Original Article

Current Diagnostic and Prognostic Applications of Cardiopulmonary Exercise Testing in Heart Failure with Preserved Ejection Fraction – A Narrative Review

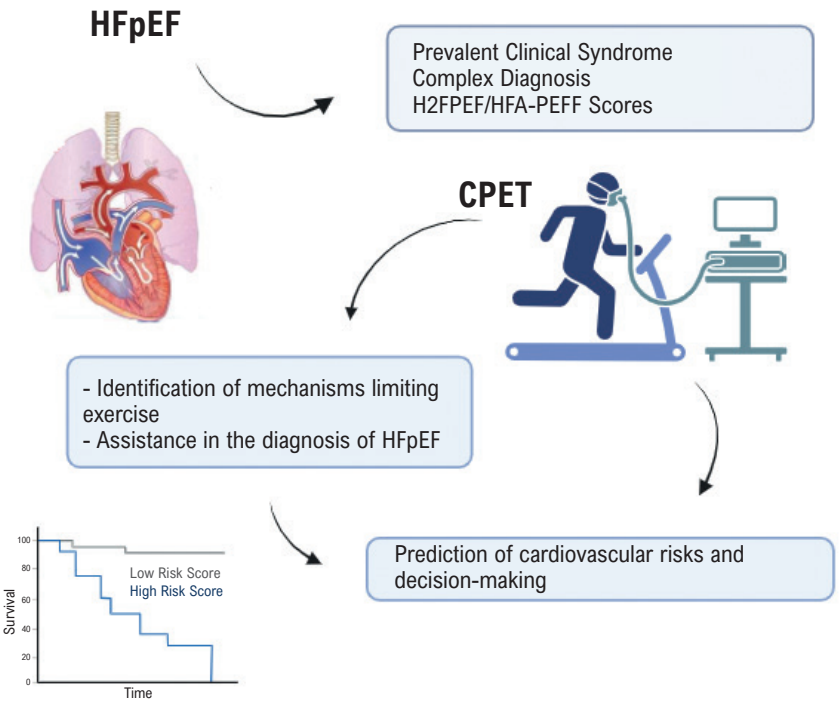
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Central Illustration: Current Diagnostic and Prognostic Applications of Cardiopulmonary Exercise Testing in Heart Failure with Preserved Ejection Fraction – A Narrative Review



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Diagnostic and prognostic applications of the CPET in HFpEF. Source: Author's own work.

Keywords

Prognosis; Heart Failure; Exercise Test

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a prevalent clinical syndrome with a complex diagnosis, associated with various comorbidities and high rates of cardiovascular events. Cardiopulmonary exercise testing (CPET) plays an essential role in understanding the mechanisms of exercise limitation and in complementing the diagnosis of HFpEF, but it presents several gaps to be explored in risk prediction. This article reviews the literature on current pathophysiological, diagnostic, and prognostic aspects of

HFpEF. Subsequently, the role of CPET in diagnosis and prognostic prediction in HFpEF is explored. A critical analysis of the main observational and cohort studies that used CPET in this setting is performed, selected after a qualified search on the PubMed platform. For diagnostic purposes, peak VO2 is not very specific, with a high diagnostic probability for values <14 ml/kg/min and a low probability for values >20 ml/kg/min. However, when peak VO2 is evaluated together with other ventilatory parameters, there is an increase in the diagnostic value of CPET in HFpEF. For prognostic purposes, variables such as peak VO2, VE/VCO2 slope, and the presence of periodic ventilation correlate with a higher risk prediction. However, there are notable sample differences between studies in HFpEF, hindering the generalization of the use of CPET in clinical practice. This review concludes that conducting prospective studies with more rigorous patient selection and using some variables adjusted for body composition differences, such as lean VO2, may allow for better incorporation of CPET in risk stratification in HFpEF.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome with a high prevalence, accounting for approximately half of all heart failure patients. In Brazil, HFpEF is one of the leading causes of hospitalizations, with a high rate of readmissions.[1-8] Recent clinical studies have demonstrated that obesity and associated cardiometabolic alterations, such as dyslipidemia and increased insulin resistance, predispose to HFpEF, with a higher risk of developing the disease in female patients.[9,10]

The diagnosis of HFpEF is a complex process, given the high prevalence of cardiovascular and non-cardiovascular comorbidities in this population and the fact that the signs and symptoms of HFpEF are not specific.[1] Recently, different clinical scores have been developed to assist in identifying patients with HFpEF, notably the H2FPEF and HFA-PEFF,[3-8] allowing for more accurate and less costly non-invasive diagnosis of the disease.

Exercise intolerance represents a central problem experienced by patients with HFpEF, impacting their quality of life. Considering that multiple pathophysiological mechanisms contribute to exercise limitation in HFpEF, cardiopulmonary exercise testing (CPET) becomes a fundamental tool for its proper understanding.[11] CPET has a well-recognized prognostic value in patients with heart failure with reduced ejection fraction (HFrEF), assisting in the identification of higher-risk patients and in clinical decision-making.[12] In contrast, in HFpEF, the prognostic value of CPET variables is not well established, which hinders the clinical incorporation of this test in the risk assessment of these patients.

In this article, we initially conducted a literature review on pathophysiological and diagnostic aspects of HFpEF, including the limitations of traditional clinical examinations and the role of the H2FPEF and HFA-PEFF scores in the non-invasive diagnosis of the disease. Subsequently, we analyze the role of the CPET in the interpretation of the pathophysiological mechanisms of exercise intolerance and in diagnostic complementation in HFpEF, and we will perform a critical analysis of the main studies that used CPET in predicting the risk of events in this population, intending to evaluate its importance and applications in this HFpEF scenario.

Etiological and pathophysiological aspects in heart failure with preserved ejection fraction

HFpEF is a complex clinical syndrome with increasing prevalence, accounting for approximately half of all heart failure patients. Risk factors for the development of HFpEF include: advanced age, obesity, systemic arterial hypertension, diabetes mellitus, atrial fibrillation (AF), kidney disease, and female sex.[5,8,13,14] Recent clinical studies have demonstrated that obesity and associated cardiometabolic alterations, such as dyslipidemia and increased insulin resistance, predispose to HFpEF, with a higher risk of the disease in female patients.[9]

Obesity has been proposed as the main contributor to systemic inflammation and subsequent ventricular remodeling in HFpEF, with multiple deleterious effects on myocardial structure, function, and metabolism, as well as effects on the lungs, skeletal muscle, kidneys, and liver, collectively mediated by systemic inflammation, neurohormonal activation, autonomic dysregulation, and altered hemodynamic load.[15] Systemic arterial hypertension occurs in most patients with HFpEF, and there is evidence that suboptimal control of hypertension is one of the pathophysiological pathways for the development of HFpEF, inducing ventricular hypertrophy and myocardial fibrosis[14] (Figure 1).

Physiopathologically, ventricular diastolic dysfunction, with increased filling pressures, constitutes the central alteration in HFpEF, occurring both at rest and induced by hemodynamic stress (examples: exercise and pressure overload). Recently, other pathophysiological mechanisms have been linked to the development of HFpEF, such as endothelial dysfunction secondary to frequently associated comorbidities, increased arterial resistance, and decreased ventricular systolic compliance.[9]

Patients with HFpEF demonstrate altered left ventricular relaxation and increased diastolic stiffness, resulting in higher filling pressures for a given LV volume at rest or with increased flow, as occurs during exercise. In addition to myocardial factors, ventricular interdependence may contribute to elevated filling pressures at rest and during exercise, especially in obese patients, who exhibit greater plasma volume expansion, LV and RV volumes, pulmonary hypertension (PH), RV dysfunction, and epicardial fat.[16]

Diagnostic aspects in HFpEF

Diagnosing HFpEF is challenging, given the high prevalence of cardiovascular and non-cardiovascular comorbidities in this population and the fact that the signs and symptoms of HFpEF are not specific.[1,10] In the context of signs and symptoms suggestive of chronic heart failure, in a patient with risk factors and electrocardiographic abnormalities, the diagnostic process for HFpEF is based on a probabilistic model according to echocardiographic findings and/or natriuretic peptide levels (Figure 2).[10,17] Around 30-35% of patients with HFpEF present with dyspnea on exertion, without showing evident signs of congestion on physical examination or resting

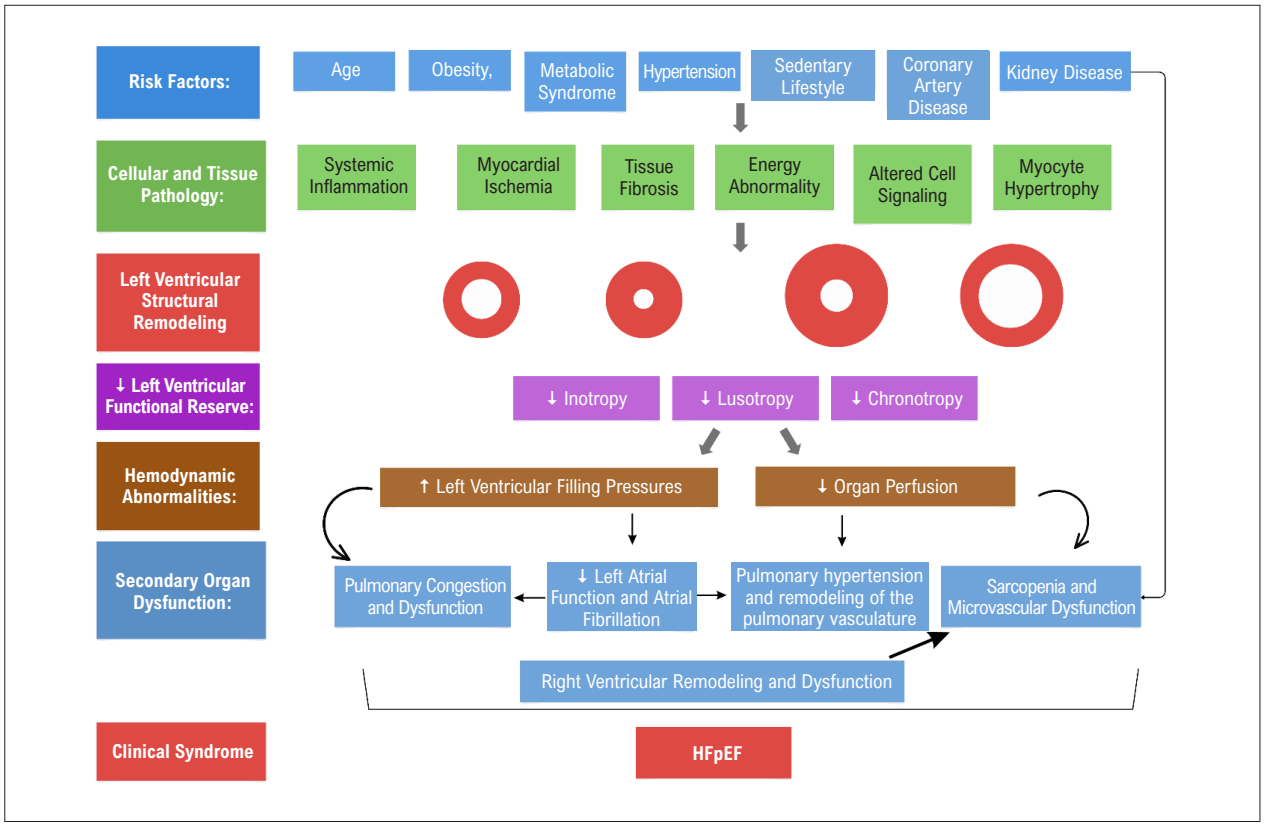


Figure 1 – *Pathophysiological Mechanisms in Heart Failure with Preserved Ejection Fraction (HFpEF). Source: Adapted from Pfeffer et al.*[13]

imaging studies. In these cases of indefinite diagnosis, only through measurements of filling pressures during physical exertion, either in the form of stress echocardiography or cardiac catheterization, is it possible to confirm the diagnosis of HFpEF.[3]

Recently, different clinical scores have been developed to assist in the non-invasive identification of patients with HFpEF, notably the H2FPEF and HFA-PEFF.[14,18-37] Through a disease probability model, based on clinical and echocardiographic variables, both scores stratify patients into low, intermediate, and high probability of HFpEF diagnosis and help define the need for further specific tests, such as stress echocardiography or cardiac catheterization (Figure 2). The H2FPEF score was developed from a cohort of patients with an invasive diagnosis of HFpEF by cardiac catheterization combined with physical exercise and subsequently validated in a second cohort, including patients with and without HFpEF.[28] The HFA-PEFF score was developed from a consensus of recommendations from the European Society of Cardiology and is based on a sequential diagnostic approach.[30-32] The HFA-PEFF score was subsequently validated in cohorts of outpatients and inpatients.[34,35]

The population of clinical studies with HFpEF is quite heterogeneous, including patients with varying diagnostic criteria and clinical markers, such as previous hospitalizations, natriuretic peptide levels, and altered functional capacity, making subsequent reproducibility of results difficult[21-24] (Table 1). Currently, the existence of different clinical phenotypes in HFpEF is recognized, including those related to obesity/metabolic syndrome, atrial fibrillation, and pulmonary hypertension, which present different stages of cardiac involvement, clinical presentations, and hemodynamic conditions.[21,23,24] Due to its clinical heterogeneity and the absence of universal diagnostic markers, in many cases, the diagnosis of HFpEF requires the use of invasive hemodynamic measurements that demonstrate increased left ventricular filling pressures and pulmonary circulation pressures both at rest and during exertion. However, the adoption of this invasive strategy is impractical and costly, remaining restricted to specialized research centers.[25,26]

Prognostic assessment in HFpEF

Randomized clinical trials with patients with HFpEF have described high cardiovascular mortality rates, around 60-70% of total deaths in this population, slightly lower than those in HFrEF. Among the predominant cardiovascular causes are sudden death (30-40% of causes) and worsening heart failure (20-30% of causes). The cardiovascular mechanisms leading to terminal events in these patients have not yet been elucidated and are related to restrictive cardiomyopathy, right ventricular dysfunction, tachyarrhythmias and bradyarrhythmias, acute myocardial infarction, and others. Non-cardiovascular causes of death, which account for 30-40% of the total, include advanced kidney disease, respiratory failure, pulmonary hypertension, obstructive pulmonary disease, sepsis, and multiple organ dysfunction.[44]

Traditionally, parameters used in the diagnosis of HFpEF, such as serum natriuretic peptide levels and echocardiographic

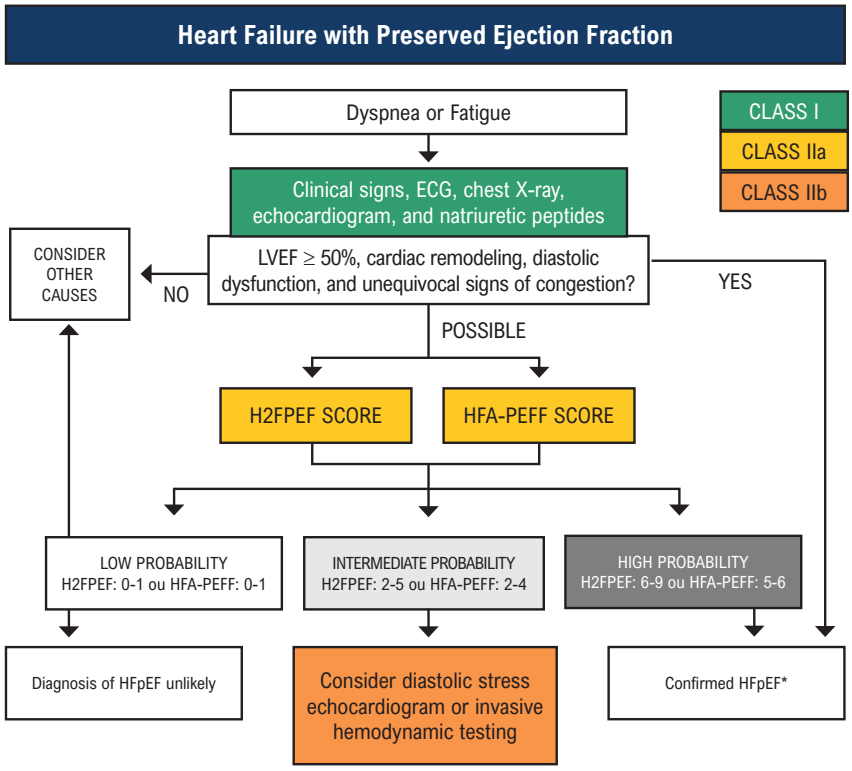


Figure 2 – *Current probabilistic diagnostic model for Heart failure with preserved ejection fraction (HFpEF). Source: Marcondes-Braga FG et al.*[17]

changes, are used to assess severity and prognosis.[18,45] Echocardiographic measurements of structural and functional cardiac changes have limited value for predicting mortality and hospitalizations due to HF, with contradictory results in the literature.[46] A recent meta-analysis of clinical trials investigating the role of echocardiographic parameters used in the assessment of diastolic dysfunction in HFpEF, including indexed left atrial volume, indexed left ventricular mass, tricuspid regurgitation velocity, myocardial tissue velocity, and E/e' ratio, demonstrated only a moderate correlation of the latter parameter with combined outcomes of all-cause mortality and hospitalizations due to cardiovascular causes.[19] Other echocardiographic parameters, such as left ventricular global longitudinal strain (LGS), were not systematically included in these clinical trials, but may provide additional prognostic information.[19,47]

Some studies have analyzed the use of the H2FPEF and HFA-PEFF scores in the prognostic evaluation of patients with HFpEF, with conflicting results.[27,29,36] In the case of H2FPEF, its component variables, such as age, obesity, atrial fibrillation, and pulmonary hypertension, are individually associated with a higher risk of cardiovascular outcomes in different clinical studies. Regarding HFA-PEFF, its component factors, indexed left ventricular mass, E/e' ratio, indexed left atrial volume, pulmonary arterial systolic pressure, and BNP are also associated with a higher risk of cardiovascular events.[29]

CPET and its diagnostic applications in HFpEF

In HFpEF, exercise intolerance is the central clinical manifestation, resulting from a reduction in the functional reserve of different organs, both cardiac and extracardiac, including alterations in respiratory gas exchange with reduced pulmonary vascular reserve (PV), lower central and peripheral vascular reserve, musculoskeletal dysfunction, anemia, and other factors.[48] Inefficient O2 transport, associated with inadequate peripheral extraction, whether due to inflammatory and microvascular aspects or skeletal muscle inefficiency, are the main causes of exercise intolerance[49,50] (Figure 3).

Thus, peak oxygen consumption (VO2peak), which represents the objective measure of aerobic capacity through CPET, is markedly reduced in patients with HF.[50] Ventilatory abnormalities and changes in the efficiency of respiratory gas exchange are also described in patients with HF. Ventilatory efficiency, measured by the VE/VCO2 ratio, is altered, with a disproportionate increase in ventilation (VE) relative to CO2 production, and is related to the lung ventilation/perfusion ratio and pulmonary artery pressure. Periodic ventilation (EOV) consists of a cyclical pattern of respiratory kinetics, present in up to 20% of patients with symptomatic HF, and is characterized in CPET as the fluctuation of gas exchange measurements in amplitude, frequency, and duration; however, its prevalence in HFpEF appears to be lower.[50]

Considering that the CPET is the gold standard for assessing functional capacity, its use is recommended for confirming

Table 1 – Diagnostic criteria for HFpEF according to different guidelines and clinical trials

	ACC/ AHA	ESC	HFSA	TOPCAT	PARAGON	I-PRESERVE	RELAX
Reference	Yancy C, Circ, 2013[38]	Ponkowskand P, EHJ, 2016[1]	Lindenfeld J, JCF, 2010[39]	Pitt B, N England J Med, 2014[40]	Solomon SD, JACC HF, 2017[41]	Massie B, N Engl J Med, 2008[42]	Redfield MM, JAMA, 2013[43]
Symptoms	✓	✓	✓	✓	✓	✓	✓
Signs		✓	✓	✓		Alt. on admission by HF	✓
LVEF	≥50%	≥50%	≥50%	≥45%	≥45%	≥45%	≥50%
Structural heart disease		LVH, LAO, or DD, and non-dilated LV	LVH, LAO (without AF), DD		LAO or LVH	LAO or LVH	LAO and use of diuretics (Altered admission due to heart failure)
Hospitalization for heart failure or cardiovascular disease			✓ (CV)	✓ (HF)		✓ (HF)	✓ (HF)
Exclusion	Non-cardiac causes		Non-myocardial disease				
NT pro-BNP		≥125		>360 (Altered admission by HF)	Different cut-offs for hospitalization and AF		≥400 or higher filling pressures
CPET						VO2 peak <14 ml/kg/min (Alt on admission due to heart failure)	Predicted peak VO2 ≤ 60%
Invasive		Alt: PAOP >15mmHg					↑ pressures filling (Alt. admission by HF)
Other HF criteria					Chronic diuretic and age > 50	Age > 60	

Source: Adapted from Ho et al.[21] Alt.: alternative; CV: cardiovascular; DD: diastolic dysfunction; AF: atrial fibrillation; LVH: left ventricular hypertrophy; PAOP: pulmonary artery occlusion pressure; LAO: left atrial overload; LVEF: left ventricular ejection fraction; CEPT: Cardiopulmonary exercise testing; HF: heart failure

and measuring the degree of exercise limitation and also provides diagnostic and prognostic information in patients with HFpEF.[51] Peak VO2, a parameter used as the gold standard for estimating functional capacity, shows a reduced value in patients with HFpEF,[52,53] comparable to that of patients with HFrEF.[51] However, the reduction in peak VO2 is not very specific for the diagnosis of HFpEF, with a high diagnostic probability for values <14 ml/kg/min and a low probability for values >20 ml/kg/min, making it difficult to incorporate CPET into recent diagnostic algorithms for HFpEF (Figure 4).

When peak VO2 is evaluated together with other ventilatory parameters obtained in the CPET, including ventilatory equivalents (peak respiratory quotient (R), VE/VCO2 slope), there is an increase in the diagnostic value of the exercise test in HFpEF, allowing differentiation of the contribution of cardiac and pulmonary components in exercise limitation and identification of specific disease phenotypes, such as those related to involvement of the right heart chambers and pulmonary hypertension.[48]

CPET and its prognostic applications in HFpEF

Regarding the prognostic value of CPET in HFpEF, the application of its different variables still presents important limitations, unlike what occurs in HFrEF, whose prognostic value is already well recognized, assisting in the identification of patients with a higher risk of cardiovascular events, including hospitalization for HF and mortality from general and cardiovascular causes. As well observed by Ozemek,[54] there are notable differences in the

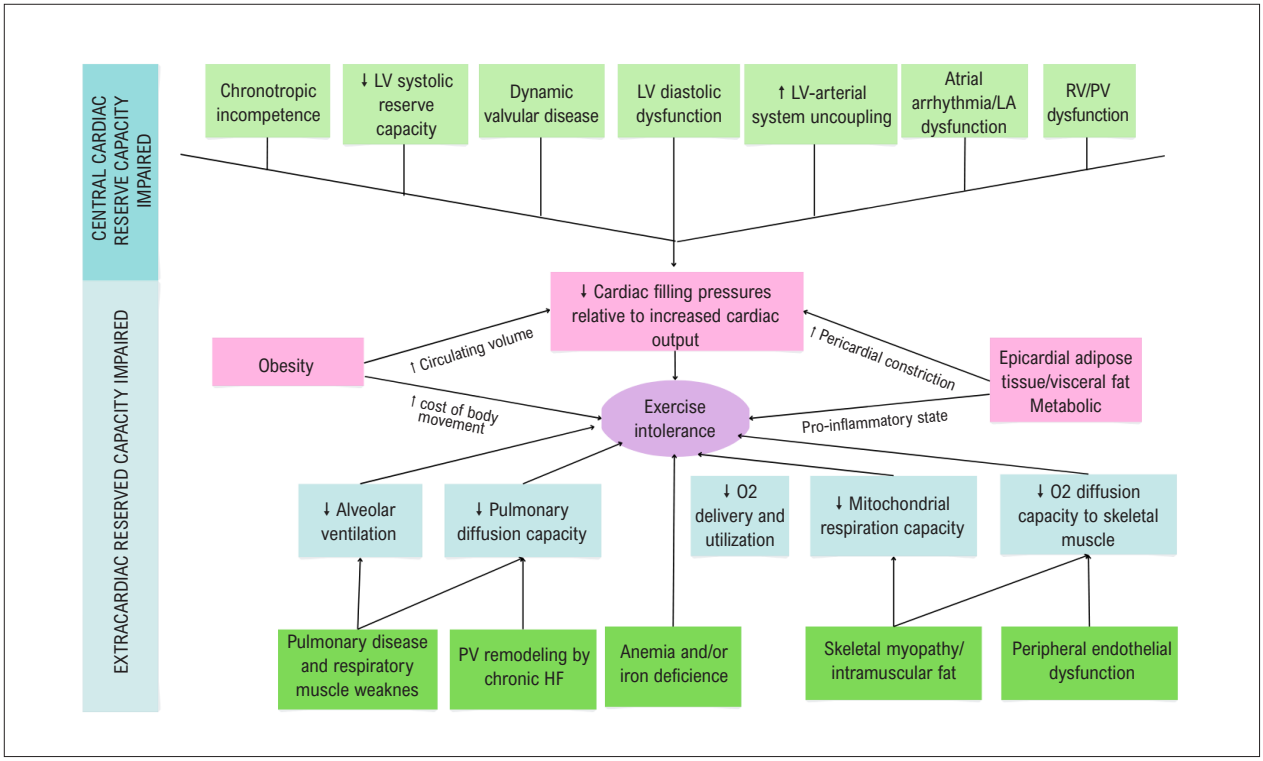


Figure 3 – *Pathophysiological Mechanisms of Exercise Intolerance in HFpEF. Source: Adapted from Nayor et al.[51] LA: left atrium; HF: heart failure; RV: right ventricle; LV: left ventricle; PV: pulmonary vasculature.*

different studies between the samples of patients with HFpEF regarding age, sex, and definition, diagnosis, and stage of the disease, which directly impact the values of the variables obtained in CPET. Considering, for example, the VE/VCO2 slope variable, while some studies[55-57] described cutoff points > 35-36 as indicative of a higher risk of events, others[58] identified average values > 30 for the same variable, which makes its incorporation with other clinical variables difficult.

A systematic search was conducted using the PubMed platform, including the descriptors "Heart Failure with Preserved Ejection Fraction", "Prognostic", and "Cardiopulmonary Exercise Testing", selecting observational and cohort clinical studies that evaluated CPET variables in predicting risk in patients with HFpEF, without restriction by publication date. Table 2 summarizes the main prognostic studies in HFpEF using CPET, with clinical characteristics of the samples, main prognostic findings, and limitations of each study.

One of the initial studies that evaluated the prognostic role of CPET in HFpEF investigated 409 patients with NYHA II or III HF, of whom 145 had EF >40%, and compared different cutoff points for defining preserved EF at the time (>40%, >45%, and >50%), of which only 46 had EF >50%.[55] Peak VO2 and VE/VCO2 slope were shown to be predictors of hospitalization and mortality for patients with HF and EF >50% in univariate analysis. In multivariate analysis, only the VE/VCO2 slope was a marker of worse prognosis independent of EF, with a cutoff point of 33.3, demonstrating a worse prognosis with EF >50%. In addition to the small population of patients with HFpEF by current criteria (n=46), the percentage of women included was low, unlike what is shown in clinical studies with larger samples.

Another important study in determining the prognostic role of CPET in HFpEF[59] included 151 patients and demonstrated that, as in HFrEF, the presence of periodic ventilation and an elevated VE/VCO2 slope are markers of cardiovascular events. Importantly, this study used a cutoff point of > 50% for EF as a diagnostic criterion for HFpEF. However, the use of different exercise modalities in the study (treadmill and cycle ergometer) introduced biases in the maximum ventilatory values obtained, in addition to the predominance of males again (67% of the sample). In the study,[60] Guazzi et al. sought to demonstrate the prognostic role of CPET in HFpEF, matching 34 patients with HFpEF and 34 with HFrEF by age, sex, functional class, natriuretic peptide, and CPET variables (peak VO2, VE/VCO2 slope, and the presence of periodic ventilation). Positive correlations were identified between the CPET variables in both groups, most strongly for the VE/VCO2 slope, suggesting a similar severity of the disease. Limitations of the study include a small sample size and a predominant percentage of male individuals (76%).

In a retrospective study in 2016, Shafiq et al.[58] demonstrated in 103 patients with HFpEF that predicted peak VO2 percent and peak VO2 were predictors of a composite outcome of all-cause mortality, while VE/VCO2 slope and the presence of periodic ventilation were not predictors, unlike the studies cited. In addition to the use of an EF >50% cutoff point for diagnostic inclusion, there was a sample with a lower predominance of males (55%) and a longer follow-up time (median of 5.2 years), which may

Table 2 – Summary of the main prognostic studies using the CPET in HFpEF

Studies of CPET at HFpEF	N	Primary outcomes and other results	Clinical limitations, biases, and relevance of the study
Guazzi et al. (2005)[55]	46	- VE/VCO2 slope >33.3 associated with overall mortality and hospitalization for heart failure.	- Small N - Predominantly male (83%)
Guazzi et al. (2008)[59]	151	- VE/VCO2 slope and periodic ventilation associated with worse prognosis	- Predominantly male (67%) - Use of different types of CPET (treadmill and bicycle)
Yan et al. (2011)[56]	224	-Peak VO2 (<16.9 ml/min/kg) and VE/VCO2 (>34.7) associated with overall mortality	- Predominantly male (71%)
Shafiq et al. (2016) [58]	103	-Predicted peak VO2 percentile (<58%) and peak VO2 (<13.9 ml/min/kg) associated with worse prognosis.	- Lower predominance of men (55%) - Longer average follow-up (5.2 years)
Palau et al. (2017) [57]	74	A 10% decrease in predicted peak VO2 percent was associated with a 32% increased risk of readmission.	-Representative sample of HFpEF, despite small N - Short average follow-up (276 days)
Nadruz et al. (2017)[61]	195	-Peak VO2 (<14.0 ml/min/kg) and VE/VCO2 slope (>30) are associated with higher overall mortality and hospitalization for heart failure.	- Lower predominance of men (53%)
Sato et al. (2017)[62]	438	Peak VO2 and periodic ventilation are associated with a worse prognosis.	- Only hospitalized patients / recently discharged (<3 days)

CPET: Cardiopulmonary exercise testing; HFpEF: Heart failure with preserved ejection fraction. Source: Author's own work

justify the different prognostic findings of the variables. Another study in 2017[57] demonstrated that a reduction in predicted peak VO2 percent was associated with an increase in overall and cardiovascular mortality and risk of rehospitalization in a sample of 74 patients with stable HFpEF who had previously been hospitalized for heart failure decompensation. A 10% reduction in predicted peak percent VO2 was associated with a 32% increase in the risk of readmission, remaining significant in the multivariate model.[54] Although the sample had similar clinical characteristics to larger clinical studies in HFpEF (elderly patients, predominantly female, and with multicomorbidities), the mean follow-up time was short (276 days).

Recently, two studies evaluated the role of CPET in HFrEF, HFpEF, and HFpEF-R. The study by Nadruz et al.,[61] with 969 patients with HF, demonstrated that both peak VO2 and the slope of the VE/VCO2 ratio showed greater risk discrimination in patients with HFpEF (total of 195 patients) when added to clinical variables and EF. The study by Sato et al. compared 1190 patients with the same diagnoses.[62] The HFrEF group had a higher rate of cardiovascular events and mortality than the other groups. The prognostic variables of CPET were more altered in the HFrEF group. The main predictor of all-cause mortality and cardiovascular events in all groups was peak VO2. In the HFrEF and HFpEF-R groups, the OUES was a predictor of cardiovascular events, which was not observed in the HFpEF group. In the HFpEF group (total of 438 patients), in addition to peak VO2, only the presence of periodic ventilation was an independent predictor of death or cardiovascular events.

Established variables such as peak VO2 and the presence of periodic ventilation can be considered reliable prognostic markers. However, the role of other prognostic variables of interest, such as VE/VCO2 slope, O2 pulse, and OUES, is still controversial, and further prospective studies in this area are needed for better definition.[63]

Among the clinical factors particularly associated with the more heterogeneous behavior of CPET variables in HFpEF, obesity plays a central role in this scenario, given its high prevalence in this population and its direct influence on the evaluation of cardiopulmonary exercise test parameters, such as relative peak VO2 and lean VO2.[64] According to previous studies, patients with HFpEF present marked alterations in their body composition resulting from obesity, such as an increase in total fat mass disproportionate to the increase in lean mass, which is associated with a reduction in cardiorespiratory fitness and functional limitation.[64-66] There may also be an increase in total lean mass due to increased fluid retention in cases of chronically decompensated HF.[64] Compared to non-obese patients with HFpEF, those with obesity and HFpEF present a greater elevation of ventricular filling pressures during exertion, greater pericardial restriction with increased ventricular interdependence, reduced extracardiac functional reserve due to inflammation, and a higher metabolic cost due to physical activity.[29]

Particularly regarding peak oxygen consumption, this variable can traditionally be corrected for total body mass (relative peak VO2) or alternatively for lean mass (lean VO2). In individuals with higher total body mass, such as obese individuals, relative peak VO2 may be underestimated.[64] On the other hand, the use of lean VO2 may be a more reliable parameter for assessing peak VO2 in patients with HFpEF, with better prognostic discrimination capacity in this population.[67] As pointed out by Krachler et al.,[68] correcting peak VO2 for lean

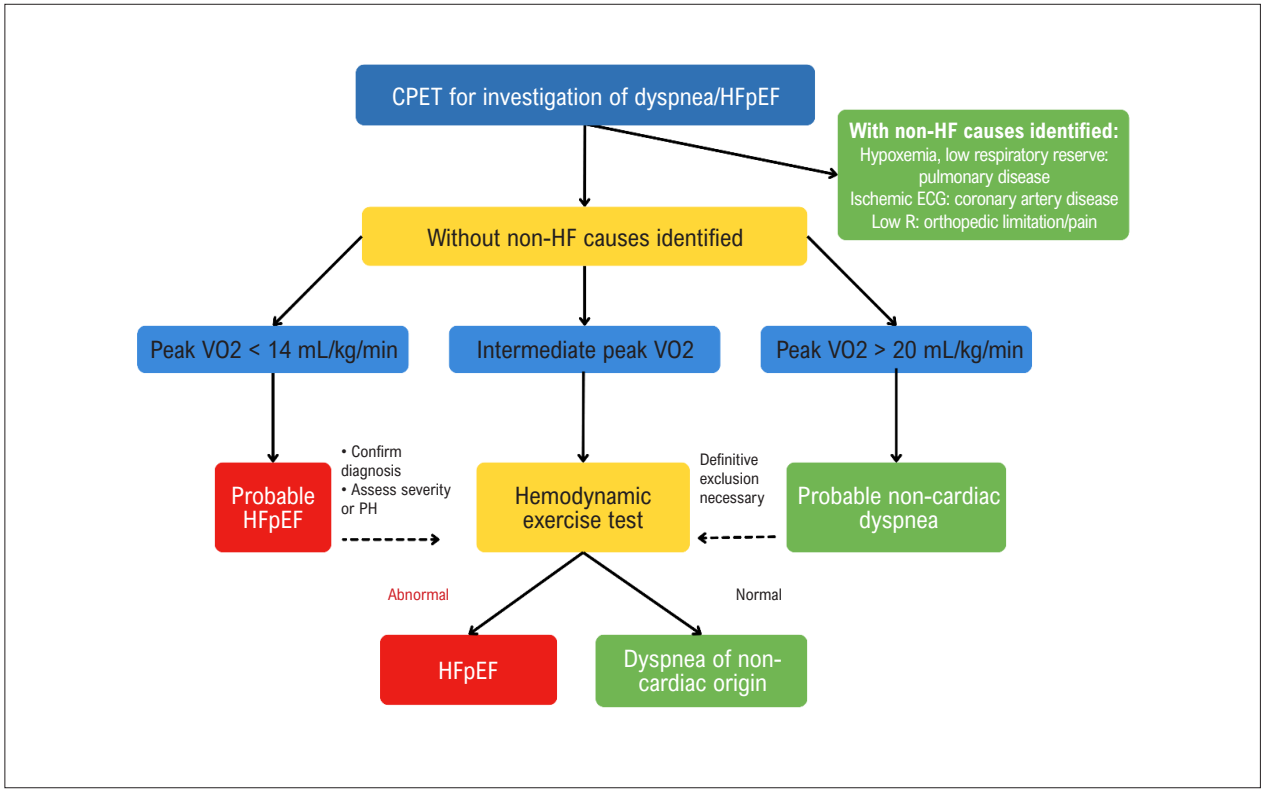


Figure 4 – *Diagnostic flowchart for dyspnea/HFpEF using CPET. Source: Adapted from Reddy et al.[52] HP: pulmonary hypertension; HF: heart failure; R: respiratory quotient; CPET: cardiopulmonary exercise test; VO2: oxygen consumption.*

mass implies a stronger association in the curve of the increase in peak VO2 per kg of mass. The use of lean mass reduces the bias associated with obesity and increased total body mass. In the study by Haykowsky et al.,[66] it was observed that lean VO2 was significantly reduced in the group of patients with HFpEF (25.1±5.6 ml/kg/min), correlated with the loss of lean mass in this group.

Conclusions

As demonstrated, CPET is valuable in complementing the diagnosis of HFpEF. The combined use of peak VO2 with other ventilatory parameters can help differentiate between cardiac and pulmonary components of exercise limitation. For prognostic purposes, variables such as peak VO2, VE/VCO2 slope, and the presence of periodic ventilation correlate with a higher risk prediction; however, there are notable differences in studies between samples of patients with HFpEF, hindering the clinical incorporation of CPET variables. Therefore, we believe that the use of contemporary diagnostic criteria and the performance of prospective studies with more appropriate patient selection can reduce these biases observed in previous studies.

Due to the high prevalence and central role of obesity in the heterogeneous behavior of CPET variables in HFpEF, we believe that the use of some variables adjusted for body differences, such as VO2 lean, can reduce the heterogeneity of the measurements and allow for better incorporation of CPET in risk stratification in HFpEF.

Author Contributions

Conception and design of the research: Barros FC, Cezaro JC, Menegazzo WR, Silveira AD; Acquisition of data: Barros FC, Cezaro JC; Analysis and interpretation of the data: Barros FC, Scolari FL, Silveira AD; Statistical analysis: Barros FC, Silveira AD; Writing of the manuscript: Barros FC; Critical revision of the manuscript for content: Barros FC, Pianca EG, Silveira AD.

Potential conflict of interest

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

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Study association

This article is part of the thesis of doctoral submitted by Fernando Colares Barros, from Universidade Federal do Rio Grande do Sul.

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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