Dx and Rx of HF*p*EF
Diastolic Heart Failure

Jae K. Oh, MD

Torino, Italy
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MAYO CLINIC

With contribution from M. Redfield, MD and B. Borlaug, MD

ORIGINAL CONTRIBUTION

Systolic and Diastolic Heart Failure in the Community

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Context The heart failure (HF) syndrome is heterogeneous. While it can be defined by ejection fraction (EF) and diastolic function, data on the characteristics of HF in the community are scarce, as most studies are retrospective, hospital-based, and rely on clinically indicated tests. Further, diastolic function is seldom systematically assessed based on standardized techniques.

Objective To prospectively measure EF, diastolic function, and brain natriuretic peptide (BNP) in community residents with HF.

Main Outcome Measures Echocardiographic measures of EF and diastolic function, measurement of blood levels of BNP, and 6-month mortality.

Design, Setting, and Participants Olmsted County residents with incident or prevalent HF (inpatients or outpatients) between September 10, 2003, and October 27, 2005, were prospectively recruited to undergo assessment of EF and diastolic function by echocardiography and measurement of BNP.

Results A total of 556 study participants underwent echocardiography at HF diagnosis. Preserved EF (≥50%) was present in 308 (55%) and was associated with older age, female sex, and no history of myocardial infarction (all $P<.001$). Isolated diastolic dysfunction (diastolic dysfunction with preserved EF) was present in 242 (44%) patients. For patients with reduced EF, moderate or severe diastolic dysfunction was more common than when EF was preserved (odds ratio, 1.67; 95% confidence interval [CI], 1.11-2.51; $P=.01$). Both low EF and diastolic dysfunction were independently related to higher levels of BNP. At 6 months, mortality was 16% for both preserved and reduced EF (age- and sex-adjusted hazard ratio, 0.85; 95% CI, 0.61-1.19; $P=.33$ for preserved vs reduced EF).

Conclusions In the community, more than half of patients with HF have preserved EF, and isolated diastolic dysfunction is present in more than 40% of cases. Ejection fraction and diastolic dysfunction are independently related to higher levels of BNP. Heart failure with preserved EF is associated with a high mortality rate, comparable to that of patients with reduced EF.

JAMA. 2006;296:2209-2216 www.jama.com

HEART FAILURE (HF) IS A highly prevalent syndrome with diverse etiologies that may be associated with reduced or preserved ejection fraction (EF). The pathophysiology of HF with reduced EF has been extensively studied and management strategies are well defined.[1] Conversely, while clinical series, epidemiological surveys, and clinical trials have improved our understanding of HF and preserved EF,[2,3] controversy remains on many key elements of this entity, including its prevalence, clinical characteristics, and outcome.[4] To this end, the prevalence and distribution of diastolic dysfunction among patients with HF and reduced or preserved EF has not, to the best of our knowledge, been reported. Further, previous studies share key limitations, including retrospective design, inclusion of prevalent cases, inconsistent assessment of EF, infrequent assessment of diastolic function, and m

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County residents presenting with HF at Mayo Clinic inpatient and outpatient facilities. Our objective was to determine the prevalence of preserved and reduced EF and that of diastolic dysfunction among all patients with HF in a contemporary community cohort. Further, we sought to define key clinical characteristics associated with preserved and reduced EF and to determine 1-year survival according to EF and diastolic dysfunction. The central hypothesis was that the community prevalence of HF with preserved EF is high, and that among patients with preserved EF, most have diastolic dysfunction of moderate to severe degree. The prevalence of diastolic dysfunction in the general population of Olmsted County (assessed with a method similar to the one we used) has previously been reported,[5] thereby provid-

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See also pp 2217 and 2259.

JAMA 2006;296:2209-2216

Systolic and Diastolic Heart Failure in the Community

Francesca Bursi et al

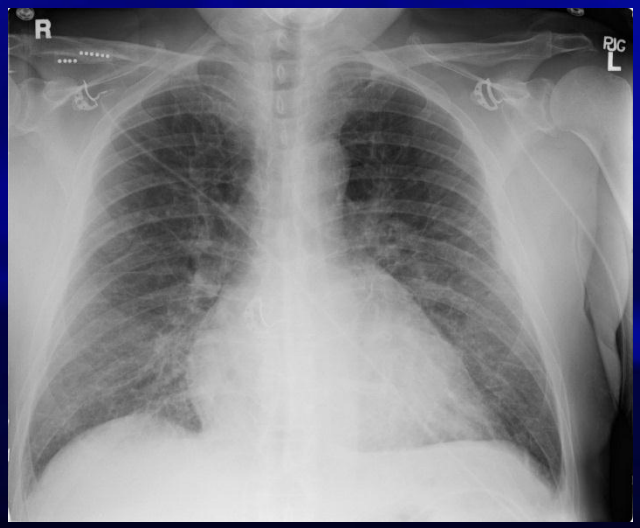
Olmsted County residents with incident or prevalent HF (in-patients or outpatients) between Sept 10, 2003 and Oct 27, 2005.

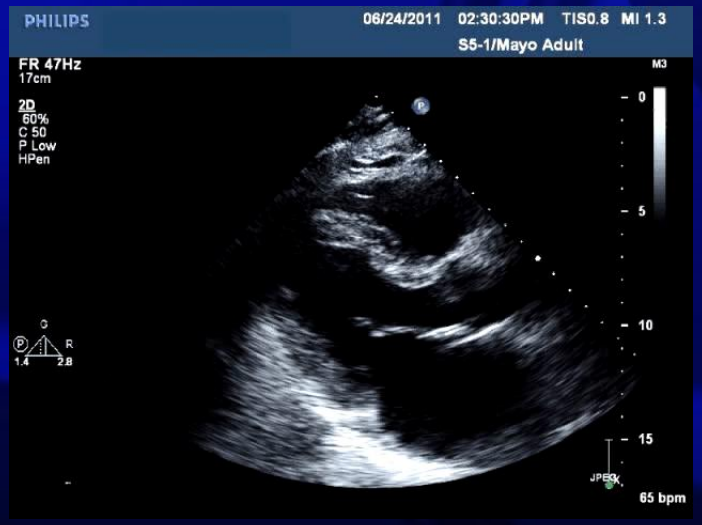
A total of 556 participants had echocardiography at HF Dx.

EF was preserved (≥50%) in 308(55%) and was reduced in 45%. Patients with systolic heart failure had worse diastolic function.

Case Presentation

- 73 yo woman with dyspnea in 2000
- Risk factors: Age, HTN, Lipids
- CXR: PVH, Cardiomegally
- PFT: Normal
- Echo: Nl EF, Mild MR,RVSP 45 mmHg
- Cath: Nl Coronaries

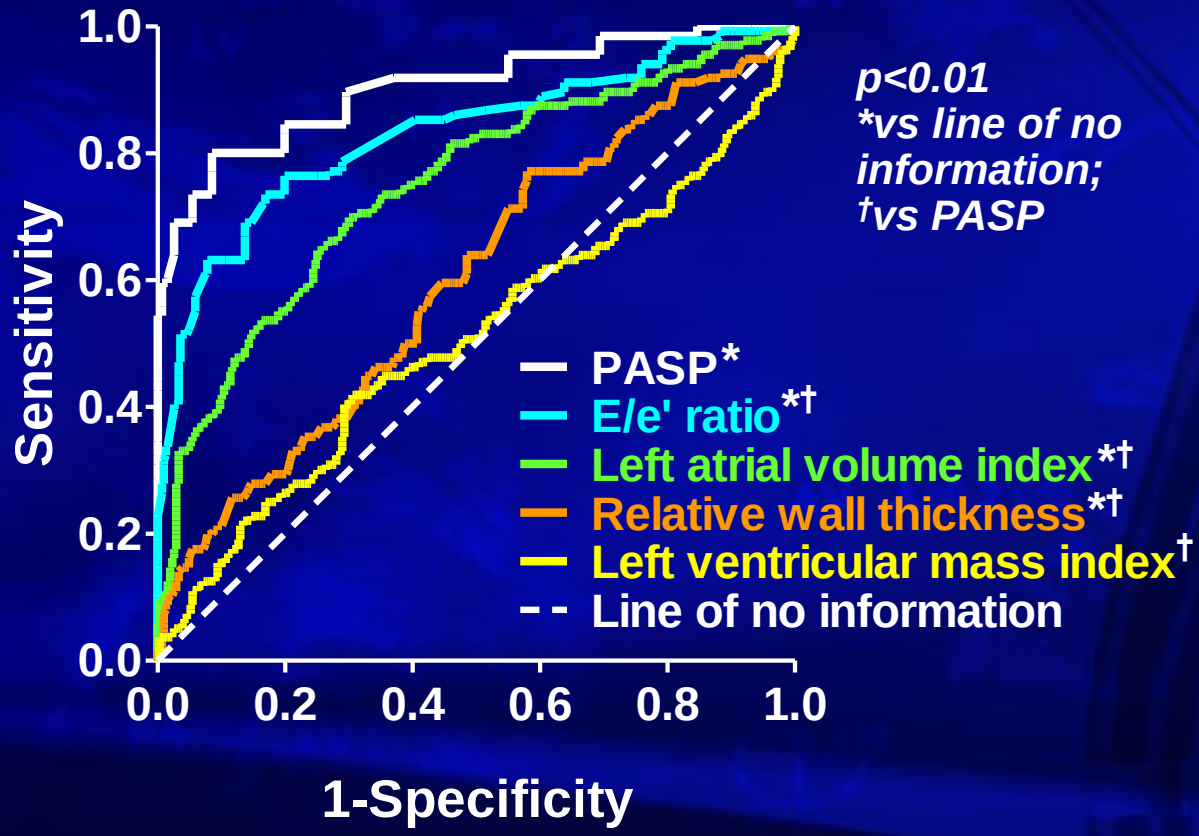




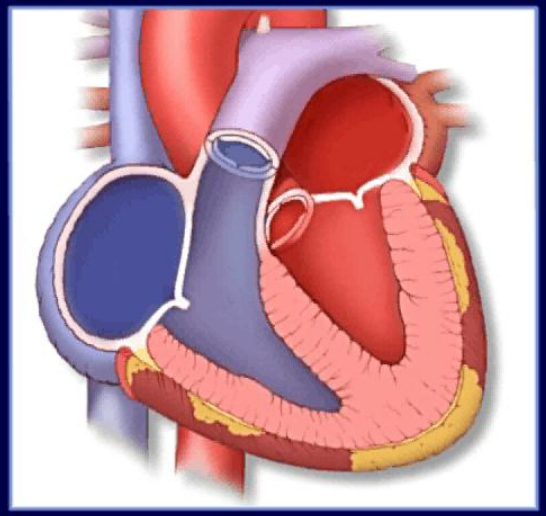
Additional tests to diagnose HF*p*EF?

- Cardiac MRI for LV mass
- Echo Doppler for filling pressure
- BNP ?
- Right heart cath?

Distinguishing Hypertensive Heart Disease from HFpEF

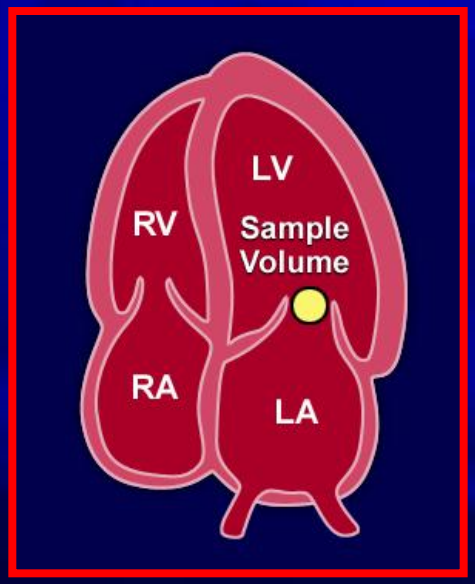


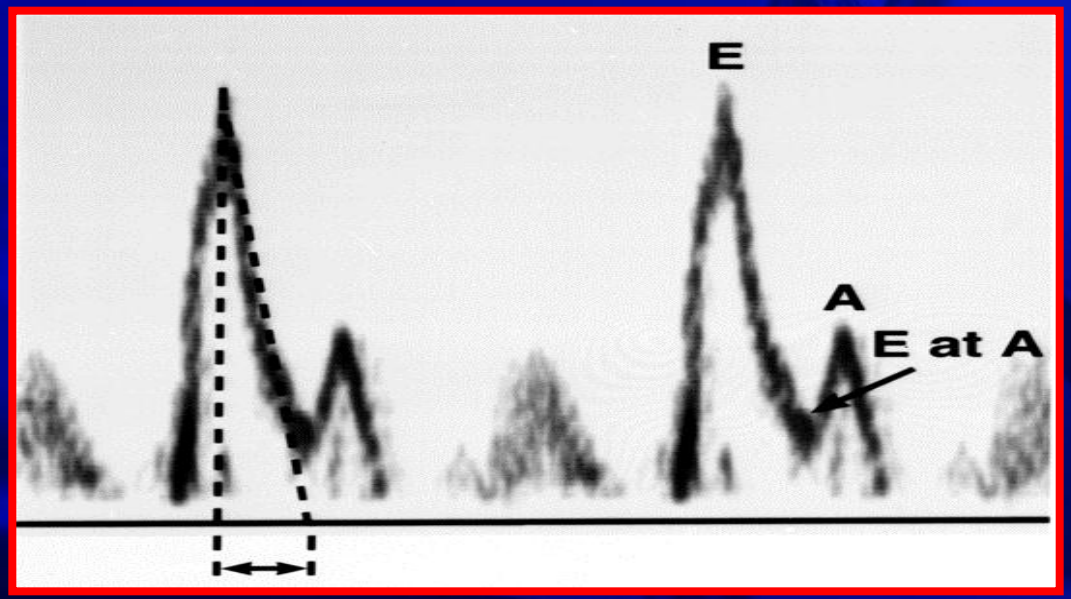
Lam C et al, JACC, 2009



Diastolic Filling Mitral Inflow

E velocity, A velocity, E/A ratio, DT

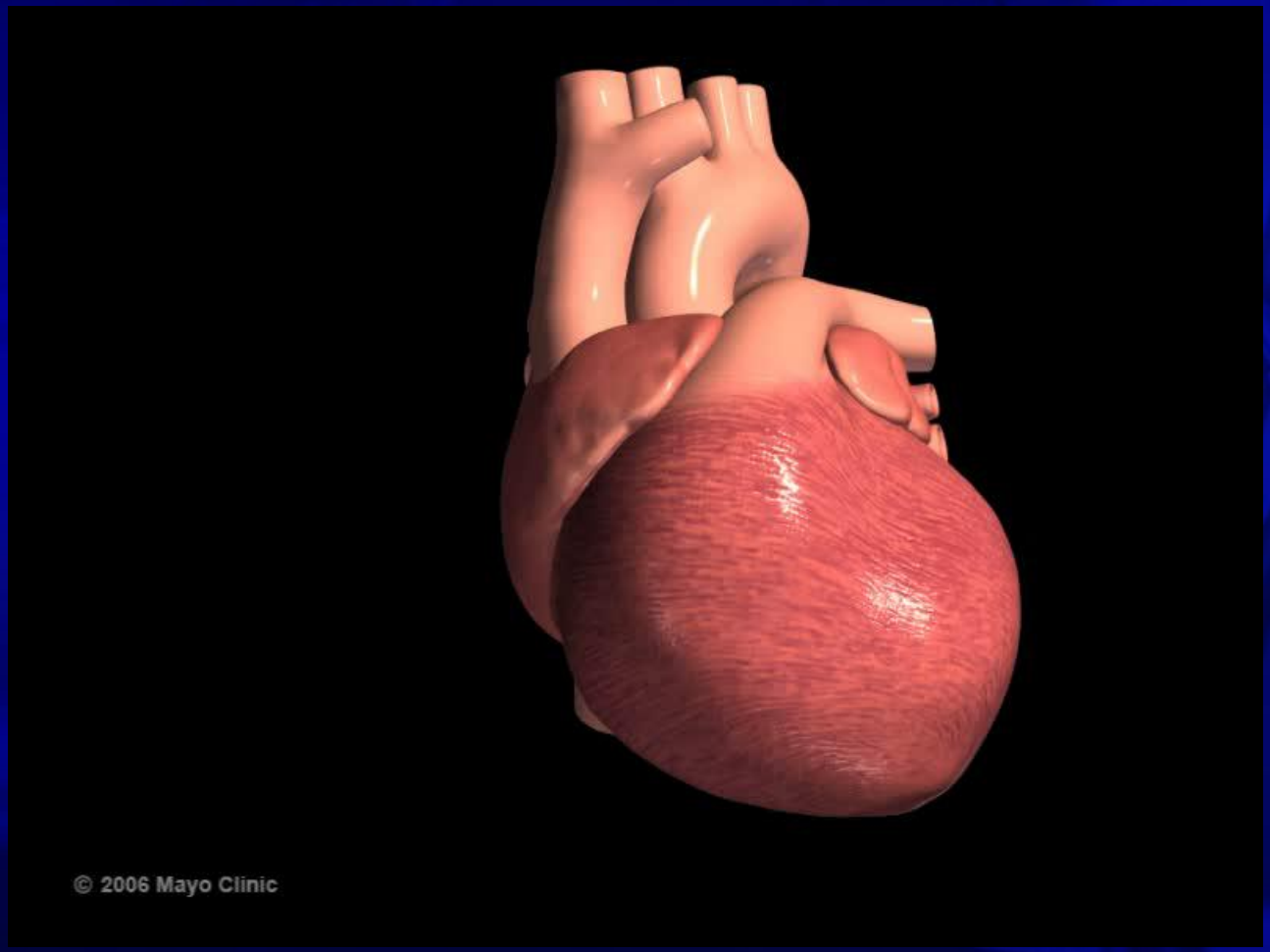




Deceleration time(DT)

Diastolic Function Assessment

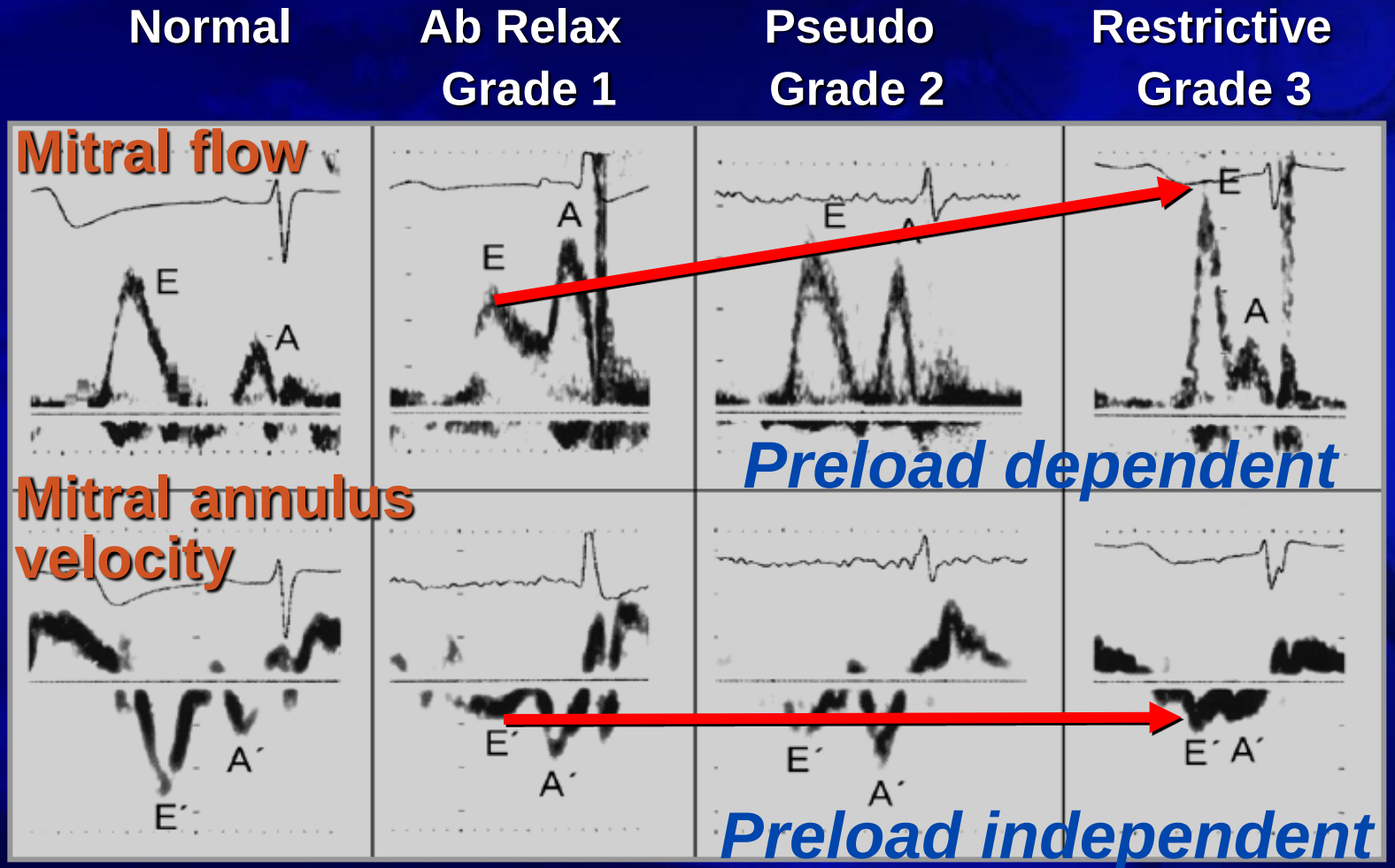
Echocardiography



Myocardial Relaxation is the Key for Diastole

Evaluation of Diastolic Function

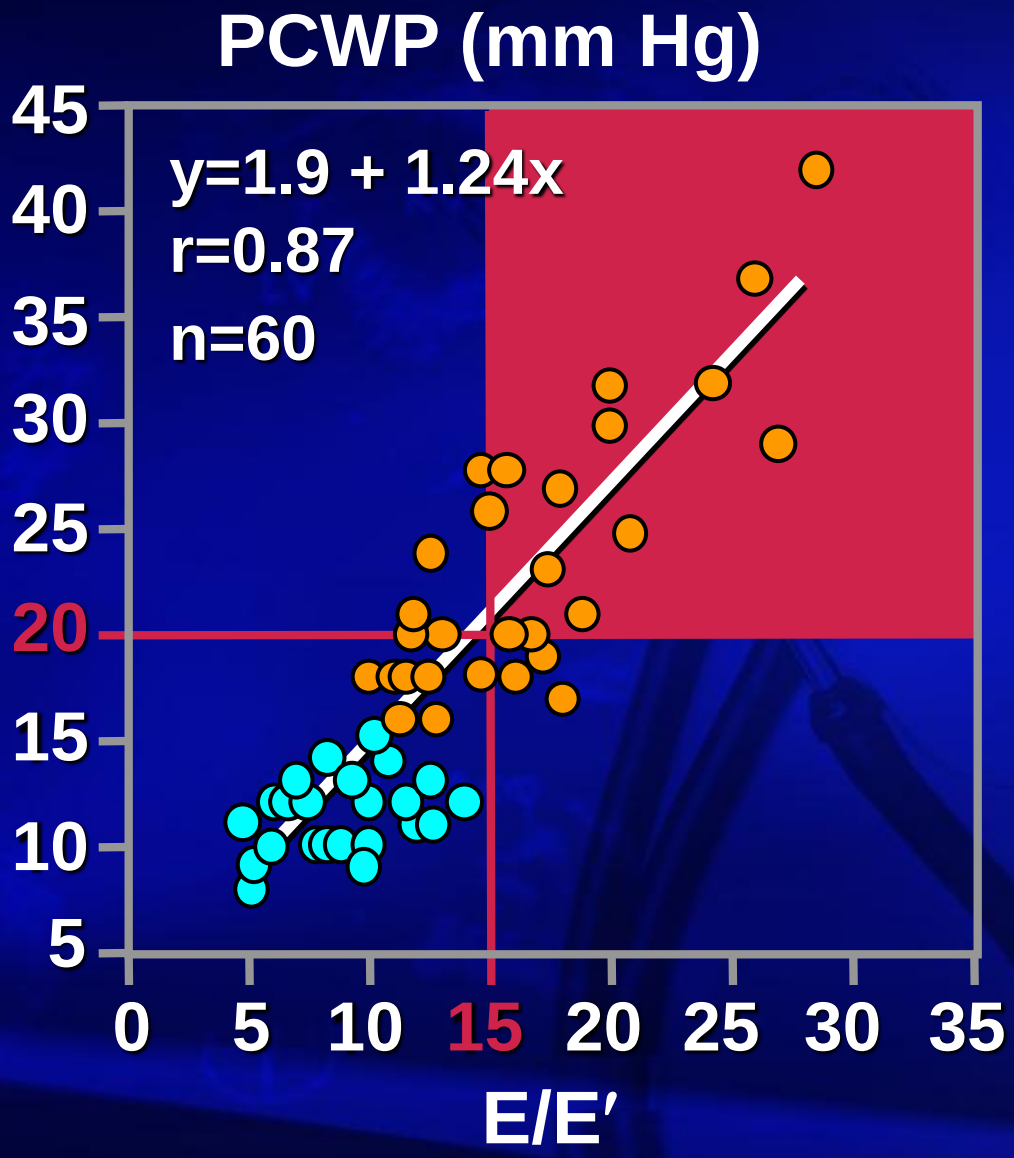
Mitral Inflow and Annulus Velocity



Sohn et al: JACC, 1997

As LV filling pressure ↑

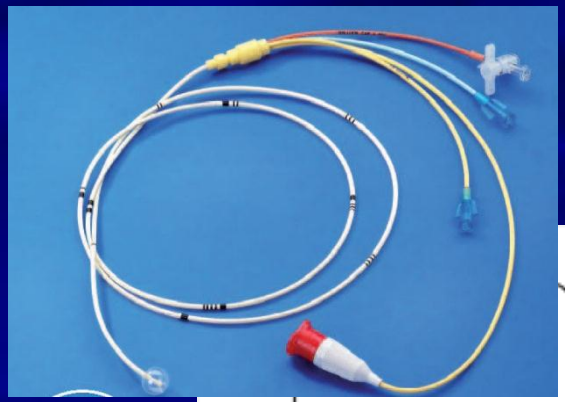
- Mitral E ↑
- Annulus E′ ↓
- E/E′ ↑

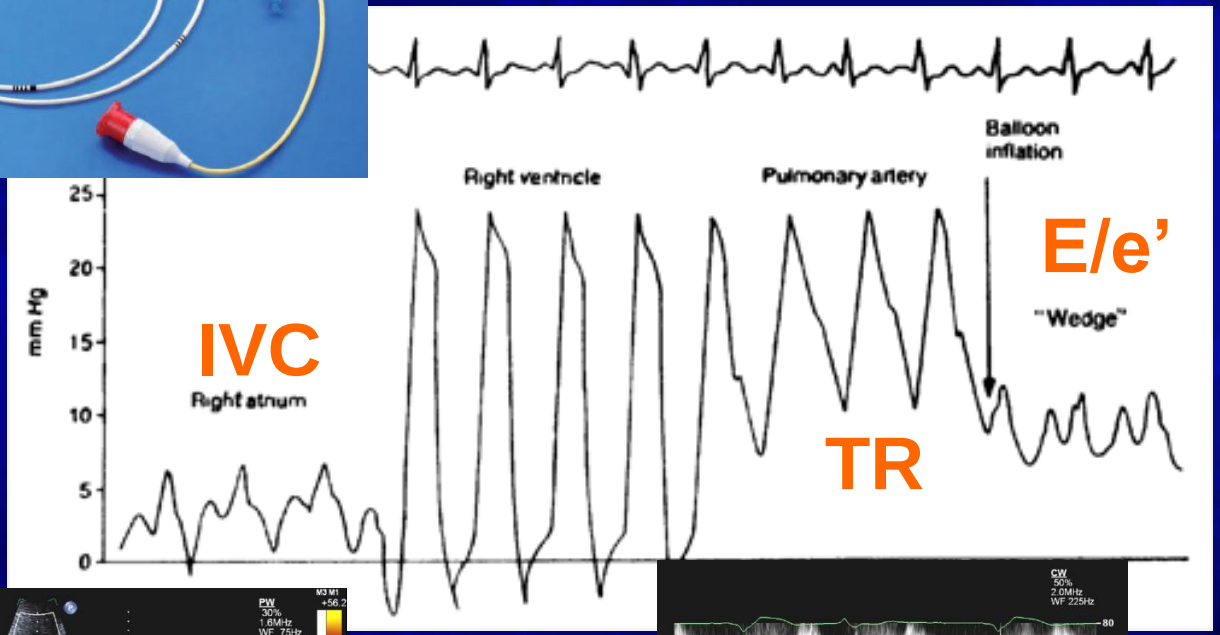


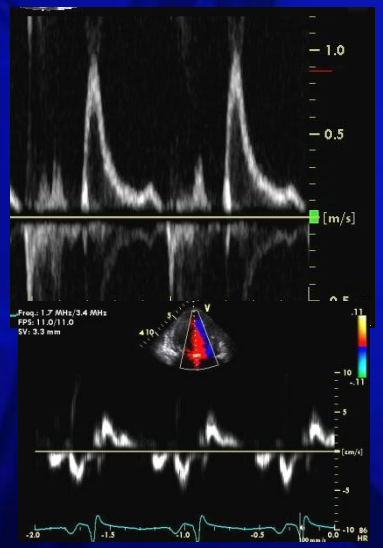
Nagueh et al: JACC, 1997
Ommen et al: Circ, 2000

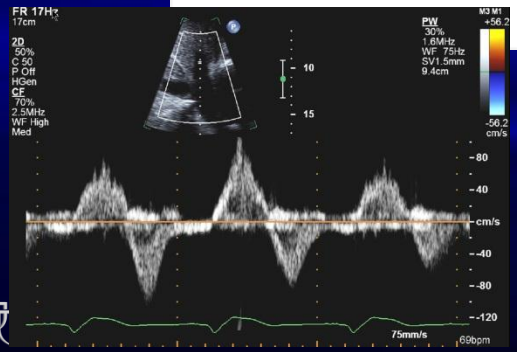
Doppler Evaluation of Filling Pressure

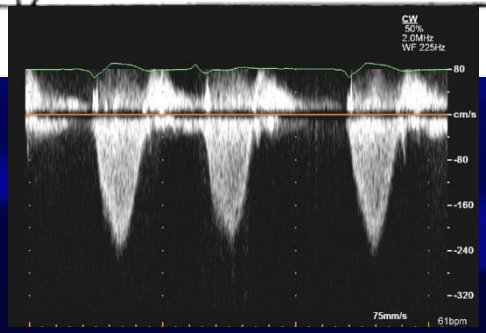
Non-invasive Swan-Ganz Catheter











Case Presentation continued

- 2004

  73 yo woman with dyspnea

  Risk factors: Age, HTN, Lipids

  Comorbidities: No autoimmune

  CXR: PVH, Cardiomegally

  PFT: Normal

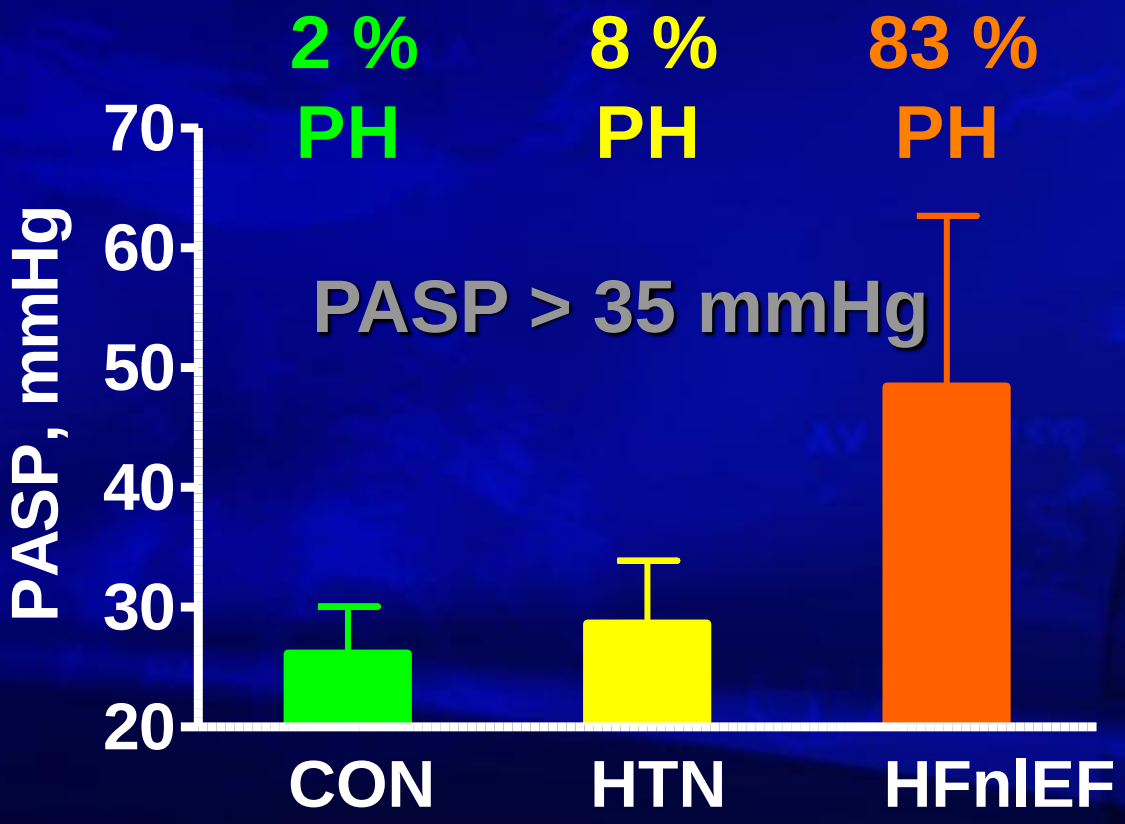
  Echo: Nl EF,

  E/e' = 16 RVSP 45 mmHg

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*



Case Presentation – Follow up

- 2011 back to Mayo

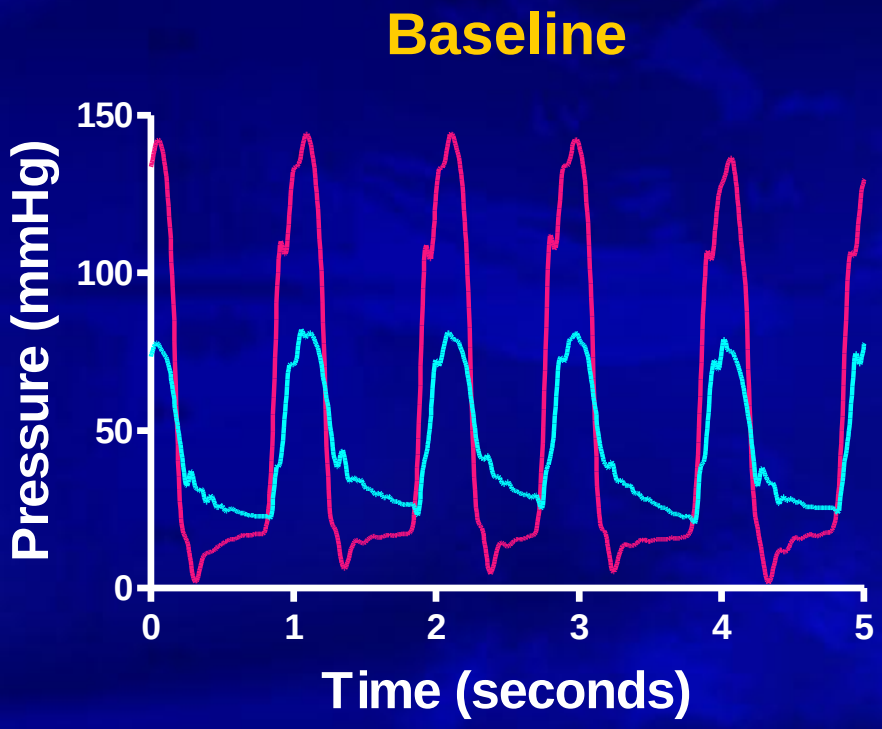
  Now 84

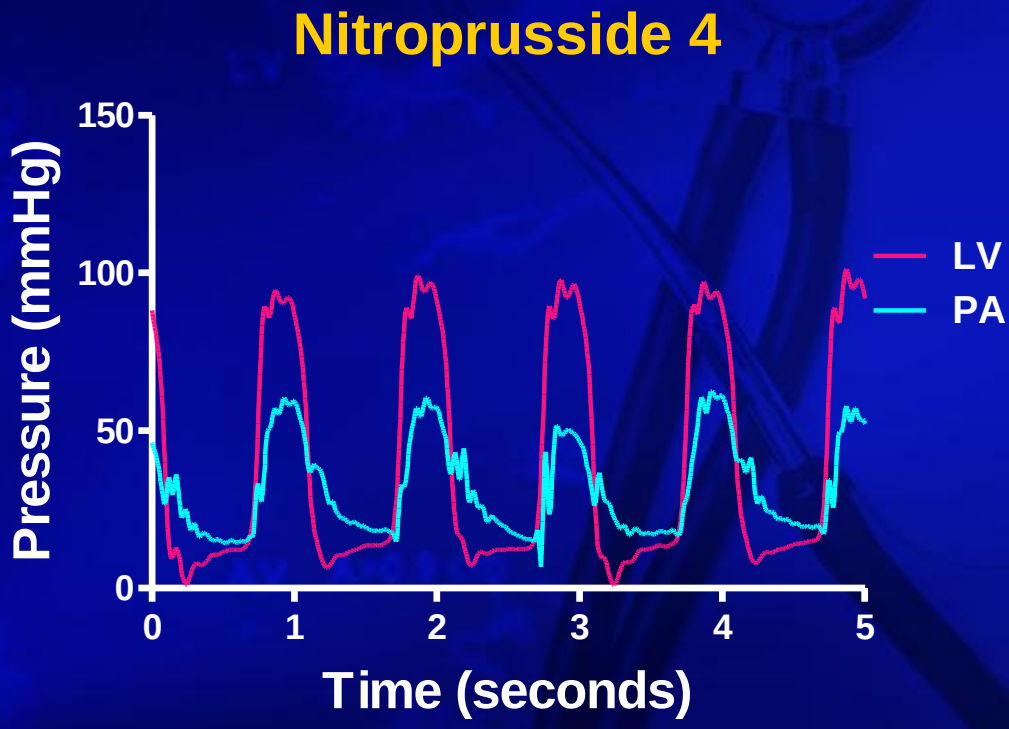
  Chronic severe dyspnea, AF

  Multiple evaluations for dyspnea

  2011 Echo – Nl EF, RVSP = 64 mmHg, E/e' = 25

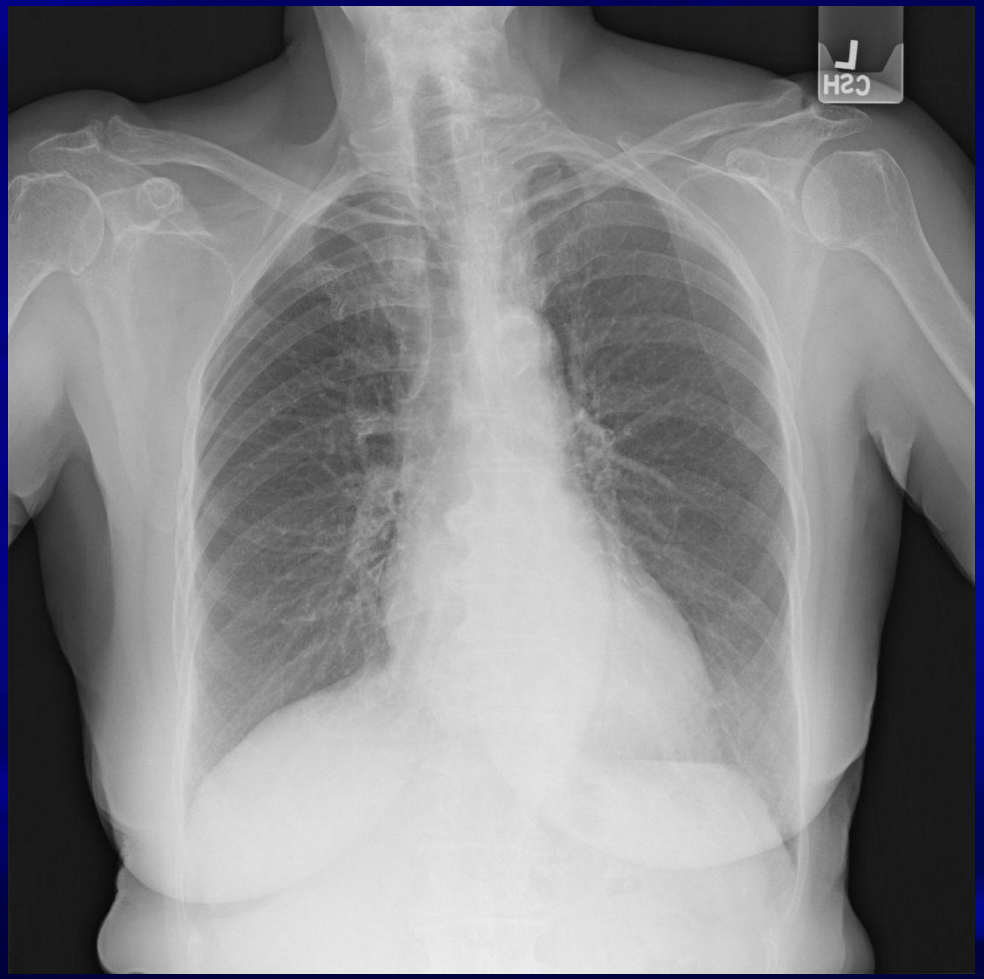
Right and left heart catheterization





Dx: HFpEF

Why is this pt short of breath?



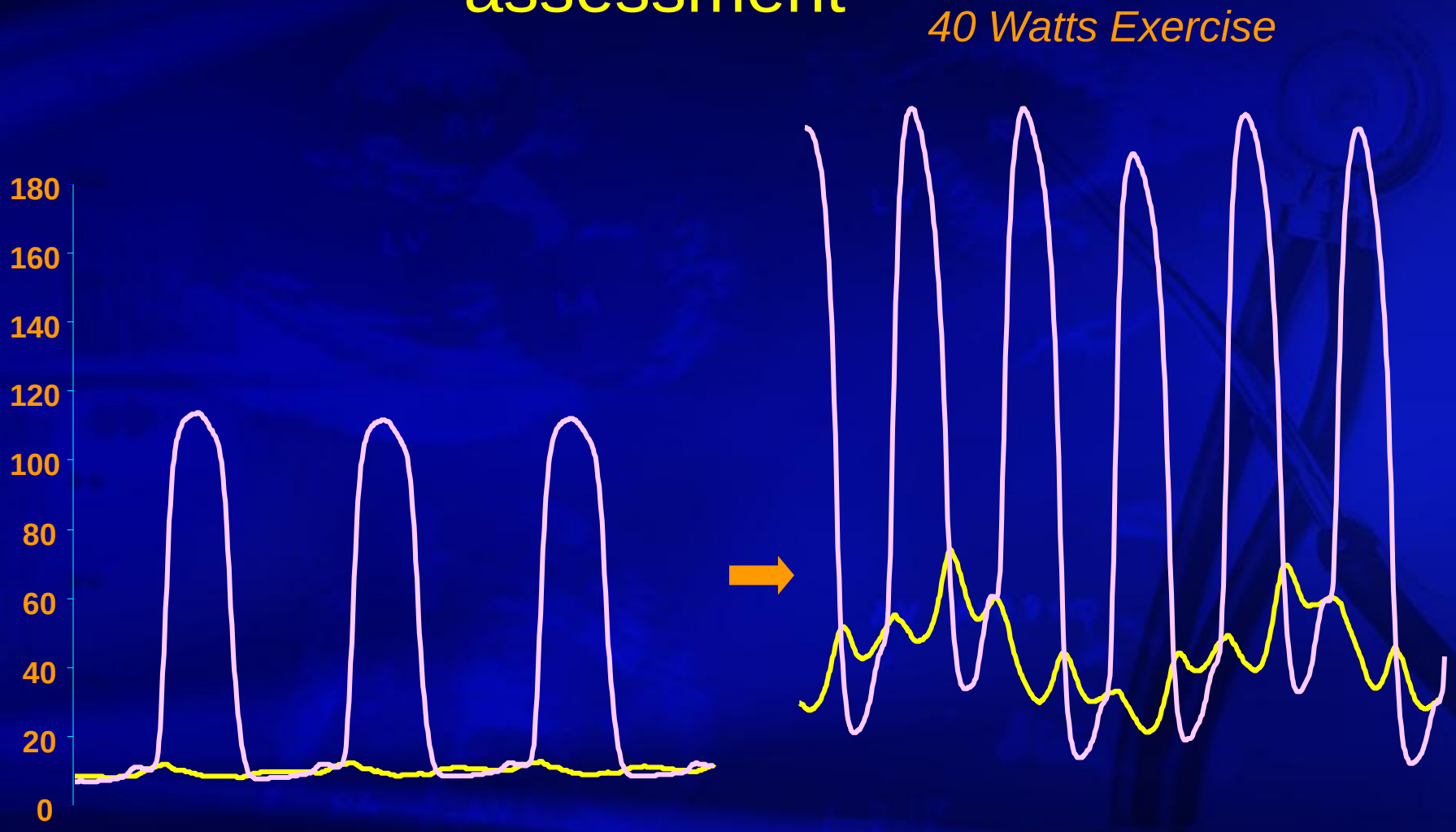
- **70 yo f, NYHA II DOE**
- **BMI 32, JVP 7, trace edema, no gallop**
- **Normal ECG & BNP**
- **Echo:**

  Nl LV size, EF 65%

  E/A 1.2, DT 160, E/e' 9

  PASP 37 mmHg

Referred to cath lab for hemodynamic assessment



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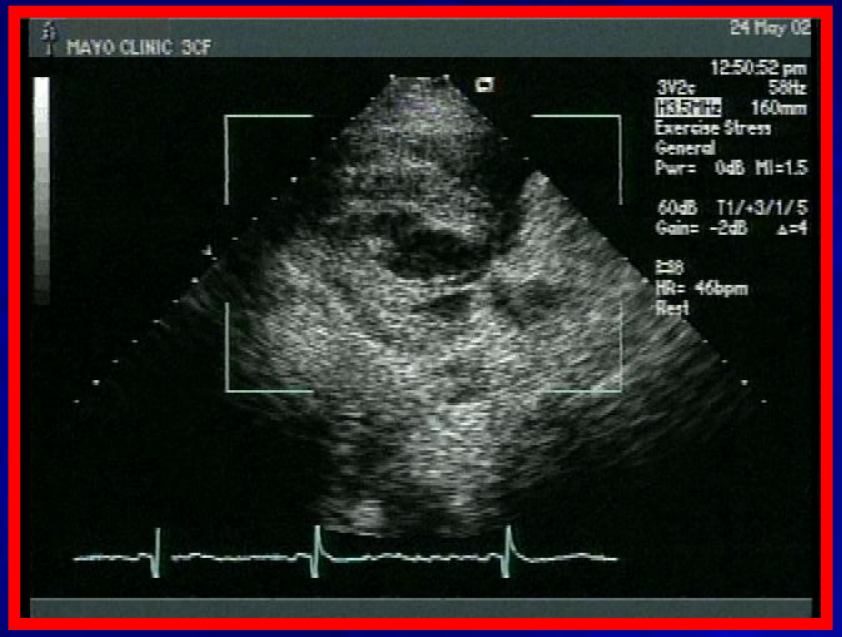
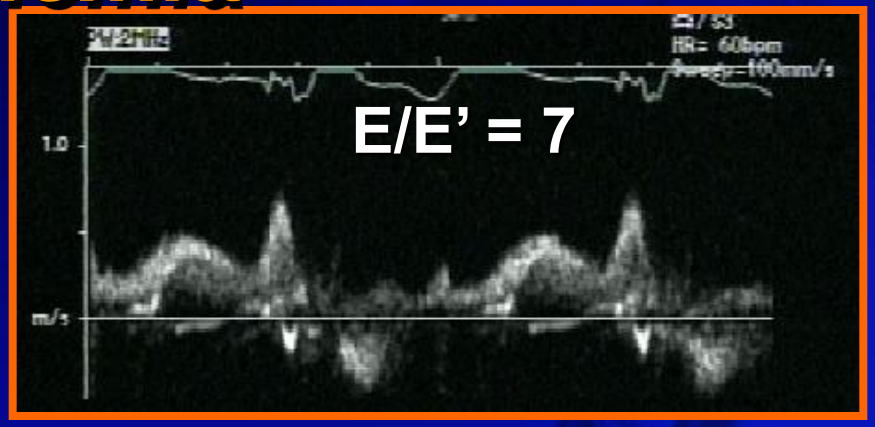
Courtesy of B. Borlaug, MD

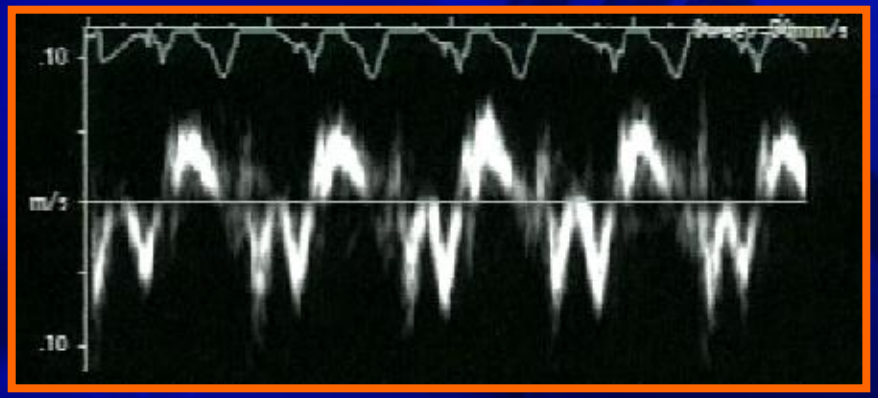
Hypertension and Exertional Dyspnea

No ischemia





E = 50 cm/s DT = 250 ms

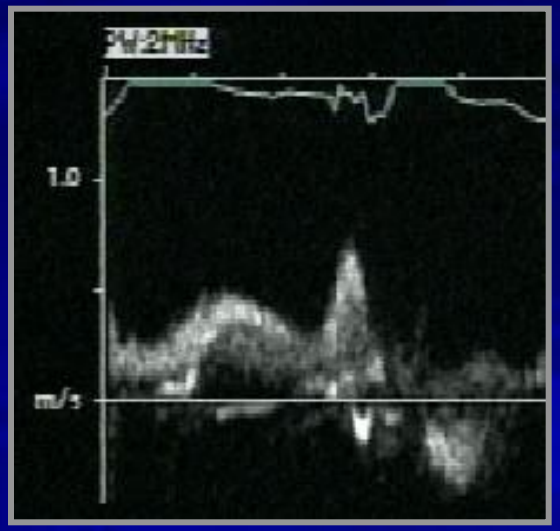


E' = 7 cm/s

"This patient has delayed myocardial relaxation, but filling pressure is not increased at rest"

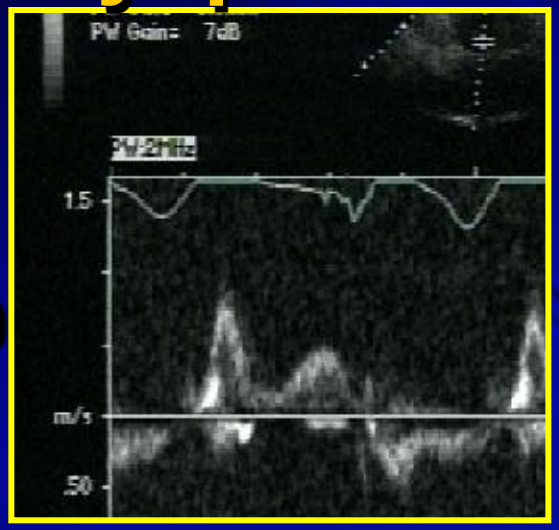
Ha , Oh et al. JASE 2004

Exertional Dyspnea



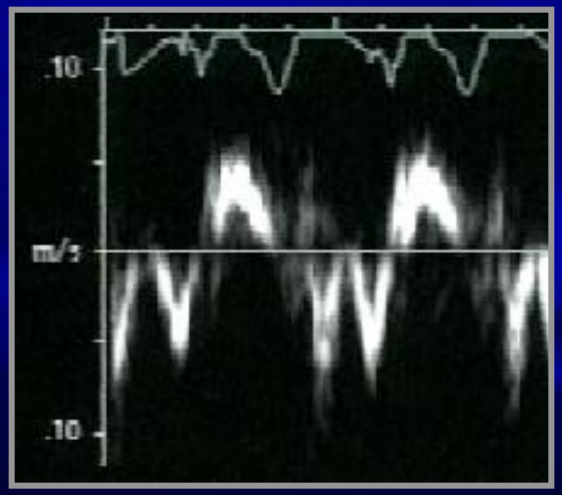
E = 50

DT = 250



E = 85

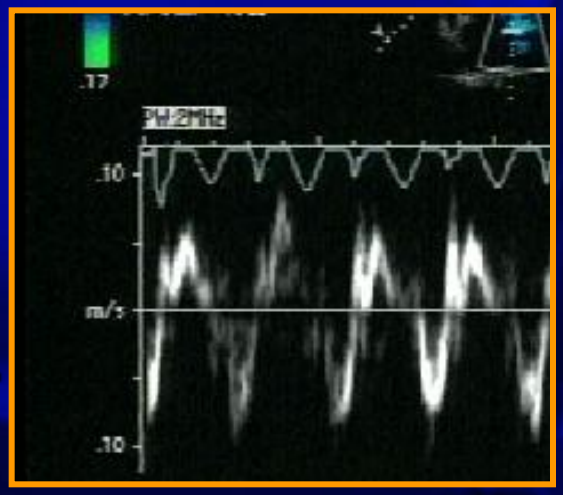
DT = 140



E' = 7

E/E' = 7

TR = 2.4



E' = 7

E/E' = 12

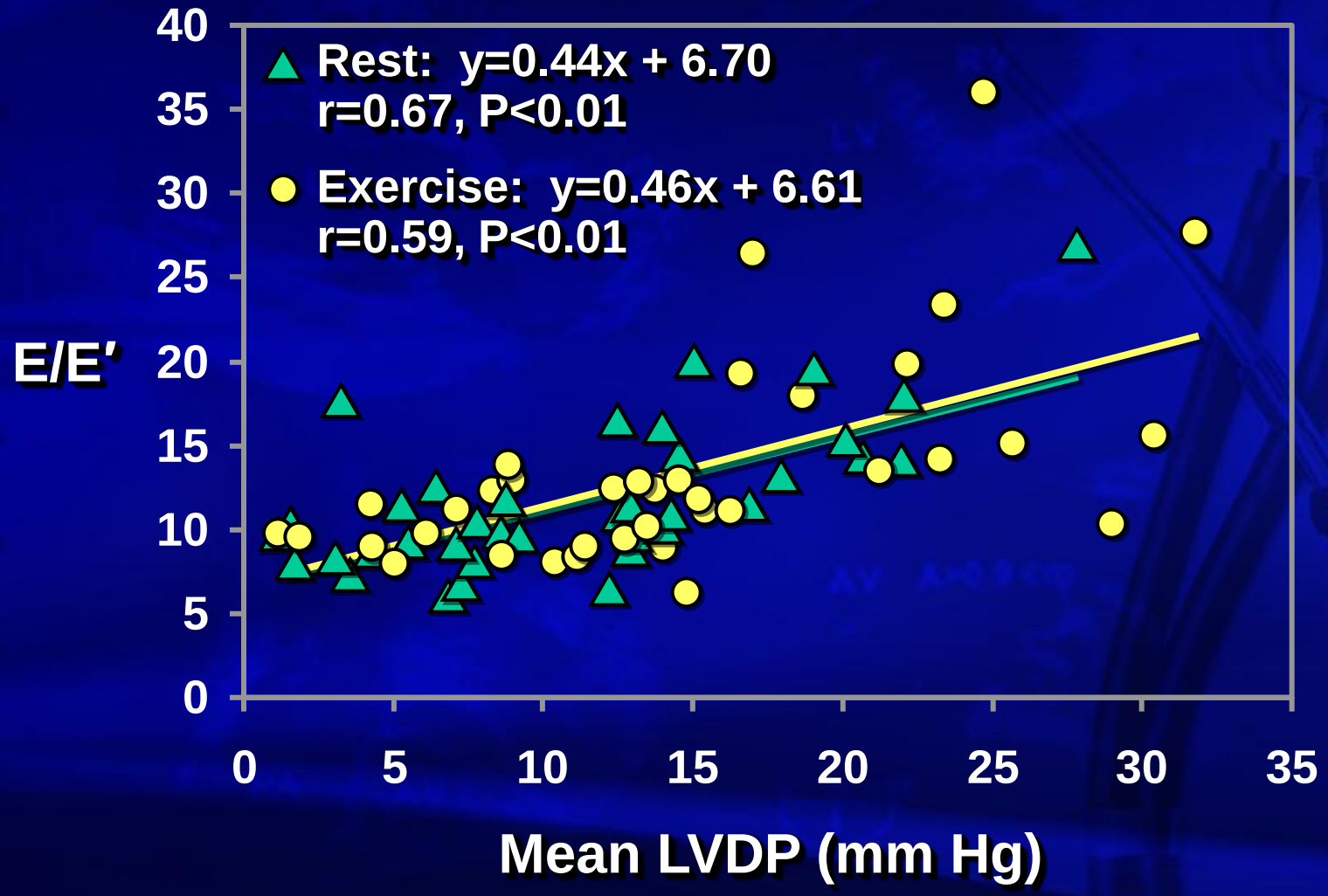
TR = 3.8

Baseline

Supine Bike

Mean LVDP vs E/E'

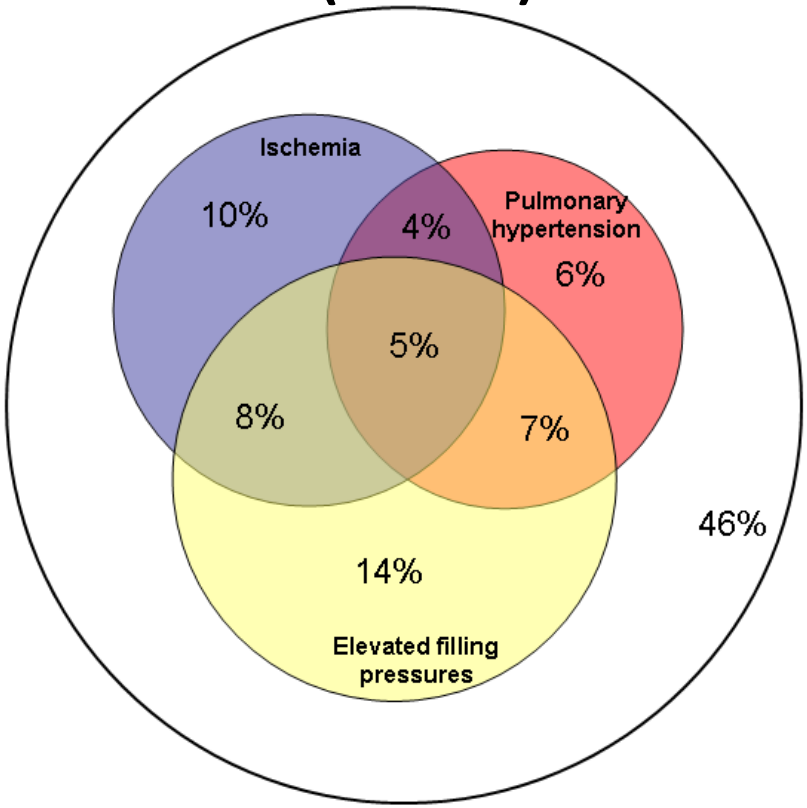
Rest and Exercise



Burgess et al: JACC 47:1891, 2006

Diastolic Function Initiative of 2006

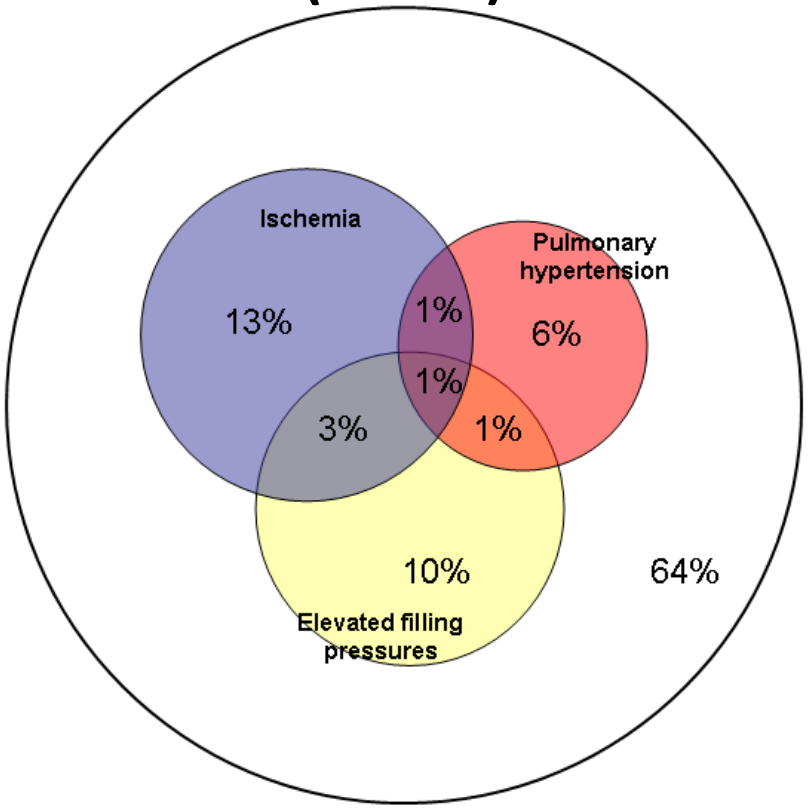
Exercise-limiting Dyspnea (n= 630)



Ischemia 27%

Any abnormality 54%

Other (n=908)



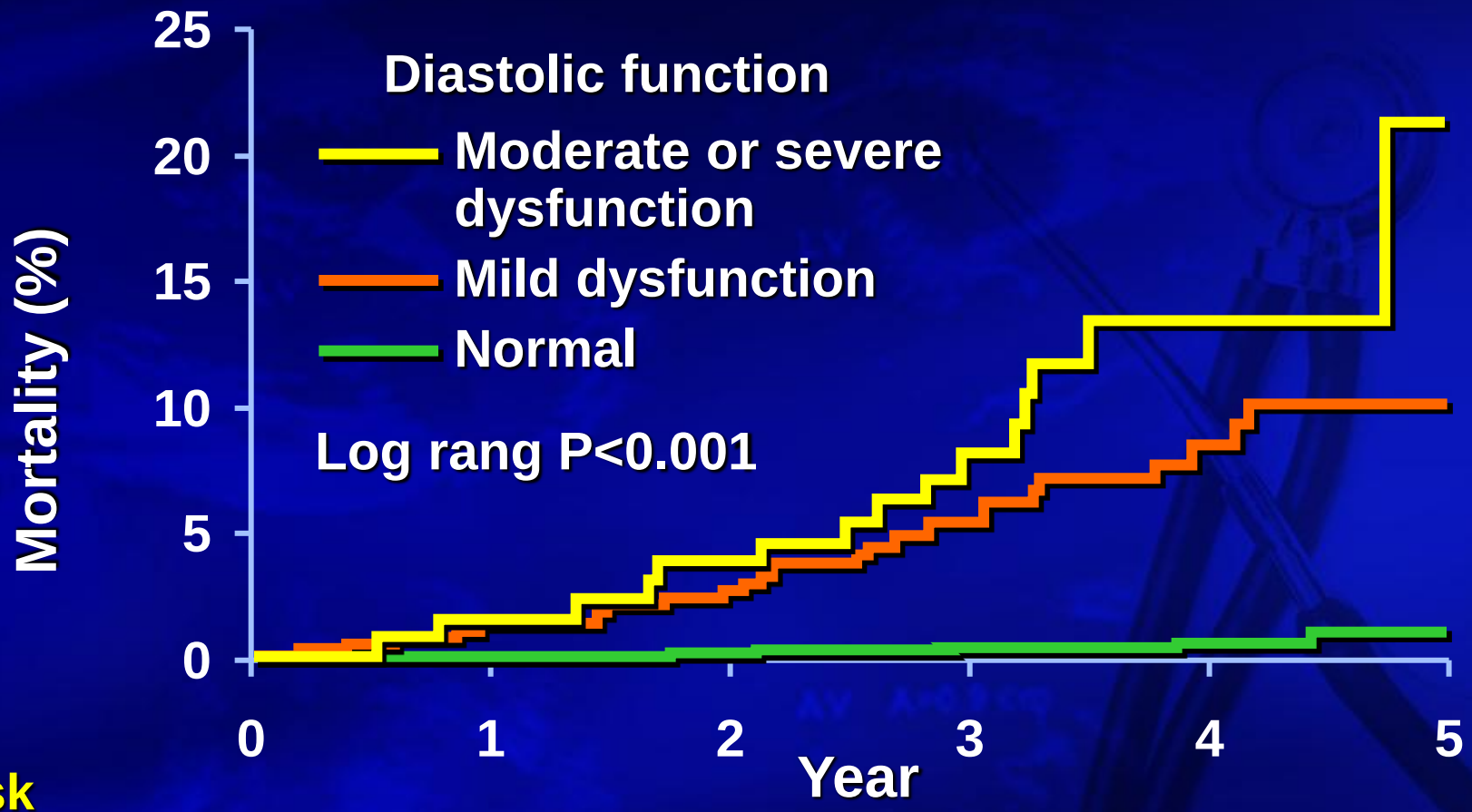
Ischemia 18%

Any abnormality 36%

Pulmonary HTN: RVSP ≥50 mm Hg with exercise
Elevated filling pressures: E/e' >13 with exercise

Courtesy of R. McCully, MD

Diastolic Function and Mortality



No. at risk						
Normal	1,277	1,277	1,275	885	404	38
Mild	371	366	361	246	122	8
Modeate or severe	131	129	126	94	39	5

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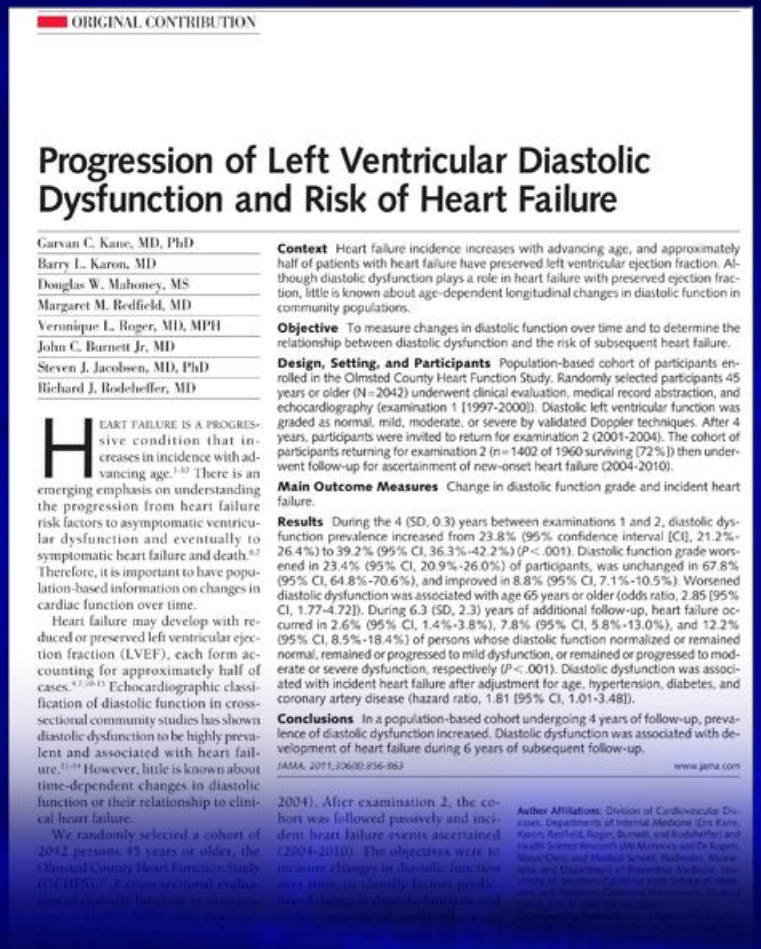
Redfield et al JAMA, 289(2), January 8, 2003

CP1095635-3

Study Flow



ORIGINAL CONTRIBUTION

Progression of Left Ventricular Diastolic Dysfunction and Risk of Heart Failure

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Context Heart failure incidence increases with advancing age, and approximately half of patients with heart failure have preserved left ventricular ejection fraction. Although diastolic dysfunction plays a role in heart failure with preserved ejection fraction, little is known about age-dependent longitudinal changes in diastolic function in community populations.

Objective To measure changes in diastolic function over time and to determine the relationship between diastolic dysfunction and the risk of subsequent heart failure.

Design, Setting, and Participants Population-based cohort of participants enrolled in the Olmsted County Heart Function Study. Randomly selected participants 45 years or older (N=2042) underwent clinical evaluation, medical record abstraction, and echocardiography (examination 1 [1997-2000]). Diastolic left ventricular function was graded as normal, mild, moderate, or severe by validated Doppler techniques. After 4 years, participants were invited to return for examination 2 (2001-2004). The cohort of participants returning for examination 2 (n=1402 of 1960 surviving [72%]) then underwent follow-up for ascertainment of new-onset heart failure (2004-2010).

Main Outcome Measures Change in diastolic function grade and incident heart failure.

Results During the 4 (SD, 0.3) years between examinations 1 and 2, diastolic dysfunction prevalence increased from 23.8% (95% confidence interval [CI], 21.2%-26.4%) to 39.2% (95% CI, 36.3%-42.2%) ($P<.001$). Diastolic function grade worsened in 23.4% (95% CI, 20.9%-26.0%) of participants, was unchanged in 67.8% (95% CI, 64.8%-70.6%), and improved in 8.8% (95% CI, 7.1%-10.5%). Worsened diastolic dysfunction was associated with age 65 years or older (odds ratio, 2.85 [95% CI, 1.77-4.72]). During 6.3 (SD, 2.3) years of additional follow-up, heart failure occurred in 2.6% (95% CI, 1.4%-3.8%), 7.8% (95% CI, 5.8%-13.0%), and 12.2% (95% CI, 8.5%-18.4%) of persons whose diastolic function normalized or remained normal, remained or progressed to mild dysfunction, or remained or progressed to moderate or severe dysfunction, respectively ($P<.001$). Diastolic dysfunction was associated with incident heart failure after adjustment for age, hypertension, diabetes, and coronary artery disease (hazard ratio, 1.81 [95% CI, 1.01-3.48]).

Conclusions In a population-based cohort undergoing 4 years of follow-up, prevalence of diastolic dysfunction increased. Diastolic dysfunction was associated with development of heart failure during 6 years of subsequent follow-up.

JAMA. 2011;306(8):856-863 www.jama.com

HEART FAILURE IS A PROGRESSIVE condition that increases in incidence with advancing age.[1-10] There is an emerging emphasis on understanding the progression from heart failure risk factors to asymptomatic ventricular dysfunction and eventually to symptomatic heart failure and death.[6,7] Therefore, it is important to have population-based information on changes in cardiac function over time.

Heart failure may develop with reduced or preserved left ventricular ejection fraction (LVEF), each form accounting for approximately half of cases.[4,7,10-13] Echocardiographic classification of diastolic function in cross-sectional community studies has shown diastolic dysfunction to be highly prevalent and associated with heart failure.[11-14] However, little is known about time-dependent changes in diastolic function or their relationship to clinical heart failure.

We randomly selected a cohort of 2042 persons 45 years or older, the Olmsted County Heart Function Study (OCHFS), [illegible] 2004). After examination 2, the cohort was followed passively and incident heart failure events ascertained (2004-2010). The objectives were to measure changes in diastolic function over time, to identify factors predic[illegible]

Author Affiliations: Division of Cardiovascular Diseases, Departments of Internal Medicine (Drs Kane, Karon, Redfield, Roger, Burnett, and Rodeheffer) and Health Sciences Research (Mr Mahoney and Dr Roger), Mayo Clinic and Mayo Medical School, Rochester, Minnesota, and Department of Preventive Medicine, University of Southern California Keck School of Medicine, [illegible]

4,203 individual randomly invited to participate

→ 2,161 excluded (did not participate in examination 1

2,402 participated in examination 1 (1997-2000)

→ 640 excluded
558 did not return for examination 2
82 died before examination 2

1,402 returned for examination 2 (2001-2004)

1,151 classifiable diastolic function
139 indeterminate diastolic function
112 diastolic dysfunction, determinate grade

Kane et al: JAMA 2011;306(8):856-863

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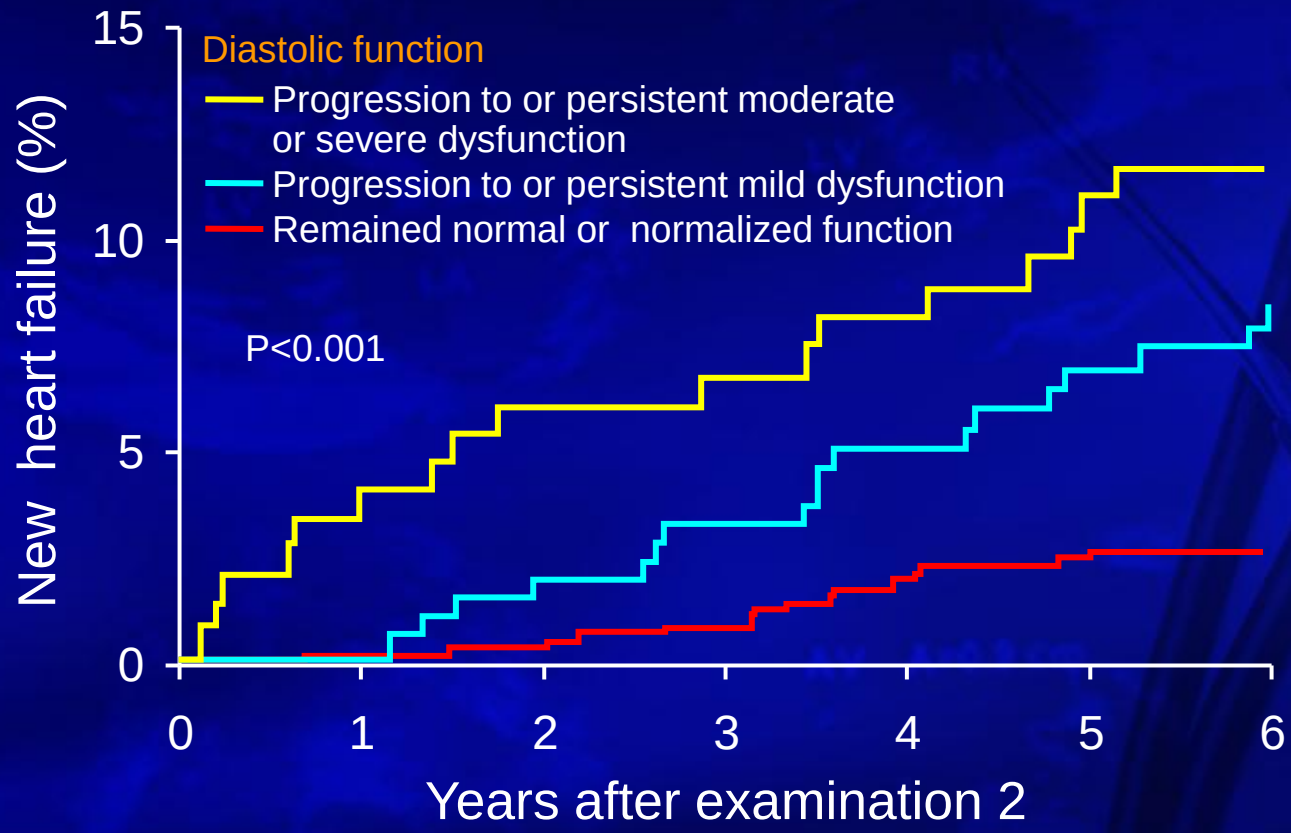
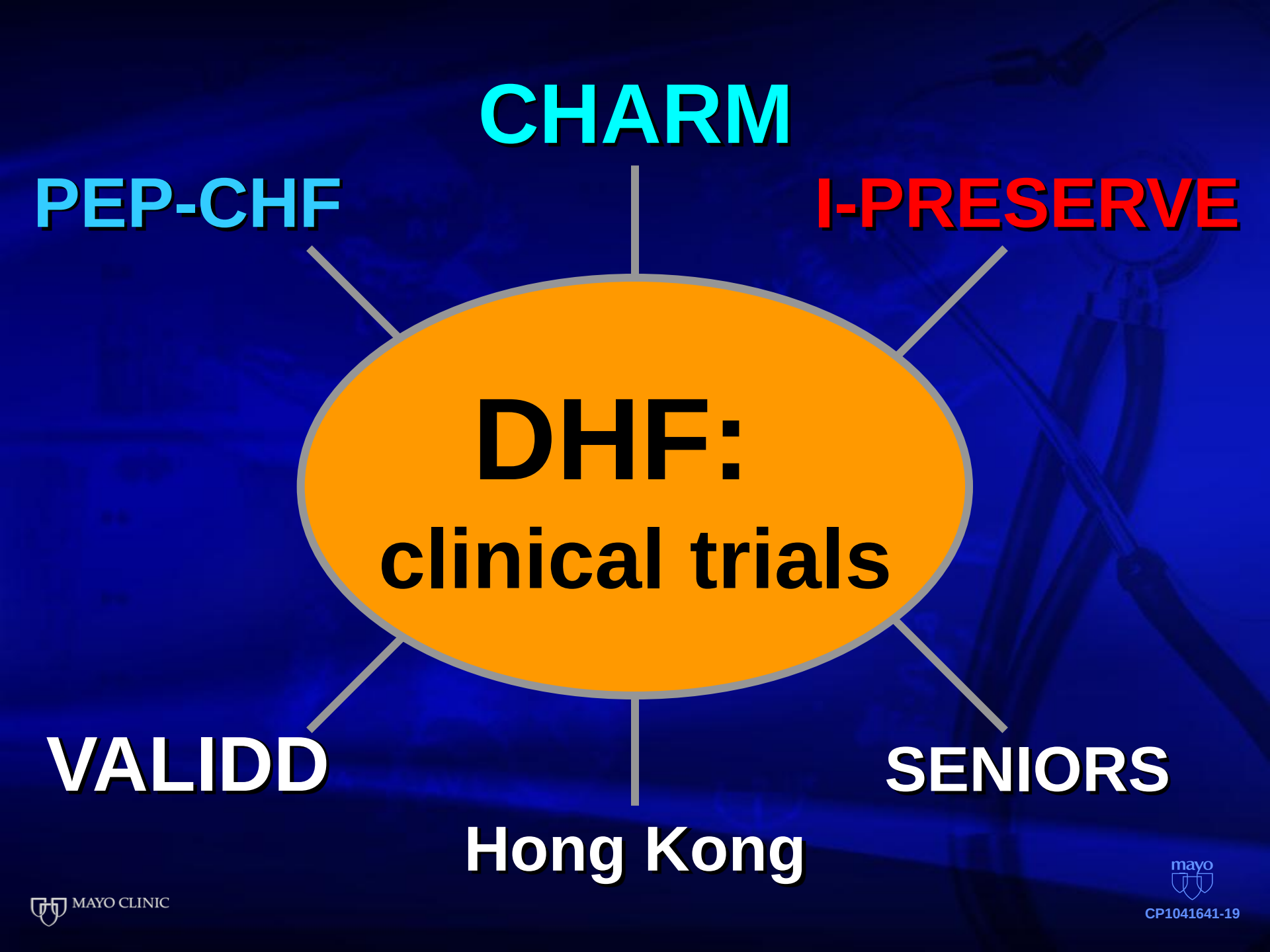
Cumulative Incidence of Heart Failure After Examination 2



No. at risk

Moderate or severe	160	146	140	136	129	124	114
Mild	239	233	222	216	208	198	182
Normal/normalized	648	608	600	584	566	537	499

Kane et al: JAMA 2011;306(8):856-863


CHARM
PEP-CHF
I-PRESERVE
DHF:
clinical trials
VALIDD
SENIORS
Hong Kong

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

Barry M. Massie, MD, Peter E. Carson, MD, John J. McMurray, MD, Michael Komajda, MD, Robert McKelvie, MD, Michael R. Zile, MD, Susan Anderson, MS, Mark Donovan, PhD, Erik Iverson, MS, Christoph Staiger, MD, and Agata Ptaszynska, MD, for the I-PRESERVE Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

Barry M. Massie, M.D., Peter E. Carson, M.D., John J. McMurray, M.D., Michel Komajda, M.D., Robert McKelvie, M.D., Michael R. Zile, M.D., Susan Anderson, M.S., Mark Donovan, Ph.D., Erik Iverson, M.S., Christoph Staiger, M.D., and Agata Ptaszynska, M.D., for the I-PRESERVE Investigators*

ABSTRACT

BACKGROUND

Approximately 50% of patients with heart failure have a left ventricular ejection fraction of at least 45%, but no therapies have been shown to improve the outcome of these patients. Therefore, we studied the effects of irbesartan in patients with this syndrome.

METHODS

We enrolled 4128 patients who were at least 60 years of age and had New York Heart

of at least 45%

acebo per day.

talization for a

le angina, ar-

eart failure or

cardiovascular

During a mean follow-up of 49.5 months, the primary outcome occurred in 742 patients in the irbesartan group and 763 in the placebo group. Primary event rates in the irbesartan and placebo groups were 100.4 and 105.4 per 1000 patient-years, respectively (hazard ratio, 0.95; 95% confidence interval [CI], 0.86 to 1.05; P=0.35). Overall rates of death were 52.6 and 52.3 per 1000 patient-years, respectively (hazard ratio, 1.00; 95% CI, 0.88 to 1.14; P=0.98). Rates of hospitalization for cardiovascular causes that contributed to the primary outcome were 70.6 and 74.3 per 1000 patient-years, respectively (hazard ratio, 0.95; 95% CI, 0.85 to 1.08; P=0.44). There were no significant differences in the other prespecified outcomes.

CONCLUSIONS

Irbesartan did not improve the outcomes of patients with heart failure and a preserved left ventricular ejection fraction. (ClinicalTrials.gov number, NCT00095238.)

dation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom (J.J.M.); Université Paris 6

*Committee members and investigators in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

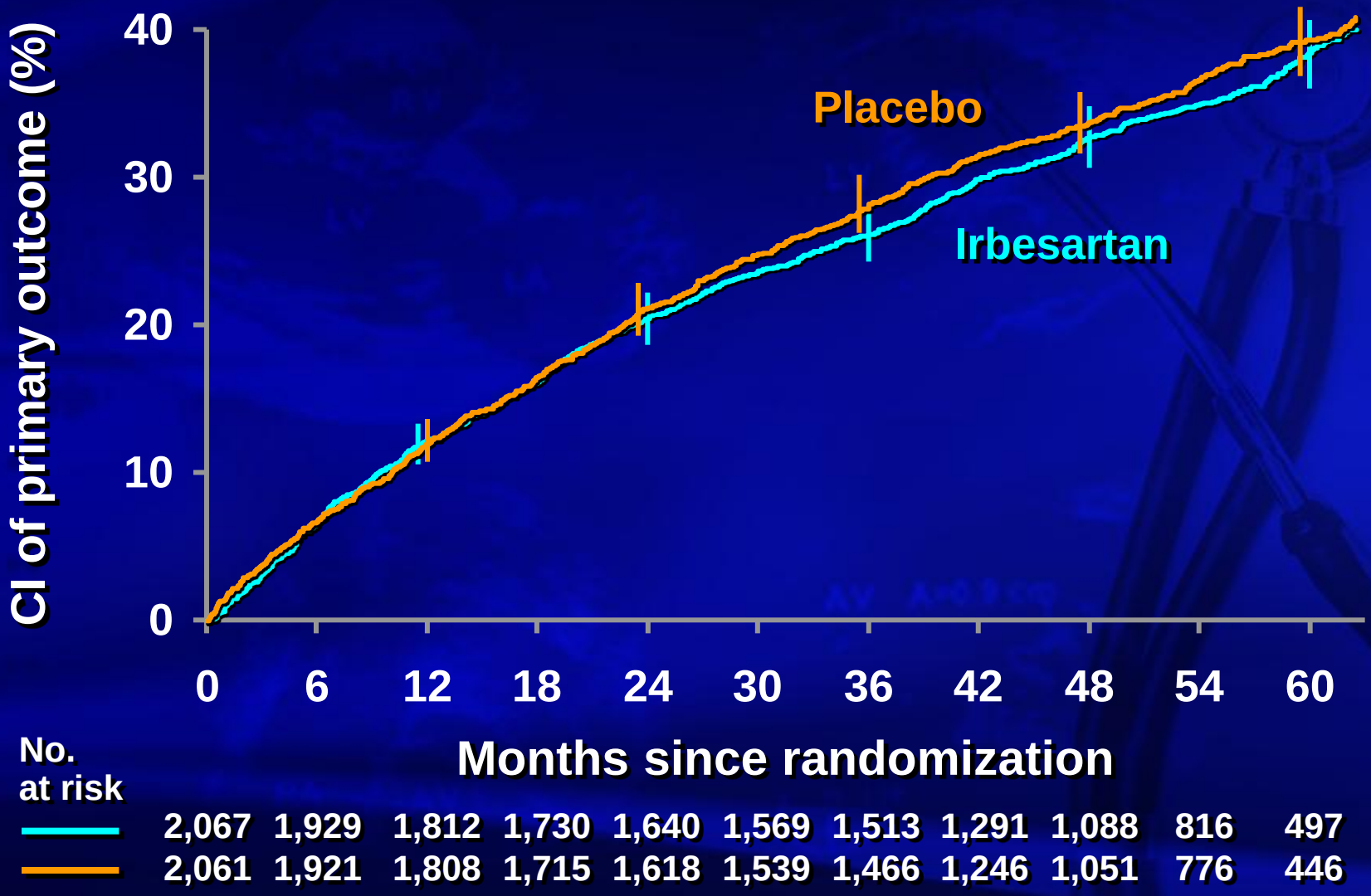
This article (10.1056/NEJMoa0805450) was published at www.nejm.org on November 11, 2008.

N Engl J Med 2008;359:2456-67.

Conclusions – Irbesartan did not improve the outcomes of patients with HF and a preserved LVEF.

N Engl J Med 2008; 359:2456-67

Kaplan-Meier Curves for Primary Outcome



Massie et al: NEJM 359:2456, 2008

nature medicine

Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy

Eiki Takimoto[1,5], Hunter C Champion[1,5], Manxiang Li[1,5], Diego Belardi[1], Shuxun Ren[2], E Rene Rodriguez[3], Djahida Bedja[4], Kathleen L Gabrielson[4], Yibin Wang[2] & David A Kass[1]

Sustained cardiac pressure overload induces hypertrophy and pathological remodeling, frequently leading to heart failure. Genetically engineered hyperstimulation of guanosine 3′,5′-cyclic monophosphate (cGMP) synthesis counters this response. Here, we show that blocking the intrinsic catabolism of cGMP with an oral phosphodiesterase-5A (PDE5A) inhibitor (sildenafil) suppresses chamber and myocyte hypertrophy, and improves *in vivo* heart function in mice exposed to chronic pressure overload induced by transverse aortic constriction. Sildenafil also reverses pre-established hypertrophy induced by pressure load while restoring chamber function to normal. cGMP catabolism by PDE5A increases in pressure-loaded hearts, leading to activation of cGMP-dependent protein kinase with inhibition of PDE5A. PDE5A inhibition deactivates multiple hypertrophy signaling pathways triggered by pressure load (the calcineurin/NFAT, phosphoinositide-3 kinase (PI3K)/Akt, and ERK1/2 signaling pathways). But it does not suppress hypertrophy induced by overexpression of calcineurin *in vitro* or Akt *in vivo*, suggesting upstream targeting these pathways. PDE5A inhibition may provide a new treatment strategy for cardiac hypertrophy and remodeling

In hearts exposed to sustained pressure overload, cellular, molecular and morphologic changes are activated that often become maladaptive and contribute to progressive cardiac dysfunction and heart failure. This response involves the stimulation of multiple signaling and transcription pathways that induce hypertrophic remodeling[1,2]. Potential therapeutic targets aimed at inhibiting these enzymes have been proposed[3–5], but so far most have been only tested using genetically engineered animals, whereas small-molecule approaches remain scarce.

The heart also has an intrinsic signaling system coupled to cGMP that can inhibit myocardial proliferative responses. As revealed in models with enhanced cGMP synthesis resulting from genetic upregulation

function. PDE5A is expressed in the myocardium[16,17] and see active; however, its role in the heart has been questioned as its in has minimal effects on resting heart function[18]. Here, we much greater role of PDE5A in hearts subjected to sustain sure load and show that PDE5A inhibition in this setting prev reverses cardiac chamber, cellular and molecular remodeling by this stimulus.

RESULTS

PDE5A inhibition blunts hypertrophy, remodeling and fibrosis

We subjected adult C57Bl/6 mice to constriction of the transverse

nature medicine **Feb 2005**

Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy

Eiki Takimoto et al

PDE5A inhibition may provide a new treatment strategy for cardiac hypertrophy and remodeling.

Oral phosphodiesterase-5A (PDE5A) inhibitor (sildenafil) suppresses chamber and myocyte hypertrophy, and improves in vivo heart function in mice exposed to chronic pressure overload induced by transverse aortic constriction, Sildenafil also reverses pre-established hypertrophy induced by pressure load while restoring chamber function to normal.

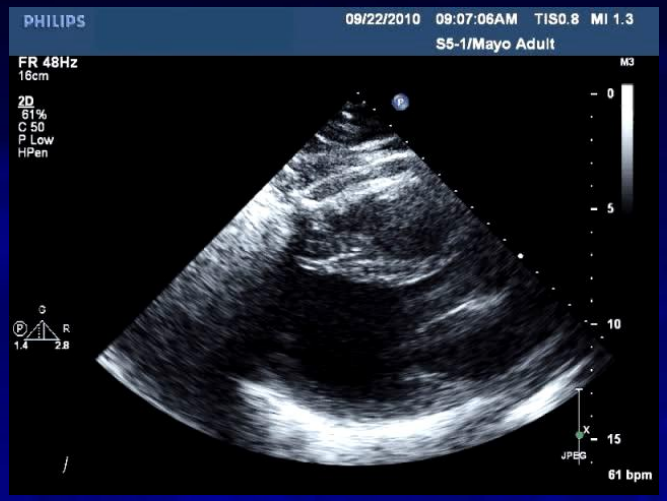
PhosphodiesteRasE-5 Inhibition to Improve CLinical Status And EXercise Capacity in Diastolic Heart Failure

RELAX

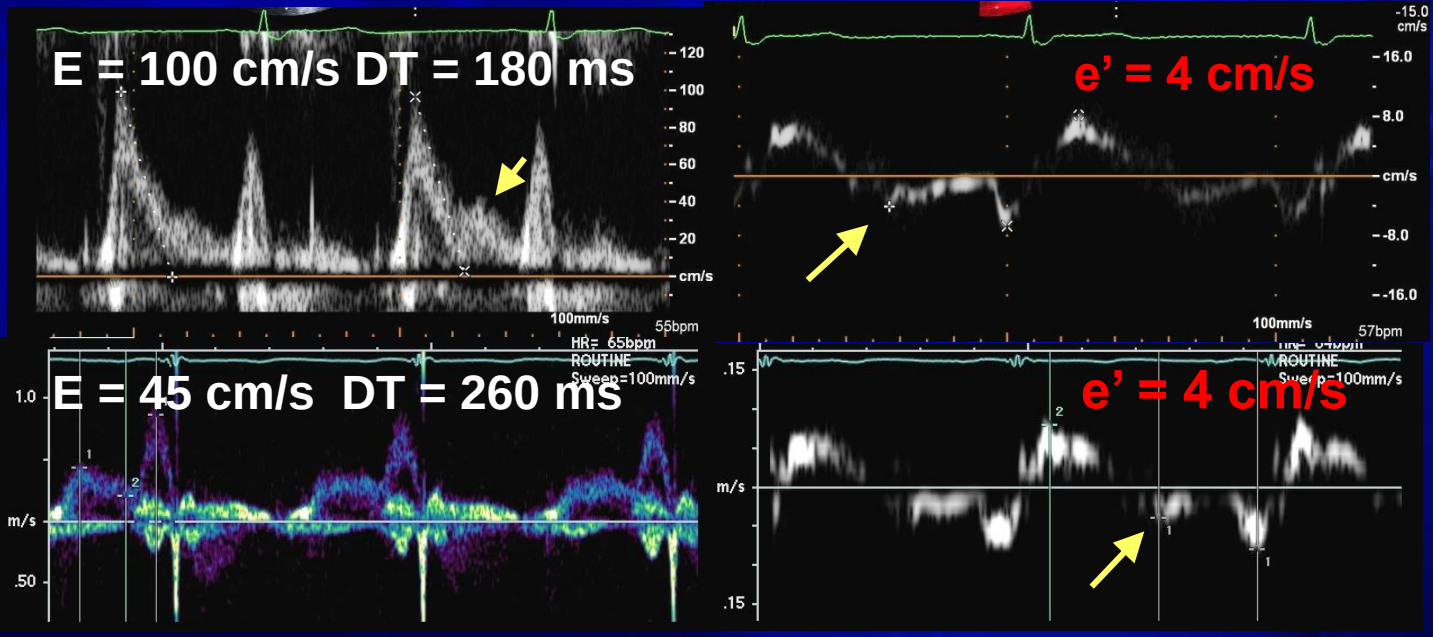
in Progress

NIH Heart Failure Clinical Research Network

MAYO CLINIC



Before and after treatment of HF Diuretic and ARB 6 days apart



E/e' 25

E/e' 11

E velocity 100 to 45

No change in e' velocity

Does this patient with "HF symptoms" and EF>50% have HF?

- ✓ Elevated PASP?
- ✓ Doppler DD consistent with symptoms?
- ✓ LA enlargement?
- ✓ LVH or Concentric Remodeling?
- ✓ Elevated BNP?
- ✓ Response to diuretics?
- ✓ CXR and Physical Exam cw HF

The more items checked, the ↑ the probability, but no single parameter necessary or sufficient.

If Dx uncertain, Assessment with Exercise

"Once you start studying medicine you never get through with it."

Charles H. Mayo, MD

Thanks for listening !

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European Heart Journal (2005) 26, 1115–1140
doi:10.1093/eurheartj/ehi204

ESC Guidelines

Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005)

The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology

Authors/Task Force Members: Karl Swedberg, Chairperson,* Göteborg (Sweden) *Writing Committee:* John Cleland, Hull (UK), Henry Dargie, Glasgow (UK), Helmut Drexler, Hannover (Germany), Ferenc Follath, Zurich (Switzerland), Michel Komajda, Paris (France), Luigi Tavazzi, Pavia (Italy), Otto A. Smiseth, Oslo (Norway).
Other Contributors: Antonello Gavazzi, Bergamo (Italy), Axel Haverich, Hannover (Germany), Arno Hoes, Utrecht (The Netherlands), Tiny Jaarsma, Gronigen (The Netherlands), Jerzy Korewicki, Warsaw (Poland), Samuel Lévy, Marseille (France), Cecilia Linde, Stockholm (Sweden), José-Luis Lopez-Sendon, Madrid (Spain), Markku S. Nieminen, Helsinki (Finland), Luc Piérard, Liège (Belgium), Willem J. Remme, Rhoon (The Netherlands)

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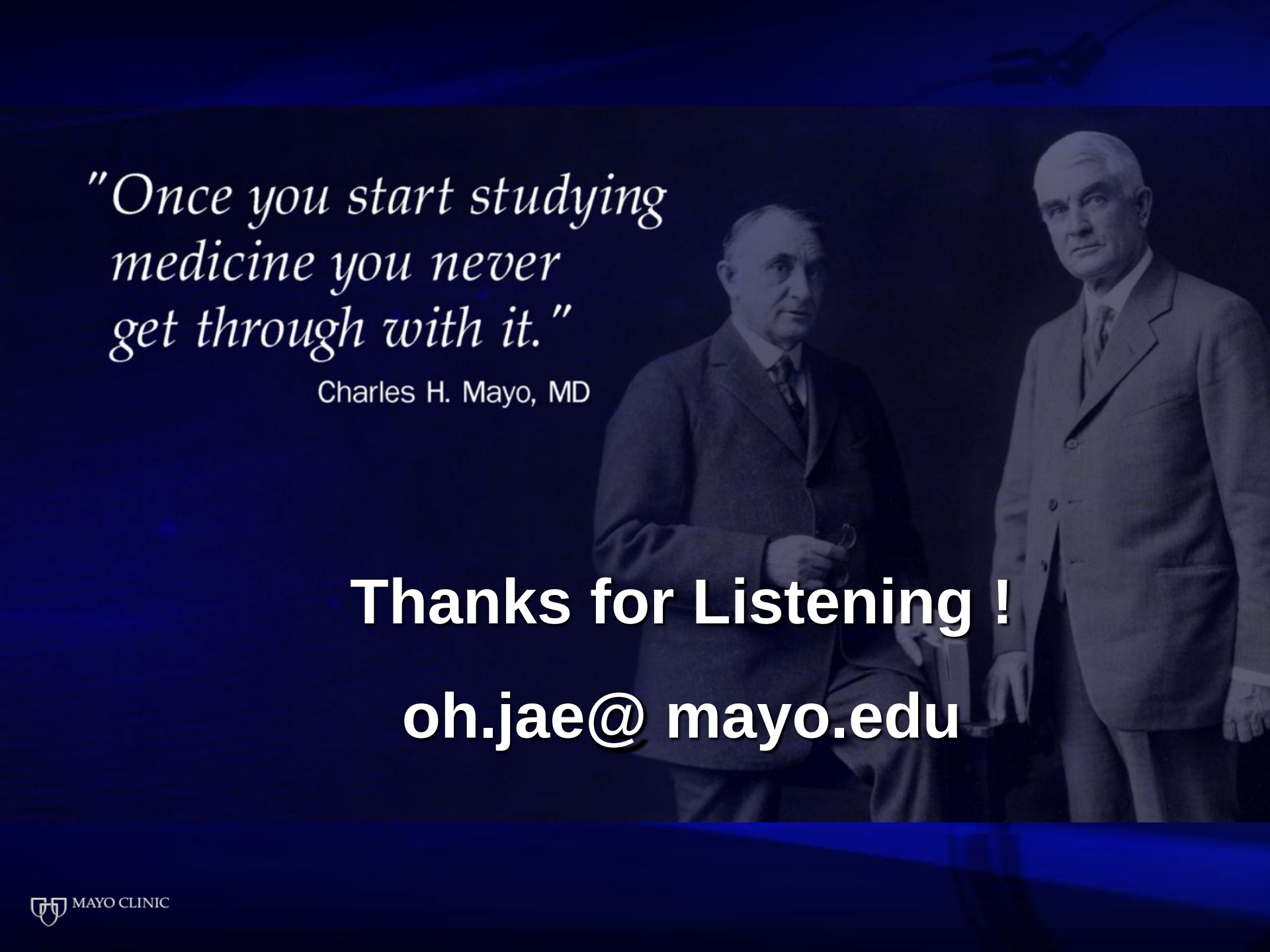
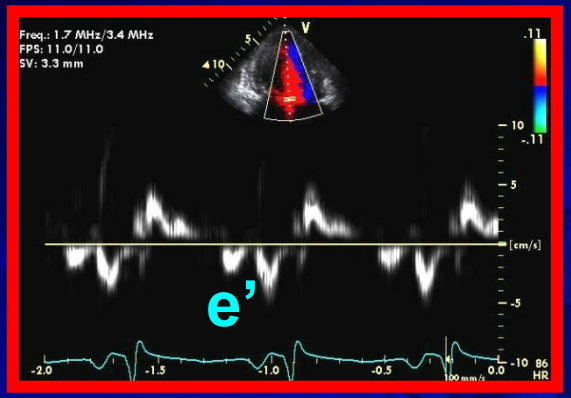
European Heart J
26:1115, 2005

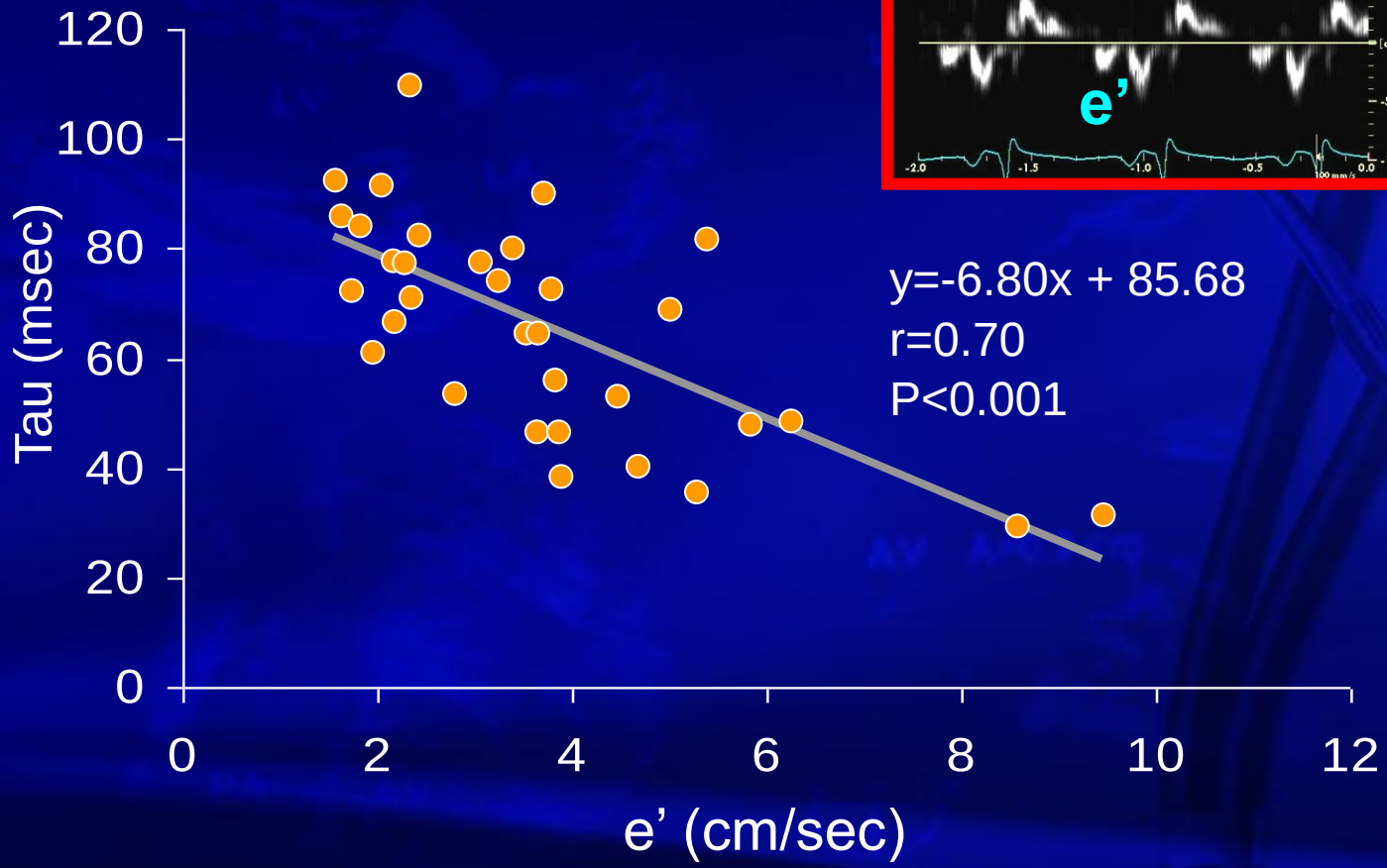


Thanks for Listening !

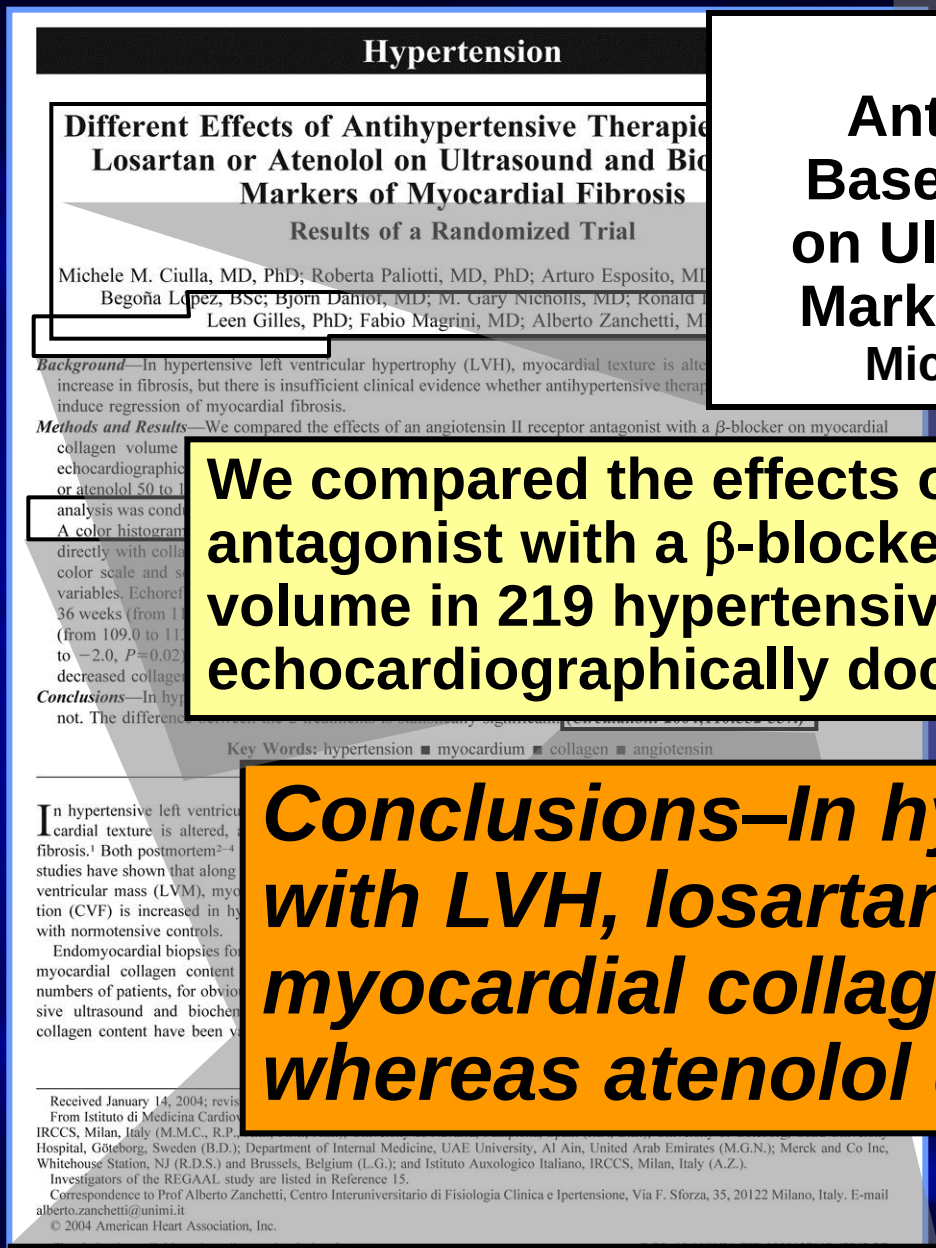
oh.jae@ mayo.edu

Relationship Between e' and τ





Firstenberg et al: J Appl Physiol 90:299, 2001, Nagueh et al: JACC 1997
Oki et al: AJC 1997 , Sohn et al:JACC 1997, Ommen et al: Circ 2000
Opdahl et al: Circulation 119:2578, 2009, and more


Hypertension

Different Effects of Antihypertensive Therapie
Losartan or Atenolol on Ultrasound and Bio
Markers of Myocardial Fibrosis

Results of a Randomized Trial

Michele M. Ciulla, MD, PhD; Roberta Paliotti, MD, PhD; Arturo Esposito, MD
Begoña López, BSc; Bjorn Dahlof, MD; M. Gary Nicholls, MD; Ronald
Leen Gilles, PhD; Fabio Magrini, MD; Alberto Zanchetti, M

Background—In hypertensive left ventricular hypertrophy (LVH), myocardial texture is alte
increase in fibrosis, but there is insufficient clinical evidence whether antihypertensive therap
induce regression of myocardial fibrosis.

Methods and Results—We compared the effects of an angiotensin II receptor antagonist with a β-blocker on myocardial
collagen volume
echocardiographic
or atenolol 50 to
analysis was cond
A color histogram
directly with colla
color scale and s
variables, Echoref
36 weeks (from 1
(from 109.0 to 11
to −2.0, P=0.02
decreased collage

Conclusions—In hy
not. The differenc

Key Words: hypertension ■ myocardium ■ collagen ■ angiotensin

In hypertensive left ventricu
cardial texture is altered,
fibrosis.[1] Both postmortem[2–4]
studies have shown that along
ventricular mass (LVM), myo
tion (CVF) is increased in hy
with normotensive controls.
Endomyocardial biopsies fo
myocardial collagen content
numbers of patients, for obvio
sive ultrasound and biochem
collagen content have been v

Received January 14, 2004; revis
From Istituto di Medicina Cardiov
IRCCS, Milan, Italy (M.M.C., R.P.
Hospital, Göteborg, Sweden (B.D.); Department of Internal Medicine, UAE University, Al Ain, United Arab Emirates (M.G.N.); Merck and Co Inc, Whitehouse Station, NJ (R.D.S.) and Brussels, Belgium (L.G.); and Istituto Auxologico Italiano, IRCCS, Milan, Italy (A.Z.).
Investigators of the REGAAL study are listed in Reference 15.
Correspondence to Prof Alberto Zanchetti, Centro Interuniversitario di Fisiologia Clinica e Ipertensione, Via F. Sforza, 35, 20122 Milano, Italy. E-mail alberto.zanchetti@unimi.it

Different Effects of Antihypertensive Therapies Based on Losartan or Atenolol on Ultrasound and Biochemical Markers of Myocardial Fibrosis

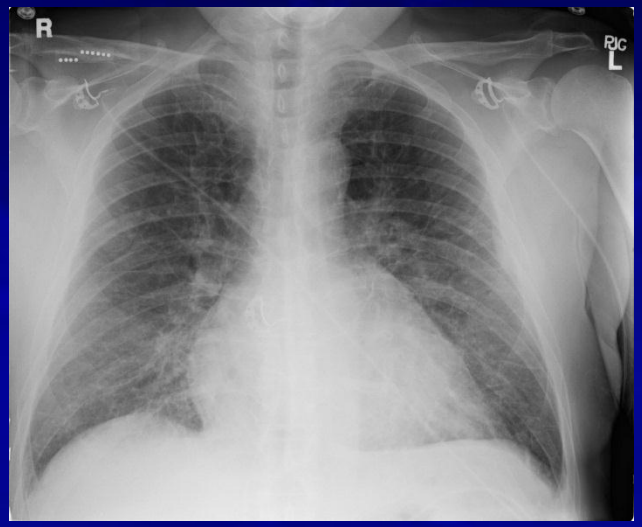
Michele M. Ciulla, MD, PhD, et al

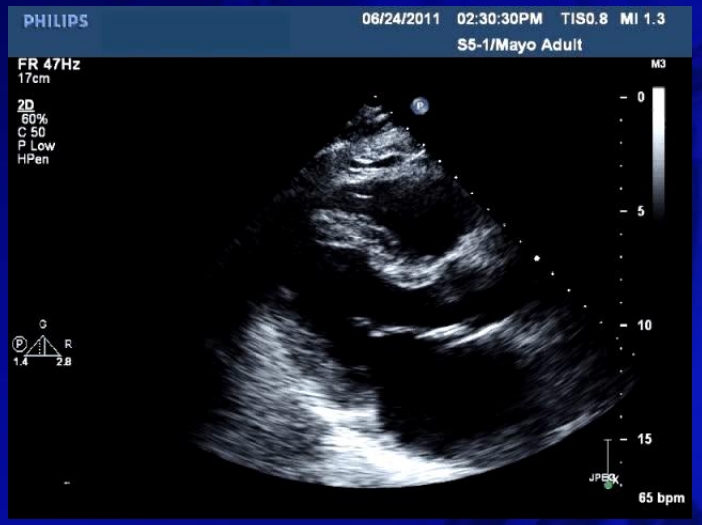
We compared the effects of an angiotensin II receptor antagonist with a β-blocker on myocardial collagen volume in 219 hypertensive patients with echocardiographically documented LVH.

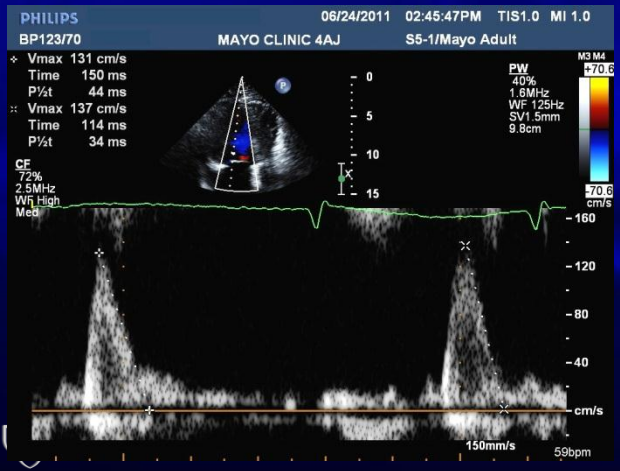
Conclusions–In hypertensive patients with LVH, losartan decreases myocardial collagen content, whereas atenolol does not.

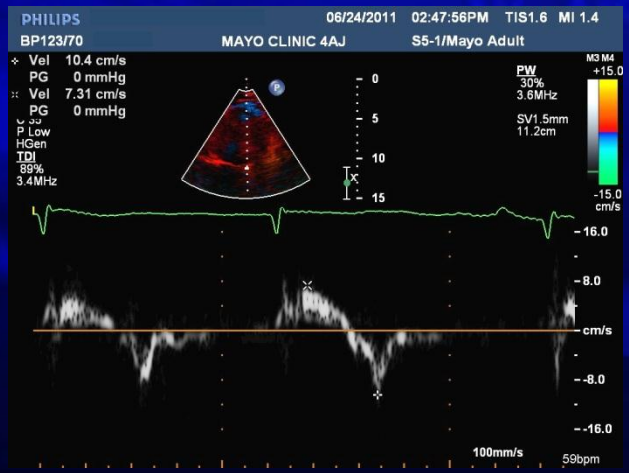
(Circulation. 2004;110:552-557.)

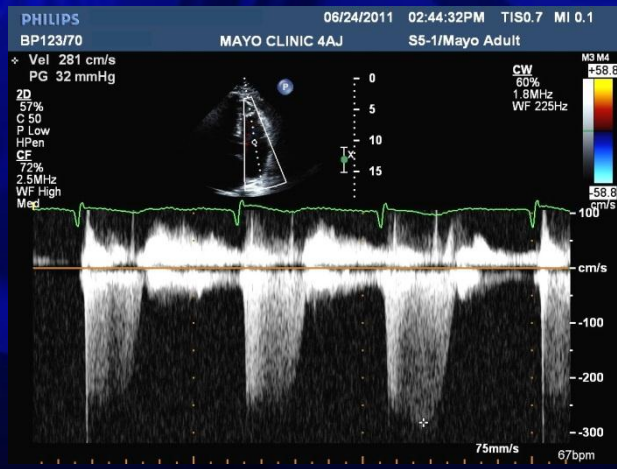
Case Example
70 year old man presents with dyspnea



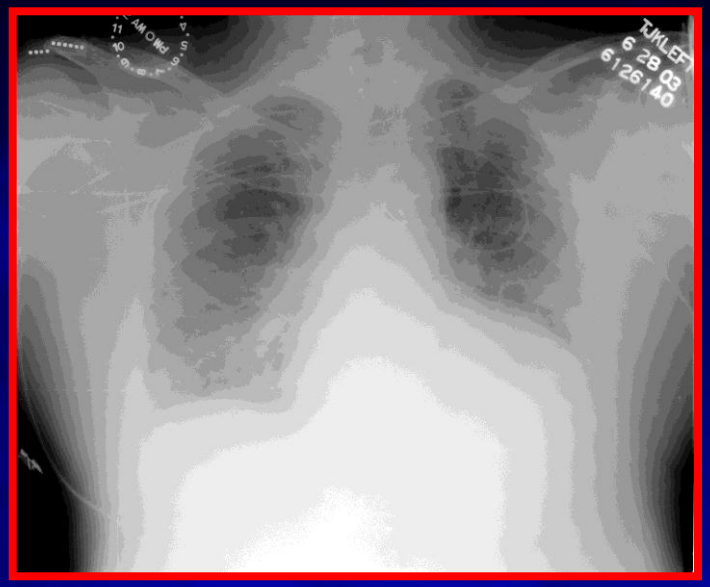


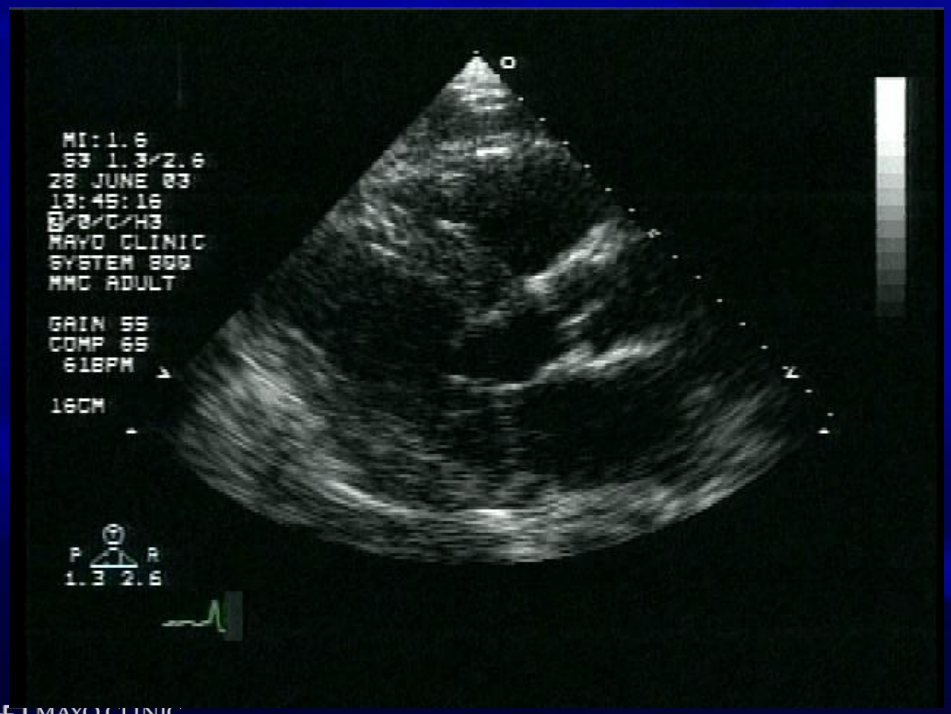


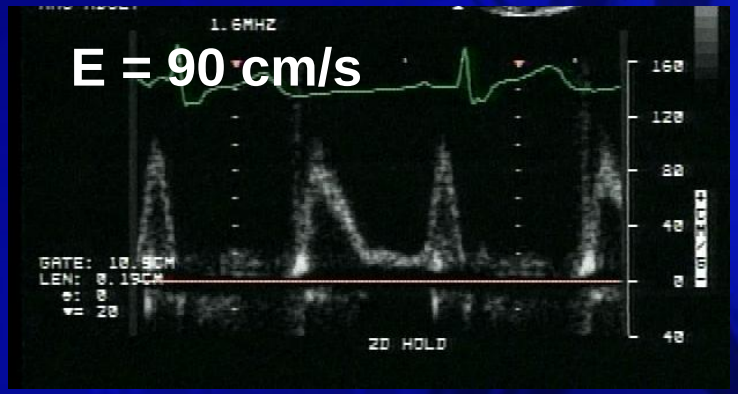


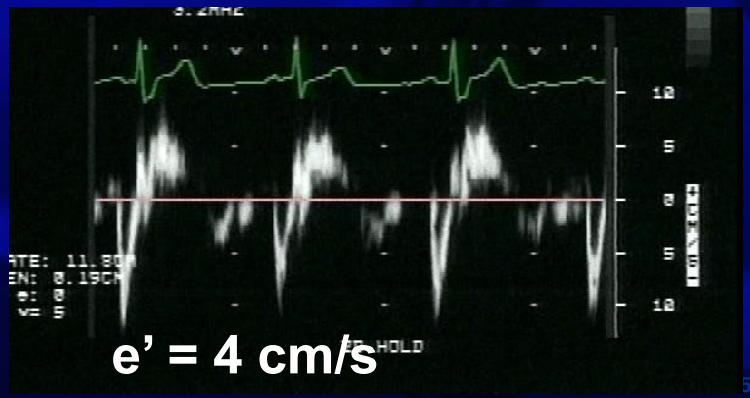


70-Year-Old Man with Dyspnea and LVEF 65 %









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.

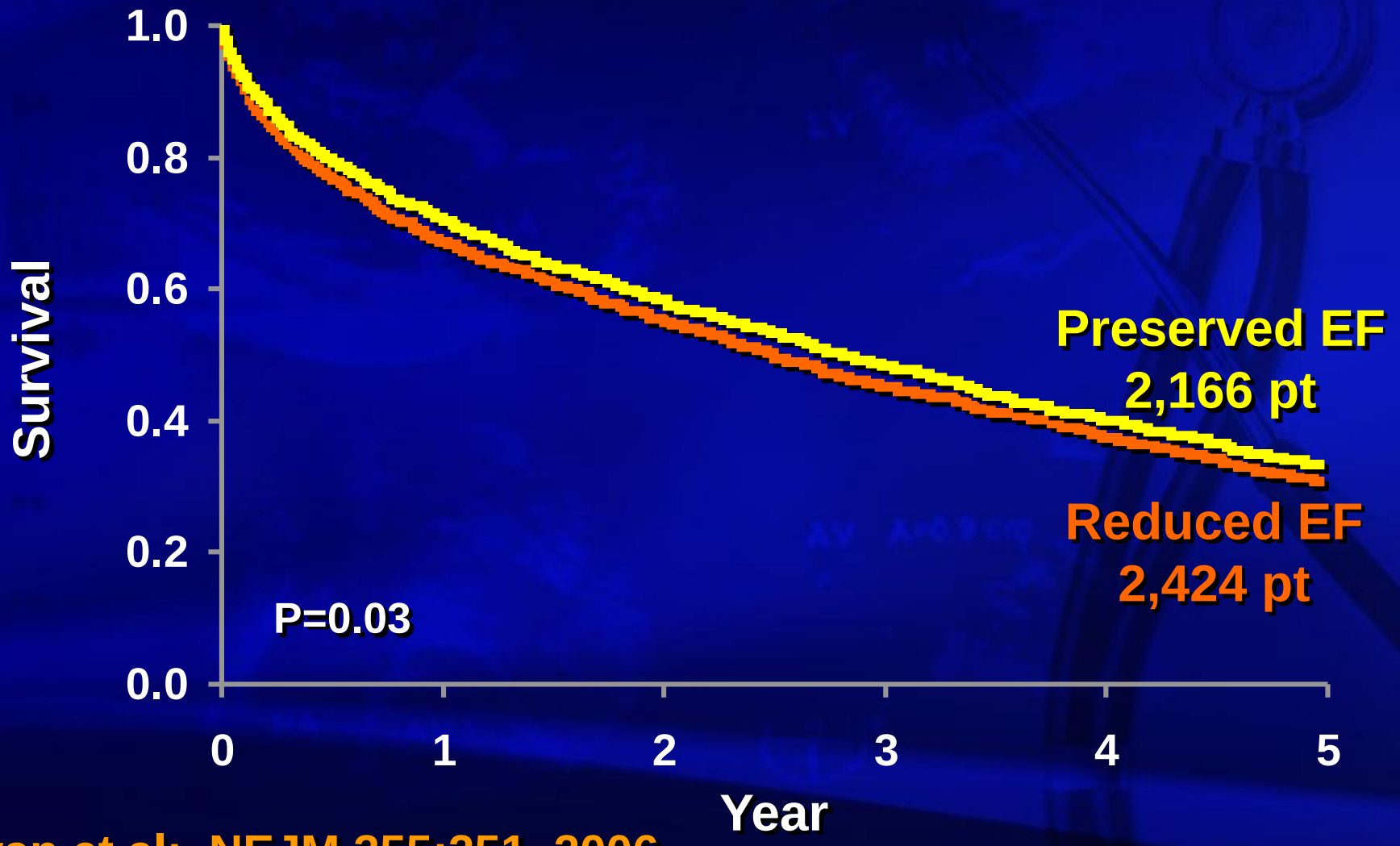
Methods and Results—Patients with exertional dyspnea and ejection fraction >50% were referred for hemodynamic catheterization. Those with no significant coronary disease, normal brain natriuretic peptide assay, and normal resting hemodynamics (mean pulmonary artery pressure <25 mm Hg and pulmonary capillary wedge pressure [PCWP] <15 mm Hg) (n=55) underwent exercise study. The exercise PCWP was used to classify patients as having HFpEF (PCWP ≥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 ≥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.**)

Key Words: heart failure ■ exercise ■ hemodynamics ■ diastole ■ diagnosis

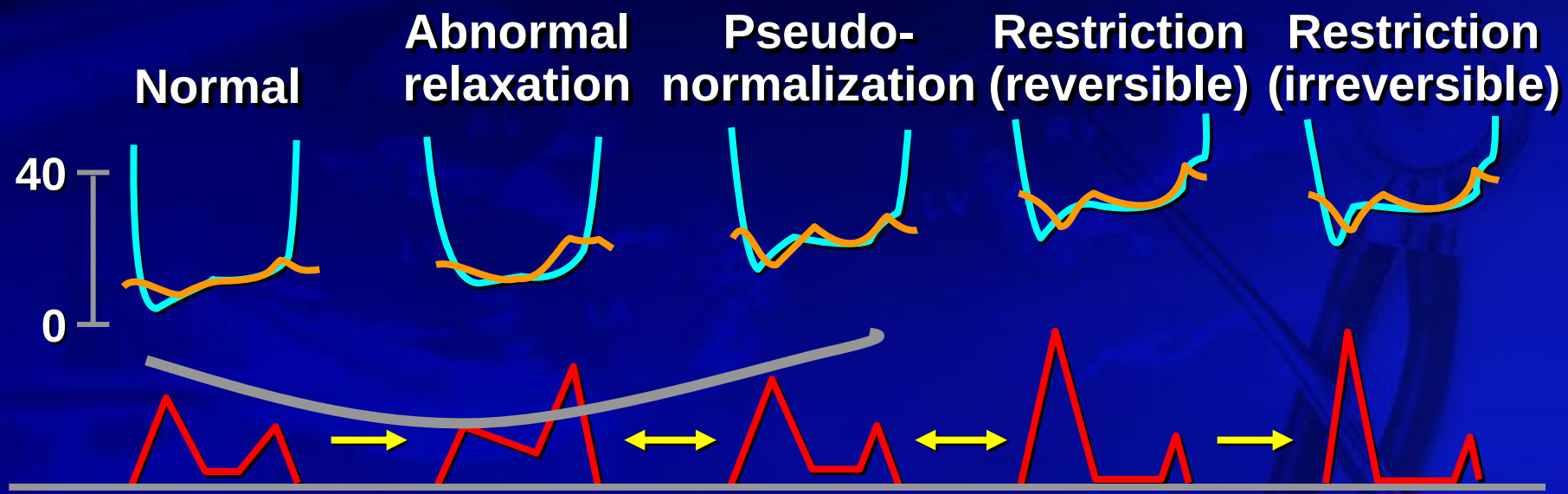
58% of pts with normal exam, echo, BNP & resting hemos have HF by exercise

Heart Failure and Preserved or Reduced Ejection Fraction



Owan et al: NEJM 355:251, 2006

Diastolic Function



Mean LAP	N-↑	↑↑	↑↑↑	↑↑↑
TAU	normal	↑	↑	↑↑	↑↑
Grade	I	II	III	IV

The NEW ENGLAND JOURNAL of MEDICINE

Diastolic Heart Failure — Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle

Michael R. Zile, M.D., Catalin F. Baicu, Ph.D., and William H. Gaasch, M.D.

METHODS

We prospectively identified 47 patients who met the diagnostic criteria for definite diastolic heart failure; all the patients had signs and symptoms of heart failure, a normal ejection fraction, and an increased left ventricular end-diastolic pressure. Ten patients who had no evidence of cardiovascular disease served as controls. Left ventricular diastolic function was assessed by means of cardiac catheterization and echocardiography.

RESULTS

The patients with diastolic heart failure had abnormal left ventricular relaxation and increased left ventricular chamber stiffness. The mean (±SD) time constant for the isovolumic-pressure decline (τ) was longer in the group with diastolic heart failure than in the control group (59±14 msec vs. 35±10 msec, P=0.01). The diastolic pressure–volume relation was shifted up and to the left in the patients with diastolic heart failure as com-

partment of Cardiovascular Medicine, Lahey Clinic, Burlington, Mass. (W.H.G.), and the Division of Cardiovascular Medicine, University of Massachusetts Medical School, Worcester, Mass. (W.H.G.). Address reprint requests to Dr. Zile at Cardiology/Medicine, Medical University of South Carolina, 135 Rutledge Ave., Suite 1201, P.O. Box 250592, Charleston, SC 29425, or at zilem@musc.edu.

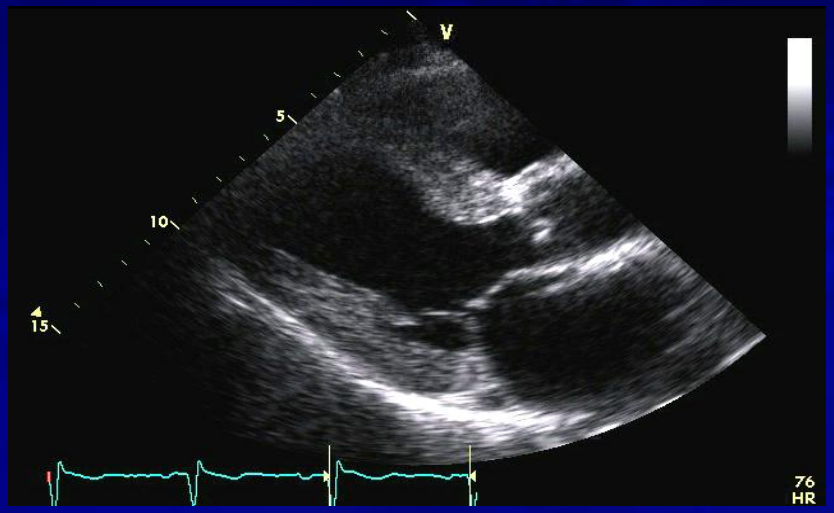
N Engl J Med 2004;350:1953-9.

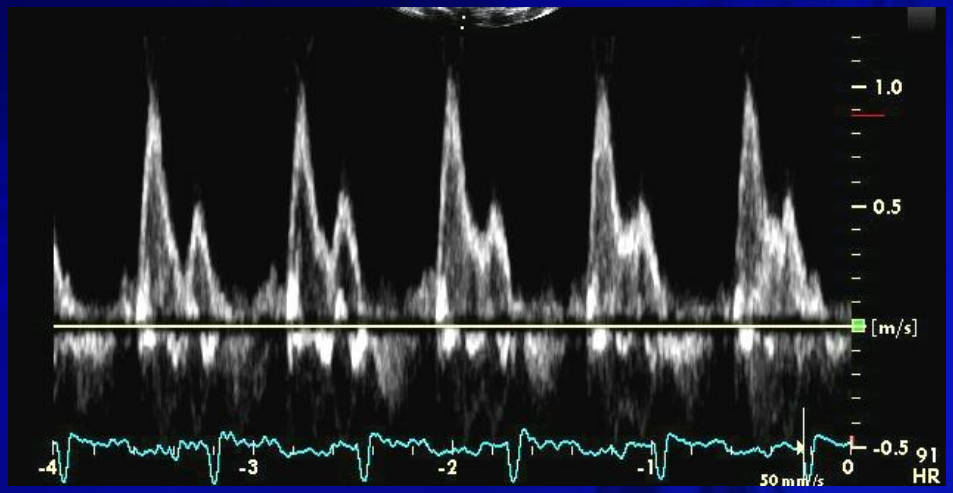
CONCLUSIONS

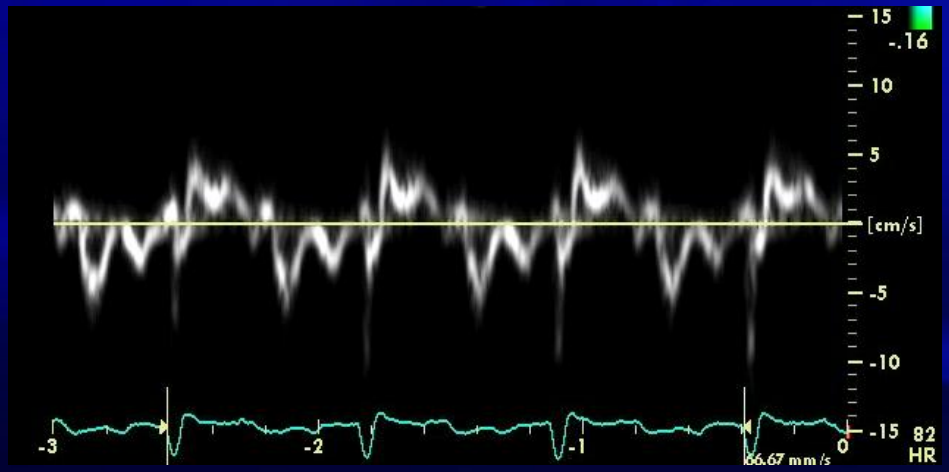
Patients with heart failure and a normal ejection fraction have significant abnormalities in active relaxation and passive stiffness. In these patients, the pathophysiological cause of elevated diastolic pressures and heart failure is abnormal diastolic function.

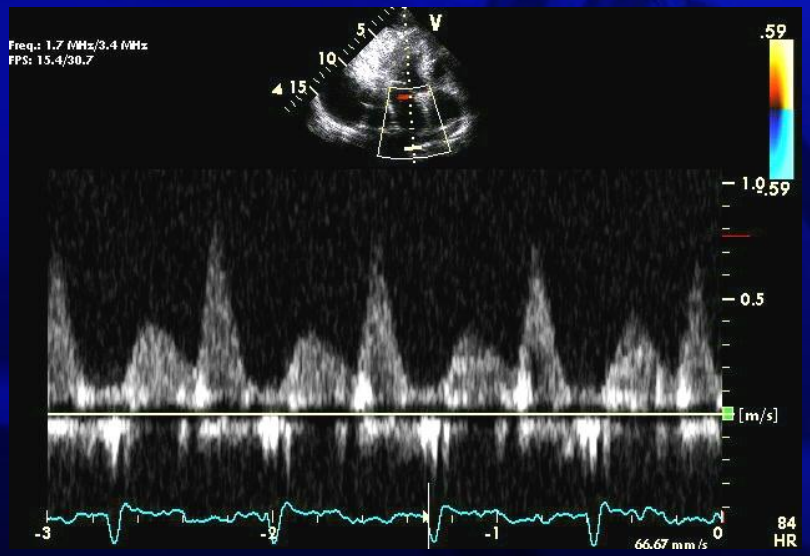
Zile et al: NEJM 350:1953, 2004

69 year old man with dyspnea for 5 months



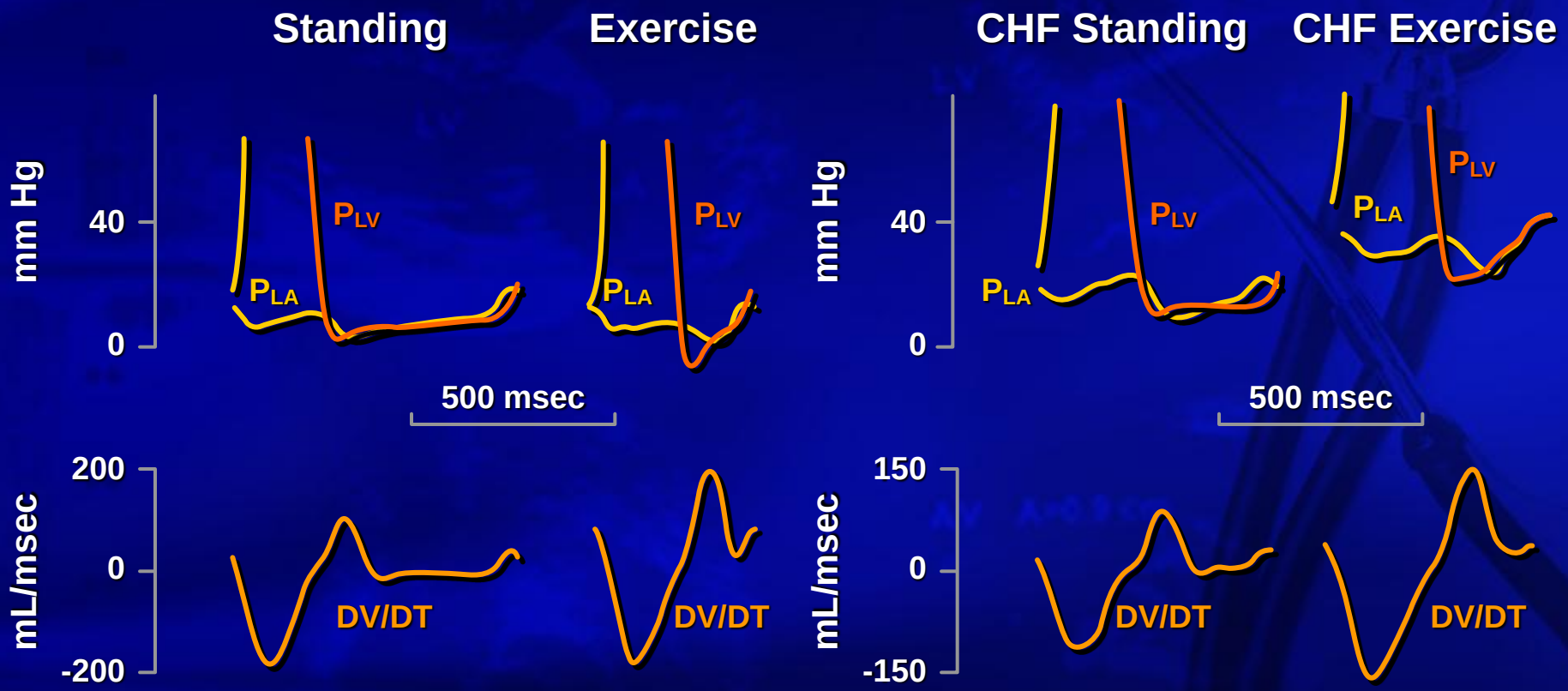






LV and LA Pressure at Rest and Treadmill Exercise

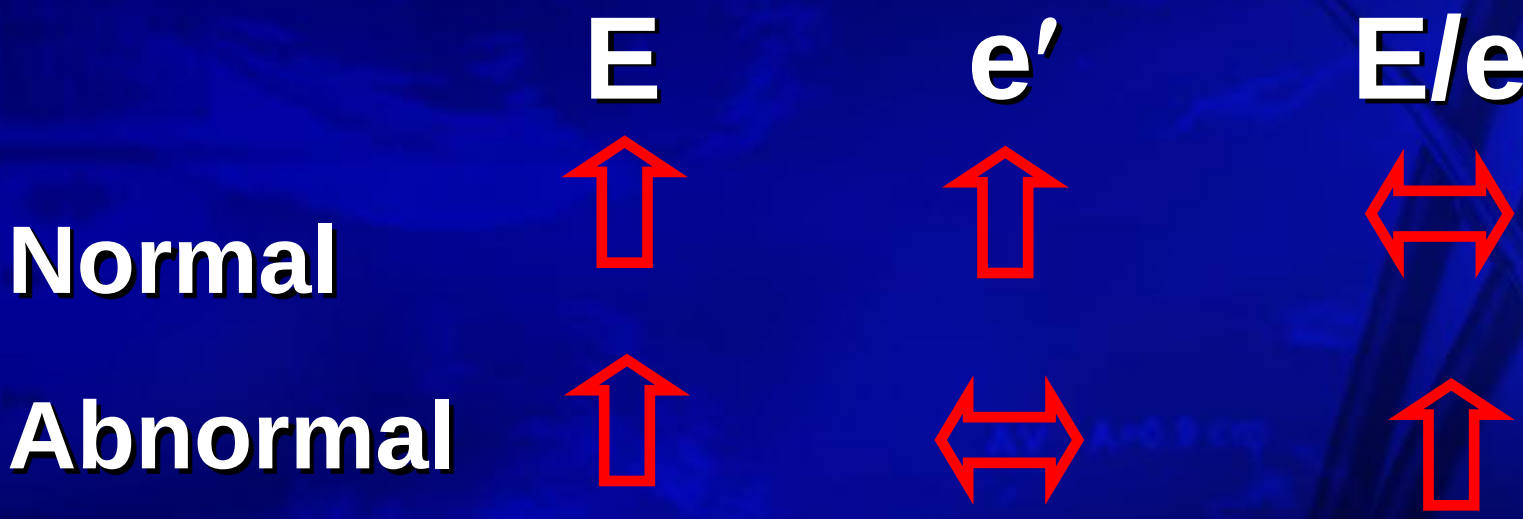
Healthy vs Heart Failure



Cheng and Little et al: Circ Res 72:795, 1993

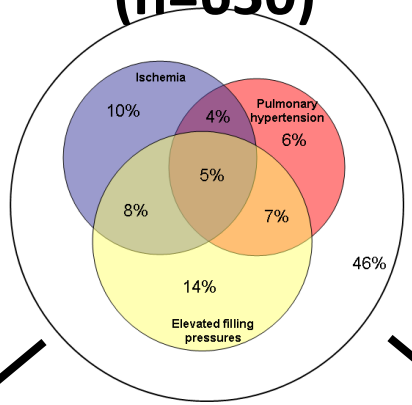
Dynamic Diastology

Filling Pressure (E/e′) with Exercise

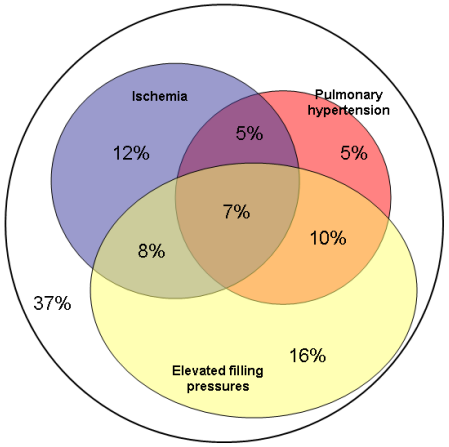


LV filling pressure (E/e') does not increase much with exercise in normal heart, but increases in symptomatic patients with diastolic dysfunction.

Exercise-limiting Dyspnea (n=630)



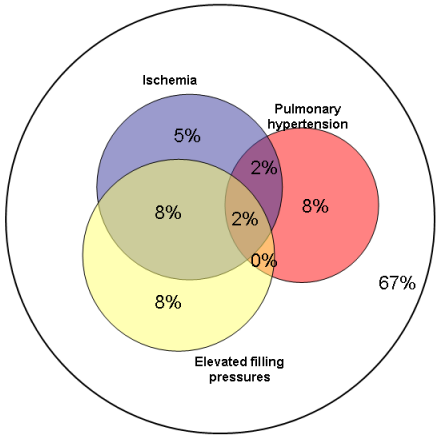
≥ 60 yrs (n=421)



Ischemia 32%

Any abnormality 63%

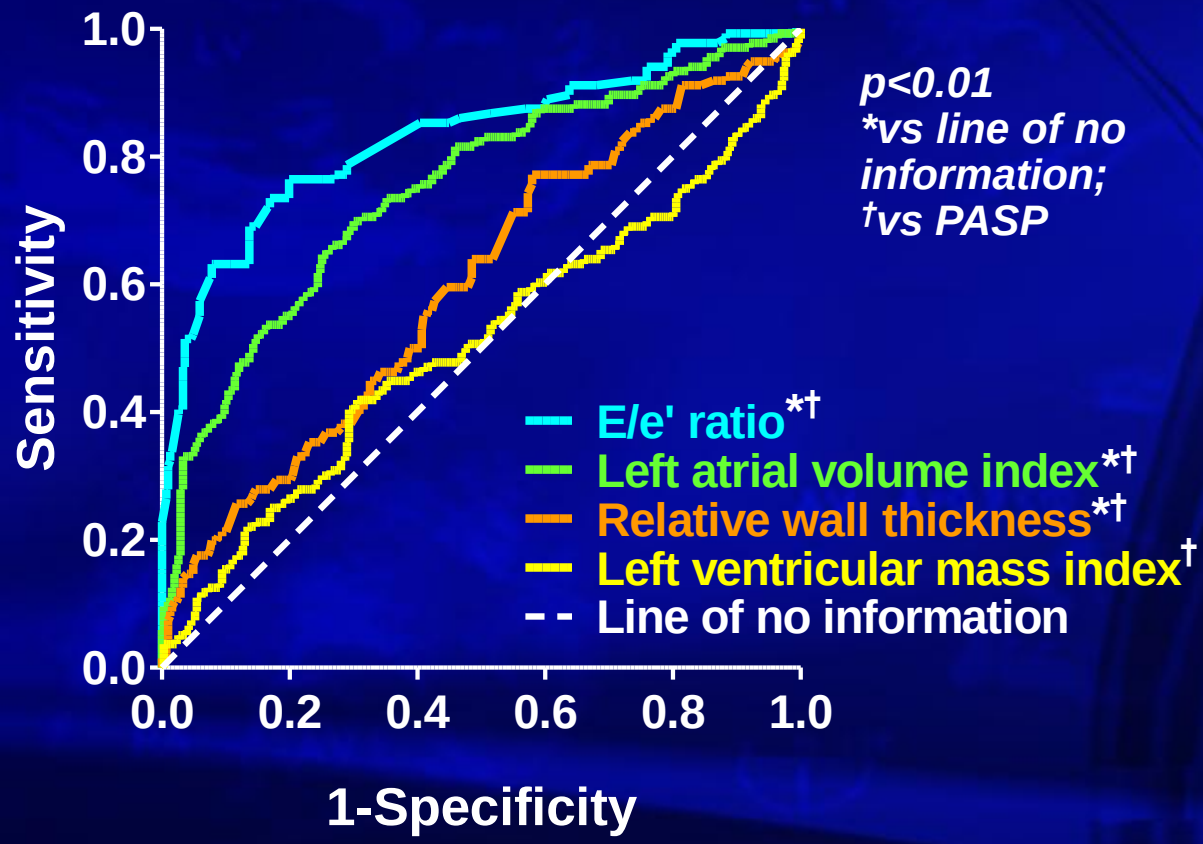
< 60 yrs (n=209)



Ischemia 17%

Any abnormality 33%

Distinguishing Hypertensive Heart Disease from HFpEF



Lam C et al, JACC, 2009

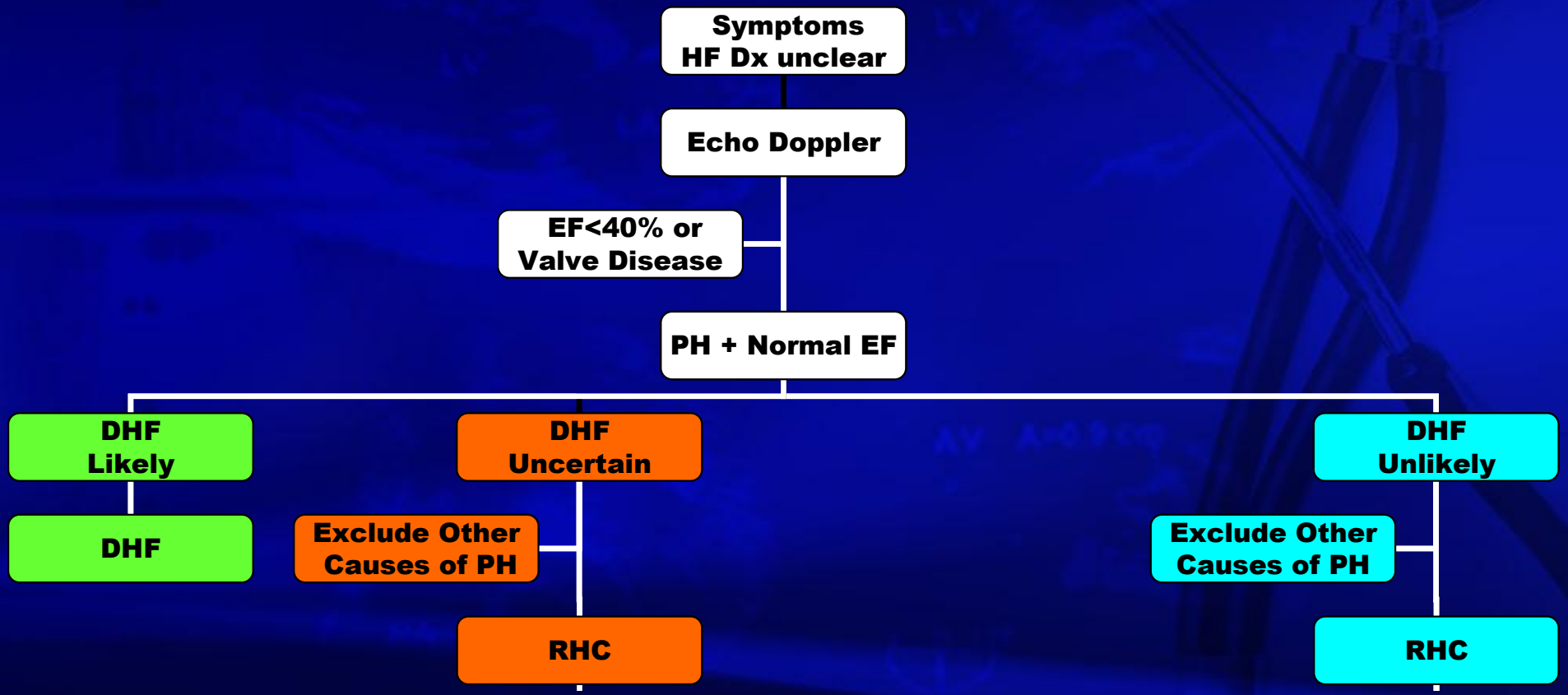
EXPERT CONSENSUS DOCUMENT

ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension

A Report of the American College of ology Foundation Task Force on
Expert Consensus Documents and ican Heart Association

"In the absence of other potential etiologies of PH, an RVSP > 40 mmHg generally warrants further evaluation in the patient with unexplained dyspnea."

Diagnosis, Assessment, and Treatment of Non-Pulmonary Arterial Hypertension Pulmonary Hypertension

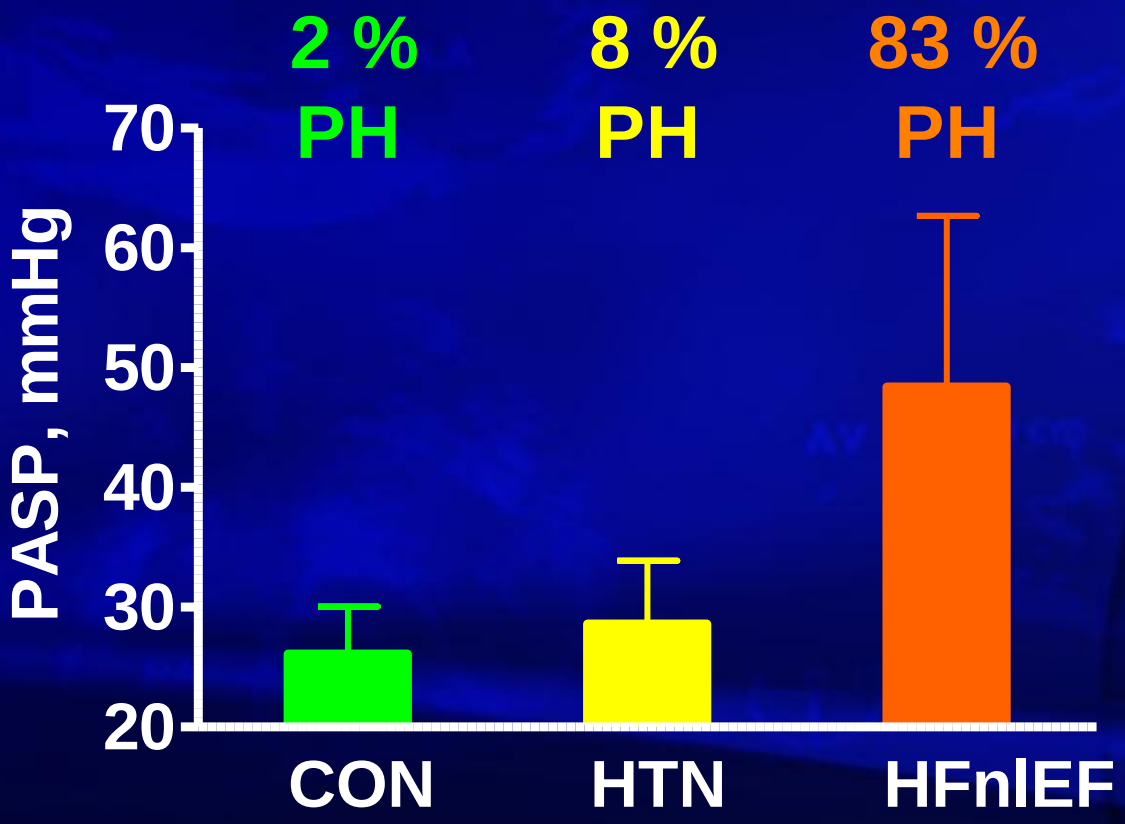


Report from the 4th World Symposium on PH: Working Group on Non-PAH pulmonary hypertension, JACC, 2009

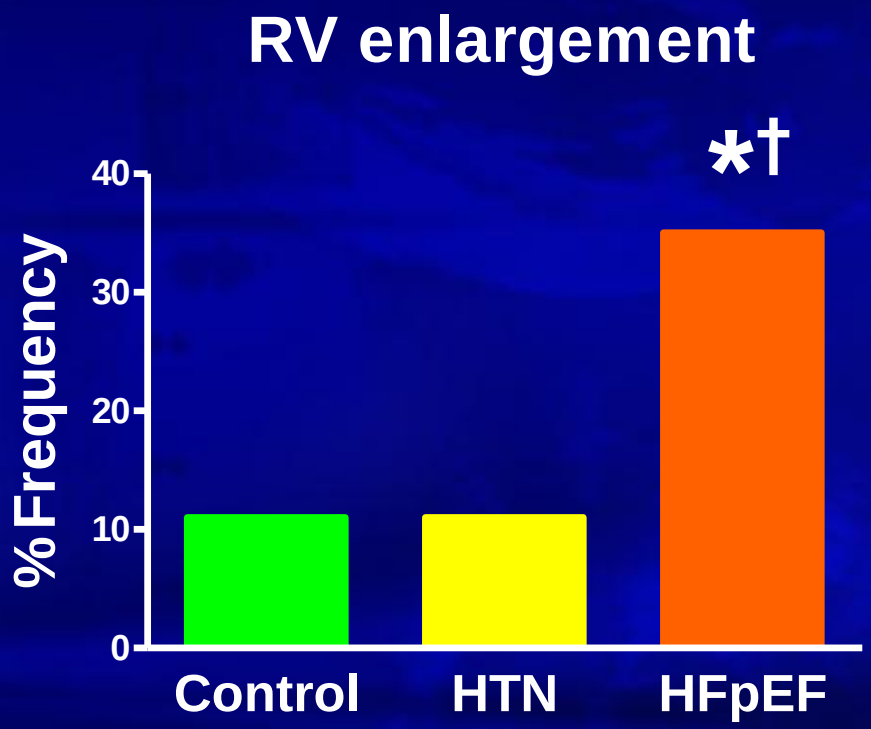
Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

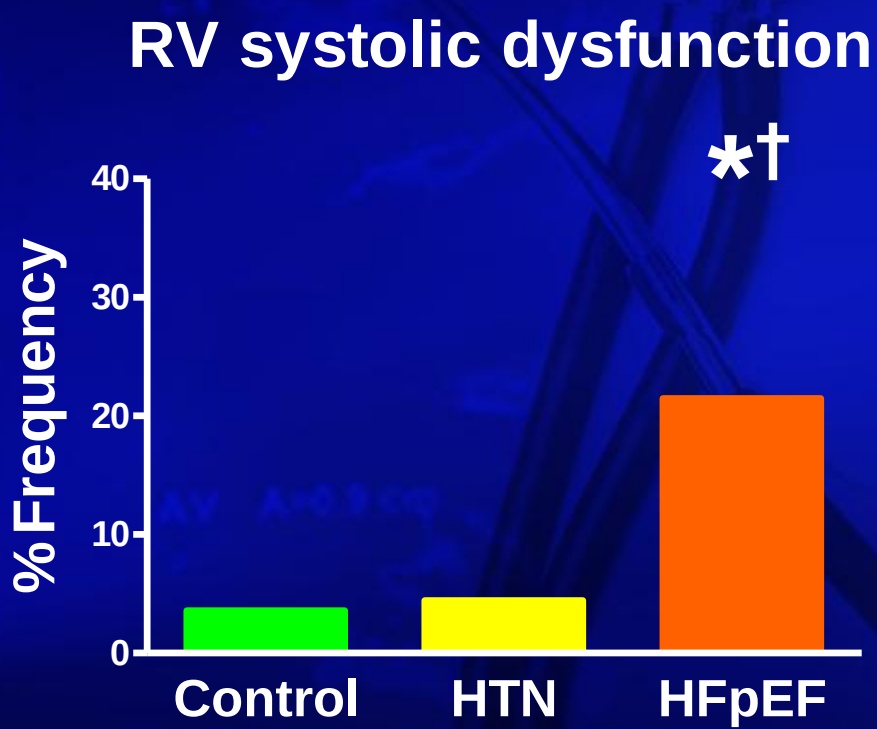
A Community-Based Study

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*



RV size and function in HFpEF
Mohammed S et al, AHA, 2011





MAYO CLINIC

p *<0.05 vs control; †<0.05 vs HTN

Hemodynamic Definitions

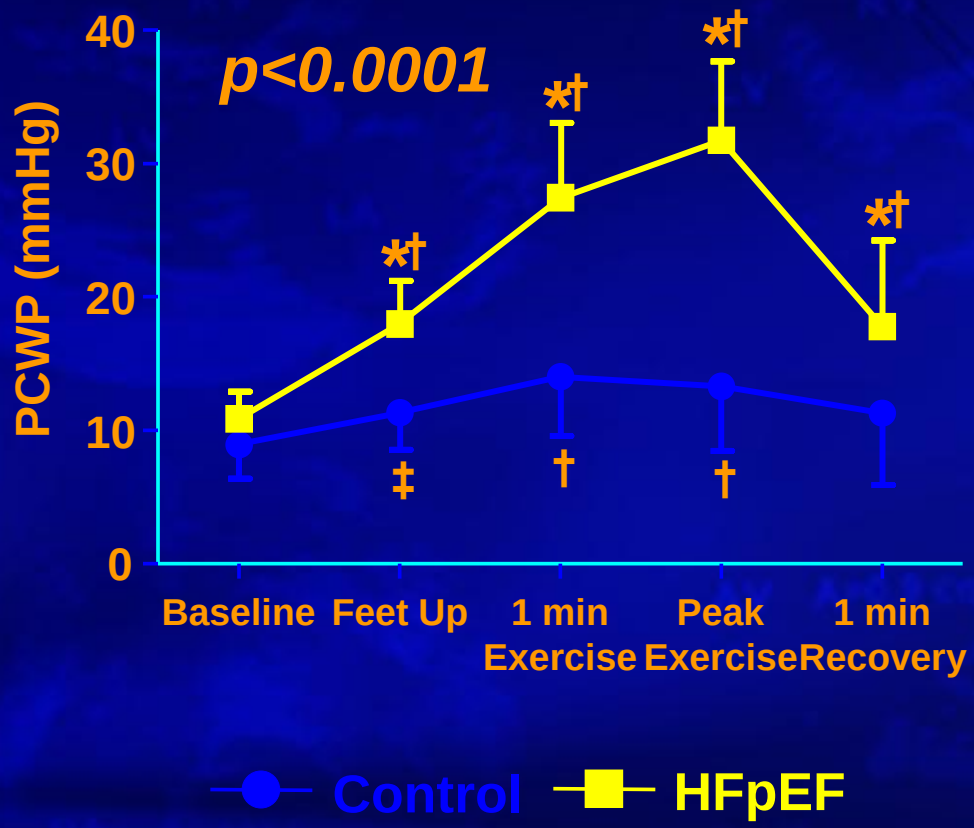
	PAH	PVH	Mixed
PASP (mmHg)	> 35		35
mPAP (mmHg)	> 25		25
mPCWP (mmHg)	< 15		15
PVR (WU)	> 3	< 3	> 3

PAH due to HFpEF

PVR mildly ↑

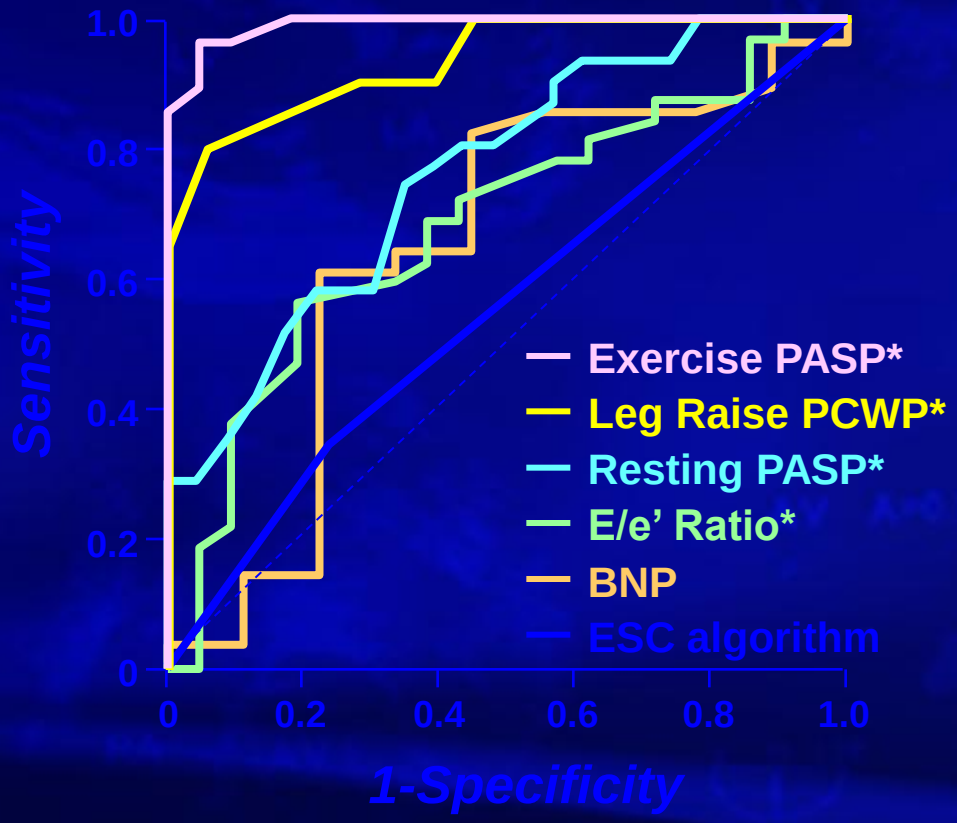
≈ 3-5 WU

↑LVFP with stress only in early HFpEF



Borlaug *Circ Heart Fail* 2010

ESC algorithm, BNP and E/e' are inadequate for early stage HFpEF



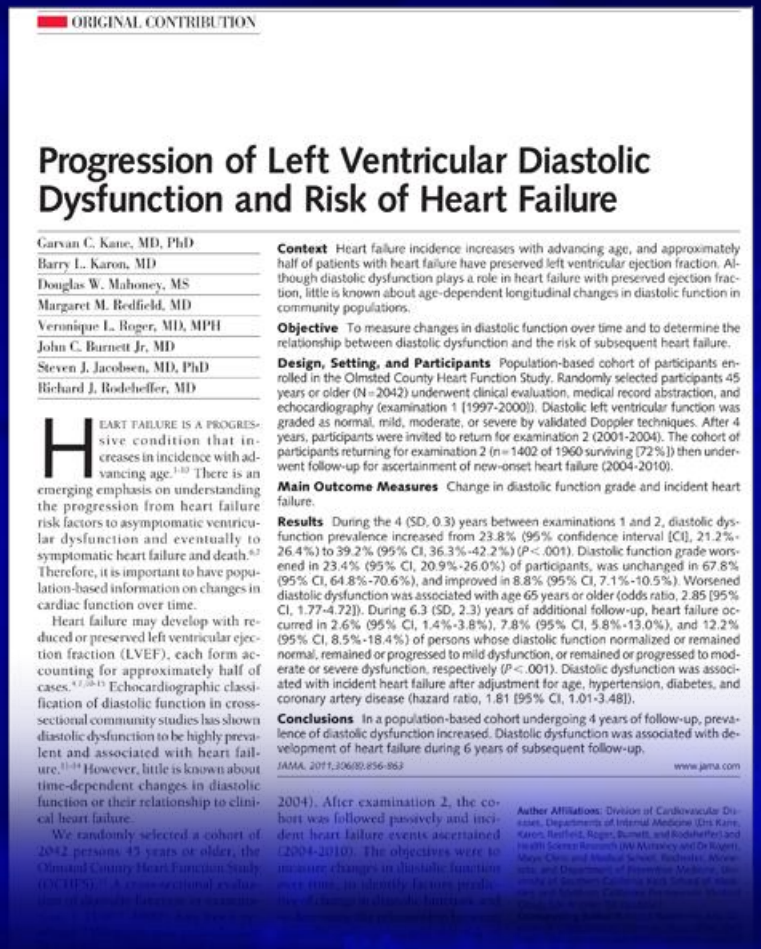
*p<0.05

MAYO CLINIC

Borlaug *Circ Heart Fail* 2010

Mayo Clinic
Locations

Study Flow



ORIGINAL CONTRIBUTION

Progression of Left Ventricular Diastolic Dysfunction and Risk of Heart Failure

Garvan C. Kane, MD, PhD
Barry L. Karon, MD
Douglas W. Mahoney, MS
Margaret M. Redfield, MD
Veronique L. Roger, MD, MPH
John C. Burnett Jr, MD
Steven J. Jacobsen, MD, PhD
Richard J. Rodeheffer, MD

Context Heart failure incidence increases with advancing age, and approximately half of patients with heart failure have preserved left ventricular ejection fraction. Although diastolic dysfunction plays a role in heart failure with preserved ejection fraction, little is known about age-dependent longitudinal changes in diastolic function in community populations.

Objective To measure changes in diastolic function over time and to determine the relationship between diastolic dysfunction and the risk of subsequent heart failure.

Design, Setting, and Participants Population-based cohort of participants enrolled in the Olmsted County Heart Function Study. Randomly selected participants 45 years or older (N=2042) underwent clinical evaluation, medical record abstraction, and echocardiography (examination 1 [1997-2000]). Diastolic left ventricular function was graded as normal, mild, moderate, or severe by validated Doppler techniques. After 4 years, participants were invited to return for examination 2 (2001-2004). The cohort of participants returning for examination 2 (n=1402 of 1960 surviving [72%]) then underwent follow-up for ascertainment of new-onset heart failure (2004-2010).

Main Outcome Measures Change in diastolic function grade and incident heart failure.

Results During the 4 (SD, 0.3) years between examinations 1 and 2, diastolic dysfunction prevalence increased from 23.8% (95% confidence interval [CI], 21.2%-26.4%) to 39.2% (95% CI, 36.3%-42.2%) ($P<.001$). Diastolic function grade worsened in 23.4% (95% CI, 20.9%-26.0%) of participants, was unchanged in 67.8% (95% CI, 64.8%-70.6%), and improved in 8.8% (95% CI, 7.1%-10.5%). Worsened diastolic dysfunction was associated with age 65 years or older (odds ratio, 2.85 [95% CI, 1.77-4.72]). During 6.3 (SD, 2.3) years of additional follow-up, heart failure occurred in 2.6% (95% CI, 1.4%-3.8%), 7.8% (95% CI, 5.8%-13.0%), and 12.2% (95% CI, 8.5%-18.4%) of persons whose diastolic function normalized or remained normal, remained or progressed to mild dysfunction, or remained or progressed to moderate or severe dysfunction, respectively ($P<.001$). Diastolic dysfunction was associated with incident heart failure after adjustment for age, hypertension, diabetes, and coronary artery disease (hazard ratio, 1.81 [95% CI, 1.01-3.48]).

Conclusions In a population-based cohort undergoing 4 years of follow-up, prevalence of diastolic dysfunction increased. Diastolic dysfunction was associated with development of heart failure during 6 years of subsequent follow-up.

JAMA. 2011;306(8):856-863 www.jama.com

HEART FAILURE IS A PROGRESSIVE condition that increases in incidence with advancing age.[1-10] There is an emerging emphasis on understanding the progression from heart failure risk factors to asymptomatic ventricular dysfunction and eventually to symptomatic heart failure and death.[6,7] Therefore, it is important to have population-based information on changes in cardiac function over time.

Heart failure may develop with reduced or preserved left ventricular ejection fraction (LVEF), each form accounting for approximately half of cases.[4,7,10-13] Echocardiographic classification of diastolic function in cross-sectional community studies has shown diastolic dysfunction to be highly prevalent and associated with heart failure.[11-14] However, little is known about time-dependent changes in diastolic function or their relationship to clinical heart failure.

We randomly selected a cohort of 2042 persons 45 years or older, the Olmsted County Heart Function Study (OCHFS), [illegible] 2004). After examination 2, the cohort was followed passively and incident heart failure events ascertained (2004-2010). The objectives were to measure changes in diastolic function over time, to identify factors predic[illegible]

Author Affiliations: Division of Cardiovascular Diseases, Departments of Internal Medicine (Drs Kane, Karon, Redfield, Roger, Burnett, and Rodeheffer) and Health Sciences Research (Mr Mahoney and Dr Roger), Mayo Clinic and Mayo Medical School, Rochester, Minnesota, and Department of Preventive Medicine, [illegible] School of Medicine, [illegible]

4,203 individual randomly invited to participate

→ 2,161 excluded (did not participate in examination 1

2,402 participated in examination 1 (1997-2000)

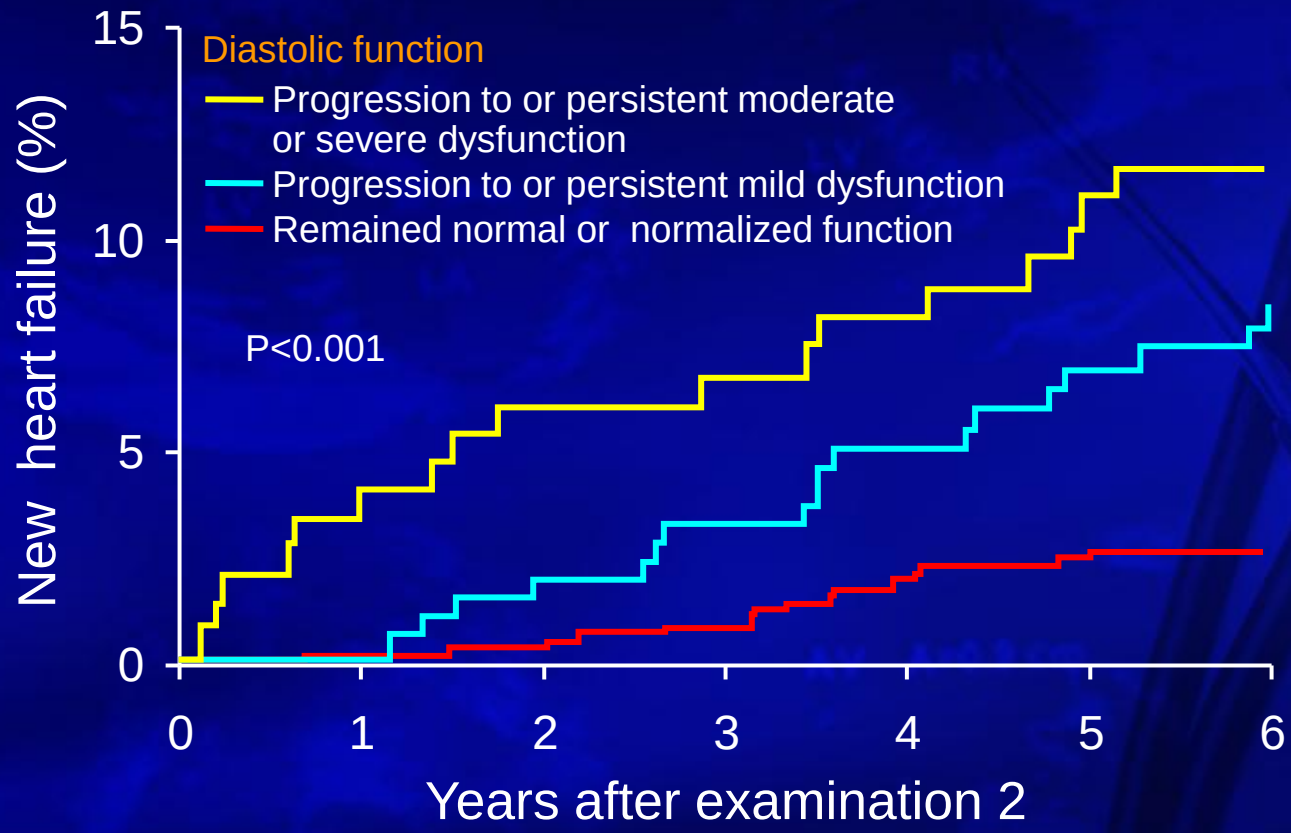
→ 640 excluded
558 did not return for examination 2
82 died before examination 2

1,402 returned for examination 2 (2001-2004)

1,151 classifiable diastolic function
139 indeterminate diastolic function
112 diastolic dysfunction, determinate grade

Kane et al: JAMA 2011;306(8):856-863

Cumulative Incidence of Heart Failure After Examination 2



No. at risk

Moderate or severe	160	146	140	136	129	124	114
Mild	239	233	222	216	208	198	182
Normal/normalized	648	608	600	584	566	537	499

Kane et al: JAMA 2011;306(8):856-863

JACC: CARDIOVASCULAR IMAGING
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CVN Interview

ORIGINAL RESEARCH

Serial Doppler Echocardiography and Tissue Doppler Imaging in the Detection of Elevated Directly Measured Left Atrial Pressure in Ambulant Subjects With Chronic Heart Failure

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Christopher F. Frampton, PHD,* Iain C. Melton, MD,† Robert N. Doughty, MD,‡
James T. Stewart, MD,‡ Neal Eigler, MD,§‖ James Whiting, PHD,§‖
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Christchurch and Auckland, New Zealand; Los Angeles, California; Minneapolis, Minnesota; Columbus, Ohio; and Queensland, Australia

OBJECTIVES This study sought to determine the accuracy of Doppler echocardiography and tissue Doppler imaging (TDI) measurements in detecting elevated left atrial pressure (LAP) in ambulant subjects with chronic heart failure using directly measured LAP as the reference.

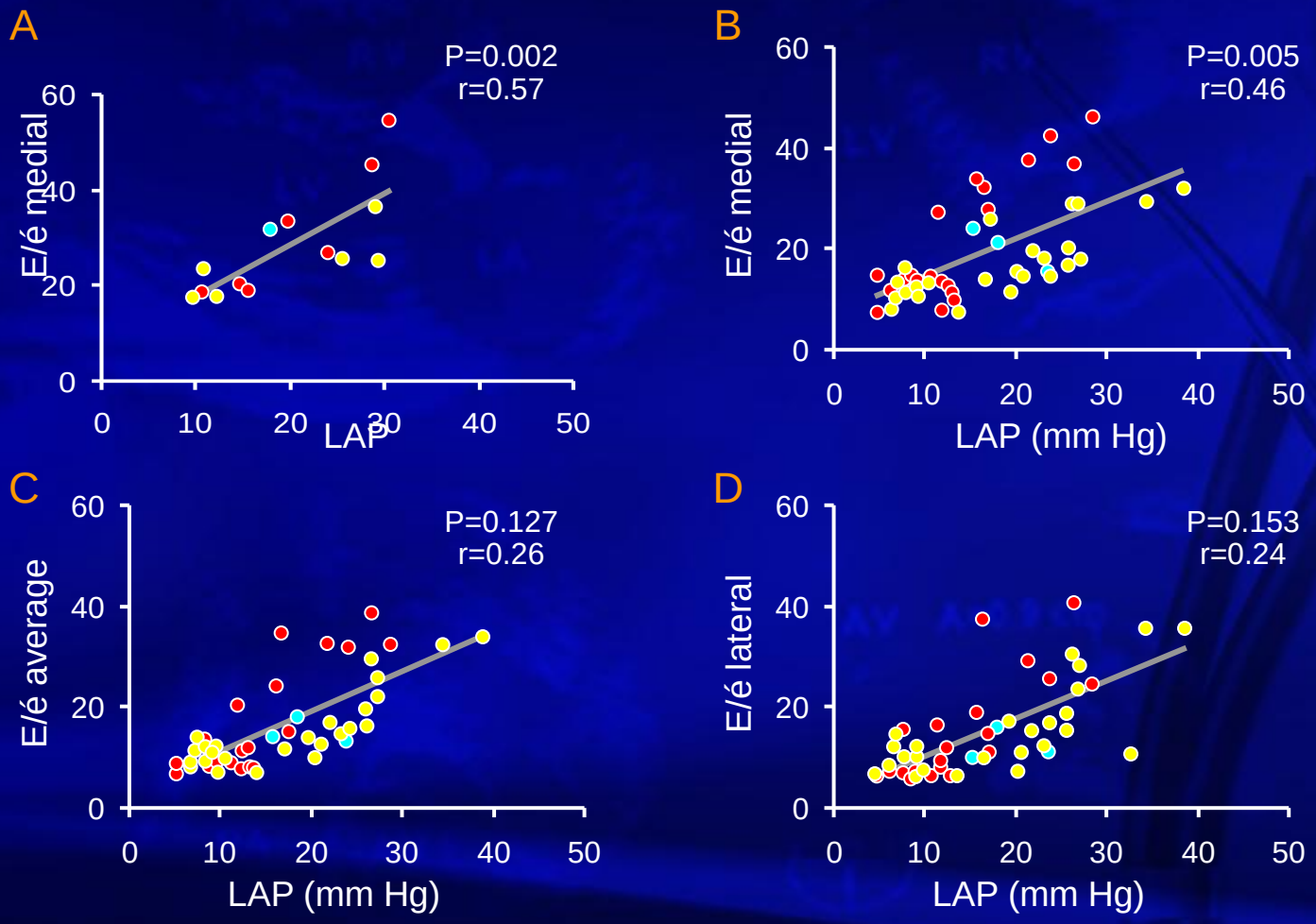
BACKGROUND Echocardiographic indexes including the ratio of transmitral to annular early diastolic velocities (E/e') may identify raised invasively measured left ventricular filling pressures when tested in cross-sectional studies in some populations. The accuracy of these indexes when measured sequentially remains untested. We determined the accuracy of Doppler echocardiography and TDI measurements in detecting elevated directly measured LAP in ambulant subjects with stable chronic heart failure.

METHODS Fifteen patients with New York Heart Association functional class II to III heart failure and a permanently implanted direct LAP monitoring device underwent serial echocardiography. Simultaneous resting mean LAP, Doppler mitral inflow, mitral annular TDI, and pulmonary venous inflow velocities were obtained on each occasion. Receiver-operator characteristic curve analysis was used to compare the accuracy of the Doppler variables to detect an elevated device LAP ≥15 and ≥20 mm Hg.

RESULTS The patients (13 men, mean age: 71 years, mean left ventricular ejection fraction: 32 ± 12%) underwent 60 simultaneous echocardiographic studies and LAP measurements with a median of 4 (1 to 7) studies per patient. Mean LAP was 16.9 (range 5 to 39 mm Hg) at echocardiography (n = 60). E/e' had the greatest accuracy for detection of LAP ≥15 mm Hg with an area beneath the receiver-operator characteristic curve >0.9. In comparison, area under the curve for mitral E velocity and mitral E/A were 0.77 and 0.76, respectively ($p < 0.008$ vs. E/e' medial and average).

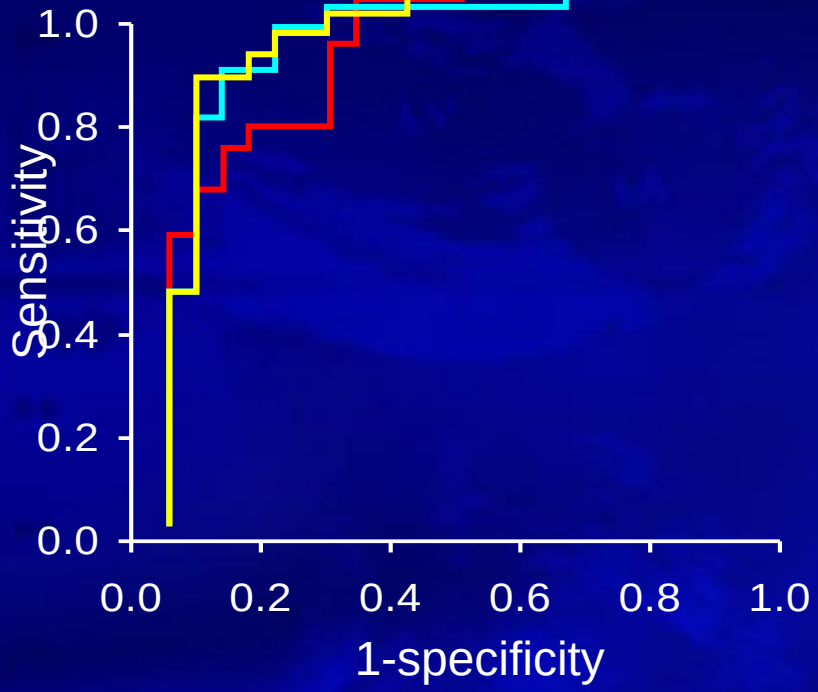
CONCLUSIONS Single and serial measurements of mitral inflow and mitral annular TDI velocities (E/e') can reliably detect raised directly measured LAP in ambulant subjects with compensated chronic heart failure. (Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients [HOMEOSTASIS]: NCT00547729) (J Am Coll Cardiol Img 2011;4:927–34) © 2011 by the American College of Cardiology Foundation

Intrapatient Correlation of E/é with Simultaneous LAP

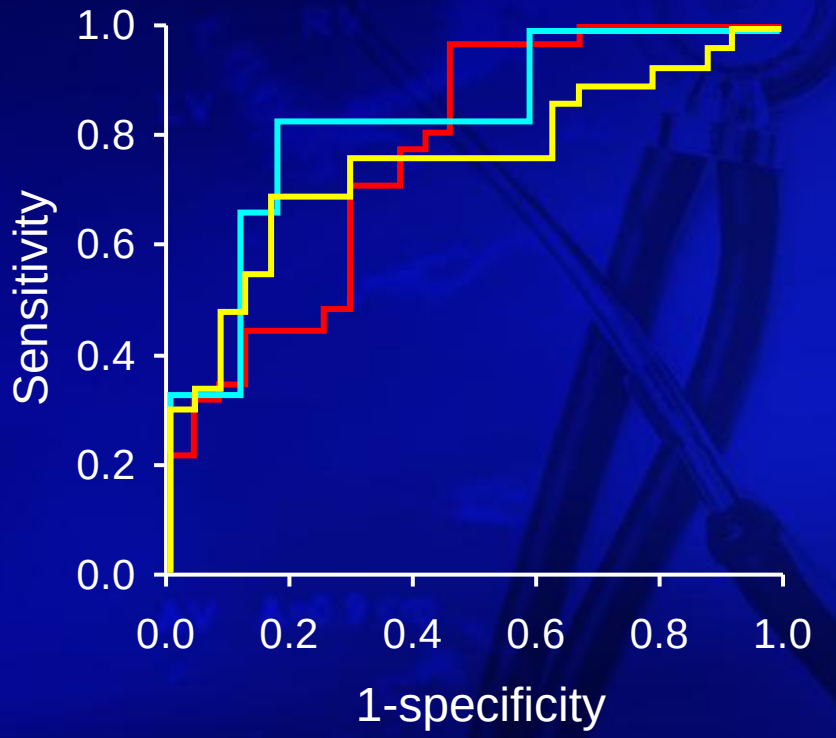


Ritzema et al: JACC: Cardiovasc Imaging 2011;4(9):927-934

ROC Curves for the Prediction of LAP ≥15 mm Hg Using Echo Doppler Indexes



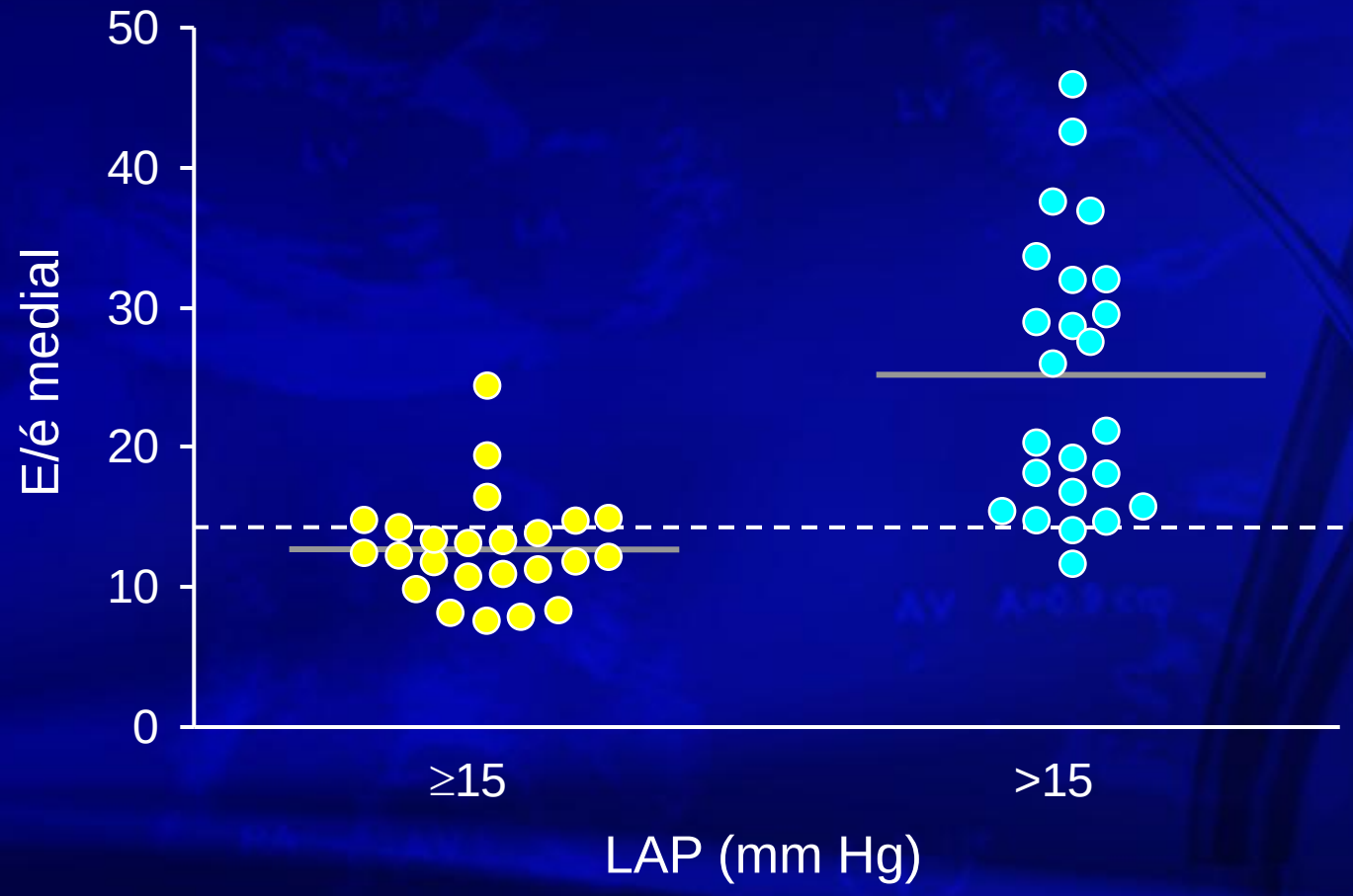
E/é average (cutpoint ≥14, AUC 0.94)
E/é medical (cutpoint ≥15, AUC 0.93)
E/é lateral (cutpoint ≥12, AUC 0.9)



E/A (cutpoint ≥1, AUC 0.76)
PV/Adur-Adur (cutpoint ≥25, AUC 0.83)
E velocity (cutpoint ≥60, AUC 0.78)

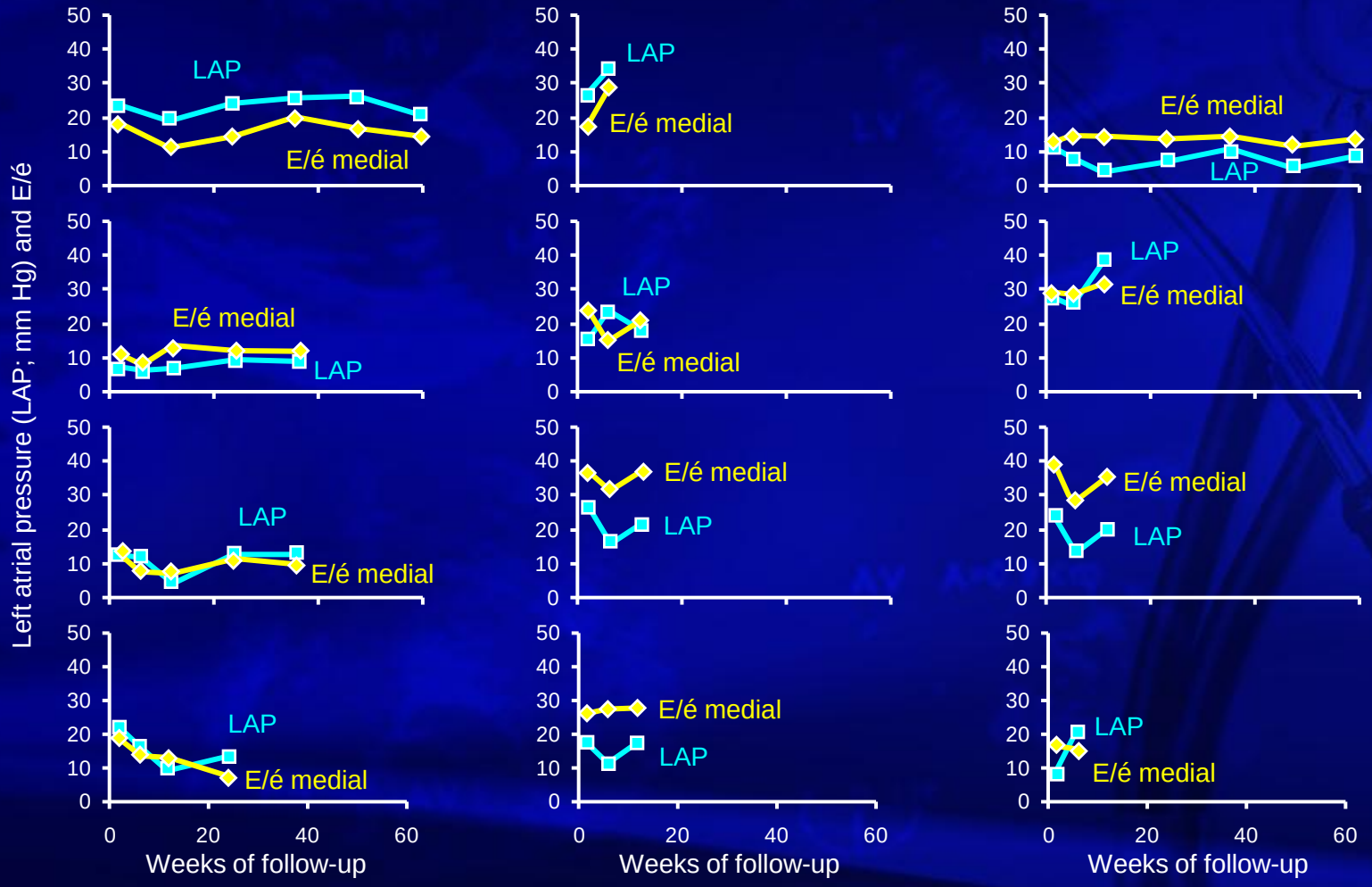
Ritzema et al: JACC: Cardiovasc Imaging 2011;4(9):927-934

Mean LAP vs Categorical E/é Medial Ratio (≤15 and >15) for All Studies (n=48)



Ritzema et al: JACC: Cardiovasc Imaging 2011;4(9):927-934

Concordant Temporal Changes in Left Atrial Pressure (mm Hg) and E/é Medial Ratio in 12 Subjects with 2 or More Echocardiogram Studies



Ritzema et al: JACC: Cardiovasc Imaging 2011;4(9):927-934

Why is BNP lower (or Nl) in HFpEF?

Transient ↑ in Atrial Pressure (Early HFpEF)

Obesity (↓ production; ↑ clearance)

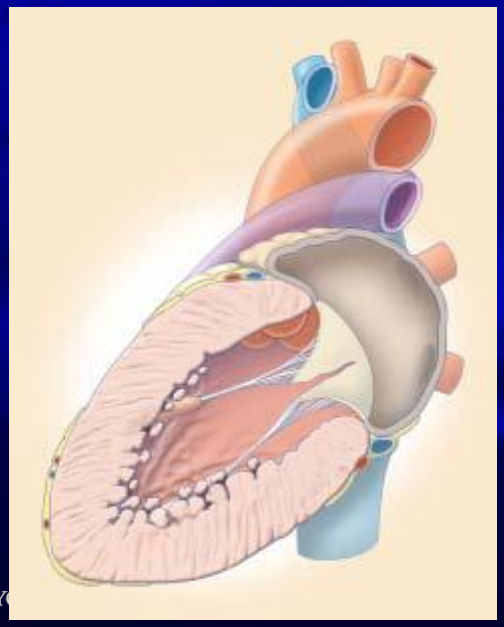
Why is BNP lower (or Nl) in HFpEF?

Transient ↑ in Atrial Pressure (Early HFpEF)

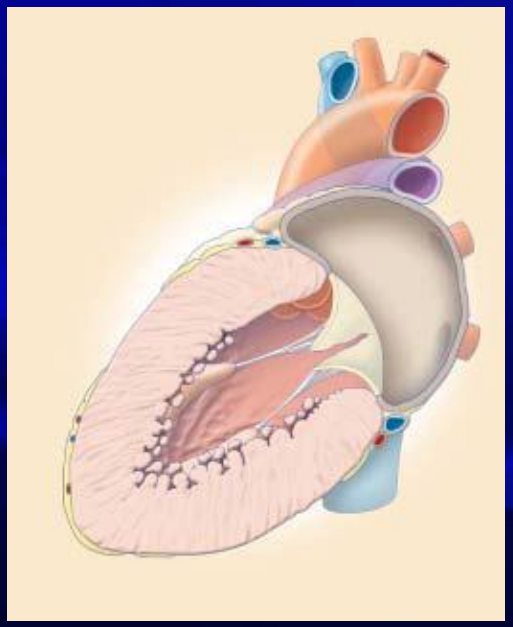
Obesity (↓ production; ↑ clearance)

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

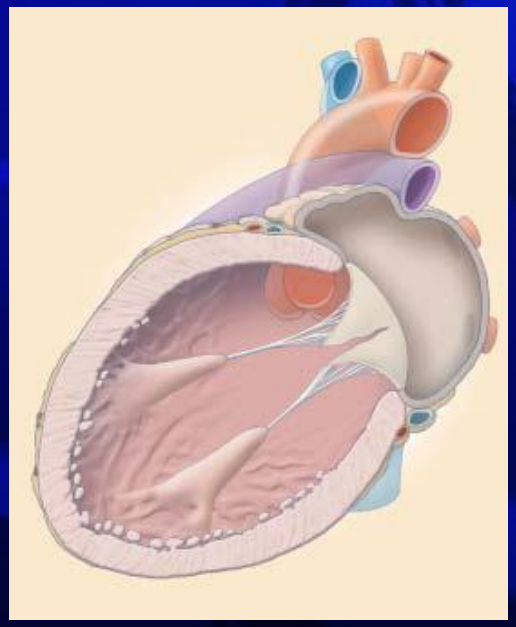
Normal



HFpEF

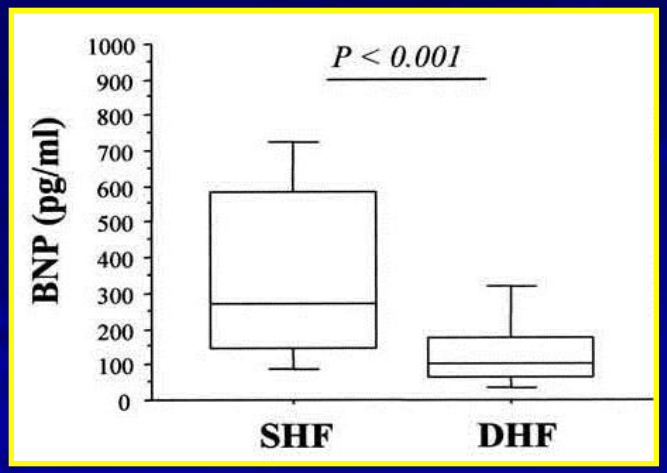


SHF

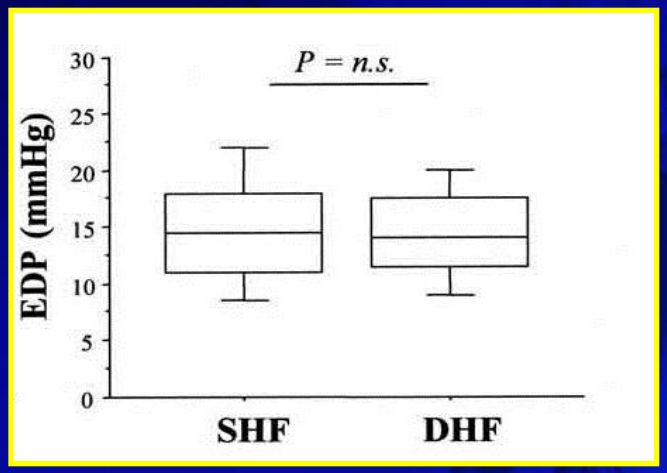


Wall Stress (~ (P*r)/h) → Production
Stretch→ Release

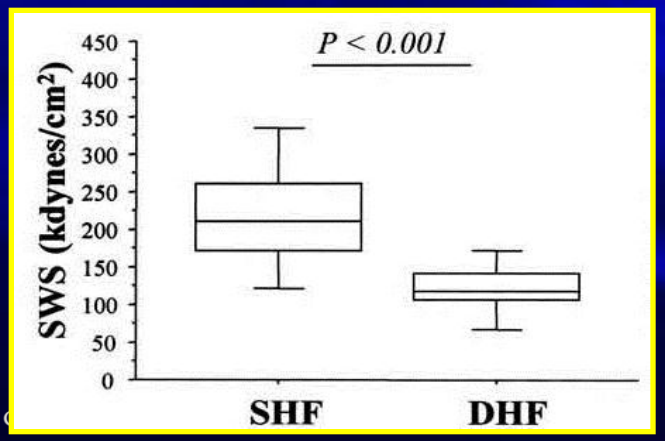
BNP



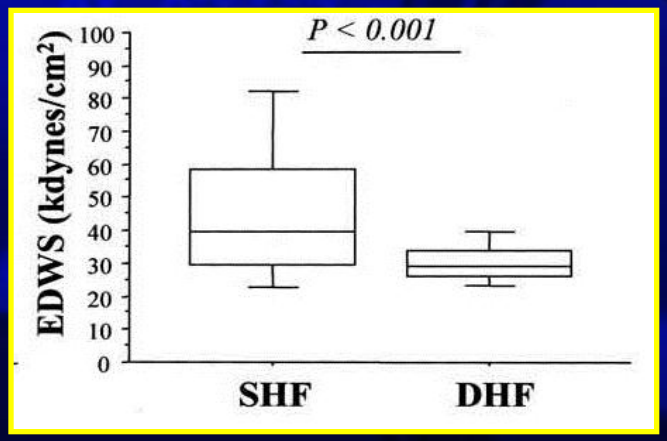
End Diastolic Pressure



Systolic Wall Stress



End Diastolic Wall Stress



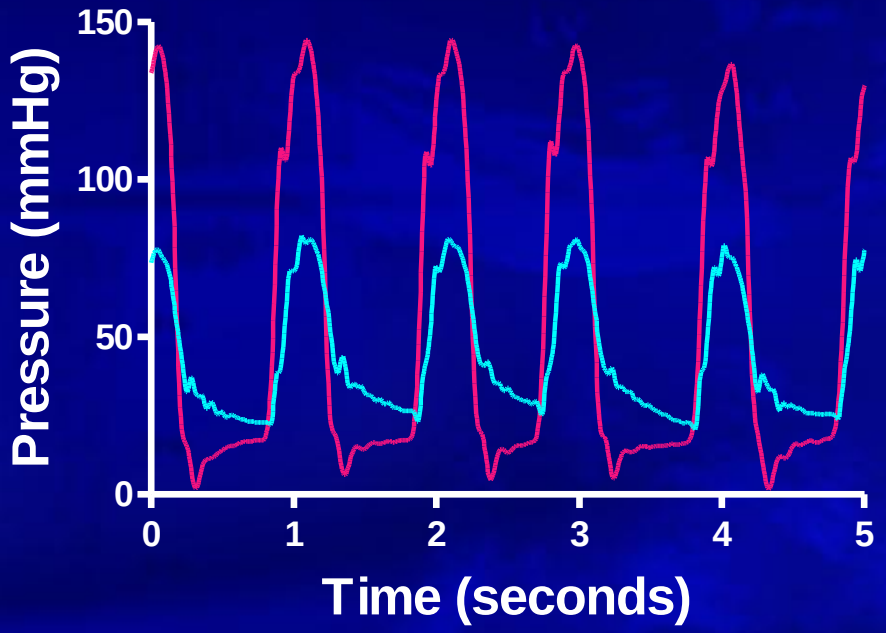
Iwanaga Y et al. *JACC*. 2006; 47:742-8.

Additional evaluation should include:

A. MRI for LV mass calculation
B. Doppler Echo Diastolic Function
C. BNP
D. Right heart cath

Does this patient have HFpEF?

Right and left heart catheterization
Coronaries normal



LVSP = 140

RAm = 17

PA = 85/25 (47)

PCWP = 22

CO = 5.53 l/m

PVR = 8.5 wu

Right and left heart catheterization

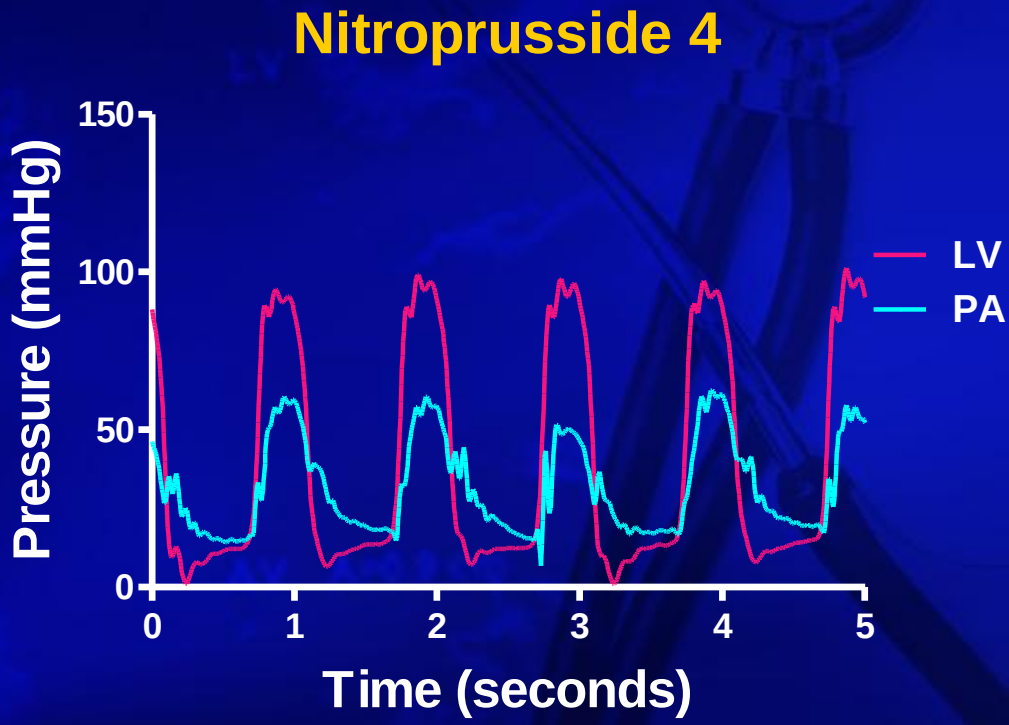
LVSP = 104

PA = 47/12 (28)

PCWP = 19

CO = 6.49 l/m

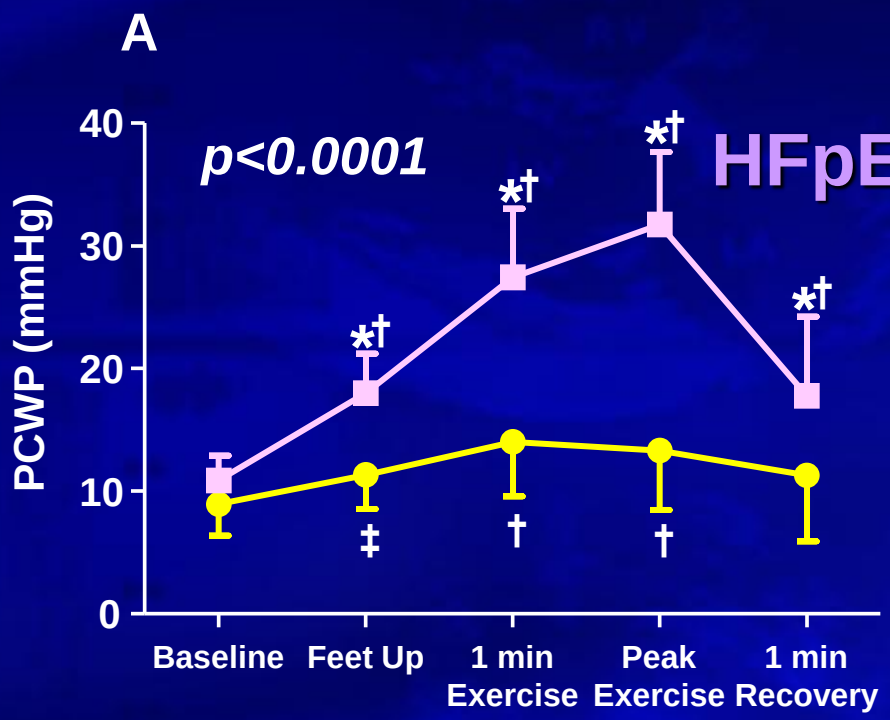
PVR = 1.39 wu

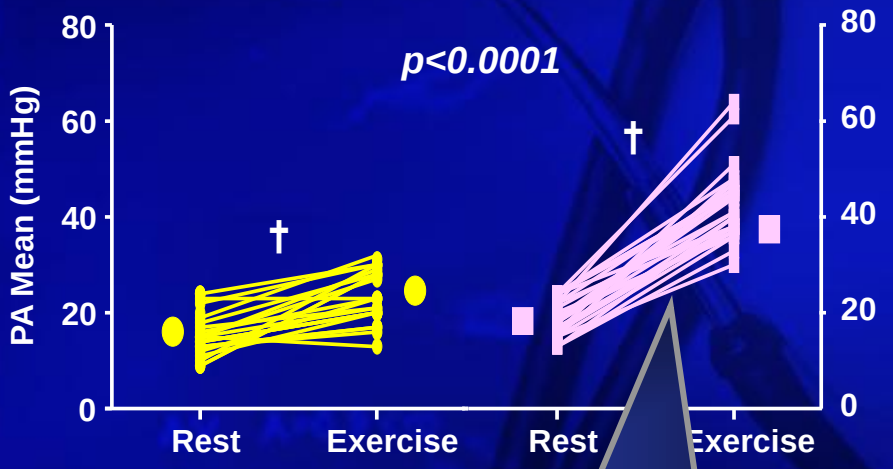


Evolution of PVH to PAH
"Post-Capilliary" to "Mixed"

Pulmonary Venous HTN	↑ PASP	NI PVR
Reactive PAH	↑ PASP	$_{rev}$↑PVR
Chronic PA Remodeling	↑ PASP	$_{fix}$↑PVR

“Exercise induced PH” in Earlier HFpEF





? Exc Echo with Exc RVSP

Borlaug et al. Circ HF, 2010

Does this patient with "HF symptoms" and EF>50% have HF?

- ☐ Elevated PASP?
- ☐ Doppler DD consistent with symptoms?
- ☐ LA enlargement?
- ☐ LVH or Concentric Remodeling?
- ☐ Elevated BNP?
- ☐ Sx correlate with onset Atrial Fib?
- ☐ Response to diuretics?
- ☐ CXR and Physical Exam cw HF

The more boxes checked, the ↑ the probability but no single parameter necessary or sufficient.

If Dx uncertain, Invasive Assessment + Exercise

PhosphodiesteRasE-5 Inhibition to Improve CLinical Status And EXercise Capacity in Diastolic Heart Failure

RELAX

NIH Heart Failure Clinical Research Network

MAYO CLINIC

MAYO CLINIC

Hemodynamic Definitions

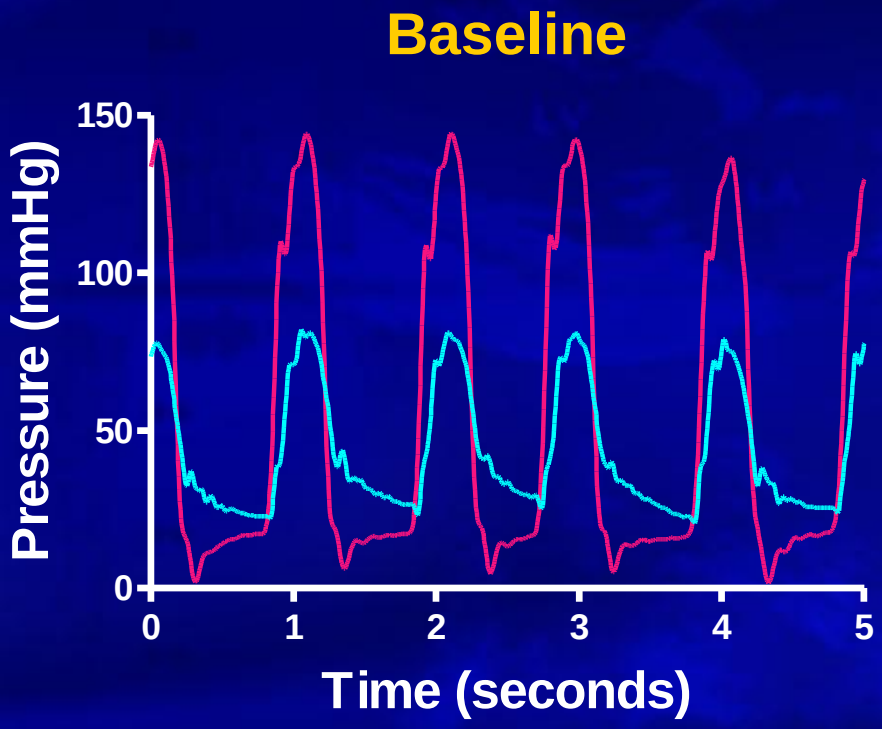
	PAH	PVH	Mixed
PASP (mmHg)	> 35		35
mPAP (mmHg)	> 25		25
mPCWP (mmHg)	< 15		15
PVR (WU)	> 3	< 3	> 3

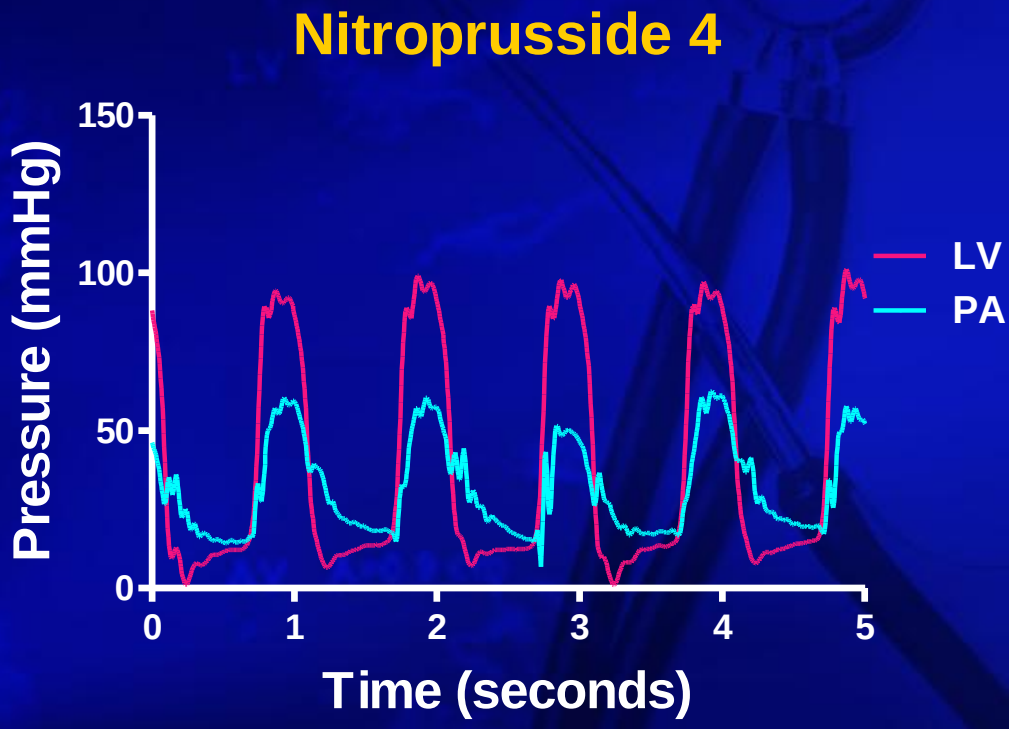
PAH due to HFpEF

PVR mildly ↑

≈ 3-5 WU

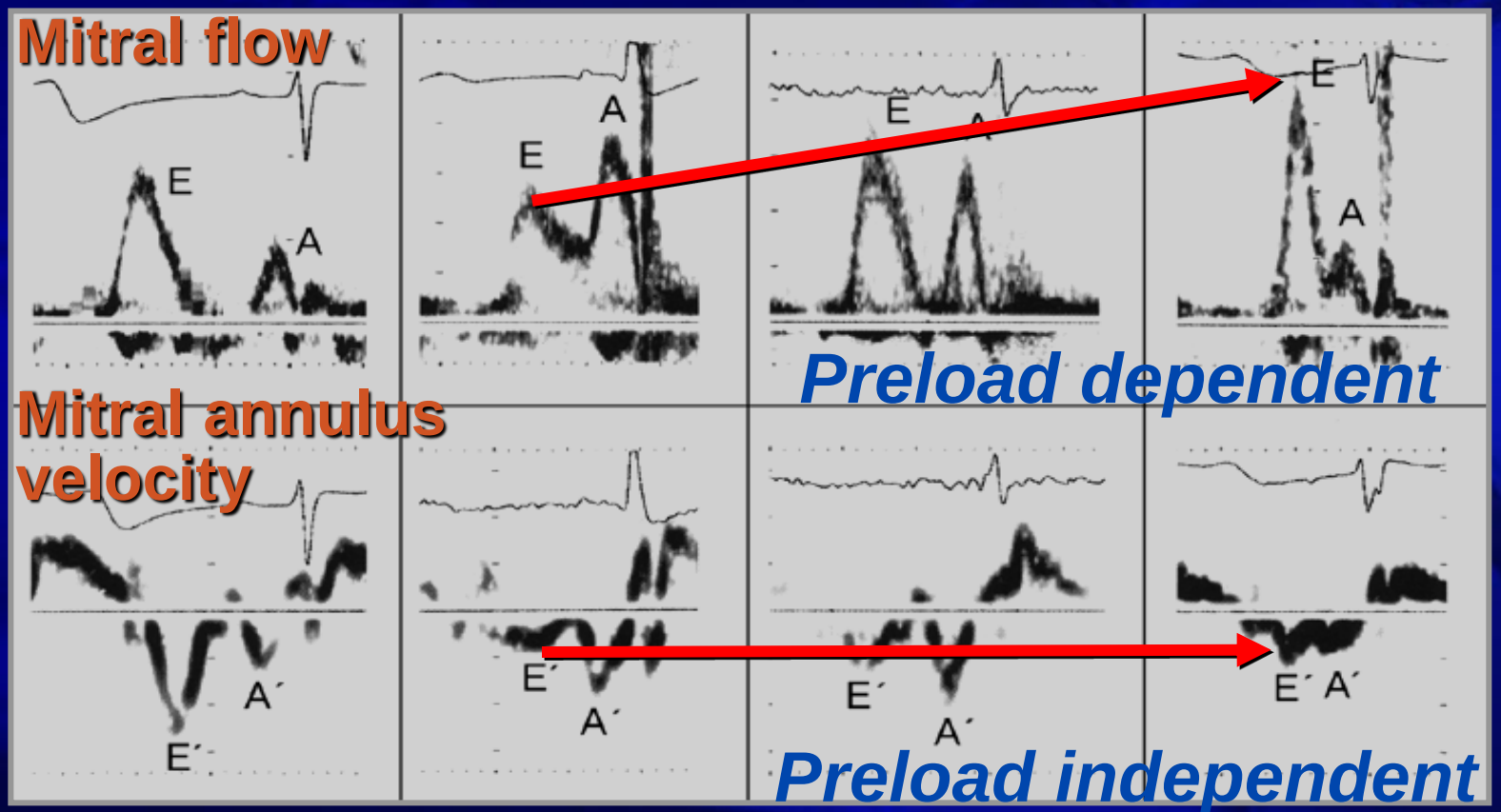
Right and left heart catheterization





Evaluation of Diastolic Function

Mitral Inflow and Annulus Velocity



Sohn et al: JACC, 1997

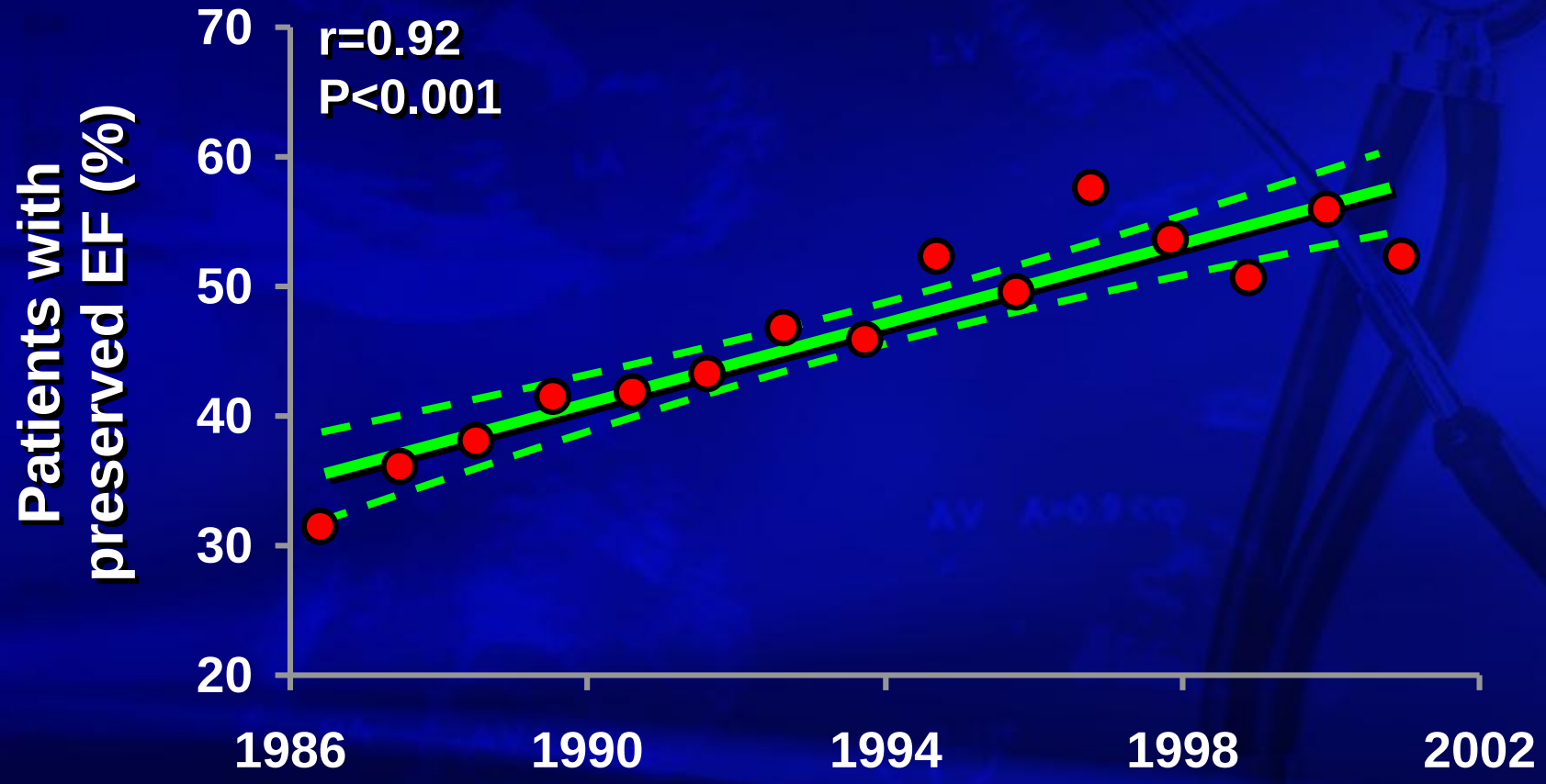
Heart Failure *is*

"A complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with (diastolic) or eject blood (systolic)"

ESC guidelines for heart failure
European Heart Journal 2005

Normal diastolic function allows adequate filling of the heart without excessive increase in diastolic filling pressure at rest and with stress

Secular Trends in Prevalence of Heart Failure with Preserved LVEF



Owan et al: NEJM 355:251, 2006

Do all patients with HFpEF have LVH?

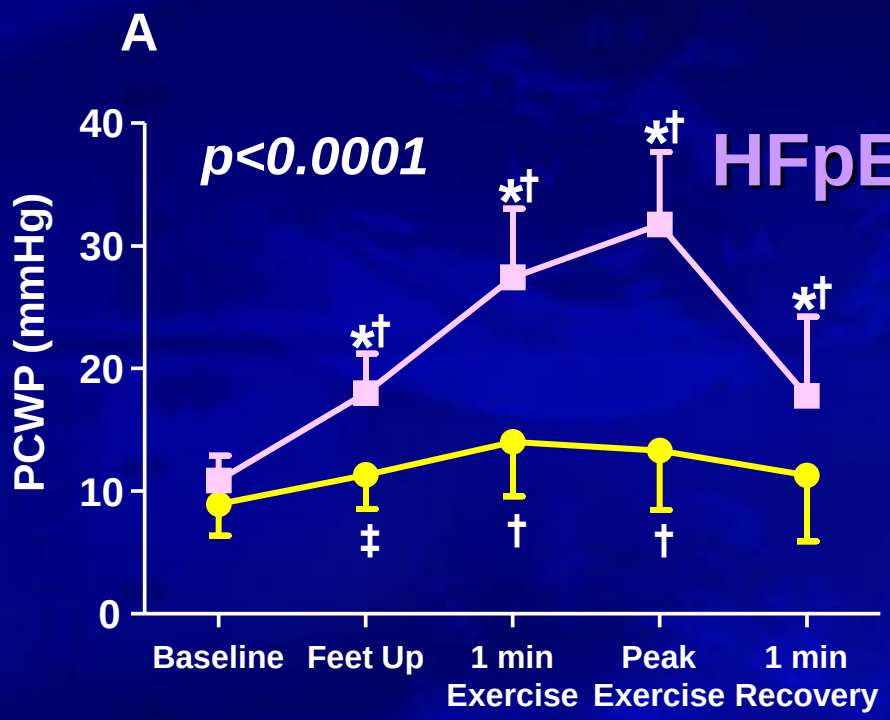
- No!
- Numerous observational studies
- On average: LV $mass_{HFpEF}$ > LV $mass_{HTN}$ >LV $mass_{Normal}$
- Only ≈ 40-50% pts fulfill echo criteria for LVH (LV mass)

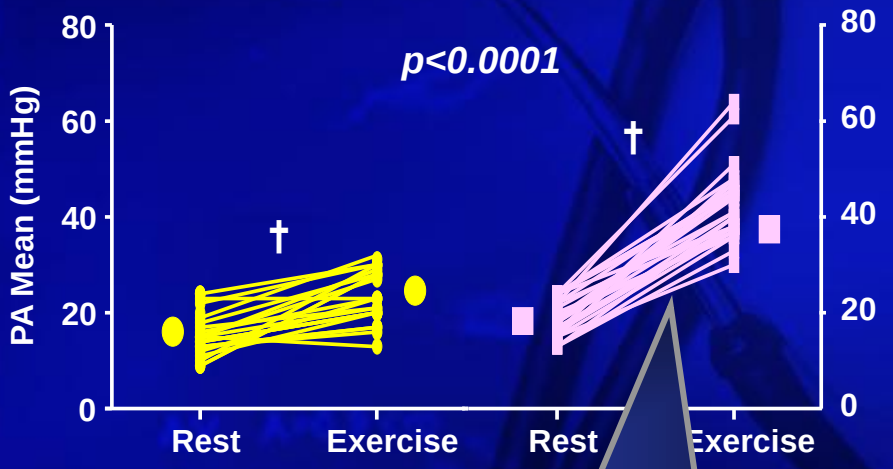
Case Presentation

LVEDP = 27

- 2000
  - 73 yo woman with dyspnea, AF
  - Risk factors: Age, HTN, Lipids
  - CXR: PVH, Cardiomegally
  - PFT: Normal
  - Echo: Nl EF, RVSP 45 mmHg
  - Cath: Nl Coronaries, Mild MR
  - Dx = Deconditioning, Age

“Exercise induced PH” in Earlier HFpEF



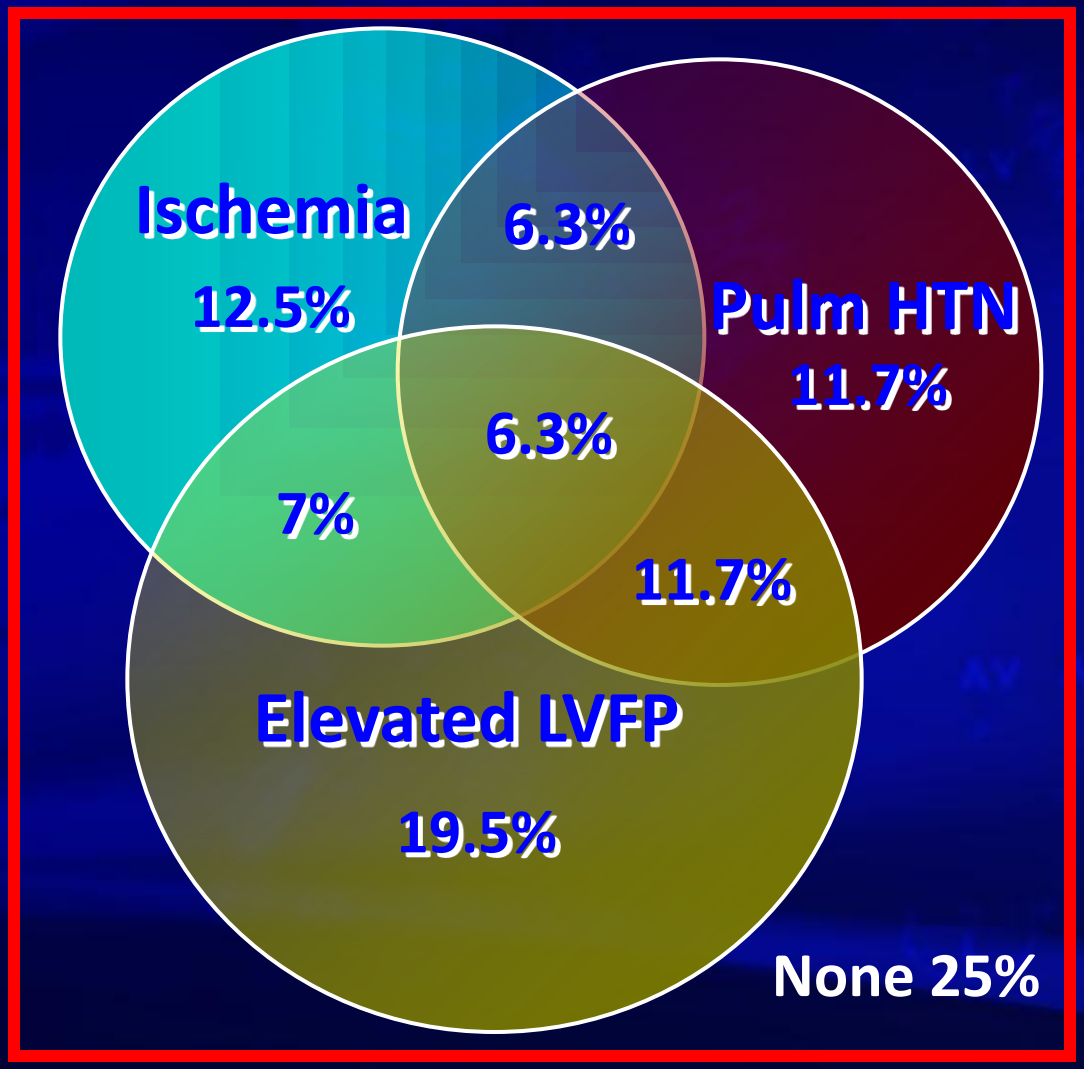


? Exc Echo with Exc RVSP

Borlaug et al. Circ HF, 2010

Reduced Exercise Capacity

Women <5 METs, Men <7 METS (n=128)



Ischemia 32%

Elevated LVFP 45%

Pulmonary HTN 36%

Any abnormality 75%

MAYO CLINIC

G. Kane, MD for Mayo Diastolic Stress Group