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

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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 (V_{O_2}), carbon dioxide production (V_{CO_2}) and minute ventilation (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);

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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 individuals[39] 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 prognostic 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 ($P_{ET}CO_2$). 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 V_{O_2} and 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 $P_{ET}CO_2$. Moreover, arterial desaturation decreases oxygen delivery to working skeletal muscle, negatively impacting aerobic metabolism and contributing to the observed decrease in peak V_{O_2} and V_{O_2} at the VT with PH. The ventilatory expired gas consequences resulting from PH pathophysiology are illustrated in Figure 1.

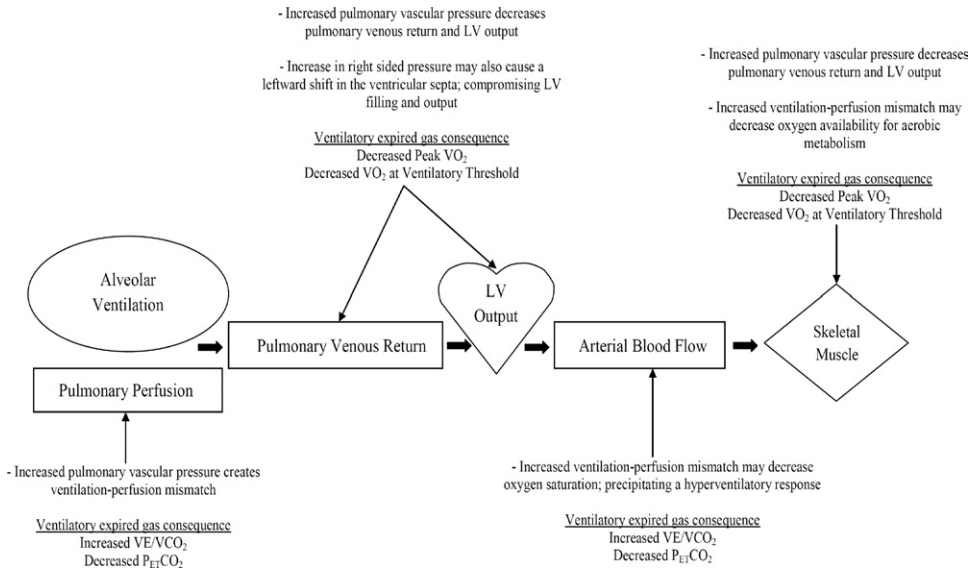

Figure 1 Impact of pulmonary hypertension pathophysiology on ventilatory expired gas exchange.