



2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations

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In the past several decades, cardiopulmonary exercise testing (CPX) has seen an exponential increase in its evidence base. The growing volume of evidence in support of CPX has precipitated the release of numerous scientific statements by societies and associations. In 2012, the European Association for Cardiovascular Prevention & Rehabilitation and the American Heart Association developed a joint document with the primary intent of redefining CPX analysis and reporting in a way that would streamline test interpretation and increase clinical application. Specifically, the 2012 joint scientific statement on CPX conceptualized an easy-to-use, clinically meaningful analysis based on evidence-vetted variables in color-coded algorithms; single-page algorithms were successfully developed for each proposed test indication. Because of an abundance of new CPX research in recent years and a reassessment of the current algorithms in light of the body of evidence, a focused update to the 2012 scientific statement is now warranted. The purposes of this update are to confirm algorithms included in the initial scientific statement not requiring revision, to propose revisions to algorithms included in the initial scientific statement, to propose new algorithms based on emerging scientific evidence, to further clarify the application of oxygen consumption at ventilatory threshold, to describe CPX variables with an emerging scientific evidence base, to describe the synergistic value of combining CPX with other assessments, to discuss personnel considerations for CPX laboratories, and to provide recommendations for future CPX research.

Keywords AHA Scientific Statements • diagnosis • exercise test • physical exertion • prognosis

In the past several decades, cardiopulmonary exercise testing (CPX) has seen an exponential increase in its evidence base. From the long-lasting vision of test indications limited to a narrowed study of certain pathophysiological conditions, CPX now has the potential to become more intrinsic to daily clinical practice as a result of a growing awareness of the considerable amount of valuable information provided. Accordingly, indications for ventilatory expired gas analysis during exercise have broadened to a wide array of confirmed or suspected cardiopulmonary and musculoskeletal conditions and to individuals without a medical diagnosis.^{1–6}

The growing volume of evidence in support of CPX has precipitated the release of numerous scientific statements by societies and associations.^{4,7,8} Despite these advances and endorsements, CPX application in the clinical setting has lagged behind the evidence base. This disconnect may be due in part to the historical approach to CPX data reporting, which commonly includes all potential variables derived from the test without assessment of the literature to determine whether this practice is warranted. In other words, do all possible variables derived from CPX portend clinically valuable information? In fact, a majority of CPX variables described in

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traditional reports, in either tabular or graphical form, are poorly understood by the typical practitioner in terms of their clinical value for many test indications. This approach has led to a large volume of data that clinicians less versed in CPX find difficult to navigate, which may be at the core of why this valuable assessment of cardiopulmonary exercise performance is underused.

In 2012, the European Association for Cardiovascular Prevention & Rehabilitation and the American Heart Association (AHA) developed a joint document with the primary intent of redefining CPX analysis and reporting in a way that would streamline test interpretation and increase clinical application.¹ Specifically, the 2012 joint scientific statement on CPX conceptualized an easy-to-use, clinically meaningful analysis based on evidence-validated variables in color-coded algorithms; single-page algorithms were successfully developed for each proposed test indication.

Since release of the 2012 scientific statement, the body of evidence assessing the applicability of CPX has continued to grow significantly.^{6,9,10} Because of an abundance of new CPX research in recent years and a reassessment of the current algorithms in light of the body of evidence, a focused update to the 2012 scientific statement is now warranted. The purposes of this update are to confirm algorithms included in the initial scientific statement not requiring revision, to propose revisions to algorithms included in the initial scientific statement, to propose new algorithms based on emerging scientific evidence, to further clarify the application of oxygen consumption ($\dot{V}O_2$) at ventilatory threshold (VT), to describe CPX variables with an emerging scientific evidence base, to describe the synergistic value of combining CPX with other assessments, to discuss personnel considerations for CPX laboratories, and to provide recommendations for future CPX research.

2012 algorithms not requiring revision

The writing group reviewed the CPX literature that has emerged since the 2012 scientific statement was released.¹ In addition, a broader perspective was taken, reassessing CPX literature that was published before the 2012 scientific statement. From this review, it was determined that the following CPX algorithms included in the 2012 scientific statement did not require revision at this time: heart failure (HF), confirmed or suspected hypertrophic cardiomyopathy, confirmed or suspected pulmonary arterial hypertension/secondary pulmonary hypertension (PH), suspected myocardial ischemia, and suspected mitochondrial myopathy. The reader is therefore referred to the 2012 scientific statement for continued use of these algorithms.¹

2012 CPX universal reporting sheet and algorithms requiring revision

Universal reporting sheet

The revised universal CPX reporting sheet is illustrated in Appendix 1. As described in the initial scientific statement,¹ the universal reporting sheet is to be completed for all CPX indications. In the

revised version, a section for comparing and reporting the relationship between the exercise tidal volume loop and maximal flow-volume loop has been added. This comparison is used to identify a possible expiratory flow limitation (EFL), which could be a primary or contributing mechanism for exercise intolerance and abnormal symptomatology (i.e. exertional dyspnea); a detailed account of the pathophysiological premise of an EFL is given elsewhere.^{13–17} The writing group recognizes that performing flow-volume loop analysis may not be possible in all CPX laboratories; we therefore do not view this addition as a required measurement. However, there is sufficient and long-standing literature to indicate that flow-volume loop assessment during CPX improves interpretive resolution and should be considered in laboratories capable of this assessment from both an equipment and a personnel perspective. The Figure 1 illustrates an example of a normal exercise tidal volume loop, within the maximal flow-volume loop envelope, and an example of an EFL.

Unexplained exertional dyspnea and chronic obstructive pulmonary disease or interstitial lung disease

Algorithms for unexplained exertional dyspnea, chronic obstructive pulmonary disease, and interstitial lung disease were included in the 2012 scientific statement.¹ The use of CPX to assess unexplained exertional dyspnea is particularly common in clinical practice. The use of CPX in both of these patient populations is still endorsed in this focused update; all variables included in the initial algorithm continue to be key elements for assessing the cardiopulmonary response to aerobic exercise. In the revised algorithms, which are illustrated in Appendixes 2 and 3, flow-volume loop assessment has been added. For patients with unexplained exertional dyspnea, the presence and magnitude of an EFL further elucidate a pulmonary mechanism for exertional limitations and abnormal symptomatology. In patients with confirmed chronic obstructive pulmonary disease or interstitial lung disease, some degree of EFL is to be expected in the majority of cases.^{13,14} The assessment of flow-volume loops during exercise in these patients would allow the quantification of the magnitude of the EFL when present, providing further resolution of disease severity.

New CPX indications and algorithms

CPX to assess perisurgical and postsurgical risk and long-term prognosis

Accurately assessing an individual's risk for untoward events perioperatively or postoperatively provides important guidance on surgical eligibility. Accurately determining long-term prognosis after a surgical procedure with presurgical assessments also provides valuable information. Literature demonstrating the significant prognostic value of CPX before several surgical procedures has emerged.^{18–21} Surgical procedures in which CPX has demonstrated prognostic value include abdominal aortic aneurysm repair,^{22–25} radical cystectomy,²⁶ liver transplantation,²⁷ hepatic resection,²⁸ lung resection,^{29–33} bariatric surgery,^{34,35} and colorectal surgery.^{36,37} In fact, the American

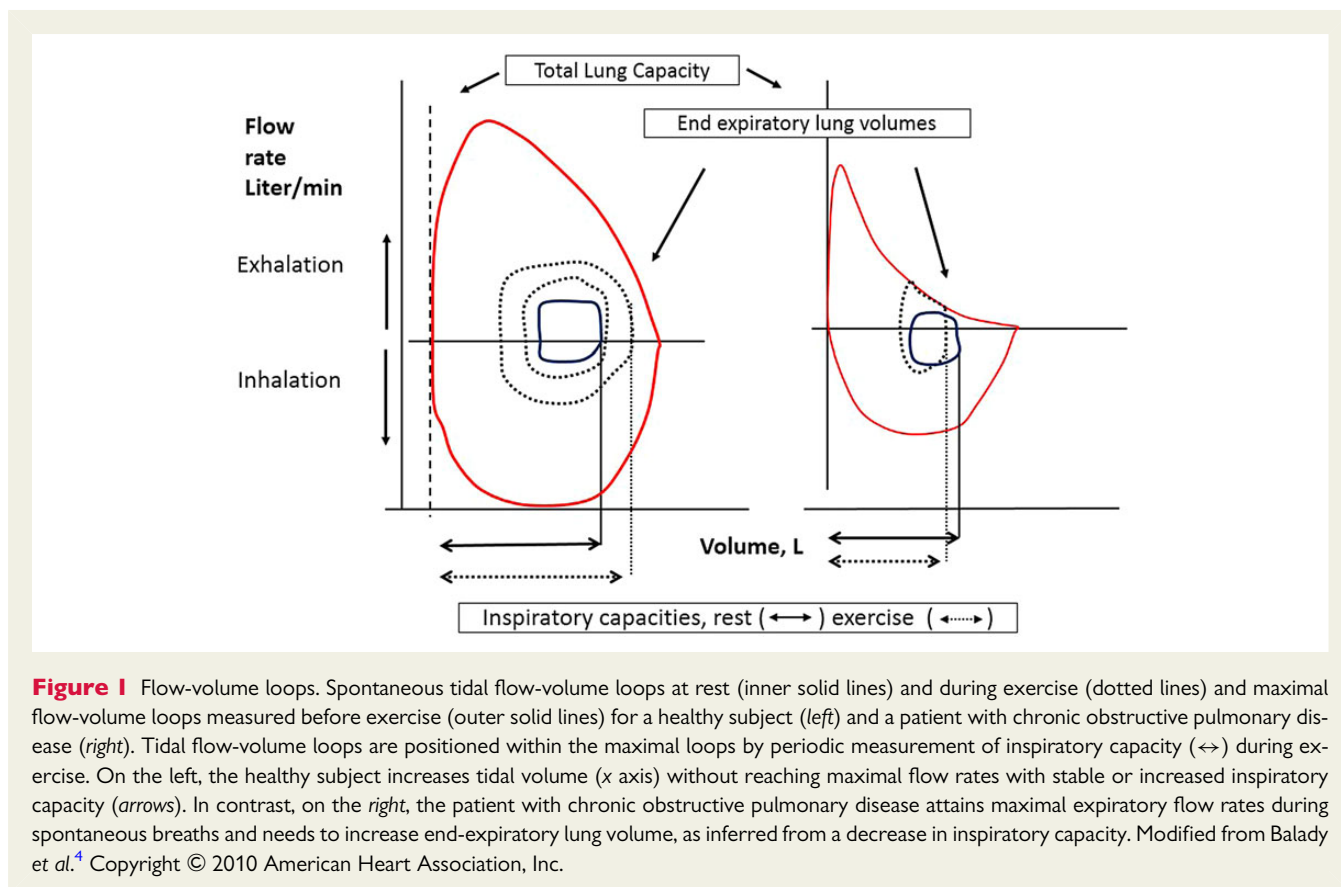


Figure 1 Flow-volume loops. Spontaneous tidal flow-volume loops at rest (inner solid lines) and during exercise (dotted lines) and maximal flow-volume loops measured before exercise (outer solid lines) for a healthy subject (*left*) and a patient with chronic obstructive pulmonary disease (*right*). Tidal flow-volume loops are positioned within the maximal loops by periodic measurement of inspiratory capacity (\leftrightarrow) during exercise. On the left, the healthy subject increases tidal volume (x axis) without reaching maximal flow rates with stable or increased inspiratory capacity (*arrows*). In contrast, on the *right*, the patient with chronic obstructive pulmonary disease attains maximal expiratory flow rates during spontaneous breaths and needs to increase end-expiratory lung volume, as inferred from a decrease in inspiratory capacity. Modified from Balady *et al.*⁴ Copyright © 2010 American Heart Association, Inc.

College of Chest Physicians clinical practice guidelines for evaluation procedures of patients with lung cancer being considered for surgical resection recommend the use of CPX to assess risk.³⁸ The 2014 American College of Cardiology/AHA guidelines on the perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery also give CPX a Class IIb (Level of Evidence B) rating.³⁹ Specifically, this guideline recommends, “CPX may be considered for patients undergoing elevated risk procedures in whom functional capacity is unknown.”³⁹ From this body of original literature and practice guidelines, the 3 CPX variables that consistently demonstrate prognostic significance are peak \dot{V}_{O_2} ; \dot{V}_{O_2} at VT, which is often referred to as anaerobic threshold; and the minute ventilation/carbon dioxide production (\dot{V}_E/\dot{V}_{CO_2}) relationship (i.e. ventilatory efficiency).

Appendix 4 illustrates a proposed CPX algorithm for presurgical risk assessment. The Ventilatory⁴⁰ and Weber⁴¹ classification systems, included in Appendix 4, provide an appropriate 4-level system for incrementally quantifying increasing risk. Using \dot{V}_{O_2} at VT was not recommended for any CPX algorithm in the 2012 scientific statement.¹ However, the prognostic value of \dot{V}_{O_2} at VT has been assessed extensively in the literature evaluating presurgical risk using CPX and has consistently been found to be a significant prognostic marker.^{20,42} Thus, the writing group recommends the inclusion of \dot{V}_{O_2} at VT for the presurgical risk assessment algorithm. In the calculation of \dot{V}_{O_2} at VT, the writing group recommends using rigorous and established guidelines; visually verifying this measure

by at least 1 experienced reviewer, although 2 or 3 blinded reviewers are preferred; and using multiple graphical detection techniques with appropriate data sampling (i.e. 10-second rolling averages).^{4,43} Moreover, a valid and reliable identification of \dot{V}_{O_2} at VT is not always possible; this has been well documented in patients with HF.⁴⁴ If \dot{V}_{O_2} at VT is unidentifiable, the validity of the CPX should be confirmed by ensuring that the subject effort reached a sufficient level (i.e., peak respiratory exchange ratio ≥ 1.00). Assessment of hemodynamics, the electrocardiogram, and subjective symptoms is standard practice with universal prognostic implications and therefore is included in this algorithm.^{3,45}

CPX to assess valvular disease/dysfunction

Normal right- and left-sided valvular function is critical to aerobic exercise performance. Disease or dysfunction in any of the 4 cardiac valves can have a significant impact on cardiopulmonary function. Two major effects of valvular heart disease (VHD) are retrograde pressure elevation (i.e. PH) and diminished cardiac output (CO). CPX may be of value in a wide spectrum and stages of VHD, particularly for its ability to gauge pulmonary hemodynamic status through the assessment of ventilatory efficiency and augmentation of CO through the assessment of aerobic capacity. In particular, ventilatory efficiency, commonly assessed by the \dot{V}_E/\dot{V}_{CO_2} slope, plays an important role in detecting elevated pulmonary pressures.^{2,46,47} Given that PH is often a consequence of left-sided VHD,⁴⁸ the assessment of the \dot{V}_E/\dot{V}_{CO_2} slope may be particularly advantageous.

In asymptomatic patients with severe aortic stenosis, the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines consider the development of symptoms during exercise or a decrease in blood pressure (BP) during exercise compared with resting values abnormal responses, representing a Class I and IIA, respectively, Level of Evidence C indication for aortic valve replacement.⁴⁹ In a series of patients with asymptomatic severe aortic stenosis, Levy *et al.*⁵⁰ demonstrated that an elevated \dot{V}_E/\dot{V}_{CO_2} slope and decreased peak \dot{V}_{O_2} were consistently present in those with an abnormal exercise response and subsequently underwent an aortic valve replacement. In another investigation, an elevated \dot{V}_E/\dot{V}_{CO_2} slope was found to be a significant predictor of decompensated HF or mortality in asymptomatic patients with severe aortic stenosis.⁵¹

The relationship between mitral valve disease/dysfunction and CPX responses has also been examined. Izumo *et al.*⁵² categorized an HF cohort into those with and those without concomitant exercise-induced mitral regurgitation (MR). Subjects with exercise-induced MR presented with a significantly lower peak \dot{V}_{O_2} and higher \dot{V}_E/\dot{V}_{CO_2} slope.⁵² Tanabe *et al.*⁵³ performed CPX in a symptomatic MR cohort days before and days after (2–4 days) surgical correction and in a healthy control group for comparison. Peak \dot{V}_{O_2} was significantly lower and the \dot{V}_E/\dot{V}_{CO_2} slope was significantly higher in subjects with symptomatic MR compared with healthy control subjects. Surgical correction did not immediately improve peak \dot{V}_{O_2} but significantly reduced the \dot{V}_E/\dot{V}_{CO_2} slope. However, the \dot{V}_E/\dot{V}_{CO_2} slope remained significantly higher in the experimental group compared with the control group after surgical correction. Banning *et al.*⁵⁴ also demonstrated an immediate, significant reduction in the \dot{V}_E/\dot{V}_{CO_2} slope after surgical correction in a cohort with mitral stenosis. Peak \dot{V}_{O_2} did not improve immediately but was significantly higher at the 10-week follow-up.

De Meester *et al.*⁵⁵ recently reported a significantly lower peak \dot{V}_{O_2} and significantly higher \dot{V}_E/\dot{V}_{CO_2} slope in a cohort with mild to moderate pulmonary stenosis compared with healthy control subjects. Chowdhury *et al.*⁵⁶ assessed change in CPX performance before and after pulmonary valve replacement in a mixed pulmonary VHD cohort. Six months after surgery, the \dot{V}_E/\dot{V}_{CO_2} slope was significantly reduced with no change in peak \dot{V}_{O_2} .

Appendix 5 illustrates a proposed algorithm for patients with VHD when CPX is available and used. Current evidence indicates that ventilatory efficiency (i.e. the \dot{V}_E/\dot{V}_{CO_2} slope) may be an important marker to assess VHD severity, prognosis, and improvements after surgical correction. Peak \dot{V}_{O_2} is also a marker of the degree to which VHD compromises CO and therefore aerobic capacity. It does not appear that peak \dot{V}_{O_2} is a sensitive marker for immediate improvements after surgical correction, although improvements may be realized over a longer time frame. We recommend that the \dot{V}_E/\dot{V}_{CO_2} slope be graded by the ventilatory classification system.⁴⁰ A value <30 is considered normal, and progressively higher values indicate greater severity of VHD and poorer prognosis. Patients with VHD will present with a wide range of peak \dot{V}_{O_2} values. Therefore, we propose that peak \dot{V}_{O_2} be reported with both the Weber classification system⁴¹ and the prediction equations proposed by Wasserman *et al.*¹¹ and Hansen *et al.*¹² Assessing systolic BP (SBP) is also an important consideration because a drop in SBP during CPX is indicative of a critical threshold at which VHD is compromising further increases in CO.⁵⁷ The \dot{V}_{O_2} or workload at which

a drop in SBP occurs is also important to consider in understanding the degree of functional impairment caused by VHD. Assessment of the ECG response is standard, and any abnormalities should be documented and considered an indicator of overall cardiac dysfunction. Lastly, the occurrence of angina or dyspnea is also considered an abnormal response, leading to exercise test termination.⁵⁷

CPX in apparently healthy individuals

Aerobic capacity is one of the strongest predictors of the risk for future adverse events in apparently healthy individuals.^{3,5,45,58,59} In 2013, the AHA published a policy statement calling for the development of a national aerobic capacity registry in apparently healthy individuals,⁶⁰ illustrating the recognized importance of accurately quantifying aerobic capacity in assessing an individual's overall health and risk for the development of future noncommunicable diseases and adverse events. This policy statement resulted in the establishment of the Fitness Registry and the Importance of Exercise National Database Registry, which recently published normative aerobic capacity values for the United States.⁶ Moreover, assessing the physiological response to aerobic exertion provides a wealth of information on potential underlying abnormalities that, if detected, would ideally be addressed before the subject is diagnosed with a noncommunicable disease or suffers an initial adverse event. It should be noted that an apparently healthy designation indicates the absence of a medical diagnosis as opposed to good health and high cardiorespiratory fitness. In fact, the majority of individuals in the United States who are defined as apparently healthy present with less-than-ideal cardiovascular health as a result of unhealthy lifestyle characteristics (i.e. physical inactivity, poor diet, excess body weight, smoking) and poor health metrics (i.e. dyslipidemia, hypertension, hyperglycemia).⁶¹

In a 2005 AHA scientific statement, Lauer *et al.*⁵ elucidated a compelling case for exercise testing without ventilatory expired gas in the asymptomatic population, given the value of data obtained. However, the use of exercise testing procedures, including CPX, is still not common in apparently healthy individuals receiving health care (e.g., as part of an annual checkup with a primary care physician). Clearly, research is needed to determine the clinical value of exercise testing in general, and CPX specifically, in apparently healthy populations before concrete recommendations can be made. Moreover, in the United States, both standard exercise testing and CPX are not reimbursable by government or private health insurers in this population. Nonetheless, apparently healthy individuals may undergo CPX services through gym memberships, hospital- or university-based health and wellness centers, private companies that provide CPX services for self-pay, and executive health assessments. In addition, normative aerobic capacity values, derived from large cohorts in the United States⁶ and Europe,⁶² have recently been published, demonstrating an increased recognition of the performance of this assessment in apparently healthy individuals. Given that there are avenues for apparently healthy individuals to undergo CPX and recent publications,^{6,62} the writing group felt that an evidence-based algorithm is warranted at this time. Even so, we acknowledge CPX is currently not standard practice in apparently healthy individuals. We also strongly encourage additional research that assesses the value of exercise testing in apparently healthy individuals, as proposed in the 2005 AHA scientific statement by Lauer *et al.*⁵

Appendix 6 illustrates the CPX algorithm for apparently healthy individuals. This population will present with a wide range of peak $\dot{V}O_2$ values, therefore warranting assessment of a percent-predicted value. Assessment of ventilatory efficiency provides insight into cardiopulmonary coupling and function and, when abnormal, is related to lower levels of aerobic capacity⁶² and may indicate subclinical pathophysiology that warrants further investigation.⁶³ For example, in a series of 510 subjects with differing levels of cardiovascular risk but no previous cardiovascular event enrolled in the EURO-EX trial, exercise oscillatory ventilation was observed in 17% of cases. Subjects with exercise oscillatory ventilation had a comparatively poorer CPX performance and gas exchange phenotype.⁶³ Quantifying heart rate recovery provides another dimension that improves prognostic resolution to the CPX assessment in apparently healthy individuals.^{3,5} Abnormal hemodynamic and ECG responses, as well as angina or dyspnea as primary reported symptoms for test termination, when present, should be investigated further.^{3,45,64} For example, individuals with a normal resting BP who have a hypertensive response to exercise are at increased risk for resting hypertension in the future.⁶⁴ It is important to note that heart rate recovery, hemodynamics, and electrocardiographic and subjective symptoms are accessible through standard exercise testing procedures without the use of ventilatory expired gas analysis (i.e. standard exercise test). Thus, when ventilatory expired gas is not available, analysis of these variables in conjunction with estimated aerobic capacity via metabolic equivalents has value and should be considered. In these instances, portions of the algorithm presented in Appendix 6 that do not require ventilatory expired gas analysis should be considered for test interpretation.

Use of $\dot{V}O_2$ at VT to assess tolerance to sustained aerobic activities and to prescribe an individualized exercise training intensity

Assessing $\dot{V}O_2$ at VT was included in the initial universal CPX reporting sheet proposed in 2012¹ and is maintained in this focused update. Moreover, $\dot{V}O_2$ at VT is now included in the presurgical assessment algorithm. The writing group felt that further clarification of the utility of this CPX variable was warranted. Although $\dot{V}O_2$ at VT is included in only 1 CPX algorithm at this time, it is important to note that this variable holds broad applicability in the context of assessing the capacity to perform sustained aerobic activities and determining an individualized training intensity for a structured aerobic exercise program.⁴ Thus, for individuals undergoing CPX who are deemed medically stable and are not being scheduled for follow-up testing or a surgical procedure, $\dot{V}O_2$ at VT should be used to identify the heart rate and workload that correspond to an appropriate target for aerobic exercise training.⁶⁵ For example, an individual with HF achieves a peak $\dot{V}O_2$ of $16.5 \text{ mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and a $\dot{V}O_2$ at VT of $12.0 \text{ mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; VT corresponded to a heart rate of 105 bpm and a treadmill speed and grade of 2 mph and 5%, respectively. A treadmill exercise program in

which the target training intensity was set at this speed and grade with a target heart rate goal of ≈ 105 bpm would be appropriate. As described in the section on the use of CPX for surgical candidates, an accurate, reliable determination of $\dot{V}O_2$ at VT requires certain procedures that should be followed by all laboratories.^{4,41}

Additional CPX variables demonstrating potential value

From a review of the literature, the writing group concluded that several variables derived from CPX data have demonstrated clinical promise. The evidence assessing the clinical utility of these CPX variables does not warrant inclusion in any of the proposed algorithms at this time for 2 reasons: (1) There are no firmly established threshold values, dichotomous or multilevel, for these variables, and (2) there is limited or inconclusive information on the added clinical value (i.e. multivariate modeling) of these variables in relation to more established measures obtained from CPX. However, the writing group felt that these variables merited some discussion and potential future consideration.

Oxygen uptake efficiency slope

The oxygen uptake efficiency slope (OUES) was first proposed by Baba *et al.*⁶⁶ in 1996 and has since been evaluated extensively in patients with HF. The OUES is derived from the relationship between $\dot{V}O_2$ (plotted on the y axis) and the log transformation of $\dot{V}E$ (x axis). Thus, it is a metric that expresses the ventilatory requirement for a given $\dot{V}O_2$. The log transformation of $\dot{V}E$ creates a high linearity in relation to $\dot{V}O_2$, which also has the effect of making the OUES effort independent. Patients with HF have demonstrated significantly lower OUES values compared with cohorts without HF, and the OUES is reduced in accordance with disease severity.⁶⁷ Reference equations for the OUES have been proposed,⁶⁸ although cut points for classification of risk with the OUES have not been established. Nevertheless, a consistent body of literature has demonstrated the prognostic utility of the OUES in patients with HF.^{69–73} However, the ability of the OUES to remain a significant prognostic marker in a multivariate regression with the full panel of established CPX variables is uncertain. The OUES has also been assessed before and after exercise training^{74–77} and heart transplantation.⁷⁸ It has been demonstrated to improve after these interventions, indicating that the OUES has promise as a CPX marker sensitive to clinical change.

Exercise ventilatory power

Forman *et al.*⁷⁹ proposed a novel ventilatory index called exercise ventilatory power (EVP), defined as the ratio between peak SBP and the $\dot{V}E/\dot{V}CO_2$ slope. They hypothesized that these 2 measures, one reflecting the complex interplay of peripheral (e.g., peripheral perfusion, along with skeletal muscle chemoreflexes and afferent reflexes) and pulmonary abnormalities (alveolar perfusion and ventilation) and the other reflecting systemic hemodynamics, would provide a useful integrated index to predict risk. Using $\leq/\geq 3.5$ mm Hg as a cutoff for high risk, EVP was demonstrated to have greater prognostic discrimination than traditional CPX responses. A subsequent investigation of EVP focused on the ability of this marker to reflect disease

severity and underlying pathophysiology in HF. Borghi-Silva et al.⁸⁰ considered 86 patients with HF and reduced ejection fraction (EF) who underwent CPX combined with Doppler echocardiographic recordings throughout exercise. They observed that a lower EVP reflected a highly unfavorable condition that was indicative of a severely impaired peak $\dot{V}O_2$ and CO response to exercise. The study also suggested that a low EVP was particularly indicative of impaired right heart function and pulmonary hemodynamics.

Circulatory power

The concept of cardiac power, the product of CO and mean arterial BP, was developed to characterize the relationship between cardiac-generated blood flow and peripheral perfusion pressure.⁸¹ Patients with HF who exhibit both low peak $\dot{V}O_2$ and low cardiac power have been shown to have worse outcomes than those with low peak $\dot{V}O_2$ and preserved cardiac power. Although cardiac power has compelling conceptual appeal, its application is limited by reliance on invasive cardiac assessments. The index circulatory power (CP) was introduced by Cohen-Solal et al.⁸² and is related to cardiac power but relies on CPX to achieve equivalent assessments noninvasively. With peak $\dot{V}O_2$ applied as a surrogate for CO and SBP applied for mean arterial BP, CP by CPX is calculated as the product of peak $\dot{V}O_2$ and SBP. Cohen-Solal et al.⁸² reported that peak CP was the best predictor of adverse outcomes among CPX variables. Other investigators have observed that peak CP is responsive to therapy and thus may be a valuable noninvasive marker of disease status.^{83,84}

Noninvasive determination of CO

Because peak $\dot{V}O_2$ is strongly related to the CO response to exercise, peak $\dot{V}O_2$ is often considered a surrogate for CO. In fact, one reason that peak $\dot{V}O_2$ is such a strong prognostic marker is that it closely parallels cardiac function with exercise. However, peak $\dot{V}O_2$ can be influenced by many other factors (including age, sex, motivation, obesity, deconditioning, and localized muscle fatigue).⁸⁵ Thus, it has been of interest to study whether the noninvasive determination of CO may enhance the prognostic power of CPX. A number of studies have been useful in assessing the complementary value of CO responses to exercise, along with CPX indexes, for evaluating other hemodynamic responses (e.g., exercise EF, stroke work index, and other indexes of contractility) and for assessing submaximal hemodynamic responses to exercise. Studies have demonstrated that noninvasively determined peak CO provides an independent predictor of outcomes that enhances the prognostic utility of peak $\dot{V}O_2$.^{86–90} More recent reports suggest that noninvasively determined peak cardiac index complements indexes of ventilatory inefficiency and peak $\dot{V}O_2$ and that combining these markers provides the most powerful stratification of risk.^{91,92} Although the Fick and thermodilution methods remain the gold standards for the measurement of CO,⁹³ several rebreathing methods that use CPX are available. Bioelectric impedance has also experienced a renewed interest in recent years, and along with a number of validation studies, cardiac hemodynamics with these techniques have been shown to have prognostic value in patients with HF.^{91,92,94–96}

Synergistic assessments: CPX and Doppler echocardiography

There is a strong theoretical and practical rationale supporting the simultaneous study of heart, lung, and peripheral physiology by gas exchange analysis with cardiac hemodynamics and valve function assessment by Doppler echocardiography.^{80,97} The Table 1 lists the summative advantages of combining these 2 exercise assessment techniques. Echocardiographic stress is complementary and synergic to CPX in providing information on the contractile state and relaxation of cardiac chambers, defining the corresponding contributions of left-sided versus right-sided heart hemodynamics and valve function to exercise performance.

One of the most immediate advantages of the combined CPX-echocardiographic evaluation is the possibility of calculating CO, yielding a direct comparison between CP performance ($\dot{V}O_2$ /SBP) and cardiac power output [mean arterial BP \times (stroke volume/60) \times heart rate]. Because $\dot{V}O_2$ is CO \times (A – $\dot{V}O_2$) difference, for similar impairment in $\dot{V}O_2$, the parallel assessment of these variables may allow elucidation of the respective roles of peripheral O₂ extraction deficit (i.e. CP) and the CO limitation (i.e. cardiac power).

In the presence of exercise-induced dyspnea, some individuals exhibit impaired $\dot{V}O_2$ kinetics, demonstrated by a transition from $\dot{V}O_2$ linearity to a flattened pattern during progressive exercise. This phenomenon has commonly been interpreted as the inability of the heart to adequately increase CO, especially in the presence of myocardial ischemia⁹⁸ and severely depressed left ventricular contractility.⁹⁹ However, this abnormal $\Delta \dot{V}O_2/\Delta$ work rate (WR) relationship may also be observed in patients with an exercise limitation and no evidence of left ventricular systolic dysfunction or reduced coronary reserve. A recent report⁹⁷ characterized 136 patients with various cardiovascular diagnoses referred for assessment of exertional dyspnea. CPX combined with simultaneous exercise echocardiography was used to determine the cardiac mechanisms behind a nonlinear increase in $\Delta \dot{V}O_2/\Delta$ WR. A $\Delta \dot{V}O_2/\Delta$ WR flattening was observed in 36 patients (26.5% of population) and was associated with a globally worse functional profile (reduced

Table 1 Main synergic features of CPX and Doppler echocardiography–stress assessment

CPX	Doppler echocardiography–stress
Assessment of key organ systems (cardiac, peripheral and pulmonary) involved in exercise limitations	Measurement of cardiac contractile state and relaxation
High reproducibility	Assessment of RV functional adaptation to exercise
Objective measure of therapeutic efficacy	Study of valve diseases and pattern of adaptation
Significant prognostic and diagnostic information	Significant prognostic and diagnostic information

CPX, cardiopulmonary exercise testing; RV, right ventricular.

peak $\dot{V}O_2$, $\dot{V}O_2$ at VT, and O_2 pulse and increased $\dot{V}E/\dot{V}CO_2$ slope). In univariate analysis, determinants of $\dot{V}O_2$ flattening were exercise EF, exercise MR, rest and exercise tricuspid annular plane systolic excursion, exercise pulmonary artery systolic pressure, and exercise CO. Multivariate analysis identified increased exercise pulmonary artery systolic pressure and reduced exercise tricuspid annular plane systolic excursion as the main cardiac determinants of $\Delta \dot{V}O_2/\Delta W$ flattening. This information fits with the evolving evidence that right ventricular (RV)–to–pulmonary circulation (PC) coupling is of critical importance to circulatory function and overall performance during exercise. The RV is more sensitive to pressure load increases with exercise compared with the left ventricular load, and its inability to adapt to disproportionate load may occur in different settings and stages of cardiovascular diseases not necessarily related to overt PH at rest.¹⁰⁰

Approximately 60% of patients with either reduced or preserved left ventricular EF develop PH.¹⁰¹ In left-sided heart disease, exercise-induced MR is a well-recognized determinant of PH that portends an unfavorable prognosis, especially when RV-to-PC uncoupling coexists.¹⁰² There is recent renewed interest in the role of RV-to-PC uncoupling in the natural history of HF, and its investigation during exercise through a combined echocardiography stress/CPX assessment may prove to be of value. A simplification of the RV-to-PC coupling measure may be obtained noninvasively by Doppler echocardiography looking at the relationship between pulmonary artery systolic pressure changes and tricuspid annular plane systolic excursion.¹⁰³ A worse RV-to-PC uncoupling phenotype is tightly related to ventilatory inefficiency during exercise.⁸⁰ Assessment of RV-to-PC uncoupling and its CPX correlates is likewise relevant in patients with pulmonary arterial hypertension. In a group of patients with idiopathic pulmonary arterial hypertension, the combination of stress Doppler echocardiography and CPX revealed the most important independent prognostic factors to be peak $\dot{V}O_2$ and a low pulmonary artery systolic pressure increase.¹⁰⁴ This combination is useful for therapeutic decision making by identifying patients at especially high risk and inadequate therapy. These preliminary data support the hypothesis that estimation of RV contractile reserve by Doppler echocardiography plays an adjunctive key role for the follow-up and therapeutic management of patients with pulmonary arterial hypertension.

A recent publication demonstrated that the combination of CPX and exercise Doppler echocardiography may help to identify HF with preserved EF in individuals diagnosed with hypertension who present with exertional dyspnea and normal resting left ventricular systolic and diastolic function. Numerous variables from both CPX and Doppler echocardiography at peak exercise (e.g., E/peak $\dot{V}O_2$, and the $\dot{V}E/\dot{V}CO_2$ slope) were significantly different between subjects with and without HF with preserved EF.¹⁰⁵ These findings demonstrate the potential utility of CPX and exercise Doppler echocardiography in identifying HF with preserved EF at an earlier time point, prompting more aggressive medical management and improving clinical outcome.¹⁰⁶

We recognize the combined CPX–Doppler echocardiographic assessments do not hold broad applicability at this time. Most CPX laboratories do not have the capacity, from either an equipment or a personnel perspective, to integrate Doppler

echocardiographic assessments. The converse is likely true for echocardiography laboratories. Perhaps the most feasible approach in the current clinical and research environment is for CPX and echocardiography laboratories that are in close proximity (i.e. in the same center, on the same floor) to agree to jointly perform exercise assessments in patient populations in whom the combined data would be of clinical or research value. To a degree, equipment from both laboratories is easily mobile if housed in close proximity (i.e. down the hall from one another). Research assessing the value of combining CPX and Doppler echocardiography is needed to provide more definitive clinical recommendations.

Supervision of CPX

In 2014, the AHA published a scientific statement on supervision of exercise testing by nonphysicians.¹⁰⁷ This document made the clear case that exercise testing can be conducted safely and competently by appropriately qualified nonphysician health professionals. The medical director of an exercise testing laboratory must continue to make the final decision as to the level of physician supervision needed for exercise testing services (i.e. direct versus proximity). This scientific statement, for the first time, provided guidance on education and practical experiences that qualify nonphysician health professionals to conduct an exercise test safely and competently. Readers of this focused update should consider the 2014 scientific statement¹⁰⁷ a valuable companion publication that provides guidance on CPX laboratory personnel decisions, competency training and ongoing experience expectations to maintain competency, and level of test supervision.

Recommendations for future CPX research

The CPX evidence base for numerous test indications continues to expand, which will allow further refinement of clinical recommendations in the future. Some specific recommendations for future research are described below.

A review of the literature shows an apparent lack of examination in terms of how CPX alters the trajectory of patient management and clinical decision making. Specifically, there is a need to determine the benefits of clinically implementing CPX, which then spurs future research questions warranting additional investigation.¹⁰⁸ For example, in patients with HF, can a poor CPX response be used to trigger more aggressive clinical management and subsequently reduce mortality and hospitalizations? The writing group recommends that assessing the clinical impact of CPX become a high research priority.

The writing group was still unable to recommend a weighting system for specific CPX variables in any of the algorithms. Some work has been done to assess CPX scores with variable weighting, depending on the prognostic strength of a given variable included in a multivariate Cox regression.^{72,109,110} More work is needed in this area to allow weighted scoring systems to be integrated into the CPX algorithms. Such approaches would most certainly improve the prognostic and diagnostic resolution of CPX. In

addition, further research is needed to determine the value of the emerging CPX variables described in this update. Such analyses will help determine whether inclusion of ≥ 1 of these emerging variables in any of the current or future CPX appendixes is warranted. To achieve these research objectives, the writing group proposes that strong consideration be given to developing a national/international CPX registry that includes tests performed for all indications described in the 2012 scientific statement¹ and the present update. Many high-quality laboratories (i.e. following current practice recommendations⁴³) around the world are performing CPX evaluations; collecting data on parallel assessments such as echocardiography, nuclear imaging, and catheterization; and tracking major adverse events. If resources were pooled, key research questions needed to refine CPX applications would be addressed with high statistical power. The procedures followed to establish the Fitness Registry and the Importance of Exercise National Database registry, elucidated in the 2013

AHA policy statement,⁶⁰ can be used to create the expanded CPX registry called for in this update.

Conclusions

CPX is a valuable clinical assessment and has a number of indications. The 2012 scientific statement¹ and the present focused update possess evidence-based CPX algorithms for these test indications. The continued intent is to streamline test interpretation while optimizing data visualization through a color-coded approach. Although the CPX literature is robust, important knowledge gaps remain that, if addressed, would further improve the clinical impact of CPX. The European Association for Cardiovascular Prevention & Rehabilitation and AHA will continue to monitor the CPX literature and will provide additional algorithm updates when warranted.

Disclosures

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

Exercise Modality: <input type="checkbox"/> Treadmill <input type="checkbox"/> Lower extremity ergometer		
Exercise Protocol:		
Peak $\dot{V}O_2$ (mlO ₂ ·kg ⁻¹ ·min ⁻¹): □□.□	Percent-Predicted Peak $\dot{V}O_2$ (%)* □□.□	$\dot{V}E/\dot{V}CO_2$ Slope [†] : □□.□
$\dot{V}O_{2at VT}$ (mlO ₂ ·kg ⁻¹ ·min ⁻¹): □□.□	Peak RER: □.□□	EOV [‡] <input type="checkbox"/> Yes <input type="checkbox"/> No
VT as % Peak $\dot{V}O_2$: □□		
P_{ET}CO₂ (mmHg): Resting: □□.□ Increase during ET: □.□	$\dot{V}E/\dot{V}O_2$ at peak ET: □□.□	$\Delta Q/\Delta \dot{V}O_2$ [§] □□.□
$\dot{V}E/MVV$: □.□□ PEF (L/min): Pre ET - □□.□ Post ET: □□.□ FEV ₁ (L/min): Pre ET - □□.□ Post ET: □□.□		
Flow Volume Loops: Compare Maximal Flow Volume Loop to Exercise Tidal Volume Loop		
Normal <input type="checkbox"/> or Expiratory Flow Limitation <input type="checkbox"/> [¶]		
O₂ pulse trajectory#: <input type="checkbox"/> Continual rise throughout ET <input type="checkbox"/> Early and sustained plateau <input type="checkbox"/> Decline		
$\Delta \dot{V}O_2/\Delta W$ trajectory#: <input type="checkbox"/> Continual rise throughout ET <input type="checkbox"/> Early and sustained plateau <input type="checkbox"/> Decline		
Resting HR (beats/min): □□	Resting BP (mmHg): □□□/□□□	Resting Pulse Oximetry (%): □□
Peak HR (beats/min): □□□	Peak BP (mmHg): □□□/□□□	Peak Pulse Oximetry (%): □□
Percent of Age Predicted Maximal HR ^{**} : □□□	Maximal Workload <input type="checkbox"/> Treadmill speed/grade: □□.□/□□.□ <input type="checkbox"/> Cycle ergometer Watts: □□□	
HRR at 1 minute (beats): □□		
ECG Criteria <input type="checkbox"/> No arrhythmias/Ectopy/ST segment changes <input type="checkbox"/> Arrhythmias/Ectopy/ST segment changes: not exercise limiting <input type="checkbox"/> Arrhythmias/Ectopy/ST segment changes: exercise limiting		ECG Description
Subjective Symptoms (check box for primary termination criteria) Fatigue <input type="checkbox"/> Leg Fatigue <input type="checkbox"/> Angina <input type="checkbox"/> Dyspnea <input type="checkbox"/> Other _____ Peak RPE _____		
Additional Notes		

BP, blood pressure; CPX, cardiopulmonary exercise testing; ECG, electrocardiogram; EOv, exercise oscillatory ventilation; ET, exercise test; HR, heart rate; HRR, heart rate recovery; O₂, oxygen; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide production; PEF, peak expiratory flow; $\Delta Q/\Delta O_2$, change in cardiac output/change in oxygen consumption; RER, respiratory exchange ratio; RPE, rating of perceived exertion; E/MVV, peak minute ventilation/maximal voluntary ventilation; E/CO₂, minute ventilation/carbon dioxide production; E/O₂, minute ventilation/oxygen consumption; O₂, oxygen consumption; $\Delta O_2/\Delta W$, change in oxygen consumption/change in Watts; VT, ventilator threshold.

*Use equations proposed by Wasserman.^{11,12}

[†]Use all exercise data to calculate the E/CO₂ slope; from initiation to maximal effort.^{11,12}

[‡]Definition of EOv: Oscillatory pattern at rest that persists for $\geq 60\%$ of the exercise test at an amplitude of $\geq 15\%$ of the average resting value.^{11,12}

[§]Requires additional equipment for assessment of Q response to exercise through non-invasive rebreathing technique.

[¶]Directly measure MVV at baseline (typically FEV₁ × 40).

[¶]Refer to Figure for example of normal response and expiratory flow limitation.

[#]Requires O₂ pulse and $\Delta O_2/\Delta W$ plot from initiation to end of ET. If these variables are required for assessment, electronically braked cycle ergometer should be used for testing.

^{**}Use equation: (% peak HR achieved/220-age) × 100.

Appendix 2 Diagnostic stratification for patients with unexplained exertional dyspnea

Primary CPX Variables			
\dot{V}_E/\dot{V}_{CO_2} Slope	Percent Predicted Peak \dot{V}_{O_2} *	P_{ETCO_2}	\dot{V}_E/MVV^\dagger
Ventilatory class I \dot{V}_E/\dot{V}_{CO_2} slope <30.0	≥100% predicted	Resting P_{ETCO_2} 36–42 mm Hg 3- to 8-mm Hg increase during ET	≤0.80
Ventilatory class II \dot{V}_E/\dot{V}_{CO_2} slope 30.0–35.9	75%–99% predicted		
Ventilatory class III \dot{V}_E/\dot{V}_{CO_2} slope 36.0–44.9	50%–74% predicted	Resting P_{ETCO_2} <36 mm Hg <3-mm Hg increase during ET	>0.80
Ventilatory class IV \dot{V}_E/\dot{V}_{CO_2} slope ≥45.0	<50% predicted		
Primary PFT Variables: Flow-Volume Loop and FEV ₁ and PEF [‡]			
exT _v loop: normal		exT _v loop: expiratory flow limitation	
No change in FEV ₁ and/or PEF from before to after CPX		≥15% reduction in FEV ₁ or PEF from before to after CPX	
Standard ET Variables			
Hemodynamics	ECG		Pulse Oximetry
Rise in systolic BP during ET: 10 mm Hg/3.5–mL O ₂ ·kg ⁻¹ ·min ⁻¹ increase in \dot{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 mm Hg/3.5-mL O ₂ ·kg ⁻¹ ·min ⁻¹ increase in \dot{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			
<ul style="list-style-type: none"> • Progression of percent predicted peak \dot{V}_{O_2} from green to red reflects degree of functional impairment regardless of mechanism • As \dot{V}_E/\dot{V}_{CO_2} slope progresses from yellow to orange to red and P_{ETCO_2} progresses to red, consider an elevation in pulmonary pressure, resting or exercise induced, as a mechanism • Pulse oximetry progression to red indicative of ventilation-perfusion mismatch • \dot{V}_E/MVV, FEV₁, PEF, and flow-volume loop in red indicative of pulmonary mechanism; worsening FEV₁ and PEF response through first several minutes of recovery suggestive of EIB; FEV₁ response in the red, regardless of PEF response, also suggestive of EIB • Hemodynamic and/or ECG response in red indicative of cardiovascular mechanism 			

BP, blood pressure; CPX, cardiopulmonary exercise testing; EIB, exercise-induced bronchospasm; ET, exercise test; exT_v, exercise tidal volume; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; P_{ETCO_2} , partial pressure of end-tidal CO₂; PFT, pulmonary function test; SpO₂, saturation of peripheral O₂; \dot{V}_E/\dot{V}_{CO_2} , minute ventilation/CO₂ production; \dot{V}_E/MVV , minute ventilation at peak exercise/maximal voluntary ventilation (maximal voluntary ventilation should be directly measured before ET); \dot{V}_{O_2} , O₂ consumption.

*Peak \dot{V}_{O_2} valid if peak respiratory exchange ratio is at least 1.00 or test is terminated secondary to abnormal hemodynamic or ECG exercise response. Percent predicted values derived from formulas proposed by Wasserman et al.¹¹ and Hansen et al.¹²

†MVV should be directly measured before CPX; the majority of CPX systems allow MVV measurement.

‡Expiratory flow limitation indicates a pulmonary mechanism for unexplained dyspnea. After CPX, measurement of FEV₁ and PEF should be conducted at 1, 3, 5, 7, 10, 15, and 20 minutes.

Appendix 3 Prognostic and diagnostic stratification for patients with chronic obstructive pulmonary disease or interstitial lung disease

Primary CPX Variables			
\dot{V}_E/\dot{V}_{CO_2} Slope	Peak \dot{V}_{O_2} *	P_{ETCO_2}	
Ventilatory class I \dot{V}_E/\dot{V}_{CO_2} slope <30.0	Weber class A Peak \dot{V}_{O_2} >20.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹	Resting P_{ETCO_2} ≥33.0 mm Hg 3- to 8-mm Hg increase during ET	
Ventilatory class II \dot{V}_E/\dot{V}_{CO_2} slope 30.0–35.9	Weber class B Peak \dot{V}_{O_2} =16.0-20.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹		
Ventilatory class III \dot{V}_E/\dot{V}_{CO_2} slope 36.0–44.9	Weber class C Peak \dot{V}_{O_2} =10.0-15.9 mL O ₂ ·kg ⁻¹ ·min ⁻¹	Resting P_{ETCO_2} <33.0 mm Hg <3-mm Hg increase during ET	
Ventilatory class IV \dot{V}_E/\dot{V}_{CO_2} slope ≥45.0	Weber class D Peak \dot{V}_{O_2} <10.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹		
Flow-Volume Loops			
exT _v loop: normal		exT _v loop: expiratory flow limitation	
Standard ET Variables			
Hemodynamics	ECG	HRR	Pulse Oximetry
Rise in systolic BP during ET	No sustained arrhythmias, ectopic foci, or ST-segment changes during ET 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, or ST-segment changes during ET 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, or ST-segment changes during ET or in recovery: led to test termination		
Interpretation			
<ul style="list-style-type: none"> All variables in green: excellent prognosis in next 1–4 y <ul style="list-style-type: none"> -Maintain medical management and retest in 4 y Greater number of CPX and standard exercise test variables in red/yellow/orange indicative of progressively worse prognosis <ul style="list-style-type: none"> -All CPX variables in red: risk for major adverse event extremely high in next 1–4 y Expiratory flow limitation during exercise indicates respiratory muscle fatigue contributing to exercise limitations Greater number of CPX and standard ET variables in red/yellow/orange indicative of increasing interstitial lung disease severity <ul style="list-style-type: none"> -As \dot{V}_E/\dot{V}_{CO_2} slope and P_{ETCO_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 			

BP, blood pressure; CPX, cardiopulmonary exercise testing; ET, exercise test; exT_v, exercise tidal volume; HRR, heart rate recovery; P_{ETCO_2} , partial pressure of end-tidal CO₂; SpO₂, saturation of peripheral O₂; \dot{V}_E/\dot{V}_{CO_2} , minute ventilation/CO₂ production; \dot{V}_{O_2} , oxygen consumption.

*Peak \dot{V}_{O_2} valid if peak respiratory exchange ratio is at least 1.00 or test is terminated secondary to abnormal hemodynamic or ECG exercise response.

Appendix 4 Presurgical assessment

Primary CPX Variables		
$\dot{V}_E\dot{V}_{CO_2}$ Slope	Peak \dot{V}_{O_2} *	\dot{V}_{O_2} at VT
Ventilatory class I $\dot{V}_E\dot{V}_{CO_2}$ slope <30.0	Weber class A Peak \dot{V}_{O_2} >20.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹	≥11.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹
Ventilatory class II $\dot{V}_E\dot{V}_{CO_2}$ slope 30.0–35.9	Weber class B Peak \dot{V}_{O_2} =16.0–20.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹	
Ventilatory class III $\dot{V}_E\dot{V}_{CO_2}$ slope 36.0–44.9	Weber class C Peak \dot{V}_{O_2} =10.0–15.9 mL O ₂ ·kg ⁻¹ ·min ⁻¹	<11.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹
Ventilatory class IV $\dot{V}_E\dot{V}_{CO_2}$ slope ≥45.0	Weber class D Peak \dot{V}_{O_2} <10.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹	
Standard ET Variables		
Hemodynamics		ECG
Rise in systolic BP during ET		No sustained arrhythmias, ectopic foci, or ST-segment changes during ET or in recovery
Flat systolic BP response during ET		Altered rhythm, ectopic foci, or ST-segment changes during ET or in recovery: did not lead to test termination
Drop in systolic BP during ET		Altered rhythm, ectopic foci, or ST-segment changes during ET or in recovery: led to test termination
Patient Reason for Test Termination		
Lower-extremity muscle fatigue		Angina or dyspnea
Interpretation		
<ul style="list-style-type: none"> • All variables in green: excellent prognosis and low risk for perisurgical/postsurgical complications • Greater number of CPX and standard ET variables in red/yellow/orange indicative of progressively worse prognosis and higher risk for perisurgical/postsurgical complications <ul style="list-style-type: none"> -All CPX variables in red: risk for major adverse event or perisurgical/postsurgical complications is extremely high and long-term prognosis is poor 		

BP, blood pressure; CPX, cardiopulmonary exercise testing; ET, exercise test; $\dot{V}_E\dot{V}_{CO_2}$, minute ventilation/carbon dioxide production; \dot{V}_{O_2} , oxygen consumption.

*Peak \dot{V}_{O_2} valid if peak respiratory exchange ratio is at least 1.00 or test is terminated secondary to abnormal hemodynamic or ECG exercise response.

Appendix 5 Valvular heart disease/dysfunction

Primary CPX Variables		
\dot{V}_E/\dot{V}_{CO_2} Slope	Peak \dot{V}_{O_2} *	Percent Predicted Peak \dot{V}_{O_2} †‡
Ventilatory class I \dot{V}_E/\dot{V}_{CO_2} slope <30.0	Weber class A Peak \dot{V}_{O_2} >20.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹	≥100% predicted
Ventilatory class II \dot{V}_E/\dot{V}_{CO_2} slope 30.0–35.9	Weber class B Peak \dot{V}_{O_2} =16.0–20.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹	75–99% predicted
Ventilatory class III \dot{V}_E/\dot{V}_{CO_2} slope 36.0–44.9	Weber class C Peak \dot{V}_{O_2} =10.0–15.9 mL O ₂ ·kg ⁻¹ ·min ⁻¹	50%–75% predicted
Ventilatory class IV \dot{V}_E/\dot{V}_{CO_2} slope ≥45.0	Weber class D Peak \dot{V}_{O_2} <10.0 mL O ₂ ·kg ⁻¹ ·min ⁻¹	<50% predicted
Standard ET Variables		
Hemodynamics	ECG	
Rise in systolic BP during ET	No sustained arrhythmias, ectopic foci, or ST-segment changes during ET or in recovery	
Flat systolic BP response during exercise	Altered rhythm, ectopic foci, or ST-segment changes during ET or in recovery: did not lead to test termination	
Drop in systolic BP during ET	Altered rhythm, ectopic foci, or ST-segment changes during ET or in recovery: led to test termination	
Patient Reason for Test Termination		
Lower-extremity muscle fatigue	Angina or dyspnea	
Interpretation		
<ul style="list-style-type: none"> • All variables in green: excellent prognosis • Greater number of CPX and standard ET variables in red/yellow/orange indicative of progressively worse prognosis • Greater number of CPX and standard ET variables in red/yellow/orange warrants strong consideration of more aggressive medical management and surgical options 		

BP, blood pressure; CPX, cardiopulmonary exercise testing; ET, exercise test; \dot{V}_E/\dot{V}_{CO_2} , minute ventilation/carbon dioxide production; \dot{V}_{O_2} , oxygen consumption.

*Peak \dot{V}_{O_2} valid if peak respiratory exchange ratio is at least 1.00 or test is terminated secondary to abnormal hemodynamic or ECG exercise response.

†If peak \dot{V}_{O_2} is Weber class A, calculate percent predicted value and include in interpretation.

‡Use equations proposed by Wasserman et al.¹¹ and Hansen et al.¹²

Appendix 6 Apparently healthy individuals

Primary CPX Variables		
Percent Predicted Peak $\dot{V}O_2^{*†}$	$\dot{V}_E/\dot{V}CO_2$ Slope	EOV
≥100% predicted	<u>Ventilatory class I</u> $\dot{V}_E/\dot{V}CO_2$ slope <30.0	Not present
75%–99% predicted	<u>Ventilatory class II</u> $\dot{V}_E/\dot{V}CO_2$ slope 30.0–35.9	
50%–74% predicted	<u>Ventilatory class III</u> $\dot{V}_E/\dot{V}CO_2$ slope 36.0–44.9	Present
<50% predicted	<u>Ventilatory class IV</u> $\dot{V}_E/\dot{V}CO_2$ slope ≥45.0	
Standard ET Variables		
Hemodynamics	ECG	HRR
Rise in systolic BP during ET: 10 mm Hg/3.5–mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_2$ and no change/slight decrease in diastolic BP	No sustained arrhythmias, ectopic foci, or ST-segment changes during ET or in recovery	>12 beats at 1 min recovery
Hypertensive response: excessive rise in systolic BP during exercise: ≥20 mm Hg/3.5–mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_2$ or increase in diastolic BP: did not lead to test termination	Altered rhythm, ectopic foci, or ST-segment changes during ET or in recovery: did not lead to test termination	≤12 beats at 1 min recovery
Hypertensive response: Excessive rise in systolic BP during exercise: ≥20 mm Hg/3.5–mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ increase in $\dot{V}O_2$ or increase in diastolic BP: led to test termination Hypotensive response: flat response or decrease in systolic BP during exercise: led to test termination	Altered rhythm, ectopic foci, or ST-segment changes during ET or in recovery: led to test termination	
Patient Reason for Test Termination		
Lower-extremity muscle fatigue	Angina or dyspnea	
Interpretation		
<ul style="list-style-type: none"> • All variables in green: normal exercise response and excellent prognosis • Greater number of CPX and standard ET variables in red/yellow/orange indicative of abnormal exercise response <ul style="list-style-type: none"> -Abnormal response indicative on possible subclinical pathophysiology, increased risk for noncommunicable disease and poor prognosis -Explore mechanisms for abnormal response 		

BP, blood pressure; CPX, cardiopulmonary exercise testing; EOV, exercise oscillatory ventilation; ET, exercise test; HRR, heart rate recovery; $\dot{V}_E/\dot{V}CO_2$, minute ventilation/carbon dioxide production; $\dot{V}O_2$, oxygen consumption.

*Use equations proposed by Wasserman et al.¹¹ and Hansen et al.¹²

†Peak $\dot{V}O_2$ valid if peak respiratory exchange ratio is at least 1.00 or test is terminated secondary to abnormal hemodynamic or ECG exercise response.