

# Cardiopulmonary Exercise Testing in Heart Failure: Updating the Theory into Clinical Practice

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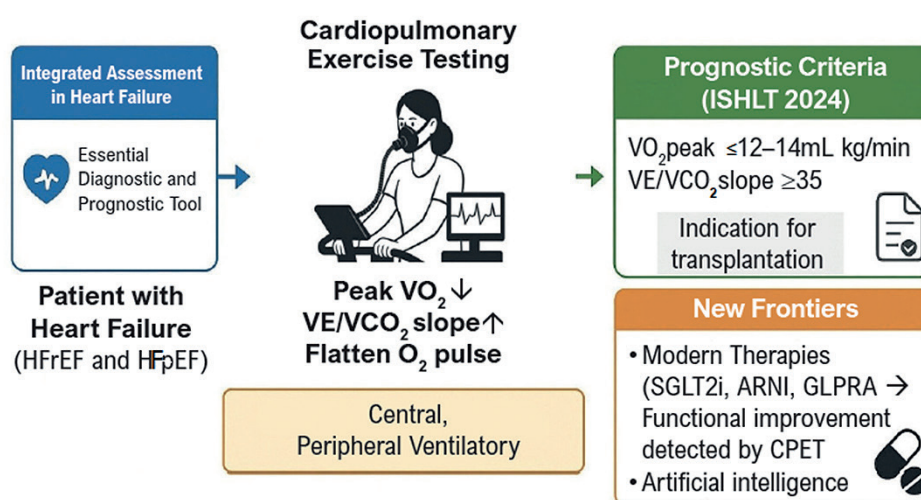
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**Central Illustration:** Cardiopulmonary Exercise Testing in Heart Failure: Updating the Theory into Clinical Practice



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Integrated representation of the role of cardiopulmonary exercise testing (CPET) in heart failure (HF). CPET integrates central, ventilatory, and peripheral responses, allowing functional assessment in patients with heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). Key variables, such as peak exercise oxygen consumption ( $VO_2$  peak), slope of the ventilation/minute-carbon dioxide production ratio ( $VE/VCO_2$  slope), and oxygen pulse ( $O_2$  pulse), support prognostic stratification and identification of transplant candidates according to the International Society for Heart and Lung Transplantation (ISHLT) 2024 ( $VO_2$  peak  $\leq 12$ – $14$  mL/kg/min;  $VE/VCO_2$  slope  $\geq 35$ ). The figure also illustrates new applications of CPET, including the assessment of response to sodium-glucose cotransporter 2 (SGLT2) inhibitors, angiotensin-neprilysin receptor (ARNI) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists, as well as artificial intelligence (AI)-based approaches. VE: minute/ventilation;  $VCO_2$ : carbon dioxide production;  $VO_2$ : oxygen consumption.

## Keywords

Exercise Test, Heart Failure, Gas Exchange, Prognosis, Cardiac Rehabilitation

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## Abstract

Cardiopulmonary exercise testing (CPET) is a central tool in the functional assessment of heart failure (HF), integrating cardiovascular, ventilatory, and metabolic responses into a single examination. In light of evidence published between 2023 and 2025, its diagnostic and prognostic role has been expanded, incorporating more refined pathophysiological foundations, submaximal parameters, and updated criteria for heart transplantation according to ISHLT 2024. This narrative review, based on studies indexed in PubMed, international consensus statements, and contemporary analyses, addresses

the main mechanisms of exercise limitation in HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), as well as the clinical relevance of key CPET variables, including peak  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  slope, OUES,  $\text{O}_2$  pulse, chronotropic response, and  $\text{VO}_2$  recovery kinetics.

The body of evidence confirms that the CPET is the most comprehensive tool for characterizing cardiocirculatory, ventilatory, and peripheral limitations, with reduced peak  $\text{VO}_2$  and elevated  $\text{VE}/\text{VCO}_2$  slope remaining the most robust prognostic markers, even in submaximal tests. Recent studies also demonstrate that emerging therapies — such as SGLT2 inhibitors, ARNIs, and GLP-1 agonists — promote functional benefits detectable by CPET before cardiac structural changes, highlighting its role as a monitor of therapeutic response. Additionally, CPET remains fundamental in risk stratification and transplant decision-making, following the updated thresholds of the ISHLT. Thus, the examination is consolidated as an essential instrument in modern HF practice, integrating diagnosis, prognosis, and therapeutic monitoring, as well as guiding rehabilitation strategies and the selection of advanced therapies.

## Historical aspects

Cardiopulmonary exercise testing (CPET) began to be applied clinically in the 1960s–1970s, when Wasserman et al.<sup>1</sup> systematized ventilatory principles and introduced the concept of cardiorespiratory integration. In cardiology, it was consolidated in the 1980s after Weber and Janicki<sup>2</sup> demonstrated the prognostic value of peak oxygen consumption ( $\text{VO}_2$ ) in heart failure (HF). Since then, CPET has evolved from a diagnostic tool to a central prognostic and therapeutic instrument. Contemporary publications, such as those by Guazzi et al.<sup>3</sup> and Puttini et al.,<sup>4</sup> have reaffirmed its role as the gold standard in integrated functional assessment, including stable patients, those in advanced stages, or post-rehabilitation.

## Pathophysiological basis of exercise limitation

The CPET assesses  $\text{VO}_2$  according to Fick's equation,  $\text{VO}_2 = [\text{cardiac output (CO)} \times \text{peripheral oxygen extraction (CaO}_2 - \text{CvO}_2)]$ , integrating CO and  $(\text{CaO}_2 - \text{CvO}_2)$ . CO — determined by heart rate (HR) and stroke volume (SV) — represents the central contribution, while adequate ventilation ensures efficient gas exchange; mechanical alterations or increased dead space can lead to ventilation-perfusion mismatch. Thus,  $\text{VO}_2$  reflects, in an integrated way, cardiac function, pulmonary ventilation, and muscle metabolism<sup>4</sup> (Central Illustration).

In HF, exercise limitation is characterized by reduced peak  $\text{VO}_2$ , high carbon dioxide ( $\text{CO}_2$ ) ventilatory efficiency ( $\text{VE}/\text{VCO}_2$  slope), flattened oxygen pulse ( $\text{VO}_2/\text{HR}$ ), chronotropic incompetence, and limited effort. Recent evidence has detailed distinct mechanisms: in HF with reduced ejection fraction (HFrEF), invasive cardiopulmonary exercise testing (CPET) shows increased filling pressures and ventilatory inefficiency, indicating contractile dysfunction.<sup>5</sup> In HF with preserved ejection fraction (HFpEF), dynamic congestion with variation in pulmonary capillary wedge pressure ( $\Delta\text{PCWP}$ )  $\geq 5$  mmHg<sup>6</sup> stands out, in addition to specific profiles such

as engine-chassis mismatch in obese individuals,<sup>7</sup> early submaximal limitation,<sup>8</sup> and the impact of muscle quality on exercise tolerance.<sup>9</sup> These findings reinforce CPET as a tool for functional phenotyping and identification of the main determinants of exercise intolerance. Table 1 summarizes the key parameters of the examination and their clinical reference values.

Table 1 shows the main variables of the CPET, their pathophysiological significance, and clinical cutoff/reference values.

## Practical interpretation of the CPET

CPET may seem complex, but its interpretation can be systematized through a few fundamental steps (Figure 1).

These parameters can be interpreted as a “functional map of heart failure”, capable of distinguishing limitations of central, ventilatory, or peripheral origin (Table 2).<sup>10</sup>

- **Central route:** Peak  $\text{VO}_2$  expresses the maximum limit of oxygen consumption and summarizes the overall performance of the heart pump, while the  $\text{O}_2$  pulse ( $\text{VO}_2/\text{HR}$ ) represents the effective stroke volume during exertion. It is important to highlight that, in the central pathway, the ventilatory reserve is generally normal; however, the ventilatory efficiency of  $\text{CO}_2$  ( $\text{VE}/\text{VCO}_2$  slope) is usually increased, as its alteration derives from cardiocirculatory imbalance—and not from pulmonary limitation—reflecting the severity of HF (prognostic value: the higher, the worse).
- **Ventilation route:**
  - The  $\text{VE}/\text{VCO}_2$  slope quantifies the ventilatory efficiency in eliminating carbon dioxide (the lower the ventilation required to eliminate  $\text{CO}_2$ , the more efficient the system);
  - The respiratory exchange ratio (RER), which at rest is typically 0.7–0.8, indicates the degree of exertion and the predominant metabolic activity (aerobic or anaerobic);
  - Ventilatory reserve (VR) reflects the range of lung recruitment at the end of exercise, and is useful for identifying patterns of ventilatory inefficiency and ventilation-perfusion mismatch, usually associated with ventilatory limitation or concomitant lung disease.<sup>10–13</sup>
- **Peripheral route:**
  - The anaerobic threshold (VT1 or LV1) marks the beginning of the anaerobic metabolic contribution;
  - Oxygen uptake ventilation efficiency (OUES) estimates the overall efficiency of oxygen uptake, even in submaximal tests;
  - $\text{VO}_2$  recovery kinetics reflect the rate of energy restitution and muscle mitochondrial performance, characterizing peripheral metabolic efficiency.<sup>14,15</sup>

The Brazilian study by Costa RVC et al.<sup>11</sup> demonstrated a significant correlation between functional class according to the New York Heart Association (NYHA) and CPET parameters, reinforcing the usefulness of the test to refine daily clinical assessment.

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**Table 1 – Main variables of the cardiopulmonary exercise test (CPET), their pathophysiological significance, and clinical cutoff/reference values**

| Variable (CPET)                                                           | Physiopathological significance                                                                                                                       | Cutoff value / clinical reference                                                                                                  |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <b>Peak <math>\text{VO}_2</math> (mL/kg/min)</b>                          | It reflects the maximum oxygen consumption and overall performance of the heart pump; it integrates cardiac output, perfusion, and muscle metabolism. | $\leq 14$ mL/kg/min (without beta-blocker) or $\leq 12$ mL/kg/min (with beta-blocker); severe limitation and transplant criterion. |
| <b><math>\text{O}_2</math> pulse (<math>\text{VO}_2/\text{HR}</math>)</b> | It expresses the effective stroke volume and $\text{O}_2$ transport capacity; flattening indicates central limitation.                                | $< 85\%$ of predicted or flattened curve: ventricular dysfunction / low SV                                                         |
| <b><math>\text{VE}/\text{VCO}_2</math> slope</b>                          | It measures ventilatory efficiency and ventilation-perfusion coupling; high values indicate compensatory hyperventilation.                            | $> 34$ (moderate inefficiency); $> 45$ (high risk).                                                                                |
| <b>RER (<math>\text{VCO}_2/\text{VO}_2</math>)</b>                        | It indicates the degree of effort and the predominant metabolic activity (aerobic vs. anaerobic).                                                     | $\geq 1.05$ : maximum effort;<br>$< 1.05$ : consider submaximal.                                                                   |
| <b>Ventilatory reserve (%MVV)</b>                                         | This represents the lung recruitment margin; low values suggest ventilatory limitation.                                                               | $< 15\text{--}20\%$ : ventilatory limitation.                                                                                      |
| <b>Anaerobic threshold (VT1)</b>                                          | It defines the metabolic transition point and exercise tolerance; reduced in peripheral limitation.                                                   | $< 40\%$ of predicted $\text{VO}_2$ : low functional capacity.                                                                     |
| <b>OUES</b>                                                               | Quantifies the overall efficiency of $\text{O}_2$ uptake; useful in submaximal tests.                                                                 | $< 1.4$ (low); $< 1.0$ indicates severe inefficiency.                                                                              |
| <b><math>\text{VO}_2</math> recovery kinetics</b>                         | It reflects the rate of energy restitution and muscle mitochondrial function.                                                                         | $\text{VO}_2$ takes $> 90$ s to reduce by 50%: abnormal recovery.                                                                  |

**$\Delta\text{PCP}$  in effort** It estimates dynamic congestion and diastolic compliance. Increase  $\geq 5$  mmHg: typical of HFpEF.

**Heart rate and chronotropic response** They indicate the autonomic reserve and responsiveness of the sinus node. Chronotropic incompetence: Heart rate  $< 80\%$  of predicted or attenuated curve.

*$\text{VO}_2$ : oxygen consumption; HR: heart rate; VE: ventilation;  $\text{VCO}_2$ : carbon dioxide production;  $\text{VE}/\text{VCO}_2$  slope:  $\text{CO}_2$  ventilatory efficiency; RER: respiratory exchange ratio; MVV: maximum voluntary ventilation; OUES: oxygen ventilatory efficiency;  $\Delta\text{PCWP}$ : change in pulmonary capillary wedge pressure; HFpEF: heart failure with preserved ejection fraction.*

Furthermore, recent reviews emphasize that the CPET complements clinical judgment and should not be replaced by isolated hemodynamic indices, as per Motiwala & Naylor.<sup>12</sup> Peak  $\text{VO}_2$  remains the main marker of aerobic capacity and clinical outcome in all forms of HF.<sup>13</sup> However, complementary variables — especially  $\text{VE}/\text{VCO}_2$  slope, OUES,  $\text{O}_2$  pulse, and chronotropic response — add independent prognostic value, even when the effort is submaximal.<sup>14,15</sup>

Recent studies reinforce this importance. The  $\text{VE}/\text{VCO}_2$  slope, according to Guazzi et al.<sup>3</sup> and Buber & Robertson,<sup>16</sup> is the ventilatory marker with the highest isolated predictive value for mortality in both forms of HF. A slope above 34 indicates significant ventilatory inefficiency, and values above 45 reflect advanced dysfunction and an increased risk of hospitalization.<sup>17</sup>

The OUES was revalued by Chiang et al.,<sup>18</sup> who demonstrated its independent prognostic power, especially when indexed to body surface area.

The  $\text{O}_2$  pulse, in turn, indirectly reflects stroke volume and is particularly useful in patients on beta-blockers, whose chronotropic response is attenuated.<sup>19</sup>

Finally, studies by Edward et al.<sup>5</sup> and Naito et al.<sup>20</sup> showed that combining CPET with invasive hemodynamics or stress echocardiography increases diagnostic and prognostic accuracy, allowing differentiation between dynamic congestion and ventilatory limitation.

### Differences in the interpretation of cardiopulmonary exercise testing between HFrEF and HFpEF

The CPET allows distinguishing limiting mechanisms in the two main forms of HF — HFrEF and HFpEF.<sup>3,5-7,10,14</sup>

In HFrEF, a central limitation predominates, characterized by peak  $\text{VO}_2 < 14$  mL/kg/min, flattened  $\text{O}_2$  pulse, attenuated chronotropic response, and  $\text{VE}/\text{VCO}_2$  slope  $> 40\text{--}45$ .<sup>5-7</sup> There is slow recovery of  $\text{VO}_2$  and a disproportionate increase in ventilation, phenomena associated with contractile dysfunction and greater neuro-hormonal activation.<sup>5,6</sup>

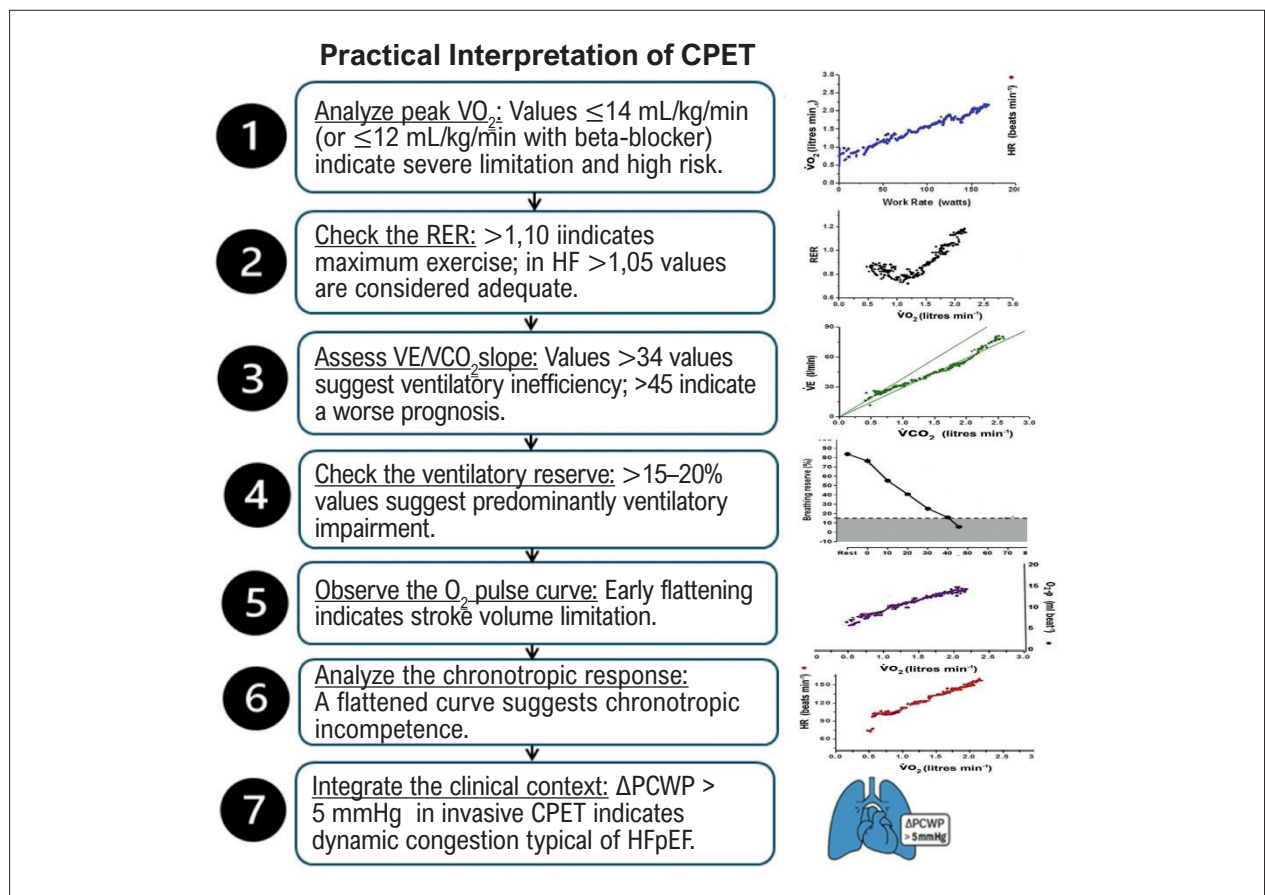


**Figure 1** – Diagram for interpreting the cardiopulmonary exercise test (CPET) in heart failure (HF). The seven steps summarize the integrated analysis of the CPET, including peak exercise oxygen consumption ( $\dot{V}O_2$  peak), respiratory exchange ratio (RER), slope of the ventilation/minute-carbon dioxide production relationship ( $VE/\dot{V}CO_2$  slope), ventilatory reserve (VR), oxygen pulse ( $\dot{V}O_2$  pulse), chronotropic response (CR), and clinical-hemodynamic integration. VE: ventilation/minute;  $\dot{V}CO_2$ : carbon dioxide production;  $\dot{V}O_2$ : oxygen consumption.

In HFpEF,  $\dot{V}O_2$  is usually moderately reduced (13–16 mL/kg/min), the  $\dot{V}O_2$  pulse tends to be preserved, and  $\Delta PCWP$  increases  $>5$  mmHg, reflecting dynamic congestion and diastolic dysfunction.<sup>7–10,13</sup> The anaerobic threshold occurs early, and ventilatory efficiency is only moderately compromised.

Thus, while HFrEF shows a predominantly cardiocirculatory pattern, HFpEF presents a hemodynamic-peripheral pattern, useful for therapeutic stratification and transplant decision.<sup>14,15,21–23</sup>

#### CPET and new therapies for HF

CPET has become a sensitive tool for detecting early functional benefits of new therapies, often before significant structural cardiac changes occur.

#### Sodium-glucose cotransporter 2 inhibitors (SGLT2) and hemodynamics

Borlaug et al.<sup>24</sup> demonstrated that dapagliflozin reduces left ventricular filling pressures at rest and during exercise, even without an immediate increase in peak  $\dot{V}O_2$ . These

findings indicate hemodynamic and ventricular compliance improvement, rather than direct aerobic gain.

Subsequently, Takahashi & Fukumoto<sup>25</sup> confirmed this effect, highlighting autonomic stability and metabolic improvement, reinforcing that the benefit of CPET may reflect cardiac efficiency rather than maximum power.

#### GLP-1 receptor agonists (GLP-1RAs) and metabolism

In the STEP-ICFEP study, Borlaug et al.<sup>26</sup> observed that semaglutide promoted a significant improvement in the 6-minute walk distance (6MWT) and in the quality of life score (KCCQ-CSS), correlating with weight loss and metabolic improvement. Although peak  $\dot{V}O_2$  remained stable, the CPET revealed improved ventilatory efficiency and early cardiovascular adaptation, demonstrating the sensitivity of the method to detect submaximal responses.

#### Neprilysin and Angiotensin Receptor Inhibitor (INRA) and verify

The REAL.IT study, conducted by Sarullo et al.,<sup>27</sup> showed improved functional capacity with the use of sacubitril/

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**Table 2 – Central, ventilatory, and peripheral limitations for exercise**<sup>3,4,10,11</sup>

| Limitation  | Main structure                                                     | Key parameters                                                                                                        |
|-------------|--------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| Central     | Heart (CO and chronotropic response)                               | Reduced peak $\text{VO}_2$<br>Flattened $\text{O}_2$ pulse<br>Inadequate chronotropic response                        |
| Ventilatory | Lungs (gas exchange, ventilation, and ventilation/perfusion ratio) | Elevated $\text{VE}/\text{VCO}_2$ slope<br>Ventilation disproportionate to the effort.<br>Reduced ventilatory reserve |
| Peripheral  | Skeletal muscle (extraction and oxidative metabolism)              | Early anaerobic threshold<br>Reduced metabolic efficiency<br>Slow $\text{VO}_2$ recovery                              |

CO: cardiac output;  $\text{VO}_2$ : oxygen consumption; VE: ventilation;  $\text{VECO}_2$ : carbon dioxide production;  $\text{VE}/\text{VCO}_2$  slope: ventilatory efficiency of carbon dioxide.

**Table 3 – Summary of cardiopulmonary exercise test parameters that support inclusion on the transplant list in different populations (ISHLT 2024)<sup>23</sup>**

| Patient population                                       | Parameter that supports inclusion on the transplant list.                                                                           |
|----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| With beta-blockers                                       | A lower cutoff value for $\text{VO}_2$ max is indicative of inclusion on the transplant list, generally $\leq 12$ ml/kg/min.        |
| No beta-blockers                                         | A higher peak $\text{VO}_2$ can be considered a factor that favors inclusion on the transplant list, generally $\leq 14$ ml/kg/min. |
| Patients with obesity (BMI $\geq 30$ kg/m <sup>2</sup> ) | $\text{VO}_2$ max adjusted for lean body mass $\leq 19$ ml/kg/min                                                                   |
| Everyone, especially if CPET is submaximal.              | $\text{VE}/\text{VCO}_2$ slope $>35$                                                                                                |
| Women or patients $\leq 50$ or $\geq 70$ years old       | Peak $\text{VO}_2 \leq 50\%$ of predicted                                                                                           |

BMI: body mass index; CPET: cardiopulmonary exercise test;  $\text{VE}/\text{VCO}_2$ : minute ventilation/carbon dioxide production. Maximum CPET: respiratory quotient (RER)  $>1.05$  and reaching the anaerobic threshold.

valsartan. Similarly, Zhan et al.<sup>28</sup> showed parallel results with vericiguat, reinforcing the role of the CPET as a pharmacodynamic monitoring tool.

### Combined impact

Recent reviews by Baracchini et al.<sup>21</sup> and Campodonico et al.<sup>22</sup> have consolidated the role of the CPET as an instrument capable of detecting early physiological responses to modern therapies based on hemodynamic and metabolic mechanisms.

More recently, Puttini et al.<sup>4</sup> emphasized that integrating CPET parameters with biomarkers and hemodynamic data allows for personalized therapeutic monitoring, offering an integrated functional assessment of clinical evolution.

In summary, CPET allows for the quantification of integrated therapeutic responses, reflecting improvements in filling pressure, ventilatory efficiency, and exercise tolerance, even when peak absolute  $\text{VO}_2$  does not change.

### Risk stratification and heart transplantation

The most recent guideline from the International Society for Heart and Lung Transplantation (ISHLT 2024) reinforced the CPET as a cornerstone in the evaluation of candidates for heart transplantation (Tx).<sup>23</sup> The updated criteria include peak  $\text{VO}_2$  thresholds  $\leq 12$ – $14$  mL/kg/min (adjusted for beta-blocker use) and  $\text{VE}/\text{VCO}_2$  slope  $\geq 35$  as classic indicators of high risk and worse prognosis (Table 3).

Studies by Landsteiner et al.<sup>19</sup> and Brawner & Lazar<sup>29</sup> confirm that these parameters remain the most reliable markers of mortality and need for Tx in patients with advanced HF.

Furthermore, Brás et al.<sup>30</sup> showed that the use of sex-adjusted predicted percentages can correct for eligibility bias, especially in women, optimizing the selection for advanced therapies.

### Contemporary advances

#### Rehabilitation and training guided by CPET

Cardiac rehabilitation has evolved from generic protocols to individualized programs based on objective CPET data. Aerobic training prescribed according to ventilatory thresholds (VT1 and VT2) improves peak  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  slope, and quality of life.

Recent studies — Sakellaropoulos & Mitsis<sup>31</sup> and Sugita et al.<sup>32</sup> — confirm the benefit of structured rehabilitation in patients with chronic HF, including those with HFpEF.

The OptimEx-Clin trial, conducted by Mueller et al.,<sup>33</sup> demonstrated that combined and interval training (HIIT) modalities provide superior  $\text{VO}_2$  gains compared to moderate continuous exercise, particularly for patients with chronotropic incompetence.

Furthermore, serial analysis of the CPET allows monitoring of autonomic and ventilatory recovery. Velmeden et al.<sup>34</sup> showed that slow heart rate recovery (HRR) after exertion reflects autonomic dysfunction and predicts worse survival. Similarly, Nasser et al.<sup>35</sup> documented significant

improvement in chronotropic response and peak  $\text{VO}_2$  after supervised training, reinforcing the CPET as a guide for personalized rehabilitation.

### Contemporary phenotyping and new pathophysiological frontiers

The CPET has become established as an integrated phenotyping tool, allowing the distinction between hemodynamic, ventilatory, and peripheral mechanisms of exercise limitation. In the study by Miller et al.,<sup>36</sup> four exercise response clusters were identified: (1) efficient, with good  $\text{O}_2$  uptake and recovery; (2) ventilatory, marked by high  $\text{VE}/\text{VCO}_2$  and reduced ventilatory reserve; (3) peripheral, with low peak  $\text{VO}_2$  and reduced OUES; and (4) central, characterized by a flattened  $\text{O}_2$  pulse and attenuated chronotropism. These patterns showed significant differences in mortality and HF progression (worse for central and peripheral), reinforcing the role of CPET in the individualized physiological classification of patients.

In a complementary way, in the study by Skow et al.,<sup>37</sup> the reduction in peripheral oxygen extraction was directly quantified by the smaller arteriovenous  $\text{O}_2$  difference, while ventilatory inefficiency was identified by an elevated  $\text{VE}/\text{VCO}_2$  slope and reduced end-expiratory partial pressure of carbon dioxide ( $\text{PETCO}_2$ ), demonstrating that the limitation of effort in HFpEF is mainly due to peripheral and ventilatory mechanisms. The combination of CPET with biological and molecular markers, as demonstrated by Shah et al.<sup>38</sup> and Dixon et al.,<sup>39</sup> revealed that alterations in inflammatory (Interleukin-6, Tumor Necrosis Factor- $\alpha$ , C-reactive protein), metabolic [carnitine, nicotinamide adenine dinucleotide and oxidized and reduced adenine ( $\text{NAD}^+/\text{NADH}$ )] and cardiac [N-terminal B-type natriuretic peptide (NT-proBNP), galectin-3] biomarkers are associated with distinct patterns of functional limitation. This integration defines the concept of exercise-based molecular phenotyping, allowing the identification of physiological subgroups and guiding more personalized therapies in HF.

### Artificial intelligence and machine learning

The study by Kato et al.<sup>40</sup> demonstrated that machine learning models applied to submaximal parameters of CPET ( $\text{VO}_2$  at the anaerobic threshold,  $\text{VE}/\text{VCO}_2$ , HR, and OUES) predict exercise intolerance with >85% accuracy, even without maximal effort. These approaches allow for the early identification of high-risk patients and the automation of complex cardiopulmonary exercise test interpretations in high-volume clinical settings.

Tepetes et al.<sup>41</sup> proposed integrating the CPET with clinical and laboratory variables in artificial intelligence models to predict progression to advanced HF. The algorithm, which included peak  $\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  slope,  $\text{O}_2$  pulse, NT-proBNP, and functional class, showed superior accuracy to traditional clinical scores, allowing for early identification of at-risk patients and optimizing the timing of referral to advanced therapies such as transplantation or ventricular assist.

The convergence of CPET, artificial intelligence, and multimodal data represents one of the main frontiers of personalized medicine in HF.

### Cardiopulmonary exercise testing in acute HF and in the post-hospitalization period

Traditionally, CPET was reserved for clinically stable patients; however, recent evidence demonstrates its usefulness soon after hospital discharge, when there is hemodynamic stability and absence of active congestion.

Ding et al.<sup>42</sup> showed that serial CPET during early rehabilitation in decompensated HF detects progressive improvement in peak  $\text{VO}_2$  and ventilatory efficiency, reflecting hemodynamic and muscle recovery in the first weeks post-discharge. Chen et al.<sup>43</sup> complemented these findings, showing that simple variables derived from CPET can predict early readmissions and mortality, guiding clinical follow-up and therapeutic adjustments. Furthermore, Zimerman et al.<sup>44</sup> and Hosoda et al.<sup>45</sup> observed that patients with mild or recovering HF exhibit subclinical changes in  $\text{VE}/\text{VCO}_2$  and  $\text{O}_2$  pulse, which precede detectable functional decline, reinforcing CPET as a post-decompensation surveillance tool.

Therefore, post-hospitalization CPET should be viewed as an early functional surveillance strategy, capable of anticipating deterioration, adjusting therapies, and guiding rehabilitation based on ventilatory thresholds and chronotropic response.

### Extracardiac conditions and CPET

In patients with associated chronic obstructive pulmonary disease, recent reviews demonstrate that dynamic hyperinflation and early ventilatory limitation reduce performance on CPET, with increased  $\text{VE}/\text{VCO}_2$  and disproportionate dyspnea, potentially simulating or masking cardiac dysfunction.<sup>46</sup> In advanced HF scenarios, systemic comorbidities such as renal and hepatic disease and metabolic disorders contribute to a reduction in overall functional reserve, resulting in low peak  $\text{VO}_2$  regardless of isolated ventricular function.<sup>47</sup> Furthermore, cachexia and sarcopenia, mediated by chronic inflammation, reduce peripheral muscle mass and efficiency, compromising oxygen extraction and leading to significant changes in CPET even with relatively preserved hemodynamics.<sup>48</sup> Conditions such as anemia/iron deficiency and renal disease tend to reduce peak  $\text{VO}_2$  predominantly due to peripheral limitation and reduced oxygen transport/utilization capacity; obesity reduces weight-relative  $\text{VO}_2$  and may mask hemodynamic severity; Pulmonary disease increases the  $\text{VE}/\text{VCO}_2$  slope and reduces  $\text{PETCO}_2$  due to increased dead space and V/Q mismatch; while diabetes, cancer, and frailty accentuate muscle inefficiency and exercise intolerance, with an additional impact on  $\text{O}_2$ -pulse and  $\text{VO}_2$  kinetics.<sup>49</sup> Therefore, the interpretation of cardiac output in HF should be integrated and phenotyped, using multiple variables to differentiate primary cardiac limitation from the dominant effects of comorbidities, with direct implications for prognostic stratification and therapeutic decision-making.

## Conclusion

CPET has become the primary tool for functional and prognostic assessment in HF. More than just measuring oxygen consumption, cardiopulmonary exercise testing reflects the interaction between the heart, lungs, and peripheral muscles, offering an integrated view of the patient.

In the modern era of HF — marked by multimodal therapies, advanced phenotyping, and personalized medicine — the CPET remains the physiological benchmark that guides clinical decision-making, directs treatment, stratifies risk, and anticipates prognosis.

## Author Contributions

Conception and design of the research: Rossi Neto JM, Rossi RM, Mattos VBM, Wolf PJW, Finger MAA, Santos CC; Acquisition of data, Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for

intellectual content: Rossi Neto JM; Writing of the manuscript: Rossi Neto JM, Rossi RM.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

This study is not associated with any thesis or dissertation work.

## Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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