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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

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Patients with heart failure with preserved ejection fraction (HFpEF) universally complain of exercise intolerance and dyspnoea as key clinical correlates. Cardiac as well as extracardiac components play a role for the limited exercise capacity, including an impaired cardiac and peripheral vascular reserve, a limitation in mechanical ventilation and/or gas exchange with reduced pulmonary vascular reserve, skeletal muscle dysfunction and iron deficiency/anaemia. Although most of these components can be differentiated and quantified through gas exchange analysis by cardiopulmonary exercise testing (CPET), the information provided by objective measures of exercise performance has not been systematically considered in the recent algorithms/scores for HFpEF diagnosis, by neither European nor US groups. The current clinical consensus statement by the Heart Failure Association (HFA) and European Association of Preventive Cardiology (EAPC) of the European Society of Cardiology (ESC) aims at outlining the role of exercise testing and its pathophysiological, clinical and prognostic insights, addressing the implications of a thorough functional evaluation from the diagnostic algorithm to the pathophysiology and treatment perspectives of HFpEF. Along with these goals, we provide a specific analysis of the evidence that CPET is the standard for assessing, quantifying, and differentiating the origin of dyspnoea and exercise impairment and even more so when combined with echocardiography and/or invasive haemodynamic evaluation. This will lead to improved quality of diagnosis when applying the proposed scores and may also help to implement the progressive characterization of the specific HFpEF phenotypes, a critical step toward the delivery of phenotype-specific treatments.

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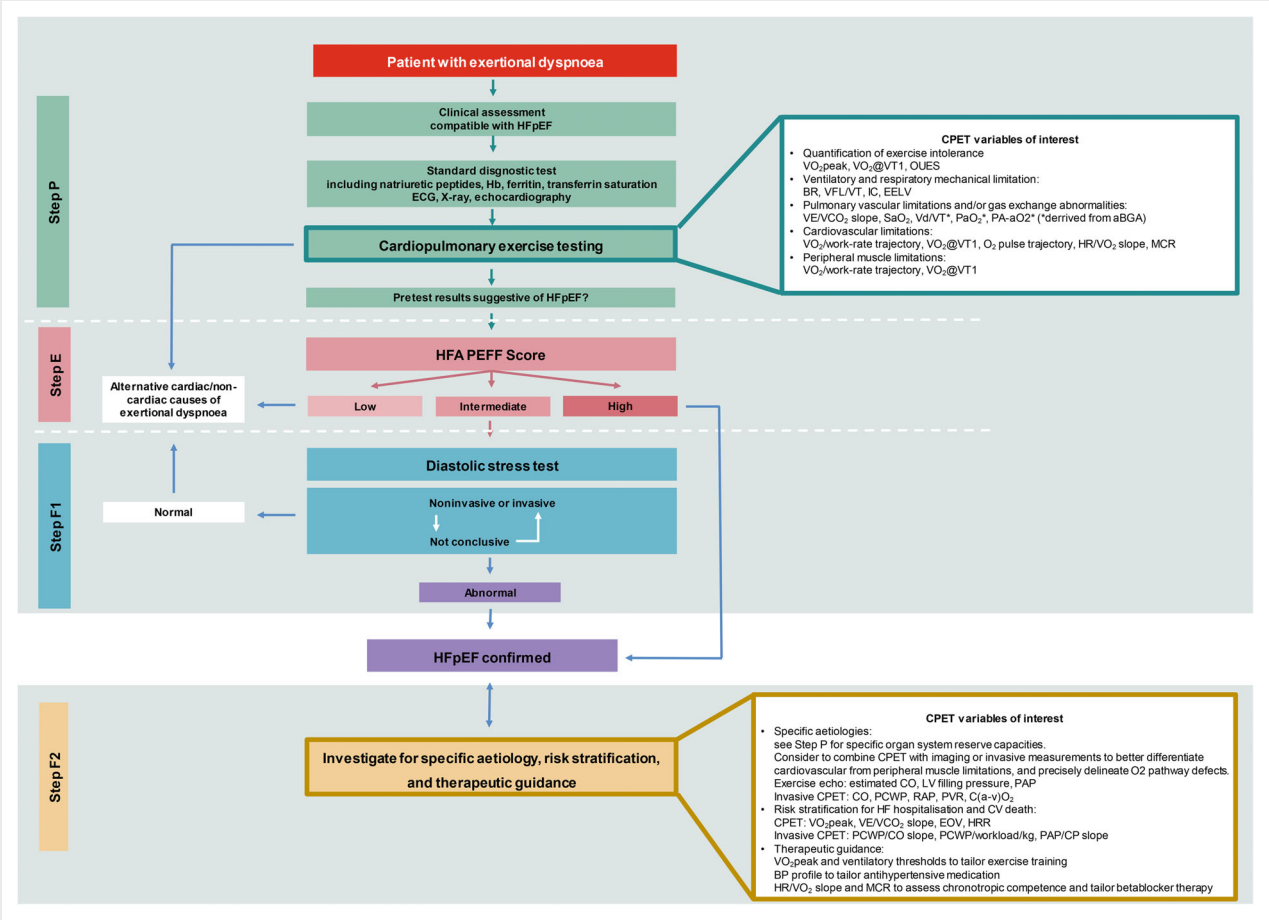
Graphical Abstract



Prioritizing cardiopulmonary exercise testing (CPET) within the HFA-PEFF diagnostic algorithm. Modified HFA-PEFF diagnostic algorithm including CPET in Step 1 (P) pre-assessment, and Step 4 (F) final aetiology. See text for details. Abbreviations: aBGA, arterial blood gas analysis; BP, blood pressure; BR, breathing reserve, ratio of VE/maximum volunatry ventilation; $C(a-v)O_2$, difference in O_2 content in arterial and mixed venous blood; CO, cardiac output; CV, cardiovascular; EELV, end-expiratory lung volume; HR, heart rate; HRR, heart rate recovery; IC, inspiratory capacity; LV, left ventricular; MCR, metabolic-chronotropic relationship; OUES, oxygen uptake efficiency slope; $PA\text{-}aO_2$, alveolar-arterial oxygen gradient; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RER, respiratory exchange ratio; SaO_2, arterial oxygen saturation; VCO_2, carbon dioxide output; VD/VT, ratio of dead-space ventilation to tidal ventilation; VE, ventilation; VFL/VT, percent of the tidal breath that expiratory air flow exceeds the maximal flow/volume envelope; VO_2, oxygen consumption; VT, ventilatory threshold.

Keywords HFpEF • Exercise • Functional limitation • Gas exchange analysis

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a common and costly clinical condition primarily affecting older adults with multiple comorbid disorders and risk factors of the metabolic syndrome, e.g. hypertension, obesity, and insulin resistance.[1] The diagnosis of HFpEF is challenging, and two influential diagnostic scores have recently been introduced into clinical practice as tools to help establish the diagnosis: the HFA-PEFF score of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)[1] and a composite score (H_2FPEF) designed by the Mayo Clinic group.[2]

Patients with HFpEF may present with typical signs and symptoms of HF, with or without increased levels of N-terminal pro-B-type natriuretic peptide,[3] left ventricular (LV) diastolic impairment, and limited contractile reserve. Most individuals also complain dyspnoea on exertion as dominant manifestation. Remarkably, in the PARAGON-HF (Prospective Comparison of

ARNI With ARB Global Outcomes in HFpEF) trial, 50% of the HFpEF population was enrolled based on the evidence of exercise limitation, and exercise-induced dyspnoea occurred in the 98% of cases.[4] The degree of exercise intolerance observed in HFpEF is similar to that seen in patients with HF with reduced ejection fraction (HFrEF), with impairments in the oxygen uptake (VO_2) cascade and in the physiological response of multiple organ systems.[5] The relative cardiac and extracardiac contributions to exercise limitation require precise recognition and objective measurements.

Gas exchange analysis by cardiopulmonary exercise testing (CPET) provides the gold standard for a non-invasive functional capacity evaluation[6] and offers a unique opportunity to investigate the role of lung mechanics and cardiopulmonary interactions with muscle weakness. In HFrEF, CPET is most frequently used to assess cardiac reserve and guide timing for advanced cardiac replacement therapies. In HFpEF, CPET may also play an important and distinct role to differentiate HFpEF from non-cardiac causes of dyspnoea. Indeed, one such main aetiology that confounds evaluation is offered by chronic obstructive pulmonary disease (COPD), a main trigger of incident HFpEF[7] and a frequent comorbidity of HFpEF.[8] A subanalysis of TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial) has identified a phenogroup with normal LV geometry, low arterial stiffness, and low natriuretic peptides with a favourable prognosis, despite non-responsiveness to spironolactone.[9] This phenogroup exhibited a COPD pattern as the main driver of dyspnoea, raising the question that HFpEF was not the true cause of symptoms in at least some of these patients.[8] Even more in the PARAGON-HF trial, one in seven patients was diagnosed with COPD and this subset presented with worse outcome.[10]

Furthermore, community-based cohort studies demonstrated a high prevalence of transthyretin amyloid cardiomyopathy in HFpEF patients with ventricular wall thickening, particularly in older men.[11] Patients with transthyretin amyloid cardiomyopathy often present with a severely reduced ventilatory efficiency and peak VO_2 compared to HFpEF.[12] While myocardial dysfunction is often cited as the predominant mechanism of gas exchange impairment in patients with cardiac amyloidosis, growing evidence points on abnormal lung function and a restrictive spirometry pattern as responsible for exercise limitation.[12]

Thus, documentation of the specific gas exchange response may lead investigators to think about underlying aetiologies, such as COPD or amyloidosis, early in the diagnostic process, which may prompt different treatments.

The algorithms proposed for the diagnosis of HFpEF within the H_2FPEF score do not explicitly include consideration of CPET as part of the probability estimation scheme, whereas the HFA-PEFF score algorithm suggests an initial gas exchange analysis approach only for the ruling out of non-cardiac-related impairment.[1]

Given that exercise impairment is the central clinical expression of HFpEF, a focused appraisal of the role of exercise functional evaluation in the diagnostic process, pathophysiological insights, and evaluation of therapeutic interventions in HFpEF is warranted. While non-invasive CPET in isolation may be insufficient to discriminate HFpEF from non-cardiac dyspnoea in some patients without adding invasive testing, its role as an early stage investigation to exclude pulmonary disease, and its potential role in more advanced phenotyping or to gauge treatment response, may be important emerging uses. The purposes of this HFA/European Association of Preventive Cardiology (EAPC) clinical consensus statement are to provide an updated document focusing on: (i) the sources of exercise limitation and its pathophysiology in HFpEF phenotypes; (ii) the role of CPET in differentiating pulmonary from cardiac mechanisms for unexplained exertional dyspnoea from the early diagnostic process to the advanced stages, highlighting its value for risk stratification and therapeutic tailoring; and (iii) the interventions that may improve exercise performance in HFpEF effectively targeting the multiple limiting steps of oxygen (O_2) kinetics.

Literature search and document approval

The writing group reviewed the exercise literature regarding HFpEF in its different phenotypes and clinical presentation highlighting the role of exercise intolerance, its pathophysiology, the diagnostic algorithms, the clinical presentation and the exercise correlates for therapies and interventions. The present HFA/EAPC clinical consensus statement has been approved and endorsed by the Clinical Practice Guidelines Committee of the ESC.

Bases of exercise limitation and symptoms in heart failure with preserved ejection fraction

The initial view that exercise limitation and symptoms are entirely due to an inadequate ventricular filling due to increased ventricular stiffness[13] has long ago been refuted. Patients with HFpEF exhibit a limited cardiac reserve on exercise[14] due to a multitude of factors including chronotropic incompetence,[15] impaired contractility,[16] atrial dysfunction,[17] atrial rhythm disorders (atrial fibrillation),[18] atrial functional mitral regurgitation[19] inducible ischaemia,[20,21] and unfavourable right ventricle to left ventricle interaction.[22,23]

The overarching hallmark of HFpEF-related exercise limitation has been expanded over the last decade by the accumulating evidence that a constellation of extracardiac pathways play a role in the impaired physiologic reserve capacity, including a limitation in gas exchange with reduced pulmonary vascular reserve,[24] impaired central and peripheral vascular reserve,[25] skeletal muscle dysfunction[26] and iron deficiency/anaemia.[27] HFpEF patients exhibit simultaneous impairment of several pathways, although one mechanism may predominate in a single patient. Historically, a comprehensive evaluation during exercise by CPET can assist in the identification and relative importance of the individual defective mechanisms[28] and the amount of information can be now further implemented by the use of combined imaging and/or invasive haemodynamic measurements.

The Fick principle states that VO_2 is equal to cardiac output (CO) multiplied by the difference in O_2 content in the arterial and mixed venous blood difference ($a-v\ O_2$), which is determined

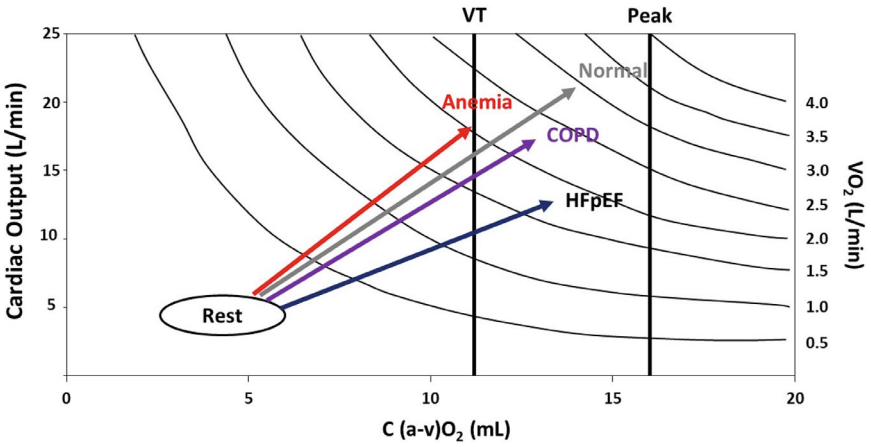


Figure 1 Plot of the Fick principle relating cardiac output to artero-venous oxygen (a−vO_2) difference and isoplets curves of oxygen uptake (VO_2). The graph describes the expected relationship of heart failure with normal control pattern along with chronic obstructive pulmonary disease (COPD) and anaemia conditions as the most common comorbidities that affect oxygen (O_2) content and delivery and may add on heart failure with preserved ejection fraction (HFpEF) haemodynamic, i.e. cardiac output, limitation. VT, ventilatory threshold.

by O_2 delivery, uptake and extraction at the cellular level. The physiological concepts behind these processes are quite complex as well as the adaptive/maladaptive response in the O_2 chain transport and utilization. Especially, O_2 delivery needs to be viewed in a broader perspective in HFpEF considering its dependency not only on the limited cardiac reserve and impaired CO distribution but also on the potential underlying conditions that facilitate a low O_2 content and limited O_2 dissociation from haemoglobin (Hb). O_2 content is actually determined by the ml of O_2 carried by 1g of Hb (1.34) times O_2 saturation and Hb concentration and decreases in hypoxia and anaemia.[6] An intriguing modality to precisely define the relative contribution of Fick principle determinants during exercise in clinical practice is to plot the relationship between CO (y-axis) and a−v O_2 difference (x-axis) trough isopleths curves of VO_2 as shown in *Figure 1*, which depicts the normal response (adequate O_2 delivery and extraction) versus the changes typically encountered in HFpEF (limited O_2 delivery and extraction), COPD (quite preserved CO response and impaired O_2 extraction) and anaemia (impaired O_2 delivery and extraction with increased compensatory CO) conditions.

Oxygen uptake kinetics and determinants

Physical performance and VO_2 kinetics are dependent on the integrated interaction between the following processes: (i) the O_2 content in inspired air; (ii) the exchange of O_2 and carbon dioxide (CO_2) through adequate alveolar ventilation (VA) and lung diffusion (DL); (iii) the O_2 delivery activity by cardiac reserve (CO), blood Hb and vascular system to supply oxygenated blood to meet the increased O_2 demand of working skeletal muscles; and (iv) the O_2 diffusion (DM) process from capillaries to cells and mitochondrial respiration capacity in skeletal muscle.

In HFpEF, the O_2 cascade can be limited at several levels and to a varied extent (*Figure 2*) as pointed out by many studies.[24,29–31] In an innovative HFpEF study performed with invasive CPET, i.e. by expired gas analysis and arterial and mixed venous blood sampling with key parameters directly measured (VA and CO) and others estimated (DL and DM), the individual limiting factors in the O_2 cascade during peak exercise were systematically evaluated by a phenomapping approach.[5] Intriguingly, the O_2 pathways causing exercise intolerance were ranked through a computational system analysis to gauge insights on the functional significance of each O_2 pathway defects, examining factors that influence the magnitude of the O_2 pathway defect and how this may impact on peak VO_2.

The vast majority of patients harboured compound mechanisms of exercise intolerance, defined as two or more defective steps in the O_2 cascade, and a wide variability of putative mechanisms was observed. These data confirm the complexity of HFpEF as a heterogeneous entity at tissue, cellular and molecular level.[32] A typical example of different defective pathways altering the O_2 chain of utilization are two subjects with the same CO increase, but distinct sets of accessory O_2 pathway defects with one showing a predominant impairment in alveolar diffusion and the other presenting with a reduced delivery of O_2 due to concomitant anaemia and/or insufficient O_2 extraction due to impaired mitochondrial oxidative capacity.

This reasoning intriguingly advocates a profiling of the O_2 cascade limitations in every patient, which then could be targeted accordingly.

Exertional limitation in HFpEF is not just related to abnormalities in the O_2 cascade (forward convective and diffusive O_2 properties), as increases in pulmonary capillary pressure also cause 'backward' induction of lung congestion resulting in changes in pulmonary mechanics, gas diffusion, and ventilation–perfusion matching.[33] These changes may occur in tandem with or independent of abnormalities in O_2 delivery. In addition, symptoms of effort intolerance in HFpEF may relate to afferent signals originating in the heart, great vessels, and skeletal muscle receptors sensitive

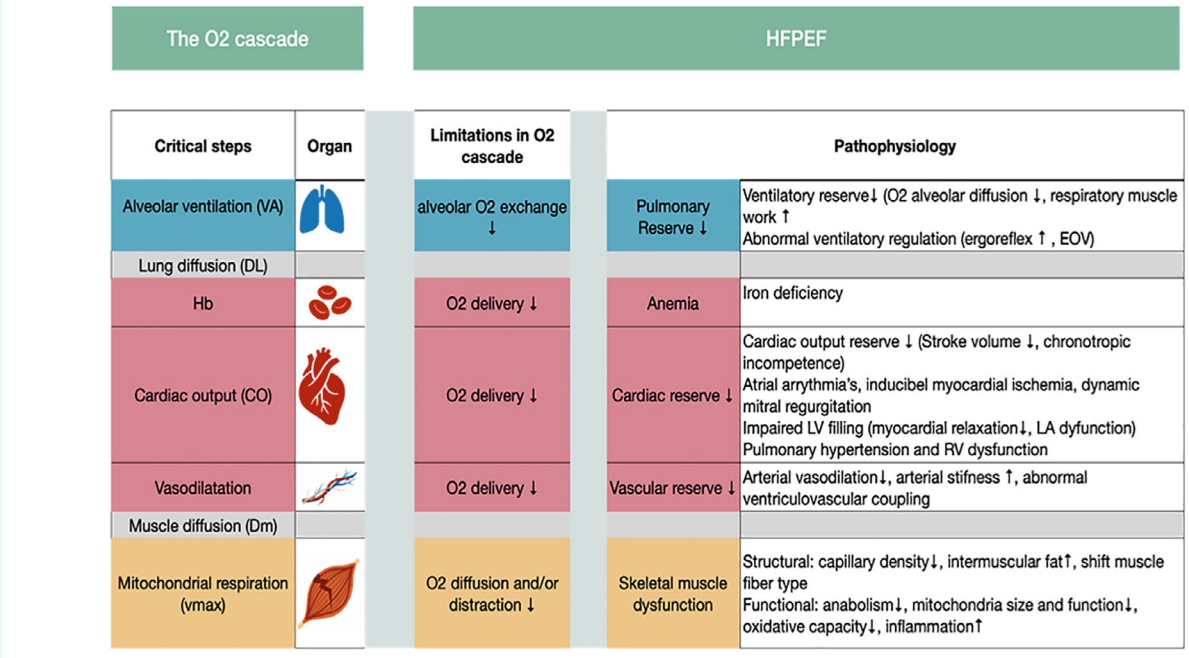


Figure 2 The oxygen (O_2) cascade during exercise. The organ systems and pathways (from air to mitochondria) involved in exercise performance are depicted along with the limiting steps and pathophysiology behind exercise limitation in heart failure with preserved ejection fraction (HFpEF). EOV, exercise oscillatory ventilation; LA, left atrial; RV, right ventricular.

to muscle contraction and metabolic byproducts of cellular respiration (ergoreflex).[34]

Ultimately, patients could be assigned to a specific exercise phenotype based on the profile displayed, and these groups may be amenable to specific and targeted therapies. This approach appears a promising avenue to be further explored and validated with precision medicine.

Cardiac contributions to impaired exercise oxygen uptake

Although stroke volume is often preserved at rest, limitations in cardiac reserve are multifold and represent the main triggers for an exercise defective exercise O_2 pathway in patients with HFpEF.[35]

Impaired myocardial performance and cardiac energetics

Landmark studies have documented a role for a biventricular myocyte stiffening as a major determinant of impaired LV relaxation and tension.[36] Ultrastructural and functional changes in the cardiac myocyte combined with fibrotic changes in the myocardium challenge effective ventricular performance, impairing coronary perfusion and ultimately yielding a cardiac energetic deficit.[37] The exercise-induced failure in LV reserve is typically driven by a progressive elevation in pulmonary capillary wedge pressure (PCWP) and CO reduction and most recent observations directly link the cardiac energetic impairment (low phosphocreatinine/ATP ratio) to the elevation in PCWP and the development of pulmonary hypertension (PH). These findings have led to the intriguing new concept of a energy-based pathway for pulmonary congestion as supported by a raised lung water content even at low workloads.[37]

Chronotropic incompetence

The exercise chronotropic response account for large part of CO increase in healthy subjects and its relative proportional contribution becomes even more relevant in HFpEF.[38] Chronotropic incompetence (CI) is usually defined as failure to attain >80% of the heart rate (HR) reserve but a more objective method to define the relationship between HR and VO_2 during exercise is the metabolic chronotropic relationship (MCR), calculated as the ratio of HR reserve to metabolic reserve during submaximal exercise.[39] MCR adjusts for age, physical fitness, and functional capacity and is unaffected by the exercise testing mode or protocol. A MCR ≤0.80 is indicative of CI.[40] CI is cardinal feature of physically untrained and deconditioned HFpEF patients[38] and basically contributes to a restricted maximal exercise performance as counter proven by the improvement in peak VO_2 after beta-blocker withdrawal.[41] Although very common, the aetiology of CI remains poorly defined with the most solid evidence pointing to an intrinsic electric conduction defect[15] and sino-atrial node dysfunction.[42]

Left atrial myopathy and atrial functional mitral regurgitation

The pathophysiological role of left atrial (LA) dysfunction in its different dynamic phases has progressively gained attention as

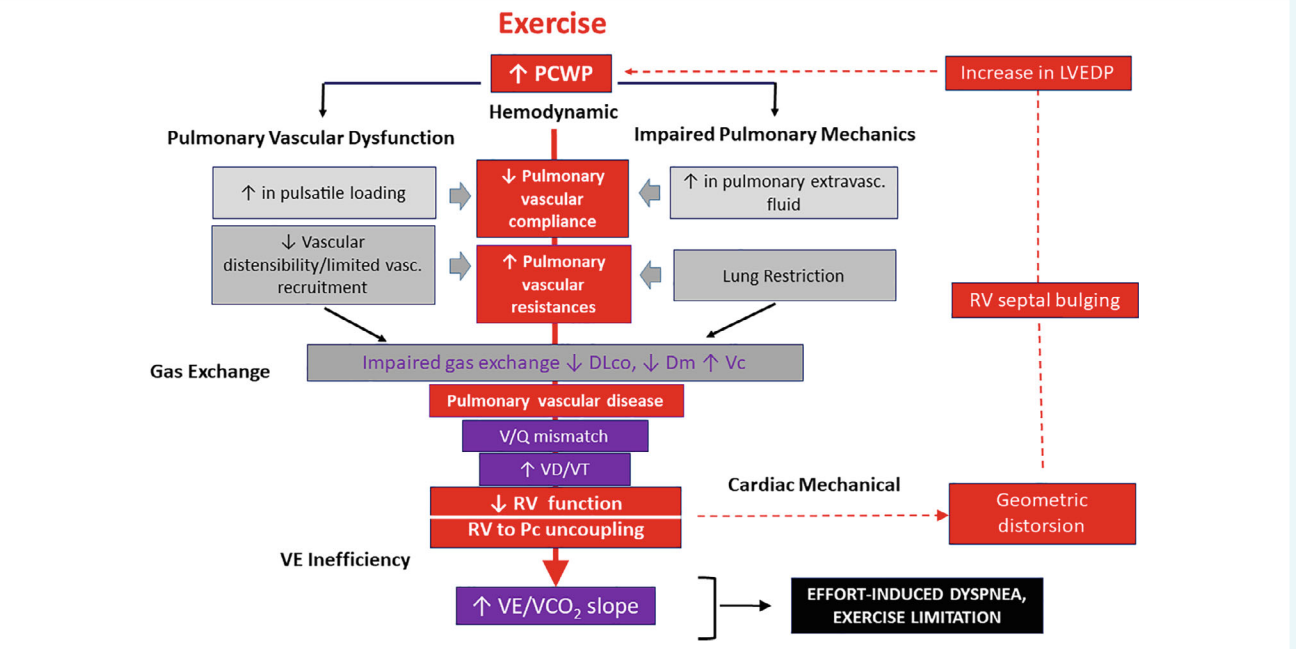


Figure 3 Cascade of the cardiac, haemodynamic and pulmonary maladaptive response under the effects of pulmonary capillary wedge pressure (PCWP) increase. DLco, exercise diffusing lung capacity for carbon monoxide; Dm, membrane diffusion; LVEDP, left ventricular end-diastolic pressure; Pc, pulmonary circulation; RV, right ventricular; Vc, capillary volume; VD/VT, dead space to tidal volume ratio; VE, minute ventilation; VE/VCO_2, minute ventilation to carbon dioxide output. V/Q, ventilation/perfusion

a trigger for symptom generation and exercise limitation.[17,43,44] The information has rapidly evolved thanks to studies performed with speckle tracking suggesting a strong association of LA reservoir impairment measured by LA strain, with peak VO_2 and an elevated ventilation (VE) to carbon dioxide (VCO_2) slope. The active role of the left atrium in CO increase during exercise has recently been addressed with studies of LA dynamics showing how an altered LA reservoir and booster function limits CO increase through combined forward and backward unfavourable haemodynamics.[45]

The vast majority of abnormalities in LA dynamics coexists with the burden of atrial functional mitral regurgitation and atrial fibrillation.[19] Indeed, LA remodelling and atrio-ventricular asynchrony favoured by atrial fibrillation contribute to a low grade mitral regurgitation development that exacerbates biventricular filling impairment and pulmonary vascular dysfunction.[19]

Comorbidities and extracardiac contributors to impaired exercise oxygen uptake impairment

Patients with HFpEF exhibit a high burden of comorbid conditions with an average of five or more coexisting comorbidities at the same time, primarily contributing to adverse outcome and critically impairing exercise capacity.[46] Peak VO_2 is impressively restrained by comorbid conditions, explaining up to 50% of the predicted increase in functional capacity after exercise training (ET) programmes.[47] Nonetheless, a precise dissection on the role of any single comorbid and extracardiac factor may be limited by the coexistence of mixed phenotypes and wide heterogeneity of O_2 pathway derangements.

Systemic arterial and venous system abnormalities

The arterial vascular system plays a central role in modulating compliance and resistances, ventriculo–vascular coupling and blood flow redistribution to the working muscles. In elderly hypertensive subjects, an impaired vascular compliance reduces the wave transit time from the LV to peripheral sites of vascular reflection and back to the aorta, generating a late systolic load which contributes to ventriculo–vascular uncoupling, increased LV filling pressures and high afterload.[48] Despite the fact that vascular stiffening is a well-known hallmark feature of the hypertensive state, only recently have the implications of this been scrutinized under maximal exercise evaluation with gas exchange measurements by applying invasive or estimated measures of arterial functional response and load pulsatility. Exercise central aortic stiffness, assessed by converting radial artery pressure waveforms to central ones, tightly correlates with peak VO_2.[25] Also non-invasive assessment of exercise blood pressure pulsatility by proportionate pulse pressure (pulse pressure/systolic blood pressure) has shown a high ratio as typical of hypertensive and obese HFpEF phenotype, correlating with peak VO_2.[49]

The microvascular peripheral circulation has an important role in O_2 delivery and utilization. Its dilator reserve is abnormal in HFpEF,

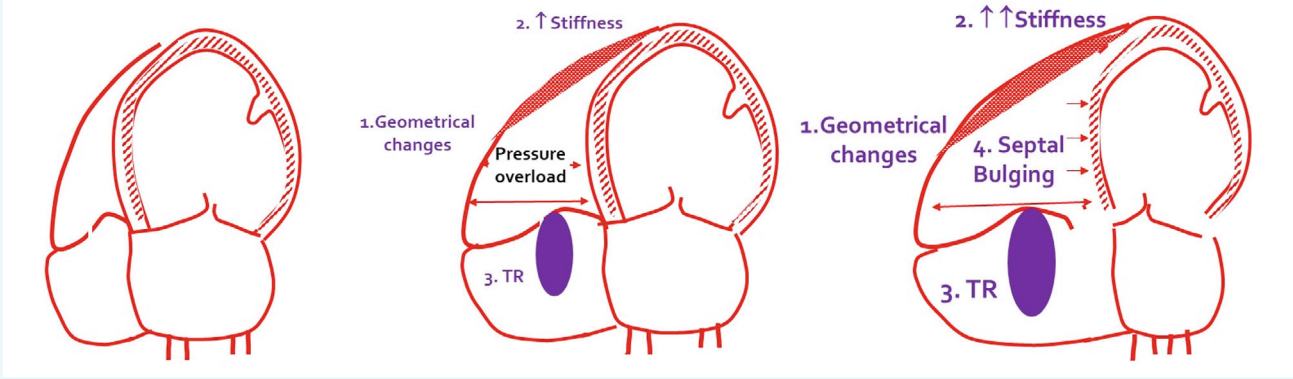


Figure 4 Continuous of mechanisms involved in right ventricular maladaptive response to increased load and pulmonary vascular disease, affecting cardiac output and exercise performance in heart failure with preserved ejection fraction. TR, tricuspid regurgitation.

due to vessel rarefaction, endothelial dysfunction and blunted response to muscle tissue hypoxic vasodilatation, all contributing to exercise limitation.[50] Recently, reports have focused also on the pathogenetic role for the venous system as a balancer in the circulating blood volume distribution. The circulating blood volume is functionally defined as the unstressed volume, which fills the vascular tree and the stressed blood volume which generates wall tension and intravascular pressure. An impairment in the venous capacitance critically shifts blood volume to the stressed blood volume pool, and exercise may further sustain this unphysiological redistribution. The obese phenotype typically exhibits an impaired venous capacitance and overload that abnormally increases the even minimal physiologic pulsatile loading imposed by the venous system, increases the systemic afterload, and may further impedes O_2 delivery and extraction.[51]

Abnormal lung mechanics, pulmonary hypertension and vascular disease

The detrimental role of PCWP elevation is key to effort-induced dyspnoea and generates a cascade of haemodynamic and functional consequences contributing to two main mechanisms common to any HFpEF phenotype, i.e. vascular dysfunction and impaired pulmonary mechanics. Both of these contribute, ultimately, to VE inefficiency and effort-induced dyspnoea[28] (*Figure 3*). Although lung dysfunction may result from concomitant lung disease, fluid swelling due to the alveolar capillary stress failure promotes a typical restrictive lung pattern responsible for a maladaptive heart–lung interaction. Lung interstitial fluid activates the inflammatory and cytokine cascade and leads to pulmonary vascular disease (PVD) in around 30% of HFpEF subjects.[33] Interestingly, PVD may progress independently of the hydrostatic-induced wall breaks pressure-injury based on the local activation of inflammatory and oxidative stress pathways as typically observed in the metabolic syndrome.[52] Pulmonary vascular remodelling involves both the venous and arterial sides of the pulmonary vasculature and critically impacts on the gas exchange process (ventilation/perfusion mismatching) and the right heart dynamics (including increased resistive load and right ventricular [RV] to pulmonary circulation [Pc] uncoupling). PVD detection relies on a thoughtful interpretation of pulmonary haemodynamics and gas exchange with analyses performed at rest and especially during exercise. An increase in resting pulmonary vascular resistance reflects PVD, a condition that can be unmasked in the earlier stages by a pulmonary vascular resistance rise >3 WU during exercise.[53] PVD can be further documented by a leftward shift of the mean pulmonary artery pressure (mPAP) versus CO relationship as a consequence of a dynamic increase in the pulmonary resistive load.[53] The right ventricle becomes stiff and is challenged in its filling and contractile properties, and uncoupling with the Pc ensues.[54]

Although technically challenging, the assessment of the exercise diffusing lung capacity for carbon monoxide (DLco) and its subcomponents, i.e. membrane diffusion (Dm) and capillary volume (Vc) in parallel with CO changes, is explanatory of the altered pulmonary perfusion pattern occurring in HFpEF,[24] definitively resulting in an increased dead space to tidal volume (VD/VT) ratio and inefficient VE.[55] Exercise-induced dynamic congestion often overlaps as an additive reason for impaired gas exchange and vascular distensibility.[56,57] The elevated afterload and RV dysfunction sustains further impairment in lung perfusion and challenges cardiac dynamics through an unfavourable RV to LV diastolic interaction. This may be observed under maximal exercise quite early and even in HFpEF patients who are otherwise asymptomatic at rest.[22] Specifically, in recent years the primary role of the right heart in the limited exercise performance due to the progressive increased load and PVD has been described under a continuum of sequential steps with initial geometrical changes and impairment in RV filling and diastolic stiffness, elongation in the free wall to septum tricuspid valve diameter, tricuspid regurgitation (TR) development and progressive unfavourable diastolic and systolic mechanical RV to LV interaction (*Figure 4*).[54]

Muscle and mitochondrial pathology

There is a clear impairment in skeletal muscle architecture and loss in mass that contribute to an impairment in O_2 transport capacity. An association between peak VO_2 and lean mass has been observed in skeletal muscle biopsy studies showing a change in fibre type

distribution with reduction in fibres type I and impaired capillary to fibre ratio.[58] Older HFpEF patients (compared to age-matched healthy subjects) exhibit an altered skeletal oxidative capacity and reduced mitochondrial content.[59]

Anaemia and iron deficiency

Anaemia and iron deficiency are common in HFpEF and importantly contribute to worsening of symptoms and exercise intolerance by reducing O_2 delivery and muscular storage (via myoglobin) in peripheral tissues.[60] Interestingly, the relative contribution of anaemia to functional capacity impairment can be calculated defining the proportion of peak VO_2 loss due to anaemic condition. As each Hb gram carries 1.34 ml of O_2, and as at peak exercise Hb desaturation is ~70%, each gram of Hb delivers to the muscle about 1 ml of O_2. In normal conditions, Hb is 15 g/dl, and, for a given peak CO (dl/min), one can easily estimate the amount of missing VO_2 attributable to anaemia at peak effort. As an example, if peak CO is 7.5 L/min, that is 75 dl/min, and Hb is 10 g/dl, the amount of VO_2 lacking because of anaemia is 15 (normal Hb) − 10 (observed Hb) × 75 = 375 ml/min. This calculation is reliable in normoxic patients with no cardiac shunt and significant O_2 desaturation. Anaemia may be compensated for by an increase in stroke volume, a mechanism which may be at work in HFpEF but still results in poor O_2 delivery.[60] Iron deficiency maintains an independent clinical role in HFpEF irrespective of anaemia, but its isolated contribution to exercise impairment has recently been questioned and overshadowed.[61,62]

Obesity

Almost half of HFpEF patients are obese or show increased visceral adiposity due to senescence and/or dysmetabolic conditions. Compared to non-obese counterpart, the HFpEF obese phenotype shows a reduced relative peak VO_2. This depends on both central and peripheral mechanisms such as LV filling pressure, lung vasculopathy and increased pulmonary pressures, which rapidly evolve to haemodynamic manifestation of RV dysfunction and superimposed pericardial constraint.[23] A causative role of impaired haemodynamics has recently been recognized in a direct pericardial fat inflammatory activity to impaired filling and increased PCWP.[63] Studies have identified an obese phenotype specific source of impaired myocardial energetics source in the abnormal ATP handling of the mitochondrial creatinine kinase shuttle.[64] Another typical defect observed in obesity is the so-called myosteatosis or excess adipose accumulation in muscle tissue, which correlates with muscle weakness, mitochondrial pathway disruption and impaired exercise performance.[65]

Diabetes mellitus

The diabetic phenotype of HFpEF combines with a higher burden of comorbidities.[66] Diabetes and worse glycaemic control is associated with higher degrees of myocardial fibrosis and myocyte dysfunction. Diabetic patients manifest exercise intolerance because of HR incompetence due to the commonly impaired sympathovagal balance, higher prevalence of anaemia, microvascular disease, endothelial dysfunction, vasoconstriction and impaired mitochondrial function.[66]

Methodology and clinical implications of exercise testing

Exercise limitation in HFpEF patients is primarily assessed with two modalities of exercise testing, the 6-min walk test (6MWT) and the CPET, also combined or not with non-invasive or invasive measurements.

Six-minute walk test

The 6MWT offers the advantage of low cost and ease of use in daily practice. However, exercise cardiac index and filling variables show only a modest correlation with 6MWT distance, indicating that 6MWT distance is influenced by extracardiac factors reducing its value in some indications for diagnostic purposes.[67] Though 6MWT performance may still provide prognostic insights[68] and it has been used for serial therapeutic evaluations,[69–71] a significant learning effect in older HFpEF patients has to be accounted for, as well as non-cardiopulmonary factors that contribute to limitation, such as orthopaedic or neurologic problems. CPET-derived variables are superior for the quantification of exercise capacity and risk stratification.[72]

Cardiopulmonary exercise test

The CPET in tandem with measurement of CO is the gold standard technique to measure aerobic capacity, and allows for interrogation of the principle organ system(s) involved in exercise limitation,[28] differentiating cardiac from pulmonary aetiologies, with the potential to enhance clinical decision-making process and objectively determine the targets for therapies. To these aims, a comprehensive lung function evaluation by spirometry and lung diffusion capacity at rest should precede CPET.

A remarkable additive value of CPET is the well-established capacity to predict outcomes across the various HF phenotypes.[6] Prerequisites for a correct test execution are a stable clinical condition in the previous 4 weeks,[28] and a test duration tailored to reach a 8–12 min maximal duration and a respiratory exchange ratio ≥1.10[73] to cope with the linear increase of gas exchange variables (peak VO_2, HR and work rate [WR])[74] and accurate detection of ventilatory thresholds and slopes (VO_2 to WR relation, VE/VCO_2 slope, oxygen uptake efficiency slope). For these goals a cycle test with a linear workload increase is preferable to treadmill testing with a less gradual increase in workload.[74] In the obese HFpEF phenotype, the excessive metabolic requirement will result in a lower expected maximal workload with equal or higher peak VO_2 than in non-obese counterparts.[23] Other factors to be considered for the test protocol selection include sex, age, cardiovascular risk factors, physical activity levels and comorbidities.

In HFpEF, peak VO_2 reduction is sensitive but not specific and it can discriminate HFpEF from non-cardiac causes of dyspnoea reliably only at very high and very low values.[75] Namely, with a peak VO_2 <14 ml/kg/min, HFpEF is very likely, whereas with a peak VO_2 >20 ml/kg/min HFpEF is very unlikely, and in the range of 14–20 ml/kg/min further testing with stress echo or exercise cath is required. Nevertheless, extending the analysis to the whole array of CPET-derived variables enables more robust delineation of cardiac versus pulmonary or other non-cardiac causes of dyspnoea.[76]

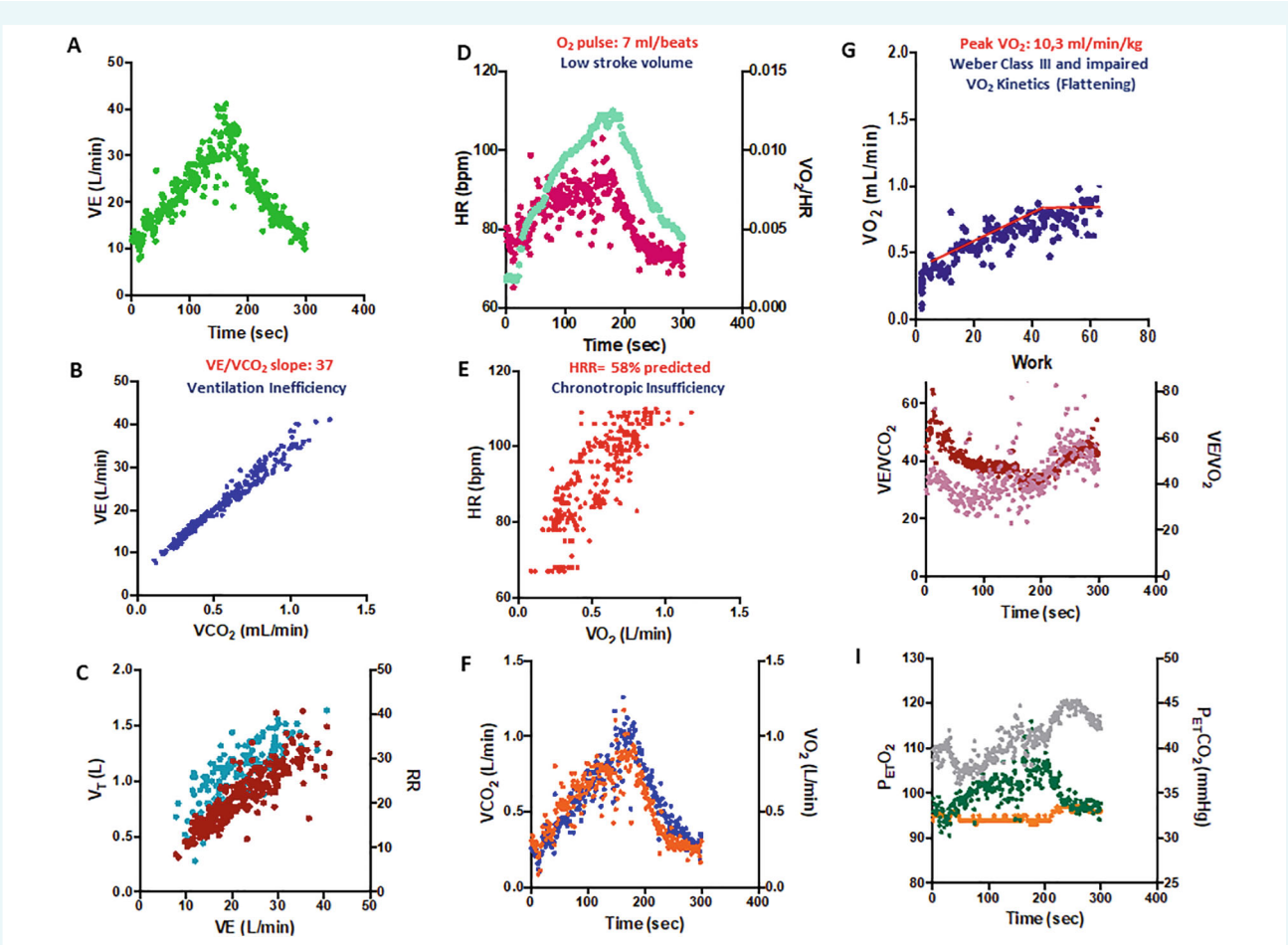


Figure 5 Nine-plot analysis (*A*–*I*) of a typical cardiopulmonary exercise test response of an old hypertensive female patient with exertional dyspnoea. See text for explanation. HR, heart rate; $PetCO_2$, end-tidal carbon dioxide tension; $PetO_2$, end-tidal oxygen tension; VCO_2, carbon dioxide output; VE, minute ventilation; VE/VCO_2, minute ventilation to carbon dioxide output; VO_2, oxygen uptake; VT, ventilatory threshold.

For example, COPD patients with significant limitation in exercise capacity will display a reduction in breathing reserve, i.e. the relative difference between the maximal voluntary ventilation (MVV) and peak exercise VE (<15% reserve indicating a mechanical ventilatory limitation); these patients will further display spirometric abnormalities such as reduced forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio.

However, the study of lung mechanics by inspiratory manoeuvres offers the most sensitive and specific diagnostic tool. The combination of operating lung volumes as measured by serial inspiratory capacity manoeuvres and breathing pattern helps to detect important inspiratory mechanical constraints, relevant to dyspnoea and exercise limitation.[77] This analysis is more sensitive than traditional assessments of breathing reserve (VE/MVV), especially in milder forms of obstructive and restrictive disorders or other cardiorespiratory conditions such as pulmonary arterial hypertension.[78]

Additionally, qualitative assessment of inspiratory and expiratory flow reserves is provided by tidal versus maximal flow–volume loops throughout exercise.[28,77] In COPD, the inefficient VE during exercise is signalled by the VE Y-intercept that increases with greater disease severity.[79] COPD patients have a higher V̇E-Y intercept than HFrEF patients[80] and presumably this is also true compared to HFpEF.

A significant elevation in VE/VCO_2 slope without an alternative explanation should prompt further diagnostic testing toward a pulmonary vascular involvement getting into a differential diagnosis of HFpEF with coexisting pre-capillary PH versus pulmonary arterial hypertension or chronic thromboembolic PH. The well-established prognostic role of VE/VCO_2 slope in HFpEF[81] seems to be similar to HFrEF, though its clinical interpretation should take into account age dependency and gender-related differences.[73]

Attention should also be paid to interstitial lung diseases, which may be suggested by gas exchange abnormalities including a low O_2 saturation (<95% at rest or >5% drop during exercise), increased VD/VT increased alveolar–arterial (A–a) O_2 pressure difference, balanced reductions in FEV_1 and FVC with normal ratio, and decrease in DLco. Patients with HFpEF may display a mild restrictive defect on spirometry, as well as reduction in DLco, so this can be difficult to distinguish, and sometimes relies upon chest computed tomography to evaluate the lung parenchyma,[82] or invasive haemodynamic testing to exclude HFpEF.[83]

However, many more patients can be distinguished without this requirement, and the ability to distinguish predominant pulmonary diseases from HFpEF is a major strength of CPET[84] and crucial to separate and objectively assess how much of the limited performance

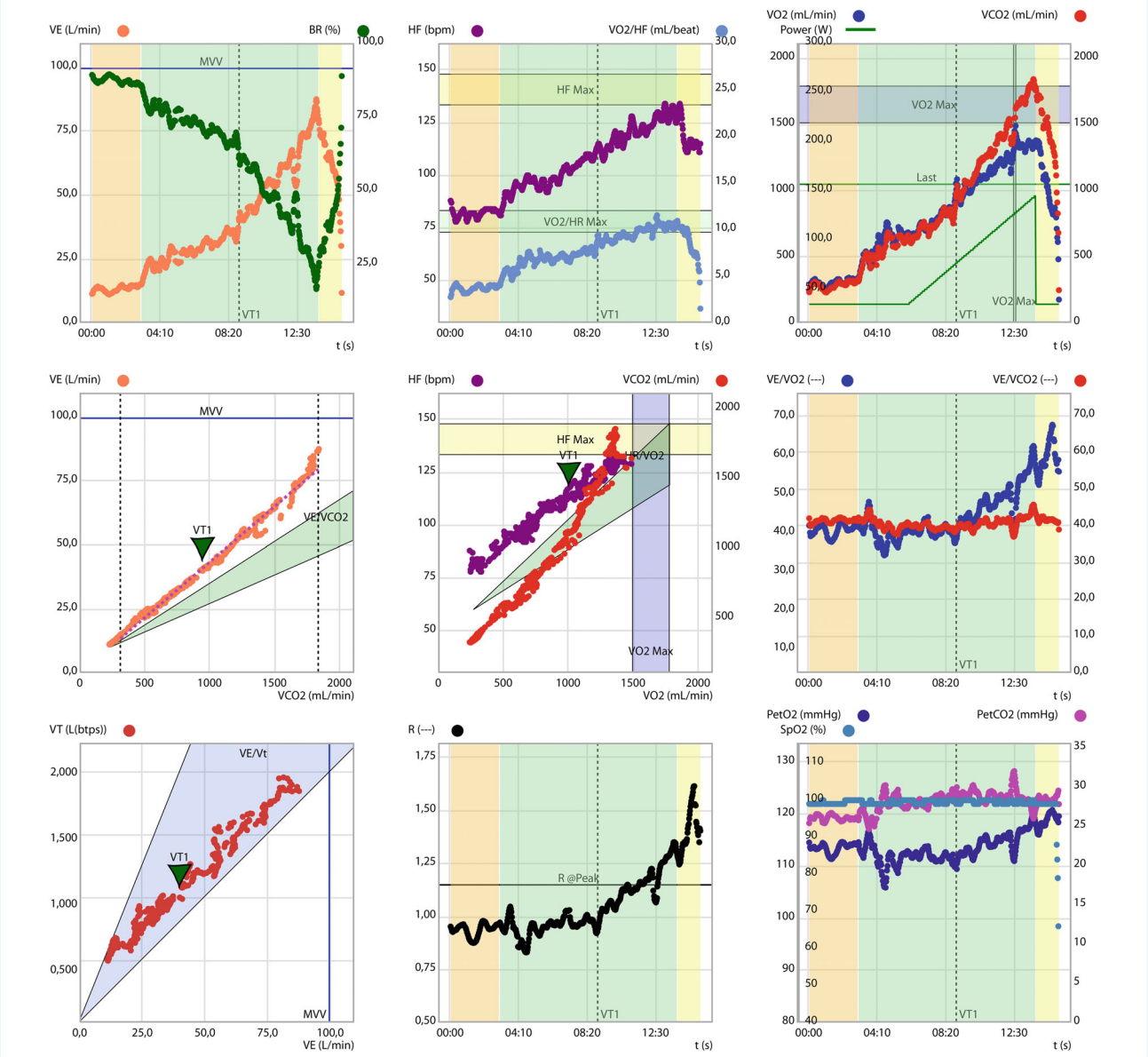


Figure 6 Nine-plot analysis of a middle aged man with initial exertional dyspnoea presenting with a different cardiopulmonary exercise test phenotype. See text for explanation. HF, heart frequency; HR, heart rate; $PetCO_2$, end-tidal carbon dioxide tension; $PetO_2$, end-tidal oxygen tension; VCO_2, carbon dioxide ouput; VE, minute ventilation; VO_2, oxygen uptake; VT, ventilatory threshold.

is pulmonary rather cardiac-related and in case is pulmonary to further detail the cause. Overall, considering that some patients may have both lung disease limitation and HFpEF, invasive CPET may be considered even though non-invasive CPET points to a primary pulmonary limitation. Comorbid chronic lung diseases are common in clinical trials of HFpEF, but the severity is not well-defined even though quite advanced in some cases and this may be a significant unmet need in the correct phenotyping of patients' enrolment in trials and treatment process.

The typical cardiac reserve limitation is signalled by a reduced O_2 pulse, a downward shift in the VO_2 to WR relationship with or without a true VO_2 flattening pattern[85] and chronotropic incompetence[76] as outlined in the 9-plot graphical representation of *Figure 5* reporting a case of a hypertensive and diabetic old lady with a HFA-PEFF score 6 points and an H_2FPEF score 0.6, which is definitively diagnostic and explanatory in terms of pathophysiology and organ system limitation. Exercise data allow phenotyping and show a typical CI (heart rate reserve (HRR) = 58% of predicted), a limited O_2 pulse (7 ml/beats) and a change in VO_2 kinetics under flattening pattern (defined as an inflection in VO_2 linearity as a function of WR in the second part of the exercise >35% compared to the first linear slope, with a duration >30 s). These CPET manifestations are typical of a cardiogenic limitation. A moderate to severe VE inefficiency was also documented by a VE/VCO_2 slope of 37.

When abnormalities in peak VO_2, O_2 pulse, VO_2/WR slope and CI combine with an elevated VE/VCO_2 slope, the coexistence of a right

heart phenotype with PH, elevated pulmonary vascular resistances[81] and RV to pulmonary circulation uncoupling[86] is very likely. A few reports have also shown that exercise oscillatory ventilation may be part of the picture of the gas exchange response during maximal exercise.[87] Thus, in the most advanced stages of HFpEF exercise limitation, a thorough analysis of VE/VCO_2 slope determinants, i.e. VD/VT ratio and $PaCO_2$ may offer valuable insights for planning therapeutic interventions.[55]

Figure 6 reports a 9-plot analysis of a 72-year-old overweight patient complaining initial exertional dyspnoea, arterial hypertension, pre-diabetes, persistent atrial fibrillation, sleep apnoea syndrome and COPD, Gold class 2. His HFA-PEFF score is 4 points and H_2FPEF score is 0.5 pointing to a 85% probability of HFpEF. His CPET performance excludes a respiratory mechanical limitation (breathing reserve of 20%) and, despite a quite relatively preserved peak VO_2 (17.3 ml/kg/min; 78% of predicted) and O_2 pulse (11.1 ml; 92% of predicted), exhibits a severely impaired ventilatory efficiency (VE/VCO_2 slope of 43.3 and end-tidal of CO_2 of 24 mmHg) with a Y-intercept in the upper normal range, a picture suggesting to investigate a potential underlying pulmonary vascular limitation due to impaired vasomotility and increased pulmonary vascular resistances.[81] CPET supported clinical management with (i) exclusion of respiratory mechanical limitation as a cause of dyspnoea, (ii) providing evidence of severe VE inefficiency and prospecting PH under exertion as a major cause of dyspnoea; (iii) showing the need for better rate control of atrial fibrillation; (iv) suggesting a relatively preserved aerobic capacity of the peripheral muscles; and (v) documenting a 10-fold increased risk for incident HF hospitalizations, compared to HFpEF patients with a VE/VCO_2 slope <30.

Exercise stress echocardiography

The study of LV filling adaptations/maladaptations during dynamic exercise is a priority that can be pursued by performing exercise stress echocardiography.[6] Most of the interest has been focused on diastolic adaptation and on the study of LV filling by E/e' changes[88] primarily for diagnostic purposes integrating also with the parallel changes in TR peak velocity and estimated pulmonary pressures during effort.[89,90] Among the technical requirements, the semi-recumbent position is suggested for a better Doppler evaluation.

Incremental ramps at low workload (8–15 W/min) are preferable for a comprehensive image acquisition. Loop storage of adequate duration (5 beats) is required in order to perform the averaging of measures, especially for Doppler parameters, accounting for physiological respiratory variations. Pulsed-wave Doppler echocardiography also enables measurement of CO at rest and during exercise, which can be of great value in distinguishing patients with predominant central versus peripheral abnormalities.[45]

The HFA-PEFF recommendations suggest to perform exercise stress echo at step 3 (F1), primarily looking at mitral E/e' and the TR peak velocity.[1] Compared to invasively determined PCWP, an E/e' >13 has been identified as a pathological cut-off.[91] The isolated increase in TR is not specific for HFpEF because it may depend on intrinsic RV dysfunction and/or PVD. Remarkably, in approximately 30% of cases, TR velocity cannot be reliably assessed.[92] Also, its correlation with the invasive RV to right atrium gradient at peak exercise is moderate ($r = 0.72$) with a small bias (−1 mmHg).[93] Echo Doppler is less consistent to measure pulmonary pressures during exercise because right atrial pressure cannot be reliably estimated and in case of RV to Pc uncoupling during effort, the contribution of right atrial pressure can be even higher than the RV to right atrium gradient estimate. Technically, an improved definition of TR velocity signal may be obtained with agitated gelofusine administration yielding to a 87% feasibility and the correlation with invasive measures is significantly improved (+2.9 mmHg).[94]

Cardiopulmonary exercise test imaging

Cardiopulmonary exercise test imaging is a comprehensive and expanding approach which combines the advantage to address the exercise physiological implications with non-invasive haemodynamic data by echocardiography. Cardiac functional reserve is extended to the integrated analysis of measures of chamber volumes, geometry, valvular status, systolic and diastolic function, including the assessment of LA dynamics and response of the right heart.[45,95] The full non-invasive nature and the considerable amount of clinical information are complementary and synergic to those obtained with invasive CPET. However, caution should be applied when comparing gas exchange information obtained in the sitting position due to the different impact of preload changes during exercise.

Application of CPET imaging in HFpEF is expanding and covers the wide spectrum of clinical presentation from the early diagnostic process to the advanced right heart involvement taking advantage of the combined pathophysiological and prognostic insights of gas exchange-derived variables.[96]

An initial study combining CPET and Doppler analysis led to the ultimate diagnosis of HFpEF in the subset of patients presenting with an elevated VE/VCO_2 slope combined with an average E/e' >15 at peak exercise.[97] Subsequent studies have implemented the interest for E/e' to the role of LV deformation primarily assessed by speckle-tracking analysis[98] and lung congestion by the analysis of exercise-induced B-lines[99] which have been shown to predict HFpEF better than standard echocardiographic estimation of filling pressure.[100] However, recent findings by invasive simultaneous study have shown that around 50% of HFpEF patients with exercise PCWP elevations do not present with B-lines.[3]

Most recent findings have also focused in depth on LA dynamics[17] highlighting the putative role of an impaired LA deformation (LA strain) during exercise as a key step in the backward and forward haemodynamic impairment and symptom cascade.[45] Indeed, among all echocardiographic data obtained at rest, abnormalities in LA strain seem to be most strongly correlated with haemodynamic abnormalities that develop during exercise.[45] Evidence has been brought also on the role of mitral regurgitation[19] and its dynamic component during maximal exercise[101] to physical limitation along with its remarkable prognostic value.[19,45]

Figure 7 reports an example of advanced CPET imaging application in HFpEF (gas exchange data in *Figure 3*) by studying LV systolic dynamics (3D strain analysis) and filling (E/A and E/e'), LA dynamics (LA strain analysis) and RV function analysis (RV to Pc coupling by tricuspid annular plane systolic excursion/systolic pulmonary artery pressure [TAPSE/PASP] ratio and RV ejection fraction by three-dimensional acquisition) at rest and at peak exercise. Data show a preserved LV deformation analysis with exercise increase in LV filling pressure (E/e': from 12.6 to 16.9); a severely limited LA strain (10.5% at rest and 9.6% at peak exercise) and a loss in RV ejection fraction (57% at rest and 45% at peak exercise) with exercise-induced PH (PASP of 41 mmHg at rest and 58 mmHg at peak exercise). The CPET-derived 9-plot analysis fits with the documentation of cardiogenic limitation and a ventilatory pattern common in left-sided PH.

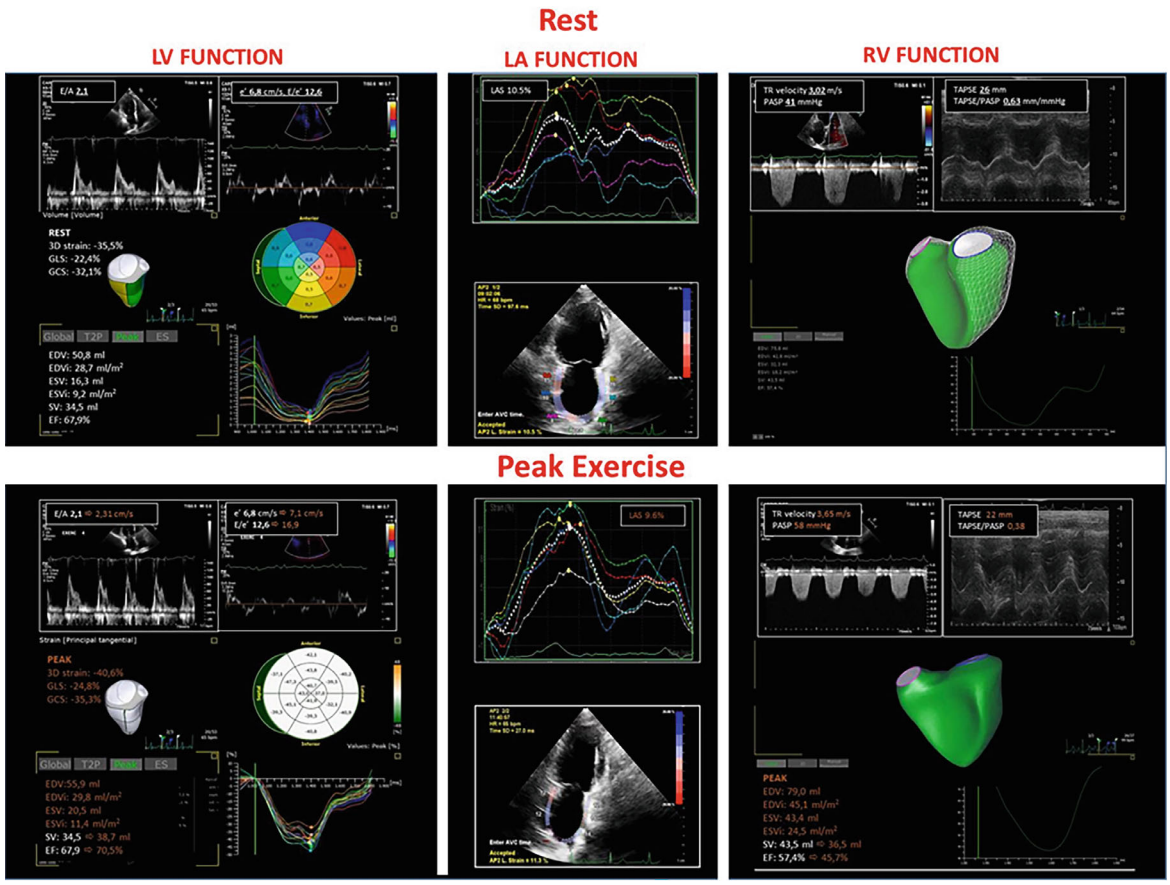


Figure 7 Cardiopulmonary exercise test imaging rest to peak exercise analysis of the same case as *Figure 5*. Measures obtained by stress echocardiography (rest to peak exercise). The analysis was performed analysing the diastolic (E/e') and systolic (three-dimensional longitudinal and circumferential strain) left ventricular (LV) function; the adaptive left atrial (LA) dynamics by LA strain (LAS); right ventricular (RV) function (RV ejection fraction 3D analysis) and its coupling with the pulmonary circulation by the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/PASP) ratio. Data are reported at rest (white) and at peak exercise (orange) with the changes occurring in the main variables from rest to peak. TR, tricuspid regurgitation.

Invasive cardiopulmonary exercise test

In the last 10 years, there has been a progressive reappraisal of invasive CPET as the gold standard approach for the thorough characterization of the haemodynamic reasons for exercise limitations, precisely dissecting central and peripheral mechanisms throughout direct measures of LV filling pressures, pulmonary haemodynamics, CO, and a−v O_2 differences. In HFpEF, pulmonary haemodynamic measurements during exercise, especially PCWP and mPAP, may yield to incremental prognostic value compared with evaluation at rest only.[102] Although technically challenging, invasive assessment of pulmonary haemodynamics is more sensitive and specific compared to fluid loading for detection of an abnormal rise.[103,104]

Borlaug *et al.*[38] first reported the potential to suspect HFpEF in subjects with unexplained dyspnoea, whilst euvolaemic with normal levels of B-type natriuretic peptide and without clear signs and symptoms of HF at rest. In half of the subjects, the observed increase in PAWP during exercise was concordant with LV end-diastolic pressure, though it was preliminary to a diagnosis. Studies have then well established that an increased mean PCWP ≥25 mmHg at peak exercise, even in the absence of elevations in pulmonary vascular resistance, indicates HFpEF.[105] Some groups have advocated for assessment of the PCWP increase during exercise to CO relationship, with a cutoff ≥2 mmHg/L/min shown to be associated with adverse outcomes. Furthermore, the analysis of biventricular interaction and changes in right atrial pressure versus PCWP implement the diagnostic information with the pressure-induced unfavourable RV to LV interaction mechanisms, intended as a decrease in the pressure gradient between the left and right ventricle, and a change in septumbecoming less convex toward the right ventricle is documented even at earlier stages of HFpEF.[22,53]

In the most advanced cases, accurate assessment of the pressure−flow relationship during exercise by plotting mPAP versus CO provides a robust indication of abnormalities in RV to Pc coupling.[53] A mPAP/CO relationship >3 mmHg/L/min is reflective of a pulmonary hypertensive response, indicating abnormalities in pulmonary vascular reserve, often associated with a high VE/VCO_2 slope.[106] Even more, the occurrence of RV to Pc uncoupling is responsible for a delayed VO_2 on kinetics during early exercise.[29]

Incorporating exercise testing within the HFA-PEFF algorithm

The HFA-PEFF algorithm includes ergometry and 6MWT, however CPET is not recommended as a typical element of the initial HFpEF workup, mainly because of the low specificity to diagnose HFpEF.[75] Nonetheless, the role of cardiac versus pulmonary predominance in generating symptoms is crucial.

The use of CPET along the steps of the HFA-PEFF appears also quite relevant for implementing the diagnostic and clinical oriented approach. Peak VO_2 should be paralleled by the VE/VCO_2 slope analysis in the search for a right heart involvement and PH coexistence, adding both specificity and specificity to HFpEF diagnosis.[81]

The CPET may then play a role in an in-depth phenotyping of the functional response assisting in the identification and relative importance of the individual defective mechanisms in the O_2 cascade, allowing assignment of patients to a specific exercise-based HFpEF phenotype.[5]

Therefore, translating these concepts to the HFA-PEFF algorithm would enable important implementations in the diagnosis and clinical workup of HFpEF. Accordingly, we propose that CPET assessment should be referred in more details in Step 1 (P, pre-assessment) to ascertain the degree of functional limitation and to address toward the primary origin of symptoms, and in Step 4 (F, final aetiology) for a comprehensive analysis of O_2 cascade organ-related defective mechanisms. This conceivable pathophysiological-oriented supported approach would certainly require dedicated studies aimed at exactly defining the prioritization order to get an ideal operationalization of gas exchange analysis even better when combined with imaging and invasive haemodynamic evaluation[76,107] (*Graphical Abstract*). Information in terms of prognosis and clinical work-up should be derived at all steps proposed.

Step 1 (P): pre-assessment

Exercise gas exchange can delineate cardiac and extracardiac reserve capacity impairments contributing to exertional intolerance.[76,77] Importantly, abnormal findings under resting (e.g. spirometry, echocardiography) may anticipate but not definitively prove their relevance to exertional dyspnoea. If the diagnosis of HFpEF is ruled out by the HFA-PEFF score (Step 2 [E]), or by a diastolic stress test (Step 3 [F1]), the collected data at CPET evaluation could provide alternative explanations of cardiac and non-cardiac reasons of exertional dyspnoea, or at least provide evidence to pursue further examinations to determine the true source of symptoms.

Step 4 (F): final aetiology

If the diagnosis of HFpEF is classified according to the HFA-PEFF criteria, CPET may additionally rank-order multiorgan system limitations, illustrate O_2 pathway defects, and support aetiological work-up, risk stratification, and therapeutic guidance.[40,108] Specifically, the combination of CPET data with findings of chronotropic incompetence, elevated PCWP,[75] PH, exercise-induced mitral regurgitation and RV dysfunction may definitively secure HFpEF diagnosis and potentially enhance care through improved phenotyping.[76] Compared to HFrEF, the heterogeneous manifestation of HFpEF phenotype[87,108,109] may well explain how a robust use of CPET-derived variables in clinical risk stratification is lacking.[110]

However, emerging evidence suggests that also in HFpEF, CPET variables, namely peak VO_2 and the VE/VCO_2 slope, provide incremental prognostic value beyond clinical variables based on the C-statistic, net reclassification improvement, and integrated diagnostic improvement.[108] Notably, in a study by Nadruz *et al.*,[108] the magnitude of association of peak VO_2 and VE/VCO_2 slope with adverse outcomes was greater in HFpEF versus HFrEF. Additional risk definition can actually be derived from invasive CPET and CPET imaging (*Table 1*).[14,40,73,76,77,81,85,87,93,96,102,105,108,111–121]

Testing effectiveness of interventions through functional evaluation

Functional capacity has been addressed as an endpoint in several interventional trials of HFpEF focusing on peak VO_2 as the main reference variable. Pharmacological trials in HFpEF have historically been unsuccessful in improving functional capacity and symptoms on effort,[70,122,123] though more recent human data on levosimendan (Reference 124) and animal model of exercise -induced PH treated with sodium–glucose cotransporter 2 inhibitor have revealed promising effects on functional capacity.[103,124]

In addition to pharmacologic treatments, ET interventions have particularly become accepted since the earlier evidence on their effectiveness to modulate dyspnoea on exertion and to increase peak VO_2.[125–127] In these studies, CPET has acquired a primary role in both planning ET interventions and measuring the extent of benefits.

In parallel, lifestyle interventions may be effective to prevent HFpEF,[128] to favourably affect several abnormalities of the HFpEF syndrome[129] and to effectively improve peak $\dot{V}O_2$, but prospective data on prevention are lacking. In patients with prevalent HFpEF, a landmark lifestyle intervention trial targeting weight loss, examined the effects of ET and caloric restriction in HFpEF versus controls on changes in peak $\dot{V}O_2$ over 20 weeks of treatment.[130] ET and caloric restriction resulted in similar changes in peak $\dot{V}O_2$ (average effect of ET: 1.2 ml/kg/min vs. diet 1.3 ml/kg/min) and weight loss. This is impactful as most patients with HFpEF are overweight or obese, and body mass index is a main determinant of peak $\dot{V}O_2$[131] and New York Heart Association functional class.[132]

Effectiveness of ET programmes in HF have been further scrutinized by performing high-intensity interval training (HIIT) in addition to traditionally prescribed moderate continuous training (MCT). The largest randomized controlled trial performed in HFpEF so far is the OptimEx trial (Optimizing Exercise in HFpEF),[133] which compared MCT versus HIIT, revealing that both ET intensities of moderate as well as high intensity may improve peak $\dot{V}O_2$ after 3 months of supervised endurance ET in stable HFpEF patients. Specifically, ET resulted in a mean increase

Table 1 Cardiopulmonary exercise testing variables delineating oxygen pathway defects, and risk stratification in heart failure with preserved ejection fraction

Variable	Cut-off	Interpretation
Quantification of exercise intolerance		
RER	<1.0 ≥ 1.0, preferably ≥1.1	Definition of submaximal or maximal exercise testing[73,112]
Peak VO_2 (ml/kg/min)	*Weber class* A >20.0, B 16.0–20.0, C 10.0–15.9 D <10.0 or age- and sex-specific cut-offs	Categorization of cardiorespiratory fitness can be used in maximal exercise tests either classified based on Weber or on healthy adult cohorts[73,113]
OUES (L/min/log[L/min])	Age- and sex-specific cut-offs	Submaximal parameter that correlates with peak VO_2[113,114]
VO_2@VT1 (ml/kg/min)	Age and sex-specific cut-offs	Submaximal parameter that correlates with peak VO_2[113]
Ventilatory mechanical limitation		
BR (%)	<15–20	Ventilatory limitation[77]
VFL/VT (%)	>50	Expiratory airflow limitation[77]
IC (ml)	Decrease >140	Dynamic hyperinflation[77]
EELV (ml)	Increase instead of decrease	Dynamic hyperinflation[77]
Pulmonary vascular limitations defined by gas exchange abnormalities and/or haemodynamics		
VE/VCO_2 slope (L/min/ml/kg/min)	>30	Reduced ventilatory efficiency due to increased ventilation and/or increased death space ventilation.[112] Elevations associated with higher PVR and more severe diseases in HFpEF patients with PH[115]
VE intercept	<2.64 L/min	May discriminate HFpEF from COPD HFpEF[116]
SaO_2 (%)	Decrease ≥5	Gas exchange abnormalities, most commonly related to V/Q mismatch[73,77]
VD/VT (%)[a]	No decrease from baseline or blunted response	Increased dead space ventilation related to V/Q mismatch and/or rapid shallow breathing,[77] associated with increased PVR and PH in HFpEF[115]
PA–aO_2[a] (mmHg)	Increase above age- and sex-specific normal values	Gas exchange abnormalities, most commonly related to V/Q mismatch[77,117]
PaO_2 (mmHg)[a]	Decrease ≥10	Gas exchange abnormalities, most commonly related to V/Q mismatch[77]
Exercise PCWP (mmHg)[b]	≥25	Cut-off for exercise-induced PH with limited validity[76,93]
ΔPAP/ΔCO (mmHg/L/min)[b]	>3	Alternative marker of exercise-induced PH[76,93]
ΔTPG/ΔCO (mmHg/L/min)[b]	>1	Pre-capillary PH[76,93]
Cardiovascular limitations defined by gas exchange abnormalities and/or haemodynamics		
VO_2/work rate trajectory (ml/kg/min/W)	Flattening or decline	LV dysfunction due to myocardial ischaemia,[118] or right-sided cardiac dysfunction and PH in HF[85]
O_2 pulse trajectory (ml/kg/min/bpm)	Flattening or decline	LV dysfunction due to myocardial ischaemia[118]
HR/VO_2 slope (bpm/ml/kg/min)	>50	Relative tachycardia to VO_2[77]
MCR	≤0.80 or <0.62 on beta-blocker	Chronotropic incompetence[40]
ΔPCWP/ΔCO slope (mmHg/L/min)[b]	>2	Impaired LV reserve capacity[76,111]
Exercise RAP (mmHg)[b]	>PCWP	RV dysfunction[76]
ΔCO/ΔVO_2 slope (ml blood/ml O_2)[b]	<4.8	Impaired CO reserve due to cardiac limitations or preload reserve failure[14]
Peripheral muscle limitations		
VO_2@VT1 (ml/kg/min)	<40% of predicted	Early first ventilatory threshold suggests peripheral muscle limitation[77]
Peak C(a–v)O_2 (ml/dl)[b]	<0.8*haemoglobin	Impaired peripheral O_2 utilization[76]
VO_2 kinetics	MRT <60 s	Impaired peripheral O_2 utilization in HFpEF,[119] may also indicate impaired RV pulmonary vascular function in HFrEF[120]

Table 1 (Continued)

Variable	Cut-off	Interpretation
Risk stratification		
VO_2peak (ml/kg/min)	<14	Predicts higher risk of HF hospitalization and the composite outcome of all-cause death, LVAD implantation, or heart transplantation, in particular when combined with VE/VCO_2 slope >30[108]
VE/VCO_2 slope	>30	Predicts higher risk of HF hospitalization and the composite outcome of all-cause death, LVAD implantation, or heart transplantation, in particular when combined with VO_2peak <14 ml/kg/min[108] Predicts mortality in HFpEF patients with PH[81]
EOV	Present	Predicts higher risk of CV death[87]
HRR at 1 min (bpm)	<12 decrease	Predicts higher risk of CV death[121]
PCWP/CO slope (mmHg/L/min)[b]	>2	Predicts higher risk of the composite outcome of CV death, HF hospitalization, or abnormal resting PCWP on future right heart catheterization[111]
PCWP/workload/kg (mmHg/W/kg)[b]	>25.5	Predicts higher risk of all-cause mortality, independently of baseline PCWP[105]
PAP/CO slope (mmHg/L/min)[b]	>3	Predicts higher risk of first HF hospitalization or all-cause mortality, both in patients with or without resting PH[96,102]

BR, breathing reserve; $C(a-v)O_2$, difference in oxygen content in arterial and mixed venous blood; CO, cardiac output; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EELV, end-expiratory lung volume; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HRR, heart rate reserve; IC, inspiratory capacity; LV, left ventricular; LVAD, left ventricular assist device; MCR, metabolic–chronotropic relationship; OUES, oxygen uptake efficiency slope; PA-aO_2, alveolar–arterial oxygen gradient; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RER, respiratory exchange ratio; SaO_2, arterial oxygen saturation; TPG, transpulmonary gradient; VCO_2, carbon dioxide output; VD/VT, ratio of dead-space ventilation to tidal ventilation; VFL/VT, percent of the tidal breath that expiratory airflow exceeds the maximal flow/volume envelope; VE, minute ventilation; VE/VCO_2, minute ventilation to carbon dioxide output; VO_2, oxygen uptake; VT, ventilatory threshold (VT1/VT2 corresponding to anaerobic threshold/respiratory compensation point).
[a]Derived from additional arterial blood gas analysis.
[b]Derived from additional invasive measurement (right heart catheterization).

of peak $\dot{V}O_2$ by +1.1 ml/kg/min for HIIT and +1.6 ml/kg/min for MCT. These changes were less compared to findings of a previous meta-analysis of six smaller studies (n = 276 patients) over 12–24 weeks of ET (+2.7 ml/kg/min; 95% confidence interval 1.79–3.65).[134] Overall, data have shown that ET carries beneficial effects that are primarily mediated by peripheral rather than central determinants, e.g. myocardial diastolic function did not change significantly.[133,135] Rather, the effects seem to be related to training adherence, as the most adherent patients exhibited the most effects on peak $\dot{V}O_2$ and diastolic function.[133] Prevention of HFpEF may be different, as recent data indicate that sustained ET can improve LV diastolic stiffness in adults without HF.[136] This may relate to greater plasticity of myocardial dysfunction prior to HF onset, or a greater dose and duration of ET applied.

Data obtained by CPET can be extremely helpful for prescribing exercise intensities in HFpEF.[28] Beyond intensity modalities, e.g. Borg rating of perceived exertion (RPE), percentage of maximal HR (%HRmax), or percentage of HRR (%HRR), ventilatory thresholds, e.g. VT_1 and VT_2, may clearly differentiate individual metabolic and respiratory exercise intensity levels. Although a rough estimate can be given for e.g. 60–70% HRR, which equals VT_1 and 80% of HRR, which equals VT_2, precise HR corridors for exercise prescription are needed. This is especially relevant in HFpEF, as these patients have a high prevalence of CI, which affects the estimation of exercise HR by using the fixed HRmax or HR reserve formula. In these cases, the prescribed HR range, e.g. for MCT, is narrow and target training intensities may be falsely calculated when using traditional parameters, e.g. %HR max.[137]

Moreover, individual responses to exercise vary widely despite similar exercise interventions as well as levels of adherence. This response heterogeneity is typical of HFpEF, as it is known to be a multifactorial and highly heterogeneous disease[138] and patients are almost exclusively suffering from multiple defects affecting the convective and diffusive O_2 delivery.[5] In the OptimEx trial, the adaptive range to improve exercise capacity varied significantly among HFpEF patients, thus suggesting the potential value of personalized prescription of exercise intensity, which can be materially aided by the evaluation of baseline CPET parameters.

Conclusions and perspectives

In HFpEF, exercise intolerance is a hallmark manifestation, characterized by impairment in the physiological reserve capacity of multiple organ systems that is the cardiac dynamics itself and/or related comorbid conditions and extracardiac factors. The relative cardiac and extracardiac deficits vary among individuals. Therefore, detailed measurements made during exercise are necessary to identify and rank-order the multiorgan system limitations in exercise reserve capacity. In this context, the value of CPET is well established in clinical practice in its ability to assess a multitude of derived variables, to address the specific phenotypes of

exercise impairment, providing insightful information in the multi-step limitation of the O_2 cascade and directing attention towards the cardiac or non-cardiac reasons for exercise limitation. While CPET is most useful to differentiate HFpEF from non-cardiac dyspnoea at the extremes of peak VO_2, it also provides valuable insight into potential pulmonary causes of dyspnoea, supporting its use earlier in the diagnostic evaluation. Advantages of the use of CPET also extend to planning of ET programmes as well as to the documentation of the effectiveness of therapeutic interventions. For these reasons an implementation of CPET use in the early and advanced diagnostic steps of the HFA-PEFF score is adopted. A similar rationale applies to patients evaluated using the H_2FPEF score, where CPET can be helpful in the initial diagnostic workup, as well as to guide medical decision making in patients where the diagnosis is secured. The use of gas exchange analysis with stress echocardiography by CPET imaging and/or invasive assessment remarkably increases the amount of diagnostic, pathophysiological and therapeutic insights. Under the European perspective, there is a need to expand CPET-derived knowledge to HFpEF by implementing in clinical cardiology with infrastructure and expertise that may be lacking. Accordingly, the new ESC/EAPC curricula for core cardiology and subspecialty training aim at these goals.[139,140]

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