HFpEF Mimics and When to Look for Them:
Plenary Session #3: Novel Concepts in the Diagnosis and Treatment of HFpEF

Heart Failure Update 2020

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Conflict of Interest Disclosures

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Outline of Discussion

- The impact of co-morbid disease in HFpEF
- Pitfalls and pearls in the diagnosis of HFpEF
- Mimics?
  - Outside of the HFpEF diagnosis
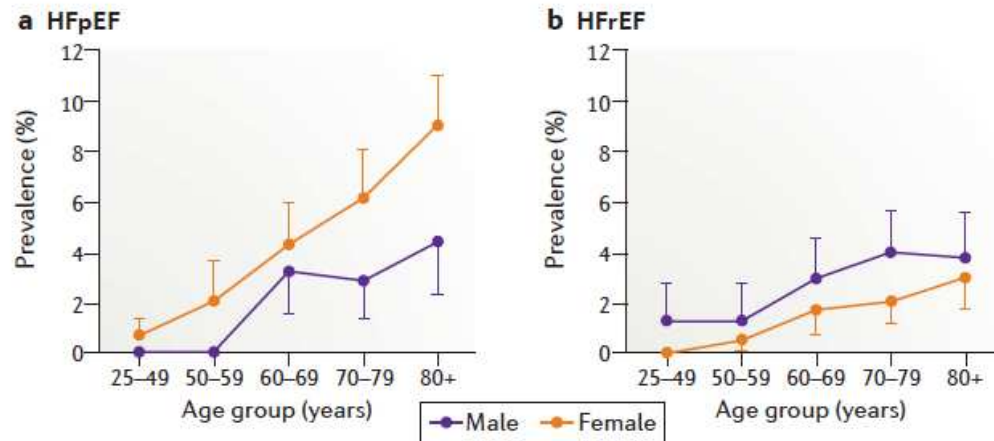 - Inside the HFpEF diagnosis
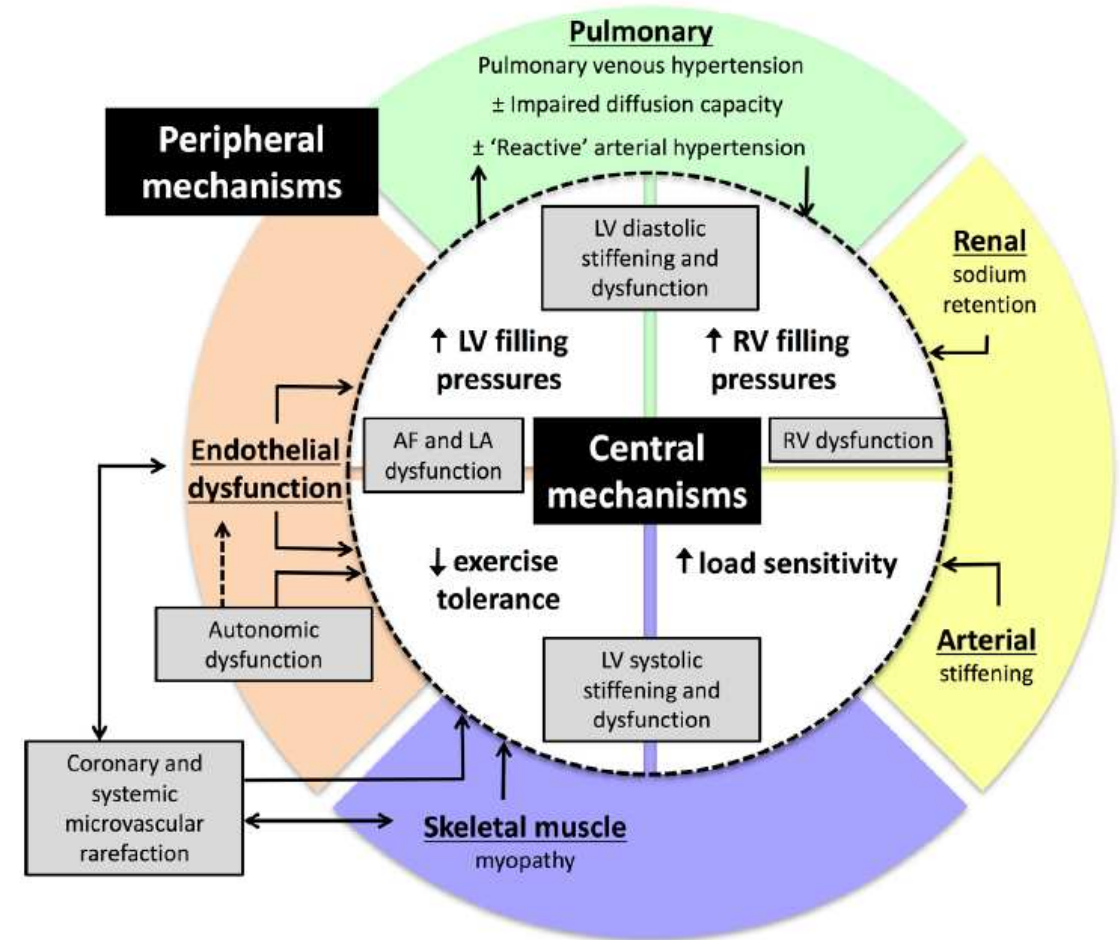
The Challenge of HFpEF

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

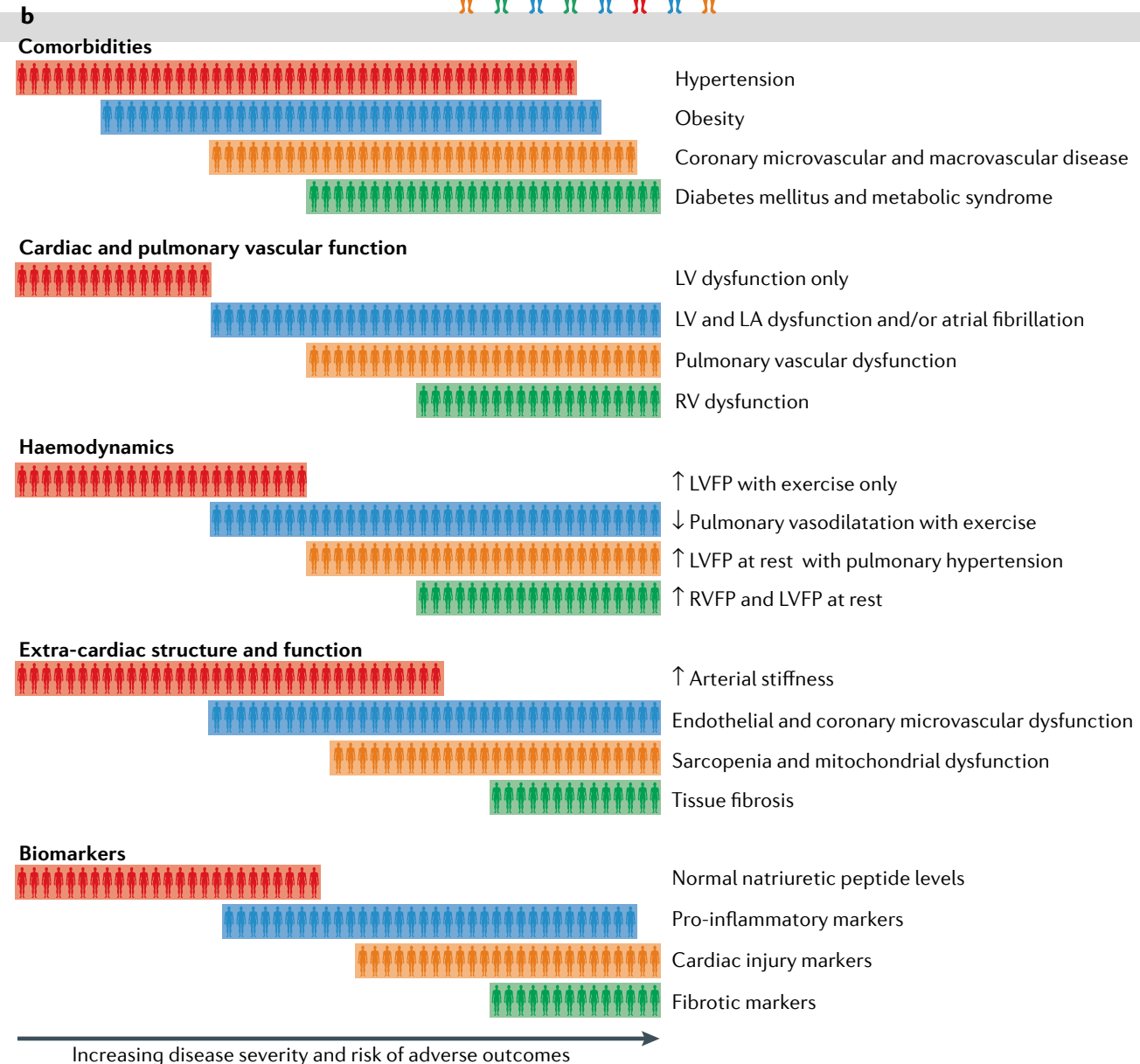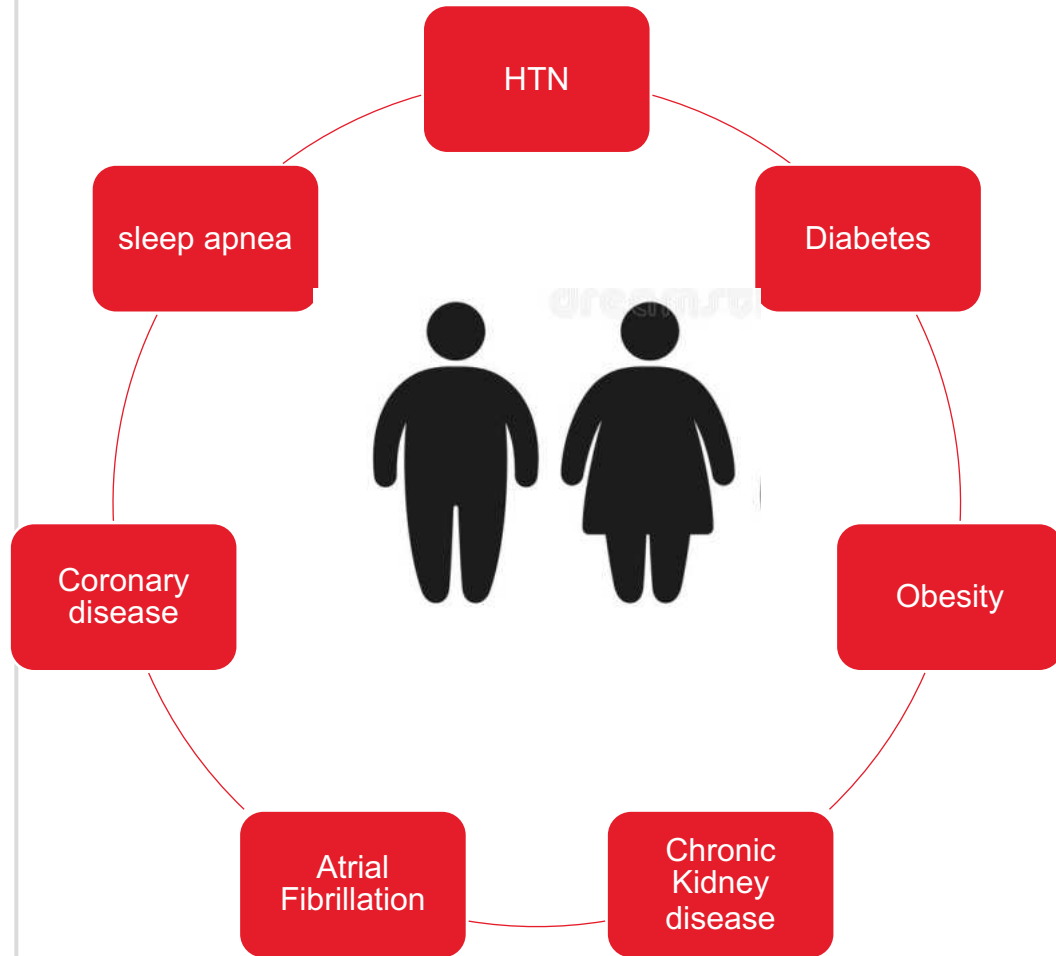| Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%

	3	–	1. Elevated levels of natriuretic peptides[b];
			2. At least one additional criterion:
			    a. relevant structural heart disease (LVH and/or LAE),
			    b. diastolic dysfunction (for details see Section 4.3.2).
				1. Elevated levels of natriuretic peptides[b];
				2. At least one additional criterion:
				    a. relevant structural heart disease (LVH and/or LAE),
				    b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.
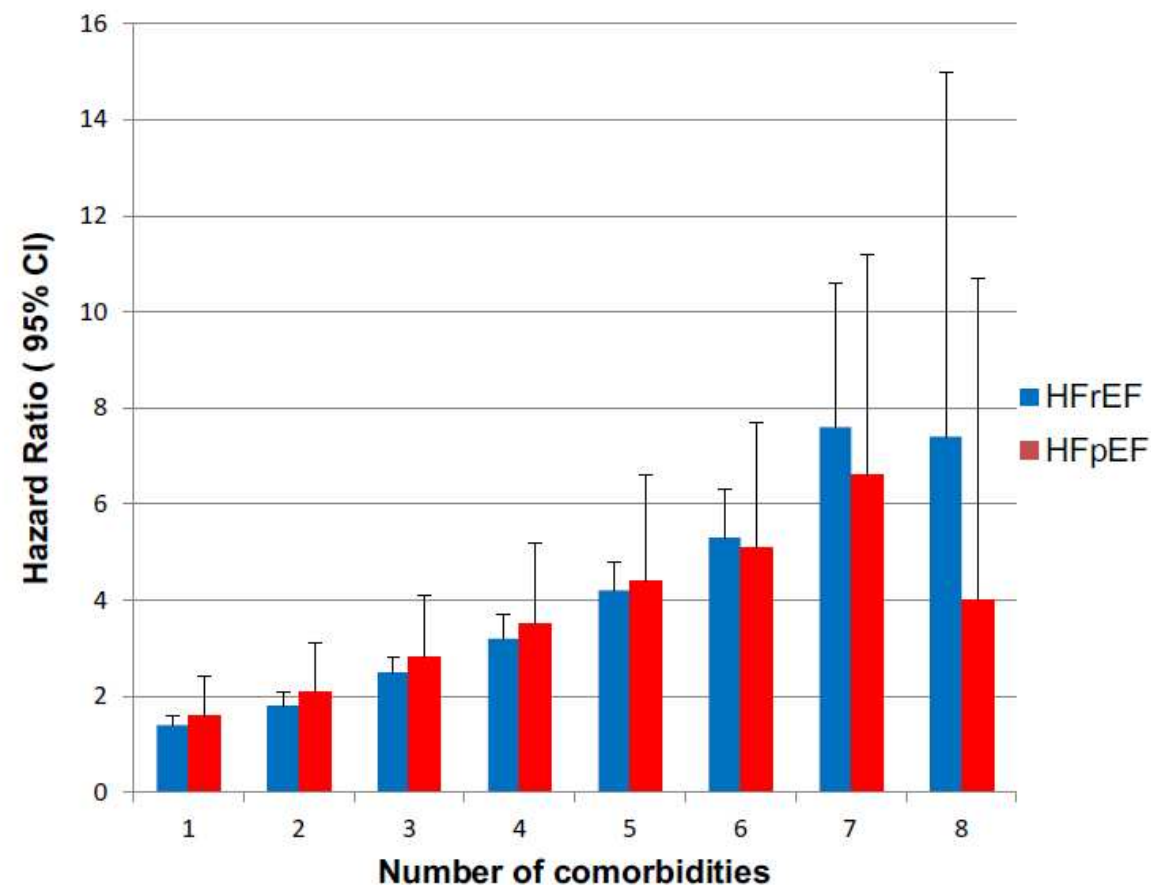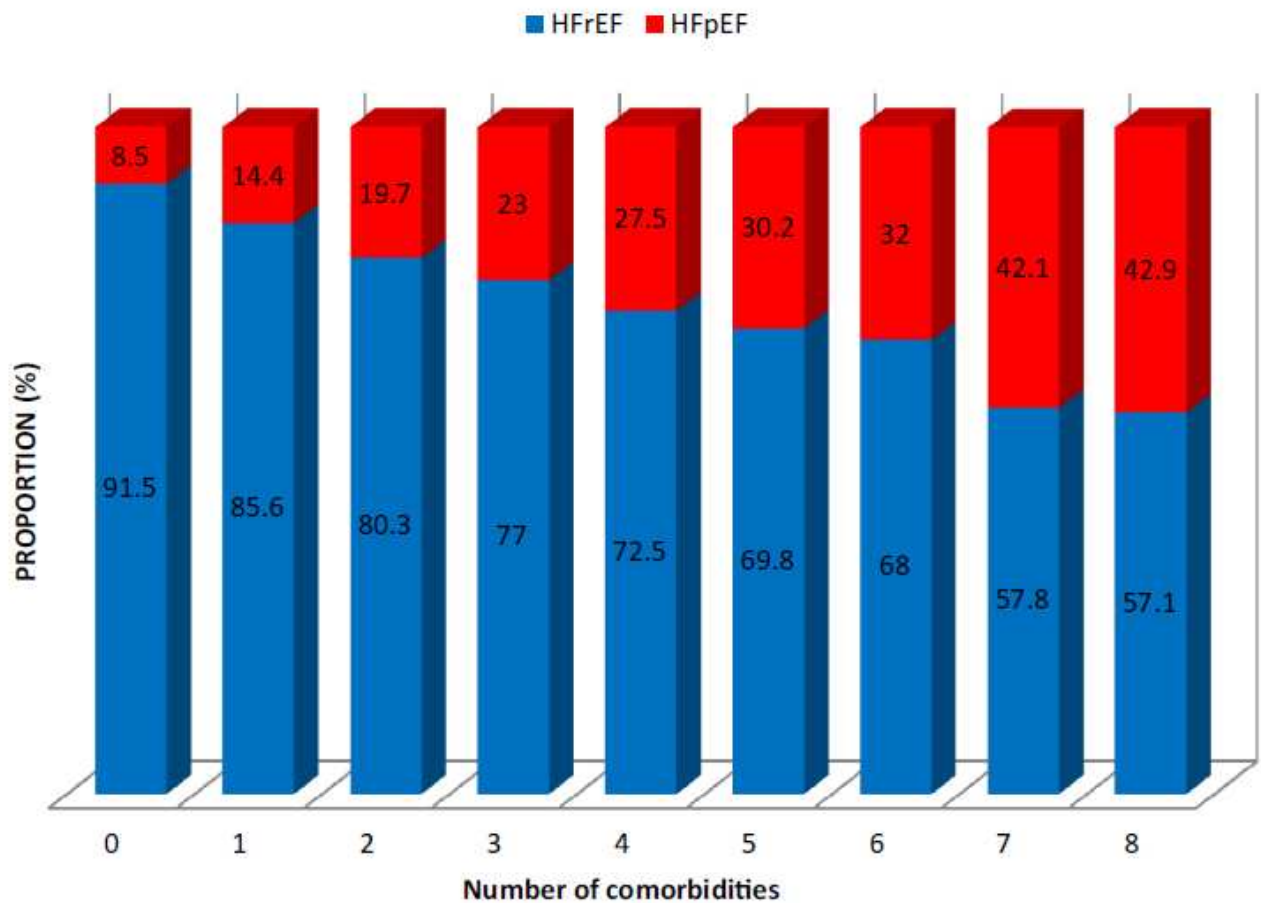[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

Dunley S. Nat Rev Cardiol 2017; 591
Zakeri et al; Heart 2018; 104:377-384

The Co-morbid Collection in HFpEF

HTN

Diabetes

Obesity

Chronic Kidney disease

Atrial Fibrillation

Coronary disease

sleep apnea

Borlaug; Nat Rev Cardiol March 2020

b

Comorbidities
- Hypertension
- Obesity
- Coronary microvascular and macrovascular disease
- Diabetes mellitus and metabolic syndrome

Cardiac and pulmonary vascular function
- LV dysfunction only
- LV and LA dysfunction and/or atrial fibrillation
- Pulmonary vascular dysfunction
- RV dysfunction

Haemodynamics
- ↑ LVFP with exercise only
- ↓ Pulmonary vasodilatation with exercise
- ↑ LVFP at rest with pulmonary hypertension
- ↑ RVFP and LVFP at rest

Extra-cardiac structure and function
- ↑ Arterial stiffness
- Endothelial and coronary microvascular dysfunction
- Sarcopenia and mitochondrial dysfunction
- Tissue fibrosis

Biomarkers
- Normal natriuretic peptide levels
- Pro-inflammatory markers
- Cardiac injury markers
- Fibrotic markers

Increasing disease severity and risk of adverse outcomes

Relationship of Comorbid Burden to Outcome in Heart Failure

Ergatoudes C; Clin Res in Cardiol 2019:108:1025-1033

Interplay Between Comorbid Disease and Underlying Molecular Mechanisms in HFpEF

Shah et al. Circ 2020; 141:1001-1026
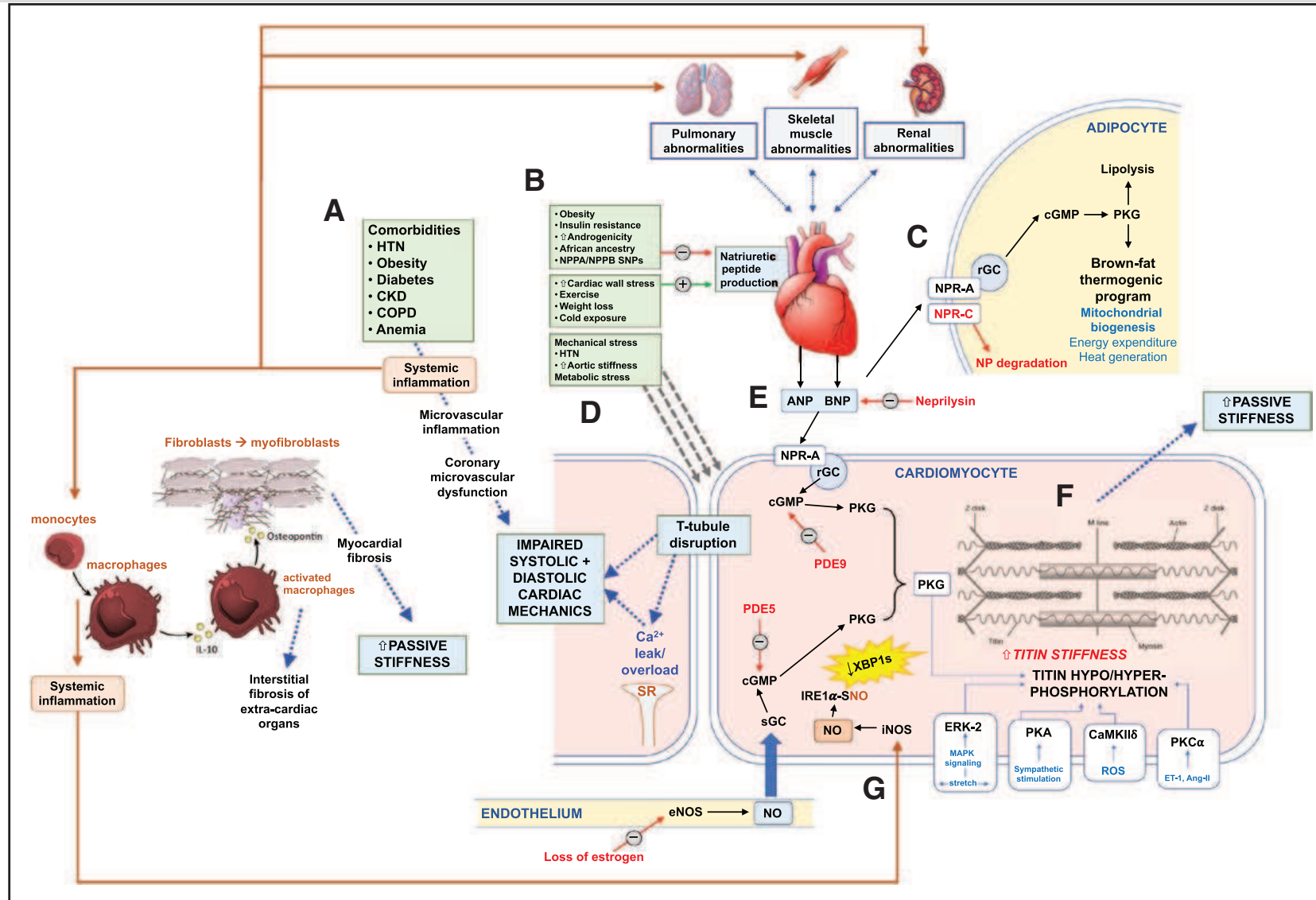
Beyond Diastolic Dysfunction: HFpEF is a Systemic Disease
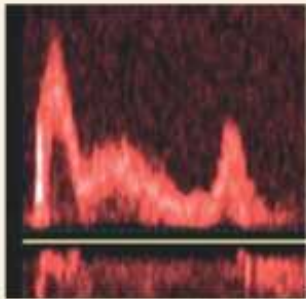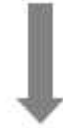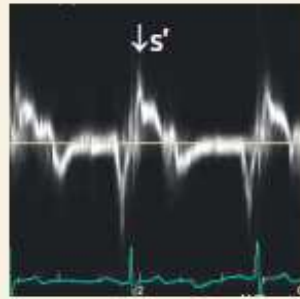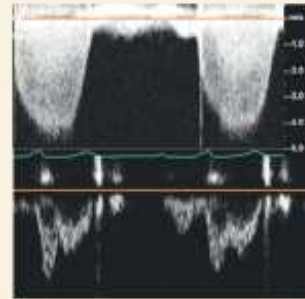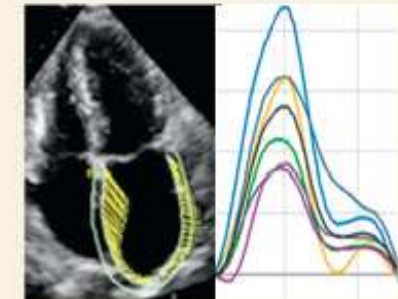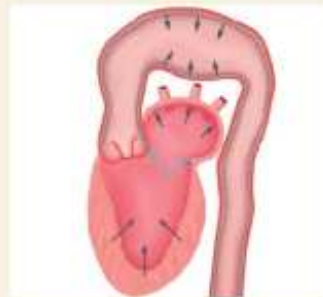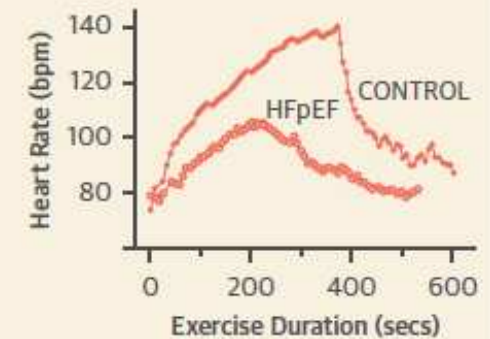
HFpEF Diagnosis: Not for the Faint of Heart….

TABLE 3 **Recent Studies Providing Sensitivity and Specificity of the Current Guidelines for the Diagnosis of HFpEF Among Patients With Unexplained Dyspnea**

First Author (Ref. #) Year	n	Guideline (Ref. #)	Sensitivity (%)	Specificity (%)	AUC	Indeterminant (%)
Reddy et al. (101) 2018	414 (HFpEF 267)	ESC (105)	57	78	0.67	0
Obokata et al. (102) 2017	74 (HFpEF 50)	ASE/EACVI (5)	34	83	0.65	24
Obokata et al. (102) 2017	74 (HFpEF 50)	ESC (105)	60	75	0.68	0

ASE/EACVI = recommendations for the evaluation of left ventricular diastolic function by echocardiography from the American Society of Echocardiography and the European Association of Cardiova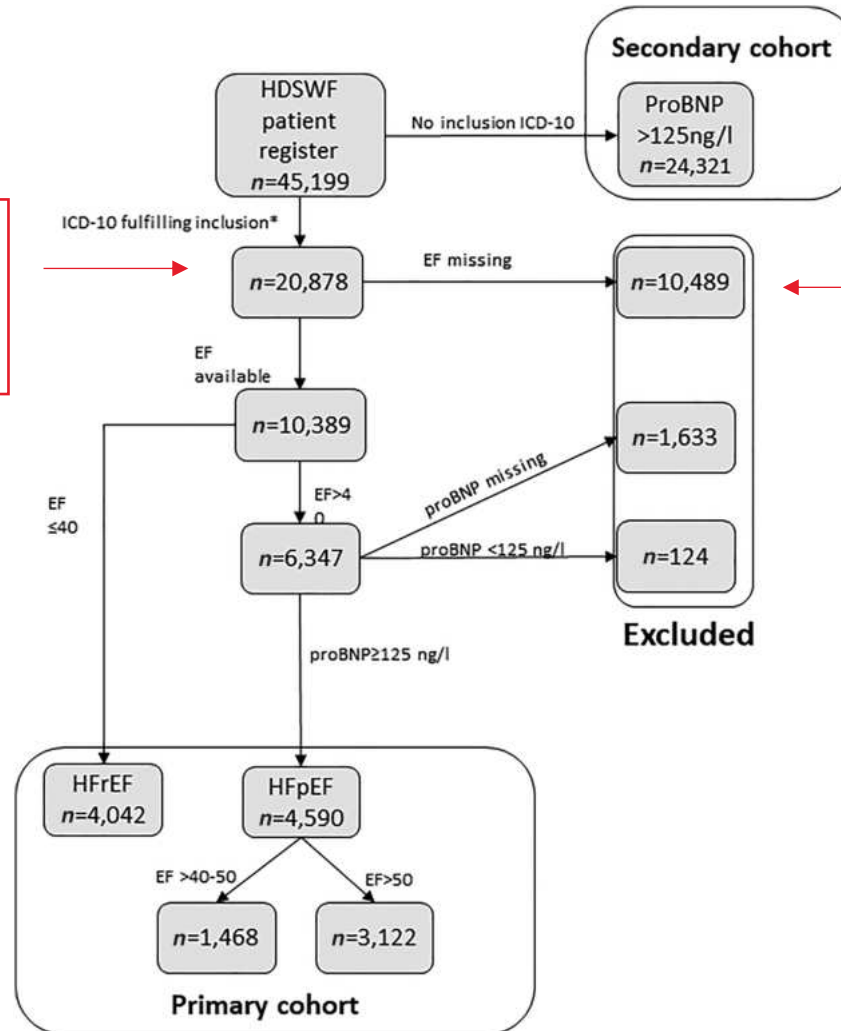scular Imaging; AUC = area under the curve; ESC = European Society of Cardiology; other abbreviations as in **Table 1**.

- Lack of a single objective marker to define the syndrome
- High frequency of comorbidities that can mimic or accompany the HF syndrome
- Natriuretic peptide levels often below typical clinical thresholds
- Notion that diastolic function required to diagnose HFpEF
- Underuse of provocative testing to elicit functional abnormalities

Real World Diagnostics of HF Patients

50% of Patients with an ICD code of HF had EF data available

50% of Patients with an ICD code of HF and no EF measurement also had no NTproBNP assessment

Secondary cohort

HDSWF patient register
n=45,199

No inclusion ICD-10 → ProBNP >125ng/l
n=24,321

ICD-10 fulfilling inclusion*

n=20,878

EF missing → n=10,489

EF available

n=10,389

EF ≤40

EF>40

n=6,347

proBNP missing → n=1,633

proBNP <125 ng/l → n=124

Excluded

proBNP≥125 ng/l

HFrEF n=4,042

HFpEF n=4,590

EF >40-50 → n=1,468

EF>50 → n=3,122

Primary cohort

Huusko et al. ESC HF Feb 2020

Use of Echocardiography After a HF Diagnosis in the Champlain LHIN

- Data obtained from ambulatory care setting 2009-2013

- In all sub regions, ~1/3 of those with HF had an echo within 6 month of prior diagnosis. This number doubled when looking at ECHO within a year of the diagnosis.

- Women were less likely than men to have an Echo within one-year of diagnosis than men.

ECHO within 6-month of prior Dx

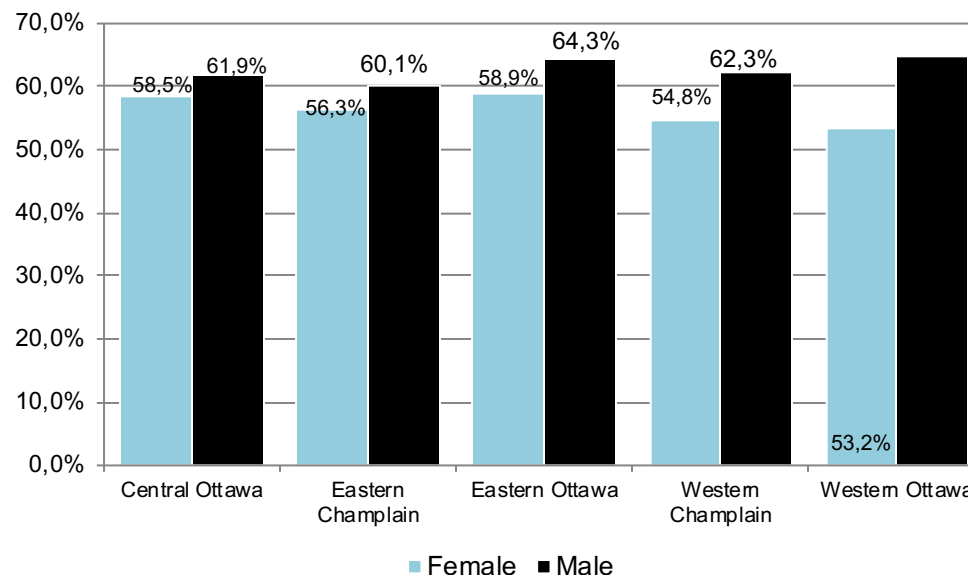| Region	Value
Central Ottawa	31.4%
Eastern Champlain	32.2%
Eastern Ottawa	33.9%
Western Champlain	30.6%
Western Ottawa	34.4%
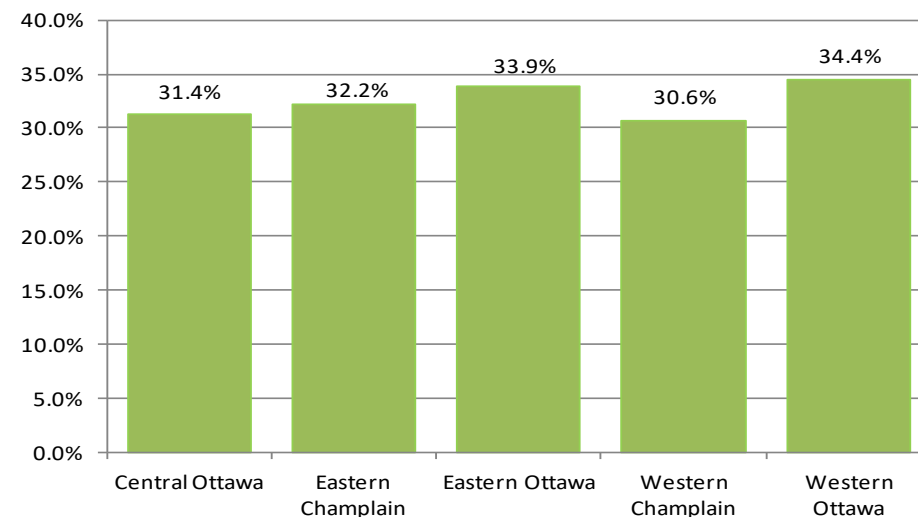
ECHO within a Year of Diagnosis

Region	Female	Male
Central Ottawa	58,5%	61,9%
Eastern Champlain	56,3%	60,1%
Eastern Ottawa	58,9%	64,3%
Western Champlain	54,8%	62,3%
Western Ottawa	53,2%	

■ Female ■ Male

Mielniczuk, Sun unpublished

Specialty Based Variability in the Diagnosis of HFpEF

TABLE 2. Physicians Who Reported Awareness of HFpEF Diagnostic Guidelines and Use of Left Ventricular Diastolic Dysfunction and BNP to Rule In or Rule Out a Diagnosis of HFpEF[a]

Diagnostic consideration	Noncardiologists n (%)	Cardiologists n (%)	P value	Question No.[b]
Aware of ESC or ACC/AHA diagnostic guidelines	49 (27.4%)	20 (62.5%)	<.001	23
Exclude HFpEF diagnosis if DD not present on TTE	66 (38.4%)	2 (6.5%)	.001	27
Diagnose HFpEF in all patients with DD present on TTE	58 (33.9%)	1 (3.2%)	.001	28
Use low BNP level to exclude a diagnosis of HFpEF	58 (33.3%)	8 (25.8%)	.41	24

[a]ACC = American College of Cardiology; AHA = American Heart Association; BNP = B-type natriuretic peptide; DD = diastolic dysfunction; ESC = European Society of Cardiology; HFpEF = heart failure with preserved ejection fraction; TTE = transthoracic echocardiography.
[b]Corresponding question number in the Supplemental Appendix.

TABLE 3. Physicians Who Reported That Certain TTE Findings Individually Would Cause Them to Consider a Diagnosis of HFpEF in the Absence of Other TTE Abnormalities[a]

| TTE finding	Noncardiologists n (%)	Cardiologists n (%)	P value	Question No.[b]
LV diastolic dysfunction	161 (89.9%)	26 (81.3%)	.15	29
Left atrial enlargement	71 (39.7%)	26 (81.3%)	<.001	29
LV hypertrophy	94 (52.5%)	19 (59.4%)	.47	29
Elevated RVSP	75 (41.9%)	20 (62.5%)	.03	29
RV enlargement	47 (26.3)	16 (50.0%)	.007	29
LV dilation	44 (24.6%)	8 (25.0%)	.96	29

[a]HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; RV = right ventricular; RVSP = right ventricular systolic pressure; TTE = transthoracic echocardiography.
[b]Corresponding question number in the Supplemental Appendix.

Saxon et al; Mayo Clin Proc 2020; 95(4)669

HFpEF Diagnosis: Not for the Faint of Heart….

Clinical History and Physical Exam

Orthopnea, PND: highly specific
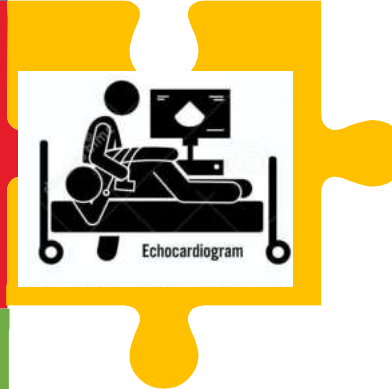Dyspnea, fatigue: more sensitive
Obesity: OR 3.46
AF: OR 12.35

Invasive/noninvasive
PWP>15 at rest and
>25 during exercise
Reduced cardiac
output reserve
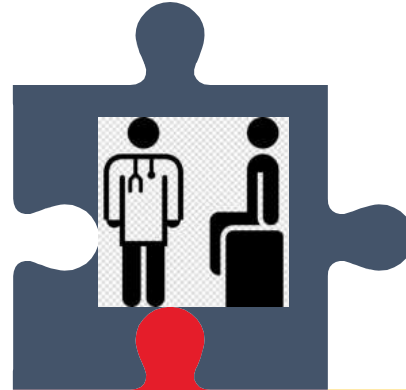
Exercise testing

Integrated Diagnostic Approach

Echo

increased E/e' and PASP
LAE, decreased e',
reduced global
longitudinal strain

Lower wall stress due to small
cavity size and thicker walls
Effect of obesity

Natriuretic peptides

H$_2$FPEF Score: A validated Diagnostic Algorithm for HFpEF

	Clinical Variable	Values	Points
H$_2$	**H**eavy	Body mass index > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	Doppler Echocardiographic E/e' > 9	1
	H$_2$FPEF score		Sum (0-9)

Total Points: 0 1 2 3 4 5 6 7 8 9

Probability of HFpEF: 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 0.95

Probability of HFpEF:
Score 0-1: Low
Score 2-5: Intermediate
Score 6-9 High

Reddy et al. Circ 2018; 138:861-870

# HFA-PEEF Algorithm: Consensus Recommendation from HFA and ESC

The HFA-PEFF Algorithm for the Diagnosis of HFpEF

| P	Initial Workup (Step 1 (P) : Pretest Assessment)	• Symptoms and/or Signs of HF • Comorbidities / Risk factors • ECG • Standard Echocardiography • Natriuretic Peptides • Ergometry / 6 min walking test or Cardiopulmonary Exercise Testing
E	Diagnostic Workup (Step 2 (E) : Echocardiographic and Natriuretic Peptide Score)	• Comprehensive Echocardiography • Natriuretic Peptides, if not measured in Step 1
F1	Advanced Workup (Step 3 (F1) : Functional testing in Case of Uncertainty)	• Diastolic Stress Test: Exercise Stress Echocardiography • Invasive Haemodynamic Measurements
F2	Aetiological Workup (Step 4 (F2) : Final Aetiology)	• Cardiovascular Magnetic Resonance • Cardiac or Non-Cardiac Biopsies • Scintigraphy / CT / PET • Genetic testing • Specific Laboratory Tests

HFA-PEFF score

Domains	Major criteria (2 points)	Minor criteria (1 point)
Functional	• Septal e' <7 cm/s • Lateral e' <10 cm/s • Average E/e' ratio ≥15 • Velocity of the tricuspid regurgitation >2.8 m/s (pulmonary artery systolic pressure >35 mmHg)	• Average E/e' ratio 9–14 • Global longitudinal strain <16%
Morphological	• LAVI >34 ml/m^2 • LVMI ≥149/122 g/m^2 (m/w) and relative wall thickness >0.42	• LAVI 29–34 ml/m^2 • LVMI >115/95 g/m^2 (m/w) • Relative wall thickness >0.42 • Left ventricular wall thickness ≥12 mm
Biomarker (sinus rhythm)	• NT-proBNP >220 pg/ml • BNP >80 pg/ml	• NT-proBNP 125–220 pg/ml • BNP 35–80 pg/ml
Biomarker (atrial fibrillation)	• NT-proBNP >660 pg/ml • BNP >240 pg/ml	• NT-proBNP 365–660 pg/ml • BNP 105–240 pg/ml

Probability of HFpEF:
Score 0-1: Low
Score 2-4: Intermediate
Score 5-6: High

Pieske et al; Eur J HF 2020; 22:391-212

HFA-PEEF Algorithm: Consensus Recommendation from HFA and ESC

Pieske et al; Eur J HF 2020; 22:391-212
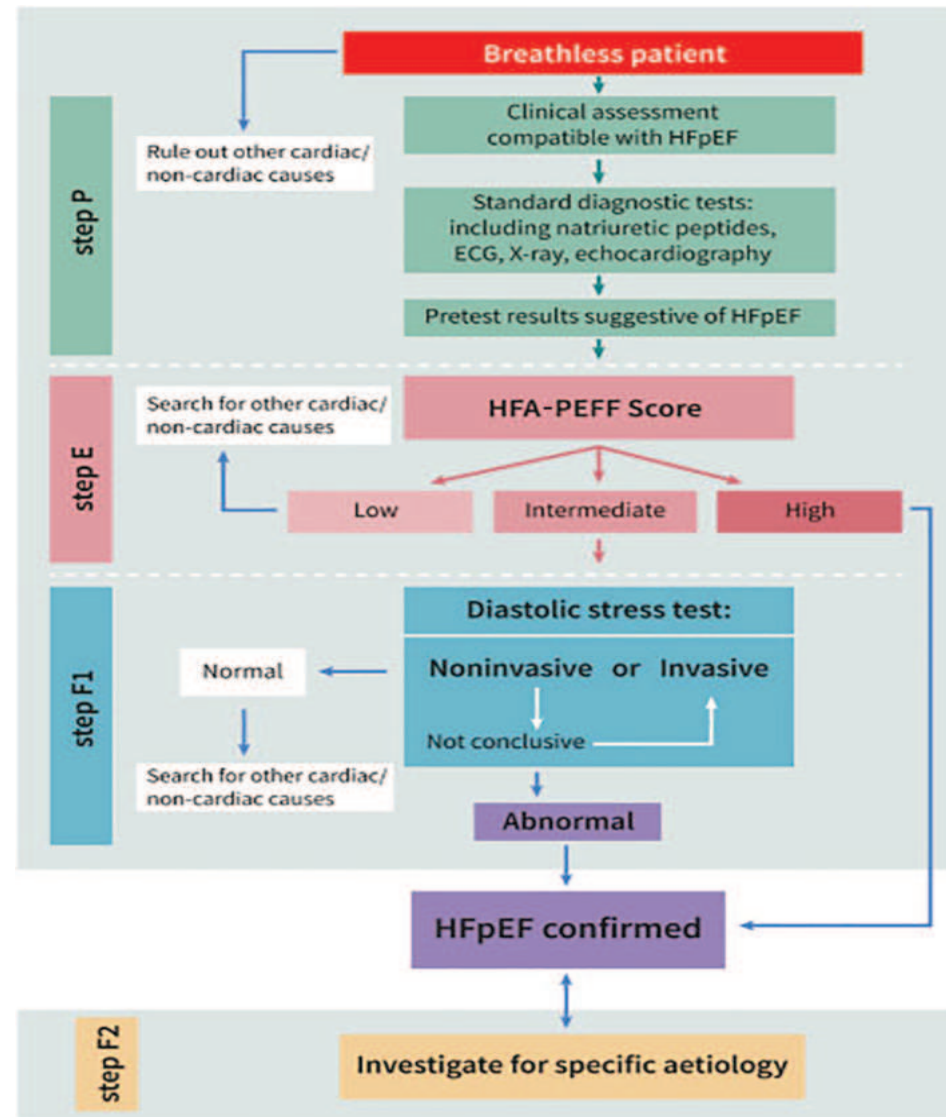
Mimics of HFpEF in a patient with Established or High Probability of HFpEF
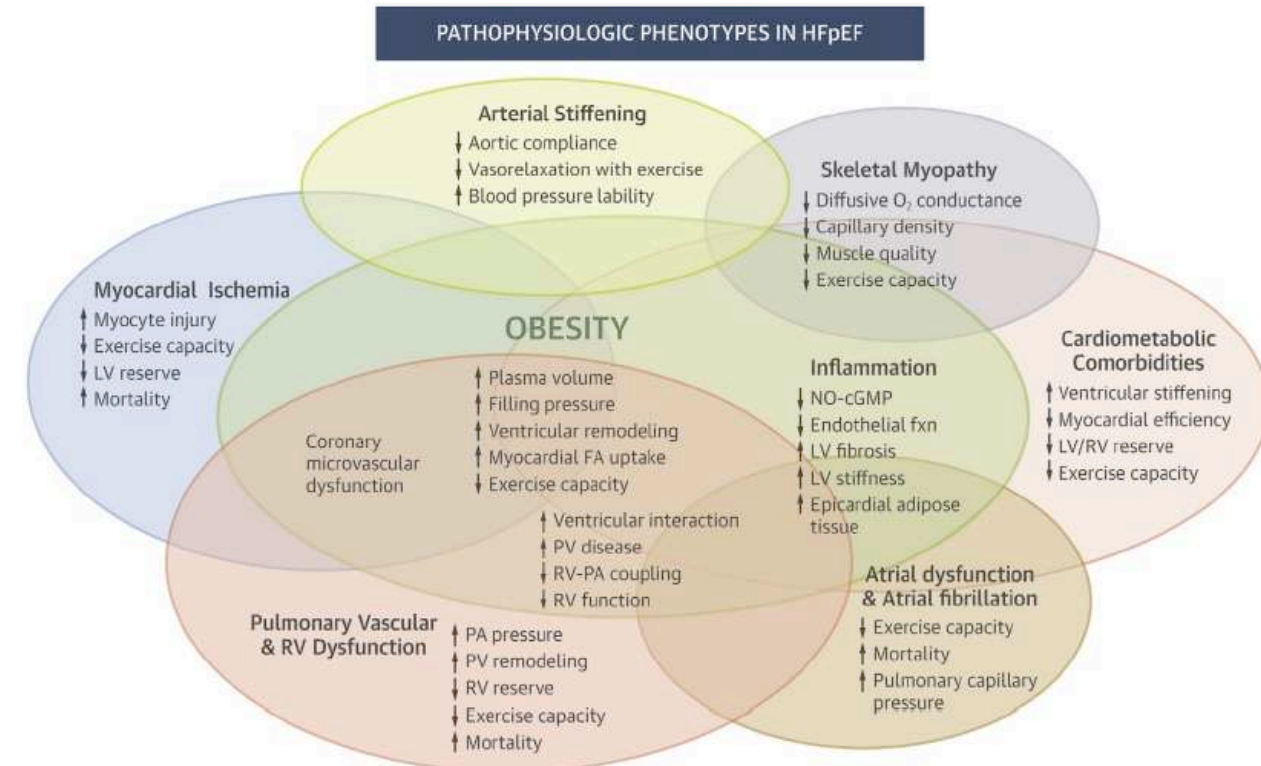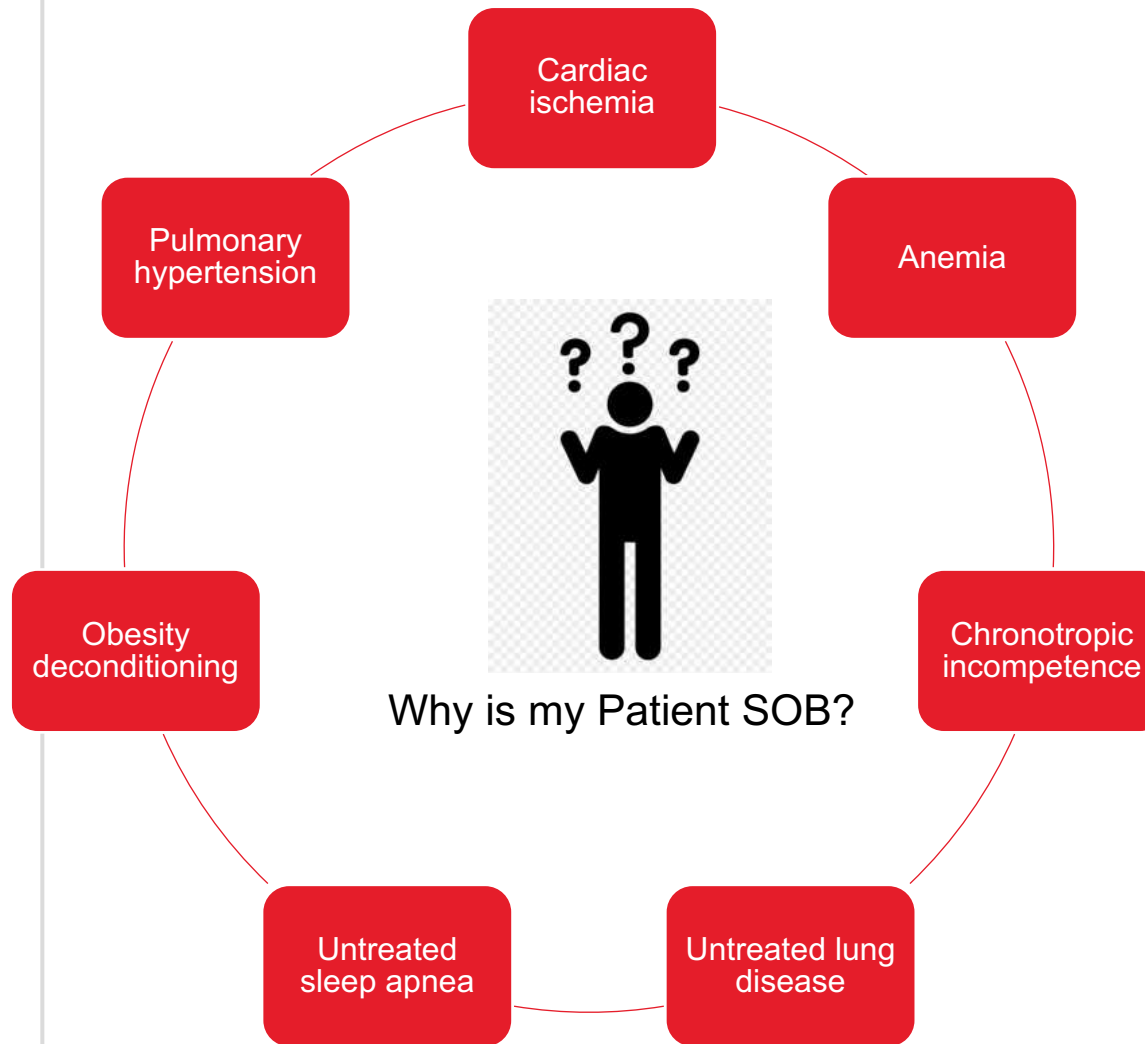
Obokata, M. et al. J Am Coll Cardiol Img. 2020;13(1):245–57.

The Role of Noninvasive Exercise Testing

Pieske et al; Eur J HF 2020; 22:391-212
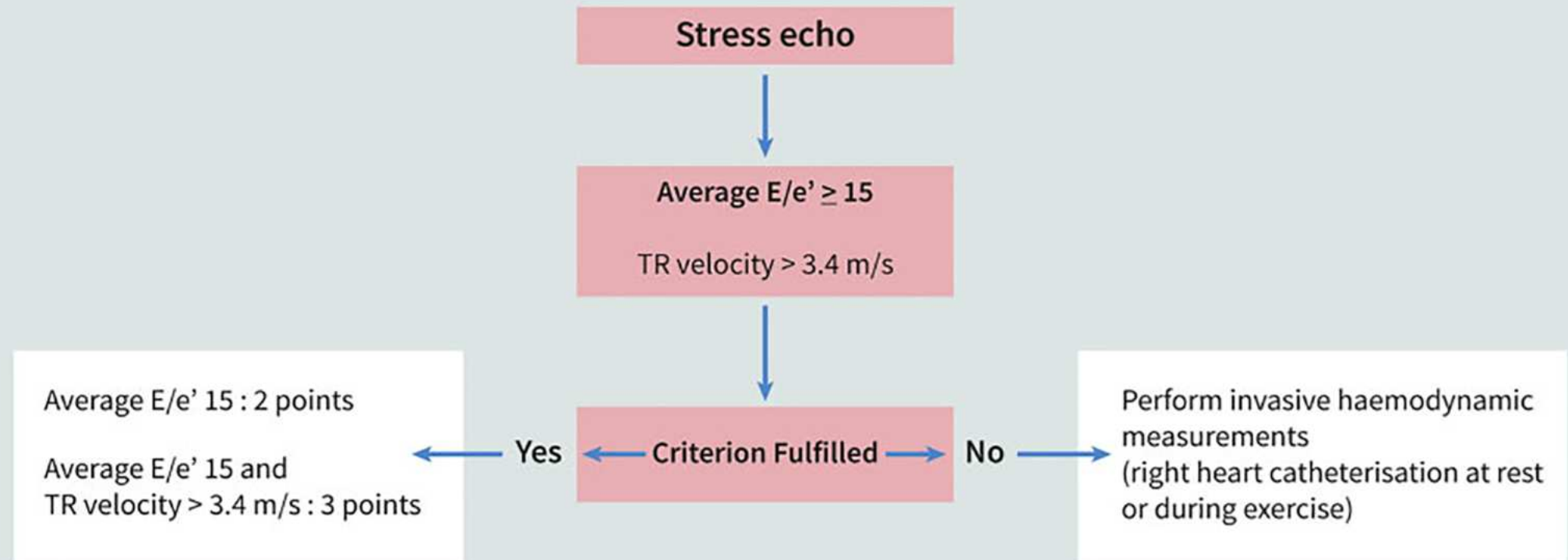
Invasive Exercise Testing in HFpEF

B

Invasive Haemodynamic Measurements (Left and Right Heart Catheterisation)

Invasive Haemodynamic Measurements at Rest

LVEDP $\geq$ 16 mmHg
or
PCPW $\geq$ 15 mmHg — No

Yes

HFpEF

Echo Stress Test
or
Invasive Stress Test

Invasive Haemodynamic Measurements during Exercise
(invasive Stress Test)

PCPW $\geq$ 25 mmHg

HFpEF

Pulmonary Artery Catheter
Registered Nurse
Supervising Physician
Exercise Physiologist
Face Mask/ Pneumotachograph
Metabolic Cart and Pressure Display
ECG Lead
Radial Artery Catheter
Pulse Oximeter
Cycle Ergometer
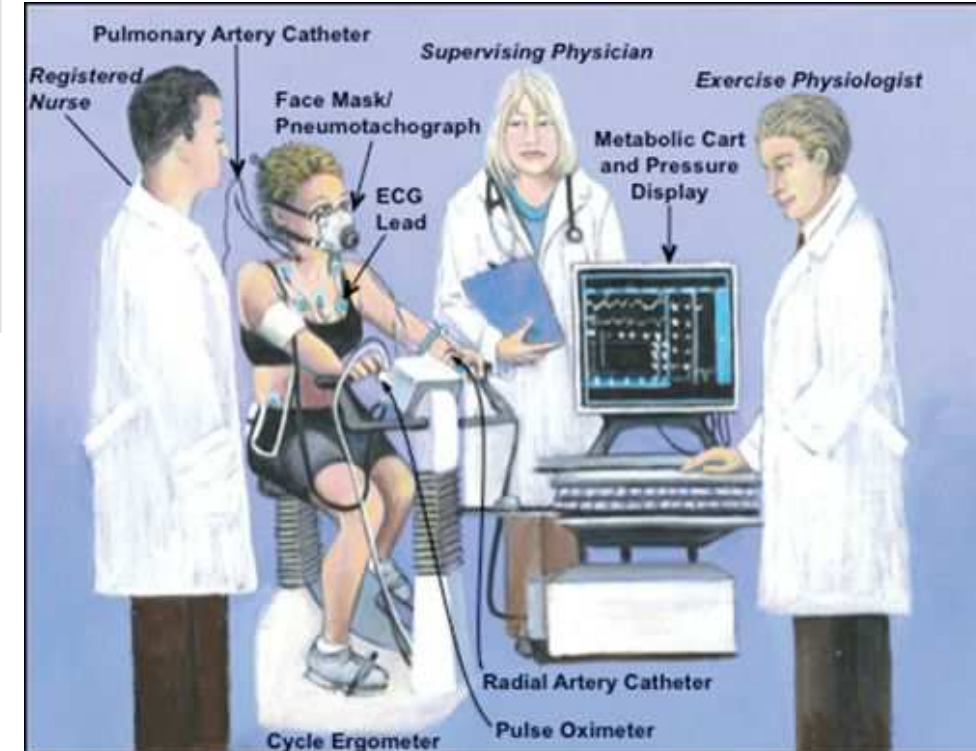
Maron; Circ 2013: 123

Pieske et al; Eur J HF 2020; 22:391-212

Pulmonary Hypertension in Left Heart Disease
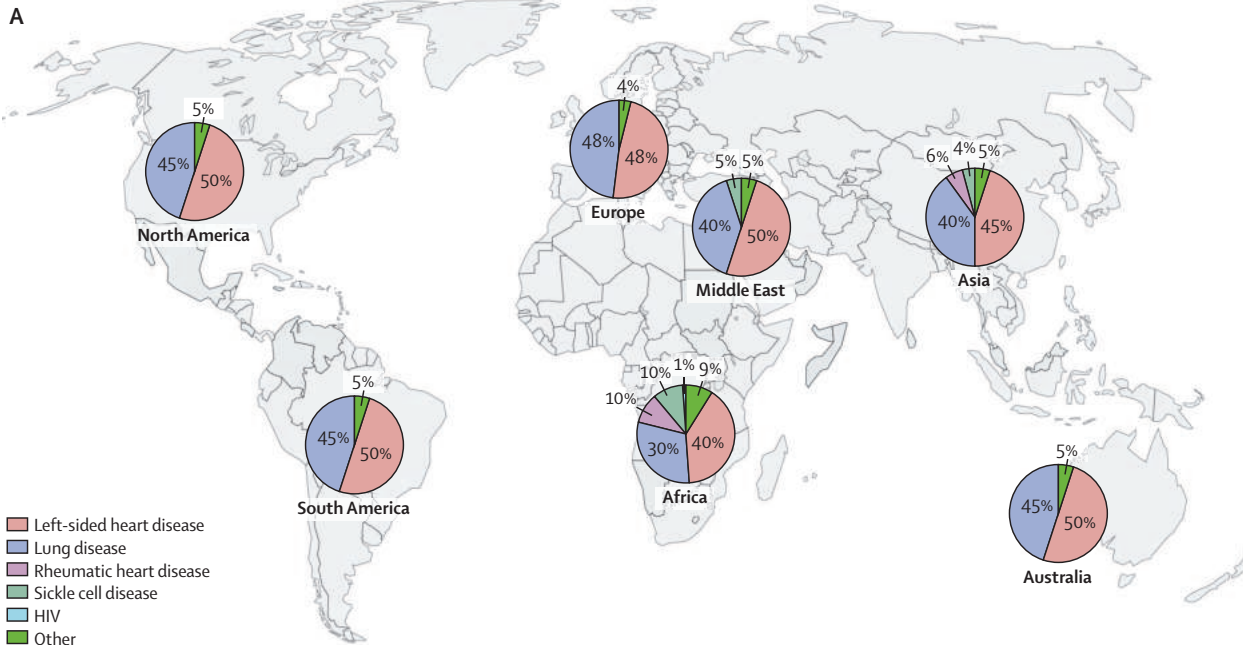
PROPOSED NEW DEFINITIONS OF PH IN LEFT HEART DISEASE:

- Isolated post capillary PH (IpcPH)
  - PCWP > 15 mmHg AND mean **PAP > 20 mmHg AND PVR ≤ 3 WU**

- Combined Post and Precapillary PH (CpcPH)
  - PCWP > 15 mmHg and **mean PAP> 20 mmHg AND PVR > 3 WU**

6th World Symposium on PH (Nice 2018)

Hoeper; Lancet Resp Med 2016; 4:306

Combined Pre and Post Capillary PH in HFpEF
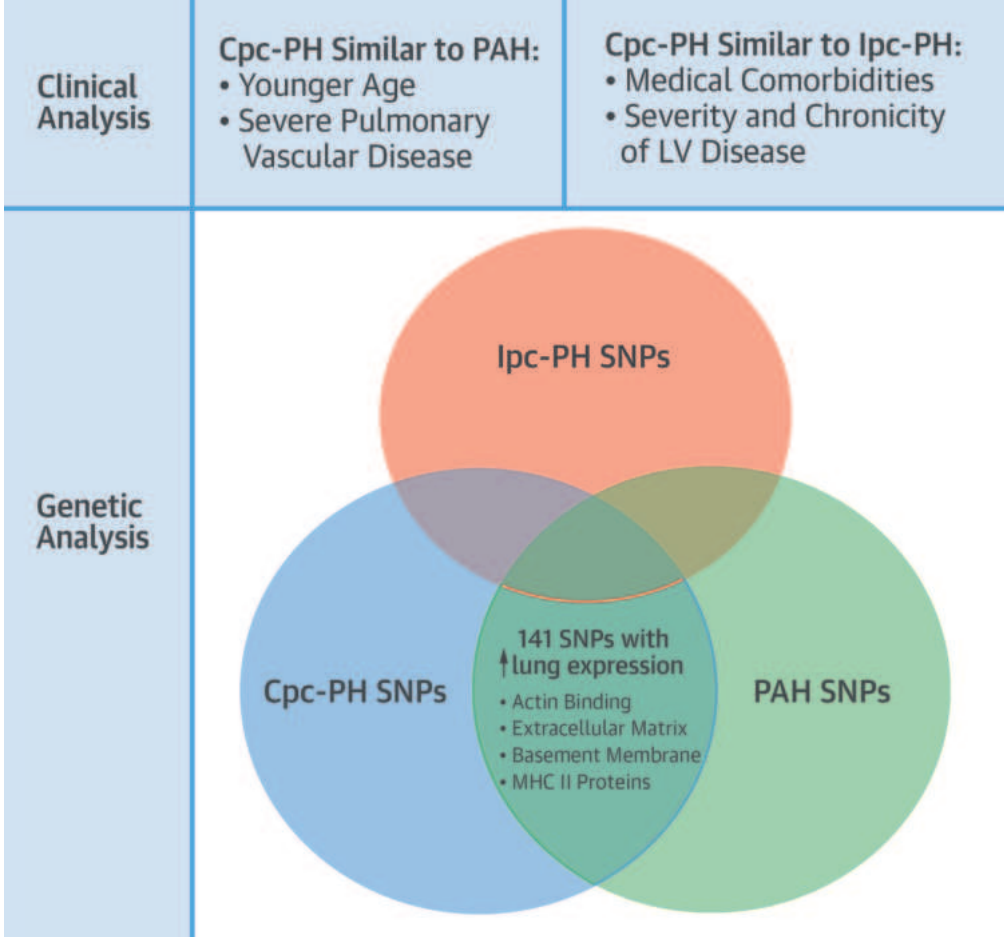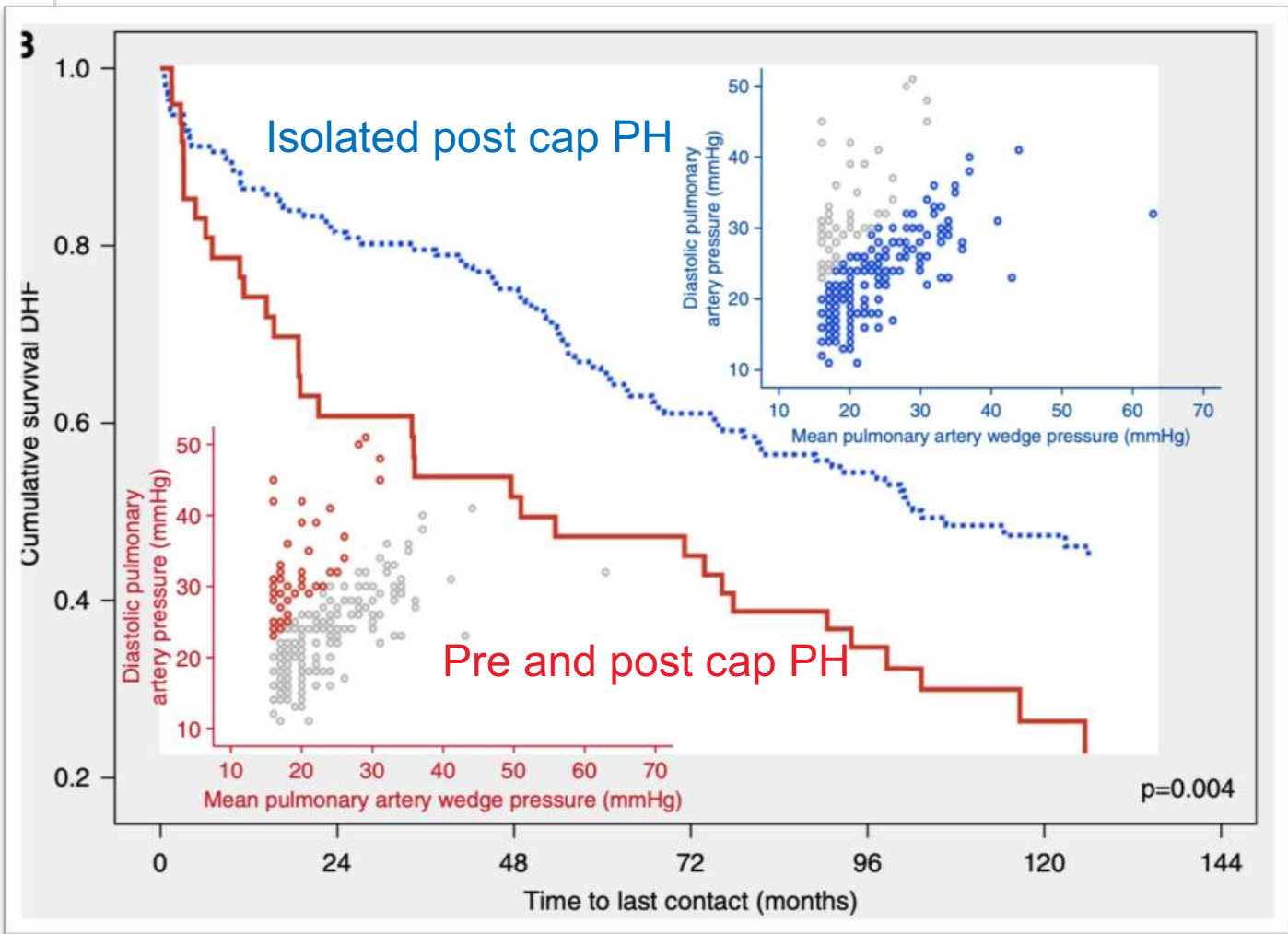
Assad, T.R. et al. J Am Coll Cardiol. 2016;68(23):2525-36.

Gerges; Am J Resp Crit Care Med; 2015; 192:1234

Assad; JACC 2016; 68:2525-36

Right Heart Failure Phenotype in HFpEF

Guazzi, Circ HF 2014;367-377
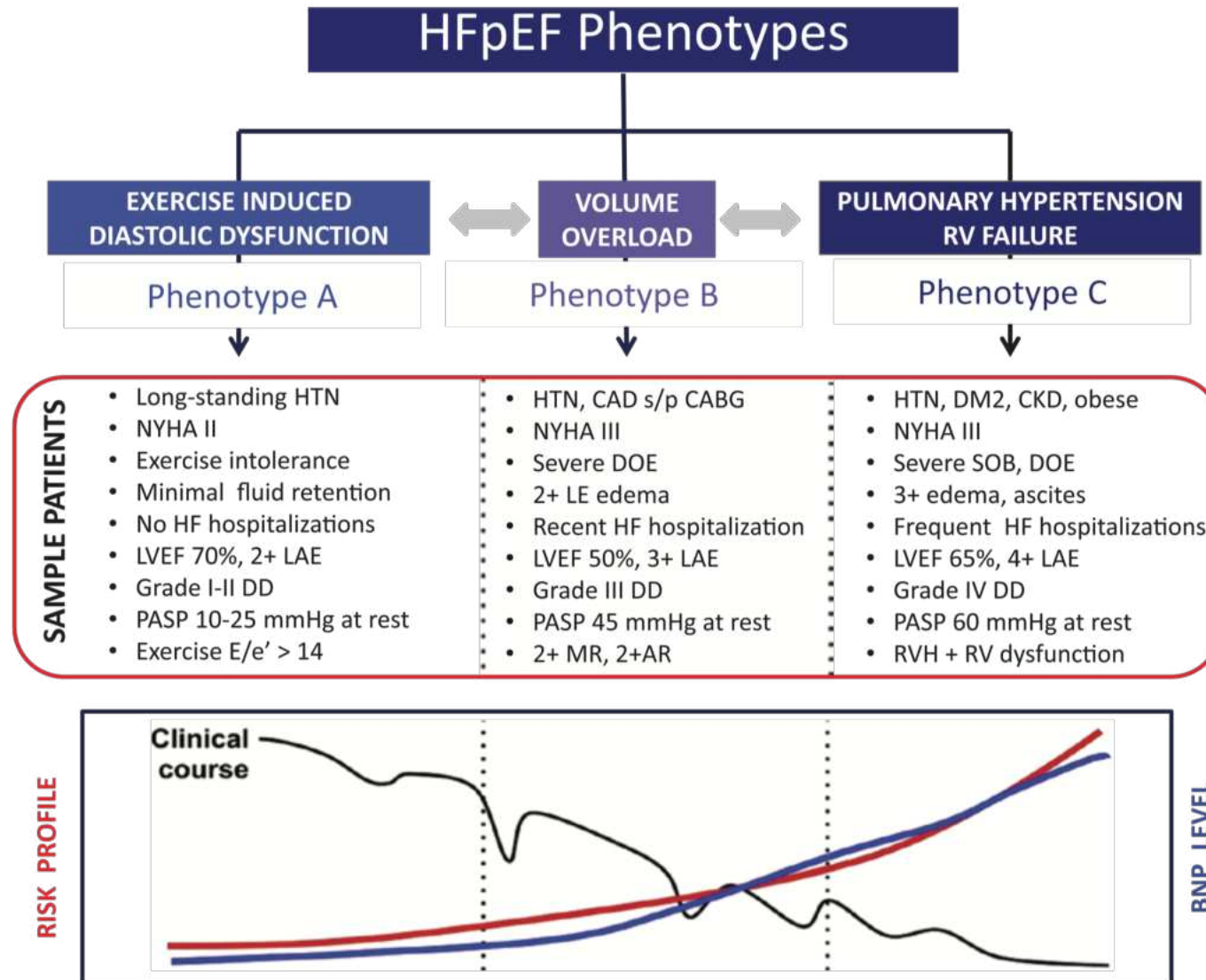
Is This "Garden Variety" HFpEF or Something Else?

Abnormalities of the Myocardium		
Ischemic		CAD
Toxic	Substance use	EtoH, cocaine, steroids
	Heavy metals	Copper, iron, lead, colbalt
Immune and inflammatory	Infection	HIV, hepatitis, parasites
	Non-infectious	Lymphocytic myocarditis, CTD, eosinophilic myocarditis
Infiltrative	Malignant	direct infiltration metastases
	Non-malignant	Amyloid, sarcoid, hemochromatosis, storage disease, Pompe, Gaucher's
Metabolic	Hormonal	Thyroid, parathyroid, Cushing, Addison, Conn's
	Nutritional	Thiamine, selenium, complex
Genetic		HCM Early muscular dystrophy
Endomyocardial		EMF, carcinoid, Pagets, endocardial fibroelastosis

Important "Mimics" of HFpEF

Differential Diagnosis	Clinical Clues	Echo Clues	Confirmatory /Ancillary Testing
Hypertrophic CM	Presyncope/syncope, arrhythmia, younger age, family history	Asymmetric hypertrophy, ⇈ wall thickness, LVOT obstruction, SAM	CMR Genetic testing
Constrictive pericarditis	Previous surgery, exposure, JVP findings	Pericardial thickening, septal bounce, increased respiratory variation in M/T flow, hepatic vein diastolic flow reversal during expiration, absence of IVC collapse	CT, CMR Right heart catheterization
Valvular heart disease	Murmur	Morphological valve abnormality, Doppler	Detailed echo assessment, TEE
CAD	Risk factors, ischemic pain	Regional WMA, thinning	Perfusion imaging Coronary angiography
High output states	Anemia, sepsis, pregnancy, AV fistula, thyrotoxicosis	Increased Doppler derived CO, increased 4 chamber volumes	Right heart catheterization

Important "Mimics" of HFpEF: Cardiac Amyloid

- 5-13% of patients considered to have HFpEF have CA
- ATTRwt CA identified in 32% of PM cases of "HFpEF" >75 years age
- All forms of amyloid can present with typical HF symptoms
- Consider:
  - Decreased exercise tolerance
  - Low BP
  - Syncope
  - Arrhythmia and conduction blocks
  - Amyloid associated neuropathy (autonomic or sensorimotor)

- Diagnostic delay associated with:
  - Increased cardiac biomarkers
  - Worsening conduction abnormalities and arrhythmia
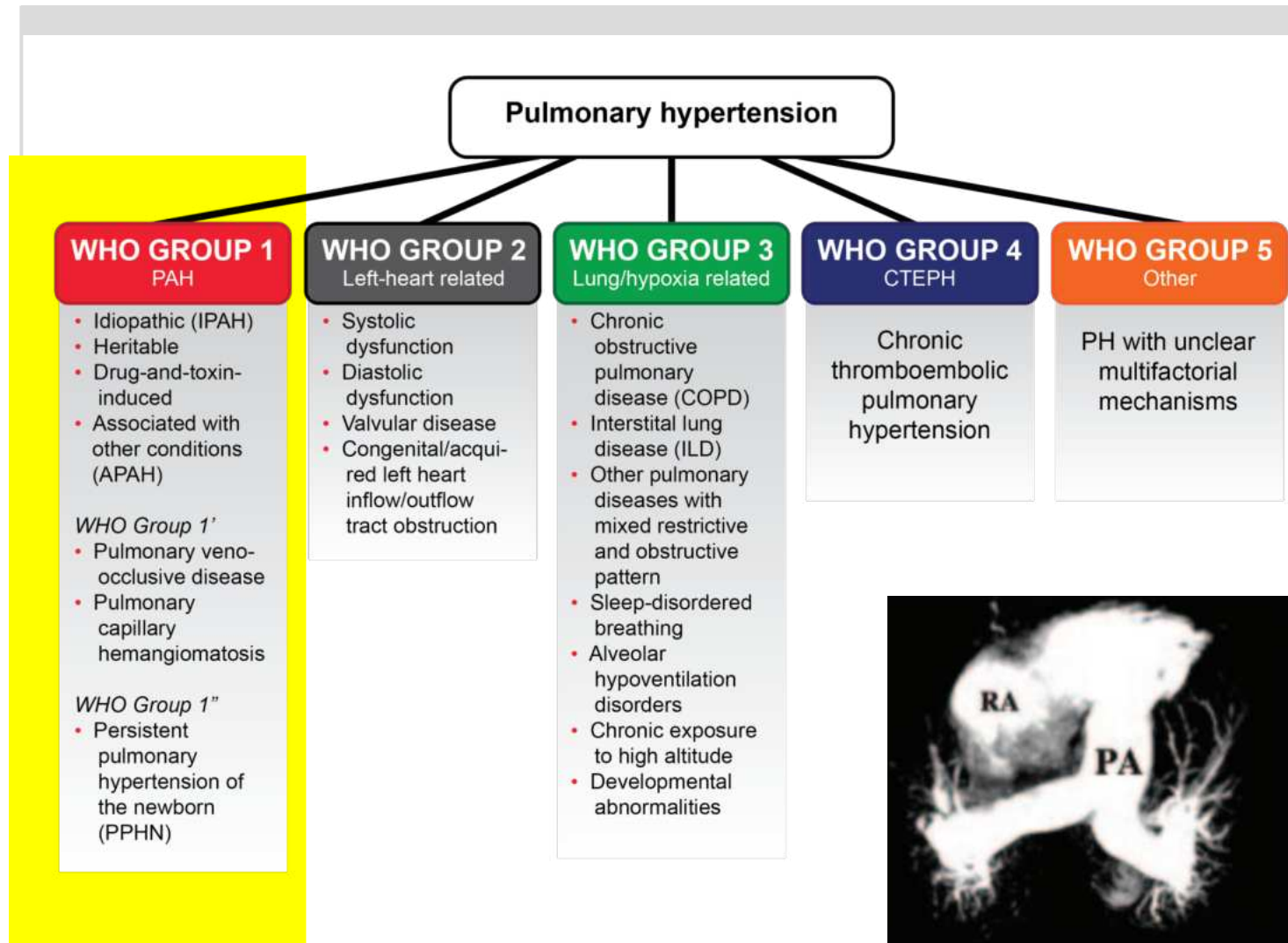 - Worse prognosis

Echo Clues:
- Small LV cavity
- Increased LV wall thickness
- Sparkling myocardium
- Apical sparing
- Severely reduced tissue doppler
- Pericardial effusion
- Hepatic vein diastolic flow reversal during inspiration

Subsequent Testing:
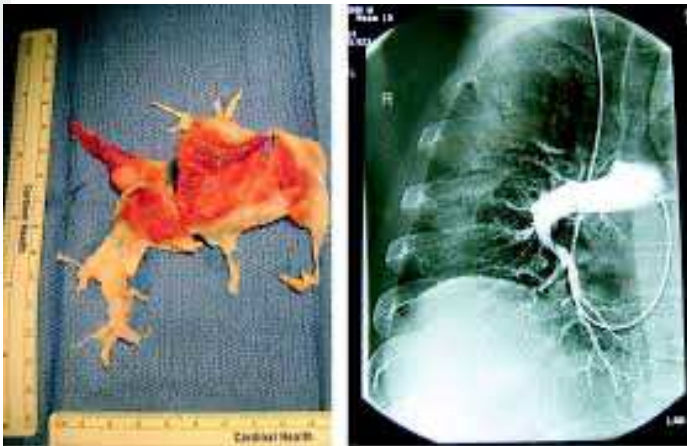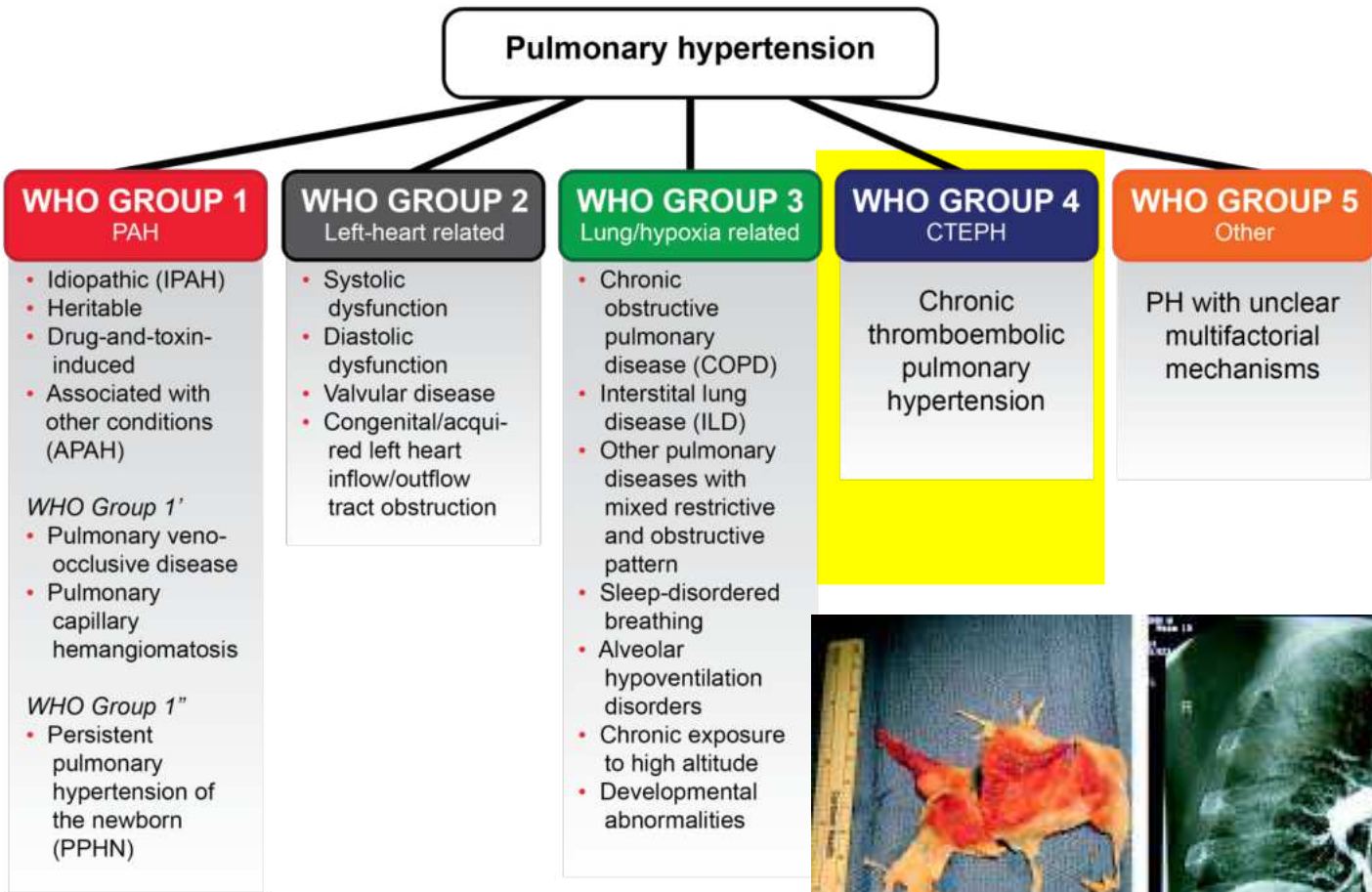CMR
Nuclear scintigraphy
Biopsy

Important "Mimics" of HFpEF: Pulmonary Arterial Hypertension

Pulmonary hypertension

WHO GROUP 1
PAH
- Idiopathic (IPAH)
- Heritable
- Drug-and-toxin-induced
- Associated with other conditions (APAH)

WHO Group 1'
- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis

WHO Group 1"
- Persistent pulmonary hypertension of the newborn (PPHN)

WHO GROUP 2
Left-heart related
- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease
- Congenital/acquired left heart inflow/outflow tract obstruction

WHO GROUP 3
Lung/hypoxia related
- Chronic obstructive pulmonary disease (COPD)
- Interstital lung disease (ILD)
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

WHO GROUP 4
CTEPH
Chronic thromboembolic pulmonary hypertension

WHO GROUP 5
Other
PH with unclear multifactorial mechanisms

Pulmonary Arterial Hypertension	
Clinical Cues	• Evidence of "Associated Conditions" • Variable age distribution
Echo Clues	• No evidence of increased LV filling pressure • Isolated right heart dilatation • PA dilatation • RV outflow tract doppler mid systolic notch
Subsequent Testing	Right Heart Catheterization

Important "Mimics" of HFpEF: Chronic Thromboembolic PH

Chronic Thromboembolic Disease

Clinical Cues	• History of DVT/PE • Hypercoaguable state
Echo Clues	• No evidence of increased LV filling pressure • Isolated right heart dilatation • PA dilatation • RV outflow tract doppler mid systolic notch
Subsequent Testing	VQ scan CT pulmonary angiogram Right heart catheterization

Summary

- HFpEF is the dominant form of HF worldwide
  - Continues to present a diagnostic and therapeutic challenge
- HFpEF diagnosis requires an integrated approach
  - Clinical evaluation
  - Biomarkers
  - Echocardiography is essential in assessing pathophysiologic mechanisms and phenotyping
  - Exercise testing may help to solicit the cause of a patients undiagnosed dyspnea
- HFpEF mimics exist inside and outside the diagnosis
  - Identification and treatment of co-morbidities
  - Functional testing
  - High index of suspicion for diagnoses with distinct natural history and management