

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



Heart Failure Update 2020

Lisa M Mielniczuk MD FRCPC
Professor of Medicine, University of Ottawa Heart Institute
Vice Chair, Quality and Clinical Care, Department of Medicine
Director, Advanced Heart Failure Program
Director, Pulmonary Hypertension Clinic

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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

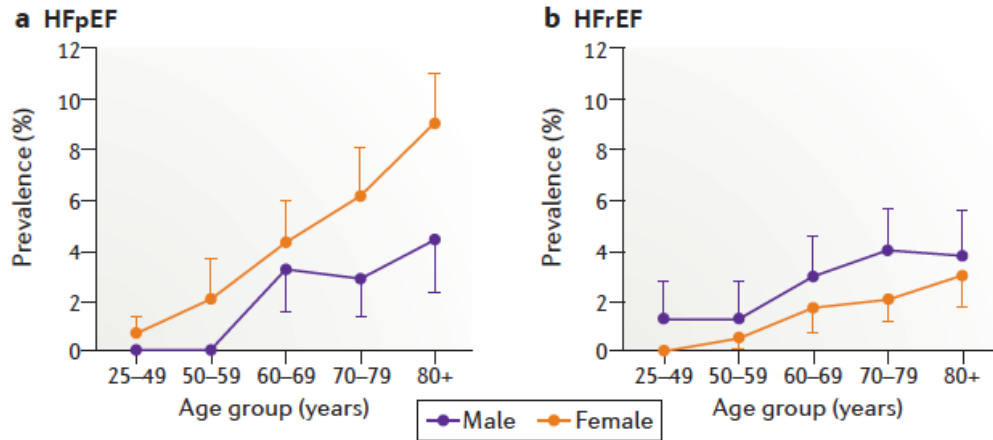


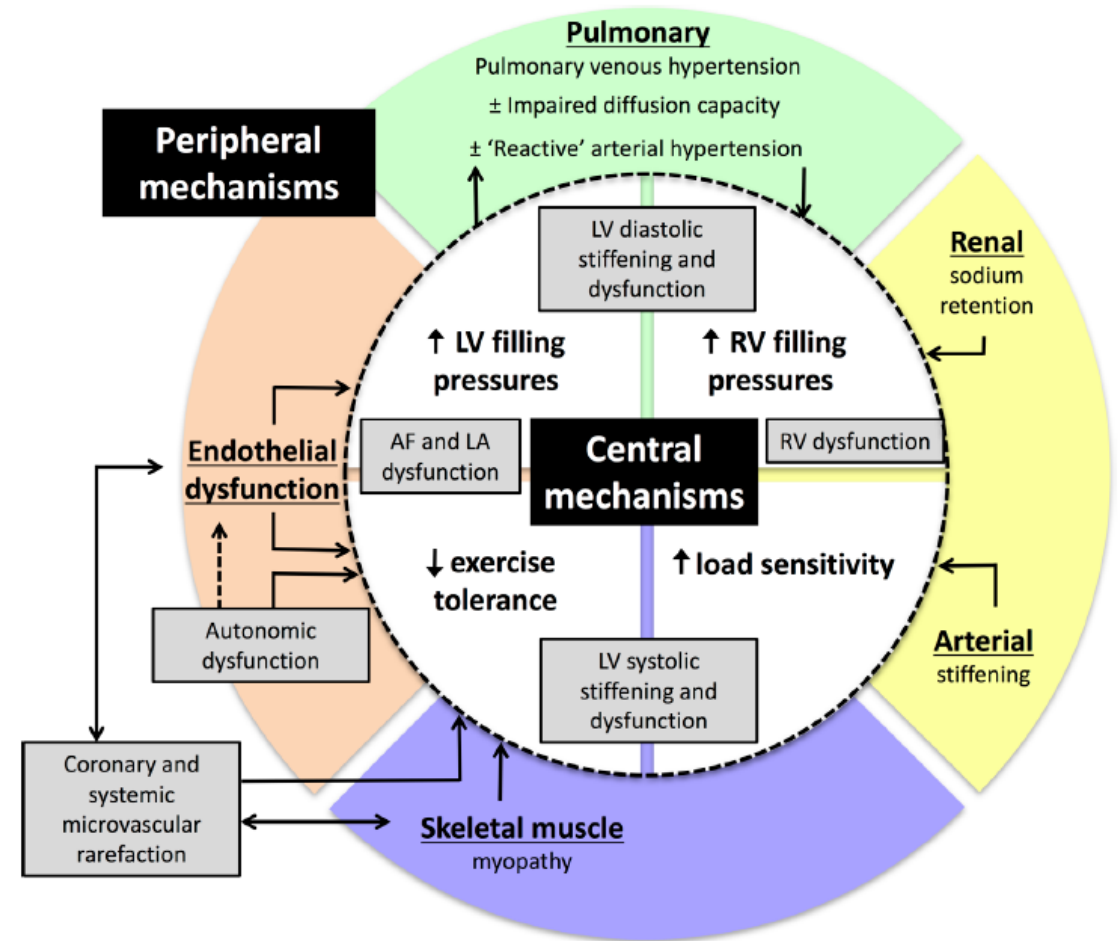
Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF	HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs ^a	Symptoms ± Signs ^a
	2	LVEF <40%	LVEF 40–49%
	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).
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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.

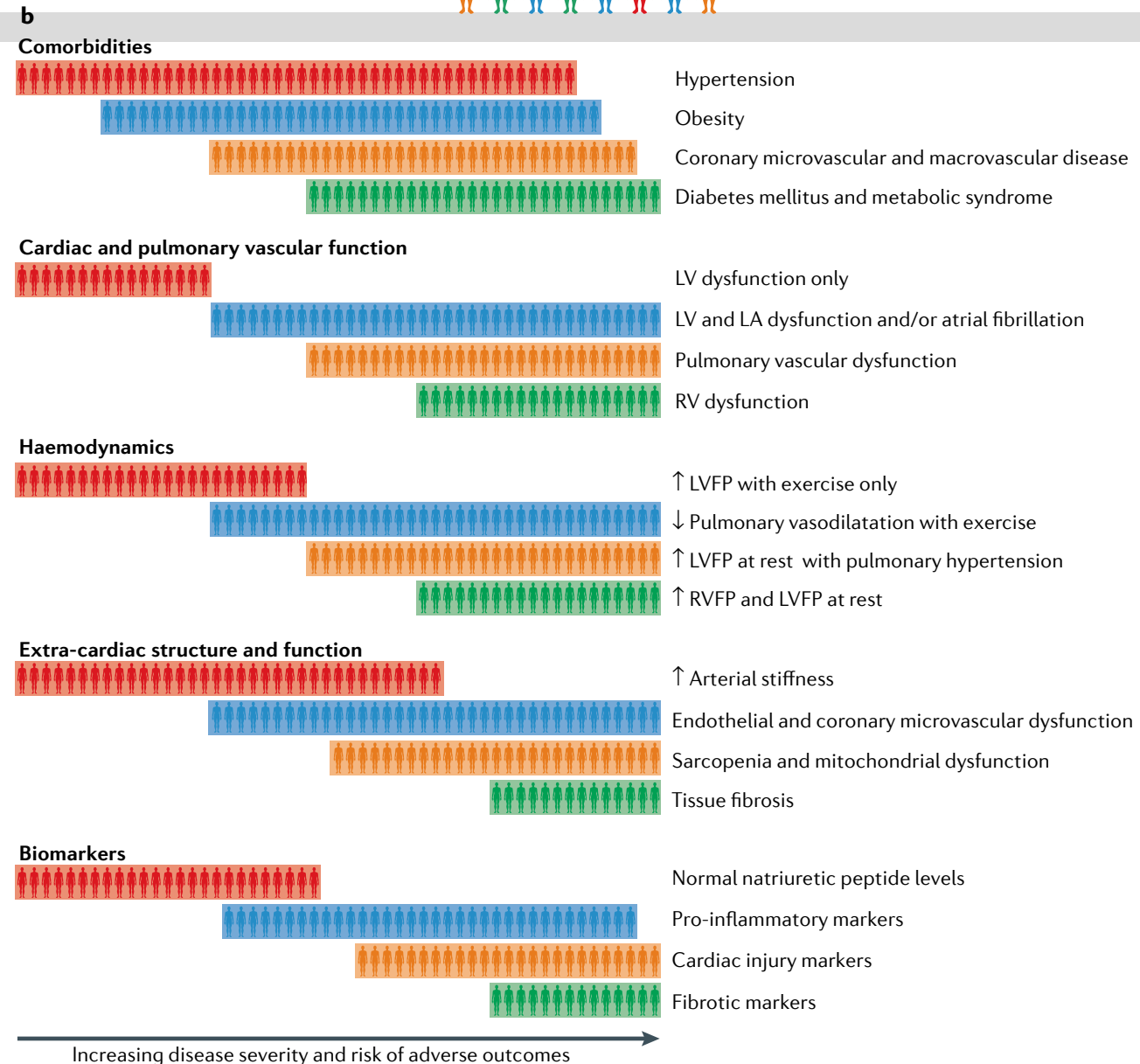
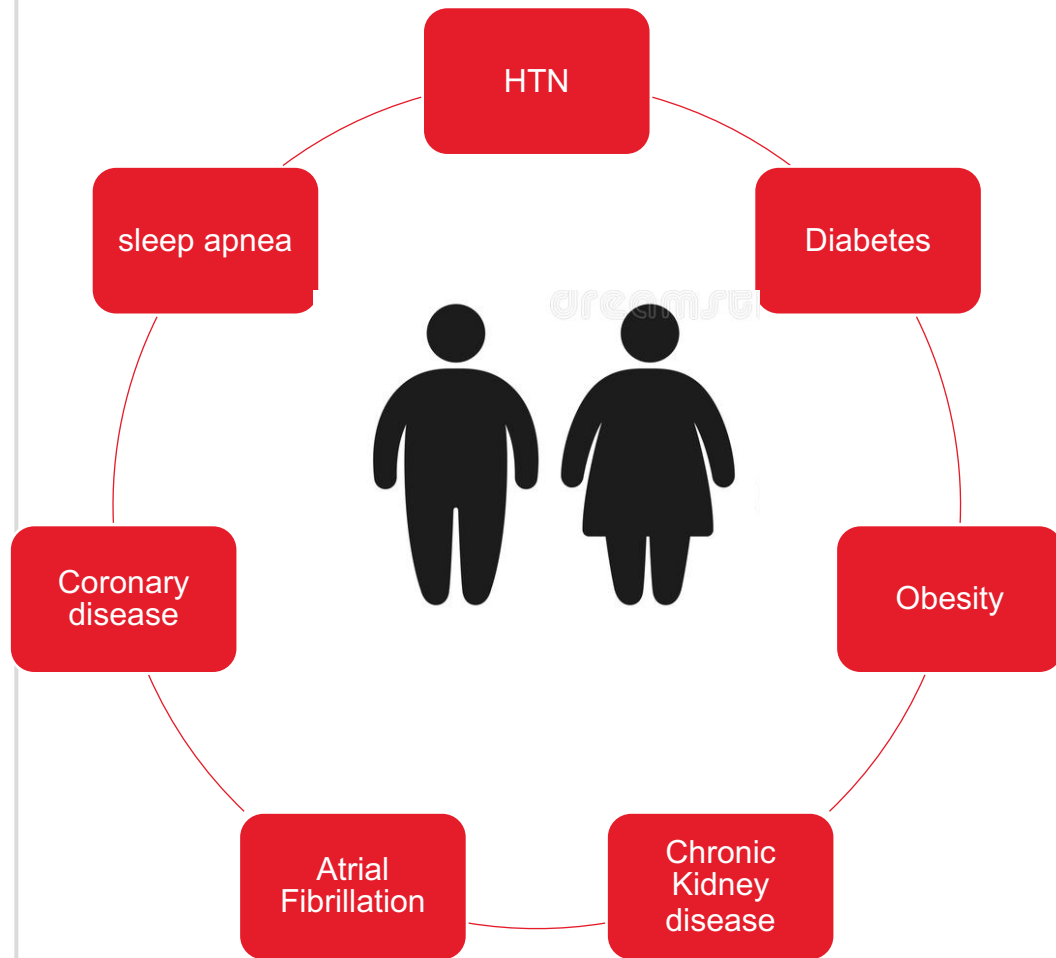
^aSigns may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

^bBNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.

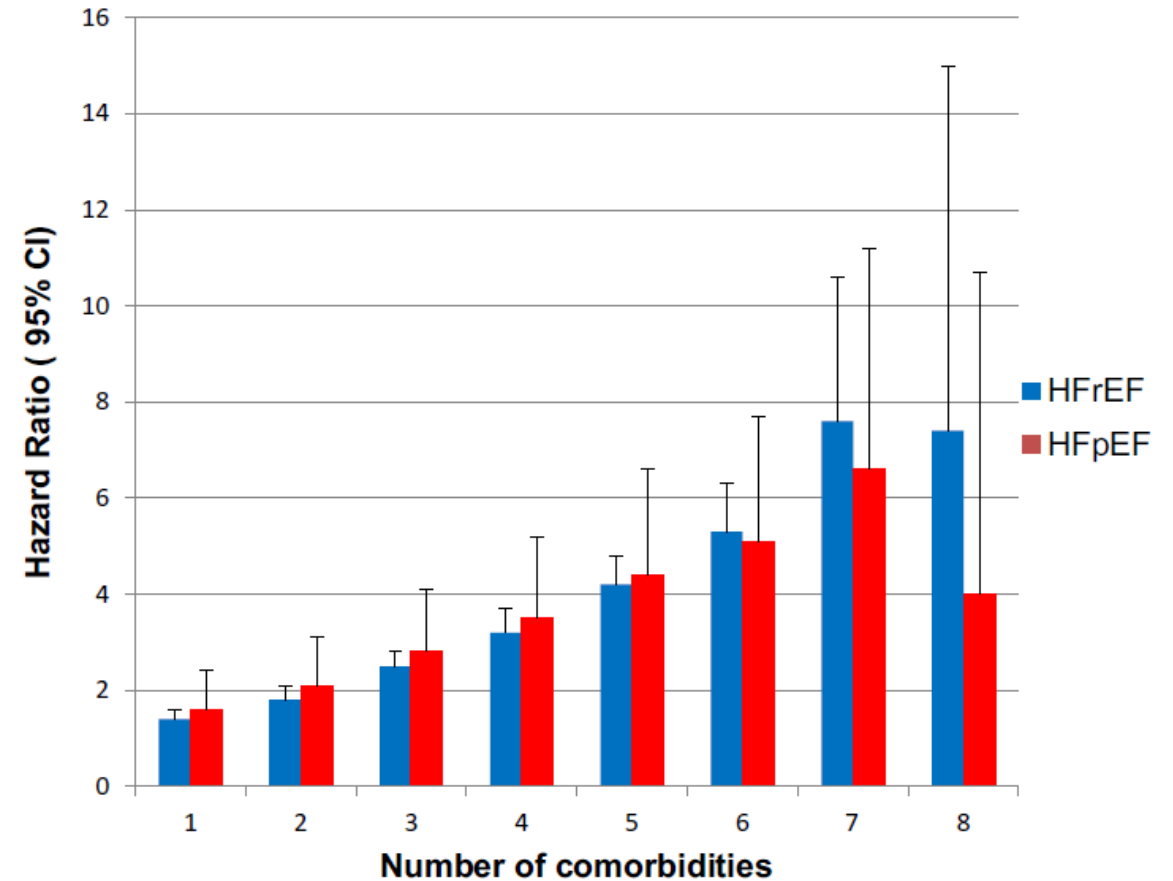
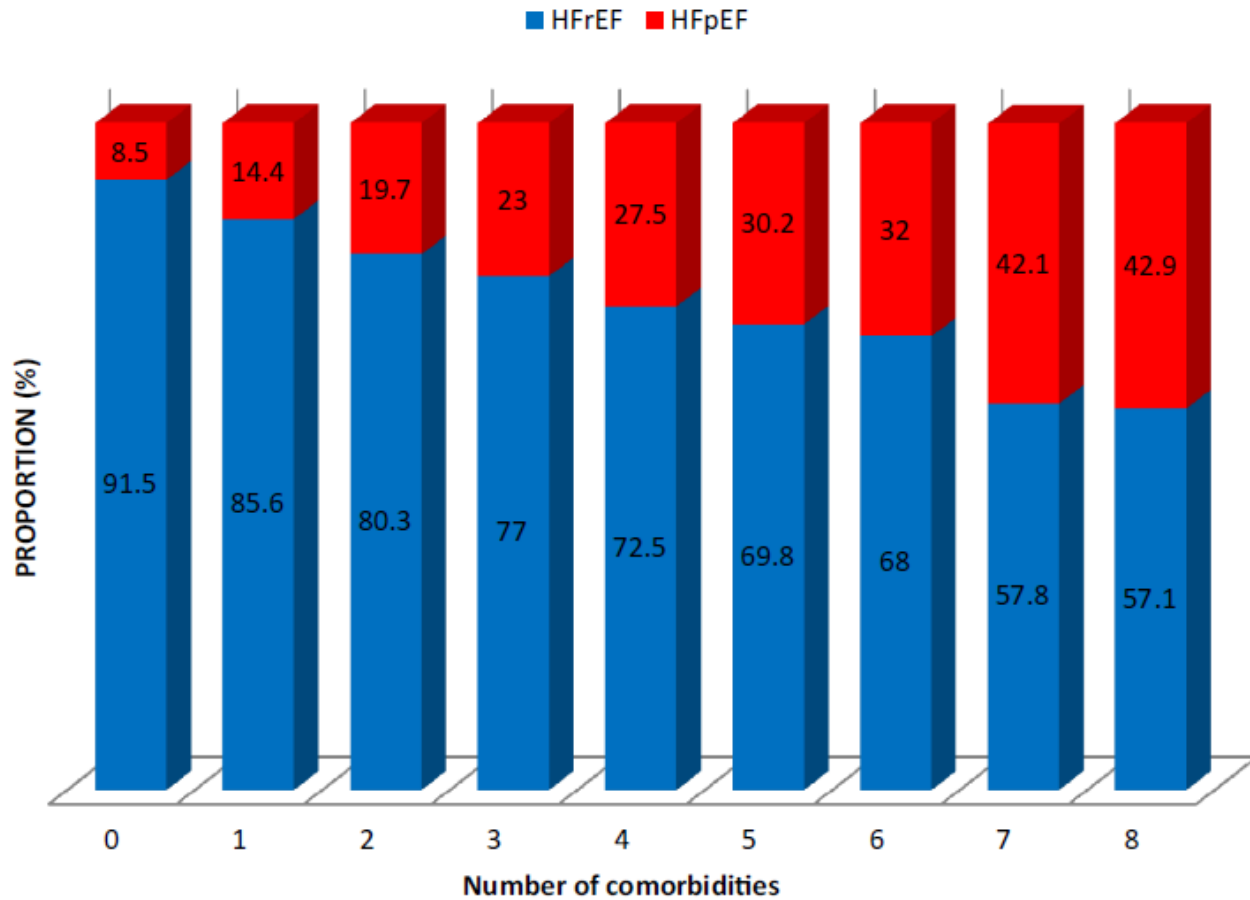


Dunley S. *Nat Rev Cardiol* 2017; 591
Zakeri et al; *Heart* 2018; 104:377-384

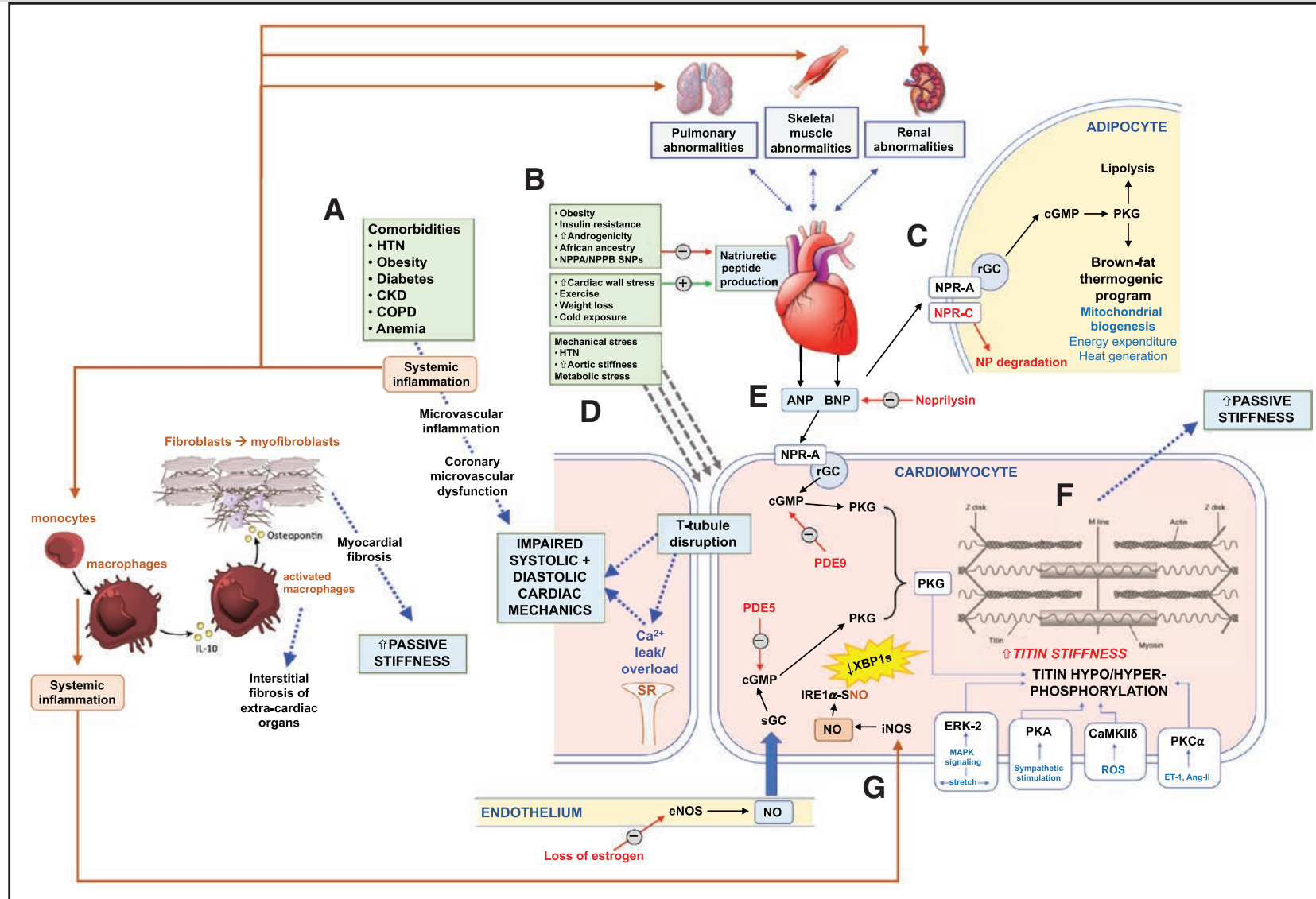
The Co-morbid Collection in HFpEF



Relationship of Comorbid Burden to Outcome in Heart Failure

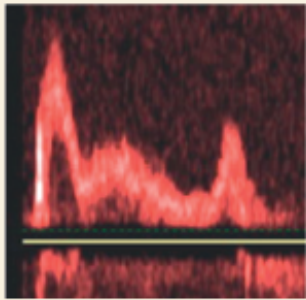


Interplay Between Comorbid Disease and Underlying Molecular Mechanisms in HFpEF

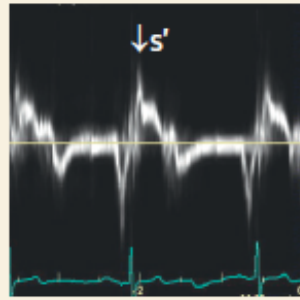


Beyond Diastolic Dysfunction: HFpEF is a Systemic Disease

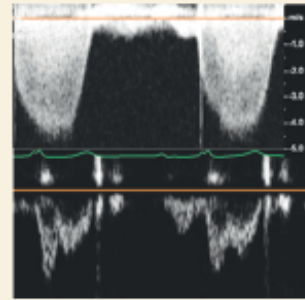
Cardiac and metabolic comorbidities
Ischemia, Atrial Fibrillation, Obesity, Hypertension, Diabetes, Anemia



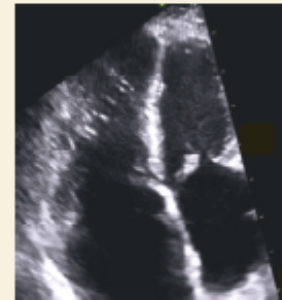
LV Diastolic Dysfunction



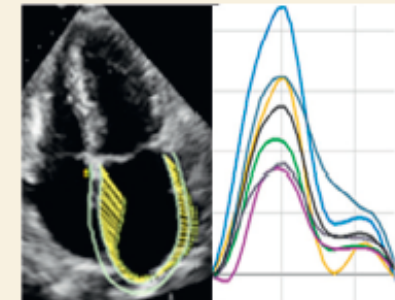
LV Systolic Dysfunction



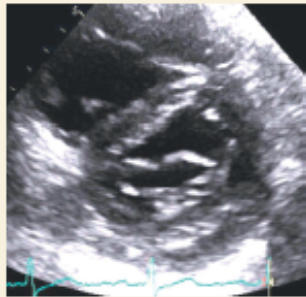
Pulmonary HT



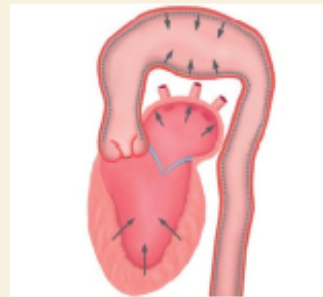
RV Dysfunction & Remodeling



LA Dysfunction



Enhanced DVI



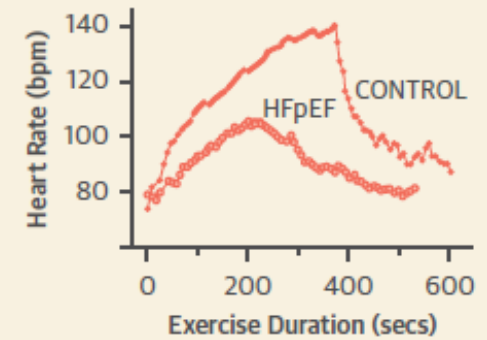
Vascular Stiffening



Microvascular Dysfunction



Peripheral Abnormalities



Chronotropic Incompetence

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

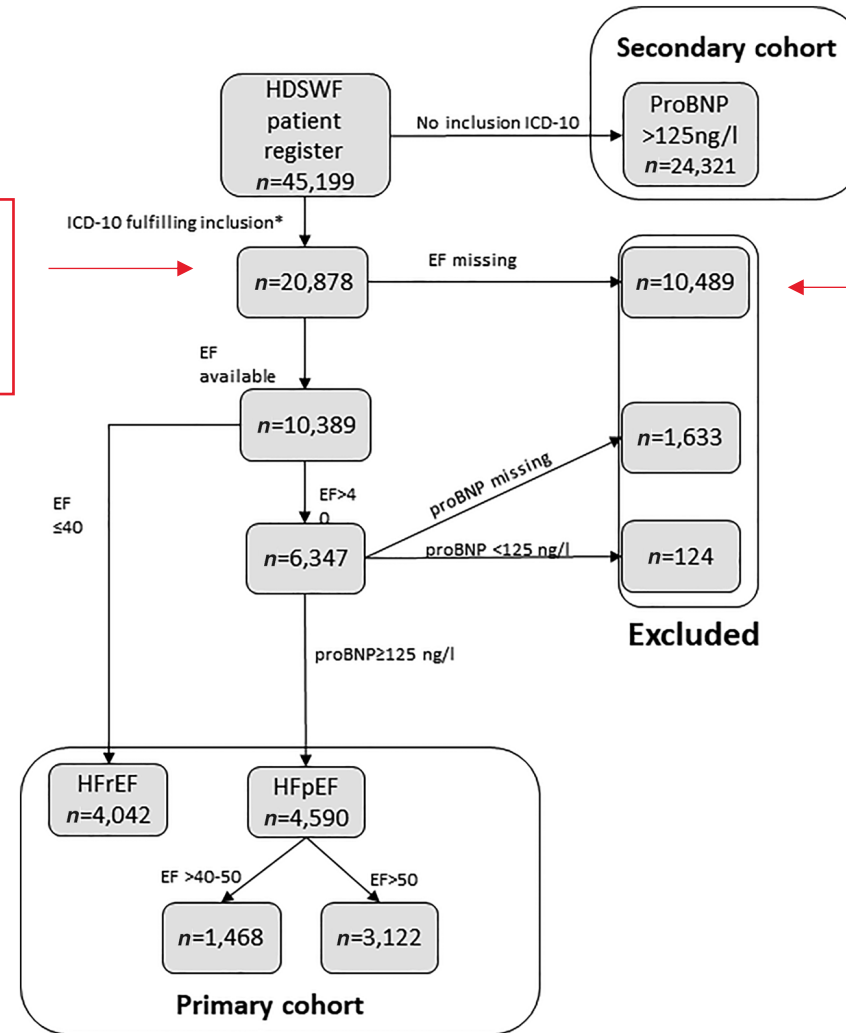
First Author (Ref. #) Year	n	Guideline (Ref. #)	Sensitivity (%)	Specificity (%)	AUC	Indeterminant (%)
Reddy et al. (101) 2018	414 (HFpEF 267)	ESC (105)	57	78	0.67	0
Obokata et al. (102) 2017	74 (HFpEF 50)	ASE/EACVI (5)	34	83	0.65	24
Obokata et al. (102) 2017	74 (HFpEF 50)	ESC (105)	60	75	0.68	0

ASE/EACVI = recommendations for the evaluation of left ventricular diastolic function by echocardiography from the American Society of Echocardiography and the European Association of Cardiovascular 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

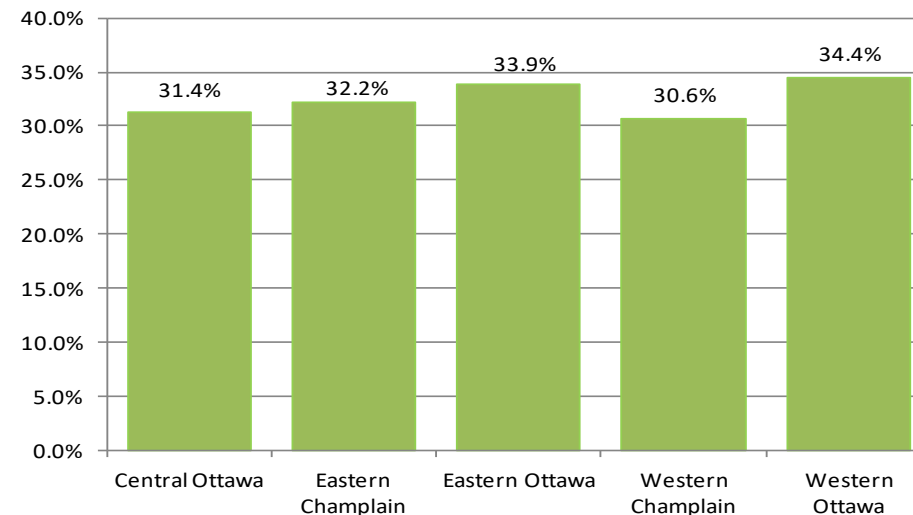


50% of Patients with an ICD code of HF and no EF measurement also had no NTproBNP assessment

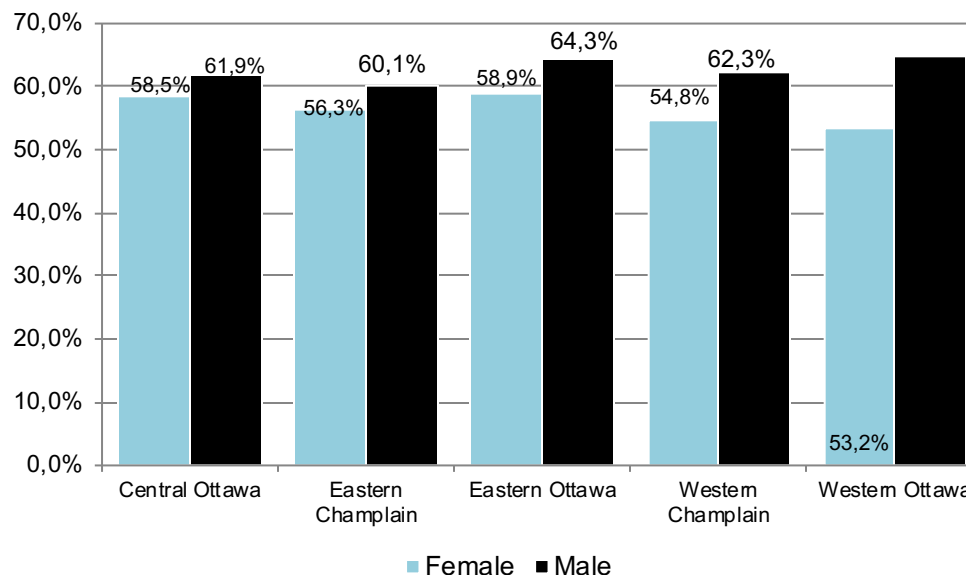
Use of Echocardiography After a HF Diagnosis in the Champlain LHIN

- 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



ECHO within a Year of Diagnosis



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

^aACC = 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.

^bCorresponding 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

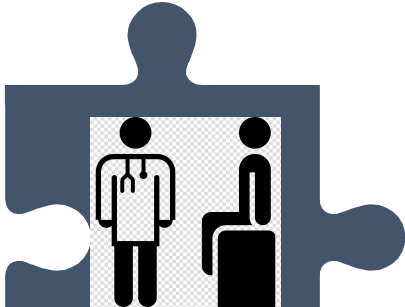
^aHFpEF = heart failure with preserved ejection fraction; LV = left ventricular; RV = right ventricular; RVSP = right ventricular systolic pressure; TTE = transthoracic echocardiography.

^bCorresponding question number in the [Supplemental Appendix](#).

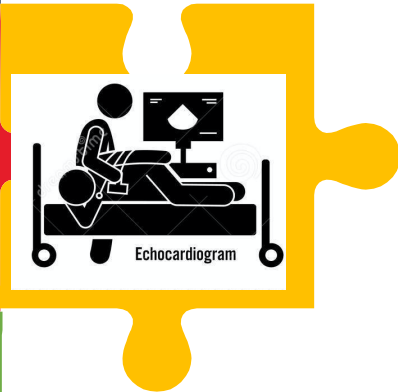
HFpEF Diagnosis: Not for the Faint of Heart....

Clinical History and Physical Exam

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



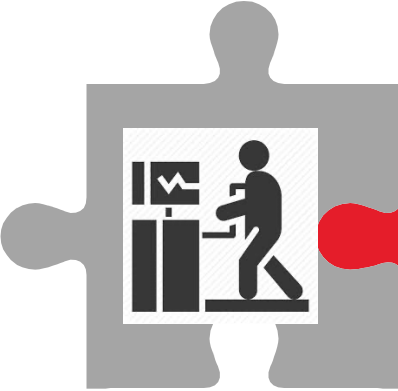
Integrated Diagnostic Approach



Echo

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

Exercise testing



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



Natriuretic peptides

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

H₂FPEF Score: A validated Diagnostic Algorithm for HFpEF

	Clinical Variable	Values	Points
H ₂	Heavy	Body mass index > 30 kg/m ²	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial Fibrillation	Paroxysmal or Persistent	3
P	Pulmonary Hypertension	Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	Doppler Echocardiographic E/e' > 9	1
H₂FPEF score			Sum (0-9)
Total Points			
Probability of HFpEF			

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

HFA-PEEF Algorithm: Consensus Recommendation from HFA and ESC

The HFA-PEEF Algorithm for the Diagnosis of HFpEF

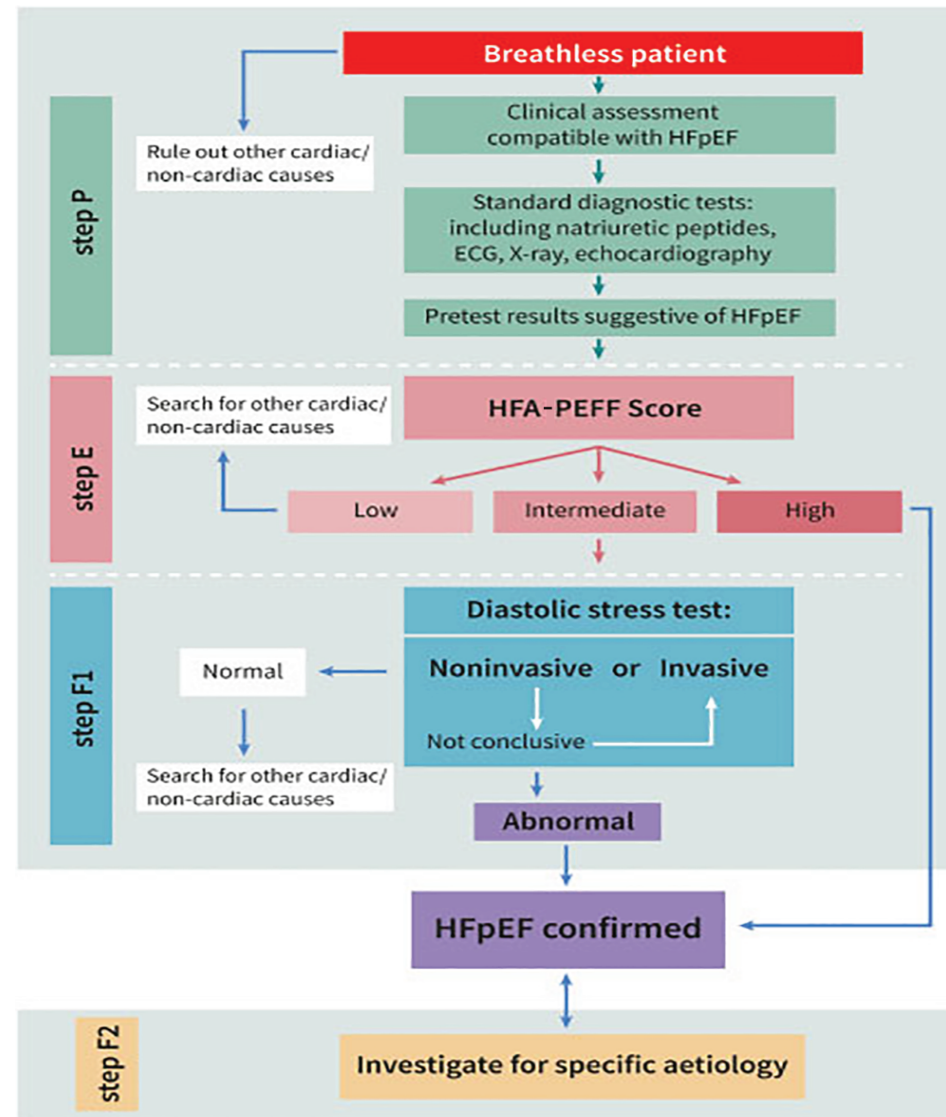
P	Initial Workup (Step 1 (P) : Pretest Assessment)	<ul style="list-style-type: none"> • Symptoms and/or Signs of HF • Comorbidities / Risk factors • ECG • Standard Echocardiography • Natriuretic Peptides • Ergometry / 6 min walking test or Cardiopulmonary Exercise Testing
E	Diagnostic Workup (Step 2 (E) : Echocardiographic and Natriuretic Peptide Score)	<ul style="list-style-type: none"> • Comprehensive Echocardiography • Natriuretic Peptides, if not measured in Step 1
F1	Advanced Workup (Step 3 (F1) : Functional testing in Case of Uncertainty)	<ul style="list-style-type: none"> • Diastolic Stress Test: Exercise Stress Echocardiography • Invasive Haemodynamic Measurements
F2	Aetiological Workup (Step 4 (F2) : Final Aetiology)	<ul style="list-style-type: none"> • Cardiovascular Magnetic Resonance • Cardiac or Non-Cardiac Biopsies • Scintigraphy / CT / PET • Genetic testing • Specific Laboratory Tests

HFA-PEEF score

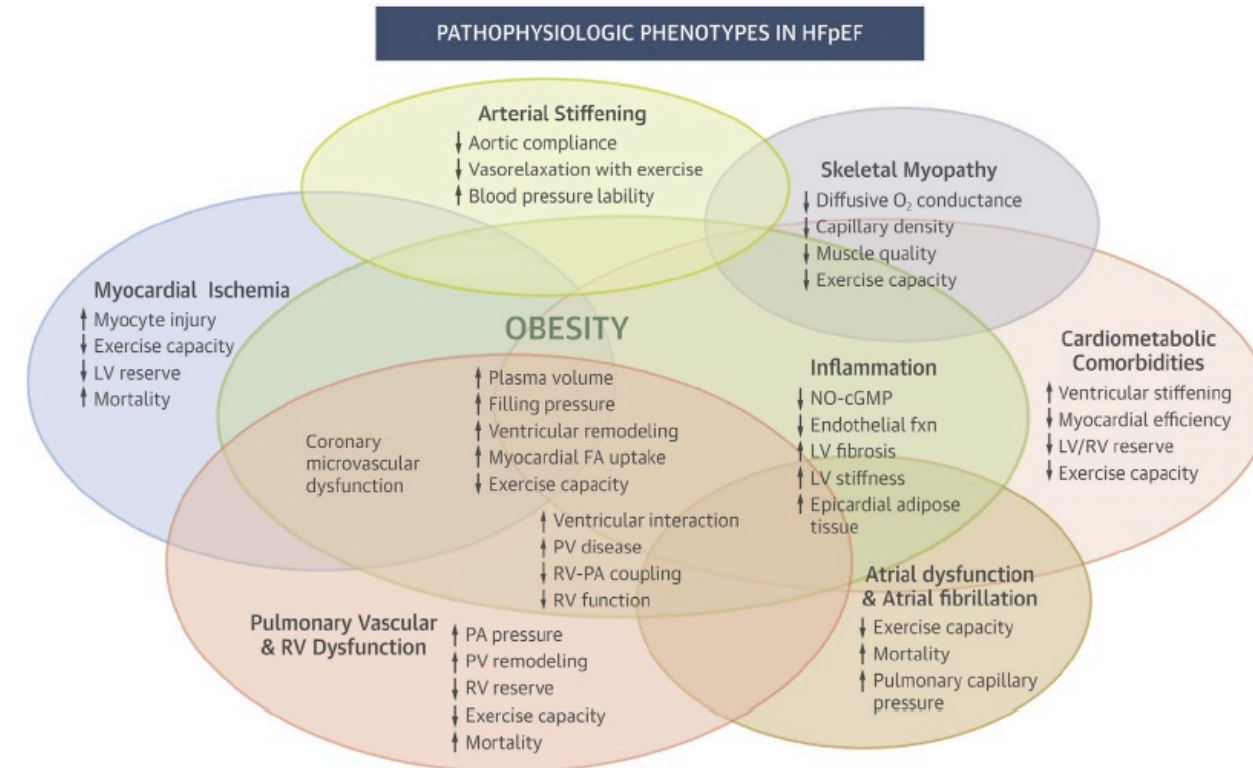
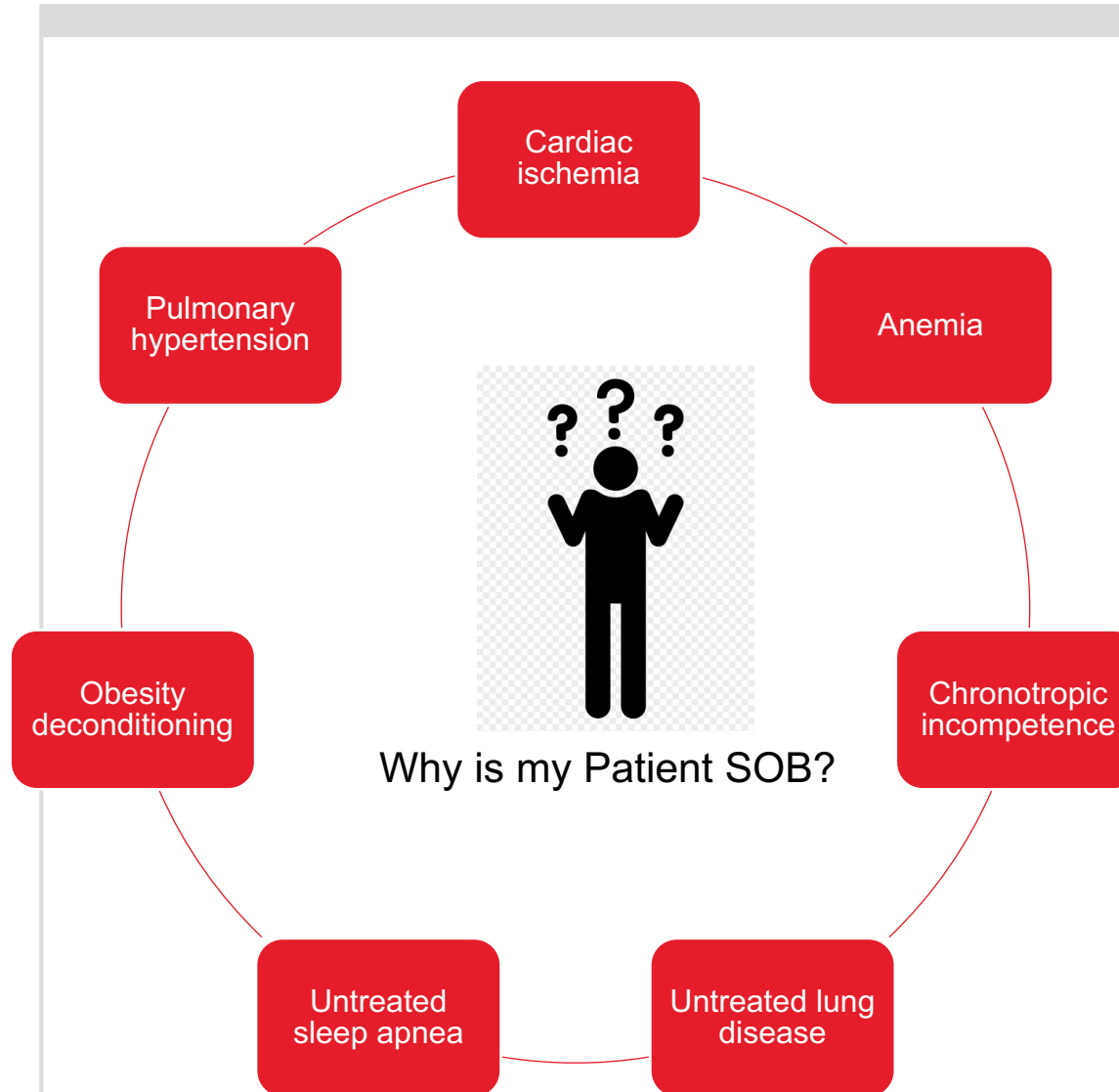
Domains	Major criteria (2 points)	Minor criteria (1 point)
Functional	<ul style="list-style-type: none"> • Septal $e' < 7$ cm/s • Lateral $e' < 10$ cm/s • Average $E/e' \geq 15$ • Velocity of the tricuspid regurgitation > 2.8 m/s (pulmonary artery systolic pressure > 35 mmHg) 	<ul style="list-style-type: none"> • Average E/e' ratio 9–14 • Global longitudinal strain $< 16\%$
Morphological	<ul style="list-style-type: none"> • LAVI > 34 ml/m² • LVMI $\geq 149/122$ g/m² (m/w) and relative wall thickness > 0.42 	<ul style="list-style-type: none"> • LAVI 29–34 ml/m² • LVMI $> 115/95$ g/m² (m/w) • Relative wall thickness > 0.42 • Left ventricular wall thickness ≥ 12 mm
Biomarker (sinus rhythm)	<ul style="list-style-type: none"> • NT-proBNP > 220 pg/ml • BNP > 80 pg/ml 	<ul style="list-style-type: none"> • NT-proBNP 125–220 pg/ml • BNP 35–80 pg/ml
Biomarker (atrial fibrillation)	<ul style="list-style-type: none"> • NT-proBNP > 660 pg/ml • BNP > 240 pg/ml 	<ul style="list-style-type: none"> • 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

HFA-PEEF Algorithm: Consensus Recommendation from HFA and ESC

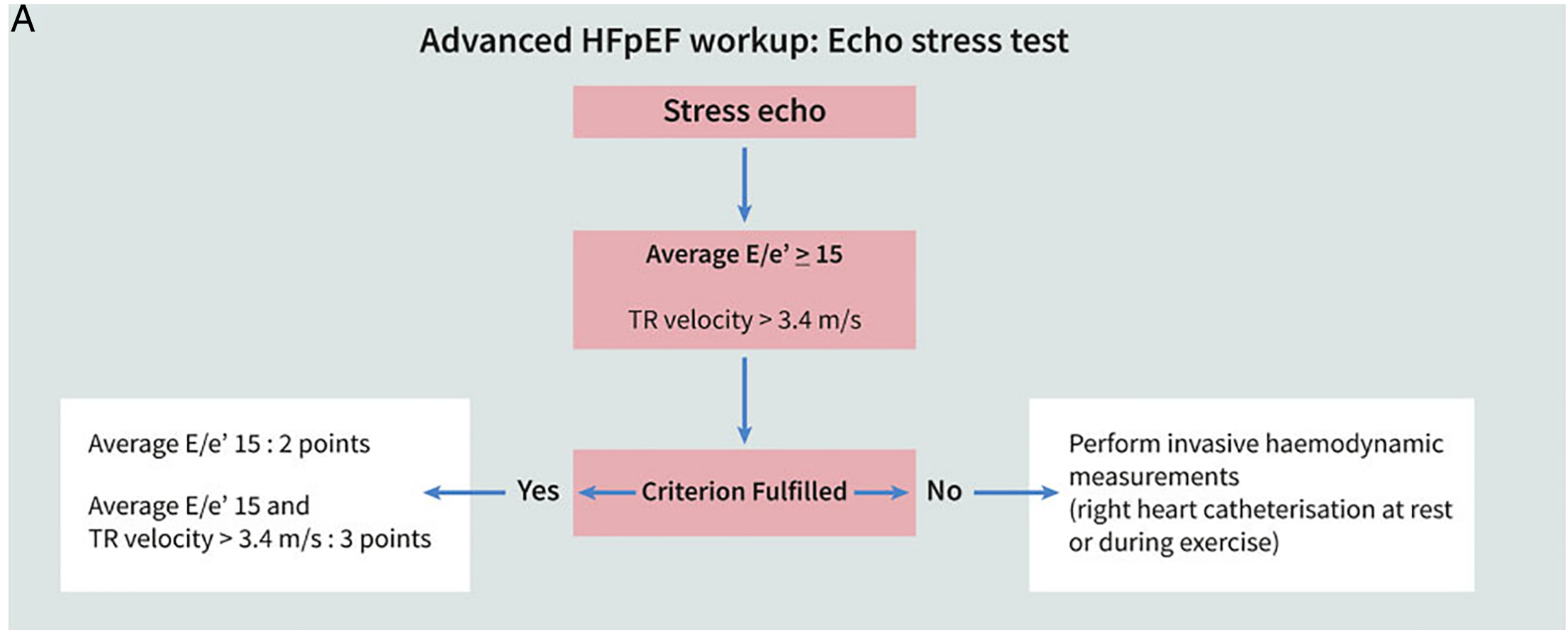


Mimics of HFpEF in a patient with Established or High Probability of HFpEF



Obokata, M. et al. J Am Coll Cardiol Img. 2020;13(1):245-57.

The Role of Noninvasive Exercise Testing



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

Yes

HFpEF

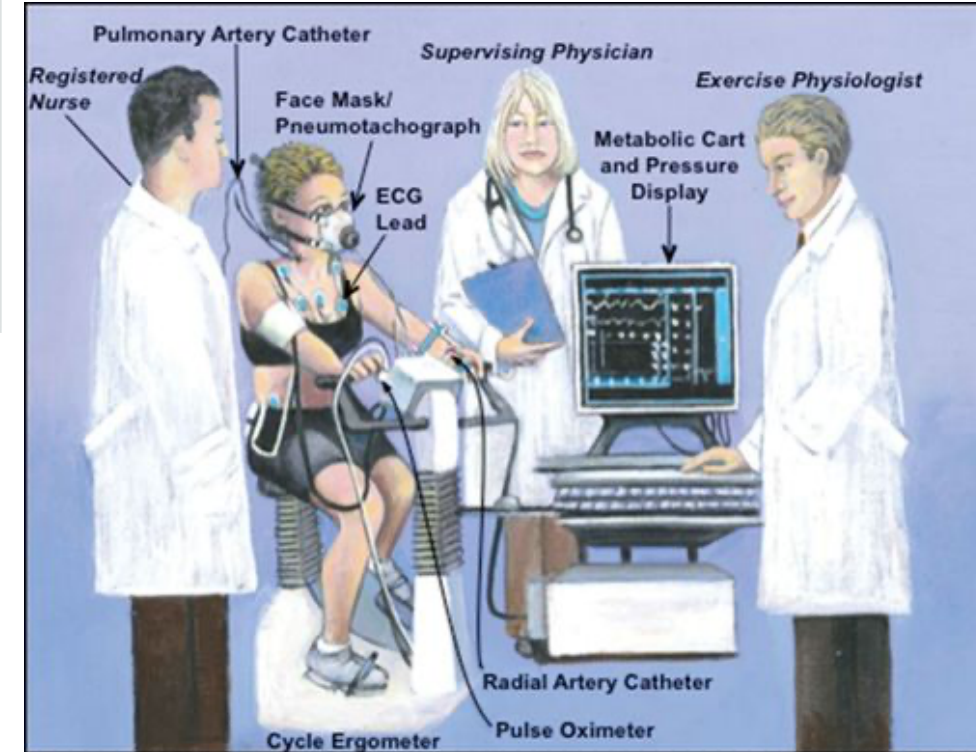
No

Echo Stress Test
or
Invasive Stress Test

Invasive Haemodynamic Measurements during Exercise (invasive Stress Test)

PCPW \geq 25 mmHg

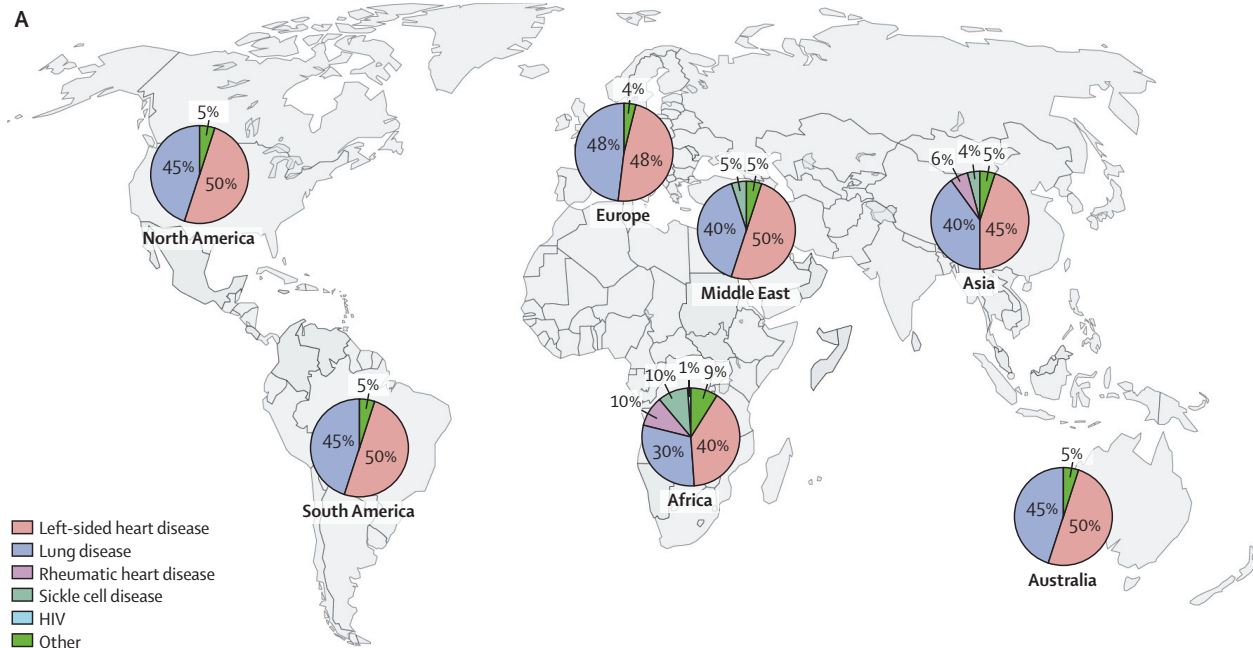
HFpEF



Maron; Circ 2013: 123

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

Pulmonary Hypertension in Left Heart Disease

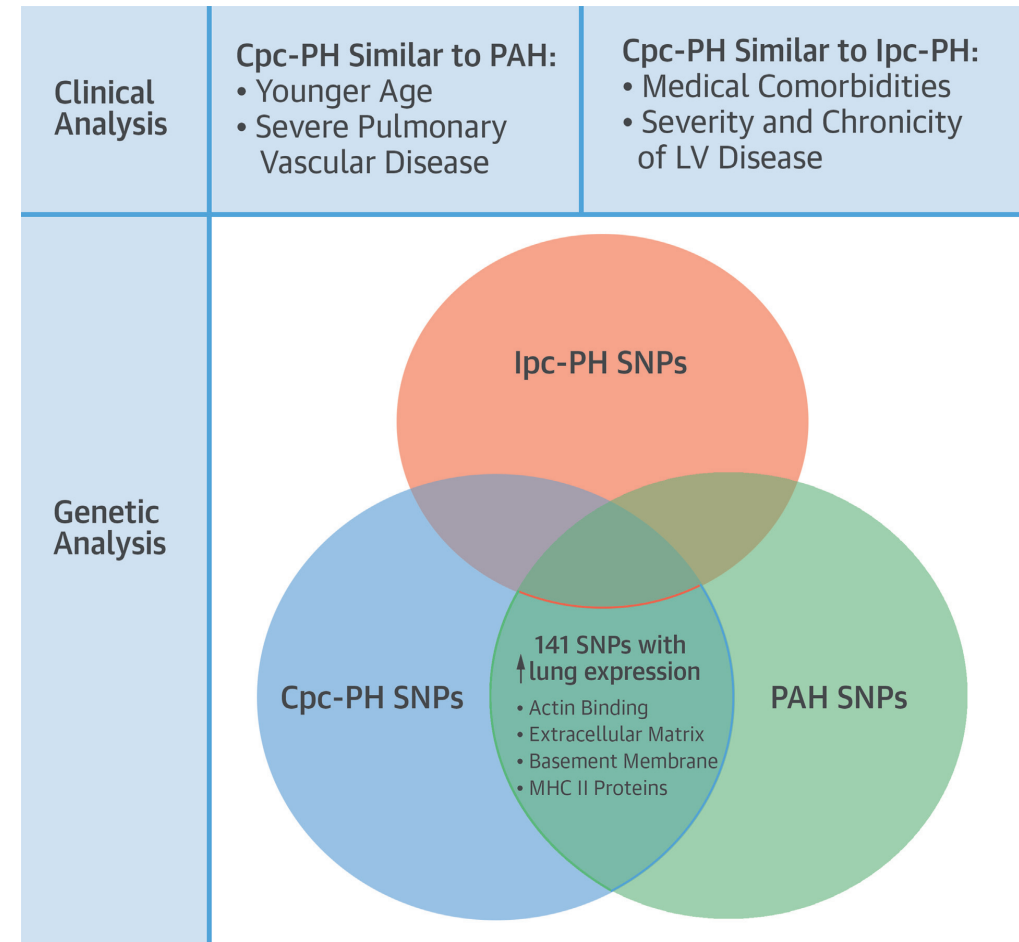
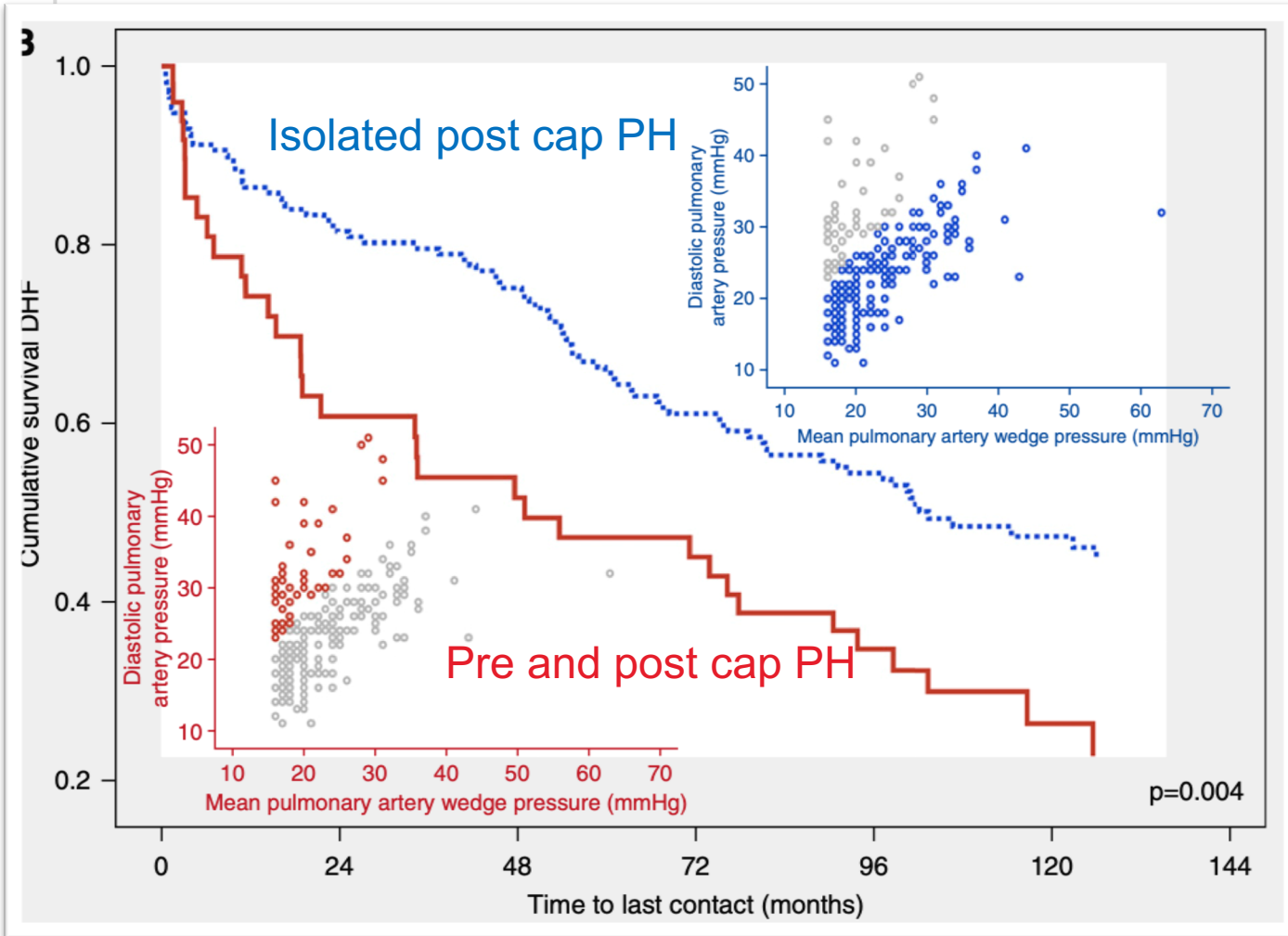


PROPOSED NEW DEFINITIONS OF PH IN LEFT HEART DISEASE:

- 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**

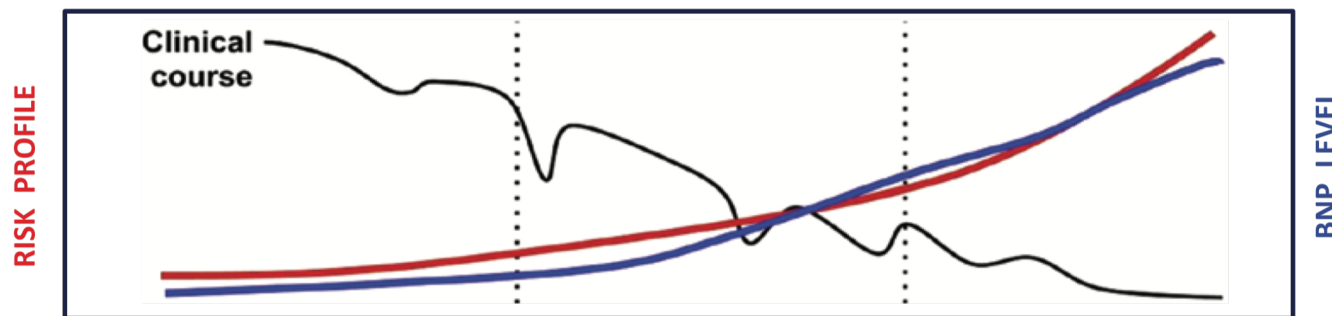
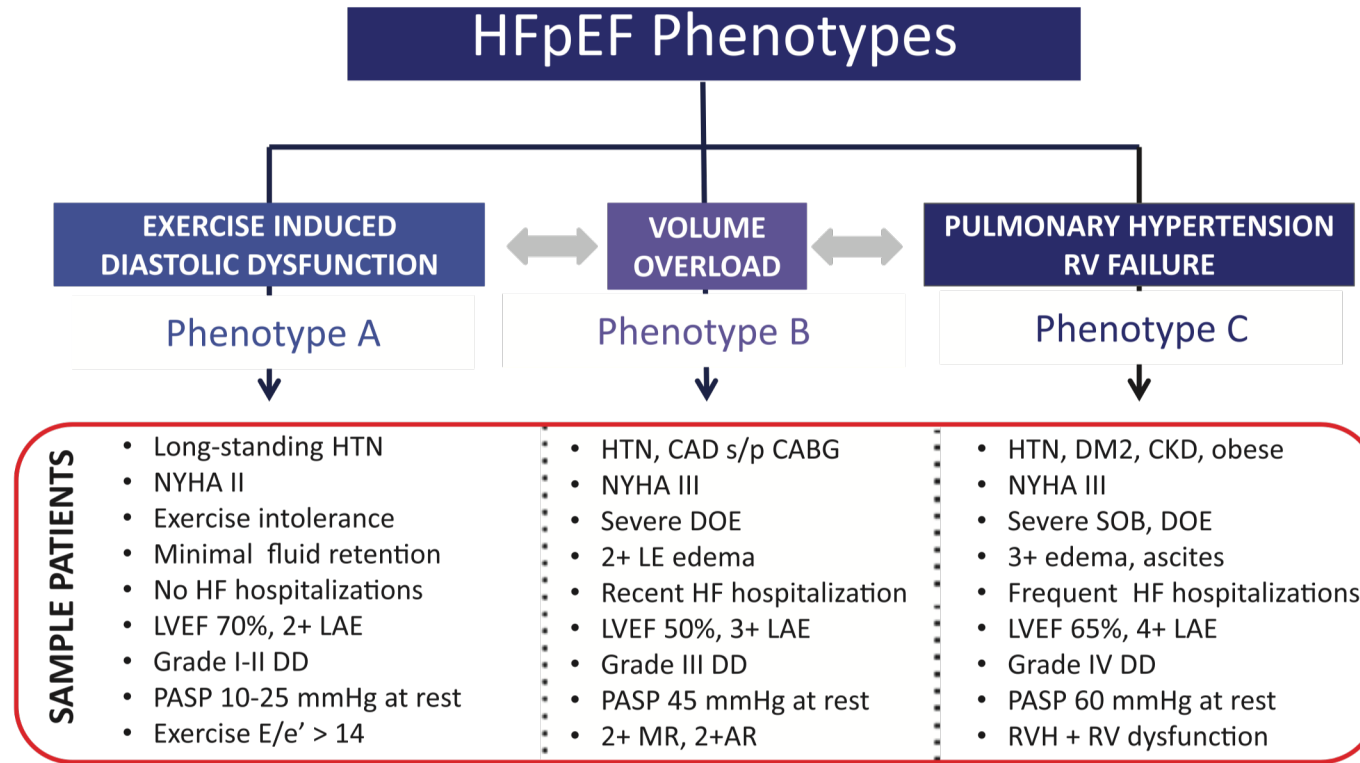
6th World Symposium on PH (Nice 2018)

Combined Pre and Post Capillary PH in HFpEF



Assad, T.R. et al. J Am Coll Cardiol. 2016;68(23):2525-36.

Right Heart Failure Phenotype in HFpEF



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:

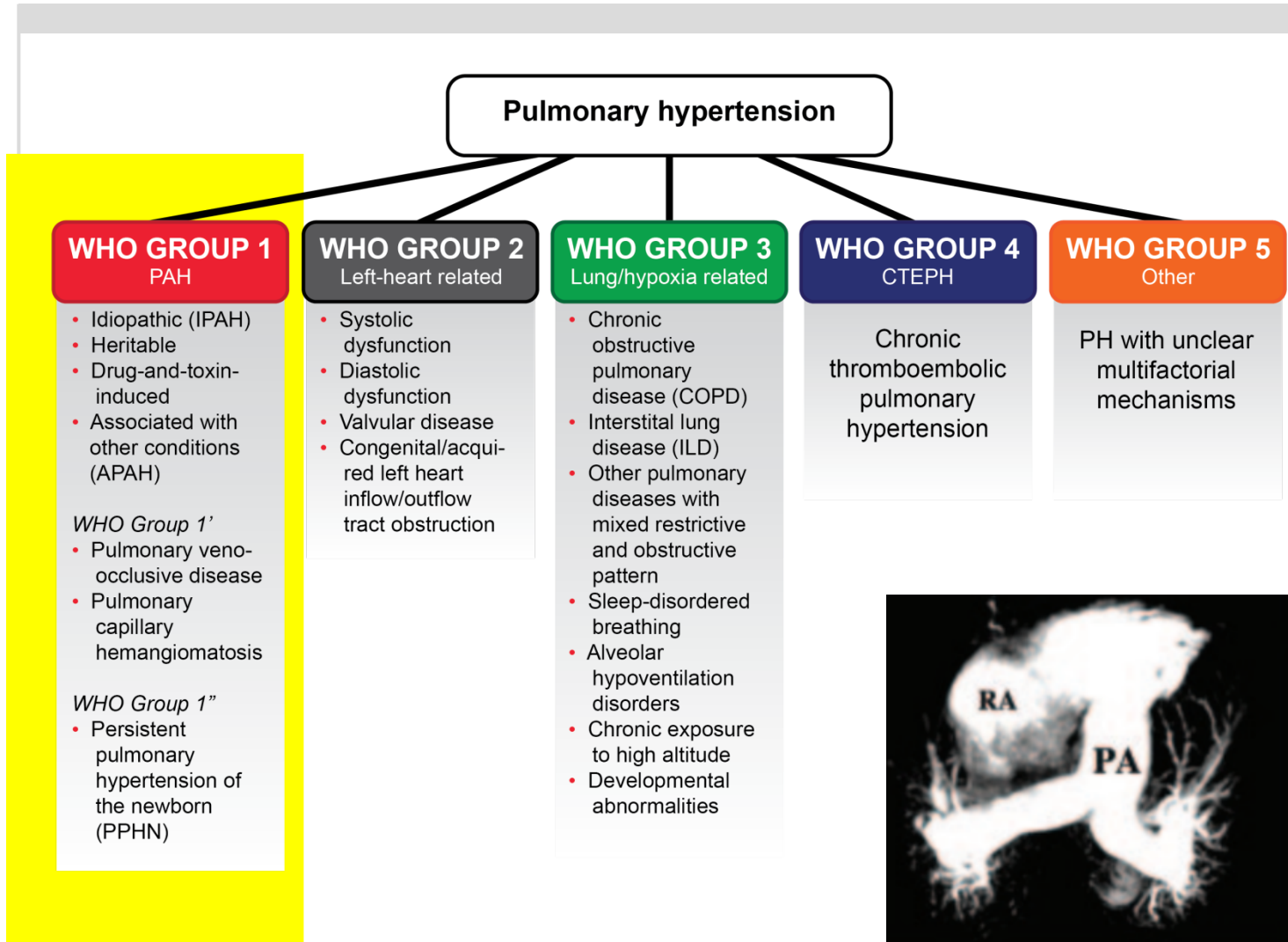
- Small LV cavity
- Increased LV wall thickness
- Sparkling myocardium
- Apical sparing
- Severely reduced tissue doppler
- Pericardial effusion
- Hepatic vein diastolic flow reversal during inspiration



Subsequent Testing:

CMR
Nuclear scintigraphy
Biopsy

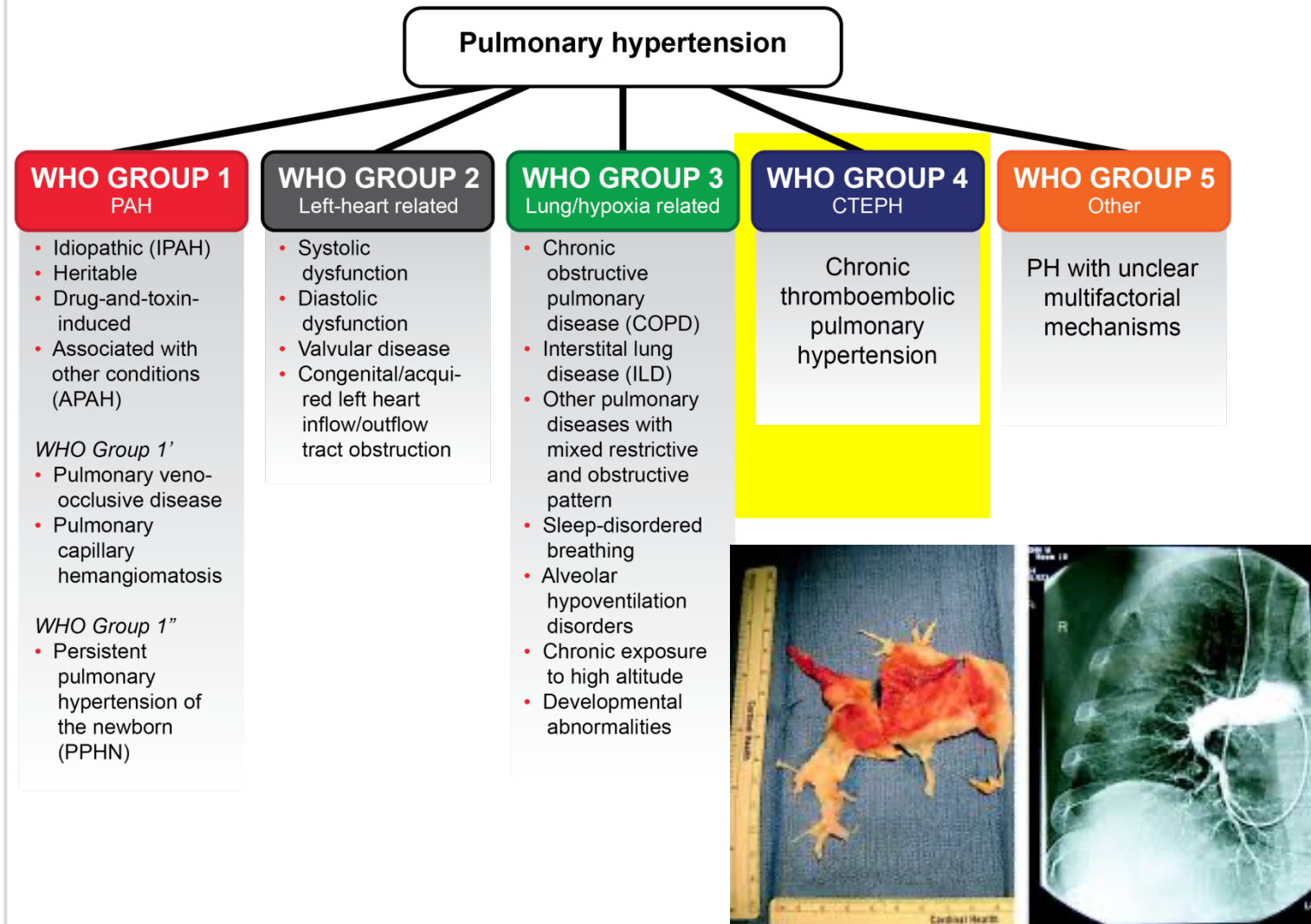
Important “Mimics” of HFpEF: Pulmonary Arterial Hypertension



Pulmonary Arterial Hypertension

Clinical Cues	<ul style="list-style-type: none"> • Evidence of “Associated Conditions” • Variable age distribution
Echo Clues	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • History of DVT/PE • Hypercoaguable state
Echo Clues	<ul style="list-style-type: none"> • No evidence of increased LV filling pressure • Isolated right heart dilatation • PA dilatation • RV outflow tract doppler mid systolic notch
Subsequent Testing	<p>VQ scan CT pulmonary angiogram Right heart catheterization</p>

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