










# Combining cardiopulmonary exercise testing with echocardiography: a multiparametric approach to the cardiovascular and cardiopulmonary systems

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## Abstract

Exercise intolerance is a prominent feature of several cardiovascular conditions. However, the physical effort requires the intertwined adaptation of several factors, namely the cardiovascular system, the lungs, and peripheral muscles. Several abnormalities in each domain may be present in a given patient. Cardiopulmonary exercise testing (CPET) has been used to investigate metabolic and ventilatory alterations responsible for exercise intolerance but does not allow for direct evaluation of cardiovascular function. However, this can readily be obtained by concomitant exercise-stress echocardiography (ESE). The combined CPET-ESE approach allows for precise and thorough phenotyping of the pathophysiologic mechanisms underpinning exercise intolerance. Thus, it can be used to refine the diagnostic workup of patients with dyspnoea of unknown origin, as well as improve risk stratification and potentially guide the therapeutic approach in specific conditions, including left and right heart failure or valvular heart disease. However, given its hitherto sporadic use, both the conceptual and technical aspects of CPET-ESE are often poorly known by the clinician. Improving knowledge in this field could significantly aid in anticipating individual disease trajectories and tailoring treatment strategies accordingly. Therefore, we designed this review to revise the pathophysiologic correlates of exercise intolerance, the practical principles of the combined CPET-ESE examination, and its main applications according to current literature.

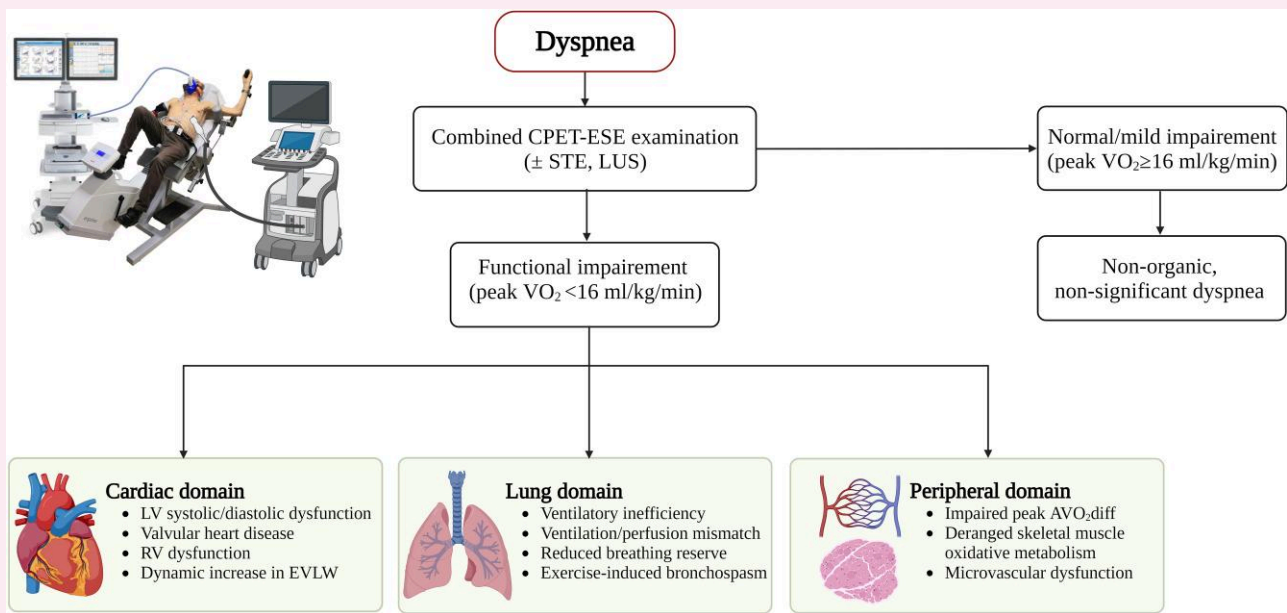
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## Graphical Abstract



The combined CPET-ESE approach to a patient with dyspnoea.  $AVO_2$ diff, peripheral oxygen extraction; CPET, cardiopulmonary exercise testing; EVLW, extravascular lung water; ESE, exercise-stress echocardiography; LV, left ventricle; RV, right ventricle;  $VO_2$ , oxygen consumption.

### Keywords

ecocardiography • stress echocardiography • cardiopulmonary function • exercise • heart failure • heart valve disease

## Introduction

Exercise intolerance, defined as the failure to perform physical activities without experiencing dyspnoea and/or fatigue, is a prominent clinical feature of cardiovascular abnormalities.<sup>1</sup> In healthy individuals, functional capacity results from the consonant interplay between cardiac and extracardiac responses to stress, including vascular and pulmonary reserve, adequate plasma haemoglobin concentration, and skeletal muscle structure and function.<sup>1,2</sup> Cardiopulmonary exercise testing (CPET) can investigate all these contributors simultaneously, allowing for an initial differentiation of cardiac and pulmonary alterations underlying exercise intolerance. However, CPET alone does not allow for a direct evaluation of cardiac determinants of impaired functional capacity [e.g. left or right ventricular (LV and RV, respectively) dysfunction, LV- or RV-arterial uncoupling, worsening valvular heart disease], which can limit the identification of the leading cause of effort intolerance, i.e. cardiac disease, lung disease, physical deconditioning, or any combination of these factors. Combining exercise-stress echocardiography (ESE) with CPET yields further data to investigate the pathophysiology behind effort intolerance.<sup>3,4</sup> The multiparametric nature of CPET-ESE provides a deep pathophysiologic characterization of the patient with dyspnoea and can refine its diagnosis and prognosis.<sup>3-5</sup> Thus, a more precise understanding of the combined CPET-ESE approach could aid the clinician in anticipating individual disease trajectories and tailoring treatment strategies accordingly. This review aims to revise the theoretical and technical aspects of CPET-ESE and dissect the main parameters analysed during a CPET-ESE evaluation.

## Pathophysiology of effort intolerance: a brief overview

The cardiovascular contributors to exercise capacity are summarized by Fick's principle, stating that oxygen consumption ( $VO_2$ ) is equal to the product of cardiac output (CO) times the arteriovenous oxygen difference ( $AVO_2$ diff); in turn, CO is the product of heart rate (HR) and stroke volume (SV). Thus, at any given time, the use of oxygen as an energy substrate depends not only on oxygen exchange across the alveolar-capillary membrane in the lungs and on cardiac pump function (i.e. CO) but also on the capacity of peripheral muscles to extract oxygen from the blood and metabolize it.<sup>2</sup> This complex system requires a coordinated interplay of numerous factors in resting conditions and is under further stress when physical effort is undertaken.<sup>2,3</sup> CPET-ESE provides essential information to understand the causes of exercise intolerance in any subject by simultaneously analysing cardiovascular, metabolic, and respiratory responses to exercise. Indeed, the patient could suffer from a dominant limitation in cardiac function, lung impairment, or inadequate peripheral oxygen extraction (*Graphical abstract*). However, the pathophysiology of effort intolerance is often multifactorial, and several abnormalities in more than one system may be present in the same patient. For example, while a marked impairment in cardiac reserve (i.e. CO increase during exercise) is a typical feature of conditions such as coronary artery disease, heart failure (HF) with reduced LV ejection fraction (HFrEF), and severe aortic stenosis (AS), subjects with HF and preserved LV ejection fraction (HFpEF) have also been found to display impaired CO increase during exercise

compared with healthy subjects.<sup>6</sup> Similarly, poor oxygen extraction (i.e. reduced peak  $AVO_2\text{diff}$ ) is typical of HFpEF, primarily due to the high prevalence of comorbidities (e.g. arterial hypertension and diabetes mellitus) driving deranged skeletal muscle oxidative metabolism and peripheral microvascular dysfunction, but it can also be observed in advanced HFpEF when skeletal muscle wasting develops due to cardiac cachexia.<sup>3,7</sup>

## The combined CPET-ESE approach

At present, there is no standardized method to perform combined CPET-ESE. However, general indications should be followed to increase the reliability and reproducibility of the findings. First, anaemia should be excluded as a potential cofactor of impaired oxygen delivery and  $AVO_2\text{diff}$ .<sup>2</sup> It is reasonable to target 8–12 min as the optimal exercise duration for the patient to achieve peak  $VO_2$ , as reported in current guidelines regarding CPET.<sup>8</sup> Similarly, a functional pulmonary evaluation with spirometry should precede CPET-ESE, in order to identify lung abnormalities associated with exercise intolerance, specifically more than moderate airflow obstruction [forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC) ratio <0.70 and FEV1 <50% of predicted] and/or restrictive pattern (FVC <80% of predicted) or exercise-induced bronchospasm.<sup>9</sup>

Incremental ramps allow for a steady, low-grade workload increase (8–15 W/min) instead of the brisk workload increments observed with the Bruce protocol stress testing. It should be remembered that the CPET-ESE examination aims to dissect the pathophysiologic mechanisms of exercise intolerance rather than investigate the presence of coronary artery disease (which is, instead, the purpose of the Bruce protocol). This method has been extensively applied to CPET-ESE in different settings.<sup>6,10–17</sup> In addition to ensuring that every patient performs an adequately challenging exercise at a constant pedalling rate, the clinician must focus on obtaining adequate echocardiographic images, taking into account each patient's acoustic window and potential modifying factors (e.g. heart movements, hyperventilation, and body motion). For this reason, the patient is usually asked to exercise in a semirecumbent position, which slightly contrasts with standard CPET protocols employing an upright cycle ergometer or treadmill. However, there seems to be little or no variation between these approaches regarding peak  $VO_2$  achieved during exercise.<sup>2</sup> The incremental ramp allows the patient to adapt to the exercise gradually and gives the clinician time to store all required echocardiographic images. Albeit the echocardiographic evaluation at rest and peak effort is mandatory, we suggest acquiring images multiple times during exercise. We usually employ a four-stage protocol<sup>3</sup>: (i) rest; (ii) low-load effort (i.e. within 4 min from the start when HR is usually <100 bpm); (iii) anaerobic threshold, i.e. when the respiratory exchange ratio [expressed by the carbon dioxide production ( $VCO_2$ )/ $VO_2$  ratio] is steadily  $\geq 1.00$ ; and (4) peak effort (i.e. when the patient reports effort-limiting symptoms; [Figure 1](#)).

During the whole exercise, blood pressure and HR are continuously monitored. Inadequate (both hypotensive<sup>18</sup> and hypertensive<sup>11</sup>) blood pressure response to effort and chronotropic incompetence (defined as the failure to achieve  $\geq 80\%$  of the difference between age-predicted maximal HR and resting HR—i.e. HR reserve—or  $>62\%$  in patients taking beta-blockers),<sup>19</sup> contribute to impaired functional capacity and carry poor prognostic significance in patients with and without cardiovascular disease.

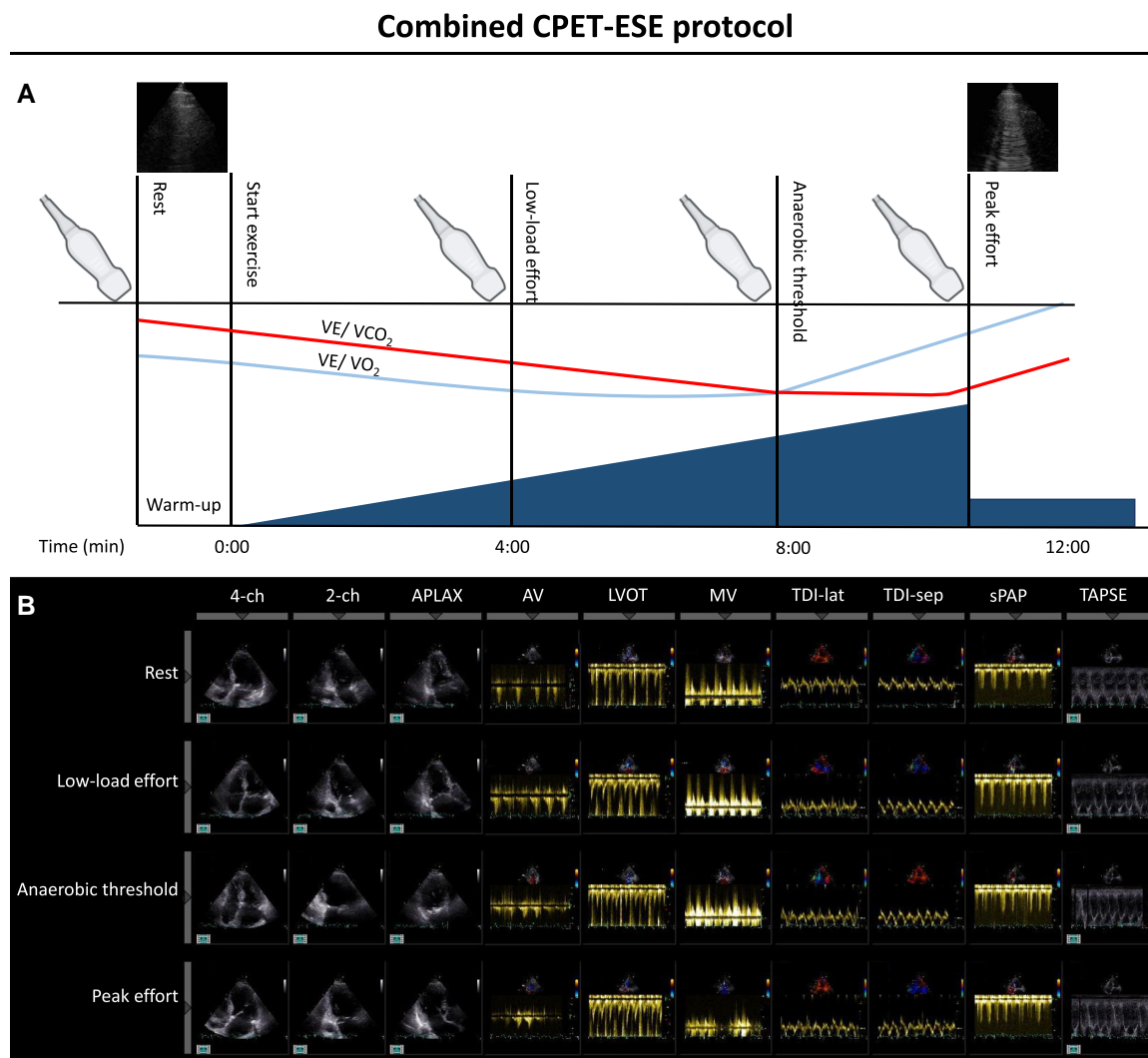
The CPET module allows breath-by-breath gas exchange measurements to analyse the respiratory determinants of effort intolerance ([Table 1](#)). It investigates ventilatory (in)efficiency by measuring exercise-induced changes in the dead space volume to tidal volume ( $V_D/V_T$ ) ratio and breathing reserve, i.e. the difference between maximum voluntary ventilation (MVV) and minute ventilation (VE). MVV is the total volume

of air exhaled during 12 s of rapid, deep breathing and can be either directly measured or estimated from FEV1 35<sup>2</sup>; MVV can be impaired in primary lung disease, especially obstructive lung disease. CPET also gives indirect evidence of ventilation/perfusion mismatch via the slope of VE to carbon dioxide production (VE/ $VCO_2$  slope). It also highlights the presence of exercise oscillatory ventilation (EOV), namely a cyclic fluctuation of ventilation and respiratory exchanges ( $VO_2$  and  $VCO_2$ ) during the exercise. The EOV sign is not a normal ventilatory response under any circumstances, and it is observed in patients with advanced HFpEF. Despite a controversial underlying mechanism, EOV is invariably associated with poor prognosis.<sup>2</sup> Other noteworthy CPET-derived parameters are the  $VO_2$ /work ratio and oxygen pulse (i.e. the  $VO_2$ /HR ratio). The  $VO_2$ /work trajectory plots the relationship between  $VO_2$  and workload; in physiological conditions, the  $VO_2$ /work presents a continual linear rise. In normal subjects, the average slope is 10 mL/min/W, independently of the load imposed and slightly changing according to exercise duration. An abnormally flat  $VO_2$ /work ratio is often observed in physical deconditioning and/or LV dysfunction.<sup>2</sup> On the other hand, the oxygen pulse represents a proxy for SV, assuming a constant  $AVO_2\text{diff}$ . It also has a linear rise throughout the exercise, with a possible plateau approaching maximal exertion. Normal peak values for the  $O_2$  pulse at peak exercise are  $>11$  mL $O_2$ /min, while they are reduced in patients with exercise-induced left ventricular dysfunction due to myocardial ischaemia.<sup>2</sup>

Key echocardiographic parameters that should be acquired during each stage include ([Figure 1](#) and [Table 2](#)):

- *Two-dimensional (2D) images.* The 2D echocardiographic examination at rest should be carried out according to current guidelines.<sup>29</sup> Throughout the exercise, apical four-, two-, and three-chamber views should be used to evaluate LV global and regional contractile function.
- *Doppler evaluation.* Measurements should include transvalvular aortic velocity, left ventricular outflow tract velocity-time integral to calculate SV, mitral inflow and tissue Doppler-derived mitral  $e'$  to evaluate the diastolic function, and tricuspid regurgitation (TR) velocity (TRV), to estimate systolic pulmonary arterial pressure (sPAP). Any valvular defect deemed significant at colour Doppler imaging should be evaluated by semiquantitative or quantitative criteria according to current guidelines,<sup>46</sup> at least at rest and peak exercise.
- *M-mode evaluation.* Tricuspid annular plane systolic excursion (TAPSE) should be measured as an index of right ventricular systolic function,<sup>29</sup> and the TAPSE/sPAP ratio should be calculated to evaluate right ventricular-pulmonary arterial (RV-PA) coupling.<sup>33</sup>
- The following ultrasound techniques can add further significant information:
- *Speckle tracking echocardiography (STE).* STE evaluates LV systolic and left atrial (LA) function [e.g. global longitudinal strain (GLS) and LA reservoir, respectively]. This technique finds its greater application at rest and low-load effort when HR is <100–120 bpm. At higher HRs, STE is prone to algorithm undersampling, and hyperventilation-related through-plane motion artefacts are usually associated with insufficient image quality for STE analysis.<sup>37,47</sup>
- *Lung ultrasound (LUS).* LUS allows for evaluating and quantifying extravascular lung water (EVLW) during exercise, counting B-lines at rest and peak effort. A dynamic increase in B-lines is virtually always diagnostic of a cardiogenic increase in EVLW.<sup>41</sup> While the complete LUS protocol at rest requires careful examination of both the anterior and posterior thorax,<sup>41</sup> simplified protocols of four- or eight-site scan acquisitions only on the anterior thorax<sup>41</sup> have been proposed during exertion and successfully integrated into the CPET examination.<sup>13,48,49</sup>

Noteworthy, three- to five-beat loops should be recorded to average parameters over different cardiac cycles, especially in patients with irregular HR, such as those with atrial fibrillation or a significant extrasystolic burden.



**Figure 1** Combined CPET-ESE protocol outline. (A) Before the beginning of the effort, an echocardiographic evaluation at rest is performed, including baseline lung ultrasound. Then, after a brief warm-up, the symptom-limited graded ramp test starts with continuous breath-by-breath gas exchange measurements. ESE images are acquired at three different stages during exercise: low load (HR <100 bpm), after reaching the anaerobic threshold, and at peak effort (when lung ultrasound is also performed). (B) ESE-derived image acquisition during each stage. Adapted from Pugliese NR, de Biase N, Balletti A, Filidei F, Pieroni A, D'Angelo G et al. Characterisation of hemodynamic and metabolic abnormalities in the heart failure spectrum: the role of combined cardiopulmonary and exercise echocardiography stress test. *Minerva Cardiol Angiol* 2022;370–84.

## CPET-ESE in specific conditions

### HFrEF and HFpEF

One of the main fields of application of CPET-ESE is HF (Figure 2).<sup>3,4,7,10–15,17,23,35,50–53</sup> CPET-ESE can aid the clinician in investigating the relative pathophysiologic and prognostic weight of the diverse cardiovascular and ventilatory alterations, resulting in exercise intolerance in a given patient with HF, a difficult task to perform relying only on clinical data, as these patients are often ailed by multiple comorbidities.<sup>54</sup> CPET is paramount in evaluating peak  $VO_2$  in patients with advanced HFrEF for transplant eligibility purposes<sup>8</sup>; at the same time, ESE can be used to highlight exercise-induced LV wall motion abnormalities and/or CO reduction. However, the combined approach has several other applications, particularly in refining the diagnosis and

prognosis of patients with (or with a suspect of) HFpEF. Indeed, CPET-ESE has been used to investigate the relationship between exercise-induced pulmonary hypertension, EVLW accumulation, ventilation/perfusion mismatch, abnormal peripheral oxygen extraction, and patient prognosis across the HF spectrum.<sup>13,49,55–57</sup> It has also been used to evaluate the role of LA function and RV-PA uncoupling on effort intolerance and prognosis.<sup>12,38</sup> More recently, the impact of impaired LV-arterial coupling<sup>14</sup> and hypertensive response to exercise<sup>11</sup> on functional capacity has been addressed by the combined approach.

Finally, attention has been drawn to the potential relationship between HF severity and acetone, an end product of beta-oxidation, in exhaled breath. This pathway is impaired in patients with acute HF due to mitochondrial energy metabolism alterations.<sup>58</sup> Therefore, implementing breath analysis during exercise with a dedicated gas chromatography coupled with mass spectrometry or a selected ion flow

**Table 1 Significant CPET parameters**

| Parameter   | Significance  | Normal value  |
|---|---|---|
| <i>Assessment of exercise intolerance</i>               |   |   |
| Peak $\text{VO}_2$                                      | The highest $\text{VO}_2$ observed during exercise, usually calculated as a 30 s average. <sup>10</sup> Index of global performance by central (i.e. cardiopulmonary) and peripheral (i.e. skeletal muscle) components, <sup>12</sup> resulting in a robust prognostic marker in HF. <sup>20,21</sup>   | Values >20 mL/kg/min indicate good functional capacity and prognosis. <sup>21</sup> To account for age, sex, weight, and height-dependent differences, peak $\text{VO}_2$ can also be expressed as a percentage of the predicted value derived from Wassermann–Hansen equations. <sup>22</sup> Normal values are >80% of predicted peak $\text{VO}_2$ (the equations might underperform in HFpEF <sup>23</sup> ). |
| RER   | The ratio between $\text{VCO}_2$ and $\text{VO}_2$ increases during exercise.   | Reliable index of exercise effort. Psychogenic hyperventilation can cause false increases, especially in the first minutes of exercise. Values $\geq 1.1$ indicate maximal effort.  |
| $\text{VO}_2/\text{work}$                               | Correlates with exercise limitation due to physical deconditioning or left ventricular dysfunction (inducible myocardial ischaemia and HF).   | In physiological conditions, the relationship is characterized by a 10 mL/min/W slope independently of workload, with minor changes according to exercise duration. In advanced HF, the slope is reduced. $\text{VO}_2/\text{work}$ flattening and downsloping indicate a significant reduction in CO (e.g. myocardial ischaemia and severe aortic stenosis).   |
| Oxygen pulse  | The ratio between $\text{VO}_2$ and HR. According to Fick's principle, the $\text{O}_2$ pulse is an indirect index of stroke volume and cardiac performance during exercise, presuming a constant $\text{AVO}_2$ diff.  | Steady rise during the exercise, possibly reaching a plateau in the final moments. Observed values are deemed normal if $\geq 80\%$ of predicted.   |
| <i>Assessment of ventilatory efficiency</i>             |   |   |
| $\text{VE}/\text{VCO}_2$ slope                          | Expression of ventilation/perfusion matching in the lung, <sup>24</sup> depending on $\text{CO}_2$ production ( $\text{VCO}_2$ ), physiological dead space/tidal volume ratio ( $V_D/V_T$ ), and arterial $\text{CO}_2$ partial pressure ( $\text{PaCO}_2$ ). $\text{VE}/\text{VCO}_2$ slope portends prognostic value in HF, <sup>25</sup> also at submaximal levels of effort. <sup>2</sup> | Optimal when <30. Values >36 indicate significant ventilation/perfusion mismatch. <sup>25</sup>   |
| $\text{P}_{\text{ET}}\text{CO}_2$                       | Indicator of ventilation/perfusion matching in the lung and a reliable non-invasive estimate of $\text{PaCO}_2$ .   | Normal values are 36–42 mmHg at rest, with a 3–8 mmHg increase before AT. Following AT, $\text{P}_{\text{ET}}\text{CO}_2$ decreases due to hyperventilation.  |
| BR  | Difference between maximal voluntary ventilation (MVV, either directly measured or calculated as $35 \cdot \text{FEV}_1$ or $40 \cdot \text{FEV}_1$ ) and VE. Index of the ventilatory response to exercise.  | Normal if BR >11 L/min Low BR (i.e. VE almost equal to MVV) is typical of patients with primary lung disease (especially obstructive lung disease).   |
| $V_D/V_T$   | The ratio between physiological dead space ( $V_D$ ) and tidal volume ( $V_T$ ) is another indicator of ventilation/perfusion matching in the lung; it decreases during exercise due to alveolar recruitment and vasodilation in the pulmonary circulation. Its regulation is impaired in numerous respiratory disorders and in left-sided pulmonary hypertension.                            | Normal values at rest are 33–34%. During exercise, the decrease is appropriate if peak $V_D/V_T \leq 25\%$ .  |
| EOV   | An oscillatory pattern of VE and expired gas kinetics is typically observed in patients with advanced HF and represents a poor prognostic indicator. <sup>2</sup>   | No agreed-upon definition is available at present. It is usually defined as an oscillatory pattern at rest persisting for $\geq 60\%$ of the exercise, at an amplitude $\geq 15\%$ of the average resting value. <sup>26</sup>  |
| <i>Haemodynamic and peripheral response to exercise</i> |   |   |
| Heart rate  | HR modifications during exercise are a good index of cardiac performance. HR reserve is the HR difference from rest to peak exercise, divided by the difference between age-predicted maximal HR and resting HR. <sup>19,27</sup> Chronotropic incompetence is defined as the inability to reach >80% of HR reserve (or >62% in patients taking beta-blockers).                               | HR continuously increases during exercise in healthy subjects; values >85% of age-predicted maximal HR indicate maximal effort.   |
| Blood pressure  | Blood pressure (BP) variations reflect the cardiovascular response to exercise.   | Systolic BP increases to 200 mmHg in healthy subjects (slightly lower in women than men). Diastolic BP may stay the same or even decrease due to vasodilation in metabolically active muscles.  |

Continued

**Table 1 Continued**

| Parameter             | Significance   | Normal value  |
|-----------------------|--|---|
| AVO <sub>2</sub> diff | It describes the difference between arterial and venous oxygen content. AVO <sub>2</sub> diff can be indirectly estimated from Fick's principle as VO <sub>2</sub> /CO, using CO measurement by invasive catheterization or ESE. | Normal resting values are in the range of 5 mL/100 mL. At peak exercise, healthy subjects can increase AVO <sub>2</sub> diff to 16 mL/100 mL by working muscles. <sup>2</sup> |

AVO<sub>2</sub>diff, arteriovenous oxygen difference; BP, blood pressure; BR, breathing reserve; CO, cardiac output; CPET, cardiopulmonary exercise testing; EOV, exercise oscillatory ventilation; FEV1, forced expiratory volume in the first second; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MVV, maximal voluntary ventilation; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; P<sub>ET</sub>CO<sub>2</sub>, end-tidal partial pressure of carbon dioxide; RER, respiratory exchange ratio; SV, stroke volume; VCO<sub>2</sub>, carbon dioxide production; VD, physiological dead space volume; VE, minute ventilation; VO<sub>2</sub>, oxygen consumption; VT, tidal volume.

**Table 2 Significant ESE parameters**

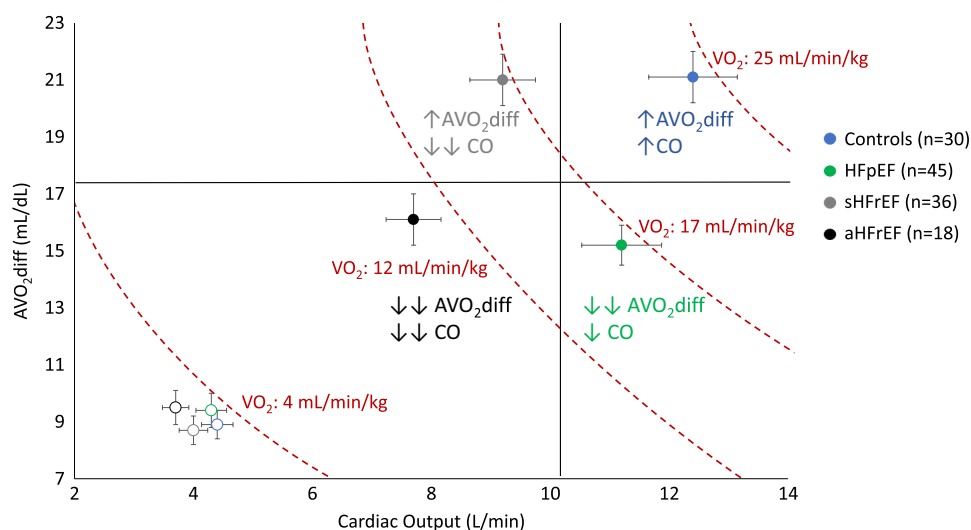
| Parameter          | Significance   | Normal value   |
|--------------------|--|--|
| LVEF               | Primary parameter to classify patients with HF and robust prognostic indicator when <50%. <sup>28</sup> However, it only highlights net differences in end-diastolic and end-systolic volumes, being highly load and geometry dependent. <sup>29</sup> It does not evaluate true myocardial contractility.   | Normal range (mean ± standard deviation) for resting LVEF is 62 ± 5%, slightly higher in women than in men. <sup>29</sup> An exercise-induced increase ≥7.5% in patients is defined as contractile reserve. The absence of contractile reserve indicates limited coronary flow reserve and myocardial damage in HF, even in patients with normal resting LVEF. <sup>30</sup> |
| LV SV              | Blood volume ejected from the LV during a single systolic phase. It can be directly calculated by multiplying the LV outflow tract area by the LV outflow tract velocity-time integral measured by pulsed-wave Doppler. It should be indexed to body surface area.   | An exercise-induced increase ≥20% is defined as flow reserve <sup>30</sup> and subtends an efficient boost in myocardial contractility via the Frank-Starling mechanism.   |
| TDI-S'             | Measured by pulsed wave-TDI, it can be expressed as a single value for each LV wall or averaged. As an index of early systolic velocity (i.e. related to the pre-ejection phase), it may be a more reliable marker of LV contractility than end-systolic indices such as LVEF. It is related to peak VO <sub>2</sub> . <sup>12</sup>   | No established cut point, especially for values at peak effort.  |
| Diastolic function | For a thorough evaluation of diastole, pulsed-wave Doppler of mitral inflow (E, A, E/A ratio), TDI-derived septal and lateral mitral annular velocities (e', E/e' ratio), and TRV must be integrated. In particular, E/e' ratio is usually considered a reliable non-invasive estimation of LV filling pressures. <sup>31</sup> However, evidence for this assumption has been questioned, especially during exercise. <sup>32</sup> | Abnormal diastolic response to exercise includes an E/e' ratio >14, septal e' velocity <7 cm/s, TRV >3.1 m/s and sPAP >50 mmHg. <sup>30</sup>  |
| TAPSE              | Valuable measure of RV longitudinal systolic function, significantly correlated with RV global function.   | Values <17 mm indicate RV systolic dysfunction. <sup>29</sup>  |
| sPAP               | Calculated by estimated right atrial pressure (usually estimated by the inferior vena cava diameter and inspiratory collapse) to continuous-wave Doppler-derived TRV. The TAPSE/sPAP ratio is a valuable index of RV-PA coupling and is related to both peak VO <sub>2</sub> and VE/VCO <sub>2</sub> slope at peak exercise. <sup>33</sup>   | Values >50–60 mmHg during exercise are associated with exercise-induced PH <sup>30</sup> ; however, this is best evaluated by analysing the slope of the multipoint mPAP/CO relationship (with values ≥3 mmHg/L/min virtually diagnostic for exercise-induced PH <sup>34,35</sup> ).   |
| LV GLS             | LV myocardium length change between end-diastole and end-systole, normalized for end-diastolic length (thus conventionally a negative number). GLS is best evaluated by STE and averaged from the three apical views. <sup>36</sup> It is an index of LV global longitudinal function and resembles true myocardial contractility more closely than LVEF. <sup>29</sup>  | GLS ≤−20% is usually deemed normal in healthy subjects. An increase of ≥2% in the absolute value of GLS during exertion indicates good LV functional reserve. <sup>30</sup>  |

Continued

**Table 2 Continued**

| Parameter   | Significance  | Normal value   |
|-------------|---|--|
| LARS        | Evaluated by STE and averaged from six segments in the apical four- and two-chamber views. It is a reliable index of LA performance and is related to RV-PA coupling, <sup>37</sup> impaired ventilatory efficiency during exercise <sup>38</sup> ; finally, it has substantial prognostic significance in both HFrEF and HFpEF. <sup>39,40</sup> The LARS/E/e' ratio has been proposed as a novel measure of LA compliance, as it seems to correlate well with LV filling pressures measured by cardiac catheterization. <sup>12</sup> | At present, there is no established cut-point for abnormal LARS at rest and during exercise.   |
| LUS B-lines | B-lines are signs of EVLW. <sup>41</sup> A dynamic increase in B-lines during exercise highly suggests cardiogenic pulmonary congestion. <sup>42,43</sup>   | No defined cut-point has been established for peak B-lines or rest-peak DB-lines to diagnose increased EVLW accurately. Nevertheless, their increase demonstrated an adverse prognostic value in HFrEF <sup>44</sup> and HFpEF. <sup>13,45</sup> |

CO, cardiac output; EF, ejection fraction; ESE, exercise-stress echocardiography; EVLW, extravascular lung water; GLS, global longitudinal strain; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LA, left atrium; LUS, lung ultrasound; LV, left ventricle; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PH, pulmonary hypertension; RV, right ventricle; sPAP, systolic pulmonary artery pressure; STE, speckle-tracking echocardiography; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging; TRV, tricuspid regurgitation velocity; VCO<sub>2</sub>, carbon dioxide production; VE, minute ventilation; VO<sub>2</sub>, oxygen consumption.



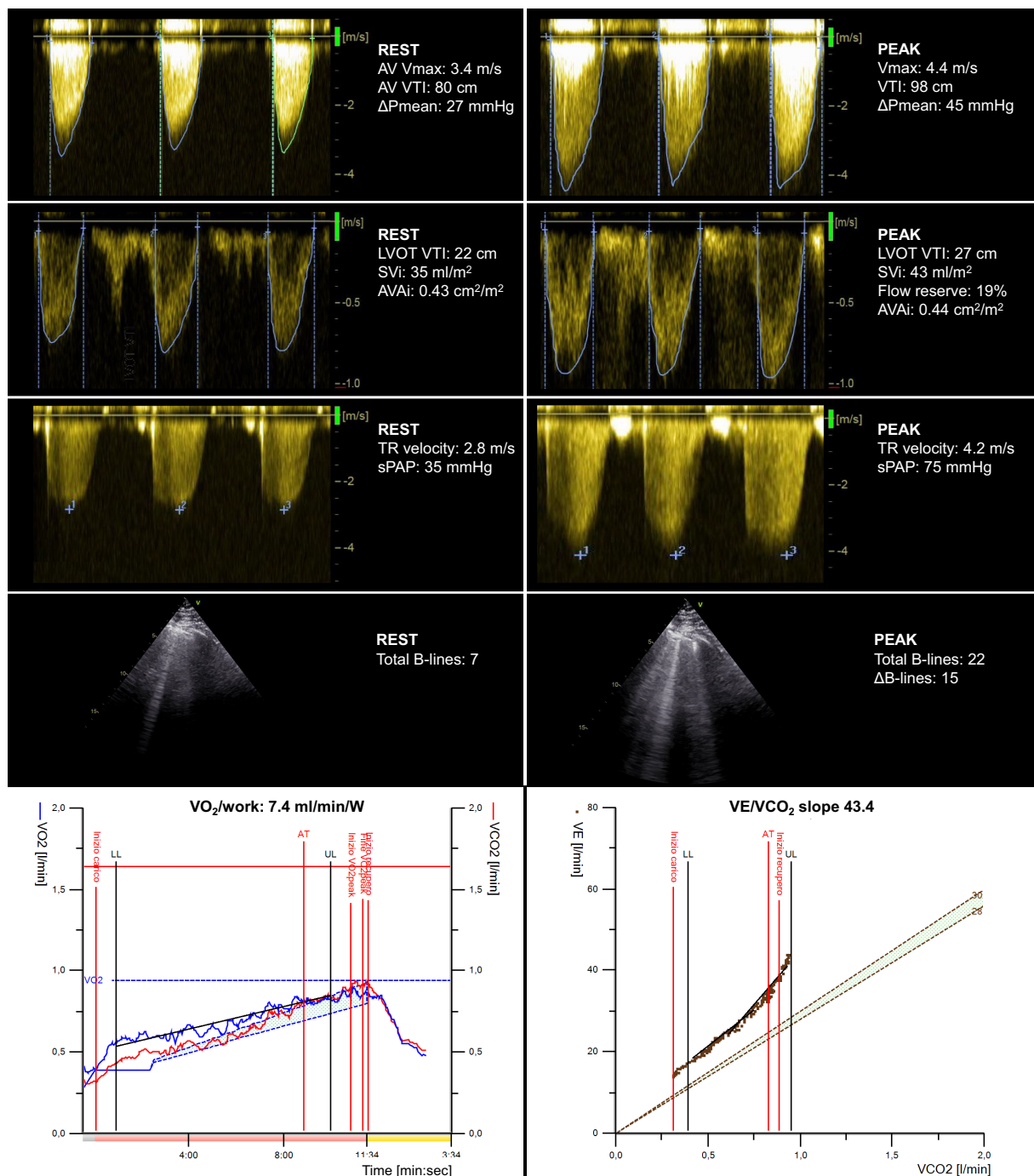
**Figure 2** Patient distribution from rest (empty dots) to peak effort (full dots) plotting AVO<sub>2</sub>diff vs. CO; error bars indicate standard error of the mean. Dashed lines join points of equal values of VO<sub>2</sub>. Compared with controls, HFpEF is characterized by reduced peak CO, with preserved peak AVO<sub>2</sub>diff in stable HFpEF (sHFpEF: peak VO<sub>2</sub> > 14 mL/min/kg) and impaired peak AVO<sub>2</sub>diff in advanced HFpEF (aHFpEF: peak VO<sub>2</sub> ≤ 14 mL/min/kg). Patients with HFpEF show preserved peak CO and reduced peak AVO<sub>2</sub>diff. Adapted from Pugliese NR, Fabiani I, Santini C, Rovai I, Pedrinelli R, Natali A *et al.* Value of combined cardiopulmonary and echocardiography stress test to characterise the haemodynamic and metabolic responses of patients with heart failure and mid-range ejection fraction. *Eur Heart J Cardiovasc Imaging* 2019;20:828–36.

tube mass spectrometer could provide additional data to CPET-ESE, unravelling early and/or worsening disease, potentially underestimated at rest.<sup>59</sup>

## Aortic stenosis

The presence of severe symptomatic AS represents *per se* an indication for aortic valve replacement (Figure 3). However, most patients with

degenerative AS in western countries are elderly, asymptomatic (usually due to self-limitation at home) or with non-specific dyspnoea due to multiple extravalvular and extracardiac comorbidities.<sup>46</sup> CPET-ESE can be particularly useful in this scenario, thanks to the unique advantage of quantifying objectively effort intolerance measuring peak VO<sub>2</sub>, which in turn can be related to the other CPET-ESE-derived parameters to better identify the cause of the dyspnoea. Indeed, the detection of effort-induced AS worsening, impaired functional capacity and/or onset

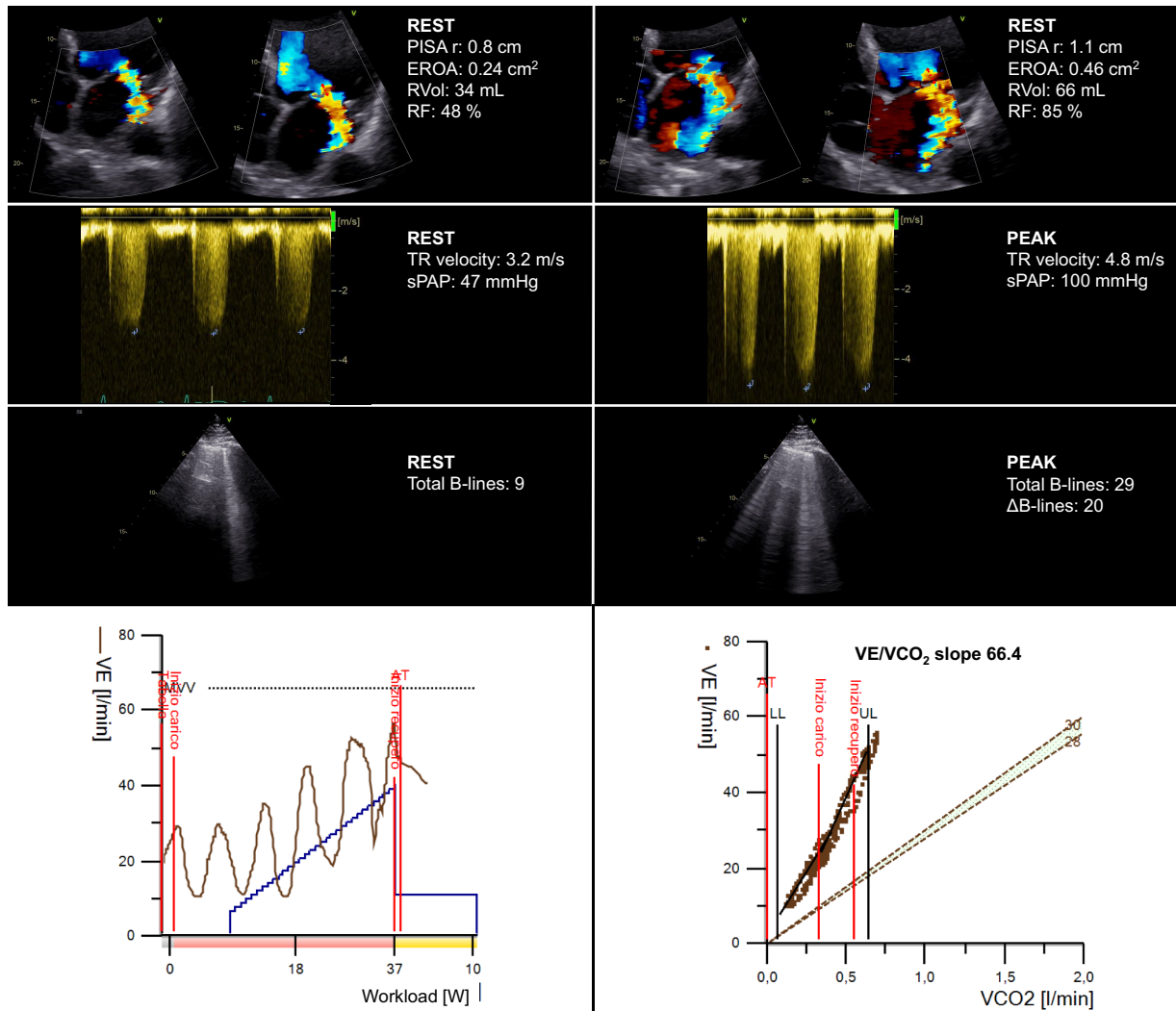


**Figure 3** Applying the combined CPET-ESE protocol to a male patient (75 years old) with moderate AV stenosis at rest and preserved left ventricle ejection fraction. ESE unravelled severe AV stenosis, significant TR worsening, and increased extravascular lung water. CPET showed a moderate reduction in peak oxygen consumption ( $\text{VO}_2 = 13.2 \text{ mL/kg/min}$ ), a reduced  $\text{VO}_2/\text{work}$  trajectory ( $7.4 \text{ mL/min/W}$ ), and a steep ventilation (VE)/carbon dioxide production slope (43.4). AVAi, indexed aortic valve area;  $\text{DP}_{\text{mean}}$ , mean aortic transvalvular gradient; LVOT, left ventricular outflow tract; sPAP, systolic pulmonary arterial pressure; SVi, indexed stroke volume;  $V_{\text{max}}$ , peak aortic transvalvular velocity; VTI, velocity-time integral.

of typical symptoms can change the therapeutic course for a given patient.<sup>46,60</sup> Thus, the ESE examination should focus on the evaluation of the haemodynamic severity of AS (peak transvalvular velocity, mean transvalvular pressure gradient, and estimated aortic valve area),

including the presence or absence of LV functional flow and/or contractile reserve (i.e. adequate SV or LV ejection fraction increase during effort<sup>30</sup>). ESE can also highlight signs of dynamic increases in sPAP and pulmonary congestion (LUS B-lines) during the whole exercise, which





**Figure 4** Applying the combined CPET-ESE protocol to a female patient (72 years old) with dilated cardiomyopathy (left ventricular ejection fraction 45%, diffuse hypokinesia) and moderate MR due to the tethering of the mitral valve posterior leaflet at rest. At peak exercise, ESE showed significant MR and TR worsening and increased extravascular lung water. CPET showed a moderate-to-severe reduction in peak oxygen consumption ( $VO_2 = 10.3$  mL/kg/min), an oscillatory ventilation pattern throughout the exercise and a very steep ventilation (VE)/carbon dioxide production slope (66.4). EROA, effective regurgitant orifice area; PISA r, proximal isovelocity surface area radius; RF, regurgitant fraction; RVol, regurgitant volume; sPAP, systolic pulmonary artery pressure.

carry an adverse prognostic significance in AS.<sup>61</sup> At the same time, CPET can indirectly assess SV response ( $VO_2$ /work slope) and correlate echographic evidence of pulmonary congestion with data regarding ventilation/perfusion mismatch (VE/ $VCO_2$  slope).

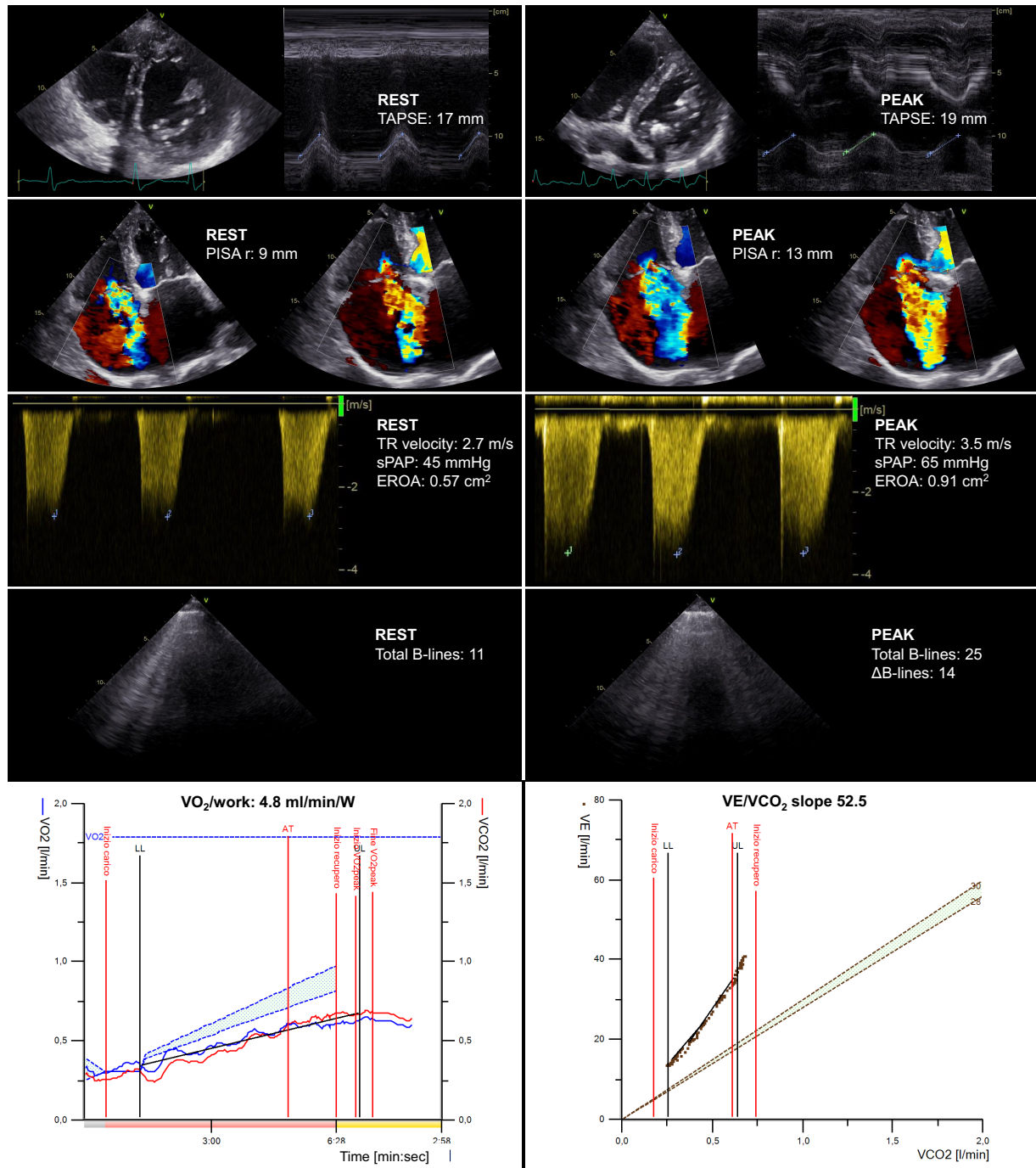
### Mitral regurgitation

In patients with asymptomatic or paucisymptomatic mitral regurgitation (MR), CPET-ESE can measure an impaired functional capacity and elucidate the mechanisms behind it (Figure 4). Indeed, MR severity can be evaluated with semiquantitative (i.e. *vena contracta*) or quantitative methods (i.e. effective regurgitant orifice area, regurgitant volume, and fraction) at rest and peak exercise to highlight the worsening of the valvular defect. Also, MR worsening is often associated with multiple supportive indirect signs, as the rise in LV filling pressure is reflected upstream in the

pulmonary circulation,<sup>30</sup> leading to increased sPAP, EVLW accumulation (measured by LUS), and ventilation/perfusion mismatch (expressed by steeper VE/ $VCO_2$  slope). In most severe cases, EOV can be observed, especially in patients with secondary MR (e.g. tethering of the mitral valve leaflets in a severely dilated and dysfunctional LV).

### Right ventricle dysfunction

CPET-ESE can be helpful for both the evaluation of functional capacity and the risk stratification of patients with RV dysfunction (Figure 5).<sup>62</sup> During the examination, several red flags can be observed, such as the flattening of the interventricular septum (leading to D-shaped LV), suggesting increased RV pressure and/or volume overload, impaired RV-PA coupling (TAPSE/sPAP ratio), TR worsening by semi-quantitative or quantitative methods, and increased LUS-derived



**Figure 5** Applying the combined CPET-ESE protocol to a male patient (77 years old) with right ventricle dilation (mildly D-shaped left ventricle during diastole) and systolic dysfunction, with severe TR at rest. At peak exercise, ESE showed a more marked D-shaped left ventricle, a significant TR worsening (which became torrential), and increased extravascular lung water. CPET showed a severe reduction in peak oxygen consumption ( $VO_2 = 9.7$  mL/kg/min), a reduced  $VO_2$ /work trajectory (4.8 mL/min/W) and a very steep ventilation (VE)/carbon dioxide production slope (52.5). EROA, effective regurgitant orifice area; PISA r, proximal isovelocity surface area radius; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

B-lines denoting increased LV filling pressures associated with enhanced ventricular interdependence. Invasive haemodynamic exercise testing has shown impaired functional capacity in severe TR is associated with elevated systemic and pulmonary venous pressures. Also,

increased ventricular interdependence leads to low LV preload and impaired CO increase.<sup>63</sup> The CPET module can non-invasively provide multiple findings supporting a significant RV dysfunction, including  $VO_2$ /work slope flattening and a steeper VE/VCO<sub>2</sub> slope.

## Other applications and future perspectives

CPET, with or without echocardiography, has been shown to refine the characterization and clinical management of other complex conditions. Indeed, the combined CPET-ESE approach has been used to investigate the pathophysiology and prognostic significance of exercise-induced pulmonary hypertension in hypertrophic cardiomyopathy,<sup>64</sup> to refine risk assessment in PA hypertension,<sup>65</sup> and to identify patients with poor functional capacity after pulmonary embolism, potentially deserving closer follow-up and/or advanced therapeutic interventions.<sup>66</sup>

## Conclusion

Combined CPET-ESE melds multiple data regarding a patient's haemodynamic response to exercise with specific insights into its cardiovascular and respiratory determinants. This allows for refined pathophysiological characterization and prognostic stratification in several cardiovascular conditions. While it is not readily available in all clinical settings due to some intrinsic limitations (e.g. time-consuming, expensive, need for specialized equipment and expertise), the thoroughness of the CPET-ESE examination and its non-invasive nature may suggest a wider acknowledgement and application of the technique (e.g. cardiomyopathies, pulmonary hypertension).

**Conflict of interest:** None declared.

## Lead author biography



I obtained my Master's degree in 'Medical Sciences' from the Sant'Anna School of Advanced Studies, and afterwards, I became a cardiology specialist at Pisa University Hospital. I undertook specific training in cardiovascular imaging, achieving multiple international certifications. I completed my PhD in 'Clinical and Translational Science' at Pisa University, where I applied several imaging techniques in the field of heart failure. My main interest and contribution to the literature lie with cardiovascular physiology and pathophysiology, combining research with intensive clinical activity. In particular, I am focusing on novel measures of cardiovascular damage to refine the stratification of patients who present different cardiovascular risk factors.

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