HFpEF Masterclasses
In centers of expertise

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FRANCE

7th November 2024 - DAY 1
8th November 2024 - DAY 2

Exercise explorations in HFpEF

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Disclosures

☑ I have the following potential disclosure to report

Affiliation/Financial Relationship	Company
Grant/Research Support	Alnylam
Consulting Fees/Honoraria	Amgen
	AstraZeneca
	Bayer
	Boehringer
	Corvia
	Novartis
	Pfizer
	Vifor

Table 3 Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

Exercise assessments : why?

Diagnosis

- Most patients with HFpEF have symptoms mainly or only on exertion
- Haemodynamic abnormalities such as reduced stroke volume, reduced CO, and elevated LV filling pressures may be absent at rest

Aetiology

- Some causes or comorbidities may require specific managements
  - Ischaemia
  - Chronotropic incompetence
  - Arrhythmias
  - Hypertensive response

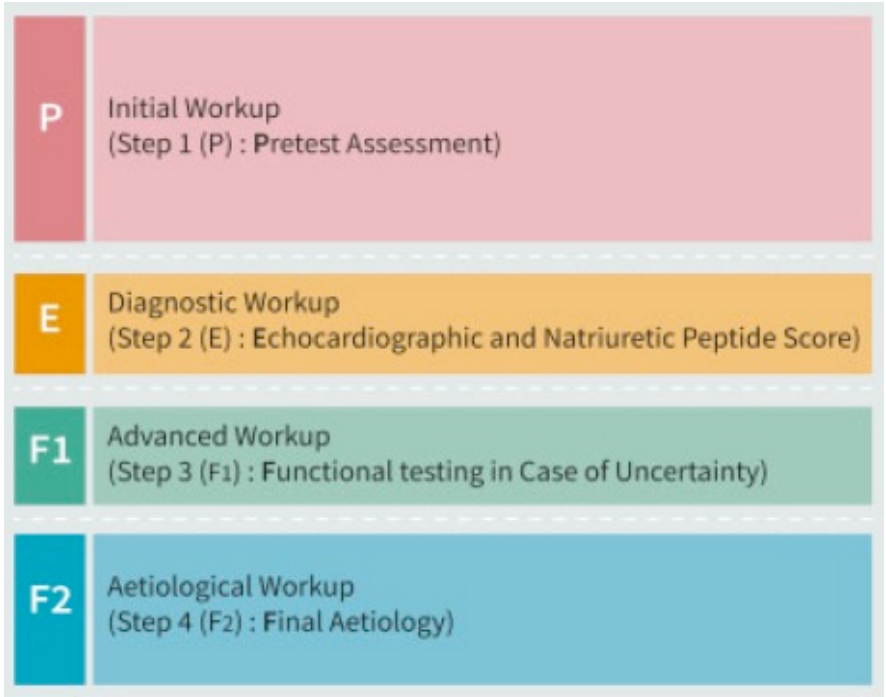
Follow-up

- Effects of treatments
- Detection of decline

Exercise assessments : when?

- The HFA-PEFF diagnostic algorithm

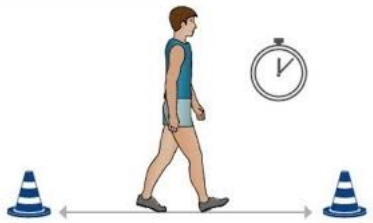
ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–21
doi:10.1093/eurheartj/ehz641

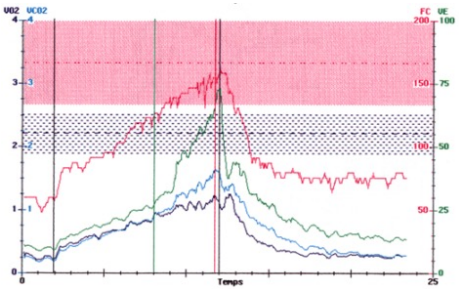


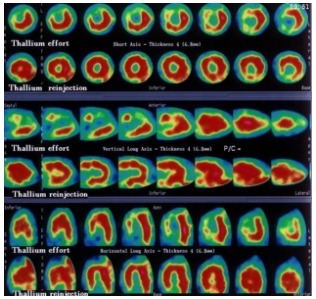
- **Step P : pre-test assessment**
  - « Cardiopulmonary exercise testing provides objective evidence of exercise capacity and may differentiate between cardiac and non-cardiac causes (pulmonary, peripheral) for dyspnoea"
- **Step F1 Functional testing**
  - "The absence of isolated cardiac structural and/or functional abnormalities at rest does not always diagnosis of HFpEF"
  - "Assessment during exercise is recommended, either by non-invasive exercise stress echocardiography or by invasive haemodynamics"
- **Step F2 : aetiological workup**
  - « Aetiological workup may include a standard exercise stress test that may identify myocardial ischaemia, an abnormal blood pressure response to exercise, chronotropic incompetence, or supraventricular and ventricular arrhythmias »
  - "These findings can immediately translate into management strategies, such as anti-ischaemic therapy, improved blood pressure control, removal of bradycardic agents (such as betablockers often prescribed for hypertension), and control of exercise-induced cardiac arrhythmias"

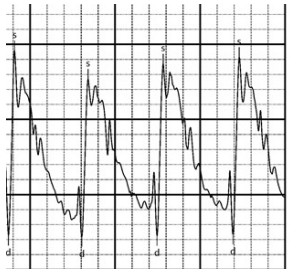
Exercise assessments : how?

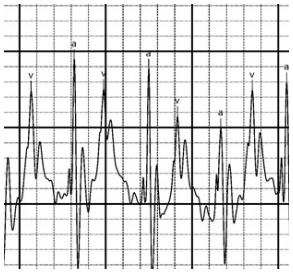
- Six-minute walking test
- Echocardiography (diastolic stress test)
- Cardiopulmonary exercise test (bicycle / treadmill)
- Imaging of ischaemia
- Right heart catheterization











ESC European Society of Cardiology

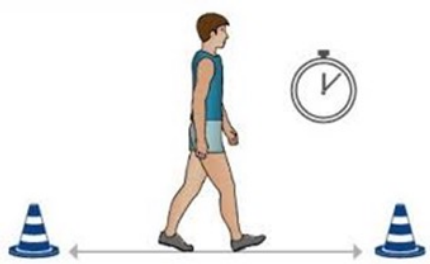
European Journal of Heart Failure (2022) 24, 1327–1345
doi:10.1002/ejhf.2601

POSITION PAPER

Exercise testing in heart failure with preserved ejection fraction: an appraisal through diagnosis, pathophysiology and therapy – A clinical consensus statement of the Heart Failure Association and European Association of Preventive Cardiology of the European Society of Cardiology

Marco Guazzi[1]*, Matthias Wilhelm[2], Martin Halle[3,4], Emeline Van Craenenbroeck[5,6], Hareld Kemps[7,8], Rudolph A. de Boer[9], Andrew J.S. Coats[10], Lars Lund[11], Donna Mancini[12,13], Barry Borlaug[14], Gerasimos Filippatos[15], and Burkert Pieske[16,17,18]

6-minute walk test



- Strengths
  - low cost and ease of use in daily practice
  - may be used for serial therapeutic evaluations
- Weaknesses
  - influenced by extracardiac factors (orthopaedic, neurologic…)
  - limited diagnostic interest

6-minute walk test in HFpEF

Predicts peak VO_2

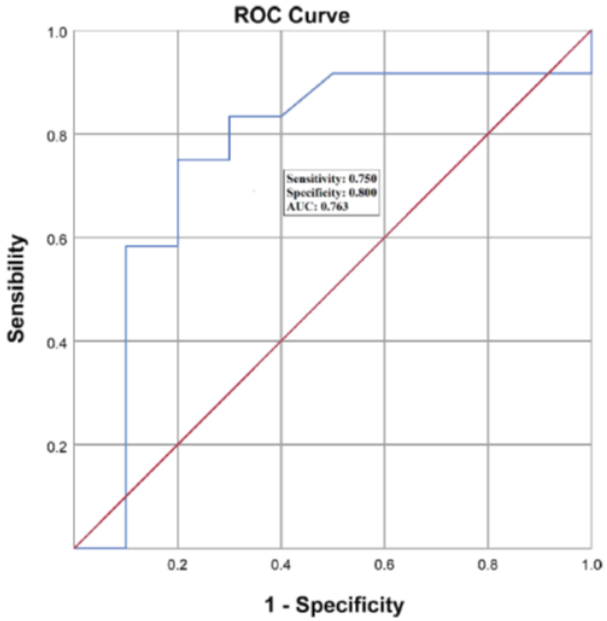
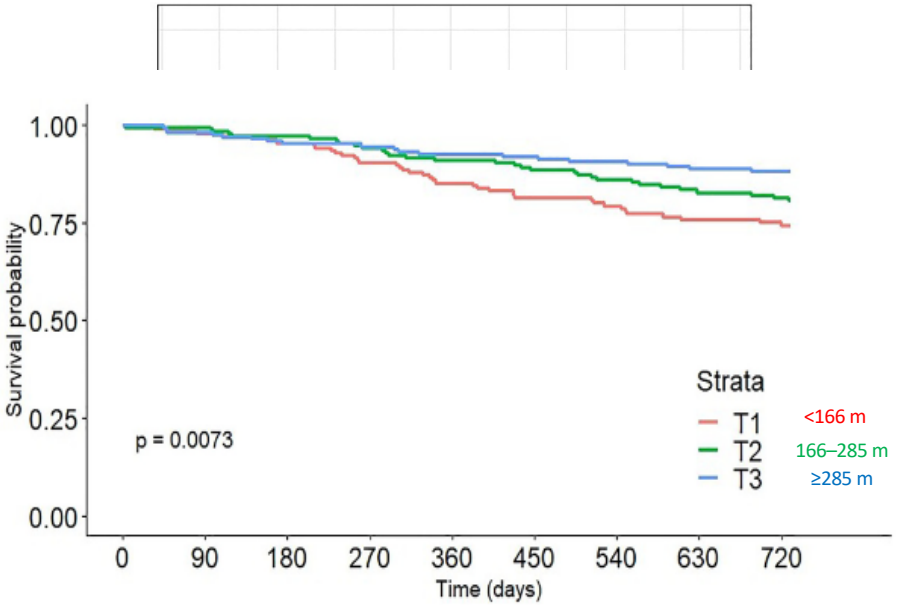


Fig. 1 ROC curve for the comparison of the 6MWT and the CPET to detect severely reduced functional capacity (VO2max<14 mL/kg/min)
Cut-off value 358.50 m. Cavero-Redondo *et al. Sports Medicine - Open* (2024)

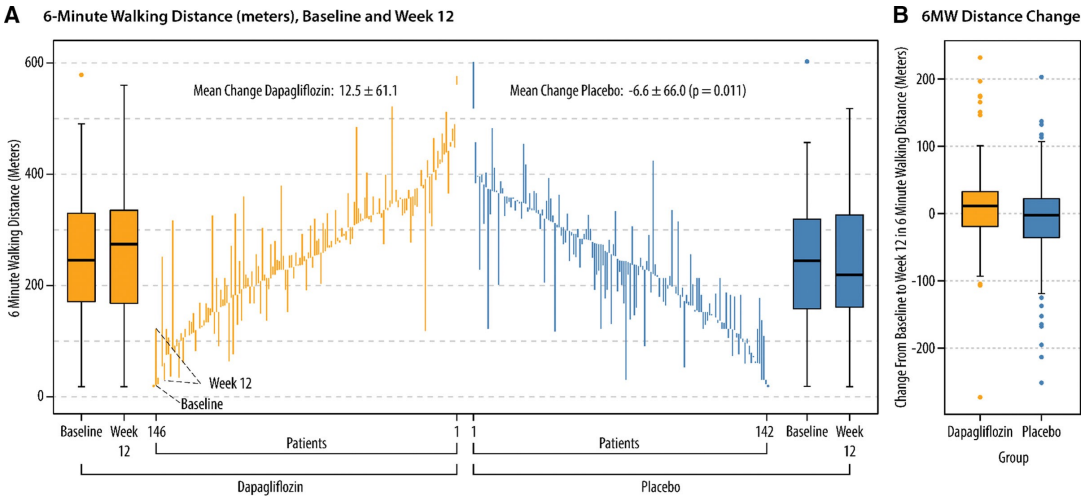
Predicts survival



Fujimoto Y. *International Journal of Cardiology* 379 (2023) 76–81

6-minute walk test in HFpEF : effects of treatments

Effect of Dapagliflozin on 6-Minute Walk Distance in Heart Failure With Preserved Ejection Fraction: PRESERVED-HF



Lewis GD. *Circ Heart Fail*. Nov 2023

Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy

Criteria for disease progression in patients with ATTR-CM

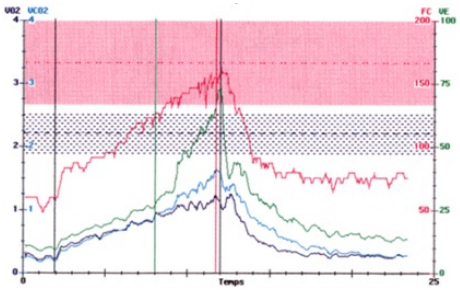
Clinical and functional	Laboratory biomarker	Imaging and ECG
Increase in HF-related hospitalization OR Increase in NYHA class OR Decline in QoL: KCCQ (5–10 pts)/ EQ-5D (10%) OR 30–40 m decline in 6MWT every 6 months	30% increase in NT-proBNP (300 pg/mL cut-off) OR 30% increase in troponin OR Advance in NAC staging scale	Increased LV wall thickness (2 mm) OR Increase in diastolic dysfunction grade OR Change in systolic measurement (≥5% decrease in LVEF; ≥5 mL decrease in stroke volume; ≥1% increase in GLS) OR New onset conduction disturbance

One marker from each domain provides the minimum requirement for assessing ATTR-CM progression

Garcia-Pavia P. *Eur J Heart Fail* (2021) 23, 895–905

Cardiopulmonary exercise test (CPET)

- Strengths
  - gold standard technique to measure aerobic capacity
  - determination of the principle organ system involved in exercise limitation
  - detection of non-cardiac causes of dyspnoea
  - well-established capacity to predict outcomes across the various HF phenotypes



- Weaknesses
  - elderly patients
  - orthopaedic / neurologic / cognitive comorbidities

Causes of exercise limitation in HFpEF

The O2 cascade		HFPEF	
Critical steps	**Organ**	**Limitations in O2 cascade**	**Pathophysiology**
Alveolar ventilation (VA)		alveolar O2 exchange ↓	Pulmonary Reserve ↓ — Ventilatory reserve↓ (O2 alveolar diffusion ↓, respiratory muscle work ↑ Abnormal ventilatory regulation (ergoreflex ↑ , EOV)
Lung diffusion (DL)			
Hb		O2 delivery ↓	Anemia — Iron deficiency
Cardiac output (CO)		O2 delivery ↓	Cardiac reserve ↓ — Cardiac output reserve ↓ (Stroke volume ↓, chronotropic incompetence) Atrial arrythmia's, inducibel myocardial ischemia, dynamic mitral regurgitation Impaired LV filling (myocardial relaxation↓, LA dyfunction) Pulmonary hypertension and RV dysfunction
Vasodilatation		O2 delivery ↓	Vascular reserve ↓ — Arterial vasodilation↓, arterial stifness ↑, abnormal ventriculovascular coupling
Muscle diffusion (Dm)			
Mitochondrial respiration (vmax)		O2 diffusion and/or distraction ↓	Skeletal muscle dysfunction — Structural: capillary density↓, intermuscular fat↑, shift muscle fiber type Functional: anabolism↓, mitochondria size and function↓, oxidative capacity↓, inflammation↑

Dyspnoea on exertion

Fick principle
$VO_2 = CO \times (a - v\ O_2)$

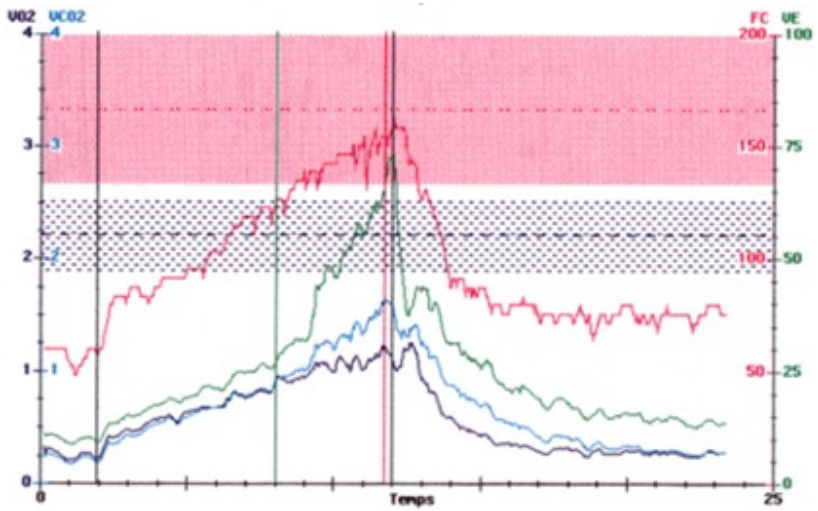
Guazzi M. *Eur J Heart Fail* 2022

Causes of exercise limitation in HFpEF

- Cardiac causes
  - Impaired myocardial performance and cardiac energetics
  - Chronotropic incompetence (33-77%)
  - Left atrial myopathy and atrial functional mitral regurgitation
- Systemic arterial and venous system abnormalities
  - Vascular stiffening
  - Endothelial dysfunction and impaired vasodilation
  - Impairment in the venous capacitance
- Abnormal lung mechanics, pulmonary hypertension and vascular disease
- Muscle and mitochondrial pathology
- Comorbidities
  - Anaemia and iron deficiency
  - Obesity

Cardiopulmonary exercise test

- Prerequisite for interpretation
  - Exercise duration 8-12 min
  - Respiratory exchange ratio $\geq$ 1.1
  - accurate detection of ventilatory thresholds and slopes
- Ventilatory limitation
  - reduction in breathing reserve (<15%)
- Pulmonary vascular involvement
  - significant elevation in VE/VCO_2 slope
  - well-established prognostic role of VE/VCO_2 slope (>40)
- Typical cardiac limitation
  - Reduced O2 pulse (VO_2/HR)
  - Chronotropic incompetence



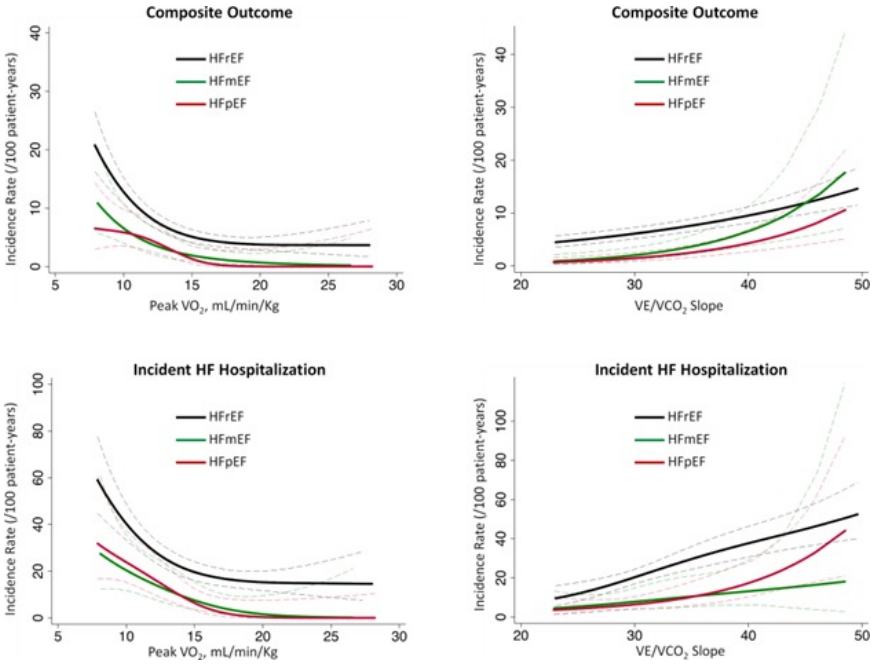
- Diagnostic value
  - peak VO_2 <14 ml/kg/min : HFpEF very likely
  - peakVO_2 >20 ml/kg/min : HFpEF very unlikely
  - 14–20 ml/kg/min : further testing with stress echo or exercise cath is required. (Guazzi M. European Journal of Heart Failure (2022) **24**, 1327–1345)

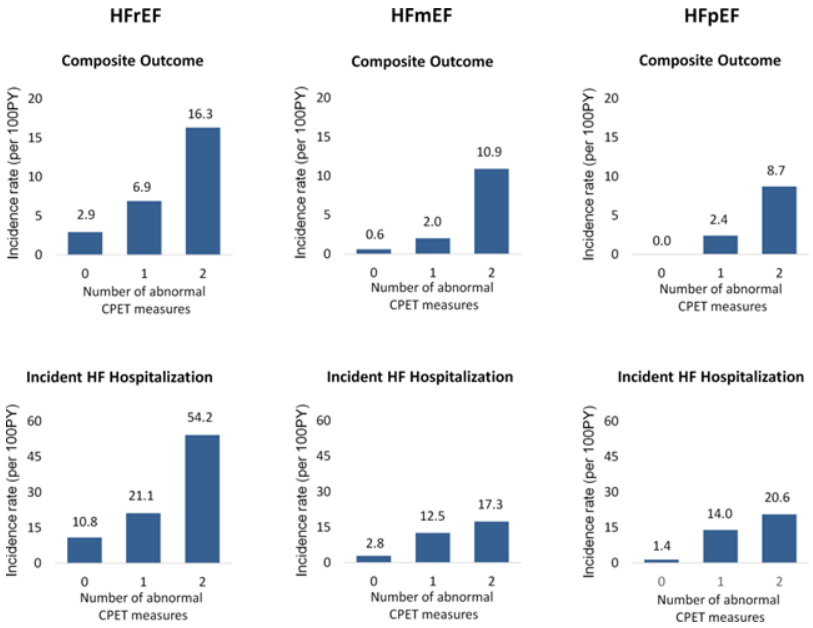
Journal of the American Heart Association
Volume 6, Issue 11, November 2017
https://doi.org/10.1161/JAHA.117.006000

ORIGINAL RESEARCH

Prognostic Value of Cardiopulmonary Exercise Testing in Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction

Wilson Nadruz, Jr, MD, PhD; Erin West, MSc; Morten Sengeløv, MB; Mário Santos, MD; John D. Groarke, MBBCh, MPH; Daniel E. Forman, MD; Brian Claggett, PhD; Hicham Skali, MD, MSc; Amil M. Shah, MD, MPH





Abnormal CPET measures

- Peak VO_2 <14 mL/kg/min
- VE/VCO_2 slope >30

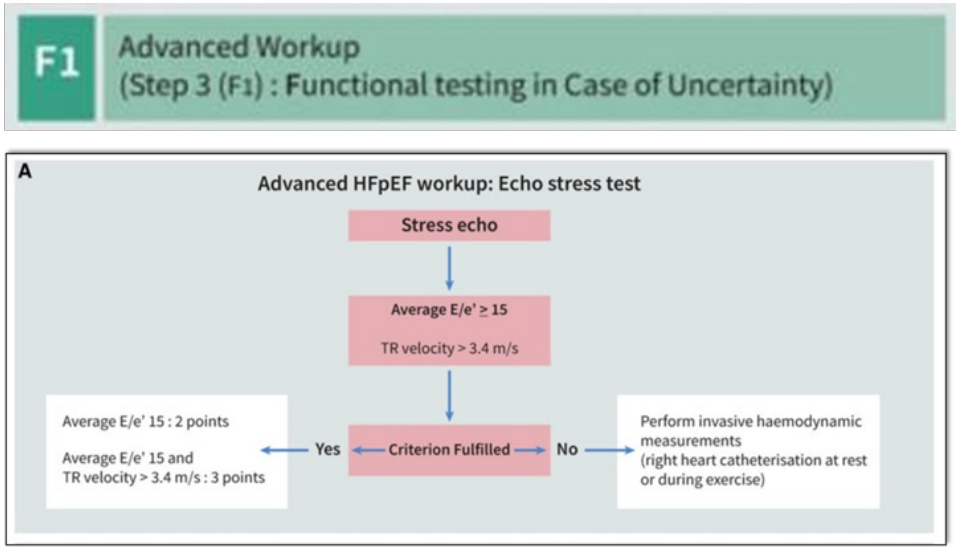
Cardiopulmonary exercise testing variables provided greater risk discrimination in HFpEF than HFrEF

Exercise echocardiography

- Step 3 (F1) of the HFA-PEFF recommendations
  - Patients with HFpEF may present with typical signs and symptoms, but without increased levels of NT-proBNP or resting LV diastolic impairment

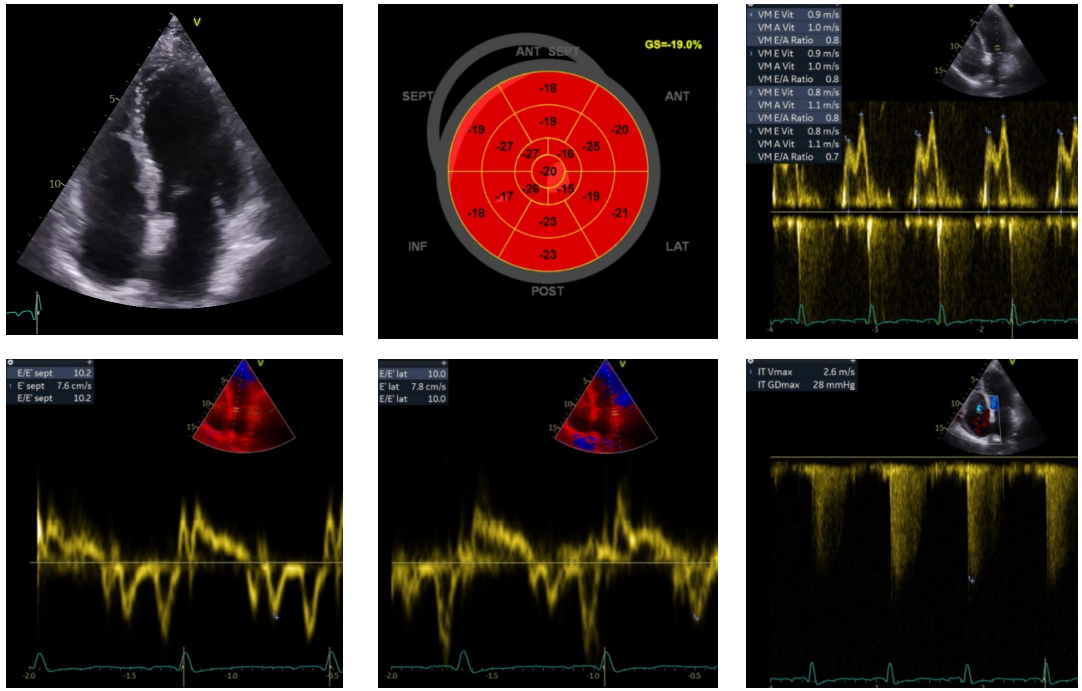
- Strengths
  - allows the study of LV filling adaptations/maladaptations during dynamic exercise
  - Simple measurements
    - Average E/e' ratio
    - TR velocity

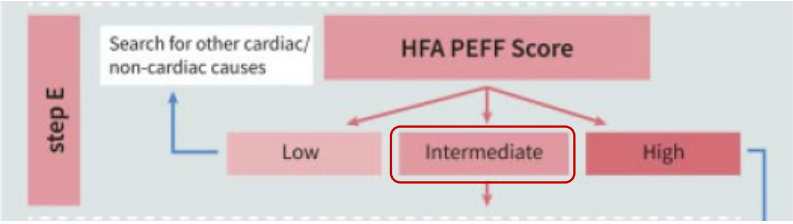
- Weaknesses
  - Mitral E velocity may be difficult to measure in case of E and A overlap
  - TR velocity cannot be reliably assessed in approximately 30% of cases



Case report 1

- 72 year-old woman
  - BMI 28 kg/m²
  - Hypertension treated with irbesartan and amlodipine
  - Paroxysmal AF treated with apixaban and amiodarone
  - NYHA II-III
  - NT proBNP 215 pg/ml
- Echocardiography
  - LVEF 64%
  - GLS -19%
  - LVMi 90 g/m², RWT 0.4
  - Septal e' 7.6 cm/s, lateral e' 7.8 cm/s
  - Average E/e' 10
  - LA volume 32 ml/m²
  - TR velocity 2.6 m/s





E Diagnostic Workup
(Step 2 (E) : Echocardiographic and Natriuretic Peptide Score)

	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

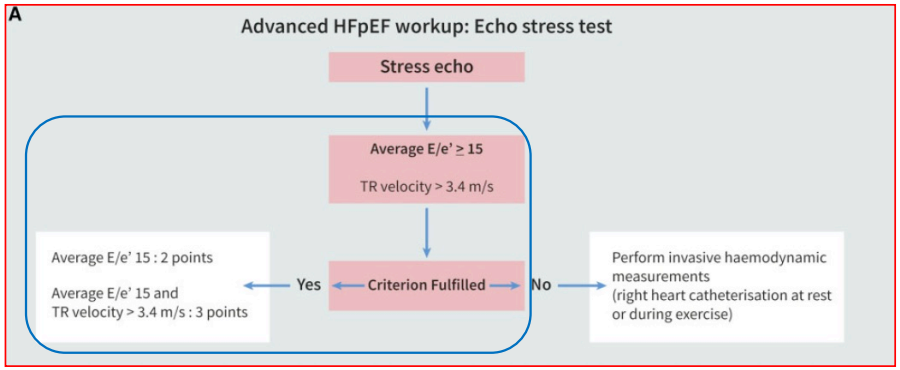
Major Criteria: 2 points
Minor Criteria: 1 point

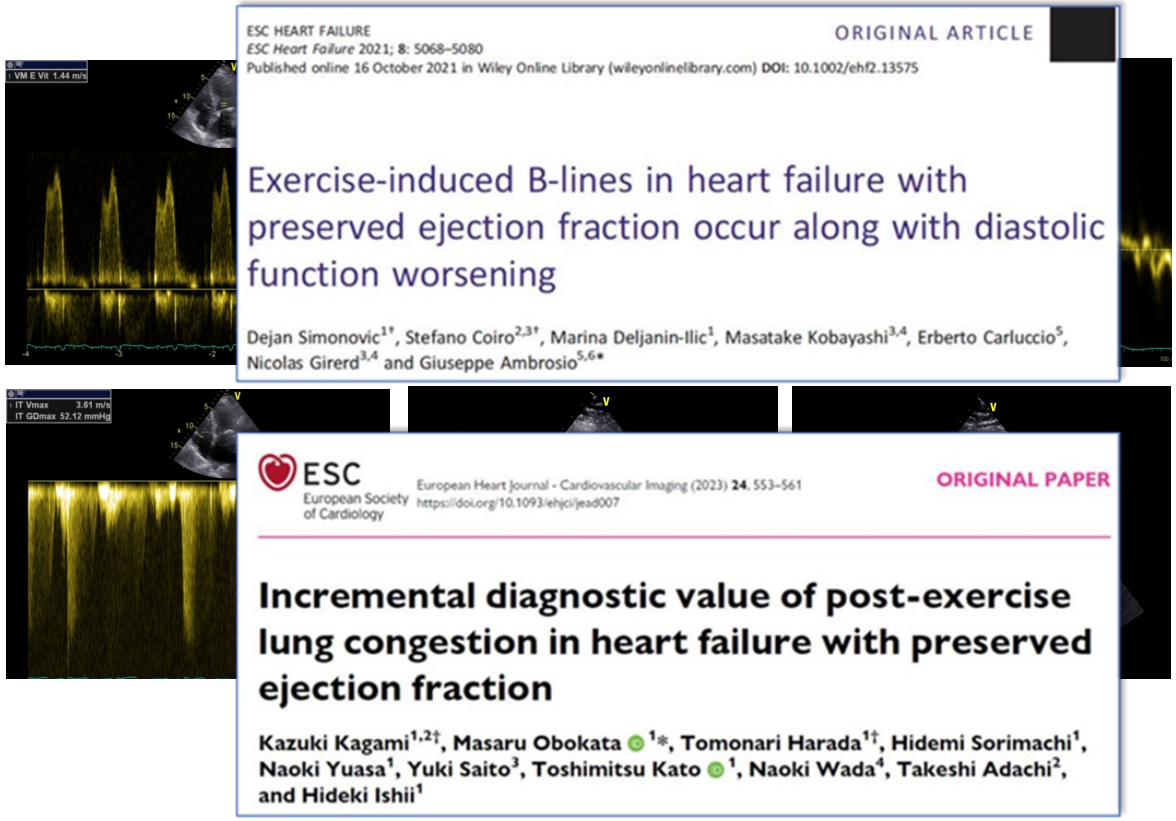
≥ 5 points: HFpEF

2-4 points: Diastolic Stress Test or Invasive Haemodynamic Measurements

Case report 1

- Diastolic stress test 60 Watts
  - Average E/e' 27
  - TR velocity 3.6 m/s
  - Bilateral pulmonary B lines





ESC HEART FAILURE
ESC Heart Failure 2021; 8: 5068–5080
Published online 16 October 2021 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.13575

ORIGINAL ARTICLE

Exercise-induced B-lines in heart failure with preserved ejection fraction occur along with diastolic function worsening

Dejan Simonovic[1†], Stefano Coiro[2,3†], Marina Deljanin-Ilic[1], Masatake Kobayashi[3,4], Erberto Carluccio[5], Nicolas Girerd[3,4] and Giuseppe Ambrosio[5,6*]

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2023) **24**, 553–561
https://doi.org/10.1093/ehjci/jead007

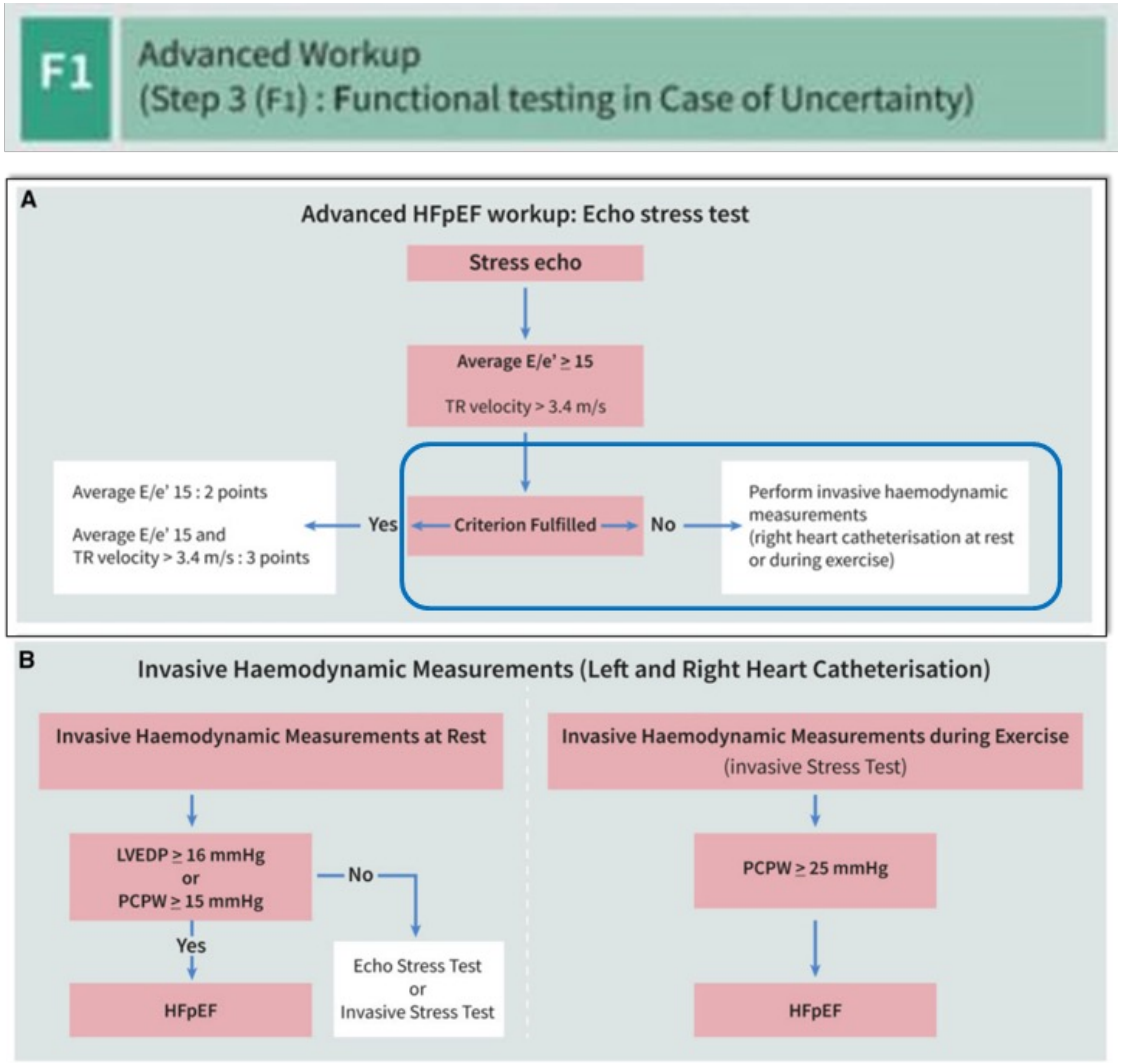
ORIGINAL PAPER

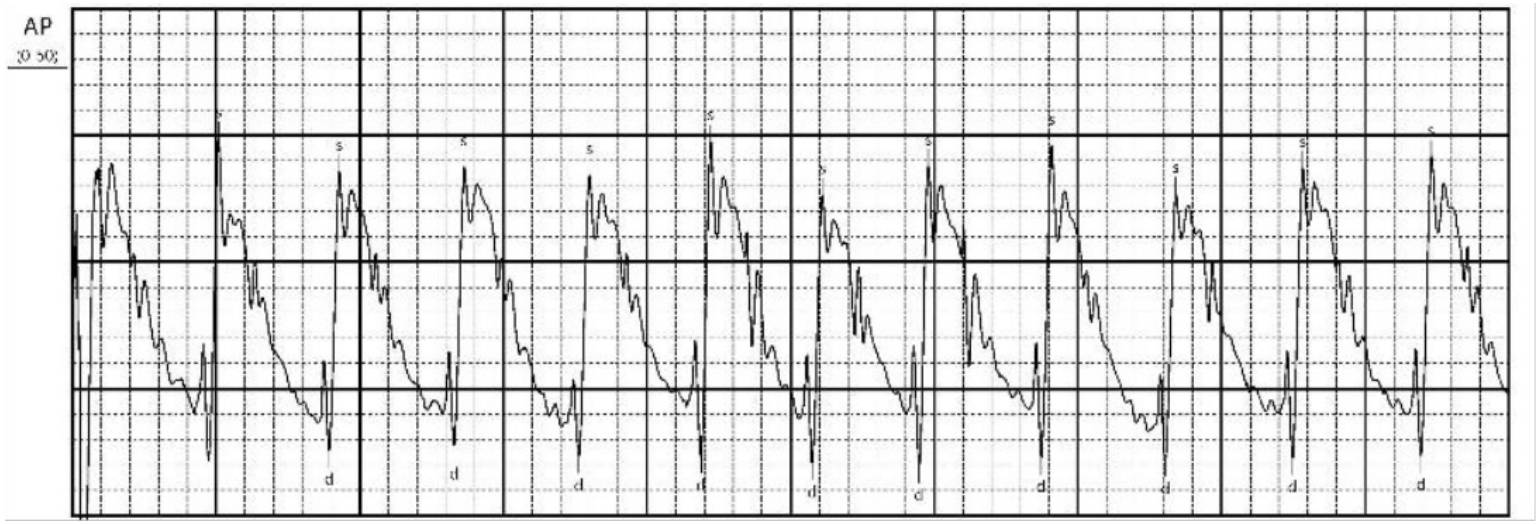
Incremental diagnostic value of post-exercise lung congestion in heart failure with preserved ejection fraction

Kazuki Kagami[1,2†], Masaru Obokata [1*], Tomonari Harada[1†], Hidemi Sorimachi[1], Naoki Yuasa[1], Yuki Saito[3], Toshimitsu Kato [1], Naoki Wada[4], Takeshi Adachi[2], and Hideki Ishii[1]

Invasive exercise test

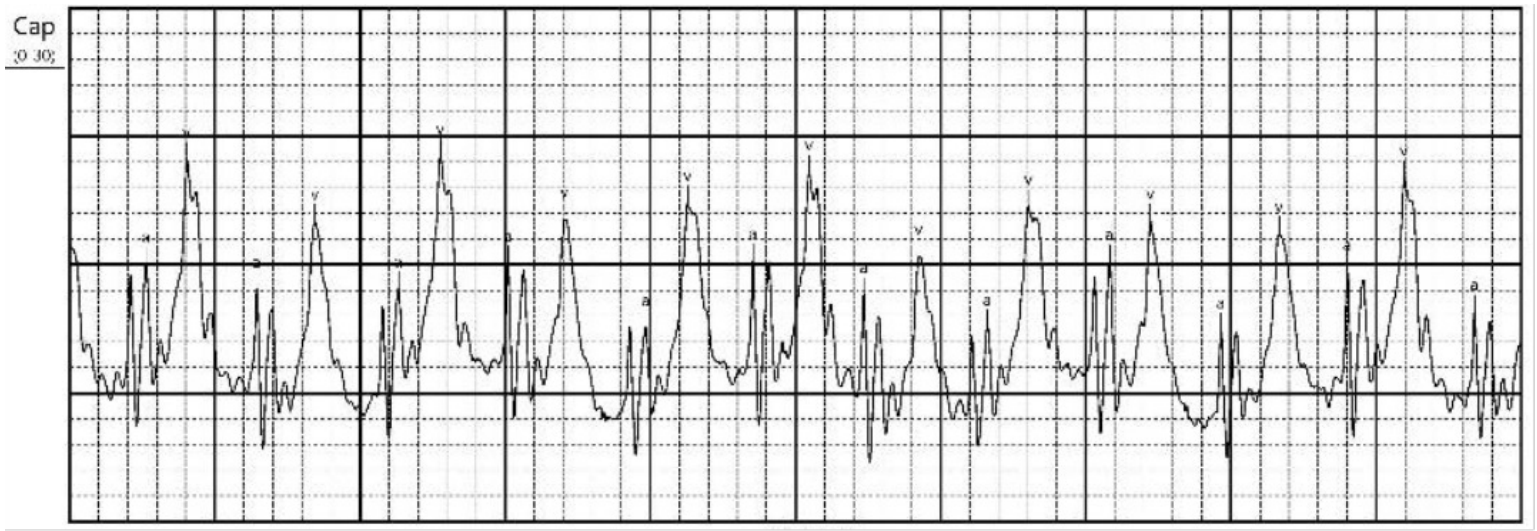
- Invasive measurement of left ventricular filling pressures in the gold standard to confirm that symptoms are due to heart failure
- However, pressures may be normal at rest
- Impaired LV filling may be disclosed by fluid challenge or exercise



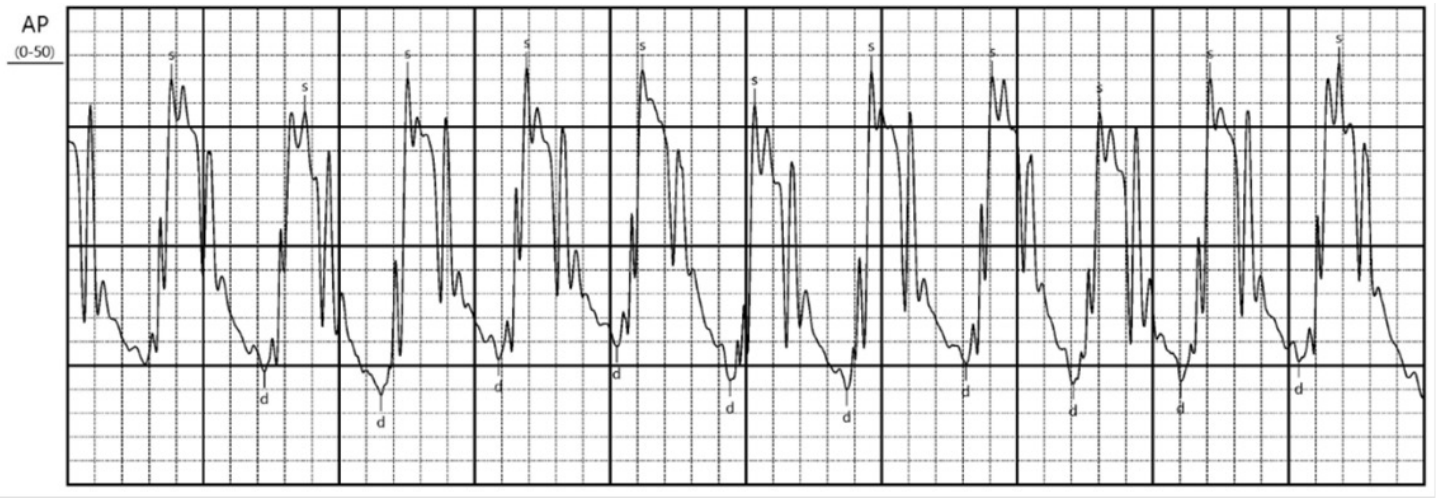


AIR REST

35/6 (19)

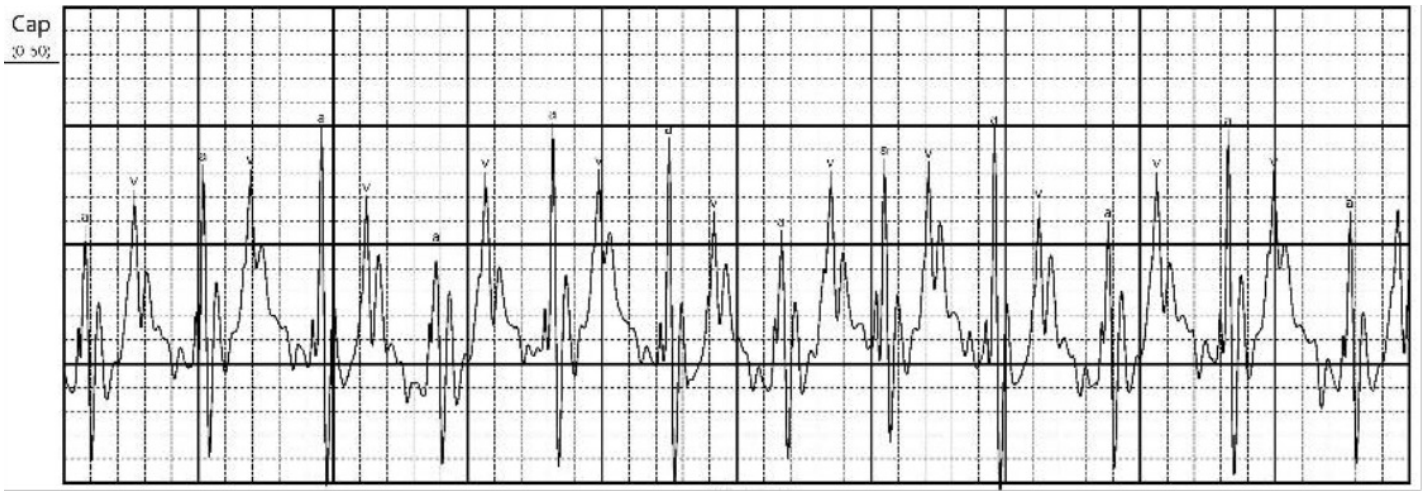


13/19 (10)



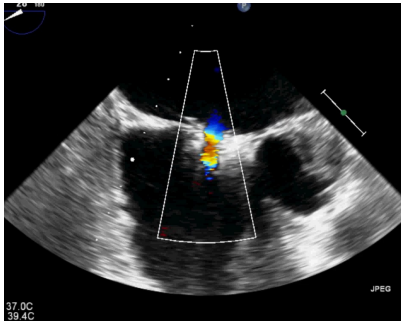
Test d'Effort 0 Pedalier

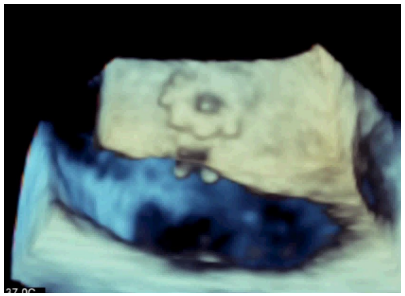
42/12 (24)



31/30 (16)

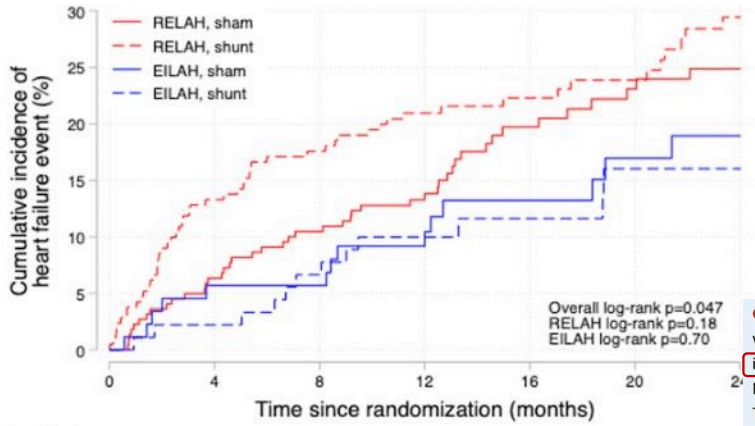
	Basal	Jambes surélevées	Effort 20W	Effort 40W	EFFORT MAX
Aorte (s/d-m) mmHg	132 / 68 - 101	135 / 68 - 101			136 / 66 -...
OG (m/a-v) mmHg			5 / 8 - 9		
Cap (m/a-v) mmHg	**10** / 13 - 19	**16** / 31 - 30	**25** / 43 - 42	**28** /.. -...	**35** /.. -...
AP (s/d-m) mmHg	35 / 6 - 19	42 / 12 - 24	61 / 12 - 33	51 / 13 - 32	58 / 20 - 29
OD (m/a-v) mmHg	**5** / 7 - 8	**5** / 8 - 9	**6** / 14-17	**10** / 14 - 17	**4** / 12 - 15
Débit (l/min)	5,54				9,6
Débit (l/min/m²)	3,4				5,8
RVS (dyn.s/cm5)	1386				
RVS index (dyn.s/cm5/m²)	2370,54				
RVP (dyn.s/cm5)	130				50
RVP index (dyn.s/cm5/m²)	222,24				85,5
RVP / RVS	0,09				

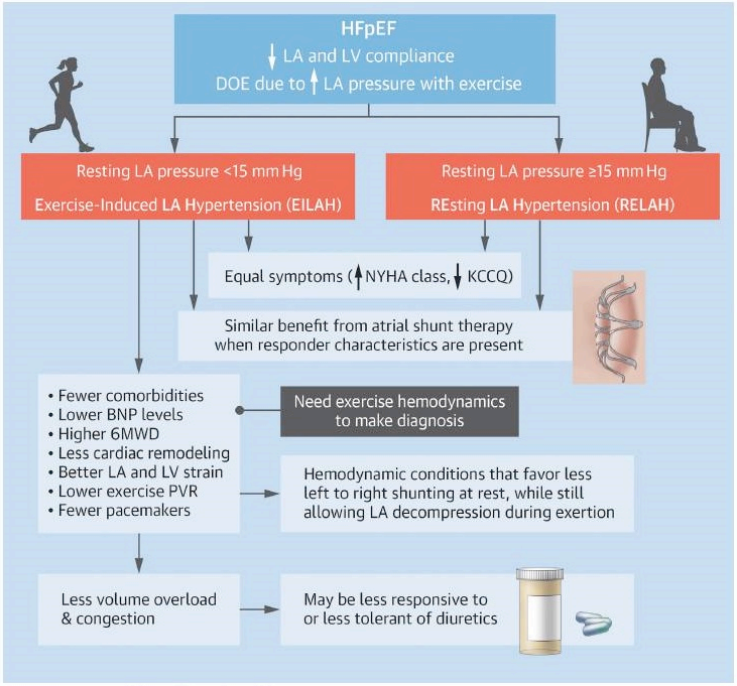




Exercise-Induced Left Atrial Hypertension in Heart Failure With Preserved Ejection Fraction

Sheldon E. Litwin, MD,[a,b] Jan Komtebedde, DVM,[c] Mo Hu, MS,[d] Daniel Burkhoff, MD, PhD,[e] Gerd Hasenfuß, MD,[f] Barry A. Borlaug, MD,[g] Scott D. Solomon, MD,[h] Michael R. Zile, MD,[a,b] Rajeev C. Mohan, MD,[i] Rami Khawash, MD,[j] Aaron L. Sverdlov, MBBS, PhD,[k,l] Peter Fail, MD,[m] Eugene S. Chung, MD,[n] David M. Kaye, MD,[o] John Blair, MD,[p] Jean-Christophe Eicher, MD,[q] Scott L. Hummel, MD,[r,s] Andreas Zirlik, MD,[t] Ralf Westenfeld, MD,[u] Christopher Hayward, MD,[v] Thomas M. Gorter, MD,[w] Catherine Demers, MD,[x] Ranjith Shetty, MD,[y] Gregory Lewis, MD,[z] Randall C. Starling, MD, MPH,[aa] Sanjay Patel, MD,[bb,cc,dd] Deepak K. Gupta, MD,[ee] Hakim Morsli, MD,[ff] Martin Penicka, MD,[gg] Maja Cikes, MD, PhD,[hh] Finn Gustafsson, MD,[ii] Frank E. Silvestry, MD,[jj] Ethan J. Rowin, MD,[kk] Donald E. Cutlip, MD,[ll] Martin B. Leon, MD,[e] Dalane W. Kitzman, MD,[mm] Franz X. Kleber, MD,[nn] Sanjiv J. Shah, MD,[d] on behalf of the REDUCE LAP-HF Investigators and Research Staff

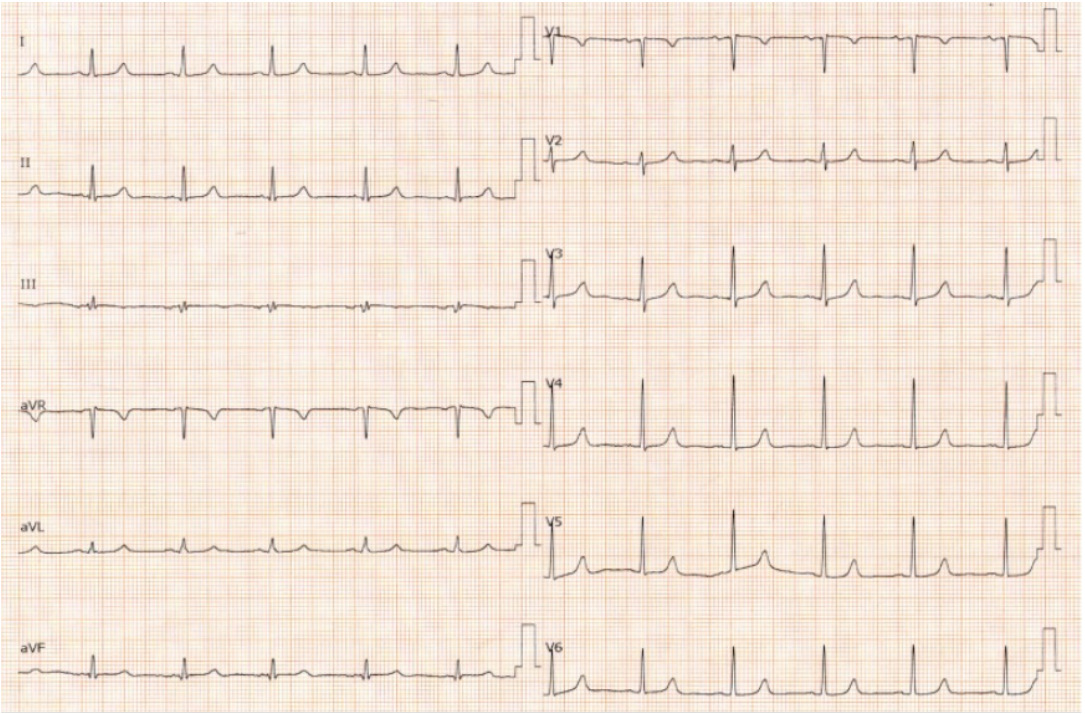




CONCLUSIONS Patients with EILAH had similar symptom severity but less advanced myocardial and pulmonary vascular disease. This important subgroup may be difficult to diagnose without invasive exercise hemodynamics, but it has characteristics associated with favorable response to atrial shunt therapy. (A Study to Evaluate the Corvia Medical, Inc. IASD System II to Reduce Elevated Left Atrial Pressure in Patients With Heart Failure [REDUCE LAP-HF TRIAL II]; NCT03088033) (J Am Coll Cardiol HF 2023;■:■–■) © 2023 by the American College of Cardiology Foundation.

Case report 2

- 74 year-old woman
  - BMI 21,6 kg/m²
  - Hypercholesterolemia treated with rosuvastatin 10
  - Intermittent LBBB
  - LAD stenting 2022 (aspirin 75 mg, bisoprolol 2,5 mg)
  - Paroxysmal exercise dyspnoea, normal coronary angiography
  - NT-proBNP 413 pg/ml

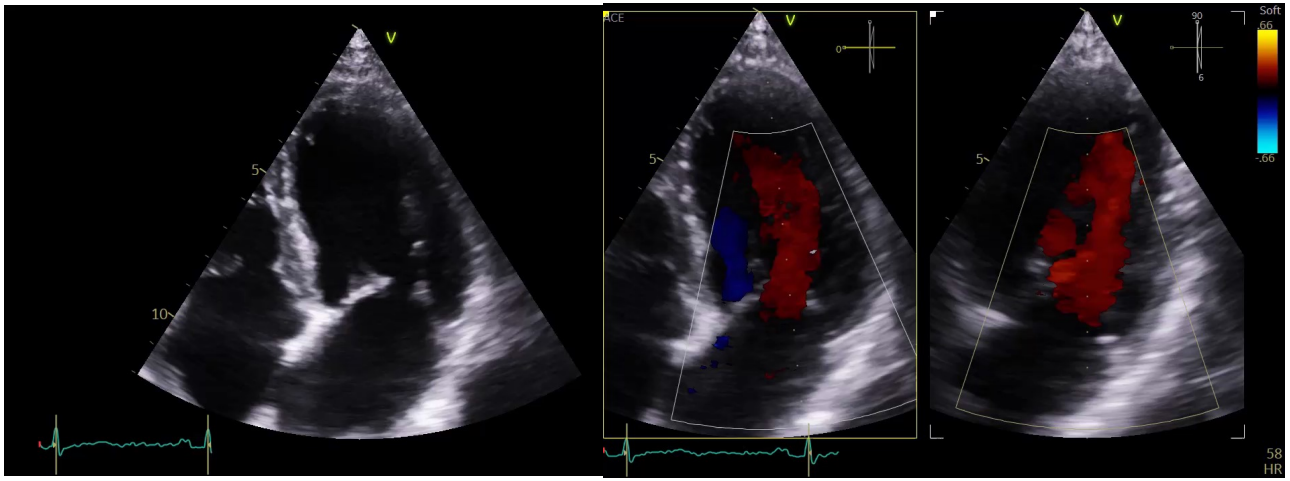


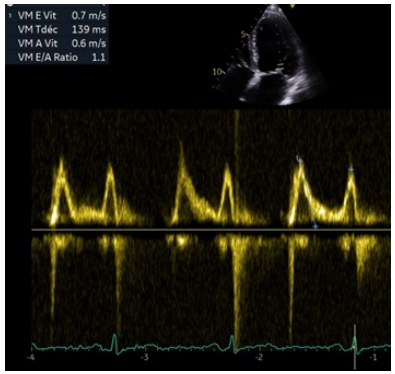
Case report 2

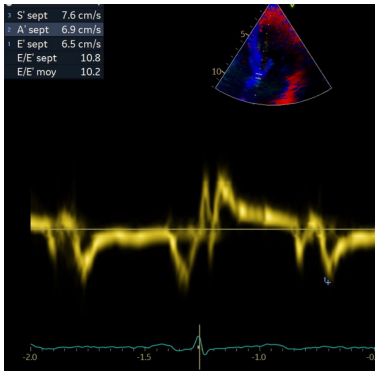
- Echocardiography
  - LVEF 71%
  - GLS -23,4%
  - Normal LVMi
  - Septal e' 6.5 cm/s,
  - Average E/e' 10.2
  - LA volume 38 ml/
  - Mild MR
  - No TR

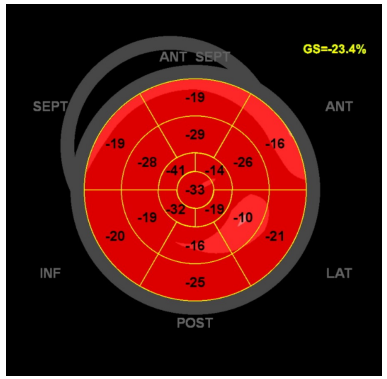
Calculate

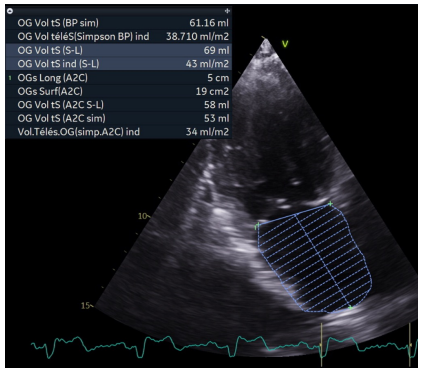
HFA-PEFF Score: 6
Diagnosis of HFpEF

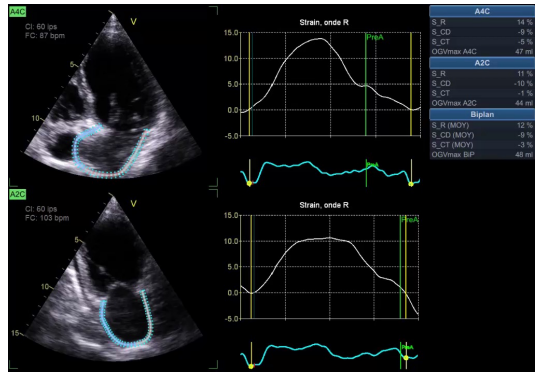






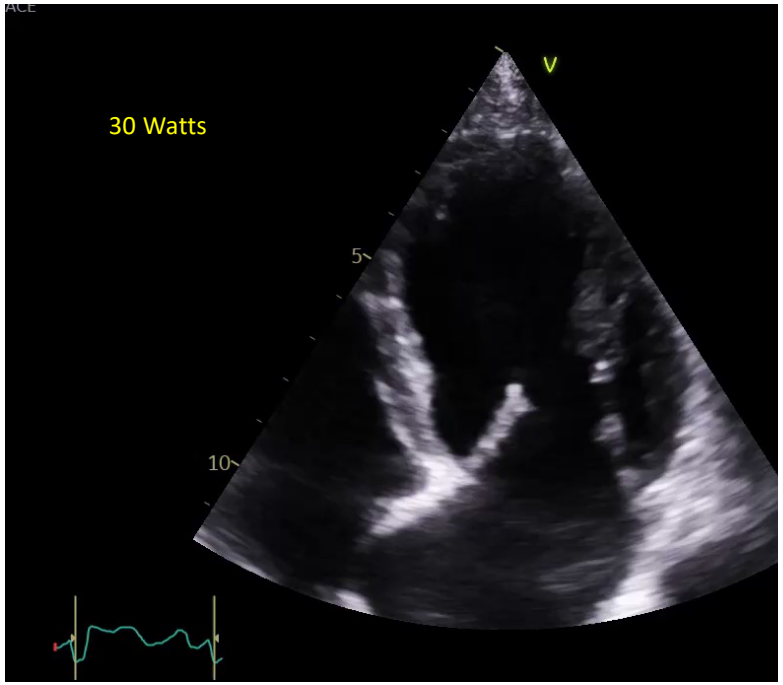


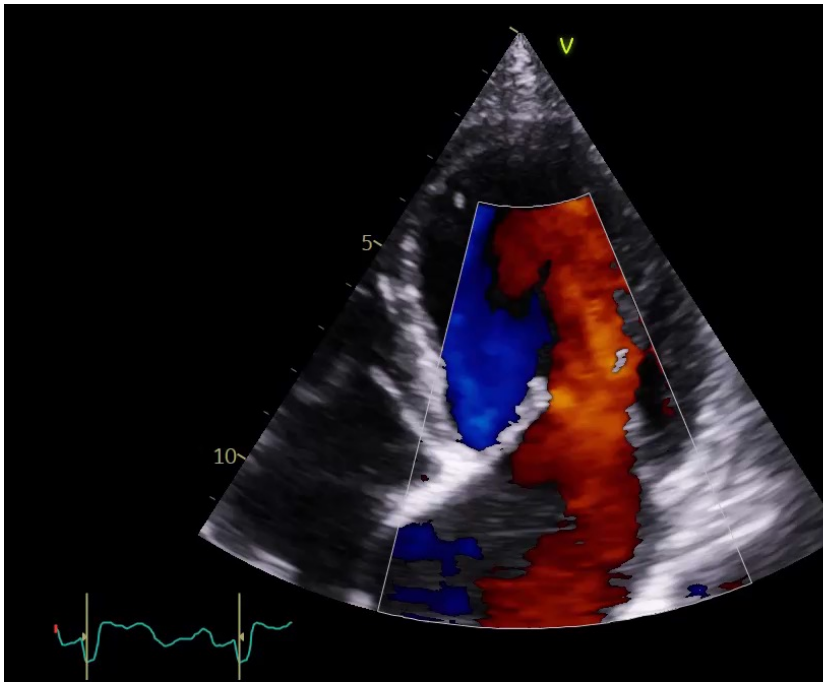


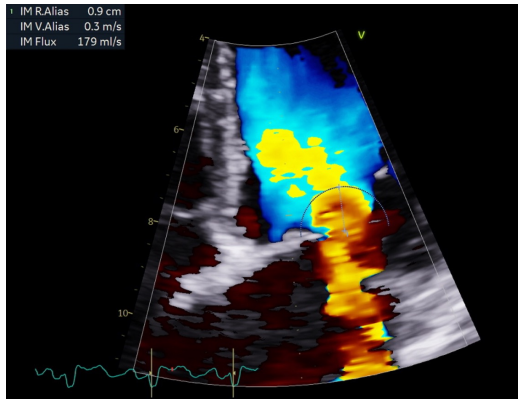


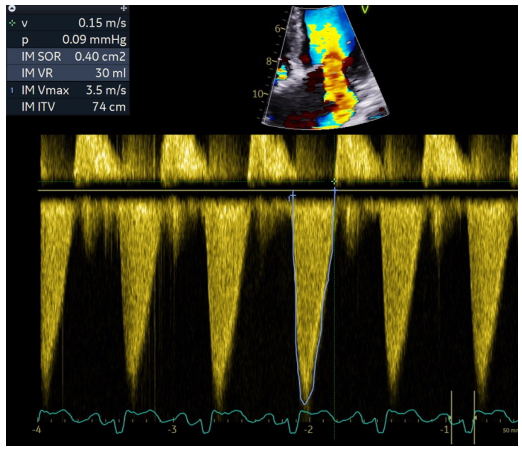
Case report 2

- Exercise echocardiography

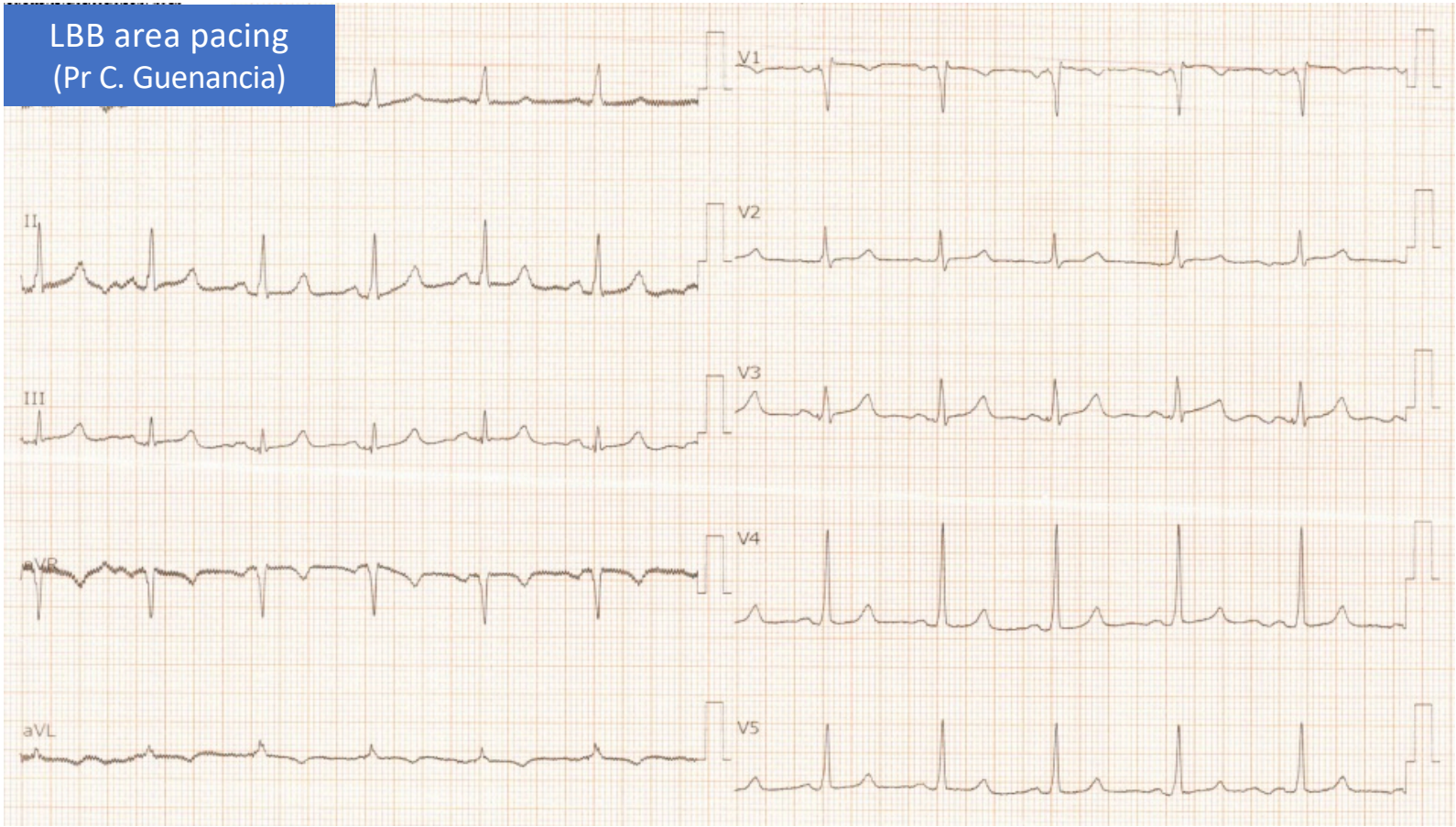








Case report 2



Take home messages

- Exercise explorations in HFpEF may be useful

1. To assess the degree of functional impairment
2. To look for differential diagnoses (respiratory causes, deconditioning)
3. To confirm diagnosis
4. To assess prognosis
5. To refine treatment (ischaemia, chronotropic incompetence, hypertension)
6. To improve follow-up