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Insights into ventilation–gas exchange coupling in chronic thromboembolic pulmonary hypertension

To the Editor:

Exercise intolerance due to excessive ventilation and dyspnoea are fundamental clinical features of patients with pulmonary vascular diseases [1]. Among these diseases, chronic thromboembolic pulmonary hypertension (CTEPH) is associated with the largest increase in exercise ventilation [2]. Understanding the mechanism(s) underlying excess exercise ventilation in CTEPH is clinically relevant when designing evidence-based therapeutic and rehabilitative strategies to improve patients' symptoms and quality of life.

Excess exercise ventilation in CTEPH has been traditionally ascribed to increased "wasted" ventilation, *i.e.* hypoperfusion of well-ventilated alveoli. In fact, the physiological dead space fraction of tidal volume (V_D/V_T ratio) at peak exercise not only predicts CTEPH after pulmonary embolism [3] but also improves after clinical [4] and surgical [5] treatment. As the end-tidal carbon dioxide tension (P_{ETCO_2}) diminishes when ventilation is excessive relative to perfusion [6], increased V_D/V_T has been mechanistically linked to inordinately low P_{ETCO_2} in CTEPH [7]. A P_{ETCO_2} lower than arterial (a) carbon dioxide tension (P_{CO_2}) (*i.e.* a positive $P_{(a\text{-}ET)CO_2}$ gradient) [6] also suggests impaired pulmonary perfusion as a potential explanation for low exercise P_{ETCO_2}in these patients [8].

Surprisingly, however, seminal studies comparing lung absorption of multiple inert gases showed no or a limited increase in V_D/V_T despite marked pulmonary arterial obstruction [9]. This prompts an alternative (or complementary) explanation for a low exercise P_{ETCO_2} in CTEPH: reduced alveolar P_{CO_2} (hyperventilation) [10]. In fact, heightened neural drive has been found in pulmonary vascular diseases secondary to increased chemosensitivity [11] and/or higher afferent stimuli from "central" baro- and mechano-receptors [12]. Thus, alveolar hyperventilation under the stress of exercise may also explain the relatively lower P_{ETCO_2} in CTEPH. A hyperbolic correlation between increasing minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2}) and decreasing arterial carbon dioxide tension (P_{aCO_2}) in CTEPH is also suggestive of heightened neural drive and consistent with the alveolar equation [13].

There is another intriguing feature of the P_{ETCO_2} response that brings additional uncertainty about the meaning of a low exercise P_{ETCO_2} in CTEPH. Similar to pulmonary arterial hypertension (PAH) [9], P_{ETCO_2} paradoxically increases (instead of further decreasing as in normal subjects) as soon as CTEPH patients enter the recovery phase. In this context, evaluation of P_{aCO_2} (or arterialised capillary (P_{cCO_2}) as its surrogate) [8] and $P_{(c\text{-}ET)CO_2}$ across the exercise-to-recovery transition might shed light on the mechanisms underlying the P_{ETCO_2} behaviour during recovery in CTEPH. Thus, we reasoned that during recovery: 1) if P_{cCO_2} remains stable or further decreases despite higher P_{ETCO_2}, a narrower $P_{(c\text{-}ET)CO_2}$ would suggest improved V_D/V_T (scenario 1); 2) conversely, if P_{cCO_2} and P_{ETCO_2} increase proportionally leading to stable $P_{(c\text{-}ET)CO_2}$, lower neural drive would explain higher P_{ETCO_2} (scenario 2); 3) but if a narrower $P_{(c\text{-}ET)CO_2}$ develops as a consequence of P_{cCO_2}, increasing less than P_{ETCO_2}, improved V_D/V_T plus lower neural drive would explain a higher P_{ETCO_2} (scenario 3).

We therefore measured P_{cCO_2} (arterialised ear lobe blood), $P_{(c\text{-}ET)CO_2}$ and plasma lactate 1 min before peak incremental exercise, at peak and in recovery at every minute up to the fifth minute of unloaded cycling. Responses from 10 patients (age 54–78 years, five males, mean±SE pulmonary arterial pressure 51.5±9.7 mmHg, pulmonary wedge pressure 9.2±3.4 mmHg, stable segmental perfusion defects after 6 months of anticoagulation) were contrasted with those from eight age- and sex-matched healthy subjects. As expected, patients had a lower peak oxygen uptake, V'_{CO_2} and arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) ($p<0.05$). Lactate corrected for peak work rate was higher in patients

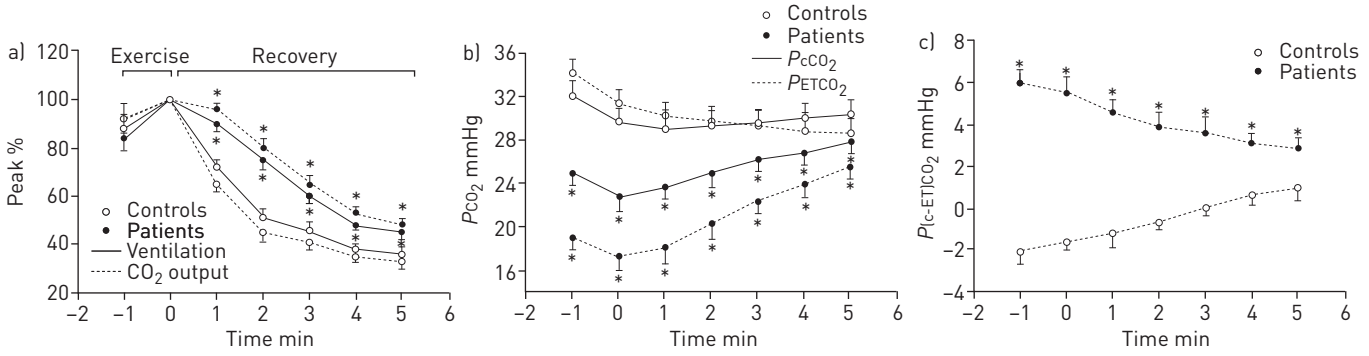

FIGURE 1 a) Ventilation, carbon dioxide (CO_2) output, b) capillary carbon dioxide tension (P_{cCO_2}) and capillary end-tidal carbon dioxide tension (P_{ETCO_2}), and c) their differences during exercise and recovery in patients with chronic thromboembolic pulmonary hypertension and healthy controls. Data are presented as mean±SE. *: p<0.05 for inter-group comparisons at a given time-point.

(0.14±0.05 *versus* 0.08±0.04 $mEq \cdot L^{-1} \cdot W^{-1}$; p<0.01). These findings were associated with lower peak P_{ETCO_2} and positive $P_{(c-ET)CO_2}$ (figure 1b).

In line with our previous observations, whereas recovery P_{ETCO_2} consistently increased throughout recovery in patients, it remained lower than peak exercise in controls (figure 1b). This increased P_{ETCO_2} was associated with a faster decline in V'_E compared with V'_{CO_2} in patients; conversely, V'_E recovered at a slower rate than V'_{CO_2} in controls (figure 1a). Lactate remained similarly increased in both groups; conversely, S_{pO_2} was lower in patients up to the third minute of recovery (91.1±3.5% *versus* 96.4±2.0%; p<0.05). In controls, P_{cCO_2} further decreased up to the second minute and remained stable thereafter, *i.e.* a negative $P_{(c-ET)CO_2}$ was found for most of recovery. In patients, P_{cCO_2} increased throughout recovery; however, as it increased less than P_{ETCO_2}, $P_{(c-ET)CO_2}$ systematically decreased in CTEPH (figure 1c). Under the logical assumption that recovery reversed the abnormalities seen during exercise, scenario 3 seems in line with the suggestions of DELCROIX *et al.* [10] and NAEIJE and VAN DE BORNE [11] that both high V_D/V_T and heightened neural drive are related to excess exercise ventilation in CTEPH.

As pointed out by the late eminent physiologist Brian J. Whipp, the transition between different rates of metabolic demand (*e.g.* exercise–recovery) provides a unique window to understand the complexities linking tissue gas exchange to pulmonary ventilation [14]. Thus, when V'_{CO_2} slowly decreased after exercise in our patients, V'_E did not lag behind as in normal subjects. Conversely, V'_E decreased consistently faster than V'_{CO_2} in patients (figure 1a). The sudden decrease in V'_E and resulting elevation in P_{cCO_2} (figure 1b) suggest an abrupt reduction in neural drive in these patients. Sluggish muscle gas exchange kinetics due to a slower rate of phosphocreatine replenishment and/or slower cardiocirculatory dynamics during recovery may have contributed to a more protracted V'_{CO_2} in patients [14]. It is also conceivable that carbon dioxide released during exercise has been slowly washed-out from carbon dioxide reservoirs, which are likely to be larger in chronically hypocapnic patients [15]. In fact, resting P_{aCO_2} and exercise-induced decrements in P_{cCO_2} were closely related to V'_{CO_2} kinetics in patients (r=0.85 and r=0.88, respectively; p<0.001). Although additional studies are needed to clarify the underlying mechanism(s), it is clear that V'_E did not "wait" for V'_{CO_2}, which resulted in post-exercise decreases in the V'_E/V'_{CO_2} ratio, thereby contributing to increase P_{ETCO_2} in CTEPH.

Another key finding relates to a $P_{(c-ET)CO_2}$ decrease after exercise in patients, which seems consistent with post-exercise improvement in V_D, likely to be secondary to enhanced pulmonary perfusion and ventilation/perfusion matching [6, 7]. ZHAI *et al.* [13] found that while V'_E/V'_{CO_2} (assumed as an index of V_D/V_T behaviour) for a given P_{aCO_2} was increased in CTEPH compared with PAH, the difference disappeared when V'_E/V'_{CO_2} was expressed as a function of P_{ETCO_2}. This suggests a greater contribution of increased V_D to the excessive exercise ventilation (and low P_{ETCO_2}) in CTEPH compared with PAH during exercise.

In conclusion, increased "wasted" ventilation (high V_D/V_T) is not the only explanation for excess exercise ventilation in CTEPH: heightened neural drive also contributes to these abnormalities. Interventions able to decrease both V_D/V_T and neural drive might prove particularly valuable in this patient population.

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Increased "wasted" ventilation and heightened neural drive explains excess exercise ventilation in CTEPH http://ow.ly/Z4YBc

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Diagnostic concordance of different criteria for exercise pulmonary hypertension in subjects with normal resting pulmonary artery pressure

To the Editor:

Pulmonary hypertension is defined by a resting mean pulmonary artery pressure (mPAP) ⩾25 mmHg [1]. Despite a better understanding of the biology of pulmonary hypertension and new therapeutic advances, pulmonary hypertension remains diagnosed late in its natural history and is largely a non-curable condition [2]. Recently, there has been renewed interest in stress-testing of the pulmonary circulation since the early stages of pulmonary vascular disease (PVD) or left heart disease (LHD) can be associated with normal resting mPAP but an abnormal haemodynamic response that is unmasked by exercise [3–5].