Breathing too much! Ventilatory inefficiency and exertional dyspnea in pulmonary hypertension

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BACKGROUND

Dyspnea and exercise intolerance are hallmarks of pulmonary hypertension (PH). Extant knowledge in the field has mostly accrued from studies involving patients with pulmonary arterial hypertension. Less is known on the determinants of exertional dyspnea in chronic thromboembolic PH, a much more frequent cause of PH in clinical practice.

OVERVIEW

A non-smoking 29-year-old woman complained of progressive dyspnea — modified Medical Research Council (mMRC) scale score = 4 — after pulmonary thromboembolism with a high clot burden two years earlier. Unremarkable spirometry coexisted with a moderate reduction in DLCO (Figure 1A). Echocardiography unveiled PH, and right heart catheterization confirmed precapillary PH. After a pulmonary CT angiogram demonstrating residual filling defects in the pulmonary arteries to the lower lobes, the patient underwent pulmonary endarterectomy (PEN). Improvement in dyspnea during activities of daily living (mMRC = 1) after surgery was accompanied by a significant increase in DLCO (Figure 1A) and O2 uptake (VO2) at a given work rate (WR) and at peak exercise (Figure 1B). A decrease in ventilation (VE) requirements for a given CO2 output (VCO2) from the start of exercise, together with a delayed respiratory compensation point (RCP) to lactic acidosis were associated with lower dyspnea scores throughout exercise (Figure 1C).

In healthy subjects, pulmonary gas exchange efficiency improves during exercise since a lower fraction of VT is wasted in the physiological (anatomical plus alveolar) dead space (Vd/Vt). Thus, less Vt is needed to clear a given amount of CO2, that is, Vt/VCO2 decreases down to a low minimum (nadir; Figure 1C, Graph 2). If Vt/VCO2 does not improve as expected (or even increases) (a) and/or the subject hyperventilates dropping PaCO2 (b), Vt/VCO2 increases, bringing shortness of breath. The relative importance of (a) or (b) to increase Vt/VCO2 seems to vary, depending on the location of the occluding clots: whereas proximal, larger-vessel disease markedly increases Vt/VCO2 since blood flow is reduced over a large portion of the vascular tree (a), increased neurochemical stimulation leading to hyperventilation (b) has a greater contributory role in distal, smaller-vessel disease.

![Graph 1](https://via.placeholder.com/150)

**Graph 1.** Resting pulmonary function (in A), tabular exercise data (in B), and selected physiologic (and sensory) responses (in C) as a function of exercise intensity before and after pulmonary endarterectomy (PEN) in a 29-year-old woman with chronic thromboembolic pulmonary hypertension. VO2: oxygen output; PtCO2: end-tidal carbon dioxide pressure; Ve: ventilation; RCP: respiratory compensation point; and VCO2: carbon dioxide output.

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End-tidal $\text{PCO}_2$ is characteristically reduced in chronic thromboembolic PH (Figure 1C, Graph 2, bottom) secondary to impaired perfusion of ventilated alveoli decreasing the rate of CO$_2$ “unloading” from mixed venous blood to alveoli (a) and/or due to alveolar hyperventilation (b). In the current patient, PEN led to a dramatic decrease in the ventilatory requirements during exercise (Figure 1C, Graphs 1 and 2) and enhanced central hemodynamics, leading to higher $\text{O}_2$ delivery to the contracting muscles (higher $\dot{V}_{\text{O}_2}/\text{WR}$), which delayed the onset of metabolic acidosis (RCP). These factors, together with lower pulmonary vascular pressures, likely contributed to decreased neural drive to breathe. Jointly, these mechanisms explain why the patient required 25 L/min less $\dot{V}E$ to clear 1 L/min $\dot{V}_{\text{CO}_2}$ at 45 W ($\dot{V}E/\dot{V}_{\text{CO}_2}$ declined from 67 L/L to 42 L/L); consequently, dyspnea intensity decreased from “very intense” to “light” (Figure 1C, Graph 3).

CLINICAL MESSAGE
Lessening the ventilatory requirements for exercise has major beneficial effects on dyspnea in patients with PH. Therapeutic approaches that improve pulmonary gas exchange efficiency and cardiocirculatory function (peripheral $\text{O}_2$ delivery) are poised to reduce breathing discomfort, enhancing exercise tolerance of patients.

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