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POSITION STATEMENT

EACPR/AHA Joint Scientific Statement

Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations

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The disclosure forms of the authors and reviewers are available in the Supplementary material at *European Heart Journal* online.

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Abbreviations

BP	blood pressure
CHD	coronary heart disease
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CPX	cardiopulmonary exercise testing
CRF	cardiorespiratory fitness
CV	cardiovascular
ECG	electrocardiogram
EIB	exercise-induced bronchospasm
EOV	exercise oscillatory ventilation
ET	exercise testing
FEV_1	forced expiratory volume in 1 s
HCM	hypertrophic cardiomyopathy
HF	heart failure
HF-PEF	heart failure-preserved ejection fraction
HR	heart rate
HRR	heart rate recovery
ILD	interstitial lung disease
LVH	left ventricular hypertrophy
MVV	maximal voluntary ventilation
O_2	oxygen
PAH	pulmonary arterial hypertension
PEF	peak expiratory flow
$P_{ET}CO_2$	partial pressure of end-tidal carbon dioxide
PH	pulmonary hypertension
Q	cardiac output
RER	respiratory exchange ratio
SpO_2	pulse oximetry
US	United States
VE	minute ventilation
V_{CO_2}	carbon dioxide production
V_{O_2}	oxygen consumption
VT	ventilatory threshold

Introduction

From an evidence-based perspective, cardiopulmonary exercise testing (CPX) is a well-supported assessment technique in both the United States (US) and Europe. The combination of standard exercise testing (ET) [i.e. progressive exercise provocation in association with serial electrocardiograms (ECGs), haemodynamics, oxygen saturation, and subjective symptoms] and measurement of ventilatory gas exchange amounts to a superior method to: (i) accurately quantify cardiorespiratory fitness (CRF), (ii) delineate the physiologic system(s) underlying exercise responses, which can be applied as a means to identify the exercise-limiting pathophysiological mechanism(s) and/or performance differences, and (iii) formulate function-based prognostic stratification. Cardiopulmonary ET certainly carries an additional cost as well as competency requirements and is not an essential component of evaluation in all patient populations. However, there are several conditions of confirmed, suspected, or unknown aetiology where the data gained from this form of ET is highly valuable in terms of clinical decision making.[1]

Several CPX statements have been published by well-respected organizations in both the US and Europe.[1–5] Despite these prominent reports and the plethora of pertinent medical literature which they feature, underutilization of CPX persists. This discrepancy is at least partly attributable to the fact that the currently available CPX consensus statements are inherently complex and fail to convey succinct, clinically centred strategies to utilize CPX indices effectively. Likewise, current CPX software packages generate an overwhelming abundance of data, which to most clinicians are incomprehensible and abstract.

Ironically, in contrast to the protracted scientific statements and dense CPX data outputs, the list of CPX variables that have proven clinical application is concise and uncomplicated. Therefore, the goal of this writing group is to present an approach of CPX in a way that assists in making meaningful decisions regarding a patient's care. Experts from the European Association of Cardiovascular Prevention and Rehabilitation and American Heart Association have joined in this effort to distil easy-to-follow guidance on CPX interpretation based on current scientific evidence. This document also provides a series of forms that are designed to highlight the utility of CPX in clinical decision-making. Not only will this improve patient management, it will also catalyze uniform and unambiguous data interpretation across laboratories on an international level.

The primary target audience of this position paper is clinicians who have limited orientation with CPX but whose caregiving would be enhanced by familiarity and application of this assessment. The ultimate goal is to increase awareness of the value of CPX and to increase the number of healthcare professionals who are able to perform clinically meaningful CPX interpretation. Moreover, this document will hopefully lead to an increase in appropriate patient referrals to CPX with enhanced efficiencies in patient management. For more detailed information on CPX, including procedures for patient preparation, equipment calibration, and conducting the test, readers are encouraged to review other publications that address these and other topics in great detail.[1–5]

What is cardiopulmonary exercise testing?

Despite advances in technologies related to diagnostic testing and the popularity of imaging techniques, the assessment of exercise responses provides critical enhancement of the evaluation of patients with or suspected of having cardiovascular (CV) or pulmonary disease.[6] The measurement of CRF from ET has many clinical applications, including diagnosis, evaluation of therapy, risk stratification, and to guide physical activity. While exercise tolerance is commonly estimated from treadmill or bicycle cycle ergometer work rate, CPX is a specialized subtype of ET that provides a more accurate and objective measure of CRF. CPX relies on the measurement of ventilatory gases during exercise, i.e. a non-invasive procedure that involves the acquisition of expired ventilation and concentrations of oxygen (O_2) and carbon dioxide (CO_2)

during progressive exercise. Admittedly, there are potential 'patient difficulties' associated with CPX (trepidation with the testing itself, mouthpiece/nose clip/mask difficulties, perception of limits in 'air' availability, etc.). However, when added to standard ET, the direct non-invasive measurement of ventilation and expired gases permits the most accurate and reproducible quantification of CRF, a grading of the aetiology and severity of impairment, and an objective assessment of the response to an intervention.[7,8] Moreover, over the last two decades, a particularly large volume of research has been directed toward the utility of CPX as a prognostic tool; these studies have established CPX as a scientifically sound and therefore clinically valuable method for accurately estimating prognosis in various disease states.[1,9,10] As will be described in this document, studies performed on the clinical applications of CPX have had an important influence on the functional assessment of patients with confirmed/suspected CV and pulmonary disease as well as those with certain confirmed/suspected musculoskeletal disorders.

Although still underutilized, CPX has gained popularity not only due to the recognition of its clear value in the functional assessment of patients with CV, pulmonary, and musculoskeletal disease/disorders, but also because of technological advances (e.g. rapid response analysers and computer-assisted data processing) which have made this modality easier to use. Once largely under the domain of the physiologist or specialized centre, CPX currently has the potential to be used for a wide spectrum of clinical applications. The basic CPX responses, O_2 consumption (V_{O_2}), minute ventilation (VE), and CO_2 production (V_{CO_2}) are now easily obtainable in the time-down spreadsheet format from most systems, providing a platform for straightforward data processing and interpretation. While standard ET has long been considered the gatekeeper to more expensive and invasive procedures (e.g. angiography, bypass surgery, transplantation, other medical management decisions), gas exchange measurements during exercise have been demonstrated to enhance the decision-making process. CPX responses have been demonstrated to be valuable in supplementing other clinical information to optimize risk stratification for cardiac transplantation listing, medical device therapy (e.g. implantable cardioverter-defibrillator and cardiac resynchronization therapy), consideration for lung resection or lung transplantation, and for a variety of pre-surgical evaluations.[1,7,9–13] Because markers of ventilatory efficiency have emerged as particularly powerful prognostic markers, risk stratification paradigms that include these indices have also been proposed in recent years.[1,13]

Defining key cardiopulmonary exercise testing variables[14–23]

The volume of data automatically generated by the software packages of CPX systems can be somewhat daunting to clinicians who do not have extensive experience with this form of ET. Moreover, the clinical significance of many of these variables, numerically and/or graphically depicted, has not been thoroughly vetted through original research. In contrast, the list of variables most pertinent in current clinical practice, and which are well substantiated by original research, is relatively concise. Key CPX variables, derived from both ventilatory expired gas analysis data and standard ET monitoring, are listed in *Table 1*. The intent of this table is to identify the key CPX variables and to provide only succinct descriptions or their significance and normal values/responses; more detailed accounts are provided elsewhere and the reader is encouraged to review these documents for additional details.[1–4,24] Of particular note, aerobic capacity is defined as peak V_{O_2} as opposed to maximal V_{O_2} in this document as the former designation is most often used in patient populations with suspected/confirmed pathophysiological processes. All of the variables listed in *Table 1* are included in the one-page, universal CPX reporting form (see Appendix 1). While some of these variables warrant assessment in all patients undergoing CPX, such as peak V_{O_2} and the peak respiratory exchange ratio (RER), others, such as the VE/V_{CO_2} slope and exercise oscillatory ventilation (EOV), are condition specific. A more refined identification of condition-specific CPX variables is described in subsequent sections and their respective appendices. The writing group hopes that this approach improves the ease by which the most pertinent data are identified and utilized by clinicians performing and interpreting CPX. Moreover, the majority of these variables are automatically included in reporting forms generated by current CPX system software packages.

Depending on system configuration, standard ET measures, such as haemodynamics and heart rate (HR), will either be reported alongside ventilatory expired gas analysis data or reported separately. In either situation, the majority of essential data is readily obtained. O_2 pulse and (change in V_{O_2}/change in Watt $(\Delta V_{O_2}/\Delta W)$ plots are often generated by customary CPX software systems. If this is not the case, the plots can be easily generated using the exercise data reported in time-down spreadsheet format. Examples of normal and abnormal O_2 pulse and $\Delta V_{O_2}/\Delta W$ plots are illustrated in *Figure 1*.

While VE data are graphically depicted, determination of EOV must be performed manually at this time. Given the importance of determining EOV in heart failure (HF), the writing group anticipates that the presence or absence of this abnormality, according to universally adopted criteria, will be automatically quantified by future CPX system software packages. The most frequently used criteria currently to define EOV are listed in *Table 1*.[16] There is initial evidence to indicate that this set of EOV criteria provides more robust prognostic insight compared with other methods.[25] For present clinical applications, the writing group recommends rest and exercise VE data be graphically depicted using 10-s averaged samples. This averaging interval allows for the removal of breath-by-breath signal noise while preventing excessive data smoothing and loss of the physiological phenomena that is brought about by averaging over longer intervals (i.e. data used for graphic illustration listed as ≥30 s averaging). A normal ventilatory pattern is contrasted to EOV in *Figure 2*.

Lastly, when the additional assessment of non-invasive cardiac output (*Q*) is performed (e.g. CPX for suspected mitochondrial myopathy), the $\Delta Q/\Delta V_{O_2}$ slope can be easily determined from the ET data in time-down spreadsheet format.

Table 1 Identification and defining normal responses for key cardiopulmonary exercise testing variables

CPX variable	**Description/significance**	**Normal value/response**
Peak V_{O_2} ($mL\ O_2 \bullet kg^{-1} \bullet min^{-1}$)	• Highest O_2 uptake obtained during exercise • Commonly designated as 'peak' value in patient populations described in this document • Expressed as a 10–60 s averaged value depending on the ET protocol (i.e. shorter averaging interval for protocols with shorter stages and longer averaging interval for protocols with longer stages)[1] • Response influenced by central (CV and/or pulmonary) and peripheral (skeletal muscle) function • Broadly reflects disease severity in a number of patient populations including HF, HCM, PAH secondary PH, COPD, ILD • Universal prognostic marker	• Wide range influenced by age and sex: ~80–15 $mL\ O_2 \bullet kg^{-1} \bullet min^{-1}$ in young elite athlete and apparently healthy 80-year-old female, respectively;[11] normal age-related decline related to decrease in central and peripheral performance across the lifespan; normal sex-related differences largely influenced by difference in maximal cardiac output • Reporting peak V_{O_2} as a per cent-predicted value using equations provided in *Table 2* recommended to account for age and sex differences. • Per cent-predicted values should be $\geq 100\%$
V_{O_2} at VT ($mL\ O_2 \bullet kg^{-1} \bullet min^{-1}$)	• Submaximal V_{O_2} where there is a dislinear rise in VE and V_{CO_2} • Generally associated with anaerobic threshold • Represents upper limit of ET workloads that can be sustained for a prolonged period • Valuable in setting intensity for exercise prescription in a highly individualized manner	• $\approx$ 50–65% of peak V_{O_2}[21] • Influenced by genetic predisposition and chronic aerobic training
Peak RER	• Defined as the V_{CO_2}/V_{O_2} ratio • Expressed as a 10–60 s averaged value depending on exercise protocol (i.e. shorter averaging interval for protocols with shorter stages and longer averaging interval for protocols with longer stages) • As exercise progresses to higher intensities, V_{CO_2} outpaces V_{O_2}, increasing the ratio • Currently is the best non-invasive indicator of exercise effort	• Peak value ≥ 1.10 widely accepted as excellent exercise effort[1]
VE/V_{CO_2} slope	• Relationship between VE, plotted on the *y*-axis, and V_{CO_2} plotted on the *x*-axis; both variables in $L\ min^{-1}$ • Most commonly calculated using all ET data[7] • Represents matching of ventilation and perfusion within the pulmonary system • Broadly reflects disease severity as well as prognosis in a number of patient populations including HF, HCM, PAH/secondary PH, COPD, ILD	<30 considered normal with slight increase with advanced age possible
EOV	• No universal definition currently available • Most commonly defined as an oscillatory pattern at rest that persists for $\geq 60\%$ of the exercise test at an amplitude of $\geq 15\%$ of the average resting value[1,16] • Recommend using 10 s averaged VE data for plotting • Reflects advanced disease severity and poor prognosis in patients with HF	This is not a normal ventilatory response to exercise under any circumstances (see *Figure* 2)
$P_{ET}CO_2$ (mmHg) at rest and during exercise	• Also represents matching of ventilation and perfusion within the pulmonary system and cardiac function • Broadly reflects disease severity in a number of patient populations including HF, HCM, PAH/secondary PH, COPD, ILD	• Rest: 36–42 mmHg • Increases between 3 and 8 mmHg by VT • Decrease following VT secondary to increased ventilation response
VE/V_{O_2} at peak exercise	• Expressed as a 10–60 s averaged value depending on the exercise protocol (i.e. shorter averaging interval for protocols with shorter stages and longer averaging interval for protocols with longer stages) • Reflects ventilatory cost of O_2 uptake at peak ET • Has diagnostic utility in patients with suspected mitochondrial myopathy	• ≤ 40 • 50 = upper limit of normal response[22]

Continued

Table 1 ***Continued***

CPX variable	Description/significance	Normal value/response
$\Delta Q/\Delta V_{O_2}$ slope	• Relationship between Q, plotted on the y-axis, and V_{O_2} plotted on the x-axis; both variables in L min^{-1} • Additional equipment needed to measure Q; through foreign gas rebreathing technique[1] • Reflects the relationship between O_2 delivery and utilization in exercising skeletal muscle • Has diagnostic utility in patients with suspected mitochondrial myopathy if anaemia is ruled out	≈5
VE/MVV	• Ratio between VE at maximal exercise and MVV obtained at rest; both variables in L min^{-1} • Although prediction equations are available ($FEV_1 \times 40$[23]), MVV should be directly measured • Has diagnostic utility in determining if unexplained exertional dyspnoea is related to a pulmonary mechanism	≤0.80
FEV_1 (L • min^{-1}) and PEF (L • min^{-1})	• Components of pulmonary function testing battery • Predicted values automatically generated by CPX unit software packages; influenced by age, sex and body habitus • Has diagnostic utility in determining if unexplained exertional dyspnoea is related to a pulmonary mechanism, particularly exercise-induced bronchospasm • When relevant, should be assessed prior to and following CPX for comparative purposes	<15% reduction from pre to post CPX for both variables
O_2 pulse trajectory (mL O_2 • beat^{-1})	• O_2 pulse defined as the ratio between V_{O_2} (mL O_2 • min^{-1}) and HR (b.p.m.) • Non-invasively reflects stroke volume response to exercise • Has diagnostic utility in patients with suspected myocardial ischemia (i.e. exercise-induced left ventricular dysfunction)	Continual linear rise throughout exercise with possible plateau approaching maximal exertion (see *Figure 1*)
$\Delta V_{O_2}/\Delta W$ trajectory (mL • min^{-1} • W^{-1})	• Plot of the relationship between V_{O_2} (y-axis in mL min^{-1}) and workload (x-axis in W) • Lower extremity ergometer should be used as exercise mode when assessed • Has diagnostic utility in patients with suspected myocardial ischaemia (i.e. exercise-induced left ventricular dysfunction)	• Continual linear rise throughout ET (see *Figure 1*) • Average slope, calculated with all exercise data, is 10 mL • min^{-1} • W^{-1}
Exercise HR (b.p.m.)	• In patients not prescribed a beta-blocking agent; provides insight into chronotropic competence and cardiac response to exercise • Peak HR should not be used as the primary gauge of subject effort given its wide variability[19,20]	• Increase ~10 beats per 3.5 mL O_2 • kg^{-1} • min^{-1} increase in V_{O_2}, achieve at least 85% of age-predicted maximal HR with good effort
HRR at 1 min (beats)	• Difference between maximal exercise HR and HR 1 min into recovery • Provides insight into speed of parasympathetic reactivation	>12 beats
Exercise BP (mmHg)	Provides insight into CV response to exercise and left ventricular afterload	• SBP increase ~10 mmHg per 3.5 mL O_2 • kg^{-1} • min^{-1} increase in V_{O_2} • Upper range of normal maximal SBP is ~210 mmHg for males and ~190 mmHg for females • DBP remains the same or slightly decreases

Continued

Table 1 ***Continued***

CPX variable	Description/significance	Normal value/response
SpO_2 (%)	• Non-invasive estimate of arterial haemoglobin saturation • Has diagnostic utility in determining if unexplained exertional dyspnoea is related to a pulmonary mechanism • Desaturation common in patients with COPD, ILD, PAH/secondary PH as disease severity advances	• ≥ 95% at rest and throughout exercise • Should not decrease >5% (absolute value)
ECG	• Insight into stability of cardiac rhythm • Identifies baseline abnormalities and exercise-induced ischaemia	• Minimal waveform changes • No significant deviation from normal sinus rhythm
Subjective symptoms	• Used to determine subjects perception of symptoms limiting exercise • Rating of perceived exertion (i.e. Borg scale)[15] as well as dyspnoea and angina (using symptom specific scales)[17] should be quantified using separate scales with unique verbal anchors • Unusual dyspnoea as primary reason for test termination (i.e. 4/4: severely difficult, patient cannot continue)[17] shown to indicate increased adverse event risk in patients assessed for myocardial ischemia[14] and HF[18]	• Limiting factor muscular fatigue with no significant dyspnoea or angina

CPX, cardiopulmonary exercise testing; V_{O_2}, oxygen consumption; ET, exercise testing; VT, ventilatory threshold; VE, minute ventilation; V_{CO_2}, carbon dioxide production; RER, respiratory exchange ratio; EOV, exercise oscillatory ventilation; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; HF, heart failure; HCM, hypertrophic cardiomyopathy; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; Q, cardiac output; MVV; maximal voluntary ventilation; PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 s; O_2, oxygen; W, watt; HR, heart rate; HRR, heart rate recovery; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, saturation of peripheral oxygen; ECG, electrocardiogram.

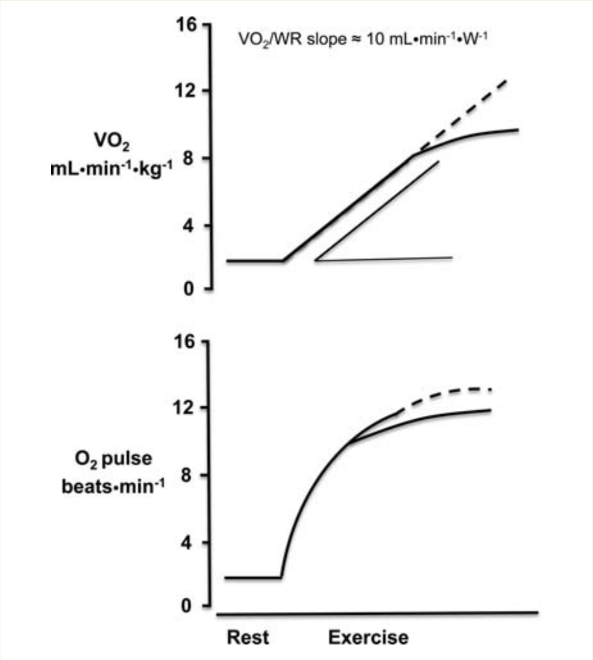


Figure 1 Normal (dashed line) and abnormal (solid line) example of oxygen pulse and $\Delta V_{O_2}/\Delta W$ plots. V_{O_2}, oxygen consumption; W, watts; O_2, oxygen.

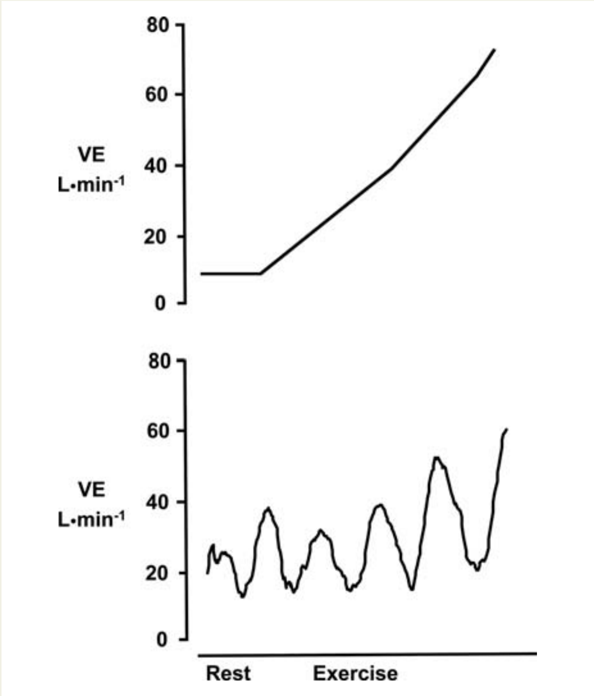


Figure 2 Examples of normal ventilatory pattern (*A*) and exercise oscillatory ventilation pattern (*B*). VE, minute ventilation.

Universal cardiopulmonary exercise testing reporting form

The ability to collect all relevant CPX data in a concise and organized manner is essential for meaningful data interpretation and clinical utilization. The universal CPX reporting form included as Appendix 1 provides clinicians with the ability to collect relevant ET data that may subsequently be used for interpretation according to a patient's specific condition/test indication. It should be noted that some of the variables in the CPX reporting form will be collected irrespective of the reason for ET. This includes peak V_{O_2}, per cent-predicted peak V_{O_2}, V_{O_2} at ventilatory threshold (VT), peak RER, HR, blood pressure (BP), ECG, and subjective symptom data. To calculate per cent-predicted peak V_{O_2}, the writing group proposes using the equations put forth by Wasserman and Hansen,[26,27] which are listed in *Table 2*. These equations account for several influencing factors including body habitus, mode of exercise, and sex. The aforementioned variables are relevant to all patients undergoing CPX because of their ability to universally reflect prognosis, maximal and submaximal functional capacity, exercise effort, and exertional physiology.[28,29] The collection of other CPX variables included in the universal CPX reporting form are dictated by test indication and described in subsequent sections and appendices.

Unique condition-related cardiopulmonary exercise testing variables according to test indication

There are several suspected/confirmed conditions where performance of a CPX would provide clinically valuable information on diagnosis, prognosis, and/or therapeutic efficacy. However, the volume of scientific evidence supporting the value of CPX is heterogeneous across the conditions identified in subsequent sections. While the clinical use of CPX is firmly established in patients with systolic HF and unexplained exertional dyspnoea, additional research, to varying degrees, is needed to further bolster support for CPX in the other patient populations identified in this document. This is not to suggest that a clinical justification for CPX cannot be made for each of the conditions listed below. Moreover, the unique condition-related CPX variables proposed for analysis are based on a sound physiological rationale, expert consensus, and current scientific evidence. The writing group feels that, based on expert opinion and currently available evidence, CPX provides valuable clinical information in all of the conditions listed in subsequent sections. Each of the following sections is accompanied by a condition-specific evaluation chart (see Appendices 2–8). These charts include key CPX variables for each test indication in a colour-coded format. Responses in the green zone indicate a normal response for a given variable, while responses in the yellow and red zones indicate progressively greater abnormalities. An interpretation, based on CPX performance for key variables, is included at the end of each chart. The intent of these condition-specific charts is to greatly simplify CPX data interpretation, thereby improving clinical utility.

Systolic heart failure

The majority of research assessing the clinical application of CPX has been performed within the systolic HF population. Beginning in the 1980s with the landmark work by Weber *et al.*,[30] followed in 1991 with the classic investigation by Mancini *et al.*,[31] a wealth of literature has been put forth that convincingly demonstrates the ability of key CPX variables to predict adverse events and gauge disease severity.[1,7,32,33] Peak V_{O_2} and the VE/V_{CO_2} slope are currently the most studied CPX variables in patients with

Table 2 **Predicted peak oxygen consumption equations**

	Sedentary male	**Sedentary Female**
Wasserman/ Hansen equations[a]	*Step 1*: Calculate Cycle factor = 50.72 − 0.372(age) Predicted weight = 0.79 (height) − 60.7 *Step 2*: Classify weight Measured weight= predicted weight *Step 3*: Select equation **Measured weight < Predicted weight** Peak V_{O_2} (mL • min^{-1}) = [(Predicted weight + Actual weight)/2] × cycle factor **Measured weight = Predicted weight** Peak V_{O_2} (mL • min^{-1}) = Measured weight × cycle factor **Measured weight > Predicted weight** Peak V_{O_2} (mL • min^{-1}) = (Predicted weight × cycle factor) + 6 × (Measured weight − predicted weight) *Step 4*: Mode of exercise consideration **If treadmill used for test** Multiply predicted V_{O_2} from step 3 × 1.11	*Step 1*: Calculate Cycle factor = 22.78 − 0.17 (age) Predicted weight = 0.65 (height) − 42.8 *Step 2*: Classify weight Measured weight = predicted weight *Step 3*: Select equation **Measured weight < Predicted weight** Peak V_{O_2} (mL • min^{-1}) = [(Predicted weight + Actual weight +86)/2] × cycle factor **Measured weight = Predicted weight** Peak V_{O_2} (mL • min^{-1}) = (Measured weight + 43) × cycle factor **Measured weight > Predicted weight** Peak V_{O_2} (mL • min^{-1}) = (Predicted weight + 43) × cycle factor + 6 × (Measured weight − predicted weight) *Step 4*: Mode of exercise consideration **If treadmill used for test** Multiply predicted V_{O_2} from step 3 × 1.11

V_{O_2}, oxygen consumption.

[a] Height in cm and weight in kg.

systolic HF and both demonstrate strong, independent prognostic value. While there is evidence to indicate the VE/V_{CO_2} slope is a stronger univariate predictive marker compared with peak V_{O_2}, there is substantial evidence to indicate that a multivariate approach improves prognostic accuracy.[7] Under current medical management strategies, a VE/V_{CO_2} slope ≥ 45 and a peak V_{O_2} < 10.0 mL $O_2 \bullet kg^{-1} \bullet min^{-1}$ are indicative of a particularly poor prognosis over the 4-year period following CPX.[34] Other CPX variables have emerged in recent years that appear to further refine prognostic resolution. Specifically, EOV and the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) during rest and exercise have both demonstrated strong prognostic value in patients with systolic HF.[16,35–37] Given these variables are readily available, their inclusion for prognostic assessment purposes is recommended. Lastly, there is some evidence to indicate the assessment of per cent-predicted peak V_{O_2} may provide prognostic information,[38–40] although it is not clear if such information supersedes/compliments the prognostic strength of measured peak V_{O_2}. Current evidence indicates that a per cent-predicted peak V_{O_2} value falling below 50% indicates a poor prognosis in patients with HF.[38] Research assessing the clinical value of per cent-predicted peak V_{O_2} assessment in patients with HF should continue. However, given the disparity in the volume of supporting evidence for the prognostic value of measured peak V_{O_2} vs. per cent-predicted peak V_{O_2}, we currently recommend the actual peak V_{O_2} value being considered in this patient population to gauge disease severity and prognosis. The prognostic and diagnostic stratification chart for patients with systolic HF is provided in Appendix 2. The peak V_{O_2}, the VE/V_{CO_2} slope, presence/absence of EOV, and rest/exercise $P_{ET}CO_2$ should all be assessed. As values for these variables progress to the red zone, disease severity worsens and the likelihood of major adverse events (i.e. death, HF decompensation to the refractory stage) becomes increasingly likely. The risk for softer endpoints, such as hospitalization due to HF, is also likely to increase as variables progress to the red zone. With respect to transplant candidacy, the peak V_{O_2} and VE/V_{CO_2} slope values in the red zone should be considered primary criteria for eligibility. Numerous investigations have demonstrated the aforementioned CPX variables respond favourably to pharmacological (i.e. sildenafil, angiotensin receptor blockade, angiotensin-converting enzyme inhibition), surgical (i.e. cardiac resynchronization therapy, left ventricular assist device implantation, and heart transplantation), and lifestyle (i.e. exercise training) interventions appropriate for patients with systolic HF.[7,41–43] Therefore, when CPX abnormalities are detected a review of the patient's clinical management strategy is recommended in order to determine whether titration of current interventions or the implementation of new interventions is warranted. In addition, standard ET variables should be included in the assessment as they may provide further information on clinical stability and prognosis. An abnormal haemodynamic and/or ECG response, as well as an abnormally low HR recovery (HRR) at 1 min post-ET and report of unusual dyspnoea (i.e. 4/4: severely difficult, patient cannot continue)[17] as the primary subjective symptom eliciting test termination, provide further evidence of poor prognosis and greater disease severity.[18,29,44,45]

Heart failure with preserved ejection fraction and congenital heart disease

Several studies are now available that support the use of CPX for gauging the level of diastolic dysfunction and assessing prognosis in patients with HF-preserved ejection fraction (HF-PEF).[46–48] VE/V_{CO_2} slope and EOV both appear to hold the prognostic value in patients with HF-PEF at a level comparable with that found in patients with systolic HF. Moreover, several investigations similarly support the prognostic importance of CPX in the congenital heart disease population.[49–51] Even so, additional research is needed in these patient populations to further elucidate the clinical value of CPX. At this time, the writing group recommends that the same reporting chart should be used for patients with systolic HF, HF-PEF, and congenital heart disease (see Appendix 2).

Hypertrophic cardiomyopathy

Cardiopulmonary ET has promising utility in regard to the assessment of patients with suspected/confirmed HCM. Ventilatory expired gas analysis during ET can be used to demarcate functional limitations, with diagnostic and prognostic implications. While the 2002 American College of Cardiology/American Heart Association ET guidelines[52] cite HCM as a relative contraindication to ET, many investigators have subsequently highlighted that the technique is safe.[53–55] Not only can peak V_{O_2} be used as criterion by which to guide HCM management, but it can also serve to distinguish left ventricular hypertrophy (LVH) associated with HCM from LVH stemming from relatively more innocuous aetiologies. Athletes may, for example, have physiological hypertrophy induced by physical activity. In this context, CPX can be applied to differentiate physiological hypertrophy from LVH in HCM simply on the basis of ET performance. While athletes achieve peak V_{O_2} that typically exceed the predicted values, only 1.5% of HCM patients have peak V_{O_2} exceeding the predicted values,[56] providing a convenient way to help recognize HCM in young adults who may have LVH but who are asymptomatic and have not been diagnosed with the condition. Measures of ventilatory efficiency, specifically the VE/V_{CO_2} slope and $P_{ET}CO_2$, may also be valuable in patients with HCM as abnormalities in these variables have been associated with increased pulmonary pressures as a consequence of advanced LVH-induced diastolic dysfunction.[57] Moreover, recent evidence indicates that aerobic capacity and ventilatory efficiency are prognostic markers in minimally symptomatic patients with obstructive HCM.[58] As a provocative exercise stimulus, CPX also provides an important assessment of ECG and haemodynamics. A blunted (≤ 20 mmHg increase in systolic BP) or hypotensive (exercise systolic BP $<$ resting values) exercise BP response is also common and indicates an increased risk of sudden death.[59,60] Moreover, prognostic implications are even worse when abnormal haemodynamic responses are coupled to a low peak V_{O_2}.[61] While exercise-induced serious ventricular arrhythmias are comparatively rare, they may also be associated with high prognostic risks in some patients.[62] The prognostic and diagnostic stratification chart for patients with confirmed or suspected HCM is provided in Appendix 3. Given the range of peak V_{O_2} values is likely to be wide in this patient population, a per cent-predicted value, which has recently demonstrated prognostic value in this population,[58] should be included in the assessment. A progressive decline in per cent-predicted values, from green to red, is indicative of worsening disease severity and prognosis. Abnormalities in standard haemodynamic (i.e. systolic blood pressure) and ECG (i.e. onset of ventricular arrhythmias) variables, progressing to the red zone, are further indication of worsening disease severity and increased risk for adverse events. As values for the VE/V_{CO_2} slope and $P_{ET}CO_2$ progress from green to red, the likelihood of secondary pulmonary hypertension (PH), induced by HCM, is increased.

Unexplained exertional dyspnoea

Cardiopulmonary exercise testing possesses the unique ability to comprehensively assess the independent and integrated exertional responses of the CV and pulmonary systems. Moreover, the majority of current CPX systems have the capability to perform pulmonary function testing. Therefore, in patients presenting with unexplained exertional dyspnoea, CPX is considered an important assessment to determine the mechanism of exercise intolerance.[1,52] When CPX is utilized for this indication, a primary goal should be to reproduce the patient's exertional symptoms in order to optimally detect any coinciding physiological abnormalities. The diagnostic stratification chart for patients with unexplained exertional dyspnoea is provided in Appendix 4. The VE/V_{CO_2} slope, per cent-predicted peak V_{O_2}, $P_{ET}CO_2$, and the peak exercise VE/maximal voluntary ventilation (MVV) ratio are primary CPX variables for this assessment. Maximal voluntary ventilation should be directly measured prior to exercise as opposed to estimated using forced expiratory volume in 1 s (FEV_1). Moreover, pulmonary function tests should be performed prior to and following CPX to determine FEV_1 and peak expiratory flow (PEF).[63–67] Following CPX, FEV_1, and PEF should be measured at 1, 3, 5, 7, 10, 15, and 20 min, as responses for these variables typically worsen several minutes into recovery when exercise induced bronchospasm (EIB) is present.[67] In addition to the standard haemodynamic and ECG monitoring procedures, pulse oximetry (SpO_2) should also be assessed at rest, throughout ET, and into recovery. Given the range of peak V_{O_2} values is likely to be wide in this patient population, a per cent-predicted value should be included in the assessment. A progressive decline in per cent-predicted values, from green to red, indicates that the physiological mechanism resulting in exertional dyspnoea is having a greater impact on functional capacity. Abnormalities in the VE/V_{CO_2} slope and $P_{ET}CO_2$, particularly progressing to the red zone, indicate ventilation–perfusion abnormalities induced by pulmonary vasculopathy[68,69] as a potential mechanism for exertional symptoms. Patients with ventilation–perfusion abnormalities may also present with a reduced SpO_2, and, in such instances, this finding portends advanced pathophysiology. Isolated abnormalities (i.e. red zone) in VE/MVV, FEV_1, and PEF are indicative of a pulmonary mechanism for the patient's unexplained exertional dyspnoea. For FEV_1 and PEF responses in the red zone, EIB should be suspected and a bronchodilator trial may be warranted. While both FEV_1 and PEF have been recommended for the assessment of EIB, FEV_1 is frequently assessed in isolation.[65,66] Thus, a decrease in FEV_1 $>15\%$ post exercise, irrespective of the PEF response, is sufficient to suspect EIB.[67] Detection of haemodynamic and/or ECG abnormalities that coincide with reproduced exertional dyspnoea are indicative of a CV mechanism for the patient's unexplained symptoms. Unique to CPX for this indication, a hypertensive response to exercise that coincides with exertional dyspnoea and exercise intolerance may be an early indicator of HF-PEF.[70,71]

Suspected or confirmed pulmonary arterial hypertension or secondary pulmonary hypertension

Although not currently a standard clinical indication for CPX, the body of evidence supporting the use of this form of ET in patients with suspected or confirmed PAH and secondary PH is growing at an impressive rate.[68,69,72–82] A key value of CPX in detecting potential pulmonary vasculopathy, or gauging disease severity once a diagnosis has been made, is the ability of this exercise approach to non-invasively quantify ventilation–perfusion abnormalities. Specifically, abnormalities in the VE/V_{CO_2} slope and $P_{ET}CO_2$ are strongly suggestive of pulmonary vasculopathy whose aetiology is either PAH or secondary PH as a consequence of other primary conditions such as HF, HCM, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or systemic connective tissue diseases. Moreover, there is emerging evidence to suggest key CPX variables portend the prognostic value in patients with PAH. The prognostic and diagnostic stratification chart for patients with suspected or confirmed PAH or secondary PH is provided in Appendix 5. Peak V_{O_2}, the VE/V_{CO_2} slope, and $P_{ET}CO_2$ are primary CPX variables in patients with suspected or confirmed PAH or secondary PH. Patients suffering from pulmonary vasculopathy, regardless of the mechanism, typically present with significantly compromised aerobic capacity. Thus, reporting peak V_{O_2} as an actual value, using the Weber classification system,[30] is warranted. In those patients without a confirmed diagnosis, the likelihood of pulmonary vasculopathy increases as values for the VE/V_{CO_2} slope and $P_{ET}CO_2$ progress from green to red. In patients with a confirmed diagnosis of PAH/secondary PH, progressively worsening abnormalities of the aforementioned ventilatory efficiency variables as well as aerobic capacity are indicative of increasing disease severity. Moreover, worsening responses in these primary CPX variables are indicative of increased risk for adverse events. With respect to mode of testing, there is evidence to suggest ventilatory efficiency abnormalities are more pronounced during treadmill ET compared with cycle ergometry.[83] Therefore, treadmill CPX may be optimal when assessing patients with suspected or confirmed pulmonary vasculopathy. In addition, patients with advanced PAH/secondary PH often present with an abnormal reduction in SpO_2. Lastly, abnormal haemodynamic and/or ECG responses further compound concerns over increasing disease severity and prognosis in these patients.

Confirmed chronic obstructive pulmonary disease or interstitial lung disease

The literature supporting the use of CPX in patients with confirmed COPD or ILD is beginning to increase, producing compelling results in support of this form of ET for these patient populations. Several investigations have demonstrated that peak V_{O_2} is predictive of adverse events in patients with COPD[84,85] and ILD.[86,87] Like patients with HF, a peak V_{O_2} $<$10 mL $O_2 \bullet kg^{-1} \bullet min^{-1}$ portends a particularly poor prognosis. The prognostic ability of peak V_{O_2} in patients with pulmonary disease has led the American College of Chest Physicians to recommend that CPX be used pre-surgically in lung resection candidates to assess post-surgical risk.[88] Initial evidence also indicates the VE/V_{CO_2} slope is a significant post-surgical prognostic marker in patients with COPD undergoing lung resection.[89] Additionally, the ability of CPX to gauge ventilatory efficiency is valuable in screening for secondary PH in patients with COPD and ILD.[90,91] As the VE/V_{CO_2} slope progressively increases and $P_{ET}CO_2$ progressively decreases above and below their normal values, respectively, the presence of secondary PH becomes more likely. The prognostic and diagnostic stratification chart for patients with COPD and ILD is provided in Appendix 6. Peak V_{O_2}, the VE/V_{CO_2} slope, and $P_{ET}CO_2$ are primary CPX variables for both COPD and ILD patients. As values for these variables progress to the red zone, there is an increased risk for adverse events and greater likelihood of secondary PH. Additionally, standard exercise variables progressing to the red zone compound the concern for poor prognosis in these patients.

Suspected myocardial ischaemia

Standard incremental ET procedures are a well-accepted and valuable clinical assessment tool in patients at high risk for myocardial ischaemia.[6,52,92] The use of ventilatory expired gas analysis for patients undergoing ET for suspected myocardial ischaemia is not commonplace in the clinical setting at this time. In recent years, however, several investigations have demonstrated the potential diagnostic utility of CPX in this setting.[93,94] Recent studies have found that the real-time change in the O_2 pulse and $\Delta V_{O_2}/\Delta W$ trajectories are most valuable when using CPX to assess exercise-induced myocardial ischaemia. Under normal physiological conditions, both of these relationships progressively rise during maximal ET. However, left-ventricular dysfunction induced by myocardial ischaemia causes both the O_2 pulse and $\Delta V_{O_2}/\Delta W$ trajectories to prematurely flatten or decline (see *Figure 1*). In a landmark study, Belardinelli *et al.*[95] performed CPX in 202 patients with a confirmed diagnosis of coronary heart disease (CHD), using 2-day stress/rest-gated SPECT myocardial scintigraphy as the gold standard for myocardial ischaemia. Using logistic regression, flattening of the O_2 pulse and $\Delta V_{O_2}/\Delta WR$ trajectories were independent predictors of exercise-induced myocardial ischaemia. The sensitivity and specificity for O_2 pulse + $\Delta V_{O_2}/\Delta W$ flattening as criteria for exercise-induced myocardial ischaemia were 87 and 74%, respectively. Comparatively, ECG criteria for exercise-induced myocardial ischaemia, defined as the onset of 1.0 mm horizontal ST-segment depression in at least two adjacent leads, produced a sensitivity and specificity of 46 and 66%, respectively. Of particular note, the addition of O_2 pulse and $\Delta V_{O_2}/\Delta W$ trajectory assessments helped to rule out ischaemia in a significant portion of individuals for whom the ECG was falsely positive. As a technical note, the majority of investigations validating the clinical applications of CPX for patients with suspected myocardial ischaemia to this point, including the landmark investigation by Belardinelli *et al.*,[95] used a lower extremity bicycle ergometry as the mode of testing. Thus, additional research should be conducted to determine whether the diagnostic utility of CPX for myocardial ischaemia is present when a treadmill is the testing mode. The diagnostic stratification chart for patients with suspected myocardial ischaemia is provided in Appendix 7. Assessment of the O_2 pulse and $\Delta V_{O_2}/\Delta W$ trajectories are primary CPX variables. As values for these variables progress to the red zone, the likelihood of exercise-induced myocardial ischaemia increases. Given that the range of peak V_{O_2}values is likely to be wide in patients undergoing CPX for this indication, a per cent-predicted value should be included in the assessment. A progressive decline in per cent-predicted values, from green to red, is indicative of poorer aerobic fitness and possibly increased coronary artery disease severity. Previous research has demonstrated lower per cent-predicted aerobic fitness values to be indicative of poor prognosis.[96] As with all ET procedures, standard haemodynamic and ECG variables should be assessed in patients with suspected myocardial ischaemia. Abnormalities in these measures progressing to the red zone further increase the likelihood of exercise-induced myocardial ischaemia and provide prognostic insight.[29] Lastly, evidence suggests patients with suspected myocardial ischaemia who report unusual dyspnoea (i.e. 4/4: severely difficult, patient cannot continue)[17] as the primary reason for exercise limitations have a poorer prognosis compared with those whose primary limiting symptom is lower extremity fatigue or angina.[14] While research demonstrating the value of CPX in this area is promising, additional investigations are needed to further substantiate CPX for this purpose, particularly in cohorts with suspected myocardial ischaemia and no prior workup bias.

Suspected mitochondrial myopathy

A number of genetic abnormalities exist which can lead to diminished CRF and a host of other exertional abnormalities uniquely captured by CPX.[22,97] The degree of impairment in peak V_{O_2} appears to correlate to the severity of genetic mutation.[22,98] Moreover, patients with mitochondrial myopathies have an elevated VE/V_{O_2} ratio at peak exercise, as the ventilatory cost of V_{O_2} dramatically rises due to aerobic inefficiency by affected skeletal muscle. The ability to non-invasively quantify Q during CPX in an accurate manner is now possible through foreign gas rebreathing methods.[1] Using this technique, the relationship between Q (y-axis) and V_{O_2} (x-axis) during ET are plotted, generating a slope value. In normal circumstances, where O_2 utilization and delivery are well matched, the $\Delta Q/\Delta V_{O_2}$ slope is 5 L min^{-1}. In subjects with mitochondrial myopathies, this slope is much higher as oxygen delivery far exceeds the capacity for utilization.[22] The diagnostic stratification chart for patients with suspected mitochondrial myopathy is provided in Appendix 8. The assessment of the $\Delta Q/\Delta V_{O_2}$ slope and peak VE/V_{O_2} are primary CPX variables.

As values for these variables progress to the red zone, the likelihood of a mitochondrial myopathy increases. Moreover, the degree of abnormality in the $\Delta Q/\Delta V_{O_2}$ slope and peak VE/V_{O_2} response is indicative of the degree of mitochondrial mutation load. Given the range of peak V_{O_2} values is likely to be wide in patients undergoing CPX for this indication, a per cent-predicted value should be included in the assessment. A progressive decline in per cent-predicted values, from green to red, when coinciding with an abnormal $\Delta Q/\Delta V_{O_2}$ slope and peak VE/V_{CO_2}, is likewise indicative of an increasingly higher mitochondrial mutation load. When these variables are abnormal, a muscle biopsy would be warranted to obtain a definitive diagnosis. Additionally, standard haemodynamic and ECG variables should be assessed in patients with suspected mitochondrial myopathy, as abnormalities in these measures are universally indicative of CV abnormalities and increased adverse event risk.[29]

Directions for future research

The current statement provides recommendations for CPX data interpretation based on currently available scientific evidence and expert consensus. However, there are other CPX variables that may emerge as clinically important measures in a number of the patient populations described herein. Examples of CPX variables demonstrating the potential value are the oxygen uptake efficiency slope,[99–101] circulatory power[102] and V_{O_2} onset[103,104] and recovery[105] kinetics. Moreover, additional research is needed to further increase support for the use of CPX in certain patient populations as previously mentioned. Additional investigations into the value of CPX in females also seem warranted across all patient populations that would benefit from this form of ET. Lastly, future investigations are needed to determine whether other patient populations would benefit from CPX as a component of their clinical assessment. For example, there is some initial data to indicate CPX may provide valuable information in patients with atrial fibrillation, a condition associated with ventilatory and functional abnormalities.[106,107] This writing group encourages continued research into the clinical utility of CPX across all patient populations where a viable case can be made for this form of ET, addressing specific questions in need of further analysis. Future investigations in this area will lead to additional refinement of CPX utilization and data interpretation as well as improve the clinical value of this assessment technique.

Conclusions

Cardiopulmonary exercise testing is well recognized as the gold standard aerobic ET assessment. The use of CPX is well established in the clinical setting for both patients with systolic HF, undergoing a pre-transplant assessment, and individuals with unexplained exertional dyspnea.[6,52] The evidence supporting the use of CPX in patients with confirmed or suspected PAH and secondary PH is also rapidly expanding and a strong case for the application of this ET assessment in this population can now be made. There is also emerging evidence to demonstrate CPX elicits clinically valuable information in a number of other patient populations, which are described in this document. Irrespective of the reason for the ET assessment, the utility of CPX currently suffers from an inability to easily interpret the most useful information in a way that is evidence based and specific to test indication. The present document attempts to rectify this issue by coalescing expert opinion and current scientific evidence and creating easily interpretable CPX charts that are indication specific. It is the hope of the writing group that this document will expand the appropriate use of CPX by simplifying data interpretation, thereby increasing the clinical value of the data obtained.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Appendix 1: Universal CPX reporting form (complete all boxes that apply for given ET indication)

Exercise modality: [ ] Treadmill [ ] Lower extremity ergometer

Protocol:		
Peak V_{O_2} (mL O_2•kg^{-1}•min^{-1}) V_{O_2} at VT (mL O_2•kg^{-1}•min^{-1})	Per cent-predicted peak V_{O_2} (%)[a] Peak RER	VE/V_{CO_2} slope EOV [ ] Yes [ ] No
$P_{ET}CO_2$ (mmHg) Resting: Increase during ET:	VE/V_{O_2} at peak ET	$\Delta Q/\Delta V_{O_2}$[b]
VE/MVV[c]:	PEF (L/min): Pre-ET	Post-ET
O_2 pulse trajectory[d] [ ] Continual rise throughout ET [ ] Early and sustained plateau [ ] Decline		
$\Delta V_{O_2}/\Delta W$ trajectory[d] [ ] Continual rise throughout ET [ ] Early and sustained plateau [ ] Decline		
Resting HR (b.p.m.) Peak HR (b.p.m.) Percent of age-predicted maximal HR[e] HRR at 1 min (beats)	Resting BP (mmHg) Peak BP (mmHg) Maximal workload [ ] Treadmill speed/grade: [ ] Cycler ergometer Watts:	Resting pulse oximetry (%) Peak pulse oximetry (%)
ECG criteria [ ] No arrhythmias/Ectopy/ST segment changes [ ] Arrhythmias/Ectopy/ST segment changes: not exercise limiting [ ] Arrhythmias/Ectopy/ST segment changes: exercise limiting		ECG description
Subjective symptoms (check box for primary termination criteria) RPE [ ] Angina [ ] Dyspnoea [ ]		
Additional notes		

CPX, cardiopulmonary exercise testing; ET, exercise testing; V_{O_2}, oxygen consumption; VT, ventilator threshold; RER, respiratory exchange ratio; VE/V_{CO_2}, minute ventilation/carbon dioxide production; EOV, exercise oscillatory ventilation; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide production; VE/V_{O_2}, minute ventilation/oxygen consumption; VE/MVV, peak minute ventilation/maximal voluntary ventilation; $\Delta Q/\Delta V_{O_2}$, change in cardiac output/change in oxygen consumption; PEF, peak expiratory flow; O_2, oxygen; $\Delta V_{O_2}/\Delta W$, change in oxygen consumption/change in Watts; HR, heart rate; BP, blood pressure; HRR, heart rate recovery; ECG, electrocardiogram; RPE, rating of perceived exertion

[a] Use equations proposed by Wasserman.

[b] Requires additional equipment of assess Q response to exercise through non-invasive rebreathing technique.

[c] Directly measure MVV at baseline.

[d] Requires O_2 pulse and $\Delta V_{O_2}/\Delta W$ plot from initiation to end of ET. If these variables required for assessment, electronically braked cycle ergometer should be used for testing.

[e] Use equation: (peak HR/220-age) * 100.

Appendix 2: Prognostic and diagnostic stratification for patients with HF

Primary CPX variables

VE/V_{CO_2} slope	Peak V_{O_2}[a]	EOV	$P_{ET}CO_2$
🟩 Ventilatory class I VE/V_{CO_2} slope <30.0	🟩 Weber class A Peak V_{O_2} >20.0 mL $O_2 \bullet kg^{-1} \bullet min^{-1}$	🟩 Not present	🟩 Resting $P_{ET}CO_2$ ≥ 33.0 mmHg 3–8 mmHg increase during ET
🟨 Ventilatory class II VE/V_{CO_2} slope 30.0–35.9	🟨 Weber class B Peak V_{O_2} = 16.0–20.0 mL $O_2 \bullet kg^{-1} \bullet min^{-1}$		
🟧 Ventilatory class III VE/V_{CO_2} slope 36.0–44.9	🟧 Weber class C Peak V_{O_2} = 10.0–15.9 mL $O_2 \bullet kg^{-1} \bullet min^{-1}$	🟥 Present	🟥 Resting $P_{ET}CO_2$ <33.0 mmHg <3 mmHg increase during exercise
🟥 Ventilatory class IV VE/V_{CO_2} slope ≥ 45.0	🟥 Weber class D Peak V_{O_2} <10.0 mL $O_2 \bullet kg^{-1} \bullet min^{-1}$		

Standard ET variables

Haemodynamics	ECG	HRR
🟩 Rise in systolic BP during ET	🟩 No sustained arrhythmias, ectopic foci, and/or ST segment changes during ET and/or in recovery	🟩 >12 beats at 1 min recovery
🟨 Flat systolic BP response during exercise	🟨 Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: did not lead to test termination	🟥 ≤12 beats at 1 min recovery
🟥 Drop in systolic BP during ET	🟥 Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: led to test termination	

Patient reason for test termination

🟩 Lower extremity muscle fatigue	🟨 Angina	🟥 Dyspnoea

Interpretation

- All variables in green: excellent prognosis in next 1–4 years (≥90% event free)
  - Maintain medical management and retest in 4 years.
- Greater number of CPX and standard ET variables in red/yellow/orange indicative of progressively worse prognosis.
  - All CPX variables in red: risk for major adverse event extremely high in next 1–4 years (>50%).
- Greater number of CPX and standard ET variables in red/yellow/orange indicative of increasing HF disease severity.
  - All CPX variables in red: expect significantly diminished cardiac output, elevated neurohormones, higher potential for secondary PH.
- Greater number of CPX and standard ET variables in red/yellow/orange warrants strong consideration of more aggressive medical management and surgical options.

VE/V_{CO_2}, minute ventilation/carbon dioxide production; V_{O_2}, oxygen consumption; EOV, exercise oscillatory ventilation; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; BP, blood pressure; CPX, cardiopulmonary exercise test; ECG, electrocardiogram; ET, exercise test; HRR, heart rate recovery; RER, respiratory exchange ratio.

[a] Peak V_{O_2} valid if peak RER is at least 1.00 or test terminated secondary to abnormal haemodynamic or ECG exercise response.

Appendix 3: Prognostic and diagnostic stratification for patients with confirmed or suspected HCM

Primary CPX variables

VE/V_{CO_2} slope	Per cent-predicted peak V_{O_2}[a]	$P_{ET}CO_2$ apex during ET[b]
Ventilatory class I VE/V_{CO_2} slope <30.0	$\geq$100% predicted	$>$37 mmHg
Ventilatory class II VE/V_{CO_2} slope 30.0–35.9	75–99% predicted	36–30 mmHg
Ventilatory class III VE/V_{CO_2} slope 36.0–44.9	50–75% predicted	29–20 mmHg
Ventilatory class IV VE/V_{CO_2} slope $\geq$45.0	$<$50% predicted	$<$20 mmHg

Standard ET variables

Haemodynamics	ECG
Rise in systolic BP during ET	No sustained arrhythmias, ectopic foci, and/or ST segment changes during ET and/or in recovery
Flat systolic BP response during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: did not lead to test termination
Drop in systolic BP during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: led to test termination

Interpretation

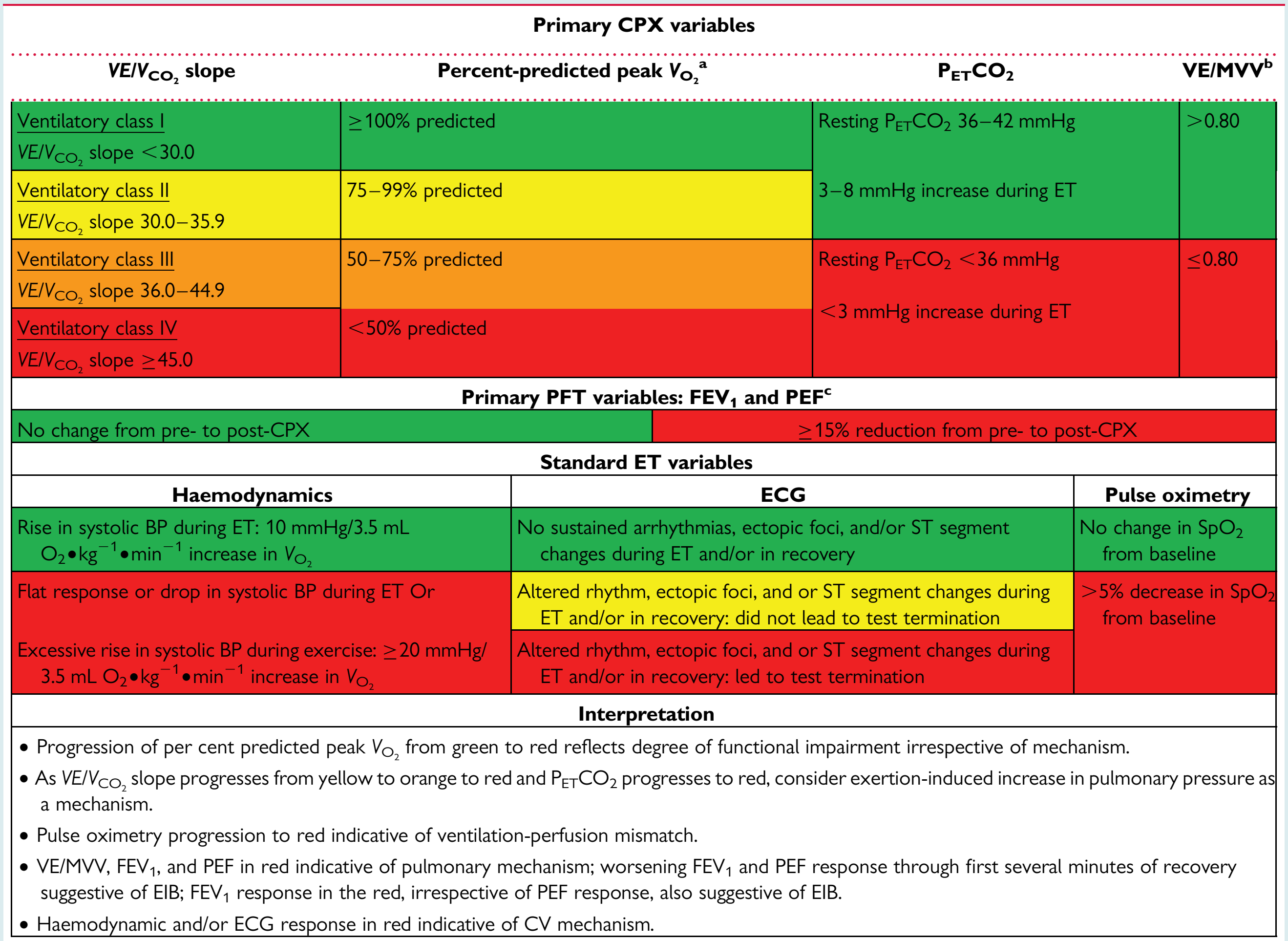
- Progressively higher VE/V_{CO_2} slope and lower per cent-predicted peak V_{O_2} and peak $P_{ET}CO_2$ indicative of greater HCM severity.
  - – CPX variables progressing from yellow to orange to red increase the likelihood of increased pulmonary pressure.
- Haemodynamic and ECG responses in yellow and red indicative of increasing risk for sudden cardiac death.

VE/V_{CO_2}, minute ventilation/CO_2 production; V_{O_2}, O_2 consumption; $P_{ET}CO_2$ apex, partial pressure of end-tidal CO_2; BP, blood pressure; CPX, cardiopulmonary exercise test; ECG, electrocardiogram; ET, exercise test; HCM, hypertrophic cardiomyopathy; VT, ventilatory threshold.

[a] Peak V_{O_2} valid if peak respiratory exchange ratio is at least 1.00 or test terminated secondary to abnormal haemodynamic or ECG exercise response. Per cent-predicted values derived from formulas proposed by Wasserman.

[b] $P_{ET}CO_2$ apex is achieved at submaximal levels during a progressive exercise test; typically immediately proceeds VT.

Appendix 4: Diagnostic stratification for patients with unexplained exertional dyspnoea



Primary CPX variables

VE/V_{CO_2} slope	Percent-predicted peak V_{O_2}[a]	$P_{ET}CO_2$	VE/MVV[b]
Ventilatory class I VE/V_{CO_2} slope <30.0	$\geq$100% predicted	Resting $P_{ET}CO_2$ 36–42 mmHg 3–8 mmHg increase during ET	>0.80
Ventilatory class II VE/V_{CO_2} slope 30.0–35.9	75–99% predicted		
Ventilatory class III VE/V_{CO_2} slope 36.0–44.9	50–75% predicted	Resting $P_{ET}CO_2$ <36 mmHg <3 mmHg increase during ET	≤0.80
Ventilatory class IV VE/V_{CO_2} slope ≥ 45.0	<50% predicted		

Primary PFT variables: FEV_1 and PEF[c]

No change from pre- to post-CPX	≥15% reduction from pre- to post-CPX

Standard ET variables

Haemodynamics	ECG	Pulse oximetry
Rise in systolic BP during ET: 10 mmHg/3.5 mL $O_2 \bullet kg^{-1} \bullet min^{-1}$ increase in V_{O_2}	No sustained arrhythmias, ectopic foci, and/or ST segment changes during ET and/or in recovery	No change in SpO_2 from baseline
Flat response or drop in systolic BP during ET Or Excessive rise in systolic BP during exercise: ≥20 mmHg/3.5 mL $O_2 \bullet kg^{-1} \bullet min^{-1}$ increase in V_{O_2}	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: did not lead to test termination	>5% decrease in SpO_2 from baseline
	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: led to test termination	

Interpretation

- Progression of per cent predicted peak V_{O_2} from green to red reflects degree of functional impairment irrespective of mechanism.
- As VE/V_{CO_2} slope progresses from yellow to orange to red and $P_{ET}CO_2$ progresses to red, consider exertion-induced increase in pulmonary pressure as a mechanism.
- Pulse oximetry progression to red indicative of ventilation-perfusion mismatch.
- VE/MVV, FEV_1, and PEF in red indicative of pulmonary mechanism; worsening FEV_1 and PEF response through first several minutes of recovery suggestive of EIB; FEV_1 response in the red, irrespective of PEF response, also suggestive of EIB.
- Haemodynamic and/or ECG response in red indicative of CV mechanism.

VE/V_{CO_2}, minute ventilation/CO_2 production; V_{O_2}, O_2 consumption; $P_{ET}CO_2$, partial pressure of end-tidal CO_2; VE/MVV, minute ventilation at peak exercise/maximal voluntary ventilation (maximal voluntary ventilation should be directly measured prior to ET); PFT, pulmonary function test; FEV_1, forced expiratory volume in one second; PEF, peak expiratory flow; BP, blood pressure; CPX, cardiopulmonary exercise test; CV, cardiovascular; ECG, electrocardiogram; ET, exercise test; RER, respiratory exchange ratio; SpO_2, saturation of peripheral O_2; EIB, exercise induced bronchospasm.

[a] Peak V_{O_2} valid if peak RER is at least 1.00 or test terminated secondary to abnormal haemodynamic or ECG exercise response. Percent-predicted values derived from formulas proposed by Wasserman.

[b] MVV should be directly measured prior to CPX; the majority of CPX systems allow for MVV measurement.

[c] Following CPX, measurement of FEV_1 and PEF should be conducted at 1, 3, 5, 7, 10, 15, and 20 min.

Appendix 5: Prognostic and diagnostic stratification for patients with suspected or confirmed PAH/secondary PH

Primary CPX variables

VE/V_{CO_2} slope	Peak V_{O_2}[a]	$P_{ET}CO_2$ apex during exercise[b]
Ventilatory class I VE/V_{CO_2} slope <30.0	Weber class A Peak $V_{O_2} > 20.0$ mL $O_2 \bullet kg^{-1} \bullet min^{-1}$	>37 mmHg
Ventilatory class II VE/V_{CO_2} slope 30.0–35.9	Weber class B Peak $V_{O_2} = 16.0–20.0$ mL $O_2 \bullet kg^{-1} \bullet min^{-1}$	36–30 mmHg
Ventilatory class III VE/V_{CO_2} slope 36.0–44.9	Weber class C Peak $V_{O_2} = 10.0–15.9$ mL $O_2 \bullet kg^{-1} \bullet min^{-1}$	29–20 mmHg
Ventilatory class IV VE/V_{CO_2} slope ≥ 45.0	Weber class D Peak $V_{O_2} < 10.0$ mL $O_2 \bullet kg^{-1} \bullet min^{-1}$	<20 mmHg

Standard ET variables

Haemodynamics	ECG	Pulse oximetry
Rise in systolic BP during ET	No sustained arrhythmias, ectopic foci, and/or ST segment changes during ET and/or in recovery	No change in SpO_2 from baseline
Flat systolic BP response during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: did not lead to test termination	$>5\%$ decrease in SpO_2 from baseline
Drop in systolic BP during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: led to test termination	

Interpretation

- All variables in green: indicative of good prognosis.
  - Maintain medical management and retest in 4 years.
- Greater number of CPX and standard ET variables in red/yellow/orange indicative of progressively worse prognosis.
  - All CPX variables in red: risk for major adverse event extremely high in next 1–4 years.
- Greater number of CPX and standard ET variables in red/yellow/orange indicative of increasing severity of pulmonary vasculopathy.
  - All CPX variables in red: expect significantly increased pulmonary arterial pressure.
- Greater number of CPX and standard ET variables in red/yellow/orange warrants strong consideration of more aggressive medical management.

VE/V_{CO_2}, minute ventilation/CO_2 production; V_{O_2}, O_2 consumption, $P_{ET}CO_2$, partial pressure of end-tidal CO_2; BP, blood pressure; CPX, cardiopulmonary exercise test; ECG, electrocardiogram; ET, exercise test; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RER, respiratory exchange ratio; SpO_2, saturation of peripheral O_2; VT, ventilatory threshold.

[a] Peak V_{O_2} valid if peak RER is at least 1.00 or test terminated secondary to abnormal haemodynamic or ECG exercise response.

[b] $P_{ET}CO_2$ apex achieved at submaximal levels; typically immediately proceeds VT.

Appendix 6: Prognostic and diagnostic stratification for patients with COPD or ILD

VE/V_{CO_2} slope	Peak V_{O_2}[a]	$P_{ET}CO_2$
Ventilatory class I VE/V_{CO_2} slope <30.0	Weber class A Peak V_{O_2} $>20.0\ \text{mL O}_2\bullet\text{kg}^{-1}\bullet\text{min}^{-1}$	Resting $P_{ET}CO_2 \geq 33.0$ mmHg
Ventilatory class II VE/V_{CO_2} slope 30.0–35.9	Weber class B Peak V_{O_2} $= 16.0–20.0\ \text{mL O}_2\bullet\text{kg}^{-1}\bullet\text{min}^{-1}$	3–8 mmHg increase during ET
Ventilatory class III VE/V_{CO_2} slope 36.0–44.9	Weber class C Peak V_{O_2} $= 10.0–15.9\ \text{mL O}_2\bullet\text{kg}^{-1}\bullet\text{min}^{-1}$	Resting $P_{ET}CO_2 < 33.0$ mmHg
Ventilatory class IV VE/V_{CO_2} slope ≥ 45.0	Weber class D Peak V_{O_2} $<10.0\ \text{mL O}_2\bullet\text{kg}^{-1}\bullet\text{min}^{-1}$	3–8 mmHg increase during ET

Standard ET variables

Haemodynamics	ECG	HRR	Pulse oximetry
Rise in systolic BP during ET	No sustained arrhythmias, ectopic foci, and/or ST segment changes during ET and/or in recovery	>12 beats at 1 min recovery	No change in SpO_2 from baseline
Flat systolic BP response during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: did not lead to test termination	≤12 beats at 1 min recovery	>5% decrease in SpO_2 from baseline
Drop in systolic BP during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: led to test termination		

Interpretation

- All variables in green: excellent prognosis in next 1–4 years.
  - Maintain medical management and retest in 4 years.
- Greater number of CPX and standard exercise test variables in red/yellow/orange indicative of progressively worse prognosis.
  - All CPX variables in red: risk for major adverse event extremely high in next 1–4
- Greater number of CPX and standard ET variables in red/yellow/orange indicative of increasing interstitial lung disease severity.
  - As VE/V_{CO_2} slope and $P_{ET}CO_2$ progress to red, likelihood of secondary PH increases.
- Greater number of CPX and standard ET variables in red/yellow/orange warrants strong consideration of more aggressive medical management and surgical options.

VE/V_{CO_2}, minute ventilation/CO_2 production; V_{O_2}, oxygen Consumption; $P_{ET}CO_2$: partial pressure of end-tidal CO_2; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CPX, cardiopulmonary exercise test; ECG, electrocardiogram; ET, exercise test; HRR, heart rate recovery; ILD, interstitial lung disease; PH, pulmonary hypertension; RER, respiratory exchange ratio; SpO_2, saturation of peripheral O_2.

[a] Peak V_{O_2} valid if peak RER is at least 1.00 or test terminated secondary to abnormal haemodynamic or ECG exercise response.

Appendix 7: Diagnostic stratification for patients with suspected myocardial ischaemia

Primary CPX variables

O_2 pulse trajectory[b]	Per cent-predicted peak V_{O_2}[a]	$\Delta V_{O_2}/\Delta W$ trajectory[b]
🟩 Continual rise throughout ET with possible plateau approaching maximal exertion	🟩 ≥100% predicted	🟩 Continual rise throughout ET
🟨 Early and sustained plateau	🟨 75–99% predicted	🟨 Early and sustained plateau
	🟧 50–75% predicted	
🟥 Early plateau then decline	🟥 <50% predicted	🟥 Early plateau then decline

Standard exercise test variables

Haemodynamics	ECG
🟩 Rise in systolic BP during ET	🟩 No sustained arrhythmias, ectopic foci, and/or ST segment changes during ET and/or in recovery
🟨 Flat systolic BP response during ET	🟨 Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: did not lead to test termination
🟥 Drop in systolic BP during ET	🟥 Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: led to test termination

Patient reason for test termination

🟩 Lower extremity muscle fatigue	🟨 Angina	🟥 Dyspnoea

Interpretation

- Progression of per cent-predicted peak V_{O_2} from green to red indicative of progressively higher level of ischaemia and functional decline.
- O_2 pulse and $\Delta V_{O_2}/\Delta W$ trajectory progressing to red indicative of myocardial ischaemia in appropriately screened patients (i.e. baseline signs/ symptoms/risk factors suggesting increased coronary artery disease risk).
- Haemodynamic and ECG responses in yellow and red indicative of abnormal exercise response and further support myocardial ischemia in appropriately screened patients (i.e. baseline signs/symptoms/risk factors suggesting increased CHD risk).

O_2 pulse, oxygen pulse; V_{O_2}, oxygen consumption; $\Delta V_{O_2}/\Delta W$, change in oxygen consumption/change in Watts; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CPX, cardiopulmonary exercise test; ECG, electrocardiogram; ET, exercise test; ILD, interstitial lung disease; PH, pulmonary hypertension; RER, respiratory exchange ratio.

[a] Per cent-predicted peak V_{O_2} valid if peak RER is at least 1.00 or test terminated secondary to abnormal hemodynamic or ECG exercise response. Per cent-predicted values derived from formulas proposed by Wasserman

[b] Requires O_2 pulse and $\Delta V_{O_2}/\Delta W$ plot from initiation to end of exercise test. If these variables required for assessment, electronically braked cycle ergometer should be used for testing.

Appendix 8: Diagnostic stratification for patients with suspected mitochondrial myopathy

Primary CPX variables

$\Delta Q/\Delta V_{O_2}$	Per cent-predicted peak V_{O_2}[a]	Peak VE/V_{O_2}
≈5	≥100% predicted	≈40
	75–99% predicted	50 = upper limit of normal
≥7	50–75% predicted	>50
	<50% predicted	

Standard ET variables

Haemodynamics	ECG
Rise in systolic BP during ET	No sustained arrhythmias, ectopic foci, and/or ST segment changes during ET and/or in recovery
Flat systolic BP response during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: did not lead to test termination
Drop in systolic BP during ET	Altered rhythm, ectopic foci, and or ST segment changes during ET and/or in recovery: led to test termination

Interpretation

- Progression of per cent-predicted peak V_{O_2} from green to red indicative of progressively higher level of mitochondrial dysfunction.
- $\Delta Q/\Delta V_{O_2}$ and peak VE/V_{O_2} in red indicative of mitochondrial myopathy; consider muscle biopsy to obtain definitive diagnosis.
- Although not diagnostic for mitochondrial myopathy, haemodynamic and ECG responses in yellow and red universally indicative of abnormal ET response.

$\Delta Q/\Delta V_{O_2}$, change in cardiac output/change in O_2 consumption; measurement requires additional equipment of assess Q response to ET through non-invasive rebreathing technique; V_{O_2}, O_2 consumption; VE/V_{O_2}, minute ventilation/O_2 consumption; BP, blood pressure; CPX, cardiopulmonary exercise test; ECG, electrocardiogram; ET, exercise test; RER, respiratory exchange ratio.

[a] Per cent-predicted peak V_{O_2} valid if peak RER is at least 1.00 or ET terminated secondary to abnormal haemodynamic or ECG exercise response. Per cent-predicted values derived from formulas proposed by Wasserman.

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