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Editorial

# Cardiopulmonary exercise testing with ventilatory gas analysis for evaluation of chronic thromboembolic pulmonary hypertension: Unmasking its role after a therapeutic intervention

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but debilitating and life-threatening complication of acute pulmonary embolism (PE). CTEPH is defined as a mean pulmonary artery pressure (mPAP) of at least 25 mmHg at rest, caused by persistent obstruction of pulmonary arteries after PE that has not resolved despite at least 3 months of therapeutic anticoagulation [1]. CTEPH results from persistent obstruction of pulmonary arteries and progressive vascular remodeling [2,3]. Non-dissolution of thromboembolic material may result in the formation of organized fibrotic scar tissue, webs and bands, which obstruct pulmonary arteries. In addition, redistribution of blood to non-occluded vessels may result in in endothelial dysfunction and vascular remodeling of precapillary arteries [3,4]. Right heart failure, as a consequence of the obstruction of pulmonary arteries and secondary pulmonary vasculopathy, is the most frequent cause of death. Surgical pulmonary endarterectomy remains the treatment of choice for CTEPH and is associated with excellent long-term results and a high probability of cure. For patients with inoperable CTEPH, various medical and interventional therapies (e.g., vasodilators, balloon pulmonary angioplasty [BPA]) are being developed. Repeat right heart catheterization (RHC) remains the gold standard to assess the response to these therapies [1,5].

In patients affected with pulmonary hypertension (PH) or CTEPH, cardiopulmonary exercise testing (CPET) is a useful tool to assess severity, and to elucidate the underlying pathophysiologic mechanisms contributing to exercise intolerance [5]. In these patients, CPET shows decreased peak oxygen uptake ($VO_2$), oxygen ($O_2$) pulse, and $VO_2$ to work rate (WR) ratio. Exercise limitation is characterized by a marked ventilatory inefficiency, which determines an increase in equivalents of $O_2$ and $CO_2$ ($EqO_2$ and $EqCO_2$, respectively), and in end tidal pressure of oxygen ($P_{ET}O_2$); and a decrease in end tidal pressure of $CO_2$ ($P_{ET}CO_2$). This decrease in $P_{ET}CO_2$ is proportional to the decrease in $VO_2$, and to the increase in the mean pulmonary arterial pressure [6,7]. Previous studies have assessed the prognostic value of CPET in patients with PH. Groepenhoff et al. [8] enrolled 115 patients with PH, of whom 18 died after a mean ± SD follow-up of 846 ± 461 days. They found that ventilatory and gas exchange parameters measured during maximal CPET predicted survival in PH patients with moderate hemodynamic abnormalities. Quezada et al. further confirmed the prognostic value of $P_{ET}CO_2$ in a cohort of 148 patients with PH from a single center in Spain [9].

In their paper, Akizuki and colleagues [10] assess whether postural changes in ventilatory gas analysis parameters were useful for assessing pulmonary hemodynamics in patients with CTEPH. They enrolled 44 patients with newly diagnosed CTEPH, 33 patients with improved CTEPH after therapy, and 25 controls (i.e., patients with suspected pulmonary hypertension but normal mPAP values). They measured various pulmonary function parameters in supine and sitting positions, and they calculated postural changes (Δ [supine minus sitting]). In addition, they examined hemodynamic and ventilatory gas analysis parameters before and after treatment with BPA in 32 patients with CTEPH. The main findings were: i) supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ were associated with mPAP; ii) supine $P_{ET}CO_2$ significantly increased after BPA, and iii) there was significant correlation between the change in mPAP and those in supine $P_{ET}CO_2$ by BPA. The strengths of the study are the use of RHC both for diagnosis and assessment of response to treatments and inclusion of a control group of patients without PH.

This study is the first to show that ventilatory gas analysis in different positions is useful for the evaluation of mPAP. In addition, Akizuki and colleagues' results suggest that CPET might be useful to assess response to therapy in patients with CTEPH. Despite the authors' best efforts, some questions persist. The role of mPAP in the prognostic assessment of patients with CTEPH remains to be elucidated. In CTEPH patients who undergo endarterectomy or BPA,

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RHC is routinely used to assess the response to these therapies. Additional research is needed to investigate whether ventilatory gas analysis in different positions may help assess response to therapy or even substitute RHC in certain CTEPH patients. Finally, the role of ventilatory gas analysis in the diagnosis of CTEPH and chronic thromboembolic disease merits further research.

Until researchers provide more and better evidence, we encourage clinicians to estimate severity of PH by combining the WHO functional class, clinical signs of right heart failure, exercise capacity and right ventricular function, among others [5]. Whenever possible, RHC should be used to assess the efficacy of medical, interventional and surgical therapies in patients with CTEPH.

## Declaration of competing interest

None.

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