HFpEF Diagnosis: Ruling Out Masqueraders

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1

Disclosures

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- Amgen

Advisory Board/Consultant:

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2

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2022 HF Guidelines - Classification of HF

Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49%Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50%Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Heidenreich PA et al. Circulation. 2022;145:e895–e1032

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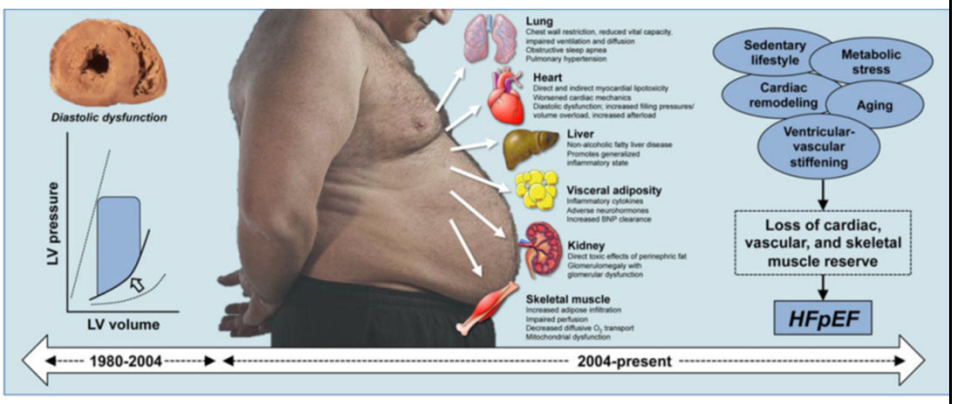
Evolving Phenotype of HFpEF



Shah S. J CV Translational Res. 2017;10(3): 233–244 .

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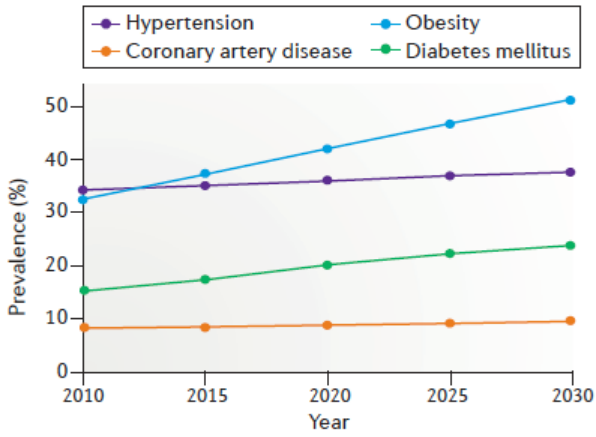
Prevalence of Co-morbidities



Dunlay SM. Nat Rev Card 2017;14:591-601

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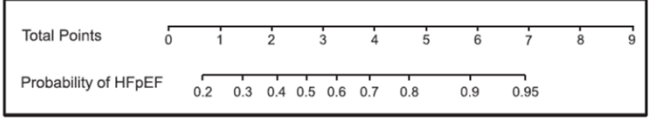
H_2FPEF Score

	Clinical Variable	Values	Points
H_2	Heavy	Body mass index > 30 kg/m²	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
	H_2FPEF score		Sum (0-9)



Reddy Y. Circulation 2018; ;138:861–870.

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HFA-PEFF Scoring Algorithm

	Functional	Morphological	Biomarker (SR)	Biomarker (AF)
Major	septal e' < 7 cm/s or lateral e' < 10 cm/s or Average E/e' ≥ 15 or TR velocity > 2.8 m/s (PASP > 35 mmHg)	LAVI > 34 ml/m² or LVMI ≥ 149/122 g/m² (m/w) and RWT > 0,42 #	NT-proBNP > 220 pg/ml or BNP > 80 pg/ml	NT-proBNP > 660 pg/ml or BNP > 240 pg/ml
Minor	Average E/e' 9 -14 or GLS < 16 %	LAVI 29-34 ml/m² or LVMI > 115/95 g/m² (m/w) or RWT > 0,42 or LV wall thickness ≥ 12 mm	NT-proBNP 125-220 pg/ml or BNP 35-80 pg/ml	NT-proBNP 365-660 pg/ml or BNP 105-240 pg/ml

Major Criteria: 2 points	≥ 5 points: HFpEF
Minor Criteria: 1 point	2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

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Pieske et al. Eur J Heart Fail. 2020 Mar;22(3):391-412.

7

Patient MPJ

- 70 year old AA female referred to JHU HFpEF Clinic for diagnosis and management of HF symptoms
- PMH:
  - Long-standing HTN
  - Paroxysmal AF
  - Obesity (BMI 48)
  - OSA, on CPAP
- Family Hx: Mother died of heart failure, maternal uncle died of SCD.

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HPI

- 2 years of progressive exercise intolerance
- Dyspnea with exertion
- LE edema
- Abdominal fullness in last 6 months
- Bendopnea
- Atypical chest pain, weekly
- 4 HF hospitalizations in the year prior to visit
  - Nuclear stress test: negative for inducible ischemia
- **Medications**: Amlodipine 10 mg daily, Labetalol 400 mg BID, Furosemide 80 mg daily, Warfarin 5 mg daily, Albuterol inhaler PRN

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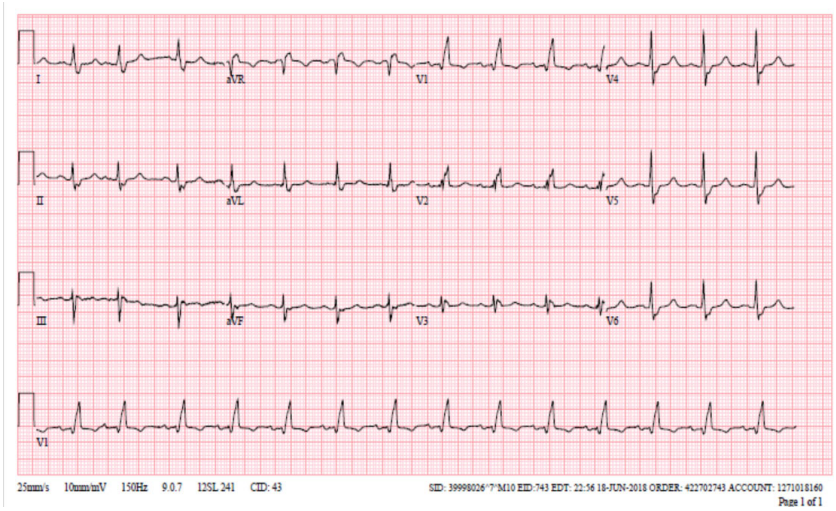
ECG



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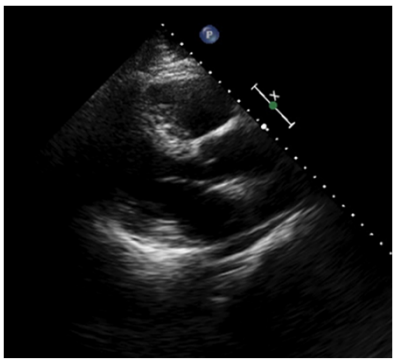

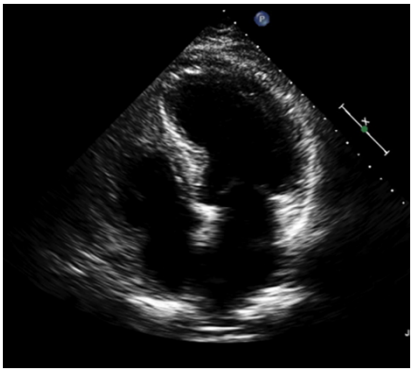

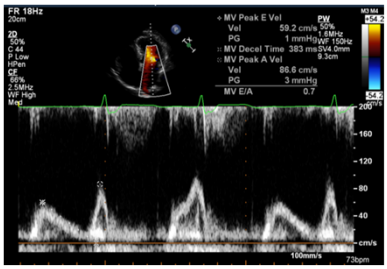

- LVEF 55%, LVEDD 5.4cm
- Impaired relaxation: E/e' 14.1
- Mild to mod LVH, sigmoid septum, IVS 1.4cm, LVPW 1.3cm
- LA diameter 5.3cm
- Normal RV size and function, TAPSE 2.7cm, RVSP 40

11

Labs

- Na 144, K 4.7, creat 1.8
- NT pro-BNP 1002
- Troponin-I 0.09

Differential Diagnosis: HFpEF, Familial CM, ischemic heart disease

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Clues this is HFpEF…

- Clinical signs/sx of HF
- Co-morbidities/risk factors: Age, female sex, HTN, CKD, obesity, OSA
- Preserved LVEF with structural heart disease
- Elevated NTproBNP
- Recent hospitalizations
- "Phenotype": HFpEF-Metabolic Syndrome

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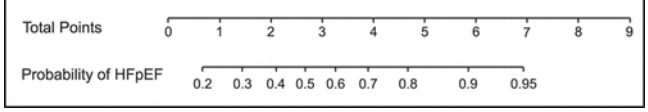

Patient score = 9

Reddy Y, Borlaug B. Circulation. 2018;138:861–870

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14

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Major Criteria: 2 points	≥ 5 points: HFpEF
Minor Criteria: 1 point	2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

Patient score = 6

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15

Additional Labs

- Kappa/Lambda LC: **105.0 / 48.8 = 2.15**
- SPEP: Quantitatively within normal limits. The gamma region is asymmetric with a spike in the gamma region, 0.26 g/dL. INTERPRETATION: The electrophoretic pattern is consistent with monoclonal gammopathy.

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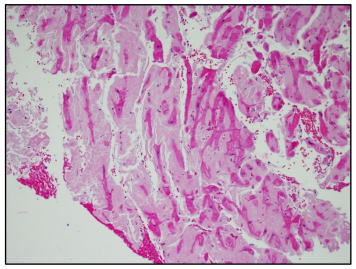
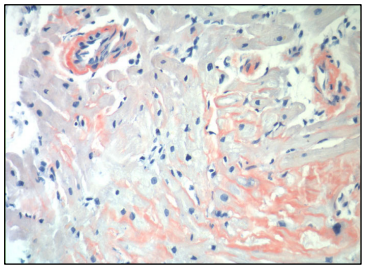
RHC and Endomyocardial Biopsy

- Rest: RA 10, PA 40/20 (mPA 27), PCWP 20
- CO 6.5 L/min; CI 2.8 L/min/m^2; BSA 2.3 m^2



H&E stain



Congo Red Stain

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- Tissue mass spectroscopy: Transthyretin (TTR) amyloidosis
- Referred for genetic testing:
  - Val122Ile – present in 3% of AA, causes TTR amyloid, typically age 65-80 years
  - Phe44Leu – rare, likely pathogenic
- *But what about the serum LC's…?*
  - *Can be elevated in elderly, those with CKD, inflammatory conditions*

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In the real world… JHU HFpEF Clinic

- LVEF ≥ 50% *and*
- Signs and symptoms of CHF *and*
- Objective evidence of a cardiac problem
  - Elevated NTproBNP *or*
  - Structural heart disease (LAE, LVH, DD) *or*
  - Resting elevated PCWP (≥ 15 mmHg) *or* elevated LV end-diastolic pressure (≥ 15 mmHg) *or*
  - Rise in PCWP with exercise to ≥ 25 mmHg
- **Rule out Masqueraders!**

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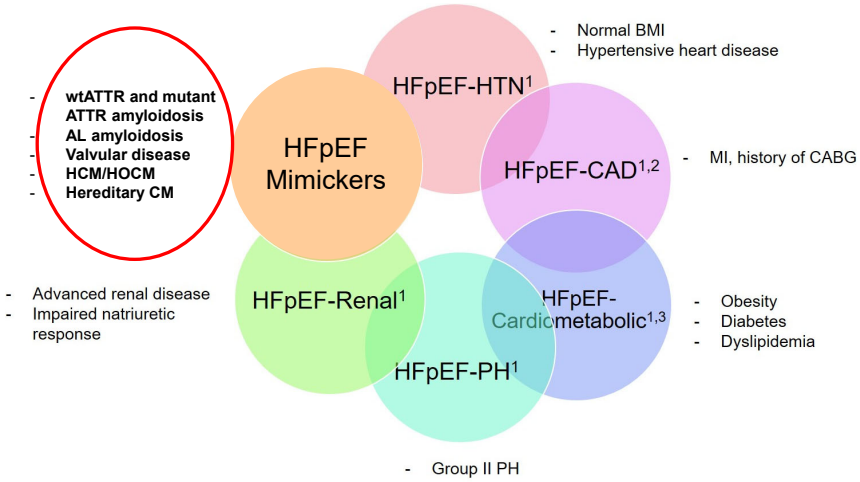
19

HFpEF Clinical Phenotypes



1. Shah SJ et al. *Circulation.* 2016;134(1):73-90. 2. Li J et al. *Cardiovasc Diabetol.* 2016;15:140. 3. Zile MR et al. *Circulation.* 2015;131(14):1247-1259. 4. Mesquita ET et al. *Arg Bras Cardiol.* 2017;109(1):71-80.

20

Histopathology characterization of HFpEF

- N=108 patients referred to JHU HFpEF Clinic from 2014-2018 underwent RHC and EM Bx (IRB protocol), for assessment of histology, compared to HFrEF (n=20) and Controls (n=13)

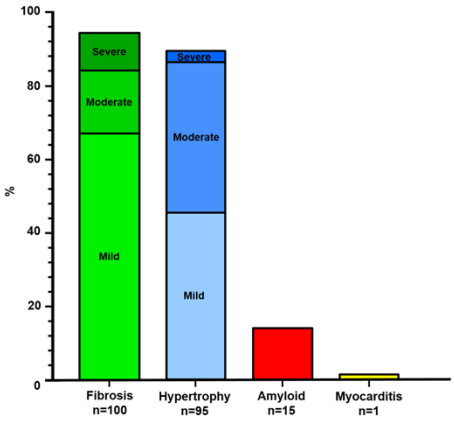


TABLE 4 Summary of CA Types Diagnosed by Endomyocardial Biopsy From a HFpEF Cohort (N = 108)

Type of CA (n = 15)	n (% of HFpEF-CA)
ATTR amyloidosis	11 (73.3)
Wild type	7 (46.7)
Mutant	4 (26.7)
Val122Ile	1 (6.7)
Leu58His	2 (13.3)
Val122Ile and Phe44Leu (presumed to be in trans)	1 (6.7)
Light-chain amyloidosis	3 (20.0)
AA (secondary) amyloidosis	1 (6.7)

ATTR = transthyretin amyloidosis; other abbreviations as in Table 1.

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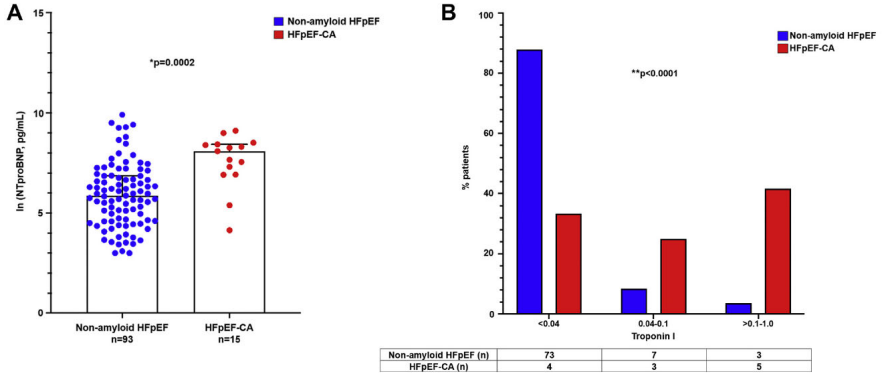
Hahn V, Sharma K. JACC-HF 2020;8:712-24.

21

Biomarkers in HFpEF-CA

FIGURE 5 Serum NT-proBNP and Troponin I in HFpEF-CA Versus Non-Amyloid HFpEF



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Hahn V, Sharma K. JACC-HF 2020;8:712-24.

22

Correlates of HFpEF-CA

TABLE 5 Multivariable Logistic Regression of Correlates of HFpEF-CA

	Odds Ratio	95% CI	p Value
Age ≥ median (66 yrs)	4.58	1.17–17.96	0.03
Female	0.43	0.13–1.43	0.17
Black or African-American race	0.78	0.23–2.68	0.69
Systolic blood pressure (per mmHg)	0.97	0.94–1.00	0.07
Body mass index (kg/m^2)	0.85	0.77–0.94	0.002
Diabetes mellitus	0.32	0.09-1.16	0.08
Glomerular filtration rate (per ml/min/1.73 m^2)	1.00	0.98–1.03	0.70
Coronary artery disease	0.54	0.10–2.97	0.48
LV mass index (per g/m^2)	1.03	1.01–1.06	0.001
Ln (NT-proBNP, pg/ml)	1.93	1.24–2.99	0.003
Troponin I ≥0.04 ng/ml	17.26	3.72–80.10	0.0003

Age, sex, and race were each adjusted for the other 2 variables. Each subsequent variable was adjusted for age, sex, and race in a separate model.
CI = confidence interval; other abbreviations as in Tables 1 and 2.

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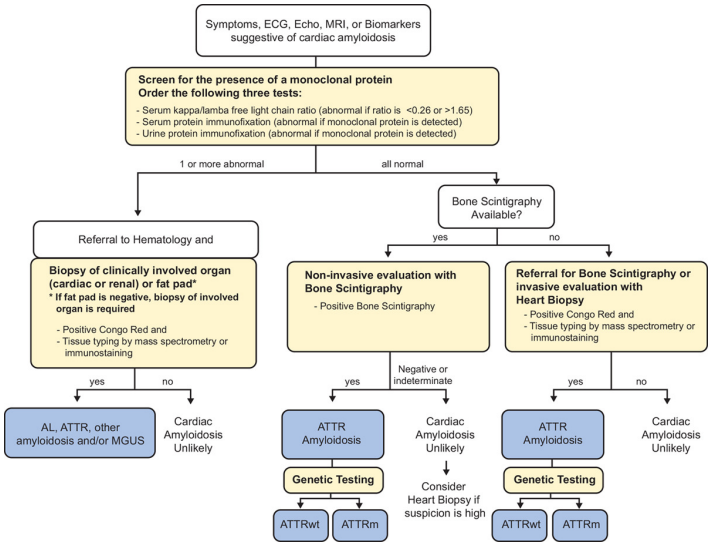
Hahn V, Sharma K. JACC-HF 2020;8:712-24.

23

When to biopsy in HFpEF?



Maurer M et al. Circulation HF. 2019.

24

Other Masqueraders…

- Ischemic heart disease – risk stratify, evaluated for occult CAD
- Hereditary cardiomyopathies – family history, genetic testing
- HCM/HOCM – Echo, MRI, genetic testing, provocative testing
- LVNC – Echo, MRI, genetic testing
- Valvular heart disease – more than moderate-severe
- Sarcoidosis – Clues: heart block, arrhythmias, extra-cardiac disease
- Amyloidosis – as discussed

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Summary

- Predominant phenotype in HFpEF is obesity/ metabolic syndrome
- HFpEF prediction scoring algorithms are helpful, but not perfect
- Need to consider “masqueraders”!
- Evaluate serum light chains/IFE, genetic testing, provocative testing
- May affect treatment plan

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THANK YOU!

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27