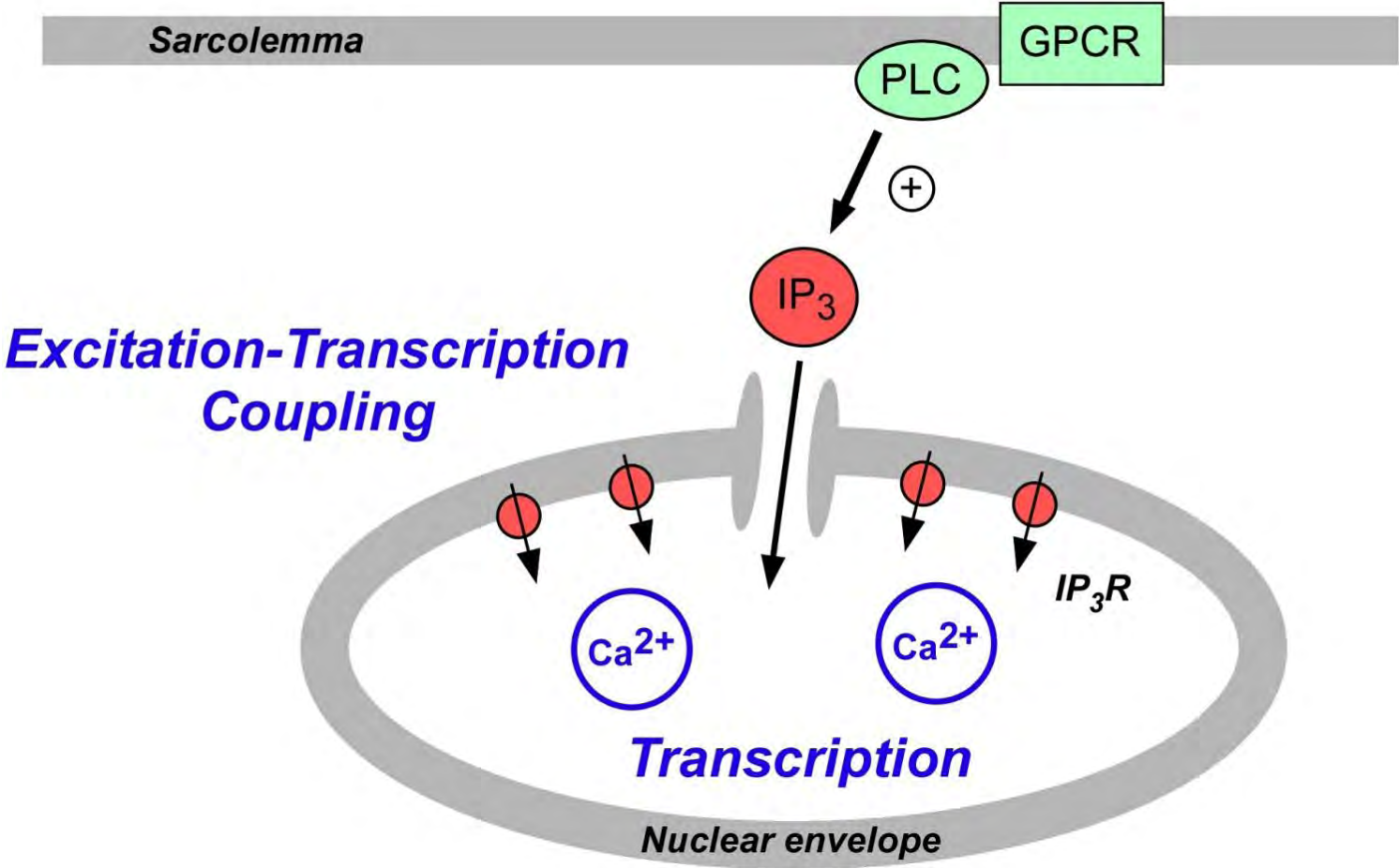


JTV-519:
69.1 ± 10.8 ng/ml (N=6)

Excitation-transcription coupling



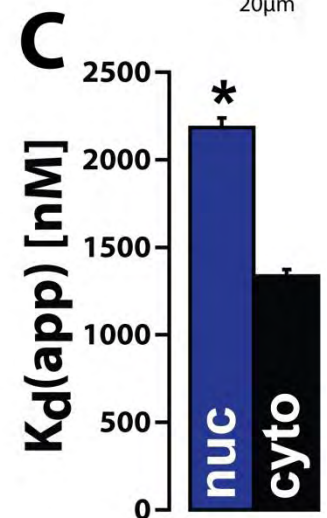
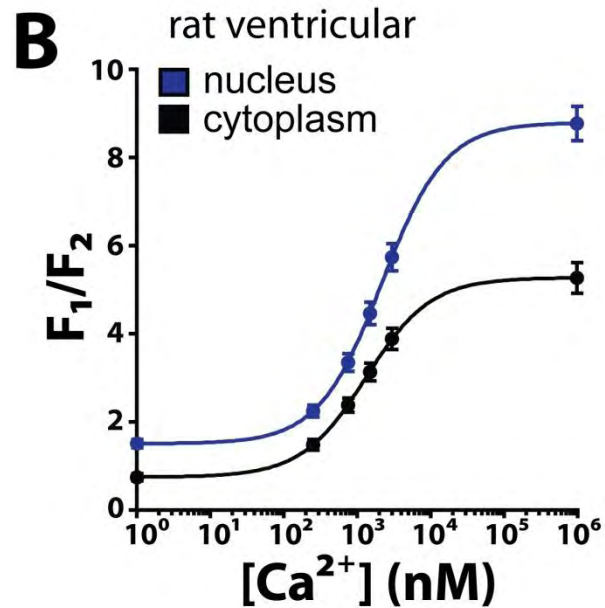
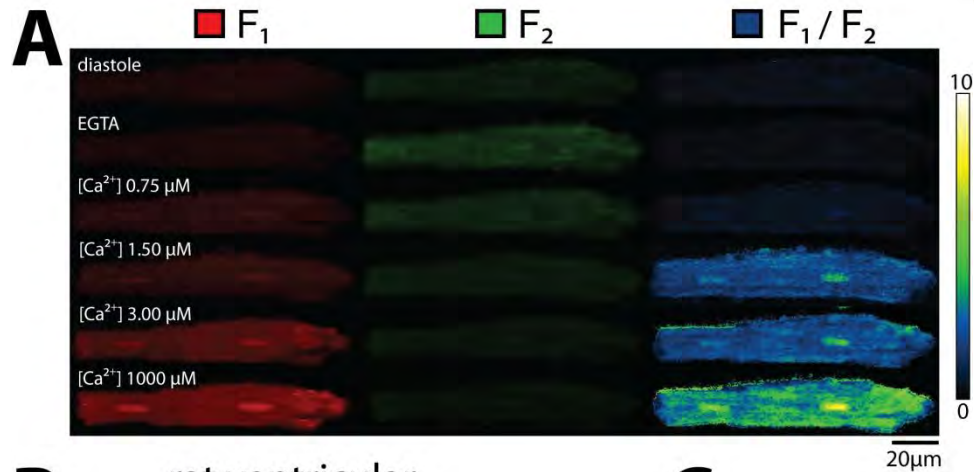
ET-1, Ang II, PE



Nuclear calcium \neq cytoplasmic calcium



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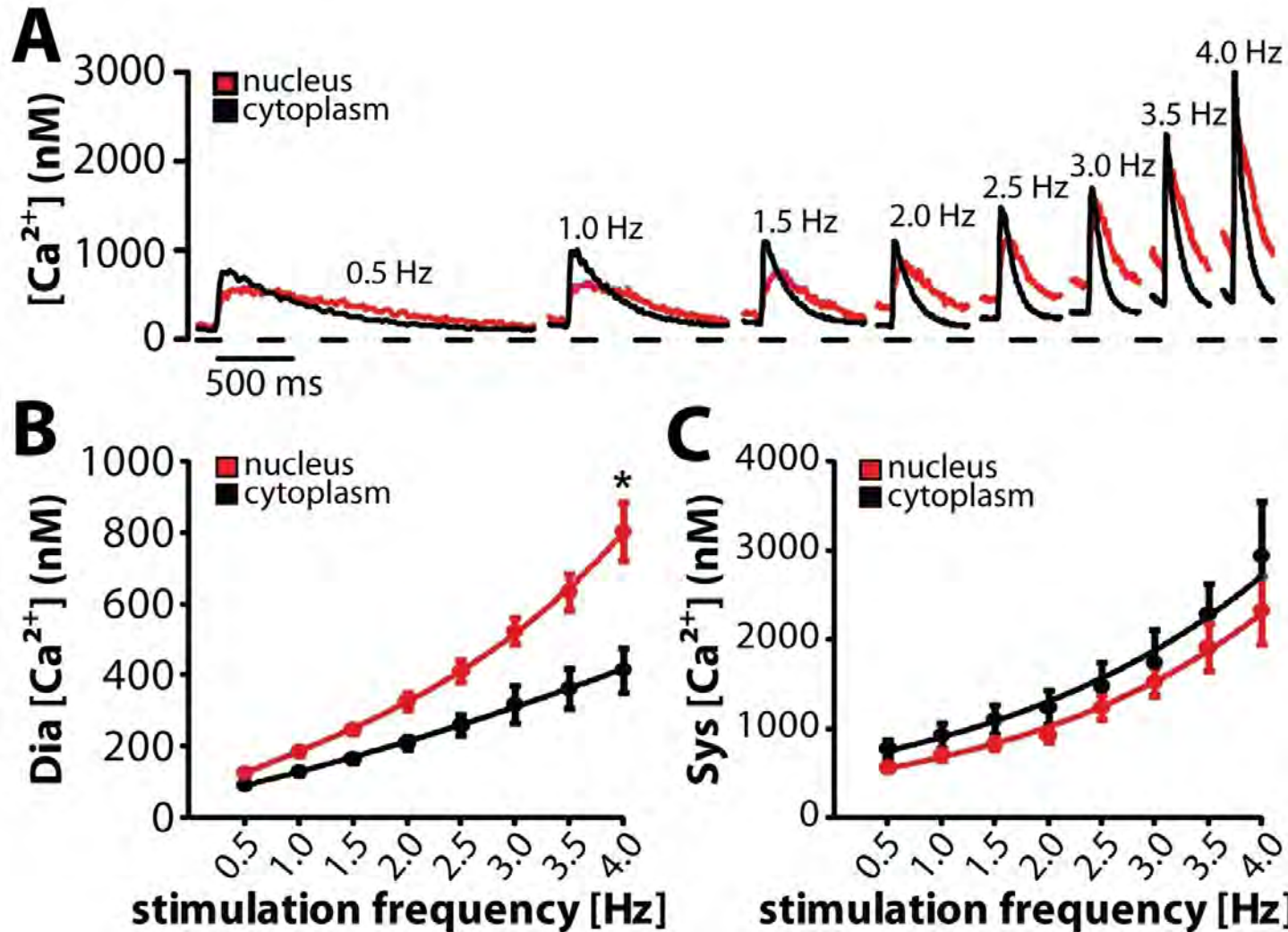


Ljubojevic et al. 2011. Biophys. J.

Nuclear calcium \neq cytoplasmic calcium



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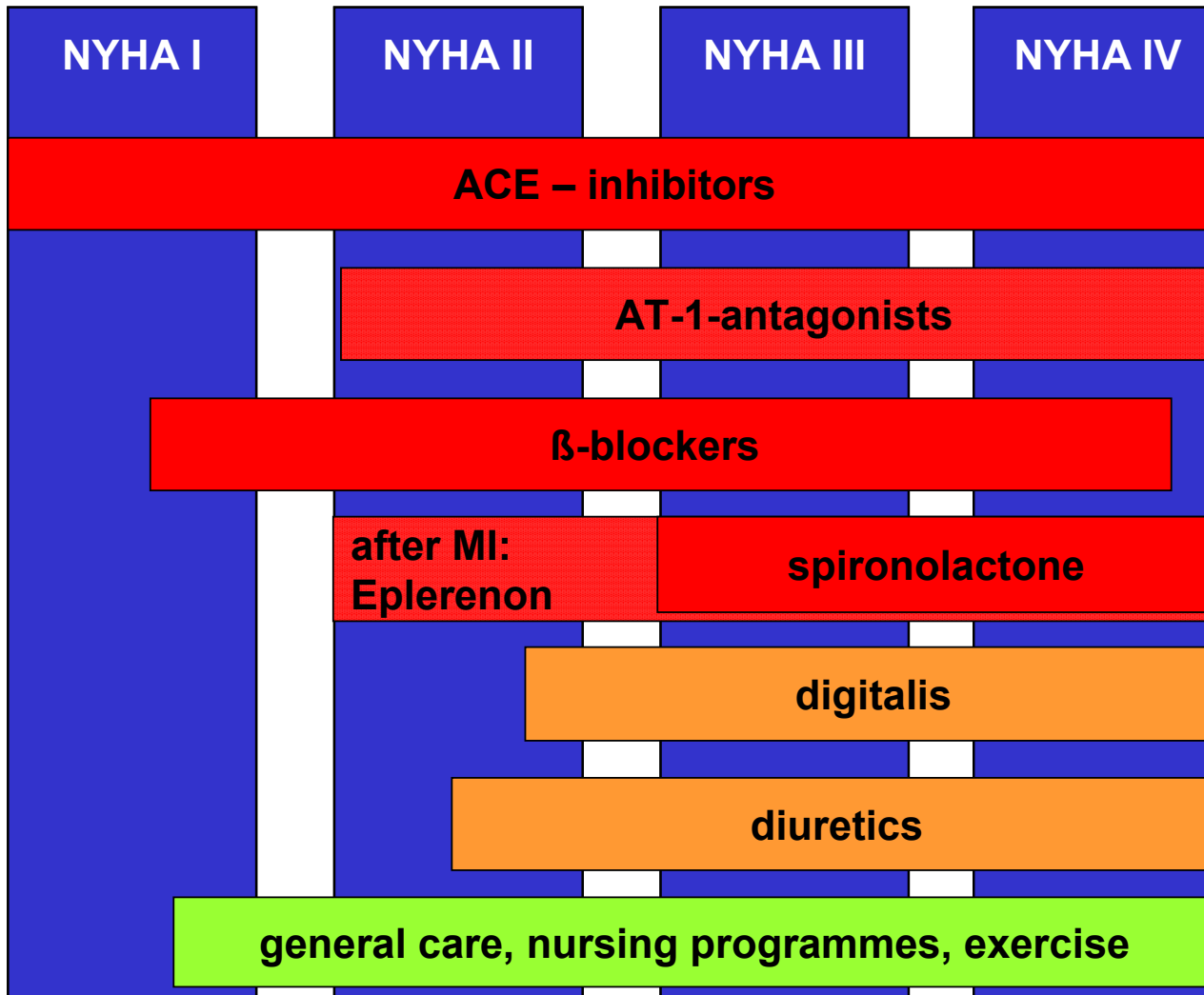


Ljubojevic et al. 2011. *Biophys. J.*

HFREF - therapy

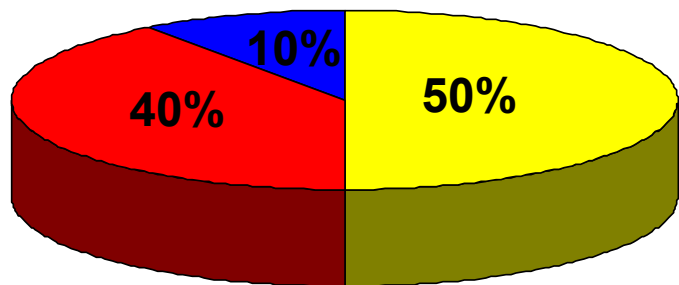


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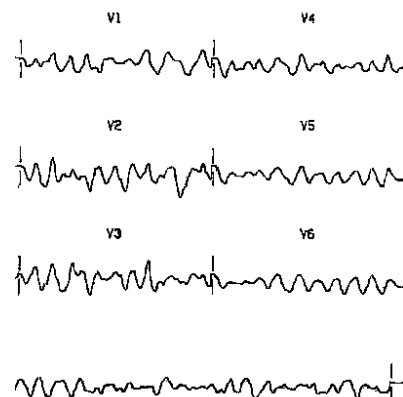
heart rate reduction:
ilvabradine?

devices: ICD and CRT



- pump failure
- arrhythmias
- other

Sudden cardiac death: ventricular fibrillation

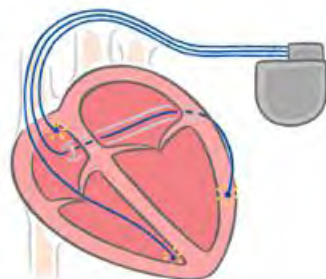


Indicated at
LV EF < 35%



left bundle branch block > 150 ms: CRT

Geb:	66 Jahre	HF	56 /min	Intervalle
Alter:	14	Achsen		RR
Geschl:	173,0 cm	P	38°	P
Grösse:	96,0 kg	QRS	14°	PQ
Gewicht:	130 / 85 mmHg	T	173°	QRS
BD:				QT
				QTc
Med:	Triflacin, Dilatrend, Sorbis, Lasix			
Bem:				



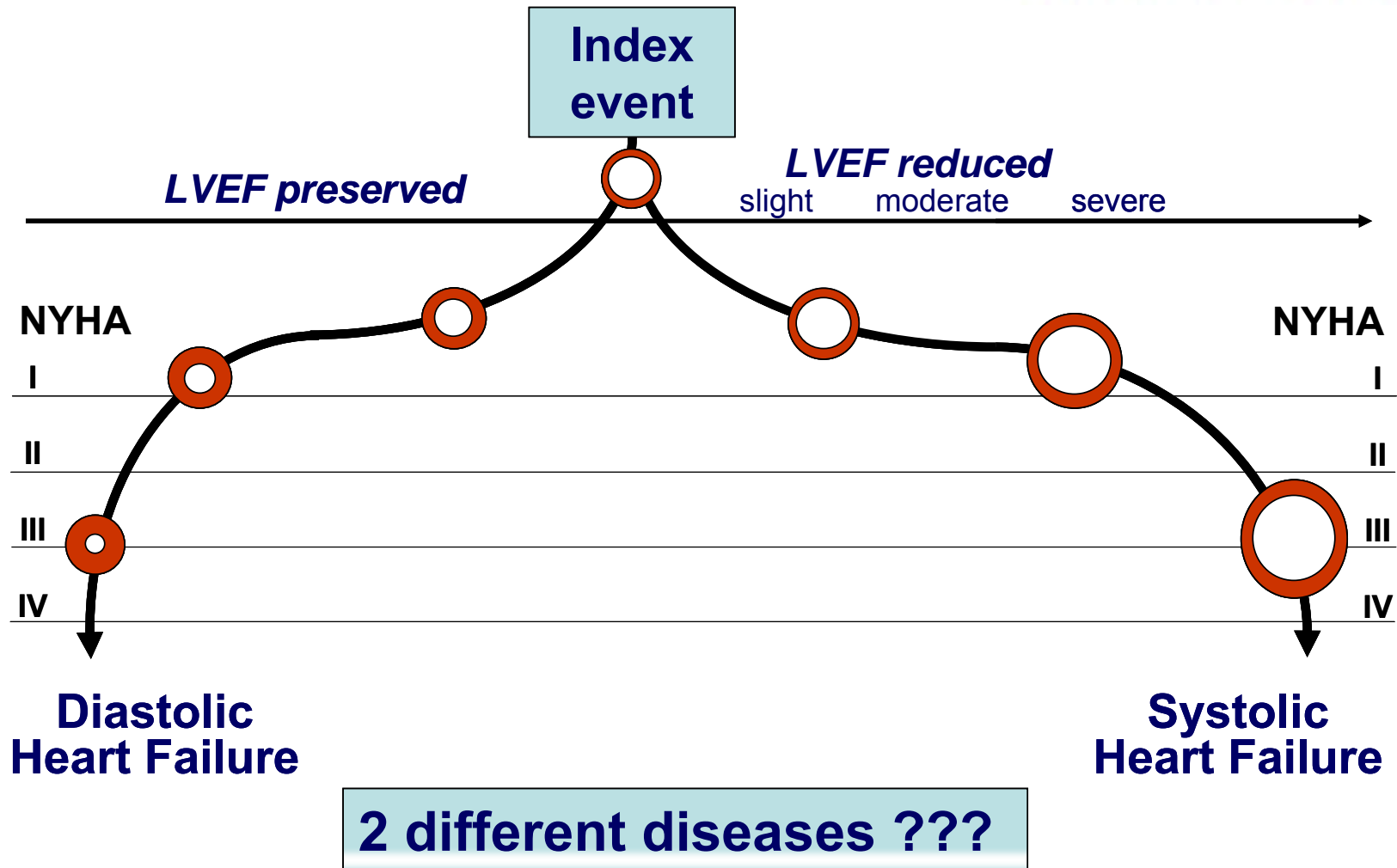
heart failure pacemaker



HFREF vs HFPEF



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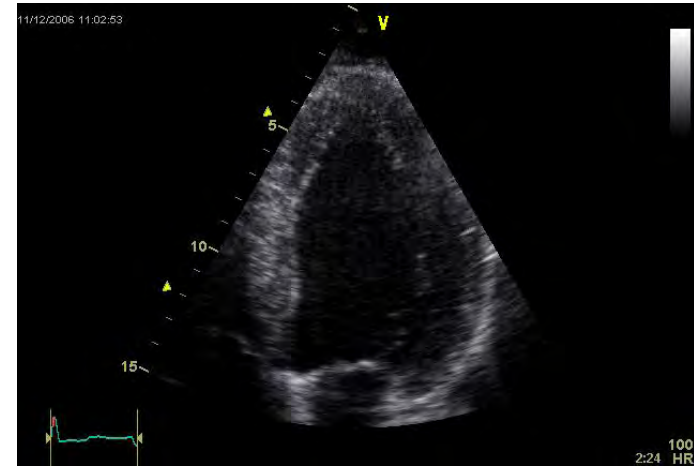
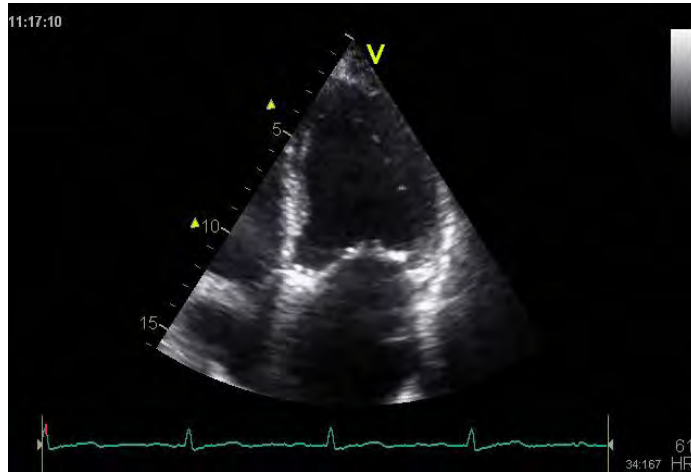


Modified after: G. De Keulenaer, 2006

HFPEF



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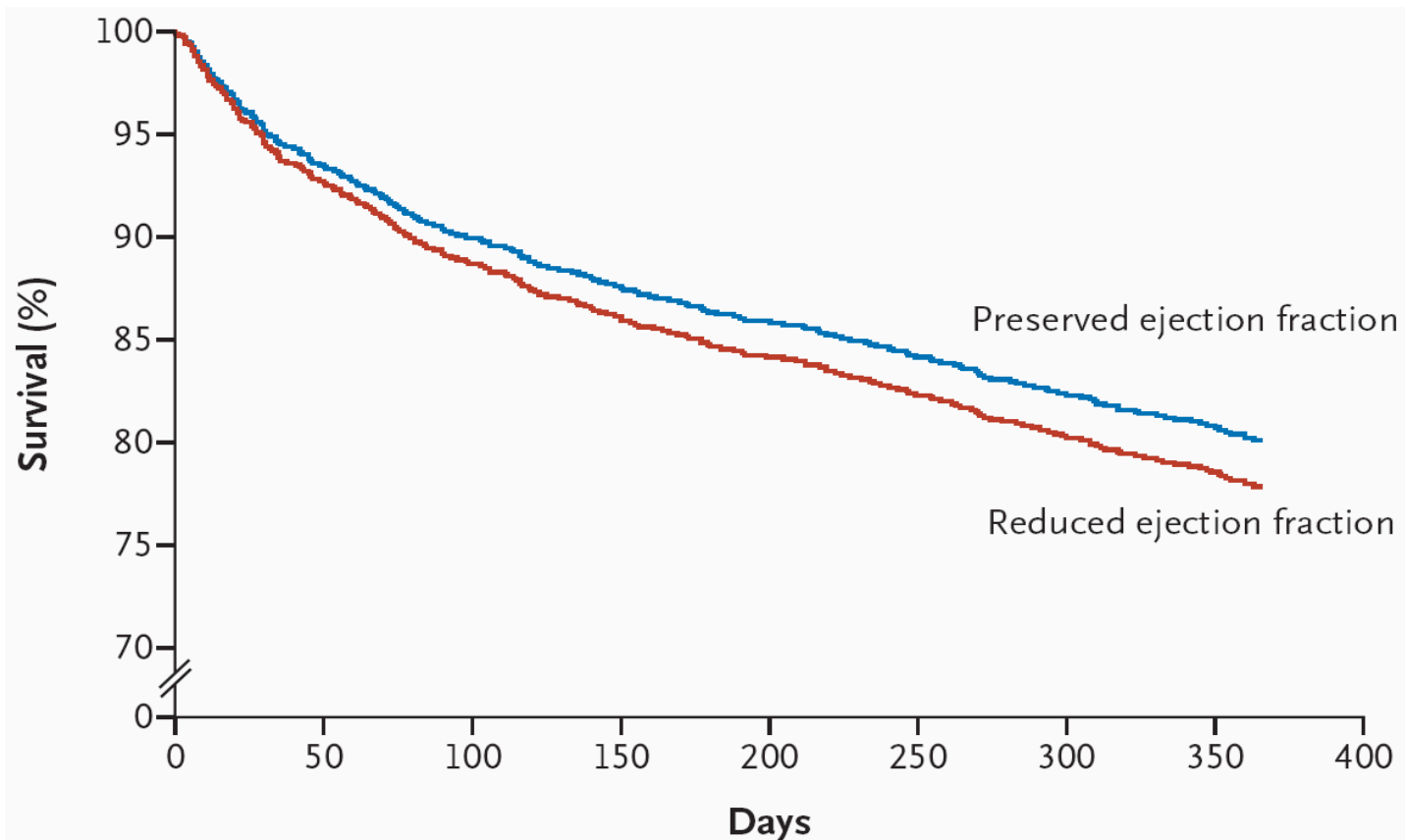
- increased wall thickness
- preserved ejection fraction
- reduced longitudinal shortening
- atrial dilatation
- atrial dysfunction

Mortality in HFPEF vs HFREF



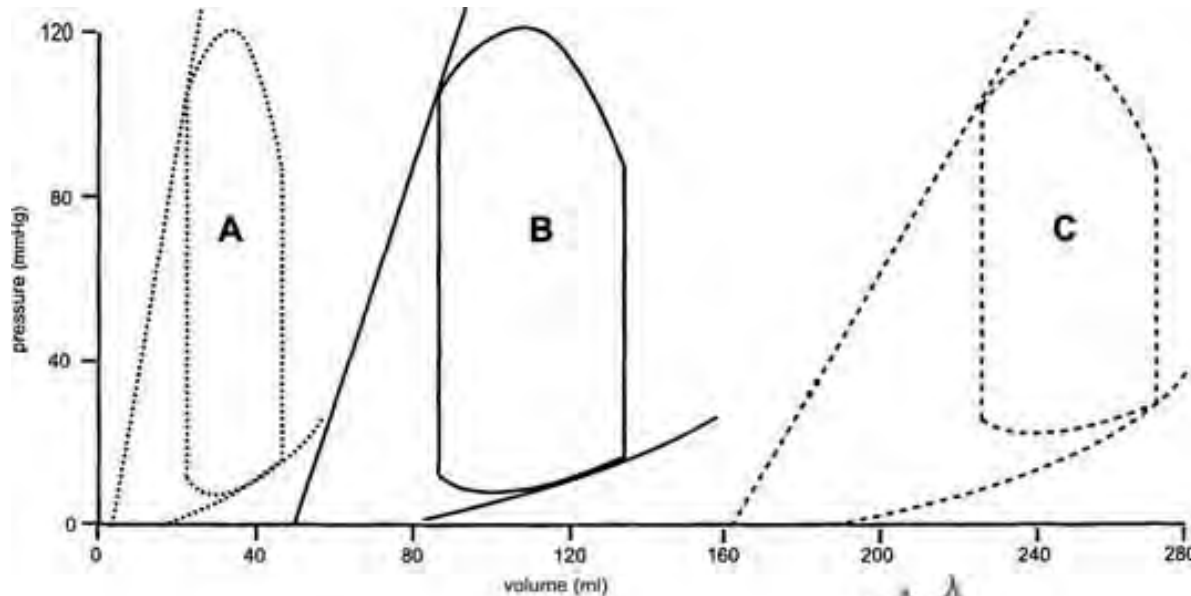
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2802 CHF patients, EF <50% vs. EF >50%



Redfield, 2003

HFPEF vs HFREF



A. Concentric



B. Normal

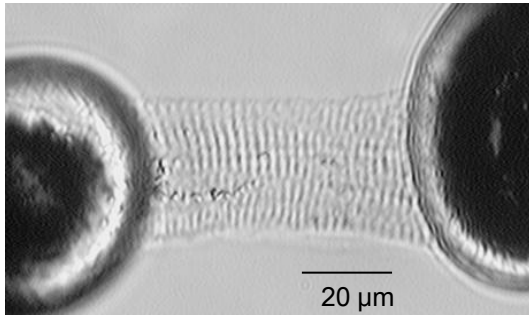


C. Eccentric

- (aortic stenosis)
- risk factors
- no animal model
- no definite trigger
- no definite treatment!

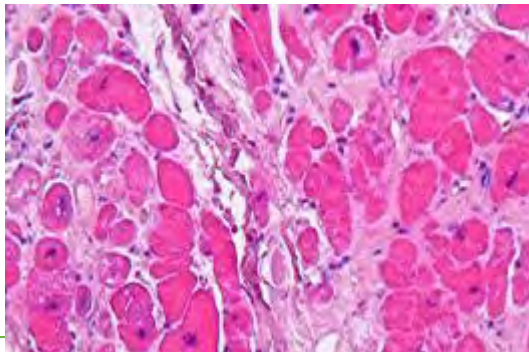
- infarction
- tachycardia
- aortic stenosis
- toxic
- shunt

HFPEF: ?



cardiomyocyte:

myocardial mechanismsn:



Extracellular Matrix:

- calcium
- metabolism
- myofilamnets (Titin)

- fibrillar collagen
- basal membran
- proteoglykanes / AGEs
- MMIP/TIMP

HFPEF: accumulation of risk factors



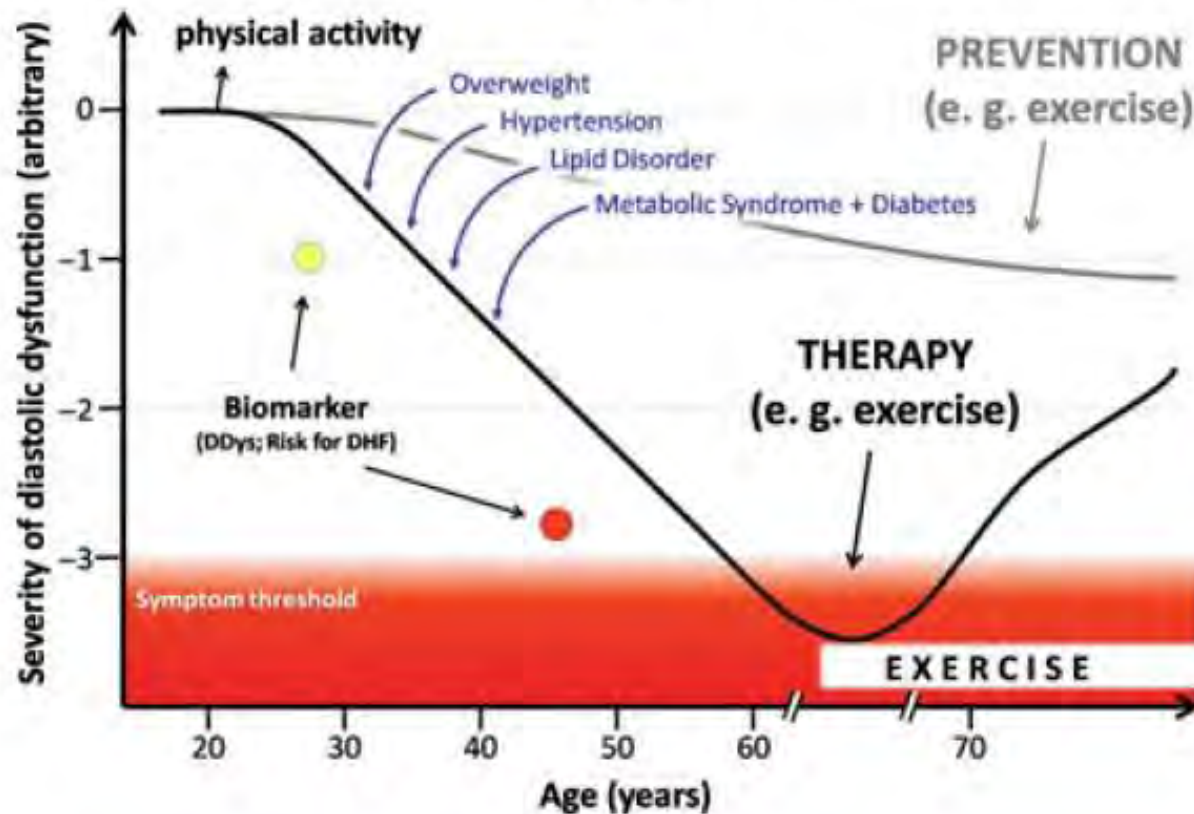
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HFPEF: accumulation of risk factors



Evolution, Prevention and Therapy of Diastolic Heart Failure



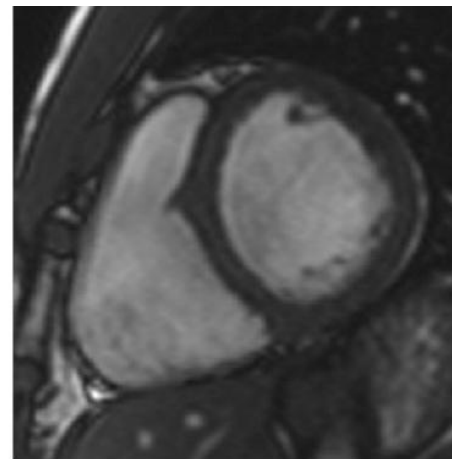
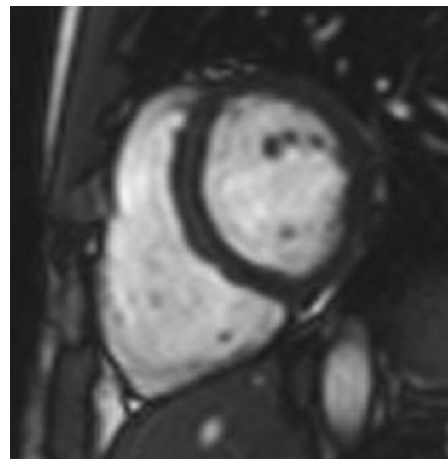
Physiological remodeling: triathletes



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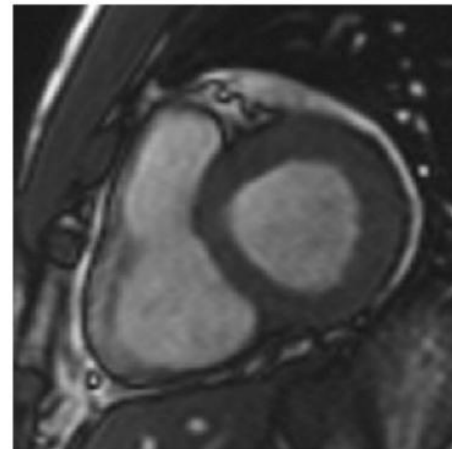
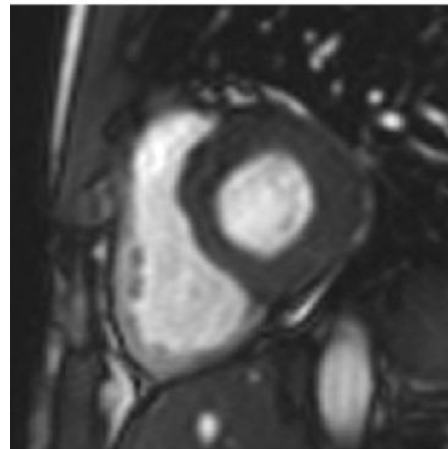
control

triathletes



a.

b.



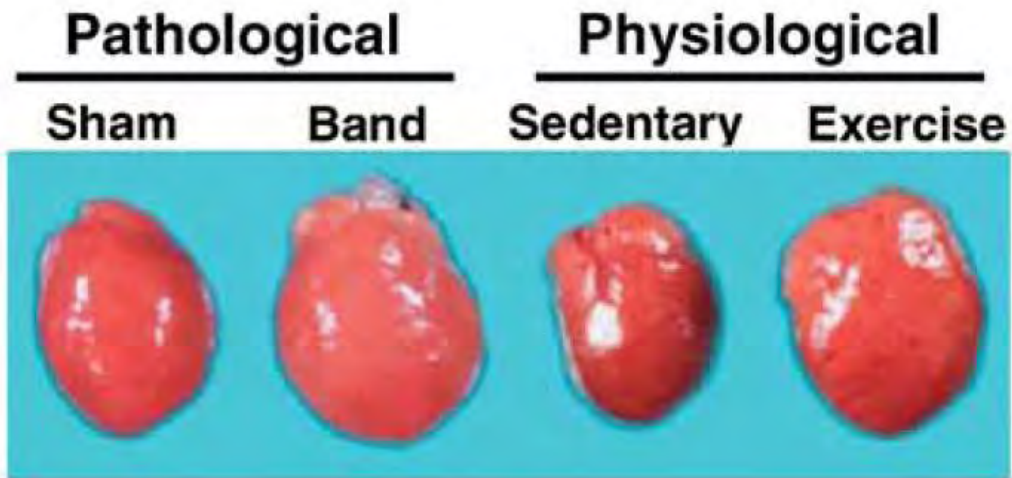
ED

ES

Parameter	Triathletes (n = 26)*	Control Subjects (n = 27)*	P Value
Left ventricle			
End-diastolic volume index (mL/m ²)	115.1 ± 12.1	90.8 ± 11.2	<.001†
End-systolic volume index (mL/m ²)	46.1 ± 9.8	36.9 ± 8.2	<.001†
Stroke volume index (mL/m ²)	69.0 ± 7.2	53.9 ± 7.7	<.001†
Mass index at end diastole (g/m ²)	83.2 ± 7.6	63.6 ± 7.1	<.001†
Wall thickness (mm)	9.8 ± 1.0	8.5 ± 0.9	<.001†
EF (%)‡	60.2 ± 5.6	59.5 ± 6.0	.679

- proportionate increase of LV volumes and wall thickness
- no fibrosis
- increased capillar density
- normal CM function

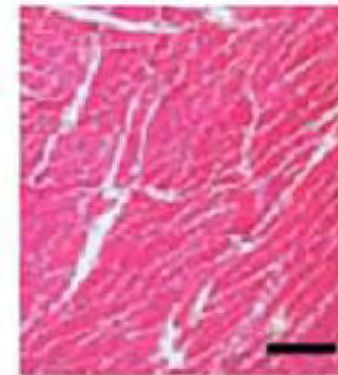
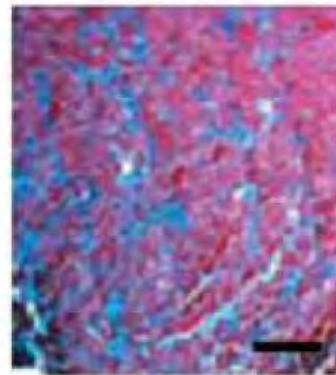
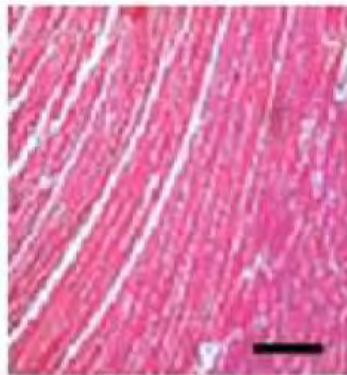
Scharf et al., Radiology, 2010



Control

**Pathological
Band**

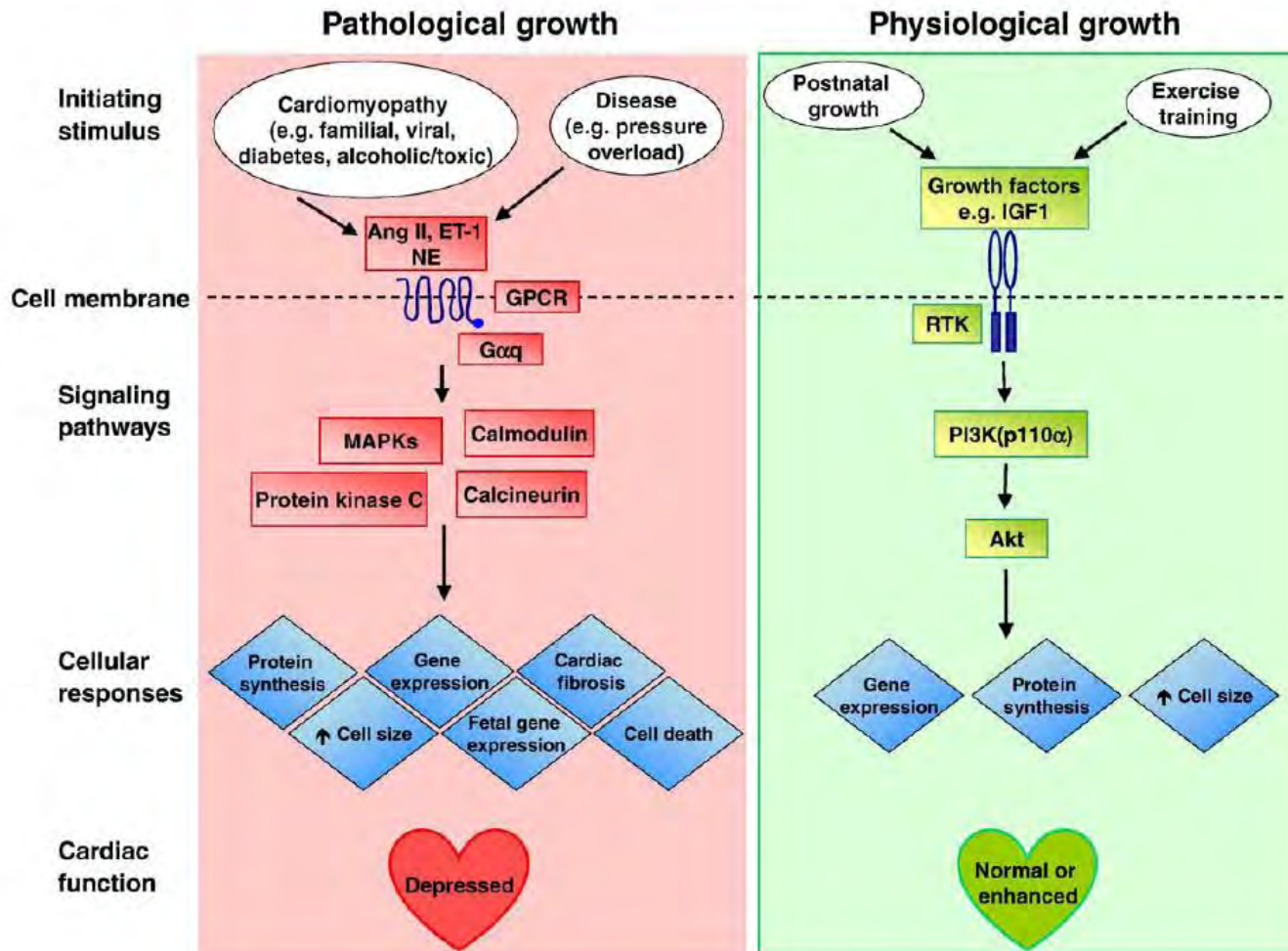
**Physiological
Exercise**



Pathological vs physiological hypertrophy: signalling



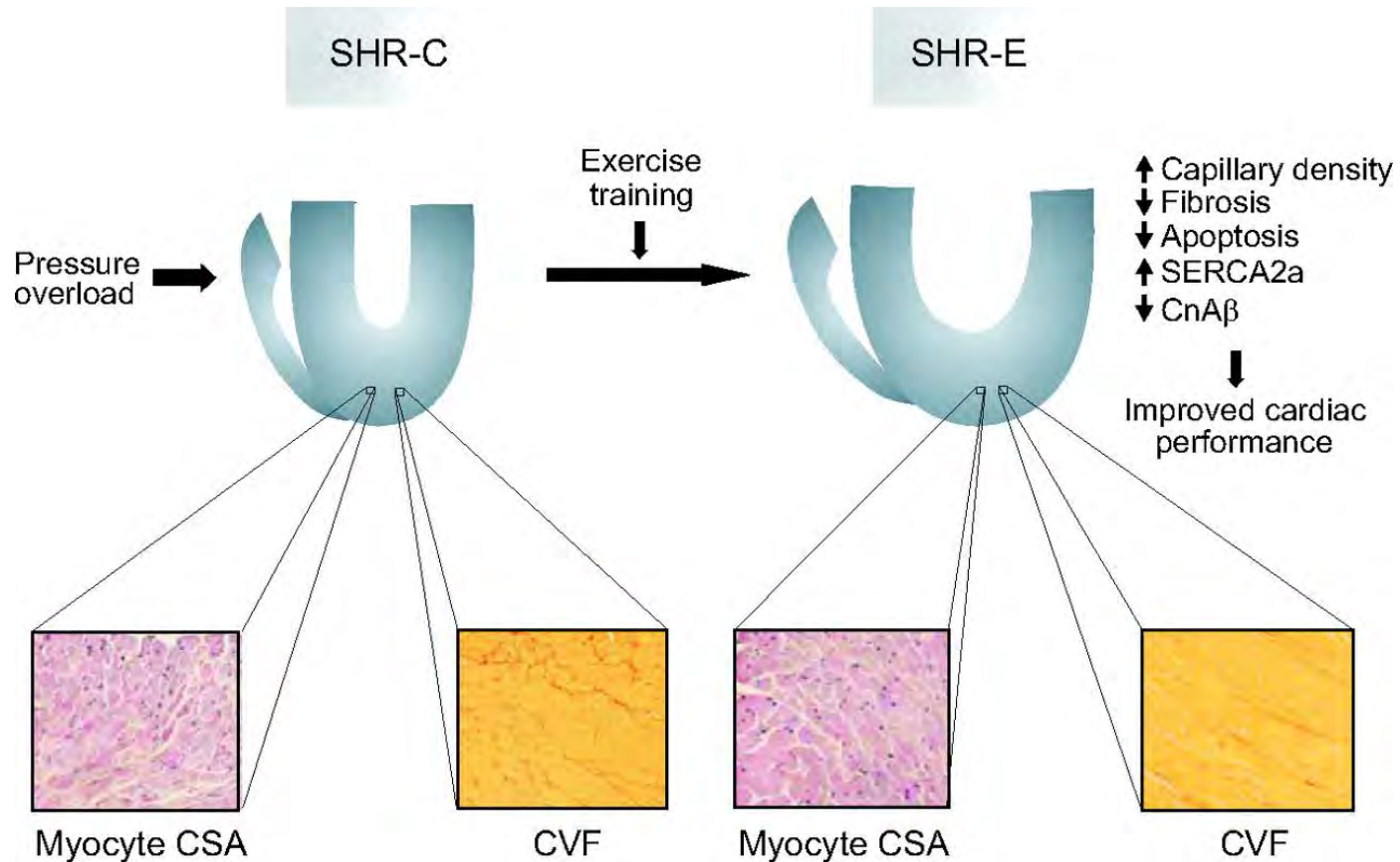
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Can physiological beat pathological hypertrophy ?

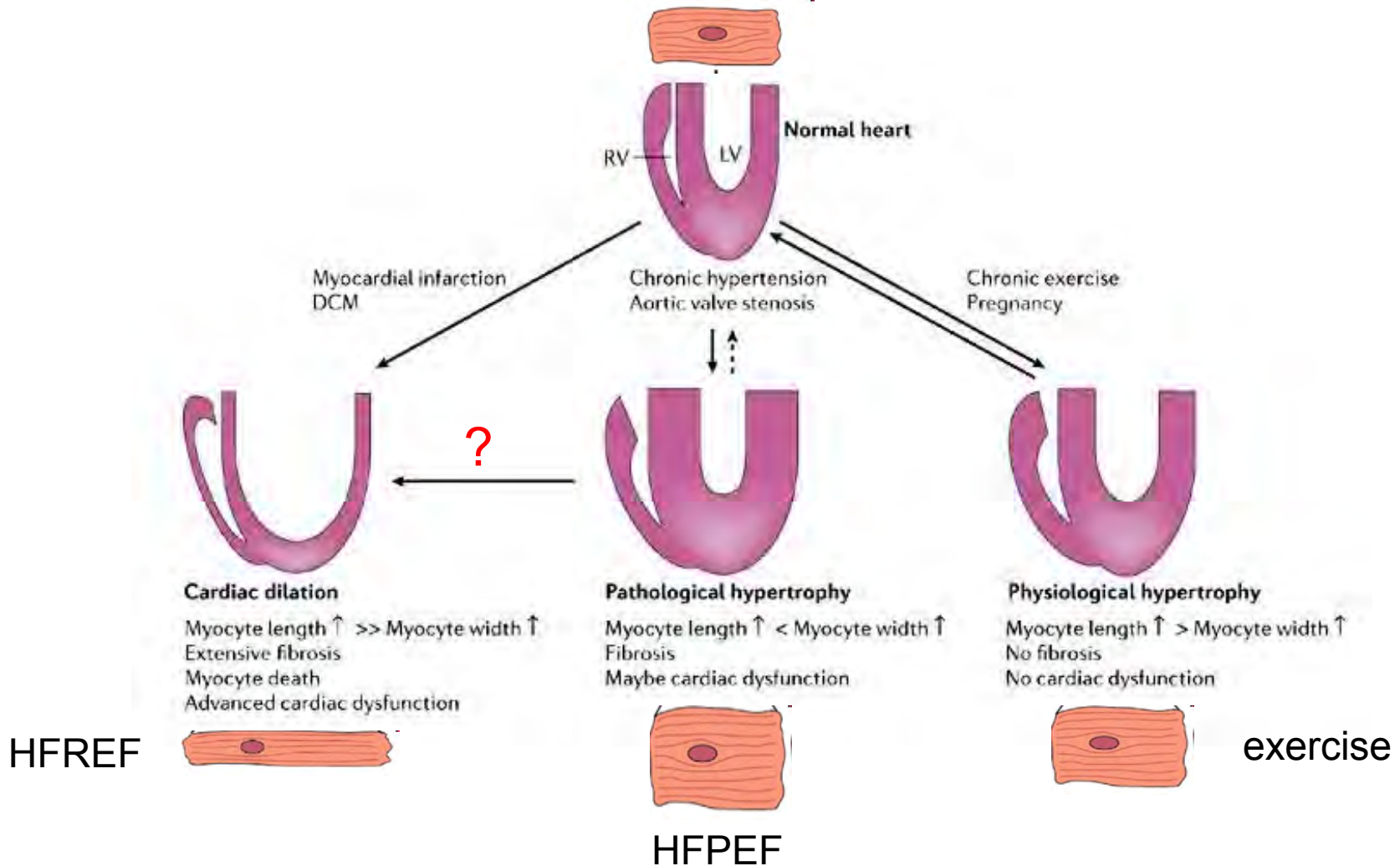


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Garciaarena et al., Hypertension 2009

Remodeling phenotypes





- remodeling during heart failure is a progressive, systemic disease
- myocardial remodeling encompasses fibrosis, apoptosis, capillaries and dysfunctional CMs

- phenotype HFREF: the dilated heart
 - CM: altered calcium handling
 - leaky RyR receptor promotes arrhythmias contractile failure and remodeling
 - nuclear calcium is an own cellular compartment

- overt heart failure can appear as HFPEF (non-dilated), same mortality as HFREF
- therapies established in HFREF do not work in HFPEF (ACEI, AT1B, β -blockers)
- there are no definite models for HFPEF, it is hardly understood

- exercise induces a healthy hypertrophy, has a distinct signalling and can counteract pathological hypertrophy
- exercise works in HFPEF, clue to signal transduction?