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Review

How to perform and report a cardiopulmonary exercise test in patients with chronic heart failure

Piergiuseppe Agostoni [a,b,*], Daniel Dumitrescu [c]

[a] Centro Cardiologico Monzino, IRCCS, Milano, Italy
[b] Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milano, Milano, Italy
[c] Heart and Diabetes Center NRW, Department of Cardiology, Bad Oeynhausen, Germany

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ABSTRACT

In the present practice review, we will explain how to perform and interpret a cardiopulmonary exercise test (CPET) in heart failure patients. Specifically, we will explain why cycle ergometer should be preferred to treadmill, the type of protocol needed, and the ideal exercise duration. Thereafter, we will discuss how to interpret CPET findings and determine the parameters that should be included. We will focus specifically on: peak VO_2 (absolute value and a percentage of its predicted value), exercise duration, respiratory exchange ratio, peak work rate, heart rate, O_2 pulse, end-tidal carbon dioxide pressure ($PetCO_2$), $PetO_2$, and -if blood gas samples are obtained-dead space to tidal volume ratio. Moreover, we will discuss the physiological and clinical value of anaerobic threshold, respiratory compensation point, ventilation vs. VCO_2 and VO_2 vs. work relationships. Finally, attention will be dedicated to exercise-induced periodic breathing. We will also discuss when and why CPET should be integrated with other measurements in the so-called complex CPET. Specifically: a) when and how to use a complex non-invasive CPET, which integrates CPET measurements with non-invasive cardiac output determination, working muscle near-infrared spectroscopy, transthoracic echocardiography, thoracic ultrasound, and lung diffusion analysis; b) when and how to use a complex minimally invasive CPET, in which CPET is combined with esophageal balloon recordings or with serial arterial blood sampling for blood gas analysis; c) when and how to use a complex invasive CPET, which usually implies the presence of a Swan Ganz catheter in the pulmonary artery and an arterial line.

Cardiopulmonary exercise testing (CPET) is probably the most comprehensive whole-body testing technique we have, allowing a holistic evaluation of human body performance [1,2]. The latter is particularly important in chronic heart failure (HF) patients. Patients with HF independent of having a preserved or reduced left ventricular ejection fraction, show alterations in multiple body functions including the cardiovascular, respiratory, muscular, sympathetic and neuro-hormonal systems [3,4]. In this practice review we will present how to choose an appropriate exercise protocol and how to interpret and report the obtained results. For this purpose, the combined use of plots and numerical tables is mandatory [5,6]. We will also discuss why, when and how a complex or second level CPET should be performed in HF patients.

1. Performing the test

As soon as the indication for the exercise test is given, it must be clear that the exercise protocol must be set for specific diseases and for specific questions. For instance, CPET protocols for patients with primary lung diseases, such as COPD, are different from those required for HF patients [6,7]. For lung diseases, an endurance test with flow/volume curve may be more suitable to answer disease-specific questions, while in the latter case a maximal self-limited ramp exercise protocol should be performed [7,8]. Furthermore, Casaburi et al. clearly showed that an intensive rehab program for COPD patients provides clinical improvement which can be appreciated with an endurance test but not with a ramp protocol [9]. Similarly, Oga et al. [10] showed a ~2% increase of distance walked with the 6 min walking test after bronchodilator therapy, improvement at a ramp exercise test between 3 and 6% among all analyzed exercise parameters, and >20% of exercise time with an endurance test.

Another starting question is whether a treadmill or bike-ergometer should be preferred in the HF population. There are several obvious differences, which includes space, safety and costs - all of which are in favor of the bike-ergometer. The most important point in favor of a

* Corresponding author at: Centro Cardiologico Monzino, IRCCS, Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Via Parea, 4, 20138 Milan, Italy.
E-mail addresses: piergiuseppe.agostoni@unimi.it, piergiuseppe.agostoni@ccfm.it (P. Agostoni).

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bike-ergometer is the linearity in workload change. Using a treadmill, it is only possible to change slope and speed, but not the workload itself, so that it is almost impossible to generate a linear increase in workload. Exceptions are the Balke exercise protocol, however it is rarely used and its application to HF patients may be challenging [11,12]. Porszasz et al. have shown a mathematical approach to generate a linear increase in work rate by simultaneous adjustment of treadmill speed and grade [13]. However, this requires multiple manual adjustment during the exercise study. The advantage of having an objective measurement of workload, the VO_2/work-rate relationship can be visualized. This is easily possible with a ramp exercise protocol on the bike-ergometer. On the other hand, a relevant issue in favor of the treadmill use is the potentially limited ability and habit of a part of the subjects to pedal. While biking is common in Europe and Eastern Asia, this is not the case in North and South America where, indeed, a treadmill is most frequently used.

The exercise ramp protocol, regardless of the ergometer used, must allow an exercise duration of ~10 min with an accepted interval ranging from 8 to 12 min [14,15]. This means that the workload increase should be personalized for each patient, in order to achieve this test duration. This is more feasible with a ramp exercise protocol performed on a bike-ergometer, where load can be easily changed. This task is more difficult and less standardized with treadmill protocols.

From a physiological point of view, a protocol is considered a ramp when the load increases with an interval of 1 min or shorter. Although this may be difficult for severely compromised HF patients, a test duration of 10 min should be attempted, because shorter or longer efforts may provide different results [14,15]). Specifically, short (5 min) and long (15 min) exercise times with a ramp protocol influenced results in HF patients, with the notable exception of VO_2 at the anaerobic threshold and ventilation (VE)/VCO_2 slope which were both unaffected by the exercise protocol applied (Table 1). In a very limited number of cases a step protocol is needed, with a minimum step duration of 3, but better 4, minutes. The step protocol is suggested when it is necessary to perform specific measurements, such as VO_2 kinetics by tau (time constant = 63% of maximal response), mean response time, R1 or t1/2 calculations, or as steady state measurements of cardiac output or Near Infra-Red Spectroscopy (NIRS) data [16–19].

1.1. Reporting the test

Data must be recorded breath by breath. For interpretation, data is usually averaged by fixed time intervals (usually 20–30 s), or by a rolling average of several breaths (usually 5–8 breaths). This allows an improved graphical display by smooth data curves. However, for specific questions in HF, it is mandatory to analyze the raw breath-by-breath data. This is needed for the assessment of respiratory gas kinetics at the beginning of a step exercise protocol and for the calculation of tau, mean response time and T1/2, [16,20]. Additionally, the identification of exercise induced periodic breathing, a clinically relevant finding associated with poor prognosis, is easier with unaveraged data. A standardized set of demographic information should be reported at the beginning of a CPET report, including name, gender, ethnic group, age, height and weight of the tested subject. Moreover, the type of ergometer, the protocol and the formula used for calculation of predicted VO_2 values must also be reported. Several formulas are available for predicted peak VO_2 calculation [21]. Prediction equations are needed to allow comparison of subjects of different gender, ethnicity, age, height and weight. It is well known that in overweight and underweight subjects, normalization for weight is mandatory [22] (Table 2). Consideration of body weight is included in most prediction formulas. At present, the prediction formulas published by Hansen and Wasserman [22], as well as the "SHIP" (study of healthy individuals in Pomerania) [23] represent the largest analyzed cohorts of healthy individuals.

Table 1
Average ± standard deviation of cardiopulmonary exercise testing parameters in 90 HF patients exercising with a fast, intermediate and prolonged exercise protocol.[a]
Reproduced from Agostoni P, Bianchi M, Moraschi A, Palermo P, Cattadori G, La Gioia R, et al. Work-rate affects cardiopulmonary exercise test results in heart failure. European journal of heart failure. (2005);7:498–504.

	5 min	10 min	15 min
Peak heart rate (beats/min)	128 ± 24*	137 ± 24	137 ± 25
Peak VO_2 (ml/min/kg)	16.9 ± 4.3*	18.0 ± 4.4	18.5 ± 5.4
Peak work-rate (W)	116 ± 44	114 ± 40	105 ± 42*
Peak O_2p (ml/beat)	10.1 ± 3.3	10.1 ± 3.3	10.1 ± 3.2
Ventilation (l/min)	47 ± 12*	54 ± 13	55 ± 16
Tidal volume (l)	1.6 ± 0.4	1.7 ± 0.4	1.7 ± 0.4
Respiratory rate (breaths × min)	30 ± 6*	33 ± 7	34 ± 7
VE/VCO_2 slope	32.9 ± 6.7	32.7 ± 6.1	32.7 ± 6.3
ΔVO_2/Δwork-rate (ml/min/W)	8.2 ± 1.1*	8.9 ± 1.5	9.5 ± 1.1*
$PetO_2$ (mm Hg) at peak exercise	115 ± 11	117 ± 11	118 ± 6
$PetCO_2$ (mm Hg) at peak exercise	35 ± 6*	33 ± 6	33 ± 5
VO_2 at anaerobic threshold (ml/min/kg)[b]	12.3 ± 4.1	12.3 ± 5.5	12.4 ± 3.9

[a] HF = heart failure; O_2p = O_2 pulse; et = end-tidal.
[b] n = 85 patients.
* p < 0.001 vs. 10-min test.

2. Interpreting the test

VO_2 at peak exercise is the most important parameter derived from a CPET [24]. It can be reported as VO_2 max or peak VO_2. Peak VO_2 describes the highest achieved VO_2 value during an exercise test (averaged over a complete 20–30 second period). Notably, this can be observed immediately after the end of active pedaling or running in patients with severe exercise limitation. The definition of VO_2 max, additionally, implies the inability of a further increase of VO_2 beyond the documented peak value, despite higher workload. Thus, a true VO_2 max measurement can only be seen in athletes or well-fit individuals and not in patients, in whom it is only possible to observe peak VO_2. For this reason, peak exercise VO_2 must be labeled peak VO_2 and not VO_2 max in HF patients. Peak VO_2 can be reported as an absolute value, i.e. in ml/min or ml/min/kg, or as a percentage of predicted. It is important to consider that the absolute peak VO_2 value is ~10% higher on a treadmill, compared to a cycle-ergometer.

Other peak exercise measurements of special interest in HF include exercise duration and subjective degree of exhaustion, respiratory exchange ratio (RER), peak work rate heart rate, O_2 pulse, $PetCO_2$, $PetO_2$, and - if blood gas samples are obtained - the fraction of dead space to tidal volume (VD/VT). Exercise duration and subjective exhaustion must be reported to confirm that an appropriate protocol was applied. RER, calculated as the ratio between VCO_2 and VO_2, is important as an indicator whether a maximal or near maximal exercise test has been performed. Exceeding an RER value of 1.05 or 1.1 indicates a good effort [25]. However, up to 50% of HF patients are not able to reach this threshold [26]. Although RER may be regarded as a time-delayed mirror image of the respiratory quotient (RQ) which is the ratio between O_2 uptake and CO_2 production at the mitochondrial level, RER and RQ are only equivalent during true steady-state conditions. In all other conditions, RER is additionally affected by CO_2 stores/buffering mechanisms, so that RER does not reflect true RQ in non-steady-state. Therefore, an RER value at peak exercise of <1.1 does not necessarily indicate that

Table 2
Correction of peak VO_2 for overweight subjects.
Data derived from Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. The American review of respiratory disease. (1984);129:S49–55.

Real weight % of predicted body weight	Correction VO_2 max%
77–99	101
100–109	91
110–119	85
120–129	77
130–160	76

Predicted body weight formula: =[0.79 × height (cm)] − 60.7.

the effort was submaximal. In this case, the exercise study should be checked for other signs of limitation, such as a ventilatory limitation pattern, a significant reduction of ventilatory inefficiency, or a low increase of work rate relative to VO_2 [27]. Peak work rate reflects the external work performed by the patient. It may be different from exercise tolerance based on peak VO_2, influenced by other conditions such as respiratory muscle work and respiratory efficiency, CO_2 set point and patient's skill. Peak heart rate must also be reported, albeit several drugs that directly affect heart rate are used in HF. It is important to keep in mind that HF patients who do not reach their predicted maximal heart rate may have given a maximal effort. On the other hand, an exercise test should not be stopped only because of reaching the predicted maximal heart rate. This is particularly relevant in patients with concomitant atrial fibrillation, who have a different heart rate increase pattern during exercise than patients in sinus rhythm, also influencing VO_2 at the anaerobic threshold (AT) [28,29]. Instead of looking at peak heart rate, chronotropic incompetence during exercise should be assessed considering the heart rate reserve, based on the heart rate increase during exercise [30,31].

The oxygen pulse (O_2pulse) is an important pathophysiological concept, reflecting efficiency of circulation during exercise. At any given timepoint during a test, O_2pulse can be calculated, dividing VO_2 by heart rate: $O_2\text{pulse} = VO_2 \div HR$. The O_2 pulse indicates how much oxygen is taken up per heartbeat. Furthermore, O_2 pulse can be calculated from the modified Fick equation: VO_2 = Heart rate x stroke volume x arteriovenous difference of oxygen content ($C(a\text{-}v)O_2$), or $VO_2 \div$ Heart rate = stroke volume $\times$ ($C(a - v)O_2$). This means that the O_2 pulse is not only an index of peak exercise stroke volume, which is frequently been proposed. It always reflects the product of stroke volume, blood flow distribution in the peripheral muscle and muscle oxygen extraction. Accordingly, the equivalence O_2 pulse = stroke volume should be used with extreme caution.

Besides peak exercise, two points of special interest must be considered in a ramp exercise test: the anaerobic threshold (AT, also referred to as VT_1 in the German literature [32]) and the respiratory compensation point (RCP, also referred to as VT_2 in the German literature [32]). The AT (VT_1) becomes visible when excess CO_2 from anaerobic metabolism in the peripheral muscles is eliminated by the lungs. AT (VT_1) is best determined using a VO_2 vs. VCO_2 plot with an equal scale on the VCO_2 and VO_2 axis (V-slope method, [39]. The AT (VT_1) is defined as the first VO_2 value on the VO_2 vs. VCO_2 plot after the slope of the VO_2 vs. VCO_2 curve rises above 1.0. Ventilatory equivalents (VE/VO_2, VE/VCO_2) and end-tidal partial pressures of O_2 and CO_2 ($PetO_2$, $PetCO_2$) may confirm the timepoint of the AT (VT_1) [33], as both ventilatory equivalents (VE/VO_2 and VE/VCO_2) and $PetO_2/PetCO_2$ behaviors represent the ventilatory response of anaerobic metabolism generated at the muscular level. It should be underlined that a dissociative behavior of muscular anaerobic metabolism and its ventilatory response has been described [34]. Finally, albeit anaerobic metabolism has been reached, in a part of HF patients, the AT (VT_1) cannot be identified regardless of the method used [28,35]. This happens in ~10% of HF patients, more specifically in patients with severe HF and is likely due to inhomogeneity of muscle O_2 delivery and muscle function [35]. The lack of AT (VT_1) identification has a strong prognostic significance suggesting poor survival [35,36].

RCP (VT_2) is identified as the end of the buffering capacity of exercise-induced acidosis. This implies an excessive increase in VE, so that VE/VCO_2 increases and $PetCO_2$ drops. Between AT (VT_1) and RCP (VT_2), the "isocapnic buffering period" takes place, where it is still possible to maintain a constant blood pH by buffering excess H^+ ions from anaerobic metabolism. Its length depends on the amount of CO_2 available for buffer acidosis. For example, at high altitude, where VE is increased driven by hypoxemia and $PaCO_2$ is low, the isocapnic buffering period disappears [37]. Similarly, pre-exercise hyperventilation may influence the amount of stored CO_2 available for acidosis buffering. In any case, at sea level, in HF patients, the amount of VO_2 increase during the isocapnic buffering period is associated with exercise performance and prognosis [38]. Notably, in chronic HF patients the absence of AT, the presence of AT but not of RCP and the presence of both AT and RCP is associated with a progressive improvement in patients survival [36]. The isocapnic buffering period is the exercise time frame when chemoreflex activity is best visualized [39]. It is therefore important to look at $PetCO_2$ during the isocapnic buffering period, and it may be used to choose the most appropriate β-blocking agent [39]. Indeed, the presence of a β_2 blocking activity is associated with a greater reduction of chemoreflex activity, compared to selective β_1 blocking agents [40]. For this purpose, it may be useful to build and analyze the VE vs. $PetCO_2$ plot. In Fig. 1 the changes in VE and $PetCO_2$ observed during a progressively increasing workload exercise test in a HF patient, in a normal subject and in an athlete (long distance runner) are reported. VE progressively increases in all cases. In all cases, $PetCO_2$ increases at the beginning of exercise up to AT, then it remains stable, and it decreases above RCP. The vertical part of the $PetCO_2$ corresponds to the isocapnic buffering period. The value of $PetCO_2$ during the isocapnic buffering period mirrors the chemoreflex activity, high in the HF patient, intermediate in the normal subject and low in the athlete.

Regardless of the causes of hyperventilation in HF the consequent reduction in $PaCO_2$ likely induces during exercise cerebral vasoconstriction as well as vasoconstriction of carotid bodies arteries. The latter, on its turn, induces a further increase in total peripheral resistance and contributes to exercise intolerance.

3. Specific aspects with relevance for clinical practice in heart failure

It is important to consider that in most HF studies, discriminative cut-off values of peak VO_2 are reported as ml/min/kg – starting from the original Weber and Janicky HF severity classification, published in the 1980s, which describes 4 classes based on peak VO_2 reported as ml/min/kg [41,42]. At that time, CPETs were mostly performed for HF severity grading in heart transplant candidates. To date, heart transplant guidelines still report peak VO_2 in ml/min/kg, specifically threshold values of 12 ml/min/kg in patients treated with β-blockers, and of 14 ml/min/kg in those not treated with β-blockers [43,44]. Indeed, in patients with severe HF, the presence of β-blockers influences the prognosis in patients with the same peak VO_2 (Fig. 2) [45]. In the general HF population, however, peak VO_2% of predicted has been suggested several times since the late 90s as more reliable than absolute values in HF patients [46–48]. Therefore the % of predicted value must be reported possibly combined with the absolute value.

In HF patients measurements of VE, respiratory rate and tidal volume are significant. Indeed, from a pathophysiological point of view, HF is characterized by a lung restrictive syndrome [49,50] so that exercise-induced tidal volume increase is hampered but modifiable by reduction of excessive lung fluids [51–54]. Moreover an expiratory flow limitation is frequently observed in HF patients [55,56]. However, the most relevant ventilatory parameter is undoubtedly the VE vs. VCO_2 slope, which has a pivotal prognostic role in HF either as a single value or in combination with other parameters [24,48,57,58]. The VE vs. VCO_2 slope is usually measured from 2 min after the beginning of loaded pedaling, to avoid erratic breathing that is sometimes observed at the onset of exercise, up to the RCP. During this period of time the VE vs. VCO_2 slope is linear. Some authors measure the VE vs. VCO_2 relationship during the entire exercise period [59], however, albeit differences are small this method is physiologically ambiguous: beyond the RCP, VE is driven by H^+, an additional stimulus independent from VCO_2, which is the driving force of VE in the first and second part of a ramp protocol exercise, respectively.

From a pathophysiological point of view, an elevated VE/VCO_2 slope is suggestive of hemodynamic abnormalities in the pulmonary circulation in HF patients [60]. A steep increase in the VE vs. VCO_2 slope at the end of exercise implies that the VE increase is mainly due to dead space increase.

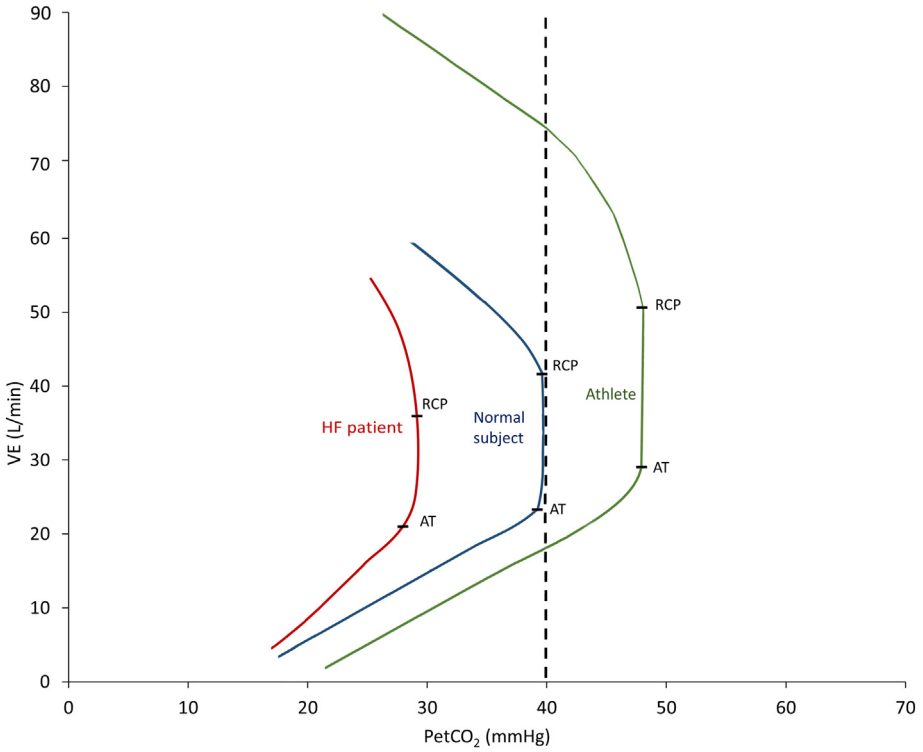

Fig. 1. Example of ventilation (VE) vs. end tidal carbon dioxide pressure ($PetCO_2$) plot in one HF patient (red line), one normal subject (blue line) and one athlete (green line). $PetCO_2$ during the isocapnic buffering period is shifted towards the left in the HF patient, and towards the right in the athlete. The $PetCO_2$ value during the isocapnic buffering period is a function of chemoreflex response and in HF is among the criteria suggested to choose the most physiologically fitting β-blocker for a specific HF patient.

The analysis of the VE vs. VCO_2 relationship must also consider the Y-axis intercept, i.e. the extrapolation of VE at $VCO_2 = 0$. In HF patients, an elevated y-intercept suggests the co-existence of COPD while a negative value may indicate the presence of pulmonary hypertension [61].

Another important pattern of pathophysiological interest is the VO_2 vs. Work relationship observed during the entire exercise. This relationship shows how well O_2 is delivered to the working muscle. Notably, it increases throughout the entire incremental exercise period, as aerobic ATP does. Its normal values are between 8 and 11 ml/min/W. A reduction of the VO_2 vs. Work relationship implies a low O_2 delivery. During exercise, the slope of this relationship can be suddenly reduced due to cardiac ischemia or mitral insufficiency [62]. An increase of the VO_2 vs. Work relationship has been observed during exercise in 50% of cases in whom exercise induced periodic breathing ceased during effort [63], suggesting a reduction in the respiratory muscle work and concomitant increase of O_2 available for working muscles.

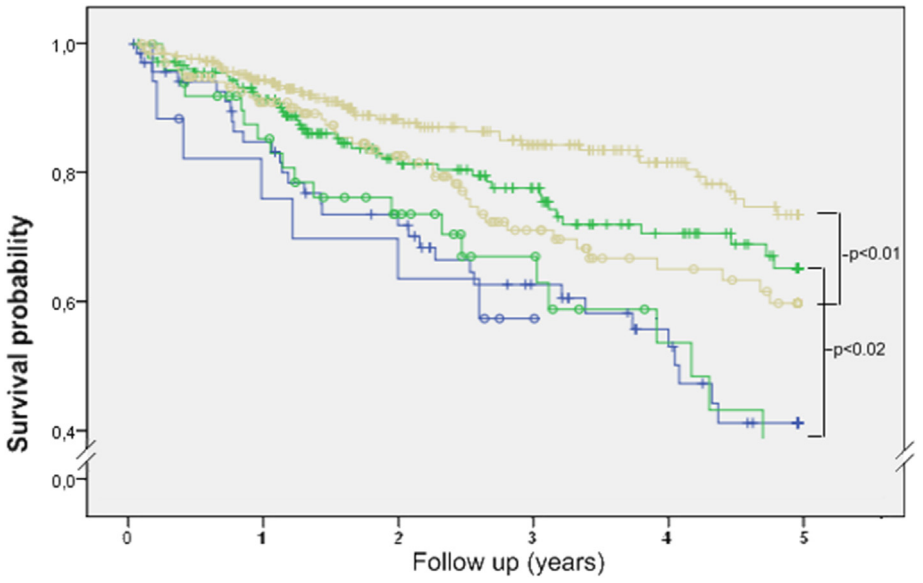

Fig. 2. Prognosis of severe HF patients treated (+) and not treated (o) with β-blockers according to peak VO_2. In yellow: peak VO_2 14–10 ml/min/kg (12–10 ml/min/kg for patients with β-blocker treatment). In green: peak VO_2 10–8 ml/min/kg. In blue: peak VO_2 < 8 ml/min/kg. β-Blocker treatment influences survival in all groups except those with peak VO_2 < 8 ml/min/kg. Data from Cattadori G, Agostoni P, Corra U, et al. Severe HF prognosis evaluation for transplant selection in the era of beta-blockers: role of peak oxygen consumption. International journal of cardiology. 2013;168:5078–5081. Ref. [45].

Exercise induced periodic breathing, known also as exercise oscillatory ventilation, is an amazing observation frequently seen in patients with severe HF in whom it bears a strong negative prognostic role [24,64–68]. Several criteria for periodic breathing identification have been proposed [69]. At present, two types of periodic breathing are recognized: one lasts throughout the entire exercise period, and one disappears during exercise. The pathophysiological mechanisms generating exercise-induced periodic breathing are still incompletely understood, albeit certainly low cardiac output, increase O_2 transit time and imbalance of the chemoreflex response play a role [17,69].

Accordingly, exercise limitation in HF has several causes. CPET is able to analyze numerous parameters looking to several aspects of exercise limitation. In Table 3 the major causes of the underlying meaning for each variable is reported.

Several other CPET derived parameters have been described including OUES, $PeCO_2$ (mean expiratory CO_2 pressure) [70] and VO_2 increase during the isocapnic buffering period, but, in our opinion, none of them have a strong physiological impactor have, or are likely to have, a widespread use in the future. Therefore, they are outside the scope of the present report [71]. Indeed, CPET reading is cumbersome and already limited to experts, so that further analysis is important for a physiological stand-point, but not useful, if not deleterious, to CPET widespread application in the clinical setting.

3.1. Complex CPET

Several other diagnostic tools may be performed in combination with CPET, aimed at adding clinical and pathophysiological information. These may be grouped in 3 categories: non-invasive complex CPET, minimally invasive complex CPET and invasive complex CPET. We will briefly report the added value to standard CPET of these measurements.

a) *Non-invasive complex CPET*

During a non-invasive complex CPET the following techniques may be added to CPET: non-invasive cardiac output determination, NIRS, transthoracic echocardiography, thoracic ultrasound and lung diffusion analysis. Several techniques for non-invasive cardiac output estimation or determination have been proposed [72]. At present, two methods are the best established during exercise: the Physioflow technique and the inert gases rebreathing technique. The former is based on thoracic bio impedance measurement, and the latter uses one blood-soluble and one blood-insoluble inert gas. The concentration of gas soluble in blood decreases during rebreathing with a rate proportional to pulmonary blood flow, while the insoluble gas is used to determine lung volume [17,73,74]. Both methods allow splitting VO_2 in its two components cardiac output and artery-venous O_2 differences, according to the Fick principle. Accordingly, it is possible to define the cause of VO_2 impairment separating the role of the heart from that of the periphery [75,76]. In addition, these techniques have been applied in HF to assess the efficacy of rehabilitation and LVAD regulation [17,77]. NIRS allows a quantitative analysis of oxygenated and de-oxygenated hemoglobin [78]. It is a promising technique to better understand the role of O_2 delivery to the working muscle and its utilization in the working muscle [17,79]. Echocardiography is frequently applied in combination with CPET. It allows analyzing exercise-induced changes in pulmonary pressure, mitral insufficiency and left ventricular performance. Finally, alveolar capillary membrane diffusion analysis at the beginning and at peak exercise has been utilized to assess the pathophysiological role of lung fluid increase during exercise with regard to alveolar gas exchange [80]. Thoracic ultrasound adds similar clinical information and can be easily performed during exercise. It allows an analysis of lung fluid changes during exercise [81].

Table 3
Physiological interpretation of altered CPET variables in HF patients.

	Alteration	Meaning of specific CPET variables in HF
Peak VO_2	↓	Overall exercise performance evaluation
VO_2 AT	↓	Overall evaluation/↓Cardiac Output
O_2 pulse	↓	↓Cardiac output/↓O_2 delivery/↓O_2 extraction
VE/VCO_2 slope	↑	Ventilation-perfusion mismatch/increase sympathetic tone
VO_2/work	↓	↓ Cardiac output/↓O_2 delivery
Periodic breathing	Presence	↓ Cardiac output/altered chemoreflex response
$PetCO_2$	↓	↑ Chemoreflex response
	↑	Concomitant lung disease
RER	↓	Not maximal exercise except in severe HF
VE/VCO_2 relation	↑	Concomitant lung disease
Y intercept	↓	Dead space increase during exercise

Peak VO_2 = oxygen uptake at peak exercise; VO_2 AT = oxygen consumption at anaerobic threshold; VE/VCO_2 slope = ventilatory efficiency (ventilation/CO_2 production); $PetCO_2$ = End-tidal CO_2 pressure; RER = respiratory exchange ratio.

b) *Minimally invasive complex CPET*

Minimally invasive complex CPET may also be utilized in HF patients. CPET is either combined with esophageal balloon recordings, or serial arterial blood sampling for blood gas analysis. Esophageal balloon recordings have been used mainly in a research setting and have allowed to demonstrate the presence of dynamic compliance reduction and its effects on cardiac function in HF [55,82]. Serial arterial blood sampling has a defined clinical role in assessing VD/VT during exercise, which can only be reliably measured with direct determination of $PaCO_2$ [83], and shows ventilatory mismatch. Indeed, Wasserman et al. showed a progressive increase in $P(a\text{-}et)CO_2$ during exercise in HF which is suggestive of poorly ventilated lung area in HF [49]. Specifically the increase in VD/VT and $P(a\text{-}et)CO_2$ in the absence of hypoxemia in patients with severe HF suggests a high mismatch of the ventilation/perfusion relationship.

c) *Invasive complex CPET*

Invasive complex CPET implies the presence of a Swan Ganz catheter in the pulmonary artery and an arterial line [72,84,85]. A few authors also added a femoral vein catheter to analyze the muscular artery – venous O_2 differences [86]. A Swan-Ganz catheter inserted in the pulmonary artery allows direct measurement of pulmonary artery and wedge pressure and direct cardiac output either by Fick principle or thermodilution both of which are of major importance in assessing HF severity and the presence of inappropriate pulmonary vascular pressure increase. The most physiologically correct way to do these measurements is by means of a cycle ergometer with the patients sitting on the bike seat. However, to date, the mode of exercise for invasive CPET is not well standardized. Besides an obvious research interest, the true clinical utility of invasive CPET is still uncertain with regard cost, availability and safety issues.

In conclusion, CPET is the most comprehensive technique which allows a holistic approach to HF. The CPET protocol must be adapted to each specific HF patient to obtain the most reliable and useful information. CPET interpretation is complex as is the pathophysiology of HF. However, a correct use of CPET implies simple questions and simple answers. A widespread use of CPET for clinical practice is feasible and reliable in the evaluation of HF patients.

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