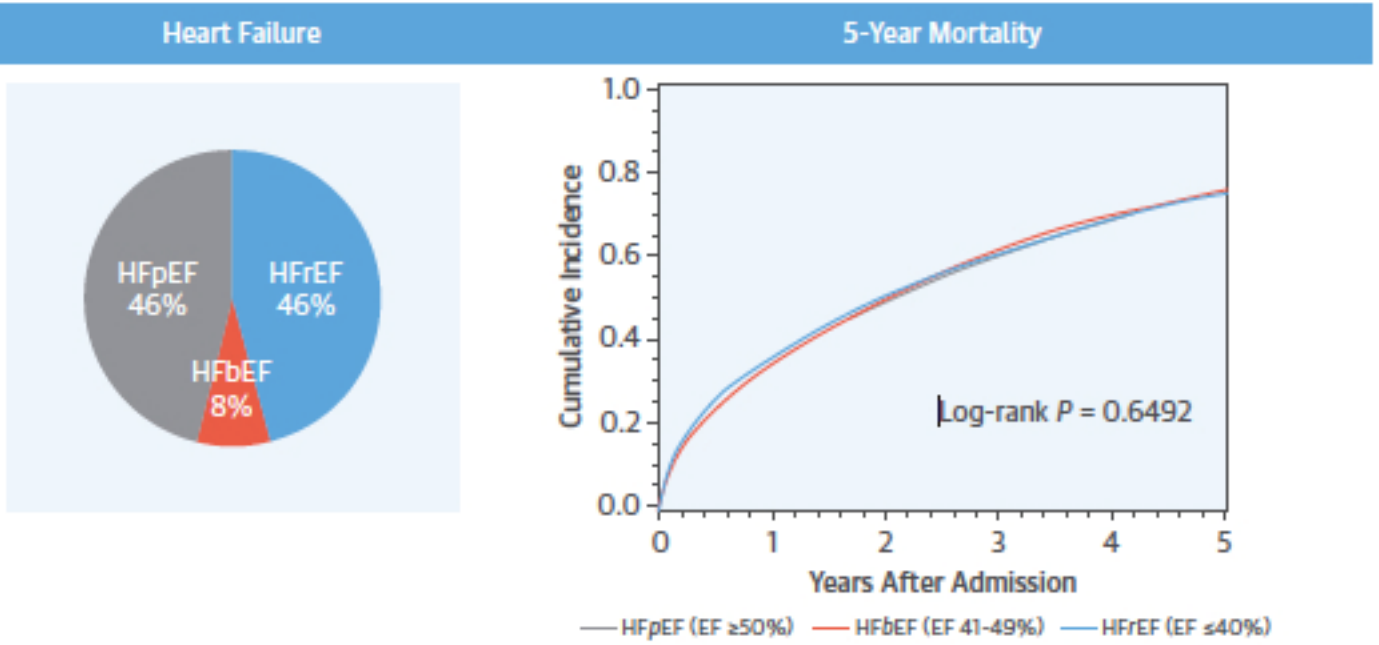
HFpEF

April 26, 2018

Definition of Heart Failure

Classification	Ejection Fraction	Description
I. Heart Failure with Reduced Ejection Fraction (HF*r*EF)	≤40%	Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HF*r*EF and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart Failure with Preserved Ejection Fraction (HF*p*EF)	≥50%	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, Borderline	41% to 49%	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HF*p*EF.
b. HF*p*EF, Improved	>40%	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

CENTRAL ILLUSTRATION **5-Year Outcomes in Patients Hospitalized With HF With Preserved, Borderline, and Reduced EF**

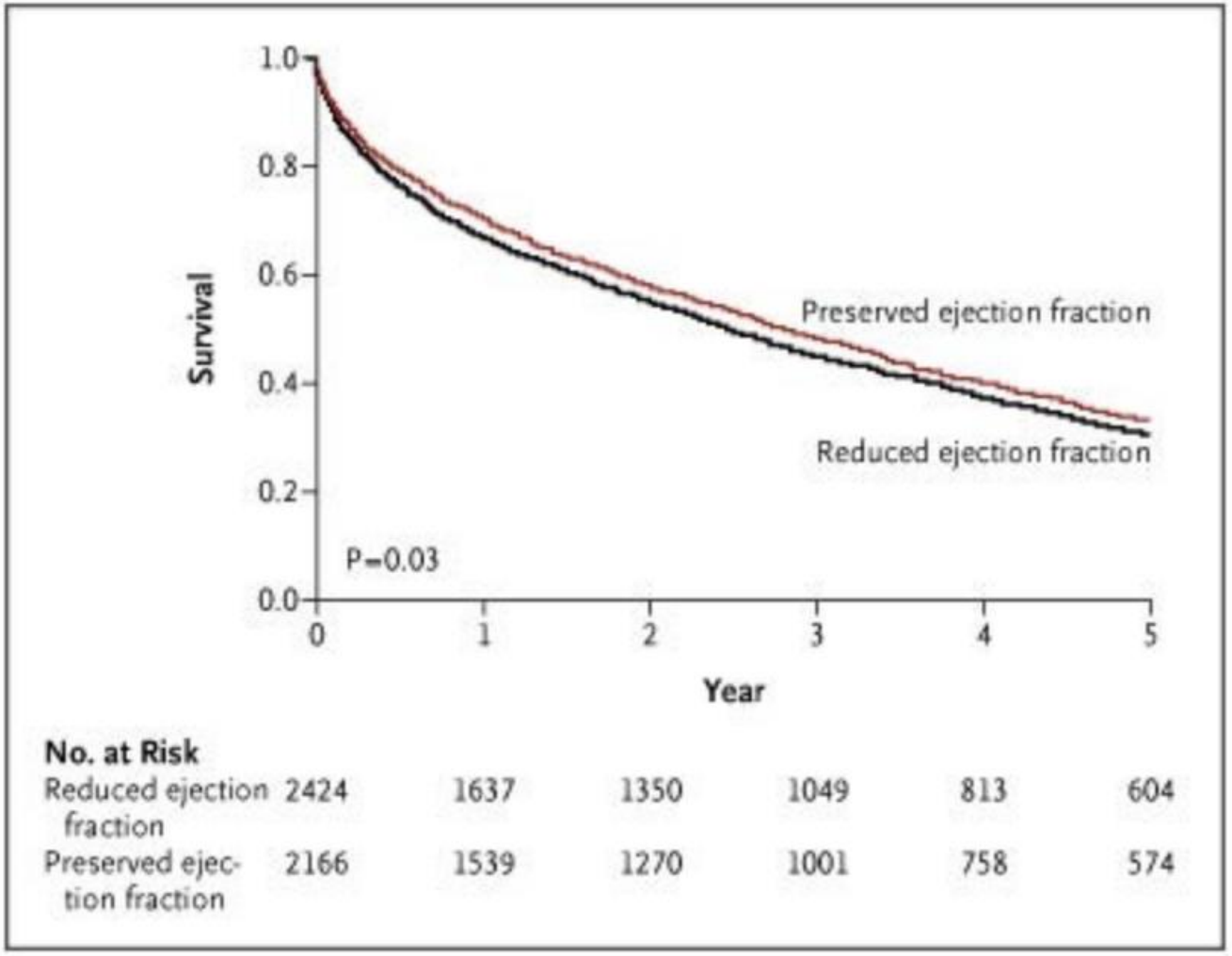


Outcomes – 5-Year Event Rates (%)					
	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3

Shah, K.S. et al. J Am Coll Cardiol. 2017;70(20):2476–86.

Patients ≥65 years of age hospitalized for decompensated heart failure (HF) in the GWTG-HF (Get With The Guidelines Heart Failure) registry had a similar percentage of preserved and reduced ejection fraction (EF), with 8% having borderline EF. The 5-year survival outcomes were poor across these subgroups, and rates of HF and cardiovascular (CV) admission were slightly greater in patients with reduced and borderline EF. The event rates for each outcome and HF subgroup are listed in the table. HFbEF = heart failure with borderline ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

(J Am Coll Cardiol 2017;70:2476–86)



No. at Risk

Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

July 20, 2006
N Engl J Med 2006; 355:251-259
DOI: 10.1056/NEJMoa052256

HFpEF

- 50% or more (40-71%) of patients with CHF have preserved LV systolic function.
- HFpEF is an increasingly frequent hospital discharge.
- Outcomes (hospitalization, death) “approach” those of HFrEF.
- “The fundamental pathophysiological perturbation leading to heart failure with a preserved ejection fraction remains incompletely defined…”

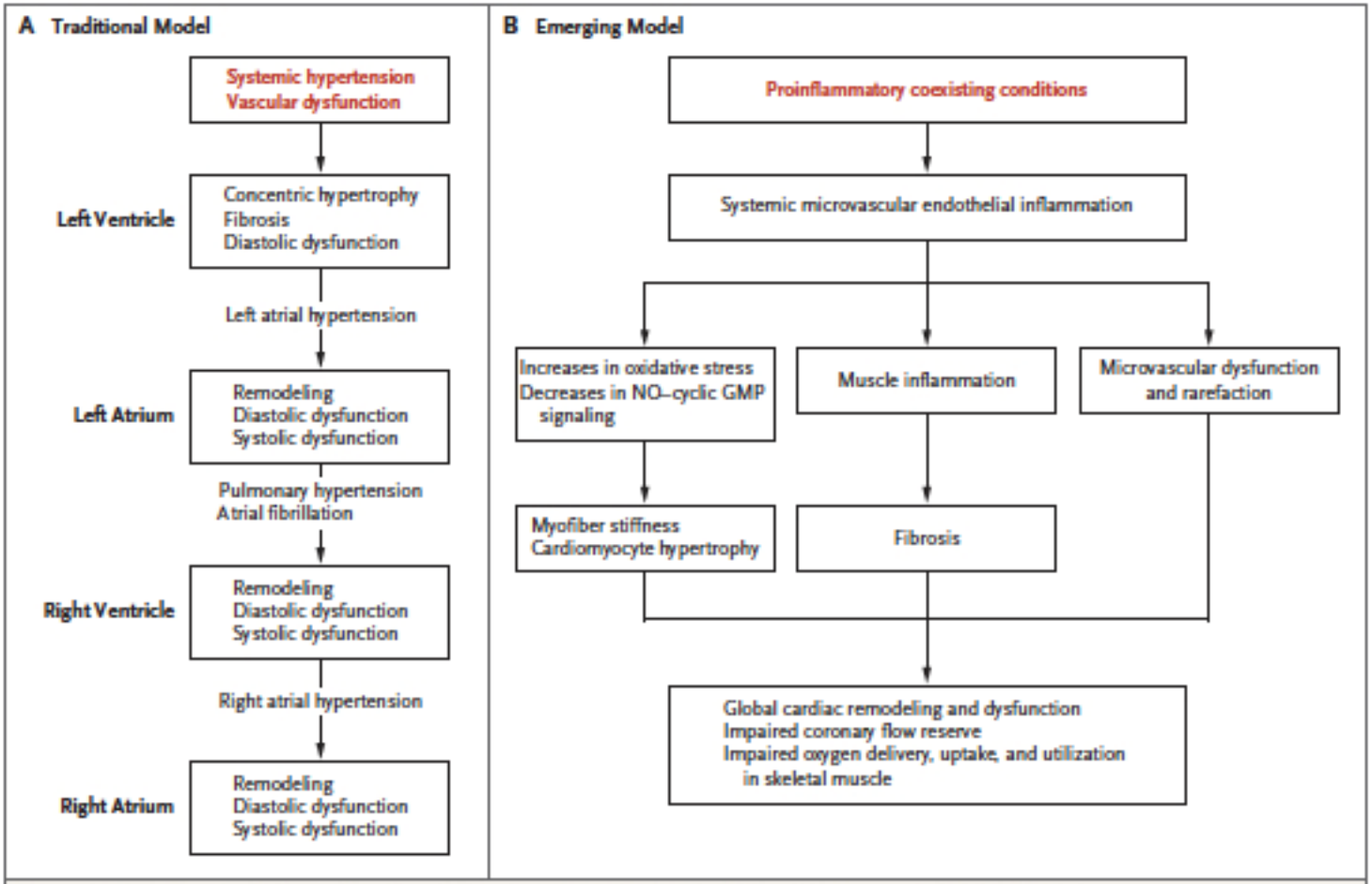
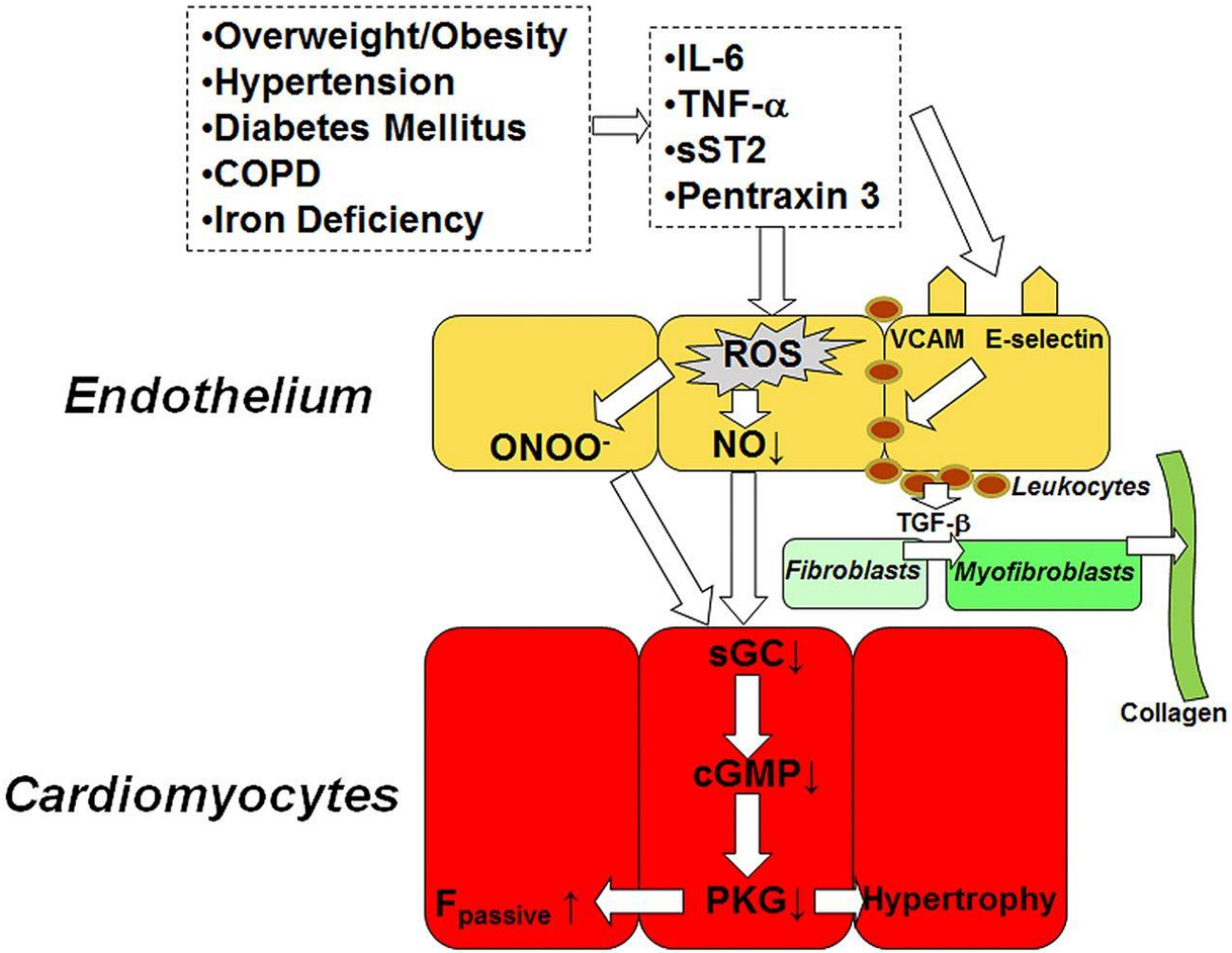


Figure 1. Traditional and Emerging Pathophysiological Models of Heart Failure with Preserved Ejection Fraction.

Most patients who have heart failure with a preserved ejection fraction have a history of hypertension. In the traditional pathophysiological model, pressure overload leads to concentric left ventricular hypertrophic and fibrotic remodeling and diastolic dysfunction. Ultimately, the left ventricular diastolic dysfunction leads to left atrial hypertension and remodeling, pulmonary venous hypertension, and right ventricular and atrial remodeling and dysfunction. Atrial fibrillation is common because of the chronic left atrial hypertension and subsequent structural and electrical remodeling. In the emerging model, proinflammatory cardiovascular and noncardiovascular coexisting conditions (e.g., hypertension, obesity, diabetes, the metabolic syndrome, lung disease, smoking, and iron deficiency) lead to systemic microvascular endothelial inflammation, global cardiac and skeletal-muscle inflammation, and subsequent fibrosis. These conditions also lead to increases in oxidative stress that limit nitric oxide–cyclic guanosine monophosphate (NO–cyclic GMP)–protein kinase G signaling, promoting global cardiomyocyte hypertrophy and intrinsic myofiber stiffness. Finally, coronary microvascular inflammation results in microvascular dysfunction and rarefaction with reduced microvascular density and coronary flow reserve. Similar changes occur in the skeletal-muscle vasculature with reduced oxygen delivery and utilization.

Myocardial Remodeling in HFPEF

Importance of Comorbidities



Walter J. Paulus, and Carsten Tschöpe JACC 2013;62:263-271

Secondary Causes of Diastolic Dysfunction

- Primary Myocardial diseases
  - Dilated cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Infiltrative cardiomyopathy
- Secondary Myocardial diseases
  - Hypertension
  - Aortic stenosis
  - Congenital heart disease
- Coronary artery disease
  - Ischemia
  - Infarction
- Pericardial disease
  - Tamponade
  - Contriction

HFpEF Epidemiology

- In the general population, patients with HFpEF are usually older women with a history of hypertension and atrial fibrillation.
- Obesity, diabetes mellitus, and hyperlipidemia are also highly prevalent in HFpEF:
  - HTN more common in patients with HFpEF
  - MI more common in patients with HFrEF
- Disordered breathing in CHF:
  - Central sleep apnea more common in HFrEF
  - Obstructive sleep apnea more common in HFpEF

JACC Vol. 43, No. 3, 2004

Table 1. Characteristics of Patients with Heart Failure and Preserved or Reduced Ejection Fraction.*

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

* Continuous variables are expressed as means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4.
† The P values are adjusted for age. NA denotes not applicable.
‡ Data on height and weight were not consistently accessible by electronic means over the course of the study; during the three consecutive five-year periods of the study, the data were available for 9 percent, 31 percent, and 83 percent of the study population, respectively. The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Obesity was defined by a body-mass index of 30 or more.

Owan T et al. N Engl J Med 2006;355:251-259

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Common Factors that Precipitate Acute Decompensated Heart Failure

- Non-adherence with medication regimen, sodium and/or fluid restriction
- Acute myocardial ischemia
- Uncorrected high blood pressure
- AF and other arrhythmias
- Recent addition of negative inotropic drugs (e.g., verapamil, nifedipine, diltiazem, beta blockers, other antiarrhythmics)
- Pulmonary embolus
- Initiation of drugs that increase salt retention (e.g., steroids, thiazolidinediones, NSAIDs)
- Excessive alcohol or illicit drug use
- Endocrine abnormalities (e.g., diabetes mellitus, hyperthyroidism, hypothyroidism)
- Concurrent infections (e.g., pneumonia, viral illnesses)
- Additional acute cardiovascular disorders (e.g., valve disease endocarditis, myopericarditis, aortic dissection)

Troponins in CHF

Table 1 Incidence of Detectable Troponin in Acute and Chronic HF

First Author, Year (Ref. #)	n	Troponin	Cut-Off Values	HF Type	HF Etiology	Incidence of Circulating Troponin
Peacock et al., 2008 (19)	67,924	TnI and TnT	TnI or TnT >0.1 μg/l	AHF	Ischemic and nonischemic	6.2%
Gheorghiade et al., 2005 (10)	51	TnI and TnT	TnI >0.03 μg/l or TnT >0.01 μg/l	AHF	Ischemic	43.5% (TnT) or 73.9% (TnI)
Del Carlo et al., 2004 (8)	62	TnT	TnT ≥0.01 μg/l	AHF	Ischemic and nonischemic	83.9%
La Vecchia et al., 2000 (14)	34	TnI	TnI >0.3 ng/ml	AHF	Ischemic and nonischemic	29.0%
Metra et al., 2007 (28)	116	TnT	TnT >0.01 ng/ml	AHF	Ischemic and nonischemic	38.0% (at baseline)
Niizeki et al., 2007 (58)	126	TnT	TnT >0.01 ng/ml	AHF	Ischemic and nonischemic	26.0%
Parenti et al., 2008 (18)	99	TnI	TnI >0.05 ng/ml	AHF	Unknown	45.0%
Perna et al., 2005 (21)	184	TnT	TnT >0.1 ng/ml	AHF	Ischemic and nonischemic	31.5%
You et al., 2007 (41)	2,025	TnI	TnI >0.5 μg/l	AHF	Ischemic and nonischemic	34.5%
Logeart et al., 2001 (16)	71	TnI	TnI >0.026 ng/ml	AHF and CHF	Nonischemic	27.0%
Horwich et al., 2003 (11)	238	TnI	TnI ≥0.04 ng/ml	CHF	Ischemic and nonischemic	49.1%
Hudson et al., 2004 (12)	136	TnT	TnT ≥0.02 ng/ml	CHF	Ischemic and nonischemic	24.0%
Latini et al., 2007 (15)	4,053	TnT and hsTnT	TnT ≥0.01 ng/ml or hsTnT ≥0.001 ng/ml	CHF	Ischemic and nonischemic	10.0% (TnT) or 92% (hsTnT)
Miller et al., 2007 (17)	190	TnT	TnT ≥0.01 ng/ml	CHF	Ischemic and nonischemic	53.0%
Missov et al., 1999 (27)	33	TnT	TnT >0.1 ng/ml	CHF	Ischemic and nonischemic	15.0%
Perna et al., 2004 (20)	115	TnT	TnT ≥0.02 ng/ml	CHF	Ischemic and nonischemic	32.0%

AHF = acute heart failure; CHF = chronic heart failure; HF = heart failure; hsTnT = high-sensitivity troponin T; TnI = troponin I; TnT = troponin T.

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

J Am Coll Cardiol 2010;56:1071–8

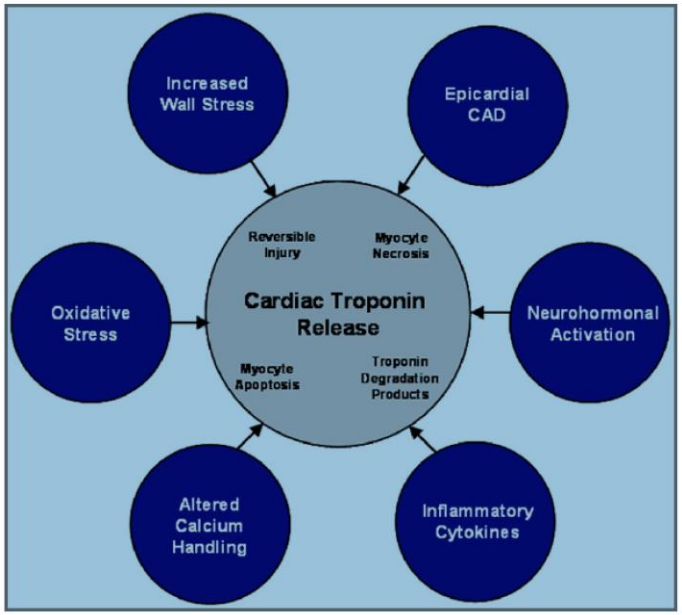


Figure 1 Mechanism of Cardiac Troponin Release in Heart Failure

Multiple mechanisms may lead to myocyte necrosis, apoptosis, or reversible injury with increased myocyte membrane permeability, all resulting in cardiac troponin release. CAD = coronary artery disease.

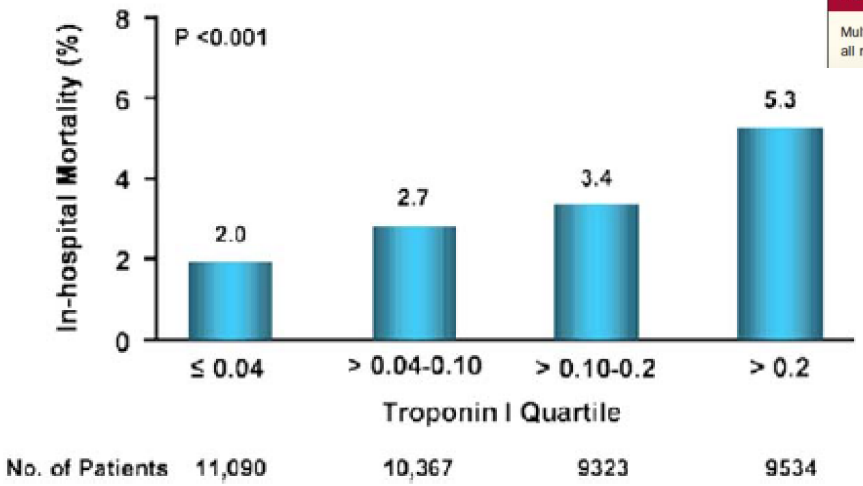


Figure 2 In-Hospital Mortality According to Troponin I Quartile

Inpatient mortality in patients with acute heart failure by troponin I quartile in the ADHERE (Acute Decompensated Heart Failure National Registry) study. Adapted from Peacock et al. (19).

Table 3 Signs and Symptoms Differentiating AMI From AHF in the Setting of Positive Troponin

	AMI (Type I NSTEMI)	AHF
Chest pain	Usually	Occasionally
Shortness of breath	Sometimes	Usually
Detectable troponin	Always	Sometimes
Troponin level >1.0 ng/ml	Usually	Occasionally
CK-MB elevation	Usually	Rarely
Troponin pattern	Rise and fall	Persistent low level elevation or gradual decline
BNP >100 pg/ml	Sometimes	Almost always
BNP >400 pg/ml	Rarely	Usually

AMI = acute myocardial infarction; CK-MB = creatine kinase–myocardial band; NSTEMI = non–ST-segment elevation myocardial infarction; other abbreviations as in Tables 1 and 2.

Diastolic dysfunction is not HFpEF

- Diastolic dysfunction is an echo finding, an aging phenomenom and a consequence of chronic disease such as HTN, diabetes, CAD, obesity, deconditioning and renal dysfunction.
- HFpEF is a clinical syndrome manifest as
  - dyspnea (DOE, orthopnea, PND, at rest),
  - fatigue, tiredness,
  - fluid retention (JVD, peripheral edema, interstitial pulmonary edema),
  - suggested by elevated markers (BNP, pro-BNP)
  - in the face of normal LV systolic function
    - absent significant contributing valvular heart disease after excluding other cardiac and non-cardiac etiologies (infiltrative/restrictive CM, PE, COPD, sleep apnea, pulmonary HTN, etc.)

Table 1. Criteria of CHF.*

Major Criteria
Paroxysmal nocturnal dyspnea or orthopnea
Neck-vein distention
Rales
Cardiomegaly
Acute pulmonary edema
S_3 gallop
Increased venous pressure ->16 cm of water
Circulation time ≥25 sec
Hepatojugular reflux
Minor Criteria
Ankle edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity ↓ ⅓ from maximum
Tachycardia (rate of ≥120/min)
Major or Minor Criterion
Weight loss ≥4.5 kg in 5 days in response to treatment

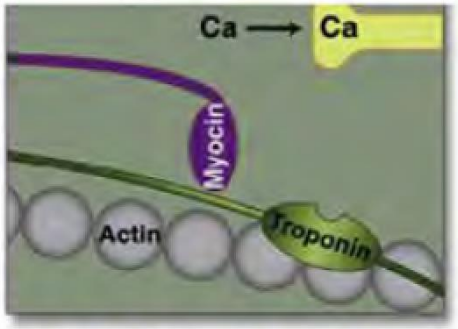
*For establishing a definite diagnosis of congestive heart failure in this study, 2 major or 1 major & 2 minor criteria had to be present concurrently.

NEJM 1971, 285, 1441-46

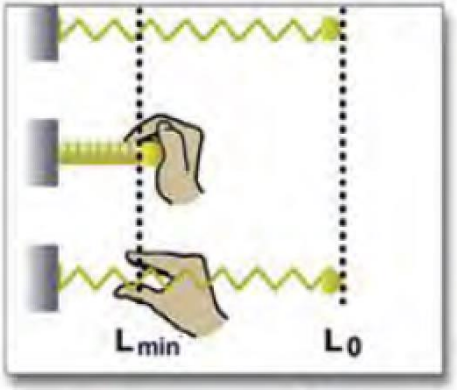
Diastolic Dysfunction

- Impaired LV relaxation
- Reduced restoring forces, reduced early diastolic suction
- Increase LV chamber stiffness
- All leading to increased LV filling pressures

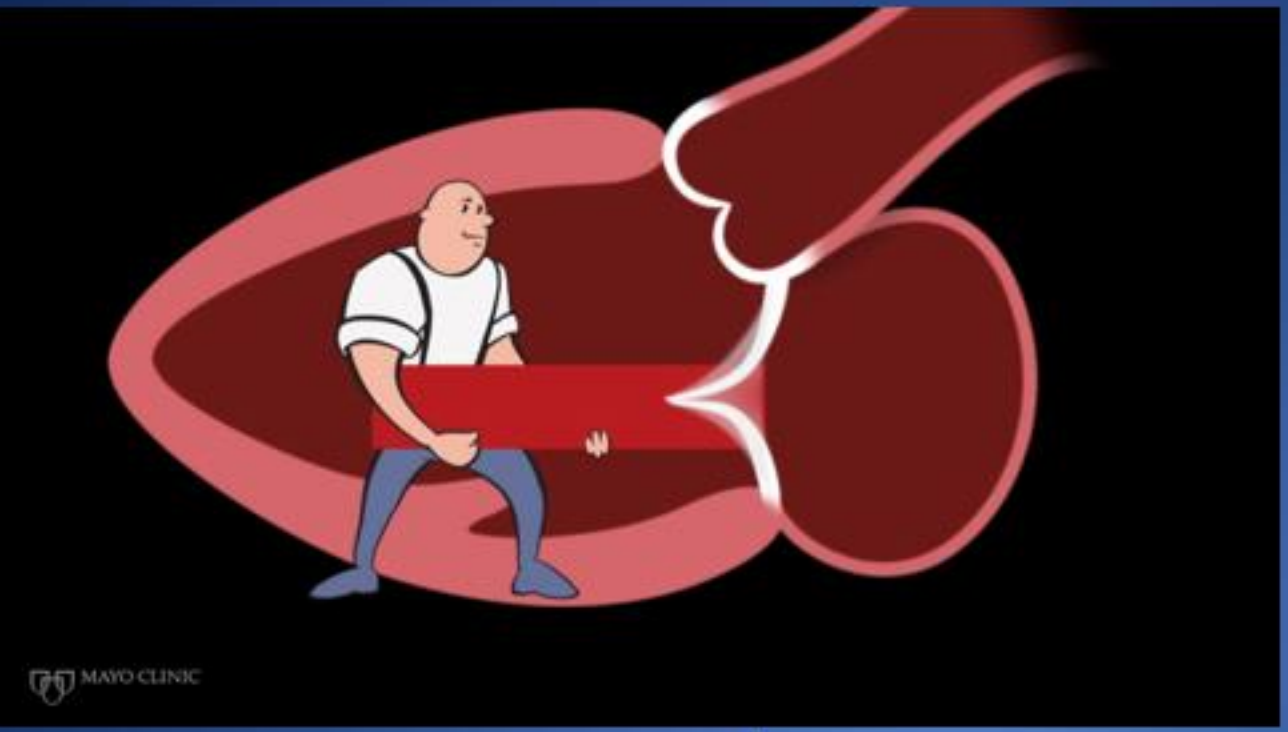
Active relaxation



Restoring forces



Lengthening load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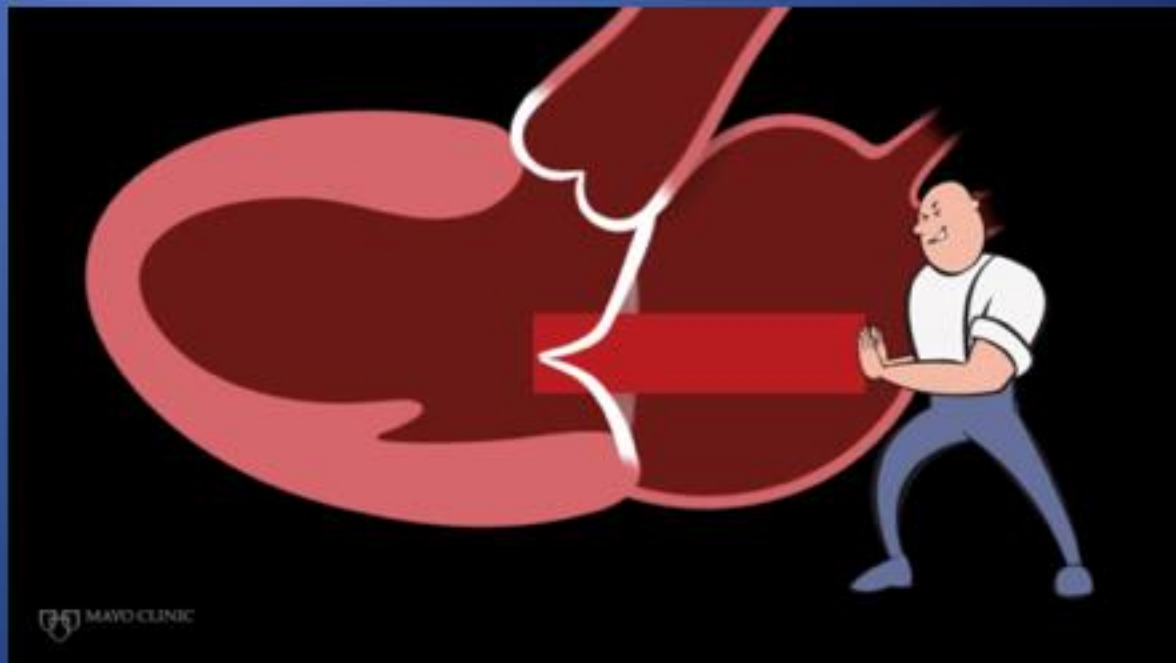
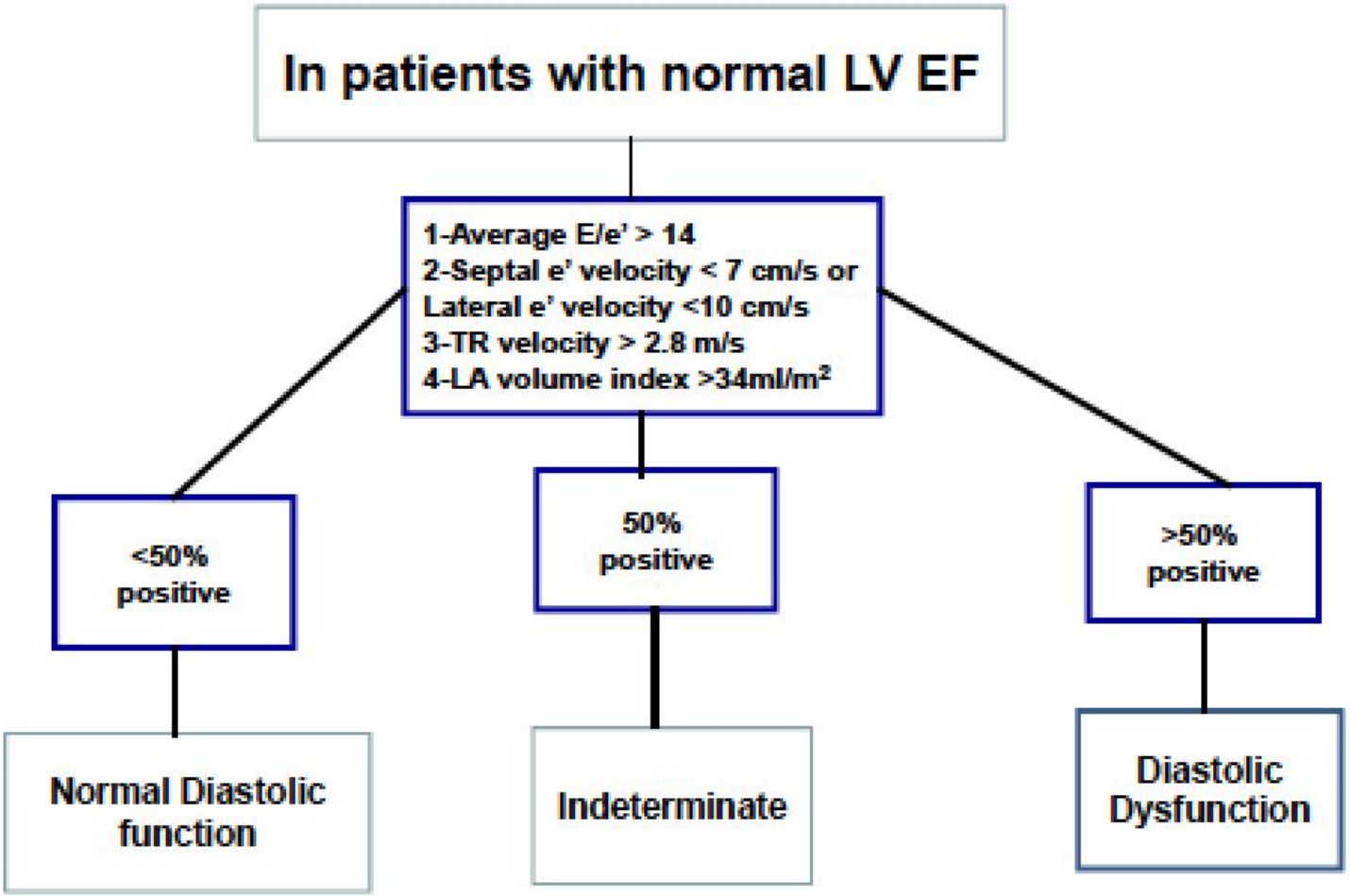
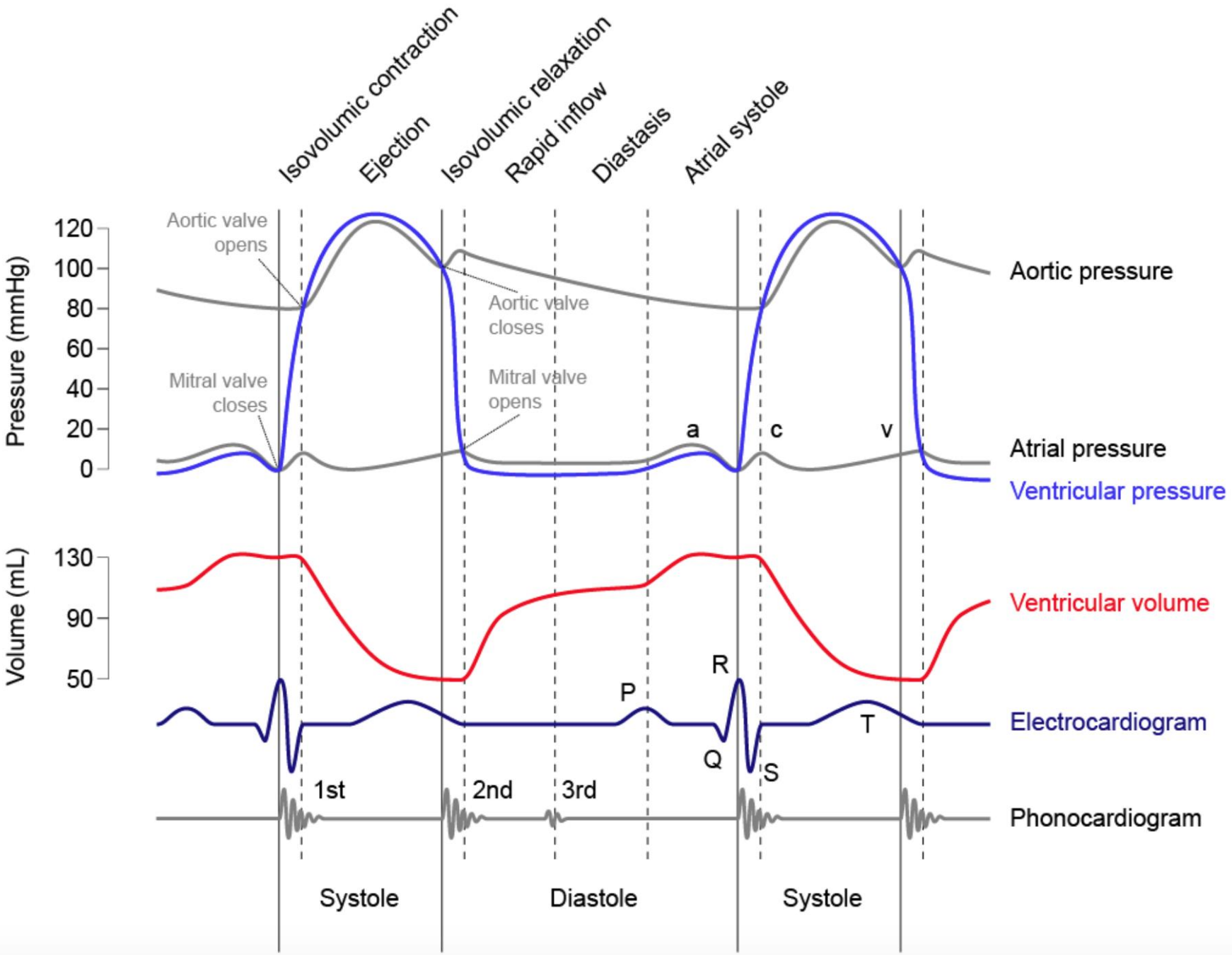

MAYO CLINIC

Is diastolic dysfunction present?

A




Isovolumic contraction
Ejection
Isovolumic relaxation
Rapid inflow
Diastasis
Atrial systole
Pressure (mmHg)
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100
80
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40
20
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Aortic valve opens
Aortic valve closes
Mitral valve closes
Mitral valve opens
a
c
v
Aortic pressure
Atrial pressure
Ventricular pressure
Volume (mL)
130
90
50
Ventricular volume
R
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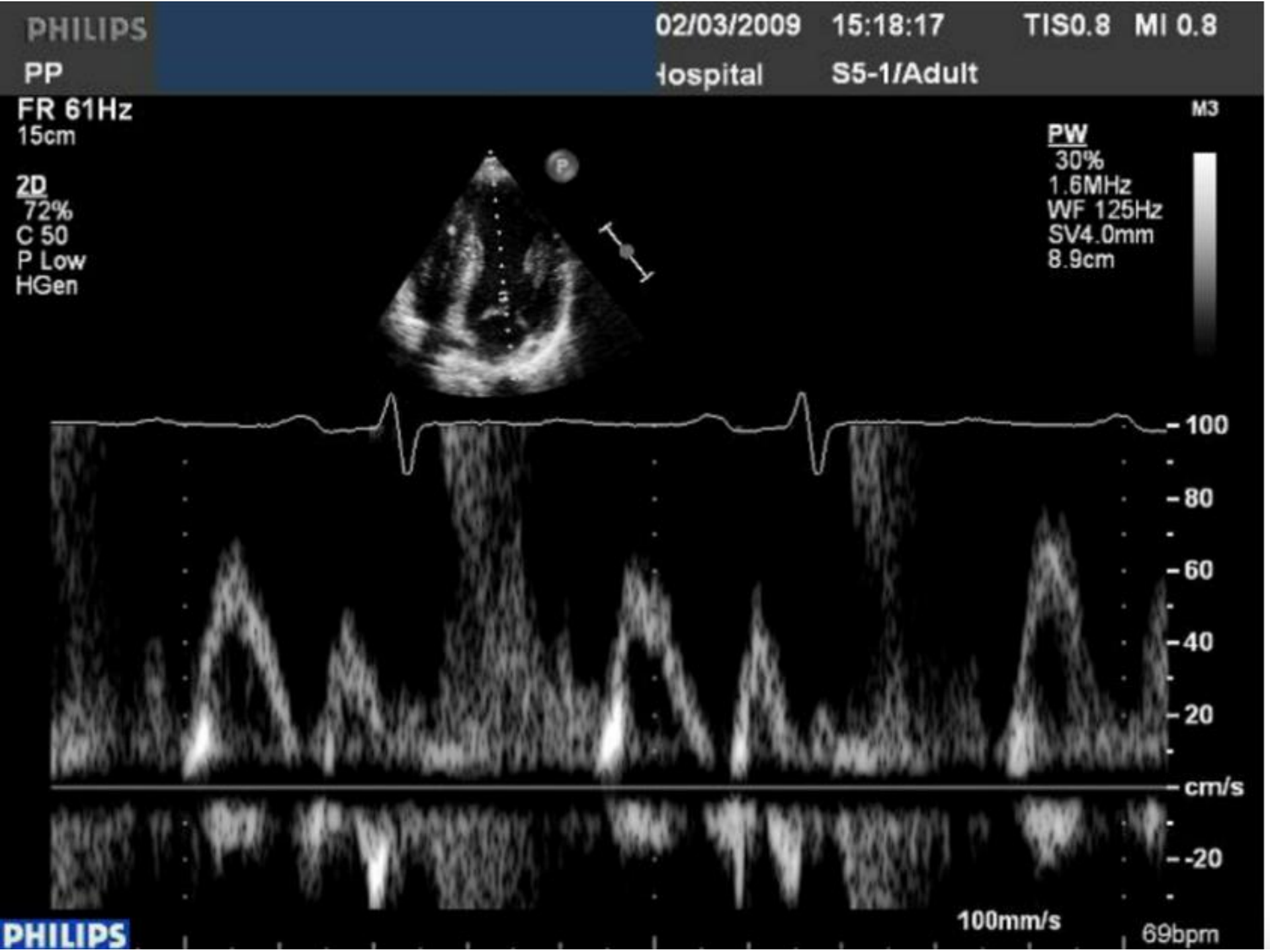
2nd
3rd
Phonocardiogram
Systole
Diastole
Systole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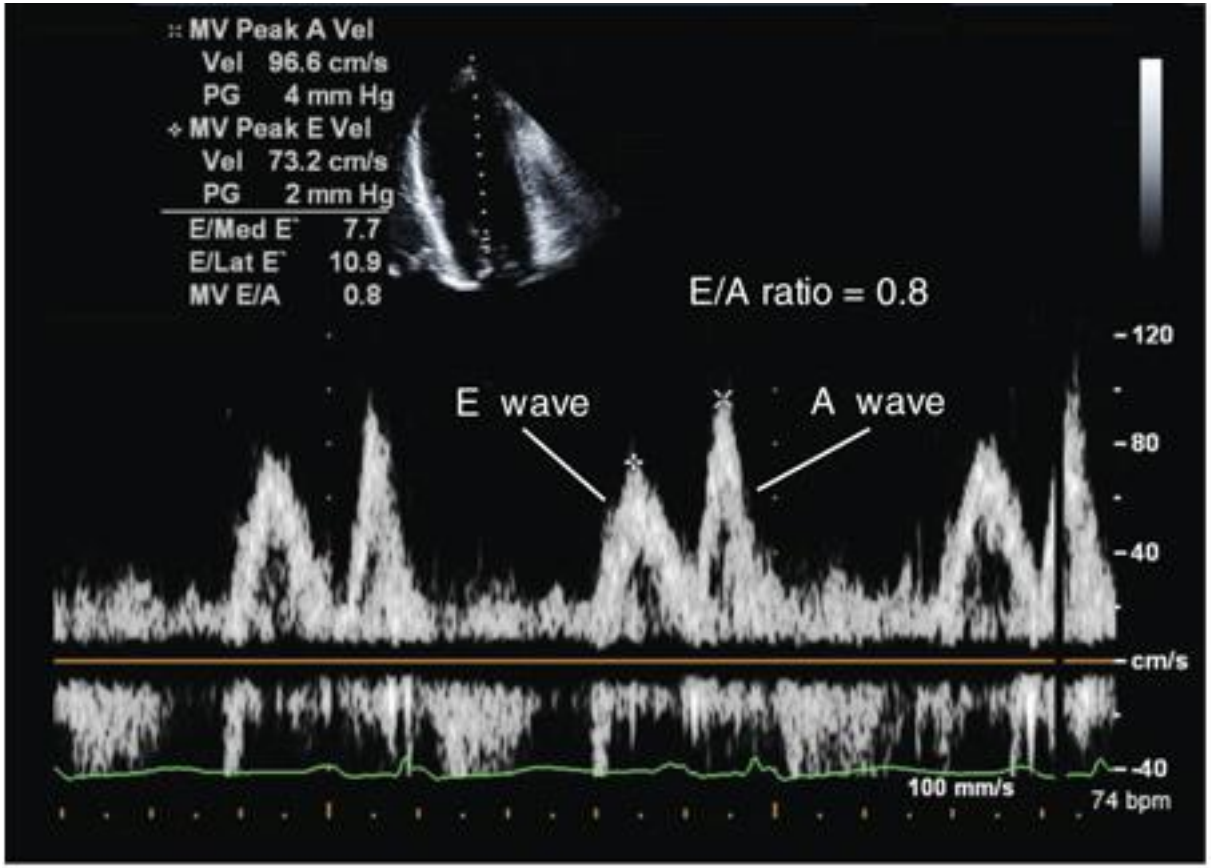
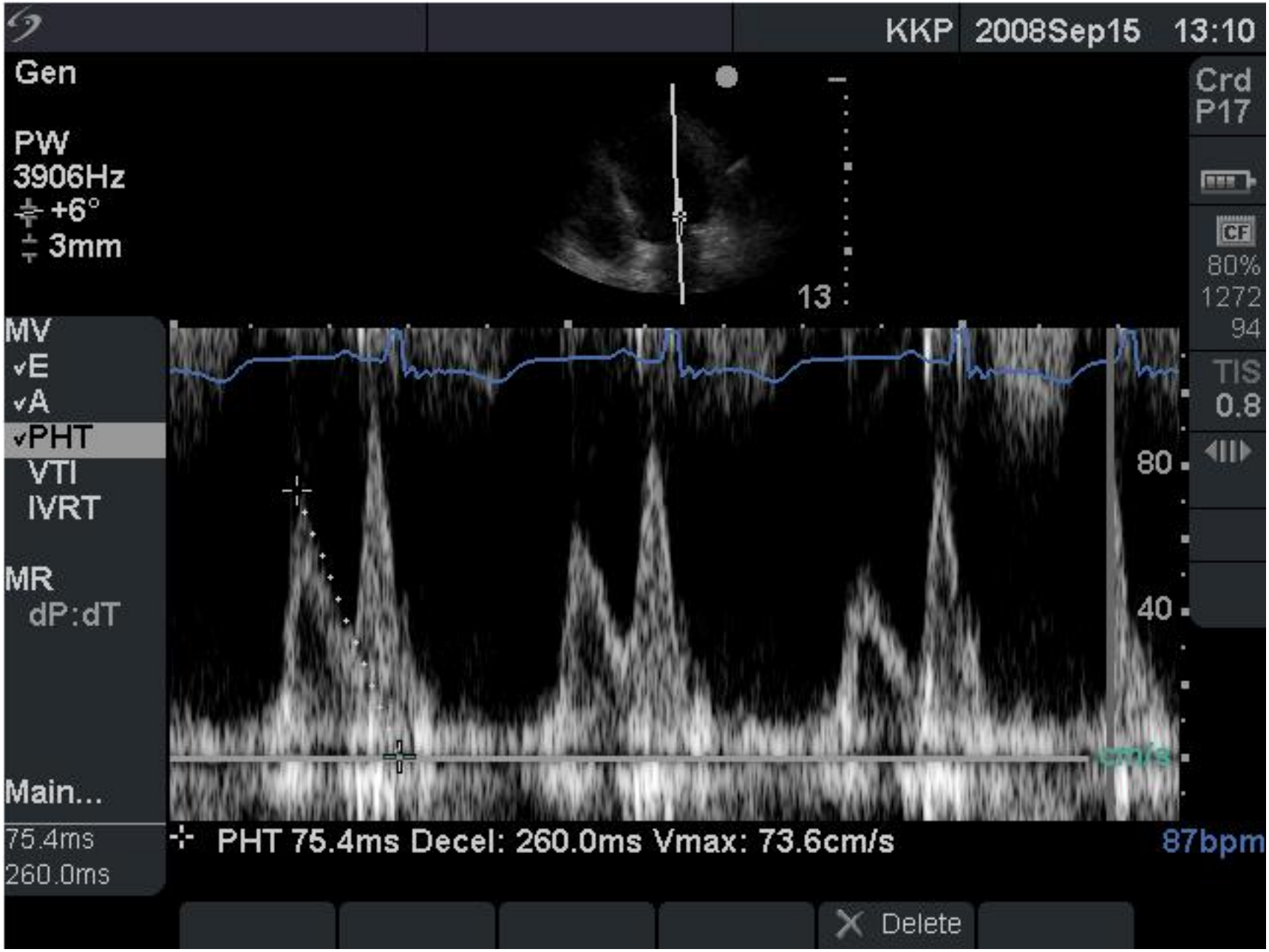


Source: Pahlm O, Wagner GS: *Multimodal Cardiovascular Imaging: Principles and Clinical Applications*: www.accessmedicine.com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80%
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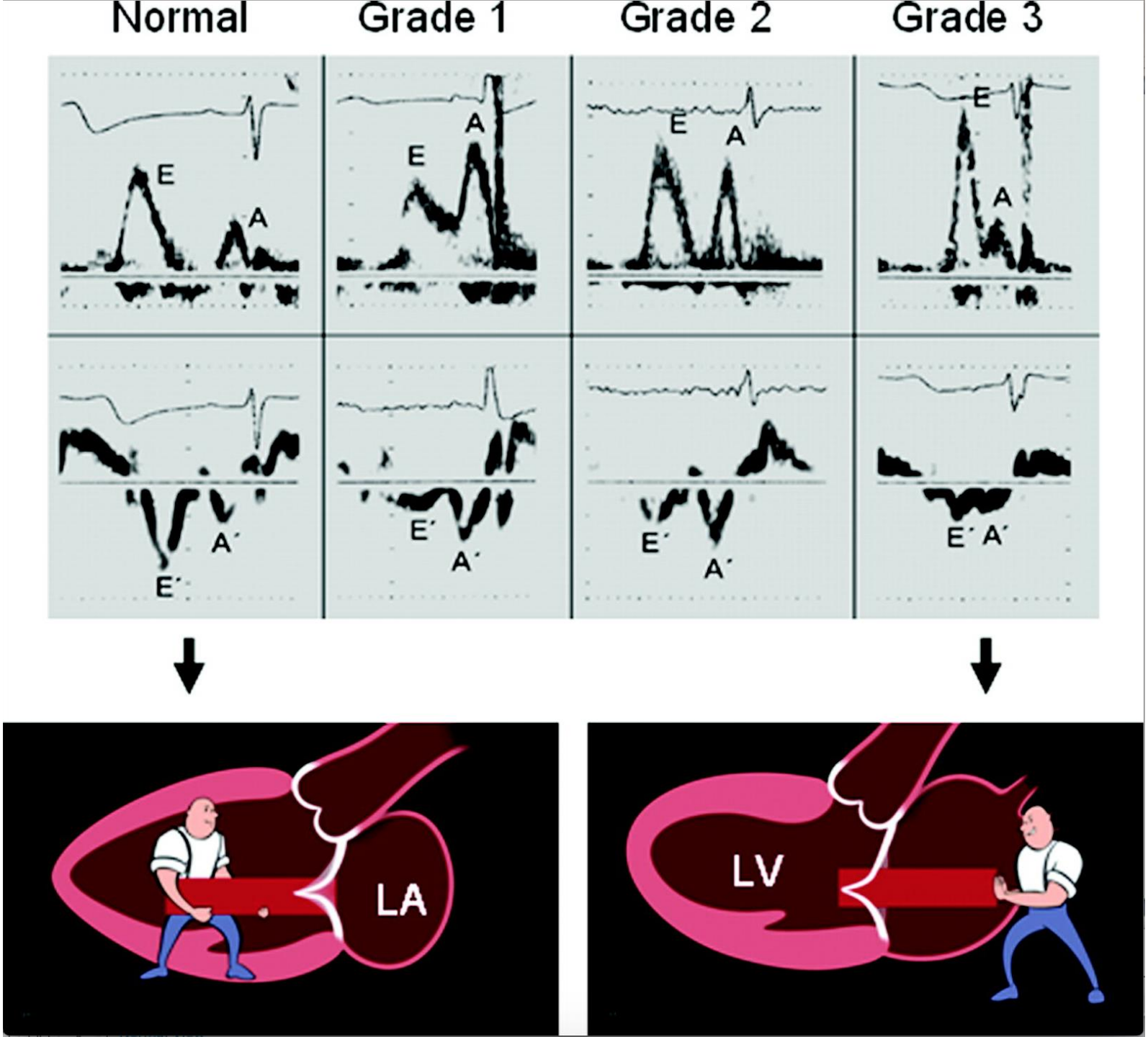
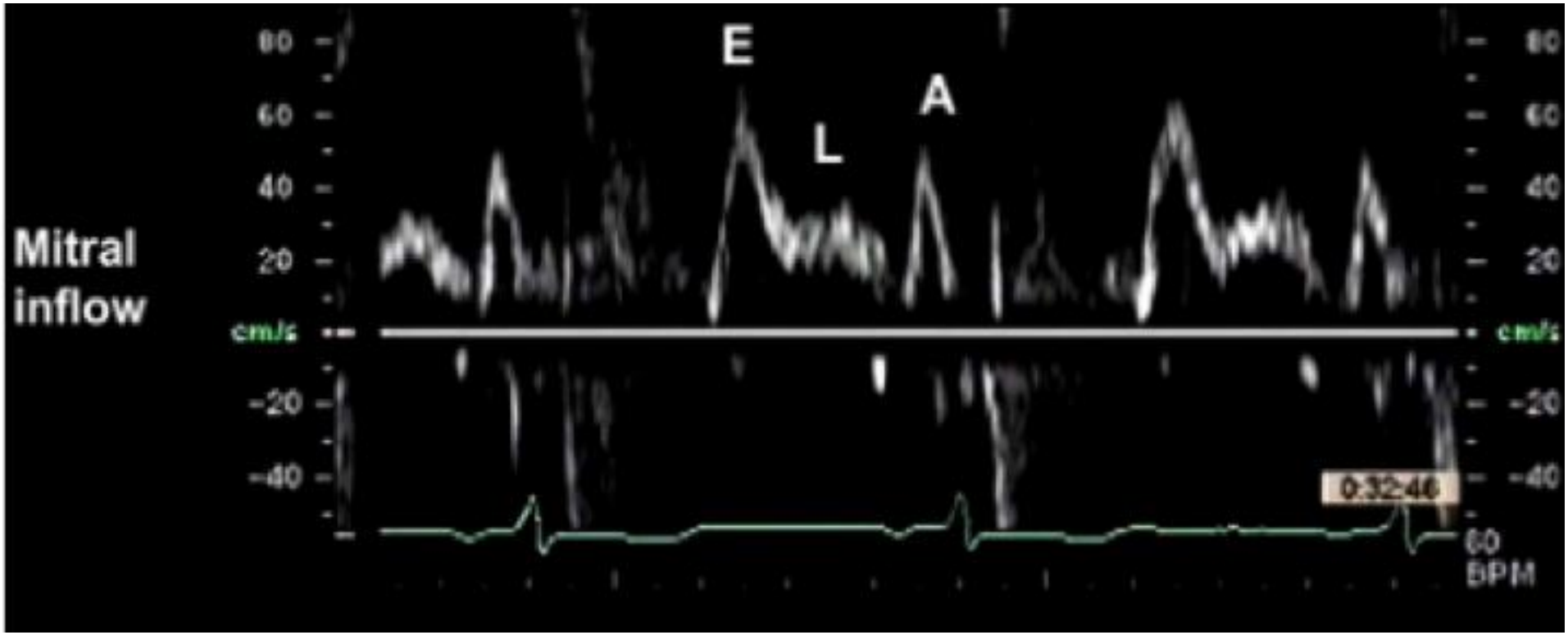

Normal
Grade 1
Grade 2
Grade 3
E
A
E´
A´
LA
LV

Exclusions!

- The approach starts with mitral inflow velocities and is applied in the absence of
  - atrial fibrillation (AF),
  - significant mitral valve disease
    - (at least moderate mitral annular calcification [MAC],
    - any mitral stenosis
    - or mitral regurgitation [MR] of more than moderate severity,
    - mitral valve repair or prosthetic mitral valve),
  - LV assist devices,
  - left bundle branch block,
  - and ventricular paced rhythm.

(J Am Soc Echocardiogr 2016;29:277-314.)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-20
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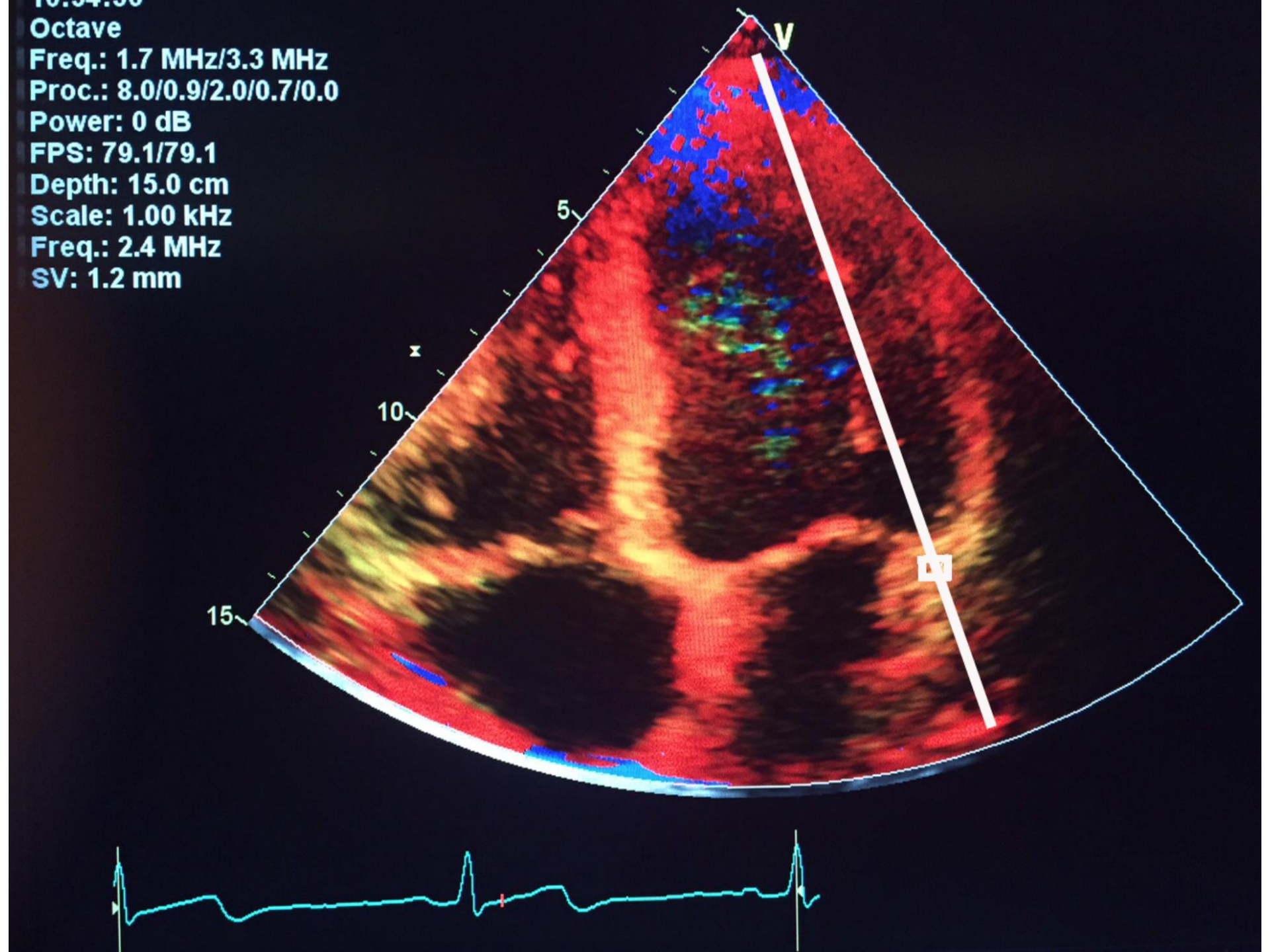
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Proc.: 8.0/0.9/2.0/0.7/0.0
Power: 0 dB
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Depth: 15.0 cm
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Freq.: 2.4 MHz
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V
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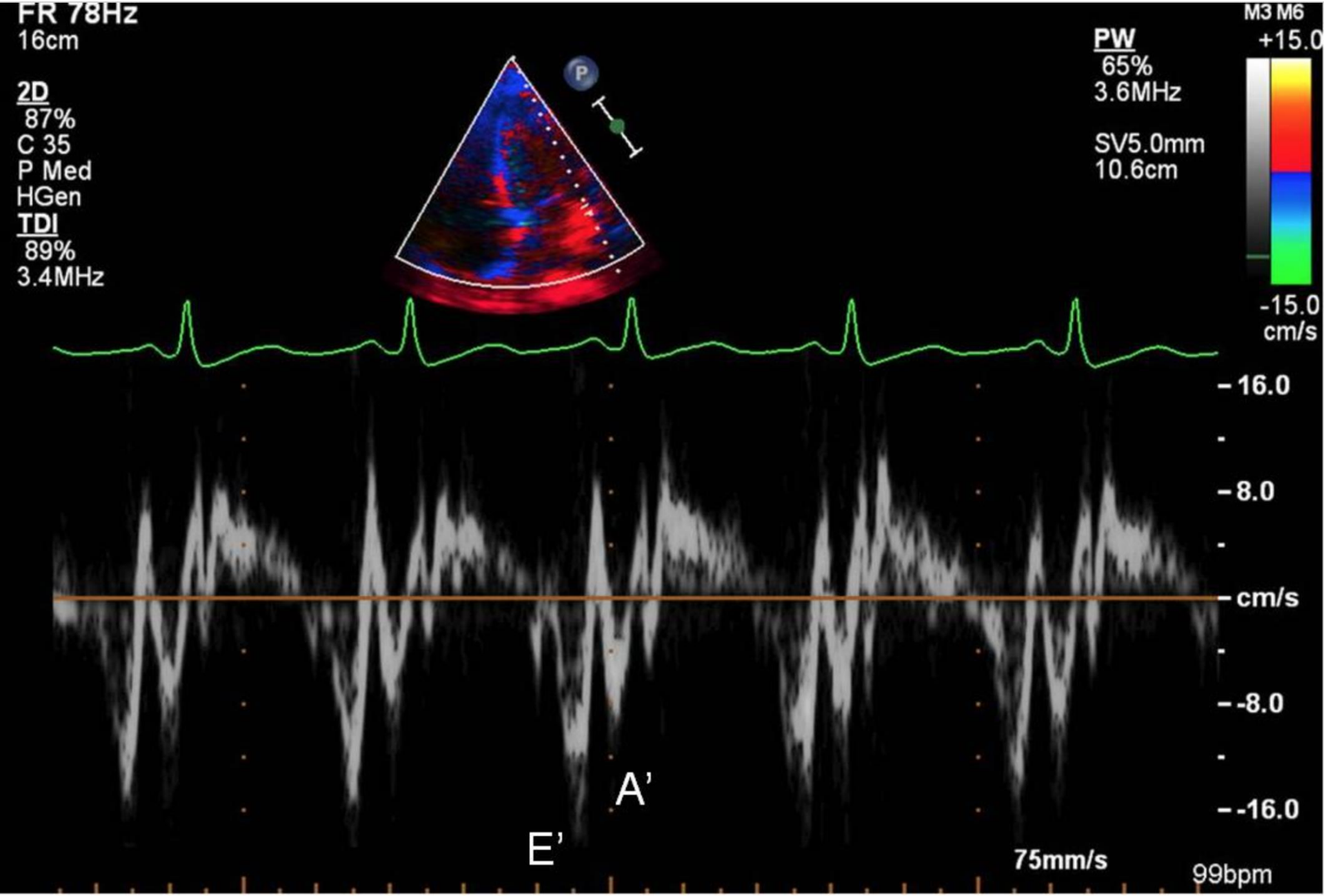
x
10
15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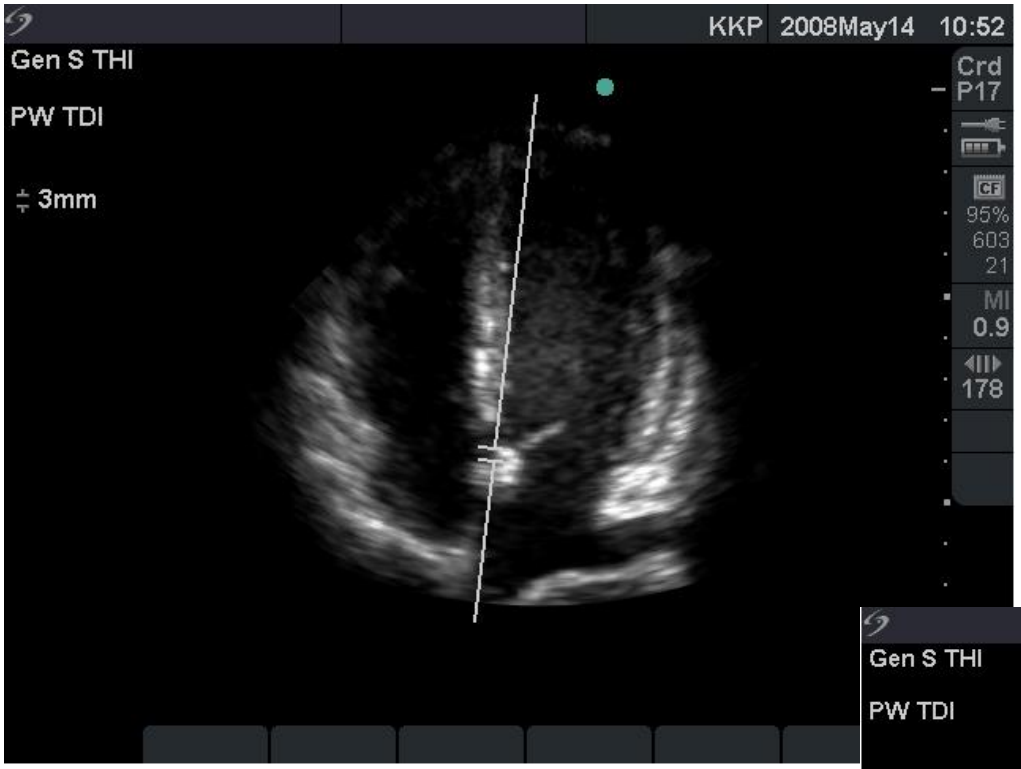
16cm
2D
87%
C 35
P Med
HGen
TDI
89%
3.4MHz
PW
65%
3.6MHz
SV5.0mm
10.6cm
M3 M6
+15.0
-15.0
cm/s
16.0
8.0
cm/s
-8.0
-16.0
A'
E'
75mm/s
99bpm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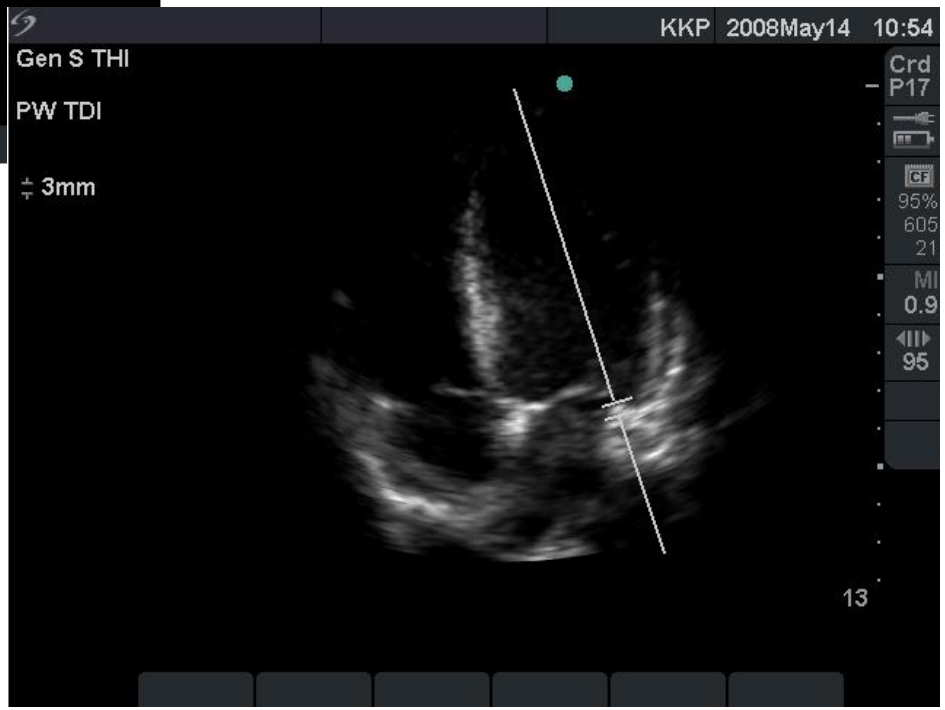
Crd
P17
CF
95%
603
21
MI
0.9
178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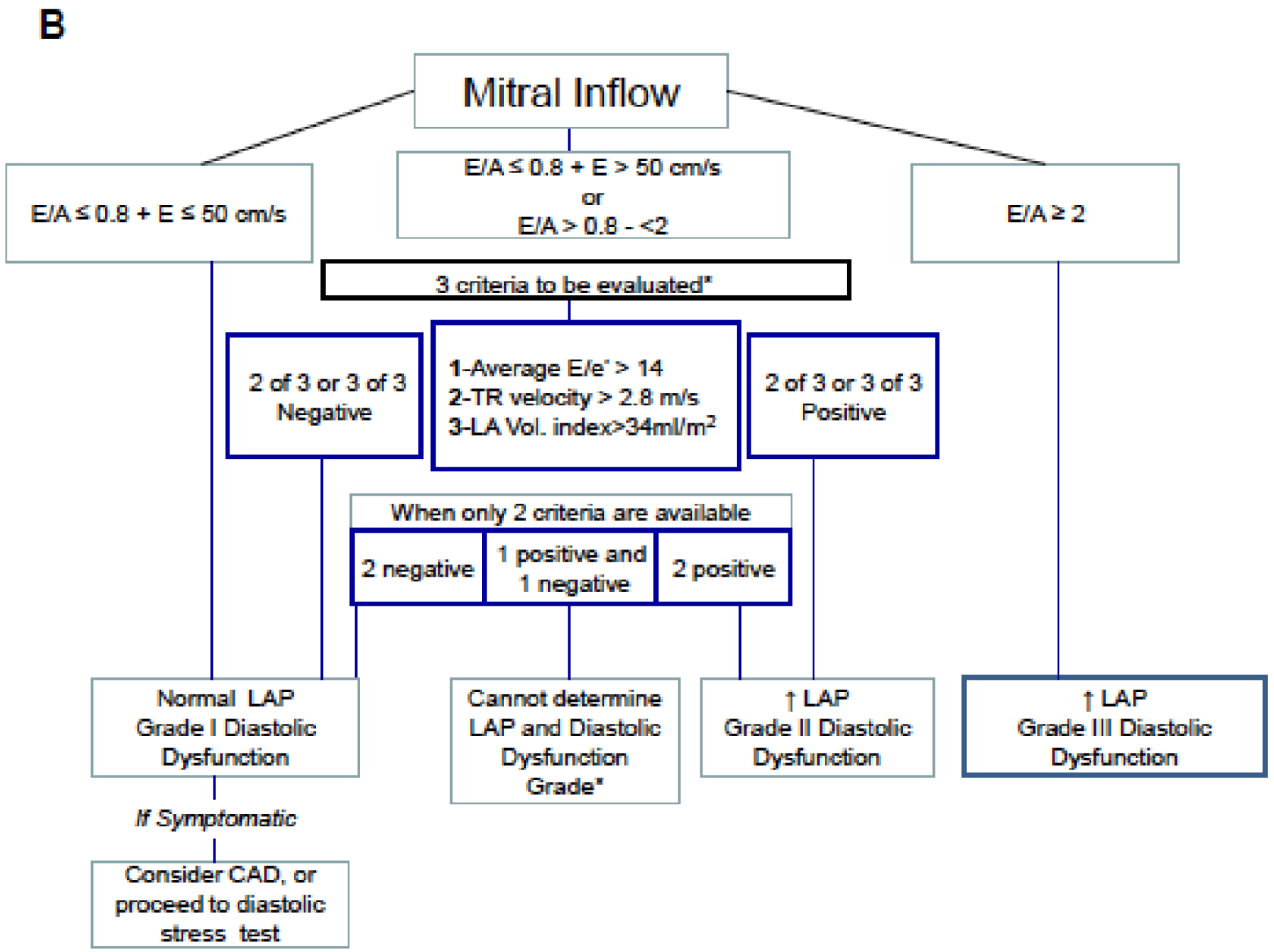
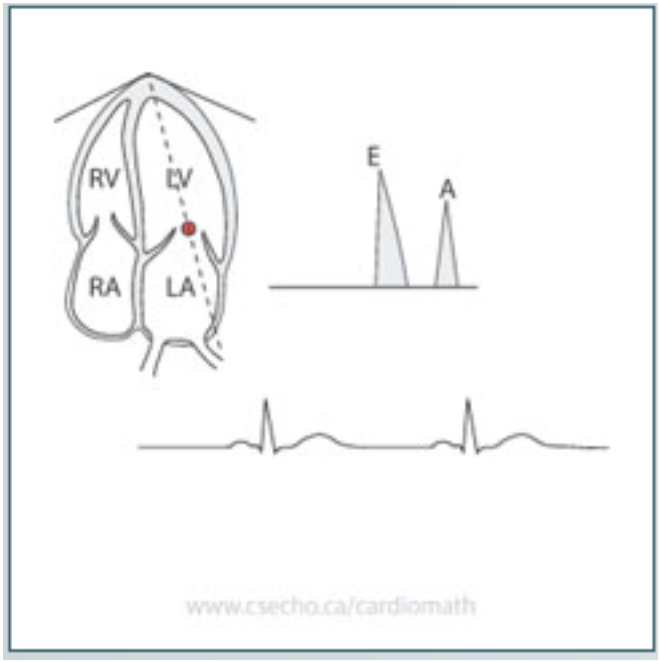
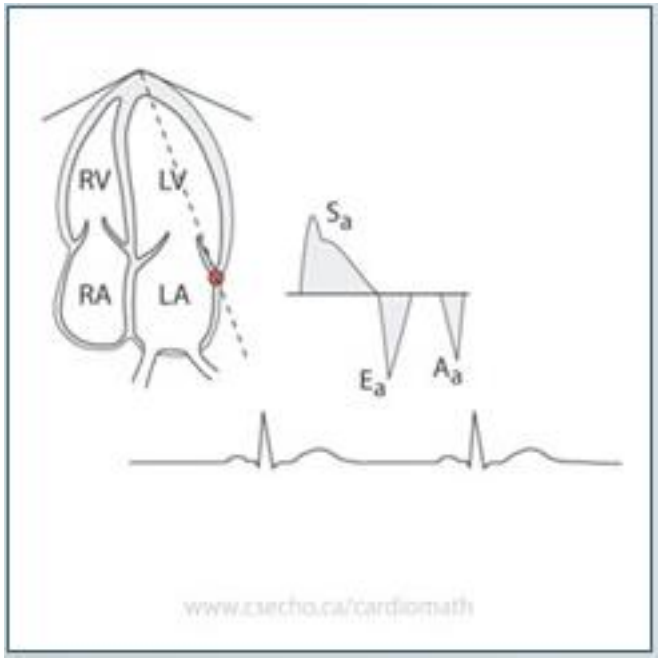
13

Is LAP elevated?



(* : LAP indeterminate if only 1 of 3 parameters available. Pulmonary vein S/D ratio <1 applicable to conclude elevated LAP in patients with depressed LV EF)

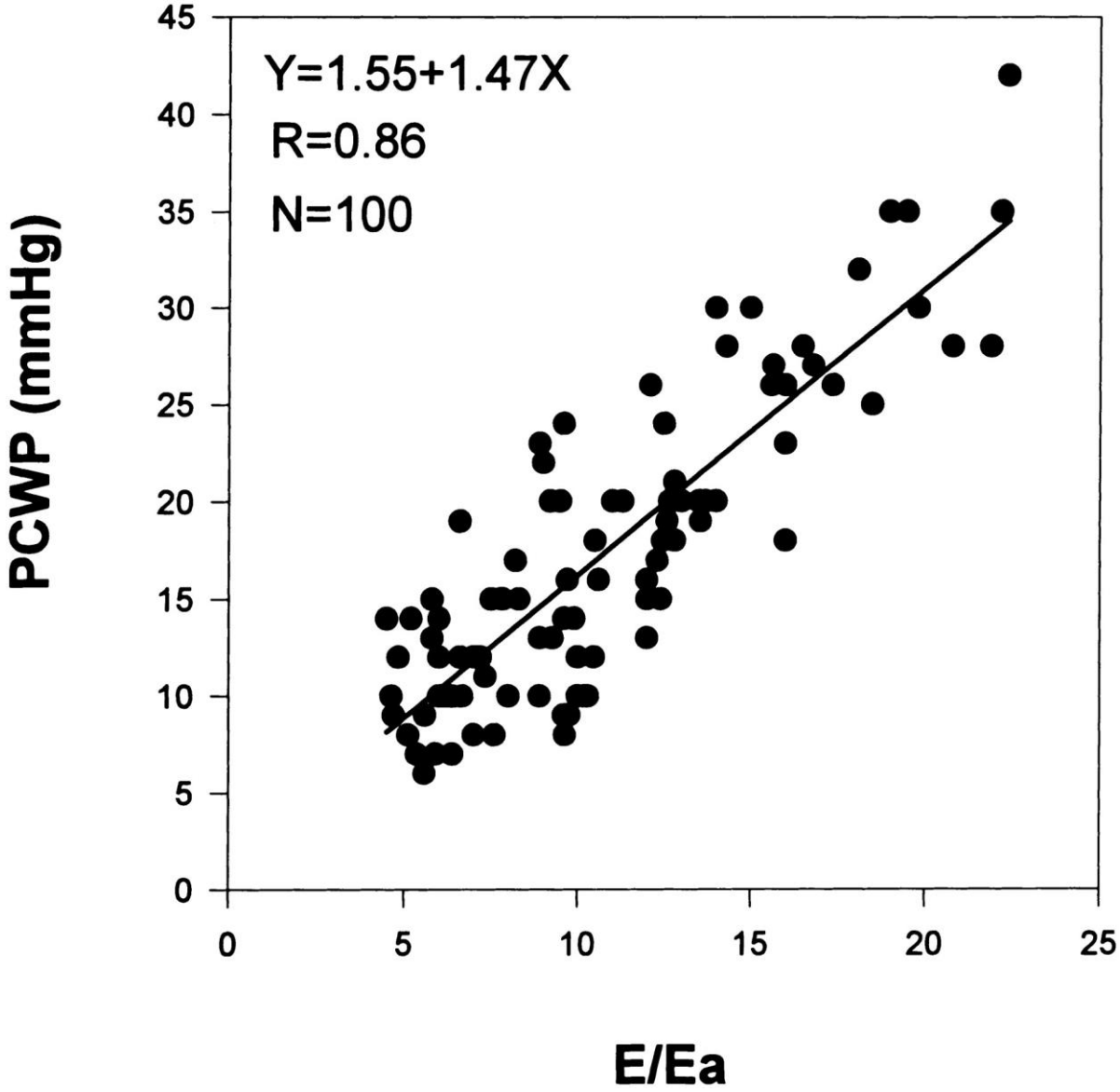




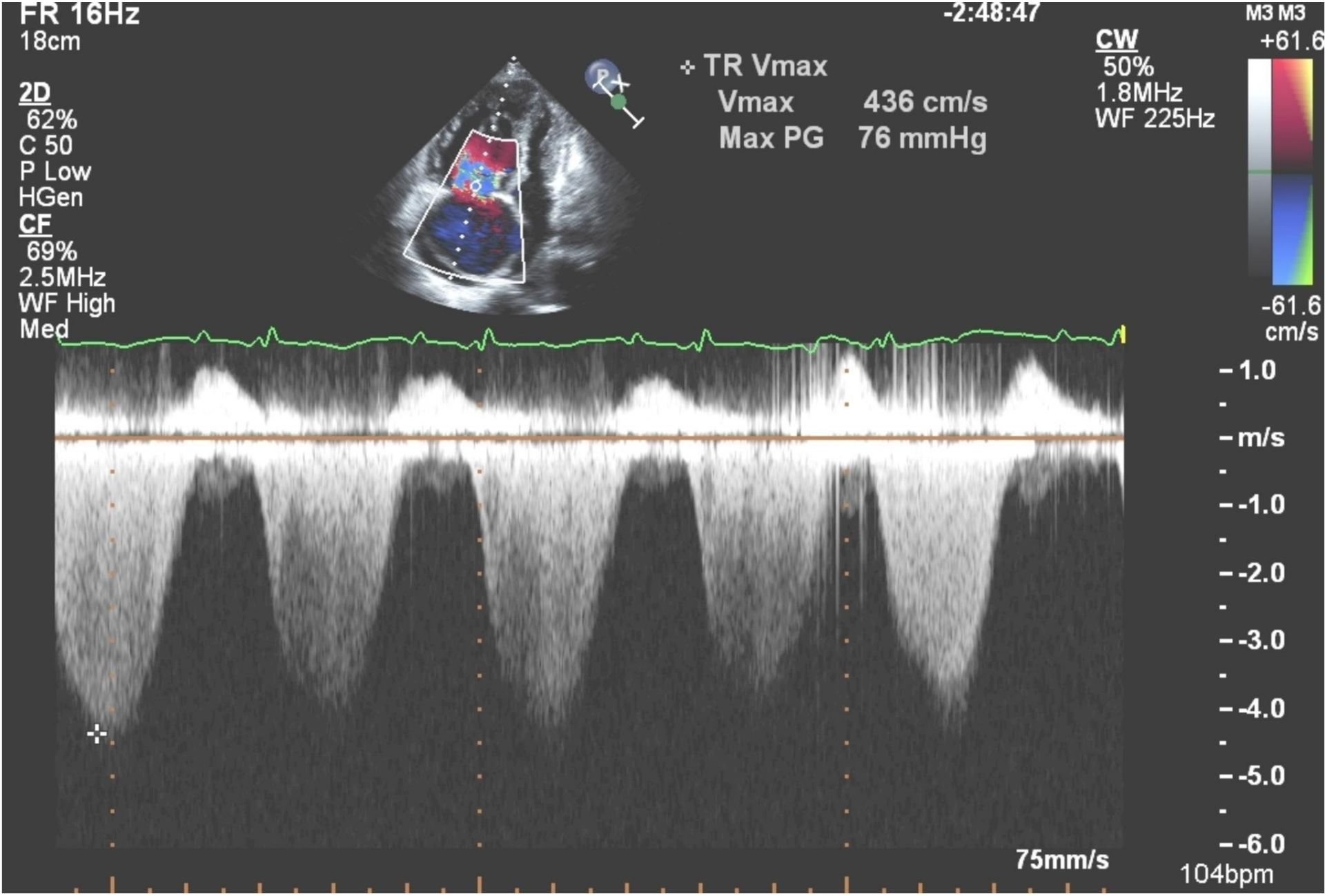
$$e' = (e'_{lateral} + e'_{septal}) / 2$$

$$PCWP = 1.24 * (E/e') + 1.9$$

Plot of PCWP vs E/Ea in 100 initial patients.

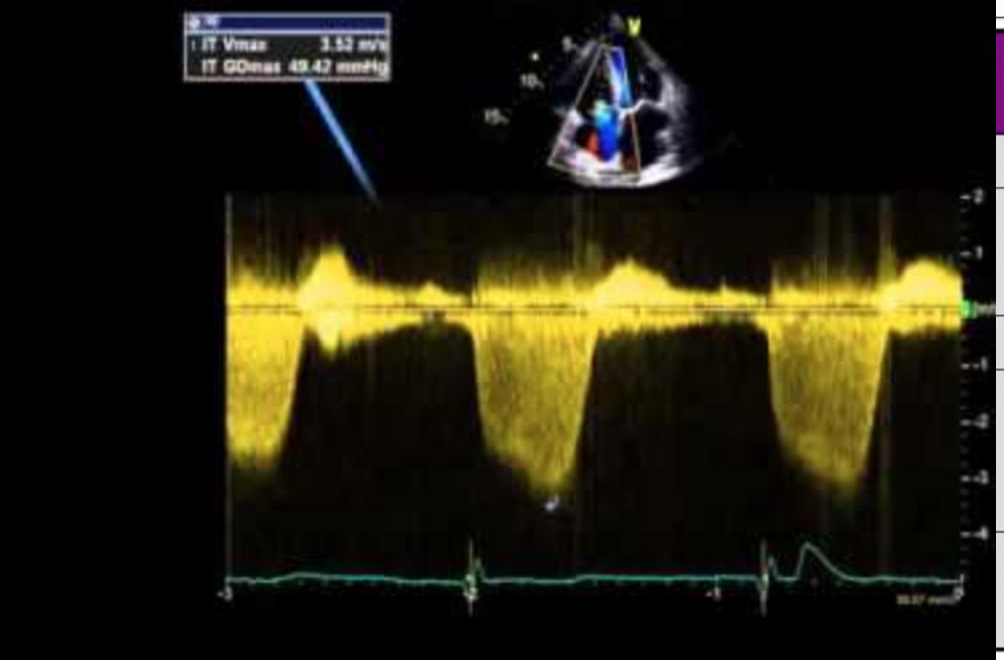


Sherif F. Nagueh et al. Circulation. 1998;98:1644-1650


FR 16Hz
18cm
2D
62%
C 50
P Low
HGen
CF
69%
2.5MHz
WF High
Med
-2:48:47
TR Vmax
Vmax 436 cm/s
Max PG 76 mmHg
CW
50%
1.8MHz
WF 225Hz
M3 M3
+61.6
-61.6
cm/s
1.0
m/s
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
75mm/s
104bpm

Pulmonary artery systolic pressure

4Vmax TR^2

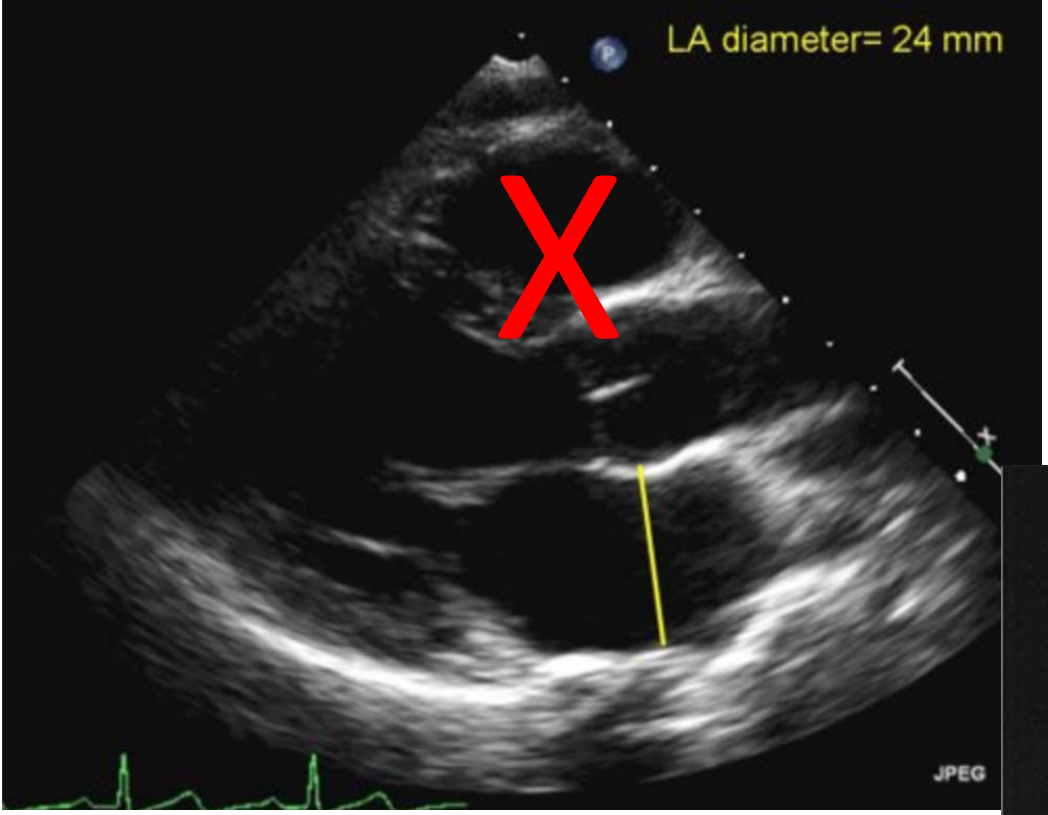


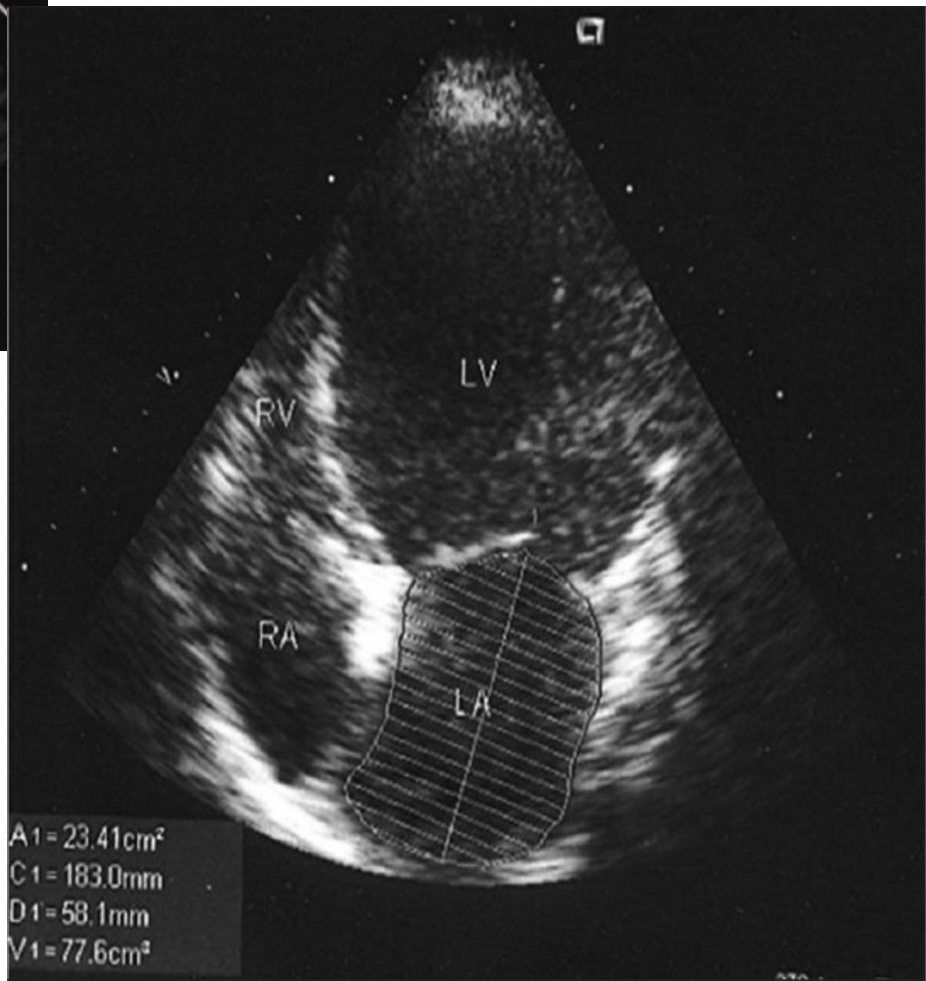
How to estimate RA pressure without a doppler probe ?

Size of IVC	IVC size On Inspiration	Right atrial pressure(mmhg)
Small < 1.5cm	Near total collapse	0 - 5
Normal (1.5-2.5cm)	Decrease > 50%	5 - 10
Normal	Decrease < 50%	10 - 15
Dilated > 2.5cms	Decrease < 50%	15 - 20
Both IVC & Hepatic veins dilated	No change	> 20

Modified from Otto C. M .Text book of clinical echocardiography W.B.Saunders .2000

PA systolic pressure = 4 X $(\text{TR velocity})^2$ + RA pressure


LA diameter= 24 mm
JPEG


LV
RV
RA
LA
A1 = 23.41cm²
C1 = 183.0mm
D1 = 58.1mm
V1 = 77.6cm³

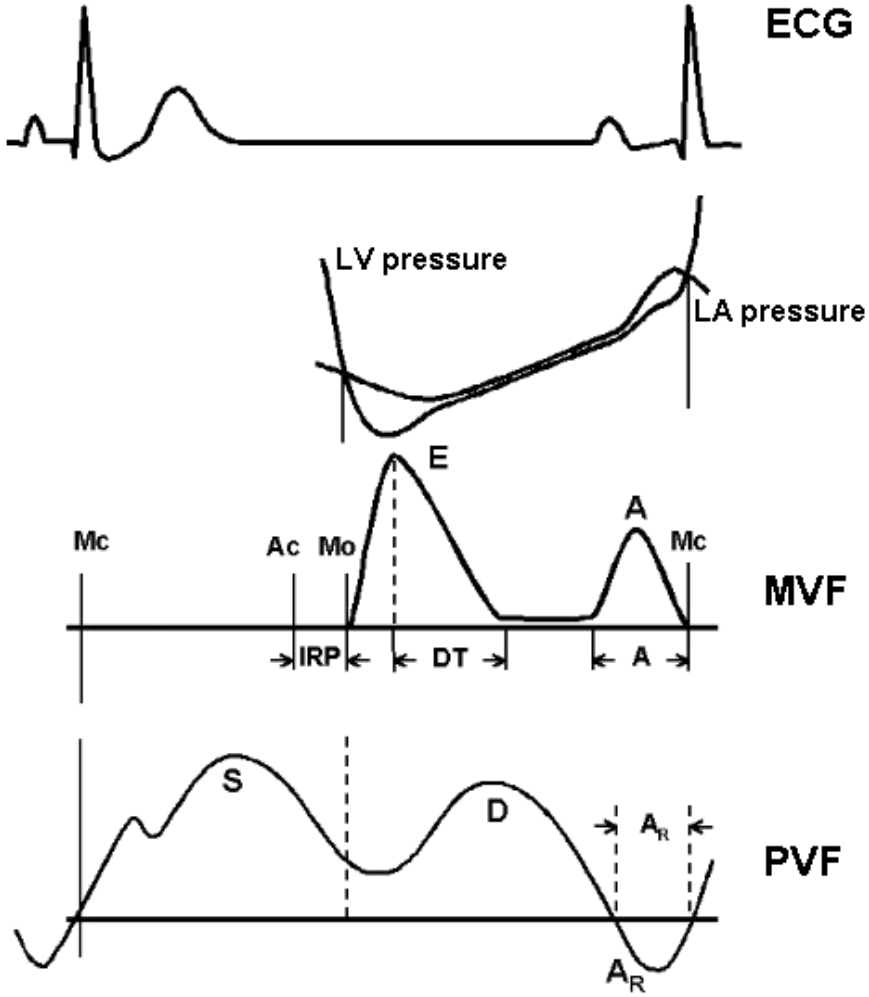
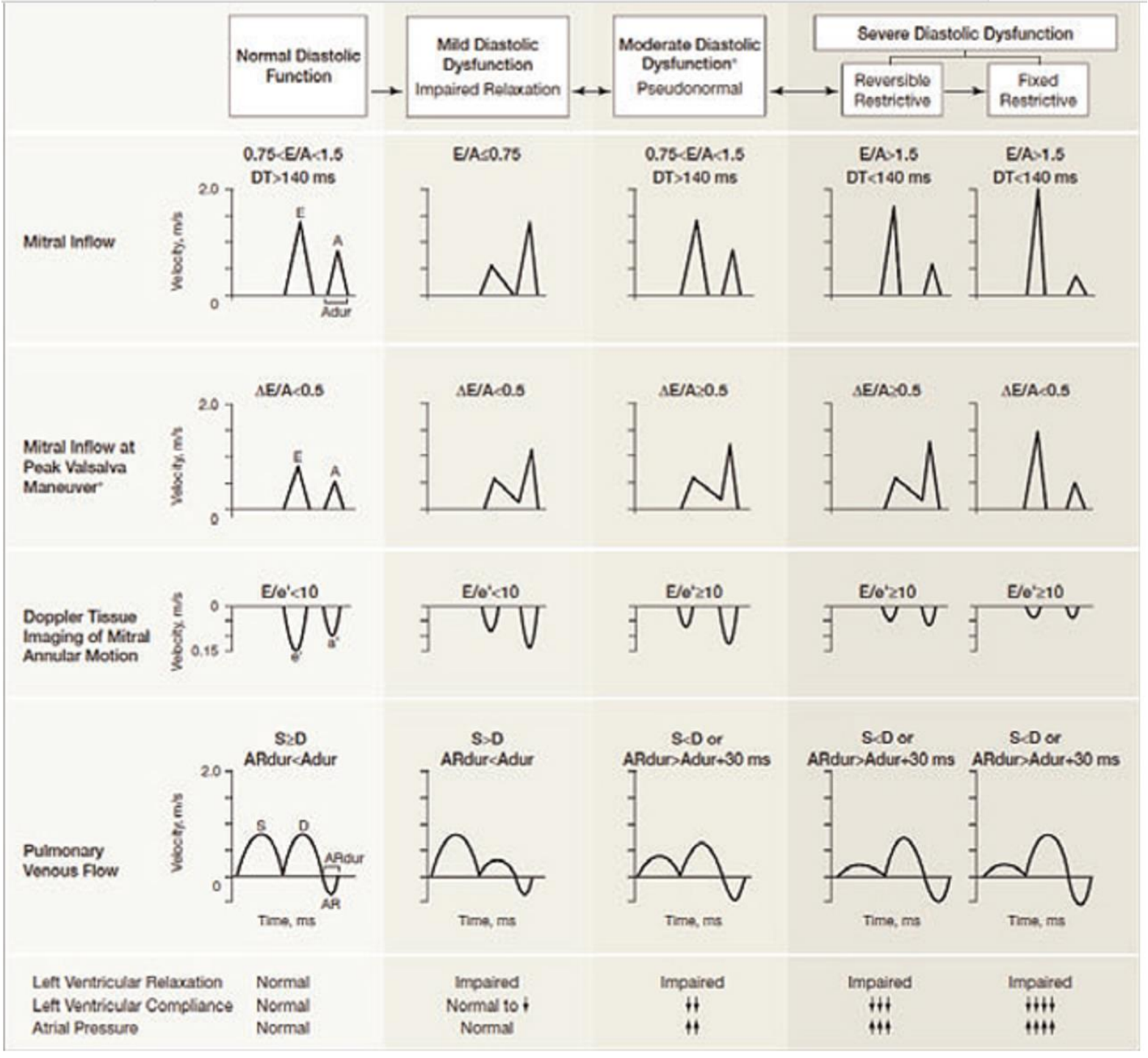


Fig.8 Timing correlates of LA pressure, mitral inflow and pulmonary venous flow:
http://www.fac.org.ar/scvc/llave/echo/roeland/roelandi.htm

Pulmonary venous flow profile:

The 2 components to note are the diastolic forward flow (D) and the diastolic flow reversal (AR). The D wave is normally equal to or smaller than the S wave. Changes in the D wave with increases in LA pressure parallel changes in the transmitral E wave, initially decreasing and then increasing to become much larger than the S wave. A S/D ratio of < 40% suggests a LA pressure more than 20mmHg. The decceleration time of the D wave also shortens with increasing LA pressures.

The atrial reversal wave increases in amplitude and duration with increasing LA pressures. An AR amplitude more than 25cms/sec and a AR duration 30ms more than the transmitral A wave duration suggest a LA pressure more than 20mmHg.


Normal Diastolic Function
Mild Diastolic Dysfunction
Impaired Relaxation
Moderate Diastolic Dysfunction*
Pseudonormal
Severe Diastolic Dysfunction
Reversible Restrictive
Fixed Restrictive
Mitral Inflow
0.75<E/A<1.5
DT>140 ms
E/A≤0.75
0.75<E/A<1.5
DT>140 ms
E/A>1.5
DT<140 ms
E/A>1.5
DT<140 ms
Velocity, m/s
2.0
0
E
A
Adur
Mitral Inflow at Peak Valsalva Maneuver*
ΔE/A<0.5
ΔE/A<0.5
ΔE/A≥0.5
ΔE/A≥0.5
ΔE/A<0.5
Doppler Tissue Imaging of Mitral Annular Motion
E/e'<10
E/e'<10
E/e'≥10
E/e'≥10
E/e'≥10
0
0.15
e'
a'
Pulmonary Venous Flow
S≥D
ARdur<Adur
S>D
ARdur<Adur
S<D or
ARdur>Adur+30 ms
S<D or
ARdur>Adur+30 ms
S<D or
ARdur>Adur+30 ms
S
D
ARdur
AR
Time, ms
Left Ventricular Relaxation
Left Ventricular Compliance
Atrial Pressure
Normal
Normal
Normal
Impaired
Normal to ↓
Normal
Impaired
↓↓
↓↓
Impaired
↓↓↓
↓↓↓
Impaired
↓↓↓↓
↓↓↓↓

Estimation of LV filling pressures

Other than in the grading of diastolic dysfunction, estimation of LV filling pressures also influence desicions on fluid resuscitation in hemodynamically unstable patients and in titrating diuretics and fluids in patients with diastolic heart failure. While the markers of an elevated LV filling pressure have been mentioned earlier and tabulated below, several formulae have been evaluated to arrive at a numerical value.

Markers of elevated LV filling pressure:

E/A > 2
Dct < 160ms
E/e' (medial) >15
E/e' (lateral) >10
PFV S/D <40%
PFV AR amplitude >25 cm/sec
PFV AR duration > 30ms more than A wave
LA enlargement
LV hypertrophy

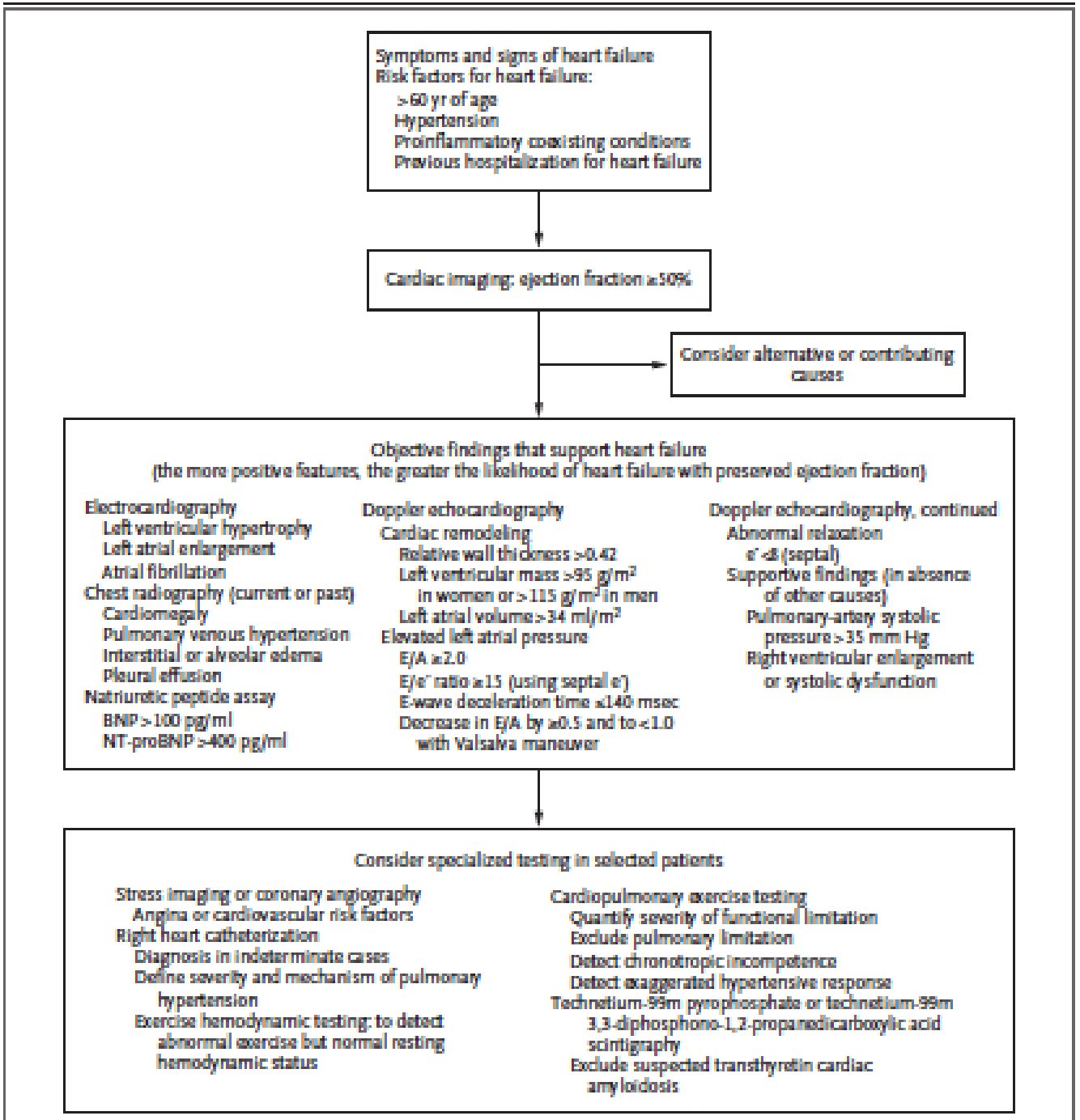
Formulae to calculate LA pressure

Sinus rhythm
2+1.2(E/e')

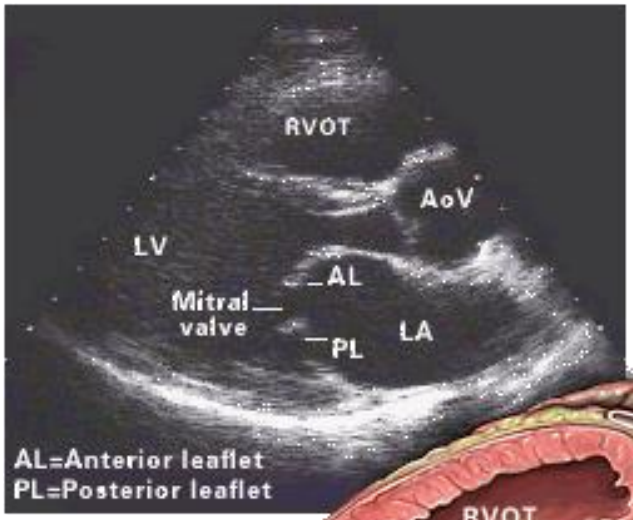
Sinus tachycardia
1.5+1.5(E/e')

Atrial fibrillation
6.5+0.8(E/e')

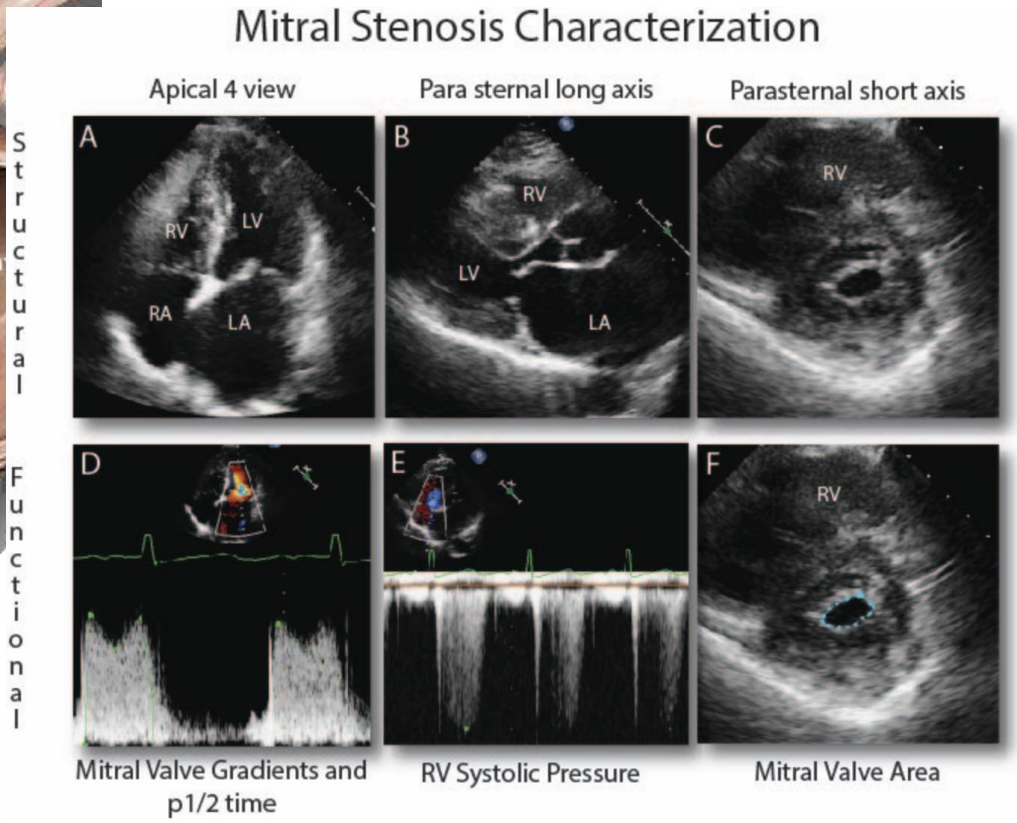
The E/e' included in the above calculations indicates that obtained from the medial mitral annulus.


Symptoms and signs of heart failure
Risk factors for heart failure:
>60 yr of age
Hypertension
Proinflammatory coexisting conditions
Previous hospitalization for heart failure
Cardiac imaging: ejection fraction ≥50%
Consider alternative or contributing causes
Objective findings that support heart failure
(the more positive features, the greater the likelihood of heart failure with preserved ejection fraction)
Electrocardiography
Left ventricular hypertrophy
Left atrial enlargement
Atrial fibrillation
Chest radiography (current or past)
Cardiomegaly
Pulmonary venous hypertension
Interstitial or alveolar edema
Pleural effusion
Natriuretic peptide assay
BNP >100 pg/ml
NT-proBNP >400 pg/ml
Doppler echocardiography
Cardiac remodeling
Relative wall thickness >0.42
Left ventricular mass >95 g/m2 in women or >115 g/m2 in men
Left atrial volume >34 ml/m2
Elevated left atrial pressure
E/A ≥2.0
E/e' ratio ≥15 (using septal e')
E-wave deceleration time ≤140 msec
Decrease in E/A by ≥0.5 and to <1.0 with Valsalva maneuver
Doppler echocardiography, continued
Abnormal relaxation
e' <8 (septal)
Supportive findings (in absence of other causes)
Pulmonary-artery systolic pressure >35 mm Hg
Right ventricular enlargement or systolic dysfunction
Consider specialized testing in selected patients
Stress imaging or coronary angiography
Angina or cardiovascular risk factors
Right heart catheterization
Diagnosis in indeterminate cases
Define severity and mechanism of pulmonary hypertension
Exercise hemodynamic testing: to detect abnormal exercise but normal resting hemodynamic status
Cardiopulmonary exercise testing
Quantify severity of functional limitation
Exclude pulmonary limitation
Detect chronotropic incompetence
Detect exaggerated hypertensive response
Technetium-99m pyrophosphate or technetium-99m 3,3-diphosphono-1,2-propanedicarboxylic acid scintigraphy
Exclude suspected transthyretin cardiac amyloidosis

Mitral Stenosis



- Enlarged LA
- Afib
- Older women



Pathophysiology

- Ejection Fraction in Mitral Regurgitation
  - >65% normal in compensated MR
  - 50-65% mild impairment
  - 40-50% moderate-severe impairment
  - <35% advanced impairment

  As ejection fraction decreases operative risk increases.

Noncardiac Comorbidities in Heart Failure With Preserved Ejection Fraction

– A Commonly Ignored Fact –

Ming Liu, PhD; Fang Fang, PhD; Cheuk-Man Yu, MD

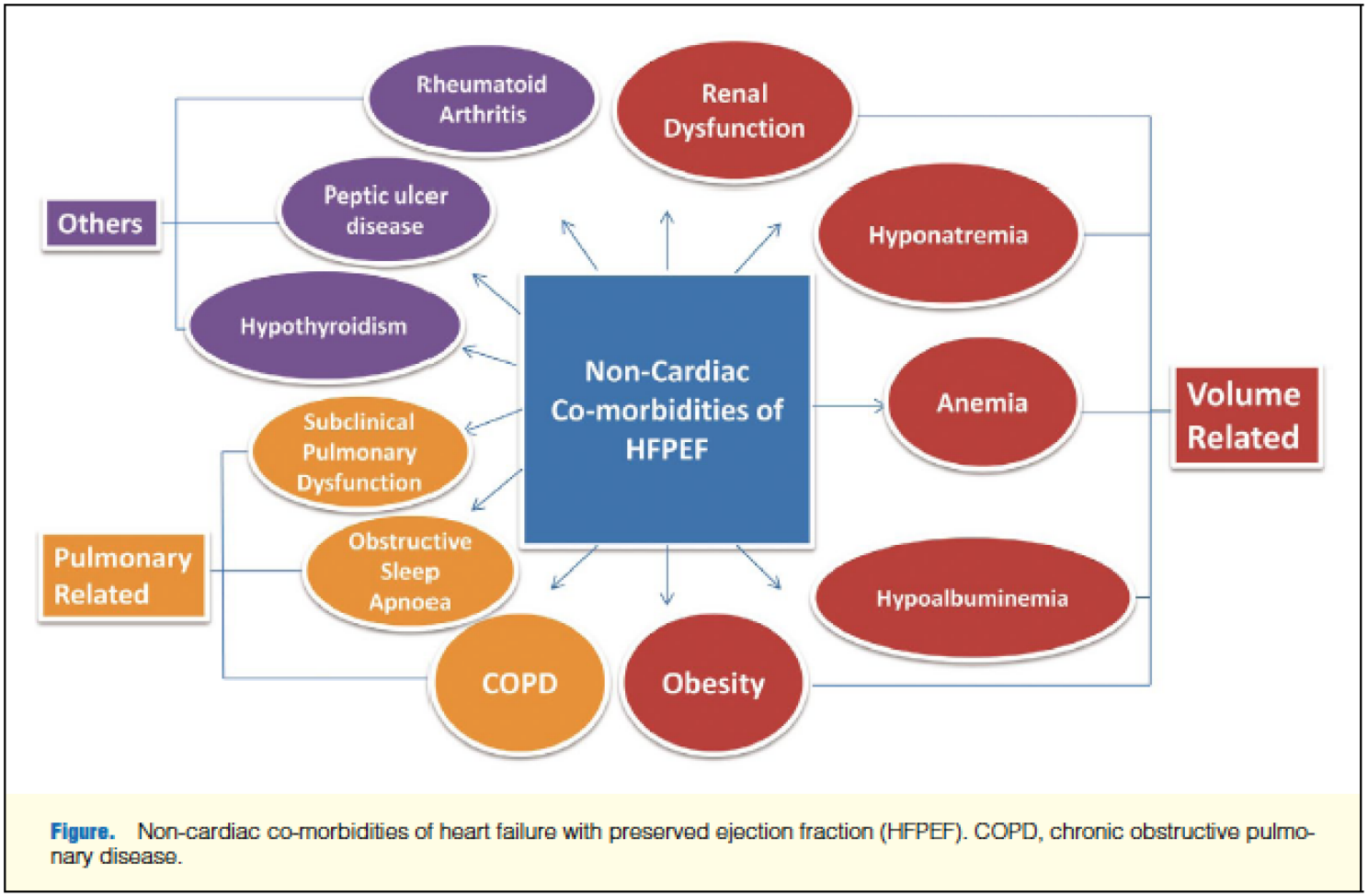


Figure. Non-cardiac co-morbidities of heart failure with preserved ejection fraction (HFPEF). COPD, chronic obstructive pulmonary disease.

(*Circ J 2015;* ***79: 954 – 959)***

Obstructive Sleep Apnea and Diastolic Dysfunction

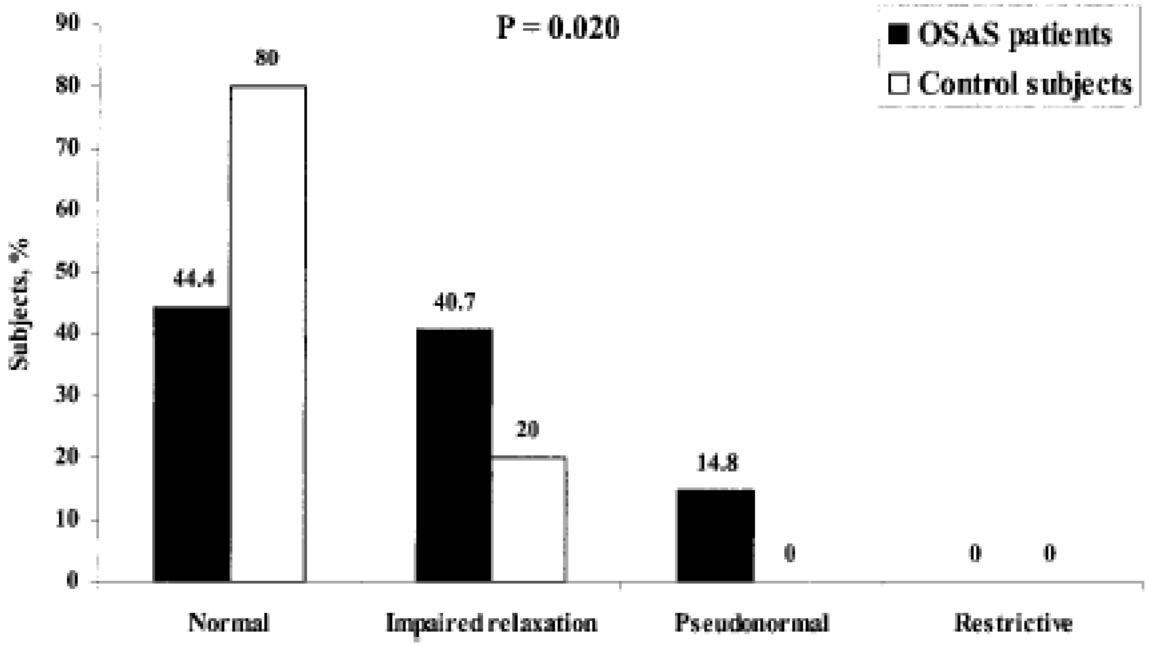


Figure 2. Left ventricular filling patterns in OSAS patients and control subjects.

(***Circulation. 2005;112:375-383.)***

Treatment of HFpEF

Table 21. Recommendations for Treatment of HF*p*EF

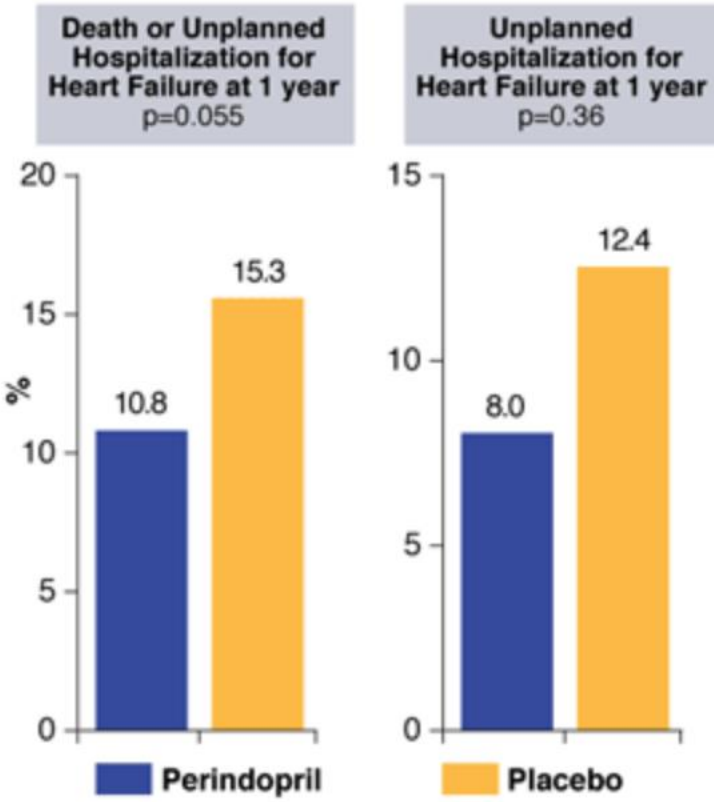
Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B (27,91)
Diuretics should be used for relief of symptoms due to volume overload.	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HF*p*EF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HF*p*EF	IIa	C
ARBs might be considered to decrease hospitalizations in HF*p*EF	IIb	B (589)
Nutritional supplementation is not recommended in HF*p*EF	III: No Benefit	C

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; C
Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fracti
LOE, and Level of Evidence.

ACEI in HFpEF

Medscape® www.medscape.com

Trial Design: PEP-CHF was a double-blind, randomized trial of perindopril 2 mg per day (n=424) or matching placebo (n=426) in patients age ≥70 years with clinical CHF and preserved left ventricular systolic function. Primary endpoint was death and unplanned hospitalizations for heart failure at median follow-up of 2.1 years.



Results

- Study drug compliance 90% at 1 year but dropped to 40% in perindopril group and 36% in 1 placebo group by 18 months
- No difference in primary endpoint of death or unplanned hospitalization for heart failure at end of study (HR 0.92, p=0.55) but trended ↓ in perindopril vs placebo group at 1 year (Figure)
- Among components at 1 year, unplanned hospitalization for HF ↓ in perindopril vs placebo group (Figure) but no difference in mortality

Conclusions

- Among patients age ≥70 years with clinical CHF and preserved LV systolic function, treatment with perindopril did not differ from placebo in primary endpoint of death or unplanned hospitalizations for HF at study end but tended to be associated with reduction in composite at 1 year
- Major limitation was high rate of discontinuation at 18 months, most of whom went on open-label ACE-inhibitors

www.cardiosource.com

Presented at ESC 2006

HONG KONG DIASTOLIC HEART FAILURE STUDY

- HFpEF patients (EF > 45%) were randomized to diuretic alone or in combination with an ACE inhibitor or ARB
- Slight reduction in LV filling pressures with ACE inhibitor/ARB
- QOL scores improved by nearly 50% in each treatment group
- Conclusion: No clinical benefit of adding an ACE inhibitor or ARB to diuretic therapy in patients with HFpEF

Heart 2008;94:573-80.

CHARM-Preserved: Candesartan

ARB

Results

Candesartan vs. Placebo

- ***Reduce hospital admission for HF***
  15.9% vs. 18.3% (p=0.047, NNT 42)
- Cardiovascular death or hospital admission for HF
  22% vs. 24%
  (adjusted HR 0.86; 95% CI 0.74 to 1.00; p = 0.051)

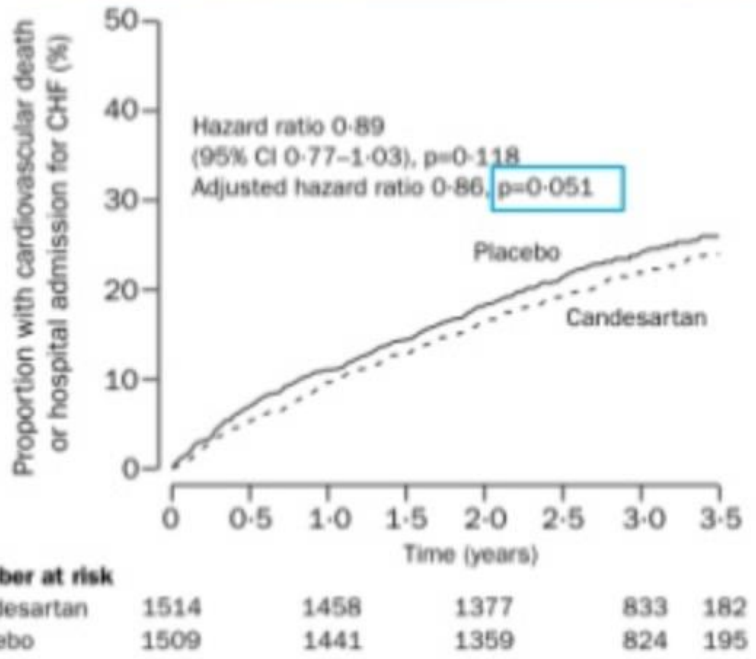


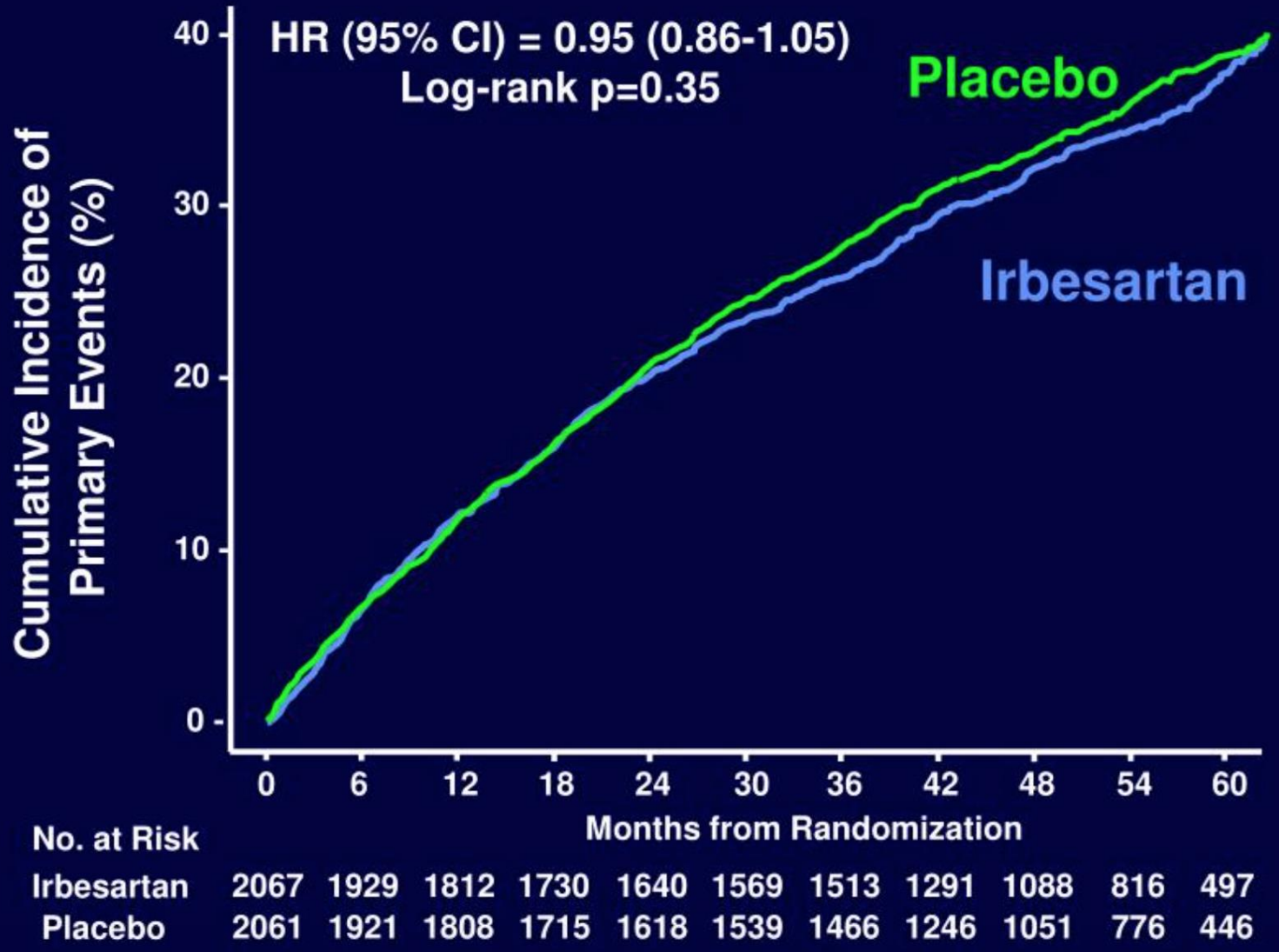
Figure 2: **Time to cardiovascular death or hospital admission for CHF**

	Candesartan (n=1514)	Placebo (n=1509)	Unadjusted hazard ratio (95% CI)	p	Adjusted hazard ratio (95% CI)*	p
Cardiovascular death or hospital admission for CHF	333 (22·0%)	366 (24·3%)	0·89 (0·77–1·03)	0·118	0·86 (0·74–1·00)	0·051
Cardiovascular death	170 (11·2%)	170 (11·3%)	0·99 (0·80–1·22)	0·918	0·95 (0·76–1·18)	0·635
Hospital admission for CHF	241 (15·9%)	276 (18·3%)	0·85 (0·72–1·01)	0·072	0·84 (0·70–1·00)	0·047
Cardiovascular death, hospital admission for CHF, MI	365 (24·1%)	399 (26·4%)	0·90 (0·78–1·03)	0·126	0·87 (0·75–1·00)	0·051
Cardiovascular death, hospital admission for CHF, MI, stroke	388 (25·6%)	429 (28·4%)	0·88 (0·77–1·01)	0·078	0·86 (0·75–0·99)	0·037
Cardiovascular death, hospital admission for CHF, MI, stroke, coronary revascularisation procedure	460 (30·4%)	497 (32·9%)	0·91 (0·80–1·03)	0·123	0·91 (0·80–1·03)	0·130

Yusuf S, Pfeffer MA, Swedberg K, et al. *Lancet*. 2003 Sep 6;362(9386):777-81

I-PRESERVE: Primary Endpoint

Death or protocol specified CV hospitalization



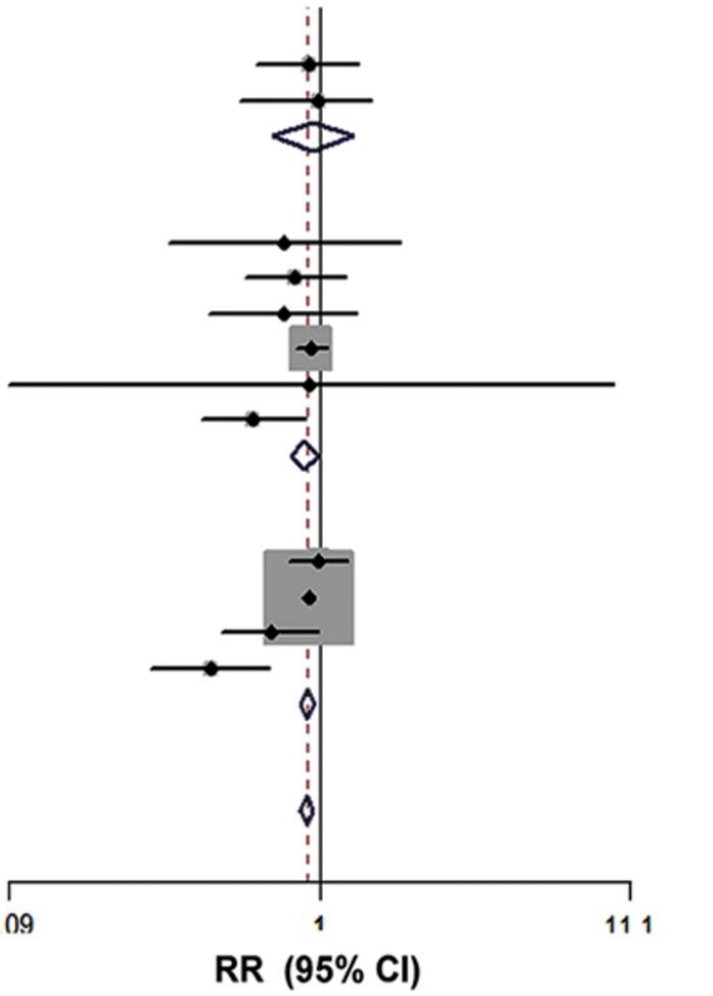
No. at Risk											
Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446

DIASTOLIC HEART FAILURE
usually due to Hemodynamic stress

- Patients with diastolic heart failure do not tolerate hemodynamic stress well
- Atrial fibrillation causes loss of atrial contraction and often leads to Diastolic CHF
- Tachycardia shortens diastole and leads to CHF
- Elevation in BP worsens myocardial relaxation
- **Ischemia worsens diastolic function raising LA and PA pressures. (This is why ischemia causes SOB)**
- **Aortic Stenosis causes worsening diastolic function.**

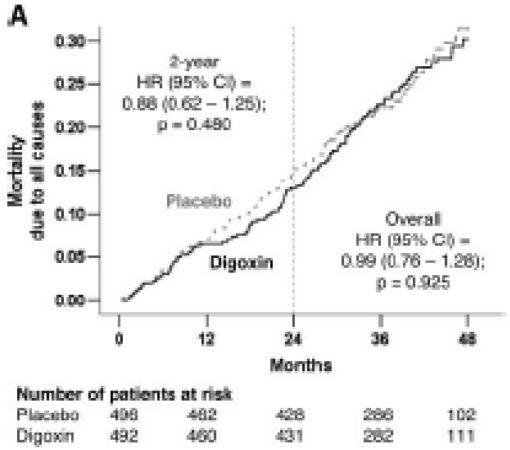
Beta blockers in diastolic dysfunction

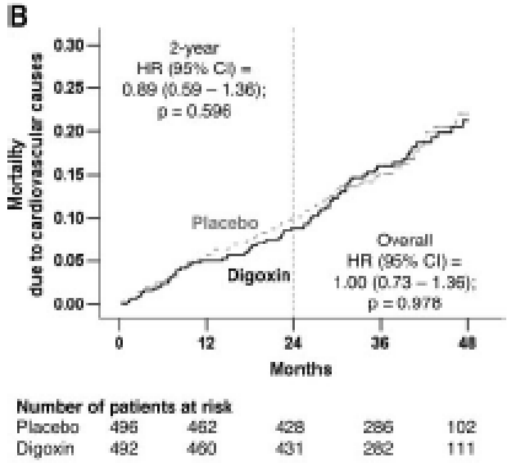
Source	% Weight	RR (95% CI)
All-cause mortality		
RCT		
SENIORS (2009)	1.34	0.92 (0.61, 1.36)
J-DHF (2013)	0.85	0.99 (0.54, 1.49)
Subtotal (I-squared = 0.0%, p = 0.823)	2.19	0.95 (0.69, 1.30)
PCS		
Fukuta H (2005)	0.27	0.76 (0.31, 1.87)
Chan, J. D (2005)	1.42	0.82 (0.56, 1.22)
Grigorian SL (2006)	0.66	0.76 (0.43, 1.34)
OPTIMIZE-HF (2009)	14.71	0.94 (0.84, 1.07)
Farasat SM (2009)	0.04	0.93 (0.09, 9.77)
Dobre D (2007)	1.31	0.60 (0.40, 0.90)
Subtotal (I-squared = 0.3%, p = 0.414)	18.40	0.89 (0.80, 0.99)
RCS		
Tehrani F (2008)	4.09	0.99 (0.79, 1.25)
R Shah (2008)	72.76	0.92 (0.87, 0.97)
Nevzorov R (2012)	1.55	0.69 (0.47, 0.99)
El-Refai M (2013)	1.01	0.43 (0.27, 0.68)
Subtotal (I-squared = 76.8%, p = 0.005)	79.41	0.91 (0.86, 0.96)
Heterogeneity between groups: p = 0.912		
Overall (I-squared = 39.4%, p = 0.078)	100.00	0.91 (0.87, 0.95)

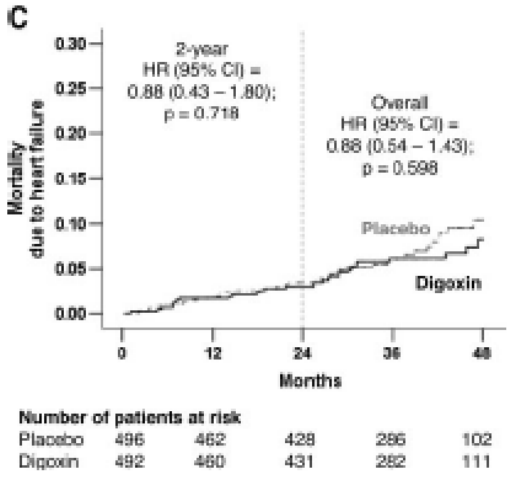


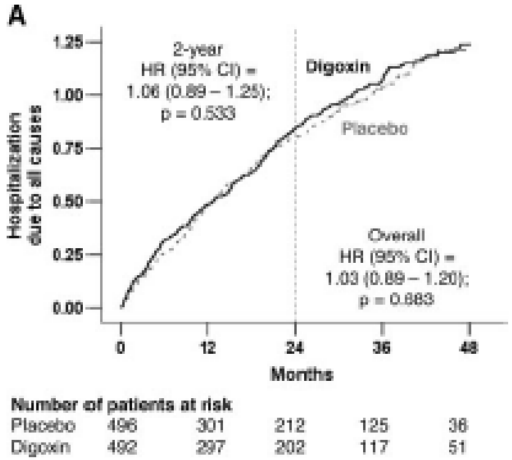
Article Source: **Effects of Beta-Blockers on Heart Failure with Preserved Ejection Fraction: A Meta-Analysis**

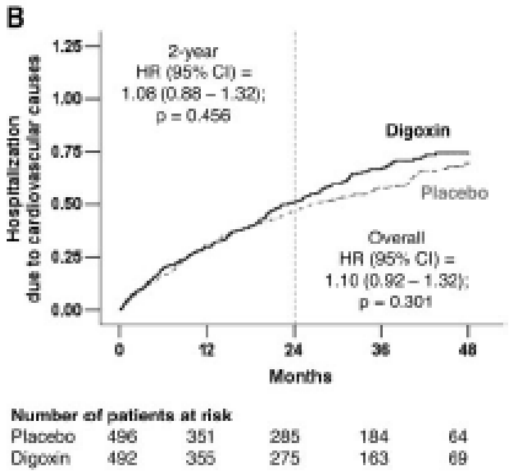
Liu F, Chen Y, Feng X, Teng Z, Yuan Y, et al. (2014) Effects of Beta-Blockers on Heart Failure with Preserved Ejection Fraction: A Meta-Analysis. PLOS ONE 9(3): e90555. https://doi.org/10.1371/journal.pone.0090555

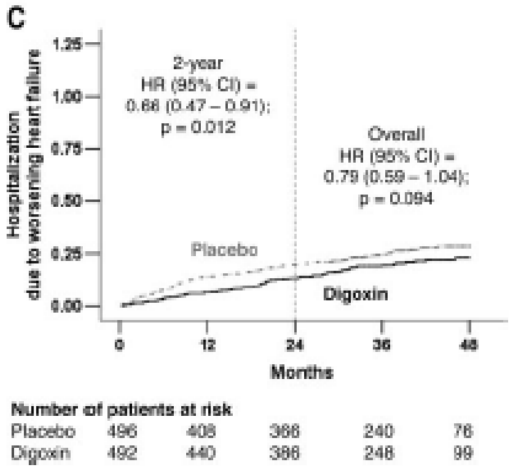












- Digoxin in HFpEF offers no significant improvement in all cause, cardiovascular or heart failure mortality or hospitalization.

(***Circulation. 2006;114:397-403.***)

Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.

Table 2. Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.*

Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI)†	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary outcome	320 (18.6)	5.9	351 (20.4)	6.6	0.89 (0.77–1.04)	0.14
Components of the primary outcome						
Death from cardiovascular causes	160 (9.3)	2.8	176 (10.2)	3.1	0.90 (0.73–1.12)	0.35
Aborted cardiac arrest	3 (0.2)	0.05	5 (0.3)	0.09	0.60 (0.14–2.50)	0.48
Hospitalization for heart failure	206 (12.0)	3.8	245 (14.2)	4.6	0.83 (0.69–0.99)	0.04
Additional secondary outcomes						
Death from any cause	252 (14.6)	4.2	274 (15.9)	4.6	0.91 (0.77–1.08)	0.29
Hospitalization for any reason	766 (44.5)	18.8	792 (46.0)	20.0	0.94 (0.85–1.04)	0.25
Myocardial infarction	65 (3.8)	1.2	64 (3.7)	1.1	1.00 (0.71–1.42)	0.98
Stroke	57 (3.3)	1.0	60 (3.5)	1.1	0.94 (0.65–1.35)	0.73

* Some participants had more than one component of the primary outcome and are included once for the primary outcome and once for each component they had.
† Shown are unadjusted hazard ratios calculated with the use of Cox proportional-hazards models.

Pitt B et al. N Engl J Med 2014;370:1383-1392

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D., Kevin J. Anstrom, Ph.D., James A. Levine, M.D., Gabe A. Koepp, M.H.A., Barry A. Borlaug, M.D., Horng H. Chen, M.D., Martin M. LeWinter, M.D., Susan M. Joseph, M.D., Sanjiv J. Shah, M.D., Marc J. Semigran, M.D., G. Michael Felker, M.D., Robert T. Cole, M.D., Gordon R. Reeves, M.D., Ryan J. Tedford, M.D., W.H. Wilson Tang, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Monica R. Shah, M.D., and Eugene Braunwald, M.D. for the NHLBI Heart Failure Clinical Research Network

METHODS

In this multicenter, double-blind, crossover study, 110 patients with heart failure and a preserved ejection fraction were randomly assigned to a 6-week dose-escalation regimen of isosorbide mononitrate (from 30 mg to 60 mg to 120 mg once daily) or placebo, with subsequent crossover to the other group for 6 weeks. The primary end point was the daily activity level, quantified as the average daily accelerometer units during the 120-mg phase, as assessed by patient-worn accelerometers. Secondary end points included hours of activity per day during the 120-mg phase,

CONCLUSIONS

Patients with heart failure and a preserved ejection fraction who received isosorbide mononitrate were less active and did not have better quality of life or submaximal exercise capacity than did patients who received placebo. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT02053493.)

December 10, 2015
N Engl J Med 2015; 373:2314-2324
DOI: 10.1056/NEJMoa1510774

Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial

Elke S. Hoendermis[1]*, Licette C.Y. Liu[1], Yoran M. Hummel[1], Peter van der Meer[1], Rudolf A. de Boer[1], Rolf M.F. Berger[2], Dirk J. van Veldhuisen[1], and Adriaan A. Voors[1]

[1]Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; and [2]Center for Congenital Heart Diseases, Department of Pediatric Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

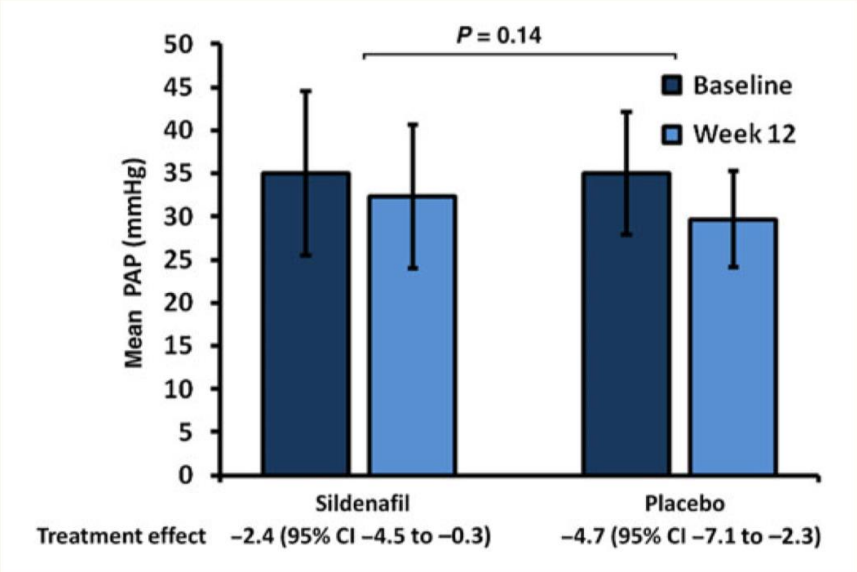
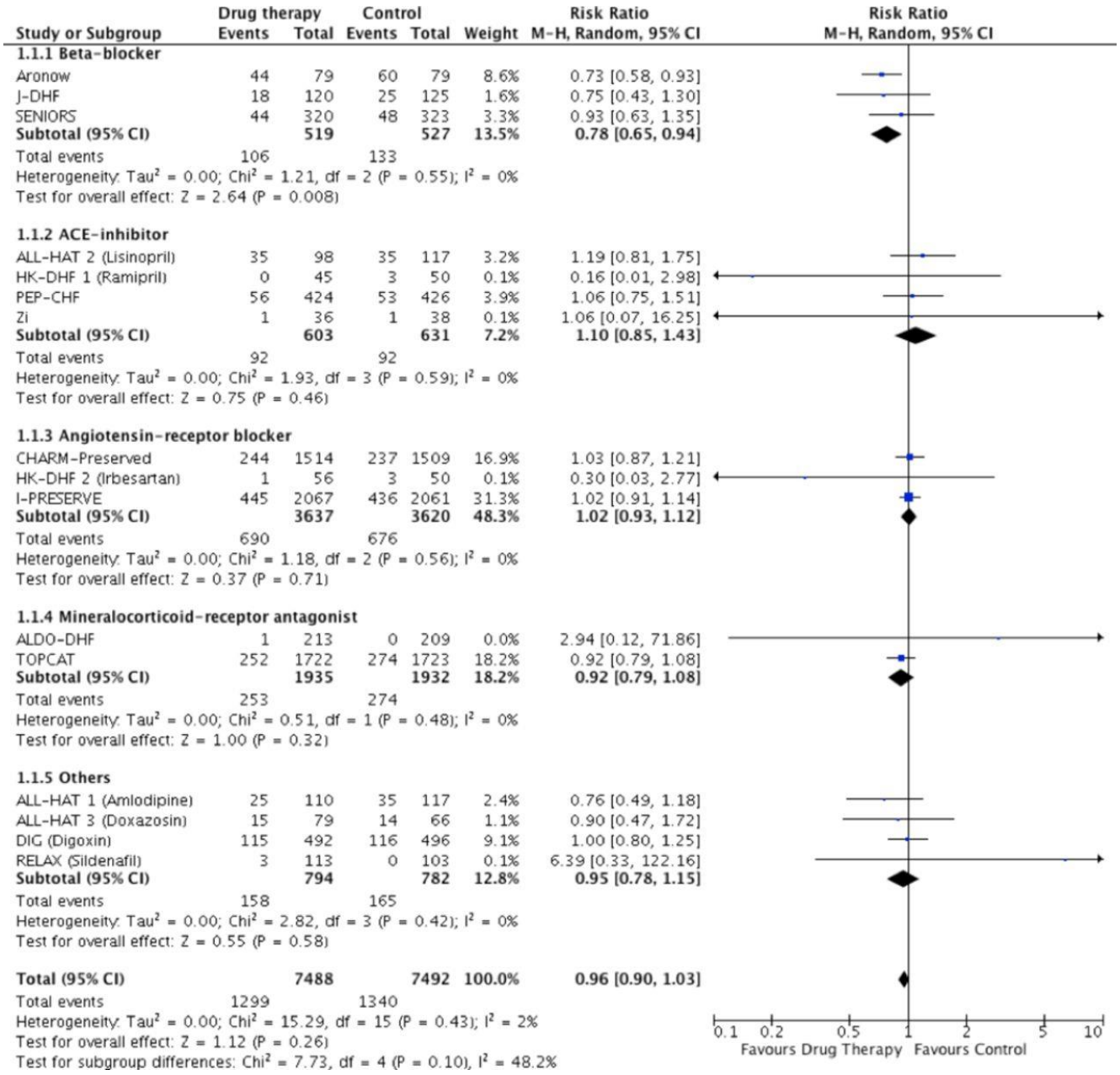


Figure 2 Change in mean pulmonary artery pressure after 12 weeks of treatment with sildenafil of placebo.

European Heart Journal (2015) **36**, 2565–2573
doi:10.1093/eurheartj/ehv336

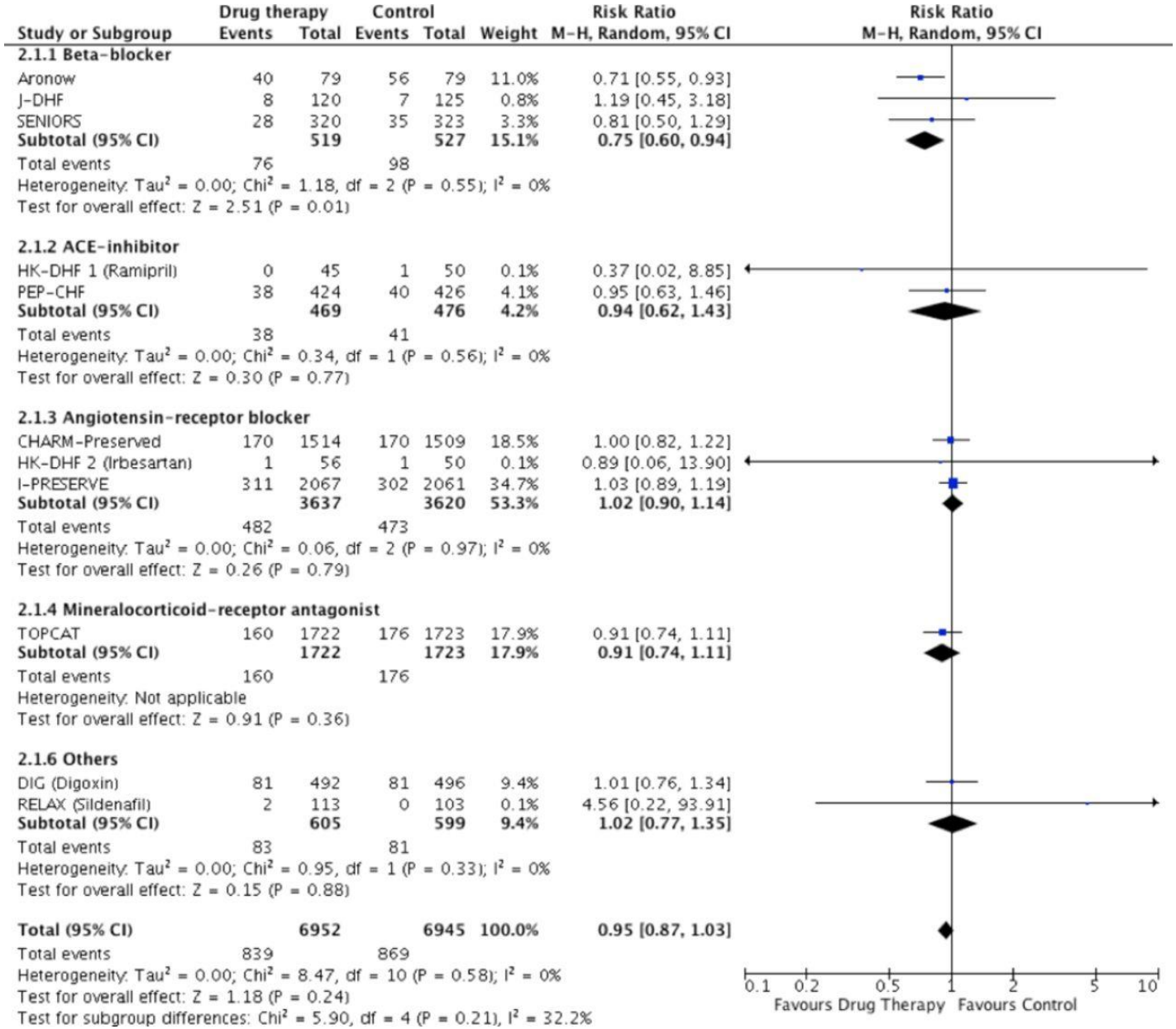
Pooled and individual estimates of relative risk (RR) and 95% CI of the primary outcome all-cause mortality for different therapies.

Heart



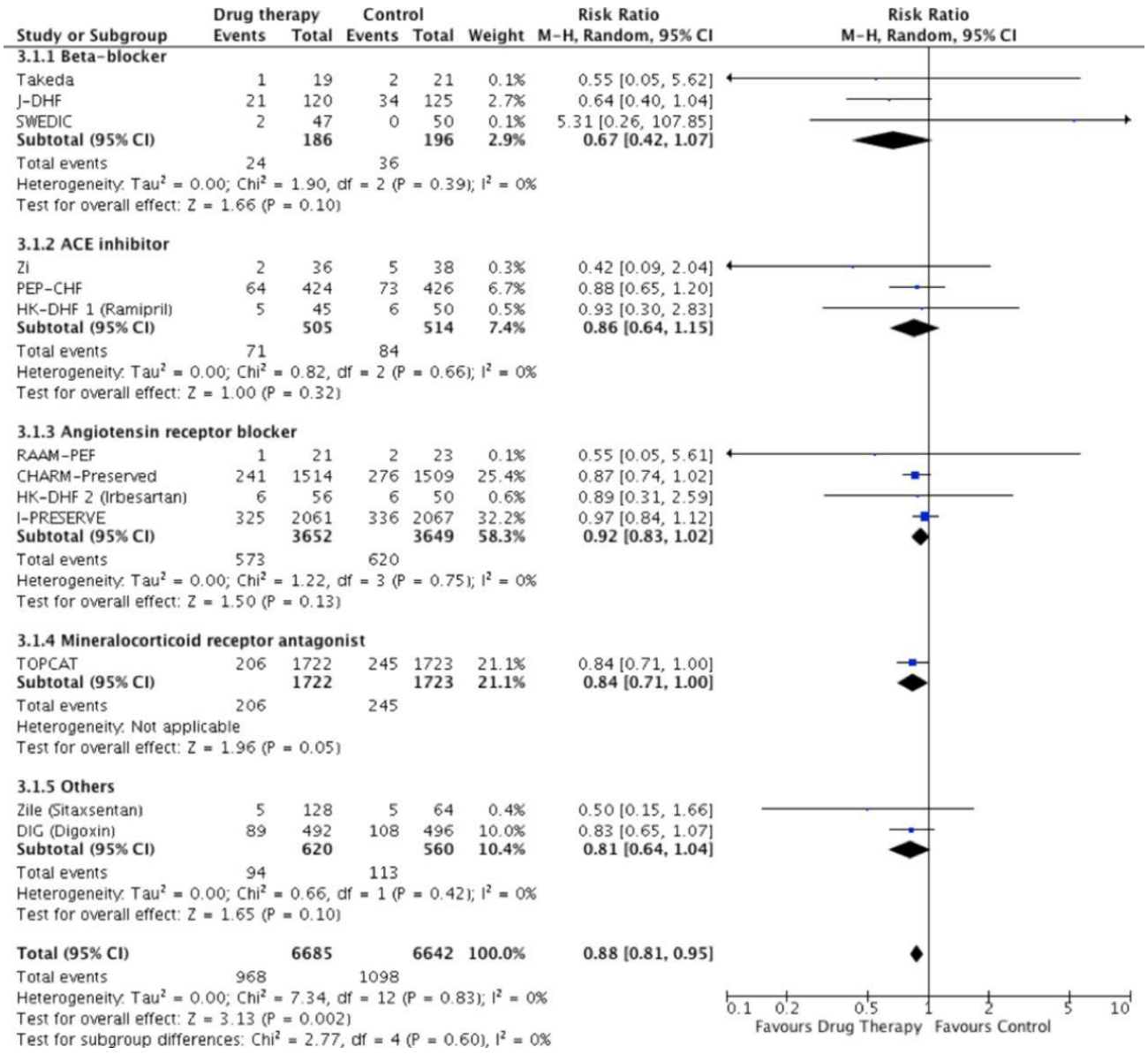
Sean Lee Zheng et al. Heart doi:10.1136/heartjnl-2017-311652

Pooled and individual estimates of relative risk (RR) and 95% CIs of the secondary outcome cardiovascular mortality for different therapies.



Sean Lee Zheng et al. Heart doi:10.1136/heartjnl-2017-311652

Pooled and individual estimates of relative risk (RR) and 95% CI of the secondary outcome heart failure hospitalisation for different therapies.



Sean Lee Zheng et al. Heart doi:10.1136/heartjnl-2017-311652

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations	Comment/ Rationale
I	B	Systolic and diastolic blood pressure should be controlled in patients with HF*p*EF in accordance with published clinical practice guidelines to prevent morbidity	2013 recommendation remains current.
I	C	Diuretics should be used for relief of symptoms due to volume overload in patients with HF*p*EF.	2013 recommendation remains current.

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations	Comment/ Rationale
IIa	C	Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic HF*p*EF despite GDMT.	2013 recommendation remains current.
IIa	C	Management of AF according to published clinical practice guidelines in patients with HF*p*EF is reasonable to improve symptomatic HF.	2013 recommendation remains current.
IIa	C	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HF*p*EF.	2013 recommendation remains current.

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations	Comment/ Rationale
IIb	B-R	In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.	NEW: Current recommendation reflects new RCT data.
IIb	B	The use of ARBs might be considered to decrease hospitalizations for patients with HF*p*EF.	2013 recommendation remains current.

Pharmacological Treatment for Stage C HF With Preserved EF

COR	LOE	Recommendations	Comment/ Rationale
III: No Benefit	**B-R**	Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective.	NEW: Current recommendation reflects new data from RCTs.
III: No Benefit	**C**	Routine use of nutritional supplements is not recommended for patients with HF*p*EF.	2013 recommendation remains current.

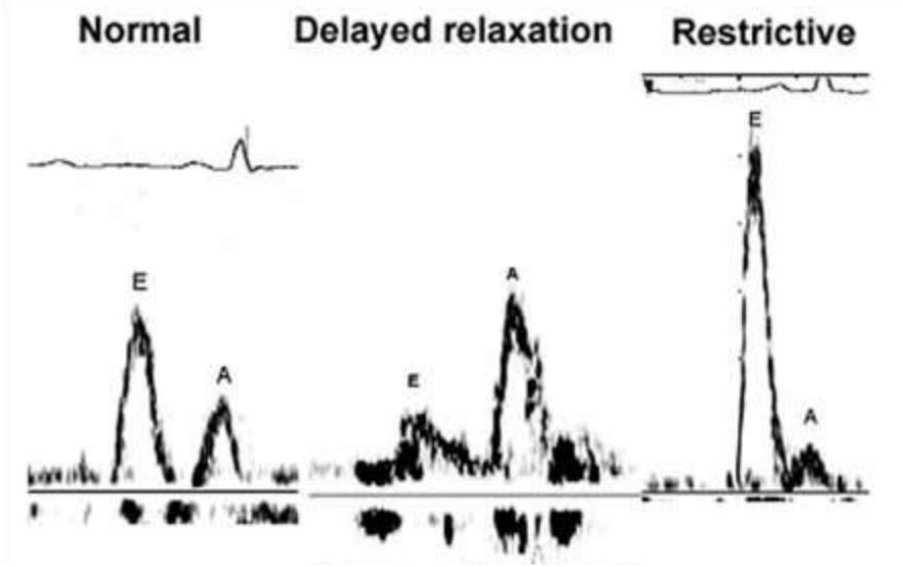
Codes

- I50 Heart failure
  - I50.1 Left ventricular failure, unspecified
  - I50.2 Systolic (congestive) heart failure
    - I50.20 Unspecified systolic (congestive) heart failure
    - I50.21 Acute systolic (congestive) heart failure
    - I50.22 Chronic systolic (congestive) heart failure
    - I50.23 Acute on chronic systolic (congestive) heart failure
  - I50.3 Diastolic (congestive) heart failure
    - I50.30 Unspecified diastolic (congestive) heart failure
    - I50.31 Acute diastolic (congestive) heart failure
    - I50.32 Chronic diastolic (congestive) heart failure
    - I50.33 Acute on chronic diastolic (congestive) heart failure
  - I50.4 Combined systolic (congestive) and diastolic (congestive) heart failure
    - I50.40 Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
    - I50.41 Acute combined systolic (congestive) and diastolic (congestive) heart failure
    - I50.42 Chronic combined systolic (congestive) and diastolic (congestive) heart failure
    - I50.43 Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
  - I50.8 Other heart failure
    - I50.81 Right heart failure
      - I50.810 …… unspecified
      - I50.811 Acute right heart failure
      - I50.812 Chronic right heart failure
      - I50.813 Acute on chronic right heart failure
      - I50.814 …… due to left heart failure
    - I50.82 Biventricular heart failure
    - I50.83 High output heart failure
    - I50.84 End stage heart failure
    - I50.89 Other heart failure
  - I50.9 Heart failure, unspecified

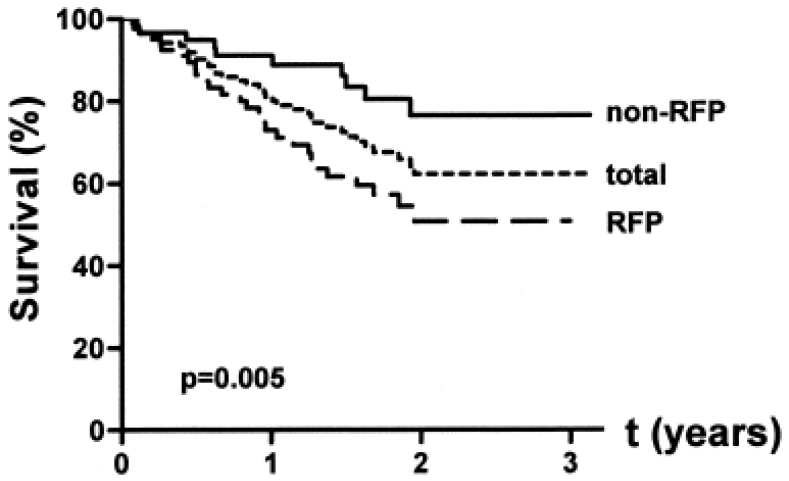
Prognostic Value of Doppler Echocardiographic Mitral Inflow Patterns: Implications for Risk Stratification in Patients With Chronic Congestive Heart Failure

Alexander Hansen, MD,* Markus Haass, MD,* Christian Zugck, MD,* Carsten Krueger, MD,* Kristina Unnebrink, PHD,† Rainer Zimmermann, MD,* Wolfgang Kuebler, MD, FACC,* Helmut Kuecherer, MD*

Heidelberg, Germany



	Total	Survivors	Non-survivors
LVEF (%)	24 +/- 12	25 +/- 13	19 +/- 10



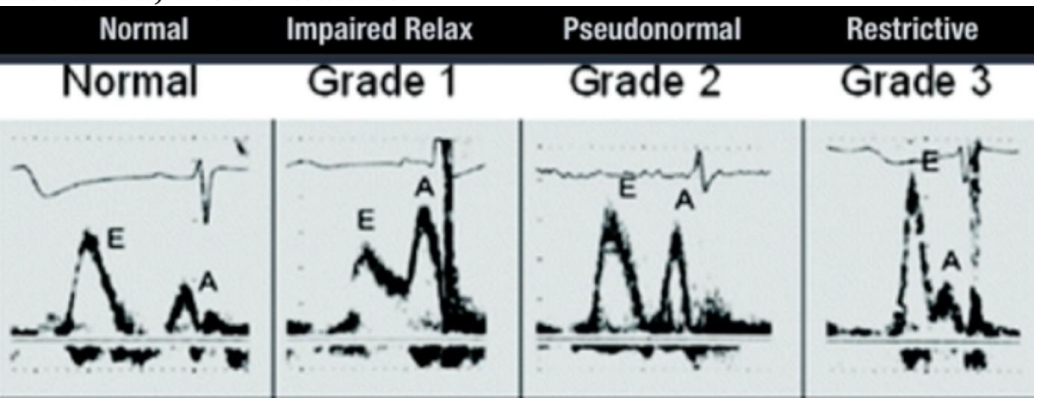
total	n = 140	84	34	6
non-RFP	n = 61	45	20	4
RFP	n = 79	41	14	3

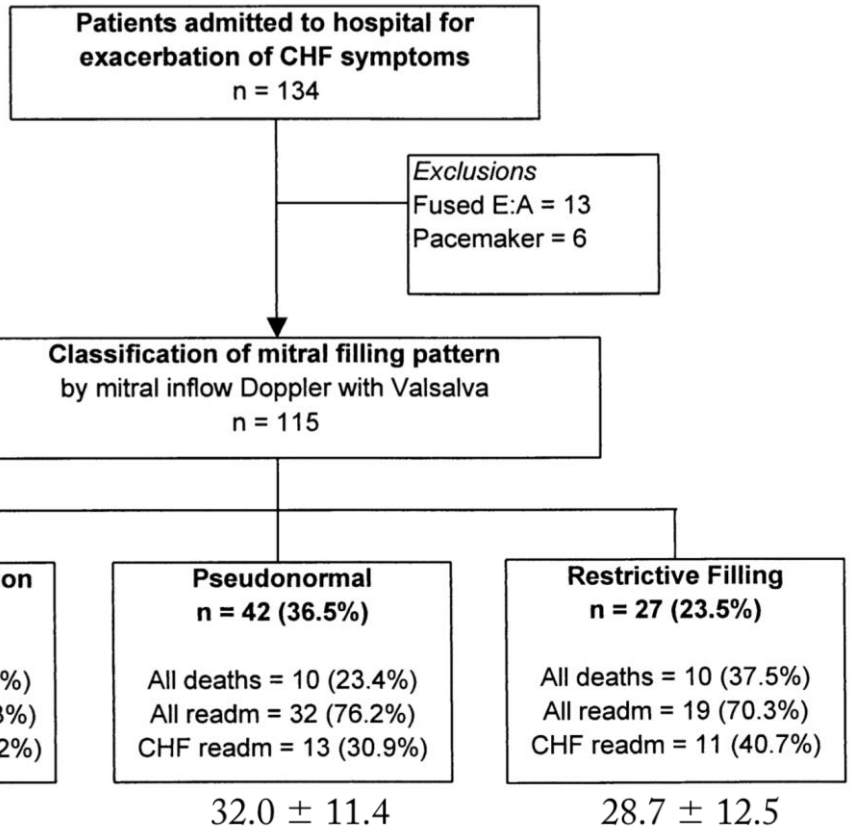
Journal of the American College of Cardiology Vol. 37, No. 4, 2001

Pseudonormal Mitral Filling Pattern Predicts Hospital Re-Admission in Patients With Congestive Heart Failure

Gillian A. Whalley, MHSc, Robert N. Doughty, MB BS, MRCP, FRACP, MD, Greg D. Gamble, MSc, Susan P. Wright, MBChB, MMedSc, Helen J. Walsh, RN, BSc, Stephanie A. Muncaster, RN, Norman Sharpe, MD, FRACP, FACC

Auckland, New Zealand





LVEF (%)	32.8 ± 13.6	32.0 ± 11.4	28.7 ± 12.5

Journal of the American College of Cardiology Vol. 39, No. 11, 2002

Summary

- HFpEF is similar in frequency and prognosis to HFrEF.
- HFpEF is defined by clinical symptoms, lab and radiographic findings in the absence of alternative (valvular/OSA/comorbidities) explanations, with normal LVEF and mitral inflow, tissue Doppler, pulmonary vein inflow findings consistent with diastolic dysfunction.
- Echo findings of elevated left atrial pressures indicate opportunity for improvement in symptoms with diuretic therapy.

Summary (continued)

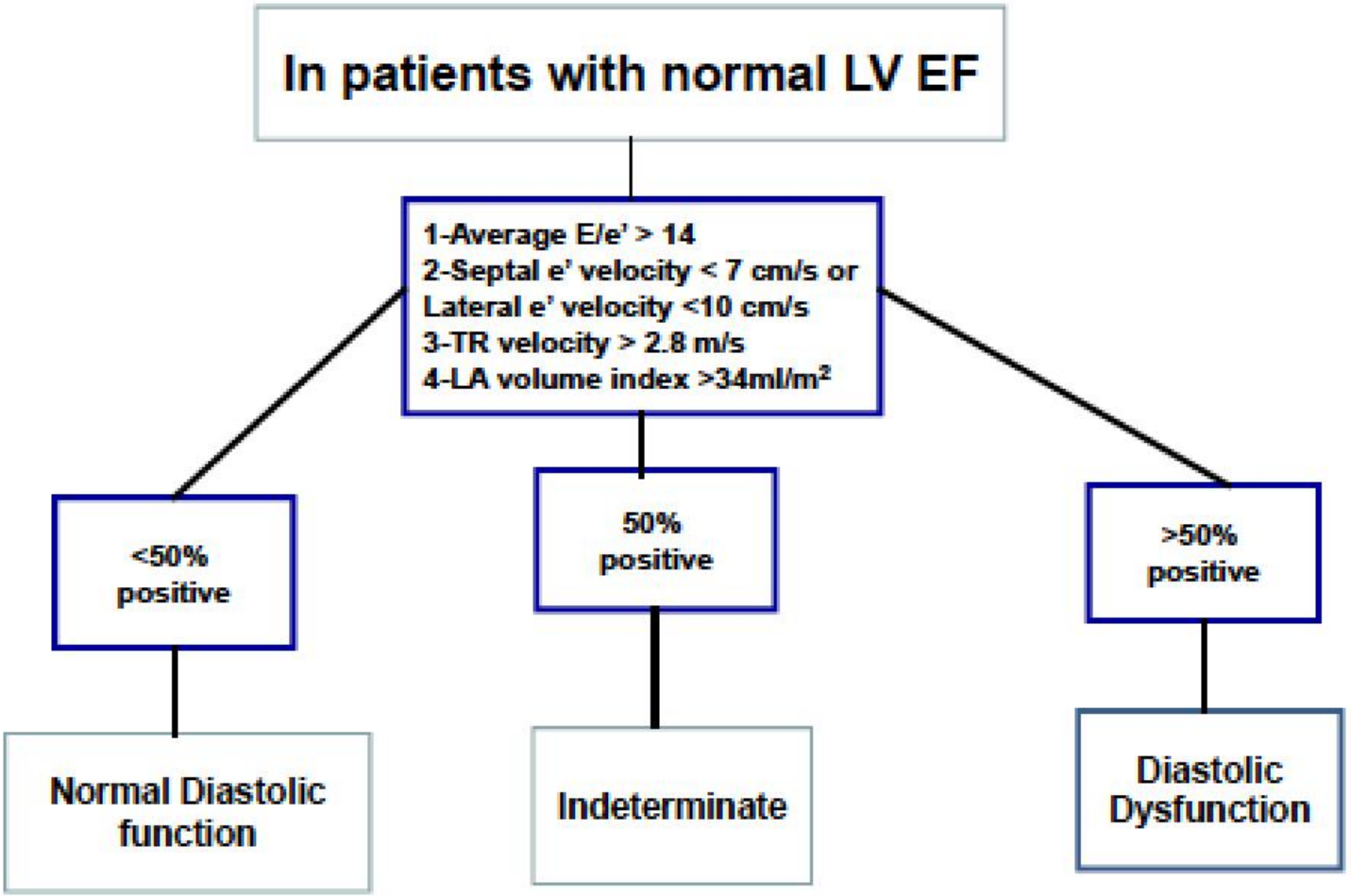
- Medical therapy of HFrEF cannot be extrapolated to HFpEF:
  - ACEI, ARB, BB, spironolactone do NOT improve mortality risk:
  - ARB, BB and spironolactone offer minimal evidence in reducing hospitalization;
  - Control of BP and HR (esp in Afib), myocardial revascularization are LOE Class C recommendations.

Summary (continued)

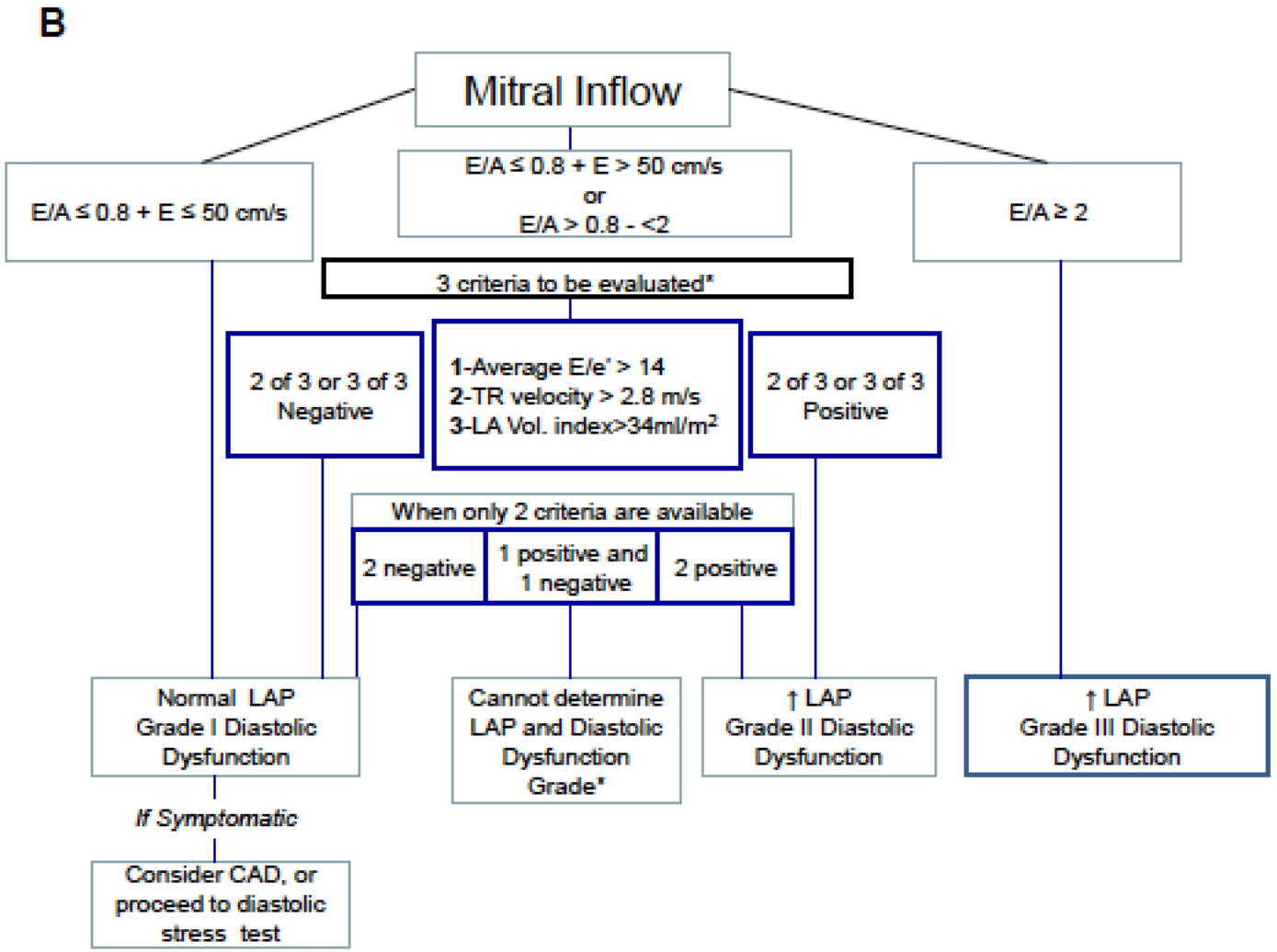
- The four recommended variables for identifying diastolic dysfunction and their abnormal cutoff values are
  - annular e’ velocity: septal e’ < 7 cm/sec, lateral e’ < 10 cm/sec,
  - average E/e’ ratio > 14,
  - LA volume index > 34 mL/m2,
  - and peak TR velocity > 2.8 m/sec.

Summary (continued)

A



Summary (continued)



(* : LAP indeterminate if only 1 of 3 parameters available. Pulmonary vein S/D ratio <1 applicable to conclude elevated LAP in patients with depressed LV EF)

Summary (continued)

- Markers for diastolic dysfunction in patients with systolic dysfunction offer evidence of prognostic significance.

References

ASE/EACVI GUIDELINES AND STANDARDS

Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Sherif F. Nagueh, Chair, MD, FASE,[1] Otto A. Smiseth, Co-Chair, MD, PhD,[2] Christopher P. Appleton, MD,[1] Benjamin F. Byrd, III, MD, FASE,[1] Hisham Dokainish, MD, FASE,[1] Thor Edvardsen, MD, PhD,[2] Frank A. Flachskampf, MD, PhD, FESC,[2] Thierry C. Gillebert, MD, PhD, FESC,[2] Allan L. Klein, MD, FASE,[1] Patrizio Lancellotti, MD, PhD, FESC,[2] Paolo Marino, MD, FESC,[2] Jae K. Oh, MD,[1] Bogdan Alexandru Popescu, MD, PhD, FESC, FASE,[2] and Alan D. Waggoner, MHS, RDCS[1], *Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liège, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri*

(J Am Soc Echocardiogr 2016;29:277-314.)

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PRACTICE GUIDELINE

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/
American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society and International Society for Heart and Lung Transplantation

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

WRITING COMMITTEE MEMBERS*

Clyde W. Yancy, MD, MSc, FACC, FAHA, Chair†‡;
Mariell Jessup, MD, FACC, FAHA, Vice Chair*†; Biykem Bozkurt, MD, PhD, FACC, FAHA†;
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W. H. Wilson Tang, MD, FACC*†; Emily J. Tsai, MD, FACC†;
Bruce L. Wilkoff, MD, FACC, FHRS*††

References

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Heart Failure with Preserved Ejection Fraction

Margaret M. Redfield, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

N Engl J Med 2016;375:1868-77.

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Heart Online First, published on August 5, 2017 as 10.1136/heartjnl-2017-311652

OPEN ACCESS

ORIGINAL RESEARCH ARTICLE

Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis

Sean Lee Zheng,[1,2,3] Fiona T Chan,[3] Adam A Nabeebaccus,[1,2] Ajay M Shah,[1,2] Theresa McDonagh,[1,2] Darlington O Okonko,[1,2] Salma Ayis[4]