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REVIEW

Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review

Ross Arena, PhD,^a Carl J. Lavie, MD,^b Richard V. Milani, MD,^b
Jonathan Myers, PhD,^c and Marco Guazzi, MD, PhD^d

From the ^aDepartments of Internal Medicine, Physiology and Physical Therapy, Virginia Commonwealth University, Richmond, Virginia;

^bDepartment of Cardiovascular Diseases, Ochsner Medical Center, New Orleans, Louisiana;

^cCardiology Division, VA Palo Alto Health Care System, Palo Alto, California; and

^dCardiopulmonary Laboratory, Cardiology Division, University of Milan, San Paolo Hospital, Milan, Italy.

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BACKGROUND: There is an increasing recognition of the potential value of cardiopulmonary exercise testing (CPX) in patients with pulmonary hypertension (PH). Key CPX characteristics in these patients include: (1) a diminished aerobic capacity; (2) an abnormally elevated minute ventilation–carbon dioxide production relationship; and (3) an abnormally diminished partial pressure of end-tidal carbon dioxide. Given the burgeoning number of original research investigations utilizing CPX in patients with PH, a summation of the presently available body of literature seems timely.

METHODS: A literature search was conducted in PUBMED using “cardiopulmonary exercise testing” and “pulmonary arterial hypertension” as key phrases. Only studies conducting exercise testing with simultaneous ventilatory expired gas analysis in subjects with a confirmed diagnosis of pulmonary arterial hypertension were included. Twenty-three investigations were included in this review. Nineteen of the investigations assessed cohorts with resting pulmonary arterial hypertension as the sole diagnosis. Two investigations assessed subjects with chronic obstructive pulmonary disease and pulmonary arterial hypertension: one assessed subjects with pulmonary fibrosis and pulmonary arterial hypertension, and another included groups with exercise-induced pulmonary arterial hypertension and resting pulmonary arterial hypertension.

RESULTS: Collectively, these investigations indicate variables obtained from CPX: (1) reflect varying degrees of PH severity; (2) positively respond to several pharmacologic and surgical interventions; and (3) may provide prognostic value.

CONCLUSIONS: Currently, CPX is not widely utilized in patients with PH. Although more research is required in a number of areas, the present evidence-based review indicates this exercise testing technique may provide valuable information in the PH population.

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Cardiopulmonary exercise testing (CPX) employs ventilatory expired gas analysis to quantify oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and minute ventilation (\dot{V}_E) both at rest and during exercise. Among the wealth of information provided, this technology allows for: (1) the most accurate non-invasive assessment of aerobic capacity; (2) determination of sub-maximal, sustained exercise performance (i.e., ventilatory/anaerobic threshold);

Reprint requests: Ross Arena, PhD, Department of Physical Therapy, Virginia Commonwealth University, Health Sciences Campus, Box 980224, Richmond, VA 23298-0224. Telephone: 804-828-0234. Fax: 804-828-8111.

E-mail address: raarena@vcu.edu

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and (3) assessment of ventilatory efficiency (i.e., matching of pulmonary ventilation and perfusion).¹ CPX is presently a well-accepted and widely utilized diagnostic test in patients with heart failure (HF) and for those individuals presenting with unexplained exertional dyspnea.^{2–4} With respect to patients with HF, there is a robust body of literature demonstrating the diagnostic^{5–9} and prognostic^{10–14} utility of CPX as well as its ability to gauge the response to interventions.^{15–23} The body of original research supporting the value of CPX in HF has resulted in the publication of several reviews^{24–26} and consensus statements.^{27–30}

More recently, the potential utility of CPX in patients with mitochondrial myopathy,^{31–33} coronary artery disease^{34,35} and suspected or confirmed pulmonary hypertension (PH)^{36–38} has garnered attention. In addition to significantly diminished aerobic capacity, these particular patient populations present with an assortment of ventilatory expired gas abnormalities unique to each pathophysiologic process. Presently, evidence supporting the utility of CPX in patients with PH, a condition with a prevalence of 1 or 2 cases per million individuals³⁹ and a high short-term mortality if left untreated,⁴⁰ is more robust compared with either other condition. Moreover, a statement jointly put forth by the American Thoracic Society and American College of Chest Physicians advocates the use of CPX during the assessment of patients with PH.⁴¹ A recent review, “Diagnostics in Pulmonary Hypertension,” by Schannwell et al,³⁹ also listed CPX as a valuable assessment technique in this population, although only one original research reference was cited supporting its use. At the present time, there do not appear to be any available publications providing a thorough analysis of the literature supporting the use of CPX in PH. Such a review is particularly timely given the growing clinical interest in PH.⁴² Therefore, the goals of this evidence-based review were to: (1) assess the pathophysiologic mechanisms accounting for an abnormal CPX response in PH; (2) describe key CPX findings in diagnostic/comparative, interventional and prog-

nostic PH investigations; (3) identify CPX variables with the highest degree of clinical/research relevance; and (4) identify current gaps in the literature, providing a basis for future research.

Link Between PH Pathophysiology and Abnormal CPX Response

The ventilatory expired gas abnormalities precipitated by PH are multifactorial and associated with disease severity.^{43,44} Increased pulmonary artery pressure (PAP), the primary pathophysiologic consequence of this condition, creates a ventilation–perfusion mismatch (i.e., acceptable ventilation/diminished perfusion). This results in an increase in physiologic dead space, which, from a ventilatory expired gas perspective, is reflected by an elevated V_E/V_{CO_2} ratio or slope and diminished partial pressure of end-tidal carbon dioxide (P_{ETCO_2}). Increased PAP can also decrease blood flow to the left side of the heart, resulting in a lower cardiac output (CO). The increase in PAP may shift the ventricular septum leftward, negatively impacting left ventricular (LV) filling, which can also contribute to a decrease in CO. These secondary consequences lead to decreased peak $\dot{V}O_2$ and $\dot{V}O_2$ at the ventilatory threshold (VT) that parallels the decline in CO. Increasing PH severity also eventually decreases red blood cells’ transit time in the pulmonary circulation to the point where oxygen diffusion is no longer able to match the needs required for a given level of physical exertion. The ensuing arterial desaturation will further exaggerate the ventilatory response to exercise, compounding the elevated V_E/V_{CO_2} ratio and slope and decreased P_{ETCO_2} . Moreover, arterial desaturation decreases oxygen delivery to working skeletal muscle, negatively impacting aerobic metabolism and contributing to the observed decrease in peak $\dot{V}O_2$ and $\dot{V}O_2$ at the VT with PH. The ventilatory expired gas consequences resulting from PH pathophysiology are illustrated in Figure 1.

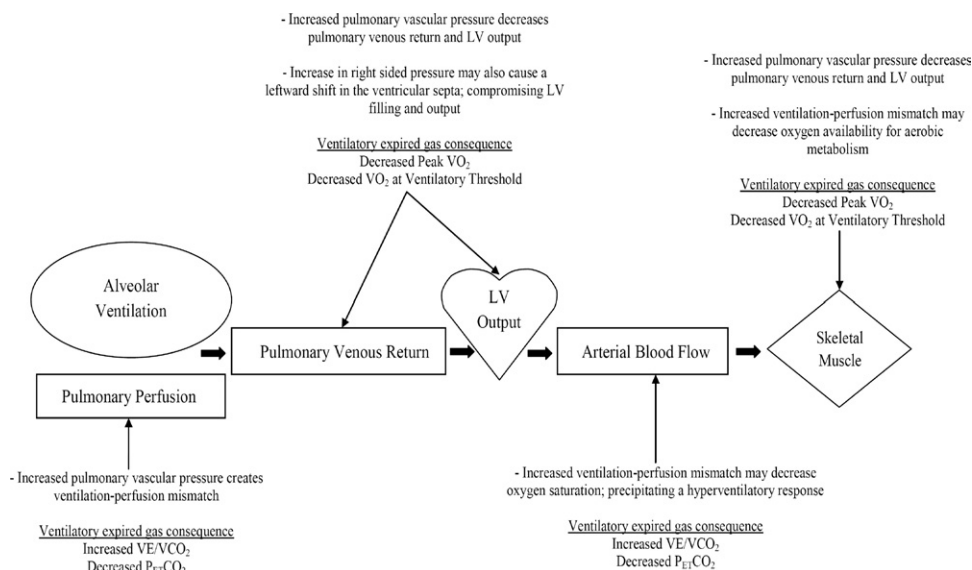


Figure 1 Impact of pulmonary hypertension pathophysiology on ventilatory expired gas exchange.

Evidence Supporting Utility of CPX in Patients with PH

A literature search was conducted in PUBMED using “cardiopulmonary exercise testing” and “pulmonary arterial hypertension” as key phrases. Only studies conducting exercise testing with simultaneous ventilatory expired gas analysis in subjects with a confirmed diagnosis of pulmonary arterial hypertension were included. The 23 presently available investigations addressing this area of research are listed in Table 1. Nineteen of the investigations assessed cohorts with resting pulmonary arterial hypertension as the sole diagnosis. Two investigations assessed subjects with chronic obstructive pulmonary disease and pulmonary arterial hypertension: one assessed subjects with pulmonary fibrosis and pulmonary arterial hypertension, and the other included groups with exercise-induced pulmonary arterial hypertension and resting pulmonary arterial hypertension. Irrespective subject characteristics, the exercise testing protocols and CPX variables assessed were similar. The majority of these studies assessed a higher percentage of females, which is consistent with gender trends in the overall PH population.⁴⁰ Although the number of subjects assessed in individual studies tends to be low, consistent results across several investigations adds strength to the abnormal CPX findings in patients with PH. The following sections summarize the key findings.

Diagnostic/comparative CPX investigations in PH

Eleven of the 22 investigations listed in Table 1 fall into the diagnostic/comparative investigation category. Compared with control groups, patients with resting PH consistently present with a significantly: (1) lower peak $\dot{V}O_2$; (2) higher $\dot{V}_E/\dot{V}CO_2$ ratio and slope; and (3) lower $P_{ET}CO_2$. Moreover, there appears to be a significant correlation between increasing pulmonary pressures and a worsening CPX response. Peak $\dot{V}O_2$ and $P_{ET}CO_2$ progressively decreased and the $\dot{V}_E/\dot{V}CO_2$ ratio and slope progressively increased as PH disease severity worsened from mild to severe. In addition to peak exercise measurements, $P_{ET}CO_2$ and $\dot{V}_E/\dot{V}CO_2$ abnormalities were apparent at rest and sub-maximal exercise. Figure 2 shows the $P_{ET}CO_2$ and $\dot{V}_E/\dot{V}CO_2$ ratio and slope responses in an apparently healthy individual and patients with PH of varying disease severity. Note that, in the patient with PH, abnormalities are already apparent at rest and do not normalize at any point during CPX.

Only one investigation has examined the ability of CPX to detect exercise-induced PH. Tolle et al⁵⁰ assessed the ability of the differing graphical relationships between PAP (y-axis) and $\dot{V}O_2$ (x-axis) to detect PH. A plateau in this relationship as a subject progressed toward maximal exercise was deemed an abnormal response, whereas a dislinear increase (“take-off”) from sub-maximal to maximal exertion defined a normal response. A majority of control subjects exhibited a normal response, whereas a majority of subjects with resting PH, conversely, demonstrated a plateau. The percentage of subjects with a normal vs abnormal

PAP- $\dot{V}O_2$ response was more evenly distributed in subjects with exercise-induced PH. Aerobic capacity and maximal CO were significantly lower, whereas PAP was significantly higher in exercise-induced PH subjects with an abnormal response compared with those presenting with a normal relationship. Although the $\dot{V}_E/\dot{V}CO_2$ ratio was compared among control, resting PH and exercise-induced PH groups, its ability to detect changes in PAP during exercise was not assessed.

Sun et al⁶⁵ assessed the ability of CPX to detect the development of a right-left atrial shunt [patent foramen ovale (PFO)] during physical exertion in subjects with primary pulmonary hypertension (PPH). A sudden and sharp decline in $P_{ET}CO_2$ accompanied by a sudden and sharp increase in the $\dot{V}_E/\dot{V}CO_2$ ratio were among the key CPX characteristics used to define an abnormal response consistent with a shunt. The pathophysiologic rationale for this abnormal response included: (1) physical exertion dramatically increases PAP; (2) in patients with a PFO, blood shunts to arterial circulation when right atrial pressure exceeds left atrial pressure; and (3) in response to the rise in carbon dioxide in the arterial circulation, a sudden exaggerated ventilatory response ensues, which is detectable by CPX. Figure 3 illustrates a ventilatory expired gas response in a patient with PPH and a right-left shunt. The positive and negative predictive values of a normal vs abnormal $\dot{V}_E/\dot{V}CO_2$ ratio and $P_{ET}CO_2$ response to diagnose a PFO identified by echocardiography were >90%.

CPX to assess response to an intervention in PH

Nine interventional investigations have utilized CPX to gauge the therapeutic response in patients with PH. Three of the investigations included a control group, further illustrating the consistent CPX abnormalities in patients with PH. Seven of the 9 investigations were single-center studies that included ≤ 30 subjects. The two multicenter investigations, conducted by the same research group, included ≥ 10 sites and >100 subjects each. Heart-lung transplantation appears to significantly reduce the $\dot{V}_E/\dot{V}CO_2$ slope. In 5 of the pharmacologic single-center studies, prostacyclin, iloprost, beraprost, epoprostenol and sildenafil, all vasodilatory agents, were shown to significantly improve the CPX response. Inhaled nitric oxide, which does not appear to reduce PAP in patients with PH, had no impact on CPX variables. The impact of pharmacologic interventions on CPX in the multicenter trials was far less dramatic. Sitaxsentan, an endothelin receptor antagonist, significantly improved percent-predicted $\dot{V}O_2$ in the high-dose group (300 mg) only. This agent also had no impact on the $\dot{V}_E/\dot{V}CO_2$ ratio. In the second multicenter trial, beraprost demonstrated a non-significant trend in delaying the reduction in peak $\dot{V}O_2$ over 12 months compared with control. Changes in the $\dot{V}_E/\dot{V}CO_2$ ratio or slope were not assessed in that investigation. A follow-up analysis by investigators conducting the multicenter trials discovered that centers less experienced in conducting CPX in the sitaxsentan investigation, representing the majority of the 23 sites, produced less reliable data.⁶⁶

Table 1 Summary of Studies Assessing Cardiopulmonary Exercise Testing in Patients With Pulmonary Hypertension

Study	Number of subjects and characteristics	Mean/range in age and number of males/females	Mode of exercise and protocol	Major findings ^{a,b}
Diagnostic/comparative investigations				
Data from D'Alonzo et al ⁴⁵	11 subjects with PPH; 11 apparently healthy controls matched for age and gender	PPH group: ~43 years, gender not specified; control group: characteristics not specified	Lower extremity ergometer; progressively increasing workload (20 W/min) to maximal exertion	<ul style="list-style-type: none"> • Peak $\dot{V}O_2$ was significantly lower in PPH subjects (~13 mLO_2 kg⁻¹ min⁻¹) compared with control subjects (~28 mLO_2 kg⁻¹ min⁻¹) • $\dot{V}_E/\dot{V}CO_2$ slope was significantly higher in PPH subjects compared with control group; actual values not provided
Data from Reybrouck et al ⁴⁶	10 subjects with PH; 37 subjects with normal pulmonary artery pressure who underwent surgical closure of right-left shunt	PH group: 23 years, gender not specified; surgical repair group: 10–30 years, gender not specified	Treadmill; used for pediatric patients, constant speed (3.5 mph) with 2% grade increase/minute to target heart rate of 170 bpm; lower extremity ergometer; progressively increasing workload (16 W/min) to maximal exertion	<ul style="list-style-type: none"> • $\dot{V}_E/\dot{V}CO_2$ slope was significantly higher in PH subjects (~45) compared with surgical repair group (~30) • Significant correlation between the $\dot{V}_E/\dot{V}CO_2$ slope and mean pulmonary artery pressure in subgroup of 17 subjects from both groups ($r = 0.92$)
Data from Miyamoto et al ⁴⁷	43 subjects with PPH; 16 apparently healthy controls matched for age and gender	PPH group: ~37 years, 13 males/30 females; control group: characteristics not specified	Lower extremity ergometer; progressively increasing workload (15 W/min) to maximal exertion; 6-minute walk test also performed	<ul style="list-style-type: none"> • 16 of 43 PPH subjects did not perform cardiopulmonary exercise testing secondary to being unable to tolerate maximal exertion • Peak $\dot{V}O_2$ was significantly lower in PPH subjects (~13 mLO_2 kg⁻¹ min⁻¹) compared with control subjects (~36 mLO_2 kg⁻¹ min⁻¹) • $\dot{V}_E/\dot{V}CO_2$ slope was significantly higher in PPH subjects (~43) compared with controls (~25) • 6-minute walk test distance significantly correlated with both peak $\dot{V}O_2$ ($r = 0.70$) and the $\dot{V}_E/\dot{V}CO_2$ slope ($r = -0.63$)
Data from Riley et al ⁴⁸	9 subjects with PPH; 9 apparently healthy controls	PPH group: ~35 years, 3 males/6 females; control group: ~34 years, 3 males/6 females	Lower extremity ergometer; progressively increasing workload (5 or 10 W/min for PPH subjects and 20 W/min for controls) to maximal exertion	<ul style="list-style-type: none"> • Peak $\dot{V}O_2$ was significantly lower in PPH subjects (~14 mLO_2 kg⁻¹ min⁻¹) compared with control subjects (~37 mLO_2 kg⁻¹ min⁻¹) • $\dot{V}_E/\dot{V}CO_2$ ratio at rest, VT and peak exercise significantly higher in PPH group (~57, 46 and 49) compared with controls (~47, 30 and 35) • $P_{ET}CO_2$ at rest, VT and peak exercise significantly lower in PPH group (~31, 31 and 30 mm Hg) compared with controls (~38, 44 and 32 mm Hg)
Data from Sun et al ³⁷	53 subjects with PPH; 20 apparently healthy control subjects	PPH group: ~42 years, 6 males/47 females; control group: not specified, similar age and gender characteristics	Lower extremity ergometer; progressively increasing workload (5–15 W/min) to maximal exertion	<ul style="list-style-type: none"> • $\dot{V}_E/\dot{V}CO_2$ slope was significantly higher in PPH subjects (~47) compared with controls (~25) • Peak $\dot{V}O_2$ was significantly lower in PPH subjects (~12 mLO_2 kg⁻¹ min⁻¹) compared with control subjects (~30 mLO_2 kg⁻¹ min⁻¹) • The $\dot{V}_E/\dot{V}CO_2$ slope highest (~60) and peak $\dot{V}O_2$ lowest (~8 mLO_2 kg⁻¹ min⁻¹) in patients with severe PPH

Table 1 Continued

Study	Number of subjects and characteristics	Mean/range in age and number of males/females	Mode of exercise and protocol	Major findings ^{a,b}
Data from Sun et al ³⁸	68 subjects diagnosed with PPH; 20 apparently healthy control subjects	PPH group: ~41 years; 60 males/8 females; control: 42 years; 17 males/3 females	Lower extremity ergometer; progressively increasing workload to maximal exertion	<ul style="list-style-type: none"> • Peak $\dot{V}O_2$ significantly lower in PPH subjects (~44% predicted) compared with control subjects (~104% predicted) • Peak $\dot{V}O_2$ in PPH subjects with a right-left exercise induced shunt (~40% of predicted) and PPH subjects with no evidence of a shunt (~46% of predicted) was comparable • $\dot{V}_E/\dot{V}CO_2$ slope (calculated using data to VT) and the $\dot{V}_E/\dot{V}CO_2$ ratio at VT were significantly higher in subjects with PPH (no right-left exercise induced shunt: 137% of predicted for slope and 151% of predicted for ratio; right-left exercise induced shunt: 210% of predicted for slope and 205% of predicted for ratio) compared with controls (88% of predicted for slope and 98% of predicted for ratio) • $P_{ET}CO_2$ at rest, VT and peak exercise was significantly lower in subjects with PPH compared with controls (mean values not reported) • PPH subjects with a right-left exercise induced shunt had a significantly lower $P_{ET}CO_2$ and significantly higher $\dot{V}_E/\dot{V}CO_2$ slope and the $\dot{V}_E/\dot{V}CO_2$ ratio at VT compared to PPH subjects with no-evidence of a shunt • Abrupt and sustained changes in $P_{ET}CO_2$ (abrupt decrease), and the $\dot{V}_E/\dot{V}CO_2$ ratio (abrupt increase) during exercise testing were able to identify a patent foramen ovale (by echocardiography) with a average sensitivity and specificity of 90% and 96%, respectively
Data from Yasunobu et al ³⁶	52 subjects diagnosed with PPH; 9 apparently healthy controls	PPH group: 43.5 years; 7 males/45 females; control: 39.9 years; 3 males/6 females	Lower extremity ergometer; progressively increasing workload (5–15 W/min) to maximal exertion	<ul style="list-style-type: none"> • PPH group divided into four subgroups based on decrease in percent-predicted peak $\dot{V}O_2$ achieved (mild: 65–79%; moderate: 50–64%; severe: 35–49%; very severe: <35%) • Peak $\dot{V}O_2$ was significantly lower in all PPH subgroups (~71%, 56%, 43% and 26% predicted) compared to control (~93% predicted) • $\dot{V}_E/\dot{V}CO_2$ ratio at VT significantly higher in moderate (~42), severe (~45) and very severe (~67) PPH subgroups compared with control (~27) • $\dot{V}_E/\dot{V}CO_2$ ratio at VT significantly higher in very severe PPH subgroup compared to all other PPH subgroups • $P_{ET}CO_2$ at VT was significantly lower in all PPH subgroups (~33, 28, 26 and 18 mm Hg) compared with control (~42 mm Hg)

Table 1 Continued

Study	Number of subjects and characteristics	Mean/range in age and number of males/females	Mode of exercise and protocol	Major findings ^{a,b}
Data from Holverda et al ⁴⁹	10 subjects with COPD and PH; 15 subjects with COPD but without PH	COPD with PH: ~64 years, 5 males/5 females; pulmonary fibrosis without PH: ~66 years, 7 males/8 females	Lower extremity ergometer; progressively increasing workload to maximal exertion	<ul style="list-style-type: none"> • Mean P_{ETCO_2} at rest and peak exercise was significantly lower in moderate (~30 and 26 mm Hg), severe (~27 and 24 mm Hg) and very severe (~22 and 14 mm Hg) PPH subgroups compared with control (~36 and 37 mm Hg) • P_{ETCO_2} at rest and during exercise became progressively lower as PPH severity increased • P_{ETCO_2} at rest ($r = -10.51$), VT ($r = -10.53$) and peak exercise ($r = -10.53$) significantly correlated with mean pulmonary artery pressure in PPH group • V_E/V_{CO_2} slope was significantly higher in COPD with PH subjects (~51) compared with COPD without PH subjects (~36) • V_E/V_{CO_2} ratio nadir was significantly higher in COPD with PH subjects (~55) compared with COPD without PH subjects (~31) • Peak V_{O_2} was comparable in COPD with PH subjects compared to COPD without PH subjects (~13 mL O₂ kg⁻¹ min⁻¹) • V_E/V_{CO_2} ratio nadir was significantly correlated with mean pulmonary artery pressure ($r = 0.43$)
Data from Tolle et al ⁵⁰	78 subjects with exercise-induced PH; 15 subjects with PH at rest; 16 apparently healthy controls	Exercise-induced PH group: ~59 years, 27 males/51 females; PH at rest group: ~59 years, 8 males/7 females; control: ~46 years, 5 males/11 females	Lower extremity ergometer; progressively increasing workload (6.25–25 W/min) to maximal exertion; pulmonary artery catheter in place during exercise to measure pressures	<ul style="list-style-type: none"> • Peak V_{O_2} significantly lower in exercise-induced PH (~67% predicted) and resting PH (~56% predicted) compared with control subjects (~92% predicted) • Peak V_{O_2} significantly lower in resting PH group compared to exercise-induced PH group • V_E/V_{CO_2} ratio at VT significantly higher in resting PH group (~43) compared with control (~36); exercise-induced PH group (~39) not significantly different from either group • Relationship between mean pulmonary artery pressure (y-axis) and V_{O_2} (x-axis) throughout exercise: <ul style="list-style-type: none"> (a) 41% of subjects with exercise-induced PH and 60% of subjects with resting PH demonstrated a plateau in this relationship during exercise; only 1 control subject demonstrated this plateau; deemed an inappropriate response (b) 88% of control, 59% of exercise-induced PH and 40% of resting PH subjects demonstrated a dislinear increase in this relationship as subjects progressed to maximal exertion; deemed a normal response

Table 1 Continued

Study	Number of subjects and characteristics	Mean/range in age and number of males/females	Mode of exercise and protocol	Major findings ^{a,b}
Data from Vonbank et al ⁵¹	32 subjects with COPD and PH; 10 subjects with COPD but without PH	COPD with PH: ~63 years, 21 males/11 females; COPD without PH: ~59 years, 7 males/3 females	Lower extremity ergometer; progressively increasing workload (5–15 W every 2 min) to maximal exertion	<p>(c) Comparing normal vs abnormal response in subjects with exercise-induced PH: those with abnormal response had significantly higher pulmonary vascular resistance and significantly lower percent-predicted $\dot{V}O_2$ and percent-predicted cardiac output at maximal exercise</p> <ul style="list-style-type: none"> • $\dot{V}_E/\dot{V}CO_2$ ratio at rest and during exercise was significantly higher in COPD with PH subjects (~46 and 47) compared with COPD without PH (~38 and 39) • Peak $\dot{V}O_2$ was significantly lower in COPD with PH subjects (~785 ml/min, 48% of predicted) compared with COPD without PH subjects (~1,052 ml/min, 59% of predicted)
Data from Glaser et al ⁵²	16 subjects with pulmonary fibrosis and PH; 18 subjects with pulmonary fibrosis but without PH	Pulmonary fibrosis with PH: ~63 years, 12 males/4 female; pulmonary fibrosis without PH: ~56 years, 10 males/8 females	Lower extremity ergometer; progressively increasing workload (5 W/min) to maximal exertion	<ul style="list-style-type: none"> • $\dot{V}_E/\dot{V}CO_2$ slope was significantly higher in pulmonary fibrosis with PH subjects (~45) compared with pulmonary fibrosis without PH subjects (~30) • Peak $\dot{V}O_2$ was significantly lower in pulmonary fibrosis with PH subjects (~10 mlO₂ kg⁻¹ min⁻¹) compared with pulmonary fibrosis without PH subjects (~18 mlO₂ kg⁻¹ min⁻¹) • Significant correlation between the systolic pulmonary artery pressure and the $\dot{V}_E/\dot{V}CO_2$ slope ($r = 0.77$) and peak $\dot{V}O_2$ ($r = 0.52$) in the pulmonary fibrosis with PH group only
Interventional investigations				
Data from Theodore et al ⁵³	10 subjects with PH; 12 apparently healthy controls	PH group: 20–41 years, 7 male/3 females; control: 20–65 years, 10 males/3 female	Treadmill; series of 7-min steady-rate stages at progressively increasing workloads to maximal exertion	<ul style="list-style-type: none"> • The $\dot{V}_E/\dot{V}CO_2$ slope was significantly higher in pre-heart-lung transplant PH subjects (~58) compared with controls (~22) • The $\dot{V}_E/\dot{V}CO_2$ slope significantly reduced and comparable to the control group in the same 10 PH subjects after heart-lung transplant (~25)
Data from Wax et al ⁵⁴	16 subjects with PPH	PH group: 24 years, 6 male/10 female	Lower extremity ergometer; progressively increasing workload (5 W/min) to maximal exertion	<ul style="list-style-type: none"> • Long-term intravenous prostacyclin therapy (mean follow-up: ~20 months) significantly increased peak $\dot{V}O_2$ (~39 vs ~59%-predicted)
Data from Riley et al ⁵⁵	9 subjects with PPH; 9 apparently healthy control subjects	PPH group: ~35 years; 3 males/6 females; control: ~34 years; 3 males/6 females	Lower extremity ergometer; 6 min of steady-rate exercise slightly above anaerobic threshold for subjects with PPH; workload for controls matched to PPH group	<ul style="list-style-type: none"> • $\dot{V}_E/\dot{V}CO_2$ ratio at rest and end of steady-rate exercise significantly higher in PPH group (~53 and 46) compared with controls (~47 and 33) • $P_{ET}CO_2$ at rest and end of steady-rate exercise significantly lower in PPH group (~31 and 29 mm Hg) compared with controls (~37 and 43 mm Hg)

Table 1 Continued

Study	Number of subjects and characteristics	Mean/range in age and number of males/females	Mode of exercise and protocol	Major findings ^{a,b}
Data from Wensel et al ⁵⁶	10 subjects with PPH and 1 with PH	PPH/PH group: ~41 years, gender not specified	4 subjects: lower extremity ergometer; progressively increasing workload (16 W/min) to maximal exertion; 7 subjects: treadmill; modified Naughton protocol to maximal exertion	<ul style="list-style-type: none"> Inhaled nitric oxide did not improve V_E/V_{CO_2} ratio or P_{ETCO_2} at rest or during exercise in PPH group Significant increase in peak $\dot{V}O_2$ (12.8 vs 14.2 mL O₂ kg⁻¹ min⁻¹) and significant reduction in the V_E/V_{CO_2} slope (58 vs 51) after inhalation of iloprost Resting P_{ETCO_2} (~24 vs 24 mm Hg) and V_E/V_{CO_2} ratio (58 vs 56) were unchanged after the intervention
Data from Ting et al ⁵⁷	10 subjects diagnosed with PPH; 9 apparently healthy controls	PPH group: 45.1 years; 2 males/8 females; control: 42.0 years; 2 males/7 females	Ventilatory expired gas analysis performed at rest	<ul style="list-style-type: none"> V_E/V_{CO_2} ratio at rest significantly higher in PPH group (~51) compared with control (~31) V_E/V_{CO_2} ratio at rest significantly correlated with total pulmonary vascular resistance ($r = 0.70$) in PPH group Intravenous epoprostenol administration significantly reduced the V_E/V_{CO_2} ratio at rest (~51 vs 48) in PPH group
Data from Nagaya et al ⁵⁸	30 patients with PH receiving beraprost for 1–7 months	PH group: 51 years, 10 males, 20 females	Lower extremity ergometer; progressively increasing workload (15 W/min) to maximal exertion	<ul style="list-style-type: none"> Significant increase in peak $\dot{V}O_2$ (14.9 vs 16.9 mL O₂ kg⁻¹ min⁻¹) and significant reduction in the V_E/V_{CO_2} slope (42 vs 37) after beraprost treatment
Data from Barst et al ⁵⁹	116 patients with PH randomized to placebo or beraprost for 12 months; multicenter study (10 sites)	Beraprost group: 42 years, 8 males/52 females; placebo group: 42 years, 9 males/47 females	Lower extremity ergometer; progressively increasing workload to maximal exertion	<ul style="list-style-type: none"> Baseline peak $\dot{V}O_2$ not significantly different between placebo (892 mL/min) and beraprost group (955 mL/min) Both beraprost (–68.8 mL/min) and placebo (–156 mL/min) groups demonstrated a reduction in peak $\dot{V}O_2$ at 12 months; trend in lesser peak $\dot{V}O_2$ decline in beraprost group ($p = 0.08$) that did not reach statistical significance
Data from Barst et al ⁶⁰	178 patients with PH randomized to placebo or 100 or 300 mg/day of sitaxsentan for 3 months; multicenter study (23 sites)	100 mg sitaxsentan group: 45 years, 8 male/47 female; 300 mg sitaxsentan group: 44 years, 16 males/47 females; placebo group: 48 years, 13 males/47 females	Lower extremity ergometer; progressively increasing workload to maximal exertion	<ul style="list-style-type: none"> Baseline percent-predicted peak $\dot{V}O_2$ was not significantly different among placebo (48%), 100 mg (45%) and 300 mg (45%) sitaxsentan groups Significant post-intervention increase in percent-predicted peak $\dot{V}O_2$ in the 300-mg sitaxsentan group (+3.1%) compared with placebo (–10.1%) No difference in post-intervention change in percent-predicted peak $\dot{V}O_2$ in the 100-mg sitaxsentan group (–10.4%) compared with placebo (–10.1%) Baseline V_E/V_{CO_2} ratio at VT was not significantly different among placebo (50), 100 mg (60) and 300 mg (50) sitaxsentan groups

Table 1 Continued

Study	Number of subjects and characteristics	Mean/range in age and number of males/females	Mode of exercise and protocol	Major findings ^{a,b}
Data from Oudiz et al ⁶¹	14 subjects with pulmonary artery hypertension receiving sildenafil for ~4 months; 14 subjects with pulmonary artery hypertension serving as control	sildenafil group: ~41 years; 1 male/13 females; control: ~45 years; 1 male/13 females	Electronically braked lower extremity ergometer; progressively increasing workload to maximal exertion	<ul style="list-style-type: none"> • No difference in post-intervention change in V_E/V_{CO_2} ratio at VT among placebo (4), 100 mg (-17) and 300 mg (-12) sitaxsentan groups • V_E/V_{CO_2} ratio at VT not significantly different between sildenafil and control group at baseline (~50) • Significant reduction in V_E/V_{CO_2} ratio at VT (~14%) after ~4 months of sildenafil therapy, no change in control group • P_{ETCO_2} at VT not significantly different between sildenafil and control group at baseline (~27 mm Hg) • Significant increase in P_{ETCO_2} at VT (~10%) after ~4 months of sildenafil therapy, no change in control group • Peak V_{O_2} not significantly different between sildenafil and control group at baseline (~11 mlO₂ kg⁻¹ min⁻¹) • Increase in peak V_{O_2} (~9%) after ~4 months of sildenafil therapy that trended toward statistical significance, no change in control group
Prognostic investigations Data from Wensel et al ⁶²	86 subjects with PPH; 70 undergoing exercise testing	Overall group: ~46 years, 28 males/58 females	17 subjects: lower extremity ergometer; progressively increasing workload (5–20 W/min) to maximal exertion; 53 subjects: treadmill; modified Naughton protocol to maximal exertion	<ul style="list-style-type: none"> • P_{ETCO_2} at rest (24 mm Hg) and peak V_{O_2} (~11 mlO₂ kg⁻¹ min⁻¹) were abnormally low whereas the V_E/V_{CO_2} slope (54) was abnormally high; the V_E/V_{CO_2} slope only assessed in 47 patients without a patent foramen ovale • 28 deaths and 16 lung transplants over 3-year follow-up in the overall group; peak V_{O_2}, the V_E/V_{CO_2} slope and P_{ETCO_2} at rest were all significant univariate predictors of composite end-point • Peak V_{O_2}, systolic and diastolic blood pressure, and uric acid level all retained in multivariate analysis; the V_E/V_{CO_2} slope not included in multivariate analysis
Data from Yetman et al ⁶³	40 subjects with PH; 66 apparently healthy controls	PH group: 13 years, 21 males/ 19 females; control group: 14 years, gender not specified; matched to PH group	Lower extremity ergometer; ramp protocol to maximal exertion	<ul style="list-style-type: none"> • Peak V_{O_2} was significantly lower in PH subjects (~21 mlO₂ kg⁻¹ min⁻¹) compared with controls (~36 mlO₂ kg⁻¹ min⁻¹) • V_E/V_{CO_2} slope was significantly higher PH subjects (~47) compared with controls (~34) • 1 death and 11 PH subjects required intravenous prostacyclin therapy • Peak V_{O_2} was significantly lower in PH subjects (~15 vs 27 mlO₂ kg⁻¹ min⁻¹) and the V_E/V_{CO_2} slope was significantly higher (55 vs 39) in the 12 PH subjects who suffered an adverse event compared with the 18 who were event-free

Table 1 Continued

Study	Number of subjects and characteristics	Mean/range in age and number of males/females	Mode of exercise and protocol	Major findings ^{a,b}
Data from Groepenhoff et al ⁶⁴	115 subjects with PH	48 years, 35 males/80 males	Lower extremity ergometer; progressively increasing workload (5–20 W/min) to maximal exertion; 6-minute walk test also performed	<ul style="list-style-type: none"> • P_{ETCO_2} at rest (~ 27 mm Hg) and VT (~ 27 mm Hg) and peak $\dot{V}O_2$ (~ 15 mL O_2 kg^{-1} min^{-1}) were abnormally low while the $\dot{V}_E/\dot{V}CO_2$ slope (~ 49) was abnormally high • Right atrial pressure, mean pulmonary artery pressure and total pulmonary vascular resistance all significantly correlated with peak $\dot{V}O_2$, the $\dot{V}_E/\dot{V}CO_2$ slope, the $\dot{V}_E/\dot{V}CO_2$ ratio and P_{ETCO_2} ($r = -10.22$ to 0.50) • 18 deaths during ~ 2-year follow-up; peak $\dot{V}O_2$, the $\dot{V}_E/\dot{V}CO_2$ slope, the $\dot{V}_E/\dot{V}CO_2$ ratio, change in oxygen pulse with exercise and 6-minute walk distance all significant univariate predictors of death • Only 6-minute walk distance and change in oxygen pulse with exercise were retained in multivariate survival analysis

PPH, primary pulmonary hypertension; VT, ventilatory threshold.

^aWith the exception of correlation coefficients, values represent reported means.

^bSignificant difference ($p < 0.05$).

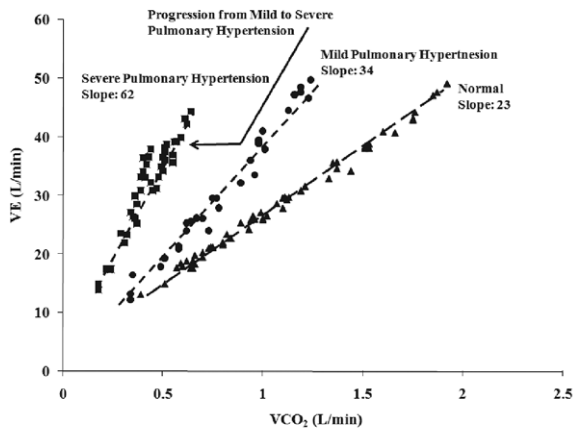
Prognostic value of CPX in PH

Three investigations have examined the prognostic utility of CPX in patients with PH. The investigation involving a pediatric PH cohort also assessed apparently healthy controls, again demonstrating a significant difference in CPX variables. From a prognostic perspective, all investigations included small cohorts (≤ 115 subjects) with a limited number of events (≤ 44), dramatically limiting the conclusions that can be drawn from these analyses. In 2 investigations, peak $\dot{V}O_2$, the $\dot{V}_E/\dot{V}CO_2$ ratio or slope and P_{ETCO_2} all demonstrated prognostic value as univariate markers. Peak $\dot{V}O_2$ was retained in one investigation's multivariate regression, whereas none of these CPX variables were retained in the other. Although standard prognostic statistics were not employed in the third investigation examining a pediatric PH cohort, peak $\dot{V}O_2$ was significantly lower, whereas the $\dot{V}_E/\dot{V}CO_2$ slope was significantly higher in subjects who suffered an adverse event compared with those who were event-free, implying potential prognostic value for these CPX variables.

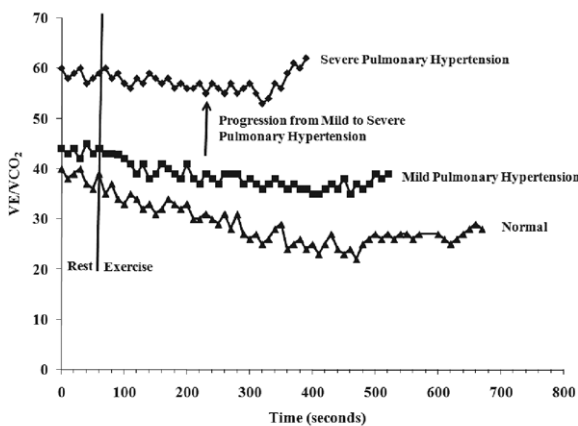
Summary of presently available body of evidence and clinical assessment implications

Although the body of literature investigating the utility of CPX in patients with PH continues to expand, well-founded recommendations based on the currently available evidence

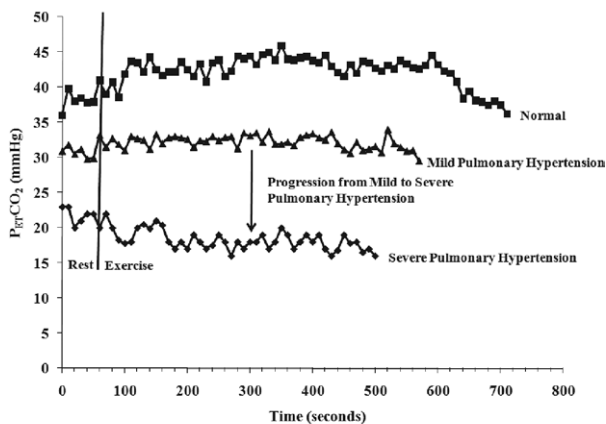
are limited.⁶⁷ Table 2 provides current CPX assessment recommendations in the PH population. These recommendations are meant to complement guidelines for heart rate, blood pressure, pulse oximetry and subjective symptom monitoring, which have been described elsewhere.^{1,4,41} Peak $\dot{V}O_2$, peak respiratory exchange ratio (RER), the $\dot{V}_E/\dot{V}CO_2$ ratio or slope and P_{ETCO_2} , all of which demonstrate a high level of reliability in patients with PH,⁶⁸ should be included in the assessment of patients with PH. Peak $\dot{V}O_2$ should be reported relative to body weight and as a percent-predicted value. The peak $\dot{V}O_2$ prediction equations proposed by Wasserman and Hansen^{69,70} account for the greatest number of explanatory variables and may therefore best approximate an individual's normally expected aerobic capacity. Peak RER allows for an assessment of subject effort during a progressive exercise test to maximal tolerance. Low peak RER values may be indicative of poor subject effort or severe PH, where hemodynamic deterioration limits the ability to adequately stress the skeletal muscle. It is unclear which, if either, $\dot{V}_E/\dot{V}CO_2$ expression (ratio vs slope) provides optimal clinical information. Both expressions are abnormal in PH, favorably respond to certain interventions, and may be prognostic. These trends in $\dot{V}_E/\dot{V}CO_2$ expression are comparable to what has been found in patients with HF.^{24,71} Tracking the $\dot{V}_E/\dot{V}CO_2$ ratio at rest and throughout exercise may be preferable in patients with PH as it allows for clearer identification of right-left shunt development during exercise.³⁸ Current evidence clearly indicates peak



(a) VE/VCO_2 slope



(b) VE/VCO_2 ratio



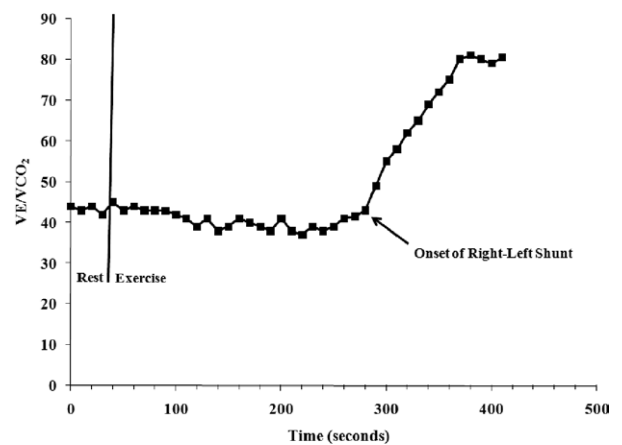
(c) $P_{ET}CO_2$

Figure 2 Examples of ventilatory expired gas responses in an apparently healthy individual and patients with pulmonary hypertension during a progressive maximal exercise test. (a) VE/VCO_2 slope. (b) VE/VCO_2 ratio. (c) $P_{ET}CO_2$.

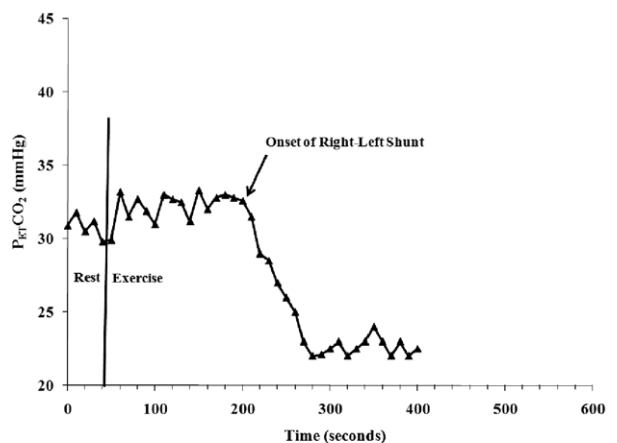
VO_2 and $P_{ET}CO_2$ are significantly diminished, whereas the VE/VCO_2 ratio and slope are significantly elevated in patients with PH. These CPX variables can therefore be used to assess disease severity in patients diagnosed with resting PH. Moreover, worsening CPX abnormalities reflect pro-

gressively higher PAP in patients with resting PH. Although only one investigation supporting the use of CPX to diagnose a right-left shunt in patients with PH has been performed, its robust findings support the ability of dramatic and sudden shifts in the VE/VCO_2 ratio and $P_{ET}CO_2$ during exercise to diagnose a PFO in patients with resting PH. Presently available evidence supporting the use of CPX to detect exercise-induced PH is lacking.

Improvements in peak VO_2 , the VE/VCO_2 ratio and slope and $P_{ET}CO_2$ may be evident in pre/post-intervention assessments, particularly treatments that improve pulmonary hemodynamics. These CPX variables may allow for a non-invasive, cost-efficient situation by which the response to an intervention can be assessed in a serial fashion, although more research is required in this area to solidify this recommendation. For multicenter trials planning to use CPX as an end-point, each site should undergo training to ensure testing procedures are standardized across all sites. Moreover, incorporation of a core CPX laboratory should be considered for multicenter trials. Initial evidence indicates CPX may provide prognostic value, although the limited research in this area does not permit the use of CPX as a



(a) VE/VCO_2 ratio response



(b) $P_{ET}CO_2$ response

Figure 3 Example of a VE/VCO_2 ratio and $P_{ET}CO_2$ response in a patient with primary pulmonary hypertension who developed a right-to-left shunt during exercise testing. (a) VE/VCO_2 ratio response. (b) $P_{ET}CO_2$ response.

Table 2 Cardiopulmonary Exercise Test Considerations in Patients With Confirmed Pulmonary HypertensionPeak $\dot{V}O_2$

- Report in $\text{mlO}_2 \text{ kg}^{-1} \text{ min}^{-1}$ and as a percent-predicted value
- Both expressions will be diminished and reflect disease severity
Percent-predicted range: $\sim 70\%$ to 25% of age- and gender-predicted normal values depending on disease severity
- May improve with interventions and provide prognostic value

Peak RER

- Assess to determine subject effort
- Value >1.10 indicative of excellent effort
- Value >1.00 should be considered a minimal threshold for an indication of exertion that substantially increases blood lactate
- Values <1.00 indicative of sub-maximal effort or a high level of disease severity in the pulmonary vasculature, limiting the ability to reach/surpass anaerobic threshold

 $\dot{V}_E/\dot{V}CO_2$ ratio

- Ratio at ventilatory threshold normally <30
Values may be in low 30s in apparently healthy elderly individuals
Normal slope values comparable to ratio expression
- Increased in pulmonary hypertension and reflects disease severity
Abnormal values range from middle 30s to 60s
Abnormalities can be apparent at rest and continue throughout exercise
Abnormal slope values comparable to ratio expression
- Abrupt rise in the $\dot{V}_E/\dot{V}CO_2$ ratio during exercise test indicative of right-left shunt
- May improve with interventions and provide prognostic value

 $P_{ET}CO_2$ (units: mm Hg)

- Resting values normally in upper 30s to low 40s
- Normally an 3–8-mm Hg increase from rest to ventilatory threshold
- Decreased in pulmonary hypertension and reflects disease severity
Abnormal values range from low 30s to low 20s at rest and low 30s to ~ 18 at ventilatory threshold
As disease severity increases: $P_{ET}CO_2$ from rest to ventilatory threshold transitions from flat to decreasing value (increasing value is normal)
- Abrupt decline in $P_{ET}CO_2$ during exercise test indicative of right-left shunt
- May improve with interventions and provide prognostic value

primary indication for the assessment of prognosis in PH. When performing CPX to gauge PH severity or response to a given intervention, an increased risk for adverse events should be considered as the peak $\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$ ratio and slope and $P_{ET}CO_2$ responses worsen. Clearly, more research is required in the prognostic arena to clinically support CPX primarily for this purpose in patients with PH.

Other CPX Procedural Considerations and Uses In Patients with PH

Safety of CPX in patients with PH: sub-maximal vs maximal exercise testing

None of the investigations listed in Table 1 reported adverse events with CPX. Similarly, no adverse events with CPX were reported in a small pediatric cohort with PH.⁷² Severe PH with accompanying syncopal episodes, cardiac arrhythmias or acute right ventricular failure do, however, serve as contraindications to maximal exercise testing.⁴¹ Both the $\dot{V}_E/\dot{V}CO_2$ ratio and $P_{ET}CO_2$ demonstrate abnormalities at rest and sub-maximal exercise that are reflective of PH disease severity and potentially respond to interventions and provide prognostic value. Sub-maximal exercise testing proto-

cols may therefore provide clinically valuable information when performance of maximal exercise testing creates safety concerns. Although already recommended as a viable option,⁴⁴ future research is required to further solidify the value of sub-maximal CPX protocols in the PH population.

Mode of exercise testing

Most investigations listed in Table 1 employed lower extremity ergometry as the mode of exercise. In a group of patients with PH, Valli et al⁷³ demonstrated that, although abnormal with both ergometry and treadmill exercise testing, the $\dot{V}_E/\dot{V}CO_2$ ratio and slope and $P_{ET}CO_2$ responses were significantly worse with the latter mode compared to the former. The investigators concluded that ventilation-perfusion abnormalities were further accentuated with treadmill ambulation compared with cycle ergometry. It is therefore plausible to hypothesize that treadmill testing provides a more accurate depiction of PH disease severity, perhaps because higher work rates are generally achieved on the treadmill. However, either mode exposes ventilatory expired gas abnormalities in patients with PH, making both acceptable for CPX. Values obtained from CPX should, however, not be considered interchangeable between exercise modes. Moreover, serial CPX assessments should be conducted using the same exercise mode.

Identifying undiagnosed patients with PH using CPX

Use of CPX to assess unexplained dyspnea upon exertion is considered a Class I indication by the American Heart Association.^{3,4} Given that profound dyspnea with physical activity is a common occurrence in patients with PH, this pathophysiologic mechanism should be considered. As in patients with PH, an abnormally elevated \dot{V}_E/\dot{V}_{CO_2} ratio or slope and diminished aerobic capacity is typically present in patients with HF,^{10,71} hypertrophic cardiomyopathy,⁷⁴ chronic obstructive pulmonary disease (COPD)^{49,75} and interstitial lung disease.⁷⁶ Pre-CPX assessments and additional measurements during CPX assist in determining the pathophysiologic mechanism underlying ventilatory expired gas abnormalities. Patients with HF or hypertrophic cardiomyopathy will obviously present with LV abnormalities on echocardiography, a varying degree of diminished aerobic capacity, and an elevated \dot{V}_E/\dot{V}_{CO_2} ratio and slope reflective of disease severity, and maintain normal oxygen saturation throughout CPX. Patients with COPD or interstitial lung disease will present with obstructive or restrictive abnormalities on pulmonary function testing, a varying degree of diminished aerobic capacity, and an elevated \dot{V}_E/\dot{V}_{CO_2} ratio and slope reflective of disease severity, and may desaturate during CPX. Thus, PH should be considered as a potential mechanism in patients with unexplained dyspnea upon exertion who: (1) have no LV abnormalities on echocardiography; (2) a normal pulmonary function test; (3) exhibit CPX abnormalities, including a diminished aerobic capacity, abnormally elevated \dot{V}_E/\dot{V}_{CO_2} ratio and slope and diminished P_{ETCO_2} ; and (4) possibly desaturate during exercise.

It should also be noted that patients with HF,⁶ hypertrophic cardiomyopathy,⁷⁴ COPD⁴⁹ and pulmonary fibrosis⁷⁷ may also develop PH as a secondary consequence of their primary pathophysiologic condition. If PH coexists with these primary cardiac or pulmonary conditions, ventilatory expired gas abnormalities (peak $\dot{V}O_2$, the \dot{V}_E/\dot{V}_{CO_2} ratio and slope and P_{ETCO_2}) are typically more severe and reflect the degree of elevated PAP.

Use of CPX for functional assessment and exercise prescription

The resultant decrease in peak $\dot{V}O_2$ and $\dot{V}O_2$ at the anaerobic threshold in PH results in a decreased ability to perform activities of daily living. CPX can therefore be used to assess the degree of disability and provide the patient, caregiver or employer with guidance regarding those activities of daily living that can be performed safely and those that should be avoided due to symptoms associated with PH.^{1,41,78} Tables defining the oxygen cost of common occupational and recreational activities are available.⁷⁸ The CPX response, particularly $\dot{V}O_2$ at the VT,⁷⁹ if detectable, can be matched to these oxygen costs to provide guidance on aerobic activities that the patient will be able to perform safely. Moreover, exercise training appears to safely im-

prove symptoms and functional capacity in patients with PH.⁸⁰ CPX provides for the ability to individualize the appropriate training intensity, particularly if VT is identified, and optimize clinical outcomes.⁴¹

CPX is a clinically accepted modality in the evaluation and management of patients with HF.²⁴ Current evidence indicates that CPX provides an accurate depiction of PH disease severity and may provide information on the response to therapeutic interventions and prognosis. Moreover, the exercise testing procedures employed (i.e., conservative exercise protocols) and the key variables attained from ventilatory expired gas analysis (peak $\dot{V}O_2$, \dot{V}_E/\dot{V}_{CO_2} and P_{ETCO_2}) are strikingly similar between patients diagnosed with HF and PH. Research using CPX in PH should continue to better determine the clinical utility of this exercise assessment.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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