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

José Alberto Neder[1], Danilo Cortozi Berton[2], Denis E O'Donnell[1]

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.[1] Less is known on the determinants of exertional dyspnea in chronic thromboembolic PH,[2] 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 DL_{CO} (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 DL_{CO} (Figure 1A) and O_2 uptake ($\dot{V}O_2$) at a given work rate (WR) and at peak exercise (Figure 1B). A decrease in ventilation ($\dot{V}E$) requirements for a given CO_2 output ($\dot{V}CO_2$) 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 ($V_{D_{phys}}$). Thus, less $\dot{V}E$ is needed to clear a given amount of CO_2, that is, $\dot{V}E/\dot{V}CO_2$ decreases down to a low minimum (nadir; Figure 1C, Graph 2). If $V_{D_{phys}}$ does not improve as expected (or even increases) (a) and/or the subject hyperventilates dropping $PaCO_2$ (b), $\dot{V}E/\dot{V}CO_2$ increases, bringing shortness of breath.[3] The relative importance of (a) or (b) to increase $\dot{V}E/\dot{V}CO_2$ seems to vary, depending on the location of the occluding clots: whereas proximal, larger-vessel disease markedly increases $V_{D_{phys}}$ 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.[4]

A	Pre PEN	% pred	Post PEN	% pred
FVC, L	3.50	91	3.42	89
FEV_1, L	3.02	94	2.85	88
FEV_1, FVC	0.86		0.83	
DLco, mmol/min/kPa	4.71	51	8.04	88

B	Pre PEN	% pred	Post PEN	% pred
Peak $\dot{V}O_2$, L/min	0.706	42	1.230	74
Peak WR, W	44	29	96	65
$\Delta\dot{V}O_2/\Delta WR$, mL/min/W	5.7	57	9.3	93
Peak SpO_2, %	95		94	

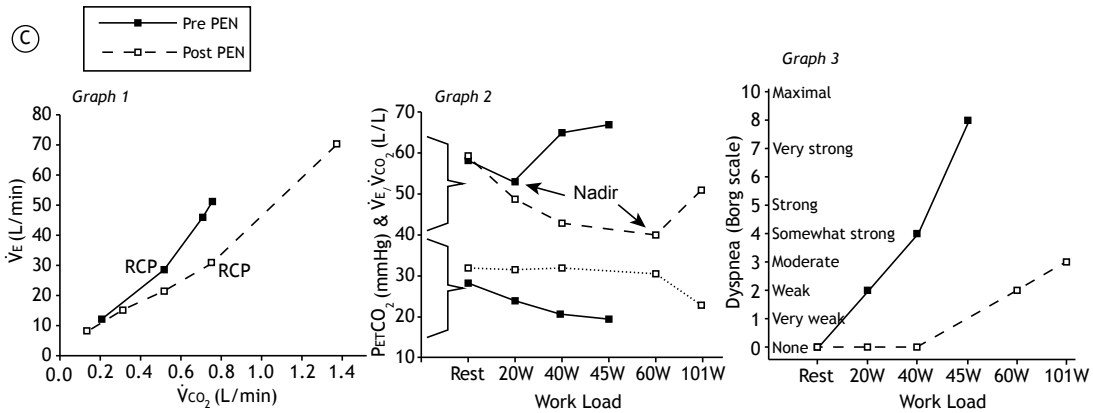

Figure 1. Resting pulmonary function (in A), tabular exercise data (in B), and selected physiologic (and sensory) responses (in C) as a function of exercise intensity before and after pulmonary endarterectomy (PEN) in a 29-year-old woman with chronic thromboembolic pulmonary hypertension. $\dot{V}O_2$: oxygen output; $P_{ET}CO_2$: end-tidal carbon dioxide pressure; $\dot{V}E$: ventilation; RCP: respiratory compensation point; and $\dot{V}CO_2$: carbon dioxide output.

1. Pulmonary Function Laboratory and Respiratory Investigation Unit, Division of Respirology, Kingston Health Science Center & Queen's University, Kingston, ON, Canada.
2. Unidade de Fisiologia Pulmonar, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

End-tidal $P_{ET}CO_2$ 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).[5] 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 O_2 delivery to the contracting muscles (higher $\dot{V}O_2$/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 $\dot{V}CO_2$ at 45 W ($\dot{V}E/\dot{V}CO_2$ 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 O_2 delivery) are poised to reduce breathing discomfort, enhancing exercise tolerance of patients.

REFERENCES

1. Neder JA, Ramos RP, Ota-Arakaki JS, Hirai DM, D'Arsigny CL, O'Donnell D. Exercise intolerance in pulmonary arterial hypertension. The role of cardiopulmonary exercise testing. Ann Am Thorac Soc. 2015;12(4):604-612. https://doi.org/10.1513/AnnalsATS.201412-558CC
2. Ramos RP, Ferreira EVM, Valois FM, Cepeda A, Messina CMS, Oliveira RK, Araújo ATV, et al. Clinical usefulness of end-tidal CO_2 profiles during incremental exercise in patients with chronic thromboembolic pulmonary hypertension. Respir Med. 2016;120:70-77. https://doi.org/10.1016/j.rmed.2016.09.020
3. Neder JA, Berton DC, O'Donnell DE. Out-of-proportion dyspnea and exercise intolerance in mild COPD. J Bras Pneumol. 2021;47(3):e20210205. https://doi.org/10.36416/1806-3756/e20210205
4. Zhai Z, Murphy K, Tighe H, Wang C, Wilkins MR, Gibbs JSR, et al. Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Chest. 2011;140(5):1284-1291. https://doi.org/10.1378/chest.10-3357
5. Neder JA. Residual Exertional Dyspnea in Cardiopulmonary Disease. Ann Am Thorac Soc. 2020;17(12):1516-1525. https://doi.org/10.1513/AnnalsATS.202004-398FR