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**Title:** Clinical usefulness of end-tidal CO<sub>2</sub> profiles during rapidly-incremental exercise in patients with idiopathic and chronic thromboembolic pulmonary hypertension

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**Body:** Rationale: Low CO<sub>2</sub> set-point and inequalities in ventilation/perfusion distribution can lead to reduced end-tidal partial pressure for CO<sub>2</sub> during incremental exercise in pulmonary arterial hypertension (PAH). Whether progressive or sudden decreases in exercise PETCO<sub>2</sub> could be helpful in indicating more severe disease remains unclear. Methods: 43 patients with chronic thromboembolic pulmonary hypertension (CTEPH) (50 ± 13 yrs, mPAP 53 ± 11 mmHg) and 18 with idiopathic PAH (39 ± 14 yrs, mPAP 63 ± 17 mmHg) performed a ramp-incremental exercise test. According to PETCO<sub>2</sub>, they were separated into: 1) Group A with a normal response; 2) Group B, showing an abrupt decrease and other signs of exercise-induced right-to-left shunt (EIS); and 3) Group C, showing a progressive decrease but without EIS. Results: In CTEPH, Group B (n = 21/43, 48%) had worse haemodynamics (cardiac index= 1.9±0.6 vs 2.3±0.6 L/min/m<sup>2</sup>), more impaired exercise performance (peak O<sub>2</sub> uptake= 12±2 vs 14±2 mL/kg/min) and higher ventilatory response ( $\Delta V'E/VCO_2 = 70 \pm 22$  vs  $47 \pm 8$ , p<0.05) compared to Group A. Similar findings were observed in IPAH. Of note, Group C pattern was more frequent in CTEPH than in IPAH (28% vs 11%, p<0.05) and associated with functional impairments at rest and exercise at same extent of those found in Group B. Conclusion: Abnormal decrease in PETCO<sub>2</sub> during exercise is more commonly found in CTEPH than PAH and regardless its association with right-to-left shunt, should be clinically valued as a non-invasive marker of disease severity in both diseases.