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Cardiopulmonary exercise testing in the assessment of pulmonary hypertension

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Abstract

The assessment of patients with suspected or confirmed pulmonary arterial hypertension (PAH) and secondary pulmonary hypertension (PH) continues to evolve and, in recent years, evidence demonstrating that cardiopulmonary exercise testing (CPX) provides valuable information has grown at an impressive rate. The key premise supporting the use of CPX is that certain variables obtained provide insight into the degree of ventilation/perfusion mismatching secondary to altered pulmonary hemodynamics. In this article, we discuss the pathophysiology of PAH and secondary PH and its impact on cardiac function, review the clinical presentation of patients with elevated pulmonary pressures and outline a case for the use of CPX as an integral assessment technique, discuss CPX technology and testing procedures, and review the current state of available evidence and provide clinical recommendations for CPX in the setting of known or suspected PAH and secondary PH.

Keywords

aerobic capacity; carbon dioxide production; diagnosis; minute ventilation; prognosis; pulmonary vasculopathy; ventilatory efficiency

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Pulmonary arterial hypertension (PAH), a disease that primarily impacts women [1,2], is defined by a mean pulmonary artery pressure (PAP) of >25 mmHg at rest as determined by right heart catheterization [3]. PAH is a disease of the small pulmonary arterioles, which results in pulmonary vasculopathy and increased pulmonary vascular resistance (PVR), and often causes exertional dyspnea and/or fatigue and progresses to right ventricular (RV) hypertrophy, RV failure and eventual death [2,4]. The prototype form of PAH is idiopathic, but PAH may also occur secondary to toxins, including anorexigen use, familial or hereditary, HIV positivity, portal hypertension, congenital heart disease and connective tissue diseases (scleroderma in particular). A substantial percentage of secondary pulmonary hypertension (PH) is due to advanced cardiovascular (CV) diseases that lead to elevations in left heart filling pressures (heart failure [HF] and advanced valvular heart disease), end-stage pulmonary diseases, especially chronic obstructive pulmonary lung disease (COPD) and pulmonary fibrosis, which have numerous etiologies, as well as chronic thromboembolic disease [5–7].

Due to the relatively low prevalence of primary PAH (approximately one to two cases per 1 million people), the diagnosis of this disease is often markedly delayed and, as such, patients experience symptoms for approximately 2 years before a definitive diagnosis is made [2,8]. In fact, well over half of patients with primary PAH present with a substantial functional limitation at the time of diagnosis. This delay in the diagnosis of PAH is problematic, especially since the prognosis of this disease, previously thought to be progressive and almost formerly fatal, has improved in recent years with various medical therapies when identified at its early stages. Moreover, PAH is associated with considerable disability, which can also be improved with early identification and treatment [9]. When considering the relatively high prevalence of advanced CV and pulmonary diseases, however, the total prevalence of secondary PH is markedly higher, but still most likely underdiagnosed. The lack of recognition of secondary PH is again problematic in that its presence worsens prognosis in patients with both HF and COPD [10–12].

The failure to identify pulmonary vasculopathy early in the disease process has been partly due to the lack of standardization for defining PAH severity. Commonly, clinicians have subjective functional classifications to stratify patients with various PAH severity, which does have value in both prognostication and for many decisions regarding treatment modalities. However, many other modalities have been utilized, including cardiopulmonary hemodynamics, usually acquired from right and left heart catheterization, serum biomarkers, such as N-terminal pro-brain natriuretic peptide [13], and noninvasive tests such as Doppler echocardiography [14].

Certainly an evolving approach to assess PAH and secondary PH presence/severity has been through exercise assessments [9,15,16]. While use of the 6-min walk test has historically been the exercise assessment of choice in pulmonary populations [15], the use of cardiopulmonary exercise testing (CPX) is evolving as a more precise way to quantify cardiopulmonary limitations in patients with suspected or confirmed PAH and secondary PH. CPX is a well-accepted modality to evaluate patients with HF and unexplained dyspnea on exertion [17]. Even so, the possibility of CPX abnormalities indicating PAH or secondary PH has not been frequently considered in the past. However, there is increasing recognition

that CPX has a potentially valuable role in evaluating PAH and secondary PH, given the decline in function and abnormalities in the physiologic response to exercise are central issues in patients with this condition. Therefore, exercise assessment is potentially valuable, and CPX provides the ideal way to simultaneously assess all of the systems (heart, lung and their integration) that are impacted by PAH and secondary PH.

In this article, we discuss the pathophysiology of PAH and its impact on pulmonary and CV function, review the clinical presentation of patients impacted by this condition and outline a case for the use of CPX in these patients, discuss CPX technology and testing procedures, and review the current state of available evidence and provide clinical recommendations for CPX in the setting of known or suspected PAH or secondary PH.

Pathophysiologic mechanisms leading to an abnormal exercise response

Patients with PAH exhibit a CPX profile similar to that observed in HF patients as documented by a series of abnormal variables such as reduced work rate, diminished aerobic capacity and impaired ventilatory efficiency. Moreover, the CPX response of patients with advanced PAH and patients with advanced HF and concomitant left-sided PH may appear strikingly similar. However, the pathophysiologic mechanisms that lead to these exercise-related abnormalities are different.

Patients with primary PAH are typically exercise limited by deleterious remodeling of the pulmonary vasculature, resulting in an increased ventilatory requirement and profound dyspnea at low levels of exercise. The underlying pathophysiology consists of an intrinsic abnormality of the pulmonary vasculature due to intimal fibrosis, medial hypertrophy and formation of plexiform lesions. These changes sustain an increased vascular resistance and failure to perfuse ventilated alveoli resulting in:

- Ventilation/perfusion (V/Q) mismatching with an increased dead space ventilation;
- Decreased left-sided cardiac output (CO);
- Failure of O₂ to be appropriately delivered to working skeletal muscle both as a result of diminished O₂ diffusion within the pulmonary system and diminished left-sided CO [18].

Exercise ventilation inefficiency & blood gas response

The occurrence of exercise ventilation inefficiency in patients with PAH is reflected by several CPX variables, including an increase in the minute ventilation/carbon dioxide production (VE/VCO₂) slope [9]. The steepness with which VE rises with respect to VCO₂ is described by the modified alveolar equation [19]:

$$VE = \frac{VCO_2 \times 863}{PaCO_2 \times \left(1 - \frac{VD}{VT}\right)}$$

where PaCO_2 is the partial pressure of carbon dioxide in the blood and VD/VT is the ventilatory dead space to tidal volume ratio. Accordingly, two major factors may determine the VE/VCO_2 slope; the VD/VT ratio and the behavior of arterial CO_2 tension. An abnormal pattern of both of these determinants plays a pathogenic role in the excessive ventilatory response observed in patients with PAH.

D'Alonzo *et al.* first examined the ventilatory and arterial blood gas tension response to exercise in PAH, thus providing initial insight into this phenomenon [20]. They reported an important occurrence of V/Q mismatch as suggested by a significant increase in the alveolar arterial partial pressure of oxygen (PO_2) gradient from rest to peak exercise leading to hypoxemia. Another important observed mechanism in this study was the significant reduction of PaCO_2 at peak exercise, in part due to the increased ventilatory response and in part related to the ensuing metabolic acidosis due to muscle underperfusion. Interestingly, a progressively lower PaCO_2 at rest correlated with a progressively higher VE/VCO_2 slope during exercise. Other studies have focused attention on changes occurring in the partial pressure of end-tidal CO_2 (P_{ETCO_2}), a variable that reflects both PaCO_2 and the degree of V/Q mismatch. In a study by Yasunobu *et al.* among 52 patients with PAH, a severity-dependent reduction in P_{ETCO_2} was observed both at rest and at peak exercise [21]. These authors postulated increased V/Q mismatch was a primary mechanism for the abnormal P_{ETCO_2} response observed in this cohort.

In a significant percentage of patients with PAH, a right-to-left shunt through the patent foramen ovale (PFO) may develop with exercise as right-sided pressure exceeds left-sided pressure. The CPX response in this instance, which has been shown to possess a high degree of diagnostic accuracy for a right-to-left shunt in these patients, is characterized by an abrupt decrease in P_{ETCO_2} associated with an increase in the respiratory exchange ratio and in the ventilatory requirement for CO_2 [22]. Thus, monitoring P_{ETCO_2} from rest to maximal exercise may be of special pathophysiologic and clinical value for detecting an abnormal pattern indicative of right to left shunting in patients with PAH. Moreover, P_{ETCO_2} in conjunction with VE/VCO_2 both at rest and during exercise provide insight into the degree of V/Q mismatching and thus disease severity in patients with PAH.

Diminished left-sided CO response

An appropriate rise in left-sided CO during aerobic exercise is essential to a normal peak oxygen consumption (VO_2) response as defined by the modified Fick equation [23]:

$$\text{VO}_2 = \text{CO} \times \text{arterial venous O}_2 \text{ difference}$$

Peak VO_2 is clearly diminished in patients with PAH to varying degrees in accordance with disease severity [9]. In patients with PAH, increased PVR blunts RV output, which ultimately leads to an insufficient increase in left-sided CO and O_2 transport during exercise. This yields to left ventricular underfilling, with a resultant decrease in stroke volume, which is also accentuated by the compression of the enlarged RV against the left one [24]. In the presence of inadequate O_2 delivery, anaerobic metabolism ensues in an attempt to meet the increasing energy demands as exercise intensity increases toward maximum. Unfortunately,

anaerobic metabolism is grossly inefficient in comparison to its aerobic counterpart and there is a rapid onset of fatigue at an abnormally low workload. The exaggerated increase in CO_2 production relative to O_2 consumption due to bicarbonate dissociation for lactic acid also provides a further stimulus to the ventilatory drive as detected by an increased VE/VCO_2 slope [18,25].

Peripheral factors contributing to the abnormal exercise response

Recent evidence also indicates patients with PAH possess a lower proportion of type 1 (i.e., aerobic) skeletal muscle fibers and diminished maximal voluntary contraction compared with healthy controls [26]. These skeletal muscle alterations also correlated with peak VO_2 in patients with PAH. Moreover, while there is established documentation that increased physiologic dead space and premature lactic acidosis are involved in the elevated exercise VE/VCO_2 slope, the potential role of an impaired peripheral reflexogenic control from muscular fibers (i.e., ergoreflex activation) has not been tested specifically in PAH. There is, however, the intriguing suggestion that some of the positive changes in exercise ventilation and dyspnea sensation after PAH therapies may be related to modulation of the excessive ergoreflex response [27]. If this hypothesis is confirmed in appropriately designed trials, this would provide the intriguing possibility that muscle disuse and deconditioning is an additional pathogenetic mechanism sustaining exercise ventilation inefficiency and breathlessness in PAH populations.

Clinical presentation of patients with PAH & the importance of exertional assessments

Patients with either resting or exercise-induced PAH present at variable times along the disease process continuum (i.e., initial/mild-to-late/severe). Owing to convenience, diagnostic tests of PAH have traditionally been performed at rest. However, since most patients are asymptomatic at rest, diagnostic tests in this state do not explain a patient's condition as thoroughly as exertional assessments. Moreover, the early detection of PAH will likely depend on exertional testing, a point in the disease process where dyspnea and abnormal physiologic processes only manifest during higher levels of physical activity. To this end, patients early in the PAH disease process may go undiagnosed if they remain asymptomatic at rest and during low-intensity bouts of physical exertion. This may be particularly true for patients who lead a sedentary lifestyle and perform a minimal amount of physical activity on a daily basis. Identification of patients early in the PAH disease process is imperative given that even mild elevations in PAP reflect substantial vascular damage [5].

Regardless of time of presentation, almost all patients describe exertional dyspnea at variable exercise intensities relative to a given individual's aerobic capacity. Patients early in the disease course may tolerate significant activity before experiencing dyspnea, while the late stages of PAH are characterized by dyspnea with minimal activity. Recognition of the importance of this spectrum of dyspnea led to the development of the WHO classification of Functional Status of patients with PAH, which is listed in Box 1 [28]. On this scale, WHO class I patients have no symptoms with ordinary physical activity, while WHO class IV patients have dyspnea with minimal activity, such as bending over or walking a few feet.

Previous research has demonstrated the WHO functional class is prognostic in patients with PAH [29,30].

The use of the WHO classification of functional status to quantify symptoms with physical exertion is limited by the fact that it relies largely on subjective interpretation. In fact, previous research has demonstrated wide inter-rater variability in WHO classification [31]. Moreover, the WHO classification system is not equipped to identify patients with symptoms at higher levels of physical exertion. Given the limitations of subjectively assessing exertional symptoms in conjunction with the importance of accurately detecting abnormal physiologic responses during physical activity as early into the disease process as possible, the use of an objective exercise assessment in the patient with suspected/confirmed PAH is clearly warranted. To this end, the use of CPX as the exertional assessment of choice possesses numerous potential clinical advantages.

Cardiopulmonary exercise testing is a well-established technique for the assessment of unexplained dyspnea on exertion [17], a symptom commonly encountered in patients with resting as well as activity-induced PAH. CPX has been proven to be safe, reliable and reproducible in numerous patient populations, including those diagnosed with PAH [9,16,32]. Unlike the 6-min walk test, CPX is able to provide insight into the physiologic response to exercise with much greater precision. For example, measurements from CPX can accurately quantify patient effort, aerobic capacity and, perhaps most importantly to the PAH population, V/Q matching during exercise. Unsurprisingly, variables from CPX have been shown to significantly correlate with pulmonary vascular pressure and thus aid in the diagnosis of PAH, accurately reflect disease severity, predict adverse events and reflect the response to therapeutic interventions [9,33].

CPX technology & testing procedures

Basic operation of exercise testing with ventilatory expired gas analysis

The determination of O_2 uptake and related ventilatory responses requires the ability to measure three variables during exercise: the fraction of O_2 in the expired air, the fraction of CO_2 in the expired air, and the volume of the inspired or expired air. From these basic measurements, a multitude of indices related to cardiopulmonary functions that are associated with the diagnosis and prognosis of cardiopulmonary disease can be derived. Prior to the computerization era, measuring these CPX responses to exercise was a cumbersome process requiring a great deal of laboratory space, technician time and time directed towards data reduction. Today, ventilatory expired gas analysis is commonly performed 'online', and rapidly responding systems permit the measurement of detailed gas exchange data on a breath-by-breath basis, with some systems no larger than a laptop. With these systems, the patient's responses are available immediately, and rapid computations can be made and displayed continuously during the test. CPX responses can be readily integrated with standard variables measured during exercise testing, including heart rate, blood pressure, workrate, ECG findings and symptoms to provide a comprehensive assessment of exercise tolerance and exercise responses.

Mode of exercise & protocol selection

While there are many modes of exercise, clinical exercise testing is most appropriately performed using a progressively incremented test with a treadmill or a cycle ergometer. Exercise capacity is typically 10–20% lower on the cycle ergometer due to the smaller muscle mass employed [23]. Some studies have suggested that test sensitivity is slightly higher on the treadmill [34], but these differences are relatively minor. Supine exercise is often used for imaging studies, such as echocardiography, but the exercise response is restricted by mechanical limitations and the smaller muscle mass available to perform the test. The majority of studies in PAH have been performed using the cycle ergometer; just one study to our knowledge has compared the treadmill and cycle ergometer in PAH. Valli *et al.* demonstrated that both the VE/VCO₂ slope and P_{ET}CO₂ responses were significantly worse when patients with PAH were tested on the treadmill compared with the cycle ergometer [35]. The authors suggested that V/Q abnormalities related to PAH were accentuated with the treadmill compared with cycle ergometry, perhaps because higher workrates are generally achieved on the treadmill.

A consistent recommendation in the various guidelines on exercise testing over the last two decades has been that the exercise protocol should be individualized for the subject being tested. This is in contrast to common clinical practice, in which a single protocol is applied to all subjects in a given laboratory [36]. This may be a particularly important principle to apply to patients with PAH as functional limitations are heterogeneous, limiting the use of a universal exercise protocol. Another consistent recommendation has been that large and unequal work increments should be avoided, particularly in clinical settings. Exercise test protocols with large stage-to-stage increments in energy requirements generally have a weaker relationship between measured VO₂ and workrate. Protocols which involve only modest increases in workrate per stage such as the Balke and Ware [37], Naughton [38] and individualized ramp protocols [39], are recommended for this reason. Regardless of the specific protocol chosen, the protocol should be tailored to the individual to yield a fatigue-limited exercise duration of approximately 8–12 min. Even with exercise test protocols using modest increases in workrate, the relationship between VO₂ and workrate is comparatively poor when test duration is <6 min. Conversely, when the protocol results in an exercise duration >12 min, subjects may terminate exercise because of specific muscle fatigue or orthopedic factors rather than cardiopulmonary end points.

Key CPX responses in PAH & secondary PH

Aerobic capacity—As in other conditions, peak VO₂ is the standard metric that defines the limits of the cardiopulmonary system in PAH. Because peak VO₂ parallels CO, and pulmonary blood flow must equal CO, CPX provides a reliable reflection of a patient's ability to increase pulmonary blood flow during exercise. A hallmark of PAH is deleterious remodeling of small pulmonary arteries [40], leading to alveolar hypoperfusion; because normal O₂ exchange at the alveolar level is critical to exercise performance, peak VO₂ has been repeatedly shown to be reduced in patients with PAH [9,25,41–45]. The reduction in aerobic capacity in PAH has been demonstrated to be comparable to or lower than that in patients with HF of similar age [9,45]. Thus, while quantification of the level of impairment in aerobic capacity is important in patients with PAH, it cannot provide discriminatory value

in relation to other conditions. Sun *et al.* reported that two-thirds of PAH patients had peak VO_2 levels <50% of the age-predicted value, an impairment in aerobic capacity similar to other studies in patients with PAH [9,25,41–45]. The impairment in peak VO_2 in PAH has been shown to parallel a reduction in CO [46], and peak VO_2 is inversely associated with PAP at rest and during exercise [47,48]. Although there are a limited number of such studies, both peak VO_2 and submaximal endurance capacity have been shown to be powerful prognostic markers in PAH [15,42,49].

Ventilatory efficiency—Indices of ventilatory inefficiency have become well established for their prognostic value in CV and pulmonary disease in recent years [34]. Ventilatory inefficiency describes the degree to which ventilation is heightened relative to the demands of the work rate, and is caused by one or more of the following:

- V/Q mismatching (adequate ventilation and poor perfusion), usually due to impaired CO;
- Elevated chemo- and muscle-receptor sensitivity;
- Early lactate accumulation;
- Elevated pulmonary pressures causing decreased alveolar–capillary membrane conductance [9,33,50–52].

While most previous studies in this area have focused on chronic HF, several of these factors may contribute to ventilatory inefficiency in PAH. The hallmark index for ventilatory inefficiency, the VE/VCO_2 slope or ratio, is heightened in accordance with the increase in PAP in PAH [9,44]. In addition, a higher VE/VCO_2 is associated with the degree of dyspnea during exercise in patients with PAH [44] and is associated with a marked reduction in exercise performance [9,25,44,53]. The VE/VCO_2 slope has been demonstrated to be markedly higher even among patients with interstitial pulmonary disease when secondary PH is present (~48 in PH patients vs ~31 without PH) [53]. Although there are a limited number of studies in this area, the VE/VCO_2 slope/ratio has also been shown to be a strong predictor of outcomes in PAH [9,42].

End-tidal CO_2 —The P_{ETCO_2} is normally determined by CO_2 production (metabolism), alveolar ventilation, pulmonary perfusion (circulation) and the degree of V/Q matching in the lung. Both resting and exercise P_{ETCO_2} have been shown to be highly correlated with CO [54,55], and to be strong prognostic markers in various cardiopulmonary conditions [33]. Recent studies have shown that abnormal P_{ETCO_2} in the presence of dyspnea of unknown etiology may reflect PAH [21,32,56]. P_{ETCO_2} may also provide evidence of exercise-induced right-to-left shunting in PAH [22]. In the most detailed study addressing this issue, Yasunubo *et al.* demonstrated that P_{ETCO_2} during exercise decreased in proportion to the decrease in age-predicted peak VO_2 , and P_{ETCO_2} values at rest and at the anaerobic threshold were reduced as mean PAP increased [21]. In addition, P_{ETCO_2} at rest and during exercise was reduced in proportion to the severity of PAH, and directional changes in the P_{ETCO_2} profile during exercise and recovery occurred in the opposite direction of those expected in either normal subjects or patients with HF. Hansen *et al.* observed that the pattern of the change in P_{ETCO_2} during exercise could be used to

distinguish disease states with V/Q mismatching, including those due to inadequate perfusion related to PAH versus airway defects related to other pulmonary diseases [43]. When low resting $P_{ET}CO_2$ values or abnormal $P_{ET}CO_2$ patterns occur during exercise, PAH should be considered as a possible diagnosis to account for dyspneic symptoms.

Pulse oximetry—Pulse oximeters, which provide an estimation of O_2 saturation at rest and during exercise, can be a valuable supplement to other CPX responses in PAH. Pulse oximeters rely on differential absorption of varying wavelengths of light in order to noninvasively estimate the proportion of arterial capillary hemoglobin in the oxygenated form. A $>5\%$ decrease in the pulse oximeter estimate of arterial saturation during CPX suggests abnormal exercise-induced hypoxemia [57]. O_2 desaturation is common in PAH, and can be a marker of the severity the condition. The extent to which O_2 desaturation occurs generally reflects the degree of pulmonary pressure elevation and disease severity [21,47]. Paciocco *et al.* demonstrated that a decrease in O_2 saturation 10% during submaximal exercise was associated with a threefold increase in mortality among patients with PAH [49]. Ridruejo *et al.* observed that 4–6-month mortality was higher among PAH patients exhibiting a $>10\%$ desaturation compared with those who did not exhibit a desaturation response to submaximal exercise [58].

Hemodynamics—Pulmonary arterial hypertension is fundamentally characterized by increased PVR, which leads to impairment of the normal pulmonary vasodilator response to exercise. Because of heightened PAP, the right ventricle cannot adequately increase pulmonary blood flow, furthering the mismatching of V/Q and heightening the dead space ventilation. The inability to adequately increase pulmonary, and therefore systemic, blood flow results in a failure to meet the O_2 requirements of exercise. A small number of studies have measured CPX and right heart catheterization responses simultaneously, and demonstrated severely blunted CO and stroke volume increases with exercise [59]. Some patients exhibit normal resting PAP, but exhibit PAH only with exercise; it has been suggested that exercise-induced PAH is an early and more treatable phase that precedes resting PAH [60,61]. Thus, in combination with direct hemodynamic measurements, CPX can be used to quantify both the degree of cardiac impairment and pulmonary pressure abnormalities, and can distinguish between resting and exercise PAH [46].

Symptoms during exercise in PAH—The WHO has established a symptom classification system for PAH (Box 1) that is similar to those developed for patients with symptoms of angina and HF. Although the WHO classification system provides a general depiction of function in patients with PAH, CPX provides a more precise and physiologic evaluation of symptoms and a given patient's functional capabilities. An abnormally increased ventilatory response to exercise is a uniform finding in patients with PAH. This heightened ventilatory response underlies dyspnea, the hallmark symptom in PAH; virtually every study assessing the CPX response in PAH has reported inefficient ventilation and early breathlessness compared with subjects without PAH [9,25,44,45,48]. The degree of dyspnea with exercise testing is directly related to the increase in PAP and ventilatory inefficiency in PAH [44]. Sun *et al.* studied 64 patients with PAH and observed that peak VO_2 decreased and the VE/VCO_2 slope increased in accordance with increasing New York Heart

Association symptoms [25]. PAH may also manifest itself as fatigue or chest pain with CPX, and lower limb edema may also limit the exercise response. Symptoms of PAH have been shown to improve with structured programs of exercise training [62].

Additional exercise testing assessments

Echocardiography—Echocardiography in association with CPX may provide a more thorough evaluation of CV and pulmonary physiology in patients with suspected PAH, although research is needed in this area. A specific research hypothesis of particular interest would be: does the combination of echocardiography and CPX variables reflecting ventilatory efficiency improve the diagnostic sensitivity and specificity for PAH? Standard assessment includes both 2D imaging as well as Doppler interrogation of the tricuspid valve regurgitant flow. The 2D imaging provides assessment of RV size and systolic function. Doppler assessment is primarily used to measure tricuspid valve regurgitant flow velocity, for instance, data used to calculate the pulmonary artery systolic pressure (PASP) by the following equation:

$$PASP = (4 \times [\text{tricuspid regurgitant velocity}]^2) + \text{right arterial pressure}$$

This formula assumes that tricuspid valve gradient equals $(4 \times \text{flow velocity})^2$, which is an application of the modified Bernoulli equation. Right atrial pressure is added to the tricuspid gradient, with the right atrial pressure value (5–10 mmHg) usually determined according to the respiratory diameter of the inferior vena cava and/or right atrial and RV size and function [63–65].

Principles of exercise stress echocardiography are similar to rest echo, except that post-exercise echocardiographic interrogation of the heart is restricted to a short window (usually 1 min or less) immediately after exercise is completed, for instance, to assess tricuspid regurgitant velocity before the effects of exercise provocation diminish. Whereas exercise echocardiography techniques are used most commonly used to diagnose coronary ischemia (i.e., based on 2D assessments of left ventricle wall motion provoked by exercise), exercise-associated PAH is assessed by shifting the priorities of post-exercise assessments to Doppler measurements of tricuspid valve flow.

A key limitation of this technique is the narrow time window available to acquire suitable echocardiographic images immediately after the exercise stimulus. Moreover, this challenge is often compounded by the poor echocardiographic images that result from COPD and other lung diseases that are widespread in the PAH population. To overcome these limitations, it is now common to inject echocardiographic contrast agents, for instance, albumin solutions with microscopic air bubbles. Contrast-enhanced images have been demonstrated to improve echo signals in general, and specifically to enhance the tricuspid valve flow assessments required in these calculations [66].

Level 3 cardiopulmonary assessment—An alternate technique to assess exercise-induced PAH is to perform CPX in combination with right heart and arterial line catheterizations, a technique also referred to as level 3 CPX. Just as in standard CPX, a level

3 CPX utilizes ventilatory expired gas exchange measurements to facilitate reliable quantification of exercise performance as well as the capacity to discern cardiac and ventilatory components underlying functional capacity. Adding right heart and arterial line catheterizations may enhance the assessment by facilitating precise evaluation of pulmonary arterial pressures and CO in relation to function [46,67]. Research is needed to determine if the invasive nature and added complexity of level 3 CPX provides additional and clinically meaningful diagnostic value in comparison to standard CPX procedures.

Current state of available evidence & translation to clinical practice

The current body of evidence supporting the clinical value of CPX in patients whose primary medical concern is suspected or confirmed PAH is rather compelling and continues to expand [9,68]. Present evidence more strongly supports the ability of CPX to gauge disease severity in patients with confirmed resting PAH. Several investigations also support the potential use of CPX to determine the response to a given intervention. While initial studies also indicate the prognostic value of CPX in patients with resting PAH, additional investigations are needed to support clinical utilization for this purpose. Initial evidence further indicates CPX may assist in the diagnosis of exercise-induced PAH in those patients presenting with unexplained exertional dyspnea. Lastly, there are other cardiopulmonary conditions, such as HF, hypertrophic cardiomyopathy, COPD and pulmonary fibrosis, where elevated pulmonary pressure may become a secondary consequence as disease severity worsens. CPX may again prove valuable in identifying an increased likelihood of elevated pulmonary pressure in this latter scenario. This section will describe the body of scientific evidence in support of CPX as a clinical tool for the assessment of pulmonary hemodynamic status.

Patients with confirmed PAH at rest—The majority of evidence demonstrating the value of CPX for pulmonary hemodynamic assessment has been conducted in cohorts with confirmed PAH at rest. Several CPX variables have been demonstrated to reflect the level of disease severity and functional impairment in this patient population. Sun *et al.* performed CPX in 53 subjects with resting PAH and 20 apparently healthy controls and found the VE/VCO₂ slope was significantly higher and peak VO₂ was significantly lower in the PAH group [25]. Moreover, these CPX variables became progressively more abnormal as PAH increased. Reybrouck *et al.* also reported a highly significant positive correlation ($r = 0.92$; $p < 0.001$) between the VE/VCO₂ slope and mean PAP determined by catheterization in 17 patients with resting PAH [53]. Miyamoto *et al.* found a similarly abnormal CPX response in 43 subjects with resting PAH compared with 16 apparently healthy controls [69]. While Riley *et al.* found similar trends in peak VO₂ and VE/VCO₂, they also reported P_{ET}CO₂ at rest and during exercise was significantly lower in patients with resting PAH compared with controls [70]. Yasunobu *et al.* also found significantly lower P_{ET}CO₂ values at rest and during exercise in patients with resting PAH, and the magnitude by which P_{ET}CO₂ was diminished was reflective of disease severity determined by catheterization [21]. Several other investigations have also confirmed a significantly diminished aerobic capacity and abnormal ventilatory response to exercise in patients with resting PH [20,22,46].

Cardiopulmonary exercise testing may also aid in the diagnosis of exercise-induced cardiopulmonary pathophysiology in patients with confirmed resting PAH. Sun *et al.* assessed the utility of CPX in diagnosing the onset of a right–left atrial shunt (PFO) in subjects with resting PAH. A sudden and sharp decline in $P_{ET}CO_2$ and an increase in the VE/VCO_2 ratio were key CPX characteristics consistent with a shunt [22]. These CPX responses possessed both a high sensitivity and specificity (>90%) for detecting a PFO confirmed by resting 2D. The proposed pathophysiologic rationale for this abnormal CPX response were:

- A marked rise in PAP;
- In the presence of a PFO, blood shunts to the arterial circulation when the right atrial pressure becomes greater than the left atrial pressure;
- The rise in CO_2 in the arterial circulation precipitates a sudden and exaggerated ventilatory response that is detectable by CPX.

Several pharmacologic agents are used in an attempt to reduce pulmonary pressure in this patient population and CPX may reflect the degree of hemodynamic improvement post-intervention. In 30 patients with resting PAH receiving beraprost over several months, Nagaya *et al.* reported a significant increase in peak VO_2 and a reduction in the VE/VCO_2 slope [71]. Oudiz *et al.* reported a significant reduction in VE/VCO_2 slope and significant increase in $P_{ET}CO_2$ following 4 months of sildenafil therapy in 14 patients with resting PAH [72]. In the latter study, the increase in peak VO_2 post-intervention trended toward but did not reach statistical significance.

Patients diagnosed with resting PAH carry a poor prognosis and CPX may assist in identifying those individuals at greatest short-term risk for adverse events. In 115 patients with resting PAH, Groepenhoff *et al.* found that the peak VO_2 and the VE/VCO_2 slope were both significant univariate predictors of mortality over a 2-year period post-CPX [15]. Oudiz *et al.* also found that an abnormally elevated VE/VCO_2 slope was a significant predictor of adverse events in a group of 103 patients with resting PAH [73]. Other investigations also indicate CPX may provide prognostic information in this patient population [42,74].

In conclusion, patients with resting PAH present with an abnormal CPX response, primarily reflected by a diminished aerobic capacity and abnormal ventilatory efficiency. As such, peak VO_2 , the VE/VCO_2 slope and $P_{ET}CO_2$ appear to be key CPX variables. A significantly diminished peak VO_2 is common to a number of chronic disease populations and should therefore not be viewed in isolation in patients with resting PAH undergoing CPX. The degree of V/Q mismatching within the pulmonary system is a primary issue in patients with PAH and CPX variables that more uniquely assess this dysfunction (i.e., the VE/VCO_2 slope and $P_{ET}CO_2$) provides for a more comprehensive assessment as to how this pathophysiologic process impacts the response to exercise. The degree of CPX abnormalities generally reflect disease severity (i.e., the magnitude of elevation in resting pulmonary pressure). Thus, current evidence supports the use of CPX to quantify functional limitations and disease severity in present-day clinical practice. Initial evidence also indicates that CPX may also hold promise as a clinical tool to determine therapeutic responsiveness and

prognosis. However, additional research is needed to support the clinical application of CPX as a tool for interventional or prognostic assessment.

Exercise-induced PAH—Exercise-induced PAH is the term used to describe a patient whose PAP is within normal limits at rest but abnormally rises with physical exertion [46]. Patients suffering from this condition often complain of exertional dyspnea, although other mechanisms may be the cause of this complaint [23]. It is believed that exercise-induced PAH is a precursor to resting PH and, given the poor survival rate in its advanced state, detection of elevated pulmonary pressure in its earliest form (i.e., during exercise) is advantageous [61]. CPX may be valuable in the detection of exercise-induced PAH through the assessment of ventilatory efficiency during exercise. While research examining the potential value of CPX in this context is lacking, a small investigation by Raeside *et al.* shows promise [75]. A total of ten patients with suspected PAH underwent a submaximal CPX test on a cycle ergometer at 30 W with simultaneous assessment of mean PAP via catheterization. There was a significant correlation between VE/VCO₂ and mean PAP during exercise ($r = 0.80$; $p = 0.005$). The authors concluded that an abnormal ventilatory response to exercise was the result of an increase in physiologic dead space secondary to increased PAP. The work by Chenivesse *et al.* supports this hypothesis by demonstrating that subjects with exercise-induced PAH fail to either decrease, which is the normal response, or increase physiologic dead space ventilation at maximal exercise [76]. Research in this area should continue to solidify the diagnostic value of CPX in patients being assessed for exercise-induced PAH.

Detecting elevated pulmonary pressures caused by other cardiopulmonary conditions—Pulmonary hypertension is a secondary consequence in a number of other cardiac and pulmonary conditions, particularly as the disease severity of the primary condition progresses [77–80]. There appears to be differences in the CPX response in these patient populations according to the presence or absence of secondary PH. In 57 patients with HF, Reindl *et al.* demonstrated a significant correlation between the VE/VCO₂ slope and mean PAP ($r = 0.69$; $p < 0.001$) [48]. More recently, Ukkonen *et al.* reported a significant correlation between right ventricular oxidative metabolism and the VE/VCO₂ slope ($r = 0.61$; $p > 0.01$), a relationship theoretically resulting from the impact of increasing pulmonary pressure on this CPX variable [81]. Lastly with respect to the HF population, the VE/VCO₂ slope is also a powerful predictor of adverse events, as demonstrated by numerous original investigations [82,83]. In a group of 87 patients diagnosed with hypertrophic cardiomyopathy, Arena *et al.* found an elevated VE/VCO₂ at peak exercise (>35) was an effective indicator (sensitivity: 83%; specificity: 79%) of a resting mean PAP 20 mmHg as determined by right heart catheterization [84]. Vonbank *et al.* reported that subjects with COPD and PH had a significantly higher resting and exercise VE/VCO₂ and significantly lower peak VO₂ compared with subjects with this pulmonary condition who did not have PH [85]. In a separate COPD cohort, Holverda *et al.* also reported a significantly higher VE/VCO₂ slope when PH was present [86]. Peak VO₂ was, however, similar between COPD groups with and without PH. In a pulmonary fibrosis cohort, divided by the presence or absence of PH, Glaser *et al.* likewise demonstrated a significantly higher VE/VCO₂ slope and significantly lower peak VO₂ in subjects with an elevated pulmonary

pressure [44]. In patients with pulmonary fibrosis and PH, the correlation between systolic PAP and both the VE/VCO₂ slope ($r = 0.77$; $p < 0.001$) and peak VO₂ ($r = -0.52$; $p < 0.05$) were significant. It should be noted that the aforementioned CV and pulmonary conditions frequently result in abnormalities in ventilatory efficiency and diminished aerobic capacity in the absence of PH. However, the available evidence indicates that CPX abnormalities accelerate when PH develops as a secondary consequence. Thus, when performing CPX in these patient populations, clinicians may want to consider the potential for secondary PH and more definitive diagnostic tests to determine pulmonary pressure, particularly when the VE/VCO₂ slope is < 40 . The early identification of PH may be particularly valuable given its ominous prognostic impact in these chronic disease populations [79,80].

Current clinical recommendations for CPX to assess pulmonary hemodynamics

Cardiopulmonary exercise testing is a firmly established and broadly utilized clinical assessment tool in patients with HF being considered for transplantation and individuals with unexplained exertional dyspnea [17]. The use of CPX to assist in the diagnosis of elevated pulmonary pressure, either as a primary pathophysiologic process or a consequence of another cardiopulmonary condition, is currently not as prevalent in clinical practice. However, the scientific evidence in support of CPX continues to grow in this area, which may result in greater clinical utilization in the future. Moreover, a number of patients with the potential for PAH (i.e., exertional dyspnea) currently undergo CPX assessment, although its value in reflecting pulmonary hemodynamics may be underappreciated. The true value of CPX in discerning the likelihood for PAH primarily lies within two easily obtained variables: VE/VCO₂ and P_{ET}CO₂. Both variables reflect V/Q matching in the pulmonary system, which is negatively impacted by PAH such that VE/VCO₂ and P_{ET}CO₂ are abnormally elevated and diminished, respectively. The potential value of these CPX variables is highlighted by an algorithm for determining the likelihood of PAH as a mechanism for unexplained exertional dyspnea proposed by Yasunobu *et al.* (Figure 1) [21]. As VE/VCO₂ at ventilatory threshold progressively rises past 30 and P_{ET}CO₂ at anaerobic threshold progressively declines below 36 mmHg, PAH as a mechanism for dyspnea should be considered. At ventilatory threshold, which is typically the nadir for VE/VCO₂ and high point for P_{ET}CO₂ during a progressive exercise test, a VE/VCO₂ of 57 or more and a P_{ET}CO₂ of < 20 mmHg or less may be strongly suggestive of PAH in subjects presenting with unexplained exertional dyspnea. The clinical utilization of CPX in this fashion may be particularly valuable in patients with autoimmune conditions, such as systemic sclerosis, where exertional dyspnea is a common patient complaint and PAH is a potential mechanism [87].

Table 1 further expands considerations for CPX in the context of pulmonary pressure assessment based on the current body of evidence. In all patient scenarios listed, the assessment of VE/VCO₂ and P_{ET}CO₂ is considered central in determining the potential for PAH or to gauge disease severity in those individuals already diagnosed with an elevated pulmonary pressure at rest. The importance of these two CPX variables in the link between pathophysiology and clinical interpretation is further illustrated in Figure 2. While not listed

in Table 1, peak VO_2 should be assessed in all patient populations to quantify the degree of functional impairment and for a more refined prognostic assessment. However, the decline in aerobic capacity is not unique to the pathophysiologic process associated with PAH and therefore does not assist in identification of this condition. This premise holds true for other CPX variables including pulse oximetry, hemodynamics and subjective symptomatology, all of which are described in previous sections. While abnormal responses in any of these are not specific to PAH, they do assist in better describing the patient's response to aerobic exercise. Moreover, patients with advanced PAH more often demonstrate arterial O_2 desaturation in conjunction with a severely elevated VE/VCO_2 slope and diminished P_{ETCO_2} [21].

Conclusion

Cardiopulmonary exercise testing provides the unique ability to noninvasively assess V/Q coupling within the pulmonary system. This is of particular importance in patients with suspected or confirmed PAH and secondary PH as V/Q mismatching progressively worsens as pulmonary pressure continues to rise. There is a growing body of evidence demonstrating the clinical value of CPX in the assessment of pulmonary hemodynamics. As such, clinical acceptance of CPX when suspected or confirmed PAH is a primary indication may continue to grow. In the current clinical setting, CPX is well established in patients with HF as well as in those with unexplained exertional dyspnea. Secondary PH is an important component of disease progression in HF and is a potential mechanism for unexplained dyspnea. As such, the potential for the presence of secondary PH in these patient cohorts should be considered, primarily through the assessment of VE/VCO_2 and P_{ETCO_2} .

Expert commentary

The exercise assessment provides a wealth of valuable clinical information in patients with suspected or confirmed PAH and secondary PH. CPX provides for the most comprehensive assessment of functional capacity and exclusively allows for the assessment of V/Q dynamics, which is particularly relevant to the PAH/secondary PH population. As a noninvasive, first-line assessment, CPX may be valuable in diagnosing resting and exercise-induced PAH in patients with unexplained exertional dyspnea. In patients with confirmed PAH, CPX provides information on disease severity above that which is obtained during a resting assessment. As such, we highly recommend the clinical utilization of CPX for PAH assessment. Although the focus of this article was to examine the value of a single test, the role of serial CPX in assessing the response to a given intervention (i.e., exercise training, surgical, pharmacologic) in the PAH/secondary PH population demonstrates promise [9,62]. However, additional work is needed given that not all interventional trials demonstrate a favorable CPX adaptation following treatment [9,88].

Five-year view

We anticipate original scientific research supporting the use of CPX for PAH assessment will continue to grow in the coming years. The growth in supporting evidence will probably increase the utilization of CPX in patients with suspected or confirmed PAH, and scientific

statements from leading organizations will endorse this practice. As such, we envision that CPX may someday become a core assessment for the PAH population.

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- of interest
- of considerable interest

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Box 1.**WHO classification of functional status in patients with pulmonary arterial hypertension****Class I**

Patients with PAH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain or presyncope

Class II

Patients with PAH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain or presyncope

Class III

Patients with PAH who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain or presyncope

Class IV

Patients with PAH who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity

PAH: Pulmonary arterial hypertension.

Adapted from [28].

Key issues

- Pulmonary arterial hypertension (PAH) significantly diminishes functional capacity and carries a poor prognosis as pathophysiologic severity advances.
- Regardless of time of presentation, almost all patients with PAH describe exertional dyspnea at variable exercise intensities relative to a given patient's aerobic capacity. Patients early in the disease course may tolerate significant activity before experiencing dyspnea, while the late stages of PAH are characterized by dyspnea with minimal activity.
- Given the limitations of subjectively assessing exertional symptoms in conjunction with the importance of accurately detecting abnormal physiologic responses during physical activity as early into the disease process as possible, the use of an objective exercise assessment in the patient with suspected/confirmed PAH is clearly warranted.
- Cardiopulmonary exercise testing is proving valuable in aiding in the diagnosis of PAH as well as gauging disease severity and prognosis.
- As minute ventilation/carbon dioxide production (VE/VCO_2) at ventilatory threshold progressively rises past 30 and partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) at anaerobic threshold progressively declines below 36 mmHg, PAH as a mechanism for dyspnea should be considered.
- At ventilatory threshold, a VE/VCO_2 of 57 or more and a $P_{ET}CO_2$ of <20 mmHg or less may be strongly suggestive of PAH in subjects presenting with unexplained exertional dyspnea.
- The assessment of VE/VCO_2 and $P_{ET}CO_2$ is considered central in determining the potential for PAH or to gauge disease severity in those individuals already diagnosed with an elevated pulmonary pressure at rest.
- Peak VO_2 should be assessed in all patient populations to quantify the degree of functional impairment and for a more refined prognostic assessment. However, the decline in aerobic capacity is not unique to the pathophysiologic process associated with PAH and therefore does not assist in identification of this condition.

Unlikely $P_{ET}CO_2@VT >37 \text{ mmHg}$ $VE/VCO_2@VT <30$	Consider $P_{ET}CO_2@VT = 36-30 \text{ mmHg}$ $VE/VCO_2@VT = 30-38$	Likely $P_{ET}CO_2@VT = 29-20 \text{ mmHg}$ $VE/VCO_2@VT = 39-56$	Highly likely $P_{ET}CO_2@VT <20 \text{ mmHg}$ $VE/VCO_2@VT \geq 57$
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Figure 1. Likelihood of pulmonary arterial hypertension being the mechanism for unexplained exertional dyspnea.

$P_{ET}CO_2$: Partial pressure of end-tidal carbon dioxide; VCO_2 : Carbon dioxide production; VE: Minute ventilation; VT: Ventilatory threshold. Adapted from [21].

Figure 2. Relationship between pathophysiology and clinical interpretation of key cardiopulmonary exercise testing variables.

$P_{ET}CO_2$: Partial pressure of end-tidal carbon dioxide; VCO_2 : Carbon dioxide production; VE : Minute ventilation.

Table 1.

The value of cardiopulmonary exercise testing in assessing pulmonary hemodynamics[†].

Patient population or chief complaint	Clinical significance of abnormal cardiopulmonary exercise testing response
Confirmed resting PAH	Progressively increasing VE/VCO ₂ and progressively decreasing P _{ET} -CO ₂ indicative of worsening pulmonary hemodynamics. Abnormal response may indicate increased risk for adverse events. Sudden and sharp decline and increase in P _{ET} -CO ₂ and the VE/VCO ₂ ratio, respectively, may be indicative of right-left atrial shunt
Unexplained exertional dyspnea	Progressively increasing VE/VCO ₂ and progressively decreasing P _{ET} -CO ₂ increase the likelihood that PAH is the mechanism of exertional dyspnea
Heart failure	Progressively increasing VE/VCO ₂ and progressively decreasing P _{ET} -CO ₂ increase the likelihood that elevated pulmonary pressures have developed as a secondary consequence of the primary cardiac condition Abnormal response is strongly indicative of increased risk for adverse events
Hypertrophic cardiomyopathy	Progressively increasing VE/VCO ₂ and progressively decreasing P _{ET} -CO ₂ increase the likelihood that elevated pulmonary pressures have developed as a secondary consequence of the primary cardiac condition
Chronic obstructive pulmonary disease and pulmonary fibrosis	Progressively increasing VE/VCO ₂ and progressively decreasing P _{ET} -CO ₂ increase the likelihood that elevated pulmonary pressures have developed as a secondary consequence of the primary pulmonary condition

[†]Normal values for key cardiopulmonary exercise testing variables: VE/VCO₂: slope or submaximal ratio expressions are both typically <30; P_{ET}-CO₂: at rest = 36-42 mmHg, increases by 3-8 mmHg by anaerobic threshold.

PAH: Pulmonary arterial hypertension; P_{ET}-CO₂: Partial pressure of end-tidal carbon dioxide production; VE/VCO₂: Minute ventilation/carbon dioxide production.