



In vivo hemodynamics

1. Cardiac effects of mild hypothermia
2. Hemodynamics of systolic and diastolic heart failure

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MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

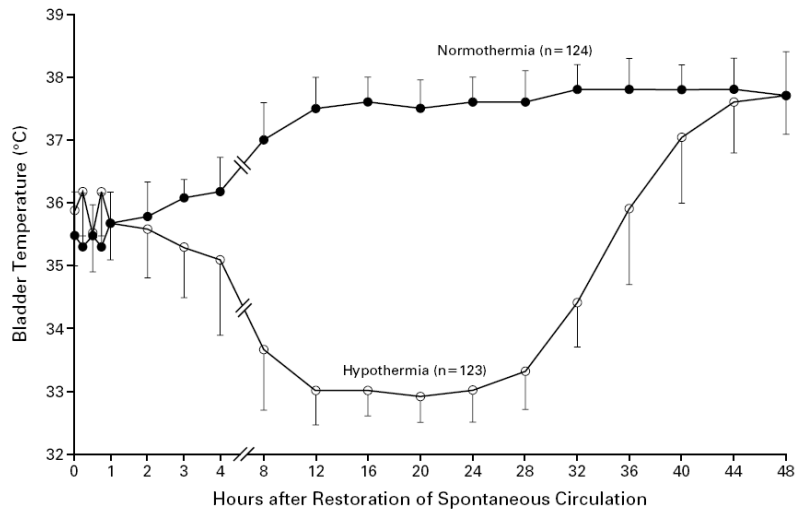


Figure 1. Bladder Temperature in the Normothermia and Hypothermia Groups.

The T bars indicate the 75th percentile in the normothermia group and the 25th percentile in the hypothermia group. The target temperature in the hypothermia group was 32°C to 34°C, and the duration of cooling was 24 hours. Only patients with recorded temperatures were included in the analysis.



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24 h MH (33°C) after cardiac arrest

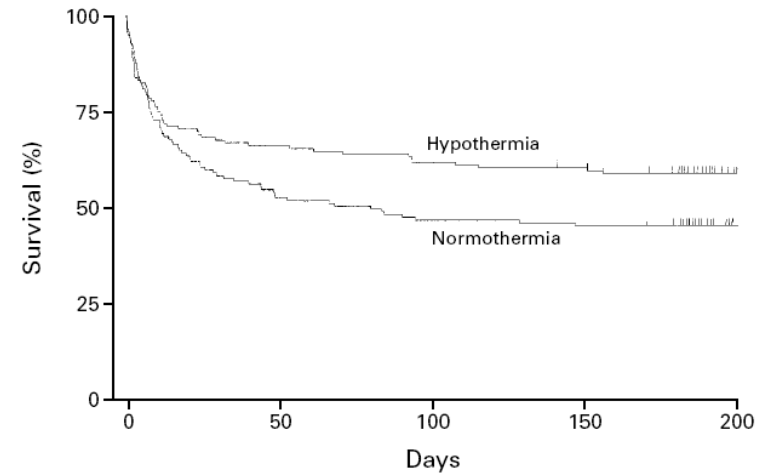


TABLE 2. NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.

OUTCOME	NORMOTHERMIA	HYPOTHERMIA	RISK RATIO (95% CI)*	P VALUE†
	no./total no. (%)			
Favorable neurologic outcome‡	54/137 (39)	75/136 (55)	1.40 (1.08–1.81)	0.009
Death	76/138 (55)	56/137 (41)	0.74 (0.58–0.95)	0.02

*The risk ratio was calculated as the rate of a favorable neurologic outcome or the rate of death in the hypothermia group divided by the rate in the normothermia group. CI denotes confidence interval.

†Two-sided P values are based on Pearson's chi-square tests.

‡A favorable neurologic outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability). One patient in the normothermia group and one in the hypothermia group were lost to neurologic follow-up.

Oscar Langendorff

(*1853, †1908)



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(Aus dem physiologischen Institut in Rostock.)

Untersuchungen am überlebenden Säugethierherzen.

Mitgetheilt von

O. Langendorff.

II. A b h a n d l u n g.

Ueber den Einfluss von Wärme und Kälte auf das Herz der warmblütigen Thiere.

(Nach Versuchen von O. Langendorff und Dr. Czeslaw Nawrocki.)

Hierzu Tafel V, VI, VII u. VIII und 14 Textfiguren.

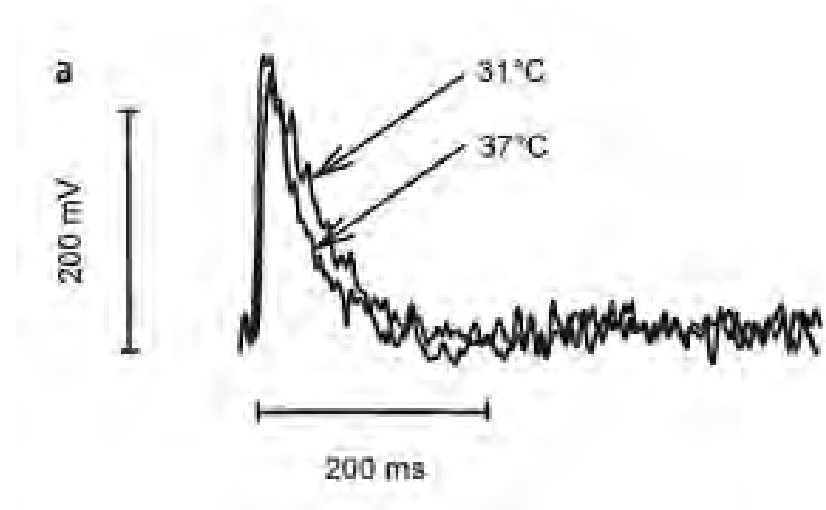
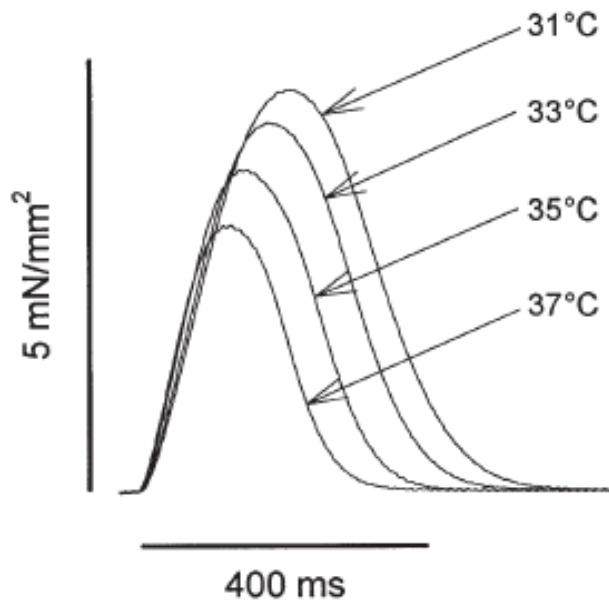
In meiner ersten Mittheilung über das isolirte Warmblüterherz (1) habe ich gezeigt, dass es gerade so wie das Froschherz von der Temperatur beeinflusst wird. Aenderte man die Wärme des durch das Koronarsystem fließenden Blutes, so änderte sich entsprechend die Schlagzahl; dem rapiden Ablauf der Zusammenziehungen des warmen stand die träge Kontraktion des abgekühlten Herzens gegenüber. Ich zeigte ferner, dass das Herz noch bei Speisung mit stark abgekühltem Blut seine Schläge nicht einstellt.

Langendorff O (1897) Untersuchungen am überlebenden Säugetierherzen. Über den Einfluss von Wärme und Kälte auf das Herz der warmblütigen Tiere. Pflügers Arch 66: 355–400

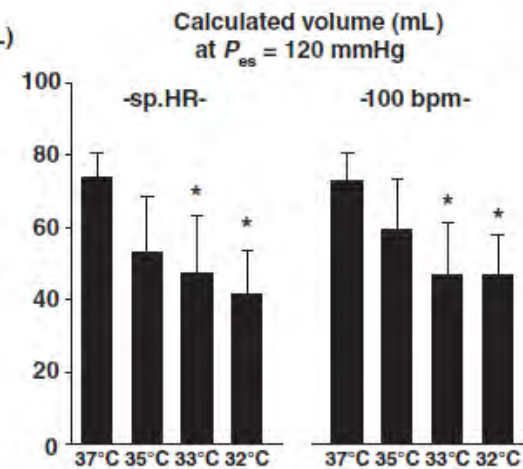
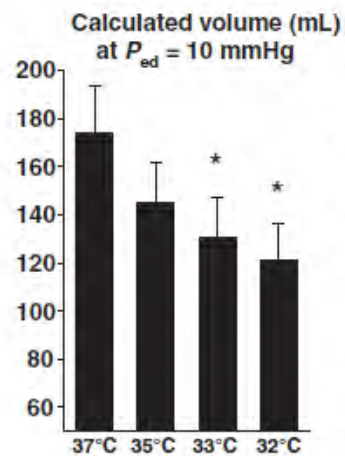
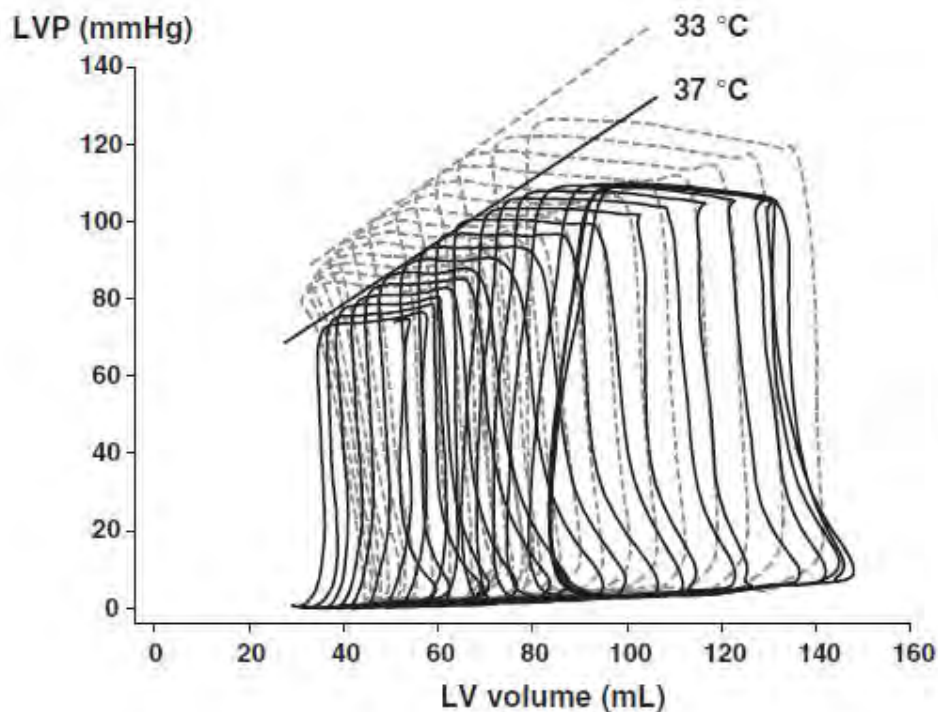
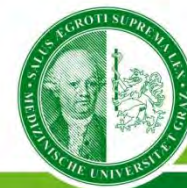
MH is a positive inotrope



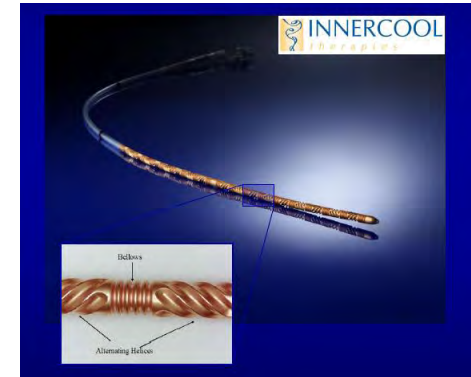
Isolated human heart muscle strips



MH in normal pigs:
improved systolic, but decreased diastolic function



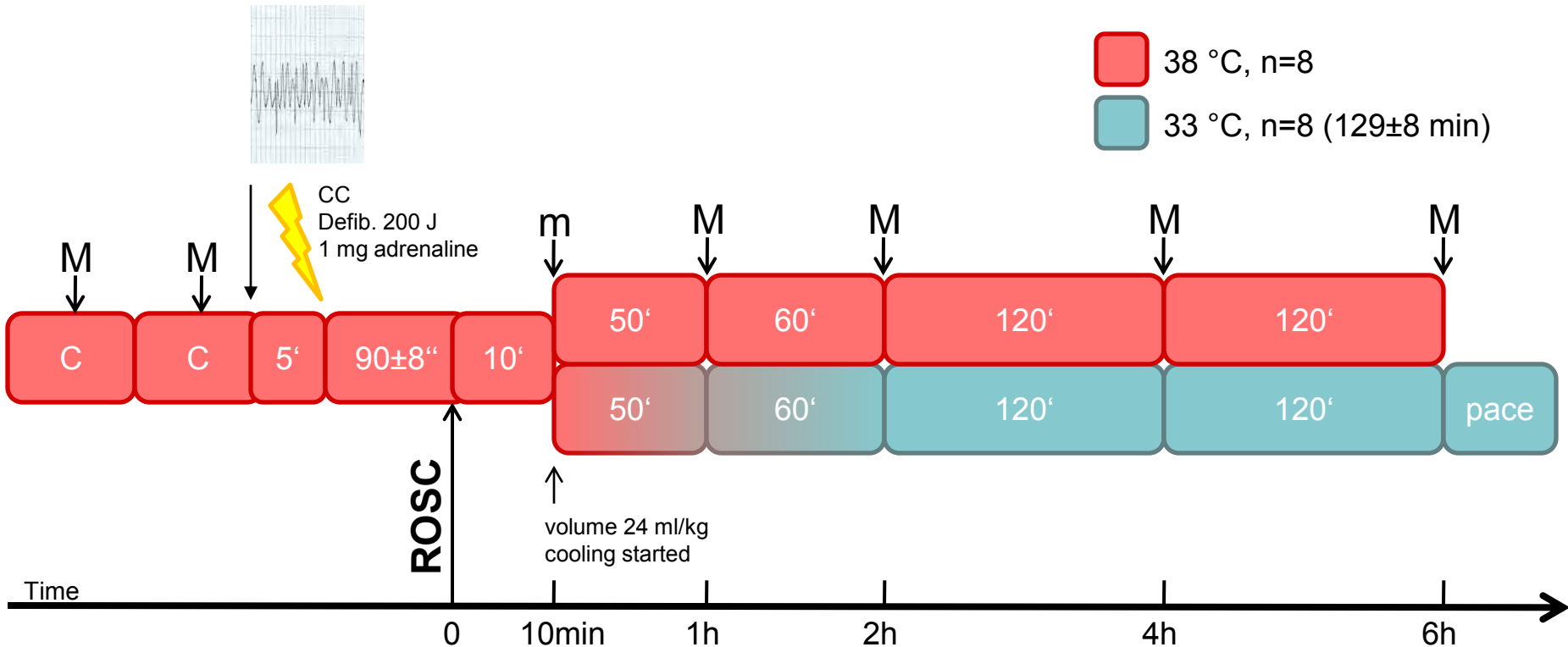
- 16 female, landrace pigs (63.6±1.8 kg)
- closed chest
- Swan-Ganz catheter
- PV catheter
- right atrial pacing probe
- aortic ballon catheter
- intravascular cooling device



MH after cardiac arrest



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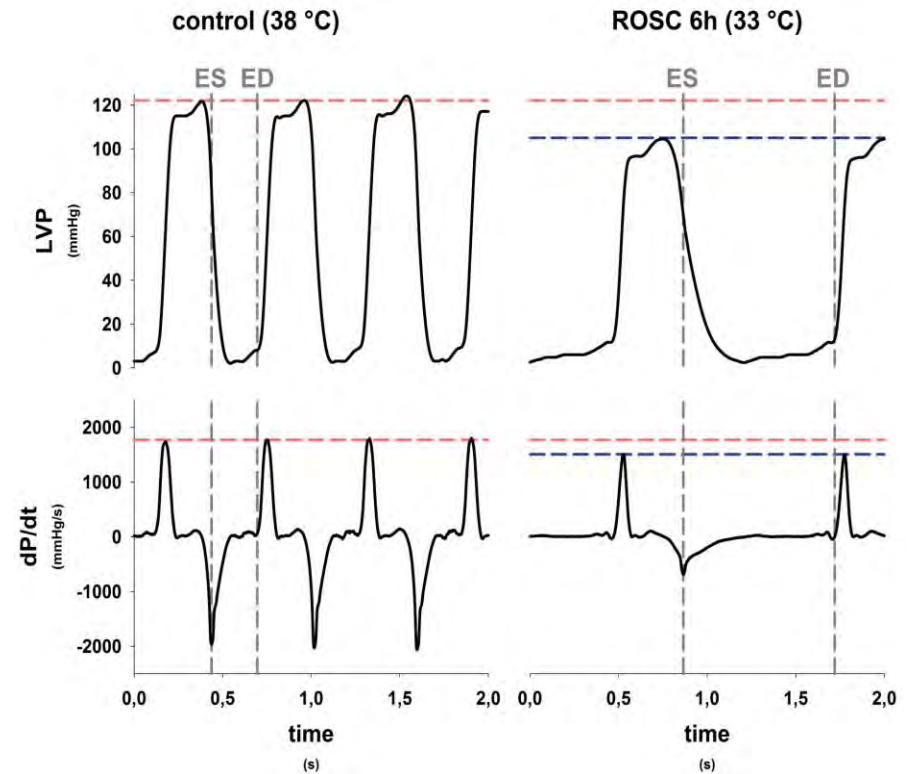
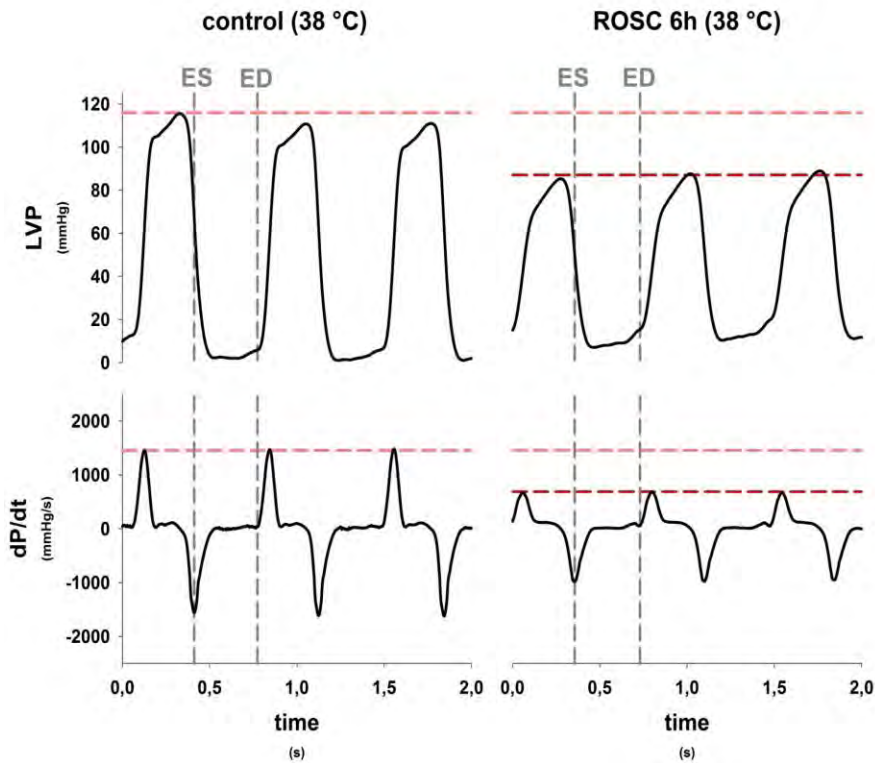


M: saline, CO, BGA art./ven., blood samples, aortic occlusion
m: saline, CO, BGA art./ven., blood samples

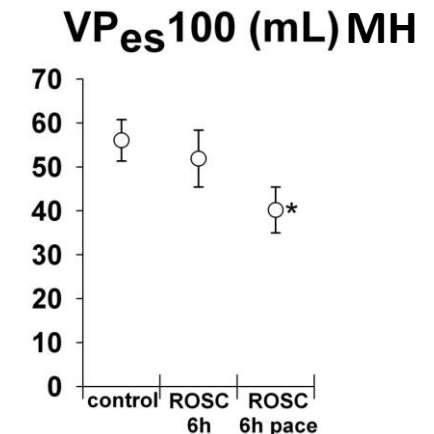
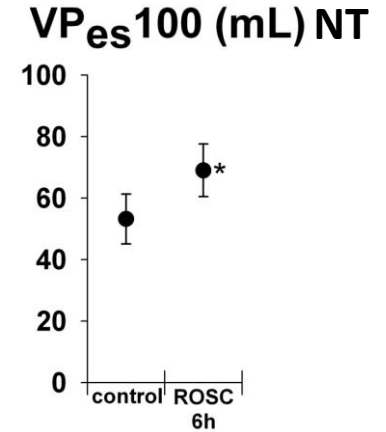
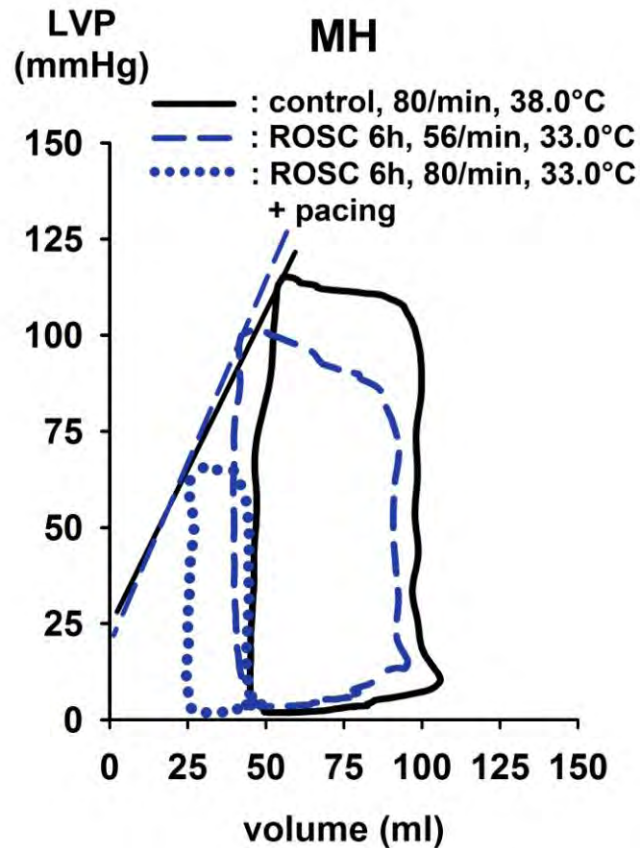
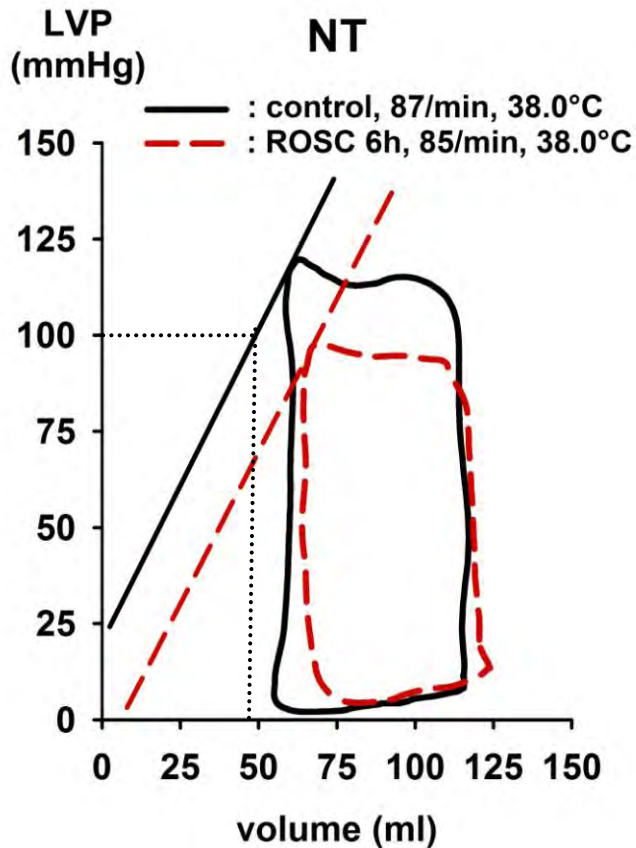
MH after cardiac arrest



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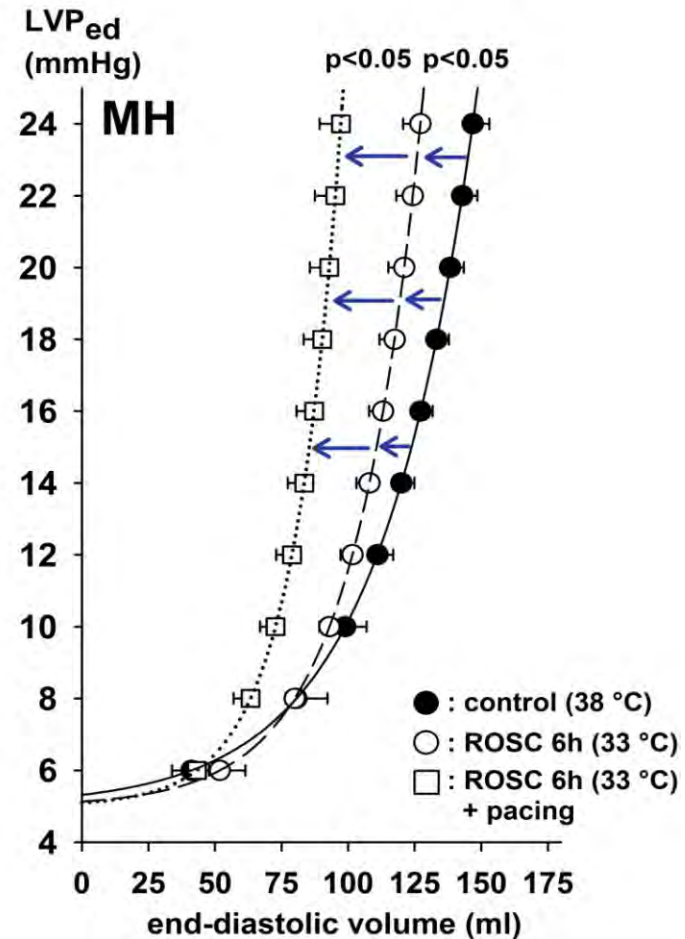
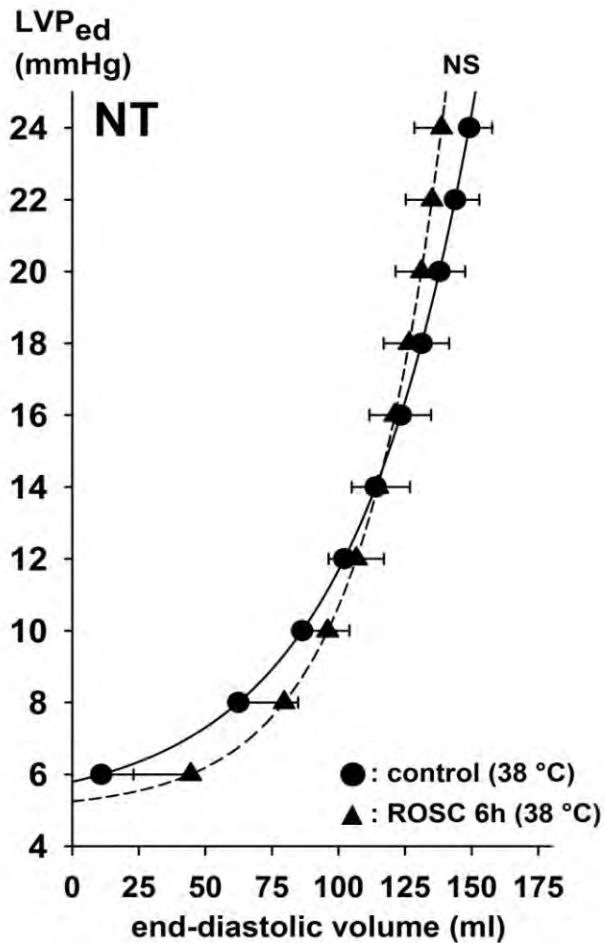
MH after cardiac arrest



MH after cardiac arrest



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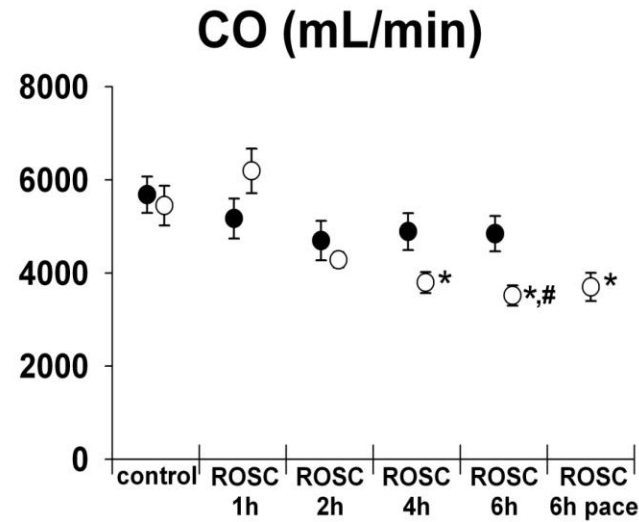
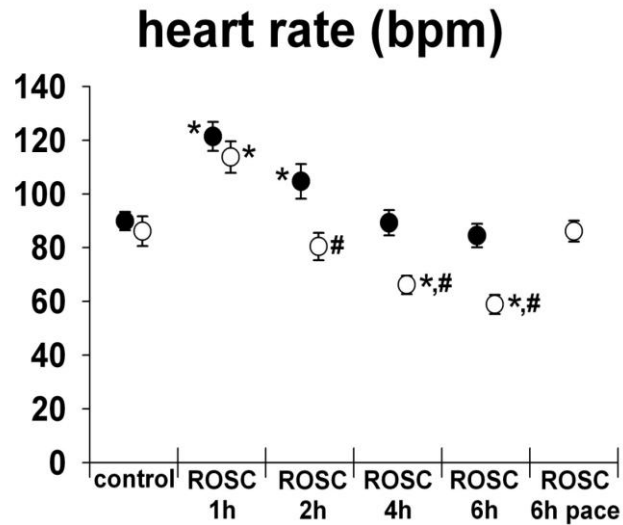


Schwarzl et al., Acta Physiol 2011

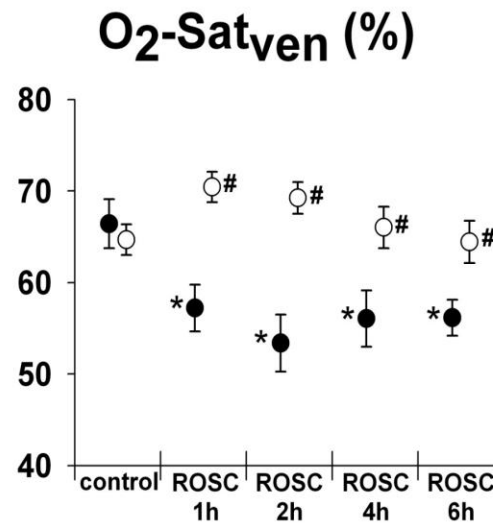
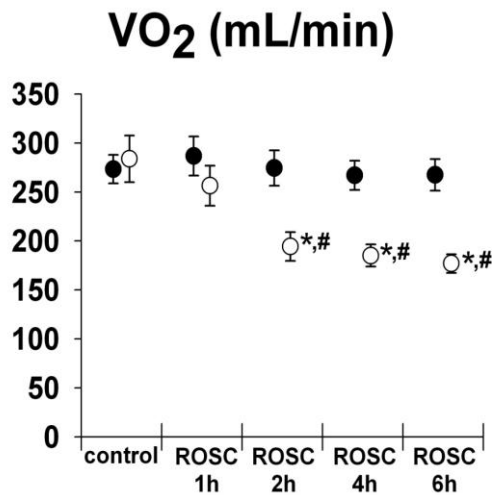
MH after cardiac arrest



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● NT (38 °C)
○ MH (33 °C)
* p < 0.05 vs. control
p < 0.05 vs. NT



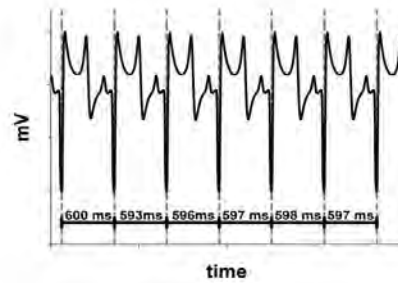
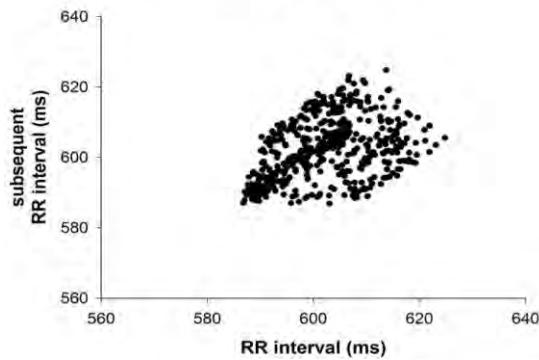
Schwarzl et al., Acta Physiol 2011

Heart rate variability

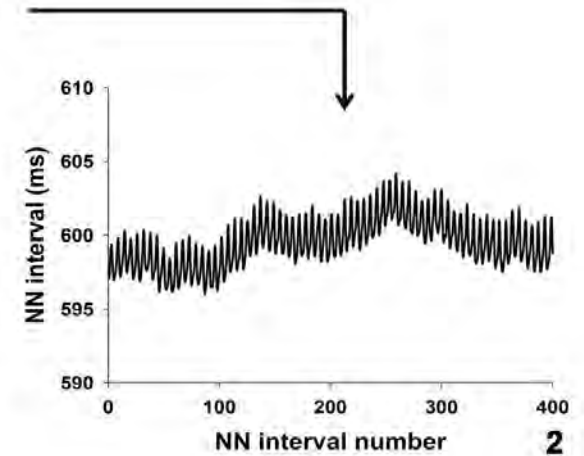


Poincaré plot

control (38 °C)

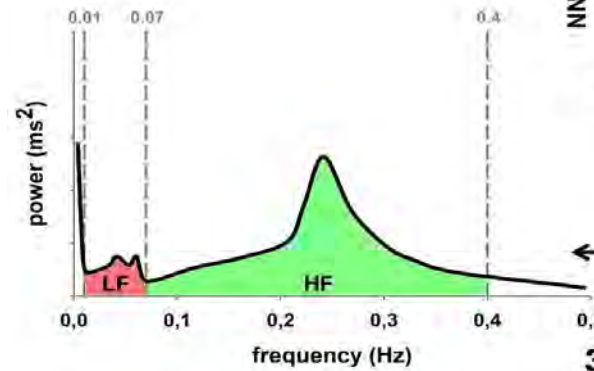
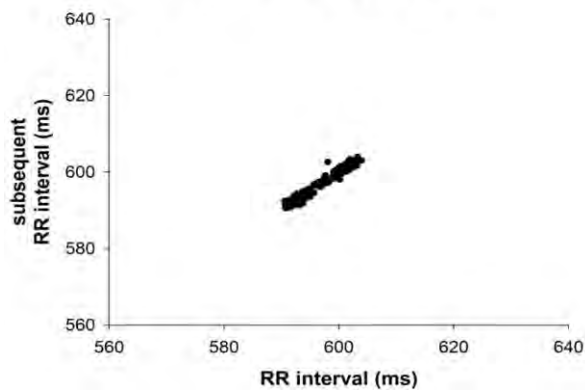


1



2

ROSC + 1h (38 °C)

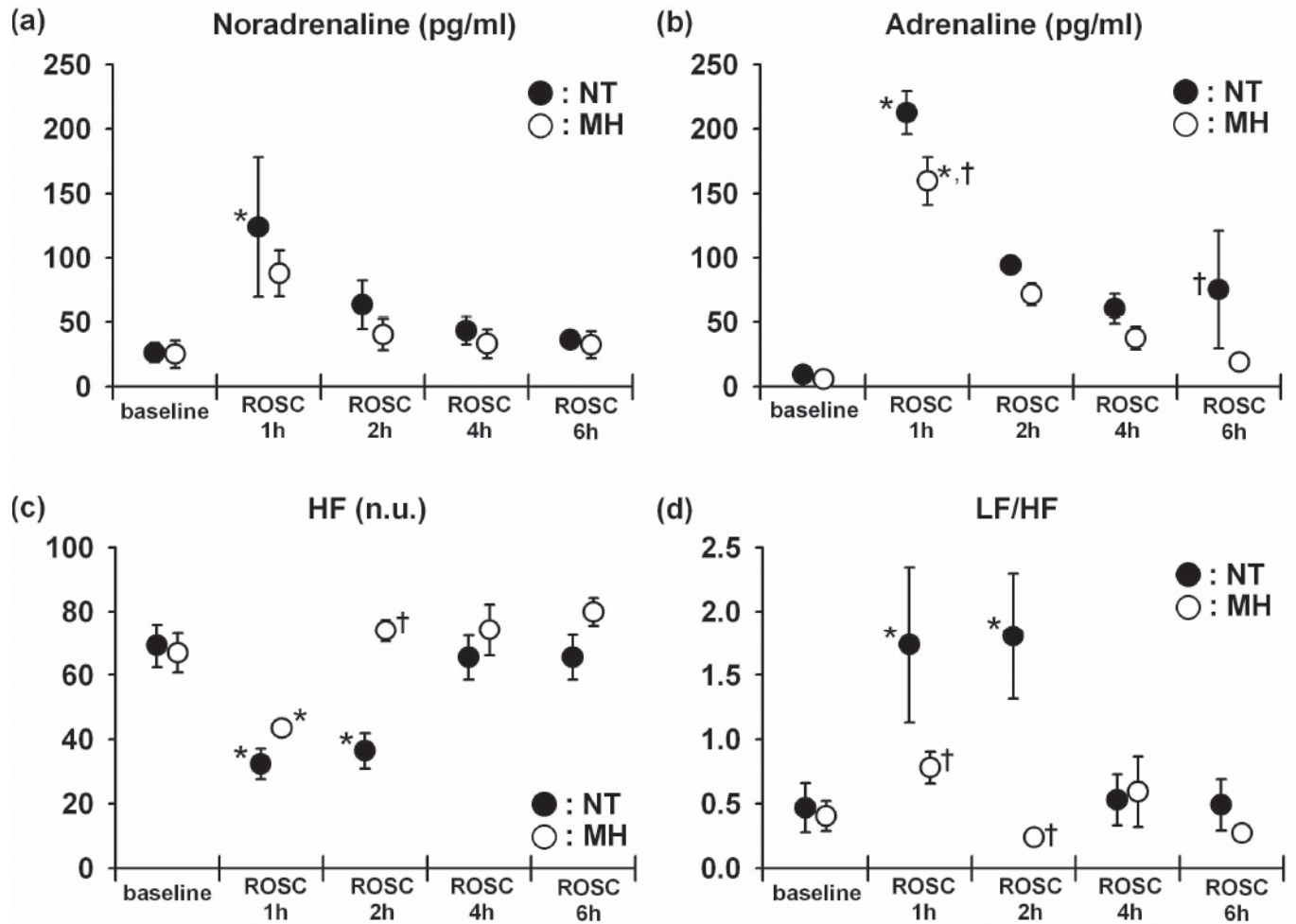


3

MH after cardiac arrest



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Schwarzl et al., Acta Physiol 2011

MH after cardiac arrest



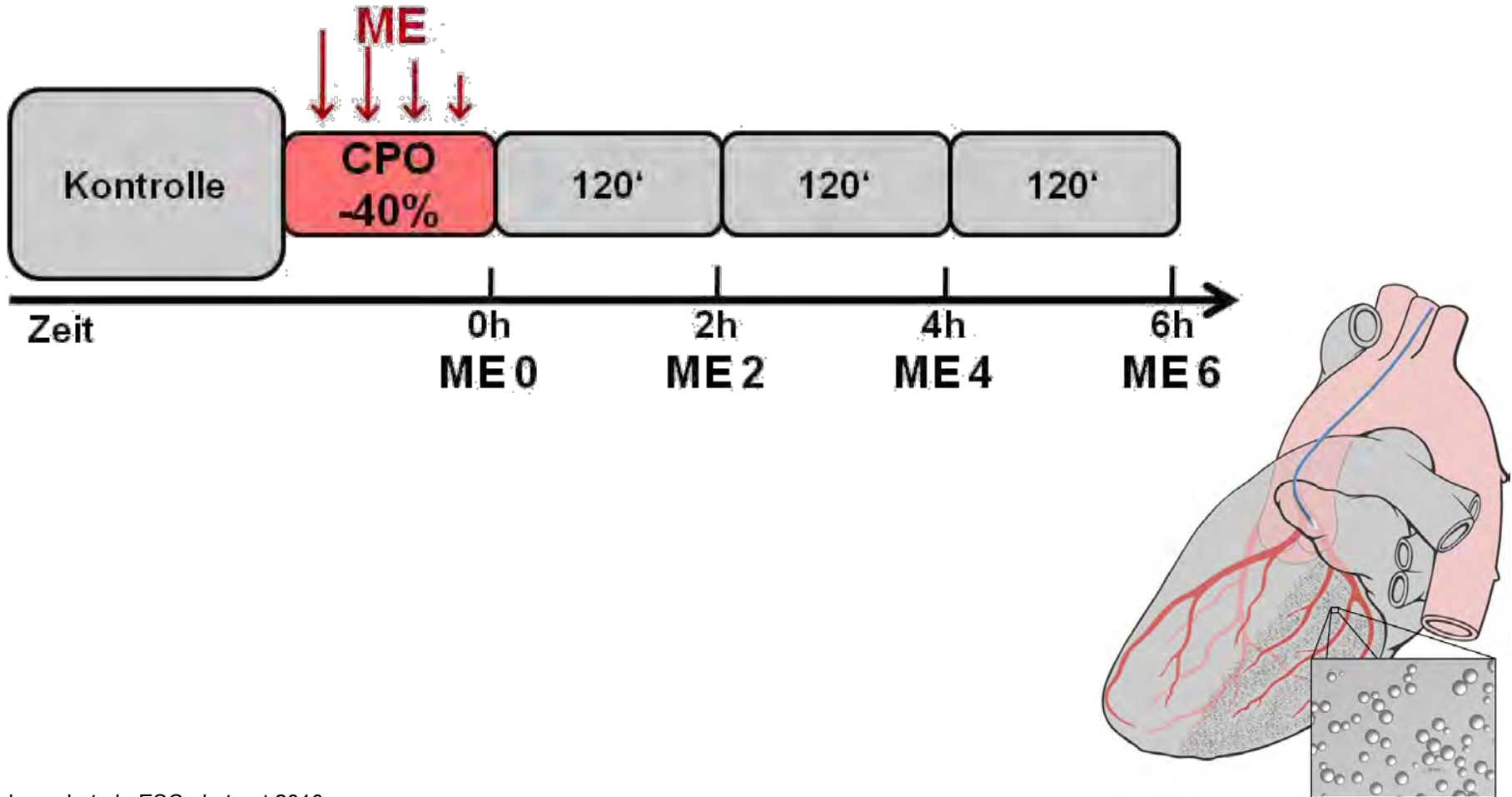
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- increases contractility
- decreases diastolic function – compensated by bradycardia
- improves oxygen-supply demand
- does not potentiate sympathetic activation

NO-reflow myocardial infarction



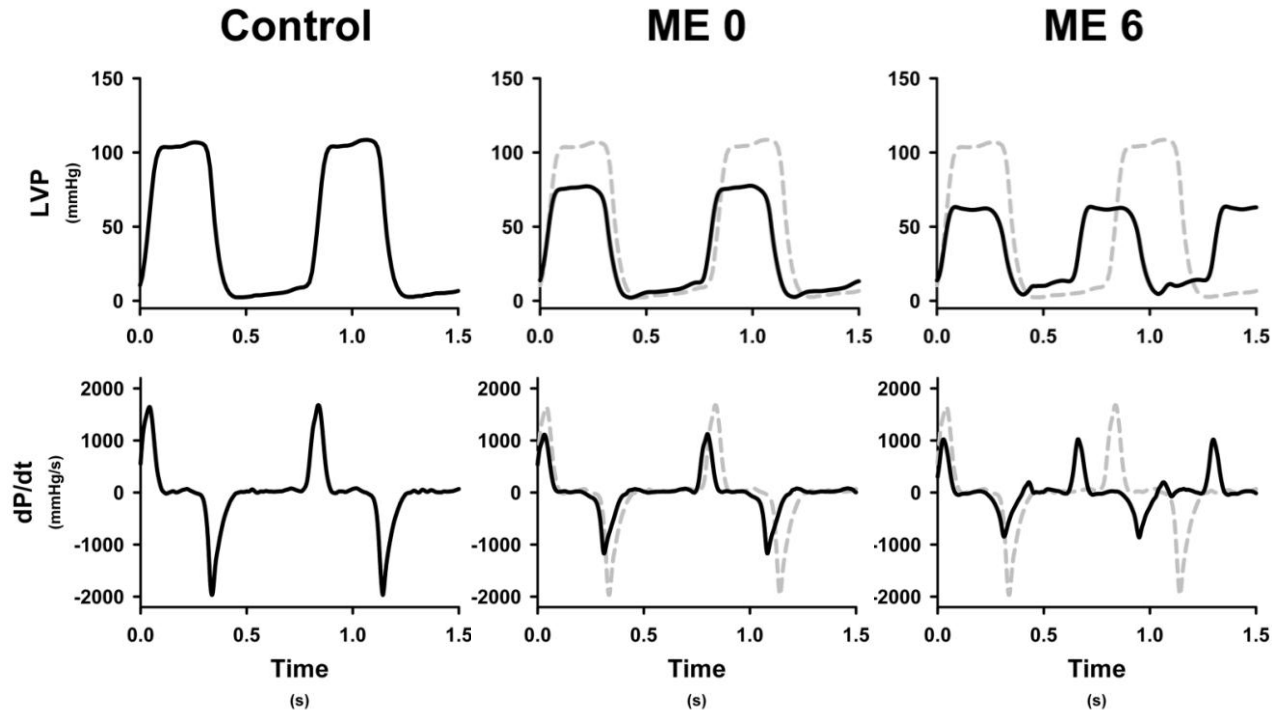
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Acute heart failure after CME

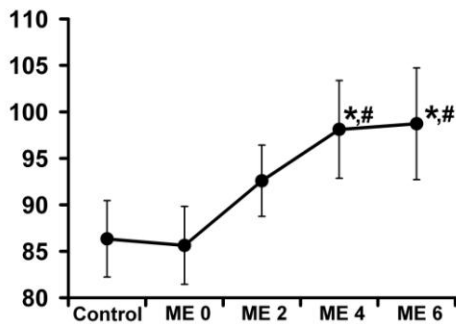


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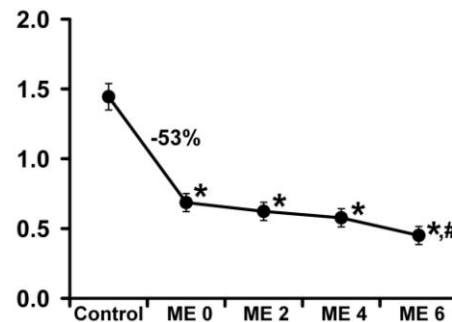


* p<0.05 vs. control
p<0.05 vs. ME 0

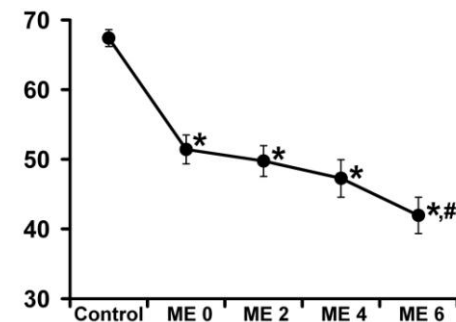
heart rate (bpm)



Cardiac Power Output (W)



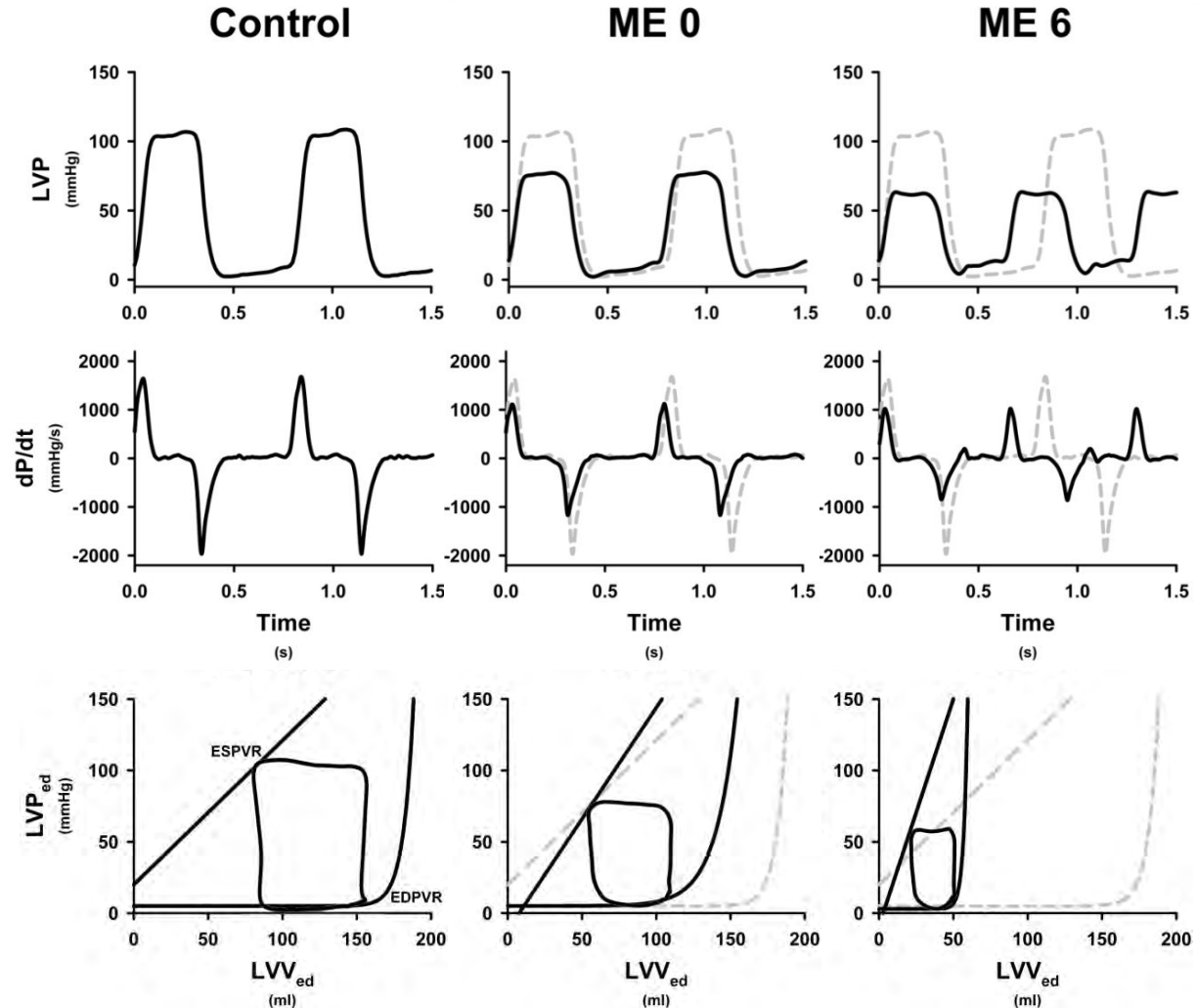
mixed venous sO₂ (%)



Acute systolic and diastolic heart failure after CME

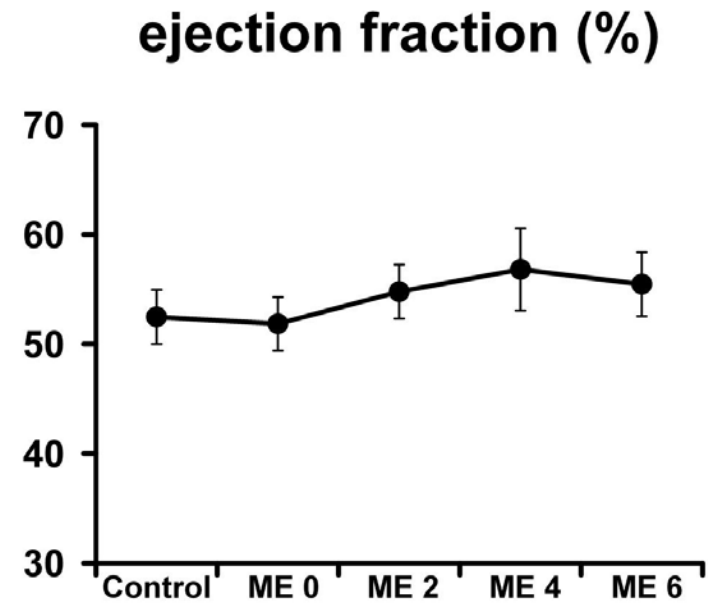
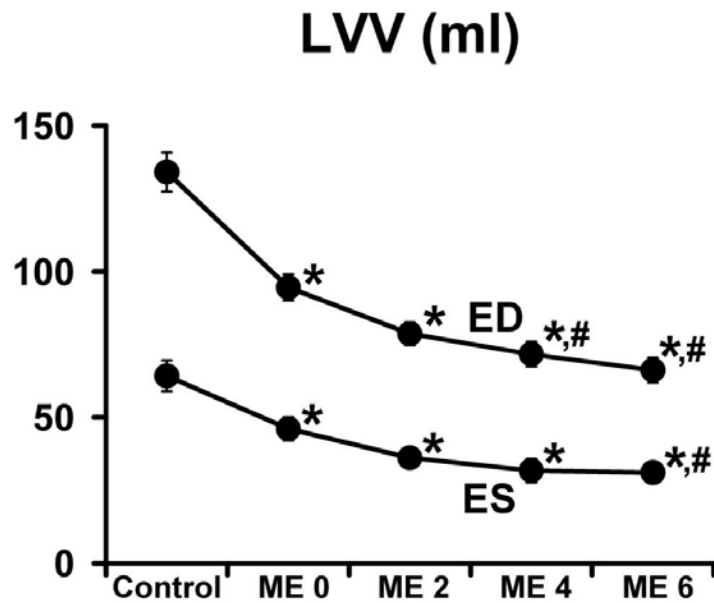


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Schwarzl et al., ESC abstract 2011

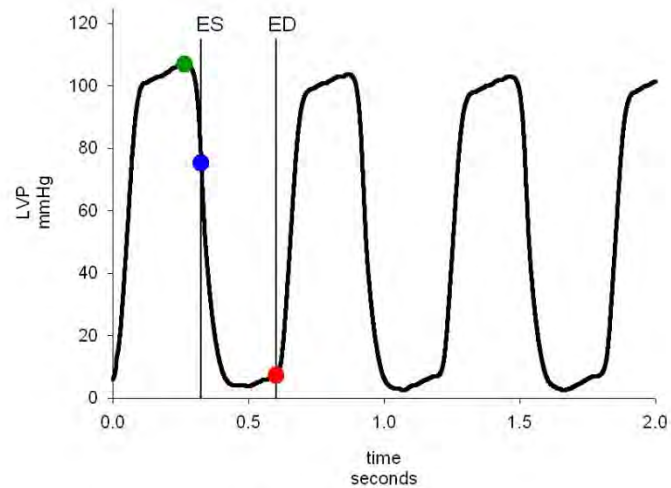
Ejection fraction after CME



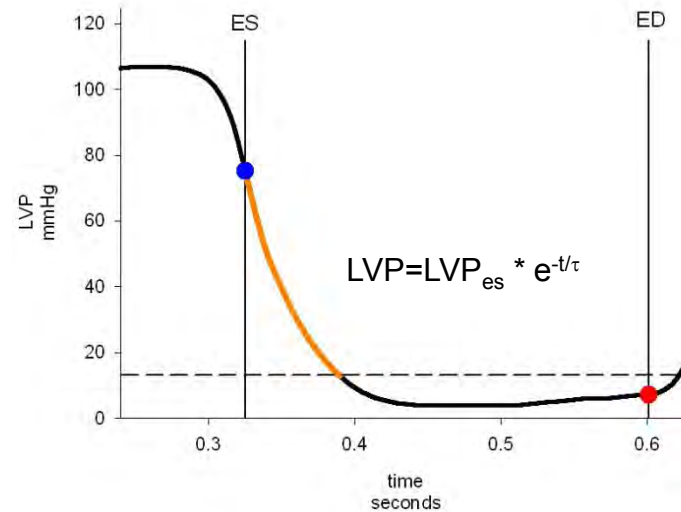
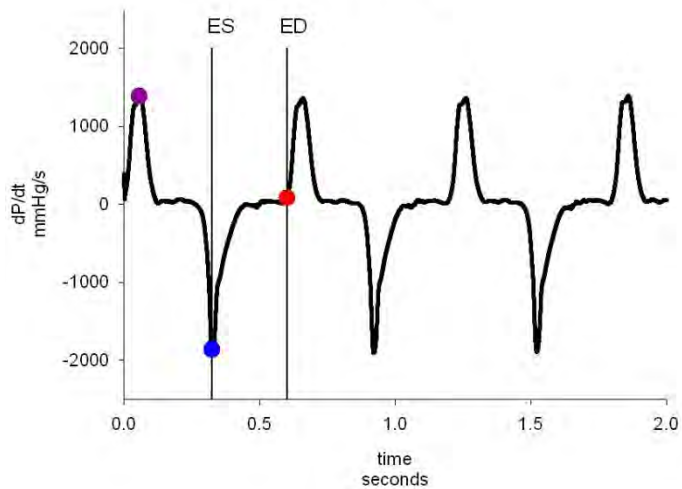
Pressure-time derived indices



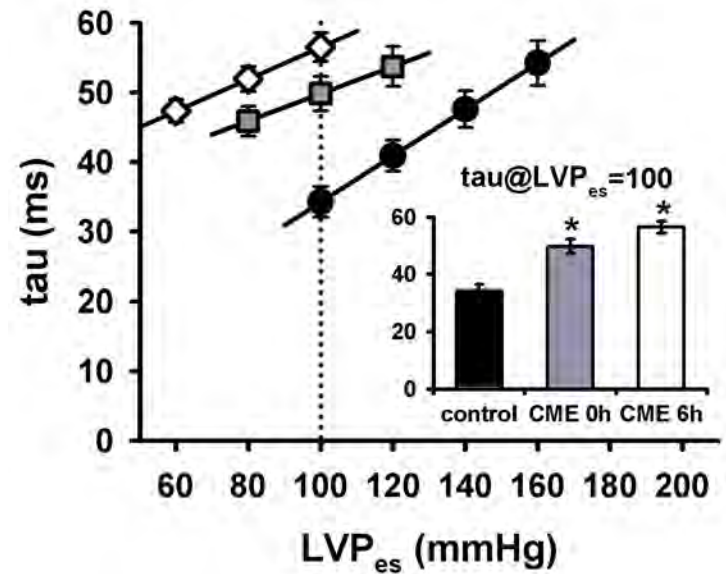
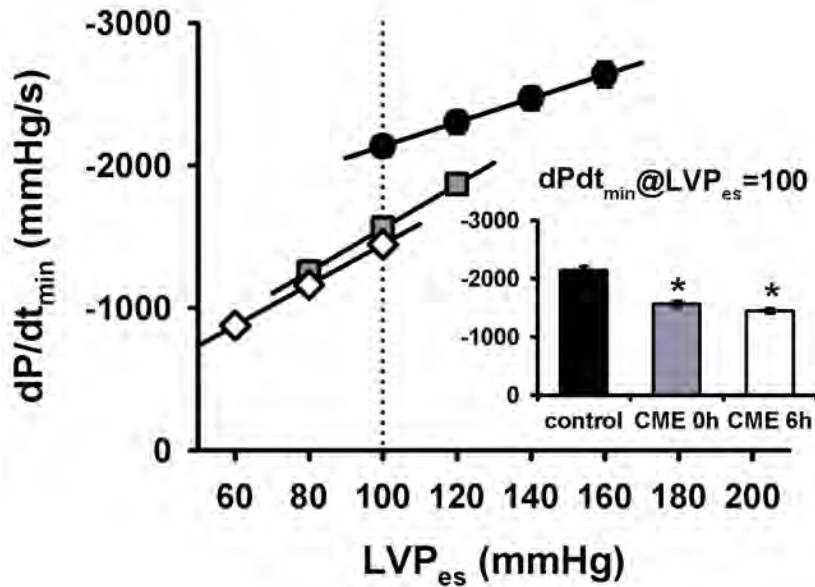
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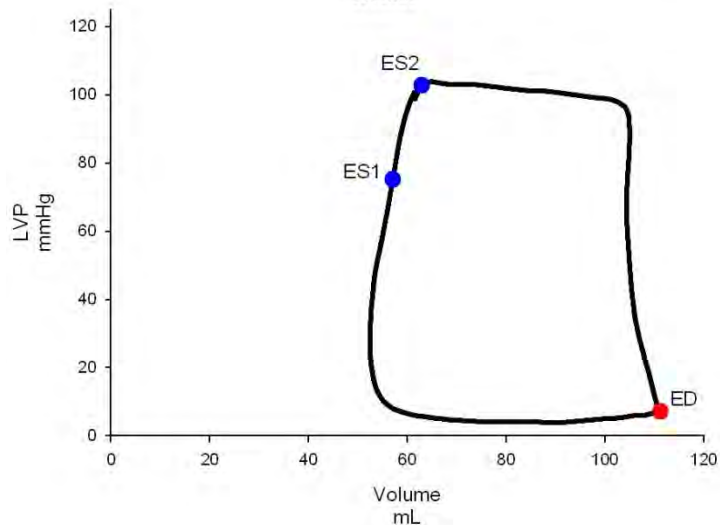
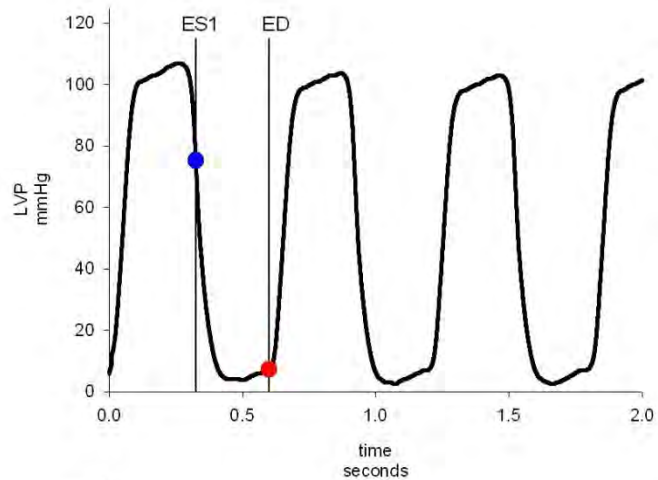
- LVP_{max}
- LVP_{es}
- LVP_{ed}
- dP/dt_{max}
- dP/dt_{min}
- τ



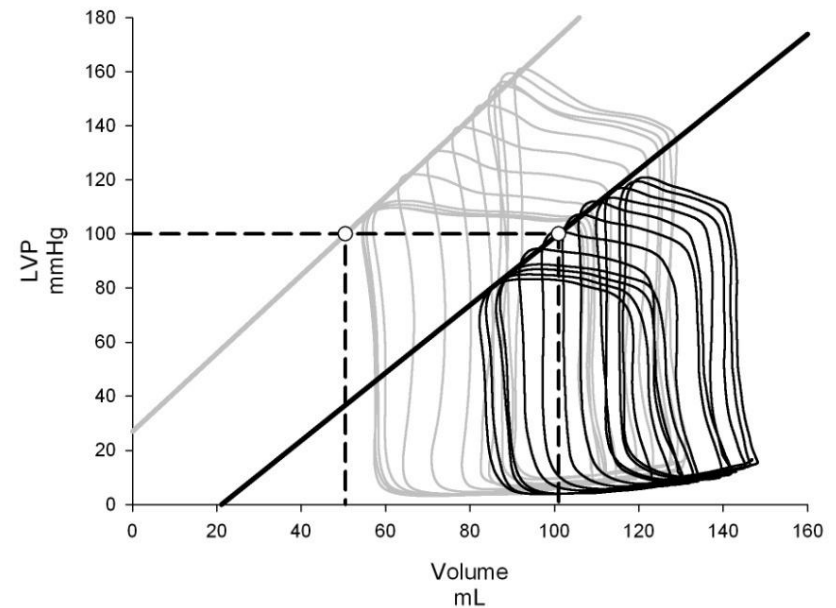
Active LV relaxation after CME



Pressure-volume derived indices



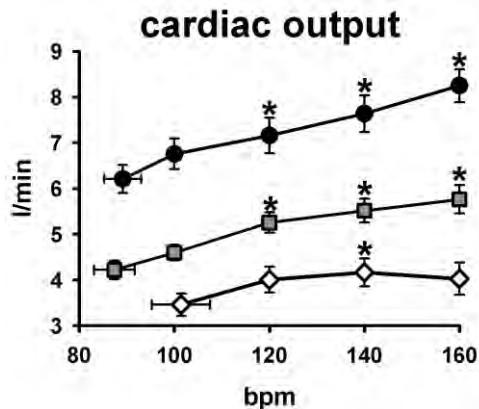
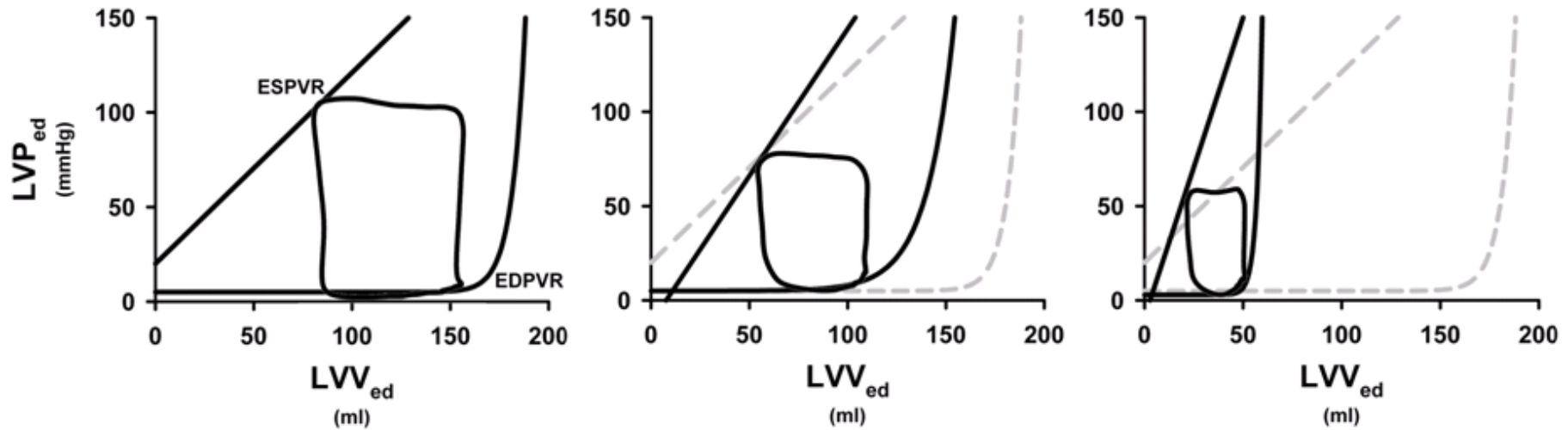
- LVP_{es}, V_{es}
- LVP_{ed}, V_{ed}
- end-systolic pressure-volume relationship (ESPVR, $VP_{es} 100$)



Acute systolic and diastolic heart failure after CME: how to treat?

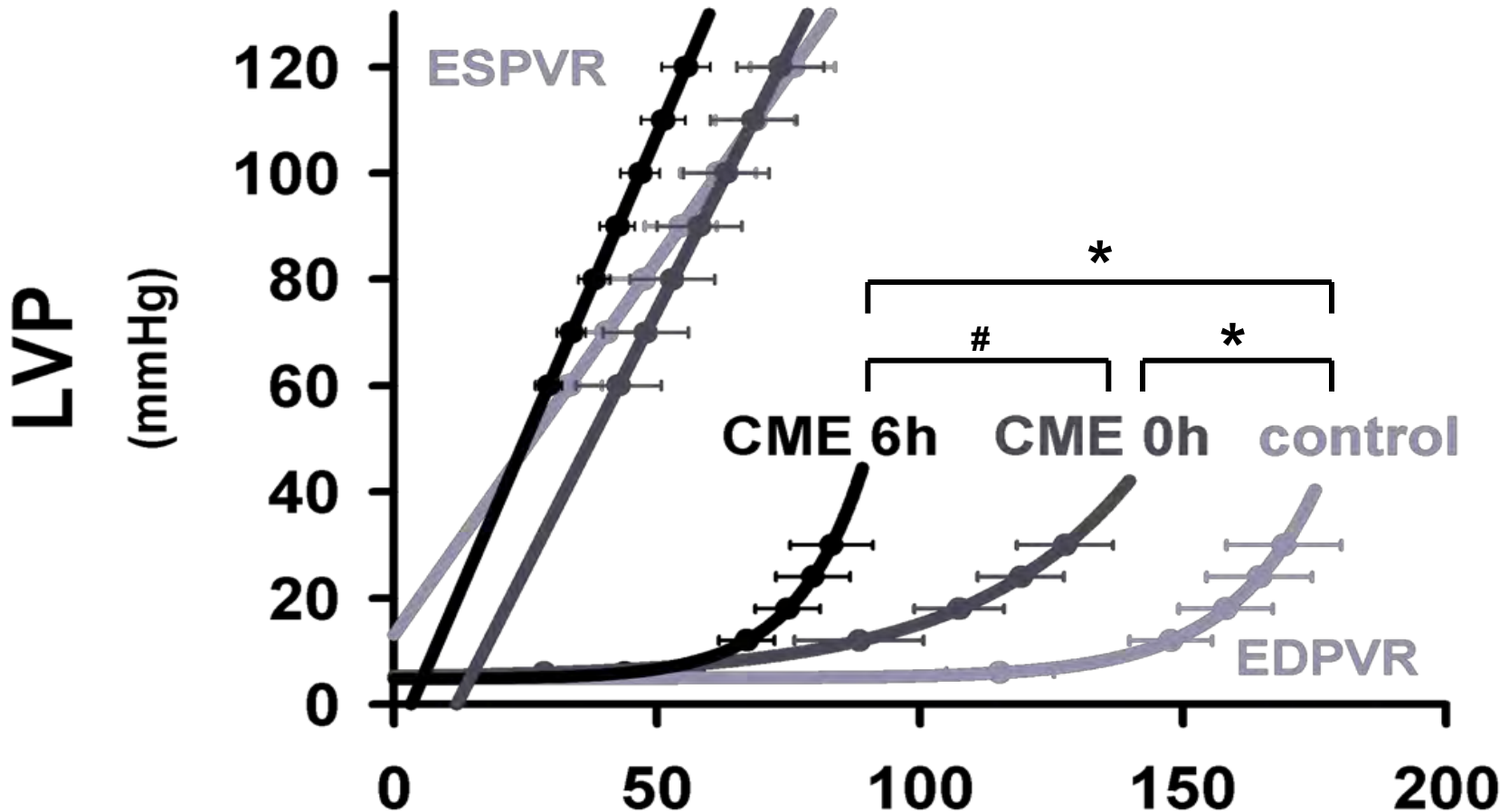


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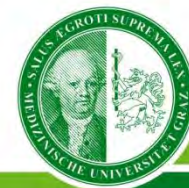


Increase preload – pulmonary edema
 Increase inotropy – ES volume already small
 Decrease afterload – ES volume is already small
 Increase heart rate – no effect
 IABP – no reflow, ES volume is already small

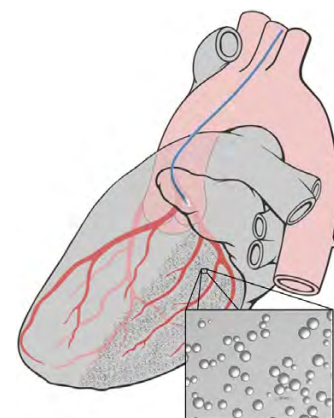
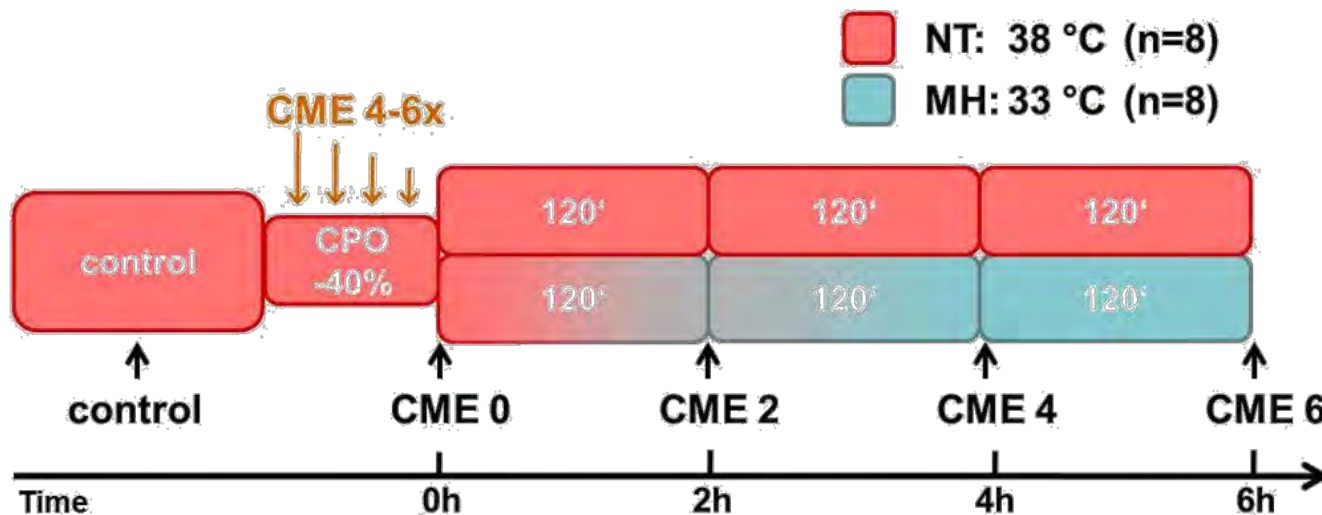
PV-relationships after CME



Effect of cooling on acute heart failure after CME



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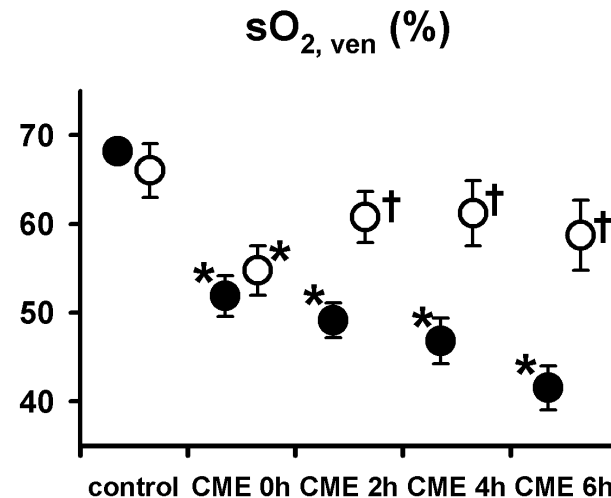
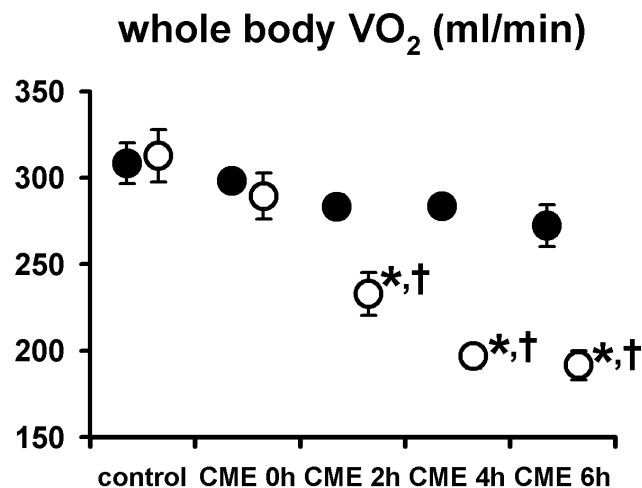
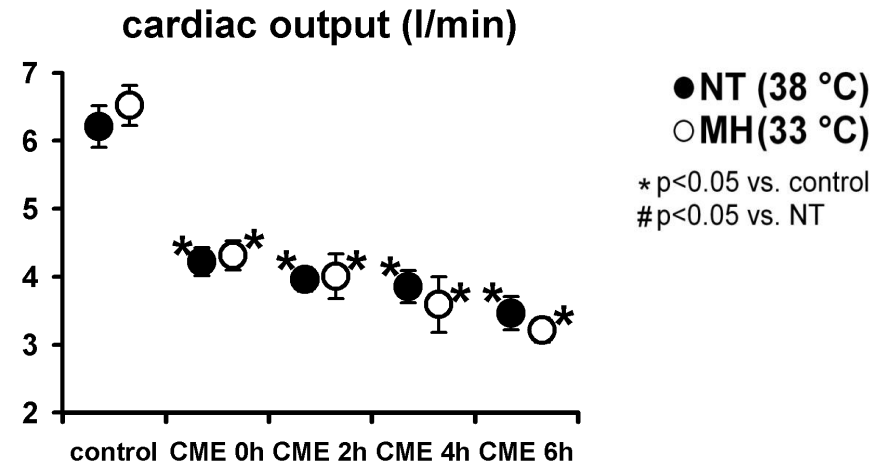
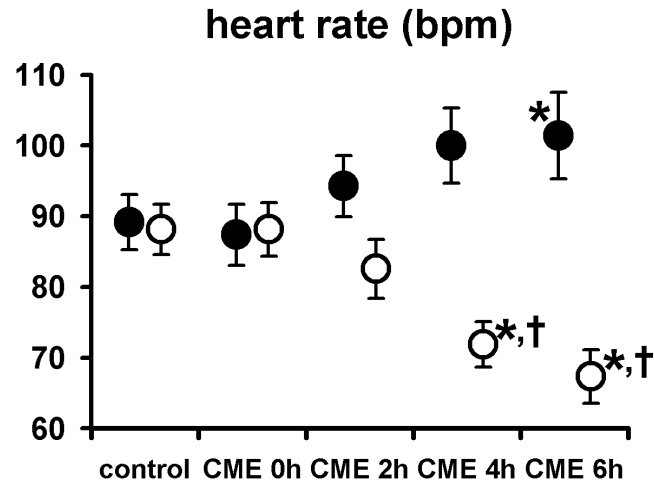


Schwarzl et al., ESC abstract 2011

Effect of cooling on acute heart failure after CME



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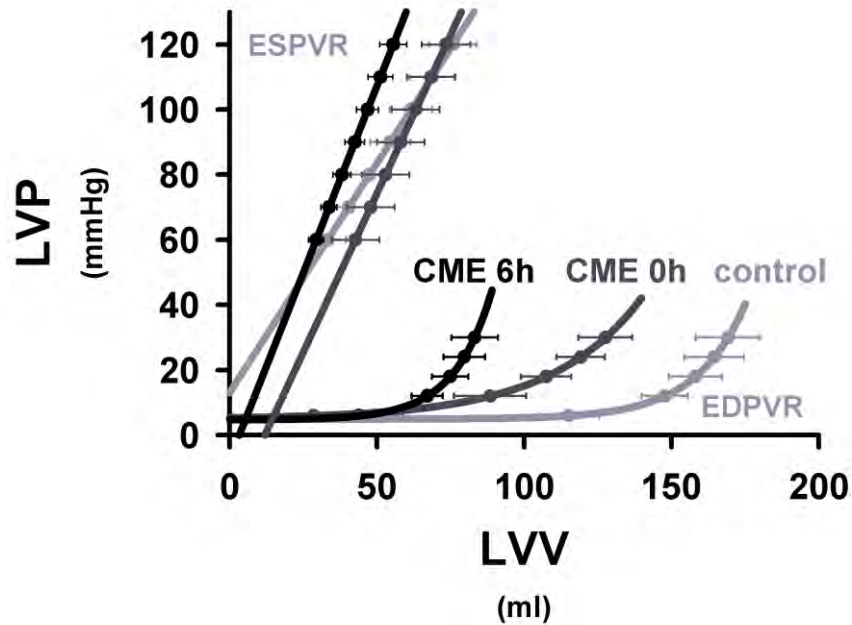


Effect of cooling on acute heart failure after CME: PV-relationships

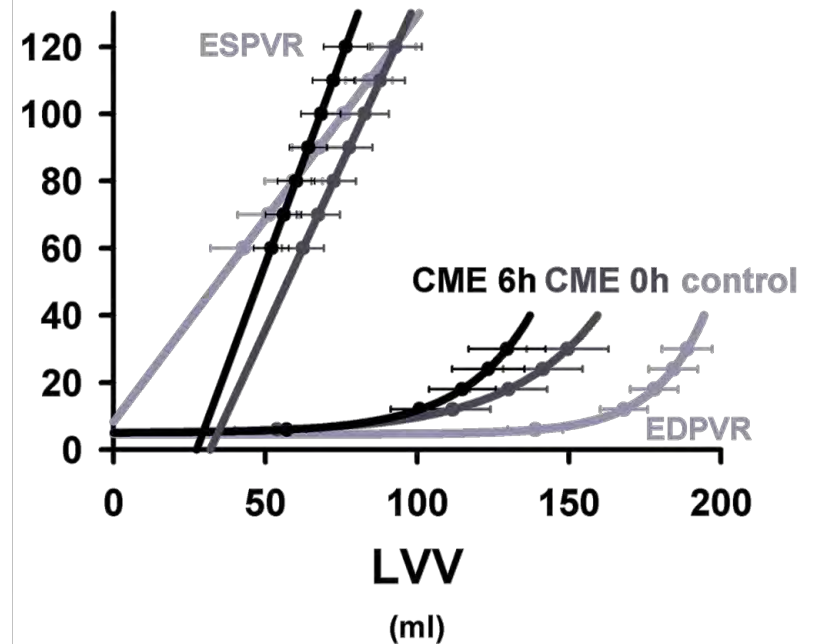


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38,0°C



33,0°C after CME

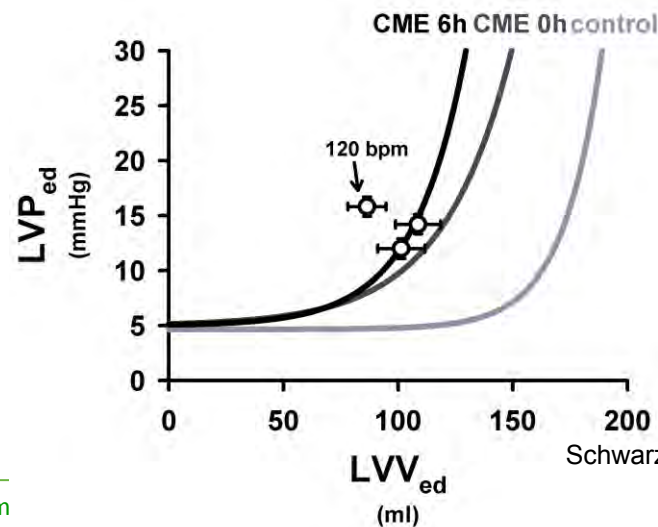
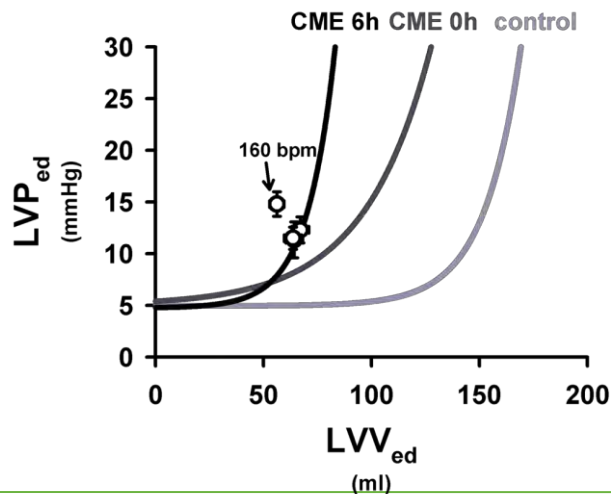
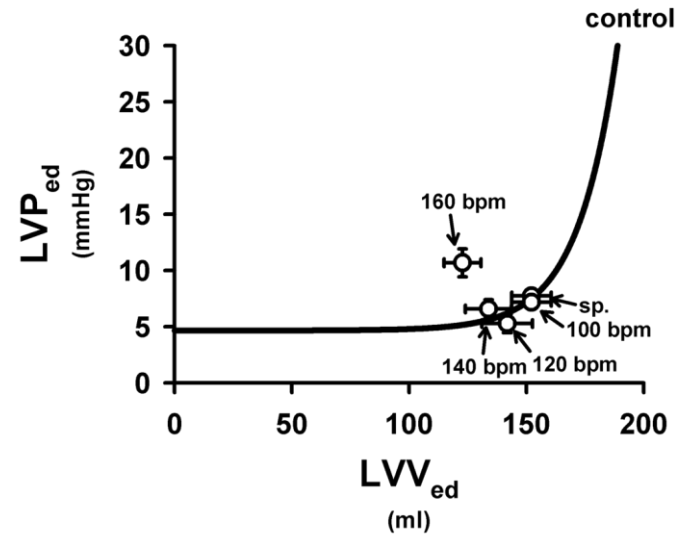
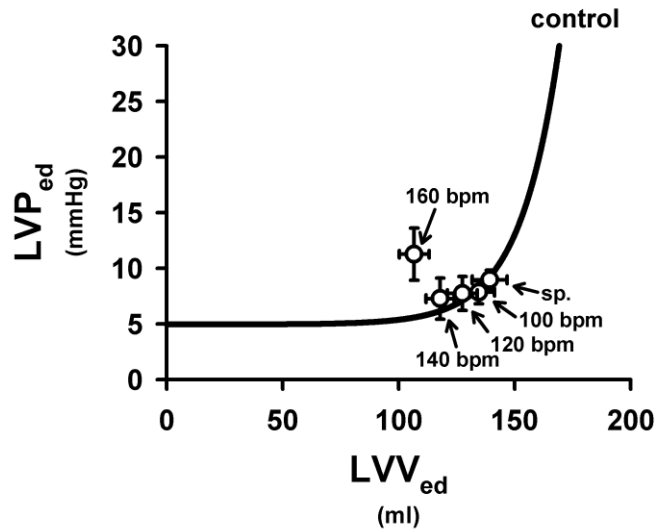


Schwarzl et al., ESC abstract 2011

Effect of cooling on acute heart failure after CME: challenging relaxation



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Schwarzl et al., ESC abstract 2011

Mild hypothermia in acute heart failure



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O_2 -demand

hypothermia



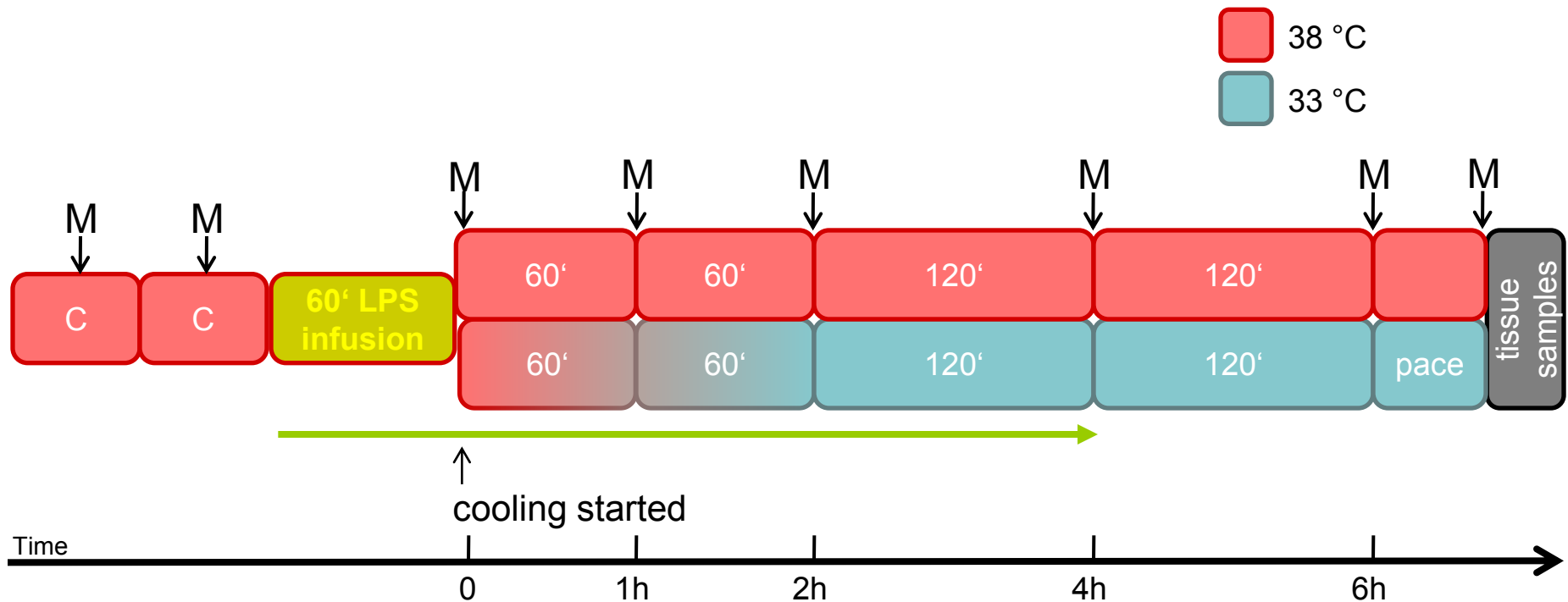
O_2 -delivery

preload
inotropics
pacing
devices:
(IABP, Impella
ECMO)

Sepsis/inflammation model



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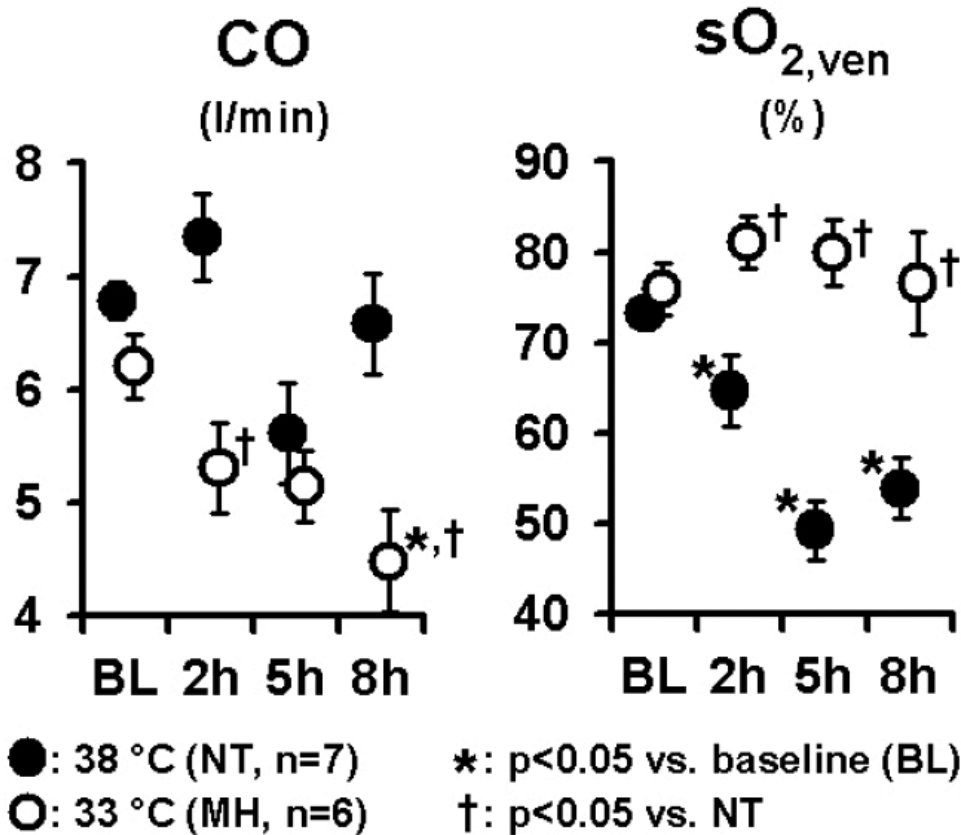
LPS: lipopolysaccharide, inductor of sepsis

M: saline, CO, BGA art./ven., blood samples, aortic occlusion

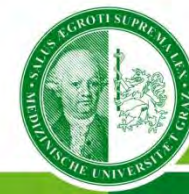
MH and LPS/sepsis: improved oxygen supply-demand balance



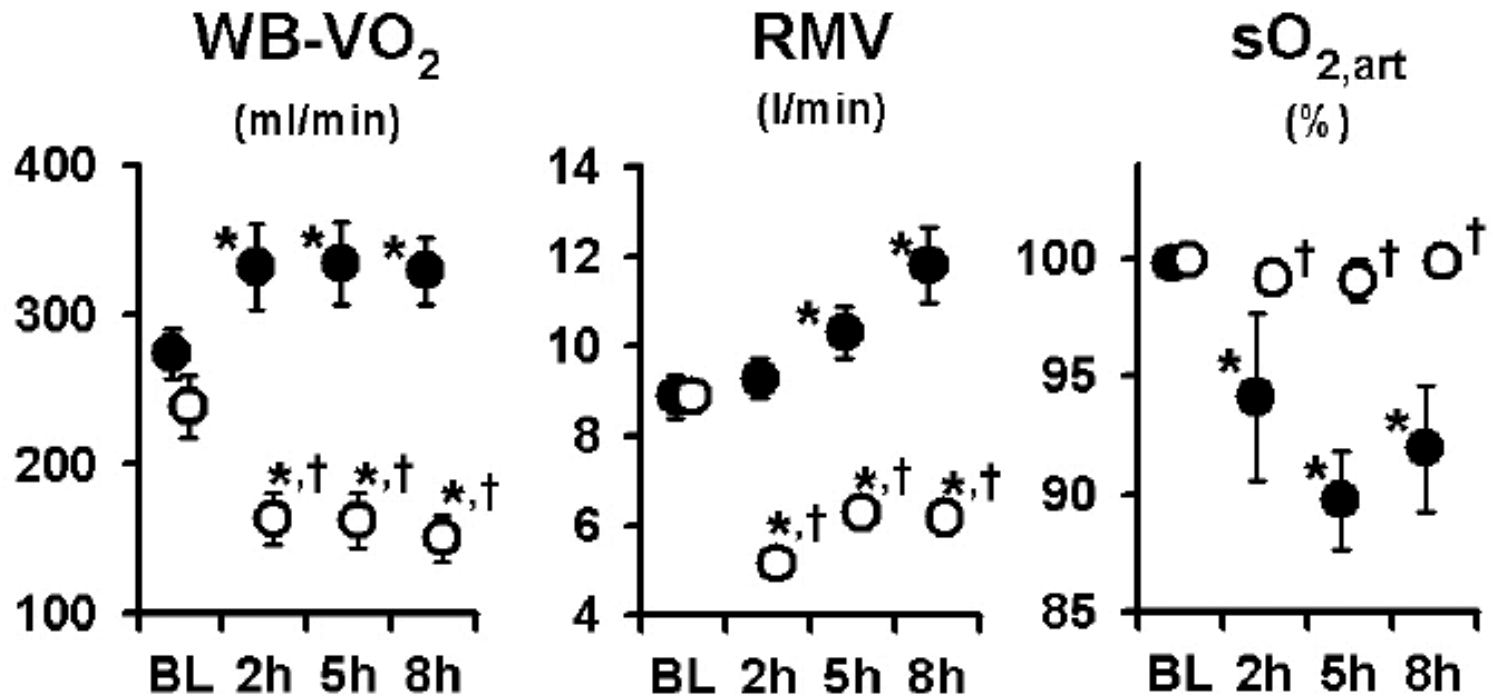
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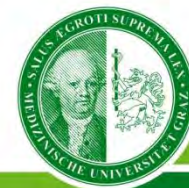
MH and LPS/sepsis: preserved pulmonary function



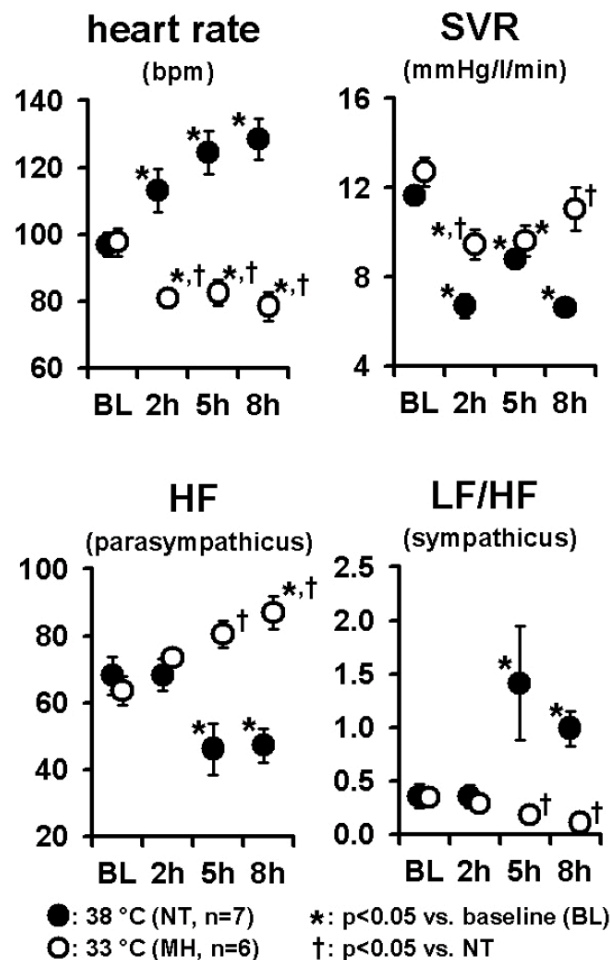
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MH and LPS/sepsis: decreased symp. activation, preserved myocardial β -response

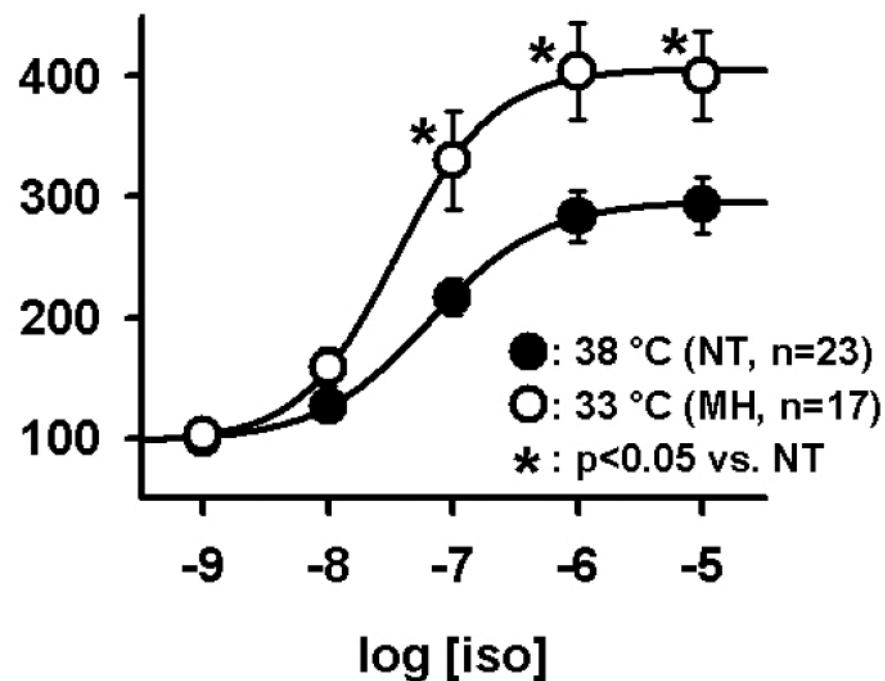


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isolated muscle strips:

Developed force (%) in response to isoproterenol

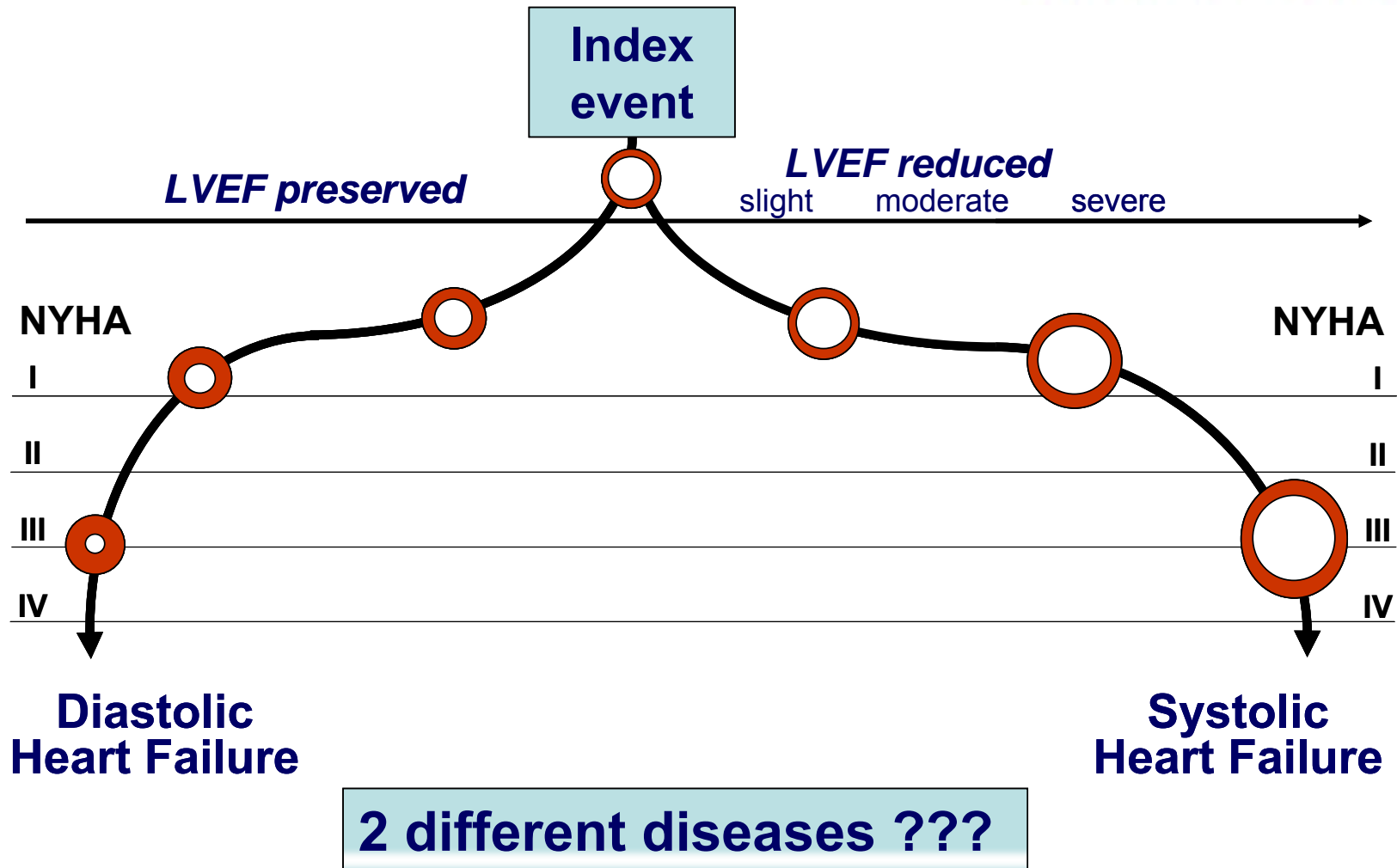




- reduces reperfusion injury
- positive inotrope
- decreases relaxation and distensibility, compensated by bradycardia
- improves systemic oxygen/supply balance, even at decreased cardiac output
- decreases sympathetic activation
- hypothesis: anti-inflammatory effects
- may evolve as a new therapy for
 - acute myocardial infarction
 - ICU: critical acute (but potentially transient) heart failure



Systolic (HFREF) vs diastolic (HFPEF) heart failure - Hemodynamics -

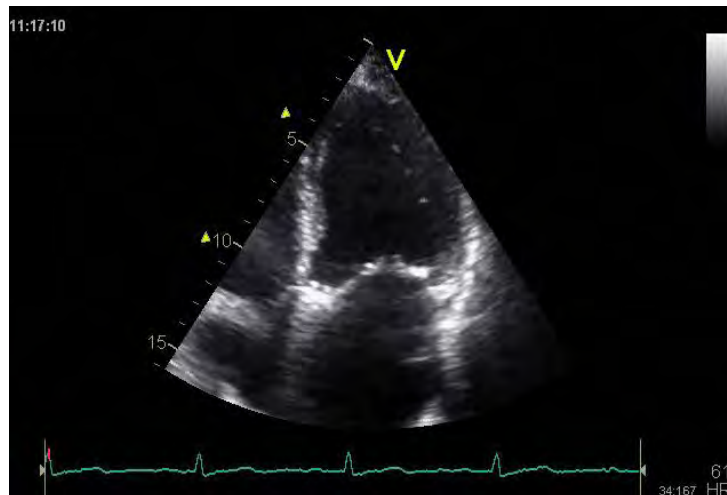


Modified after: G. De Keulenaer, 2006

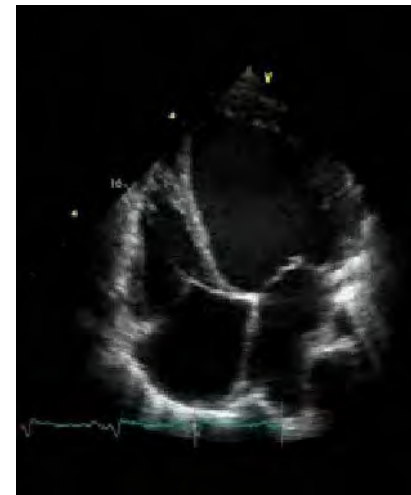
healthy



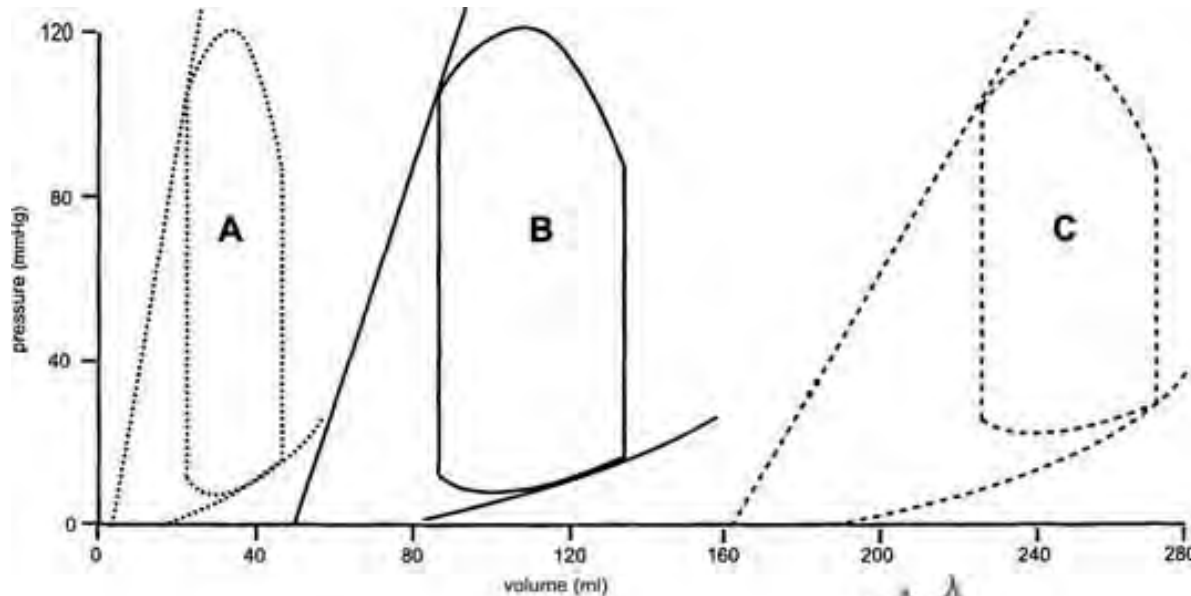
HFPEF



HFREF



HFPEF vs HFREF



A. Concentric



B. Normal



C. Eccentric

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

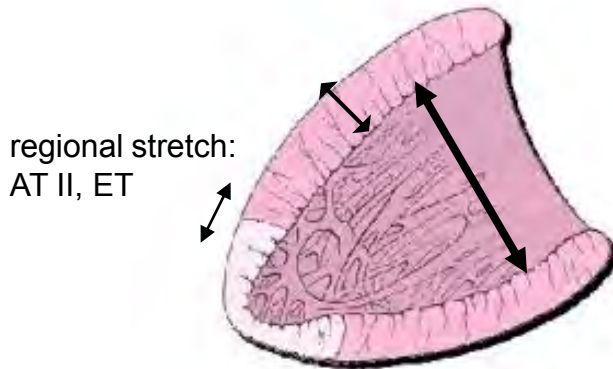
- infarction
- tachycardia
- aortic stenosis
- toxic
- shunt

Remodeling in HFREF



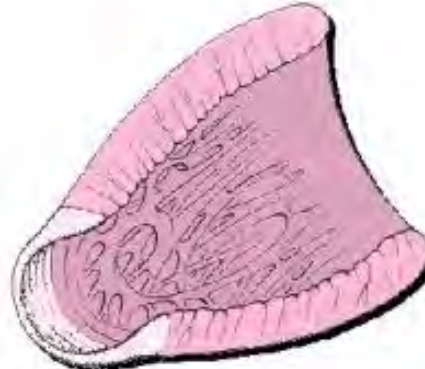
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Acute MI

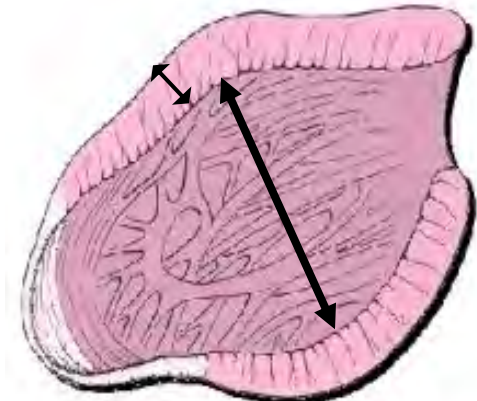


regional stretch:
AT II, ET

Extension



Dilatation



wall tension:
LaPlace

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

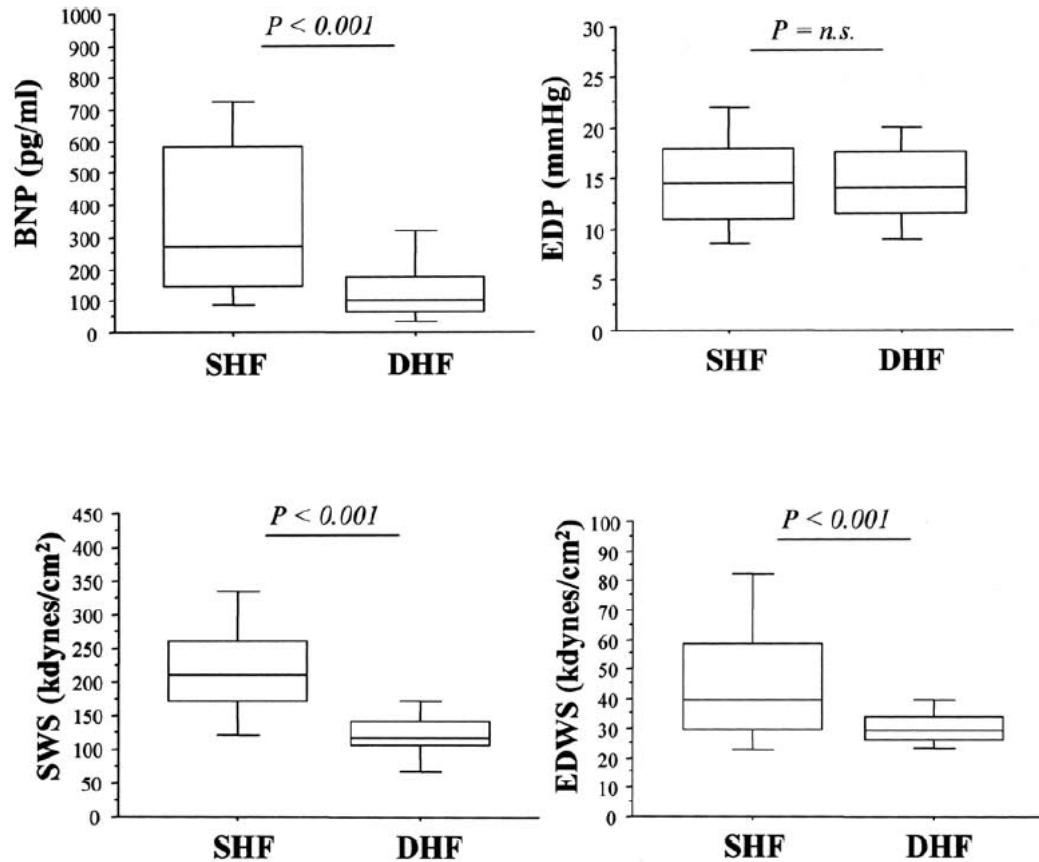
- diameter ↑
- wall thickness ↓
- ejection fraction ↓
- wall tension ↑↑

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

Wall stress in HFPEF vs HFREF



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Iwanaga, JACC 2006

HFPEF: not only a LV disease

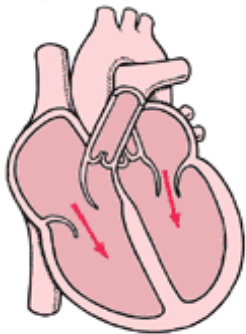


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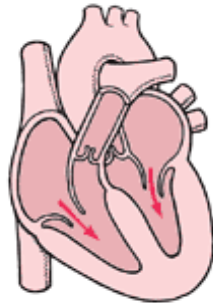


Systolic Dysfunction

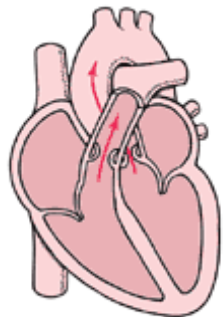
Diastolic Dysfunction



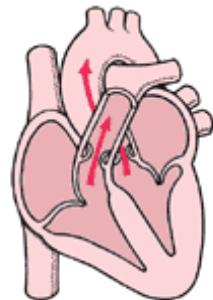
The enlarged ventricles fill with blood.



The stiff ventricles fill with less blood than normal.



The ventricles pump out less than 40 to 50% of the blood.



The ventricles pump out about 60% of the blood, but the amount may be lower than normal.

pulmonary hypertension

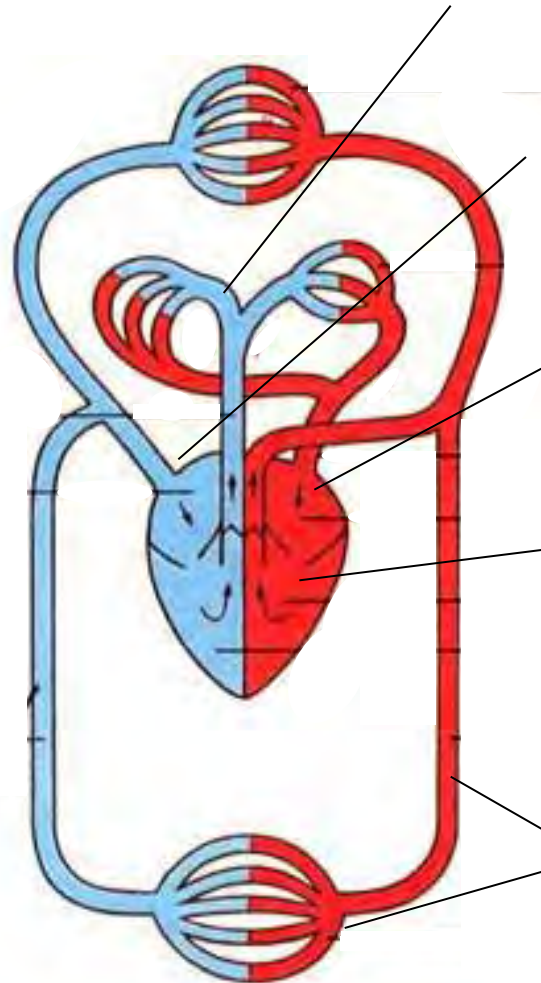
chronotropic incompetence

left atrial dysfunction

left ventricle:
- relaxation
- stiffness
- torsion

VA
coupling

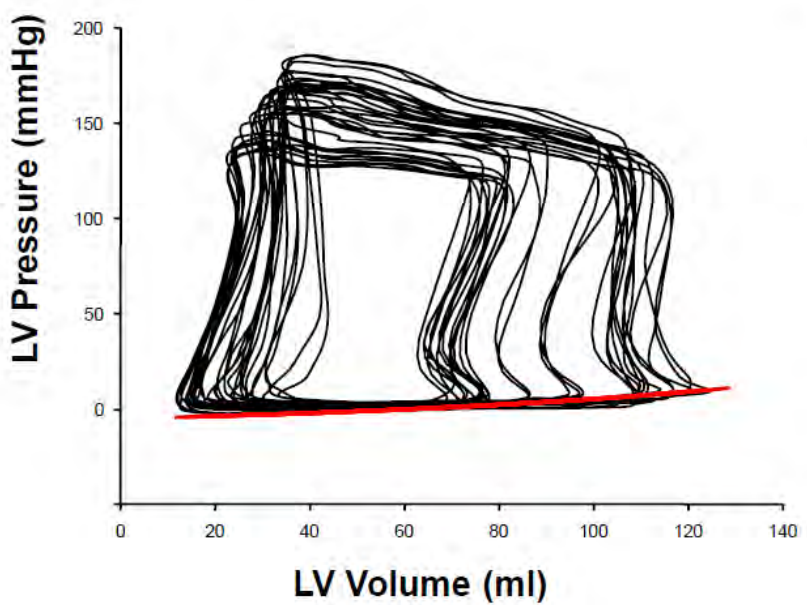
arterial stiffening



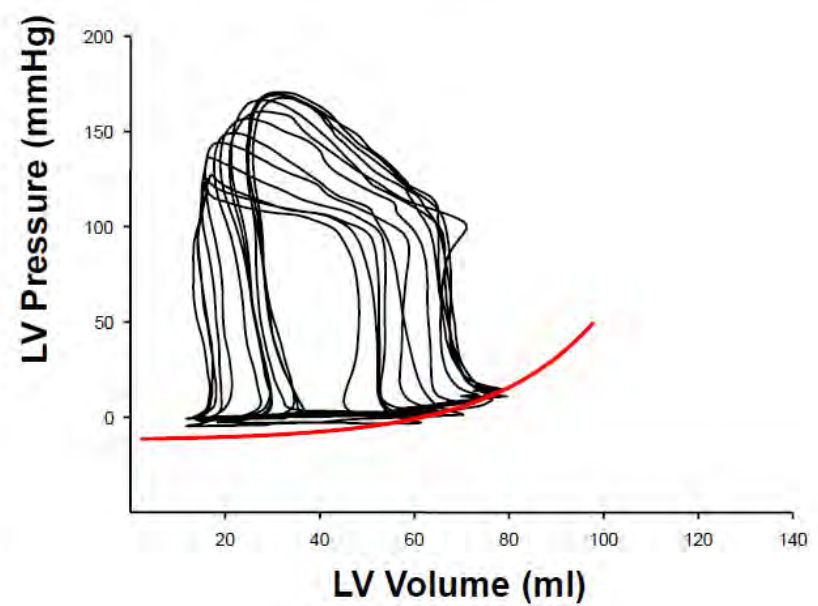
Pressure-volume analysis in HFPEF: patients



Control



HFNEF

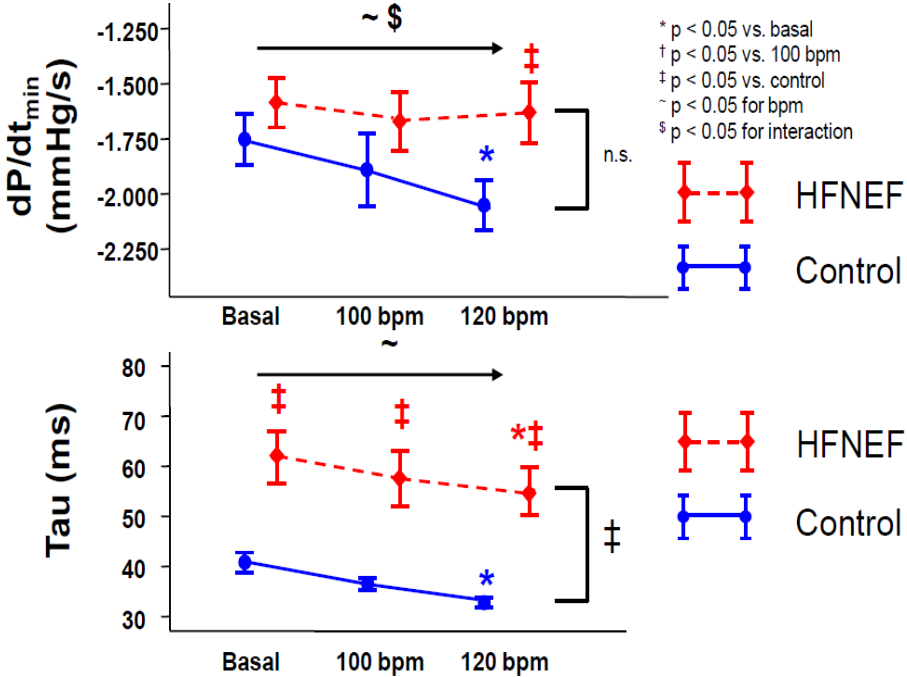
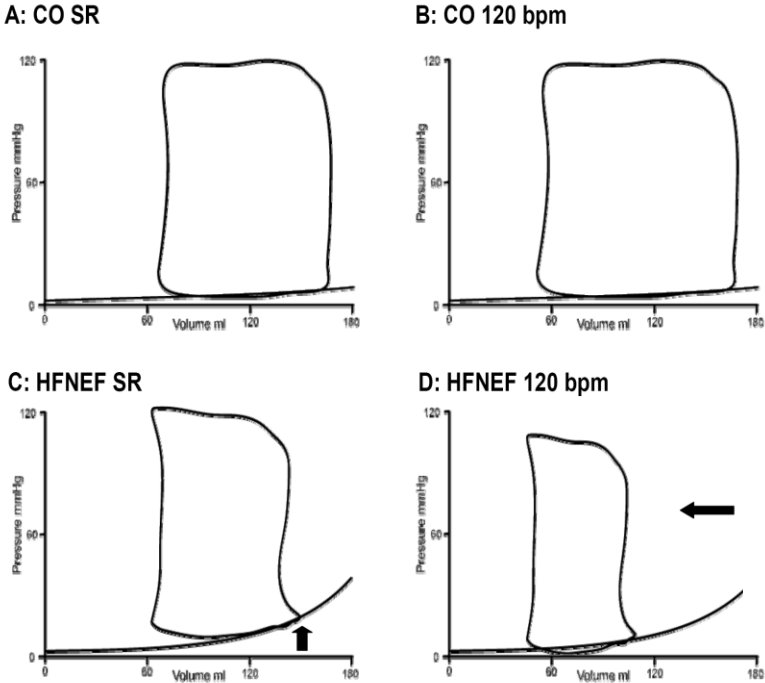


Pressure-volume analysis in HFPEF



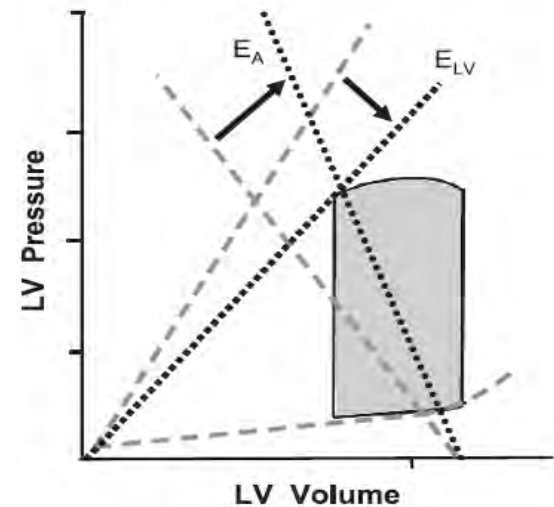
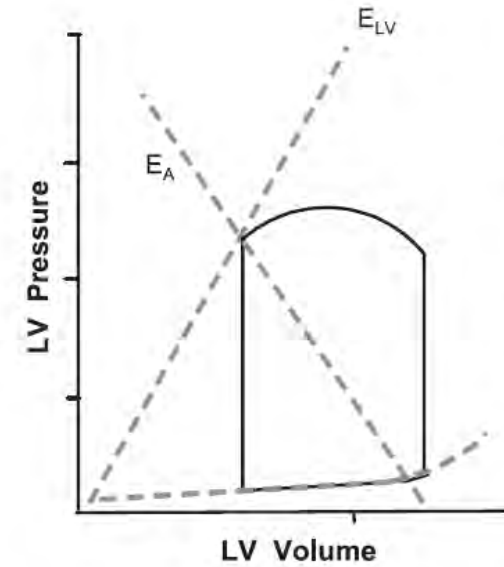
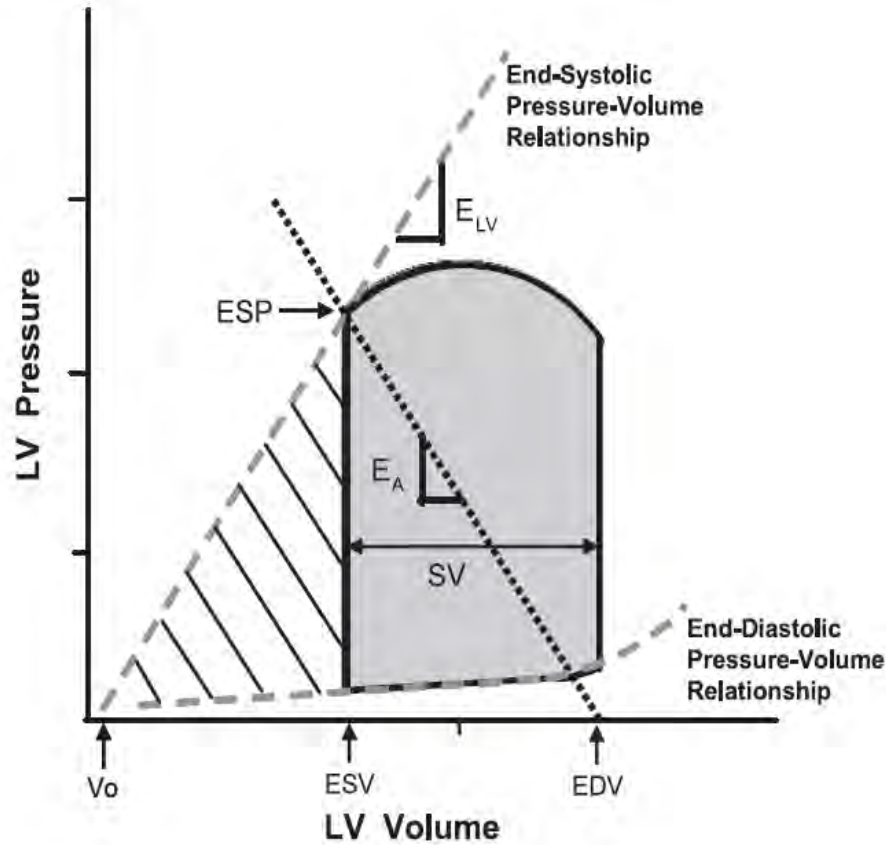
leftward shift of EDPVR

slowed LV relaxation



Westermann et al., Circ 2008; Wachter et al., EHJ 2009

Ventricular-arterial coupling in HFREF

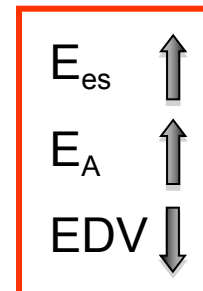
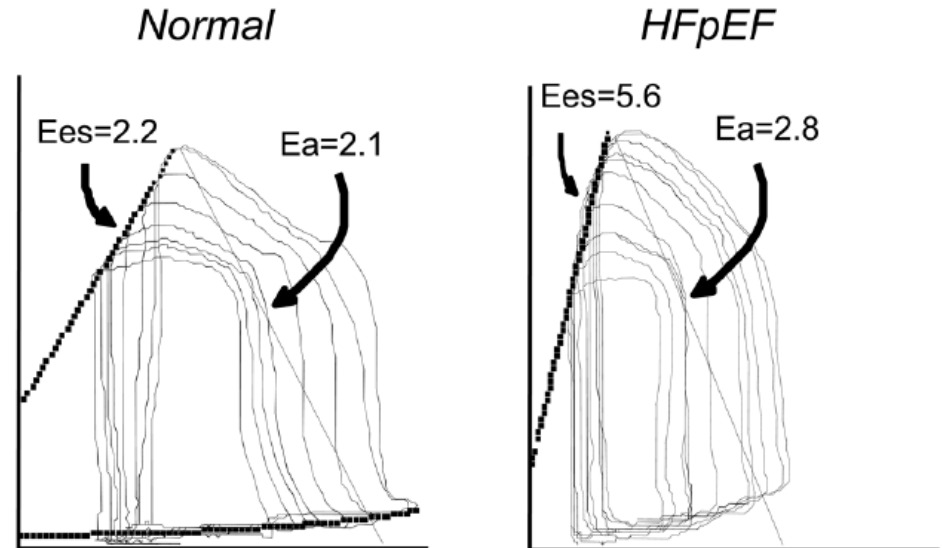
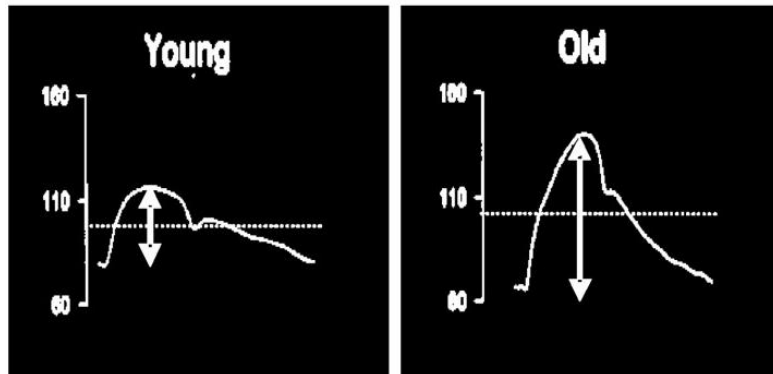
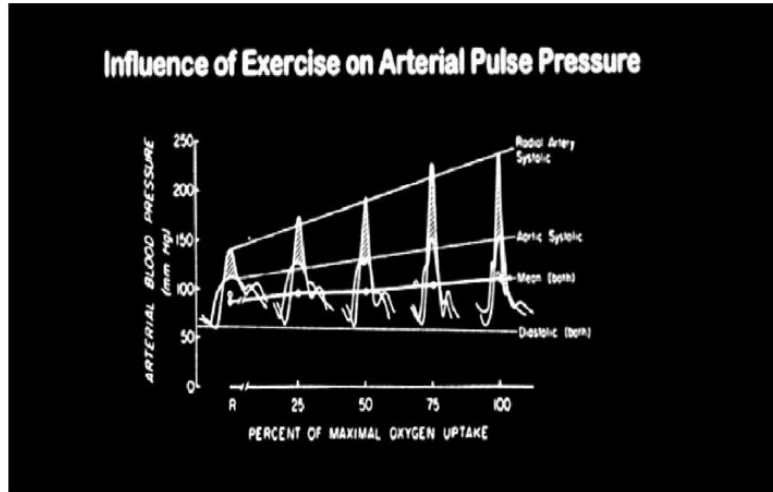


- | | |
|----------|---|
| E_{es} | ↓ |
| E_A | ↑ |
| EDV | ↑ |

Ventricular-arterial coupling in HFPEF



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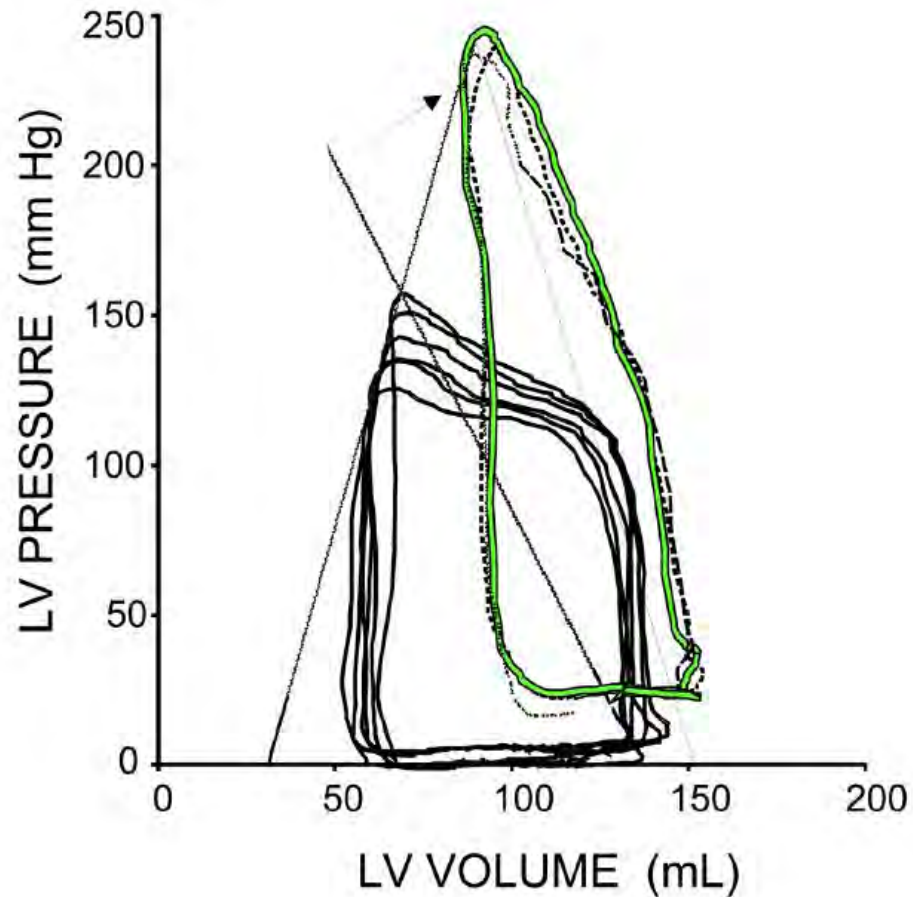


Borlaug et al., Heart Fail Clin 2008

PV-loops in HFPEF: exercise



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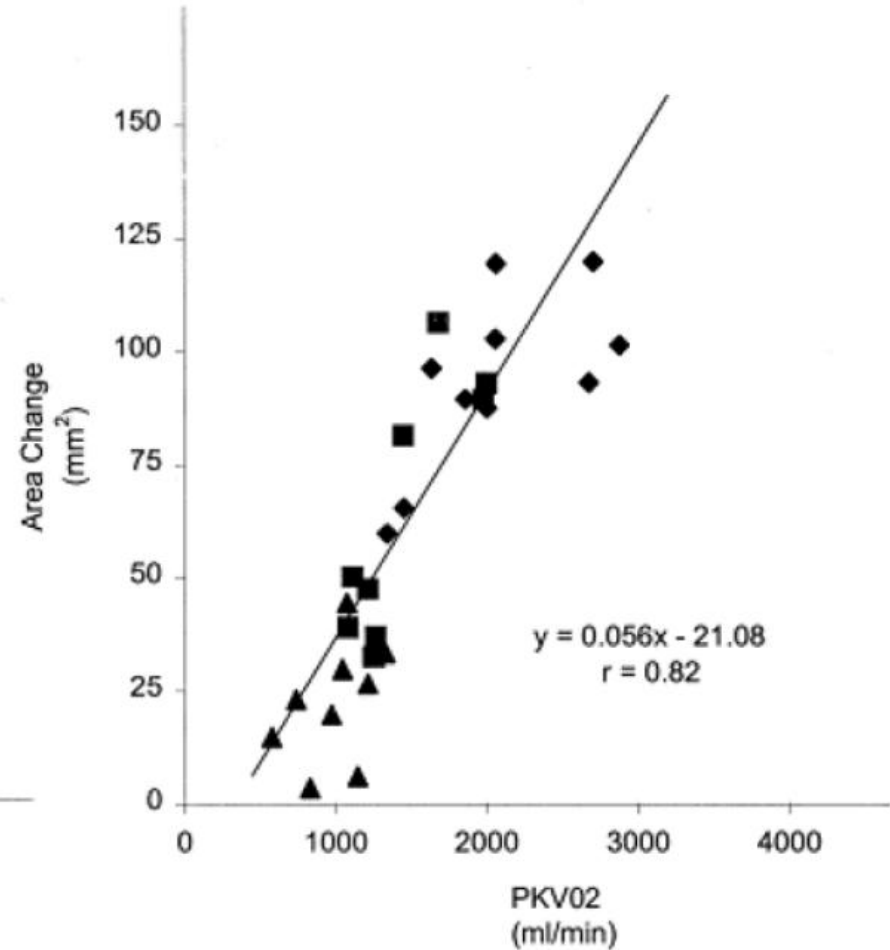
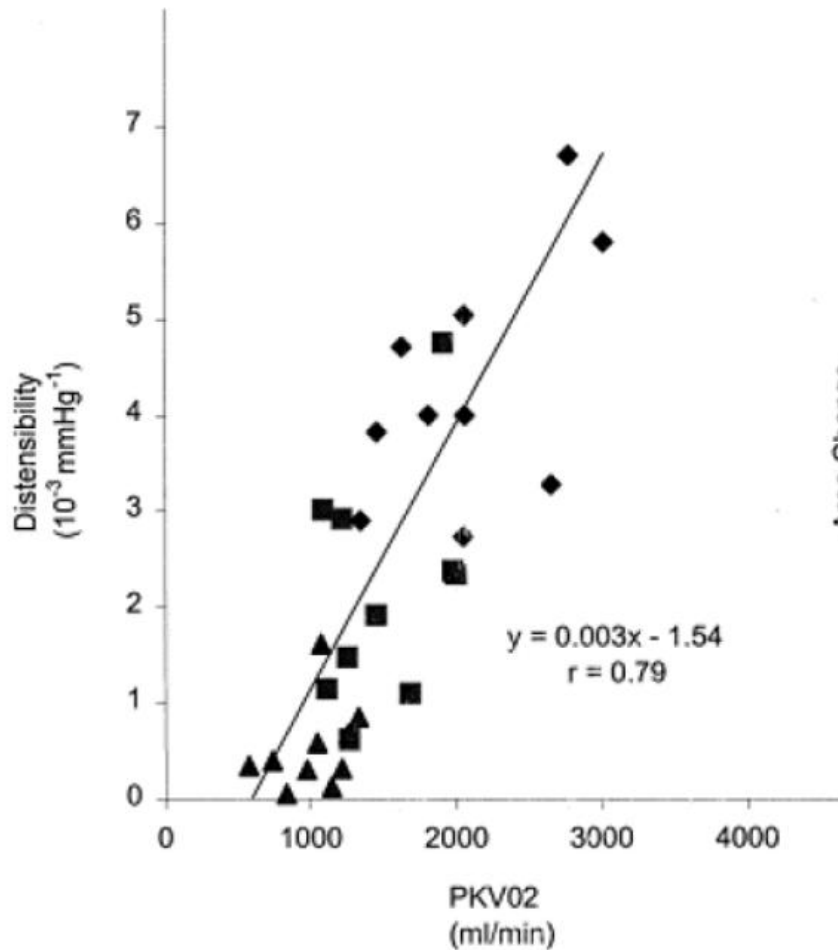
$E_{es} =$
 $E_A \uparrow$
 $EDV =$

Kawaguchi et al., Circ 2003

Aortic distensibility determines exercise capacity



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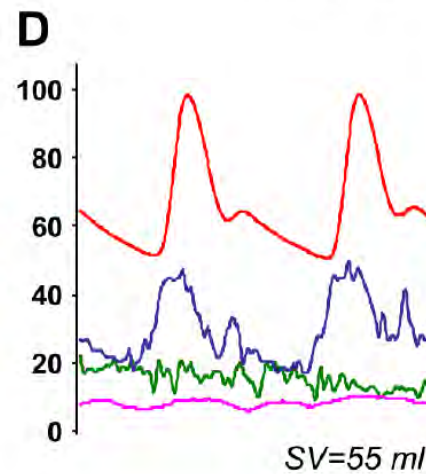
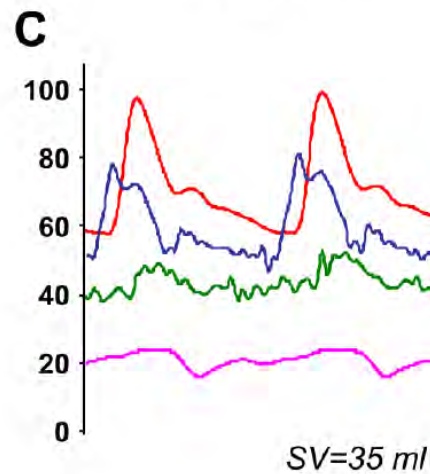
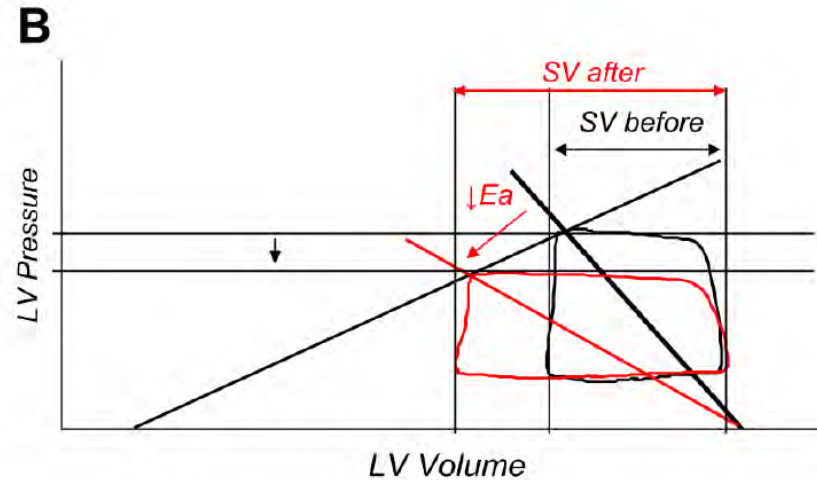
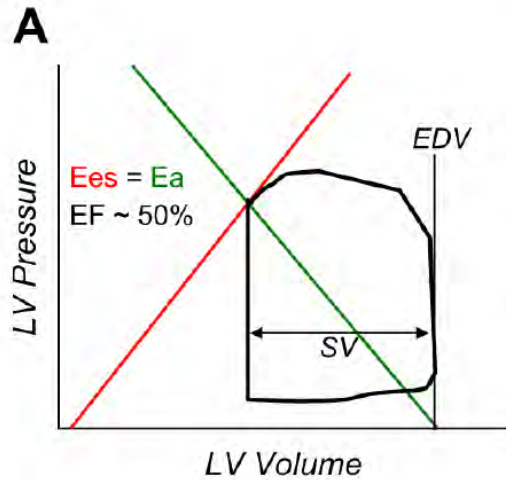


Hundley et al., JACC 2001

HFREF, RR 100/60 mmHg : give a lot vasodilatator: SNP 7 $\mu\text{g}/\text{kg}/\text{min}$



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radial artery
pressure

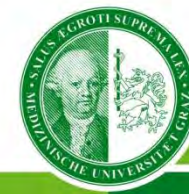
pulm. pressure

wedge pressure

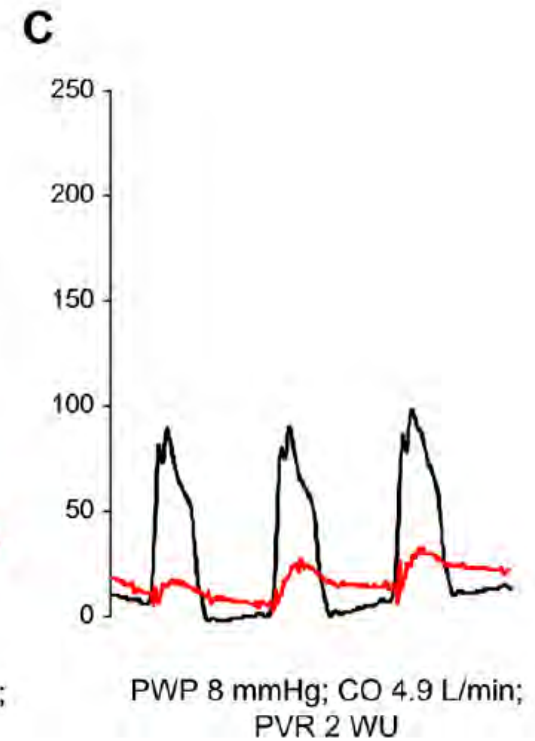
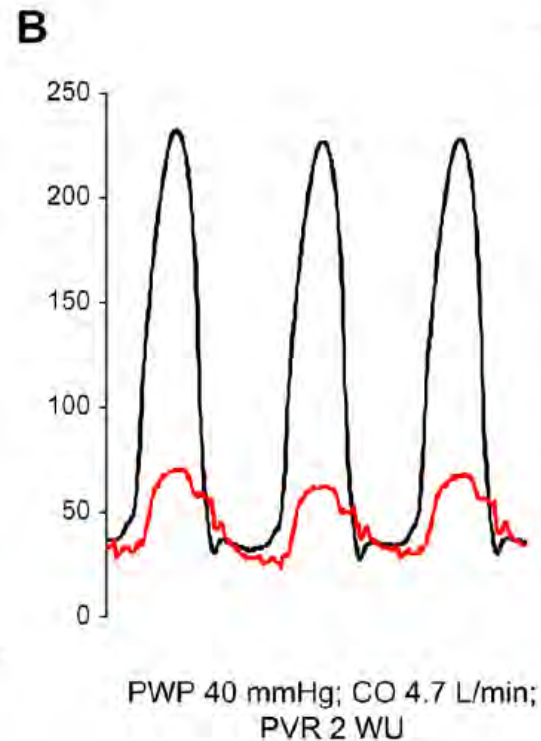
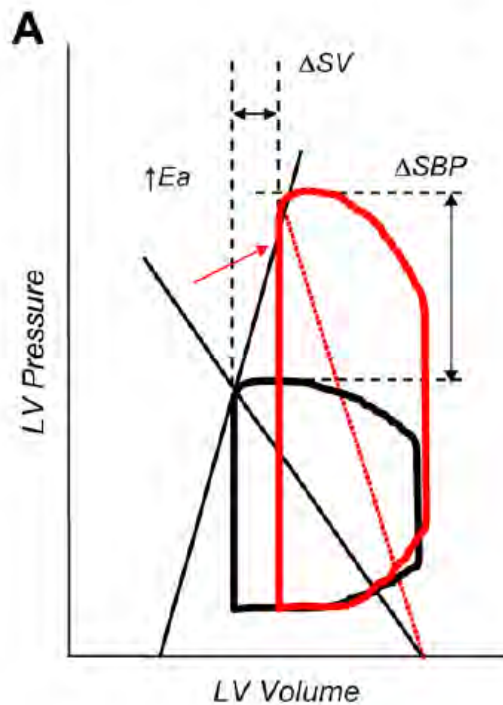
RA pressure

Borlaug et al., Heart Fail Clin 2009

HFPEF, RR 230/90 mmHg give a little vasodilator: SNP 2 $\mu\text{g}/\text{kg}/\text{min}$

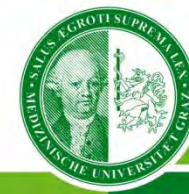


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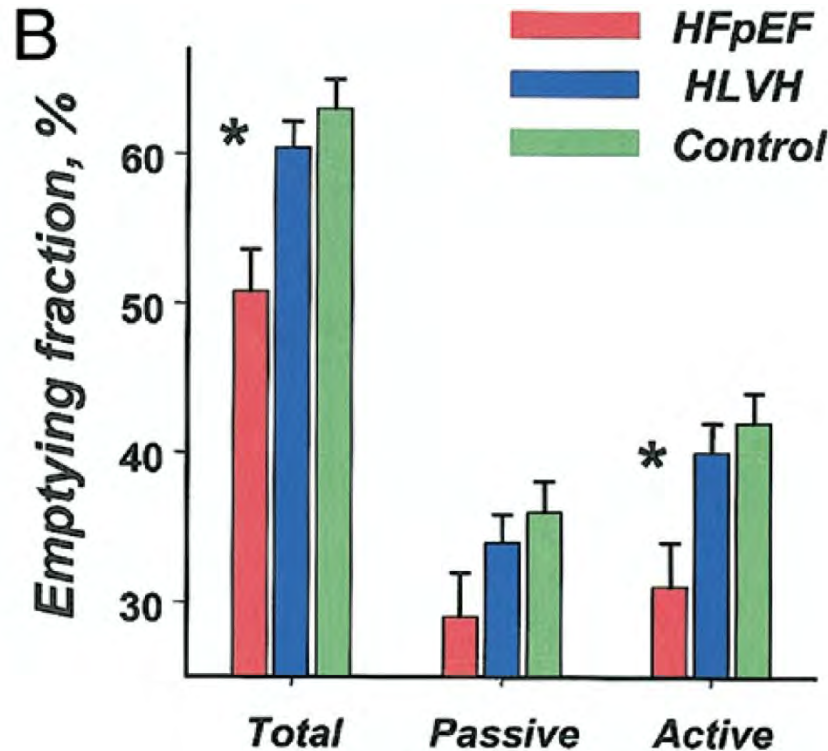


Borlaug et al., Heart Fail Clin 2009

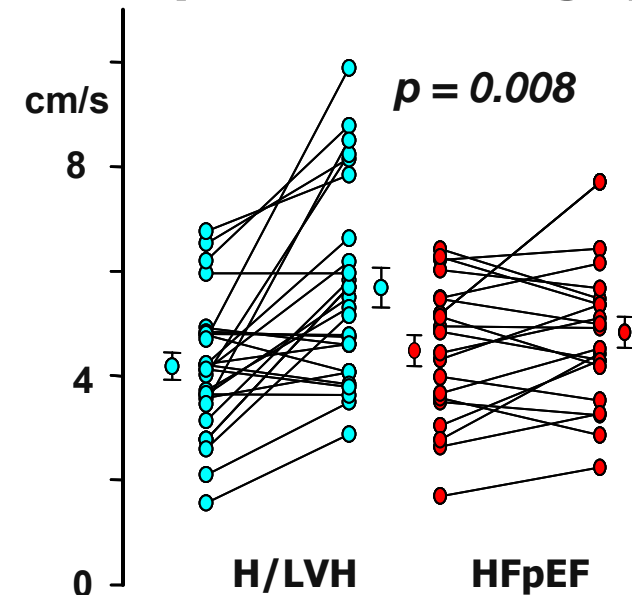
Atrial function: HFPEF



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Annular A' velocity response to handgrip



■ Reduced left atrial active emptying (LA EF) in HFpEF

■ Patients with HFpEF have decreased LA contractile reserve during stress

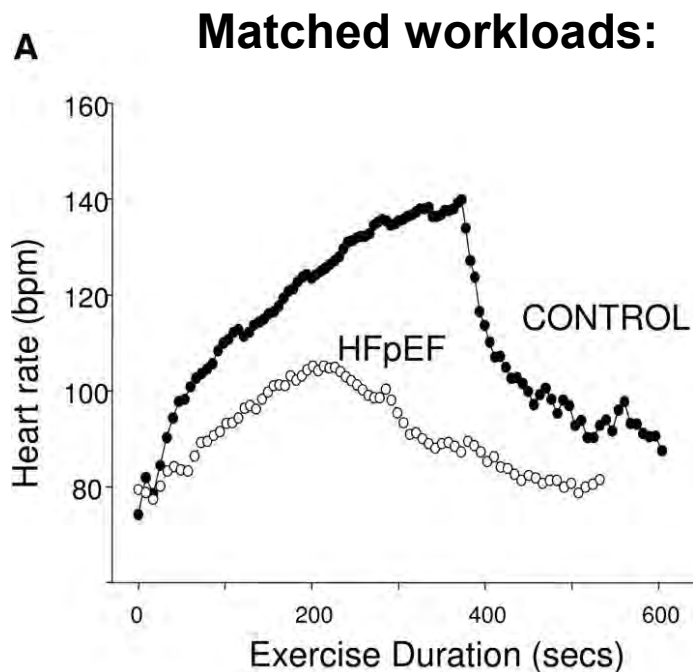
Melenovsky V, JACC 2007; 49: 198-207

Chronotropic incompetence



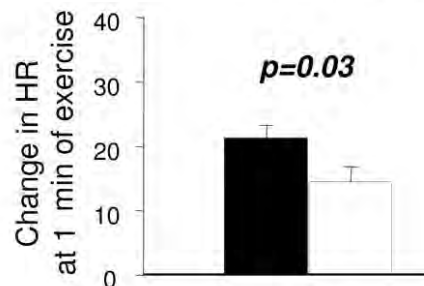
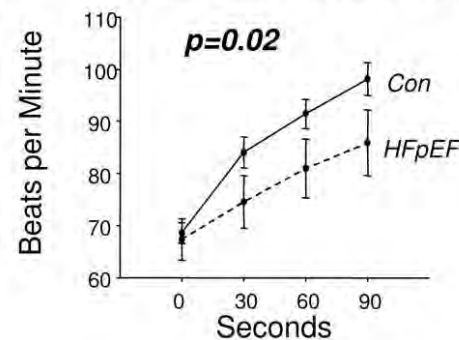
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HFpEF (n=17) and matched controls (n=19): maximal effort upright cycle ergometry & radionuclide-ventriculography

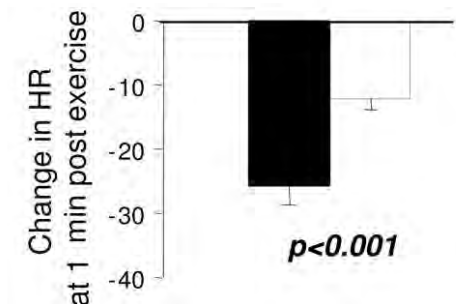
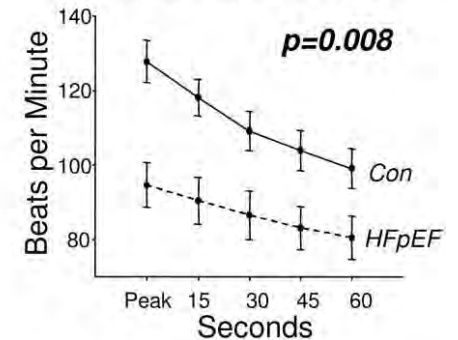


Reduced chronotropic, vasodilator, and cardiac output reserve during exercise

B Heart Rate Acceleration



Heart Rate Deceleration

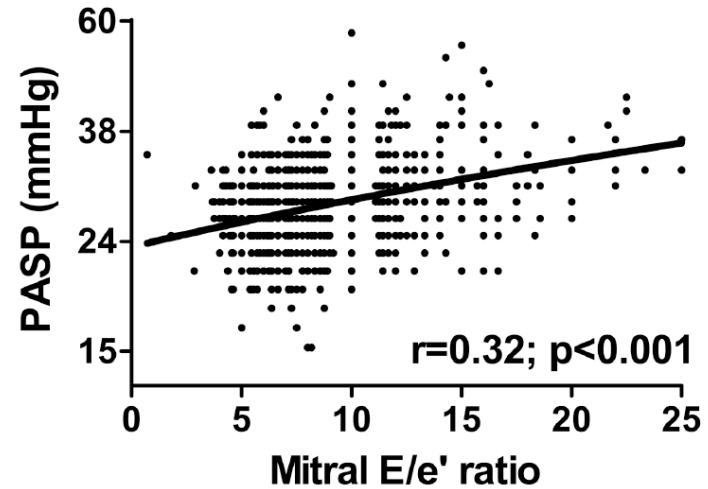
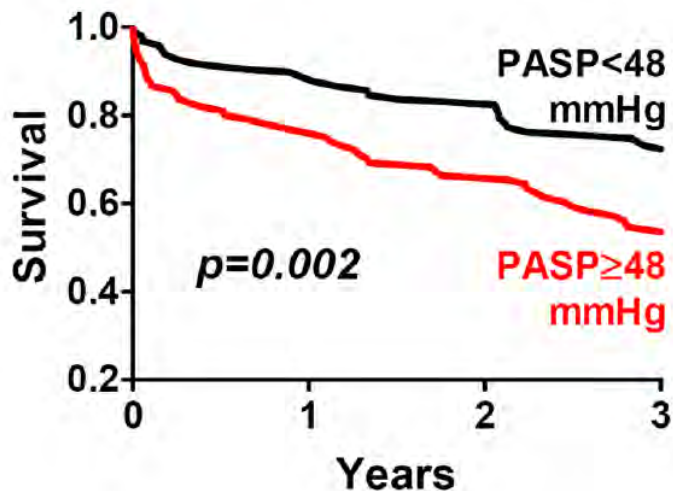
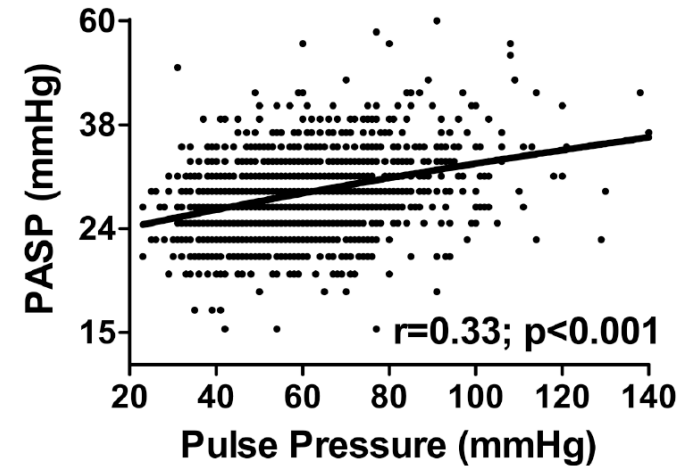
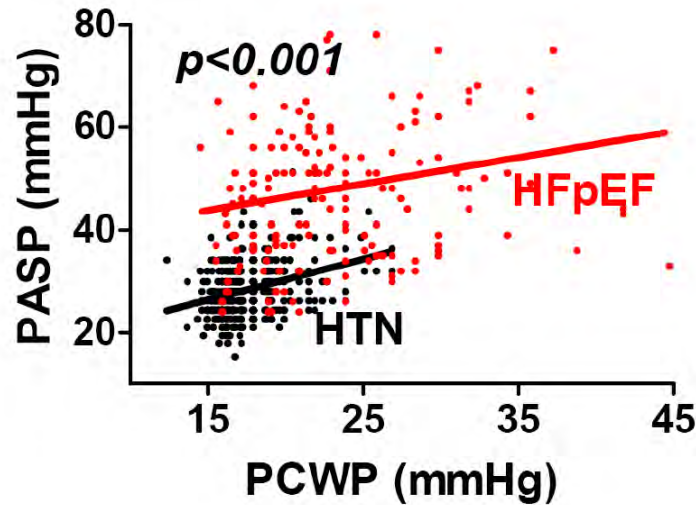


Borlaug et al., Circulation 2006; 114(20)

Pulmonary hypertension



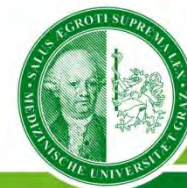
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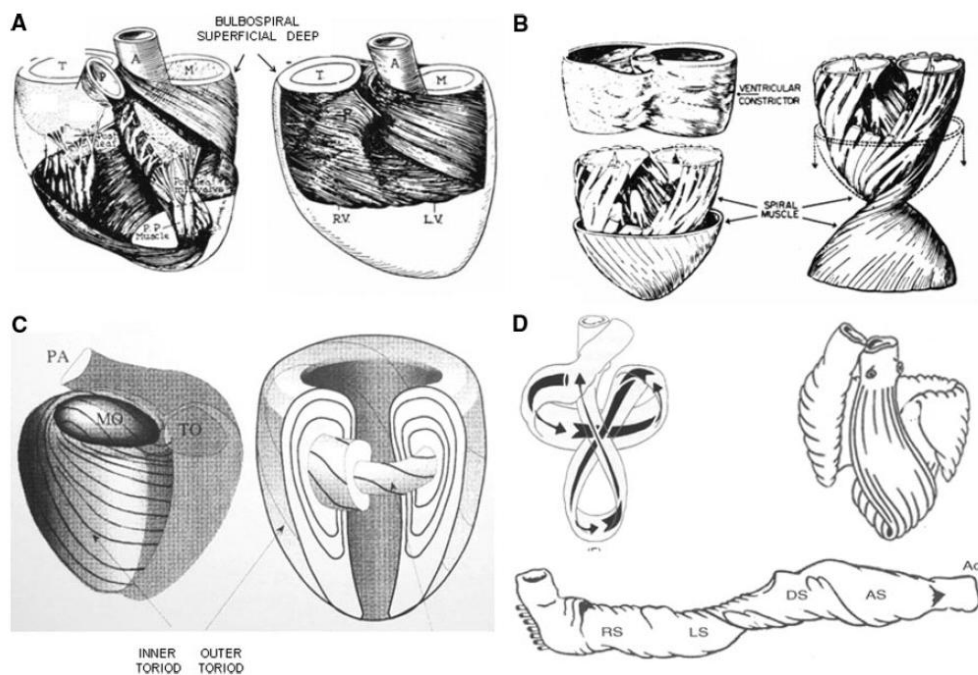
Lam et al., JACC 2009

Lam et al., Circ 2009

The contracts like a towel



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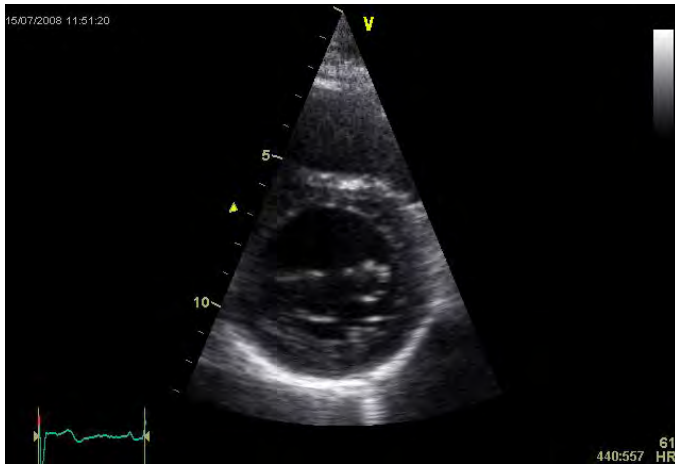
Buckberg, Circulation 2008

Rotation and twist

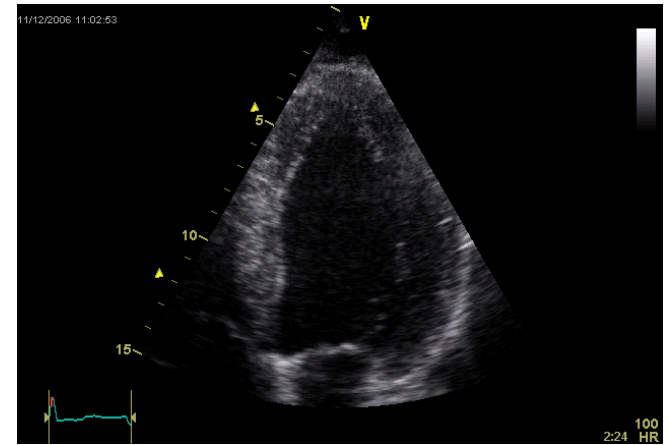


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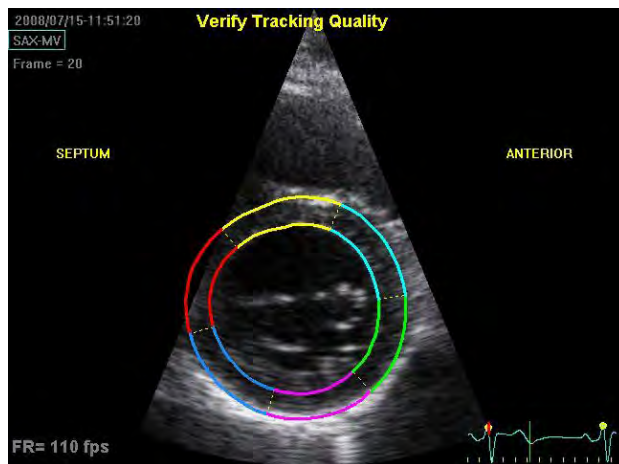
Control



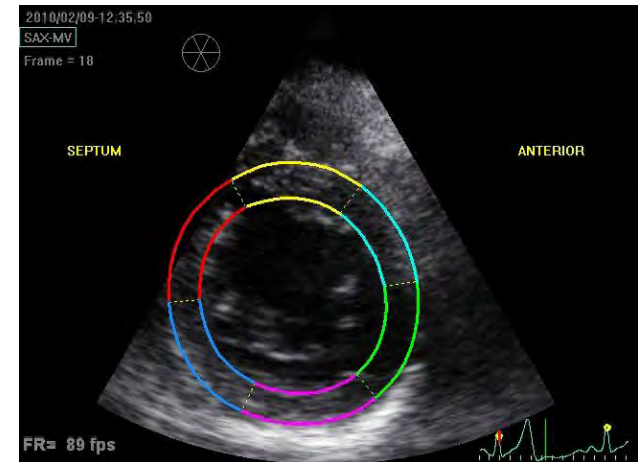
HFPEF



Control



HFPEF



Rotation is decreased in HFPEF

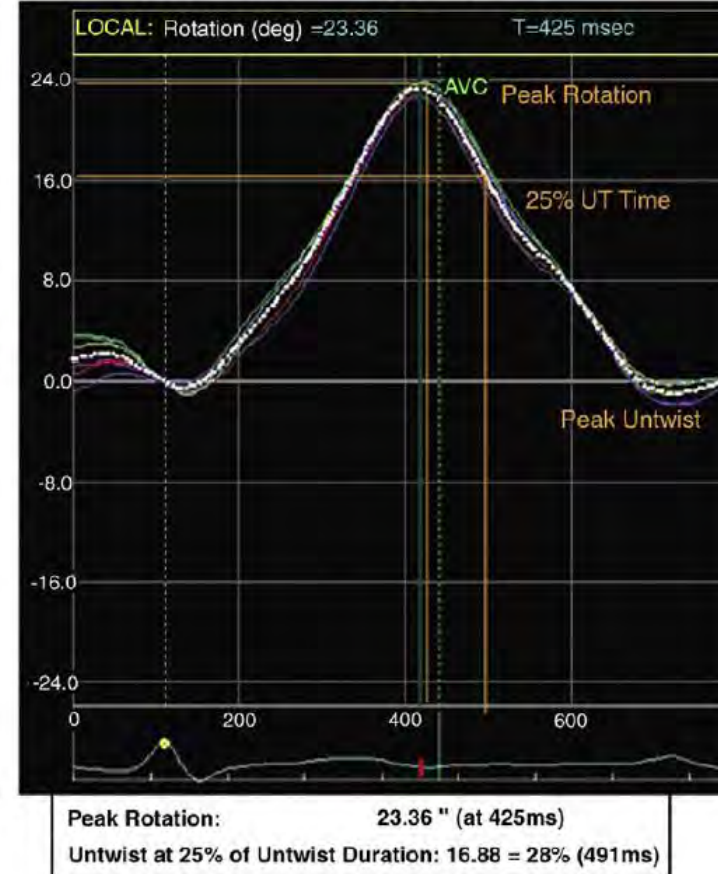


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Patient, ♂ 62 years

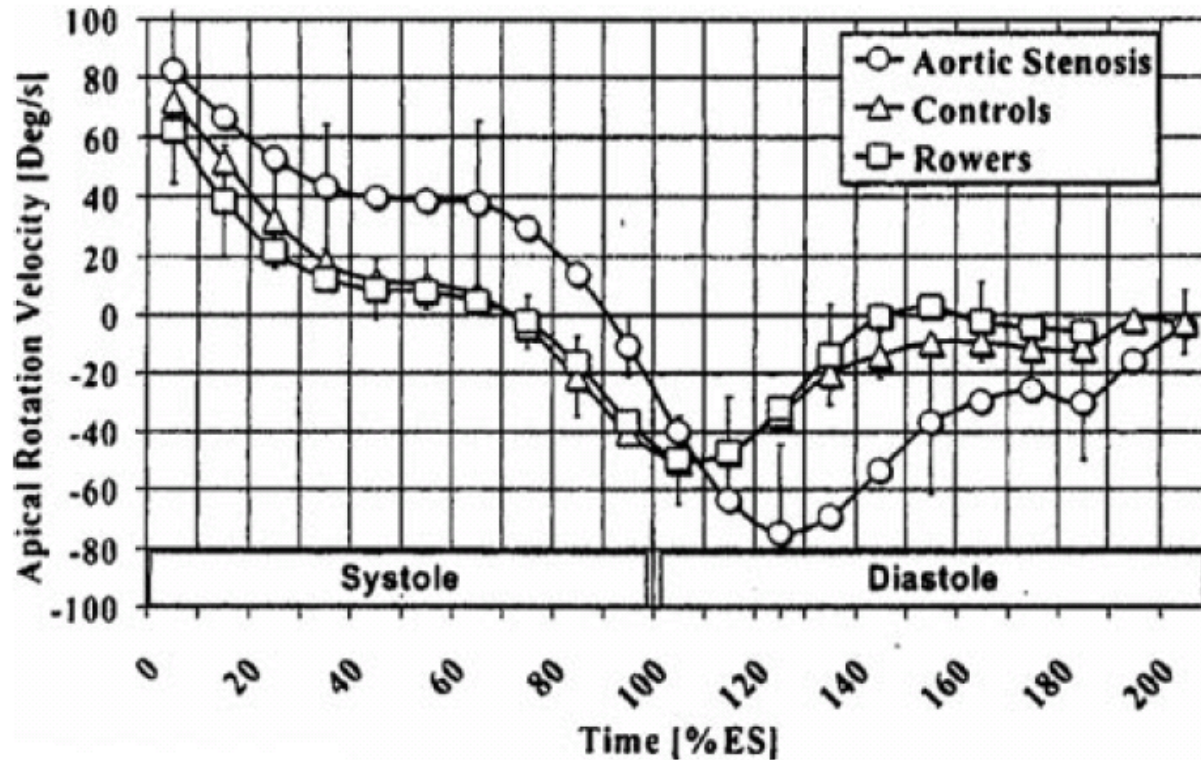


Control, ♀ 61 years



Tan et al., JACC 2009

Rotation in physiol. vs path. hypertrophy



Pts. with AST, all LV EF > 50%

LV biopsies during surgery

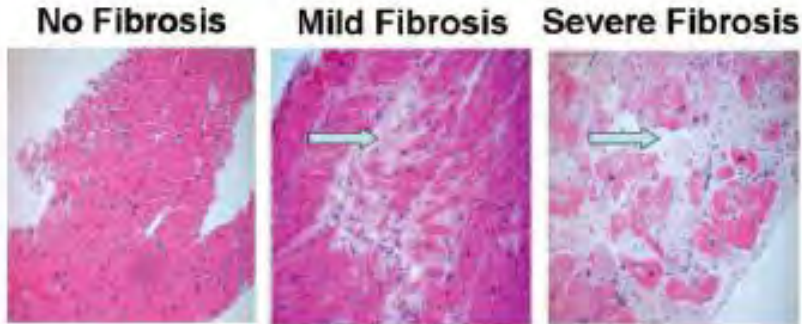
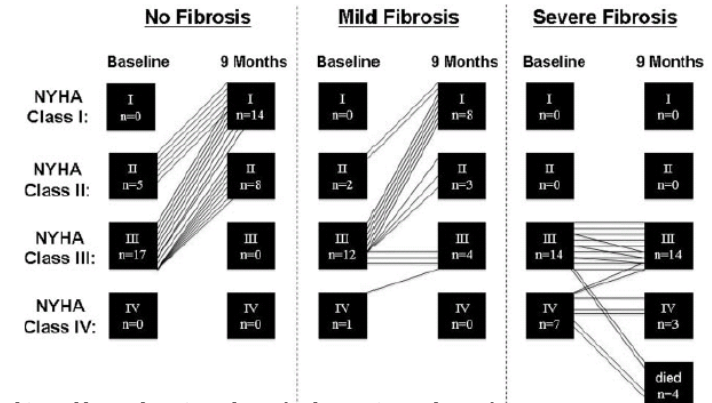
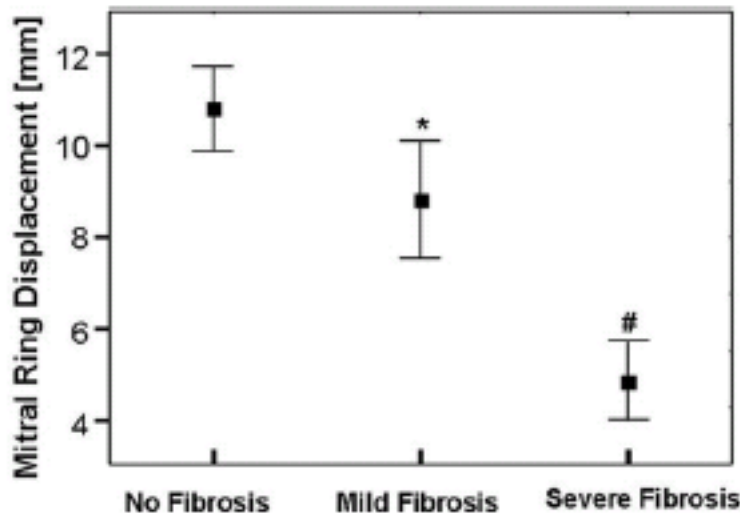


Table 2. Change in Radial and Longitudinal LV Function After AVR

	Baseline	10 Days	9 Months	P*	P†
No fibrosis					
Radial strain, %	31 (11)	44 (16)	55 (16)	0.001	<0.001
Radial strain rate, s ⁻¹	1.7 (0.4)	2.3 (0.6)	2.5 (0.5)	<0.001	<0.001
Longitudinal strain, %	-19 (5)	-19 (5)	-22 (5)	0.836	<0.001
Longitudinal strain rate, s ⁻¹	-1.2 (0.2)	-1.3 (0.4)	-1.5 (0.2)	0.142	0.008
Mild fibrosis					
Radial strain, %	29 (9)	41 (15)	40 (15)	0.004	0.003
Radial strain rate, s ⁻¹	1.7 (0.4)	2.3 (0.6)	2.3 (0.5)	0.004	0.006
Longitudinal strain, %	-15 (6)	-15 (4)	-18 (5)	0.852	0.021
Longitudinal strain rate, s ⁻¹	-0.9 (0.3)	-1.1 (0.3)	-1.3 (0.4)	0.157	0.009
Severe fibrosis					
Radial strain, %	26 (11)	31 (14)	34 (11)	0.492	0.021
Radial strain rate, s ⁻¹	1.6 (0.3)	1.6 (0.5)	1.7 (0.4)	0.843	0.245
Longitudinal strain, %	-10 (5)	-11 (6)	-14 (5)	0.853	0.079
Longitudinal strain rate, s ⁻¹	-0.6 (0.2)	-0.8 (0.3)	-0.8 (0.2)	0.044	0.040

Fibrosis = longitudinal function



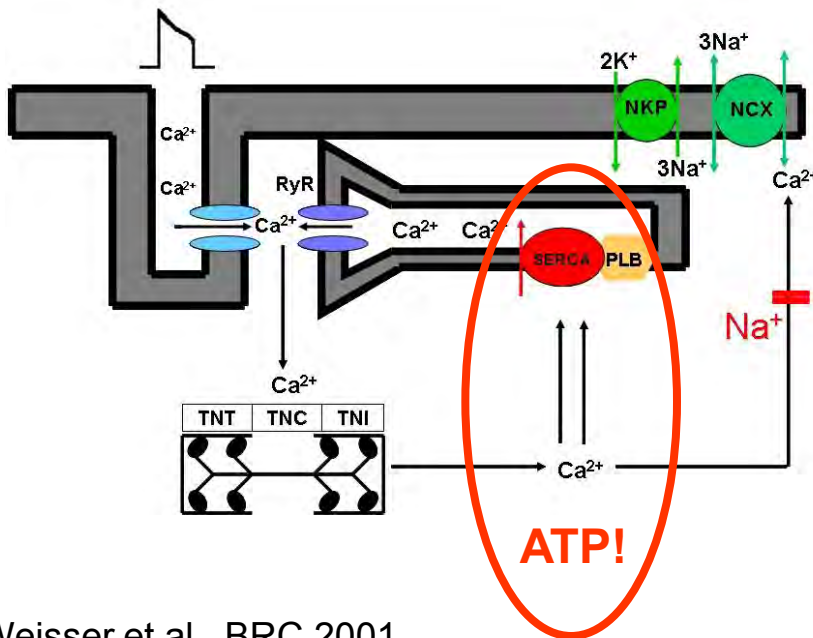
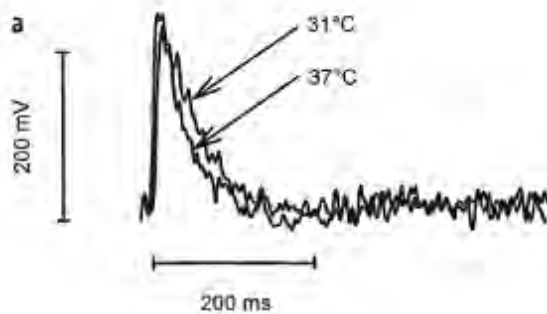
Longitudinal strain (shortening):
 - negatively correlated with fibrosis
 - predicts recovery after aortic valve replacement

Disturbed LV relaxation in HFPEF: energetics

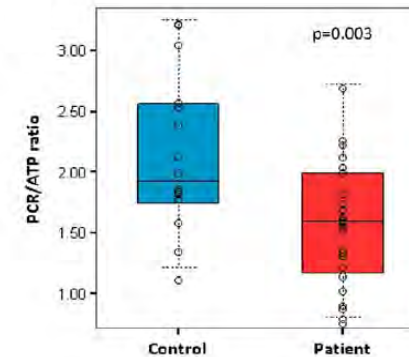


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calcium transients: unknown!



impaired myocardial energetics in DHF



Variable	Patients With HFpEF (n = 37)	Control Subjects (n = 20)	p Value
Exercise HR, beats/min	97 ± 14	114 ± 11	<0.001
Exercise SBP, mm Hg	204 ± 26	198 ± 27	0.45
Exercise DBP, mm Hg	95 ± 15	97 ± 7	0.56
Exercise MABP, mm Hg	132 ± 15	131 ± 9	0.85
Ejection fraction, %			
Rest	65 ± 9	64 ± 9	0.61
Exercise	66 ± 9	72 ± 8	0.05
Time to peak filling, RR			
Rest	0.18 ± 0.08	0.18 ± 0.09	0.84
Exercise	0.25 ± 0.09	0.16 ± 0.08	0.001
Δ nTTPF	+0.07 ± 0.11	-0.03 ± 0.12	<0.005

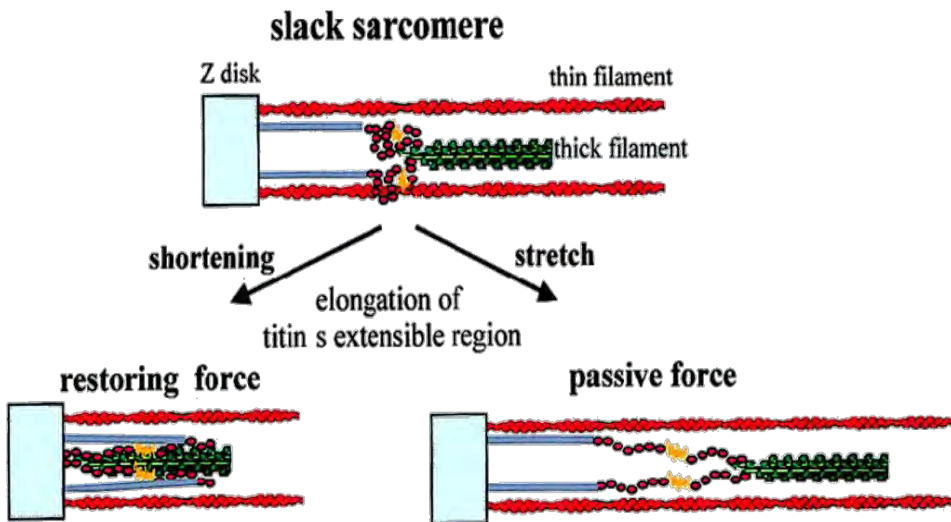
Weisser et al., BRC 2001
Pieske et al., JMCC 2002

Disturbed LV relaxation in HFPEF: myofilaments



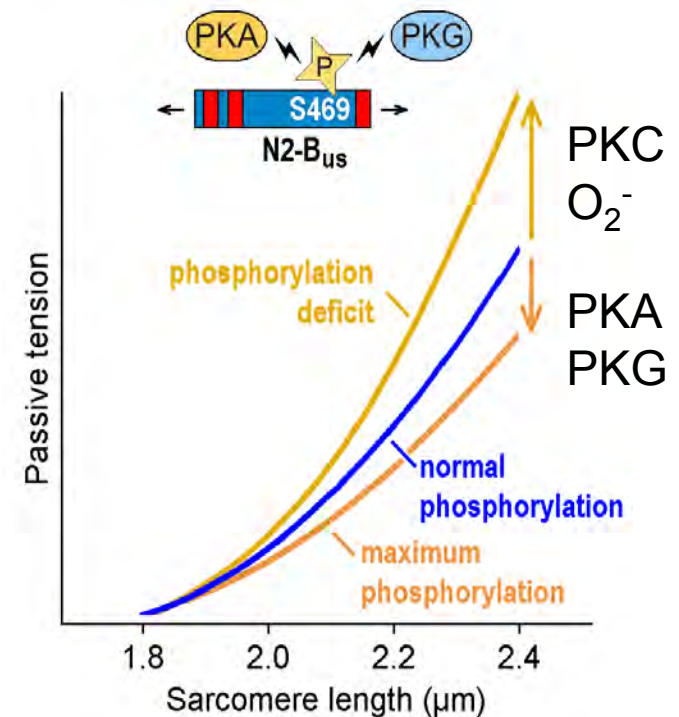
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The titin spring : restoring forces and stiffness



Bell et al., Circ Res 2000; 87:235-240

PKA or PKG mediated phosphorylation of N2B-unique sequence

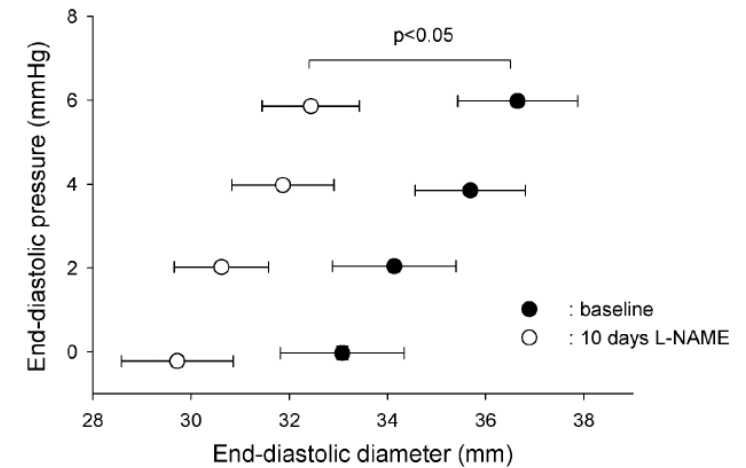
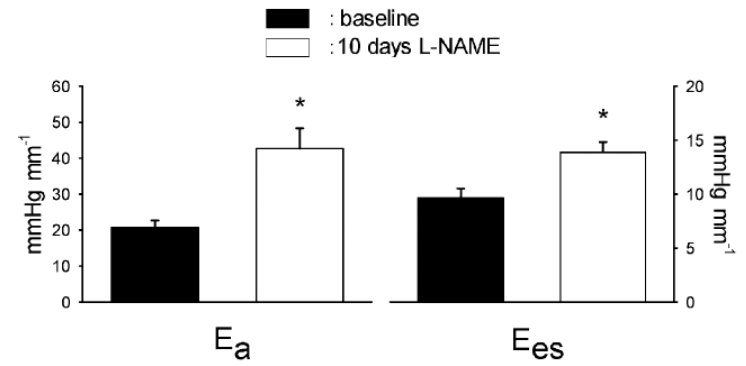
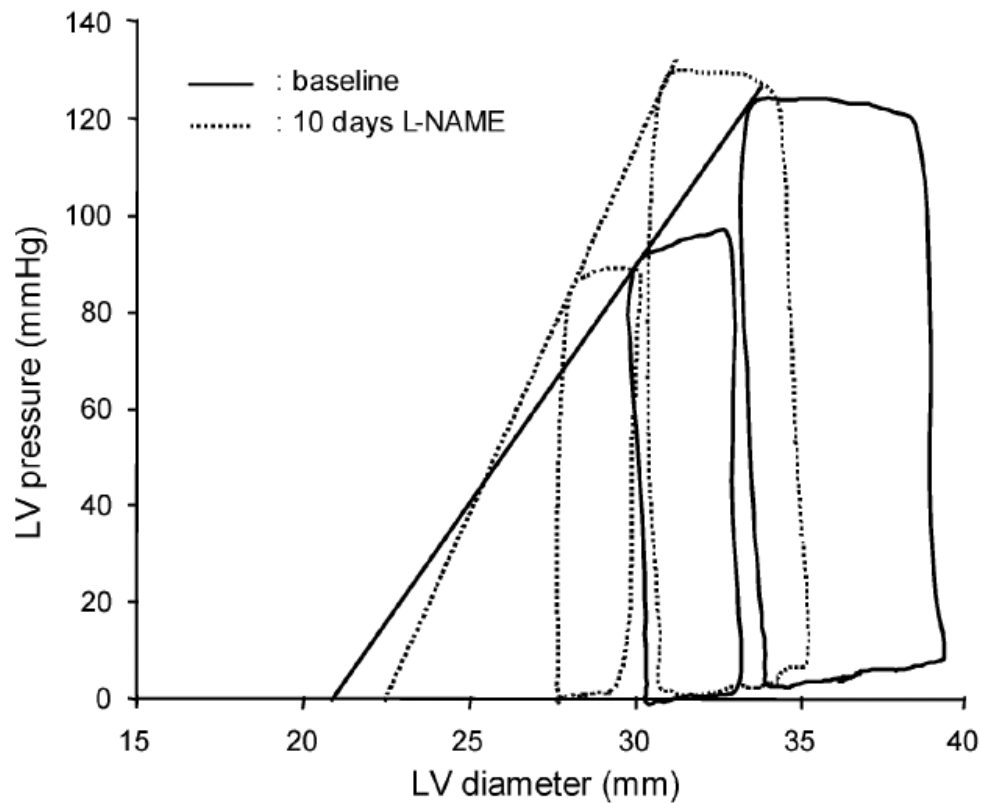


Hidalgo et al., Circ Res, 2009

10 days NOS inhibition in dogs mimicks a HFPEF phenotype



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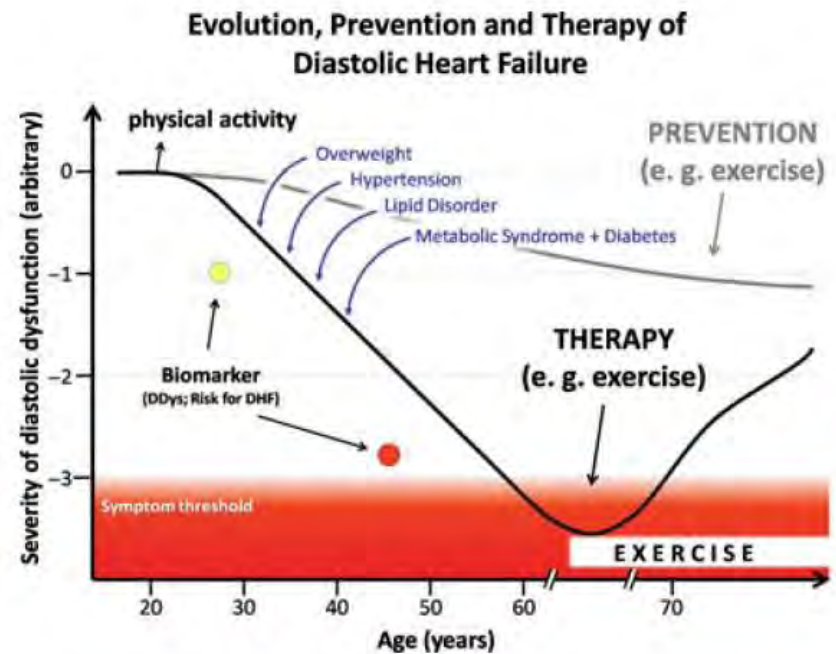
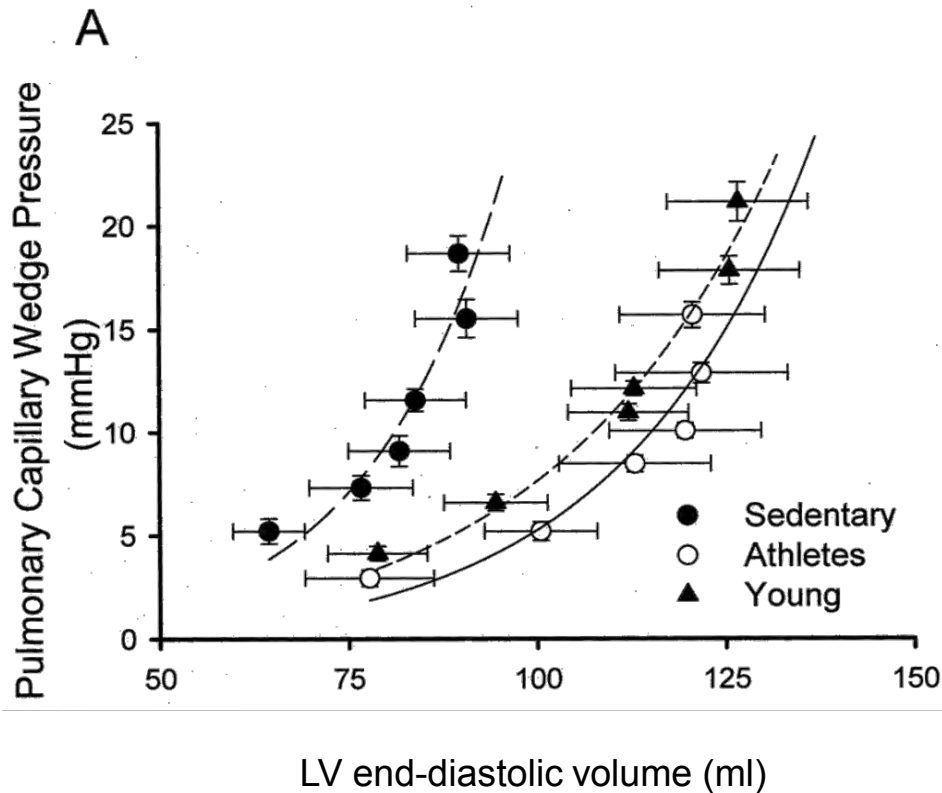


Post et al., J Physiol 2003

Exercise preserves your EDPVR!



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How to model HFPEF? „bedside-to-bench“



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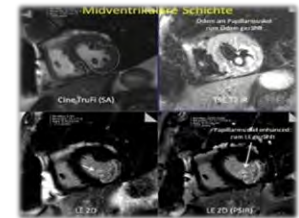
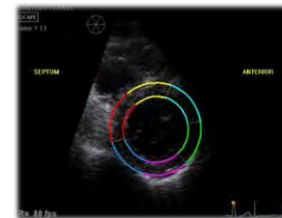
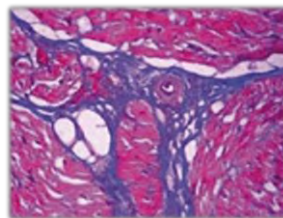
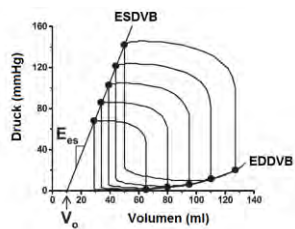
RF:

- art. HTN
- obesity
- HLP, diabetes
- sedentary lifestyle



RF:

- DOCA 100 mg/kg/90d
- McDonalds' diet:
 - high lipid/cholesterol
 - 4% salt/ 20% sugar



Take home message

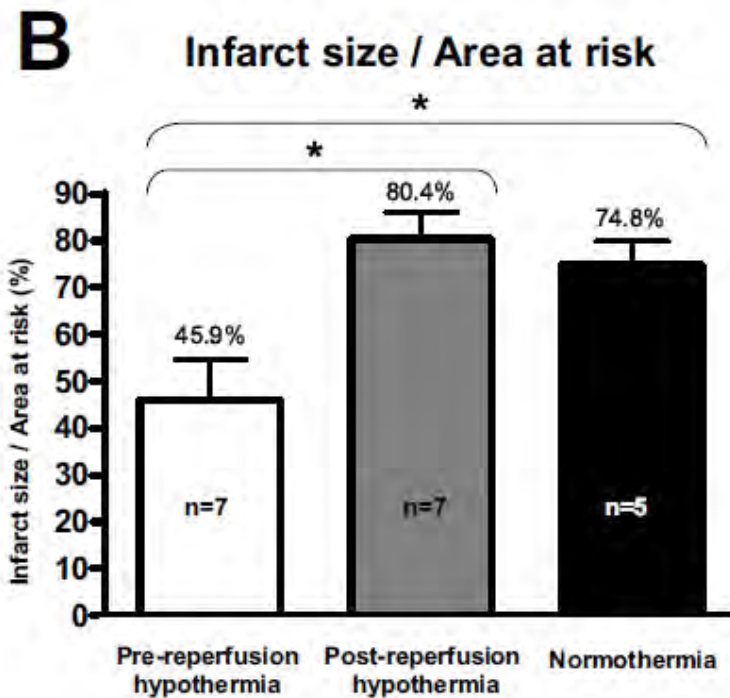
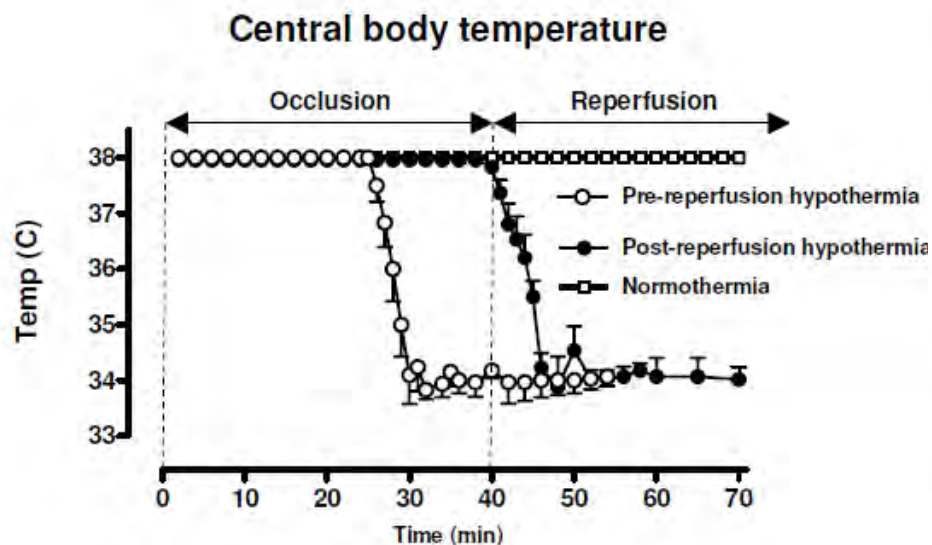
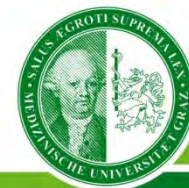


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HFPEF:

- evolves with accumulating risk factors
- small ventricles with thick walls
- slow relaxation, high end-diastolic pressures
- decreased rotation/suction, aggravated during exercise
- longitudinal LV function summarizes a complex 3-D phenotype
- systemic disease
- high Ea: very sensitive to blood pressure lowering drugs
- no uniform signal transduction
- no definite treatment
- no established experimental models

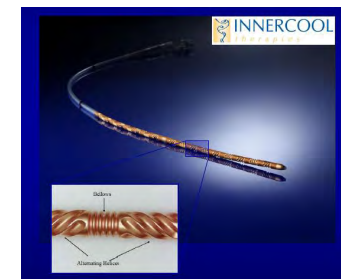
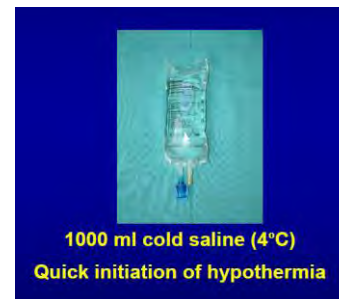
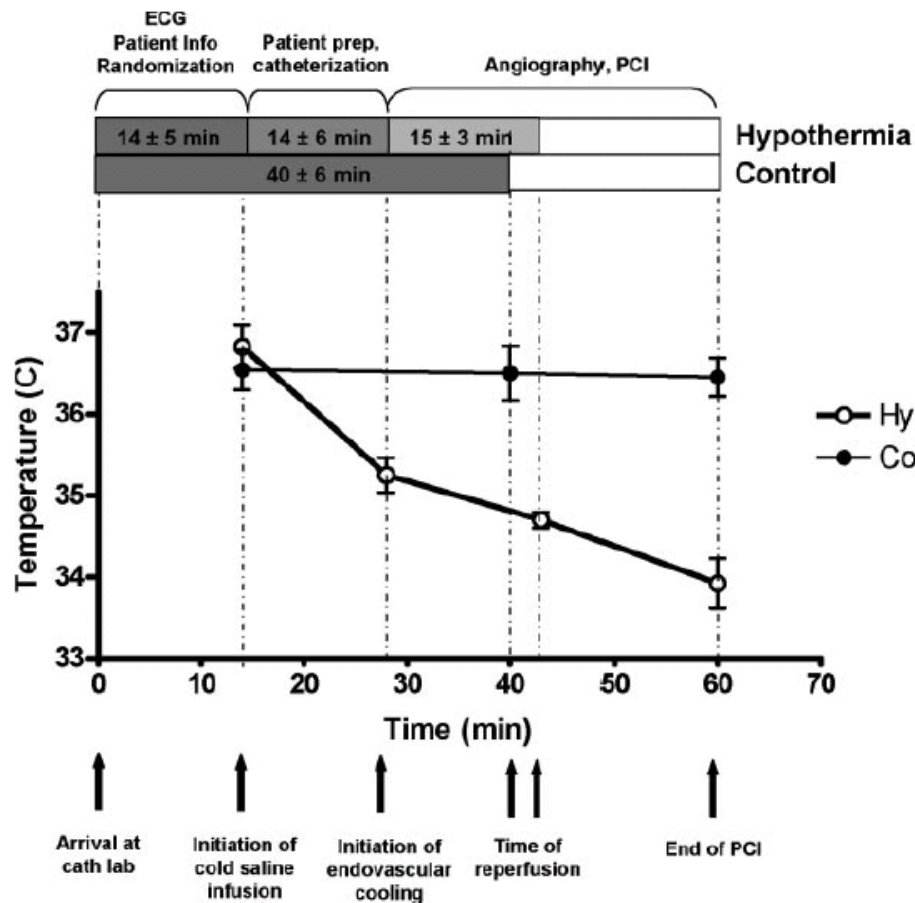
MH before reperfusion reduces infarct size



Rapid induction of MH in STEMI patients...



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Götberg, Circ CI 2010

...reduces infarct size



time to reperfusion

area-at-risk and infarct size (MRT)

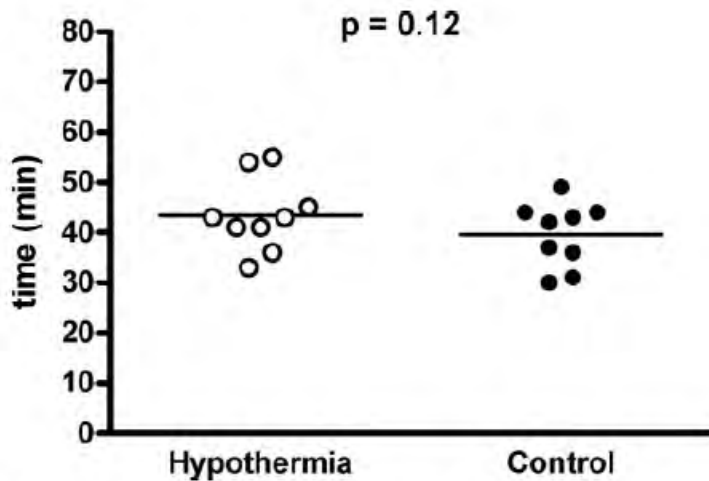
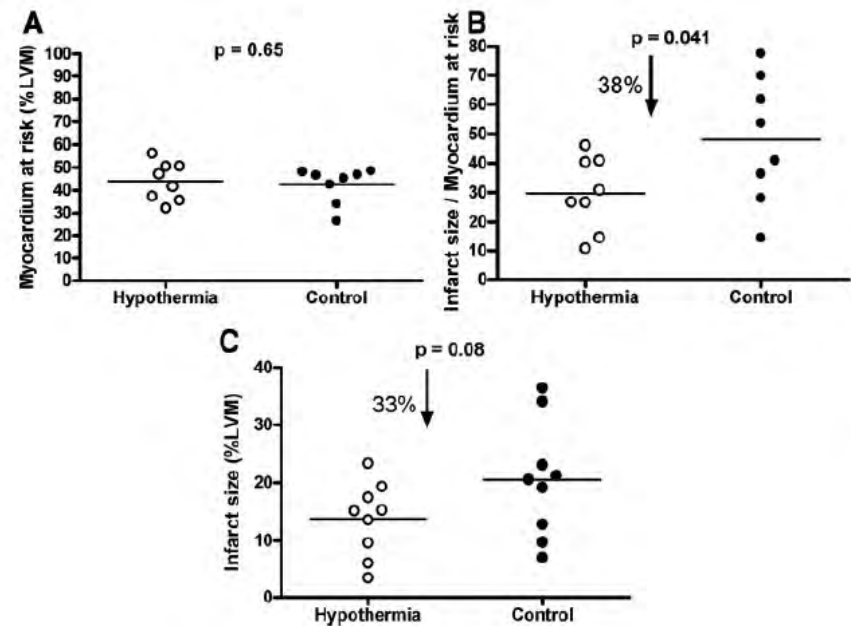


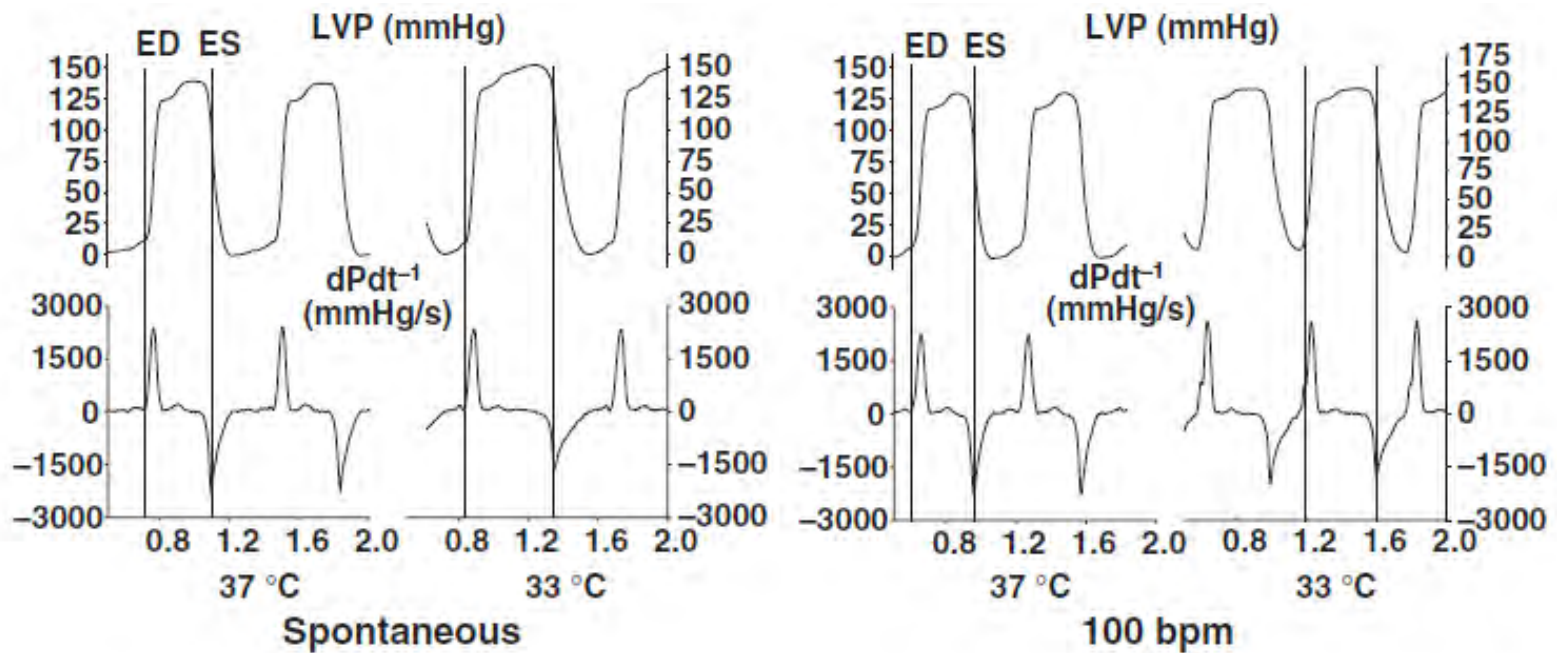
Figure 2. Time from arrival at the hospital until reperfusion (door-to-balloon time). There was no significant delay in reperfusion caused by hypothermia treatment.



MH in normal pigs



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Post et al., Acta Physiol 2010