Pathofysiologische aspecten van Heart Failure with preserved Ejection Fraction (HFpEF)

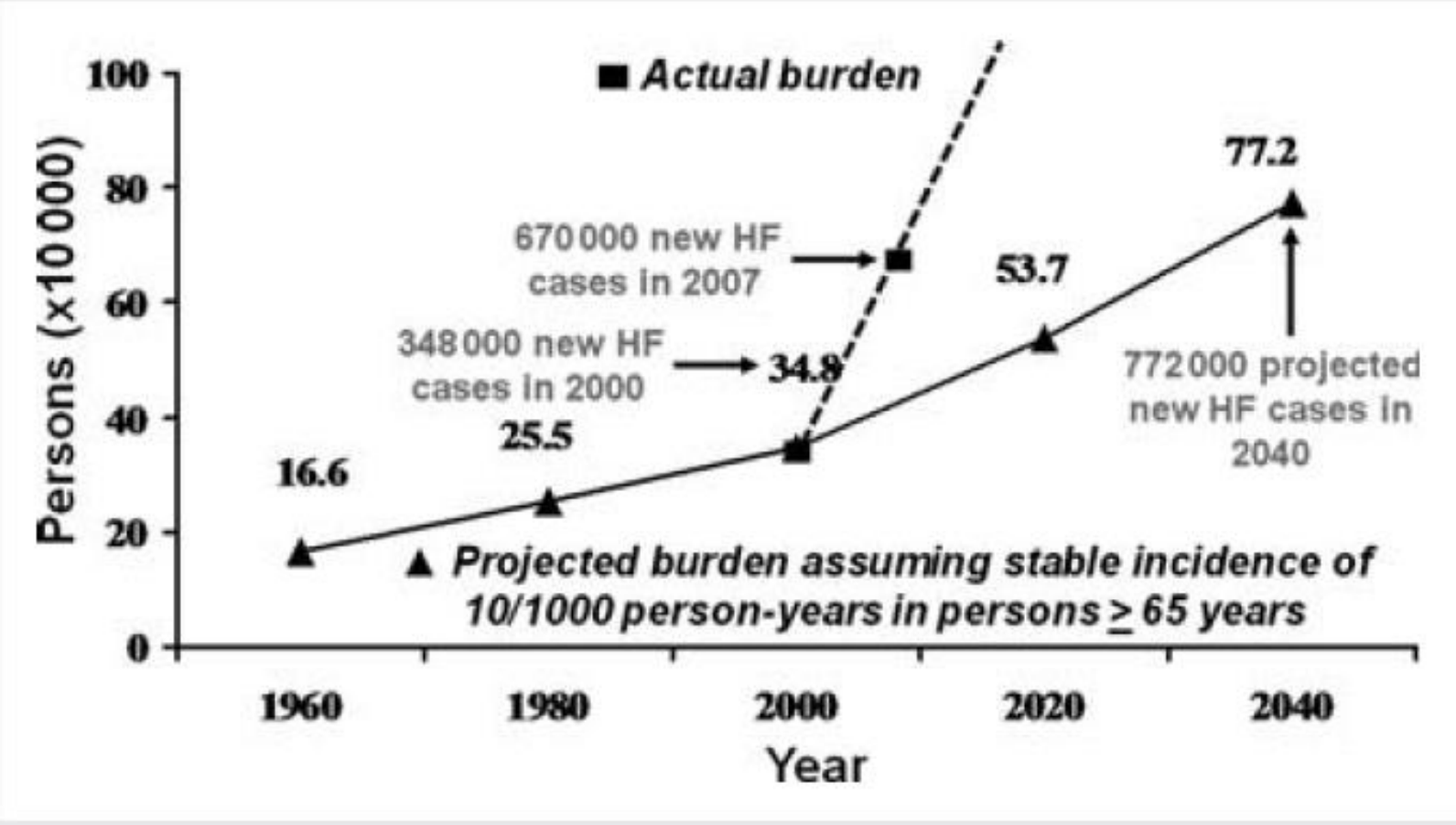
Nationale Hartfalen dag

26 september 2014

Loek van Heerebeek

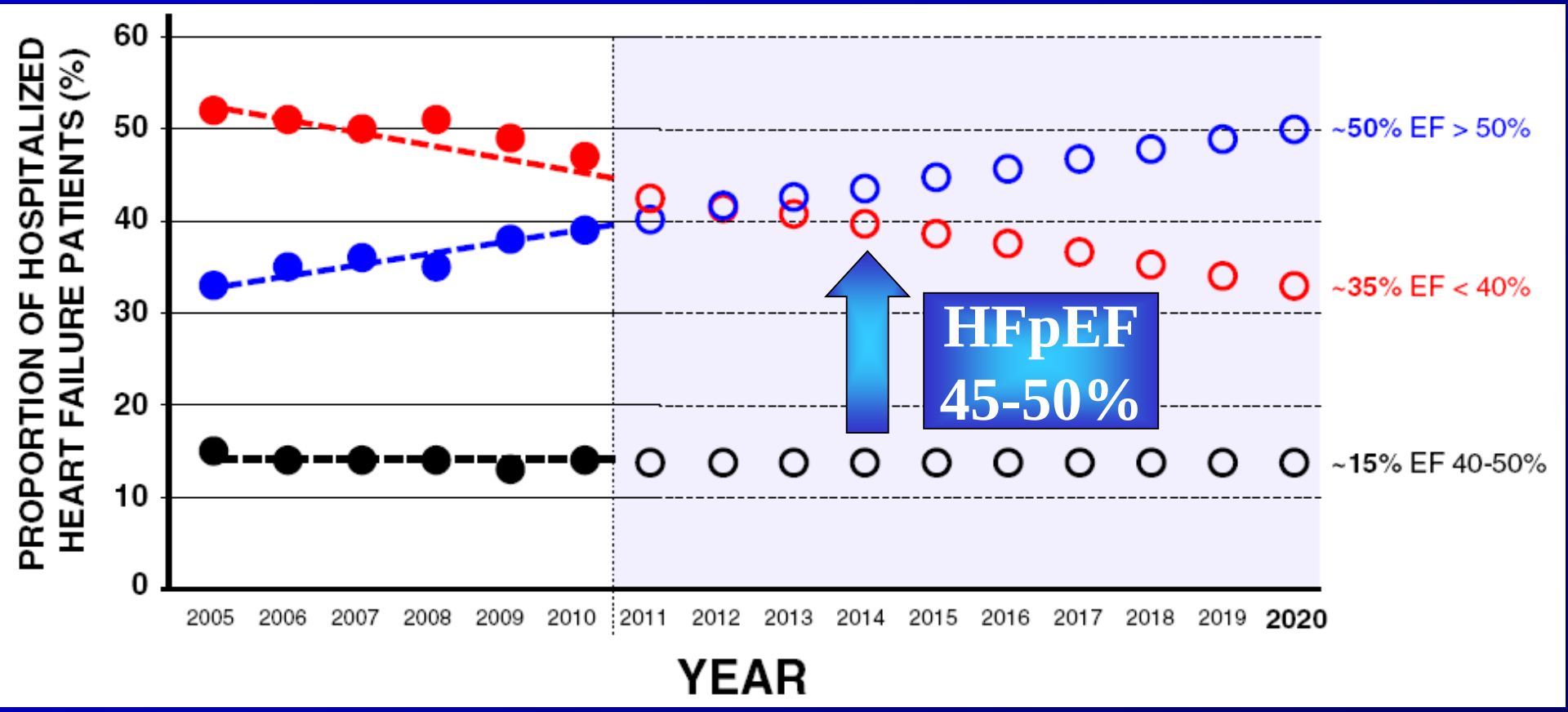
Epidemiology of heart failure (HF)

* HF affects 2% of western population
*USA: 6 million; Europe: 15 million; Asia: >35 million
*Most common cause of hospitalization in pts > 65 years



Lam CS et al. Eur J Heart Fail 2011;13:18

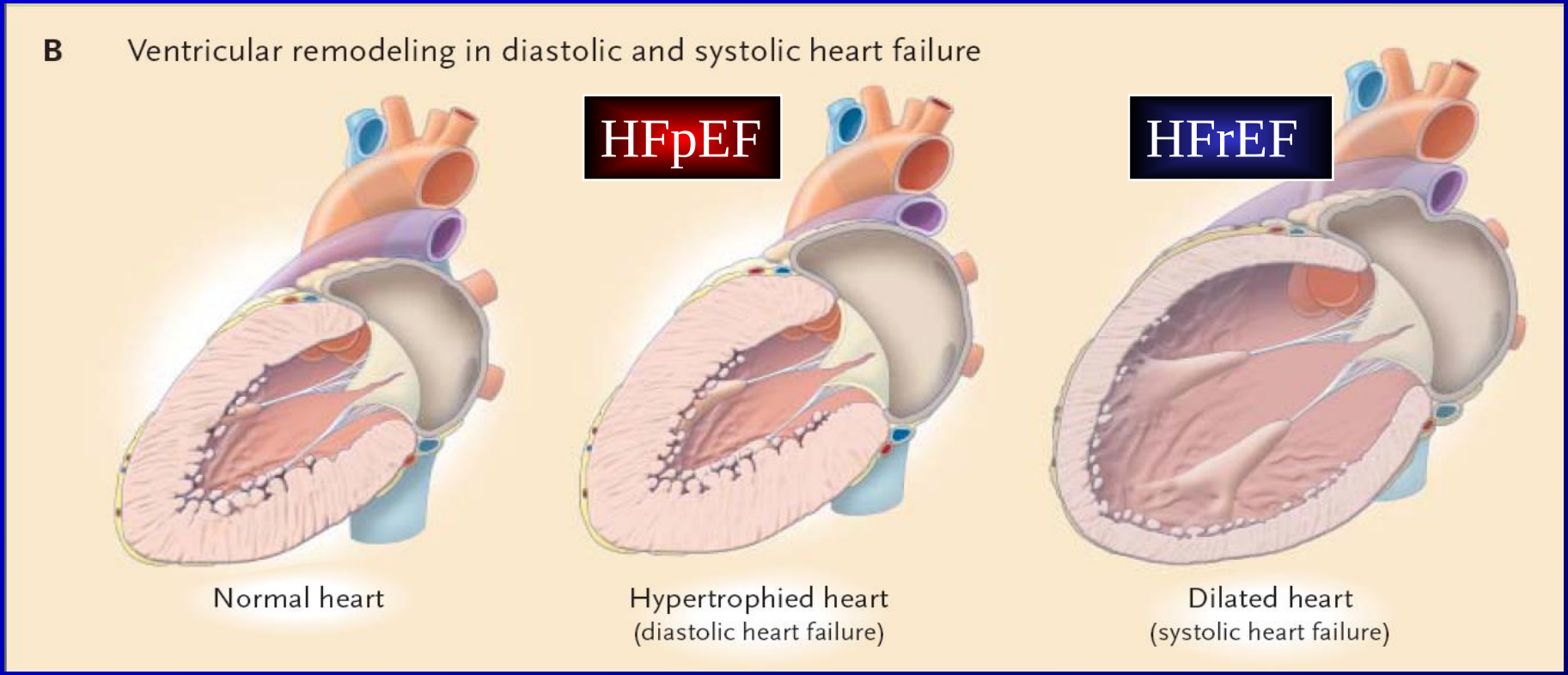
50% of patients with HF have HFpEF; still rising prevalence



110.000 pts admitted for HF in 275 US hospitals
Participating in Get With the Guidelines-HF registry (2005-2010)

Steinberg et al. Circulation 2012; Oktay Curr Heart Fail Rep 2013;10:401

HF with preserved EF (HFpEF;HFnEF;DHF) vs HF with reduced EF (HFrEF;SHF): distinct HF phenotypes



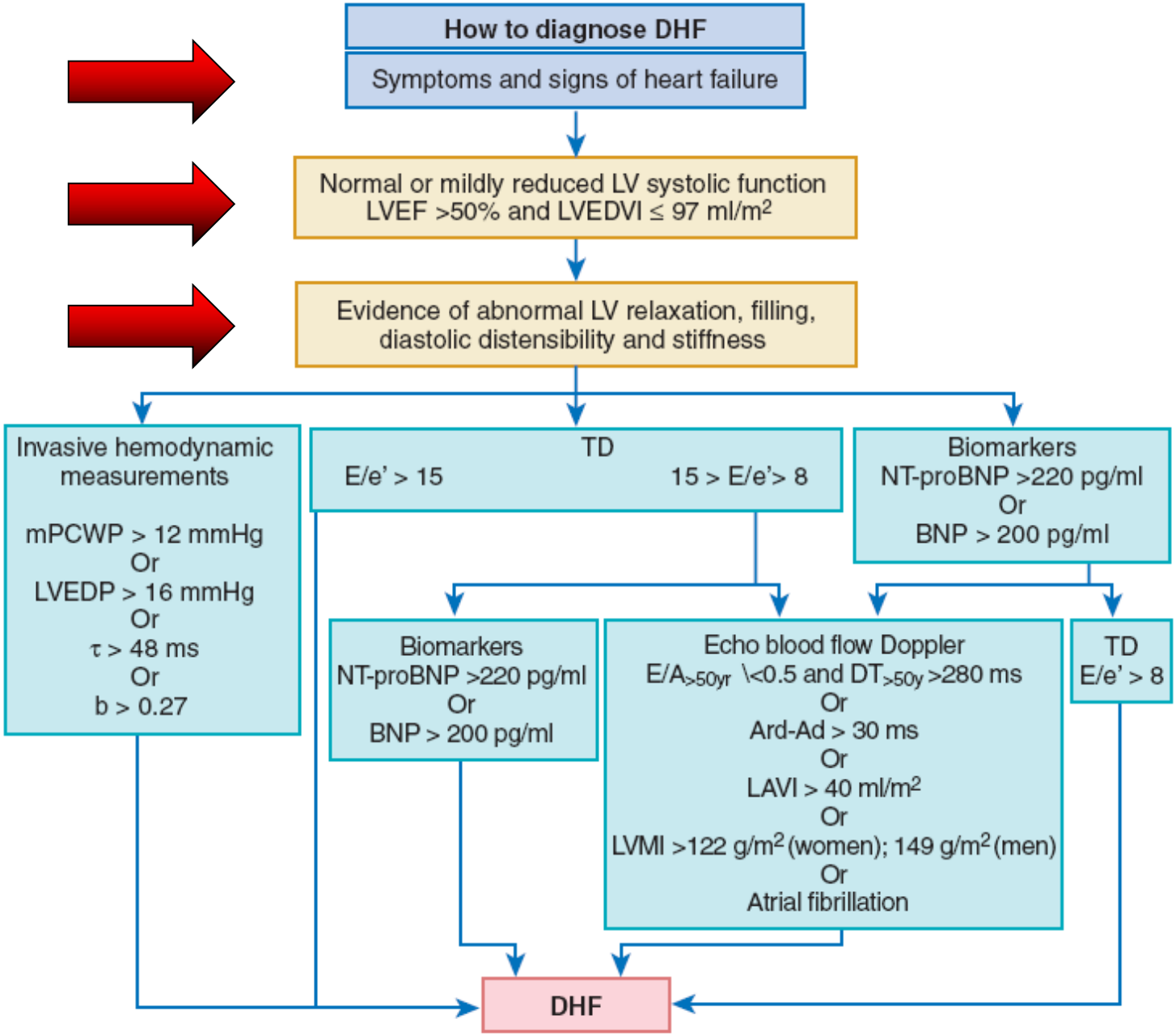
HFpEF:

* Preserved systolic LV function
* No LV dilatation
* Concentric LV remodeling/hypertrophy
* Diastolic LV dysfunction

HFrEF:

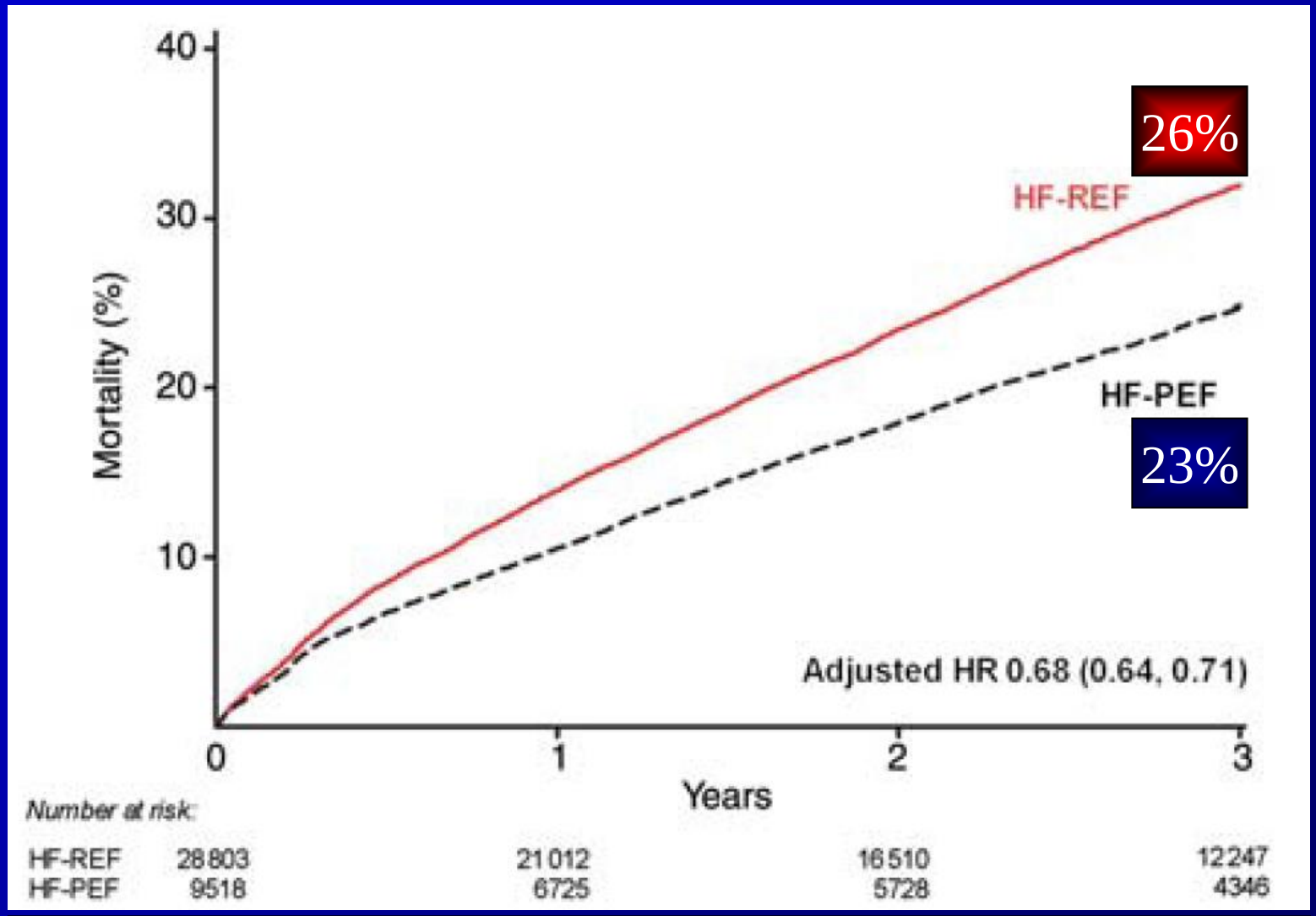
* Systolic LV dysfunction
* LV dilatation
* Eccentric LV remodeling
* Diastolic LV dysfunction

Jessup, NEJM 2003;348:2007



Modified from Paulus WJ et al. Eur Heart J 2007;28:2539

Mortality in HFpEF vs HFrEF



31 HF trials: HFpEF (n=10347) vs HFrEF (n=31625)

Eur Heart J 2012,33:1750;Oghlakian et al, Mayo Clin Proc 2011;86:531

Modern HF therapy improves mortality (in HFrEF)

ACE-I
Class IA

Betablockers
Class IA

MRAs
Class IA

Diuretics

Treatment of:
*Hypertension
*High HR
*Ischemia
*Comorbidities

HFpEF

ARBs
Class IA

HFpEF
Pathophysiology ??

ICD
Class IA (ischem)
Class IB (non-ischem)

Neutral RCTs in HFpEF

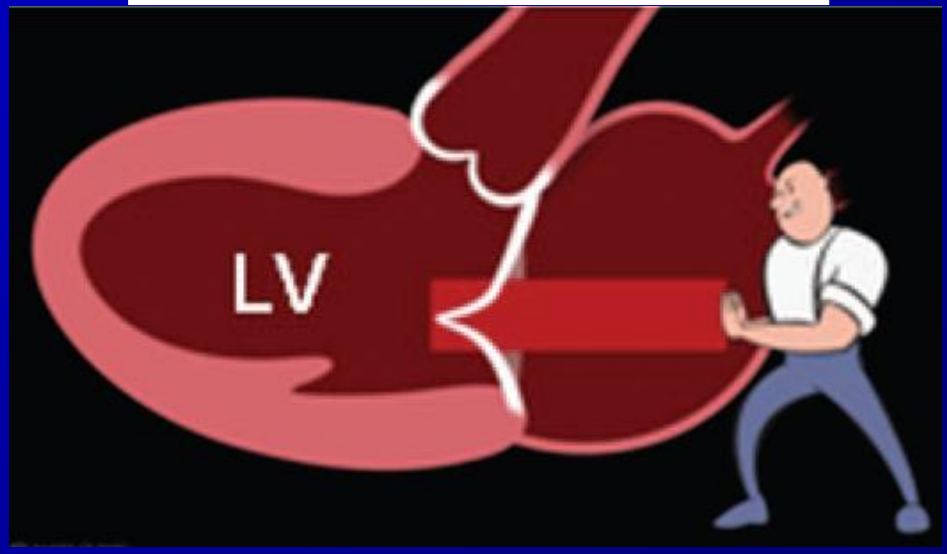
Trial	Sample size	Drug	Prim. Endpoint	Result
CHARM-preserved	3023	Candesartan	CV death, HF hospitalisation	Neutral
PEP-CHF	850	Perindopril	All cause mortality, HF hospitalisation	Neutral
SENIORS	752	Nebivolol	All cause mortality, CV hospitalisation	Neutral
DIG-PEF	988	Digoxin	HF mortality, HF hospitalisation	Neutral
I-PRESERVE	4133	Irbesartan	All cause mortality, CV hospitalisation	Neutral
ALDO-DHF	422	Spironolactone	Peak VO2, diastolic function	Neutral
TOPCAT	3445	Spironolactone	CV death, HF Hosp, cardiac arrest	Neutral
RELAX	216	Sildenafil	Peak VO2	Neutral

Diastolic LV (dys)function

Normal

*Normal LV relaxation
*Rapid fall in LV diastolic pressure
*Negative LV-LA pressure gradient
*Early diastolic "Suction"
*Normal LV compliance
*Diastolic filling at low pressures
Exercise: adequate diastolic reserve
Maintenance of low filling pressures

Diastolic dysfunction



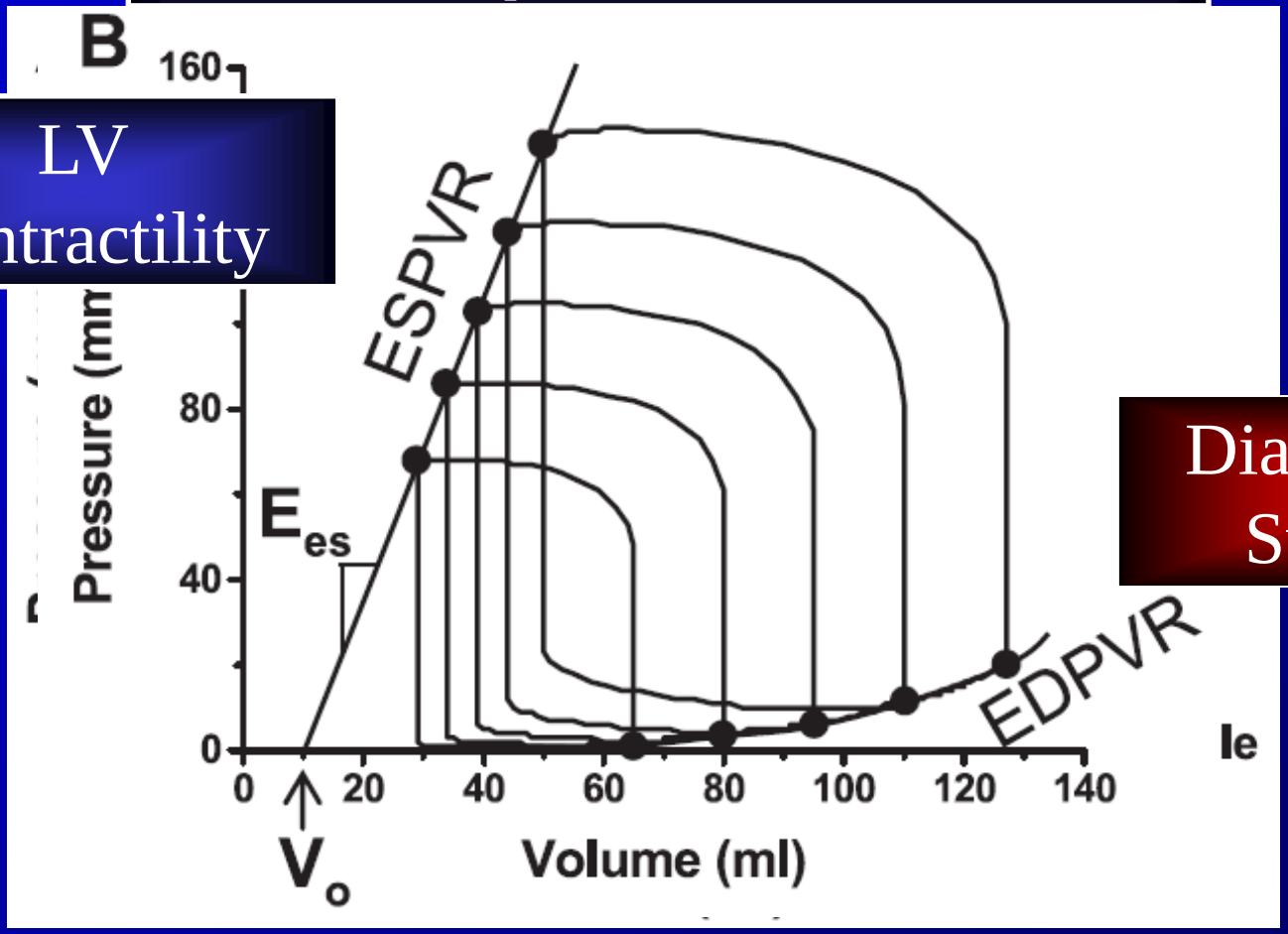
* Slow/incomplete LV relaxation
* Reduced early diastolic "suction"
*↓ LV compliance
* ↑diastolic LV filling pressures
* ↑ LA pressure; LA dilatation
* Exercise: Excessive rise in LV
Diastolic filling pressures

Oh et al. Circulation Cardiovasc Img 2011;4:444

Invasive measurement of diastology: still the gold standard

Conductance catheter: simultaneous measurement of LV pressure and volume

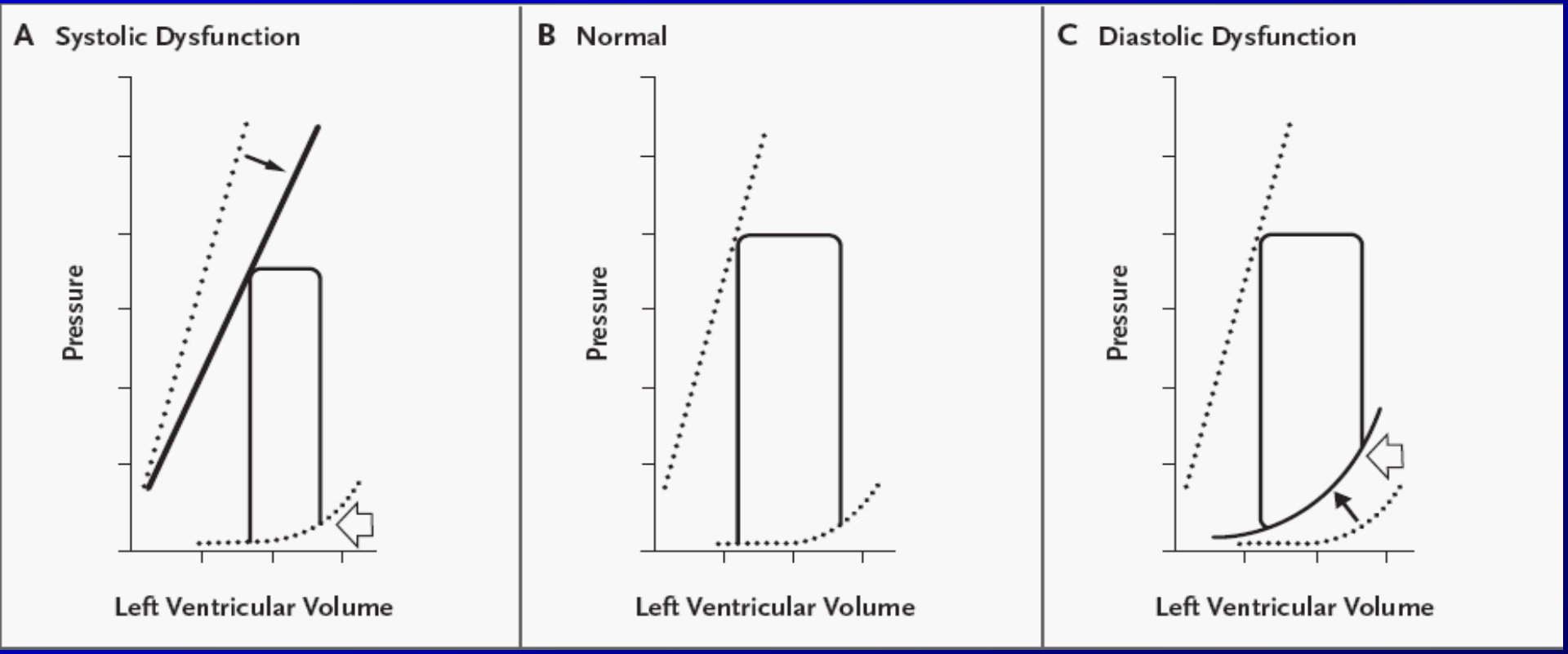
LV Contractility



Diastolic LV Stiffness

Burkhoff D et al; Am J Physiol Heart Circ Physiol 2005;289:H501

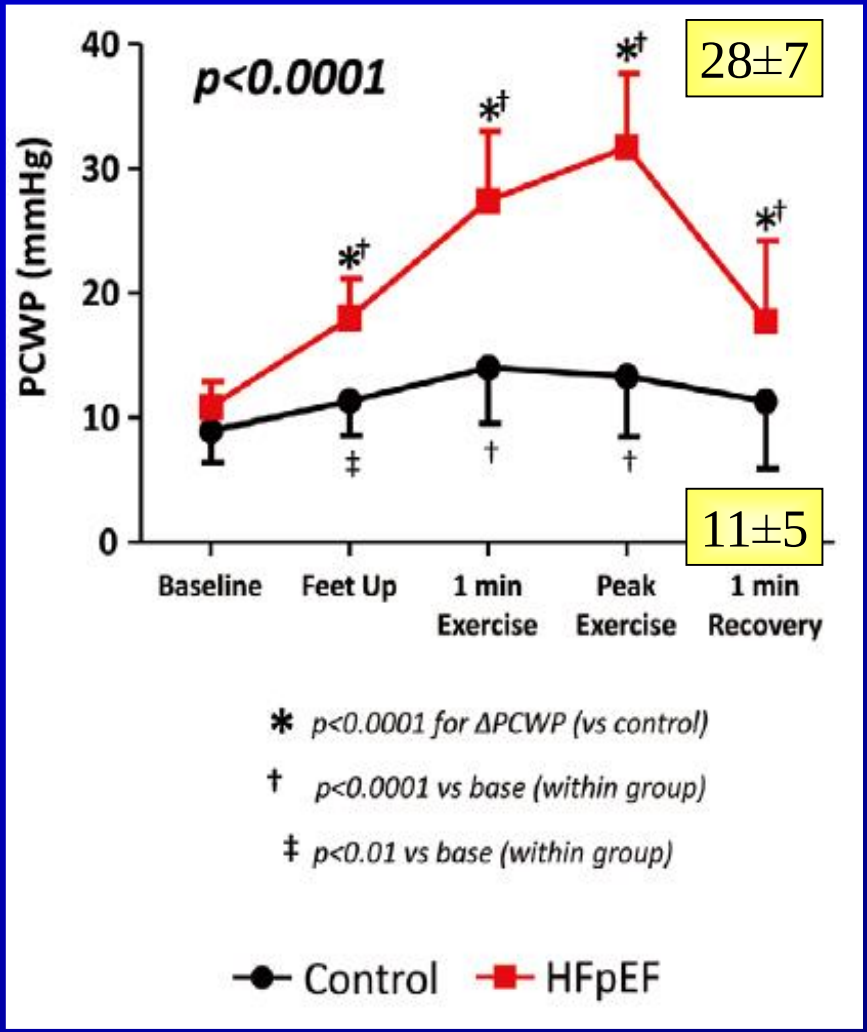
HFpEF: ↑ LV diastolic stiffness

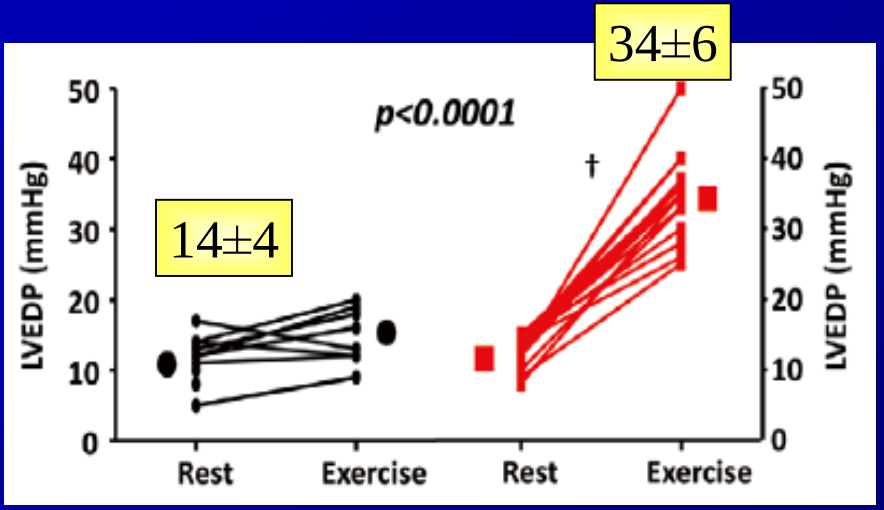


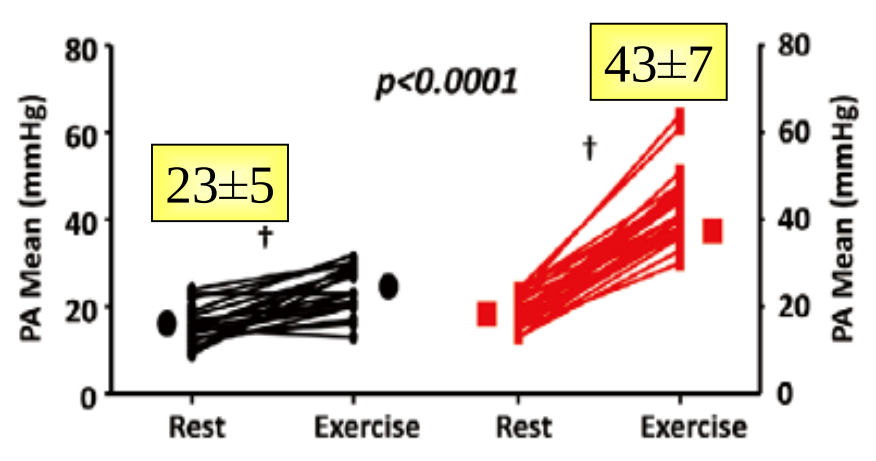
HFrEF: right and downward shift of ESPVR
→ Systolic LV dysfx

HFpEF: left and upward shift of EDPVR
→ ↑ Diastolic LV filling press.

HFpEF: ↑ PCWP/LVEDP and PAP with exercise







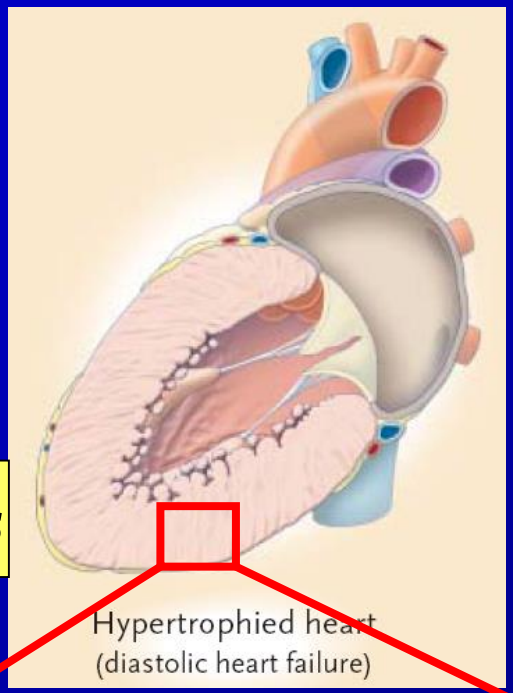
Borlaug BA, Circ J 2014;78:20

Determinants of LV and myocardial stiffness

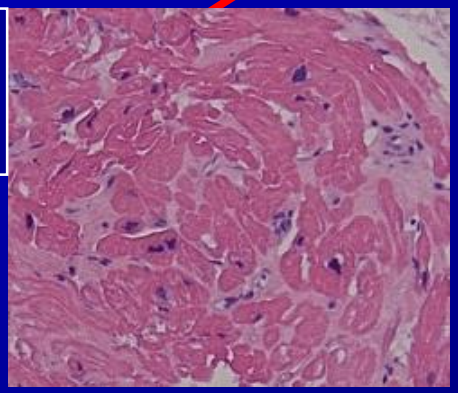
LV chamber stiffness

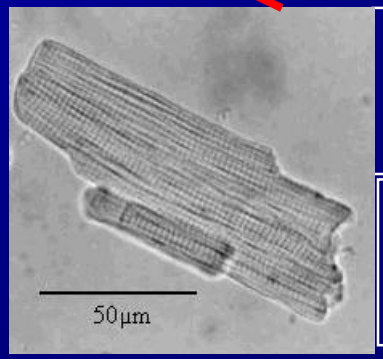
*Myocardial stiffness
*LV geometry
*LV volumes
*RV/LV interdependence
*Pericardial restraint

Myocardial stiffness



ECM





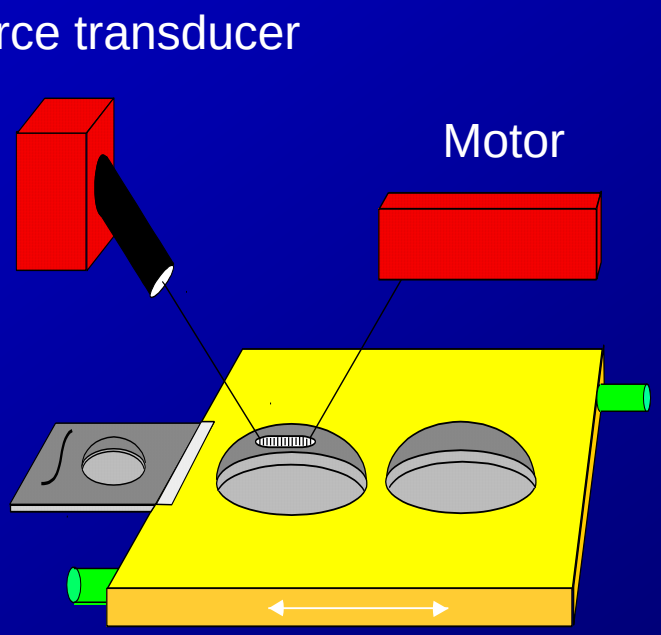
Impaired relaxation

↑ cardiomyocyte stiffness

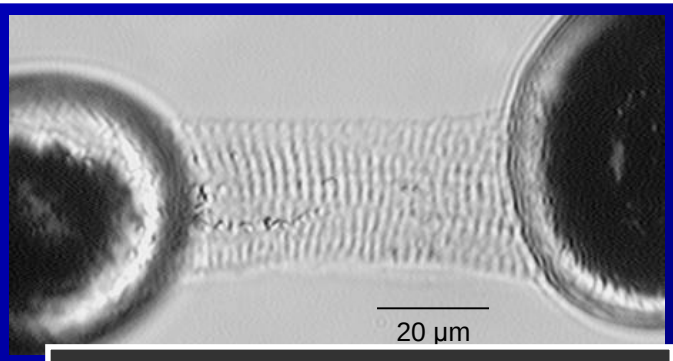
Jessup, NEJM 2003;348:2007; Borbely, Circulation 2005;111:774

HFpEF: increased cardiomyocyte stiffness

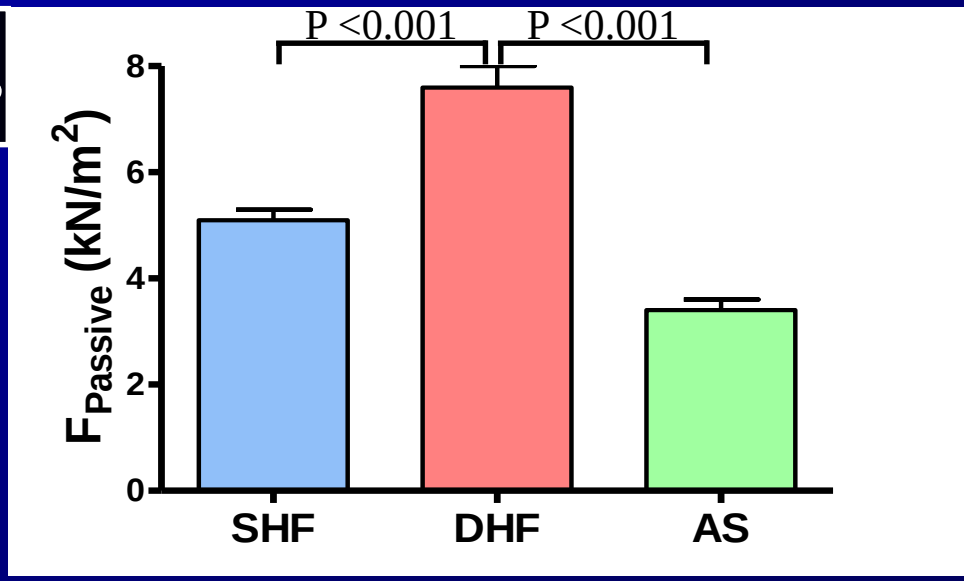
VUMC Physiology
2003-2014 (Prof dr WJ Paulus):
LV Endomyocardial biopsies:
→ Structure/function/signaling



HFpEF: ↑ Cardiomyocyte stiffness

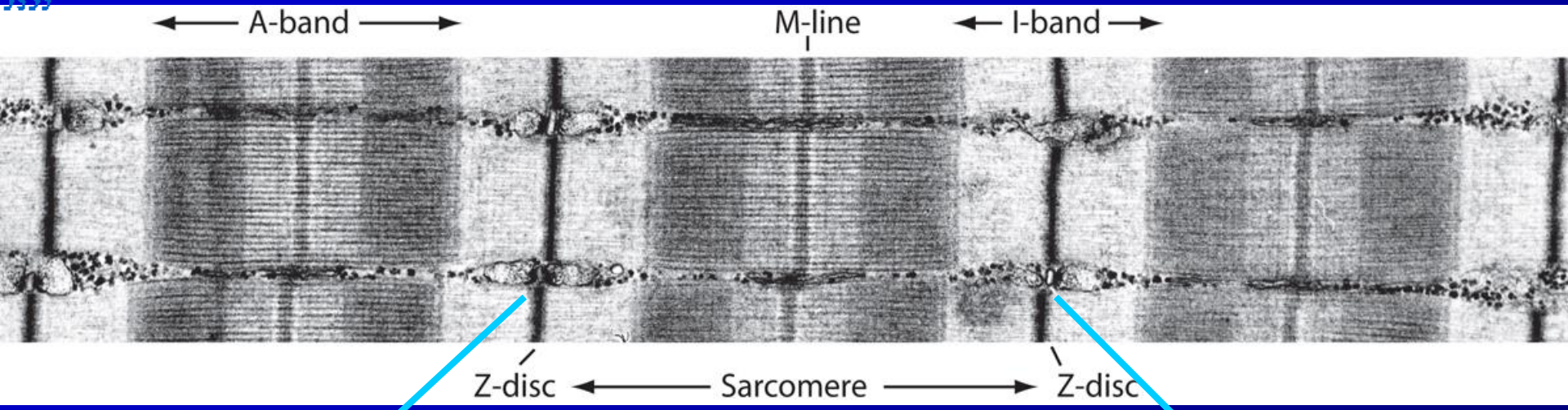


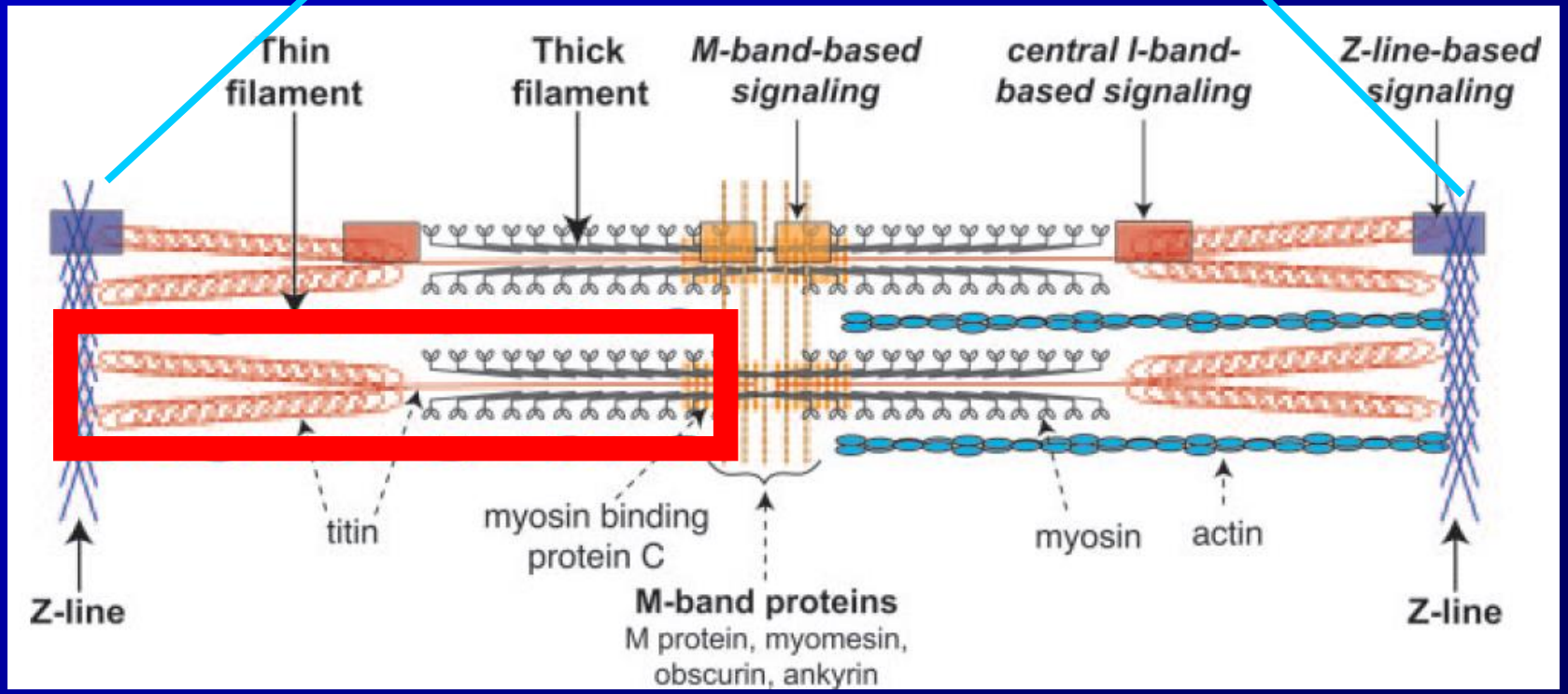
Sarcomere length 2.2 µm



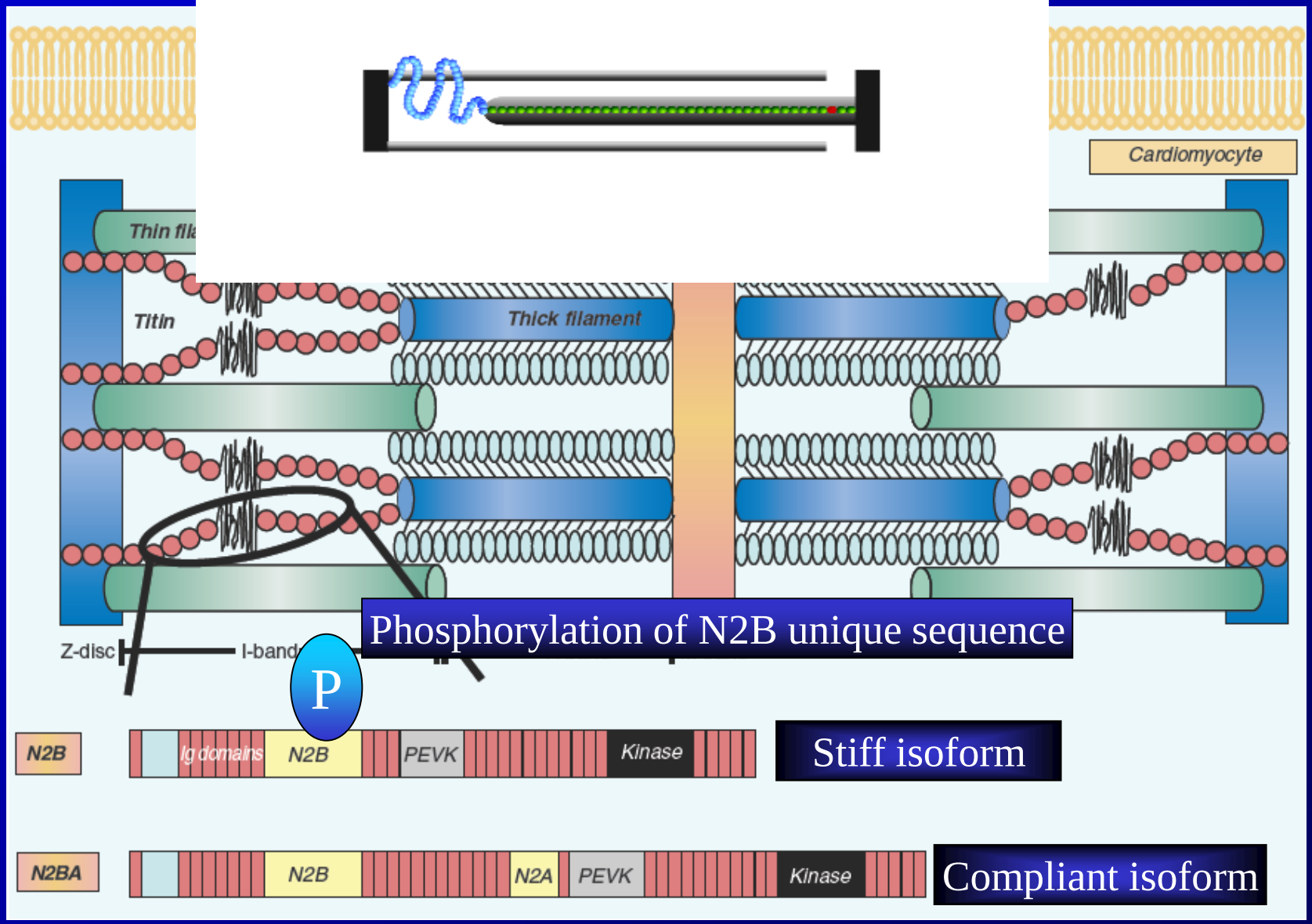
Van Heerebeek L et al., Circulation 2006;113:1966, van Heerebeek et L., Circulation 2012;126:830

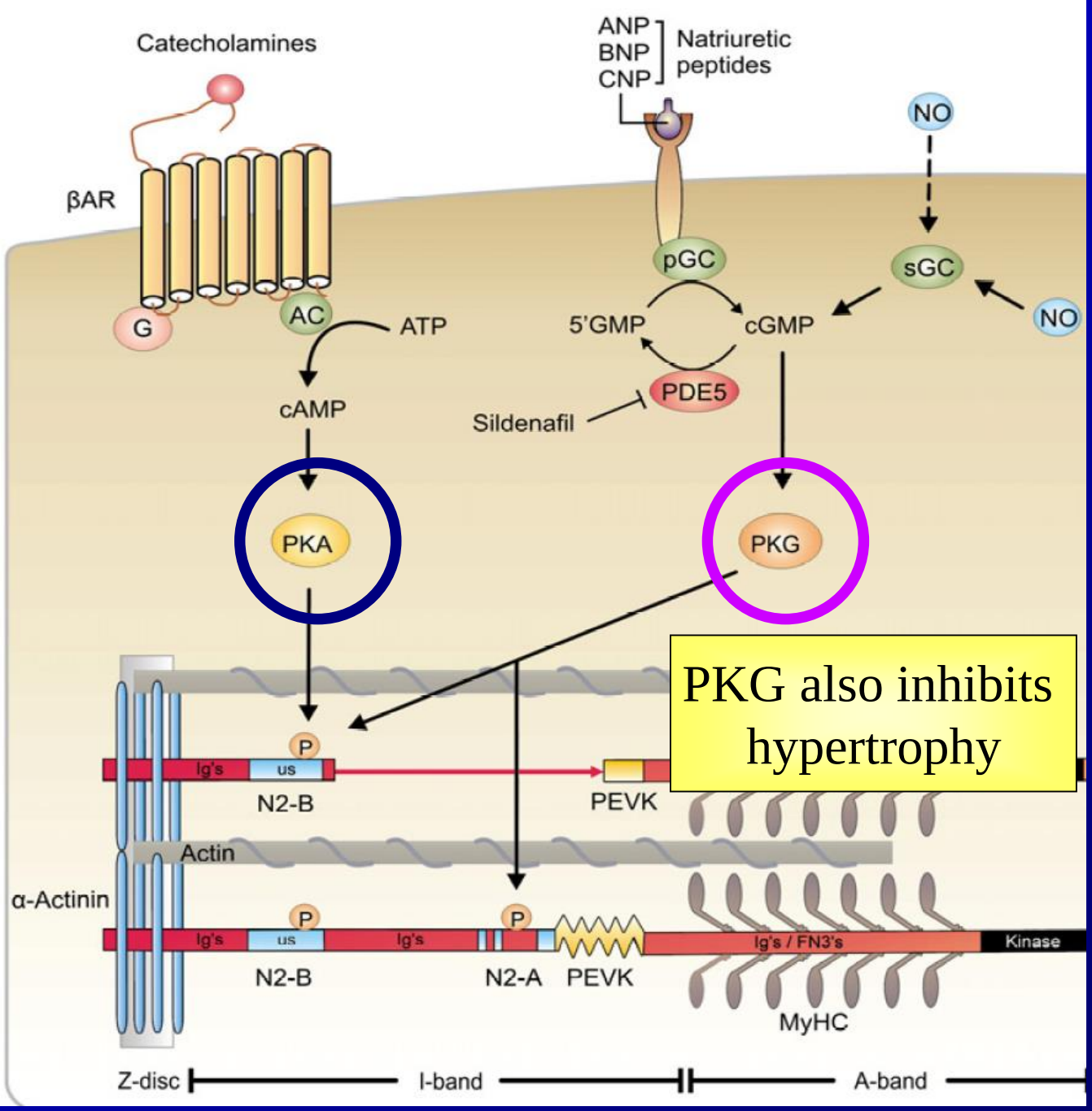
Cardiomyocyte stiffness: Titin





Titin determines cardiomyocyte stiffness





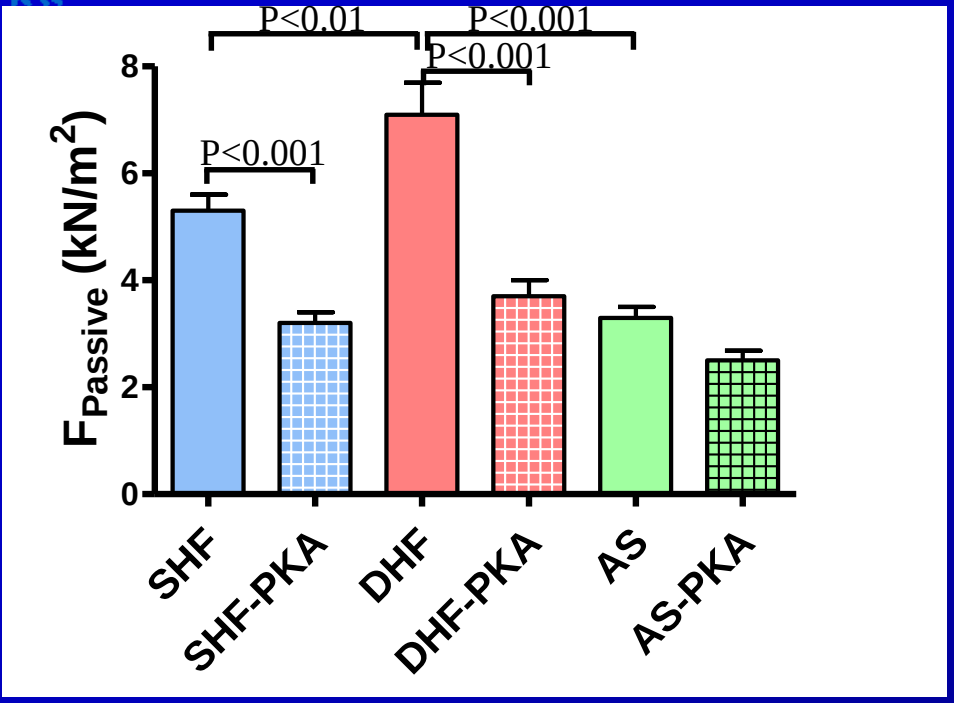
PKG also inhibits hypertrophy

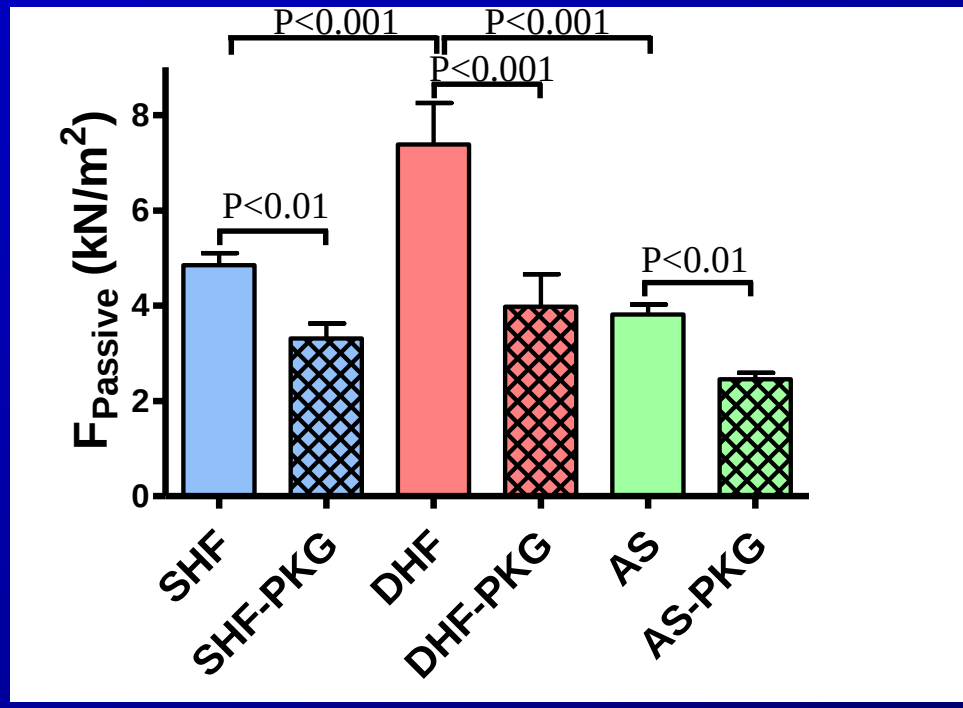
Stimulation of PKA/PKG phosph. of titin:

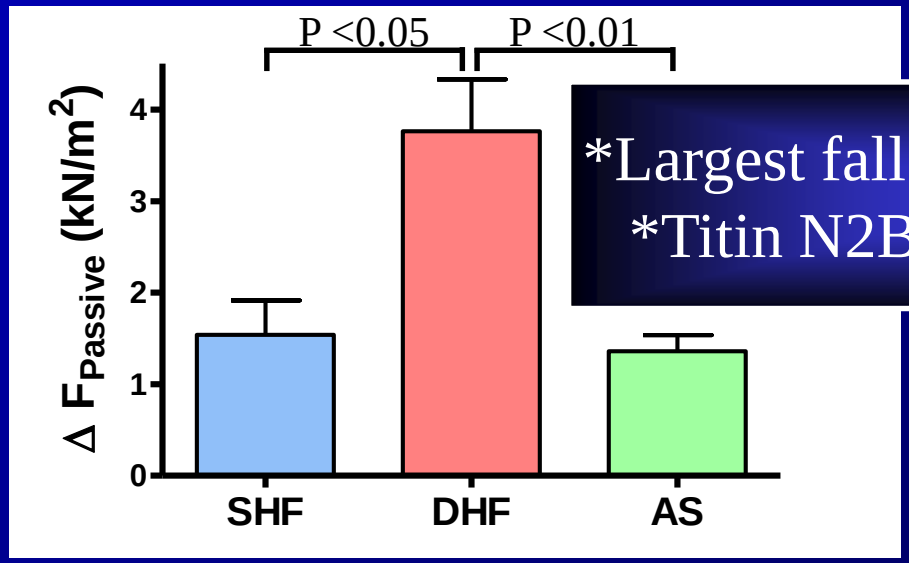
→ Lowering of CM stiffness

Krüger, J Mol Cell Cardiol 2009;46:490

CM stiffness: acute ↓ after protein kinase A (PKA) and PKG



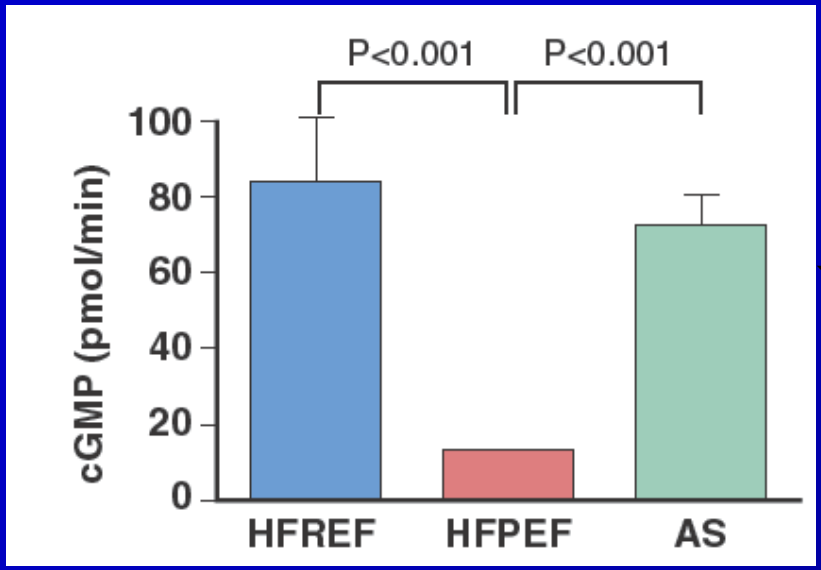


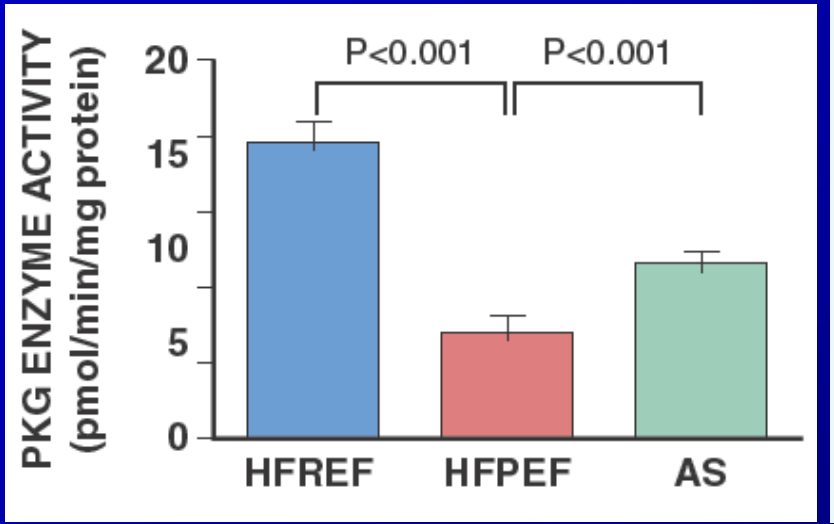


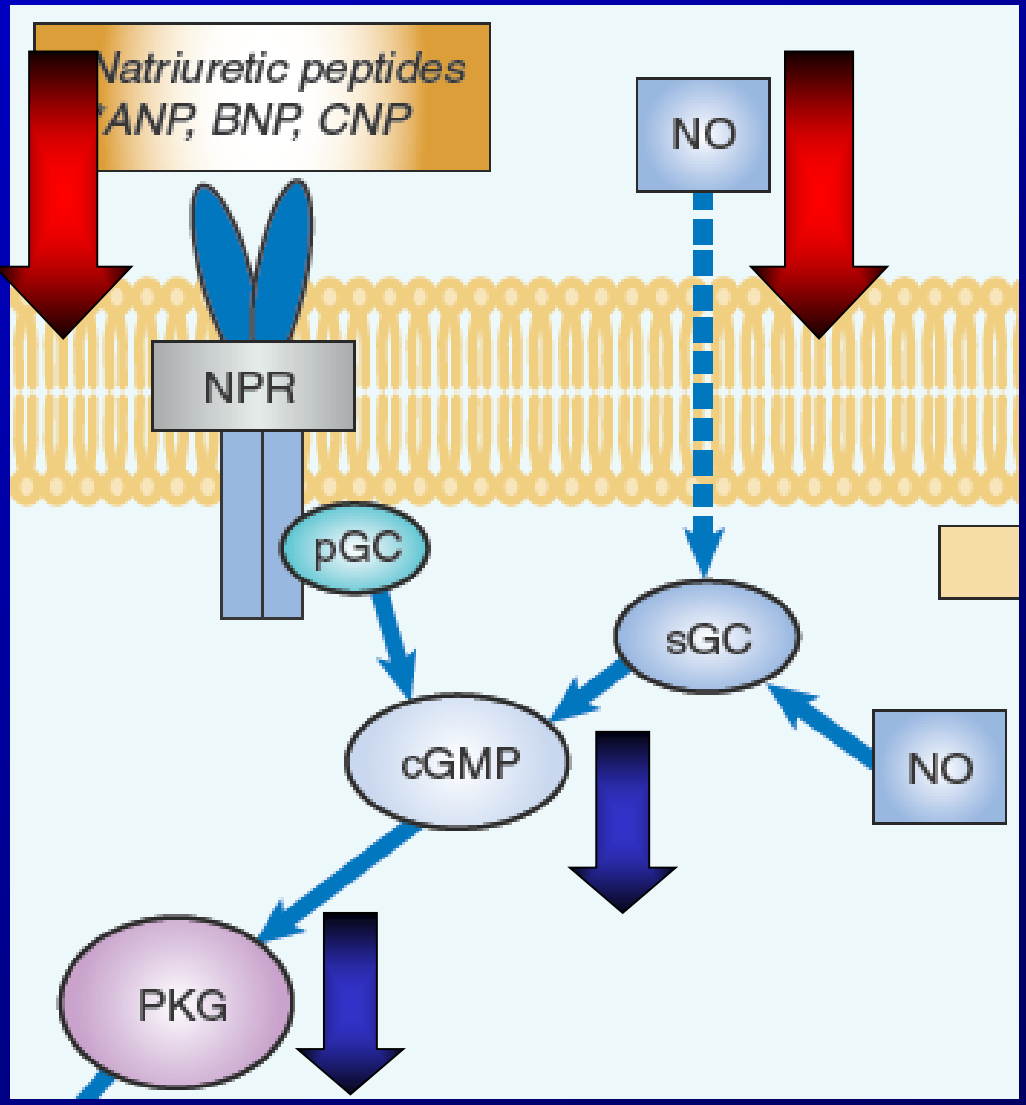
*Largest fall in stiffness in HFpEF
*Titin N2B-P deficit in HFpEF

Van Heerebeek L et al., Circulation 2006;113:1966, van Heerebeek et L., Circulation 2012;126:830

Low PKG in DHF: Stiff and hypertrophied cardiomyocytes

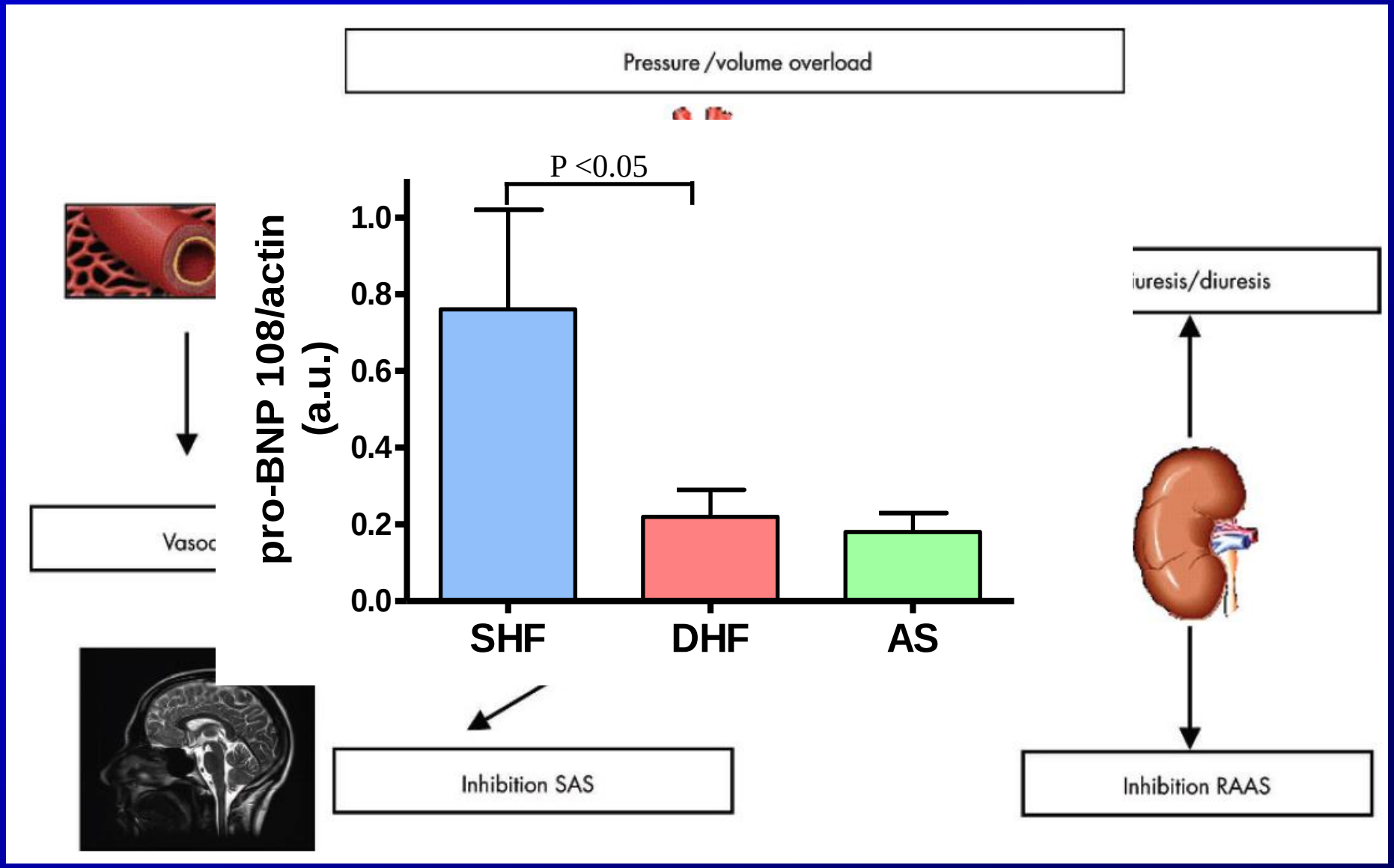






Van Heerebeek L et al, Circulation 2012;

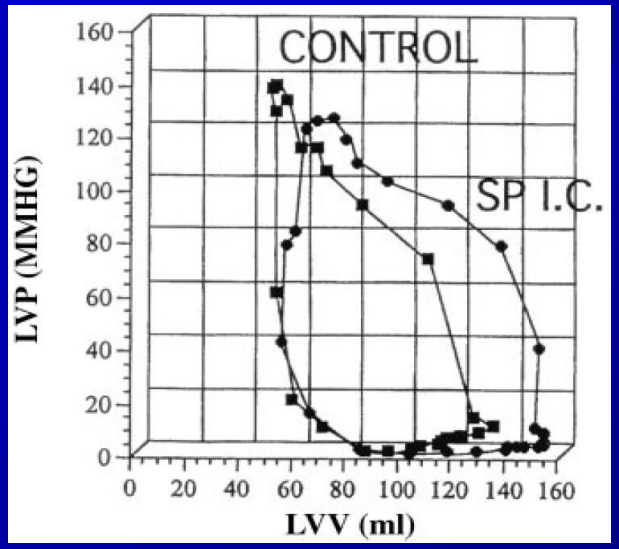
Brain Natriuretic peptide (BNP)

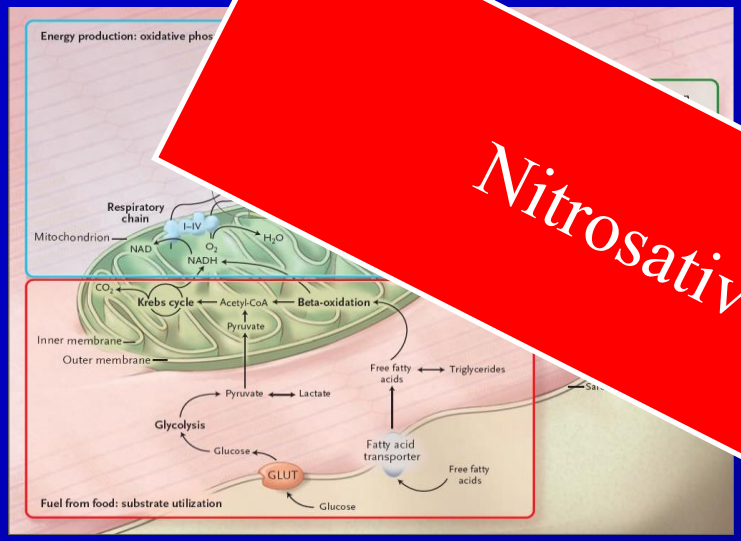


Weber et al, Heart 2006;92:843

NO is crucial for diastology

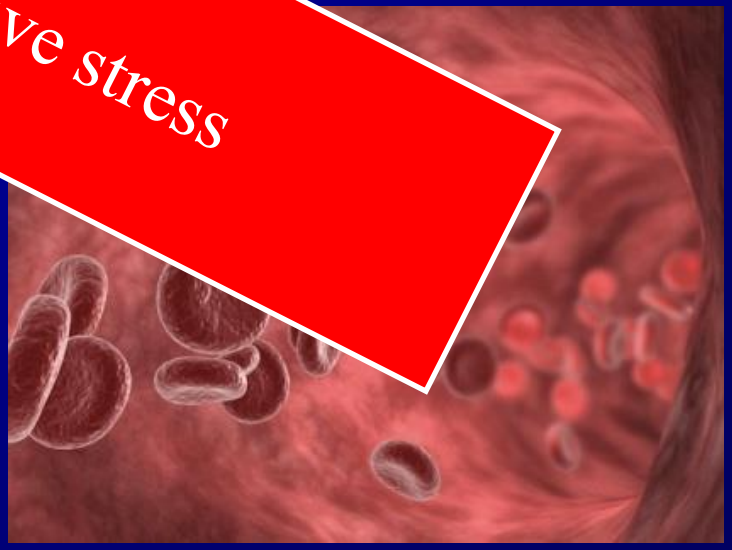
NO improves diastolic LV distensibility





Nitrosative/oxidative stress

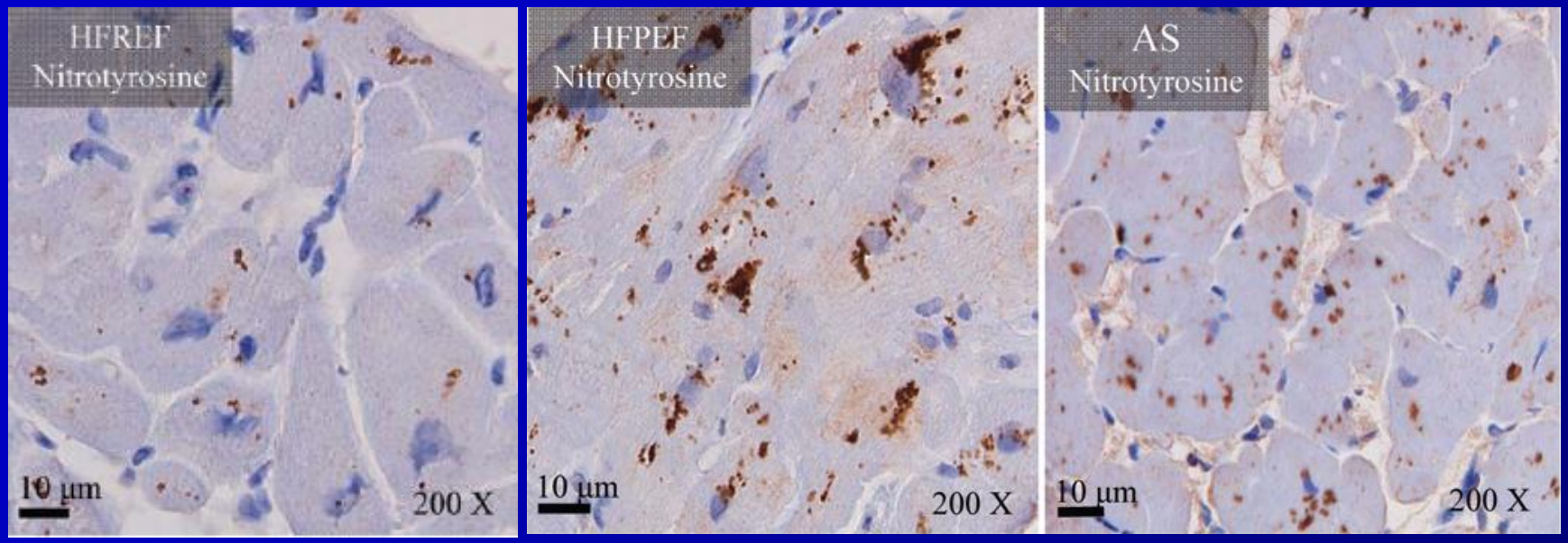
NO lowers myocardial O_2 consumption

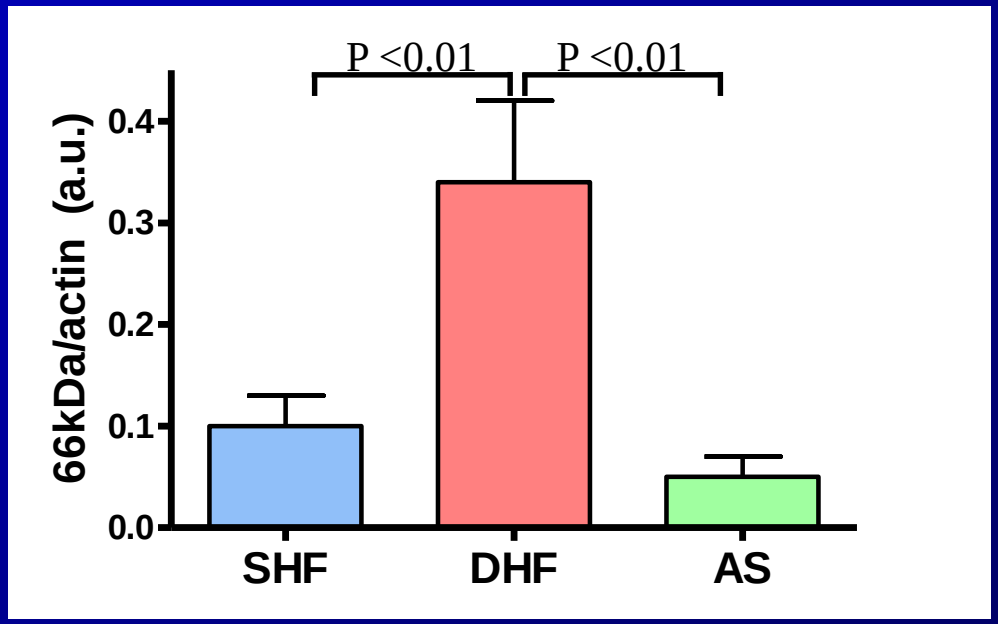


NO improves vascular distensibility

Paulus et al, Am J Physiol Heart Circ Physiol 2004;287:H8; Brutsaert Physiol Rev 2003;83:59

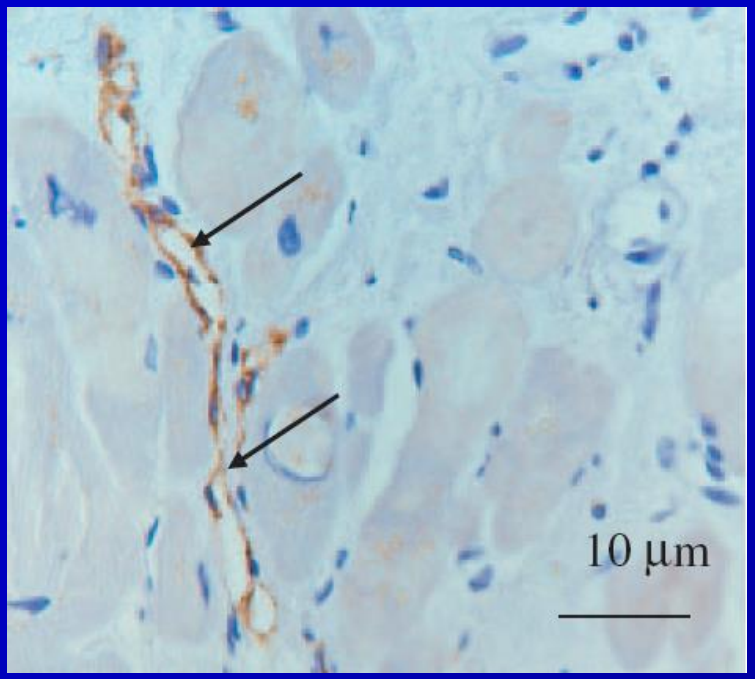
HFpEF: ↑ Nitrosative/oxidative stress



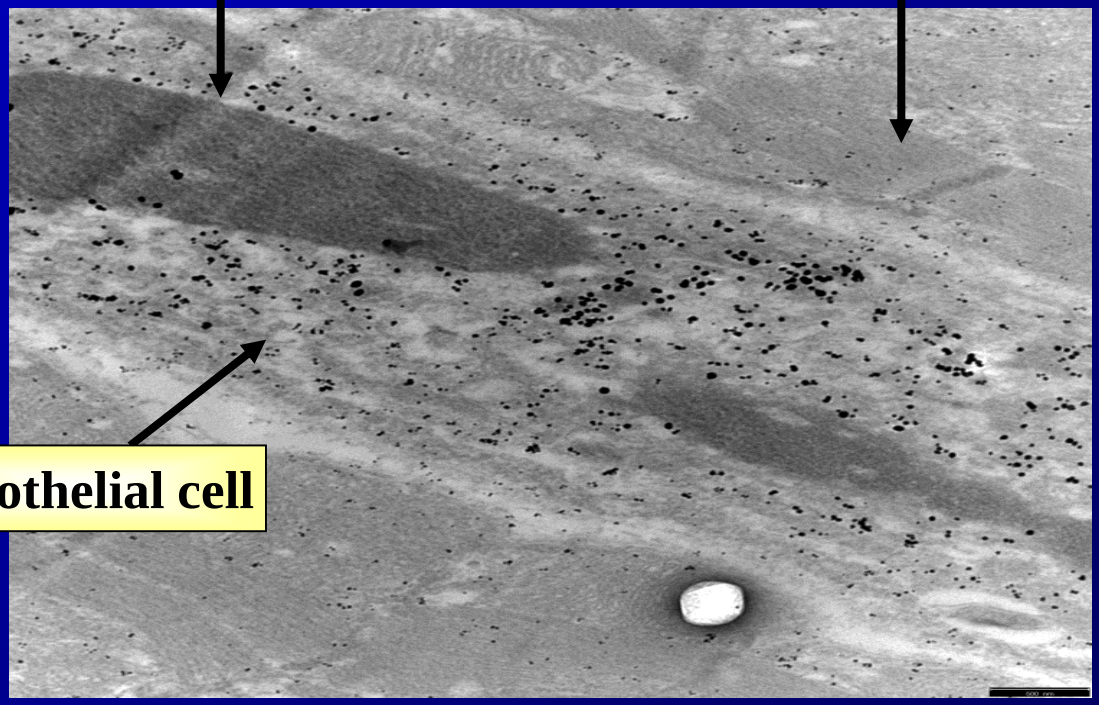


Van Heerebeek et al, Circulation 2012;126:830

HFpEF: Coronary microvascular inflammation



Van Heerebeek et al,
Circulation 2008;117:43



?

Gold-labeled antibodies against nitrotyrosine cluster in endothelial cells but not in erythrocytes or cardiomyocytes. Franssen C, … Paulus WJ Submitted.

Patient characteristics: Comorbidities

	HFrEF (n=43)	HFpEF (n=36)	AS (n=67)
Hypertension, (%)	16.3	77.8	58.3
Diabetes Mellitus, (DM, %)	30.2	47.2	25.8
Body mass index, (BMI, kg/m^2)	27.5 ± 0.8	30.4 ± 1.0	28.1 ± 0.6

Van Heerebeek et al. Circulation 2012;126:830

HFpEF and HFrEF pts: distinct risk factors

Characteristic	Reduced Ejection Fraction (N=2429)	Preserved Ejection Fraction (N=2167)	P Value	Adjusted P Value¶
Age (yr)	71.7±12.1	74.4±14.4	<0.001	NA
Male sex (% of patients)	65.4	44.3	<0.001	<0.001
Body-mass index‡	28.6±7.0	29.7±7.8	0.002	0.17
Obesity (% of patients)‡§	35.5	41.4	0.007	0.002
Serum creatinine on admission (mg/dl)	1.6±1.0	1.6±1.1	0.31	0.30
Hemoglobin on admission (g/dl)	12.5±2.0	11.8±2.1	<0.001	<0.001
Hypertension (% of patients)	48.0	62.7	<0.001	<0.001
Coronary artery disease (% of patients)	63.7	52.9	<0.001	<0.001
Atrial fibrillation (% of patients)	28.5	41.3	<0.001	<0.001
Diabetes (% of patients)	34.3	33.1	0.42	0.61
Substantial valve disease (% of patients)	6.5	2.6	<0.001	0.05
Ejection fraction (%)	29±10	61±7	<0.001	NA

6076 pts hospitalized for HF from 1987 – 2001 Mayo Clinic Hospital (Olmstead County USA)

Owan et al. NEJM 2006;355:251

HFpEF: comorbidities

Obesity
80-85%

Diabetes mellitus type 2
32% (14-50)

Metabolic syndrome

Insulin resistance

Hypertension
75% (46-93)

Female gender
59% (40-73)

COPD
25% (3-39)

HFpEF

Increased age
73 yrs (65-82)

OSAS

Atrial fibrillation
32% (5-51)

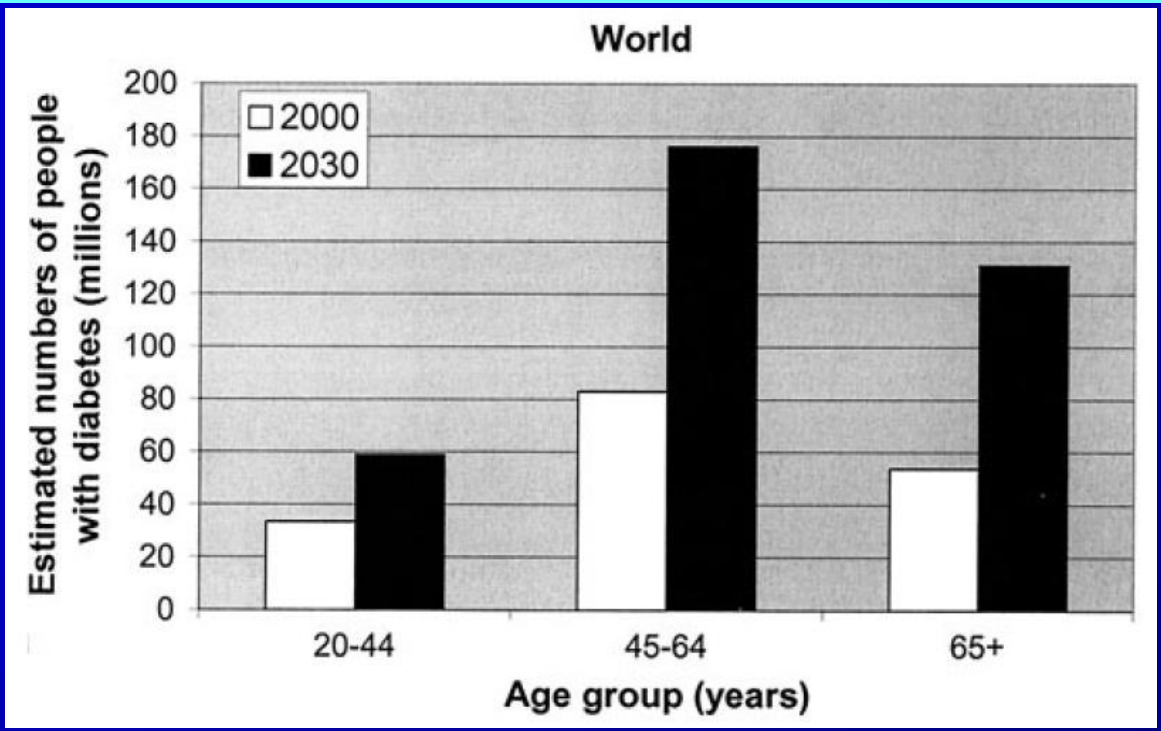
Anemia
36% (21-53)

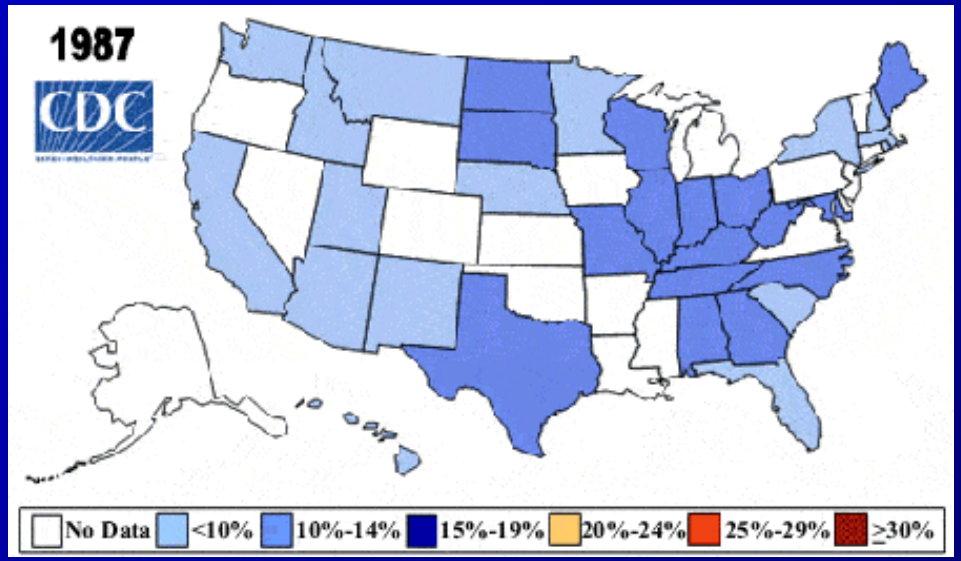
Iron deficiency

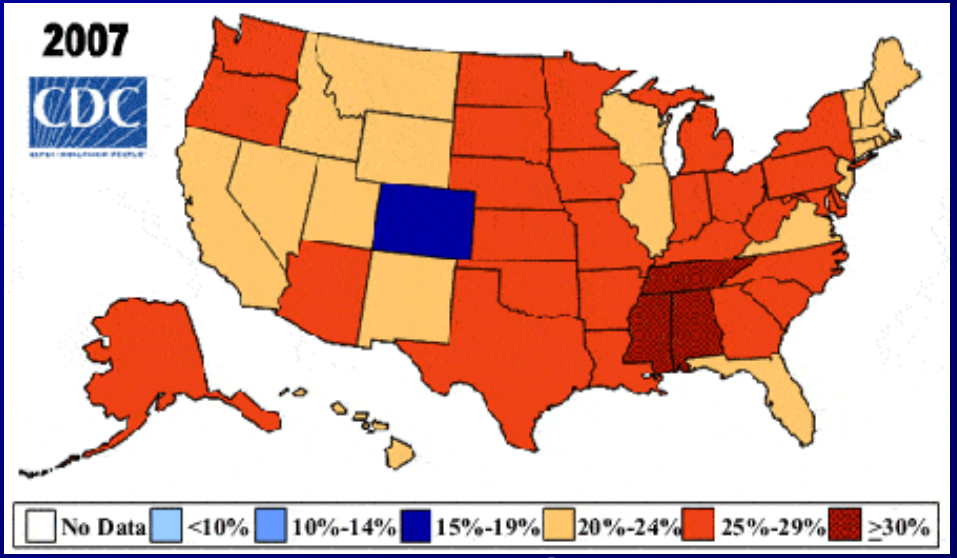
Pulmonary Hypertension
(36-85%)

Renal insufficiency
40% (22-60)

Diabetes and Obesity: global epidemic

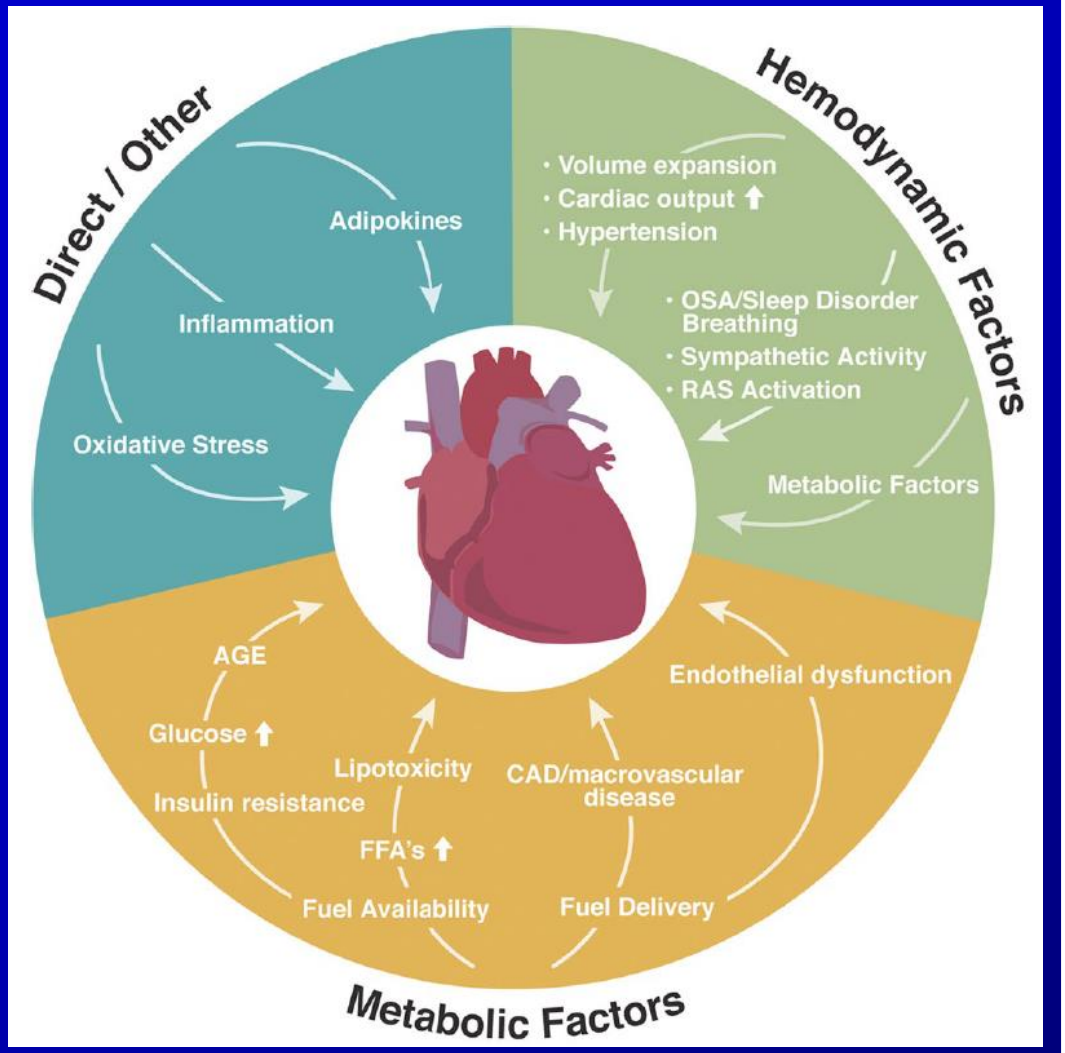






Diab Care 2004;27:1047

HFpEF: “Metabolic cardiomyopathy”?



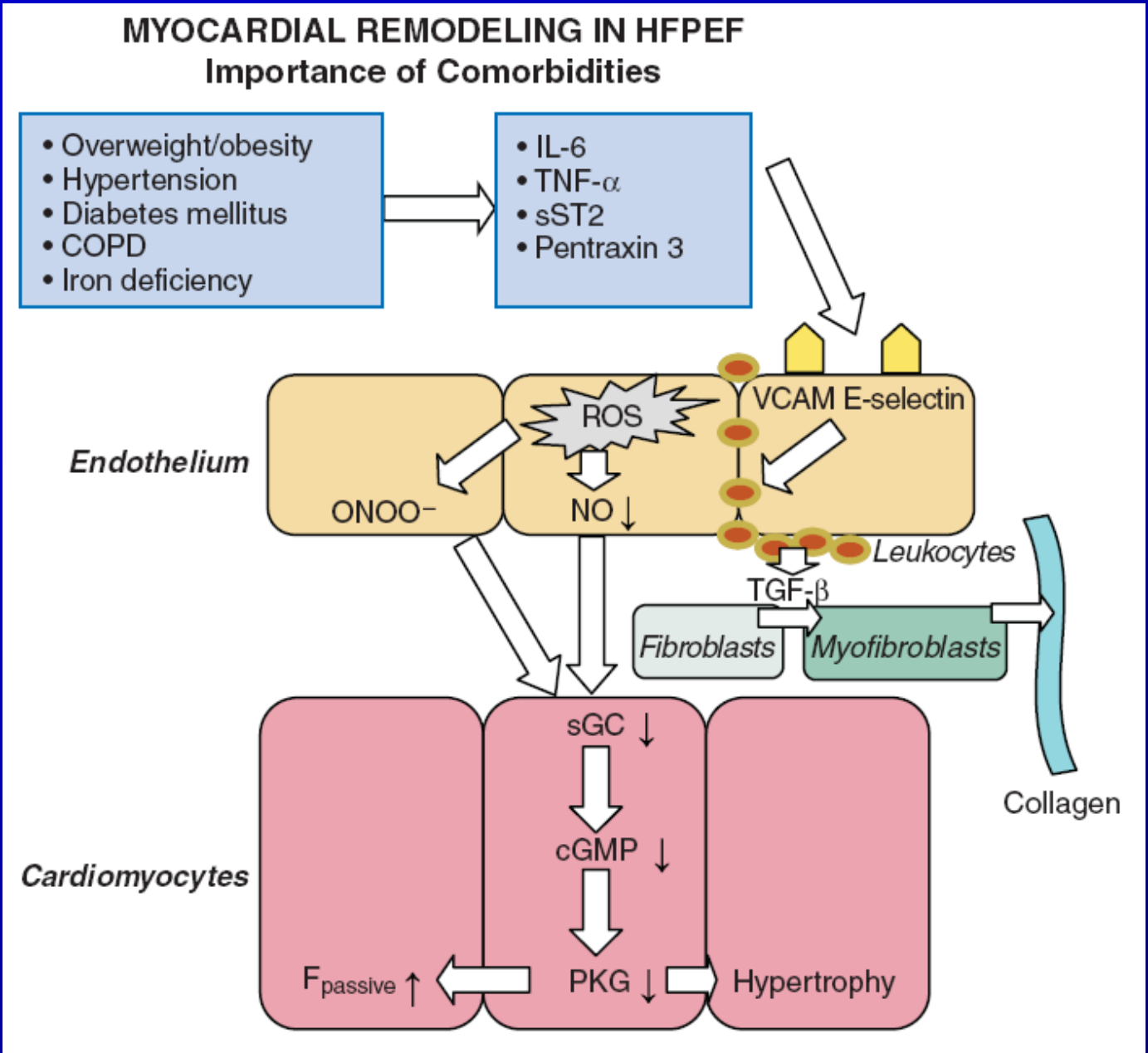
Adverse effects of Metabolic risk factors:

*Diastolic LV dysfunction

*Cardiovascular fibrosis
*Hypertrophy
*Endothelial dysfunction
*Oxidative stress/inflammation
*Mitochondrial dysfunction
*Glucose- and lipotoxicity
*Growth factor changes
*Volume changes
*Increased myocardial stiffness
*Increased cardiomyocyte stiffness

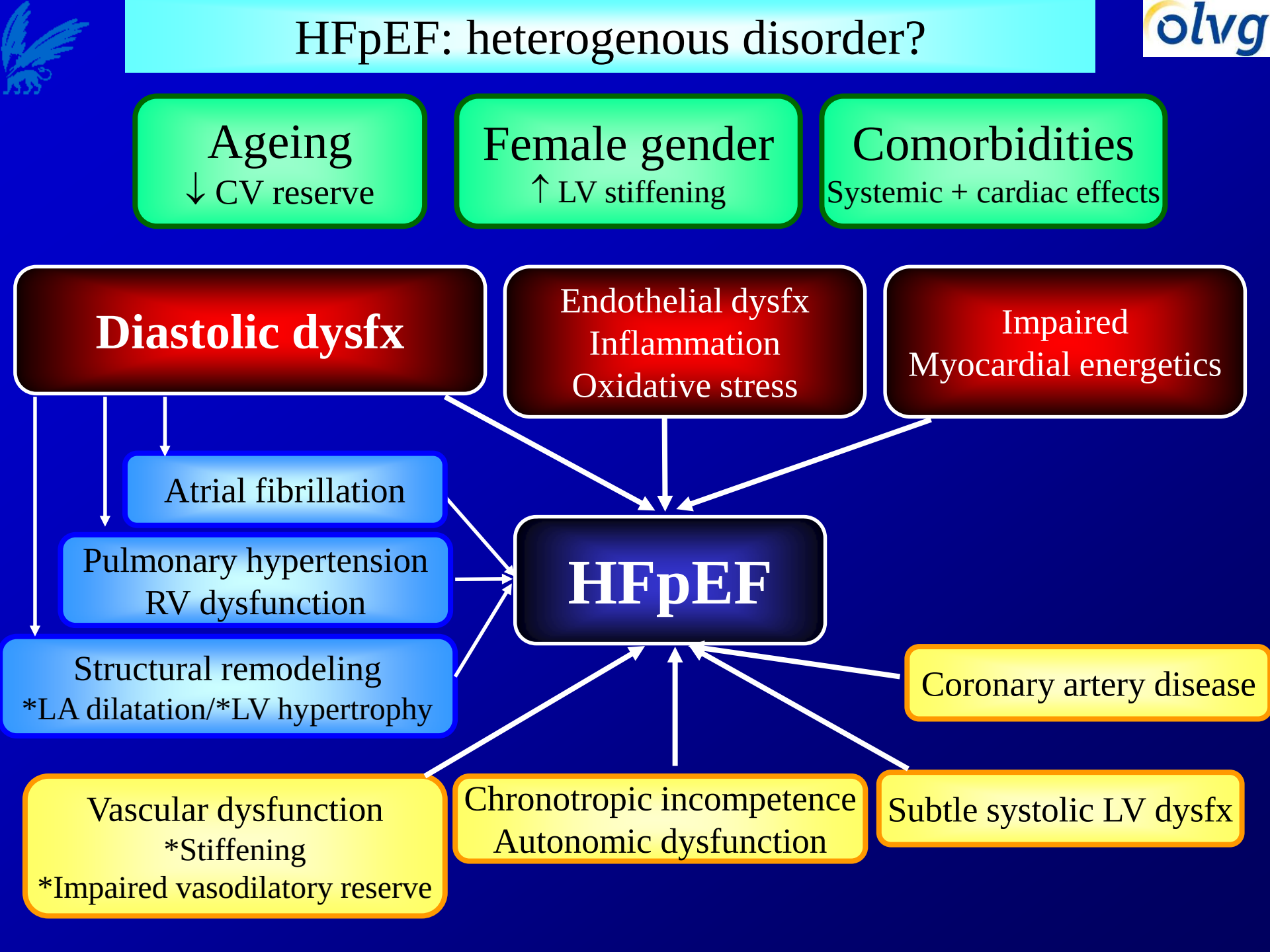
Abel et al; Physiol Rev 2008;88:389

Novel paradigm for HFpEF

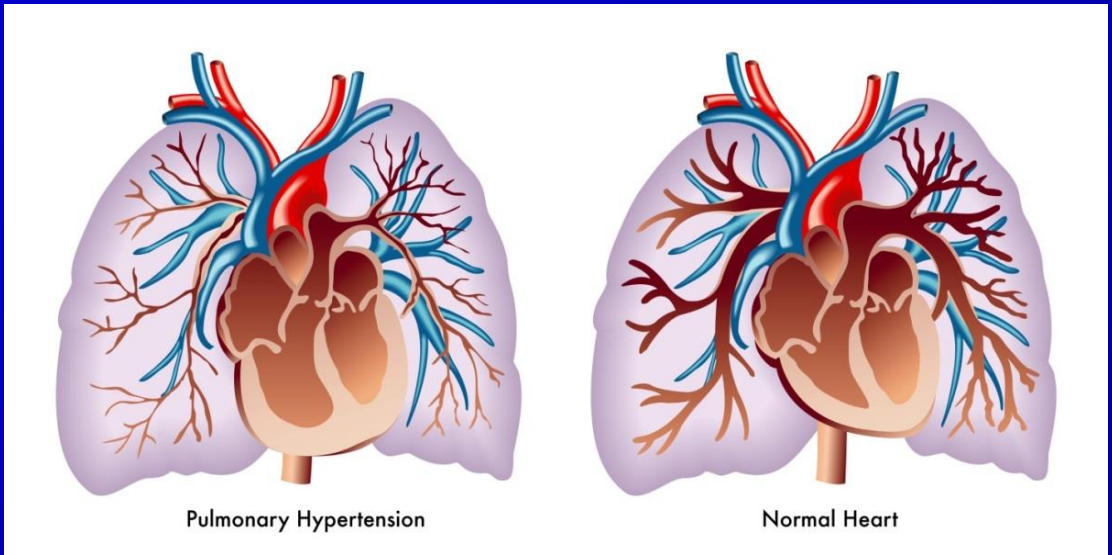


Modified from Paulus WJ et al, JACC 2013;62:263

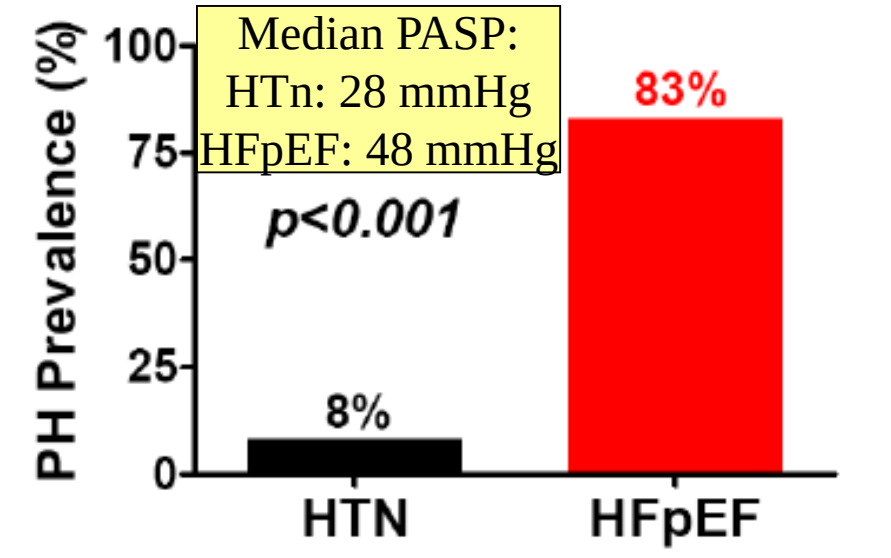
HFpEF: heterogenous disorder?

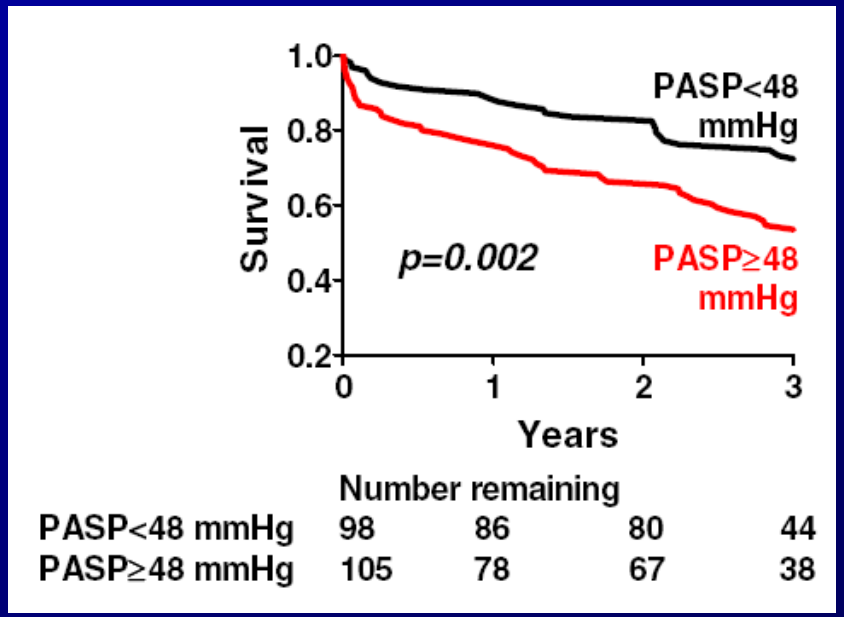


HFpEF: Pulmonary hypertension



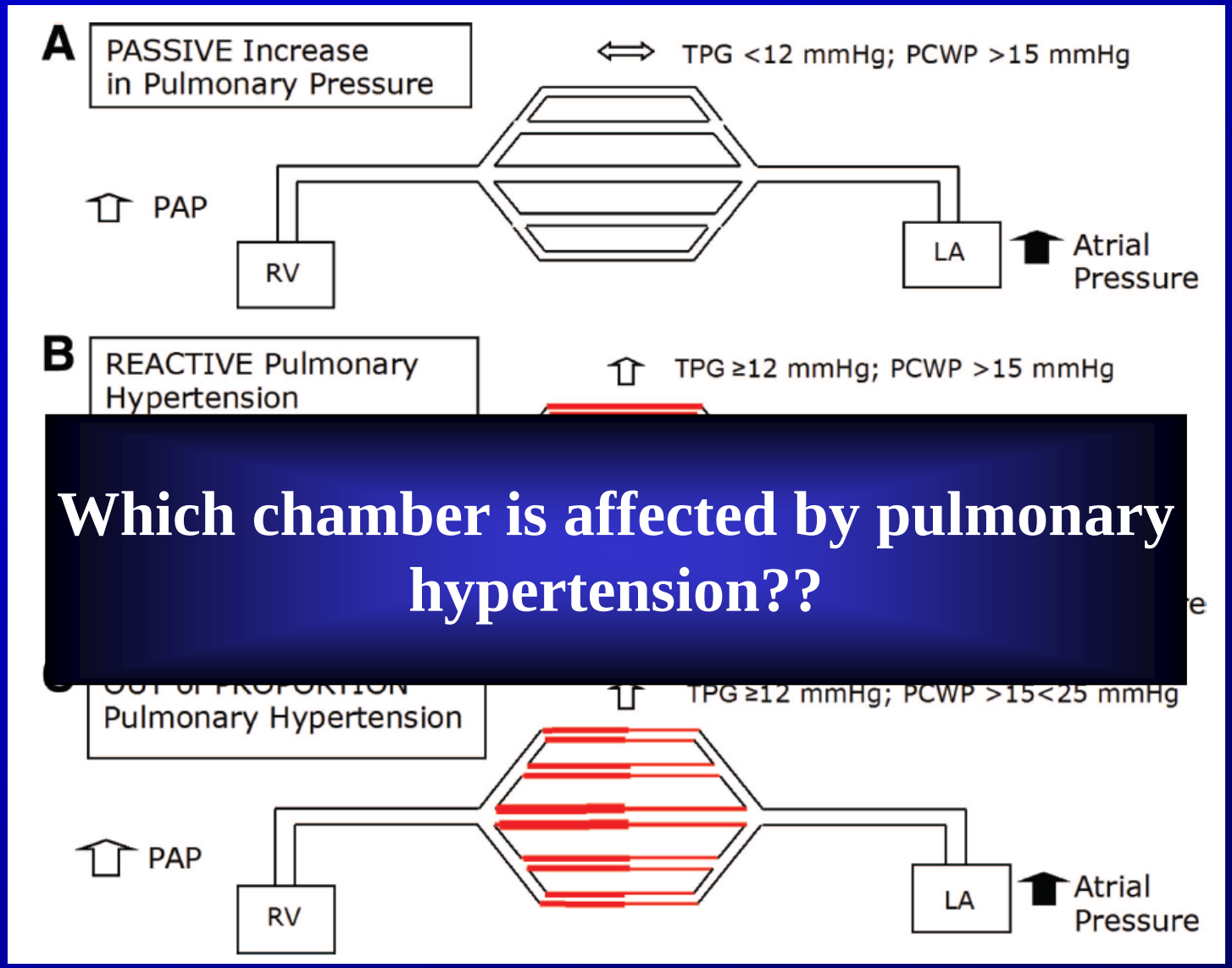
Community based study: HFpEF (n=244) vs HTn w.o. HF (n=719) pts; echo-derived PASP





Lam CS et al. JACC 2009;53:1119

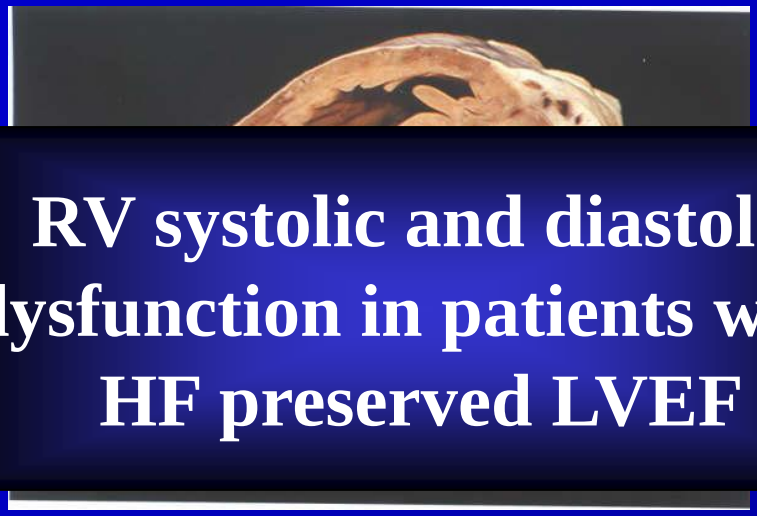
HFpEF: Pulmonary hypertension



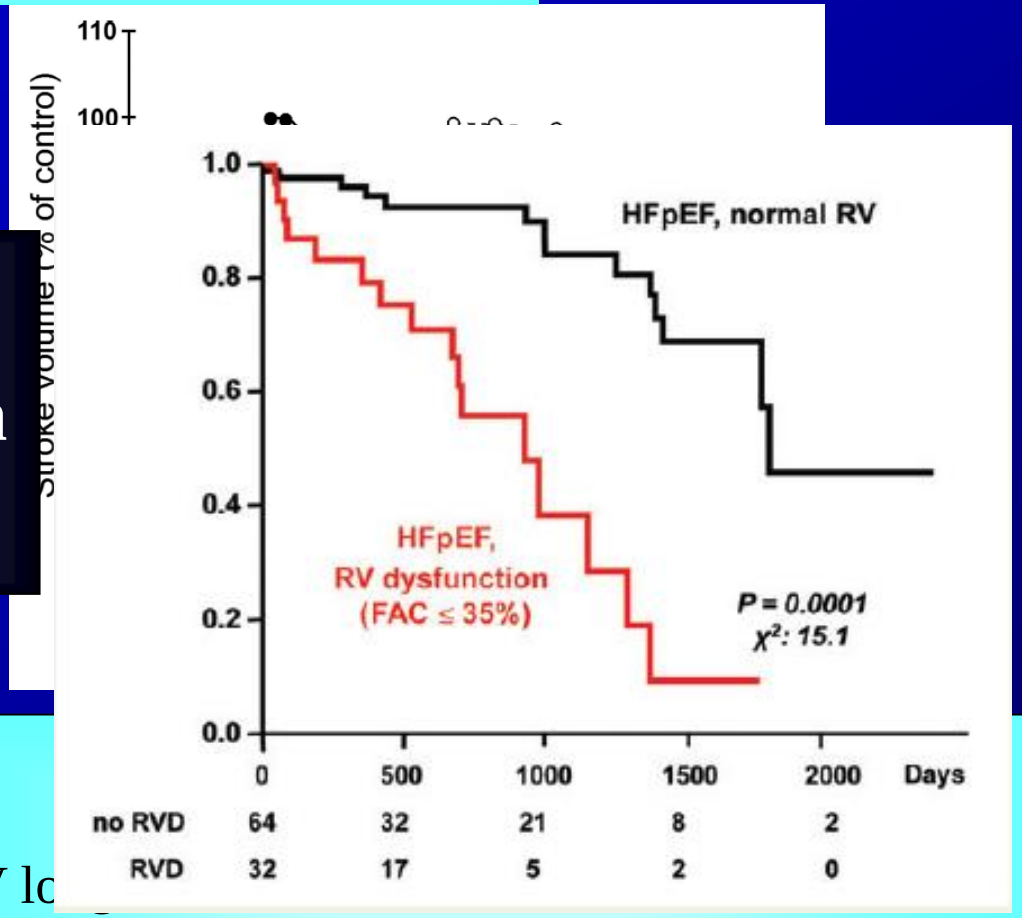
Which chamber is affected by pulmonary hypertension??

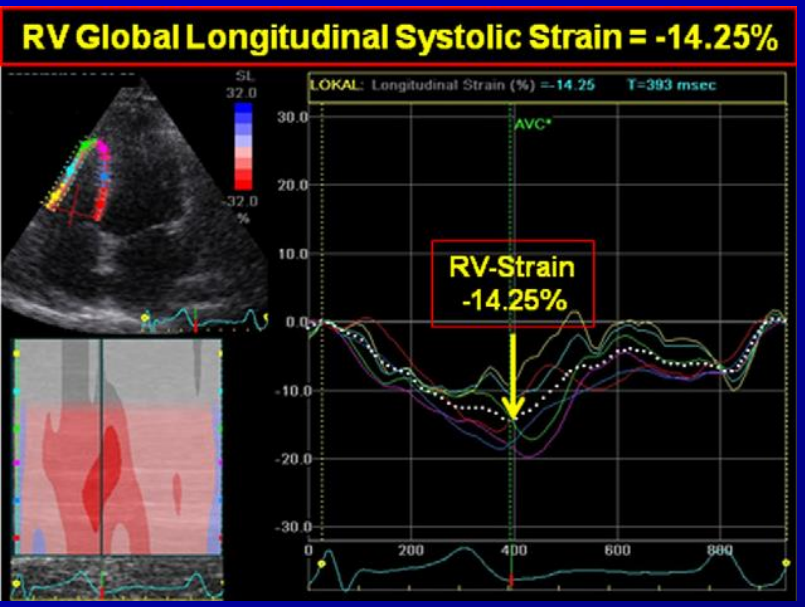
Guazzi M et al. Circulation 2012;126:975

HFpEF: RV dysfunction



RV systolic and diastolic dysfunction in patients with HF preserved LVEF

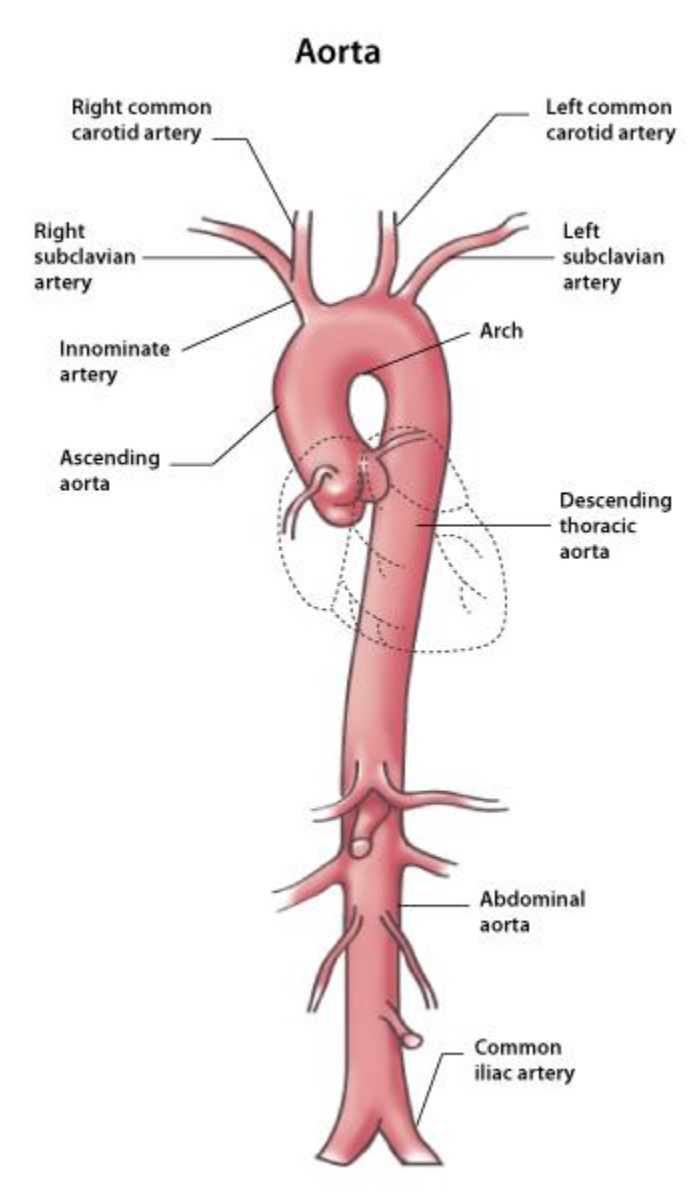


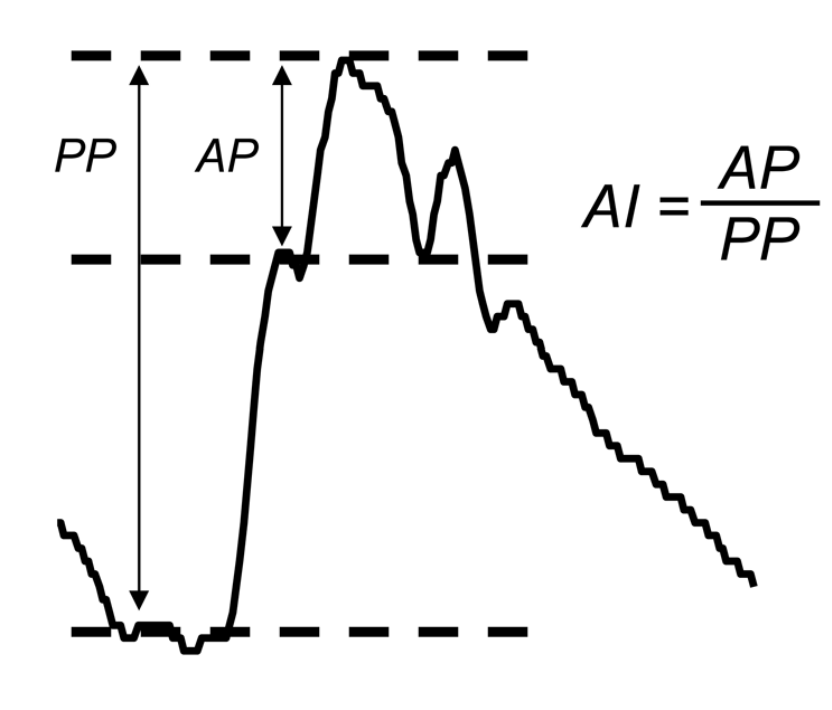


RV lo			
TAPSE	16.5 ± 3.5	18.7 ± 4.0	<0.001
RV FAC	40.1 ± 9.2	44.0 ± 8.7	<0.001
PASP	40.9 ± 10.5	32.2 ± 6.8	<0.001
PVR	1.45 ± 0.29	1.26 ± 0.24	<0.001
Mitral E/E’	17.4 ± 6	10.6 ± 3.8	<0.001

Guazzi Circulation 2012; Morris J Am Soc Echocardiogr 2011; Melenovsky Eur Heart J 2014

HFpEF: increased arterial stiffness

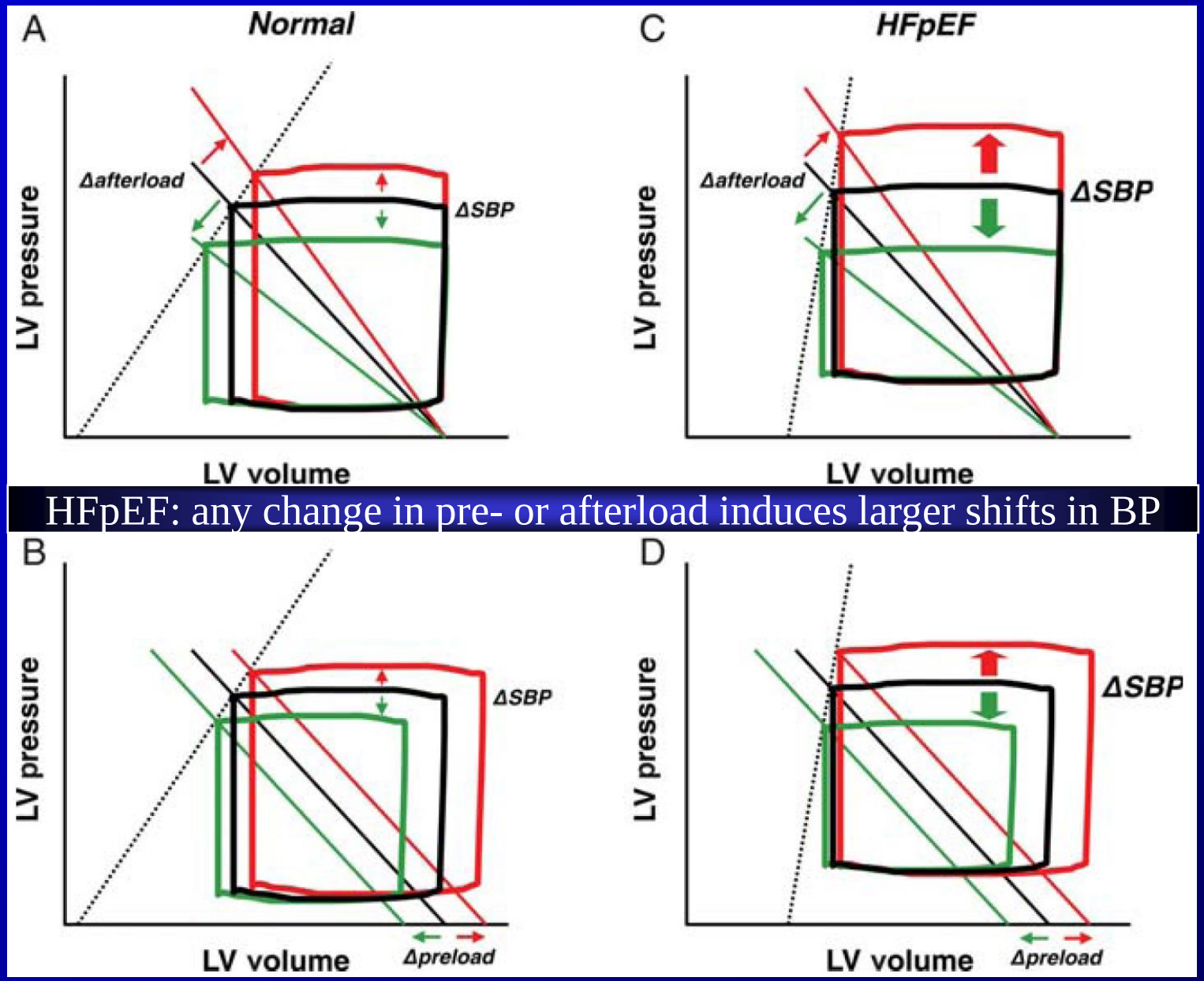




HFpEF: Stiff heart coupled to stiff arteries

Borlaug et al Heart Fail Clin 2008;4:23

Consequences of ↓ impaired ventricular-vascular reserve

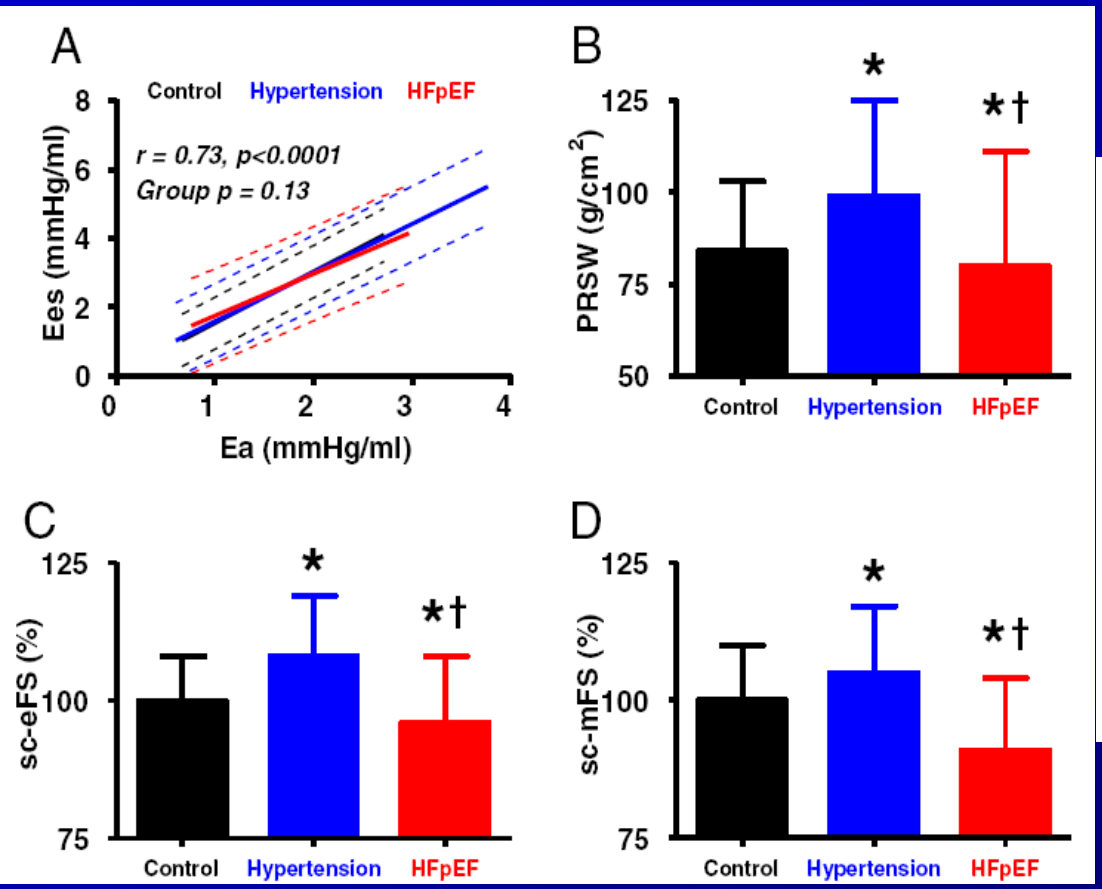


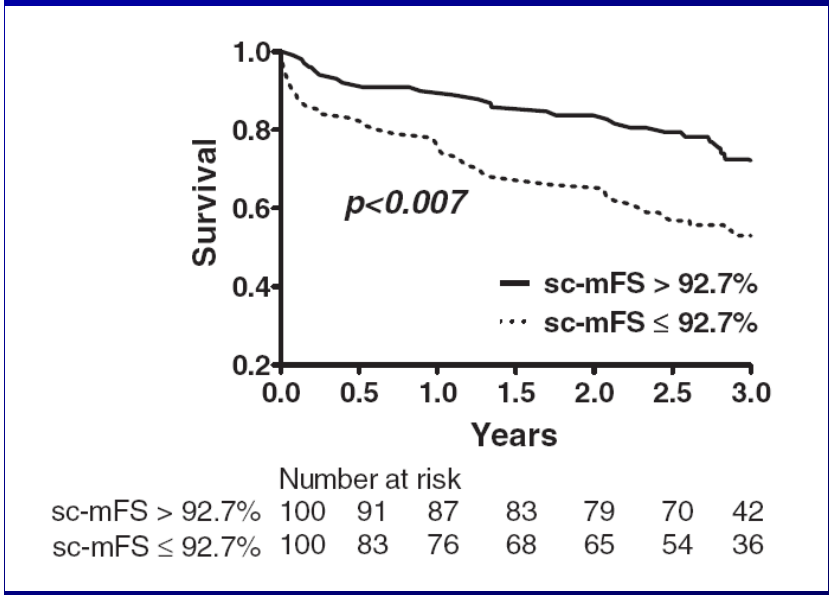
HFpEF: any change in pre- or afterload induces larger shifts in BP

Eur Heart J 2011;32:670; Heart Fail Clin 2008;4:23

HFpEF: Systolic dysfunction (predicts worse outcome)

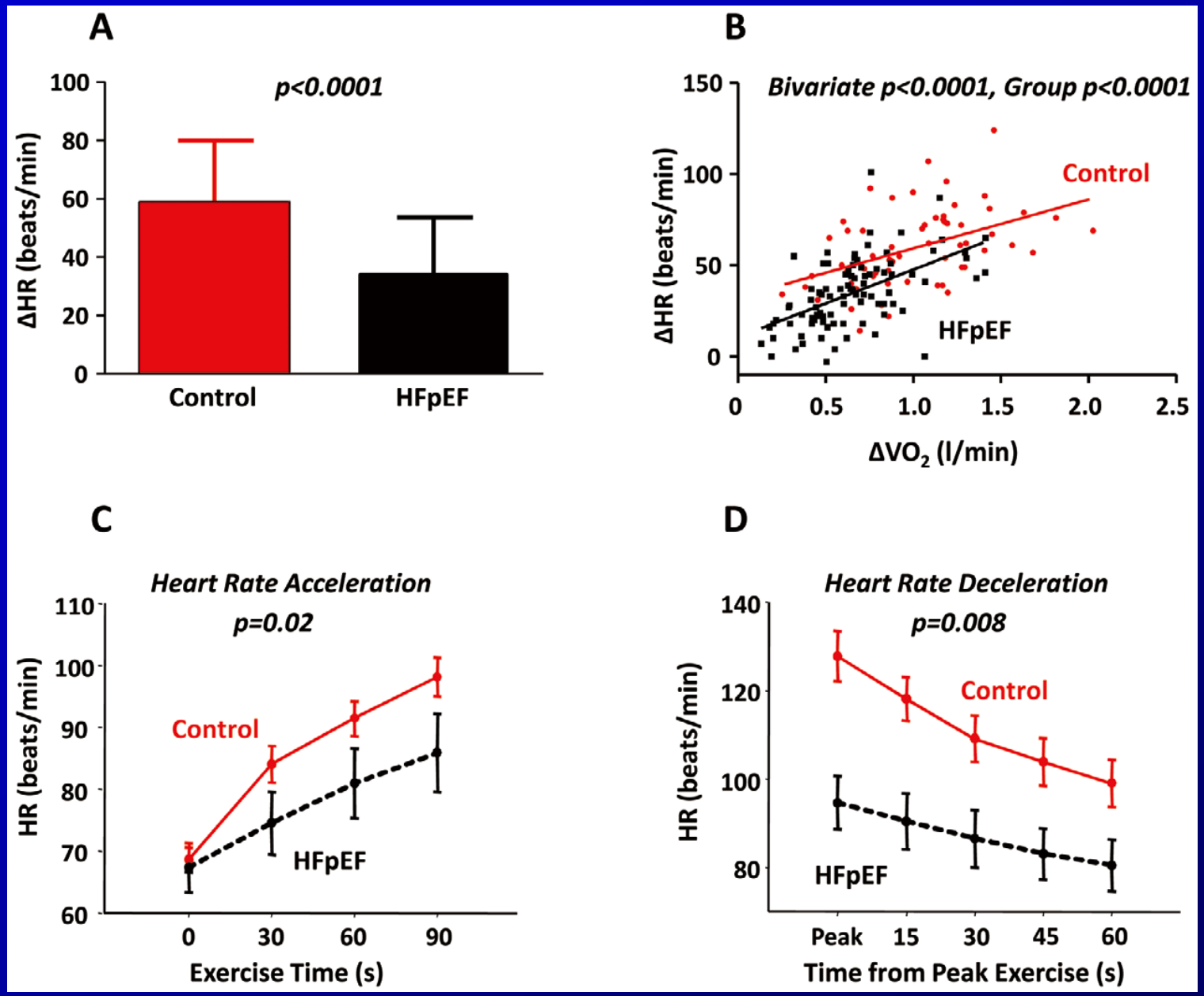
Echo-Doppler characterization of Ea, Ees and chamber and myocardial contractility (stress-corrected endocardial and midwall shortening) in Con (n=617), Hypertensives w.o. HF (n=719) and HFpEF (n=244)





Borlaug BA, et al JACC 2009;54:410

HFpEF: Chronotropic incompetence



Borlaug BA, Circ J 2014;78:20

HFpEF: Better characterize the patient

Disease duration

Comorbidities

Stage of disease

Age/Gender

Mechanisms of LV diastolic dysfunction

*Myocardial ECM
*CM characteristics
*Myocardial metabolics
*Structural remodeling
*Microvasc dysfunction

HFpEF Pathophysiology

Systemic pathology

*Inflammation
*Oxidative stress
*Endothelial dysfunction
*Skeletal muscle abnorm.
*Ventricular-vasc stiffness

HFpEF Treatment

Consequent and Concomitant pathology

*Atrial fibrillation
*Pulmonary hypertension
*RV dysfunction

Additional Pathology

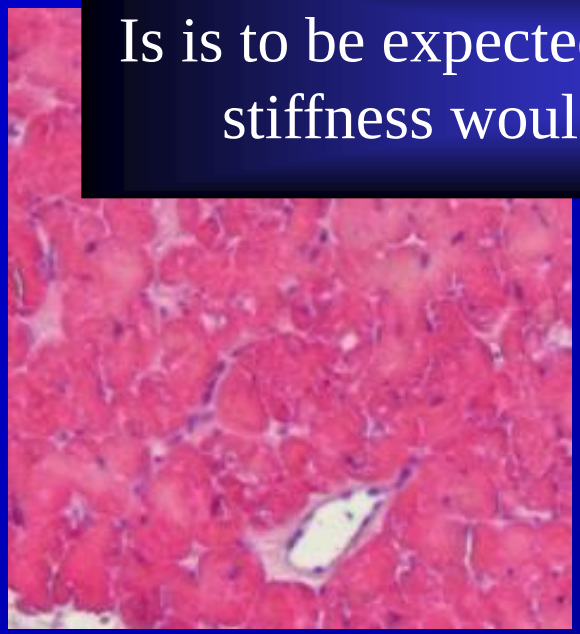
*Subtle systolic LV dysfx
*Coronary artery disease
*Autonomic dysfx
*Chronotropic incomp.

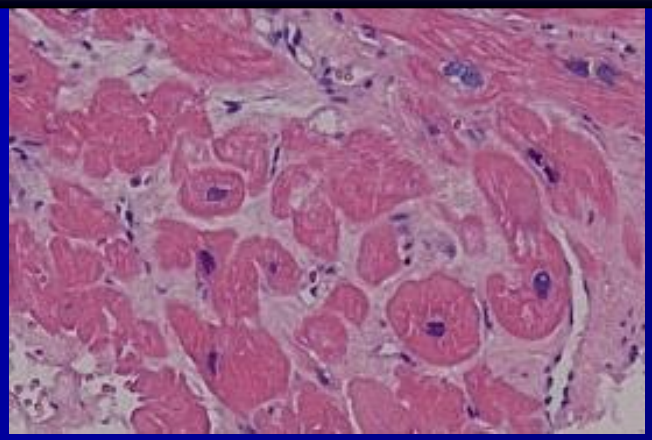
HFpEF: stage of disease?

Disease duration

Stage of disease

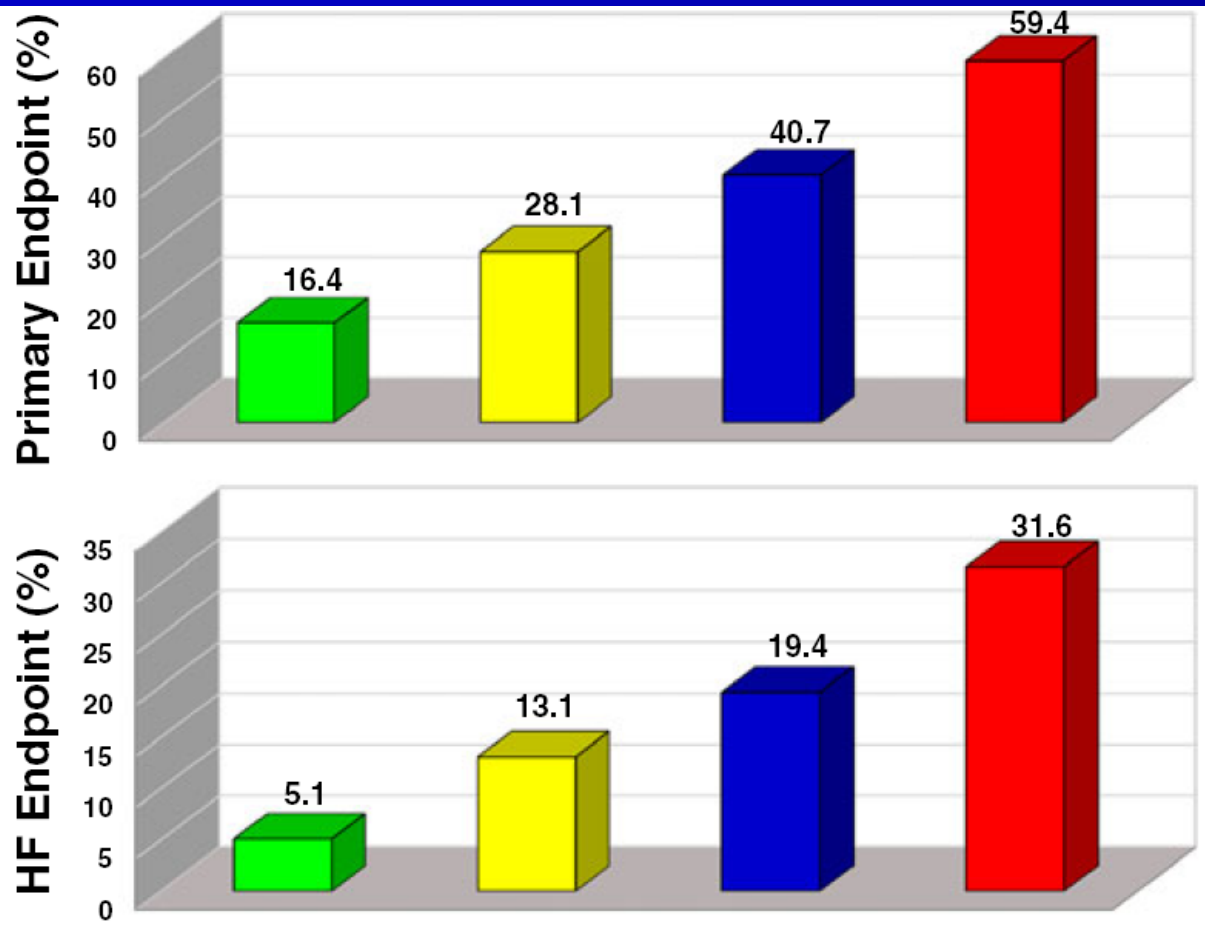
Is is to be expected that lowering of cardiomyocyte stiffness would improve diastolic stiffness??





Efficacy of:
ACE-I, ARB, aldosterone antagonists ?

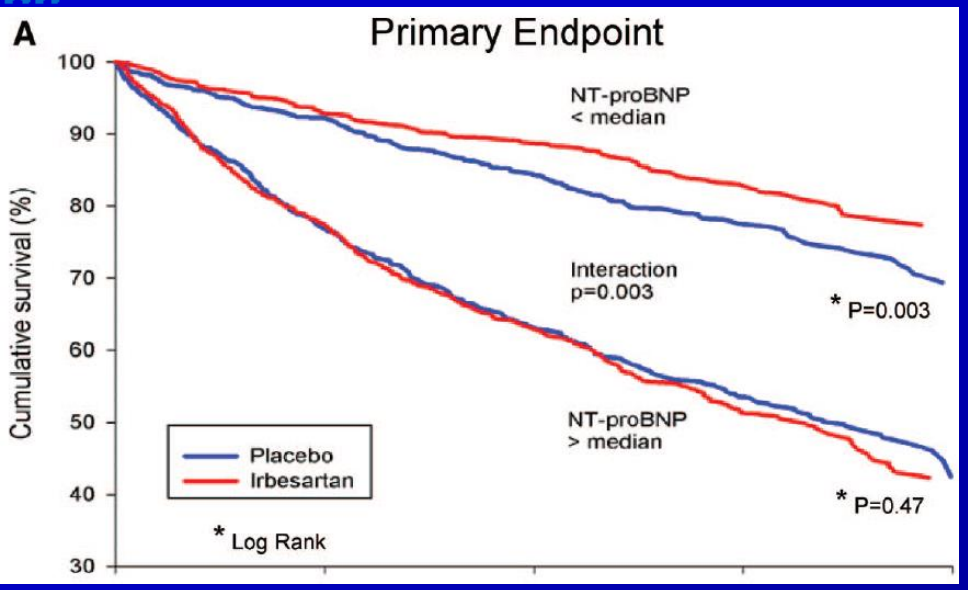
Staging of disease: role for biomarkers?; BNP

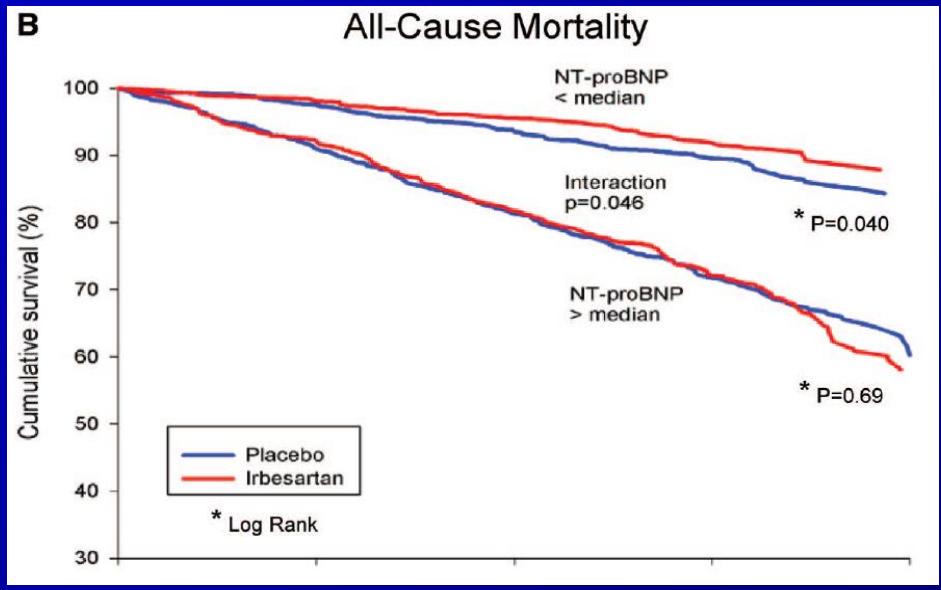


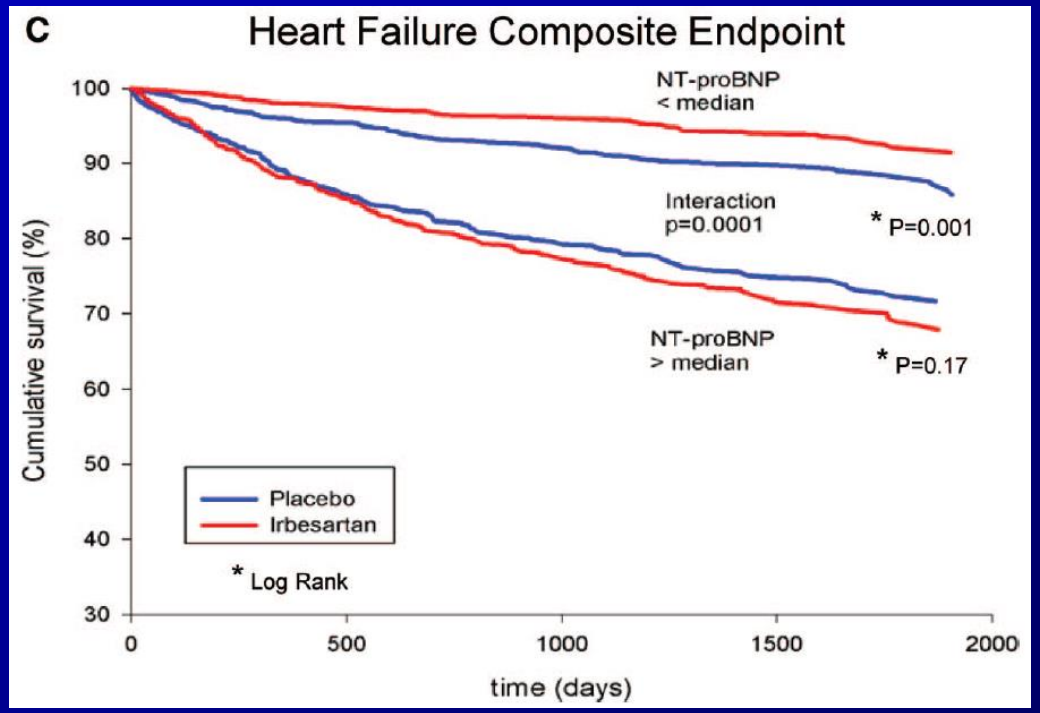
NT-pro BNP (pg/mL)	< 133	134 – 338	339 – 963	> 964
Median NT-pro BNP (pg/mL)	73	214	551	1720
# of Patients	870	867	873	870

Zile et al. J Cardiovasc Trans Res 2013

Irbesartan improves outcome in HFpEF pts with lower BNP



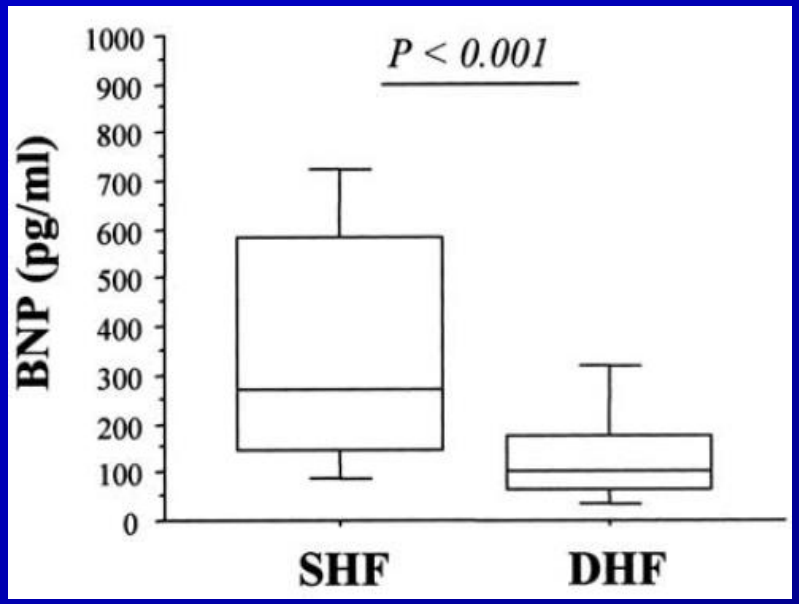


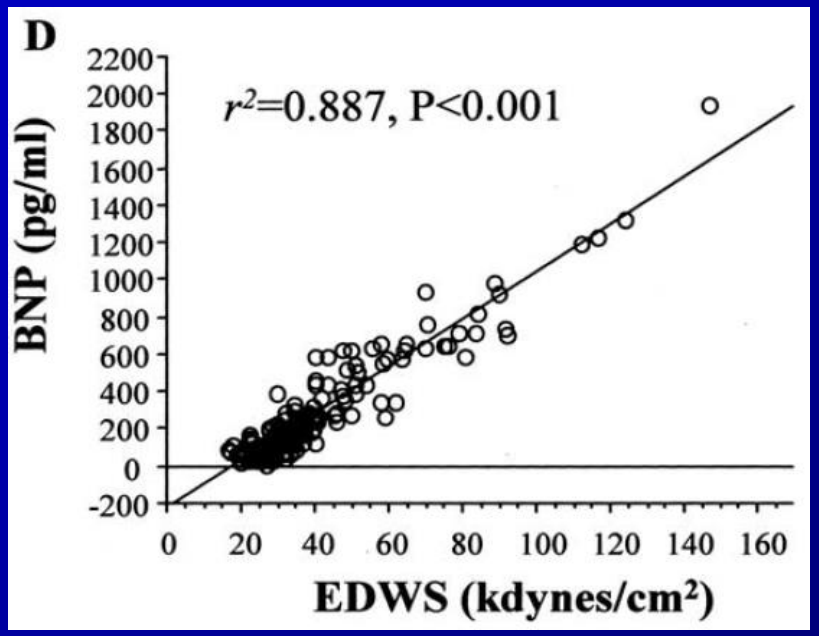


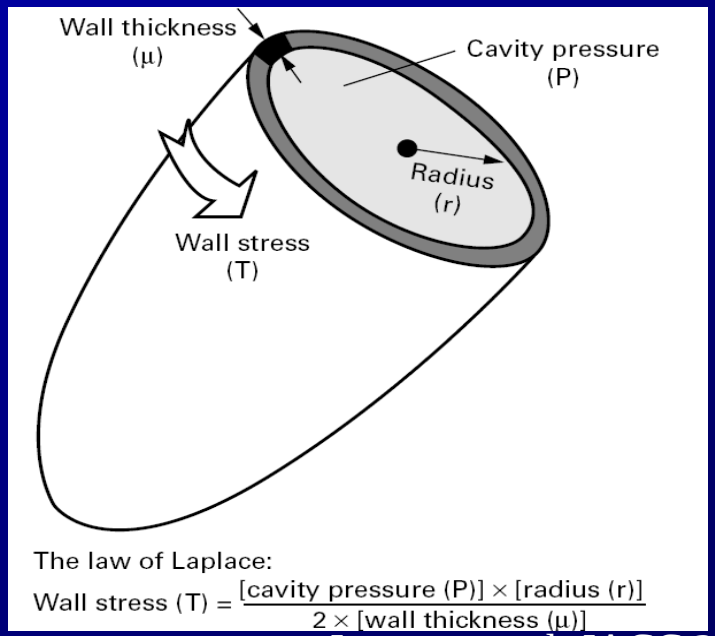
Median:
339 pg/ml
(=40 pmol/l)

Anand et al,
Circ HF 2011;4:569

Pitfalls: BNP release strongly reflects wall stress







Iwanaga et al, JACC 2006;47:742

HFpEF: staging disease: Role for biomarkers?

Inflammation	**Neurohormones**	**Extracardiac involvement**
CRP, TNF-α, TGF-β	Norepinephrine	Micro-albuminuria
IL-1, 6, 8, 10, 16, 18	Angiotensin II	Cystatin-C
Pentraxin-3	Aldosterone	NGAL, NAG
Galectin-3		T3
GDF-15	**Lipids/Adipokines**	
Oxidative stress	Adiponectin	
H2O2, malondialdehyde	Resistin, leptin, apelin	
MPO, antioxidant enzymes		
Urinay/plasma isoprostanes	**Myocyte injury/apoptosis**	
Nitrotyrosine	Troponins	
Extracellular matrix remod		
MMPs; TIMPs	**Myocyte stress**	
Collagen propeptides	(nt-pro)BNP, ANP	
Galectin-3	ST2, GDF-15	

V Kimmenade et al. Clin Chem 2012

HFpEF: Understand pathophysiology; before we can treat it!!!

Ageing
↓ CV reserve

Female gender
↑ LV stiffening

Comorbidities
Systemic + cardiac effects

Diastolic dysfx

Endothelial dysfx
Inflammation
Oxidative stress

Impaired
Myocardial energetics

Atrial fibrillation

Pulmonary hypertension
RV dysfunction

Structural remodeling
*LA dilatation/*LV hypertrophy

HFpEF

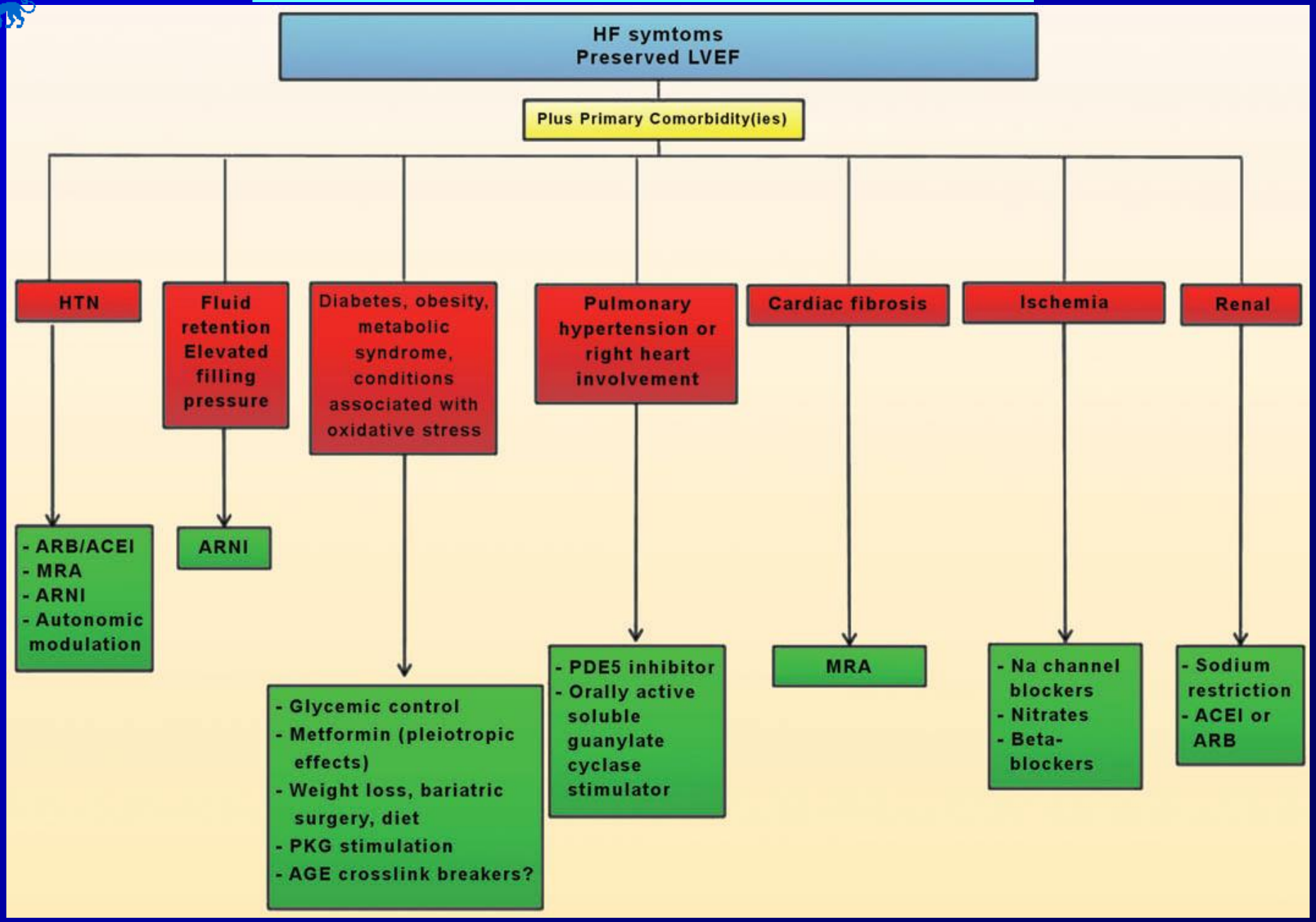
Coronary artery disease

Vascular dysfunction
*Stiffening
*Impaired vasodilatory reserve

Chronotropic incompetence
Autonomic dysfunction

Subtle systolic LV dysfx

HFpEF: patient tailored therapy



Senni M et al. Eur Heart J 2014;aug 7

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