Diastolic Heart Failure

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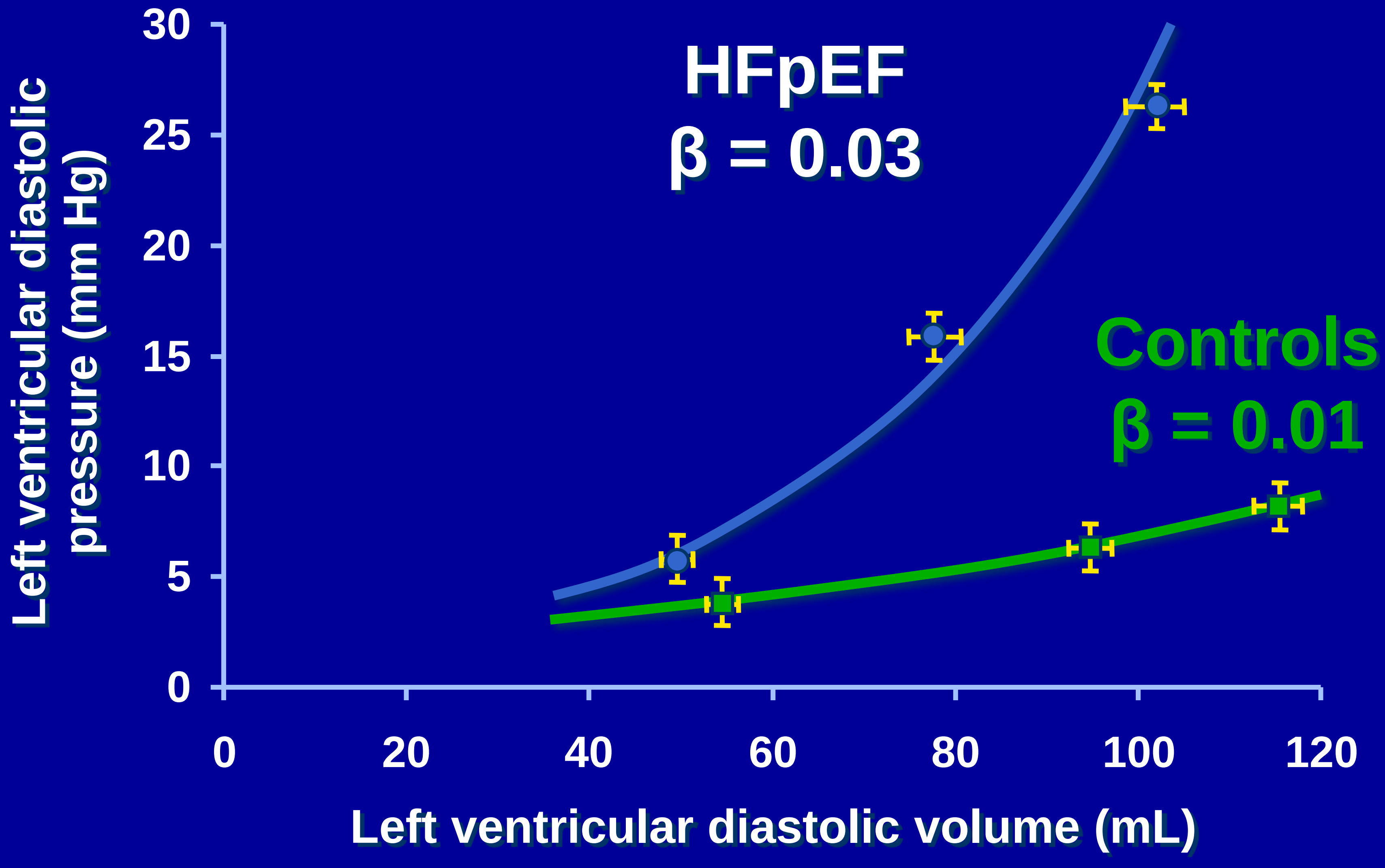
Diastolic Heart Failure
Clinical Definition

A clinical syndrome characterized by the symptoms and signs of HF, a preserved ejection fraction (≥50%), and abnormal diastolic function. Recently the most commonly used term is HFpEF.

↑ Stiffness in HFpEF



Zile M et al, NEJM, 2004

Global CV Reserve Dysfunction in HFpEF

Borlaug BA et al JACC 2010;56:845

PAT | **RHI** | **% of subjects**

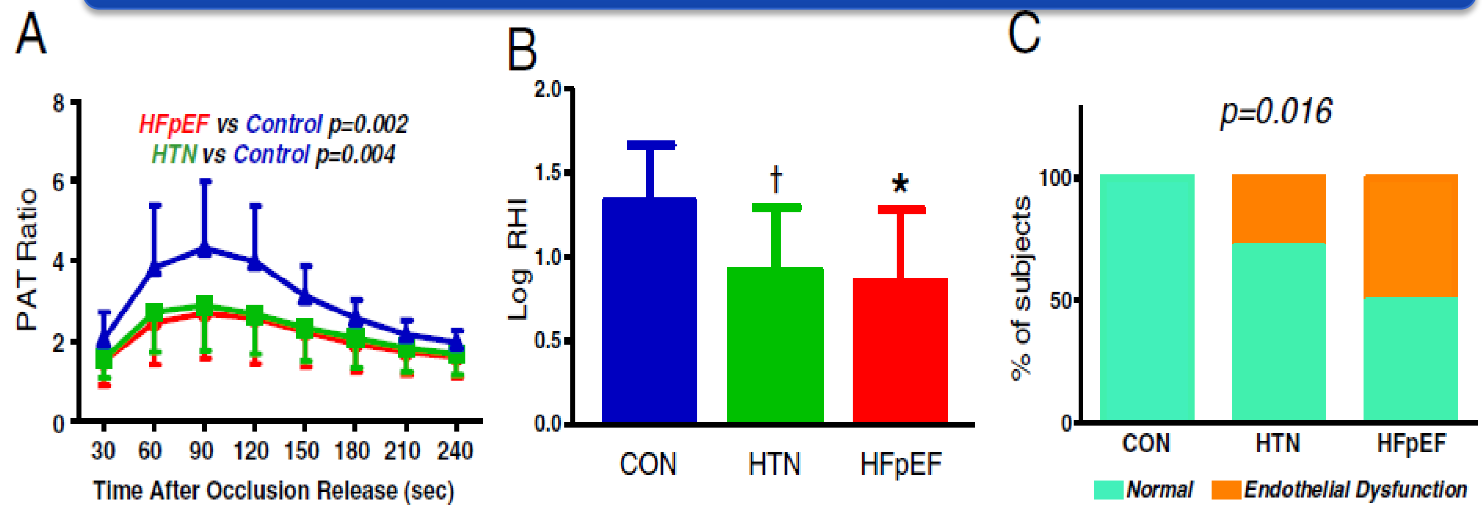


Figure 1 Assessment of Endothelial Function

PAT=Peripheral Arterial Tonometry
RHI=Reactive Hyperemia Index

(A) Increases in peripheral arterial tonometry (PAT) amplitude with reactive hyperemia are diminished in heart failure with preserved ejection fraction (HFpEF) patients **(red line)** and hypertensive subjects **(green line)** compared with control subjects **(blue line)**, consistent with endothelial dysfunction. **(B)** Mean reactive hyperemia index (log RHI) is reduced in HFpEF subjects **(red bar)** and hypertensive subjects **(green bar)** compared with control **(blue bar)**. **(C)** Compared with control, endothelial dysfunction **(orange area)** was more prevalent in HFpEF subjects (42%, $p < 0.05$) and tended to be more common in hypertensive subjects (28%, $p = 0.056$). **Green area of bars** indicates normal. *$p < 0.05$ HFpEF versus control; †$p < 0.05$ hypertension versus control. CON = control; HTN = hypertension.

Global CV Reserve Dysfunction in HFpEF

Borlaug BA et al JACC 2010;56:845

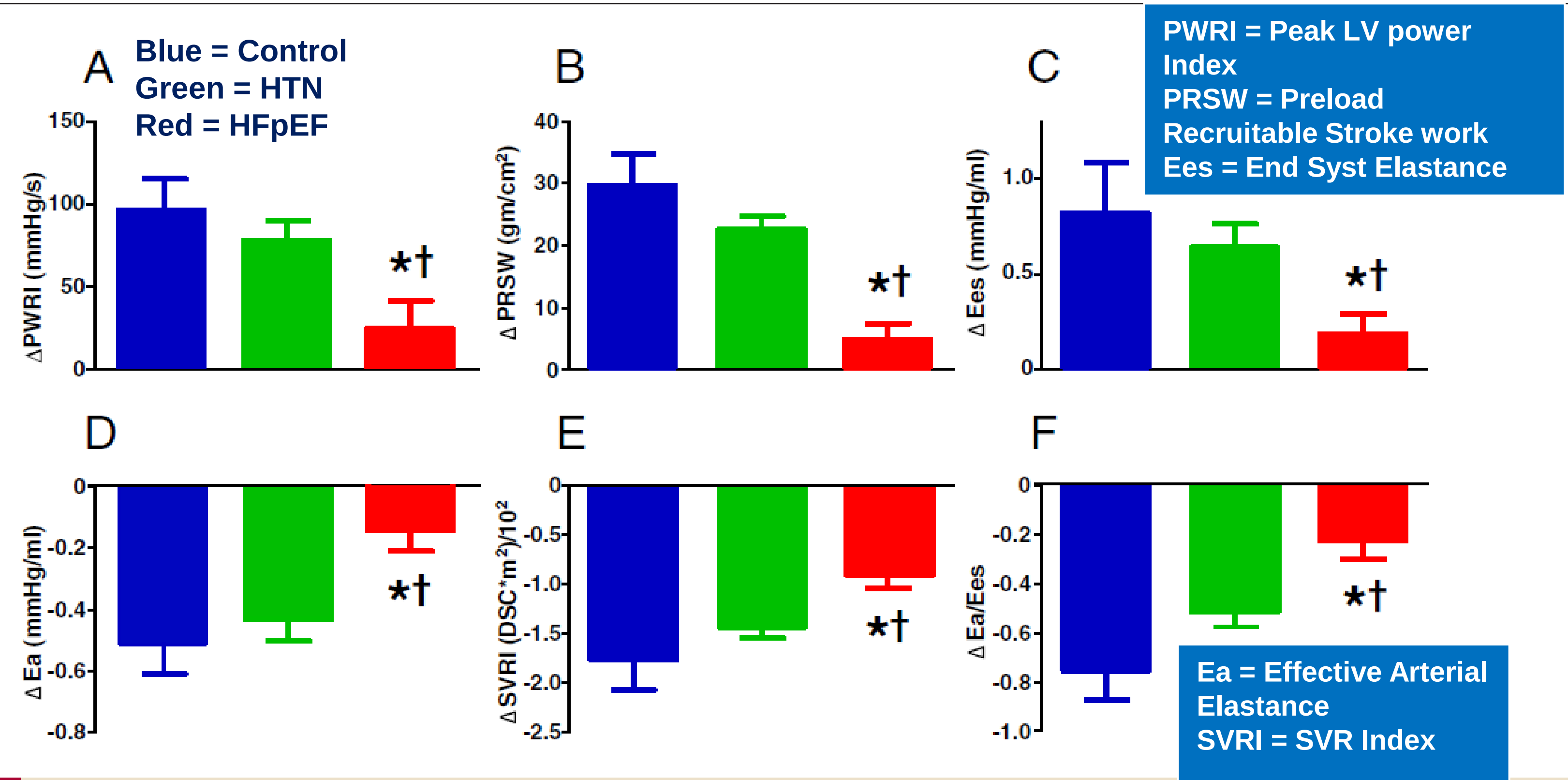


Figure 2 **Contractile, Vascular, and Coupling Reserve With Low-Level Exercise (20 W)**

(A to C) Compared with both control subjects **(blue bars)** and hypertensive subjects **(green bars)**, contractile reserve was blunted in heart failure with preserved ejection fraction (HFpEF) **(red bars)** at 20 W, evidenced by blunted increases in end-systolic elastance (Ees), pre-load recruitable stroke work (PRSW), and peak power index (PWRI). **(D, E)** Vasodilation (reduction in arterial elastance [Ea] and systemic vascular resistance index [SVRI]) was also impaired in HFpEF. **(F)** These deficits led to abnormal ventricular-arterial coupling responses (i.e., less reduction in Ea/Ees ratio) in HFpEF subjects compared with controls and hypertensive subjects. *p < 0.05 versus hypertension; †p < 0.05 versus control (analysis of variance after Bonferroni).

Vasodilation in HFrEF and HApEF

Schwarzenberg s et al JACC 2012;59:442

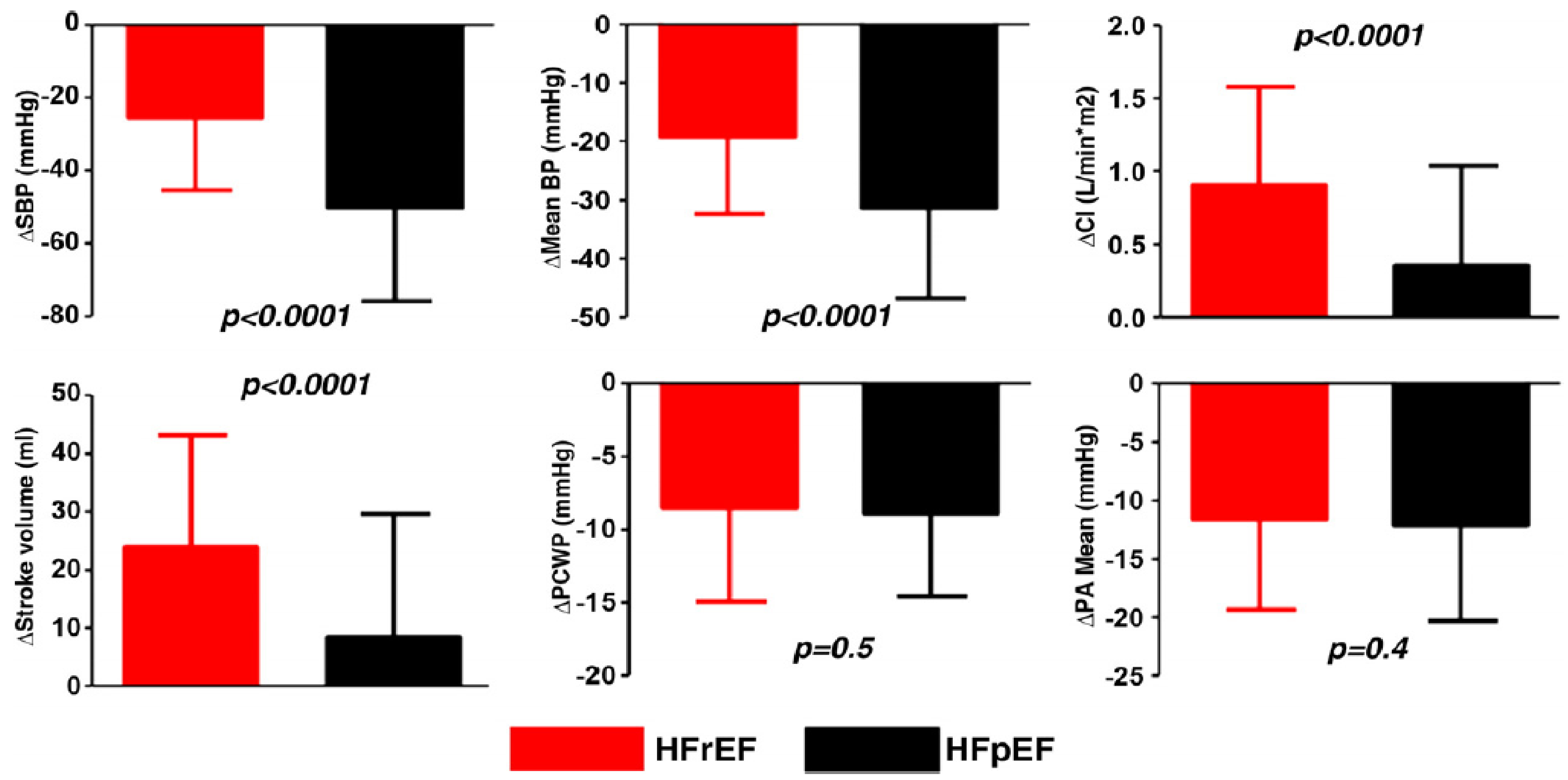


Figure 2 Peripheral and Central Hemodynamic Changes With Nitroprusside

Nitroprusside caused greater blood pressure (BP) reduction in heart failure with preserved ejection fraction (HFpEF) **(black)** compared with heart failure with reduced ejection fraction (HFrEF) **(red)**, whereas augmentation in stroke volume (SV) and cardiac output were greater in HFrEF compared with HFpEF. PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

Exercise intolerance in patients with HFpEF

Haykowski et al JACC 2011;58:265

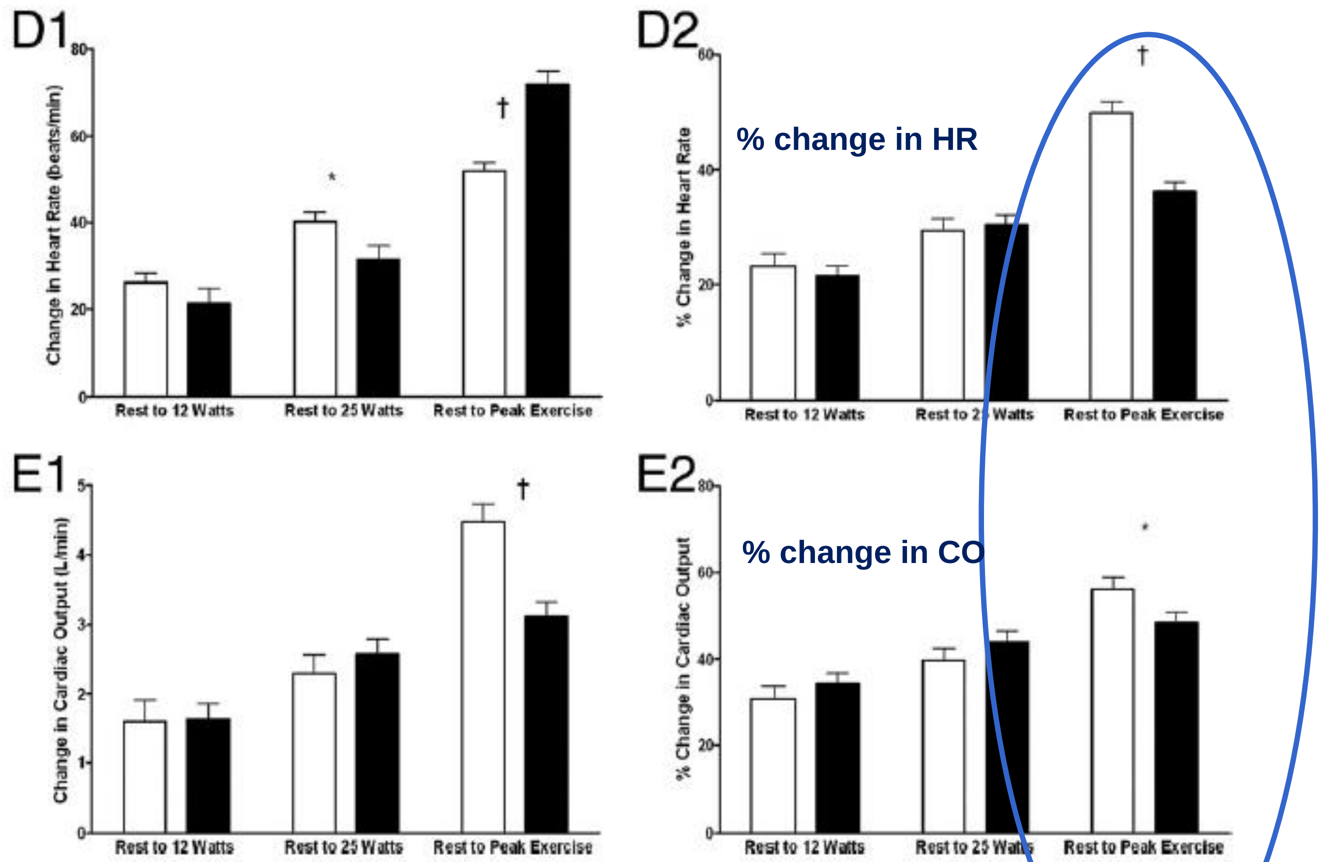


Figure 3 Comparison of Change and Percentage of Change From Rest to 12 W, Rest to 25 W, and Rest to Peak Exercise in HFPEF Patients and HCs

End-diastolic volume **(A1 and A2)**, end-systolic volume **(B1 and B2)**, stroke volume **(C1 and C2)**, and cardiac output **(E1 and E2)** adjusted for sex and body surface area. Heart rate **(D1 and D2)** adjusted for sex (*p < 0.05, †p < 0.01). **Solid bars** = HFPEF patients; **open bars** = HCs. Abbreviations as in Figure 1.

Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

A Community-Based Study

Carolyn S. P. Lam, MBBS,*† Véronique L. Roger, MD, MPH,* Richard J. Rodeheffer, MD,* Barry A. Borlaug, MD,* Felicity T. Enders, PhD,‡ Margaret M. Redfield, MD*

Rochester, Minnesota; and Singapore, Singapore

Objectives This study sought to define the prevalence, severity, and significance of pulmonary hypertension (PH) in heart failure with preserved ejection fraction (HFpEF) in the general community.

Background Although HFpEF is known to cause PH, its development is highly variable. Community-based data are lacking, and the relative contribution of pulmonary venous versus pulmonary arterial hypertension (HTN) to PH in HFpEF is unknown. We hypothesized that PH would be a marker of symptomatic pulmonary congestion, distinguishing HFpEF from pre-clinical hypertensive heart disease.

Methods This community-based study of 244 HFpEF patients (age 76 ± 13 years; 45% male) was followed up using Doppler echocardiography over 3 years. Control subjects were 719 adults with HTN without HF (age 66 ± 10 years; 44% male). Pulmonary artery systolic pressure (PASP) was derived from the tricuspid regurgitation velocity and PH defined as PASP >35 mm Hg. Pulmonary capillary wedge pressure (PCWP) was estimated from the ratio of early transmitral flow velocity to early mitral annular diastolic velocity.

Results In HFpEF, PH was present in 83% and the median (25th, 75th percentile) PASP was 48 (37, 56) mm Hg. PASP increased with PCWP ($r = 0.21$; $p < 0.007$). Adjusting for PCWP, PASP was higher in HFpEF than HTN ($p < 0.001$). The PASP distinguished HFpEF from HTN with an area under the receiver-operating characteristic curve of 0.91 ($p < 0.001$) and strongly predicted mortality in HFpEF (hazard ratio: 1.3 per 10 mm Hg; $p < 0.001$).

Conclusions PH is highly prevalent and often severe in HFpEF. Although pulmonary venous HTN contributes to PH, it does not fully account for the severity of PH in HFpEF, suggesting that a component of pulmonary arterial HTN also contributes. The potent effect of PASP on mortality lends support for therapies aimed at pulmonary arterial HTN in HFpEF. (J Am Coll Cardiol 2009;53:1119–26)

Pulmonary Hypertension and HFpEF

Lam CSP, JACC 2009;53:1119

PAS > 35 mmHg

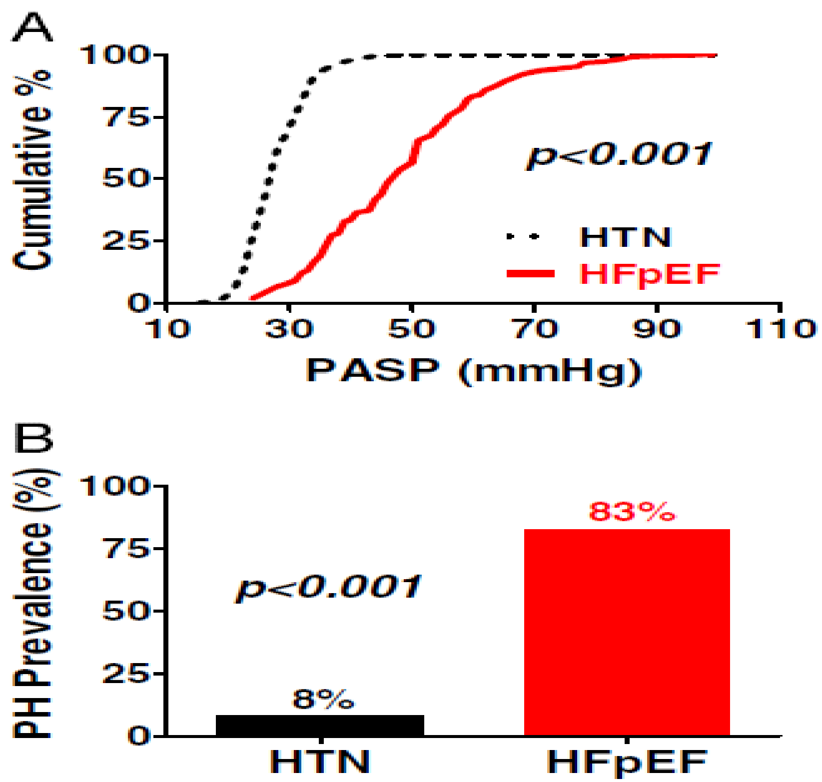


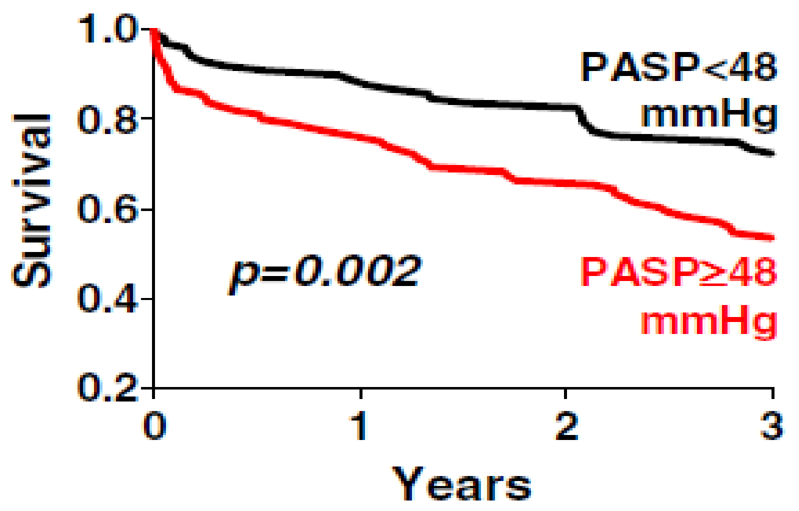
Figure 1 **Cumulative Frequency Distribution of PASP and Prevalence of PH by Subject Group**

In patients with heart failure and preserved ejection fraction (HFpEF) (in **red**), the cumulative frequency distribution of pulmonary artery systolic pressure (PASP) was shifted toward higher pressures **(A)**, whereas the prevalence of pulmonary hypertension (PH) was markedly increased **(B)** compared with subjects with hypertension (HTN) (in **black**) without heart failure in the community.

Pulmonary Hypertension and HFpEF

Lam CSP, JACC 2009;53:1119

Median PASP 48 mmHg



	Number remaining			
PASP<48 mmHg	98	86	80	44
PASP≥48 mmHg	105	78	67	38

Figure 4 Kaplan-Meier Survival Curves in HFpEF Patients With PASP Above and Below the Median

HFpEF patients with PASP above the median value of 48 mm Hg (in **red**) had reduced survival compared with patients with PASP <48 mm Hg (in **black**) over 3 years (log-rank p = 0.002). Abbreviations as in Figure 1.

Pulmonary Hypertension and HFpEF

Lam CSP, JACC 2009;53:1119

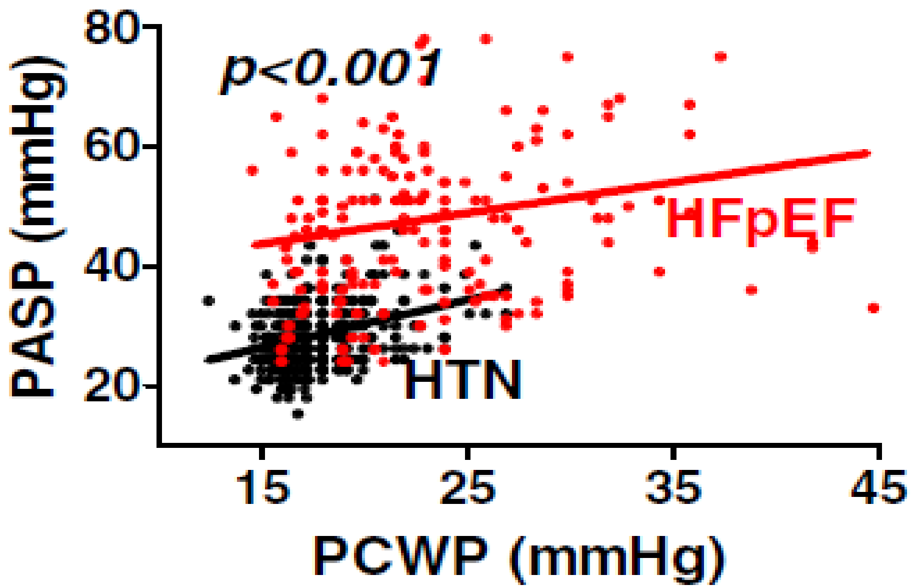
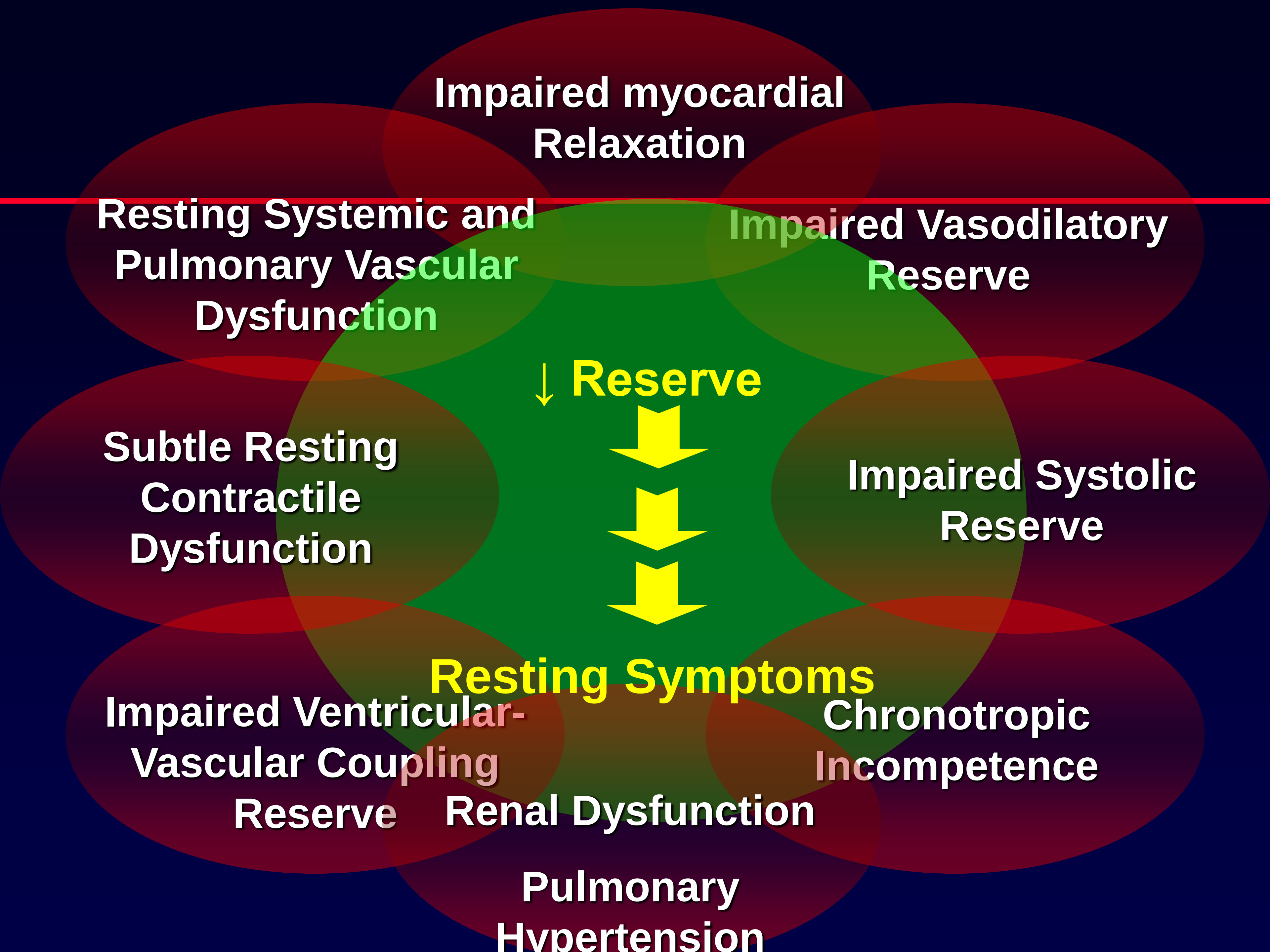
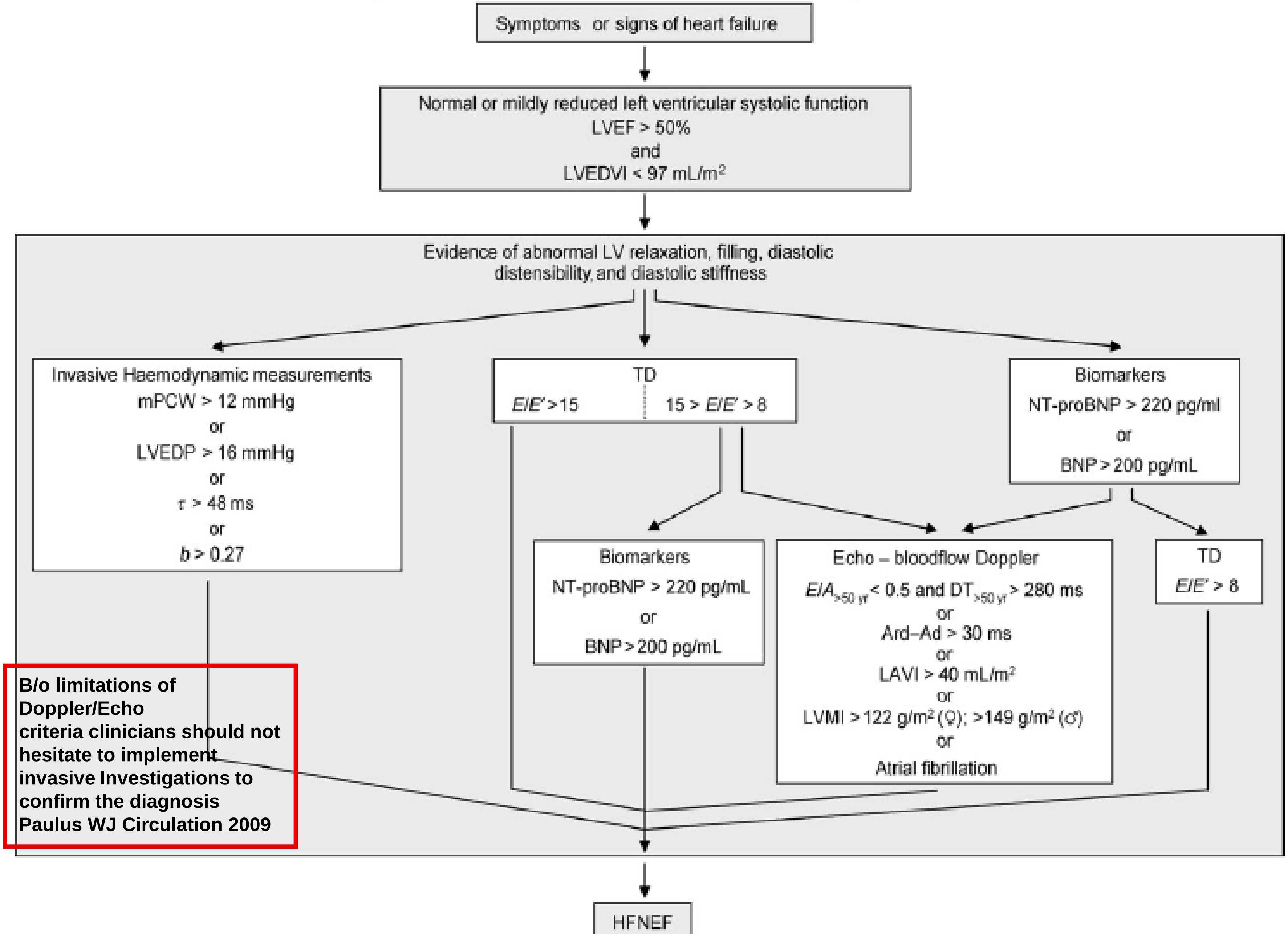


Figure 2 **Association of PASP With Pulmonary Venous Hypertension**

PASP increased with pulmonary capillary wedge pressure (PCWP) in patients with HFpEF, as well as in subjects with HTN without heart failure, but remained higher in HFpEF than HTN after adjusting for PCWP ($p < 0.001$). Raw data points and linear regression line for the association are shown for HFpEF (in **red**) and HTN (in **black**). Abbreviations as in Figure 1.


Impaired myocardial Relaxation
Resting Systemic and Pulmonary Vascular Dysfunction
Impaired Vasodilatory Reserve
↓ Reserve
Subtle Resting Contractile Dysfunction
Impaired Systolic Reserve
Resting Symptoms
Impaired Ventricular-Vascular Coupling Reserve
Chronotropic Incompetence
Renal Dysfunction
Pulmonary Hypertension

How to diagnose HFNEF

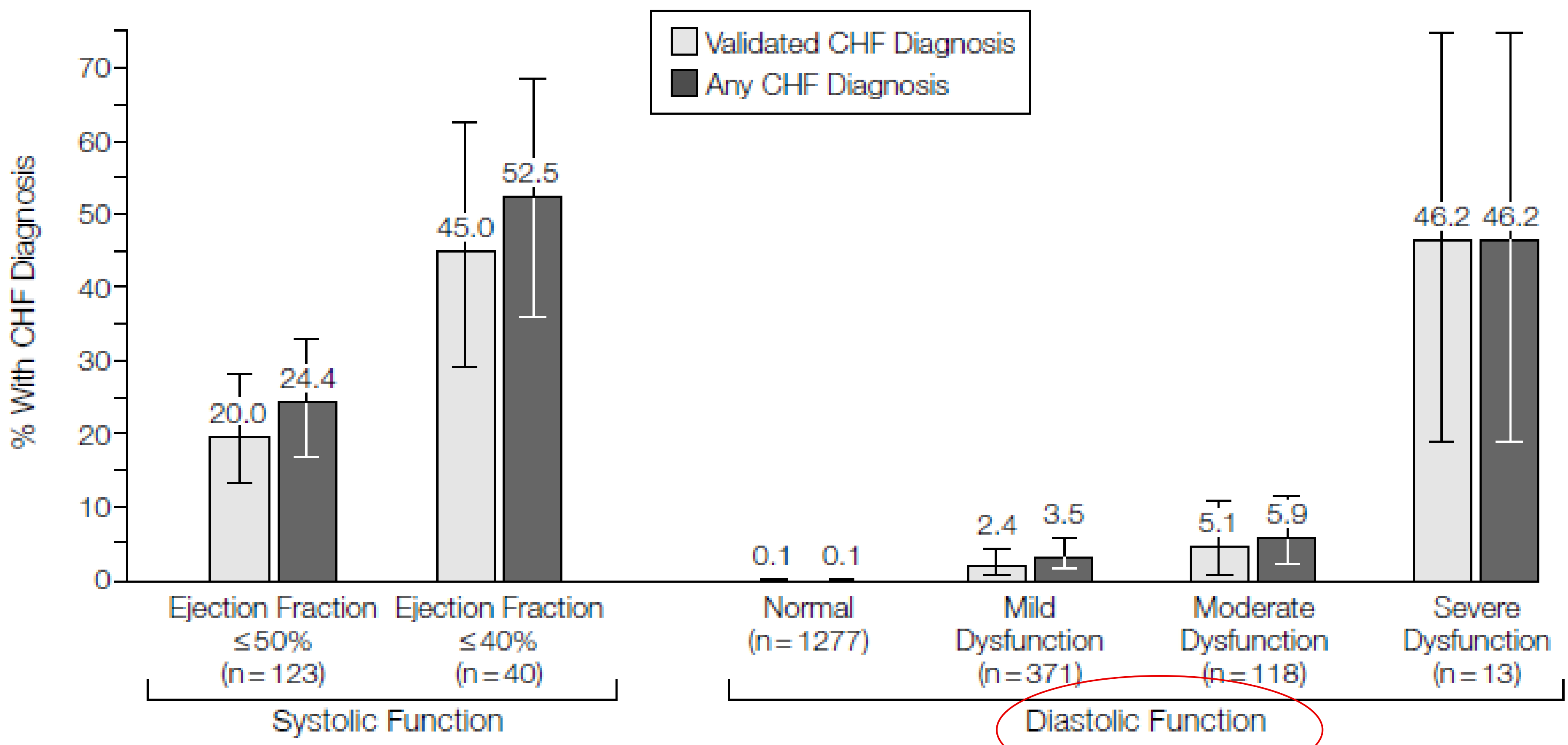


B/o limitations of Doppler/Echo criteria clinicians should not hesitate to implement invasive Investigations to confirm the diagnosis
Paulus WJ Circulation 2009

Systolic and Diastolic Dysfunction

Redfield M et al JAMA 2003;289:194

Figure 3. Relationship Between Congestive Heart Failure (CHF) Diagnosis and Ventricular Dysfunction



Systolic and Diastolic Dysfunction

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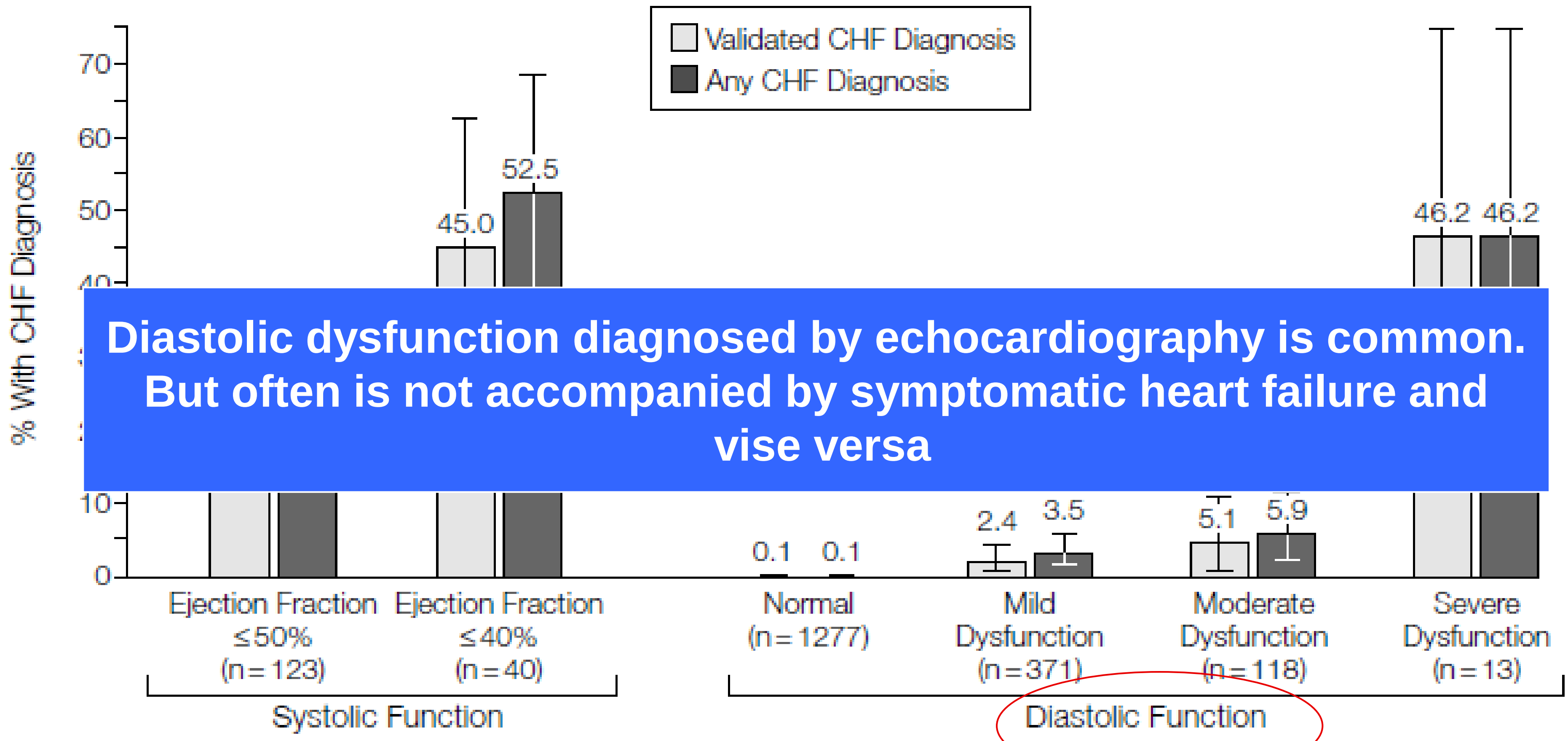
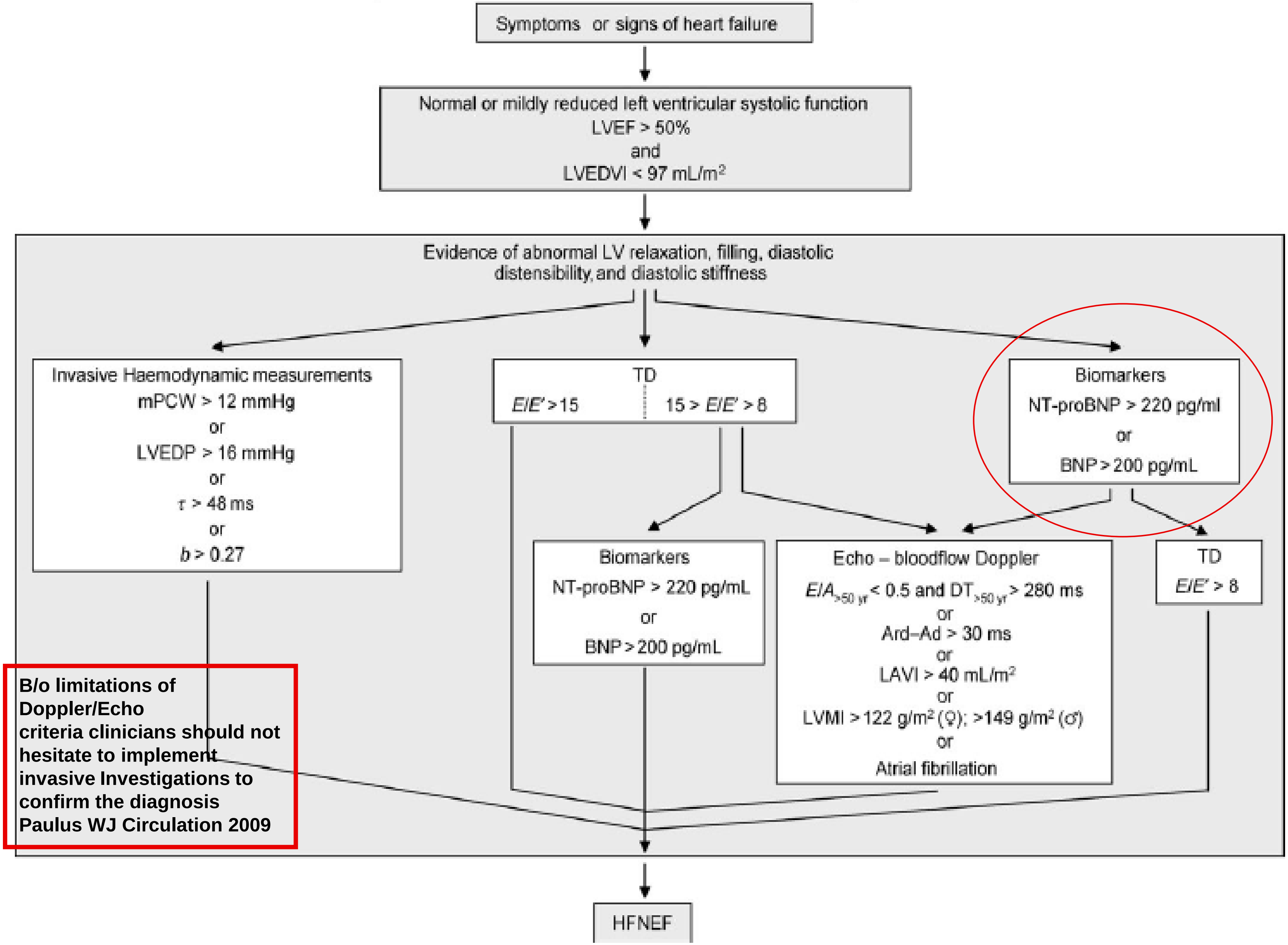
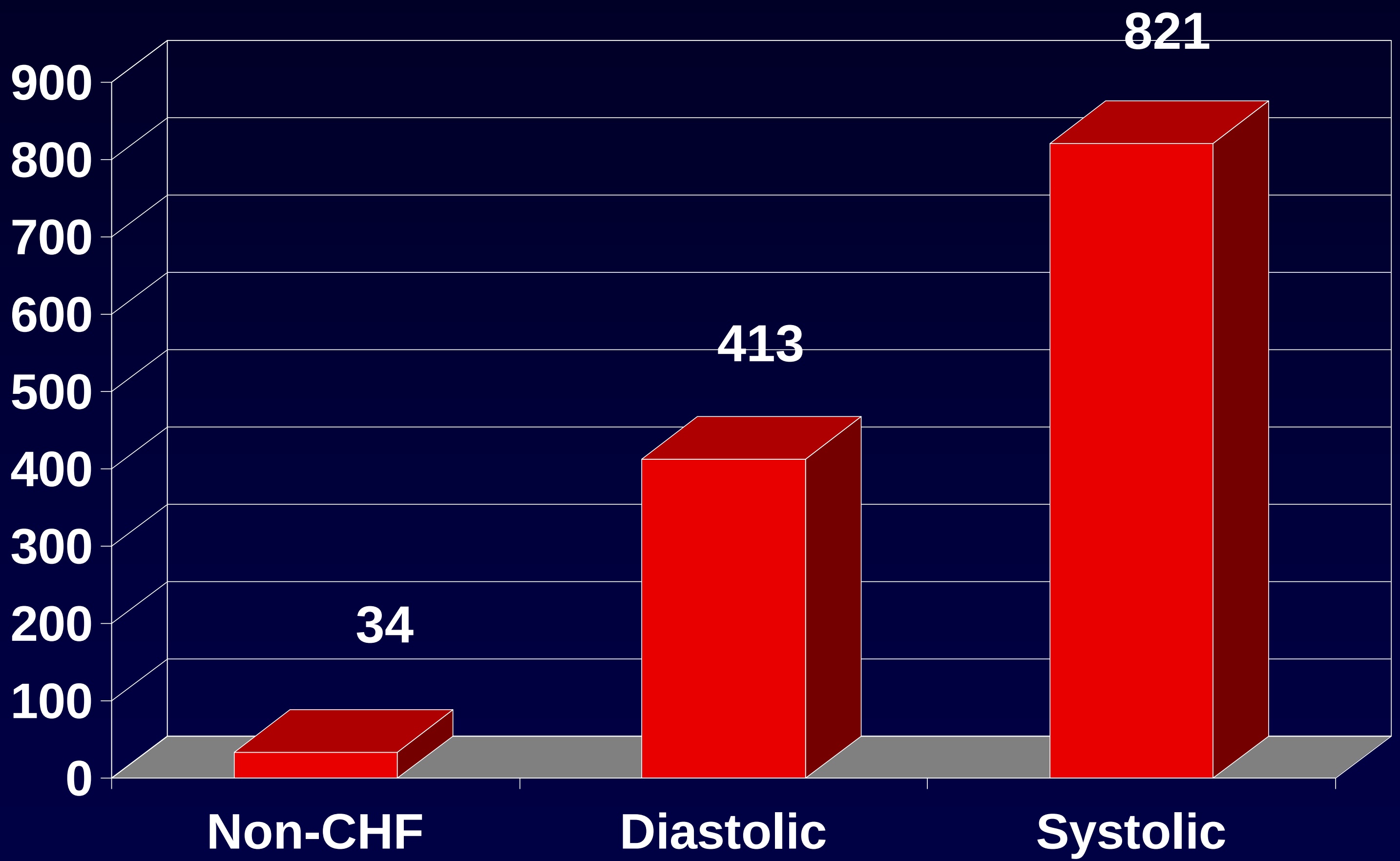


Diastolic dysfunction diagnosed by echocardiography is common. But often is not accompanied by symptomatic heart failure and vise versa

How to diagnose HFNEF



BNP IN SYSTOLIC OR DIASTOLIC DYSFUNCTION

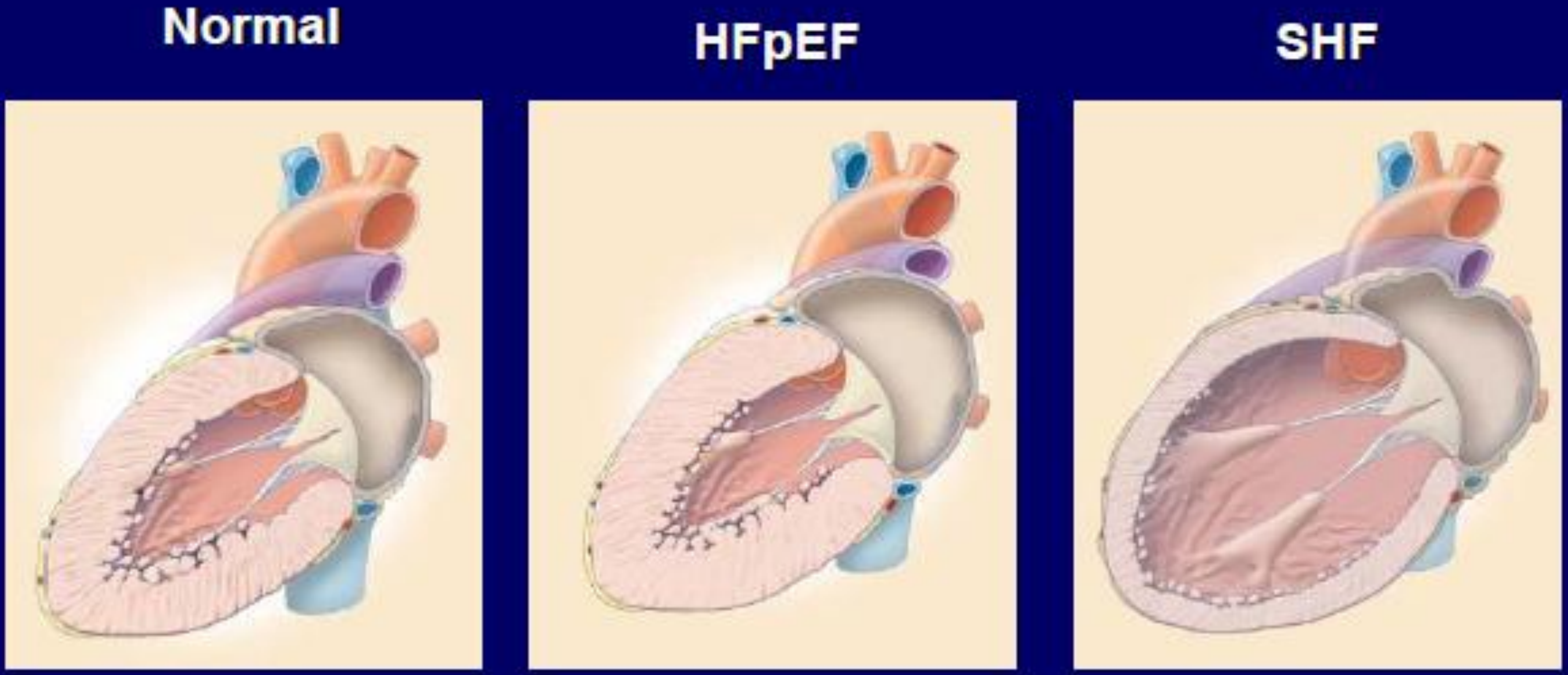


Breathing Not Properly Multinational Study – 447 patients with acute dyspnea in the ED

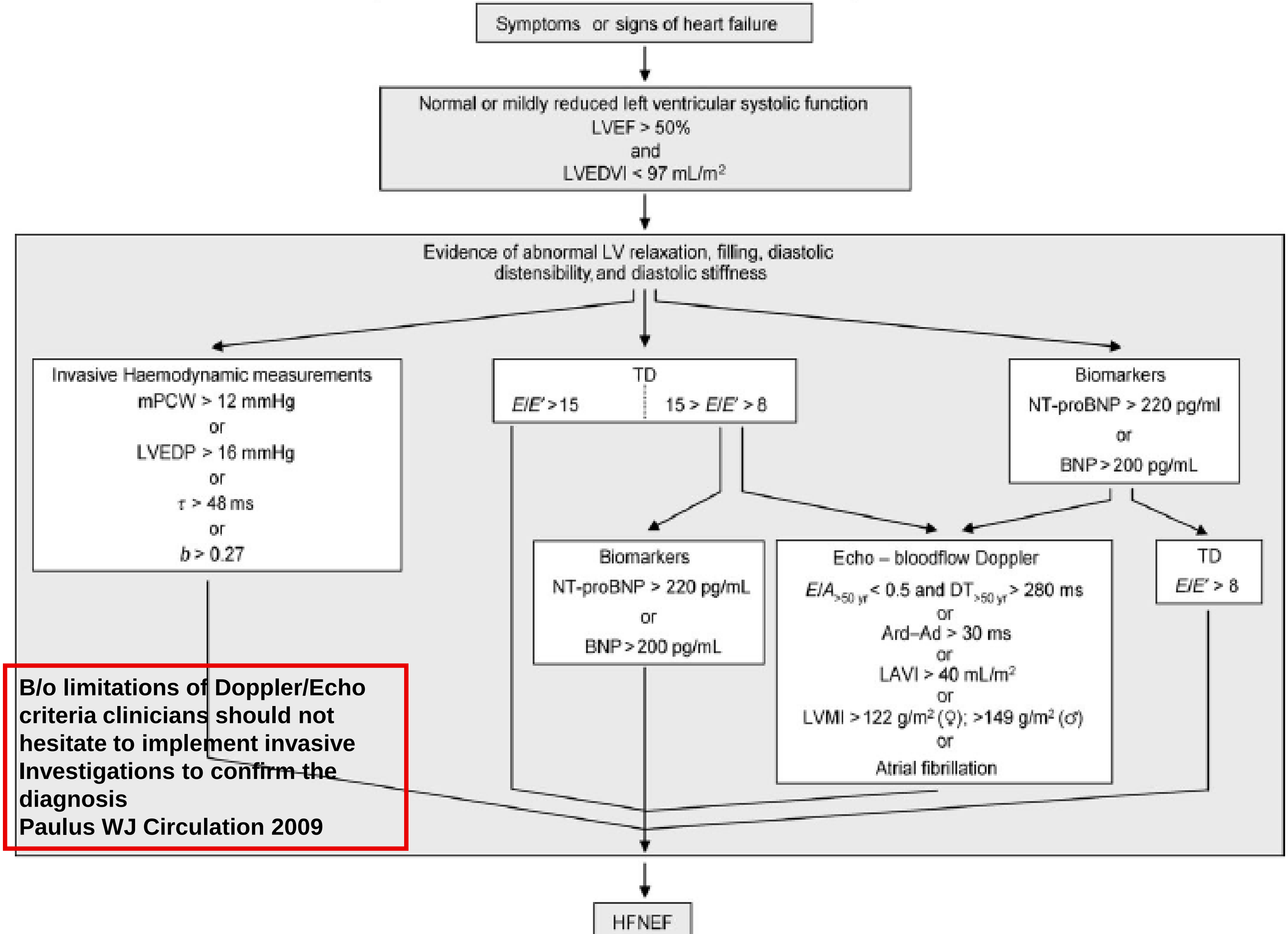
Maisel et al. JACC. 2003;41:2010-2017

Why is BNP Lower in HFpEF?

- Wall stress → BNP production
- Wall stress = P * radius/wall thickness



How to diagnose HFNEF



B/o limitations of Doppler/Echo criteria clinicians should not hesitate to implement invasive Investigations to confirm the diagnosis
Paulus WJ Circulation 2009

Exercise Hemodynamics for Early Diagnosis of HFpEF

Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure With Preserved Ejection Fraction

Barry A. Borlaug, MD; Rick A. Nishimura, MD; Paul Sorajja, MD;
Carolyn S.P. Lam, MBBS; Margaret M. Redfield, MD

Background**—**When advanced, heart failure with preserved ejection fraction (HFpEF) is readily apparent. However, diagnosis of earlier disease may be challenging because exertional dyspnea is not specific for heart failure, and biomarkers and hemodynamic indicators of volume overload may be absent at rest.

Methods and Results**—**Patients with exertional dyspnea and ejection fraction $>$50% were referred for hemodynamic catheterization. Those with no significant coronary disease, normal brain natriuretic peptide assay, and normal resting hemodynamics (mean pulmonary artery pressure $<$25 mm Hg and pulmonary capillary wedge pressure [PCWP] $<$15 mm Hg) (n=55) underwent exercise study. The exercise PCWP was used to classify patients as having HFpEF (PCWP $\geq$25 mm Hg) (n=32) or noncardiac dyspnea (PCWP $<$25 mm Hg) (n=23). At rest, patients with HFpEF had higher resting pulmonary artery pressure and PCWP, although all values fell within normal limits. Exercise-induced elevation in PCWP in HFpEF was confirmed by greater increases in left ventricular end-diastolic pressure and was associated with blunted increases in heart rate, systemic vasodilation, and cardiac output. Exercise-induced pulmonary hypertension was present in 88% of patients with HFpEF and was related principally to elevated PCWP, as pulmonary vascular resistances dropped similarly in both groups. Exercise PCWP and pulmonary artery systolic pressure were highly correlated. An exercise pulmonary artery systolic pressure $\geq$45 mm Hg identified HFpEF with 96% sensitivity and 95% specificity.

Conclusions**—**Euvolemic patients with exertional dyspnea, normal brain natriuretic peptide, and normal cardiac filling pressures at rest may have markedly abnormal hemodynamic responses during exercise, suggesting that chronic symptoms are related to heart failure. Earlier and more accurate diagnosis using exercise hemodynamics may allow better targeting of interventions to treat and prevent HFpEF progression. (*Circ Heart Fail*. **2010;3:588-595.**)

Exercise Hemodynamics for Early Diagnosis of HFpEF

Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure With Preserved Ejection Fraction

55 Patients with exertional dyspnea and LVEF ≥50%

No obstructive CAD

Normal BNP levels and

Mean PCWP <15mmHg

Underwent exercise study in the cath lab

symptoms are related to heart failure. Earlier and more accurate diagnosis using exercise hemodynamics may allow better targeting of interventions to treat and prevent HFpEF progression. (*Circ Heart Fail*. 2010;3:588-595.)

Exercise Hemodynamics for Early Diagnosis of HFpEF

Borlaug BA et al Circ HF 2010;3:588

NCD – Non Cardiac Dyspnea

Table 1. Baseline Characteristics

Characteristic	NCD (n=23)	HFpEF (n=32)	*P*
Age, y	47±17	65±13	<0.001
Female sex, %	65	72	0.6
White race, %	100	91	0.3
Body mass index, kg/m^2	27.3±5.5	32.0±5.9	0.004
Obesity, %	40	56	0.2
Hypertension, %	57	72	0.2
Diabetes, %	22	16	0.6
Atrial fibrillation, %	9	6	0.7
NYHA class II/III	20/3	27/5	0.8
Glomerular filtration rate, mL/min	95±36	86±31	0.3
BNP, pg/mL	49±54	71±49	0.3
NT-proBNP, pg/mL	38±22*	104±62†	0.07
Hemoglobin, g/dL	13.2±1.5	13.6±1.2	0.3
β-blockers, %	35	44	0.5
ACEI or ARB, %	30	38	0.6
Diuretic, %	35	53	0.18

Exercise Hemodynamics for Early Diagnosis of HFpEF

Borlaug BA et al Circ HF 2010;3:588

Table 2. Clinical Evaluation Before Hemodynamic Assessment

Evaluation	NCD (n=23)	HFpEF (n=32)	*P*
Radiographic			
Cardiomegaly, %	4	25	0.04
Echocardiographic			
LVEF, %	61±6	62±7	0.4
LV mass, g/m^2	84±22	92±20	0.16
LV hypertrophy, %	17	34	0.06
LA enlargement, %	38	65	0.06
E-wave, cm/s	80±20	80±20	0.8
A-wave, cm/s	60±30	80±30	0.08
E/A ratio	1.3±0.5	1.1±0.5	0.10
Medial E′, cm/s	10±3	9±3	0.02
E/E′ ratio	8±3	10±3	0.04
E/E′ ratio >15, %	5	9	0.5
Estimated PASP, mm Hg	31±6	33±8	0.4
PASP >35 mm Hg, %	28	26	0.9
ESC HFpEF diagnosis, %	24	34	0.4

Exercise Hemodynamics for Early Diagnosis of HFpEF

Borlaug BA et al Circ HF 2010;3:588

Table 3. Resting Hemodynamics

Hemodynamics	NCD (n=23)	HFpEF (n=32)	*P*
Heart rate, bpm	72±12	70±9	0.5
Arterial systolic pressure, mm Hg	131±19	137±23	0.3
Arterial mean pressure, mm Hg	88±12	94±14	0.4
RA pressure, mm Hg	4±2	5±2	0.04
PASP, mm Hg	24±6	31±7	0.0003
Mean PAP, mm Hg	15±4	19±4	0.001
End-expiration PCWP, mm Hg	9±3	11±2	0.002
Average PCWP, mm Hg	9±3	11±2	0.003
LVEDP, mm Hg	12±3	13±2	0.13
CI, L/min per m^2	3.2±0.8	2.8±0.6	0.04
PVRI, Wood unit×m^2	2.1±1.0	3.2±1.5	0.006
SVRI, DSC×m^2	2300±700	2800±600	0.02

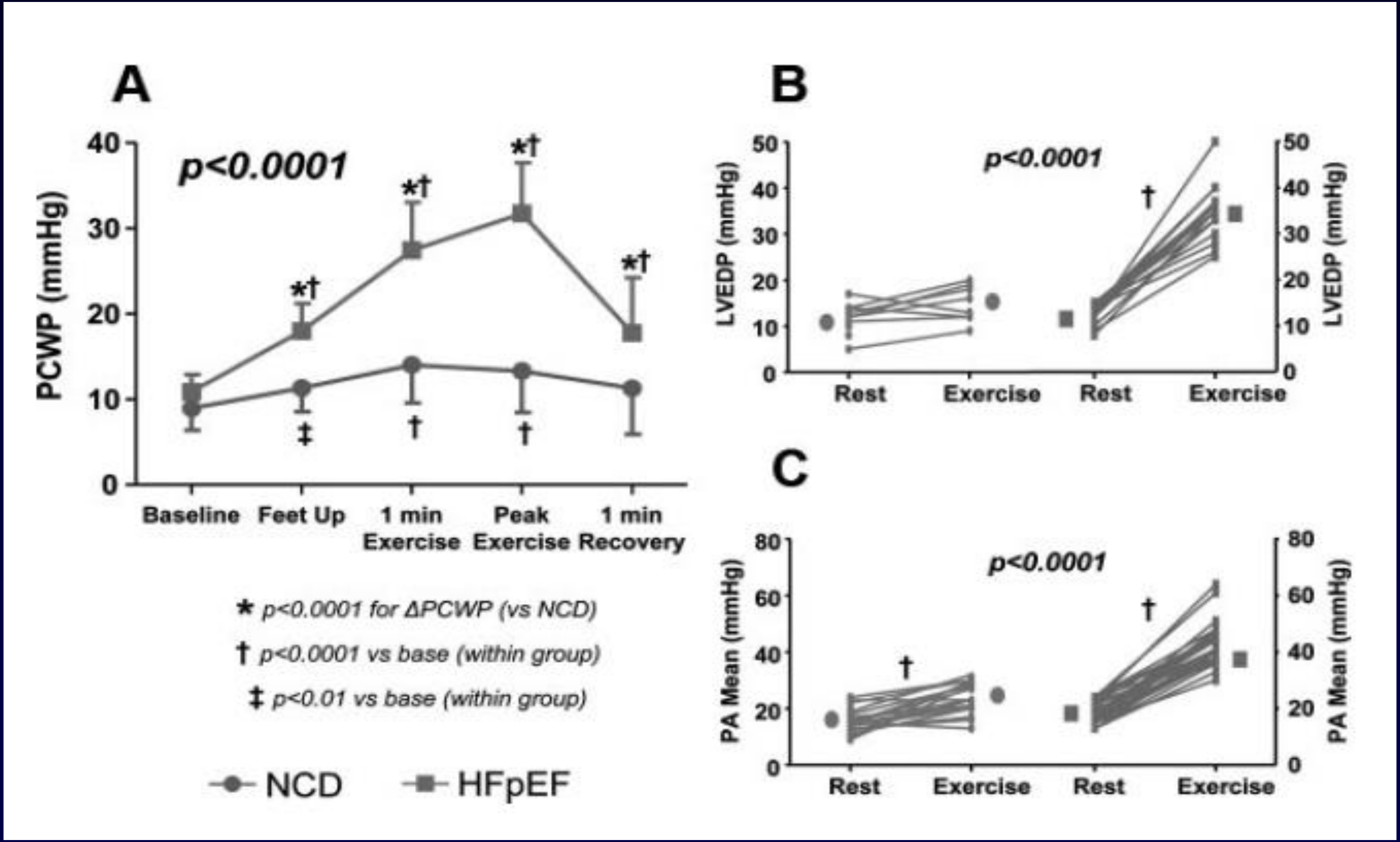
DSC indicates dynes second/cm^5.

Table 4. Exercise Hemodynamics

Hemodynamics	NCD (n=23)	HFpEF (n=32)	*P**
Arm/leg exercise	3/20	10/22	0.11
Peak leg ergometry workload, Watts	64±36	47±19	0.06
Heart rate, bpm	122±24	104±21	0.004
Arterial systolic pressure, mm Hg	153±26	182±34	0.002
Arterial mean pressure, mm Hg	101±15	125±20	0.0001
RA pressure, mm Hg	6±3†	14±4‡	0.0004
PASP, mm Hg	35±7	59±11	<0.00001
Mean PAP, mm Hg	23±5	43±7	<0.00001
End-expiration PCWP, mm Hg	13±5	32±6	<0.00001
Average PCWP, mm Hg	11±5	28±7	<0.00001
LVEDP, mm Hg	14±4	34±6	<0.00001
CI, L/min per m^2	6.7±1.4	4.9±1.0	<0.0001
PVRI, Wood unit×m^2	1.9±0.9	2.4±1.2	0.17
Exercise-induced PH, %	...	88	...
SVRI, DSC×m^2	1300±400	1900±400	0.0007

Exercise Hemodynamics for Early Diagnosis of HFpEF

Borlaug BA et al Circ HF 2010;3:588



HFpEF in Outpatients With Unexplained Dyspnea

Penica M et al JACC 2010;55:1701

RE =Rest
HG = Hand grip
LL = Leg Lifting
NI = Nitroprusside
DO = Dopamine

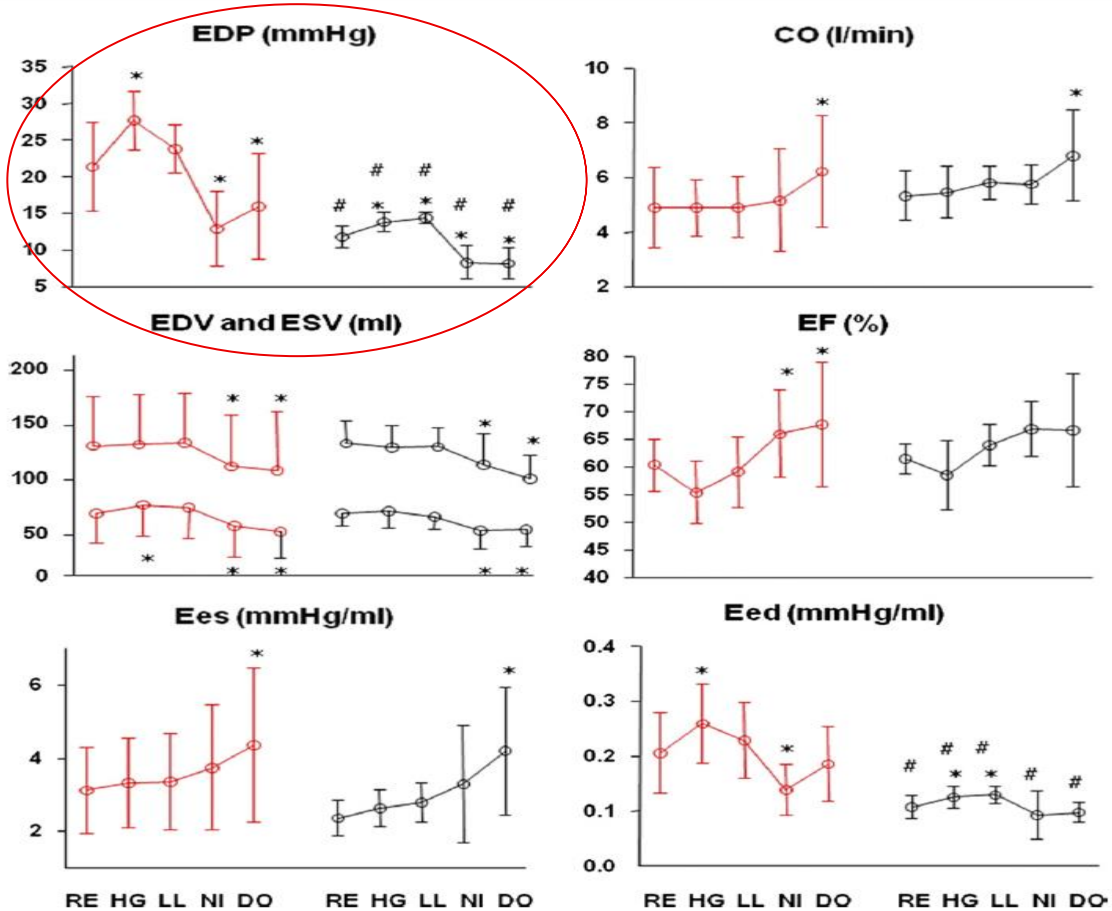


Figure 1 Hemodynamic Indices

Major hemodynamic indices at rest (RE), during hand grip (HG), leg lifting (LL), and nitroprusside (NI) and dobutamine (DO) infusions in the heart failure with preserved ejection fraction **(red)** and control **(black)** groups. *Statistically significant difference compared with baseline. #Statistically significant difference between both groups; CO = cardiac output; EDP = end-diastolic pressure; EDV = end-diastolic volume; Eed = end-diastolic stiffness; Ees = end-systolic elastance; EF = ejection fraction; ESV = end-systolic volume.

Exercise Hemodynamics in HFsEF

Maeder MT.JACC 2010;56:855

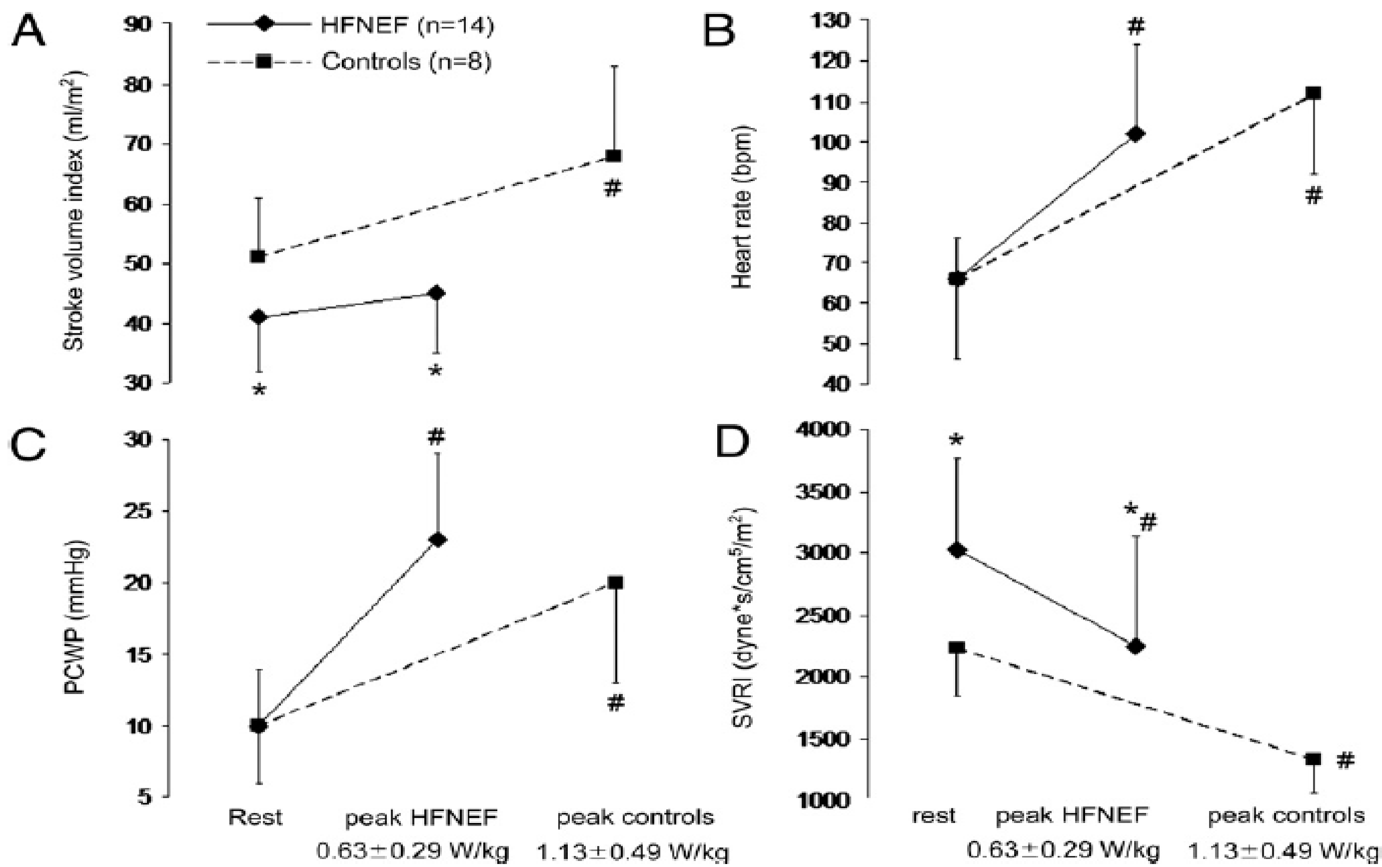


Figure 2 Hemodynamic Response to Exercise

Changes in **(A)** stroke volume index, **(B)** heart rate, **(C)** pulmonary capillary wedge pressure (PCWP), and **(D)** systemic vascular resistance index (SVRI) from rest to peak exercise in patients with heart failure and normal ejection fraction (HFNEF **[diamonds]**) and controls **(squares)**. **Error bars** represent mean and SD. *p $<$ 0.05 versus controls; #p $<$ 0.05 versus rest.

Exercise Hemodynamics in HFsEF

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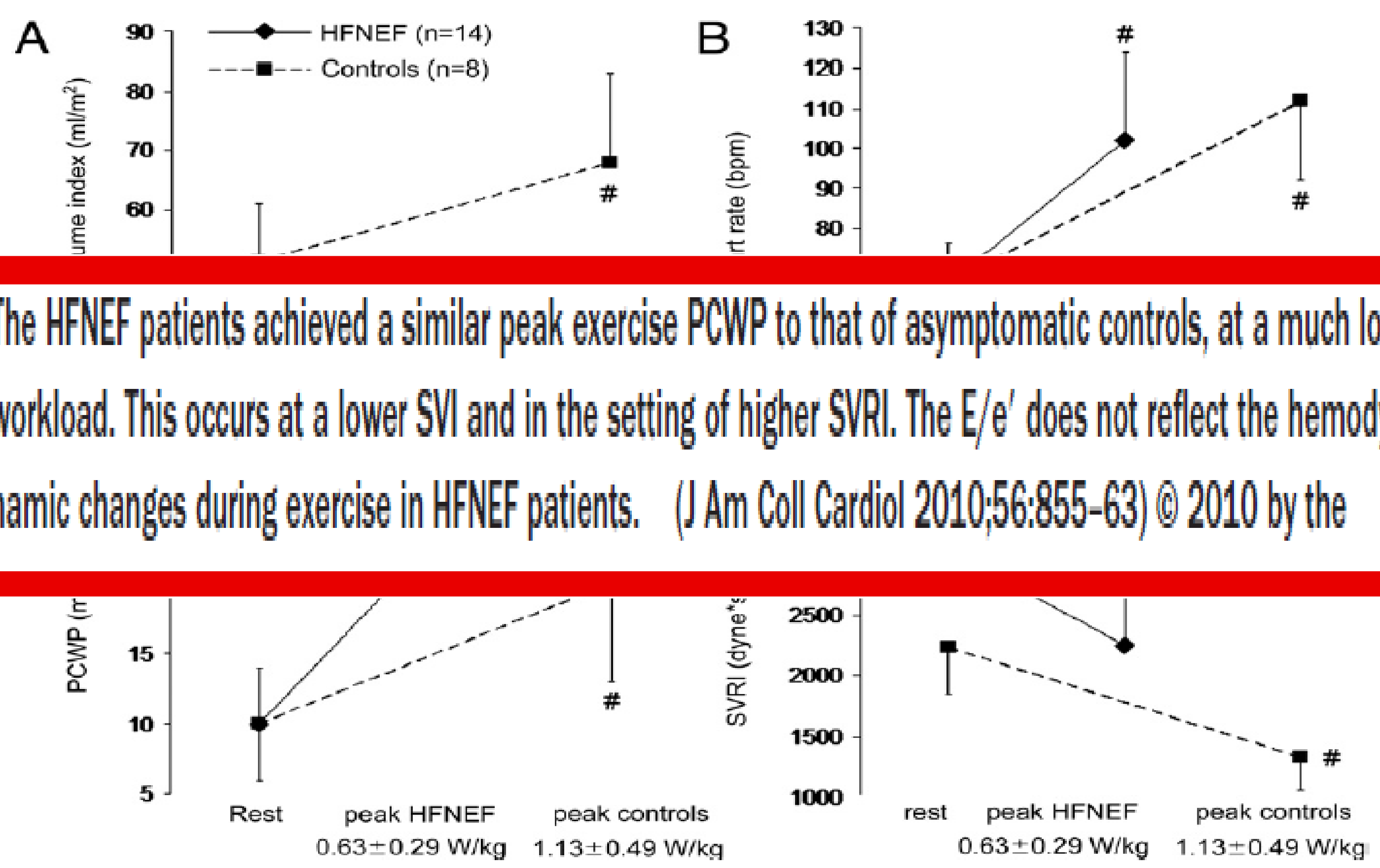

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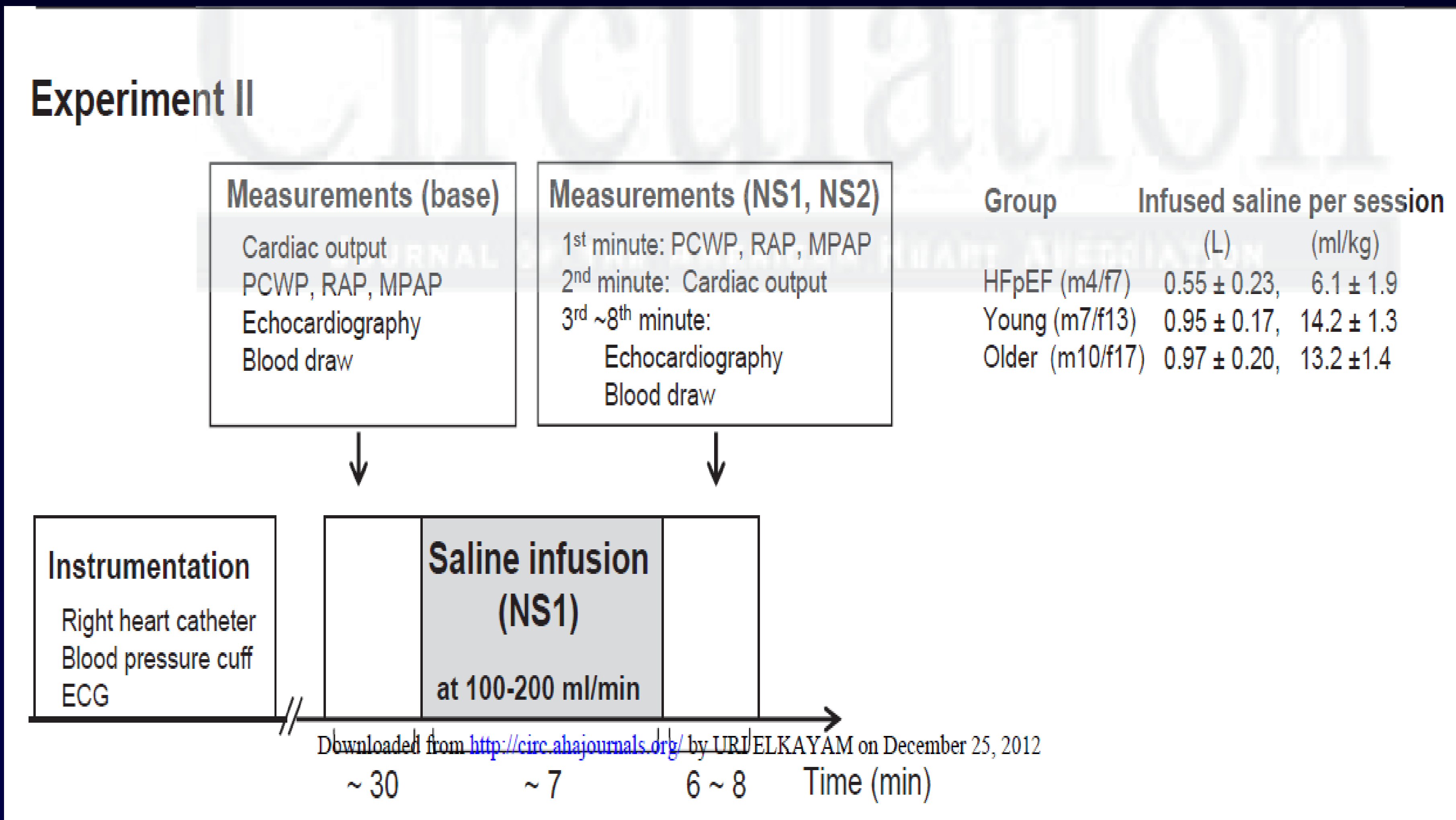
Hemodynamic Response to Rapid Saline Loading

Fujimoto N et al Circulation on line Nov 21, 2012



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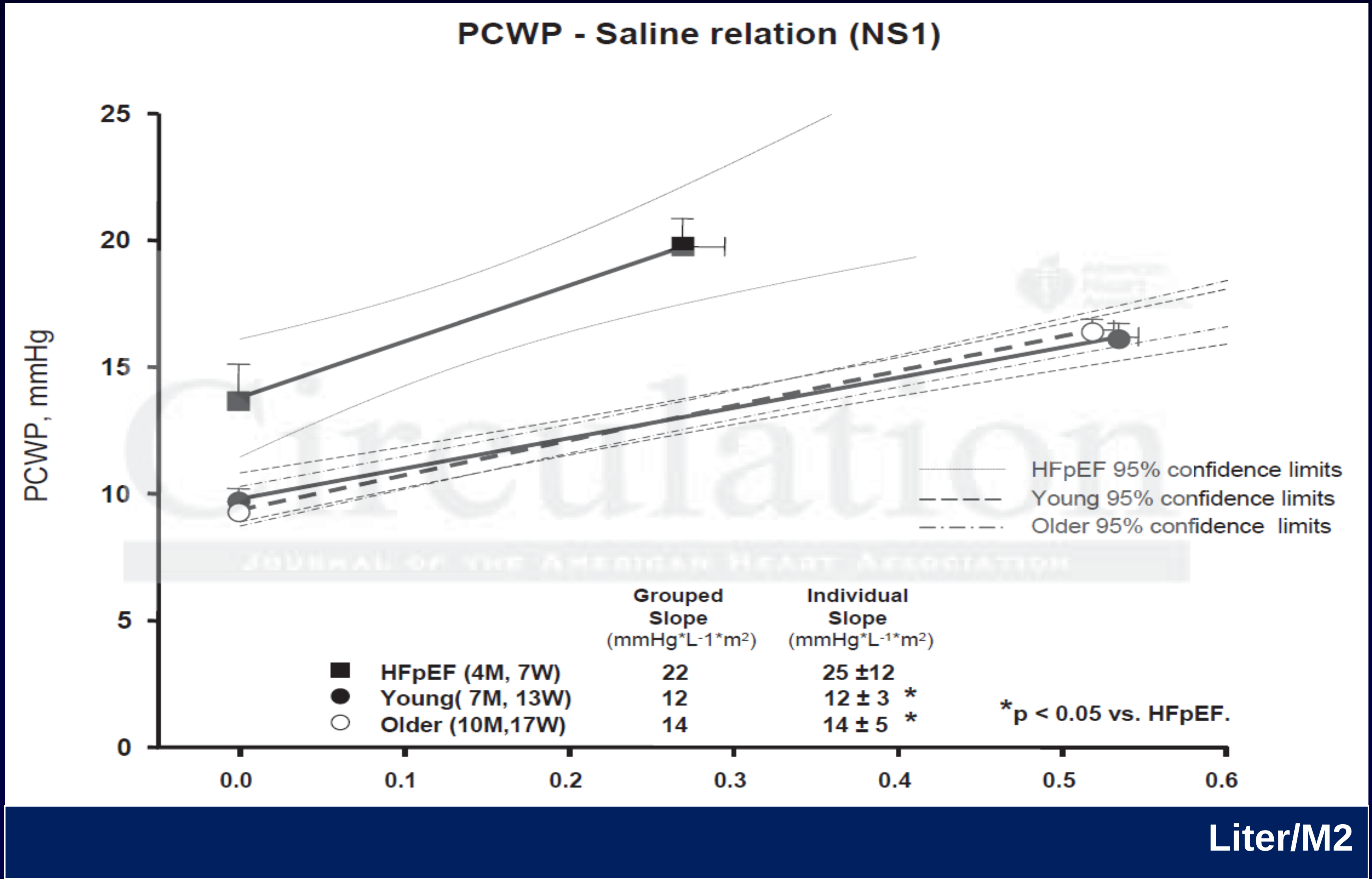
Fujimoto N et al Circulation on line Nov 21, 2012



summary

- HFpEF is a syndrome which in addition to **Impaired myocardial Relaxation is associated with endothelial dysfunction, impaired vasodilatory reserve, subtle systolic dysfunction, impaired systolic reserve, chronotropic incopmpetence, and pulmonary hypertension.All of these lead to symptoms of heart failure and worse prognosis.**

summary

- Diagnosis usually relies on non invasive criteria but can be enhanced by hemodynamic assessment of resting LV filling pressure as well as hemodynamic response to exercise (hand grip), leg raising and fluid loading.

Heart Failure with Preserved Ejection Fraction

Management

Clinical trials in HFpEF

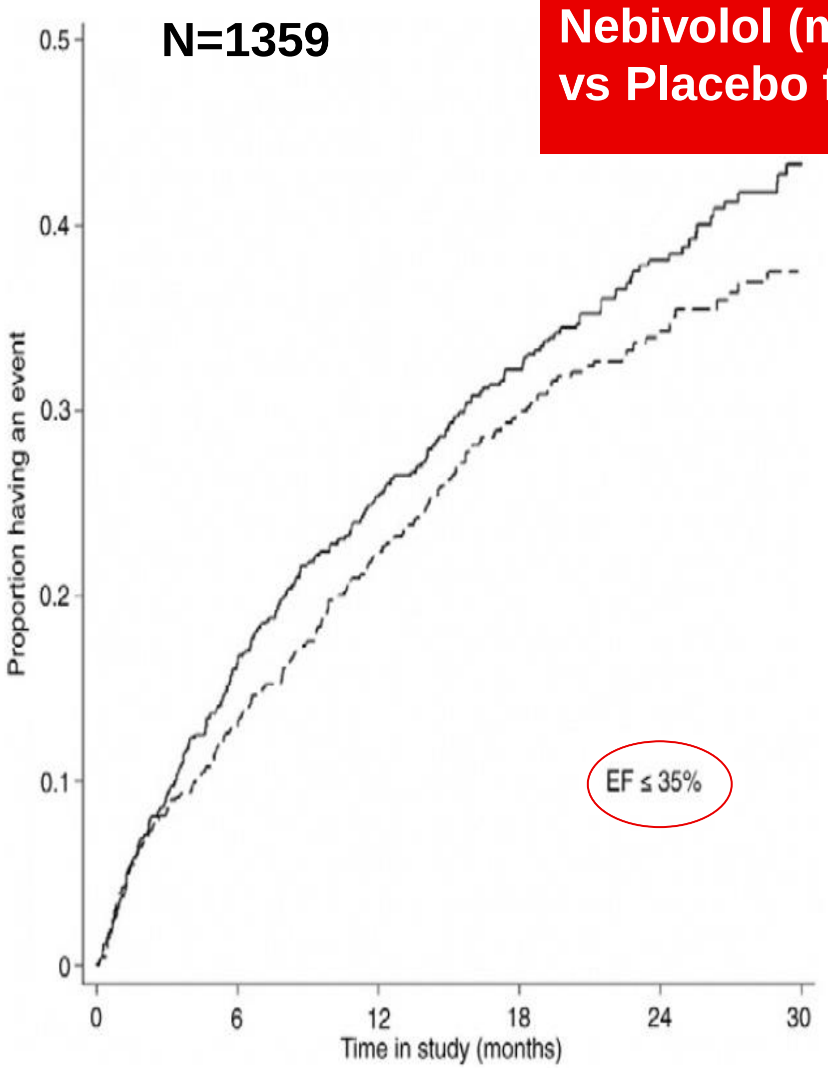
	CHARM-PHF	I PRESERVE	PEP-CHF	SENIORS
Therapy	Candesartan	Irbesartan	Perindopril	Nebivolol
Age (yrs)	>18 (67)	≥60 (72)	≥70 (76)	≥ 70 (76)
EF (%)	≥ 40 (54)	≥ 45 (59)	≥ 40 (65)	≥ 35 (49)
# of pts	3,023	4,128	850	752
Females	40%	60%	55%	38%
Death/HF hospitalizations	0.89 (0.77-1.03)	0.95 (0.86-1.05)	0.92 (0.70-1.21)	0.81 (0.63-1.04)

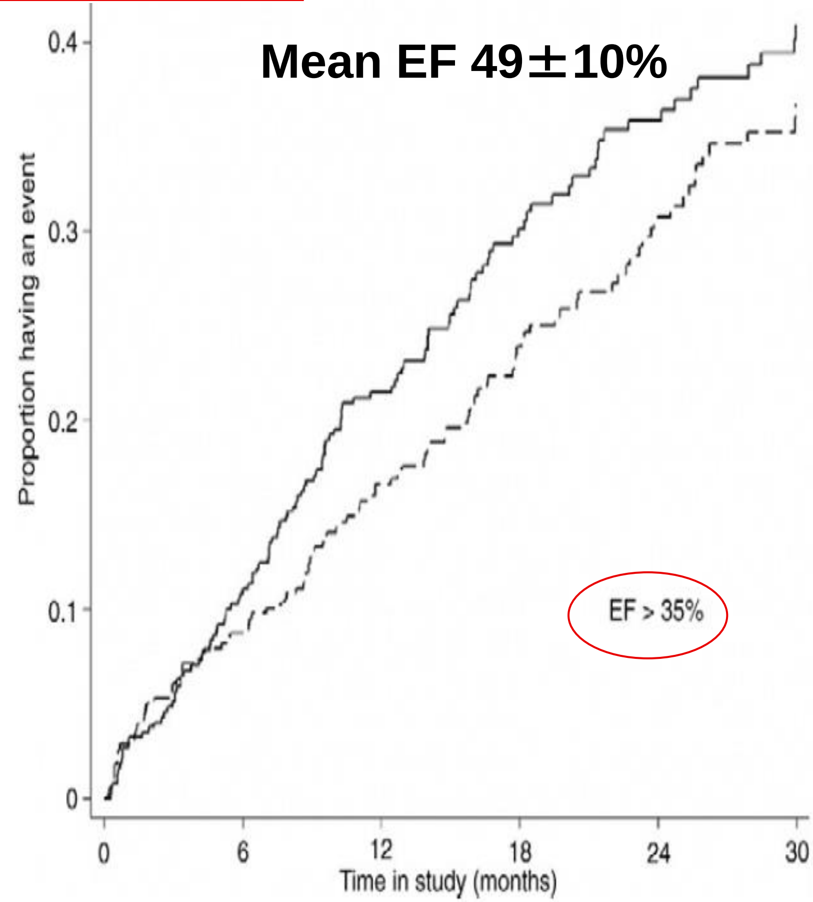
SENIORS Trial

All Cause Mortality or CV Hospitalization

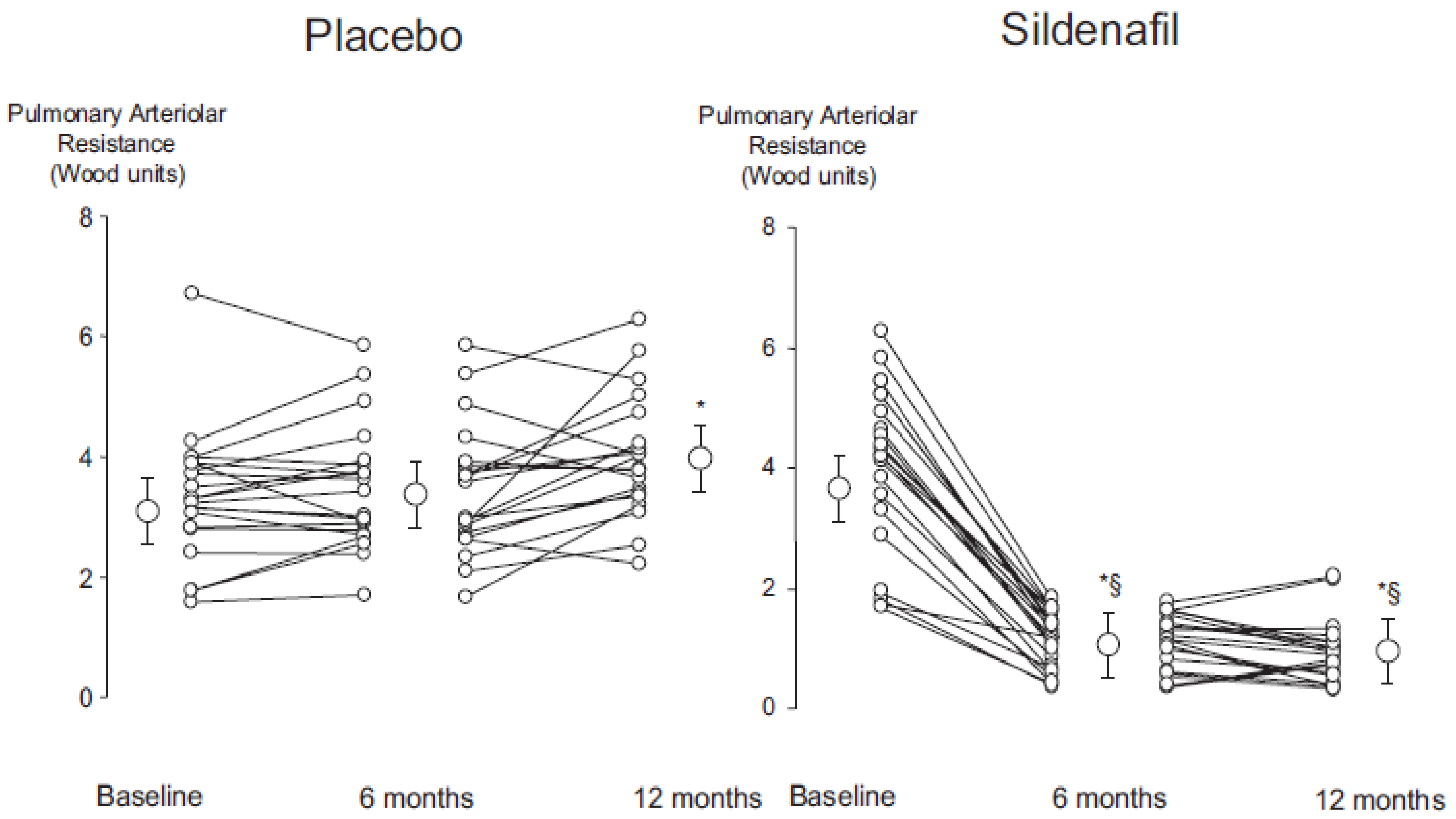
von Veldhuisen et al JACC 2009;53:2150

Nebivolol (mean dose 7.7 mg) vs Placebo for ~ 40 months





PDH in patients with HFpEF and PH
Guazzi M et al, Circulation 2011;124:164



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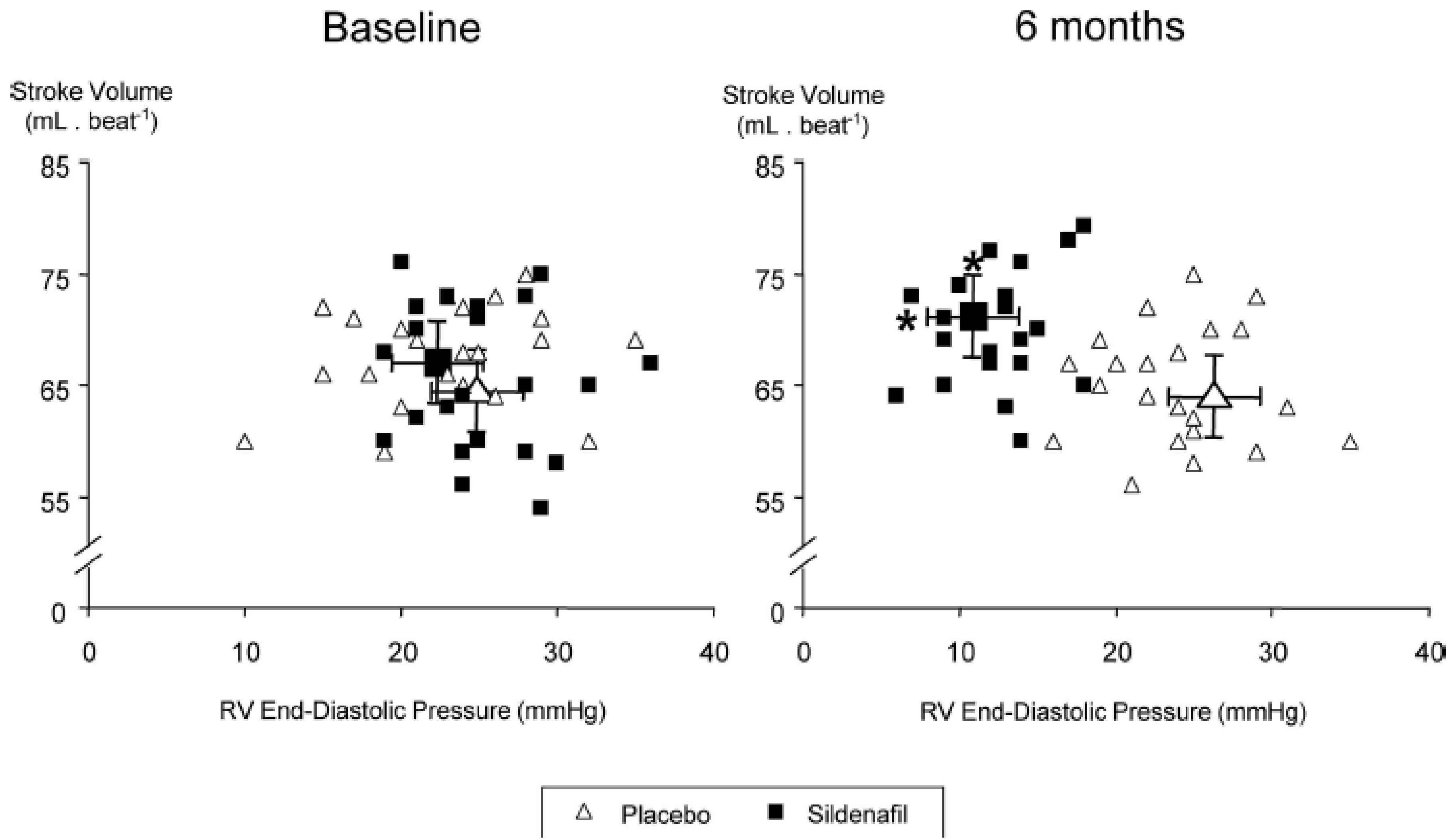

RELAX – Sildenafil in HFpEF

Redfield MM et al , JAMA 2013;309:1268

- 216 stable out patients with HFpEF (≥ 50%).
- Eleveted BNP or invasively measured LVEDP.
- Reduced exercise capacity.
- Rendomized to placebo or sidenafil 20mg tid for 12 weeks followed by 60 mg tid for 12 weeks.
- Results : No change in Peak VO_2,(primary end point), 6 minutes walk, and clinical status.

ALDO – DHF Trial

Spitonolactone in HFpEF

- 10 sites in Germany & Austria.
- 422 patients with HFpEF,NHAF class II-III.
- Echo evidence of LV diastolic dysfunction.
- Peak VO2 < 25 ml/Kg/min.
- Rendomized to spironolactone 25 mg/d vs. placebo.
- Results: Sig. improvement in diastoloc dysfunction, LV mass index and BNP level.
- No sig. change in peak VO2, symptoms and QOL.
- Deacrease in 6 min walk distance and GFR and an increase in serum potassium.

Summary

- Recent studies involving the use of aldosterone antagonists and PD5-I (Sildenafil) have been added to a long list of therapeutic interventions, effective in patients with HFrEF including ACE inhibitors , ARBs and beta blockers which have failed in patients with HFpEF.
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Heart Failure Practice Guidline

Section 11 : HF with Preserved LVEF

- Careful attention to differential diagnosis because treatment may differ (C).
- Evaluation for ischemic heart disease (C).
- Aggressive BP management (C).
- Use of low sodium diet (C).

Heart Failure Practice Guidline

Section 11 : HF with Preserved LVEF

- Diuretics to patients with evidence of volume overload but avoid excessive diuresis to prevent orthostatic hypotension and WRF (C).
- ARBs (B) or ACE inhibitors (C) should be considered.
- Measures to restore and maintain NSR should be considered in patients with symptomatic atrial flutter or fibrillation (C).