ESC European Society of Cardiology

European Heart Journal (2023) **44**, 1544–1556
https://doi.org/10.1093/eurheartj/ehad141

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Heart failure with preserved ejection fraction: relevance of a dedicated dyspnoea clinic

Jan Verwerft[1,2], Lucie Soens[3], Jokke Wynants[4], Marc Meysman[5], Siddharth Jogani [1], Danielle Plein[3], Sarah Stroobants[1], Lieven Herbots [1,2], and Frederik H. Verbrugge [3,6]*

[1]Department of Cardiology, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium; [2]Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Martelarenlaan 42, 3500 Hasselt, Belgium; [3]Centre for Cardiovascular Diseases, University Hospital Brussels, Laarbeeklaan 101, 1090 Jette, Belgium; [4]Department of Pulmonology, Jessa Hospital, Stadsomvaart 11, 3500 Hasselt, Belgium; [5]Department of Pulmonology, University Hospital Brussels, Laarbeeklaan 101, 1090 Jette, Belgium; and [6]Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Pleinlaan 2, 1050 Elsene, Belgium

Received 15 October 2022; revised 30 January 2023; accepted 21 February 2023; online publish-ahead-of-print 16 March 2023

See the editorial comment for this article 'Do we need dedicated heart failure with preserved ejection fraction clinics?', by C.S.P. Lam and J.E. Ho, https://doi.org/10.1093/eurheartj/ehad172.

Abstract

Background and aims Heart failure with preserved ejection fraction (HFpEF) is a syndrome with a heterogeneous presentation. This study provides an in-;depth description of haemodynamic and metabolic alterations revealed by systematic assessment through cardiopulmonary exercise testing combined with exercise echocardiography (CPETecho) within a dedicated dyspnoea clinic.

Methods and results Consecutive patients ($n = 297$), referred to a dedicated dyspnoea clinic using a standardized workup including CPETecho, with HFpEF diagnosed through a H_2FPEF score ≥6 or HFA-PEFF score ≥5, were evaluated. A median of four haemodynamic/metabolic alterations was uncovered per patient: impaired stroke volume reserve (73%), impaired chronotropic reserve (72%), exercise pulmonary hypertension (65%), and impaired diastolic reserve (64%) were the most frequent cardiac alterations. Impaired peripheral oxygen extraction and a ventilatory limitation were present in 40% and 39%, respectively. In 267 patients (90%), 575 further diagnostic examinations were recommended (median of two tests per patient). Cardiac magnetic resonance imaging, coronary or amyloidosis workup, ventilation–perfusion scanning, and pulmonology referral were each recommended in approximately one out of three patients. In 293 patients (99%), 929 cardiovascular drug optimizations were performed (median of 3 modifications per patient). In 110 patients (37%), 132 cardiovascular interventions were performed, with ablation as the most frequent procedure.

Conclusion Holistic workup of HFpEF patients within a multidisciplinary, dedicated dyspnoea clinic, including systematic implementation of CPETecho reveals various haemodynamic/metabolic alterations, leading to further diagnostic testing and potential treatment changes in the majority of cases.

* Corresponding author. Tel: +322 474 9657, Fax: +32 2 477 4159, Email: frederik.verbrugge@uzbrussel.be

Structured Graphical Abstract

Key Question

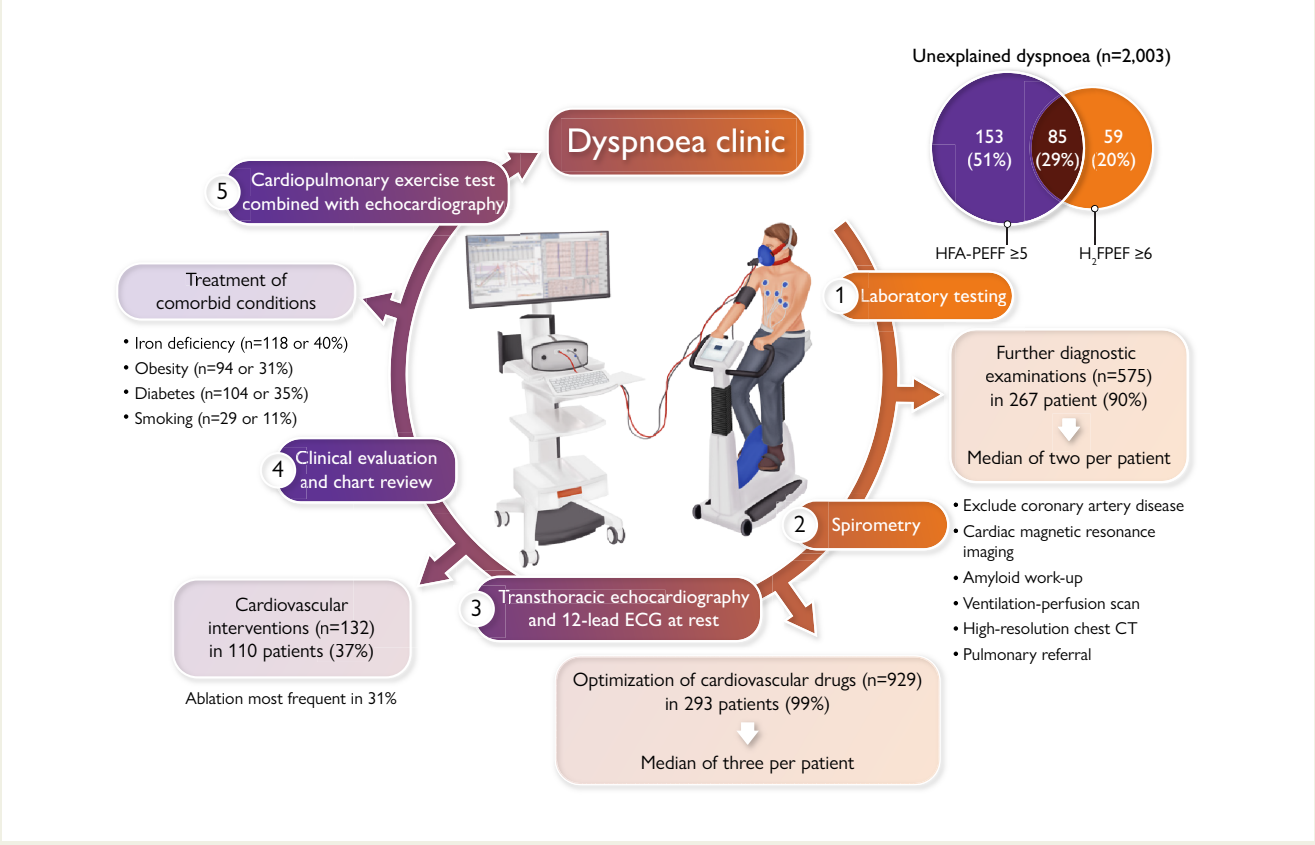
Which haemodynamic and metabolic alterations are revealed when systematic assessment including cardiopulmonary exercise testing with echocardiography (CPETecho) is performed in patients with heart failure and preserved ejection fraction (HFpEF) within a multidisciplinary, dedicated dyspnoea clinic?

Key Finding

On average, four haemodynamic/metabolic alterations were present, with a median of two further diagnostic tests recommended. Medication prescriptions were changed in virtually all patients (median of three changes per patient), while cardiovascular interventions were performed in one third.

Take Home Message

Holistic work-up of HFpEF patients within a multidisciplinary, dedicated dyspnoea clinic, including systematic implementation of CPETecho reveals various hemodynamic and metabolic alterations, leading to further diagnostic testing and potential treatment changes in the majority of cases.



Set-up of the different components of a dedicated dyspnoea clinic for heart failure with preserved ejection fraction. For patients with a confirmed diagnosis according to either the HFA-PEFF score, the H_2FPEF score, or both, downstream implications of testing are presented. CT, computed tomography; ECG, electrocardiogram.

Keywords Diastolic heart failure • Dyspnoea • Echocardiography • Exercise test • Therapeutics

Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for more than half of all heart failure cases, with a growing incidence and prevalence because of an aging population and increasing frequency of risk factors such as obesity, diabetes, hypertension, and kidney disease.[1] Despite the significant burden of HFpEF in terms of morbidity, mortality, and associated healthcare costs, current guidelines make few recommendations.[2,3] These basically comprise the use of diuretics to alleviate signs and symptoms of congestion and the treatment of relevant comorbid conditions. Only recently, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection

Fraction (EMPEROR-Preserved) became the first trial to show a significant reduction in the combined risk of cardiovascular mortality and heart failure hospitalizations with a dedicated pharmacological treatment for HFpEF.[4] The most recent American guidelines acknowledge these results with a class IIa recommendation (level of evidence B) for sodium–glucose co-transporter 2 inhibitors (SGLT2i) in HFpEF.[3] This apparent lack of therapeutic consequences for HFpEF compared with the wealth of possible treatments for patients with a reduced ejection fraction has contributed to a sense of indifference to making a correct and early diagnosis. The emergence of diagnostic HFpEF scores has definitely contributed to create awareness and allows a consistent diagnosis supported by a clear association with clinical outcomes.[5–8]

In this study, patients meeting diagnostic criteria for HFpEF according to the H_2FPEF or HFA-PEFF score underwent a standardized workup with clinical evaluation, lab testing, spirometry, transthoracic echocardiography at rest, and cardiopulmonary exercise testing combined with exercise echocardiography (CPETecho) within a multidisciplinary, dedicated dyspnoea clinic. The aim was to describe haemodynamic and metabolic alterations revealed by this approach, with their downstream impact on further diagnostic testing and treatment changes.

Methods

Study design

This is a prospective observational cohort study of consecutive patients referred for CPETecho within a multidisciplinary, dedicated dyspnoea clinic to search for haemodynamic and metabolic alterations associated with exercise intolerance and/or exertional dyspnoea. All patients underwent testing between April 2016 and December 2021, according to an identical protocol in either of two study centres (Jessa Hospital, Hasselt, Belgium, and University Hospital Brussels, Jette, Belgium). Study subjects were selected afterwards based on a H_2FPEF score ≥6 or HFA-PEFF score ≥5 (see Supplementary data online, *Methods*).[5,6] Details of the diagnostic algorithms are provided in the Supplementary data online, *Methods*. The study was conducted according to the principles outlined in the Declaration of Helsinki and approved by the local ethics committee. All study subjects provided written informed consent before evaluation in the dyspnoea clinic. All authors had full access to the data, take responsibility for its integrity, contributed to the writing of the manuscript, and have agreed to this report as written.

Study population

All patients were referred for CPETecho because of exertional dyspnoea or fatigue, corresponding to New York Heart Association functional class II or III. Only patients with a left ventricular ejection fraction ≥50% and either a H_2FPEF score ≥6 or HFA-PEFF score ≥5 were included, confirming a diagnosis of HFpEF.[5,6] Patients with a positive diastolic stress test, defined as a ratio of their early transmitral flow velocity over early diastolic tissue Doppler velocity at the septal mitral annulus (E/e') ≥ 15 during exercise, earned two or three additional points to their overall HFA-PEFF score (three points if the maximal tricuspid valve regurgitation velocity also exceeded 3.4 m/s) as recommended by the HFA-PEFF algorithm.[6] Patients with known pericardial disease; infiltrative, restrictive, or hypertrophic cardiomyopathy; high-output heart failure; more than mild valve stenosis; or more than mild primary valve regurgitation were excluded. Secondary valve regurgitations were not excluded.

Dyspnoea clinic protocol

Figure 1 summarizes the patient flow according to the dedicated dyspnoea clinic protocol.

Laboratory testing

Upon arrival in the dyspnoea clinic, all patients undergo peripheral venous cannulation with a 20 G catheter. A venous blood sample is obtained to assess a total blood count, iron, transferrin saturation, ferritin, glycated haemoglobin (HbA1c), serum creatinine, and plasma *N*-terminal of prohormone B-type natriuretic peptide (NT-proBNP). The peripheral venous cannula is left in place to ensure venous access during exercise testing.

Spirometry test

Next, patients perform a spirometry test to measure their forced expiratory volume in 1 s (FEV_1) and forced vital capacity. Maximal voluntary ventilation (MVV) is defined as 40xFEV_1.

Transthoracic echocardiography and 12-lead electrocardiogram at rest

Comprehensive 2D, Doppler, and tissue Doppler images are acquired according to contemporary guidelines, while the patient is lying in a 45° position on the semi-supine tilt table ergometer for exercise echocardiography.[9,10]

Clinical evaluation and chart review

Then, a certified cardiologist and pulmonologist perform a clinical examination chart review.

Cardiopulmonary exercise test combined with exercise echocardiography

Finally, patients perform a maximal, symptom-limited, semi-supine bicycle test with simultaneous echocardiography and continuous respiratory gas analysis (i.e. CPETecho). An individualized ramp protocol (5 W/min, 10 W/min, 15 W/min, or 20 W/min) is chosen to achieve an exercise duration of 10–15 min in total. The choice of the individual protocol is based on performance during previously available exercise tests found within the medical record or age, weight, and functional class of the patient when those are not available. An initial hold-stage at low-intensity exercise is employed to acquire the first set of echo images. This stage is preferably initiated at the first ventilatory threshold, but always with a heart rate <100–110 bpm to ensure preserved separation of the E- and A-wave on the transmitral pulsed wave Doppler signal. After acquiring a complete set of echo images during this first hold-stage, the ramp protocol is continued until exhaustion, with a second hold-stage just before peak exercise [usually defined by a respiratory exchange ratio (RER) > 1.05, although the onset of symptoms may necessitate sooner evaluation]. Patients are encouraged to reach maximal exertion with a RER >1.10. Echocardiography images acquired at every phase of the exercise test include (i–iii) four-, two-, and three-chamber 2D views of the left ventricle and atrium, (iv) a dedicated right ventricular view, (v) a four-chamber tissue Doppler view, (vi) pulsed wave Doppler sampling at the septal mitral annulus, (vii) colour Doppler of the mitral valve, (viii) pulsed wave Doppler of the mitral inflow, (ix) pulsed wave Doppler of the left ventricular outflow tract, and (x) continuous wave Doppler of the tricuspid valve regurgitation signal. Before obtaining the last image, agitated colloid is injected through the venous cannula left in place to allow optimal delineation of the signal (see Supplementary data online, *Figure S1*).[11] During the exercise test, breath-by-breath oxygen consumption, carbon dioxide production, tidal volume, and respiratory rate are measured continuously. Additionally, all patients are monitored with a 12-lead electrocardiogram and cuff blood pressure registration throughout the entire exercise and recovery phase.

Diagnostic findings and therapeutic recommendations

After all measurements have been obtained and summarized, conclusions on observed haemodynamic and metabolic alterations are reported (*Table 1*), and possible further diagnostic and therapeutic actions are proposed (*Table 2*) by a multidisciplinary team that includes a heart failure specialist, a specialist in cardiac imaging, and a pulmonologist.[11–22]

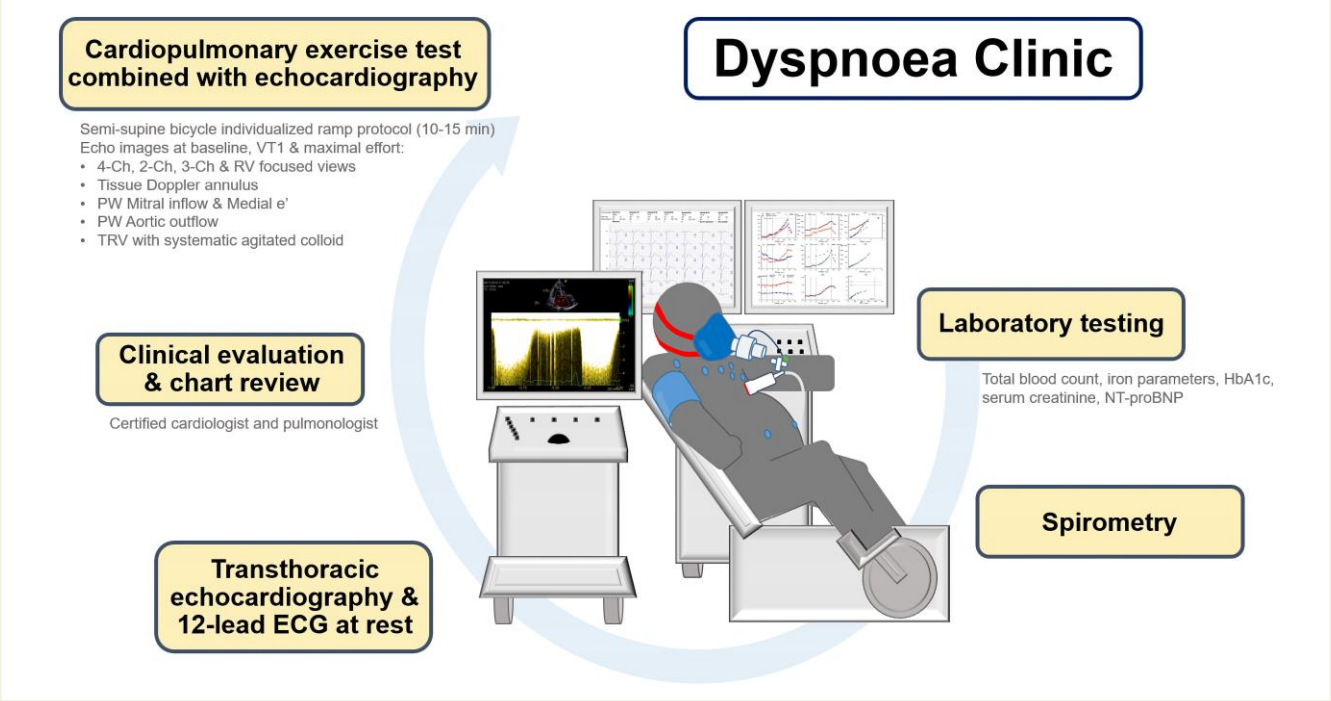


Figure 1 Patient flow in a dedicated dyspnoea clinic. This figure represents a template for a potential dyspnoea clinic. Ideally, it consists of a one-stop, multidisciplinary workup, although parts of it may be implemented according to feasibility depending on local healthcare settings. In Belgium, the two study centres are among at least six other centres that have implemented this blueprint in clinical practice, illustrating its feasibility at least in the Belgian context. Besides cardiologists and pulmonologists, general and nurse practitioners could be involved. Costs for setting up such a dyspnoea clinic are largely driven by infrastructure and equipment which may vary among regions in the world. Indications for cardiopulmonary exercise testing and exercise echocardiography overlap, yet performing them simultaneously offers complimentary information. Ch, chamber; ECG, electrocardiogram; HbA1c, glycated haemoglobin; NT-proBNP, *N*-terminal of pro-hormone B-type natriuretic peptide; PW, pulsed wave Doppler; RV, right ventricular; TRV, tricuspid regurgitation velocity; VT1, first ventilatory threshold.

Recommendations are subsequently discussed with the patient and the referring physician for shared decision-making.

Registration of proposed further diagnostic or therapeutic actions

Two certified cardiologists (J.V. for Jessa Hospital and L.S. for University Hospital Brussels) reviewed all individual patient cases in detail to register each recommended action after standardized assessment within the dyspnoea clinic. Individual actions were categorized in (i) recommendation for further diagnostic examinations, (ii) optimization of cardiovascular drugs, (iii) referral for cardiovascular interventions, (iv) treatment of non-cardiac comorbidities, and (v) rehabilitation and exercise training. The frequency of each recommendation was recorded. When multiple recommendations were made in a single patient, all of them were registered.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range) when not normally distributed. The independent-samples Student's *t*-test and Mann–Whitney U test were used for comparison between groups. Categorical data are expressed as counts and percentages. All statistics were performed using Jamovi—Stats (Version 1.6).

Results

Study population

From a total of 2003 patients referred for CPETecho during the study period at both study centres, 297 fulfilled diagnostic criteria for HFpEF according to either the H_2FPEF or HFA-PEFF score or both (*Figure 2*). Mean age was 73 ± 9 years with 64% women. Other baseline characteristics are summarized in *Table 3*. Seventy-three percent of patients had hypertension, nearly one-third was obese, 16% had diabetes, and half had a history of atrial fibrillation, while the median plasma NT-proBNP level was 400 ng/L.

Mechanisms of exercise intolerance

A median (interquartile range) of four (3–5) haemodynamic/metabolic alterations associated with exercise intolerance were found, ranging from 0 to 7 (see Supplementary data online, *Figure S2*). *Figure 3* shows the individual frequencies of all haemodynamic and metabolic alterations. Impaired chronotropic and stroke volume reserve (72% and 73%, respectively) were most frequently detected, resulting in an overall impaired cardiac output reserve in 59% of patients. Diastolic reserve was reduced in 64%, and 65% of patients fulfilled the criteria for pulmonary hypertension during exercise. Only 16% of patients had neither of these two limitations. Impaired diastolic reserve without pulmonary hypertension was present in 20% and pulmonary hypertension with a normal diastolic reserve in 19% of cases. Forty percent of patients had impaired peripheral oxygen extraction (see Supplementary data online, *Table S1*). Those patients were more likely to be women, with higher heart rates at rest. A ventilatory contribution to exercise limitation was present in 116 patients or 39% (see Supplementary data online, *Table S2*). These patients more frequently had a cardiac pacemaker.

Table 1 Haemodynamic and metabolic alterations associated with exercise intolerance or exertional dyspnoea

Haemodynamic/ metabolic alteration	Exercise echocardiography findings	CPETecho findings	References
Cardiac limitations			
Impaired CO reserve	[140×peak CO (L/min)]/predicted peak VO_2 (mL/min) < 0.8	CO/VO_2 slope <5 OR VT_1 < 40% of predicted VO_2 with exercise oscillatory ventilation	14,15,21
Impaired chronotropic reserve	(peak HR–rest HR)/[(220–age)–rest HR] < 0.8 or <0.62 (negative chronotropic medication)		13
Impaired SV reserve	Peak SV <42 mL/m^2 ΔSV <20%	Lower than predicted O_2 pulse O_2 pulse plateau	11,12,16
Impaired diastolic reserve	Exercise averaged *E*/*e*′>15 Exercise septal *E*/*e*′>14		6,16,19
Pulmonary hypertension	mPAP/CO slope >3 mmHg/L/min with mPAP >30 mmHg	V_E/VCO_2 slope >36, suggestive of pulmonary vascular disease	17,18
Ischaemia	Regional wall motion abnormalities Repolarization abnormalities	VO_2 plateau O_2 pulse decrease	14
LVOT obstruction	Systolic anterior mitral valve movement LVOT gradient >50 mmHg Systolic blood pressure rise <20 mmHg	VO_2 plateau O_2 pulse decrease	14,16
Dynamic mitral valve regurgitation	ERO increase >10–13 mm^2 during exercise	VO_2 plateau O_2 pulse decrease	16
Impaired peripheral oxygen extraction		CO/VO_2 slope >7 Peak AVO_2diff/(Hb) < 0.8 V_E/VO_2 > 50	14,20
Ventilatory limitation		V_E/MVV >0.7 with MVV = 40×FEV_1 VT_1 > 40% of predicted VO_2 with peak VO_2 < 0.85 and RER >1.10	14,15
Ventilation–perfusion mismatch		V_E/VCO_2 slope >36 $PETCO_2$ < 33 mmHg at rest and <3 mmHg increase with exercise peak V_D/V_T >0.3	14,17
Submaximal effort		RER <1.05 with V_E/VCO_2 < 30 and VO_2/Watts >8	14
Anxiety/hyperventilation		RER at rest >1.10 Rest RER >1.05 and $PETCO_2$ < 28 mmHg High V_E/VCO_2 slope with no other limitation	22

AVO_2diff, arteriovenous oxygen difference; CO, cardiac output; CPETecho, cardiopulmonary exercise test with concomitant echocardiography; ERO, effective regurgitant orifice; FEV_1, maximal expiration volume in 1 s; Hb, haemoglobin; HR, heart rate; LVOT, left ventricular outflow tract; mPAP, mean pulmonary arterial pressure; MVV, maximal voluntary ventilation; $PETCO_2$, end-tidal CO_2 pressure; RER, respiratory exchange ratio; SV, stroke volume; V_D/V_T, dead space over tidal volume; VT_1, first ventilatory threshold; V_E, peak ventilation; VCO_2, CO_2 production; VO_2, oxygen consumption.

In this group, 62 patients or 53% had a FEV_1 < 80% and 33 or 28% had an obstructive pulmonary function test with FEV <80% and FEV_1/forced vital capacity <75% of the age-, gender- and weight-predicted value. Vice versa, of all patients with a FEV_1 < 80% ($n = 136$), only 46% had a ventilatory limitation. When the peak ventilation/MVV ratio >0.7 was employed as the sole criterion, 72 or 25% had a ventilatory limitation to exercise, of which 37% had a FEV_1 < 80%. Vice versa, 63% of patients with FEV_1 < 80% had a peak ventilation/MVV ratio >0.7. Demonstration of ischaemia during exercise was uncommon (5%). Although 23% of patients ($n = 69$) had a RER <1.05, only 5% ($n = 16$) met the strict criteria for a submaximal effort. In six patients, a significant increase in mitral valve regurgitation was found.

Recommendations for further diagnostic examinations

In 267 patients (90%), 575 further diagnostic examinations were recommended, with a median of 2 tests per patient (*Figure 4* and Supplementary data online, *Figure S3*). A workup for cardiac amyloidosis with bone scintigraphy, measuring of serum light chains, and immunofixation was initiated in 97 patients (32%) because of disproportionate ventricular hypertrophy ($n = 27$), bilateral carpal tunnel syndrome ($n = 2$), or other clinical or echocardiographic suspicions ($n = 70$). For 93 patients (31%), coronary assessment with either computed tomography or invasive coronary angiography was scheduled. The indication was dynamic repolarization or

Table 2 Diagnostic and therapeutic treatment recommendations in the dyspnoea clinic

Recommendations for further diagnostic examinations	
Exclude coronary artery disease	• Regional wall motion abnormalities • Repolarization abnormalities • Positive diastolic stress test
CMR	• Suspected cardiomyopathy • High burden of ventricular ectopy • Unexplained conduction disorder
Bone scintigraphy + serum light chains + serum/urine immune fixation	• (Bilateral) carpal tunnel syndrome, spinal stenosis, biceps • Tendon rupture, polyneuropathy • Biventricular hypertrophy, especially when pericardial effusion and/or apical sparing pattern of global longitudinal strain are present • Low QRS voltage over left ventricular mass ratio
Ventilation–perfusion nuclear scan	(Exercise) pulmonary hypertension with disproportionate ventilation–perfusion mismatch (V_E/VCO_2 slope >36 or $PETCO_2$ < 33 mmHg at rest or <3 mmHg increase with exercise)
High-resolution chest computed tomography	Restrictive lung function with impaired oxygen diffusion capacity with desaturation >5% during exercise
Pulmonary referral	• Ventilatory limitation of exercise (cfr. definition in *Table 1*) • Peak V_D/V_T >0.3
Optimization of cardiovascular drugs	
SGLT2 inhibitor	• Glycated haemoglobin level >7% • Estimated glomerular filtration rate 25–60 mL/min/1.73 m^2 • NT-;proBNP >300 ng/L in sinus rhythm or >900 ng/L in atrial fibrillation
MRA	N-;proBNP >360 ng/L[23]
Increase loop diuretic	• Any clinical sign of volume overload (oedema, pleural effusion, ascites) • Elevated cardiac filling pressures at rest • Dynamic secondary atrioventricular valve regurgitation with exercise pulmonary hypertension
Stop or reduce negative chronotropic drug	Impaired chronotropic reserve [(peak HR–rest HR)/([220–age]–rest HR) < 0.62]
Improve hypertension control	• Systolic/diastolic blood pressure >130/80 mmHg at rest • Exercise systolic blood pressure rise ≥20 mmHg per 3.5 mL/kg/min rise in VO_2[14]
Improve dyslipidaemia control	• Low-;density lipoprotein cholesterol >115 mg/dL in primary prevention or >55 mg/dL in secondary prevention • Triglycerides >300 mg/dL
Anticoagulation	Atrial fibrillation or suspected thrombo-embolic pulmonary hypertension
Cardiovascular interventions	
Rhythm control	• Atrial flutter ablation when present • Pulmonary vein isolation or rhythm control medication for paroxysmal atrial fibrillation • Atrial fibrillation ablation for persistent atrial fibrillation without extensive atrial remodelling
Ventricular ectopy ablation	Significant ventricular ectopy thought to contribute to exercise limitation
Pacing strategy	• Improve rate response in patients with a pacemaker and impaired chronotropic reserve • AAI pacemaker implantation when significantly impaired exercise capacity (peak VO_2 < 65% of predicted value) due to significantly impaired chronotropic reserve [(peak HR–rest HR)/([220–age]–rest HR) < 0.62] and CO reserve [(140×peak CO)/predicted peak VO_2 < 0.65] • Cardiac resynchronization therapy when emerging left bundle branch block and systolic function decline during exercise

Continued

Table 2 *Continued*

Recommendations for further diagnostic examinations	
	• Left bundle area pacing for first degree AV block and/or left bundle branch block with marked E–A fusion at rest or immediately during exercise when proven exercise pulmonary hypertension
	• Atrioventricular node ablation with left bundle area pacing for atrial fibrillation with CO limitation of exercise [(140×peak CO)/predicted peak VO_2 < 0.8] or uncontrolled HR
Valve intervention	Severe secondary mitral and/or tricuspid valve regurgitation at rest or during exercise after other therapeutic optimizations
Treatment of comorbid conditions	
Intravenous iron therapy	• Transferrin saturation <20% and ferritin <300 µg/L
	• Ferritin <100 µg/L
Diabetes treatment	• Optimize diabetic control if glycated haemoglobin level ≥7%
	• Treat pre-;diabetes (glycated haemoglobin level ≥5.7%) with metformin if no contraindication[24]
Obesity treatment	• Glucagon-;like peptide-;1 analogue when body mass index >30 kg/m^2
	• Consider bariatric surgery
Smoking cessation program	Any current smoker
Rehabilitation and exercise training	
Consider in every patient, particularly when signs of impaired peripheral oxygen extraction (cfr. definition in *Table 1*)	

CMR, cardiac magnetic resonance; CO, cardiac output; HR, heart rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, *N*-terminal of pro-hormone B-type natriuretic peptide; $PETCO_2$, end-tidal CO_2 pressure; SGLT2, sodium-glucose linked transporter-2; V_D/V_T, dead space over tidal volume; V_E, peak ventilation; VCO_2, CO_2 production; VO_2, oxygen consumption.

regional wall motion abnormalities during CPETecho in 21 patients vs. clinical suspicion/high-risk profile in 72. In 26 (9% of all patients) significant coronary artery stenosis was found. Evaluation by pulmonology was proposed in 105 patients (35%) because of a peak ventilation over MVV ratio >0.7 ($n = 72$) or pulmonary dead space over tidal volume ratio >0.3 ($n = 44$). A ventilation–perfusion scintigraphy was scheduled in 84 patients (28%) because of exercise pulmonary hypertension with a ventilation over CO_2 production slope >36 ($n = 47$) or an end-;tidal CO_2 < 33 mmHg at rest with <3 mmHg increase during exercise ($n = 56$). Cardiac magnetic resonance imaging to exclude cardiomyopathy was recommended in 104 patients (35%) because of conduction abnormalities ($n = 71$), clinical suspicion ($n = 31$), or development of ventricular arrhythmia during exercise ($n = 14$). A high-;resolution computed tomography scan of the lungs was proposed in four patients (1%) because of a restrictive pulmonary function test with oxygen desaturation >5% during exercise.

Optimization of cardiovascular drugs

In 293 patients (99%), a total of 929 cardiovascular drug optimizations were performed with a median of 3 per patient (*Figure 5* and Supplementary data online, *Figure S4*). One hundred eighty-nine patients (64%) had an indication for starting a SGLT2i, of which 121 fulfilled the entry criteria of EMPEROR-Preserved. Of the 204 patients with available NT-proBNP levels, 112 or 55% had >360 ng/L, which conferred a beneficial effect from spironolactone in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. Only 45 (40%) of this group were already on a mineralocorticoid receptor antagonist. Signs of clinical volume overload and/or echocardiographic criteria for increased filling pressures at rest were present in 22 patients (7%), for which a loop diuretic was initiated ($n = 14$) or up-titrated ($n = 8$). Of the 230 patients (77%) on ≥1 negative chronotropic drug, 166 (56%) had impaired chronotropic reserve and a dose reduction or withdrawal was recommended. Optimization of antihypertensive medications was performed in 81% and an increase in lipid-lowering therapies in 42% (54 patients in primary prevention vs. 69 patients in secondary prevention). Eight patients had a new indication for oral anticoagulation.

Referral for cardiovascular interventions

In 110 patients (37%), a total of 132 cardiovascular interventions were performed (*Figure 6*). Ninety-three patients (31%) were referred for catheter ablation of atrial fibrillation and/or flutter: 78 had paroxysmal atrial fibrillation, while 15 had persistent atrial fibrillation with a left atrial volume index <45 mL/m^2. Seventy-seven had low heart rate reserve, while 21 had palpitations despite the use of antiarrhythmic drugs. Twelve patients (4%) were referred for ablation of ventricular ectopy, while 20 patients (7%) qualified criteria for a pacing treatment strategy. Of six patients referred for severe dynamic functional mitral regurgitation, two underwent a surgical and one a percutaneous mitral valve repair. One patient had combined mitral and tricuspid valve repair.

Treatment of comorbid conditions

Low ferritin ($n = 96$) and low transferrin iron saturation <20% ($n = 60$) revealed iron deficiency in 118 patients (40%). Diabetic treatment was improved in 104 patients (35%): metformin was started in 85 patients without previous history of diabetes and a new diagnosis of prediabetes

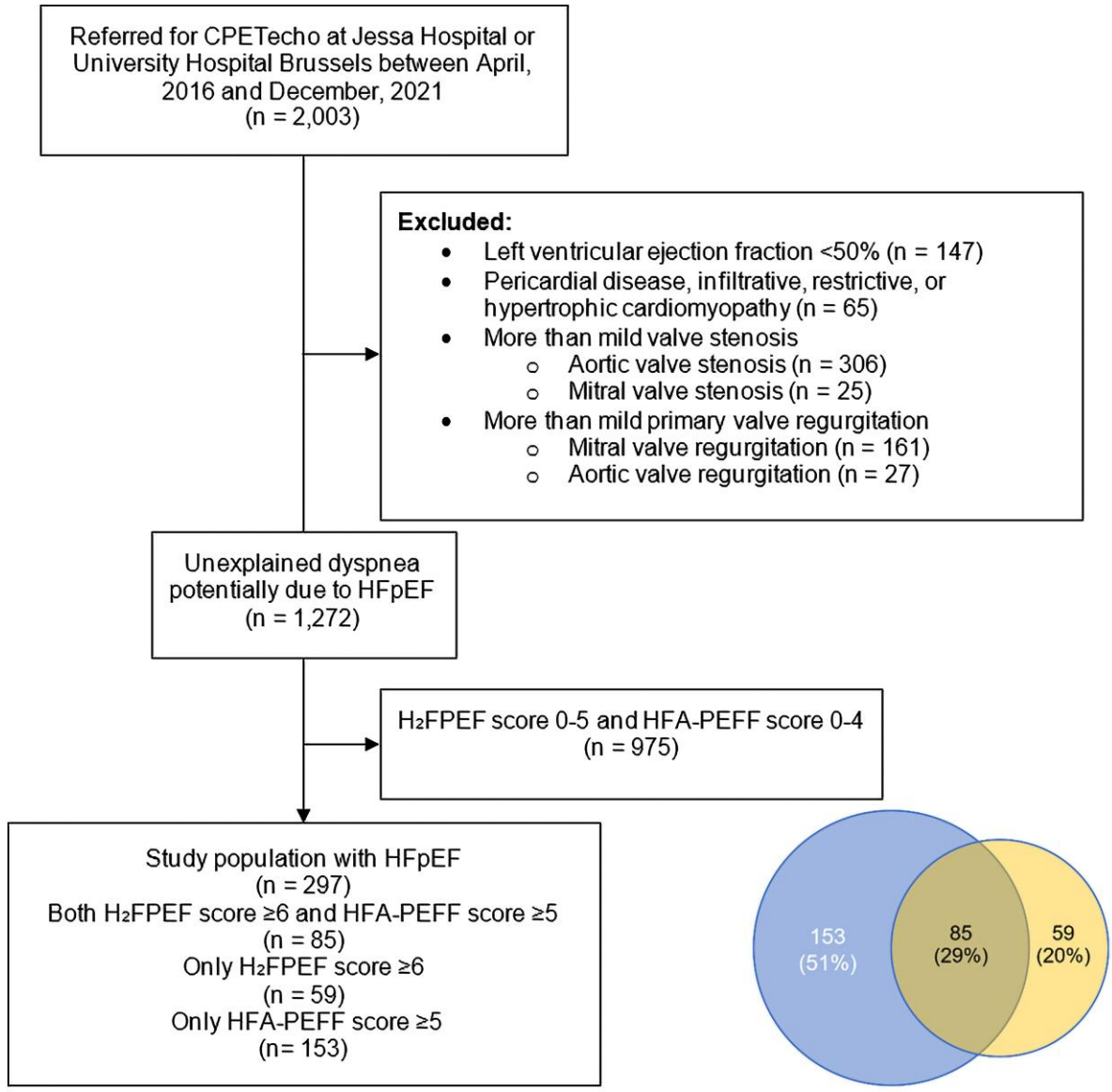


Figure 2 Study flowchart.

(HbA1c 5.7–6.5%). In four patients (2%), a new diagnosis of diabetes was made (HbA1c ≥ 6.5%). In 15 other patients with known diabetes, therapy was optimized. All 29 current smokers (11%) were referred to a smoking cessation program. Seven patients (2%) were referred for bariatric surgery because of a body mass index >40 kg/m^2, while 87 with a body mass index 30–40 kg/m^2 (29%) were put on a glucagon-like peptide-1 analogue.

Rehabilitation and exercise training

Rehabilitation and exercise training was considered particularly beneficial in 119 patients (40%) with either a cardiac output over oxygen consumption slope >7 ($n = 71$) or an impaired calculated peak oxygen extraction ($n = 100$).

Adverse events

During a median follow-up of 16 months (8–35 months), 8 patients died (3%), and 49 had at least 1 unplanned cardiovascular hospitalization (16%), while 242 (81%) had an uneventful survival. Unplanned cardiovascular hospitalizations ($n = 64$) were for heart failure ($n = 12$), atrial fibrillation ($n = 35$), or because of an ischaemic event ($n = 9$). Five of the 8 deaths were due to non-;cardiovascular causes.

Discussion

Heart failure with preserved ejection fraction is often perceived as a condition with relatively few therapeutic options due to the many failed

Table 3 Baseline characteristics of the study population ($n = 297$)

Demographics	
Age (years)	73 ± 9
Women, *n* (%)	189 (64)
Vitals and anthropometrics	
Systolic blood pressure (mmHg)	146 ± 23
Diastolic blood pressure (mmHg)	79 ± 14
Heart rate at rest (bpm)	69 ± 13
Height (cm)	165 ± 9
Weight (kg)	76 ± 15
Body mass index (kg/m^2)	27.9 ± 5.3
Ideal body weight (kg)[a]	61 ± 11
Excess body weight (kg)[a]	15 ± 15
Fat-free mass (kg)[b]	49 ± 8
Fat mass (kg)[b]	27 ± 11
Cardiovascular risk factors	
History of hypertension, *n* (%)	216 (73)
Diabetes mellitus, *n* (%)	47 (16)
Glycated haemoglobin ($n = 221$; %)	5.9 ± 0.7
Low-density lipoprotein cholesterol ($n = 280$; mg/dL)	89 ± 36
Obesity defined as a body mass index ≥30 kg/m^2, *n* (%)	94 (32)
Current smoker, *n* (%)	29 (10)
Cardiovascular history	
Any history of atrial fibrillation, *n* (%)	148 (50)
Ischaemic heart disease, *n* (%)	80 (27)
Peripheral artery or cerebrovascular disease, *n* (%)	26 (9)
History of valve intervention, *n* (%)	51 (17)
Cardiac pacemaker, *n* (%)	35 (12)
NT-proBNP ($n = 204$; ng/L)	400 (230–741)
Comorbid conditions	
Estimated glomerular filtration rate ($n = 292$; mL/min/1.73 m^2)[c]	65 ± 21
Renal replacement therapy, *n* (%)	2 (0.7)
Haemoglobin ($n = 293$; g/dL)	13.2 ± 1.6
Anaemia according to World Health Organization definition, *n* (%)	76 (26)
Ferritin ($n = 263$; ng/mL)	140 (62–220)
Transferrin saturation ($n = 219$; %)	25 ± 14
Iron deficiency ($n = 263$), *n* (%)	118 (45)
Medication use	
Sodium–glucose co-transporter-2 inhibitor, *n* (%)	2 (0.7)
Mineralocorticoid receptor antagonist, *n* (%)	86 (29)
Renin–angiotensin blocker, *n* (%)	152 (51)
Beta-blocker, *n* (%)	197 (66)
Loop diuretics, *n* (%)	78 (26)
Thiazide diuretics, *n* (%)	64 (22)
Statin, *n* (%)	166 (56)
Other lipid-lowering drugs, *n* (%)	26 (9)
Metformin, *n* (%)	23 (8)
Glucagon-;like peptide-;1 agonist, *n* (%)	1 (0.3)
Insulins, *n* (%)	12 (4)
Other diabetic drugs, *n* (%)	10 (3)
Oral anticoagulants, *n* (%)	126 (42)
Antiplatelet drugs, *n* (%)	110 (37)
Amiodarone, *n* (%)	48 (16)
Class I antiarrhythmic drugs, *n* (%)	21 (7)
Verapamil/diltiazem, *n* (%)	6 (2)
Dihydropyridine calcium channel blockers	69 (23)
Digoxin, *n* (%)	3 (1)

Numbers indicate mean ± standard deviation in case of a normal distribution or median (interquartile range) otherwise for continuous variables and absolute numbers (percentage of the population) for discrete variables NT-proBNP, *N*-terminal of pro-hormone B-type natriuretic peptide.

[a]Ideal body weight (kg) was calculated as 48 + 1.1 [height (cm)–150] in men or 45 + 0.9 [height (cm)–150] in women. Excess body weight was calculated as actual body weight minus ideal body weight.

[b]Fat-free mass was calculated as 5.1 [height (m)]$^{1.14}$ [body weight (kg)]$^{0.41}$ in men or 5.34 [height (m)]$^{1.47}$ [body weight (kg)]$^{0.33}$ in women. Fat mass was calculated as actual body weight minus fat-free mass.

[c]Calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula.

drug trials. On the other hand, many treatable comorbid conditions coincide with HFpEF, yet require a holistic rather than cardio-centric approach. This study comprehensively describes downstream diagnostic and therapeutic recommendations in patients with HFpEF who underwent a systematic workup within a multidisciplinary, dedicated dyspnoea clinic with systematic implementation of CPETecho. Key findings are as follows: (i) HFpEF patients demonstrate multiple haemodynamic and metabolic alterations associated with exercise intolerance with a median of 4 alterations found per patient; (ii) although cardiac alterations such as impaired stroke volume reserve, chronotropic incompetence, impaired diastolic reserve, and exercise pulmonary hypertension were the most frequent, a considerable proportion of patients demonstrated impaired peripheral oxygen extraction (40%) or a ventilatory limitation to exercise (39%) as well; (iii) further diagnostic workup according to predefined criteria was indicated in 9 out of 10 patients, with cardiac magnetic resonance imaging, coronary or amyloidosis workup,

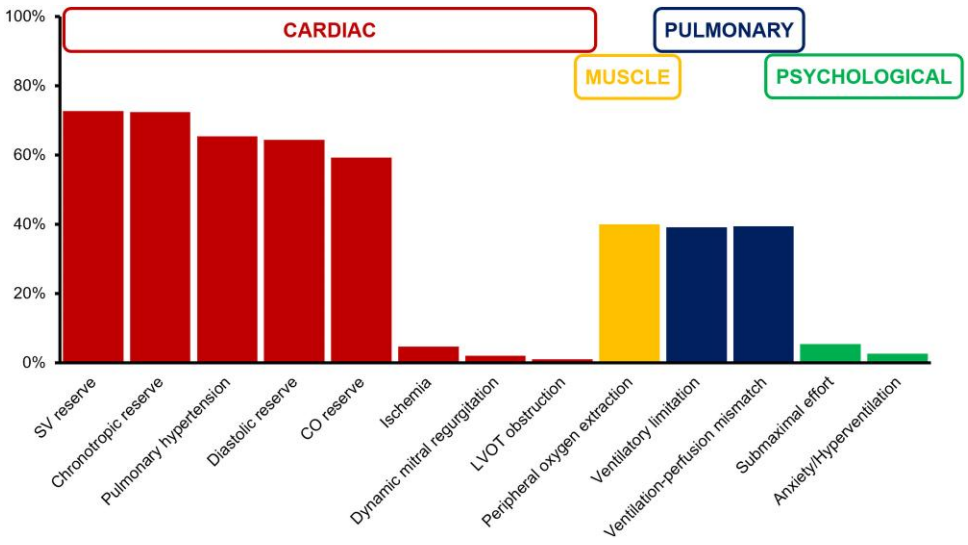


Figure 3 Haemodynamic and metabolic alterations associated with exercise intolerance. CO, cardiac output; LVOT, left ventricular outflow tract; SV, stroke volume.

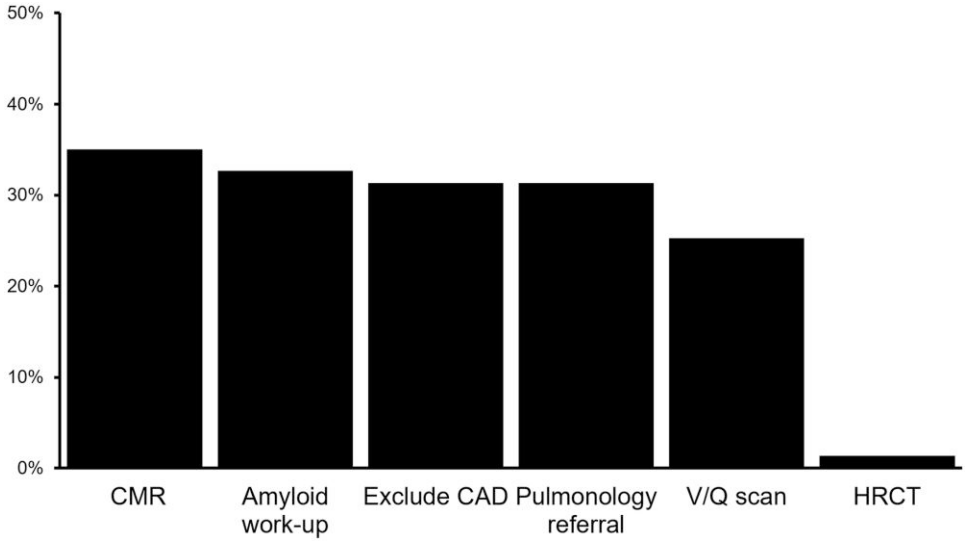


Figure 4 Frequency of recommended further diagnostic examinations. CAD, coronary artery disease; CMR, cardiac magnetic resonance; HRCT, high-resolution computed tomography; V/Q, ventilation–perfusion.

ventilation–perfusion scanning, and pulmonology referral each employed in approximately one-third of patients; (iv) in virtually all patients, cardiovascular drugs prescriptions were changed, while 1 in 3 underwent a cardiac intervention with ablation for atrial arrhythmias the most frequently performed procedure; and (v) the management of comorbid conditions such as iron deficiency, diabetes, obesity, and smoking was also frequently adapted (*Structured Graphical Abstract*). These findings highlight potential opportunities in HFpEF revealed by thorough and systematic workup within a multidisciplinary, dedicated dyspnoea clinic.

The diagnosis of HFpEF is complex, with substantial heterogeneity in clinical practice. Even among different guidelines and consensus papers, there are many inconsistencies in the proposed approach.[2,3,6] The lack of a clear definition has undoubtedly not helped an early and consistent diagnosis of HFpEF, which in turn makes therapeutic studies and trials more difficult. Two HFpEF probability scores that predict the presence of elevated cardiac filling pressures at rest and during exercise with reasonable accuracy and are associated with outcomes have facilitated and standardized the HFpEF diagnosis.[5–8,25]

This study describes in great detail the haemodynamic and metabolic alterations associated with exercise limitation (*Table 1*) in patients with HFpEF, confirmed by a high diagnostic HFpEF score. Eighty-four percent of patients demonstrated either impaired diastolic reserve or

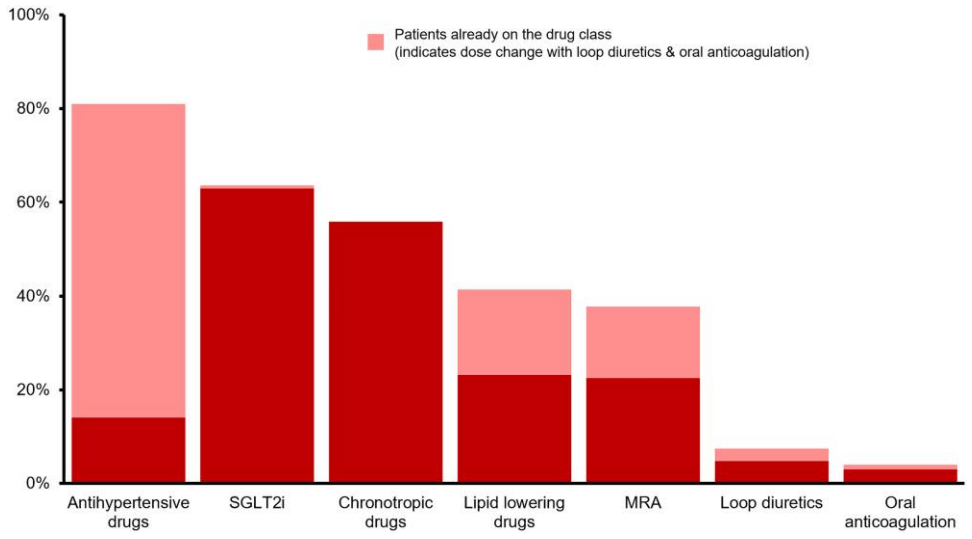


Figure 5 Frequency of cardiac medication optimizations. MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose co-transporter 2 inhibitor.

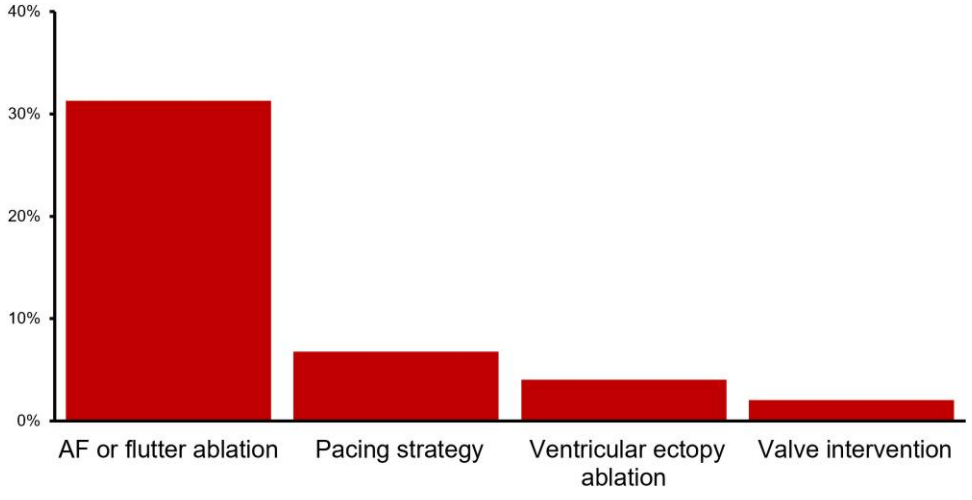


Figure 6 Frequency of referral for cardiovascular interventions. AF, atrial fibrillation. CPETecho, cardiopulmonary exercise test with concomitant exercise echocardiography; HFpEF, heart failure with preserved ejection fraction.

pulmonary hypertension during exercise, as expected in HFpEF where left ventricular diastolic dysfunction is supposed to be the central culprit. Only 64% of patients had an exercise $E/e' > 15$, which underscores the low sensitivity of this criterion for HFpEF.[19] One in five patients had isolated exercise pulmonary hypertension with an $E/e' \leq 15$. As the HFpEF scores have excellent positive predictive values to confirm HFpEF, this indicates that E/e' is a poor discriminator of pre-; vs. post-;capillary causes of exercise pulmonary hypertension and even in case of low E/e′ the presence of the latter increases the likelihood of HFpEF. It is well-known that patients with HFpEF often have an impaired systolic and chronotropic reserve as well.[1,26] Approximately 70% of patients had an impairment in each of these two components of cardiac output during exercise, which resulted in an impaired cardiac output reserve in ∼60% of the population. Identifying chronotropic incompetence has therapeutic relevance, as low heart rate reserve prompted withdrawal or down-titration of negative chronotropic drugs in 56%.

Adding cardiopulmonary exercise testing with respiratory gas analysis to exercise echocardiography in HFpEF is vital for unveiling two alternative alterations. Reduced oxygen extraction capacity was frequent, affecting 40% of the population and women in particular. Women are especially vulnerable to the haemodynamic and metabolic consequences of central obesity, potentially explaining their gender predominance within the obese HFpEF population.[27]

Notwithstanding, women remain underrepresented in cardiovascular and heart failure trials in particular, which may contribute to underutilization of guideline-directed therapies, including training programs. Alternatively, CPETecho exposed a ventilatory limitation in 39% of patients. Importantly, baseline FEV_1 at rest corresponded poorly with a ventilatory limitation during exercise, illustrating the value of cardiopulmonary exercise testing to select patients for further pulmonology evaluation.

Although key, identifying and treating the underlying disease is regularly overlooked in the HFpEF syndrome.[6] Awareness for diagnostic clues of HFpEF mimickers (*Table 2*), like coronary artery disease, amyloidosis, and myocardial or pericardial diseases, triggered appropriate workup, each in approximately one-third of our population. Changes in medication prescriptions were performed in virtually all patients with HFpEF evaluated in our dyspnoea clinics. Sixty-four percent had an indication for treatment with SGLTi according to large randomized clinical trials with reporting available at the time of the investigation. The indication was qualification for the eligibility criteria of EMPEROR-Preserved in two-thirds and diabetes or chronic kidney disease in one-third. Only two patients were already on SGLT2i as these drugs were not yet reimbursed for HFpEF in Belgium during the execution of the study with only patients with diabetes getting them at low cost. Although more controversial because of the overall negative result of the trial, patients who qualified the NT-proBNP criterion of TOPCAT (in whom treatment with spironolactone was associated with a significant reduction in cardiovascular death, aborted cardiac arrest, or heart failure readmissions) constituted 38% of our population. Despite the widespread availability of spironolactone, only 40% of this group were already on mineralocorticoid receptor antagonists.

Interestingly, the median NT-proBNP level was 400 ng/L in our population, indicating that many patients would not have been eligible for the major HFpEF trials.[4,23,28] Importantly, it has been shown recently that patients with HFpEF and normal natriuretic peptide levels, a group that makes up about one-third of the overall HFpEF population, have a significantly elevated risk of mortality or heart failure readmissions.[29] More evidence is needed on how to treat this considerable group of patients. Notably, the favourable effects of empagliflozin in HFpEF observed in the EMPERERO-Preserved trial were similar, irrespective of the NT-proBNP level.[4] Better phenotyping of patients in a dedicated dyspnoea clinic might identify a population with an impaired diastolic reserve and/or exercise pulmonary hypertension that might benefit as well from treatment with SGLT2i, but this hypothesis requires further testing in randomized clinical trials.

One-third of the population was referred for cardiac procedures after evaluation. Ablation of atrial fibrillation or flutter was the most frequently performed procedure. Recent data show that early rhythm control is safe and effective in patients with heart failure and might improve clinical outcomes.[30] Early catheter ablation of atrial fibrillation or flutter may be especially preferred in patients who demonstrate an impaired chronotropic reserve as this may render negative chronotropic drugs unnecessary while preserving atrial reserve.

In a multidisciplinary dyspnoea clinic with a holistic rather than cardio-centric perspective, our data show ample opportunities to optimize treatments of different comorbid conditions. Antihypertensive medications were intensified in 81%, lipid-lowering therapies in 42%, and diabetes treatment in 35%. The latter included starting metformin in patients with (pre)diabetes, which has been associated with slower progression of diastolic dysfunction in observational studies.[24] Although one could argue that these actions are part of any outpatient cardiology or even family health evaluation, being part of a systematic protocol in a dyspnoea clinic might help to stimulate therapeutic actions and collaboration with general practitioners. Iron deficiency (40%) and obesity (32%) were also frequent in our population and might be treated by iron suppletion and glucagon-like peptide-1 agonists or bariatric surgery, respectively. Fragmentation of care will likely result in a lack of ownership of the patient's management. By centralizing the care of patients with HFpEF, multidisciplinary dyspnoea clinics may help to overcome therapeutic inertia. As the pathophysiology of HFpEF with its associated haemodynamic and metabolic alterations is not confined to the heart, the treatment of HFpEF should probably be neither. Although the lack of a control group precludes us from making strong statements on the impact of our dyspnoea clinic on clinical outcomes, the mortality rate of 3% with an event-free survival in 81% after 16 months of follow-up looks favourable considering the average age of 73 years and frequent comorbid conditions in our population.

Study limitations

Results of the current study should be interpreted in the light of the following limitations. First, the diagnosis of HFpEF was purely based on a high H_2FPEF or HFA-PEFF score. When validated against gold standard cardiopulmonary exercise testing with invasive haemodynamic assessment, the overall accuracy of both scores to make a diagnosis of HFpEF ranges from 71% to 85%.[25] However, the positive predictive value of a high score (as used in this study) is well above 90%. Indeed, current guidelines only recommend invasive haemodynamic assessment during exercise when reasonable doubt on the diagnosis of HFpEF remains. Hence, our study population reflects a group that, in most practices, would be unambiguously labelled as HFpEF.[2,3] Nevertheless, because of the exclusion of patients with low to moderate HFpEF scores who not infrequently still have HFpEF, our results mainly apply to the group with the highest pre-test probability, somewhat limiting the external validity of the findings. From the overall group of patients referred for dyspnoea or exercise tolerance, those with a high H_2FPEF or HFA-PEFF score represented 23% in our clinics (*Figure 2*). Secondly, no data are available on the actual adherence to the different diagnostic and therapeutic recommendations made by the dyspnoea clinic team, as these were not captured in our database. However, the study's objective was to show the wealth of diagnostic and therapeutic opportunities in HFpEF rather than how they are implemented. Thirdly, many of the recommendations made by the dyspnoea clinic team (e.g. antihypertensive treatment) would not necessarily require the entire workup. However, in our experience, the likelihood that management is optimized increases by centralizing the care of patients in a holistic, patient-friendly, one-stop visit with a comprehensive assessment by a multidisciplinary team. Fourthly, although the presence of iron deficiency was systematically checked and treated based upon extrapolation of data from heart failure with reduced ejection fraction, intravenous iron therapy is currently not recommended for HFpEF since randomized clinical trials excluded these patients. Finally, further randomized studies are needed to assess whether dyspnoea clinics may improve the prognosis of patients with HFpEF.

Conclusions

A thorough and systematic workup of patients with HFpEF inside a multidisciplinary, dedicated dyspnoea clinic with routine use of CPETecho reveals many further diagnostic and potential therapeutic opportunities. Further study is needed to assess whether dyspnoea clinics improve the implementation of evidence-;based treatments for HFpEF and management of comorbid conditions and have a positive impact on hard clinical outcomes.

Acknowledgements

The authors thank all the cardiology fellows who have contributed in performing the exams in the dyspnoea clinic of Jessa Hospital (Hasselt, Belgium) over the years. In addition, a special thanks go to Nancy De Laet, Mathilde De Dobbeleer, Daisy Thys, and Peter Vanvoorden for their vital paramedic support in the clinic.

Author contributions

Jan Verwerft, M.D., Lucie Soens, M.D., Jokke Wynants, M.D., Marc Meysman, M.D., Siddharth Jogani, M.D., Danielle Plein, M.D., Sarah Stroobants, M.D., Lieven Herbots, M.D., Ph.D., and Frederik Hendrik Verbrugge, M.D., Ph.D.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

Data availability

Raw data are available upon reasonable request to the corresponding author.

Conflict of interest

All authors declare no conflict of interest for this contribution.

Funding

All authors declare no funding for this contribution.

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