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Exercise Testing in HFpEF: an Appraisal Through Diagnosis, Pathophysiology and Therapy

A Clinical Consensus Statement of the Heart Failure Association (HFA) and European Association of Preventive Cardiology (EAPC) of the European Society of Cardiology (ESC)

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Abstract

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 have not been systematically considered in the recent algorithms/scores for HFpEF diagnosis, neither by European nor US groups.

The current Clinical Consensus Statement by the HFA and EAPC Association of the ESC aims at outlining the role of exercise testing and its pathophysiological, clinical and prognostic insights, addressing the implication 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 on 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 echo and/or invasive hemodynamic evaluation is here provided. This will lead to improved quality of diagnosis when applying the proposed scores and may also help useful to implement the progressive characterization of the specific HFpEF phenotypes, a critical step toward the delivery of phenotype-specific treatments.

Key words: HFpEF, exercise, functional limitation, gas exchange anaysis

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1. Introduction

Heart failure 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 to clinical practice as tools to help establish the diagnosis: the HFA-PEFF score of the Heart Failure Association of the European Society of Cardiology [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 brain natriuretic peptide (NT-pro-BNP) [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 and 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 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 noninvasive functional capacity evaluation[6] and offers a unique opportunity to investigate the role of lung mechanics and cardiopulmonary interactions with muscle weakness. In HF with reduced EF (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 dyspnea. Indeed, one such etiology 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 the TOPCAT (treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonists) 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

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cause of symptoms in at least some of these patients.[8] Even more in the PARAGON-HF trial, 1 in 7 patients was diagnosed with COPD and this subset presented with worse outcome[10].

Furthermore, community-based cohort studies demonstrate a high prevalence of transthyretin amyloid cardiomyopathy in HFpEF patients with ventricular wall thickening, particularly in older men [11]. Patients with ATTR-CM often present with a severely reduced ventilatory efficiency and peak O_2 uptake 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 point 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 rule-out of non-cardiac-related impairment.

Because 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 noninvasive CPET in isolation may be insufficient to discriminate HFpEF from non-cardiac dyspnea in some patients without adding invasive testing, its role as an early stage investigation to exclude pulmonary disease, and potential role in more advanced phenotyping or to gauge treatment response, may be important emerging uses. The purposes of this *Clinical Consensus Statement* are to provide an updated document focusing on: (a) the sources of exercise limitation and its pathophysiology in HFpEF phenotypes; (b) the role of CPET in differentiating pulmonary versus cardiac mechanisms for unexplained exertional dyspnoea from the early diagnostic process to the advanced stages, highlighting its value for risk stratification and therapeutic tailoring; (c) the interventions which may improve exercise performance in HFpEF effectively targeting the multiple limiting steps of O_2 kinetics .

2. Literature search and document approval

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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 Clinical Consensus Statement has been approved and endorsed by the CPG Committee of the ESC.

3. Bases of exercise limitation and symptoms in HFpEF

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 (AFMR) [19] inducible ischaemia [20,21], and RV to LV 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 hemodynamic measurements.

The Fick principle states that VO_2 is equal to CO multiplied by the difference in O_2 content in the arterial and mixed venous blood difference (a-v O_2), which is determined by O_2 delivery, uptake and extractionat 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, the 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 a gram of Hb (1.34) times O_2 saturation and Hb concentration and decreases in hypoxia and anemia [6]. An

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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 (impaired O_2 extraction) and anemia (impaired O_2 delivery and extraction with increased compensatory CO) conditions.

4. O_2 Uptake Kinetics and Determinants

Physical performance and O_2 uptake kinetics is dependent on the integrated interaction between the following processes: 1) The O_2 content in inspired air; 2) The exchange of O_2 and CO_2 through adequate alveolar ventilation (VA) and lung diffusion (DL); 3) 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; 4) 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 [24,29,30,31]. 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 heterogeneic 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 anemia and/or insufficient O_2 extraction due to impaired mithocondrial oxidative capacity.

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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 the 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 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.

5. Cardiac Contributions to Impaired Exercise O_2 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 myocite 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 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 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 Insufficiency (CI)— The exercise chronotropic response account for large part of CO increase in healthy subjects and its relative proportional contribution becomes even more relevant in the HFpEF[38]. 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 ratio of the HR reserve to the metabolic reserve during submaximal exercise[39]. MCR adjusts for age, physical fitness, and functional

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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 ethiology 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 (AFMR)— The pathophysiological role of LA dysfunction in its different dynamic phases has progressively gained attention as a trigger for symptoms generation and exercise limitation [17,43,44]. The information have 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 LA in the cardiac output (CO) increase during exercise has been recently addressed with studies of LA dynamics showing how an altered LA reservoir and booster function limits the CO increase through a combined forward and backward unfavourable haemodynamics[45].

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

3. Comorbidities and Extracardiac Contributors to Impaired Exercise O_2 Uptake Impairment

HFpEF patients exhibit a high burden of comorbid conditions with an average of 5 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 programs [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 pathways derangements.

Systemic Arterial and Venous Systems Abnormalities — The arterial vascular system plays a central role in modulating compliance and resistances, ventricular-vascular coupling and blood flow redistribution to the working muscles. In the elderly hypertensive subjects an impaired vascular compliance reduces the wave transit time from the LV to peripheral sites of vascular reflection and

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back to the aorta, generating a late systolic load which contributes to ventriculo-vascular uncoupling, increased LV filling pressures and a 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 correlate with peak VO_2 [25]. Also noninvasive assessment of exercise BP 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, due to vessel rarefaction, endothelial dysfunction and blunted response to muscle tissue hypoxic vasodilation, 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 (SBV) which generates wall tension and intravascular pressure. An impairment in the venous capacitance critically shifts blood volume to the SBV 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].

<u>Abnormal Lung Mechanics, Pulmonary Hypertension and Vascular Disease (PVD) –</u> The detrimental role of PCWP elevation is key to effort-induced dyspnea and generates a cascade of hemodynamic and functional consequences contributing to two main mechanisms common to any HFpEF phenotype, i.e. vascular dysfunction and impaired pulmonary mechanics. Both of those contribute, ultimately, to VE inefficiency and effort-induced dyspnea [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 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

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stress pathways as typically observed in the metabolic syndrome [52]. Pulmonary vascular remodeling involves both the venous and arterial sides of pulmonary vasculature and critically impacts on the gas exchange process (ventilation/perfusion mismatching) and the right heart dynamics (including increased resistive load and RV to pulmonary circulation uncoupling). PVD detection relies on a thoughtful interpretation of *pulmonary hemodynamics and gas exchange* with analyses performed at rest and especially during exercise. An increase in resting PVR reflects PVD, a condition that can be unmasked in the earlier stages by a PVR rise > 3 WU during exercise [53]. PVD can be further documented by a leftward shift of the mPAP vs CO relationship as a consequence of a dynamic increase in the pulmonary resistive load [53]. The RV becomes stiff and is challenged in its filling and contractile properties, and uncoupling with the pulmonary circulation (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, [55] definitively resulting in an increased dead space to tidal volume (VD/VT) ratio and inefficient VE [56]. Exercise-induced dynamic congestion often overlaps as an additive reason for impaired gas exchange and vascular distensibility [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 stiffness, elongation in the free wall to septum tricuspid valve diameter, TR development and progressive 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 fiber type distribution with reduction in fibers 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]

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Anemia and Iron Deficiency—Anemia and iron deficiency are common in HFpEF and importantly contribute to worseining symptoms deterioration and exercise intolerance by reducing O_2 delivery and muscular storage (via myoglobin) in peripheral tissues [60]. Interestingly, the relative contribution of anemia to functional capacity impairment can be calculated defining the proportion of peak VO_2 loss due to anemic condition. As each Hb gram carries 1.34 ml of O_2, and as at peak exercise Hb desaturation is approximately 70%, each gram of Hb delivers to the muscle about 1 ml of O_2. In normal conditions, Hb is 15 g/dl, and, if peak CO (dl/min) is known, one can easily estimate the amount of missing VO_2 attributable to anemia at peak effort. As 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 anemia is 15 (normal Hb) – 10 (observed Hb) 75 = 350 ml/min. This calculation is reliable in normoxic patients with no cardiac shunt and significant O_2 desaturation. Anemia may be compensated for by an increase in stroke volume, a mechanism which may be at work in HFpEF but still results in a poor O_2 delivery [60]. Iron deficiency maintains an independent clinical role in HFpEF irrespective of anemia, but its isolated contribution to exercise impairment has been recently 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 nonobese 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 evolves to hemodynamic manifestation of RV dysfunction and superimposed pericardial constraint [23]. A causative role of impaired hemodynamics has recently been recognized in a direct pericardial fat inflammatory activity to impaired filling and increased PCWP [63]. Studies have identified an obese-phenotipe 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, distribution if mitochondrial pathways 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 patient manifest exercise intolerance because of HR incompetence due to the commonly impaired sympathovagal balance, higher

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prevalence of anaemia, microvascular disease, endothelial dysfunction, vasoconstriction and impaired mitochondrial function [66].

7. Methodology and Clinical Implications of Exercise Testing

Exercise limitation in HFpEF patients is primarily assessed with 2 modalities of exercise testing, the 6-min walk test (MWT) and the cardiopulmonary exercise test (CPET), also combined or not with noninvasive or invasive measurements.

6-MWT— 6-MWT 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 [69,70,71], 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 orthopedic or neurologic problems. CPET-derived variables are superior for the quantification of exercise capacity and risk stratification.[72]
CPET-- CPET in tandem with measurement of cardiac output 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 vs. 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 to 12 min maximal duration and a RER ≥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 (OUES)). 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.

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In HFpEF, peak VO_2 reduction is sensitive but not specific and it can discriminate HFpEF versus non-cardiac causes of dyspnoea reliably only at very high and very low values [75]. Exactly, with a peak VO_2 < 14 mmHg, HFpEF is very likely, > 20 mmHg HFpEF is very unlikely and in the range of 14-20 mmHg 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 noncardiac causes of dyspnoea[76].

For example, COPD patients with significant limitation in exercise capacity will display a reduction in breathing reserve (BR) , 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 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 (IC) 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 cardio-respiratory conditions such as pulmonary arterial hypertension[78].

Additionally, qualitative assessments of inspiratory and expiratory flow reserves is provided by tidal vs. maximal flow-volume loops throughout exercise [77,79]. In COPD, the inefficient VE during exercise is signalled by the VE Y-intercept that increases with greater disease severity [80]. COPD patients have a higher $\dot{V}E$-Y intercept than HFrEF patients [81] and presumably this is true also 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 HFpEF with coexisting precapillary PH versus PAH or CTEPH. The well-established prognostic role of VE/VCO_2 slope in HFpEF [82]seems to be similar to HFrEF though its clinical interpretation should take into account the 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

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FEV1 and FVC with normal ratio, and decrease in DLco. Patients with HF 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, or invasive hemodynamic testing to exclude HFpEF.

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[83] and crucial to separate and objectively assess how much of the limited performance 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 noninvasive CPET point on a primary pulmonary limitation. Comorbid chronic lung diseases are common in clinical trials of HFpEF, but the severity is not well-defined 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 vs WR relationship with or without a true VO_2 flattening pattern[84] and chronotropic incompetence [76] as outlined in the 9-plot graphical representation of **Figure 5** reporting a case of an hypertensive and diabetic old lady with a HFPEFF score 6 points and 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 work rate in the second part of the exercise, > 35% compared to the first linear slope, with a duration > 30 sec). These CPET manifestations are typical of a cardiogenc 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 pulmonary hypertension, elevated pulmonary vascular resistances [82] and right ventricular to pulmonary circulation uncoupling [85] 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 [86].Thus, in the most advanced stages of HFpEF exercise limitation, a thorough analysis of VE/VCO_2 slope determinants, i.e. dead

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space (VD)/ tidal volume (VT) and $PaCO_2$ may offer valuable insights for planning therapeutic interventions [56].

Figure 6 reports a 9-plot analysis of a 72-years old overweight patient complaining initial exertional dyspnea, arterial hypertension, prediabetes, persistent atrial fibrillation, sleep apnea syndrome and COPD, Gold class 2. His HFPEFF score is 4 points and H2FPEF score 0.5 point 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/min/kg; 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[82]. CPET supported clinical management with 1) exclusion of respiratory mechanical limitation as cause of dyspnoea, 2) providing evidence of severe VE inefficiency and prospecting PH under exertion as major cause of dyspnoea; 3) showing the need for better rate control of AF; 4) suggesting a relatively preserved aerobic capacity of the peripheral muscles; 5) documenting 10-fold increased risk for incident HF hospitalisations, compared to HFpEF patients with a VE/VCO_2 slope<30.

Exercise Echo Stress—The study of LV filling adaptations/maladaptations during dynamic exercise are 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 [87] primarily for diagnostic purposes integrating also with the parallel changes in tricuspid regurgitation (TR) peak velocity and estimated pulmonary pressures during effort [88, 89]. Among the technical requirements, the semirecumbent position is suggested for a better Doppler evaluation.

Incremental ramps at low workload (8 to 15 W/min) are preferable for a comprehensive images 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. Pulse wave Doppler echocardiography also enables measurement of cardiac output at rest and during exercise, which can be great value in distinguishing patients with predominant central vs peripheral abnormalities[45] .

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The HFA-PEFF recommendations suggest to perform exercise echo stress 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 [90]. The isolated increase in TR is not specific for HFpEF because it may depend on an intrinsic RV dysfunction and/or on a pulmonary vascular disease. Remarkably, in approximately 30% of cases tricuspid valve regurgitation velocity can not be reliably assessed [91]. Also, its correlation with the invasive right ventricular to atrium gradient at peak exercise is exercise is moderate (r=0.72) with a small bias (-1 mmHg) [92] Echo Doppler is less consistent to measure pulmonary pressures during exercise because right atrial pressure can not 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 right to atrium gradient estimate. Technically, an improved definition of tricuspid valve 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) [93].

CPET imaging--is a comprehensive and expanding approach which combines the advantage to address the exercise physiological implications with non-invasive hemodynamic 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 the left atrium (LA) dynamic and response of the right heart [94,45]. The full noninvasive 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.[95]

An initial study [96] 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. Subsequent studies have implemented the interest for E/e' to the role of LV deformation primarily assessed by speckle tracking analysis[97] and lung congestion by the analysis of exercise-induced B-lines [98] which have been shown to predict HFpEF better than standard

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echocardiographic estimation of filling pressure [99]. However, recent findings by invasive simultaneous study have shown that around 50% of HFpEF patients with exercise PAWP 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 hemodynamic impairment and symptoms cascade[45]. Indeed, among all echocardiographic data obtained at rest, abnormalities in LA strain seem to be most strongly correlated with hemodynamic 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 [100] 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 the LV systolic dynamics (3D strain analysis) and filling (E/A and E/e'), the LA dynamics (LA strain analysis) and the RV function analysis (RV to Pc coupling by TAPSE/PASP ratio and RVEF by 3-D acquisition) at rest and at peak exercise. Data show a preserved LV deformation analysis with exercise increase in LV filling pressure (E/e' 16,9); a severely limited LA strain (10.5% at rest and 9.6% at peak exercise) and a loss in RVEF (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 PH.

Invasive CPET—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 hemodynamic reasons for exercise limitations, precisely dissecting central and peripheral mechanisms throughout direct measures of LV filling pressures, pulmonary haemodynamics, cardiac output, and arteriovenous O_2 differences. In HFpEF, pulmonary haemodynamic measurements during exercise, especially PCWP and mean pulmonary pressure, may yield to incremental prognostic value compared with evaluation at rest only[101]. Although technically challenging, invasive assessment of pulmonary hemodynamics is more sensitive and specific compared to fluid loading for detection of an abnormal rise

Borlaug et al. [38] first reported the potential to suspect HFpEF in subjects with unexplained dyspnoea, whilst euvolemic with normal levels of B-type natriuretic peptide and without clear

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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 was preliminary to a diagnosis. Studies have then well established that an increased mean PAWP ≥25 mm Hg at peak exercise, even in the absence of elevations in pulmonary vascular resistance (PVR), indicates HFpEF [102]. Some groups have advocated for assessment of the PAWP 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 RAP vs PAWP implement the diagnostic information with the pressure-induced unfavourable RV to LV interaction mechanisms, intended as a decrease in the pressure gradient between the LV and RV, and a change in septum becoming less convex toward the RV 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 mean pulmonary artery pressure (mPAP) versus CO provides a robust indication of abnormalities in RV to pulmonary circulation 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 [103] . Even more, the occurrence of RV to Pc uncoupling is responsible for a delayed VO_2 on kinetics during early exercise [29].

8. 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 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 of a right heart involvement and PH coexistence adding both specificity and specificity to HFpEF diagnosis [82]. CPET may then play a role in an indepth 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

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assessment should be referred in more details in Step 1 (P, the pre-assessment) to ascertain the degree of functional limitation and to address toward the primary origin of symptoms, and in Step 4 (F, the 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 priorization order to get an ideal operationalization of gas exchange analysis even better when combined with imaging and invasive hemodynamic evaluation[104, 105]. **(Figure 8-Central illustration).** Information in term of prognosis and clinical work-up should be derived at all steps proposed.

Step 1 (P) the pre-assessment

Exercise gas exchange can delineate cardiac and extracardiac reserve capacity impairments contributing to exertional intolerance[77,76]. 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 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[106,40]. Specifically, the combination of CPET data with findings of chronotropic incompetence (CI), elevated PCWP [75], PH, exercise-induced MR and RV dysfunction may definitively secure HFpEF diagnosis and potentially enhance care through improved phenotyping[76]. Compared to HFrEF, the hetherogeneous manifestation of HFpEF phenotype [86, 106, 107]may well explain how a robust use of CPET-derived variables in clinical risk stratification is lacking[108]

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.[106] Notably, in a study by Nadruz et al[106] , the magnitude of association of peak VO_2 and VE/VCO_2 slope with

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adverse outcomes was greater in HFpEF versus HFrEF. Additional risk definition can actually be derived from invasive CPET [101, 102, 109] and CPET imaging [95] (see Table 1).

9. Testing Effectiveness of Interventions Through Functional Evaluation

Functional capacity has been addressed as an end point in several interventional trials of HFpEF focusing on peak VO_2 as main reference variable. Pharmacological trials in HFpEF have historically been unsuccessful in improving functional capacity and symptoms on effort [70,110,111], though more recent data on levosimendan and SGLT2 inhibitors have revealed promising effects on functional capacity [112].

In addition to pharmacologic treatments, exercise training (ET) interventions have particularly become accepted since the earlier evidence on their effectiveness to modulate dyspnoea on exertion and to increase peak VO_2 [113 114 115]. In these studies, CPET has acquired a primary role in both planning ET interventions and measuring the extent of benefits.

In parallel, life-style interventions may be effective to prevent HFpEF [116], to favourably affect several abnormalities of the HFpEF syndrome[117] 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[118]. 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 $\dot{V}O_2$ [119] and NYHA functional class[120].

Effectiveness of ET programmes in HF have been further scrutinized by performing high intensity training (HIIT) in addition to traditionally prescribed moderate-intensity continuous training (MCT). The largest randomized controlled trial performed in HFpEF so far is the OptimEx trial (Optimizing Exercise in HFpEF)[121], which compared MCT versus HIIT, revealing that both exercise training 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 of peak $\dot{V}O_2$ by +1.1 ml/min/kg for HIIT and +1.6 ml/min/kg 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 exercise training (+2.7 ml/min/kg; 95% CI 1.79–3.65)[122]. 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 [121, 123]. Rather, the

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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[121]. Prevention of HFpEF may be different, as recent data indicate that sustained ET can improve LV diastolic stiffness in adults without HF [124]. This may relate to greater plasticity of myocardial dysfunction prior to onset of HF, or to a greater dose and duration of ET applied.

Data obtained by CPET can be extremely helpful for prescribing exercise intensities in HFpEF[79]. Beyond intensity modalities e.g. rate of perceived exertion Borg (RPE), percentage of maximal heart rate (% HRmax), or percentage of heart rate reserve (%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 HR max 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[125].

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[126] 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 significantly 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.

11. 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,

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providing insightful information in the multistep 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 dyspnea at the extremes of peak VO_2, it also provides valuable insight into potential pulmonary causes of dyspnea, 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 for therapeutic interventions. For these reasons an implementation of CPET use in the early and advanced diagnostic steps of HFA-PEFF score is adopted. A similar rationale applies to patients evaluated using the H2FPEF 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 aims at these goals[127 128].

References

1. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P and Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297-3317.
2. Reddy YNV, Carter RE, Obokata M, Redfield MM and Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. *Circulation*. 2018;138:861-870.
3. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M and Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J*. 2022.
4. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong J, Anavekar N, Anker SD, Arango JL, Arenas JL, Atar D, Ben-Gal T, Boytsov SA, Chen CH, Chopra VK, Cleland J, Comin-Colet J, Duengen HD, Echeverria Correa LE, Filippatos G, Flammer AJ, Galinier M, Godoy A, Goncalvesova E, Janssens S, Katova T, Kober L, Lelonek M, Linssen G, Lund LH, O'Meara E, Merkely B, Milicic D, Oh BH, Perrone SV, Ranjith N, Saito Y, Saraiva JF, Shah S, Seferovic PM, Senni M, Sibulo AS, Jr., Sim D, Sweitzer NK, Taurio J, Vinereanu D, Vrtovec B, Widimsky J, Jr., Yilmaz MB, Zhou J, Zweiker R, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR and McMurray JJV. Baseline Characteristics of Patients With Heart Failure and Preserved Ejection Fraction in the PARAGON-HF Trial. *Circulation Heart failure*. 2018;11:e004962.
5. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD and Lewis GD. Exercise Intolerance in Heart Failure With Preserved Ejection Fraction: Diagnosing and Ranking Its Causes Using Personalized O2 Pathway Analysis. *Circulation*. 2018;137:148-161.

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6. Guazzi M, Bandera F, Ozemek C, Systrom D and Arena R. Cardiopulmonary Exercise Testing: What Is its Value? *Journal of the American College of Cardiology*. 2017;70:1618-1636.
7. Eckhardt CM, Balte PP, Barr RG, Bertoni AG, Bhatt SP, Cuttica M, Cassano PA, Chaves P, Couper D, Jacobs DR, Kalhan R, Kronmal R, Lange L, Loehr L, London SJ, O'Connor GT, Rosamond W, Sanders J, Schwartz JE, Shah A, Shah SJ, Smith L, White W, Yende S and Oelsner EC. Lung function impairment and risk of incident heart failure: the NHLBI Pooled Cohorts Study. *Eur Heart J*. 2022.
8. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CS, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B and O'Connor CM. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol*. 2014;64:2281-93.
9. Cohen JB, Schrauben SJ, Zhao L, Basso MD, Cvijic ME, Li Z, Yarde M, Wang Z, Bhattacharya PT, Chirinos DA, Prenner S, Zamani P, Seiffert DA, Car BD, Gordon DA, Margulies K, Cappola T and Chirinos JA. Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction: Detailed Phenotypes, Prognosis, and Response to Spironolactone. *JACC Heart Fail*. 2020;8:172-184.
10. Mooney L, Hawkins NM, Jhund PS, Redfield MM, Vaduganathan M, Desai AS, Rouleau JL, Minamisawa M, Shah AM, Lefkowitz MP, Zile MR, Van Veldhuisen DJ, Pfeffer MA, Anand IS, Maggioni AP, Senni M, Claggett BL, Solomon SD and McMurray JJV. Impact of Chronic Obstructive Pulmonary Disease in Patients With Heart Failure With Preserved Ejection Fraction: Insights From PARAGON-HF. *J Am Heart Assoc*. 2021:e021494.
11. AbouEzzeddine OF, Davies DR, Scott CG, Fayyaz AU, Askew JW, McKie PM, Noseworthy PA, Johnson GB, Dunlay SM, Borlaug BA, Chareonthaitawee P, Roger VL, Dispenzieri A, Grogan M and Redfield MM. Prevalence of Transthyretin Amyloid Cardiomyopathy in Heart Failure With Preserved Ejection Fraction. *JAMA Cardiol*. 2021.
12. Yunis A, Doros G, Luptak I, Connors LH and Sam F. Use of Ventilatory Efficiency Slope as a Marker for Increased Mortality in Wild-Type Transthyretin Cardiac Amyloidosis. *Am J Cardiol*. 2019;124:122-130.
13. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH and Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol*. 1991;17:1065-72.
14. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD and Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2013;15:776-85.
15. Sarma S, Howden E, Lawley J, Samels M and Levine BD. Central Command and the Regulation of Exercise Heart Rate Response in Heart Failure With Preserved Ejection Fraction. *Circulation*. 2021;143:783-789.
16. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD and Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2010;56:845-54.
17. Sugimoto T, Bandera F, Generati G, Alfonzetti E, Bussadori C and Guazzi M. Left Atrial Function Dynamics During Exercise in Heart Failure: Pathophysiological Implications on the Right Heart and Exercise Ventilation Inefficiency. *JACC Cardiovasc Imaging*. 2017;10:1253-1264.
18. Reddy YNV, Obokata M, Verbrugge FH, Lin G and Borlaug BA. Atrial Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation. *J Am Coll Cardiol*. 2020;76:1051-1064.
19. Tamargo M, Obokata M, Reddy YNV, Pislaru SV, Lin G, Egbe AC, Nishimura RA and Borlaug BA. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020;22:489-498.
20. Ahmad A, Corban MT, Toya T, Verbrugge FH, Sara JD, Lerman LO, Borlaug BA and Lerman A. Coronary microvascular dysfunction is associated with exertional haemodynamic abnormalities in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021;23:765-772.
21. Obokata M, Reddy YNV, Melenovsky V, Kane GC, Olson TP, Jarolim P and Borlaug BA. Myocardial Injury and Cardiac Reserve in Patients With Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol*. 2018;72:29-40.
22. Parasuraman SK, Loudon BL, Lowery C, Cameron D, Singh S, Schwarz K, Gollop ND, Rudd A, McKiddie F, Phillips JJ, Prasad SK, Wilson AM, Sen-Chowdhry S, Clark A, Vassiliou VS, Dawson DK and

Frenneaux MP. Diastolic Ventricular Interaction in Heart Failure With Preserved Ejection Fraction. *J Am Heart Assoc*. 2019;8:e010114.
23. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V and Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. *Circulation*. 2017;136:6-19.
24. Fermoyle CC, Stewart GM, Borlaug BA and Johnson BD. Simultaneous Measurement of Lung Diffusing Capacity and Pulmonary Hemodynamics Reveals Exertional Alveolar-Capillary Dysfunction in Heart Failure With Preserved Ejection Fraction. *J Am Heart Assoc*. 2021:e019950.
25. Reddy YNV, Andersen MJ, Obokata M, Koepp KE, Kane GC, Melenovsky V, Olson TP and Borlaug BA. Arterial Stiffening With Exercise in Patients With Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol*. 2017;70:136-148.
26. Weavil JC, Thurston TS, Hureau TJ, Gifford JR, Kithas PA, Broxterman RM, Bledsoe AD, Nativi JN, Richardson RS and Amann M. Heart failure with preserved ejection fraction diminishes peripheral hemodynamics and accelerates exercise-induced neuromuscular fatigue. *Am J Physiol Heart Circ Physiol*. 2021;320:H338-H351.
27. Martens P, Claessen G, Van De Bruaene A, Verbrugge FH, Herbots L, Dendale P and Verwerft J. Iron Deficiency Is Associated With Impaired Biventricular Reserve and Reduced Exercise Capacity in Patients With Unexplained Dyspnea. *J Card Fail*. 2021;27:766-776.
28. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J and Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J*. 2018;39:1144-1161.
29. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS and Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail*. 2015;8:286-94.
30. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Zampierollo GA, Jarolim P, Pappagianopoulos PP, Malhotra R, Nayor M and Lewis GD. Differential Clinical Profiles, Exercise Responses, and Outcomes Associated With Existing HFpEF Definitions. *Circulation*. 2019;140:353-365.
31. Haykowsky MJ, Nicklas BJ, Brubaker PH, Hundley WG, Brinkley TE, Upadhya B, Becton JT, Nelson MD, Chen H and Kitzman DW. Regional Adipose Distribution and its Relationship to Exercise Intolerance in Older Obese Patients Who Have Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail*. 2018;6:640-649.
32. Mishra S and Kass DA. Cellular and molecular pathobiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2021;18:400-423.
33. Verbrugge FH, Guazzi M, Testani JM and Borlaug BA. Altered Hemodynamics and End-Organ Damage in Heart Failure: Impact on the Lung and Kidney. *Circulation*. 2020;142:998-1012.
34. Roberto S, Mulliri G, Milia R, Solinas R, Pinna V, Sainas G, Piepoli MF and Crisafulli A. Hemodynamic response to muscle reflex is abnormal in patients with heart failure with preserved ejection fraction. *J Appl Physiol (1985)*. 2017;122:376-385.
35. Pandey A, Shah SJ, Butler J, Kellogg DL, Jr., Lewis GD, Forman DE, Mentz RJ, Borlaug BA, Simon MA, Chirinos JA, Fielding RA, Volpi E, Molina AJA, Haykowsky MJ, Sam F, Goodpaster BH, Bertoni AG, Justice JN, White JP, Ding J, Hummel SL, LeBrasseur NK, Taffet GE, Pipinos, II and Kitzman D. Exercise Intolerance in Older Adults With Heart Failure With Preserved Ejection Fraction: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2021;78:1166-1187.
36. Soetkamp D, Gallet R, Parker SJ, Holewinski R, Venkatraman V, Peck K, Goldhaber JI, Marban E and Van Eyk JE. Myofilament Phosphorylation in Stem Cell Treated Diastolic Heart Failure. *Circ Res*. 2021;129:1125-1140.
37. Burrage MK, Hundertmark M, Valkovic L, Watson WD, Rayner J, Sabharwal N, Ferreira VM, Neubauer S, Miller JJ, Rider OJ and Lewis AJM. Energetic Basis for Exercise-Induced Pulmonary Congestion in Heart Failure With Preserved Ejection Fraction. *Circulation*. 2021;144:1664-1678.
38. Borlaug BA, Nishimura RA, Sorajja P, Lam CS and Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:588-95.

Accepted Article

39. Wilkoff BL and Miller RE. Exercise testing for chronotropic assessment. *Cardiol Clin*. 1992;10:705-17.
40. Brubaker PH and Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation*. 2011;123:1010-20.
41. Palau P, Seller J, Dominguez E, Sastre C, Ramon JM, de La Espriella R, Santas E, Minana G, Bodi V, Sanchis J, Valle A, Chorro FJ, Llacer P, Bayes-Genis A and Nunez J. Effect of beta-Blocker Withdrawal on Functional Capacity in Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol*. 2021;78:2042-2056.
42. Mesquita T, Zhang R, Cho JH, Zhang R, Lin YN, Sanchez L, Goldhaber JI, Yu JK, Liang JA, Liu W, Trayanova NA and Cingolani E. Mechanisms of Sinoatrial Node Dysfunction in Heart Failure With Preserved Ejection Fraction. *Circulation*. 2022;145:45-60.
43. Singleton MJ, Nelson MB, Samuel TJ, Kitzman DW, Brubaker P, Haykowsky MJ, Upadhya B, Chen H and Nelson MD. Left Atrial Stiffness Index Independently Predicts Exercise Intolerance and Quality of Life in Older, Obese Patients With Heart Failure With Preserved Ejection Fraction. *J Card Fail*. 2021.
44. Telles F, Nanayakkara S, Evans S, Patel HC, Mariani JA, Vizi D, William J, Marwick TH and Kaye DM. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;21:495-505.
45. Sugimoto T, Barletta M, Bandera F, Generati G, Alfonzetti E, Rovida M, Gnecchi Ruscone T, Rossi A, Cicoira M and Guazzi M. Central role of left atrial dynamics in limiting exercise cardiac output increase and oxygen uptake in heart failure: insights by cardiopulmonary imaging. *Eur J Heart Fail*. 2020;22:1186-1198.
46. Pandey A, Vaduganathan M, Arora S, Qamar A, Mentz RJ, Shah SJ, Chang PP, Russell SD, Rosamond WD and Caughey MC. Temporal Trends in Prevalence and Prognostic Implications of Comorbidities Among Patients With Acute Decompensated Heart Failure: The ARIC Study Community Surveillance. *Circulation*. 2020;142:230-243.
47. Kitzman DW, Haykowsky MJ and Tomczak CR. Making the Case for Skeletal Muscle Myopathy and Its Contribution to Exercise Intolerance in Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail*. 2017;10.
48. Chirinos JA, Segers P, Hughes T and Townsend R. Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;74:1237-1263.
49. Namasivayam M, Lau ES, Zern EK, Schoenike MW, Hardin KM, Sbarbaro JA, Cunningham TF, Farrell RM, Rouvina J, Kowal A, Bhat RR, Brooks LC, Nayor M, Shah RV, Ho JE, Malhotra R and Lewis GD. Exercise Blood Pressure in Heart Failure With Preserved and Reduced Ejection Fraction. *JACC Heart Fail*. 2022;10:278-286.
50. Poole DC, Hirai DM, Copp SW and Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. *Am J Physiol Heart Circ Physiol*. 2012;302:H1050-63.
51. Sorimachi H, Burkhoff D, Verbrugge FH, Omote K, Obokata M, Reddy YNV, Takahashi N, Sunagawa K and Borlaug BA. Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021;23:1648-1658.
52. Guazzi M, Ghio S and Adir Y. Pulmonary Hypertension in HFpEF and HFrEF: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2020;76:1102-1111.
53. Gorter TM, Obokata M, Reddy YNV, Melenovsky V and Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. *Eur Heart J*. 2018;39:2825-2835.
54. Guazzi M and Naeije R. Right Heart Phenotype in Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail*. 2021;14:e007840.
55. Fermoyle CC, Stewart GM, Borlaug BA and Johnson BD. Simultaneous Measurement of Lung Diffusing Capacity and Pulmonary Hemodynamics Reveals Exertional Alveolar-Capillary Dysfunction in Heart Failure With Preserved Ejection Fraction. *J Am Heart Assoc*. 2021;10:e019950.
56. Van Iterson EH, Johnson BD, Borlaug BA and Olson TP. Physiological dead space and arterial carbon dioxide contributions to exercise ventilatory inefficiency in patients with reduced or preserved ejection fraction heart failure. *Eur J Heart Fail*. 2017;19:1675-1685.

Accepted Article

57. Reddy YNV, Obokata M, Wiley B, Koepp KE, Jorgenson CC, Egbe A, Melenovsky V, Carter RE and Borlaug BA. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. *Eur Heart J*. 2019;40:3721-3730.
58. Kitzman DW, Nicklas B, Kraus WE, Lyles MF, Eggebeen J, Morgan TM and Haykowsky M. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Physiol Heart Circ Physiol*. 2014;306:H1364-70.
59. Molina AJ, Bharadwaj MS, Van Horn C, Nicklas BJ, Lyles MF, Eggebeen J, Haykowsky MJ, Brubaker PH and Kitzman DW. Skeletal Muscle Mitochondrial Content, Oxidative Capacity, and Mfn2 Expression Are Reduced in Older Patients With Heart Failure and Preserved Ejection Fraction and Are Related to Exercise Intolerance. *JACC Heart Fail*. 2016;4:636-45.
60. Parcha V, Patel N, Kalra R, Bhargava A, Prabhu SD, Arora G and Arora P. Clinical, Demographic, and Imaging Correlates of Anemia in Heart Failure With Preserved Ejection Fraction (from the RELAX Trial). *Am J Cardiol*. 2020;125:1870-1878.
61. Barandiaran Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, Henkens M, Weerts J, Spanjers MHA, Knackstedt C and van Empel VPM. Iron deficiency impacts prognosis but less exercise capacity in heart failure with preserved ejection fraction. *ESC Heart Fail*. 2021;8:1304-1313.
62. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M and Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol*. 2018;73:115-123.
63. Koepp KE, Obokata M, Reddy YNV, Olson TP and Borlaug BA. Hemodynamic and Functional Impact of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail*. 2020;8:657-666.
64. Rayner JJ, Peterzan MA, Watson WD, Clarke WT, Neubauer S, Rodgers CT and Rider OJ. Myocardial Energetics in Obesity: Enhanced ATP Delivery Through Creatine Kinase With Blunted Stress Response. *Circulation*. 2020;141:1152-1163.
65. Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J and Kitzman DW. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Cardiol*. 2014;113:1211-6.
66. Maack C, Lehrke M, Backs J, Heinzel FR, Hulot JS, Marx N, Paulus WJ, Rossignol P, Taegtmeyer H, Bauersachs J, Bayes-Genis A, Brutsaert D, Bugger H, Clarke K, Cosentino F, De Keulenaer G, Dei Cas A, Gonzalez A, Huelsmann M, Iaccarino G, Lunde IG, Lyon AR, Pollesello P, Rena G, Riksen NP, Rosano G, Staels B, van Laake LW, Wanner C, Farmakis D, Filippatos G, Ruschitzka F, Seferovic P, de Boer RA and Heymans S. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. *Eur Heart J*. 2018;39:4243-4254.
67. Wolsk E, Kaye D, Borlaug BA, Burkhoff D, Kitzman DW, Komtebedde J, Lam CSP, Ponikowski P, Shah SJ and Gustafsson F. Resting and exercise haemodynamics in relation to six-minute walk test in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2018;20:715-722.
68. Zotter-Tufaro C, Mascherbauer J, Duca F, Koell B, Aschauer S, Kammerlander AA, Panzenboeck A, Sadushi-Kolici R, Bangert C, Laimer D, Ristl R, Lang IM and Bonderman D. Prognostic Significance and Determinants of the 6-Min Walk Test in Patients With Heart Failure and Preserved Ejection Fraction. *JACC Heart Fail*. 2015;3:459-466.
69. Maldonado-Martin S, Brubaker PH, Eggebeen J, Stewart KP and Kitzman DW. Association Between 6-Minute Walk Test Distance and Objective Variables of Functional Capacity After Exercise Training in Elderly Heart Failure Patients With Preserved Ejection Fraction: A Randomized Exercise Trial. *Arch Phys Med Rehabil*. 2017;98:600-603.
70. Armstrong PW, Lam CSP, Anstrom KJ, Ezekowitz J, Hernandez AF, O'Connor CM, Pieske B, Ponikowski P, Shah SJ, Solomon SD, Voors AA, She L, Vlajnic V, Carvalho F, Bamber L, Blaustein RO, Roessig L, Butler J and Group VI-HS. Effect of Vericiguat vs Placebo on Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The VITALITY-HFpEF Randomized Clinical Trial. *JAMA*. 2020;324:1512-1521.

Accepted Article

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71. Shah SJ, Cowie MR, Wachter R, Szecsody P, Shi V, Ibram G, Hu M, Zhao Z, Gong J and Pieske B. Baseline characteristics of patients in the PARALLAX trial: insights into quality of life and exercise capacity in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021.
72. Guazzi M, Dickstein K, Vicenzi M and Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. *Circulation Heart failure*. 2009;2:549-55.
73. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J, European Association for Cardiovascular P, Rehabilitation and American Heart A. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012;126:2261-74.
74. Agostoni P and Dumitrescu D. How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure. *Int J Cardiol*. 2019;288:107-113.
75. Reddy YNV, Olson TP, Obokata M, Melenovsky V and Borlaug BA. Hemodynamic Correlates and Diagnostic Role of Cardiopulmonary Exercise Testing in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail*. 2018;6:665-675.
76. Nayor M, Houstis NE, Namasivayam M, Rouvina J, Hardin C, Shah RV, Ho JE, Malhotra R and Lewis GD. Impaired Exercise Tolerance in Heart Failure With Preserved Ejection Fraction: Quantification of Multiorgan System Reserve Capacity. *JACC Heart Fail*. 2020;8:605-617.
77. Laveneziana P, Di Paolo M and Palange P. The clinical value of cardiopulmonary exercise testing in the modern era. *Eur Respir Rev*. 2021;30.
78. Boucly A, Morelot-Panzini C, Garcia G, Weatherald J, Jais X, Savale L, Montani D, Humbert M, Similowski T, Sitbon O and Laveneziana P. Intensity and quality of exertional dyspnoea in patients with stable pulmonary hypertension. *Eur Respir J*. 2020;55.
79. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J and Lavie CJ. 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circulation*. 2016;133:e694-711.
80. Neder JA, Arbex FF, Alencar MC, O'Donnell CD, Cory J, Webb KA and O'Donnell DE. Exercise ventilatory inefficiency in mild to end-stage COPD. *Eur Respir J*. 2015;45:377-87.
81. Teopompi E, Tzani P, Aiello M, Gioia MR, Marangio E and Chetta A. Excess ventilation and ventilatory constraints during exercise in patients with chronic obstructive pulmonary disease. *Respir Physiol Neurobiol*. 2014;197:9-14.
82. Klaassen SHC, Liu LCY, Hummel YM, Damman K, van der Meer P, Voors AA, Hoendermis ES and van Veldhuisen DJ. Clinical and Hemodynamic Correlates and Prognostic Value of VE/VCO2 Slope in Patients with Heart Failure With Preserved Ejection Fraction and Pulmonary Hypertension. *J Card Fail*. 2017;23:777-782.
83. Barron A, Francis DP, Mayet J, Ewert R, Obst A, Mason M, Elkin S, Hughes AD and Wensel R. Oxygen Uptake Efficiency Slope and Breathing Reserve, Not Anaerobic Threshold, Discriminate Between Patients With Cardiovascular Disease Over Chronic Obstructive Pulmonary Disease. *JACC Heart Fail*. 2016;4:252-61.
84. Popovic D, Arena R and Guazzi M. A flattening oxygen consumption trajectory phenotypes disease severity and poor prognosis in patients with heart failure with reduced, mid-range, and preserved ejection fraction. *Eur J Heart Fail*. 2018;20:1115-1124.
85. Guazzi M, Dixon D, Labate V, Beussink-Nelson L, Bandera F, Cuttica MJ and Shah SJ. RV Contractile Function and its Coupling to Pulmonary Circulation in Heart Failure With Preserved Ejection Fraction: Stratification of Clinical Phenotypes and Outcomes. *JACC Cardiovasc Imaging*. 2017;10:1211-1221.
86. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P and Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *European heart journal*. 2008;29:2751-9.
87. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA and Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277-314.

Accepted Article

88. Donal E, Lund LH, Oger E, Reynaud A, Schnell F, Persson H, Drouet E, Linde C, Daubert C and KaRen i. Value of exercise echocardiography in heart failure with preserved ejection fraction: a substudy from the KaRen study. *Eur Heart J Cardiovasc Imaging*. 2016;17:106-13.
89. Shim CY, Kim SA, Choi D, Yang WI, Kim JM, Moon SH, Lee HJ, Park S, Choi EY, Chung N and Ha JW. Clinical outcomes of exercise-induced pulmonary hypertension in subjects with preserved left ventricular ejection fraction: implication of an increase in left ventricular filling pressure during exercise. *Heart*. 2011;97:1417-24.
90. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V and Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. *Circulation*. 2017;135:825-838.
91. Obokata M, Kane GC, Sorimachi H, Reddy YNV, Olson TP, Egbe AC, Melenovsky V and Borlaug BA. Noninvasive evaluation of pulmonary artery pressure during exercise: the importance of right atrial hypertension. *Eur Respir J*. 2020;55.
92. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, Garcia G, Grunig E, Howard L, Humbert M, Lau E, Laveneziana P, Lewis GD, Naeije R, Peacock A, Rosenkranz S, Saggar R, Ulrich S, Vizza D, Vonk Noordegraaf A and Olschewski H. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J*. 2017;50.
93. Claessen G, La Gerche A, Voigt JU, Dymarkowski S, Schnell F, Petit T, Willems R, Claus P, Delcroix M and Heidbuchel H. Accuracy of Echocardiography to Evaluate Pulmonary Vascular and RV Function During Exercise. *JACC Cardiovasc Imaging*. 2016;9:532-43.
94. Martens P, Herbots L, Timmermans P, Verbrugge FH, Dendale P, Borlaug BA and Verwerft J. Cardiopulmonary Exercise Testing with Echocardiography to Identify Mechanisms of Unexplained Dyspnea. *J Cardiovasc Transl Res*. 2021.
95. Guazzi M, Borlaug B, Metra M, Losito M, Bandera F, Alfonzetti E, Boveri S and Sugimoto T. Revisiting and Implementing the Weber and Ventilatory Functional Classifications in Heart Failure by Cardiopulmonary Imaging Phenotyping. *J Am Heart Assoc*. 2021;10:e018822.
96. Nedeljkovic I, Banovic M, Stepanovic J, Giga V, Djordjevic-Dikic A, Trifunovic D, Nedeljkovic M, Petrovic M, Dobric M, Dikic N, Zlatar M and Beleslin B. The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. *Eur J Prev Cardiol*. 2016;23:71-7.
97. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A and Frenneaux M. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. *J Am Coll Cardiol*. 2009;54:402-9.
98. Simonovic D, Coiro S, Deljanin-Ilic M, Kobayashi M, Carluccio E, Girerd N and Ambrosio G. Exercise-induced B-lines in heart failure with preserved ejection fraction occur along with diastolic function worsening. *ESC Heart Fail*. 2021.
99. Hubert A, Girerd N, Le Breton H, Galli E, Latar I, Fournet M, Mabo P, Schnell F, Leclercq C and Donal E. Diagnostic accuracy of lung ultrasound for identification of elevated left ventricular filling pressure. *Int J Cardiol*. 2019;281:62-68.
100. Bandera F, Barletta M, Fontana M, Boveri S, Ghizzardi G, Alfonzetti E, Ambrogi F and Guazzi M. Exercise-induced mitral regurgitation and right ventricle to pulmonary circulation uncoupling across the heart failure phenotypes. *Am J Physiol Heart Circ Physiol*. 2021;320:H642-H653.
101. Ho JE, Zern EK, Lau ES, Wooster L, Bailey CS, Cunningham T, Eisman AS, Hardin KM, Farrell R, Sbarbaro JA, Schoenike MW, Houstis NE, Baggish AL, Shah RV, Nayor M, Malhotra R and Lewis GD. Exercise Pulmonary Hypertension Predicts Clinical Outcomes in Patients With Dyspnea on Effort. *J Am Coll Cardiol*. 2020;75:17-26.
102. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B and Neumann FJ. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J*. 2014;35:3103-12.

Accepted Article

103. Lewis GD, Bossone E, Naeije R, Grunig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R and Rubenfire M. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation*. 2013;128:1470-9.
104. Jain CC and Borlaug BA. Performance and Interpretation of Invasive Hemodynamic Exercise Testing. *Chest*. 2020;158:2119-2129.
105. Nayor M, Houstis NE, Namasivayam M, Rouvina J, Hardin C, Shah RV, Ho JE, Malhotra R and Lewis GD. Impaired Exercise Tolerance in Heart Failure With Preserved Ejection Fraction: Quantification of Multiorgan System Reserve Capacity. *JACC Heart Fail*. 2020.
106. Nadruz W, Jr., West E, Sengelov M, Santos M, Groarke JD, Forman DE, Claggett B, Skali H and Shah AM. Prognostic Value of Cardiopulmonary Exercise Testing in Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction. *J Am Heart Assoc*. 2017;6.
107. Shafiq A, Brawner CA, Aldred HA, Lewis B, Williams CT, Tita C, Schairer JR, Ehrman JK, Velez M, Selektor Y, Lanfear DE and Keteyian SJ. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. The Henry Ford HospITal CardioPulmonary EXercise Testing (FIT-CPX) project. *American heart journal*. 2016;174:167-72.
108. Corra U, Agostoni PG, Anker SD, Coats AJS, Crespo Leiro MG, de Boer RA, Hairola VP, Hill L, Lainscak M, Lund LH, Metra M, Ponikowski P, Riley J, Seferovic PM and Piepoli MF. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. *European journal of heart failure*. 2018;20:3-15.
109. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, Cunningham TF, Hardin KM, Baggish AL, Ho JE, Malhotra R and Lewis GD. Pulmonary Capillary Wedge Pressure Patterns During Exercise Predict Exercise Capacity and Incident Heart Failure. *Circulation Heart failure*. 2018;11:e004750.
110. Udelson JE, Lewis GD, Shah SJ, Zile MR, Redfield MM, Burnett J, Jr., Parker J, Seferovic JP, Wilson P, Mittleman RS, Profy AT and Konstam MA. Effect of Praliciguat on Peak Rate of Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: The CAPACITY HFpEF Randomized Clinical Trial. *JAMA*. 2020;324:1522-1531.
111. Abraham WT, Lindenfeld J, Ponikowski P, Agostoni P, Butler J, Desai AS, Filippatos G, Gniot J, Fu M, Gullestad L, Howlett JG, Nicholls SJ, Redon J, Schenkenberger I, Silva-Cardoso J, Stork S, Krzysztof Wranicz J, Savarese G, Brueckmann M, Jamal W, Nordaby M, Peil B, Ritter I, Ustyugova A, Zeller C, Salsali A and Anker SD. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. *Eur Heart J*. 2021;42:700-710.
112. Burkhoff D, Borlaug BA, Shah SJ, Zolty R, Tedford RJ, Thenappan T, Zamanian RT, Mazurek JA, Rich JD, Simon MA, Chung ES, Raza F, Majure DT, Lewis GD, Preston IR and Rich S. Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF: Results of the Randomized Placebo-Controlled HELP Trial. *JACC Heart Fail*. 2021;9:360-370.
113. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J and Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2012;60:120-8.
114. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Loffler M, Hasenfuss G, Halle M and Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*. 2011;58:1780-91.
115. Mueller S, Haller B, Halle M and OptimEx-Clin Study G. Effect of Training on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction-Reply. *JAMA*. 2021;326:772-773.
116. Kraigher-Krainer E, Lyass A, Massaro JM, Lee DS, Ho JE, Levy D, Kannel WB and Vasan RS. Association of physical activity and heart failure with preserved vs. reduced ejection fraction in the elderly: the Framingham Heart Study. *European journal of heart failure*. 2013;15:742-6.

Accepted Article

117. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P and Berry JD. Relationship Between Physical Activity, Body Mass Index, and Risk of Heart Failure. *Journal of the American College of Cardiology*. 2017;69:1129-1142.
118. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J and Nicklas BJ. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association*. 2016;315:36-46.
119. Wolsk E, Kaye D, Komtebedde J, Shah SJ, Borlaug BA, Burkhoff D, Kitzman DW, Lam CSP, van Veldhuisen DJ, Ponikowski P, Petrie MC, Hassager C, Møller JE and Gustafsson F. Central and Peripheral Determinants of Exercise Capacity in Heart Failure Patients With Preserved Ejection Fraction. *JACC Heart failure*. 2019;7:321-332.
120. Dalos D, Mascherbauer J, Zotter-Tufaro C, Duca F, Kammerlander AA, Aschauer S and Bonderman D. Functional Status, Pulmonary Artery Pressure, and Clinical Outcomes in Heart Failure With Preserved Ejection Fraction. *Journal of the American College of Cardiology*. 2016;68:189-199.
121. Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, Pieske-Kraigher E, Beckers P, Bobenko A, Hommel J, Van de Heyning CM, Esefeld K, von Korn P, Christle JW, Haykowsky MJ, Linke A, Wisløff U, Adams V, Pieske B, van Craenenbroeck EM and Halle M. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association*. 2021;325:542-551.
122. Pandey A, Parashar A, Kumbhani DJ, Agarwal S, Garg J, Kitzman D, Levine BD, Drazner M and Berry JD. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circulation Heart failure*. 2015;8:33-40.
123. Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, Mayo HG, de Lemos JA and Berry JD. Dose-Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis. *Circulation*. 2015;132:1786-94.
124. Hieda M, Sarma S, Hearon CM, Jr., MacNamara JP, Dias KA, Samels M, Palmer D, Livingston S, Morris M and Levine BD. One-Year Committed Exercise Training Reverses Abnormal Left Ventricular Myocardial Stiffness in Patients With Stage B Heart Failure With Preserved Ejection Fraction. *Circulation*. 2021;144:934-946.
125. Hansen D, Abreu A, Ambrosetti M, Cornelissen V, Gevaert A, Kemps H, Laukkanen JA, Pedretti R, Simonenko M, Wilhelm M, Davos CH, Doehner W, Iliou MC, Krankel N, Voller H and Piepoli M. Exercise intensity assessment and prescription in cardiovascular rehabilitation and beyond: why and how: a position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol*. 2022;29:230-245.
126. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA and Paulus WJ. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. *Circulation*. 2016;134:73-90.
127. Tanner FC BN, Fox KF et al Core curriculum for the cardiologist. . *Eur Heart J*. 2020.
128. Wilhelm M AA, Adami PE et al EACP core curriculum for preventive cardiology. *European Journal of Preventive Cardiology*. 2021.
129. Malhotra R, Bakken K, D'Elia E and Lewis GD. Cardiopulmonary Exercise Testing in Heart Failure. *JACC Heart Fail*. 2016;4:607-16.
130. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J, Eacpr and Aha. EACPR/AHA Joint Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *European heart journal*. 2012;33:2917-27.
131. Takken T, Mylius CF, Paap D, Broeders W, Hulzebos HJ, Van Brussel M and Bongers BC. Reference values for cardiopulmonary exercise testing in healthy subjects - an updated systematic review. *Expert Rev Cardiovasc Ther*. 2019;17:413-426.
132. Sun XG, Hansen JE and Stringer WW. Oxygen uptake efficiency plateau: physiology and reference values. *European journal of applied physiology*. 2012;112:919-28.

Accepted Article

133. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC and Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39:2810-2821.
134. Smith JR, Van Iterson EH, Johnson BD, Borlaug BA and Olson TP. Exercise ventilatory inefficiency in heart failure and chronic obstructive pulmonary disease. *Int J Cardiol*. 2019;274:232-236.
135. Petersson J and Glenny RW. Gas exchange and ventilation-perfusion relationships in the lung. *The European respiratory journal*. 2014;44:1023-41.
136. Belardinelli R, Lacalaprice F, Carle F, Minnucci A, Cianci G, Perna G and D'Eusanio G. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *European heart journal*. 2003;24:1304-13.
137. Hearon CM, Jr., Sarma S, Dias KA, Hieda M and Levine BD. Impaired oxygen uptake kinetics in heart failure with preserved ejection fraction. *Heart*. 2019;105:1552-1558.
138. Chatterjee NA, Murphy RM, Malhotra R, Dhakal BP, Baggish AL, Pappagianopoulos PP, Hough SS, Semigran MJ and Lewis GD. Prolonged mean VO2 response time in systolic heart failure: an indicator of impaired right ventricular-pulmonary vascular function. *Circulation Heart failure*. 2013;6:499-507.
139. Cole CR, Blackstone EH, Pashkow FJ, Snader CE and Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *The New England journal of medicine*. 1999;341:1351-7.

Legend for Figures

Figure 1. Plot of the Fick principle relating CO to a-vO_2 difference and isoplets curves of VO_2. The graph describes the expected relationship of HF versus normal control pattern along with COPD and anemia conditions as common comorbid that affect O2 content and delivery and may add on HFpEF hemodynamic, i.e. CO, limitation.

Figure 2. The O_2 cascade during exercise. The organ systems and pathways (from air to mithocondria) involved in the exercise performance are depicted along with the limiting steps and pathophysiology behind exercise limitation in HFpEF.

Figure 3. Cascade of the cardiac, hemodynamic and pulmonary maladaptive response under the effects of PCWP increase.

Figure 4. Continuous of mechanisms involved in the RV maladaptive response to increased load and PVD, affecting cardiac output and exercise performance in HFpEF

Figure 5. 9-plot analysis of a typical CPET response of an old hypertensive female patient with exertional dyspnoea. See text for explanation

Figure 6. 9-plot analysis of a middle age man with initial exertional dyspnoea presenting with a different CPET phenotype. See text for explanation

Figure 7. CPET imaging rest to peak exercise analysis of the same case of Figure 3. Measures obtained by stress echocardiography (rest to peak exercise). The analysis was performed analysing the diastolic (E/e') and systolic (3D longitudinal and circumferential strain) LV function; the adaptive LA dynamics by LA strain; RV function (RVEF 3D analysis) and its coupling with the

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pulmonary circulation by TAPSE/PASP ratio. Data are reported at rest (white) and at peak exercise (orange) with the changes occurring in the main variable rest to peak.

Figure 8. (Central Illustration). Prioritizing cardiopulmonary exercise testing within the HFA PEFF diagnostic algorithm. Modified HFA PEFF diagnostic algorithm including CPET in Step 1 (P) the pre-assessment, and Step 4 (F). Details in the text.

Abbreviations: aBGA, arterial blood gas analysis; BP, blood pressure; BR, breathing reserve, ratio of VE/maximum voluntary 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-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; VE, ventilation; VCO_2, carbon dioxide output; VO_2, oxygen consumption; VFL/VT, percent of the tidal breath that expiratory air flow exceeds the maximal flow/volume envelope; VD/VT, ratio of dead-space ventilation to tidal ventilation; VT, ventilatory thresholds (VT1/VT2 corresponding to anaerobic threshold/respiratory compensation point)

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Table 1. CPET variables delineating O2 pathway defects, and risk stratification in HFpEF

Variable	Cut-off	Interpretation
Quantification of exercise intolerance		
RER	<1.0 ≥1.0, preferably ≥1.1	Definition of submaximal or maximal exercise testing [129, 130]
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 cuf-offs	Categorization of cardiorespiratory fitness, can be used in maximal exercise tests either classified based on Weber or on healthy adult cohorts[130, 131]
OUES (l/min/log(l/min))	Age- and sex-specific cut-offs	Submaximal parameter that correlates with peak VO_2[131, 132]
VO_2@VT1 (ml/kg/min)	Age and sex-specific cut-offs	Submaximal parameter that correlates with peak VO_2[131]
Ventilatory mechanical limitation		
BR (%)	<15-20	Ventilatory limitation[77]
VFL/VT (%)	>50	Expiratory air flow 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 hemodynamics		
VE/VCO_2 slope (L/min/ml/kg/min)	>30	Reduced ventilatory efficiency due to increased ventilation and or increased death space ventilation.[129] Elevations associated with higher PVR and more severe diseases in HFpEF patients with pulmonary hypertension.[133]
VE intercept	<2.64 l/min	May discriminate HFpEF from COPD HFpEF[134]
SaO_2 (%)	Decrease≥5	Gas exchange abnormalities, most commonly related to V/Q mismatch[77, 130]
Vd/VT (%)*	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.[133]
PA-aO_2* (mmHg)	Increase above age- and sex-specific normal values	Gas exchange abnormalities, most commonly related to V/Q mismatch[77, 135]
PaO_2 (mmHg)*	Decrease≥10	Gas exchange abnormalities, most commonly related to V/Q mismatch[77]
Exercise PCWP (mmHg)#	≥25	Cut-off for exercise induced pulmonary hypertension with limited validity[92, 105]
ΔPAP/ΔCO (mmHg/L/min)#	>3	Alternative marker of exercise-induced pulmonary hypertension[92, 105]

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ΔTPG/ΔCO (mmHg/L/min)#	>1	Pre-capillary pulmonary hypertension[92, 105]
Cardiovascular limitations defined by gas exchange abnormalities and/or hemodynamics		
VO_2/work-rate trajectory (ml/kg/min/watt)	Flattening or decline	LV dysfunction due to myocardial ischemia[136], or right-sided cardiac dysfunction and pulmonary hypertension in HF[84]
O_2 pulse trajectory (ml/kg/min/bpm)	Flattening or decline	LV dysfunction due to myocardial ischemia[136]
HR/VO_2 slope (bpm/ml/kg/min)	>50	Relative tachycardia to oxygen uptake[77]
MCR	≤0.80 or <0.62 on beta blocker	Chronotropic incompetence[40]
ΔPCWP/ΔCO slope (mmHg/L/min)#	>2	Impaired LV reserve capacity[105, 109]
Exercise RAP (mmHg)#	>PCWP	RV dysfunction[105]
ΔCO/ΔVO2 slope (ml blood/ml O2)#	<4.8	Impaired cardiac output 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)#	<0.8*haemoglobin	Impaired peripheral O_2 utilisation[105]
VO_2 kinetics	MRT<60s	Impaired peripheral oxygen utilisation in HFpEF[137], may also indicate impaired RV-pulmonary vascular function in HFrEF[138]
Stratification of Risk		
VO_2peak (ml/kg/min)	<14	Predicts higher risk of heart failure hospitalisation and the composite outcome all-cause death, LVAD-implantation, or heart transplantation, in particular when combined with VE/VCO_2 slope >30.[106]
VE/VCO_2 slope	>30	Predicts higher risk of heart failure hospitalisation and the composite outcome all-cause death, LVAD-implantation, or heart transplantation, in particular when combined with VO2peak<14 ml/kg/min.[106] Predicts mortality in HFpEF patients with PH.[82]
EOV	Present	Predicts higher risk of CV death.[86]
HRR at 1 min (bpm)	<12 decrease	Predicts higher risk of CV death[139]
PCWP/CO slope (mmHg/L/min) #	>2	Predicts higher risk of composite outcome of cardiovascular death, HF hospitalization, or abnormal resting PCWP on future right heart catheterizations.[109]

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PCWP/workload/kg (mmHg/watt/kg) #	>25.5	Predicts higher risk of all-cause mortality, independently from baseline PCWP.[102]
PAP/CO slope (mmHg/L/min) #	>3	Predicts higher risk of first heart failure hospitalisation or all-cause mortality, both in patients with or without resting PH. [95 101]

For abbreviations see legend of Figure 5 – central illustration.

* derived from additional arterial blood gas analysis

derived from additional invasive measurement (right heart catheterization)

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Figure 1

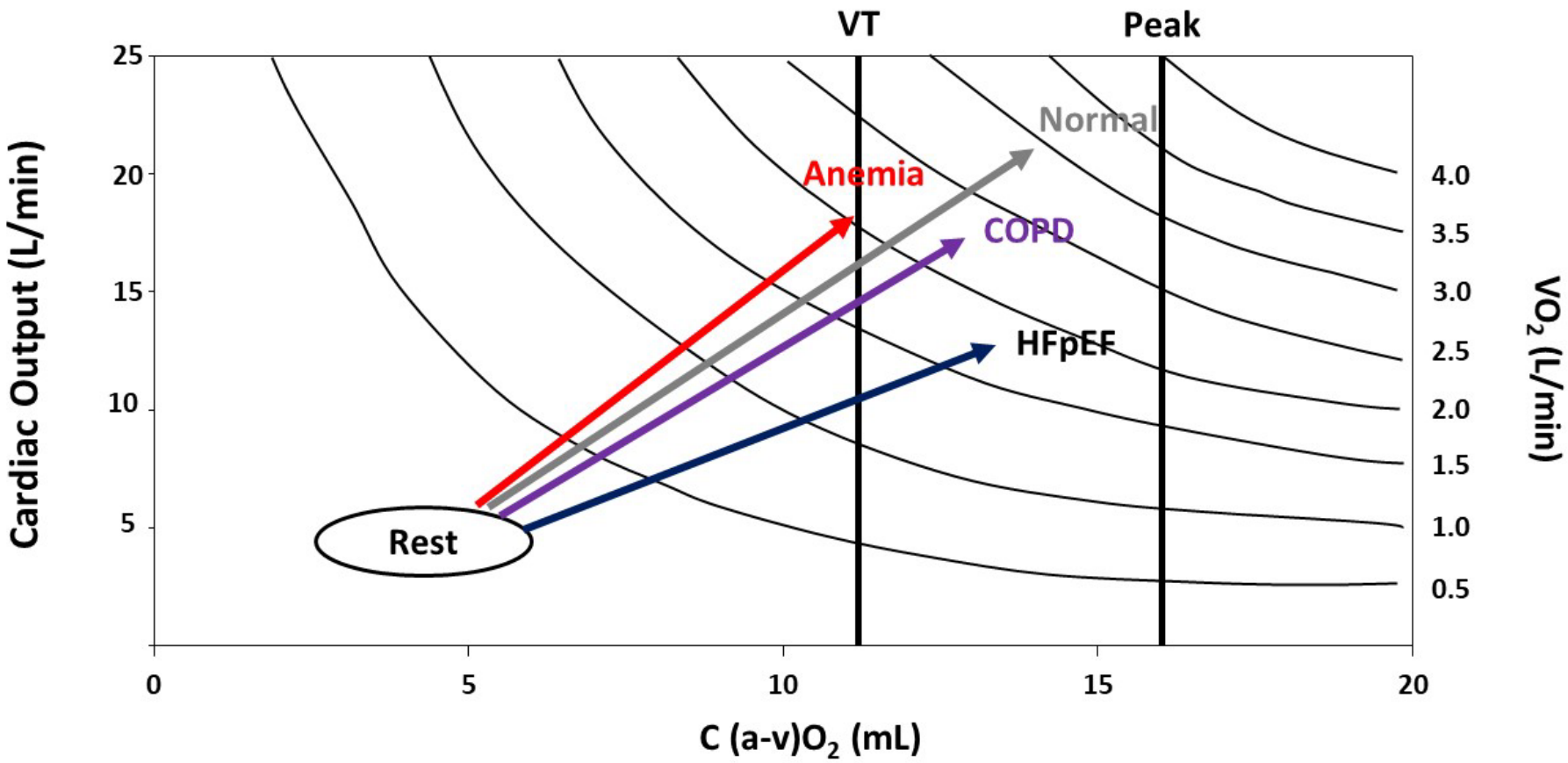

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Figure 2

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

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Figure 3

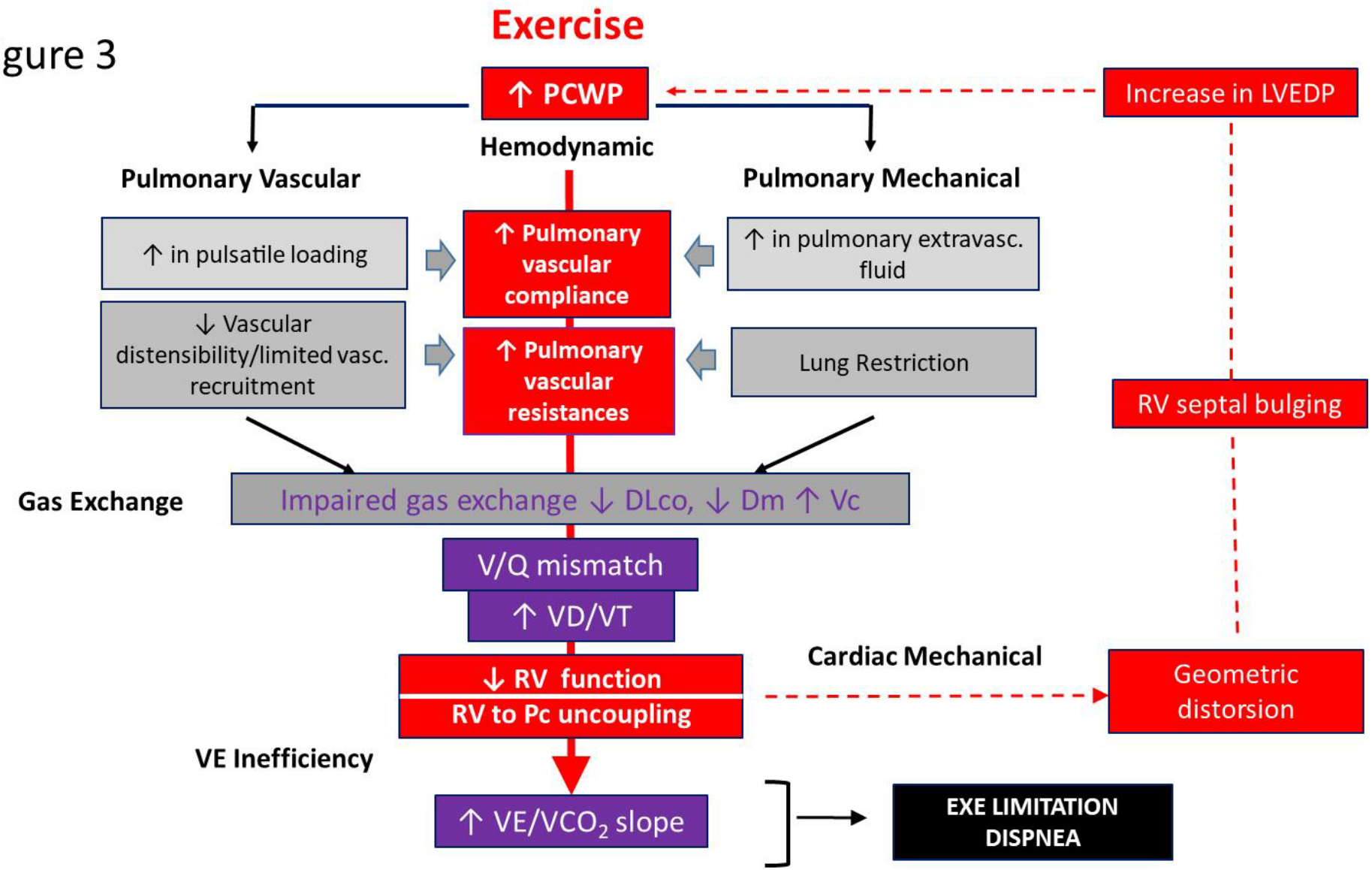

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Figure 4

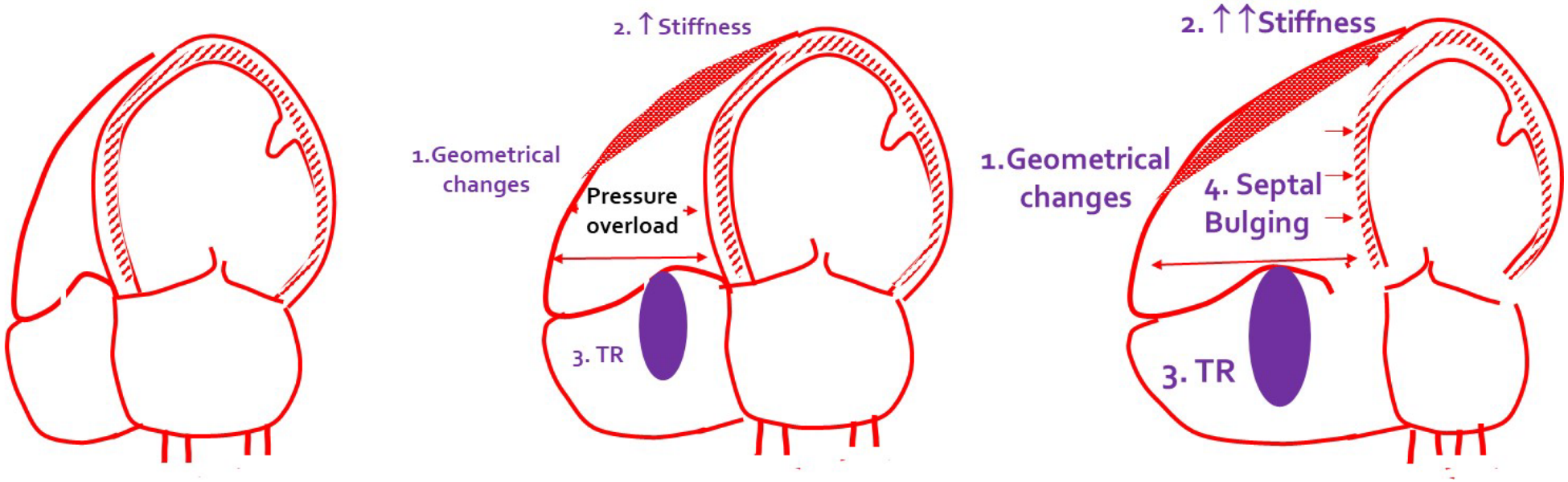

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Figure 5

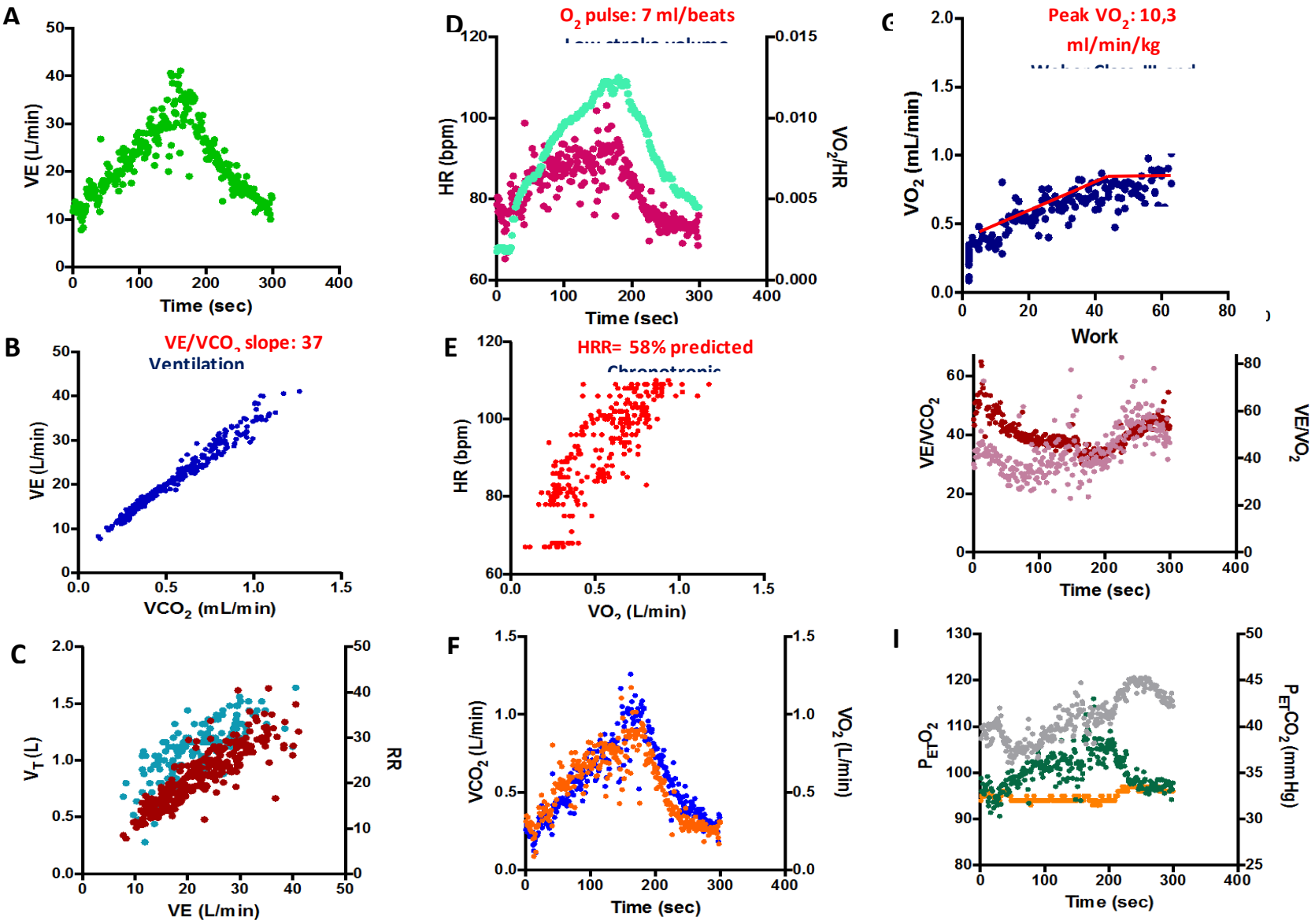

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Figure 6

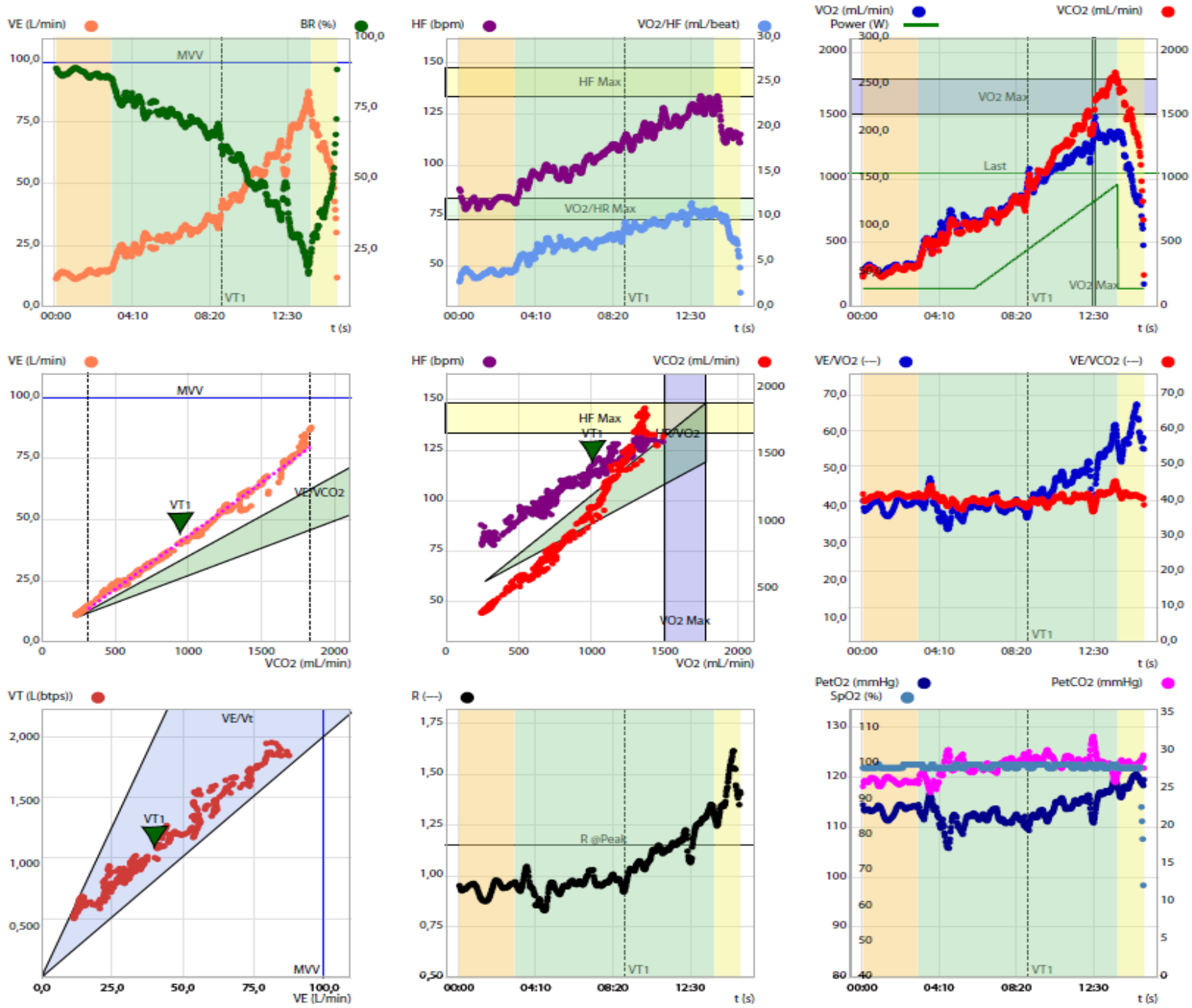

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Figure 7

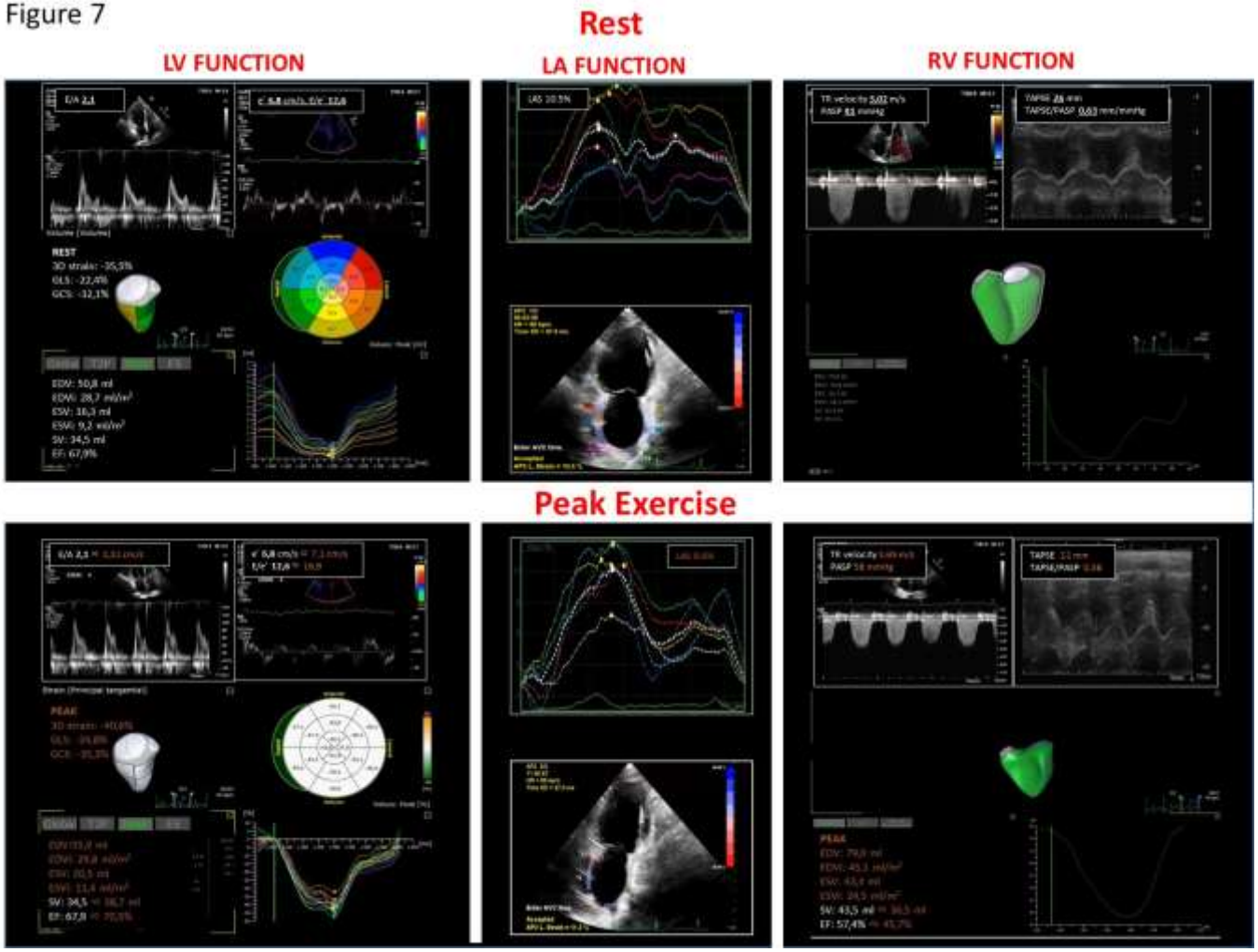

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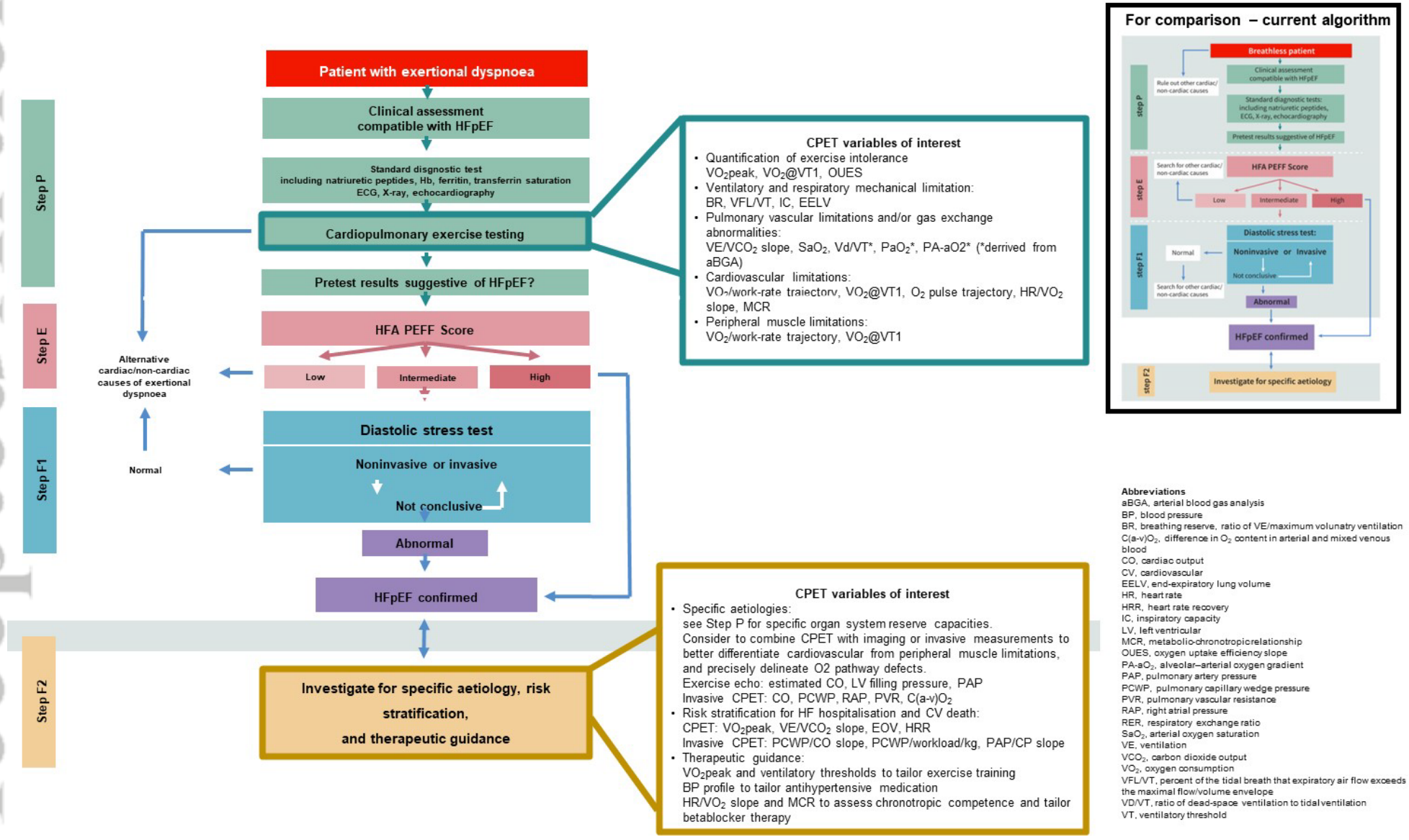
Figure 8 (Central Illustration)



Abbreviations
aBGA, arterial blood gas analysis
BP, blood pressure
BR, breathing reserve, ratio of VE/maximum volunatry ventilation
$C(a\text{-}v)O_2$, 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
VE, ventilation
VCO_2, carbon dioxide output
VO_2, oxygen consumption
VFL/VT, percent of the tidal breath that expiratory air flow exceeds the maximal flow/volume envelope
VD/VT, ratio of dead-space ventilation to tidal ventilation
VT, ventilatory threshold

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