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Exercise Training in Adverse Cardiac Remodeling

13-06-2012

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Erasmus MC, University Medical Center Rotterdam
Rotterdam, The Netherlands

Cardiac Remodeling

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Myocardial Infarction

Aortic Stenosis

Physical Exercise

LV Remodeling and Function

Perfusion ↓
Function ↓

Physical Exercise

Perfusion ↑
Function ↑

Exercise in Adverse Cardiac Remodeling

- Exercise in Chronic Heart Failure
  - Clinical Evidence
  - Mechanisms

- Exercise in Adverse Remodeling
  - Initial Observations
  - Mechanisms
  - Clinical Evidence

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Exercise in Adverse Cardiac Remodeling

- Exercise in Chronic Heart Failure
  - *Clinical Evidence*
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- Exercise in Adverse Remodeling
  - Initial Observations
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Exercise Training in Chronic Heart Failure

Key points

- Exercise training in patients with heart failure has been the subject of more than 100 studies since 1990
- Several systematic meta-analyses and systematic review have confirmed that training can improve exercise capacity by 15–20% in patients with heart failure
- Multiple randomized controlled trials have shown that exercise training improves quality of life in patients with heart failure and strongly suggest benefits in terms of major clinical outcomes
- Long-term aerobic exercise training at ≥40% of maximal capacity either at home or in hospital, combined with resistance training, is recommended for all patients with stable systolic heart failure

AJ Coats Nat Rev Cardiol 2011

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Exercise Training in Chronic Heart Failure

ESC Guidelines May 2012

Recommendations for exercise prescription and multidisciplinary management

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended that regular aerobic exercise is encouraged in patients with heart failure to improve functional capacity and symptoms.	I	A	262, 263
It is recommended that patients with heart failure are enrolled in a multidisciplinary-care management programme to reduce the risk of heart failure hospitalization.	I	A	236, 259, 264

[a]Class of recommendation.
[b]Level of evidence.
[c]References.

McMurray et al. Eur Heart J 2012

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Exercise in Adverse Cardiac Remodeling

- Exercise in Chronic Heart Failure
  - Clinical Evidence
  - *Mechanisms*

- Exercise in Adverse Remodeling
  - Initial Observations
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Exercise Training in Chronic Heart Failure

Mechanisms of Action

- Peripheral Training Effects

  - skeletal muscle adaptations

- Cardiovascular Training Effects

  - Increased dynamic heart rate range

- Interaction With Adverse Remodeling

Benito & Nattel J Physiol 2009

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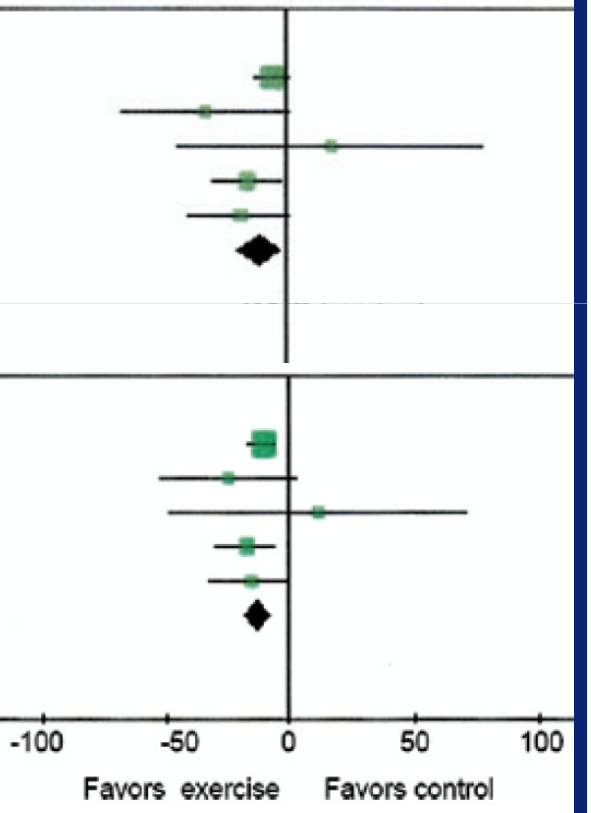
Exercise Training in Chronic Heart Failure

Aerobic Exercise

Study or sub - category	N	Exercise Mean (SD)	N	Control Mean (SD)	WMD (random) 95% CI
End-Diastolic Volume					
Belardinelli 1999	50	-7.00 (18.52)	49	-1.00 (18.52)	
Hambrecht 2000	36	-22.00 (80.47)	37	11.00 (67.02)	
Myers 2002	12	-0.70 (50.48)	12	-18.00 (96.02)	
Giannuzzi 2003	45	-7.00 (26.00)	45	9.00 (41.51)	
Passino 2006	44	-15.00 (47.83)	41	4.00 (48.34)	
Subtotal (95%CI)	187		184		
Test for heterogeneity: Chi^2=5.07, df = 4 (P=0.28),I^2= 21.1%					
Test for overall effect: Z= 2.66 (P= 0.008)					
End-Systolic Volume					
Belardinelli 1999	50	-8.00 (13.53)	49	3.00 (16.00)	
Hambrecht 2000	36	-24.00(65.51)	37	1.00 (56.00)	
Myers 2002	12	-7.70 (49.27)	12	-18.90 (94.69)	
Giannuzzi 2003	45	-10.00 (24.00)	45	8.00 (34.00)	
Passino 2006	44	-14.00 (36.93)	41	2.00 (41.99)	
Subtotal (95% CI)	187		184		
Test for heterogeneity: Chi^2 = 2.54, df = 4 (P = 0.64), I^2 = 0%					
Test for overall effect: Z = 5.11 (P < 0.00001)					



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Haykowsky et al. J Am Coll Cardiol 2007

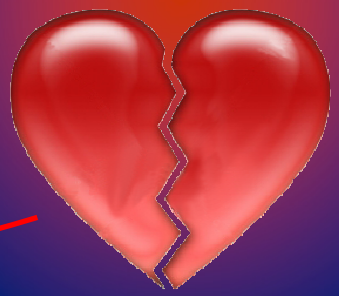
Cardiac Remodeling

Myocardial Infarction

Physical Exercise

LV Remodeling and Function

Perfusion ↓
Function ↓



Physical Exercise

Perfusion ↑
Function ↑

Exercise in Adverse Cardiac Remodeling

- Exercise in Chronic Heart Failure
  - Clinical Evidence
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Cardiac Remodeling and Dysfunction

Effect of Exercise Training After an Acute MI

- Most clinical and experimental studies reported either no effect or beneficial effects

  de Waard et al. Circ Res 2007

- Exercise training *early* after a *large* acute MI may aggravate cardiac remodeling and dysfunction

  Jugdutt et al. JACC 1988
  Kubo et al. Am Heart J 2004
  Kloner et al. Am Heart J 1983
  Gaudron et al. Circulation 1994

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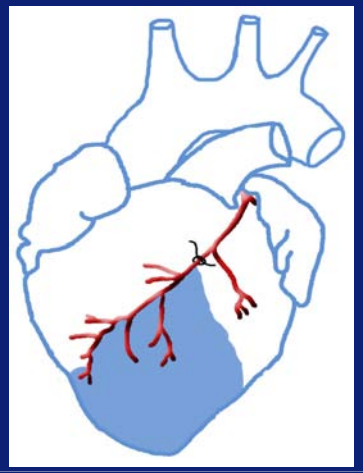
Mouse Models of Cardiac Remodeling

Myocardial infarction

8 wk Myocardial Infarction (MI) by permanent LAD ligation

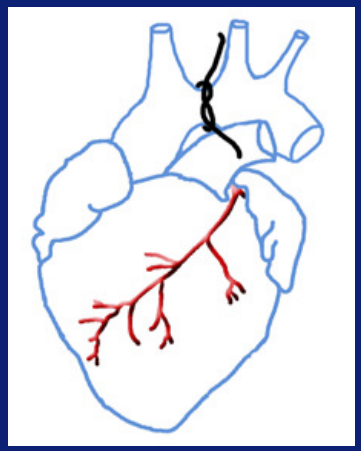
van den Bos et al. AJP 2005



Pressure overload

8 wk Transverse Aorta Constriction

van Deel et al. JMCC 2011



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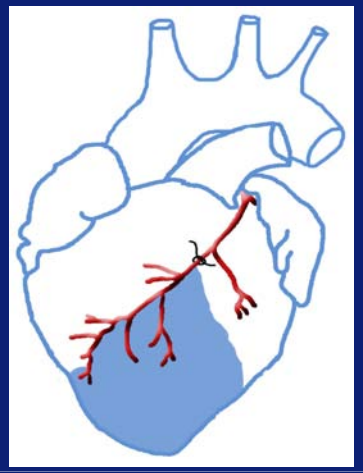

Pressure overload

8 wk Transverse Aorta Constriction

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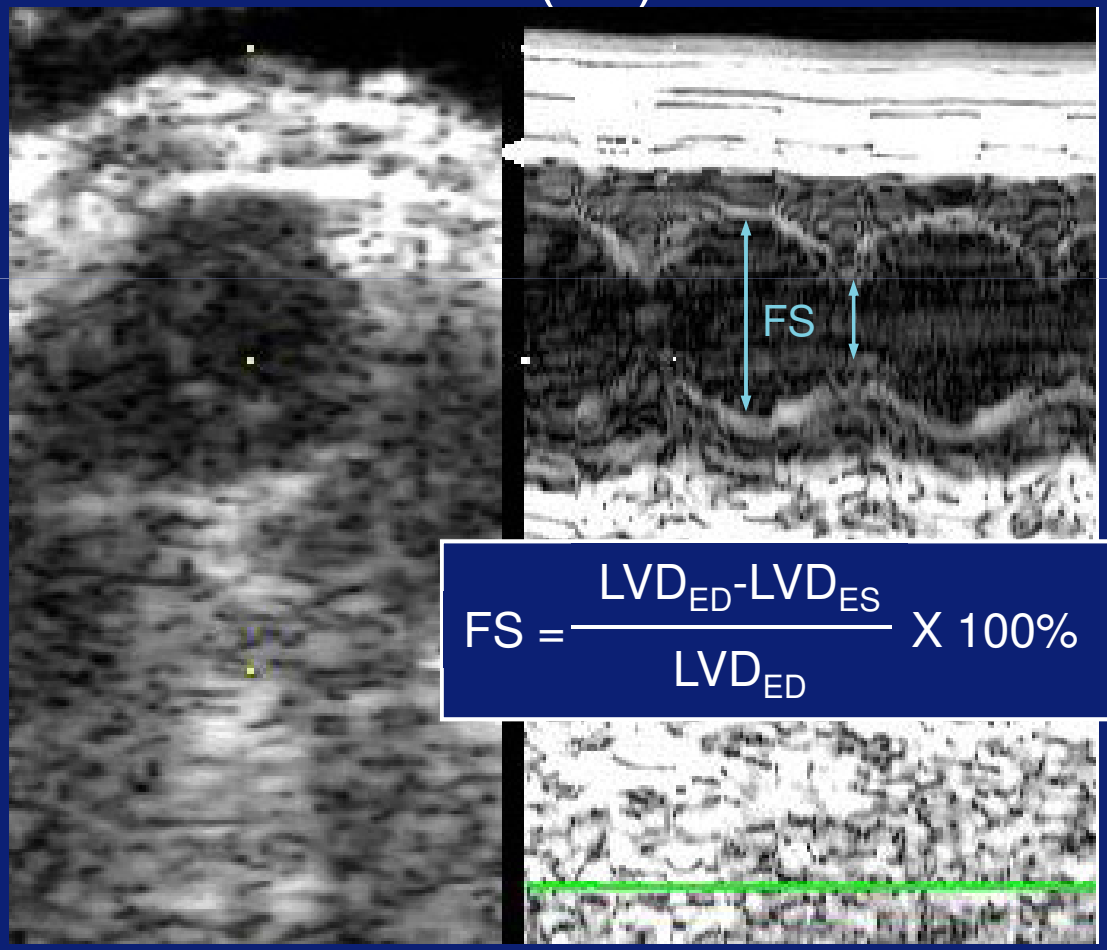
Methods

Echography

Left Ventricular (LV) dimensions



$$FS = \frac{LVD_{ED} - LVD_{ES}}{LVD_{ED}} \times 100\%$$

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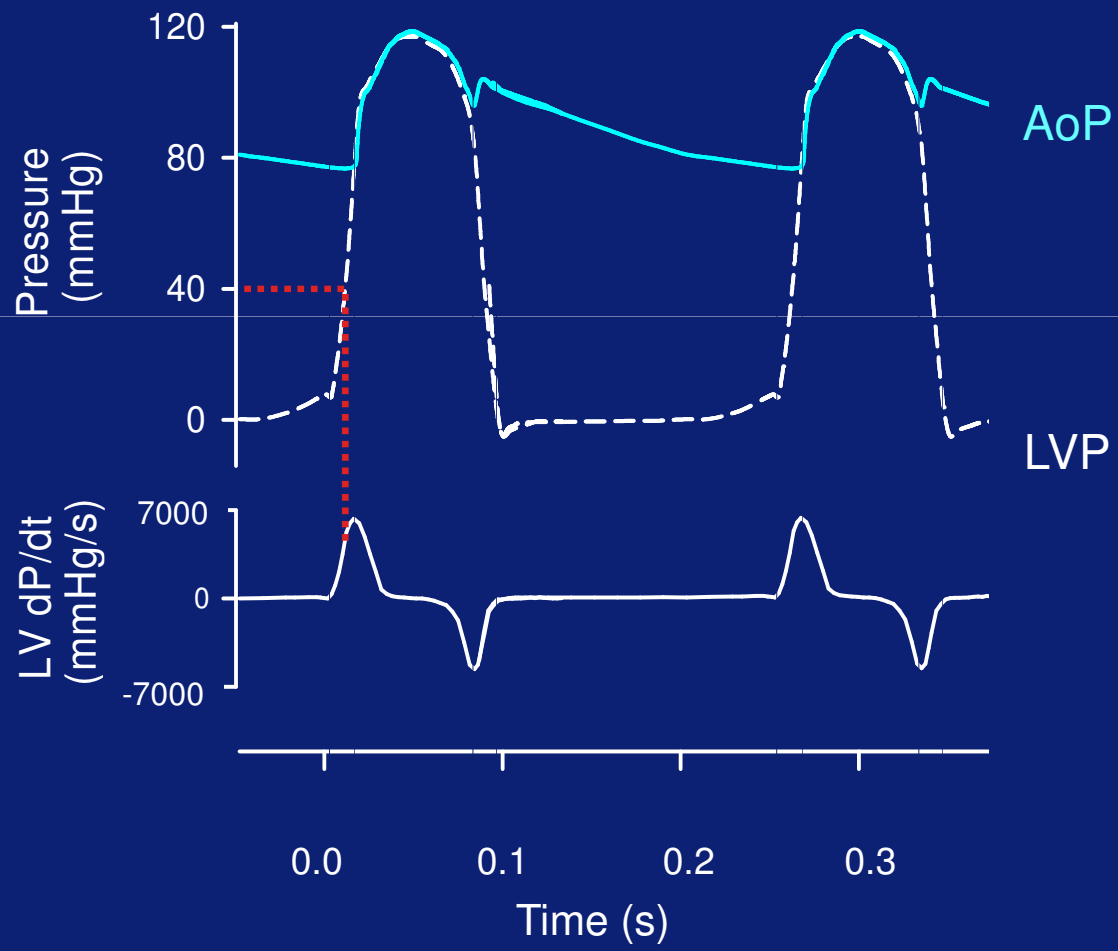
Methods

Hemodynamics



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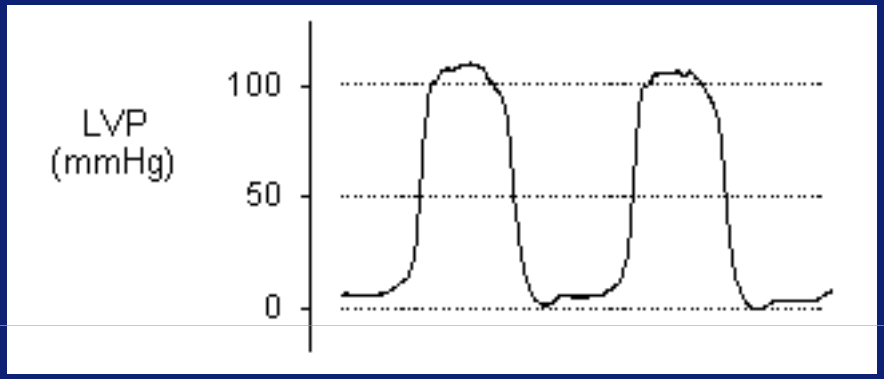
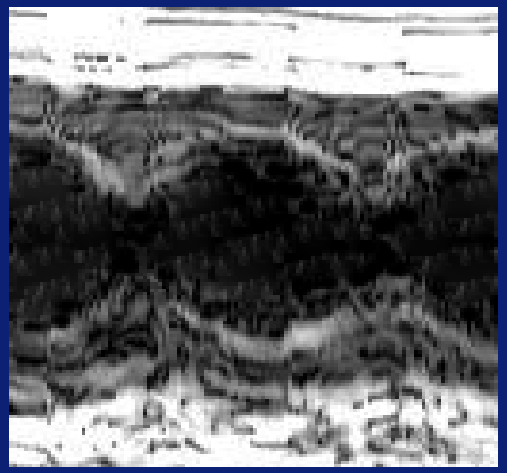
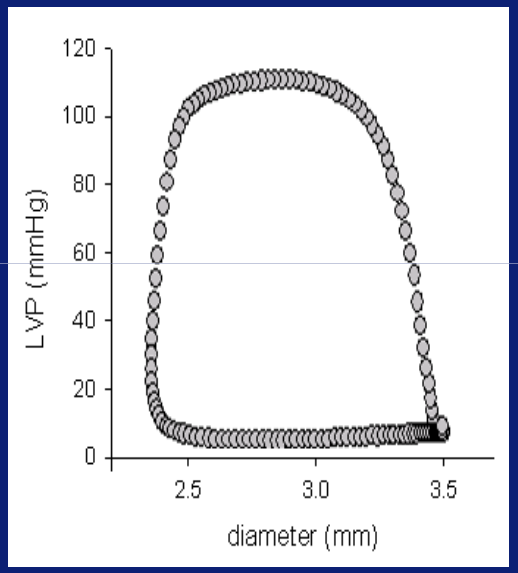
Results

Pressure Diameter Loop







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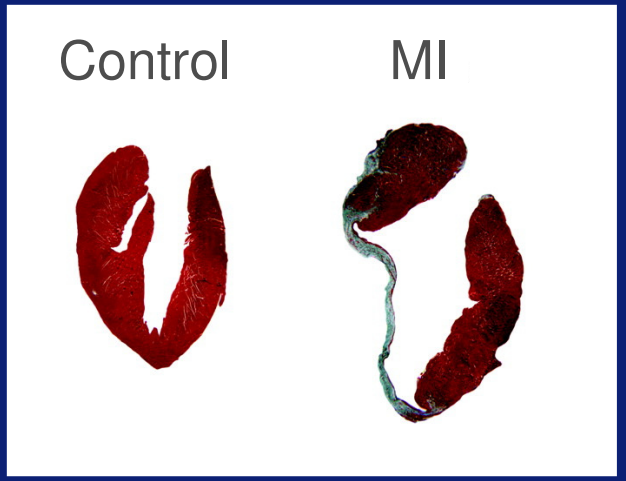
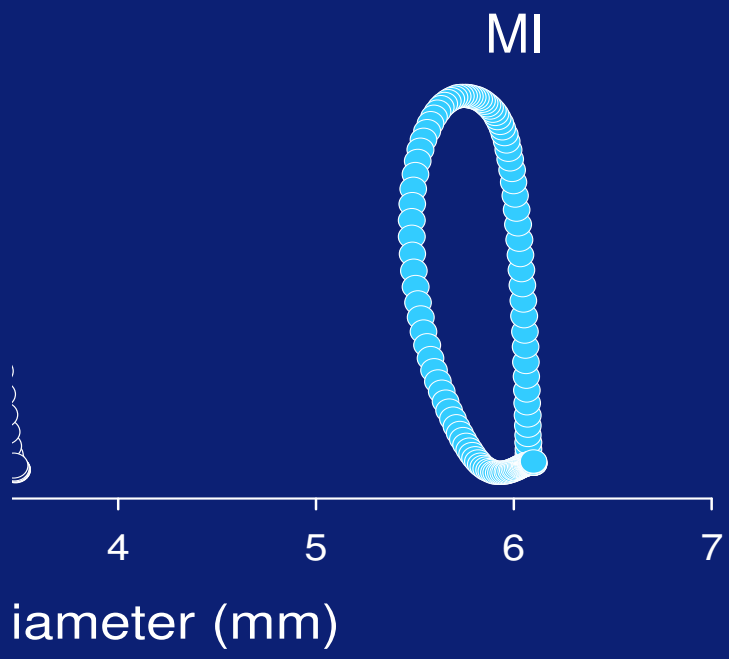
Left Ventricular Pressure-Diameter Relation





de Waard et al Circ Res 2007

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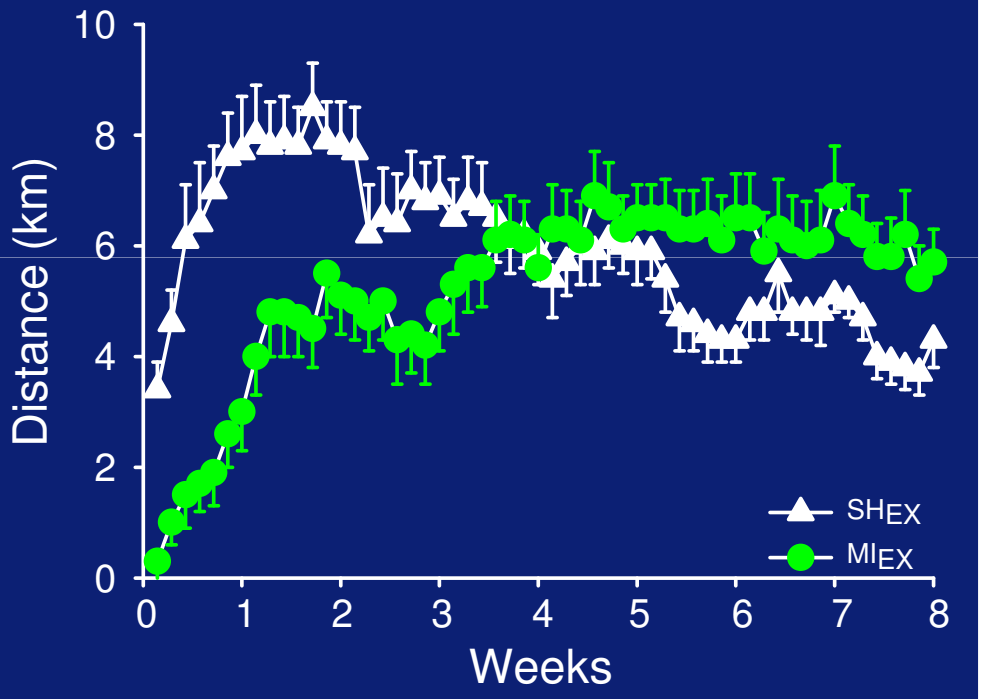
Exercise



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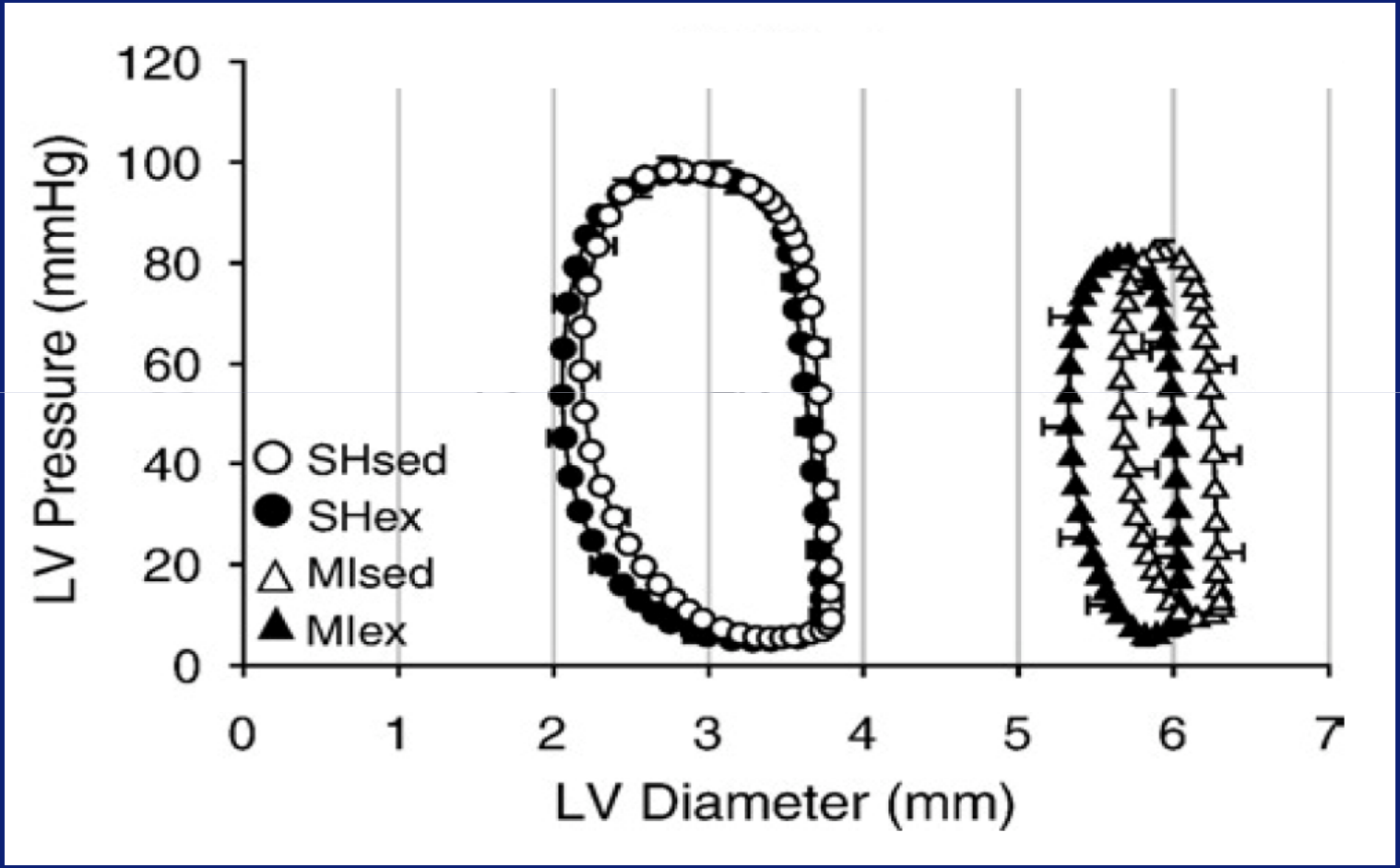
de Waard et al Circ Res 2007

Exercise and LV Dysfunction and Remodeling after MI



de Waard et al Circ Res 2007

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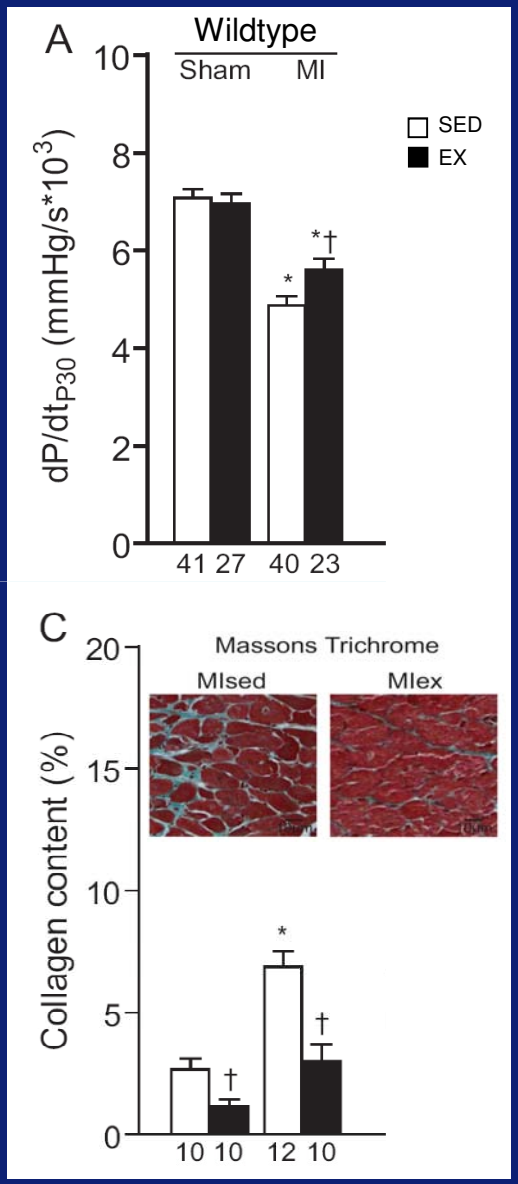
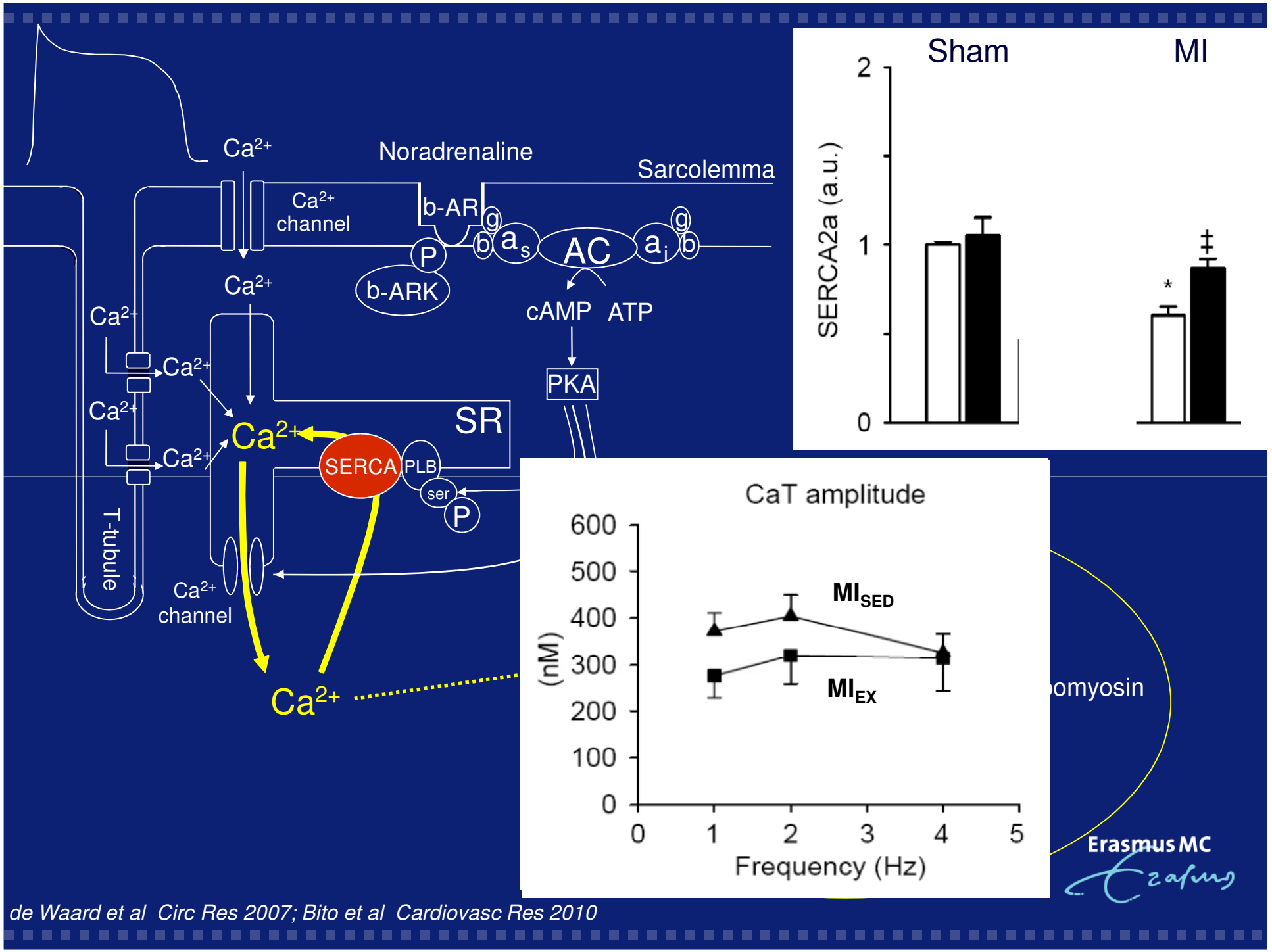
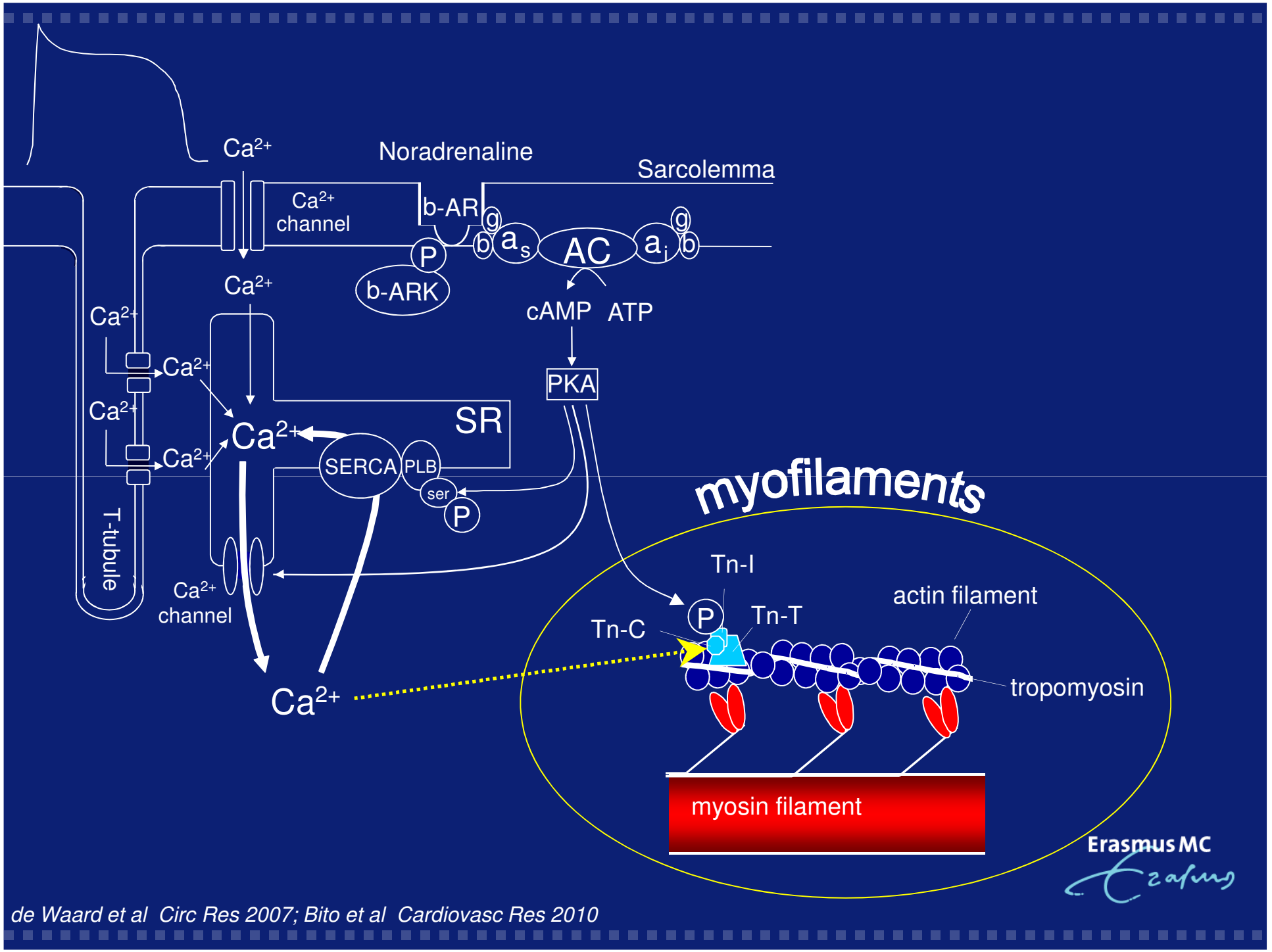
Exercise and LV Dysfunction and Remodeling after MI



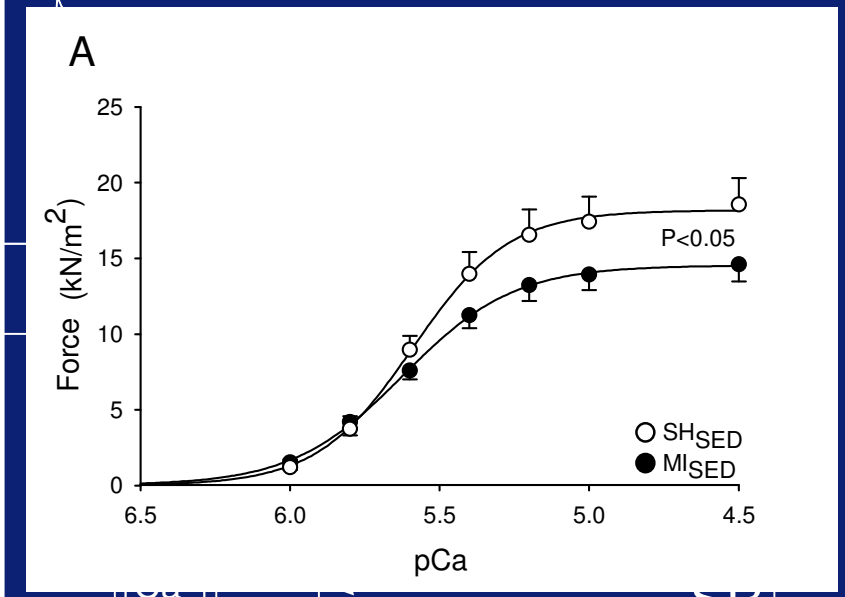
de Waard et al Circ Res 2007

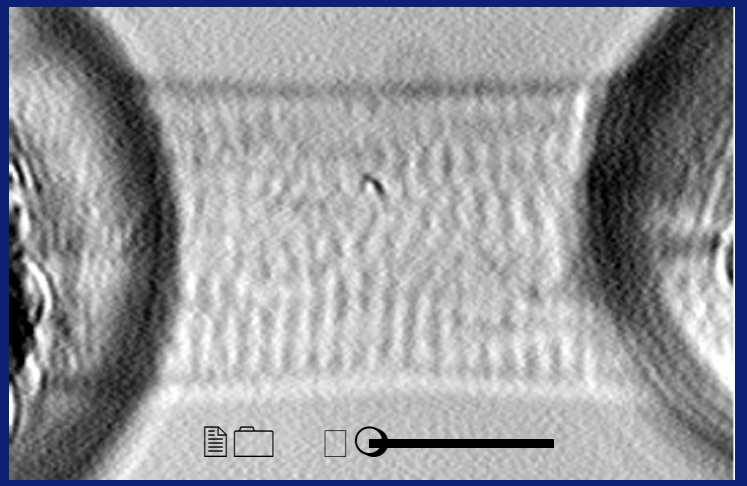


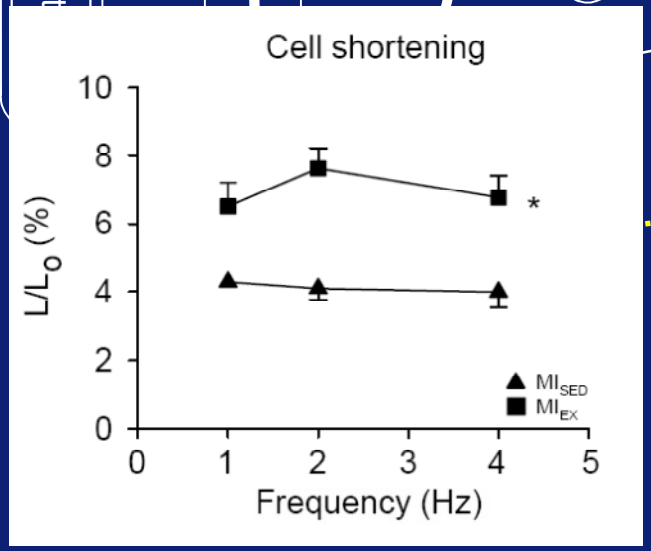
de Waard et al Circ Res 2007; Bito et al Cardiovasc Res 2010

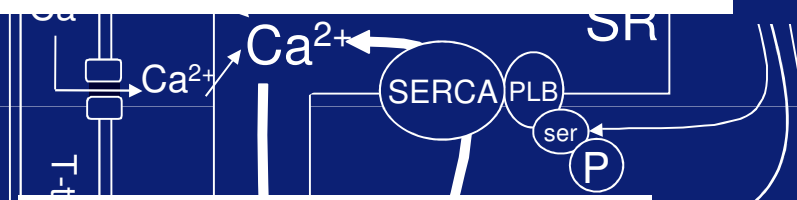


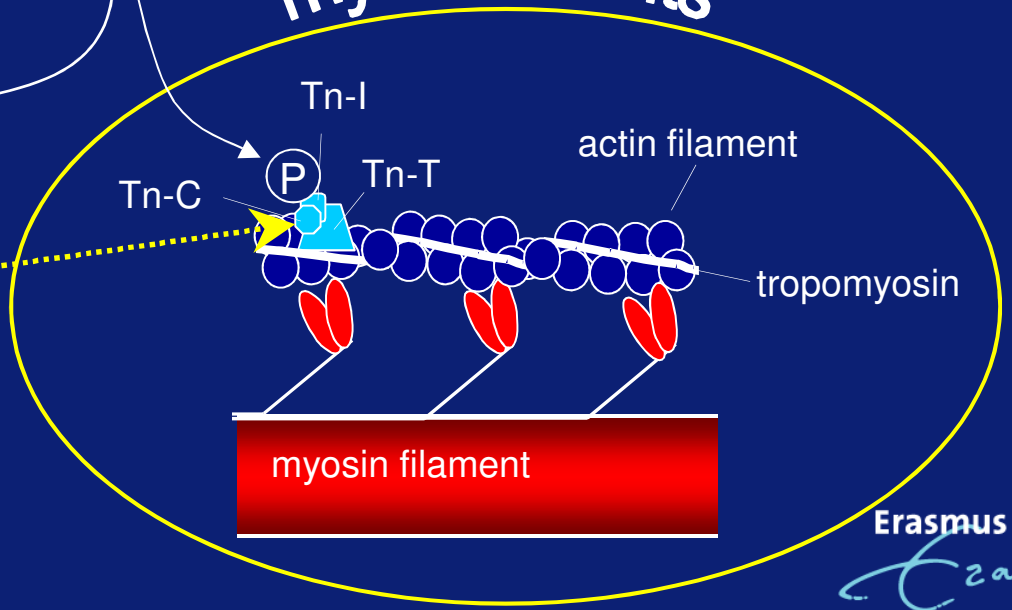
de Waard et al Circ Res 2007; Bito et al Cardiovasc Res 2010











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de Waard et al Circ Res 2007; Bito et al Cardiovasc Res 2010

Exercise in Adverse Cardiac Remodeling

- Exercise attenuates interstitial fibrosis, apoptosis, cardiomyocyte (myofilament) dysfunction, and cardiac remodeling and dysfunction after MI

de Waard et al Circ Res 2007

What are the molecular mechanisms underlying these beneficial effects of exercise training?

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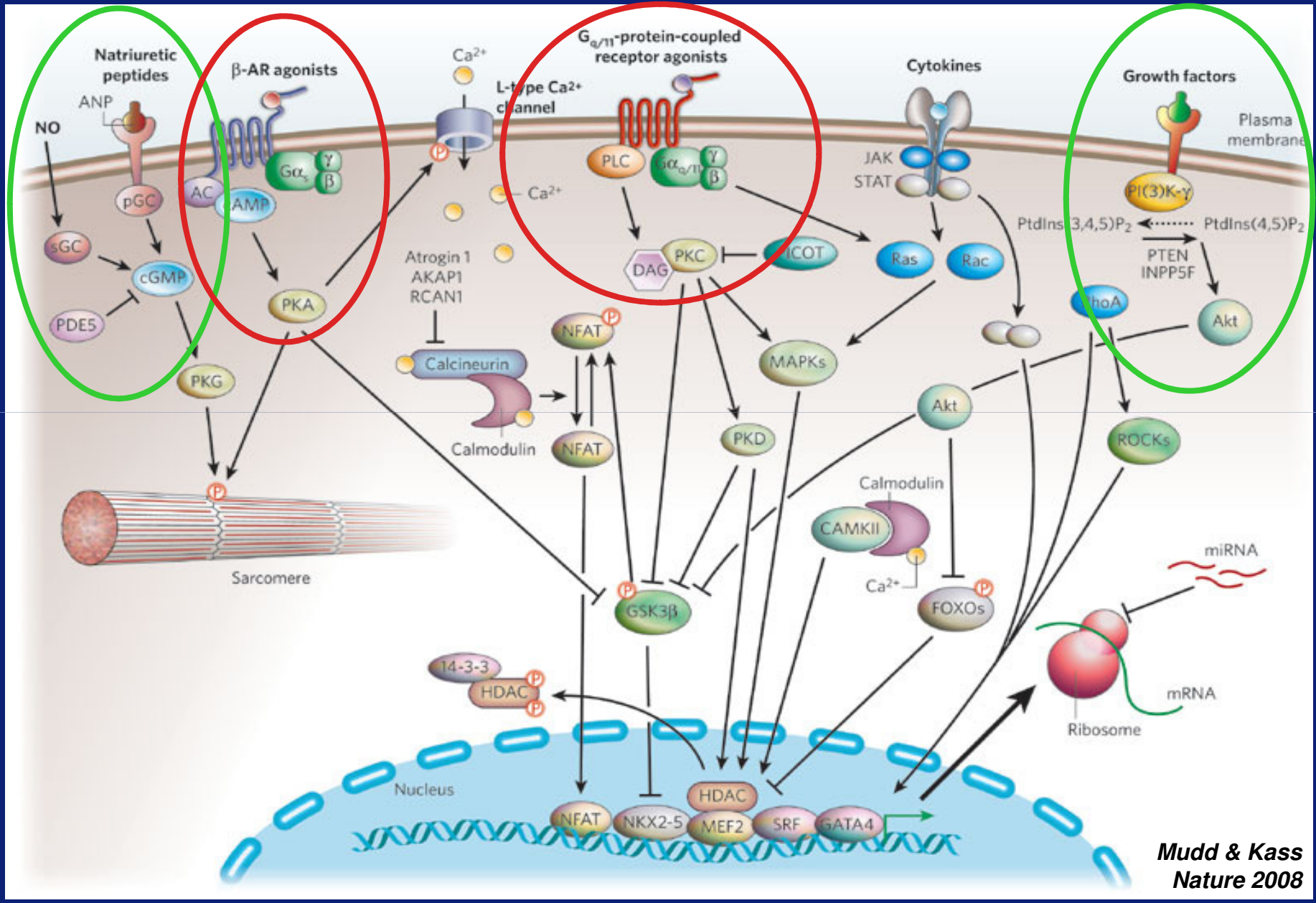
Molecular Mechanisms of Cardiac Remodeling



Mudd & Kass
Nature 2008

Exercise in Adverse Cardiac Remodeling

- Exercise attenuates interstitial fibrosis, apoptosis, cardiomyocyte (myofilament) dysfunction, and cardiac remodeling and dysfunction after MI

de Waard et al Circ Res 2007

- Exercise is mimicked, in part, by overexpression of endothelial NO synthase

Jones et al PNAS 2003; de Waard et al Am J Physiol 2009

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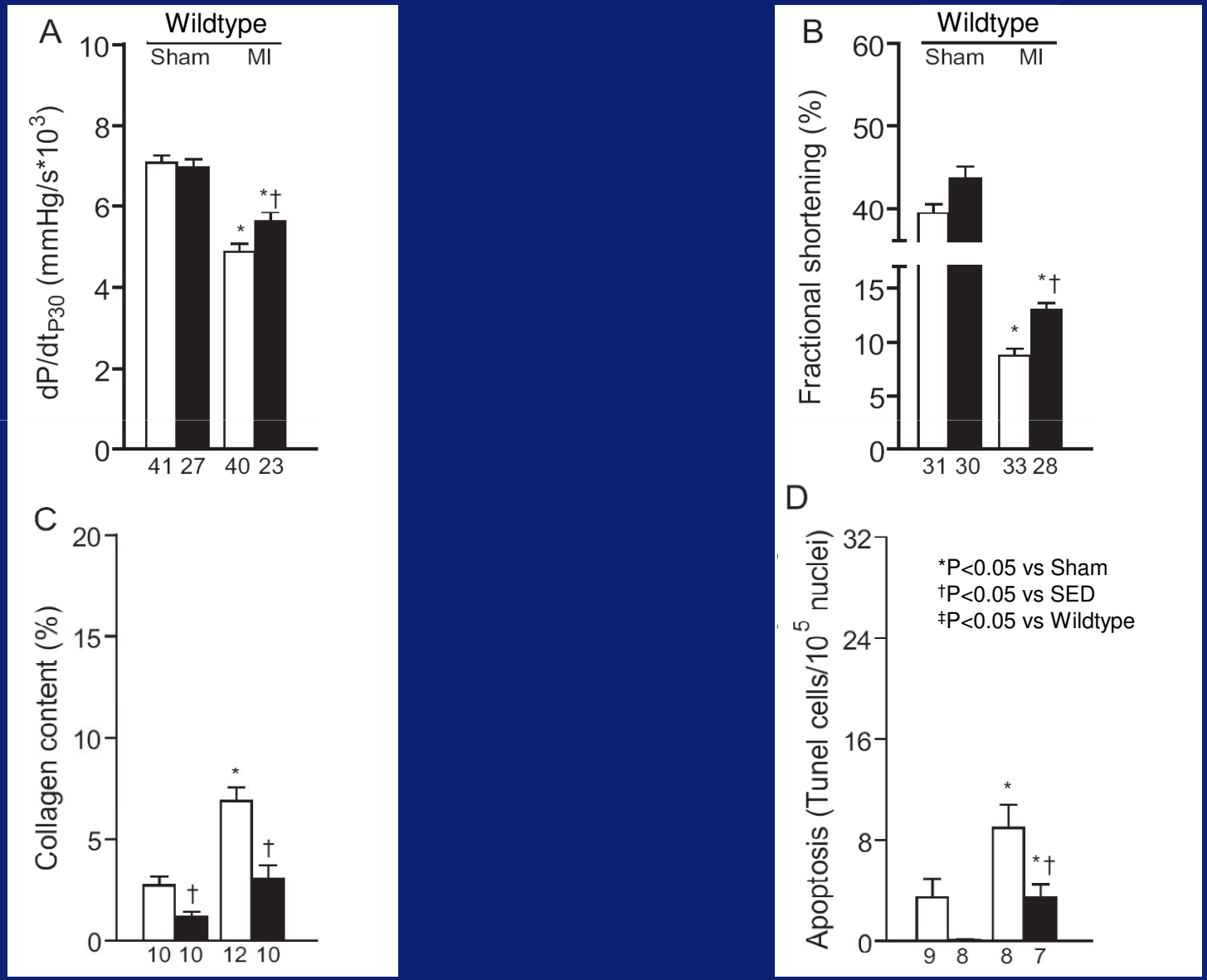
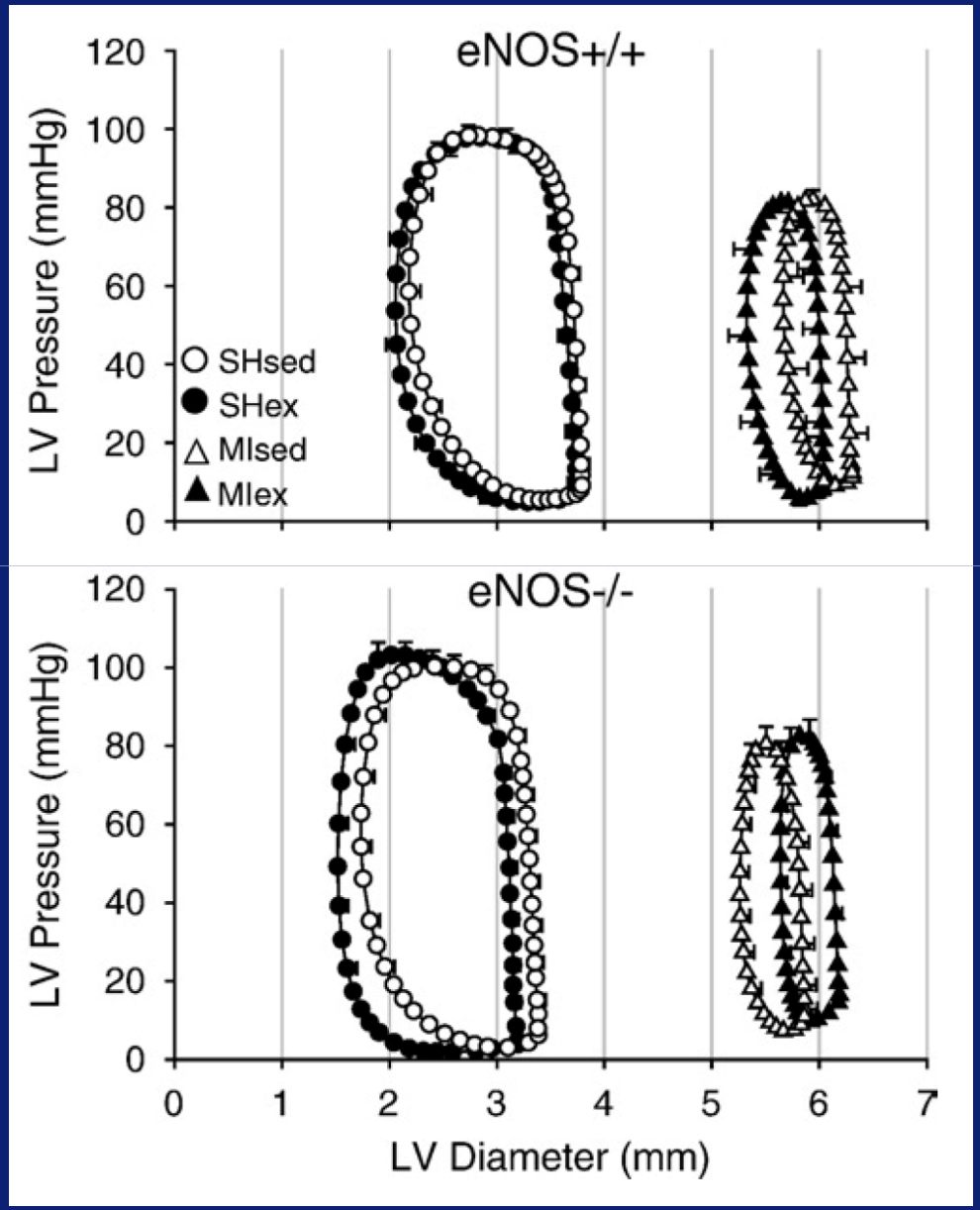
Exercise and LV Dysfunction and Remodeling after MI

Endothelial Nitric Oxide Synthase knockout



de Waard et al J Mol Cell Cardiol 2010

Exercise and LV Dysfunction and Remodeling after MI



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de Waard et al J Mol Cell Cardiol 2010

Exercise in Adverse Cardiac Remodeling

- Exercise attenuates interstitial fibrosis, apoptosis, cardiomyocyte (myofilament) dysfunction, and cardiac remodeling and dysfunction after MI

de Waard et al Circ Res 2007

- Exercise is mimicked, in part, by overexpression of endothelial NO synthase

Jones et al PNAS 2003; de Waard et al Am J Physiol 2009

- Effects of exercise appear to be fully dependent on intact eNOS expression

de Waard et al J Mol Cell Cardiol 2010

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Exercise in Adverse Cardiac Remodeling

- Exercise in Chronic Heart Failure
  - Clinical Evidence
  - Mechanisms

- Exercise in Adverse Remodeling
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  - *Clinical Evidence*

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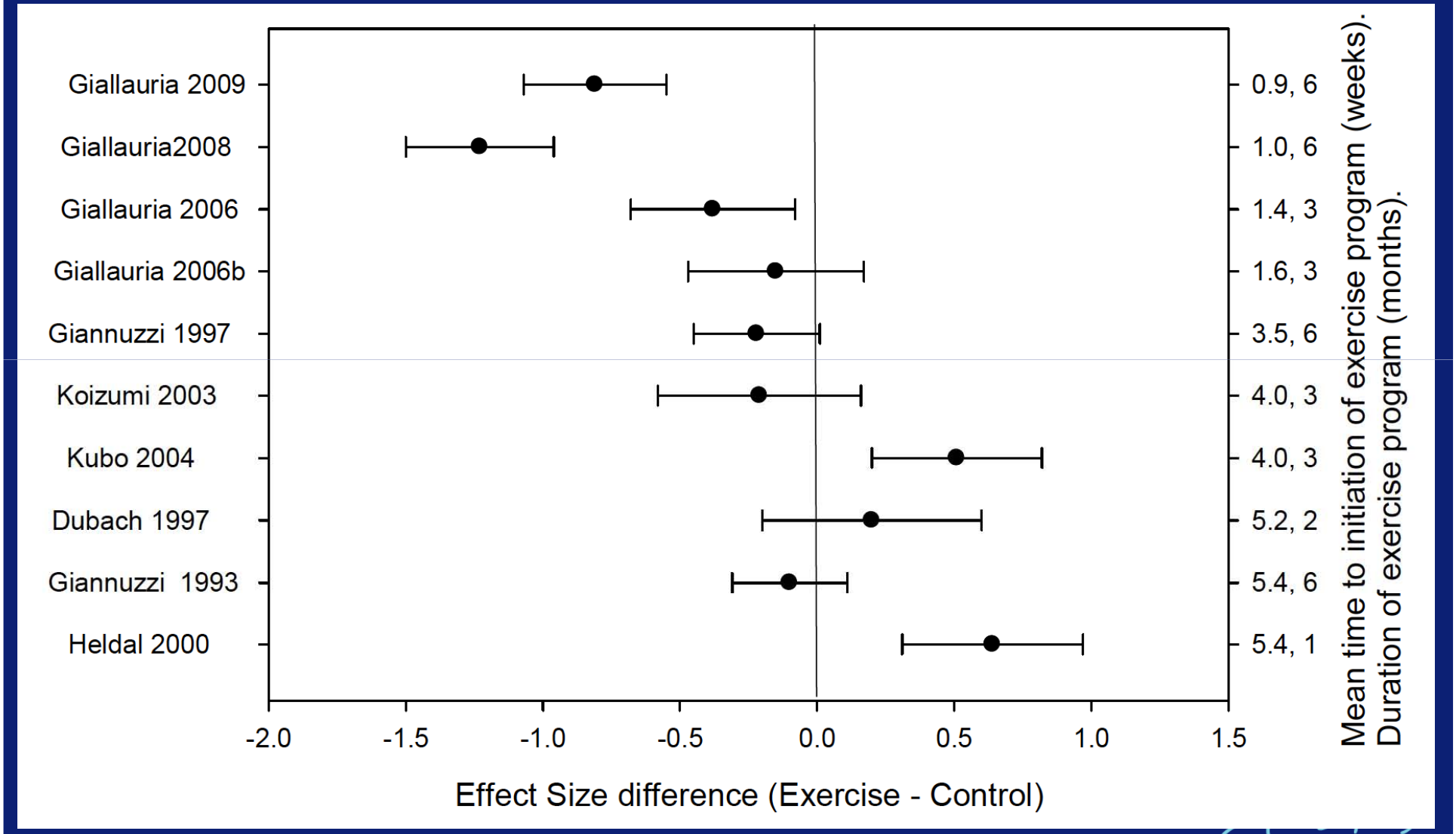
Exercise and Cardiac Remodeling after MI

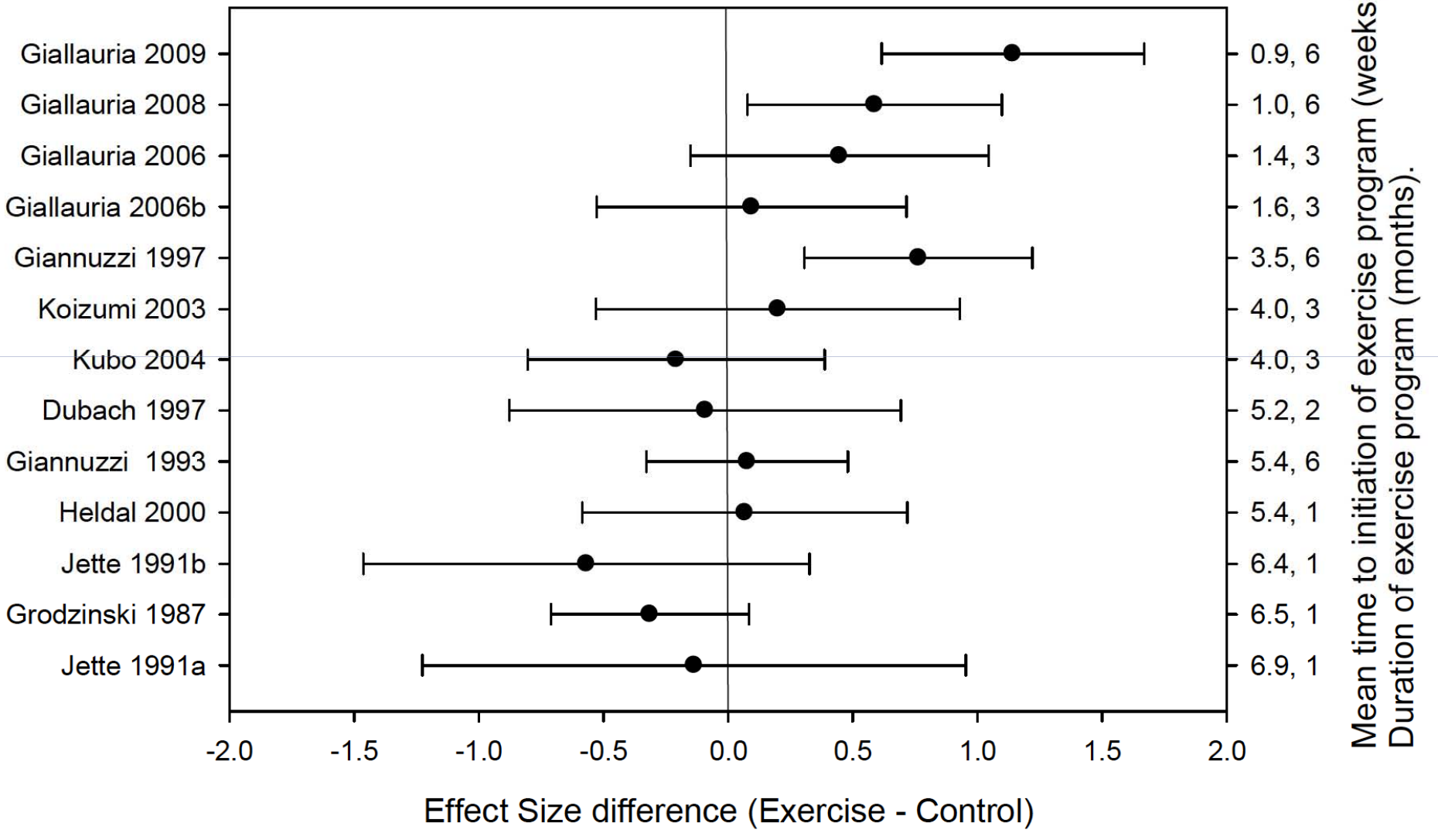
End-Diastolic Volume



Haykowsky et al. Trials 2011

Exercise and Cardiac Remodeling after MI

Ejection Fraction



Haykowsky et al. Trials 2011

Conclusions

- Exercise training improves quality of life, exercise capacity and cardiac function while blunting cardiac remodeling in patients with chronic (systolic) heart failure
- Exercise training early after AMI appears safe and effective in attenuating cardiac remodeling and improving cardiac function
- The optimal type, start, duration and intensity of exercise training remains to be established

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Acknowledgements

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Netherlands Heart Foundation (NHS)

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Take the Stairs!!

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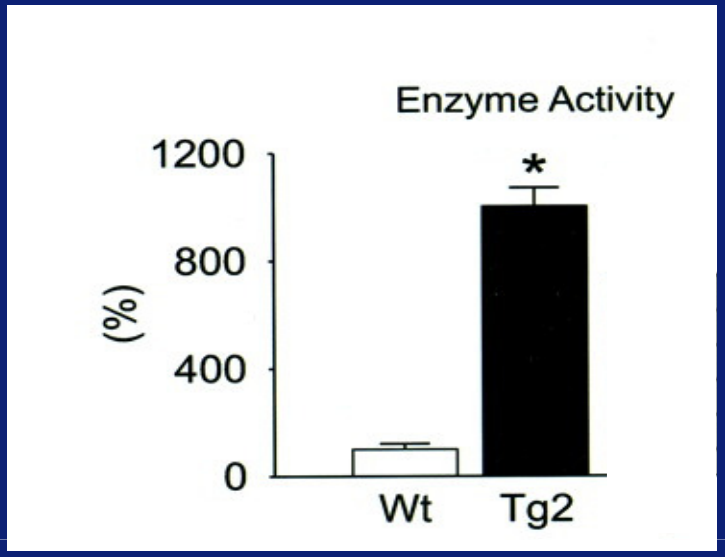
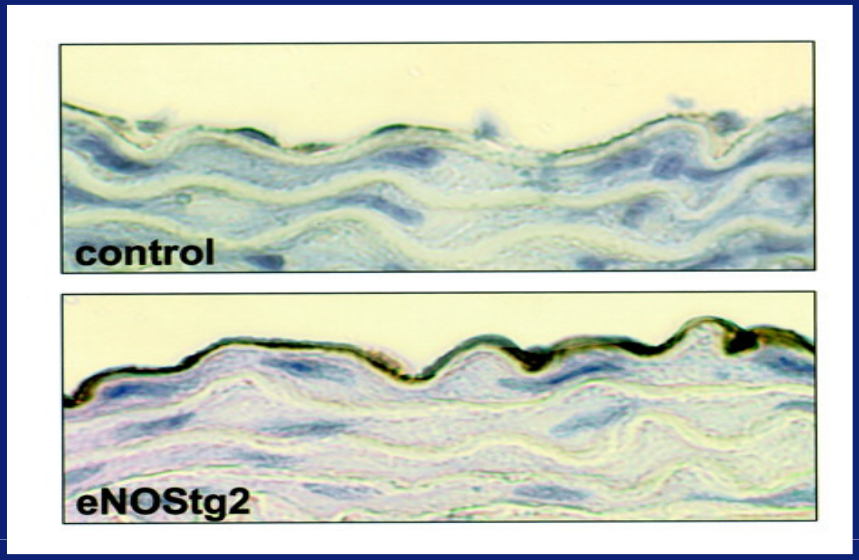
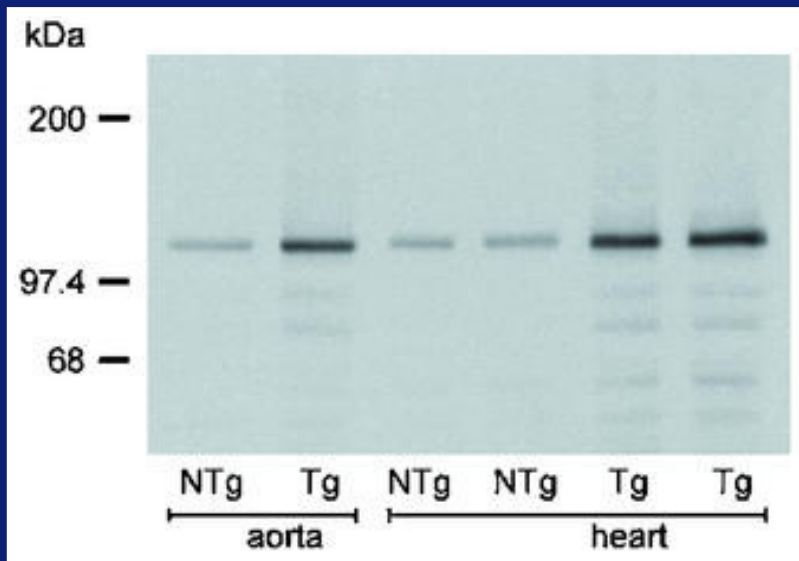
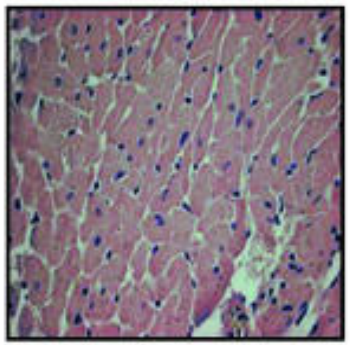
eNOS transgenic mice



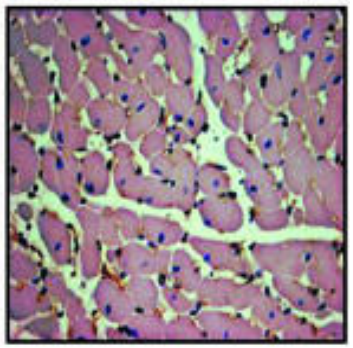


van Haperen et al. J Biol Chem 2002





Nontransgenic

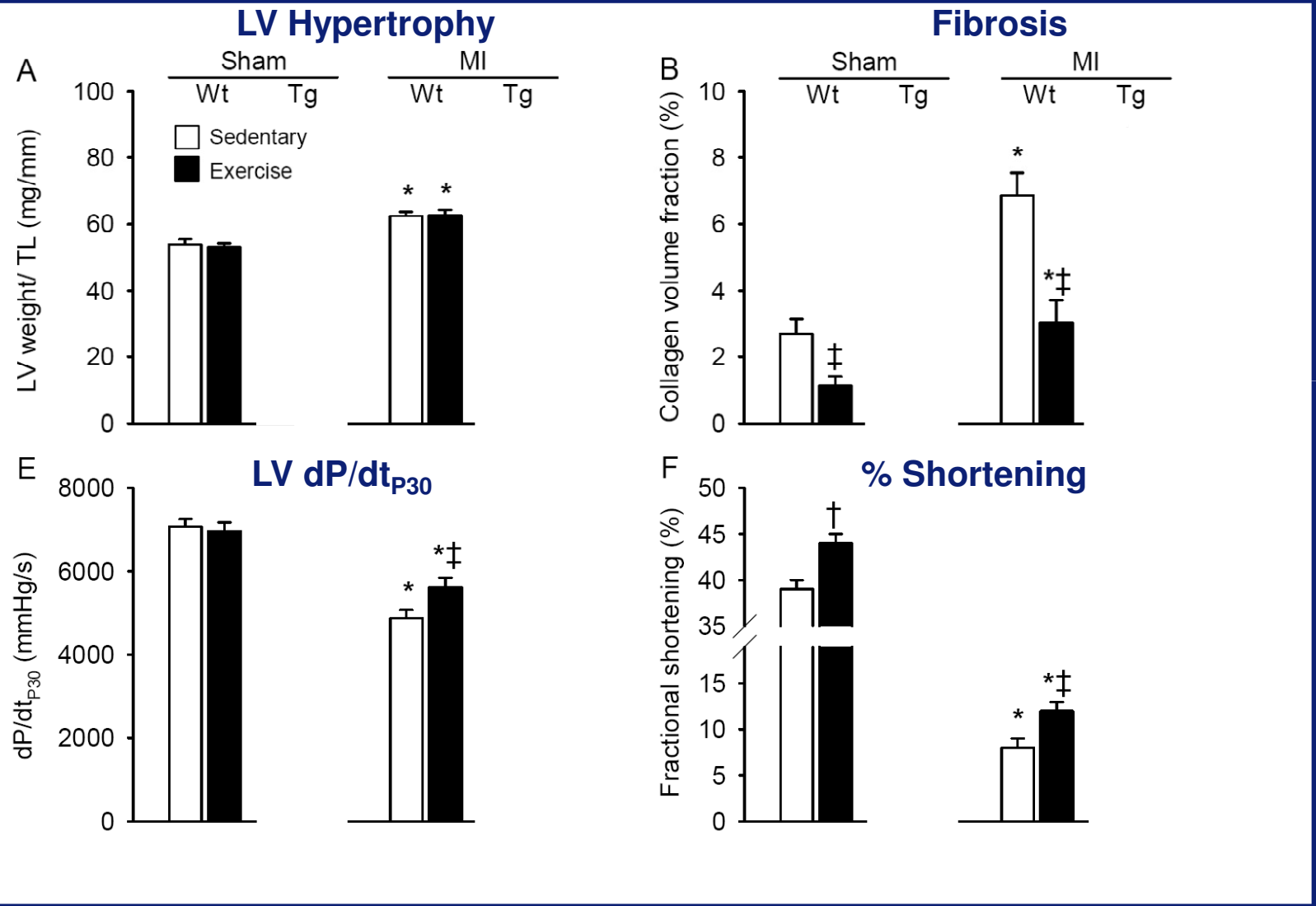


eNOS Transgenic

Jones et al. PNAS 2003

Exercise and LV Dysfunction and Remodeling after MI

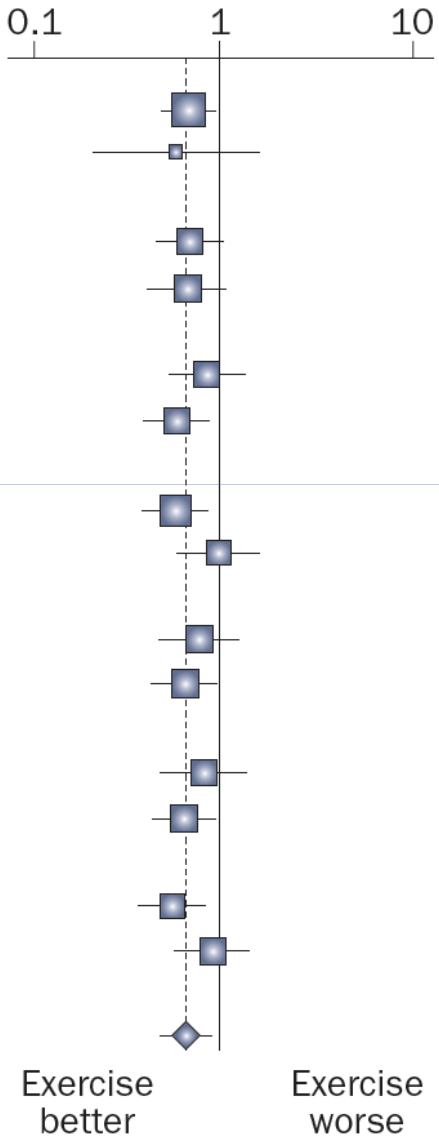
Endothelial Nitric Oxide Synthase Overexpression



Jones et al. PNAS 2003; de Waard et al. Am J Physiol 2009

Exercise Training in Chronic Heart Failure

Hospitalization Free Survival



	Hazard ratio	95% CI	Effect *P*	Interaction *P*
Male	0.73	0.57–0.95	0.02	0.73
Female	0.65	0.28–1.48	0.63	
Age ≥60 years	0.75	0.54–1.02	0.07	0.28
Age <60 years	0.73	0.50–1.06	1.01	
NYHA I–II	0.89	0.61–1.29	0.53	0.55
NYHA III–IV	0.65	0.47–0.90	0.01	
Ischemic	0.64	0.47–0.87	0.00	0.15
Nonischemic	0.99	0.66–1.47	0.94	
LVEF ≥27%	0.82	0.55–1.21	0.32	0.96
LVEF <27%	0.71	0.52–0.97	0.03	
VO_2 ≥15 ml/kg/min	0.85	0.56–1.30	0.46	0.66
VO_2 <15 ml/kg/min	0.70	0.52–0.95	0.02	
Training ≥28 weeks	0.62	0.45–0.86	0.00	0.37
Training <28 weeks	0.93	0.65–1.35	0.71	
Total	**0.72**	**0.56–0.93**	**0.011**	

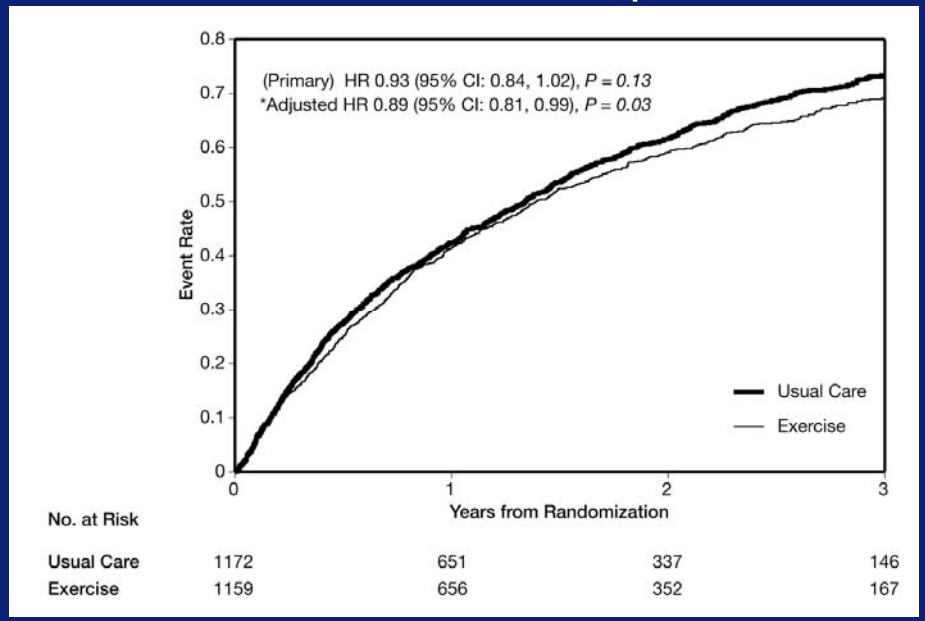
Piepoli et al. BMJ 2004

Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure: HF-ACTION Randomized Controlled Trial

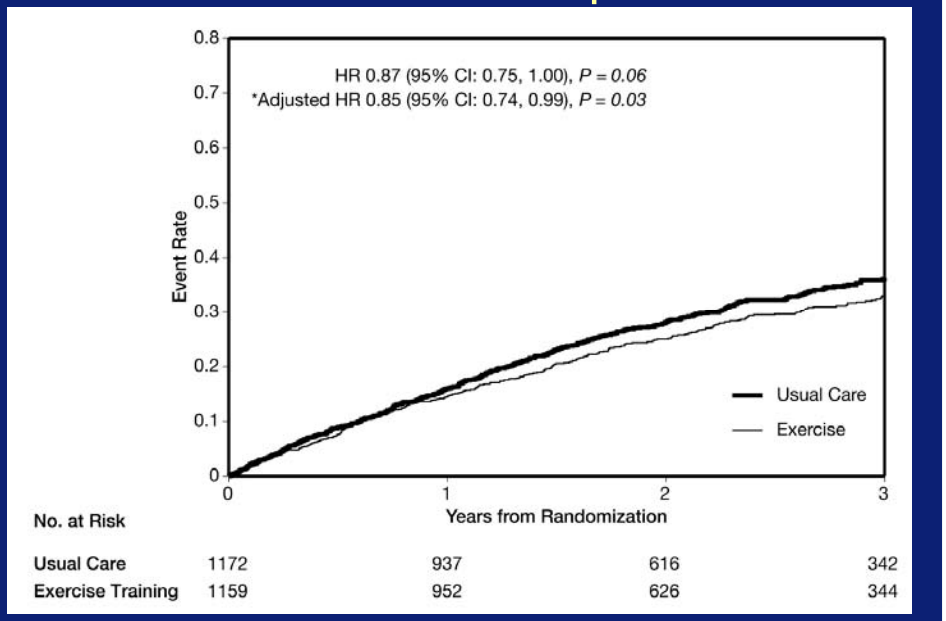
Christopher M. O'Connor, MD, David J. Whellan, MD, MHS, Kerry L. Lee, PhD, Steven J. Keteyian, PhD, Lawton S. Cooper, MD, MPH, Stephen J. Ellis, PhD, Eric S. Leifer, PhD, William E. Kraus, MD, Dalane W. Kitzman, MD, James A. Blumenthal, PhD, David S. Rendall, PA-C, Nancy Houston Miller, RN, BSN, Jerome L. Fleg, MD, Kevin A. Schulman, MD, Robert S. McKelvie, MD, PhD, Faiez Zannad, MD, PhD, and **Ileana L. Piña, MD for the HF-ACTION Investigators**

JAMA 2009;301:1439-1450

All-Cause Death or Hospitalization



CV Death or / HF Hospitalization



Adverse Cardiac Remodeling

Effect of Exercise Training

- Exercise after Myocardial Infarction

  - Role of eNOS

- *Exercise after Pressure Overload*
- Importance of Cardiac Loading Conditions

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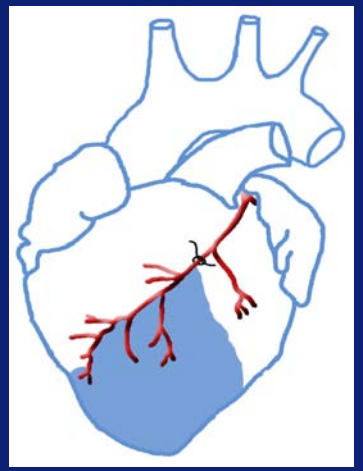
Mouse Models of Cardiac Remodeling

Myocardial infarction

8 wk Myocardial Infarction (MI)

permanent LAD coronary artery ligation

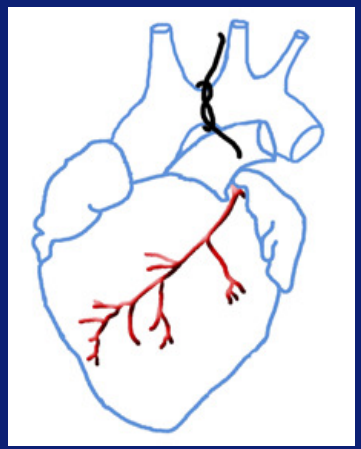


Pressure overload

8 wk Transverse Aorta Constriction (TAC)

mTAC: 25G 37± 3 mmHg

sTAC: 27G 57± 4 mmHg



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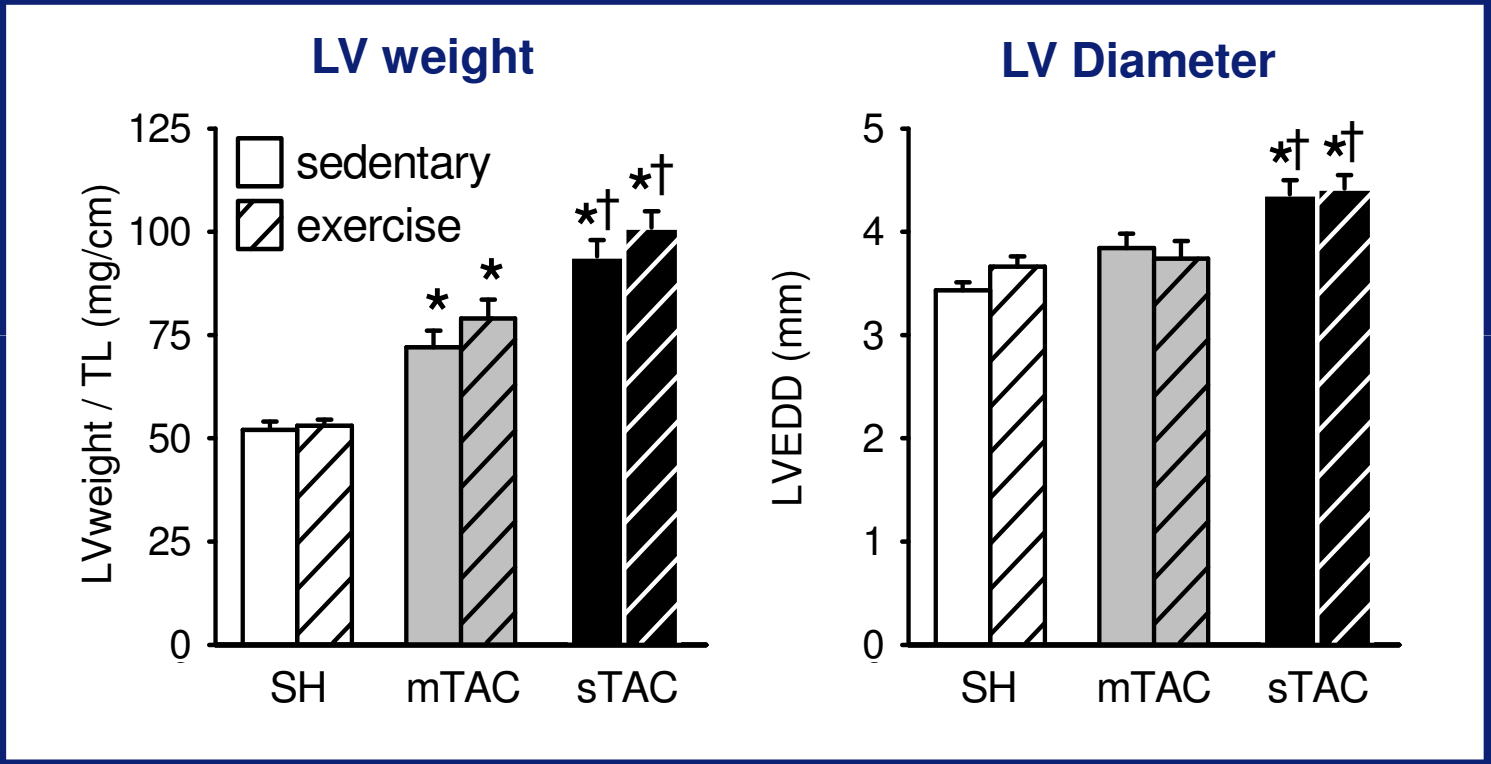
Effects of exercise in mice with TAC

Left ventricular geometry



Van Deel et al J Mol Cell Cardiol 2011

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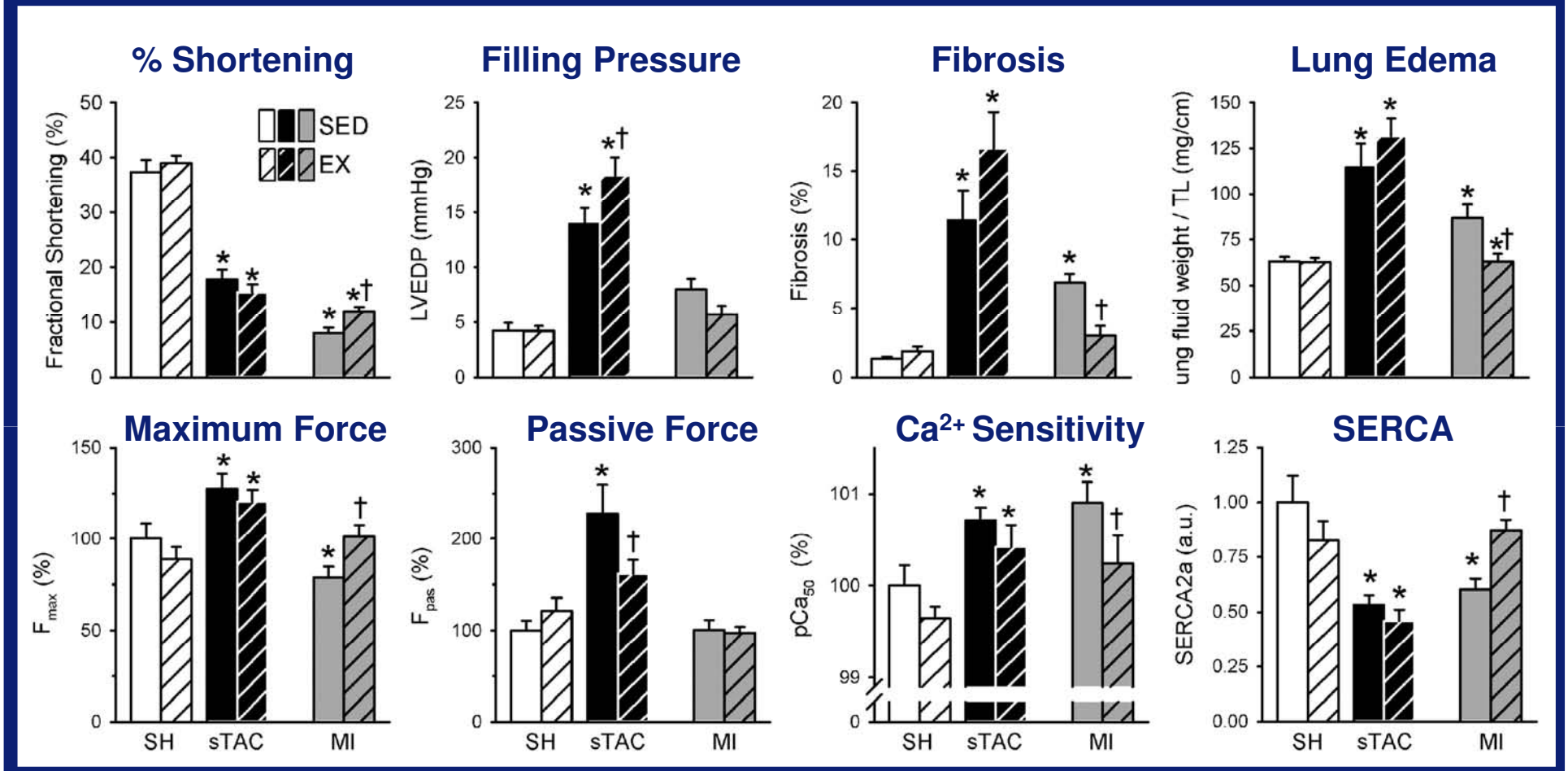
Effects of exercise in TAC versus MI



Van Deel et al J Mol Cell Cardiol 2011

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Conclusions

- Exercise training attenuates left ventricular dysfunction in post-MI remodeling, but not in pressure overload hypertrophy
  - Ø The effects of exercise training on left ventricular dysfunction appear critically dependent on the underlying cause of hypertrophy / remodeling
  - Ø *The divergent effects of exercise may be due to intrinsic differences in the remodeling phenotype, but may also be related to the different hemodynamic responses to exercise*

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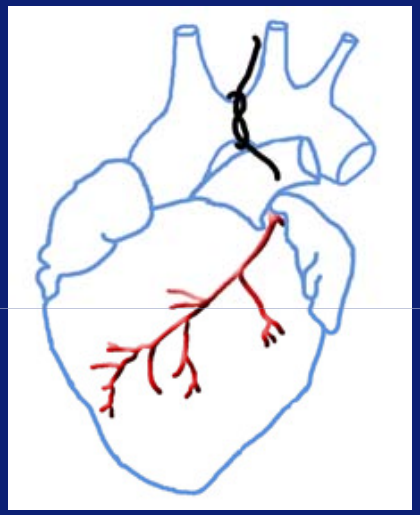
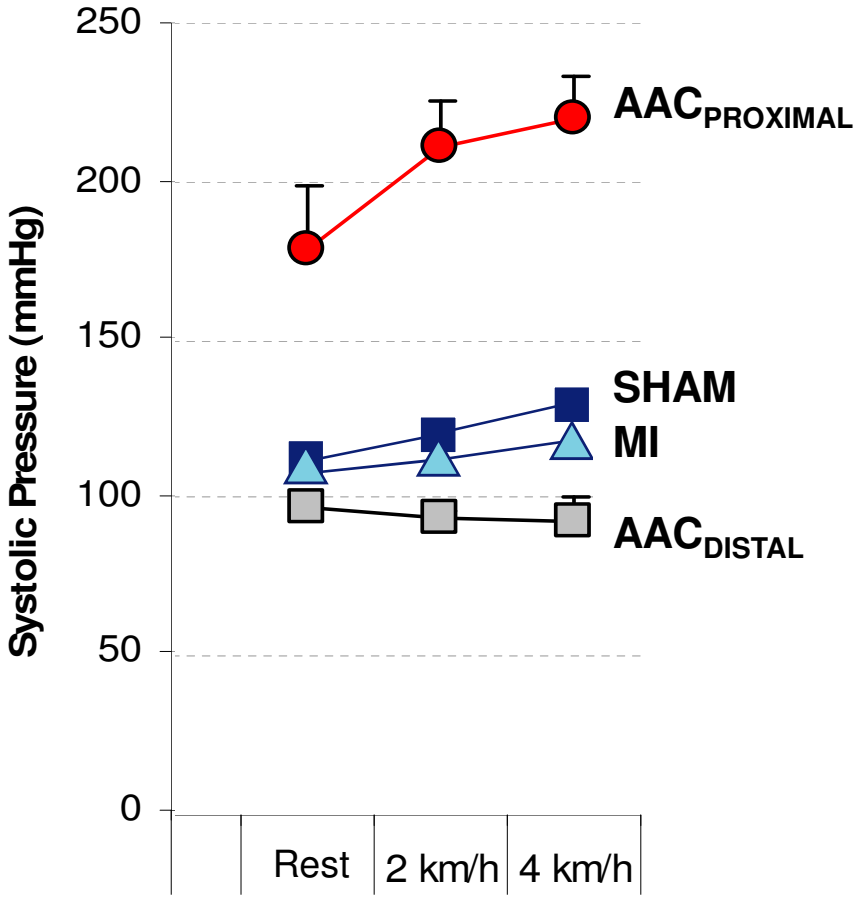
Hemodynamic Responses to Exercise



Aortic Stenosis vs Myocardial Infarction



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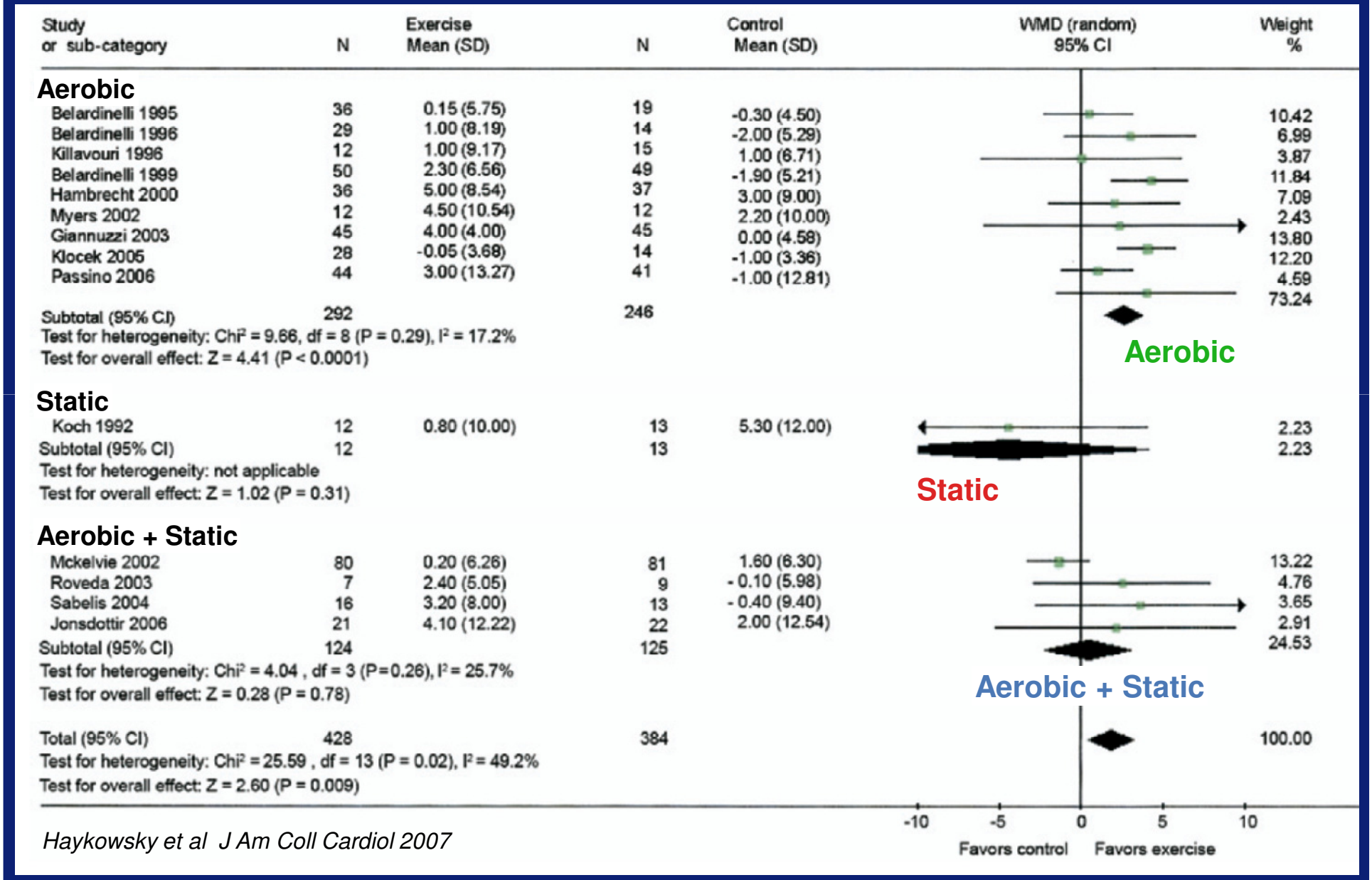
Exercise Training and Ejection Fraction



Haykowsky et al J Am Coll Cardiol 2007

Conclusions

- The lack of a beneficial effect of exercise training in mice with aortic constriction could be due to the exaggerated hemodynamic loading conditions during running

  - Ø *eNOS overexpression: The benefit of exercise without the hemodynamic overloading?*

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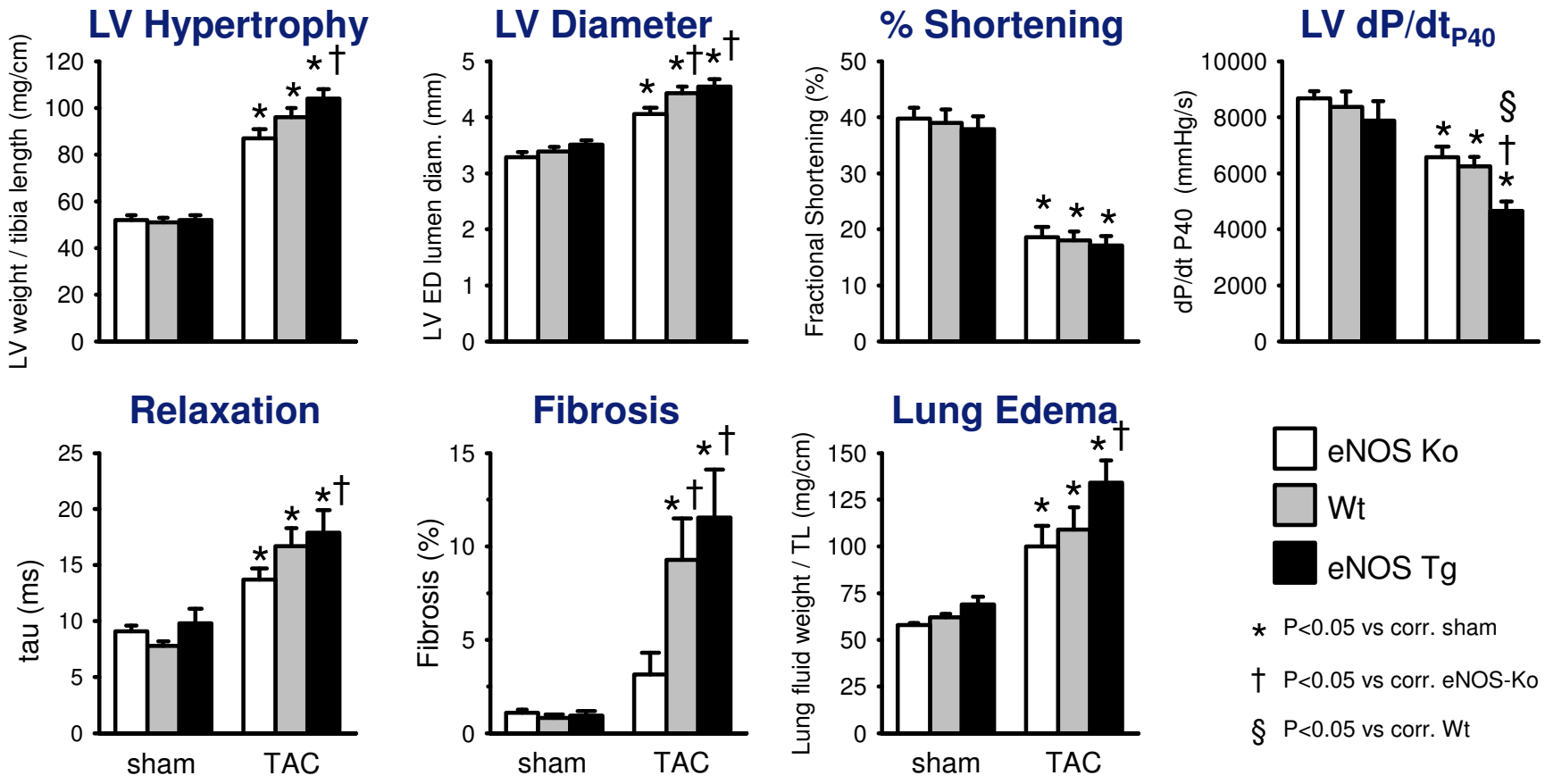
Effects of eNOS in TAC



van Deel et al in preparation

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Conclusions

- The effects of exercise training on left ventricular dysfunction appear critically dependent on the underlying cause of hypertrophic remodeling and the associated response to exercise

  - Ø These divergent effects of exercise appear to be due to different effect of eNOS in hearts with pressure-overload versus MI-induced hypertrophy subjected to exercise training

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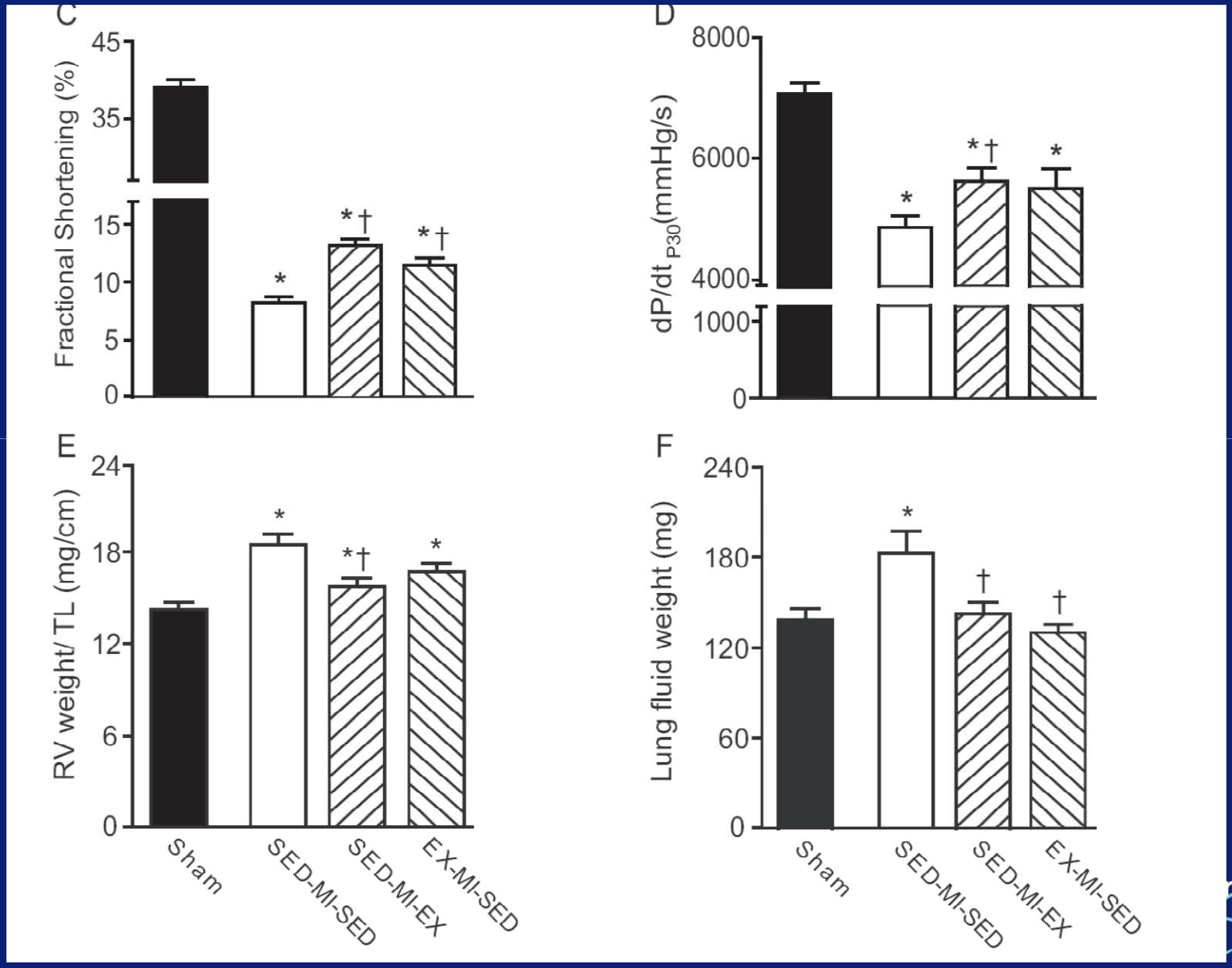
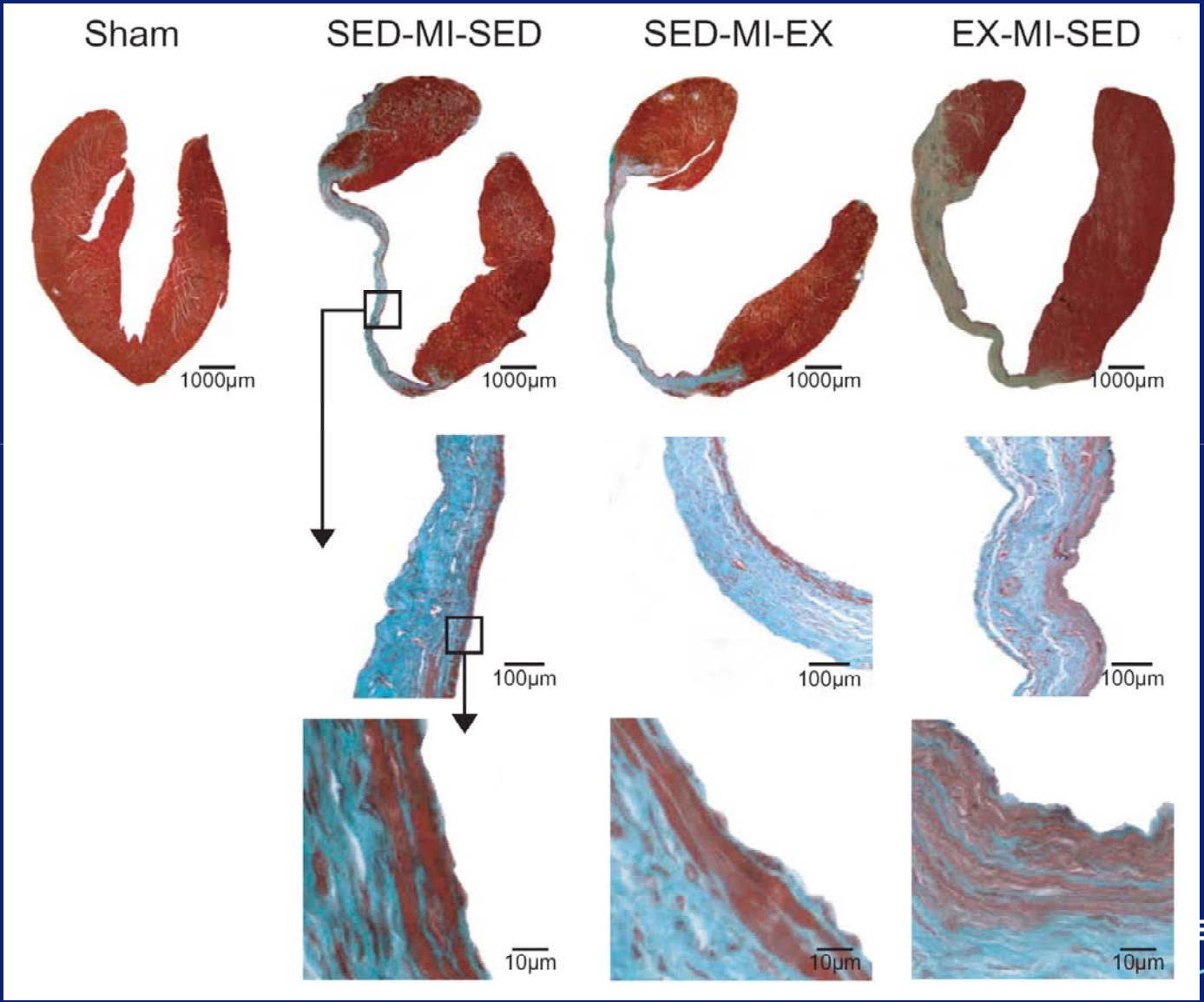
Exercise Training prior to Infarction



Exercise Training prior to Infarction



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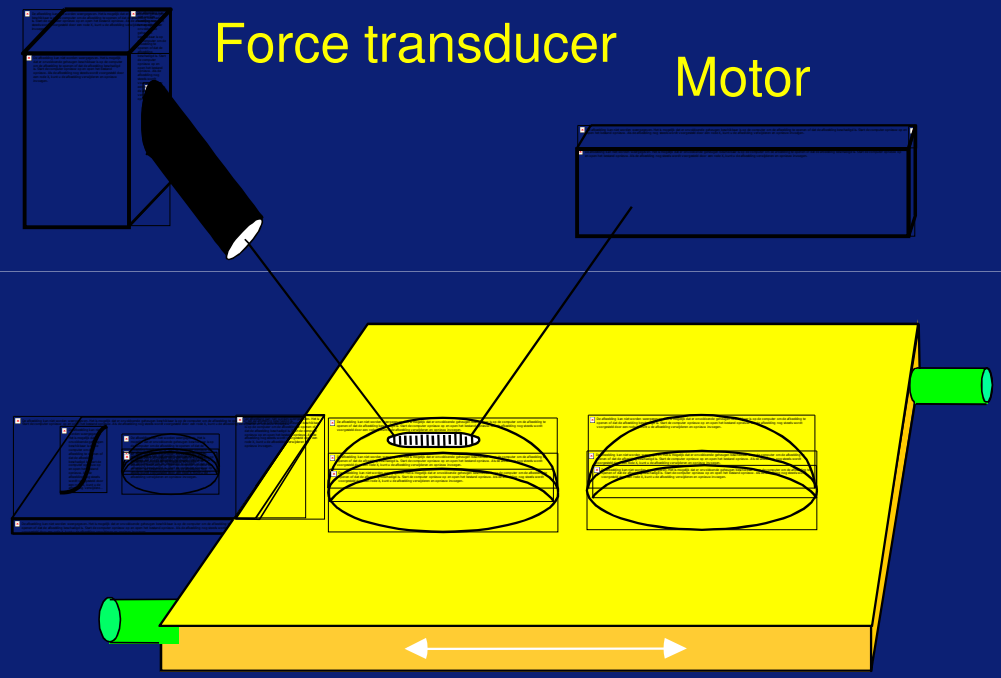
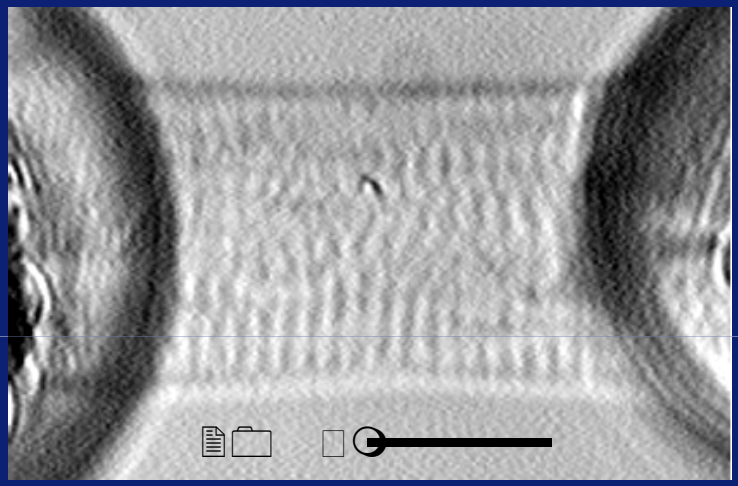
Force measurements in cardiomyocytes





Courtesy J. van der Velden / G. Stienen

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Exercise and Cardiac Remodeling after MI

Table 1 Description of exercise training program

Study	Frequency (days/week)	Intensity	Exercise duration (min/session)	Mode	Program length (mn)
Giallauria et al [6]	3	60-70% VO_{2peak}	30	Cycle	6
Giallauria et al [5]	3	60-70% VO_{2peak}	30	Cycle	6
Giallauria et al [12]	3	70% VO_{2peak}	30	Cycle	3
Giallauria et al [13]	3	60% VO_{2peak}	30	Cycle	3
Giannuzzi et al [7]	3-7	80% peak HR	30 >30 min	Cycle Walk	6
Koizumi et al [14]	7	Moderate speed	30	Walk	3
Kubo et al [9]	3	HR at VT	20 min, twice/day	Cycle Walk	3
Dubach et al [11]	4 - 7	60-70% HRR	45 120	Cycle Walk	2
Giannuzzi et al [10]	3-7	80% peak HR	30 >30	Cycle Walk	6
Heldal et al [20]	5	85% peak HR	120	Cycle Jogging	1
Jette et al [19]	7	70-80% peak HR	45-105	Cycle, Jogging Walk, Calisthenics	1
Grodzinski et al [21]	5	80% peak HR	30-180	Cycle, Jog Walk, Swim Calisthenics	1

(Heart rate; HRR: Heart rate reserve; VO_{2peak}, peak oxygen consumption; VT: Ventilation threshold).

Haykowsky et al. Trials 2011

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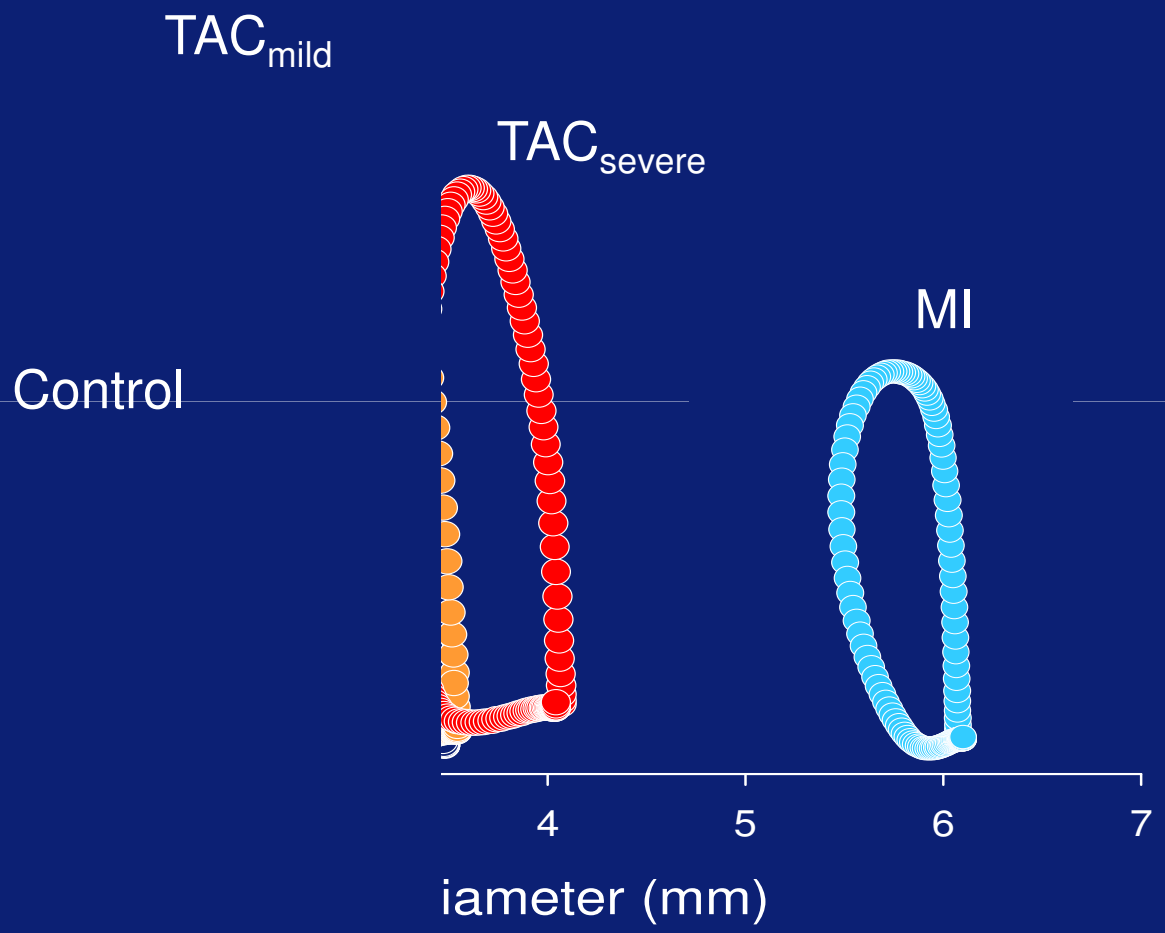
Left Ventricular Pressure-Diameter Relation



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Adverse Cardiac Remodeling

Effect of Exercise Training

- *Exercise after Myocardial Infarction*

  - Role of eNOS

- Exercise after Pressure Overload
- Importance of Cardiac Loading Conditions

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