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POSITION PAPER

Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology

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Traditionally, the main indication for cardiopulmonary exercise testing (CPET) in heart failure (HF) was for the selection of candidates to heart transplantation: CPET was mainly performed in middle-aged male patients with HF and reduced left ventricular ejection fraction. Today, CPET is used in broader patients' populations, including women, elderly, patients with co-morbidities, those with preserved ejection fraction, or left ventricular assistance device recipients, i.e. individuals with different responses to incremental exercise and markedly different prognosis. Moreover, the diagnostic and prognostic utility of symptom-limited CPET parameters derived from submaximal tests is more and more considered, since many patients are unable to achieve maximal aerobic power. Repeated tests are also being used for risk stratification and evaluation of intervention, so that these data are now available. Finally, patients, physicians and healthcare decision makers are increasingly considering how treatments might impact morbidity and quality of life rather than focusing more exclusively on hard endpoints (such as mortality) as was often the case in the past. Innovative prognostic flowcharts, with CPET at their core, that help optimize risk stratification and the selection of management options in HF patients, have been developed.

Keywords Exercise testing • Prognosis • Heart failure

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Introduction

When first introduced in cardiology, symptom-limited cardiopulmonary exercise testing (CPET) was mainly used in middle-aged male patients with heart failure (HF) due to left ventricular dysfunction, to screen candidates for heart transplantation (HT).[1] Only the results obtained in patients with severe disease, without co-morbidities but able to perform a maximal CPET [i.e. with a peak respiratory exchange ratio (RER) >1] were considered, following the recommendations of the European Society of Cardiology (ESC) guidelines on HF.[2–4]

Today, this scenario has changed.[5] Heart transplantation candidates' survival has improved, and patients (i.e. in stable condition on oral medications and able to remain out of hospital) are *de facto* excluded from listing.[6] Most of the patients with an indication for HT have recurrent HF hospitalizations and are unable to exercise because of severe symptoms at rest or with minimal exercise. The ability to perform CPET *per se* characterizes a low-risk group of patients.

CPET has an important role in HF with reduced ejection fraction (HFrEF), but nonetheless CPET and derived parameters are useful beyond risk assessment. As regards prognosis, at one end of the spectrum, where patients are unable to achieve the maximal aerobic power, submaximal CPET might also carry relevant information, whilst at the other end, more patients are able to repeat the test in the course of functional evaluation. Furthermore, new endpoints [i.e. HF hospitalization or readmission, left ventricular assist device (LVAD) implantation or implantable cardioverter-defibrillator (ICD) interventions] are meaningful to patients, physicians, and decision makers, as morbidity prediction is pertinent in terms of quality of life and costs.

The prognostic value of CPET in HFrEF, especially if combined with other key clinical parameters, has been the subject of recent papers.[7,8] Today, CPET assists in HFrEF management, underscores warning signs in symptomatic patients, and, even in asymptomatic ones, it assists in the discrimination of apparently functional weak points.[4,7] Moreover, CPET's ability to stratify risk may also support cardiac rehabilitation programmes.

The aim of the present paper is to review the prognostic role of CPET in HF considering the individual patient characteristics, the modality of CPET execution, and newer clinical endpoints. Innovative prognostic flowcharts, with CPET at their core, that help optimize risk stratification and management in HF patients are proposed.

The patient

Gender

In HFrEF, women show differences with respect to men, in terms of epidemiology, aetiology, time of disease presentation, risk factors, mechanisms of disease development, renal function, metabolism, thrombotic haemostasis, renin–angiotensin system activation, inflammatory mechanisms, co-morbidities, medical therapy prescription and response to therapy, and outcome.[9] On average, women have higher left ventricular ejection fractions (LVEF), less coronary artery disease as the primary aetiology of HF, more atrial fibrillation (AF) and fewer implanted ICDs.[9] Moreover, peak oxygen uptake (VO_2) is lower as women are generally less physically active, have a lower fat-free mass, smaller skeletal muscle fibre area, lower oxygen carrying capacity, i.e. lower haemoglobin concentration and blood volume. In addition, women show a smaller degree of stroke volume augmentation on exercise.[10] Besides, reproductive hormones can also influence parameters related to functional capacity.[11] As a consequence, HFrEF women have nearly 2 mL/kg/min (12–15%) lower peak VO_2 compared to men, after adjustment for age, peak heart rate (HR), peak RER, LVEF, and aetiology:[12] in New York Heart Association (NYHA) class II, average peak VO_2 is 16.4 mL/min/kg for men vs. 14.8 mL/kg/min in women, whereas in NYHA class III, average peak VO_2 is 13.5 mL/kg/min for men vs. 11.7 mL/kg/min in women.[13]

HFrEF women constitute a large proportion of the older-aged patient group, and the policy of non-inclusion of the elderly influences gender distribution in published studies. *Table 1* summarizes the population characteristics in studies comparing the role of CPET and outcome in HFrEF in men and women. Peak VO_2 preserved its predictive capacity in women, but the prognostic 'cut-point' values of peak VO_2 differ between genders.[14–19] In a large HFrEF population,[20] women (17%) showed lower values of peak VO_2, percentage of detectable ventilatory anaerobic threshold (VAT), VO_2 at VAT, and peak RER, whereas the ventilatory response to exercise [minute ventilation to carbon dioxide production (VE/VCO_2) slope] was comparable with respect to men. During follow-up, women showed a better survival, but the gender benefit was lost after propensity score matching analysis for most clinical, exercise and treatment characteristics, suggesting a key role of clinical and risk factors in the differences in prognosis between genders.

Elderly

Owing to the increasing longevity of human beings worldwide, the population is ageing. HFrEF is predominantly a disease of the elderly,[21] and ageing is characterized by physiological changes, with a decline of approximately 0.4–0.5 mL/kg/min of peak VO_2 per decade.[20] The rate of decline is similar between genders, but women start out at a lower peak VO_2.[22]

Most studies on CPET and risk assessment in HFrEF have been conducted in middle-aged patients,[7] excluding elderly patients (those aged ≥70 years): thus, derived predictive information is difficult in this setting. Nonetheless, symptom-limited CPET is feasible, safe and reproducible in stable elderly HFrEF patients,[23] and the decrease in peak VO_2 and the increase in VE/VCO_2 slope values are related to age.[24] CPET also predicts outcomes in the elderly with HFrEF:[25–33] key studies are summarized in *Table 2*. As mention, results must be interpreted with caution, since a sizeable number of patients were excluded because of respiratory disorders, arrhythmias, angina, joint diseases, neurological disorders, claudication, frailty, or disease severity.[34] Conclusions are far from definitive in elderly HFrEF patients as concomitant disease might limit CPET employment and number of patients enrolled is limited.

Table 1 Summary table of the main characteristics of studies evaluating cardiopulmonary exercise testing and outcomes in male and female patients with heart failure with reduced ejection fraction

	Richards *et al.*[14]		Elmariah *et al.*[15]		Guazzi *et al.*[16]		Green *et al.*[17]		Hsich *et al.*[18]		Corrà *et al.*[19]	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Patients, *n* (%)	55 (72)	21 (28)	427 (72)	167 (28)	337 (82)	75 (18)	278 (51)	274 (49)	1580 (88)	214 (12)	413 (79)	116 (21)
Age, years	51 ± 12	49 ± 9	53 ± 12	49 ± 11	57 ± 13	55 ± 12	55 ± 11	52 ± 13	51 ± 12	51 ± 12	60 ± 11	60 ± 9
NYHA class	2.7 ± 0.9	2.6 ± 0.9	NA	NA	2.2 ± 0.6	2.3 ± 0.8	NA	NA	NA	NA	NA	NA
Ischaemic aetiology of HF, %	60	33	43	15	55	52	51	26	43	22	66	55
AF, %	NA	NA	15	3	NA	NA	NA	NA	7	3	13	7
DM, %	NA	NA	26	16	NA	NA	NA	NA	25	25	NA	NA
ICD, %	NA	NA	16	5	NA	NA	NA	NA	20	17	35	28
ACEIs/ARBs, %	NA	NA	78	74	72	73	87	81	83	79	92	90
Loop diuretics, %	NA	NA	70	74	53	63	NA	NA	84	84	92	87
β-blockers, %	NA	NA	73	72	42	39	60	54	44	44	53	58
LVEF, %	19 ± 9	20 ± 11	25 ± 11	29 ± 13	33 ± 11	32 ± 13	27 ± 11	29 ± 13	20 ± 15	20 ± 15	22 ± 7	27 ± 7
Peak VO_2, mL/kg/min	18.3 ± 5	14.5 ± 2	16.6 ± 7	14 ± 4	17.1 ± 5	12.8 ± 3	17.1 ± 5	13.9 ± 5	16	15	11.4 ± 1.9	10.6 ± 1.9
%ppVO_2, %	65 ± 18	75 ± 16	NA	NA	NA	NA	NA	NA	NA	NA	42 ± 10	53 ± 15
Peak RER	1.14 ± 0.1	1.08 ± 0.1	1.11 ± 0.1	1.05 ± 0.1	1.07 ± 0.1	1.02 ± 0.1	NA	NA	1.10	1.20	1.14 ± 0.06	1.15 ± 0.07
VE/VCO_2 slope	NA	NA	NA	NA	33 ± 8	37 ± 9	NA	NA	NA	NA	37 ± 9	35 ± 8
VE/VCO_2 slope	NA	NA	NA	NA	33 ± 8	37 ± 9	NA	NA	NA	NA	37 ± 9	35 ± 8

Absolute or mean values ± SD.
ACEIs, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; DM, diabetes mellitus; ICD, implantable cardioverter-defibrillator (% of implanted patients); LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association; RER, respiratory exchange ratio; VE/VCO_2, minute ventilation to carbon dioxide production; VO_2, oxygen uptake; %ppVO_2, percentage of predicted peak VO_2.

Overweight or obese

Obesity is increasing in epidemic proportions: in HFrEF, an obesity paradox has been well described, as overweight patients show reduced cardiovascular mortality and total mortality compared to patients with normal body mass index (BMI).[35] CPET maintains its predictive value in these patients, but the adjustment of peak VO_2 to lean body mass increases its prognostic value:[36–41] the main study results are summarized in *Table 3*.

The protective role of obesity in HFrEF has been challenged by more recent data. In the Lavie's study,[36] among patients with HFrEF and with peak $VO_2 < 14$ mL/kg/min, those with BMI >30 kg/m^2 had a better prognosis than lean patients (BMI 18.5–25 kg/m^2) and intermediate outcomes compared to overweight patients (BMI 25–30 kg/m^2). On the contrary, those with peak $VO_2 \geq 14$ mL/kg/min had a good prognosis, regardless of BMI.[36] In 4623 HFrEF patients, we observed that cardiorespiratory fitness mitigates the obesity paradox: the protective power of an elevated BMI disappeared when variables such as age, gender, LVEF and percentage of predicted peak VO_2 (ppVO_2) were included in the model.[37] BMI influences the prognostic role of VE/VCO_2 slope, as well.[38]

Peak VO_2 is conventionally corrected for total body weight; however, body fat, which might represent a significant proportion of total body weight, consumes essentially no oxygen during exercise: peak VO_2 lean (i.e. peak VO_2 corrected for lean body mass) was a better predictor of outcome than peak VO_2.[39–41] Thus, peak VO_2 might be misleadingly low in the individual 'overweight-obese' HFrEF patient, and the correction of peak VO_2 value for lean body mass might provide a better measurement of exercise capacity. However, which correction should be applied is still debated.

Permanent atrial fibrillation

Atrial fibrillation is the most common arrhythmia in HFrEF.[4] Cardiopulmonary adaptation to exercise in permanent AF patients depends on complex factors, such as irregular HR, reduced left ventricular loading, irregular periods of ventricular filling, and decreased cardiac output. Peak VO_2 is by and large reduced in HFrEF patients with AF, and VAT is less frequently identified and when identified postponed likely due to altered kinetics of exercise-induced HR increases.[42] However, outcomes seem not be influenced by baseline cardiac rhythm in HFrEF patients performing symptom-limited CPET,[43] while VO_2 at VAT provided additional prognostic insights.[44] Therefore, symptom-limited CPET seems to be a valuable prognostic tool also in AF patients, but specific studies are scant.

Left ventricular assist device

Symptom-limited CPET has been performed safely in selected LVAD recipients,[45] with peak VO_2 values ranging from 11.5 to 20.3 mL/kg/min.[46] However, these findings should be considered

Table 2 Prognostic studies with cardiopulmonary exercise testing in elderly patients with heart failure with reduced ejection fraction

	Davies et al.[25]	Cicoira et al.[26]	Mejhert et al.[27]	Brubaker et al.[28] Moore et al.[29] Kitzman et al.[30]	Scardovi et al.[31]	Arena et al.[32]	Carubelli et al.[33]
Patients, *n*	50	123	9	60	227	1605	3794
Age, years	76 ± 4	77 ± 4	74 ± 6	70 ± 7	76 ± 5	59.2 ± 13.7	≥70 (990)
Subgroup analysis						≤45 years (*n* = 263) 46–65 years (*n* = 807) ≥65 years (*n* = 535)	
Female, %	16	29	34	61	30	12	16
NYHA class, I–IV	1–4	2.3 ± 0.8	1–4	1–3	2.2 ± 0.5	2.5 ± 0.55	2 (2–3)
LVEF, %	33 ± 14	38 ± 17	36 ± 11	50 ± 9	43 ± 12	32.6 ± 14.3	34 (27–40)
Ischaemic aetiology of HF, %	66	66	67	NA	49	49	58
HFrEF vs. HFpEF, %	100/0	52/48	100/0	50/50	66/34	NA	NA
ACEIs/ARBs, %	82	85	82	54	91/8	73	90
β-blockers, %	14	15	60	15	68	63	76
Loop diuretics, %	90	72	94	65	88	NA	85
% with peak RER >1	88	83	79	100	80	NA	
Peak VO_2, mL/kg/min	15.2 ± 4.5	15.4 ± 4.7	11.7 ± 3.6	13.5 ± 3	11 ± 3	16.7 ± 6.6	12.5 (10.3–15)
Main findings	Both peak VO_2 and VE/VCO_2 slope predict prognosis	CPET results predict prognosis	CPET results predict prognosis	Peak VO_2 and VAT are similar in HFrEF and HFpEF but VE/VCO_2 elevated only in HFpEF	VE/VCO_2 slope predicts prognosis	CPET results predict prognosis, irrespective of patient's age at presentation	Peak VO_2 predicts prognosis. The prognostic power of the MECKI risk score is similar in ≥70 and <70 years old patients

Values between brackets for NYHA class and LVEF are the range value.

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CPET, cardiopulmonary exercise testing; HF, heart failure; HFpEF, heart failure with preserved ejection fraction (LVEF >45% or 50%); HFrEF, heart failure with reduced ejection fraction (LVEF <45%); LVEF, left ventricular ejection fraction; MECKI, Metabolic Exercise Cardiac Kidney Indexes; NA, not available; NYHA, New York Heart Association; RER, respiratory exchange ratio; VAT, ventilatory anaerobic threshold; VE/VCO_2, minute ventilation to carbon dioxide production; VO_2, oxygen uptake.

Table 3 Prognostic studies with cardiopulmonary exercise testing in overweight/obese patients with heart failure with reduced ejection fraction

	Lavie *et al.*[36]	Piepoli *et al.*[37]	Chase *et al.*[38]	Osman *et al.*[39]	Davos *et al.*[40]	Ingle *et al.*[41]
Patients, *n*	2066	4623	704	225	135	411
Age, years	76 ± 5	61.6 ± 12.6	56.8 ± 13.7	54.3 ± 12.2	61 ± 12	64 ± 12
Female gender, %	30	17.2	21	20	0	18
NYHA class I–IV, mean or %	2.2 ± 0.5	14.7–57.6–26.5–1.2	19–41–36–4	2.4 ± 0.6	2.5 ± 0.9	NA
LVEF, %, mean or range	26/30.1	32.8 ± 7.7	33 ± 13	23 ± 13	31 ± 14	39 ± 6
Ischaemic aetiology of HF, %	36/44	46.7	51	58.1	61	NA
BMI, kg/m^2	≥18.5	26.3 ± 3.6	25 ± 4.5	28.9 ± 5.4	25 ± 4.5	27.8 ± 5.3
Obese (BMI ≥30 kg/m^2), %	35	NA	35	37	NA	27
ACEIs/ARBs, %	60/63	93.7	75	95	92	72
β-blockers, %	66/76	83.7	62	31	31	72
Loop diuretics, %	NA	80.8	60	82	NA	63
Peak VO_2, mL/kg/min	10.8/22.3	1129 ± 429 (mL/min)	16.8 ± 6.4	16 ± 5.9	18 ± 6.4	22.3 ± 8.1
VE/VCO_2 slope	30.9/39.1	32.8 ± 7.7	33.8 ± 8.7	NA	38 ± 16	33.9 ± 7.7
Main findings	In patients with low FIT, progressively worse survival was noted with BMI categories, whereas this was not noted in those with high FIT	BMI and peak VO_2 were positive predictors of survival. On multivariable analysis (age, gender, LVEF, peak VO_2), the protective role of BMI disappeared	VE/VCO_2 slope maintains prognostic value irrespective of BMI	The adjustment of peak VO_2 to lean body mass increases its prognostic value	The adjustment of peak VO_2 to lean body mass increases its prognostic value	The adjustment of peak VO_2 to lean body mass slightly increases its prognostic value, especially in obese patients

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; FIT, cardiorespiratory fitness; HF, heart failure; LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association; VE/VCO_2, minute ventilation to carbon dioxide production; VO_2, oxygen uptake.

with caution, since only optimally treated and stable LVAD recipients are selected to perform symptom-limited CPET and those with important co-morbidities are usually excluded. Furthermore, risk stratification with CPET is difficult in LVAD recipients, since mortality (and morbidity) is mainly linked to complications unrelated to exercise capacity, such as device complications (e.g. driveline infections or thrombosis), thrombo-embolic or cerebral haemorrhagic, gastrointestinal bleeding and anaemia, and acute kidney injury.[47] In summary, symptom-limited CPET is under-utilized in LVAD recipients, as is exercise training.[48]

Co-morbidities

Co-morbidities are frequent in HFrEF,[4,49,50] and are of great importance since they influence the cardiorespiratory response to exercise and (sometimes) outcome.[51–96] In chronic obstructive pulmonary disease (COPD), if concomitant pulmonary vascular disease is excluded, the exertional CPET response is characterized by a normal VAT, a reduced breathing reserve and oxyhaemoglobin desaturation during and at the end of exercise. An increased VE/VCO_2 slope usually quantifies excessive exercise VE, and mechanical constraints preclude or restrict COPD patients from attaining increased VE demands, and the slope diminishes as disease worsens.[51] In HFrEF patients with concomitant COPD, peak VO_2 is lower,[52] and these patients show a shorter CPET duration, a lower peak VO_2 and are less likely to achieve a peak RER >1.10.[53] Lower breathing reserve and higher percent predicted VO_2 efficiency slope are also associated with COPD.[54] The VE/VCO_2 slope in HF patients with concomitant COPD is peculiar and related to the severity of COPD.[55,56]

Heart failure with preserved ejection fraction

The diagnosis of HF with preserved ejection fraction (HFpEF) is challenging,[4] as the pathophysiology is heterogeneous, with different phenotypes and concomitant cardiovascular (e.g. AF, arterial hypertension, coronary artery disease, pulmonary hypertension) and non-cardiovascular pathologic conditions (diabetes, chronic kidney disease, anaemia, iron deficiency, COPD, and obesity). Exercise intolerance is the main symptom also in HFpEF.[97]

In HFpEF, abnormal ventilatory and haemodynamic responses to exercise have been described:[97–99] a marked reduction in peak VO_2 is associated with a severe impairment in peak cardiac output and stroke volume, mildly reduced peak HR, and slightly reduced peak $A–VO_2$ difference, together with mildly increased resting and markedly elevated exercise mean pulmonary capillary wedge pressures. Despite normal systolic contractile function and markedly increased left ventricular filling pressures, HFpEF patients are unable to use the Frank–Starling mechanism adequately to increase stroke volume during exercise.[97–99] Beyond that, an increased pulse pressure and markedly decreased aortic distensibility are observed while peripheral arteries must dilate early during exercise (also seen in HFrEF) to accommodate and facilitate the conveyance of increased nutritive blood flow to working skeletal muscle.[97]

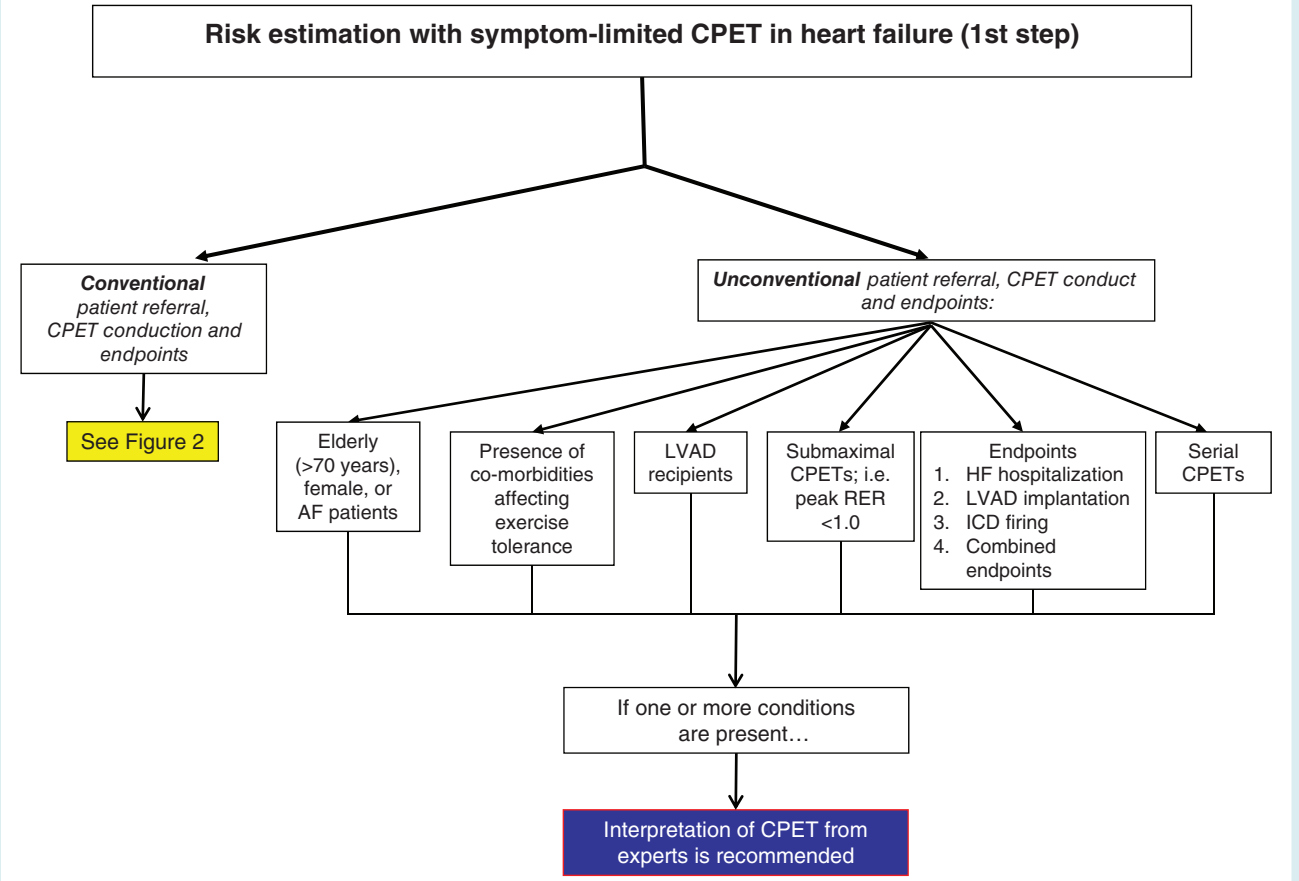

Figure 1 Risk estimation with symptom-limited cardiopulmonary exercise testing (CPET) in heart failure (HF) (1st step): differentiating conventional vs. non-conventional patient referrals, CPET conduct, and endpoints. Standard risk estimation (i.e. total or cardiovascular mortality or urgent heart transplantation) in conventional patients (i.e. middle-aged male patients) limited by muscular fatigue or dyspnoea with high respiratory exchange ratio (RER), with severe HF with reduced ejection fraction, without co-morbidities or implanted left ventricular assist device (LVAD). AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator.

In comparing HFpEF to HFrEF, the CPET-derived measures of peak VO_2 and ventilatory response (VE/VCO_2 slope) have been described to be either similarly reduced[99] or less affected.[100,101] Up to now, the predictive role of CPET-derived parameters has not been standardized for HFpEF, as data are far from being definitive. In some reports, peak VO_2, VE/VCO_2 slope and exertional oscillatory ventilation (EOV) preserved their predictive power,[101,102] whilst, in others, peak VO_2 and $ppVO_2$ were linked to outcome, but not VE/VCO_2 slope nor EOV.[103]

How to perform cardiopulmonary exercise testing for risk assessment

Body position

Posture is known to have important physiological effects on the cardiovascular system at rest and during exercise, and this applies also to patients with heart diseases: CPET recommendations for risk stratification in HFrEF are based on tests executed in the upright sitting/standing position.[6,62,63,104]

Early testing

Almost all CPETs performed for risk assessment are carried out after, at least, one month of clinical and pharmacological stability, defined as no changes in NYHA class, medications and no hospitalization for at least four weeks.[7] Consequently, CPET in HFrEF for risk assessment is usually not performed before one month from an acute episode of decompensation.[105,106]

Submaximal exercise testing

Advanced HFrEF patients are not accustomed to carrying out maximal workout during daily life, and, consequently, they are frequently afraid to perform symptom-limited CPET. Several criteria exist for defining maximal exercise effort in healthy subjects and cardiovascular disease patients:[107] (i) peak RER $\geq$1.10–1.15,

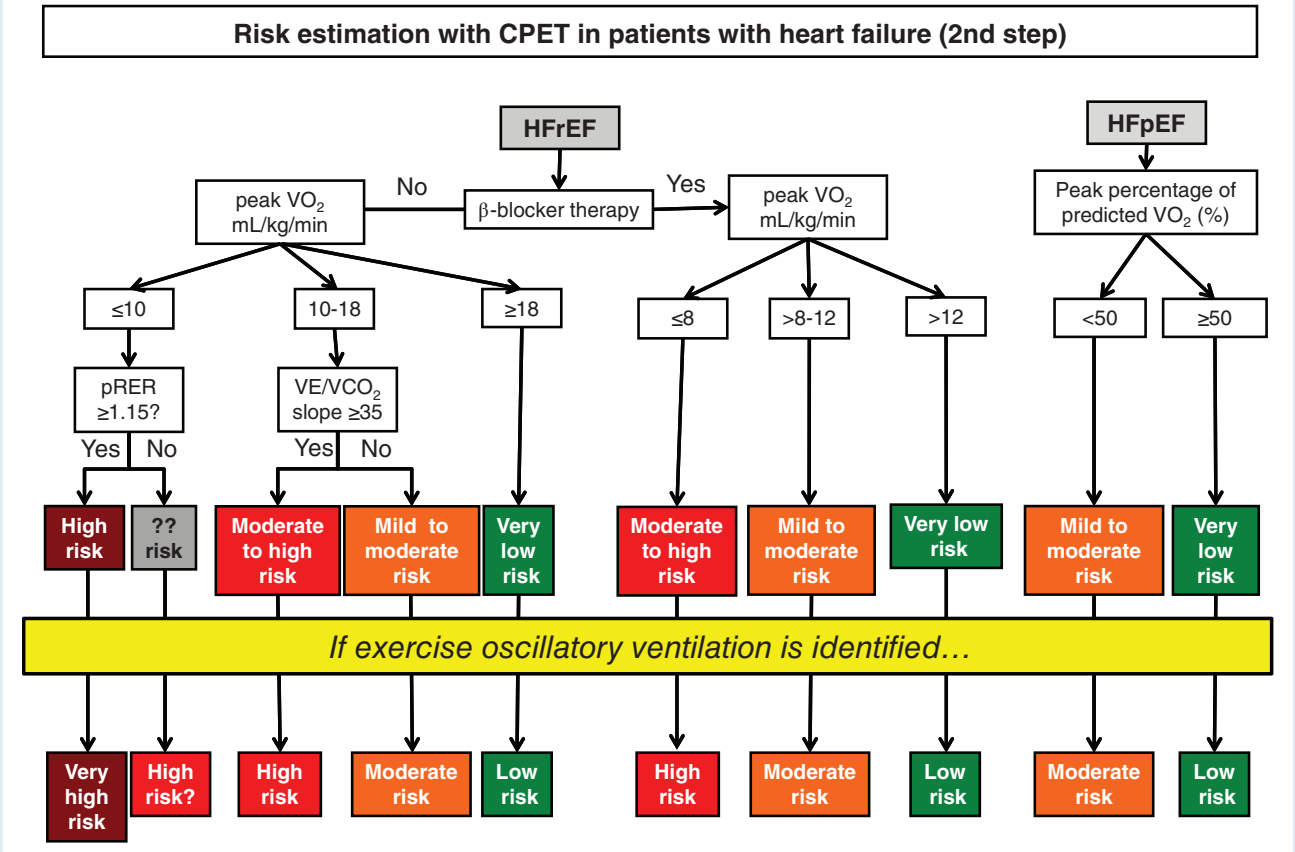

Figure 2 Risk estimation with cardiopulmonary exercise testing (CPET) in patients with heart failure (2nd step): considering specific prognostic indicators. This proposal of CPET interpretation for risk stratification is a hybrid extrapolation of the literature: therefore, it might not be fit for 'specific' individual patients, for instance, a very young patient with heart failure and reduced ejection fraction (HFrEF). In this patient, a peak oxygen uptake (VO_2) of 18 mL/kg/min might already be significantly reduced, and the integration of percentage of peak VO_2 (together with the absence of oxygen pulse increment, blood pressure increase, and/or with severe chronotropic incompetence) might be useful. Unfortunately, this attractive concept has not yet been proven by prospective studies. Up to now, no data are available for risk stratification in patients with HFrEF not treated with beta-blockers, with low peak VO_2 and low peak respiratory exchange ratio (pRER). HFpEF, heart failure with preserved ejection fraction; VE/VCO_2, minute ventilation to carbon dioxide production slope during exercise. Percent predicted peak VO_2 calculated using the Wasserman equation (Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Philadelphia: Lippincott Williams & Wilkins; 2005. p143–165).

(ii) post-exercise lactate ≥18 mmol/L, (iii) a plateau in the VO_2 to work rate relationship, (iv) HR ≥90% of predicted maximal HR, (v) perceived exertion with the Borg scale (1–10) ≥8, and (vi) patient's appearance.

Peak RER is an objective index and has traditionally been considered the gold standard in CPET, but the optimal peak RER cut-point is still debated in cardiovascular disease patients, especially in HFrEF ones. Conventionally, a peak RER >1 is believed as a marker of symptom-limited CPET capacity in HFrEF, and this limit is usually tracked. According to recent guidelines,[5] a maximal CPET is defined as one with a RER >1.05 and achievement of an anaerobic threshold on optimal pharmacological therapy (class I, level of evidence B). However, not all HFrEF patients are able to reach a high peak RER during symptom-limited CPET, and this has been attributed to muscular abnormalities (either morphological-structural or functional-metabolic), ventilatory abnormalities due to respiratory muscle fatigue, excessive cardiac dysfunction during exercise, side effects of medications, or to the occurrence of early fatigue of central origin.[108]

In HFrEF with low peak VO_2 (≤10 mL/kg/min), only those attaining a peak RER ≥1.15 have a truly unfavourable outcome.[109] Although submaximal peak VO_2 and respiratory parameters may offer prognostic information,[109] peak oxygen pulse and the occurrence of angina are related to events during follow-up when peak RER is <1.0, whereas peak VO_2 and VE/VCO_2 ratio are predictors when peak RER is ≥1.0.[110,111] On the contrary, peak VO_2 and the VE/VCO_2 slope seem to retain their significant prognostic value irrespective of peak RER in HFrEF patients.[112] Of note, as VE/VCO_2 slope can be calculated during submaximal exercise, it is an attractive parameter in those patients who are not able to complete maximal effort exercise testing.

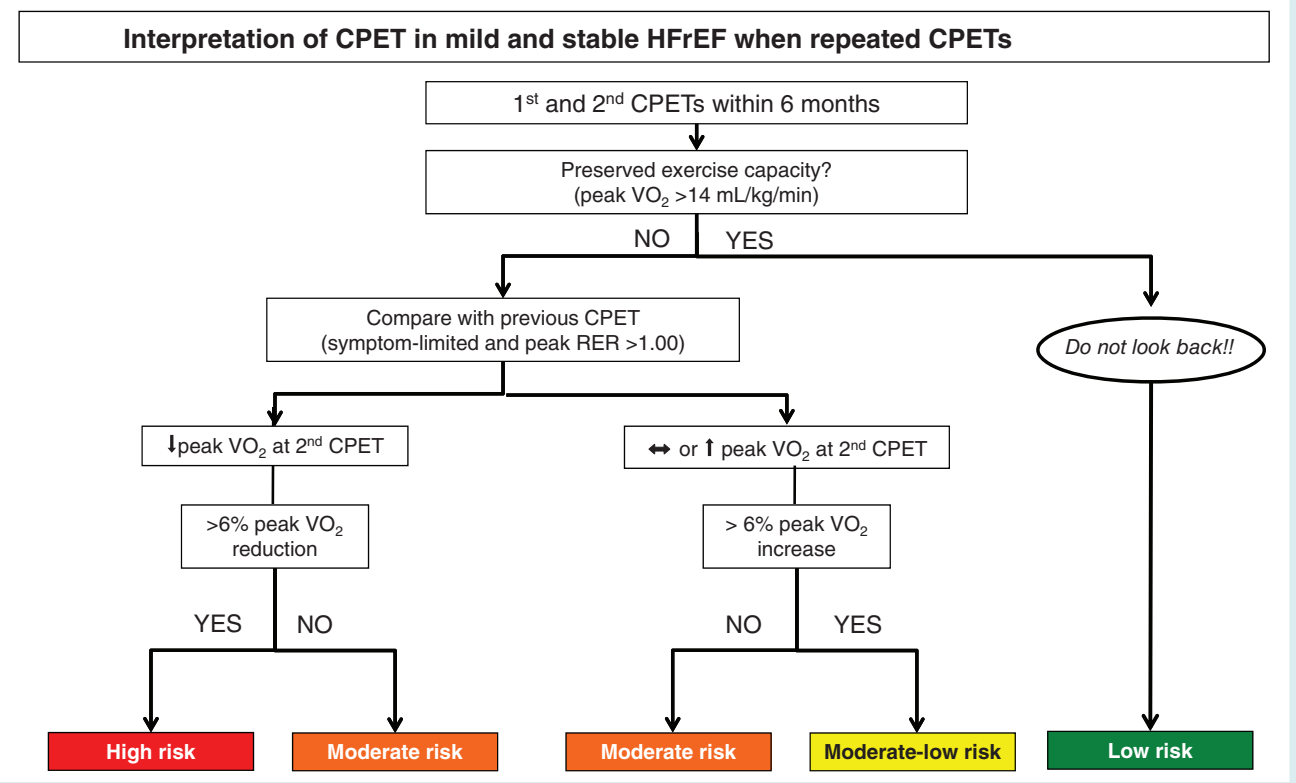

Figure 3 Interpretation of cardiopulmonary exercise testing (CPET) results in mild and stable heart failure with reduced ejection fraction (HFrEF) when test is repeated. If peak oxygen uptake (VO_2) is preserved (>14 mL/kg/min), we suggest to not 'look back'; however, we must admit that clinical deterioration can occur anytime (even without new warning signs or symptoms), therefore physicians should always be vigilant in case the patient needs renewed functional assessment. RER, respiratory exchange ratio.

Serial exercise testing

Some HFrEF patients need to repeat CPET over time, either to establish functional improvement due to additional treatments or to ascertain the stability of clinical status. Thus, some HFrEF patients are candidates for repeat CPET, and the comparison of serial tests is important.[113,114] Notably, all CPET parameters are subject to both physiological and technical variability, and the interpretation of serial CPETs can be difficult. The delta (difference between first and second CPET) peak VO_2 should be also expressed in percentage terms in order to avoid under and over-estimation:[114,115] i.e. a 2 mL/kg/min change in peak VO_2 might represent on one hand a fairly modest gain for patients with a peak VO_2 of 20 mL/kg/min (+10%), while, on the other, it is a worthwhile improvement for patients with a peak VO_2 of 10 mL/kg/min (+20%).

Several aspects should be pondered when repeated CPETs are used for risk assessment:

- the reproducibility of CPET measurements,
- the modality to express time-related CPET changes,
- the timing of repetition,
- how to judge risk if a CPET is completed with peak RER <1.00,
- how to consider background medical therapy.

In particular, the reproducibility of CPET parameters have been scantily reviewed,[116,117] and a coefficient of variability of 5.9% of test–retest reproducibility has been demonstrated in HFrEF in the Prospective Evaluation of Elastic Restraint to Lessen the Effects of Heart Failure (PEERLESS-HF) trial. Assuming that the 'noise' associated with peak VO_2 variability is ~6% in HFrEF patients with a peak VO_2 between 10 and 20 mL/kg/min, a delta peak VO_2 within this range provides little or no prognostic information. Irrespective of these issues, CPET repetition is recommended in high-risk HFrEF patients, i.e. those with low exercise capacity or who are clinically unstable.[118] Thus, a careful clinical assessment is needed, and attention should be paid to the reasons of 'new' functional capacity impairment, as CPET is precluded in patients with arrhythmias or low cardiac output (needing inotropic support, etc.).

To conclude, CPET repetition is suggested either when peak VO_2 is <14 mL/kg/min, or when a functional discrepancy (difference between what the patient reports and what the physician ascertains from interview) is evident in stable pharmacological conditions. If a new cardiovascular event (clinical instability) has occurred, clinical and pharmacological stabilization is needed before symptom-limited CEPT can be performed, similarly to what described before (see above, 'Early testing' paragraph).

Endpoints and follow-up duration

Endpoint selection is one of the most critical aspects in clinical management and risk stratification.[119] Hospitalization for worsening HF can be meaningful for patients, physicians, and decision makers, but it is often not based on objective criteria, and, in similar clinical scenarios, it can be affected by differences in healthcare organization. Furthermore, the occurrence of arrhythmias can be challenging because, if life-threatening, it might impact outcome. Nonetheless, not all episodes of ventricular tachycardia are life-threatening, and algorithms for the identification of ventricular tachycardia by ICD might differ. Finally, cardiovascular, non-cardiovascular deaths, HF hospitalizations, LVAD implantation and change in quality of life are weighted differently when calculating an outcome score. Recently, the use of composite endpoints has been recommended.[120]

Proposed flowcharts

Based on the above-mentioned data, three flowcharts describing the risk estimation by CPET in HF are here proposed, but waiting for validation.

As a first step, the physician should consider that exercise capacity is a modifiable predictor of major events, affected by several factors (such as demographic, disease-related conditions, co-morbidities, modality of execution of CPET), most of them still poorly investigated in large HF studies. These aspects are highlighted in the first flowchart (*Figure 1*). Although recent guidelines[5] recommend different CPET approaches for young patients (≤50 years), women and obese patients, unbiased data are not available and the assistance of alternative risk CPET parameters are weakly supported by evidence (class IIa, level of evidence B).

Thereafter, different flowcharts for the interpretation of CPET results in patients with HFrHF and HFpHF are proposed (*Figure 2*), based on scientific literature,[101,102,121,122] contemporary knowledge, and expert consensus.

Beta-blocker treatment is crucial since in the long term it reduces the risk in HFrEF,[4] and alters CPET response, due to the beneficial haemodynamic effects and exercise-associated haemodynamic improvement.[7] For any given peak VO_2 class, survival rate is better in β-blocker than in non-β-blocker patients.[7] Survival rates at 1–3 years were 94%–84% and 90%–76% in β-blocker patients and 91%–71% and 83%–63% in non-β-blocker patients for those with peak VO_2 > 10 mL/kg/min and 8–10 mL/kg/min, respectively:[122] except for patients with the lowest peak VO_2 (<8 mL/min/kg), HFrEF patients on β-blocker treatment show a better survival rate than age-comparable patients undergoing HT.[122] Recent published criteria for HT[5] have proposed slightly different cut-off values: without and with β-blocker, peak VO_2 of ≤14 mL/kg/min and ≤12 mL/kg/min are recommended, respectively, to guide listing to HT (class I, level of evidence B). Nonetheless, although risk cut-off values may differ,[5] the predictive role of symptom-limited CPET is still considered valuable.[7] Importantly, the International Society for Heart and Lung Transplantation guidelines[5] suggest also the use of a VE/VCO_2 slope of >35 as a determinant in listing for HT in the presence of a submaximal cardiopulmonary exercise test (RER <1.05); however, this indication is based only on experts' opinion (class IIb, level of evidence C).

HFpEF has been scanty studied, with contradictory findings:[101–103] an important prognostic power of $ppVO_2$ in this setting has been observed[103] and, consequently, a key role for this variable is here proposed (*Figure 2*).

EOV detection is a central step for risk assessment interpretation with CPET, and its occurrence, however defined, has been underscored because associated with poor outcome in HErEF, independently of beta-blocker therapy.[7] When EOV is present during symptom-limited CPET, HFrEF patients are more likely to have fatal events during follow-up.

Finally, an interpretation of repeated CPETs in mild and stable HFrEF is presented in *Figure 3*, taking into consideration the inherent variability in peak VO_2 as well as the inherent laboratory variability in multiple assessments over time (expressed as a percentage).

Conclusions

Today, risk stratification with CPET in cardiology is no longer restricted to HT candidates, but extends to all segments of the HF population. Accurate prognostic conclusions can only be derived after a full consideration of the available CPET-derived variables, including the characteristics of the cohort/patients screened, the specific timing of functional evaluation and the type/modality of CPET performed. Future research is warranted to address these topics.

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