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RESEARCH ARTICLE

Neurophysiological mechanisms of exertional dyspnea in post-pulmonary embolism syndrome

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Abstract

Following pulmonary embolism (PE), a third of patients develop persistent dyspnea, which is commonly termed the post-PE syndrome. The neurophysiological underpinnings of exertional dyspnea in patients with post-PE syndrome without pulmonary hypertension (PH) are unclear. Thus, the current study determined if abnormally high inspiratory neural drive (IND) due, in part, to residual pulmonary gas-exchange abnormalities, was linked to heightened exertional dyspnea and exercise limitation, in such patients. Fourteen participants with post-PE syndrome (without resting PH) and 14 age-, sex-, and body mass index-matched healthy controls undertook pulmonary function testing and a symptom-limited cycle cardiopulmonary exercise test with measurements of IND (diaphragmatic electromyography), ventilatory requirements for CO_2 ($\dot{V}_E/\dot{V}_{CO_2}$), and perceived dyspnea intensity (modified Borg 0–10 scale). Post-PE (vs. control) had a reduced resting transfer coefficient for carbon monoxide (K_{CO}: 84 ± 15 vs. 104 ± 14%pred, $P < 0.001$) and peak oxygen uptake ($\dot{V}_{O_{2peak}}$) (76 ± 14 vs. 124 ± 28%pred, $P < 0.001$). IND and $\dot{V}_E/\dot{V}_{CO_2}$ were higher in post-PE than controls at standardized submaximal work rates ($P < 0.05$). Dyspnea increased similarly in both groups as a function of increasing IND but was higher in post-PE at standardized submaximal work rates ($P < 0.05$). High IND was associated with low K_{CO} ($r = -0.484$, $P < 0.001$), high $\dot{V}_E/\dot{V}_{CO_2}$ nadir ($r = 0.453$, $P < 0.001$), and low $\dot{V}_{O_{2peak}}$ ($r = -0.523$, $P < 0.001$). In patients with post-PE syndrome, exercise IND was higher than controls and was associated with greater dyspnea intensity. The heightened IND and dyspnea in post-PE, in turn, were strongly associated with low resting K_{CO} and high exercise $\dot{V}_E/\dot{V}_{CO_2}$, which suggest important pulmonary gas-exchange abnormalities in this patient population.

NEW & NOTEWORTHY This study is the first to show that increased exertional dyspnea in patients with post-pulmonary embolism (PE) syndrome, without overt pulmonary hypertension, was strongly associated with elevated inspiratory neural drive (IND) to the diaphragm during exercise, compared with healthy controls. The greater IND was associated with impairments in pulmonary gas exchange and significant deconditioning. Our results help to explain why many patients with post-PE syndrome report significant dyspnea at relatively low levels of physical activity.

dyspnea; exercise capacity; inspiratory neural drive; post-PE syndrome

INTRODUCTION

Chronic activity-related breathlessness (dyspnea) occurs in up to 30% of survivors of acute pulmonary embolism (PE), even after effective anticoagulation (1). The causes of persistent dyspnea following remote PE are heterogeneous and thought to include previous cardiopulmonary disease, morbid obesity, and/or deconditioning (1–3). However, it has been recognized that some such patients report persistent dyspnea, exercise intolerance, and reduced quality of life, independent of the aforementioned comorbidities, and this has been termed the post-PE syndrome (4). Patients with this syndrome include: chronic thromboembolic pulmonary hypertension (CTEPH), chronic thromboembolic

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disease (pulmonary vascular occlusion on imaging without pulmonary hypertension [PH]), and post-PE related dyspnea (no vascular occlusion or PH) (4, 5). Although the cause of exercise limitation has been explored in CTEPH, the physiological underpinnings of dyspnea and reduced exercise capacity in patients with post-PE syndrome without resting PH are poorly understood and are the main focus of the current study.

Recent studies in various respiratory diseases (both obstructive and restrictive) have shown that exertional dyspnea intensity consistently rose in close association with excessive increases in inspiratory neural drive (measured by diaphragm electromyography, EMGdi) during exercise (6–8). In these studies, increased EMGdi during exercise was thought to reflect heightened central medullary and cortical motor command output, suggestive of compensatory responses to pulmonary gas exchange abnormalities, and to a greater extent, excessive mechanical loading and functional inspiratory muscle weakness (6–8). It is reasonable to postulate that in post-PE syndrome, where microvascular integrity is likely disrupted, increased inspiratory neural drive and dyspnea would, in part, reflect the effect of persistent ventilation-perfusion ($\dot{V}_A/\dot{Q}$) maldistribution (9), rather than abnormal dynamic mechanics that predominate in other chronic lung diseases (6, 7).

Past studies in post-PE syndrome (with and without PH) have shown reduced exercise ventilatory efficiency (abnormally high ventilatory requirements for CO_2 [$\dot{V}_E/\dot{V}_{CO_2}$]), compared with healthy controls, despite preserved resting respiratory mechanics (10, 11). In these studies, the increased $\dot{V}_E/\dot{V}_{CO_2}$ was due primarily to heightened physiological dead space (high $\dot{V}_A/\dot{Q}$ ratios) and to a lesser extent alveolar hyperventilation (i.e., low regulated level of arterial CO_2) (10–12). In CTEPH, significant abnormalities in right ventricular function and excessively high pulmonary arterial pressures can impair central hemodynamics (i.e., blunted cardiac output and capillary hypoperfusion) and may contribute to the increased exercise $\dot{V}_E/\dot{V}_{CO_2}$ (9, 13). However, in patients with dyspneic post-PE syndrome with normal right ventricular function, and preserved resting and/or mildly impaired exercise hemodynamics, we postulate that increased physiological dead space and associated compensatory increases in ventilation, may represent the effects of residual regional pulmonary capillary hypoperfusion (9, 11, 14). Thus, the resultant compromised CO_2 elimination and increased chemo-stimulation might contribute to compensatory increases in the inspiratory neural drive to breathe. In turn, the higher ventilatory requirements during exercise while preserving arterial blood gas homeostasis, may come at the cost of increased perceived breathing effort.

Accordingly, the main objective of the current study was to undertake a detailed pathophysiological characterization of the post-PE group (without resting echocardiographic PH) by comparing dyspnea intensity ratings and systematic physiological responses with incremental cycle exercise with those of healthy control participants. Secondary objectives were to explore the inter-relationships between heightened dyspnea and inspiratory neural drive, pulmonary gas-exchange, operating lung volume, and noninvasive cardiovascular responses in post-PE participants during exercise. We tested the hypothesis that greater exertional dyspnea and exercise intolerance in post-PE is consistently associated with elevated inspiratory neural drive arising, in part due to the effects of increased $\dot{V}_E/\dot{V}_{CO_2}$.

METHODS

Study Overview and Participants

The present study was a prospective, case-controlled observational study (ClinicalTrials.gov:NCT03786367) and received approval by the Health Sciences and Affiliated Teaching Hospitals Research Ethics Board at Queen's University (DMED-2208-8). After providing written informed consent, all participants complete two sessions over a 1-wk period. *Visit 1* included medical history screening, detailed pulmonary function testing (PFT), and a familiarization symptom-limited incremental cardiopulmonary exercise test (CPET) on a cycle ergometer. *Visit 2* included a symptom limited CPET with measurements of EMGdi and arterialized blood gases. Participants were asked to avoid caffeine, smoking, vigorous exercise, and alcohol 6 h before testing.

Fourteen consecutive patients referred for clinical evaluation of persistent dyspnea following a remote PE (without evidence of PH) were recruited from Respirology and PH clinics at the Kingston Health Sciences Centre (Kingston, Canada). Fourteen age-, sex-, and body mass index (BMI)-matched controls were included in the analysis. Two controls were prospectively recruited by word-of-mouth and data from 12 controls were extracted from the Respiratory Investigation Unit (Queen's University) database registry.

Diagnosis of post-PE syndrome was confirmed before enrollment by the primary treating Respirologist in accordance with major international guidelines (5, 15). All patients with post-PE syndrome were >20-yr old and clinically stable (no hospital admissions in preceding 6 wk). Patients with post-PE syndrome were included if they reported moderate chronic activity-related dyspnea [Baseline Dyspnea Index focal score (16) <9] without a clearly identified alternate diagnosis, and were able to perform study procedures. Patients were excluded if they had a contraindication to CPET, a

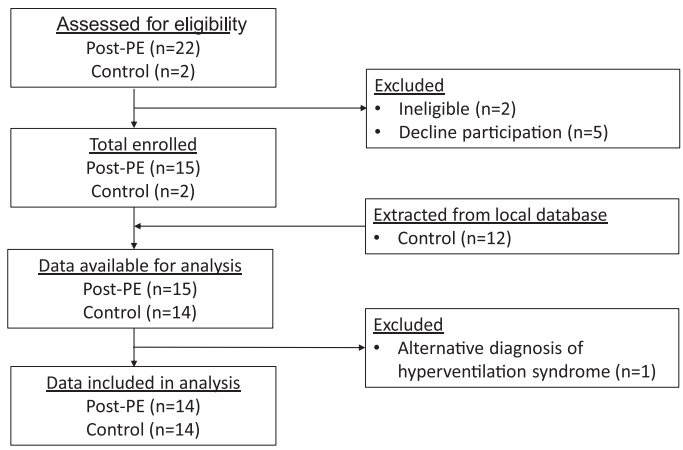

Figure 1. STROBE flow diagram for participant recruitment and study analysis. PE, pulmonary embolism.

clinical diagnosis of CTEPH, and/or a history of obstructive or restrictive lung disease.

Procedures

Spirometry, plethysmography, and diffusing capacity (D_{LCO}) and transfer coefficient (K_{CO}) for carbon monoxide measurements were performed using automated equipment following guidelines (17–19). PFT data were expressed relative to predicted normal values as appropriate (20–22). Chest computed tomography (CT) scans were available in all patients with post-PE syndrome and were qualitatively assessed by two experts (K.M.M. and D.E.O.) to *1*) determine any persistent vascular occlusion and, *2*) rule out the presence of severe emphysema and/or fibrosis. Echocardiogram results performed as a part of standard clinical care were available in all patients.

On both visits, CPET was conducted on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics, Yorba Linda, CA) using a metabolic measurement system (Vmax229d; SensorMedics), as previously described (23). Briefly, tests consisted of 6-min steady-state resting, followed by 20 W/2-min increases in work rate until symptom limitation. Measurements included standard breath-by-breath cardiorespiratory and breathing pattern parameters, pulse oximetry-derived arterial O_2 saturation, and electrocardiogram-derived heart rate. Select parameters were expressed relative to predicted normal values (24). During CPET, participants rated their perceived dyspnea and leg discomfort with the modified Borg 0–10 category-ratio scale at rest, within the last 30 s of every work rate increment and at symptom limitation (25). Inspiratory capacity (IC) maneuvers were performed at the same rest, exercise, and peak exercise intervals. Standard expired gas data were collected over the first 30 s of every second minute during CPET and were linked with the Borg ratings and IC measurements collected in the final 30 s of the respective minute to avoid contamination of the expired gas data from the IC maneuvers. Immediately following CPET, participants verbalized their main reasons for stopping (breathing, legs, combination of both).

Table 1. *Characteristics of patients with post-pulmonary emboli syndrome (n = 14) and healthy controls (n = 14)*

	Control	Post-PE
Participants (*n*)	14	14
Demographic/anthropometric/clinical		
Males/females (*n*)	3/11	3/11
Age, yr	57.4 ± 13.2	59.0 ± 14.7
Body mass index, kg/m^2	30.0 ± 4.9	31.9 ± 4.4
Smoking history, pack-years	0.1 ± 0.4	9.6 ± 15.4
Current smokers (*n*)	0	2
BDI 0–12	11.0 ± 1.3	6.4 ± 1.7*
OCD 0–100, mm	89.1 ± 14.4	53.0 ± 14.*
mMRC dyspnea scale 0–4	0.3 ± 0.4	1.7 ± 0.9*
Exercise capacity		
WR_{peak}, %pred	120 ± 26	78 ± 15*
$\dot{V}O_{2peak}$, %pred	124 ± 28	76 ± 14*
PE severity/Timing		
Massive/High risk		2
Sub-massive/Intermediate		4
Low risk		8
Time from PE to CPET months median (interquartile range)		16.7 (6.0–37.2)
Imaging		
CT-derived vascular obstruction (*n*)		9
Echocardiogram		
LV ejection fraction, %		68 ± 8
RVSP, mmHg		32 ± 11
TRV, cm/s		266 ± 52
Pulmonary function		
FVC, L	3.6 ± 0.9 (104 ± 13)	3.5 ± 0.9 (96 ± 13)
FEV_1, L	2.7 ± 0.6 (98 ± 13)	2.6 ± 0.7 (90 ± 13)
FEV_1/FVC, %	74 ± 5 (94 ± 6)	74 ± 4 (93 ± 4)
$FEF_{25–75\%}$, L/s	2.1 ± 0.8 (78 ± 32)	2.0 ± 0.9 (73 ± 21)
SVC, L	3.7 ± 0.8 (100 ± 12)	3.6 ± 0.9 (93 ± 13)
IC, L	2.8 ± 0.6 (107 ± 15)	2.8 ± 0.6 (104 ± 15)
FRC, L	2.4 ± 0.6 (86 ± 19)	2.5 ± 0.7 (81 ± 21)
RV, L	1.5 ± 0.3 (87 ± 20)	1.7 ± 0.5 (89 ± 24)
TLC, L	5.2 ± 0.9 (96 ± 11)	5.3 ± 1.1 (91 ± 14)
D_{LCO}, mL/min/mmHg	20.9 ± 5.7 (96 ± 3)	15.9 ± 3.71* (71 ± 14)*
V_A, L	4.7 ± 0.9 (93 ± 9)	4.6 ± 0.9 (85 ± 9)
K_{CO}, mL/min/mmHg/L	4.5 ± 0.7 (104 ± 14)	3.5 ± 0.6* (84 ± 15)*
V_A/TLC, %	89.6 ± 6.9	87.2 ± 8.0

Values are represented as means ± SD, absolute (% predicted) or frequency, unless otherwise stated. BDI, baseline dyspnea index; CT, computed tomography scan; D_{LCO}, diffusing capacity of the lung for carbon monoxide; $FEF_{25–75\%}$, forced expiratory flow between 25 and 75% of FVC; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; LV, left ventricle; K_{CO}, transfer coefficient for carbon monoxide; mMRC, modified medical research council; OCD, oxygen cost diagram; PE, pulmonary embolism; RV, residual volume; RVSP, right ventricular systolic pressure; SVC, slow vital capacity; TLC, total lung capacity; TRV, tricuspid regurgitant velocity; V_A, alveolar volume; $\dot{V}O_2$, oxygen uptake; WR, work rate. Data were analyzed using unpaired *t* tests. *$P < 0.05$ Control vs. Post-PE.

Diaphragm electromyography.

EMGdi data were recorded continuously at rest and during exercise. Briefly, an esophageal catheter with five multipaired electrodes (Eso101, Top Pine Technology Development Limited, Hong Kong, China) was inserted nasally and optimally positioned according to the strength of the inspiratory EMGdi signal (26, 27). EMGdi data were sampled continuously using a data acquisition system (LabChart, v8.1.2.1 and PowerLab, model ML880; ADInstruments, Castle Hill, Australia) and stored for offline analysis, as described in past publications by our group (6, 28, 29). Briefly, maximal EMGdi ($EMGdi_{max}$) was selected from the largest value measured during serial IC maneuvres (baseline, submaximal exercise, and peak exercise). EMGdi as a percentage of $EMGdi_{max}$ [EMGdi (%max)] was used as an index of the inspiratory neural drive to the crural diaphragm based on several assumptions previously described (6, 7).

Capillary blood gas.

To estimate arterial CO_2 blood gas tension, arterialized capillary blood samples were drawn in duplicate from the earlobes at rest and peak exercise (30, 31). Using a warm cloth, the earlobe was warmed for 5 min followed by a deep puncture with a lancet. Subsequently, duplicate blood samples were drawn into heparinized capillary tubes, placed on ice, and analyzed immediately (ABL, Radiometer, Copenhagen, Denmark). Total physiological dead space (V_D/V_T) was then estimated using the modified Bohr/Enghoff equation (32):

$$V_D/V_T = \left[(Pa_{CO_2} - PE_{CO_2})/Pa_{CO_2}\right] - (V_{DM}/V_T)$$

where PE_{CO_2} is the partial pressure of mixed expired CO_2, Pa_{CO_2} is the partial pressure of arterialized (capillary) CO_2, V_{DM} is the volume of the breathing valve and mouthpiece, and V_T is the tidal volume (30). Capillary blood gas data were only available in the post-PE group and were compared with previously published reference normative values (33).

Statistical Analysis

In the current study, 14 patients with post-PE syndrome and 14 controls were required to detect the minimal clinically important difference of 1.0 Borg unit (34) between groups in dyspnea intensity at the highest equivalent cycle work rate achieved by all participants (80 W), based on the assumptions of a standard deviation of 1.0 Borg units, α = 0.05, power = 0.8, and two-tailed test of significance.

Data are presented as the means ± SD unless otherwise stated. Statistical significance was set a priori at $P < 0.05$ for all analysis. Unpaired *t* tests were used to evaluate participant demographics, PFT, and selected CPET variables. Two-way repeated-measure analysis of variance, with Bonferroni corrected *t* tests, was used to evaluate the effect of group (fixed factor) on key dependent variables during incremental exercise (repeated factor). Pearson correlations were used to determine associations between continuous variables of interest. Linear regression was used to determine exertional dyspnea-to-$\dot{V}O_2$ and dyspnea-to-$\dot{V}E$ slopes. The anaerobic threshold (AT) was determined using the v-slope method, as previously described (35–38). Fisher's exact was used to compare between-group differences in the frequency of selecting breathing discomfort, alone or in combination with leg discomfort as the primary reason for stopping exercise. All data were analyzed using Statistical Package for Social Sciences (SPSS v.27, IBM).

RESULTS

Patient Characterization

Of the 22 patients identified with post-PE syndrome, 14 completed the study and were included in the final analysis with 14 age-, sex-, and BMI-matched controls (Fig. 1).

Detailed participants characteristics are provided in Table 1. Both groups were predominantly female. On average, the BMI in both groups was consistent with class I/mild obesity (i.e., BMI 30–35 kg/m^2). Seven of fourteen patients with post-PE syndrome had a smoking history (2 current smokers). One control participant had a 1.5 pack year smoking history. Most patients had an initial presentation of acute (13/14) and unprovoked (12/14) PE. All patients with post-PE syndrome were treated with long-term anticoagulation at the time of study

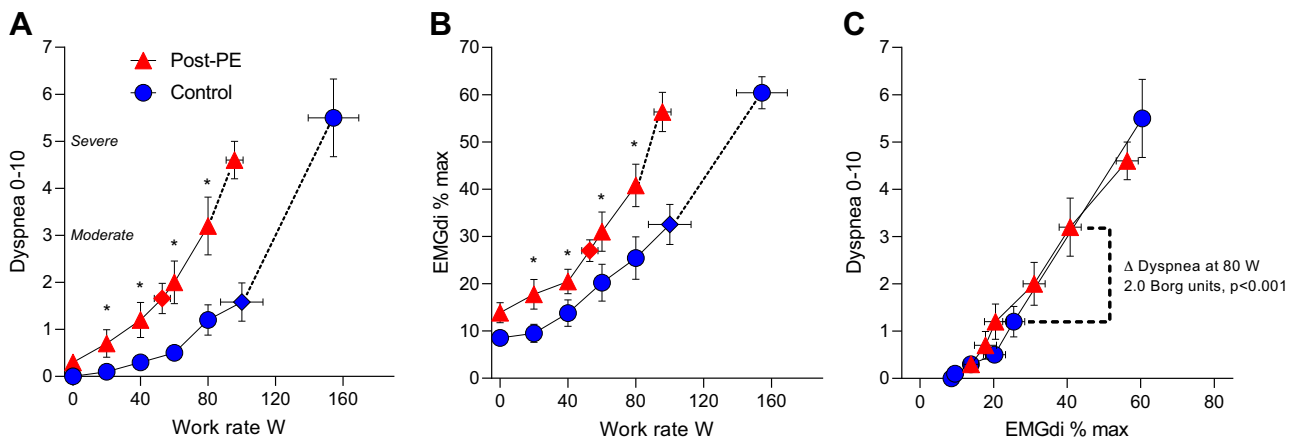

Figure 2. Perceived dyspnea and inspiratory neural drive responses to incremental cycle ergometry exercise as a function of increasing work rate (*A* and *B*), and perceived dyspnea as a function of increasing inspiratory neural drive (*C*) in patients with post-pulmonary embolism (PE) (red triangles, *n* = 14) and healthy controls (blue circles, *n* = 14). EMGdi % max, diaphragm electromyography as a percentage of maximum EMGdi (index of inspiratory neural drive). Diamond symbols within each group represent the anaerobic threshold. Data were analyzed using two-way repeated-measures analysis of variance, with Bonferroni corrected *t* tests. *$P < 0.05$ between groups at standardized submaximal work rates.

participation. Nine of fourteen patients had evidence of persistent vascular occlusive changes on serial CT scans. Moreover, echocardiograms were completed within median: 8, range: 1–44 months of study enrollment. Echocardiographic-derived resting tricuspid regurgitant velocity and right-ventricular systolic pressure values were in normal ranges for all patients with post-PE syndrome (Table 1). Resting lung function was similar between groups, however, D_{LCO} and K_{CO} were lower in post-PE compared with controls (both $P < 0.001$).

Neurosensory Responses to Exercise

Dyspnea intensity was higher at all submaximal exercise work rates in post-PE, compared with controls (all $P < 0.05$) (Fig. 2*A*). Inspiratory neural drive (EMGdi%max) was greater in post-PE than controls throughout exercise (all $P < 0.05$, Fig. 2*B*). Dyspnea increased similarly in both groups as a function of increasing EMGdi%max throughout exercise (Fig. 2*C*). Dyspnea- $\dot{V}O_2$ slopes were significantly higher in post-PE, compared with controls (4.0 ± 1.8 vs. 3.0 ± 1.8 Borg units/L/min, respectively, $P < 0.001$). There were no between-group differences in the dyspnea- $\dot{V}E$ exercise slope (Post-PE: 0.10 ± 0.05 vs. Control: 0.08 ± 0.04 Borg units/L/min, $P = 0.184$). Breathing discomfort, alone or in combination with leg discomfort was selected as the primary reason for stopping exercise in 71% post-PE versus 43% of healthy controls ($P < 0.01$).

Physiological Responses to Exercise

There were no between-group differences in $\dot{V}O_2$, $\dot{V}CO_2$, heart rate (HR), and O_2 pulse at submaximal exercise work rates (all $P > 0.05$) (Table 2). The anaerobic threshold occurred at a lower work rate and $\dot{V}CO_2$ in post-PE, compared with controls ($P < 0.001$) (Table 3). $\dot{V}E$ and $\dot{V}E/\dot{V}CO_2$ were greater and P_{ETCO_2} was lower throughout submaximal exercise in post-PE, compared with controls (all $P < 0.05$) (Fig. 3). During exercise, the nadir (lowest 30 s average) $\dot{V}E/\dot{V}CO_2$ was greater in post-PE, compared with controls (33 ± 4 vs. 27 ± 2, respectively, $P < 0.001$). At peak exercise, partial pressure of capillary CO_2 (Pc_{CO_2}) was within the normal range, whereas estimated V_D/V_T and the capillary to end-tidal CO_2 difference were abnormally high in all patients with post-PE syndrome (Table 2). The greater exercise ventilation was achieved by a compensatory increase in breathing frequency ($P < 0.05$),

Table 2. *Cardiometabolic, gas exchange, respiratory neuromechanical parameters at rest, highest equivalent work rate, and peak exercise in patients with post-pulmonary emboli syndrome (n = 14) and healthy controls (n = 14)*

Variable	Rest		HEWR (80 W)		Peak	
	Control	Post-PE	Control	Post-PE	Control	Post-PE
Work rate, W	0	0	80	80	154 ± 57	96 ± 20*
Cardiometabolic and gas exchange						
$\dot{V}O_2$, L/min	0.33 ± 0.12	0.33 ± 0.06	1.34 ± 0.12	1.26 ± 0.15	2.31 ± 0.91	1.43 ± 0.33*
$\dot{V}CO_2$, L/min	0.24 ± 0.07	0.27 ± 0.06	1.28 ± 0.15	1.31 ± 0.16	2.56 ± 0.92	1.57 ± 0.39*
RER	0.77 ± 0.09	0.81 ± 0.10	0.96 ± 0.14	1.04 ± 0.08	1.12 ± 0.11	1.09 ± 0.08
Sp_{O_2}, %	96.4 ± 1.6	96.1 ± 1.8	95.8 ± 1.6	95.5 ± 2.0	95.5 ± 1.9	95.3 ± 2.1
Heart rate, beats/min	77 ± 13	80 ± 8	123 ± 33	121 ± 10	154 ± 22	128 ± 19*
O_2 pulse, mL/beat	4.2 ± 0.8	4.4 ± 2.0	10.5 ± 1.9	11.5 ± 3.0	15.1 ± 5.5	11.4 ± 2.4*
$\dot{V}E$, L/min	9.9 ± 2.5	12.2 ± 2.7*	36.6 ± 6.1	44.7 ± 6.6*	80.4 ± 28.4	54.4 ± 11.8*
$\dot{V}E/\dot{V}CO_2$	42.5 ± 6.6	46.6 ± 7.1	28.4 ± 2.2	34.2 ± 4.5*	31.7 ± 3.7	35.1 ± 4.5*
P_{ETCO_2}, mmHg	36.6 ± 4.5	31.7 ± 4.1*	40.9 ± 4.4	33.4 ± 3.7*	35.9 ± 4.9	32.1 ± 3.3
Pc_{CO_2}, mmHg		35.1 ± 4.1				35.3 ± 3.3
Pc-ET_{CO_2}, mmHg		3.6 ± 4.6				3.5 ± 3.3
V_D/V_T		0.36 ± 0.04				0.30 ± 0.07
V_D/V_T, % predicted		118 ± 48				167 ± 49
Respiratory neuromechanics						
V_T, L	0.67 ± 0.19	0.63 ± 0.15	1.36 ± 0.14	1.48 ± 0.34	2.01 ± 0.71	1.65 ± 0.49
f_B, breaths/min	15.7 ± 4.9	20.6 ± 4.8	27.5 ± 5.7	31.6 ± 6.8	40.5 ± 7.4	34.1 ± 4.4
IC, L	2.84 ± 0.67	2.92 ± 0.72	2.99 ± 0.73	2.79 ± 0.73	2.81 ± 0.74	2.73 ± 0.74
IRV, L	2.17 ± 0.71	2.29 ± 0.66	2.25 ± 0.64	1.95 ± 0.61	0.80 ± 0.35	1.09 ± 0.50
$\dot{V}E$/MVV, %	11 ± 2	15 ± 5*	43 ± 14	55 ± 19*	63 ± 18	80 ± 14*
V_T/IC, %	23 ± 7	22 ± 5	50 ± 12	56 ± 15	71 ± 12	61 ± 12
EELV, % TLC	46 ± 7	44 ± 8	43 ± 7	46 ± 8	47 ± 9	49 ± 6
EILV, % TLC	58 ± 8	56 ± 7	70 ± 9	74 ± 10	84 ± 6	80 ± 7
V_T/T_I, L/s	0.36 ± 0.09	0.48 ± 0.15	1.32 ± 0.20	1.70 ± 0.27*	2.81 ± 0.95	2.20 ± 0.42*
V_T/T_E, L/s	0.30 ± 0.09	0.36 ± 0.07	1.09 ± 0.17	1.42 ± 0.23*	2.66 ± 0.90	1.67 ± 0.39*
EMGdi%max	8.6 ± 5.3	13.9 ± 7.9	25.5 ± 14.3	40.8 ± 14.2*	60.4 ± 10.7	56.3 ± 13.2
EMGdi%max:V_T, %IC	0.4 ± 0.2	0.5 ± 0.3	0.5 ± 0.2	0.7 ± 0.2	0.9 ± 0.3	0.9 ± 0.2
EMGdi%max:$\dot{V}E$, L/min	1.0 ± 0.7	1.1 ± 0.6	0.7 ± 0.4	0.8 ± 0.5	0.8 ± 0.3	1.0 ± 0.3
Sensory						
Dyspnea 0–10 Borg units	0.0 ± 0.1	0.3 ± 0.5	1.2 ± 1.2	3.2 ± 2.3*	5.5 ± 3.1	4.6 ± 1.5
Leg discomfort 0–10 Borg units	0.0 ± 0.0	0.4 ± 1.0	1.8 ± 1.3	3.2 ± 2.6*	5.7 ± 3.4	5.2 ± 2.1

Values are represented as means ± SD. EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; f_B, breathing frequency; EMGdi % max: diaphragm electromyography as a percentage of maximum EMGdi (index of inspiratory neural drive); HEWR, highest equivalent work rate; IC, inspiratory capacity; IRV, inspiratory reserve volume; MVV, maximal voluntary ventilation; Pc_{CO_2}, partial pressure of capillary CO_2; Pc-ET_{CO_2}, capillary to end-tidal CO_2 difference; P_{ETCO_2}, partial pressure of end-tidal CO_2; RER, respiratory exchange ratio; Sp_{O_2}, pulse oximetry derived O_2 saturation; T_E, time of expiration; T_I, time of inspiration; $\dot{V}CO_2$, carbon dioxide output; V_D/V_T, dead space to tidal volume ratio (total physiological dead space); $\dot{V}E$, minute ventilation; $\dot{V}E/\dot{V}CO_2$: ventilatory equivalent for CO_2; $\dot{V}O_2$, oxygen uptake; V_T, tidal volume. Data were analyzed using two-way repeated-measures analysis of variance, with Bonferroni corrected *t* tests. *$P < 0.05$ Control vs. Post-pulmonary embolism (PE).

Table 3. *Selected physiological and sensory parameters at the anaerobic threshold in patients with post-pulmonary emboli syndrome (n = 14) and healthy controls (n = 14)*

	Control	Post-PE
Work rate, W	100 ± 47	53 ± 18*
$\dot{V}O_2$ % peak	69 ± 11	72 ± 12
$\dot{V}O_2$ % predicted peak	84 ± 22	55 ± 13*
$\dot{V}O_2$, L/min	1.6 ± 0.6	1.0 ± 0.2
$\dot{V}CO_2$, L/min	1.5 ± 0.6	1.0 ± 0.1
$\dot{V}E$, L/min	42 ± 13	33 ± 9
RER	0.96 ± 0.04	0.95 ± 0.12
$\dot{V}E/\dot{V}CO_2$	28 ± 3	34 ± 4*
PET_{CO_2}, mmHg	41.2 ± 3.7	34.0 ± 3.8*
Sp_{O_2}, %	96 ± 2	95 ± 2
V_T, L	1.6 ± 0.6	1.3 ± 0.4
f_B, breaths/min	27 ± 6	27 ± 7
V_T/IC, %	55 ± 12	45 ± 12
IC %TLC	57 ± 7	55 ± 7
EMGdi %max	32 ± 13	28 ± 7
Dyspnea Borg 0–10	1.6 ± 1.5	1.7 ± 1.2
Leg discomfort Borg 0–10	2.0 ± 1.6	1.8 ± 1.6

Values are represented as absolute means ± SD. EMGdi: diaphragm electromyography as a percentage of maximum EMGdi (index of inspiratory neural drive); f_B, breathing frequency; IC, inspiratory capacity; PET_{CO_2}, partial pressure of end-tidal CO_2; Sp_{O_2}, pulse oximetry derived O_2 saturation; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E$, minute ventilation; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for CO_2; $\dot{V}O_2$, oxygen uptake; RER, respiratory exchange ratio; V_T, tidal volume. Data were analyzed using unpaired *t* tests. *$P < 0.05$ Control vs. Post-pulmonary embolism (PE).

while tidal volume was not different between groups ($P > 0.05$, Fig. 4, *A* and *B*). The duty cycle (% of time spent on inspiration) was similar between groups ($P > 0.05$, Fig. 4*E*), whereas the inspiratory (V_T/T_I) and expiratory (V_T/T_E) flow rates were consistently higher throughout exercise in post-PE than controls (all $P < 0.05$, Fig. 4, *C* and *D*, Table 2). There were minimal between-group differences in IC and V_T/IC throughout exercise (Fig. 4, *E* and *F*). Moreover, end-expiratory, and end-inspiratory lung volumes were not different throughout exercise (both $P > 0.05$, Table 2). EMGdi%max was similar between groups at submaximal work rates, when plotted as a function of increasing ventilation and V_T/T_I (Fig. 5, *A* and *B*).

Detailed demographic and physiological data in patients with post-PE syndrome with ($n = 9$) versus without ($n = 5$) CT-derived vascular obstruction are presented in Table 4. There were no between-group differences (with vs. without vascular obstruction) in resting forced expiratory volume in 1 s (FEV_1) and K_{CO}, peak work rate (WR), and $\dot{V}O_2$, nadir $\dot{V}E/\dot{V}CO_2$, EMGdi at 80 W, and the dyspnea-$\dot{V}O_2$ slopes (all $P > 0.05$) (Table 4).

Correlates of Increased Exertional Dyspnea

The dyspnea-$\dot{V}O_2$ slope showed significant correlations (all $P < 0.001$) with $\dot{V}O_{2peak}$ % predicted ($r = -0.523$), nadir $\dot{V}E/\dot{V}CO_2$ ($r = 0.453$), EMGdi%max-$\dot{V}O_2$ slope ($r = 0.367$), and resting K_{CO} ($r = -0.484$).

DISCUSSION

Main Findings

The current study supported our hypothesis that increased exertional dyspnea in patients with post-PE syndrome was strongly associated with elevated inspiratory neural drive (i.e., EMGdi%max) during exercise, compared with age-, sex-, and BMI-matched controls with similar resting and exercise operating lung volumes. The greater EMGdi%max, in turn, was associated with low resting K_{CO}, and abnormally high $\dot{V}E/\dot{V}CO_2$ during exercise in post-PE. Our results help to explain why many patients with a post-PE syndrome, without clinical evidence of CTEPH, continue to report abnormally high dyspnea ratings at relatively low levels of physical activity.

$\dot{V}E/\dot{V}CO_2$ was consistently elevated throughout exercise in post-PE, compared with controls, and confirms previous findings (10, 11). Remarkably, 57% of post-PE in the current sample had a $\dot{V}E/\dot{V}CO_2$ nadir (lowest 30 s measurement on CPET) that exceeded clinically relevant cut-offs (i.e., >34 and/or upper limit of normal), indicating increased risk of poor outcomes (i.e., morbidity and mortality) (39–41). Moreover, a high $\dot{V}E/\dot{V}CO_2$ nadir was associated with a low resting K_{CO} ($r = -0.55$) in post-PE. Throughout exercise, PET_{CO_2} was consistently lower in post-PE than controls, which is generally assumed to reflect alveolar hyperventilation (12). However, the capillary to end-tidal CO_2 difference at rest was positive (~3.6 mmHg) and remained positive at peak exercise (~3.5 mmHg), which suggest that areas of wasted ventilation (i.e., alveolar dead space) resulted in dilution of atmospheric CO_2 from poorly perfused alveoli (13). When combined with high estimated V_D/V_T (~167% predicted at peak), we speculate that these abnormalities point to pulmonary capillary hypoperfusion in the setting of relatively preserved alveolar ventilation (i.e., high $\dot{V}A/\dot{Q}$ ratios) and O_2 saturation, which is consistent with previous work in patients with thromboembolic obstruction (10, 11). The increased overall $\dot{V}A/\dot{Q}$ relationships may result from regional capillary hypoperfusion and/or reduced RV output to the lungs. Future studies should include invasive measurement of central hemodynamics (i.e., right heart catheterization) and regional capillary blood flow distribution (i.e., inert gas elimination or contrast-enhanced magnetic resonance imaging) to determine the mechanism of capillary hypoperfusion during exercise in post-PE syndrome. Nevertheless, we observed a consistent link between low resting K_{CO} and high exercise $\dot{V}E/\dot{V}CO_2$, which provides some indirect evidence of a pulmonary vasculopathy in this population (4, 14).

Of note, 9 of 14 patients with post-PE syndrome showed evidence of vascular obstruction on CT. It is entirely plausible that those with vascular obstruction may have more severe impairments in ventilatory efficiency (i.e., higher $\dot{V}E/\dot{V}CO_2$), and heightened inspiratory neural drive and dyspnea during exercise, compared with patients without vascular obstruction (9). Our sample of patients with post-PE syndrome was likely underpowered, but there were no differences in key variables of interest (resting K_{CO}, nadir $\dot{V}E/\dot{V}CO_2$, exertional EMGdi, and dyspnea) in patients with versus without CT-derived vascular obstruction (Table 4). Additional research in larger samples is needed to determine the pulmonary gas-exchange and neurophysiological effects of vascular obstruction in patients with post-PE syndrome.

The anaerobic threshold was significantly lower in post-PE (Table 3), suggesting that deconditioning (with earlier metabolic acidosis) contributes to exercise limitation in these patients and is consistent with previous work (2, 3).

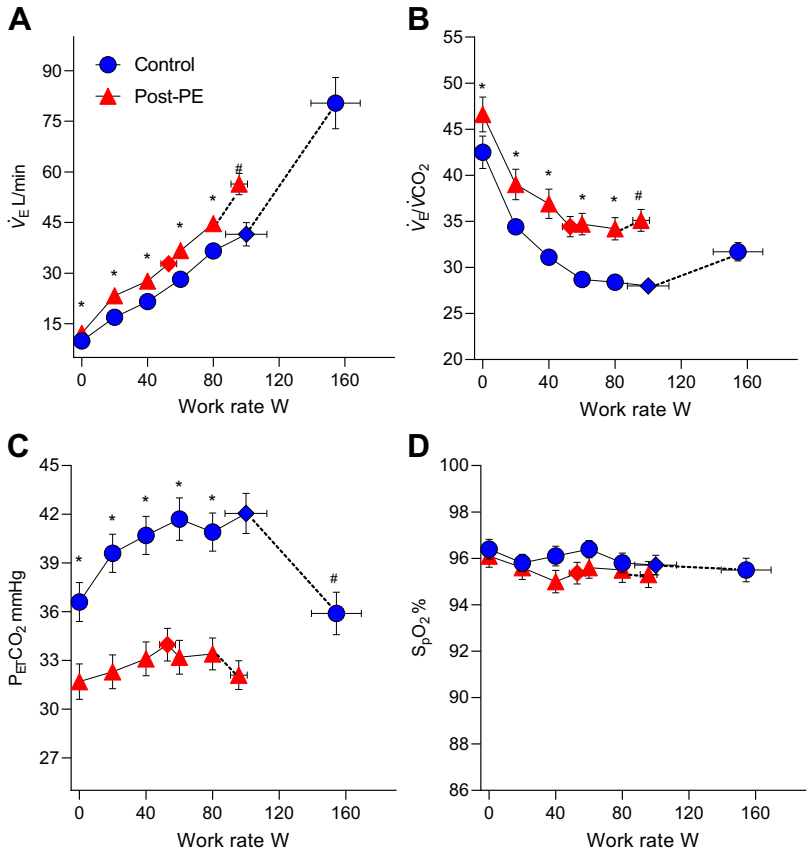

Figure 3. Ventilatory (*A* and *B*) and gas-exchange (*C* and *D*) responses to incremental cycle ergometry exercise in patients with post-pulmonary embolism (PE) (red triangles, $n = 14$) and healthy controls (blue circles, $n = 14$). $\dot{V}E$, minute ventilation; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide production; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; Sp_{O_2}, pulse oximetry-derived oxygen saturation. Data were analyzed using two-way repeated-measures analysis of variance, with Bonferroni corrected *t* tests. Diamond symbols within each group represent the anaerobic threshold. $*P < 0.05$ between groups at standardized submaximal work rates. $\#P < 0.05$ between groups at peak exercise.

However, the $\dot{V}E/\dot{V}CO_2$ at anaerobic threshold and the nadir $\dot{V}E/\dot{V}CO_2$ were significantly greater in post-PE compared with controls. Moreover, $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E$ were greater in post-PE at rest and at low standardized work rates (i.e., 20 and 40 W), before the anaerobic threshold. Taken together, these data suggest that the higher ventilatory requirements occurred independent of the level of deconditioning and are at least partially related to pulmonary gas-exchange abnormalities in this population. However, at higher work rates, the higher EMGdi and $\dot{V}E/\dot{V}CO_2$ also very likely reflects the added effect of earlier metabolic acidosis in part due to deconditioning. Importantly, the current study did not allow us to partition the relative contributions of deconditioning (i.e., early anerobic threshold) and pulmonary gas-exchange abnormalities (i.e., $\dot{V}A/\dot{Q}$ maldistribution and increased dead space) on ventilatory control during exercise in this population.

The inspiratory neural drive to breathe (estimated by EMGdi%max) during exercise was greater in post-PE, compared with controls. Interestingly, the higher EMGdi%max occurred in the absence of any between-group differences in operating lung volumes throughout exercise. Moreover, the EMGdi%max/ $\dot{V}E$ ratio was similar between groups at submaximal exercise work rates, reflecting preserved neuroventilatory coupling of the respiratory system during exercise in both groups. This, in turn, would suggest that high inspiratory neural drive in post-PE (nearly twofold greater than controls at 80 W) occurred as a compensatory adaptation needed to support the increased ventilatory requirements and maintain arterial blood gas homeostasis during exercise. These compensatory increases in EMGdi (%max) occurred even though patients had normal operating lung volume responses and maintained breathing reserve (i.e., $\dot{V}E$/maximal voluntary ventilation (MVV) at peak < 85% in 13/14 patients), highlighting the importance of increased chemical loading (i.e., pulmonary gas-exchange and CO_2 clearance abnormalities, and early anaerobic threshold) on inspiratory neural drive. The increased $\dot{V}E$ during exercise (~22% higher at 80 W) in post-PE was achieved largely by compensatory increases in breathing frequency, with significantly shorter inspiratory and expiratory time and correspondingly ~30% higher mean inspiratory and expiratory flow rates (Fig. 4*D*, Table 2). The greater reliance on breathing frequency (rather than VT) to increase $\dot{V}E$, in the setting of increased dead space in post-PE, may represent an integrative response of the central respiratory controller to minimize elastic loading, which may explain the lack of consistent between-group differences in operating lung volume (42). In both groups, EMGdi%max increased similarly as a function of increasing VT/TI. Therefore, we speculate that greater frequency and mean inspiratory flow rates increase the velocity of muscle shortening, which functionally weakens the diaphragm and requires greater electrical activation (i.e., higher neural drive) for a given tidal volume excursion during exercise (7, 43–45). Despite no between-group differences in resting spirometry, static, and operating lung volumes, we did not investigate airway dysfunction in detail (i.e., quantifying expiratory flow limitation and esophageal/transdiaphragmatic pressure swings), and

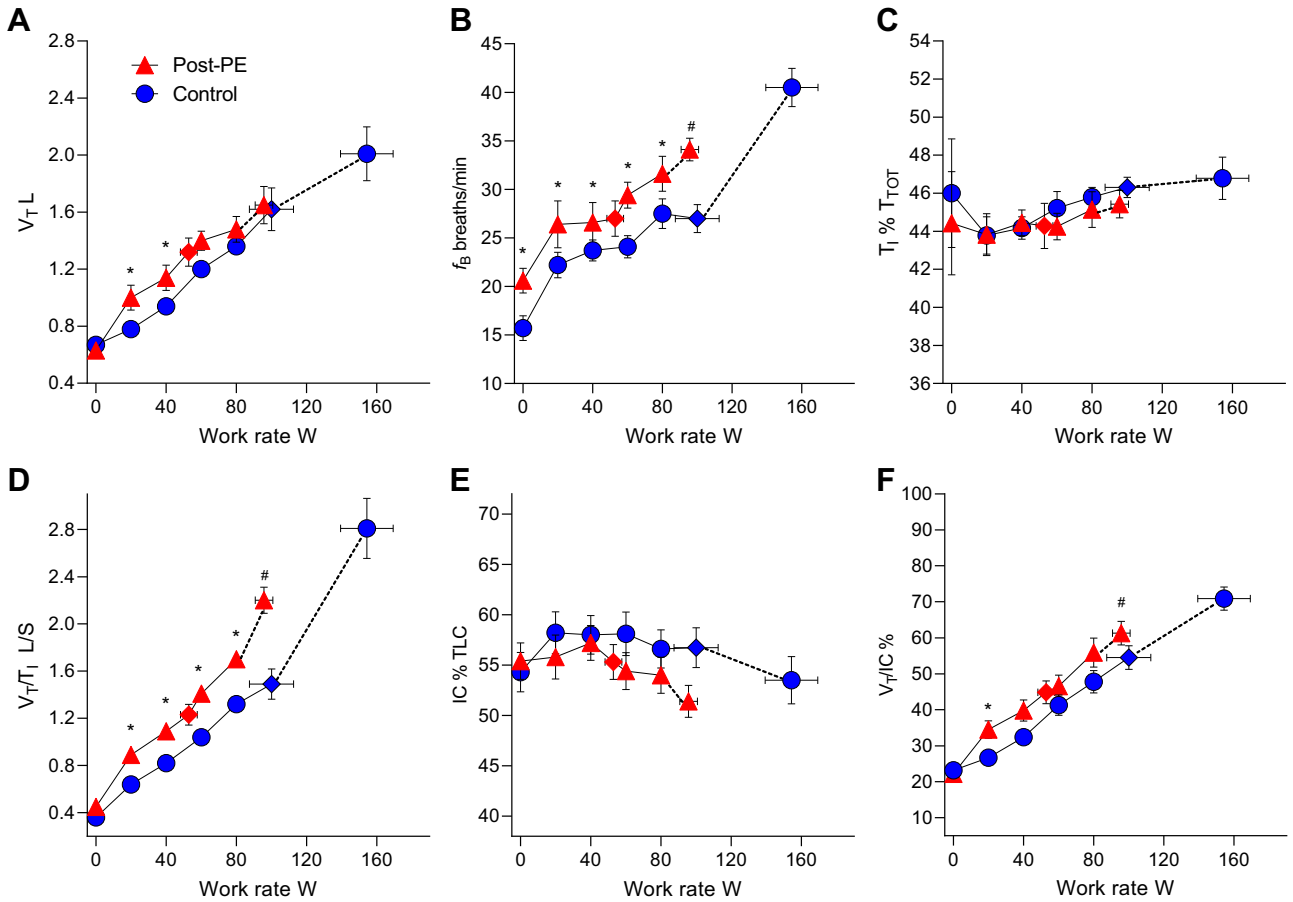

Figure 4. Breathing pattern (*A*–*D*) and dynamic lung volume (*E* and *F*) responses to incremental cycle ergometry exercise in patients with post-pulmonary embolism (PE) (red triangles, $n = 14$) and healthy controls (blue circles, $n = 14$). f_B, breathing frequency; IC, inspiratory capacity; T_I % T_{TOT}, percent of time of total breath spent on inspiration (duty cycle); T_I, time of inspiration; TLC, total lung capacity; V_T, tidal volume; V_T/T_I, mean inspiratory flow. Data were analyzed using two-way repeated-measures analysis of variance, with Bonferroni corrected *t* tests. Diamond symbols within each group represent the anaerobic threshold. *$P < 0.05$ between groups at standardized submaximal work rates. #$P < 0.05$ between groups at peak exercise.

our relatively small sample size precludes definitive conclusions.

The current study provided new insights into the neurophysiological mechanisms of exertional dyspnea in symptomatic patients following remote PE. Severe dyspnea ratings (~5 Borg units) occurred at a much lower peak work rate in post-PE than controls (96 vs. 154 W, respectively), and indicated that dyspnea was an important exercise-limiting symptom in most patients (10/14 patient stopped due to breathing discomfort). Moreover, greater exertional dyspnea (i.e., dyspnea-$\dot{V}O_2$ slope) negatively correlated with low $\dot{V}O_{2peak}$ % predicted ($r = -0.523$). In both groups, dyspnea intensity increased as a function of increasing EMGdi%max (Fig. 1*C*) during CPET, which is consistent with previous work in lung disease and in health (6, 7). The higher dyspnea ratings at standardized work rates (~2 Borg units higher at 80 W) in patients with post-PE syndrome compared with controls reflect the greater neural drive to breathe as a result

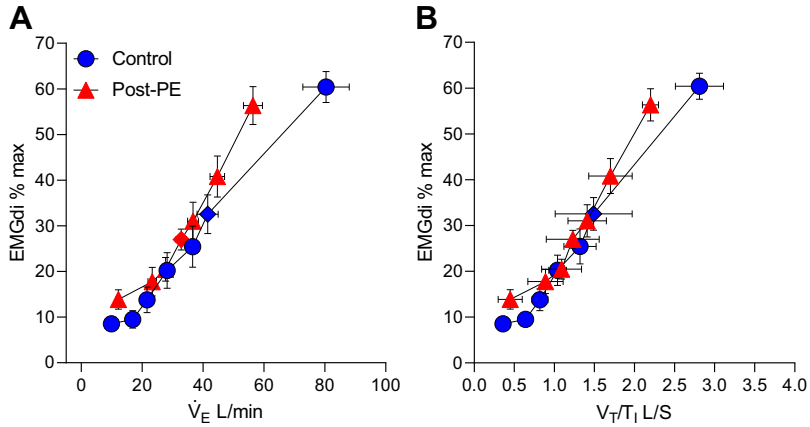

Figure 5. Inspiratory neural drive responses to incremental cycle ergometry exercise as a function of increasing ventilation (*A*) and mean inspiratory flow (*B*) in patients with post-PE (red triangles, $n = 14$) and healthy controls (blue circles, $n = 14$). EMGdi % max, diaphragm electromyography as a percentage of maximum EMGdi (index of inspiratory neural drive); $\dot{V}_E$, minute ventilation; V_T, tidal volume; T_I, time of inspiration; V_T/T_I, mean inspiratory flow. Diamond symbols within each group represent the anaerobic threshold.

Table 4. *Selected demographic and physiological parameters in patients with post-PE with or without vascular obstruction on chest computed tomography scans*

	With Vascular Obstruction	Without Vascular Obstruction
Participants (*n*)	9	5
Demographics		
Age, yr	62 ± 12	55 ± 20
Sex (Male:Female)	2:7	0:5
BMI, kg/m^2	32 ± 4	30 ± 4
Smoking history, pack years	8 ± 16	13 ± 16
Resting lung function		
FEV_1 % predicted	88 ± 16	91 ± 11
K_{CO} % predicted	82 ± 18	86 ± 11
Cardiopulmonary exercise test		
WR_{peak} % predicted	80 ± 11	75 ± 22
$\dot{V}O_{2peak}$ % predicted	73 ± 8	79 ± 23
Nadir $\dot{V}E/\dot{V}CO_2$	34 ± 3	32 ± 6
EMGdi % max at 80 W	40 ± 13	42 ± 19
Dyspnea-$\dot{V}O_2$ slope	3.9 ± 2.2	3.5 ± 1.1

Values are represented as absolute means ± SD unless otherwise stated. BMI, body mass index; EMGdi % max, diaphragm electromyography as a percentage of maximum EMGdi (index of inspiratory neural drive); FEV_1, forced expiratory volume in 1 s; K_{CO}, transfer coefficient for carbon monoxide; $\dot{V}O_{2peak}$, peak oxygen uptake; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for CO_2; WR, work rate. Between group differences assessed using unpaired *t* test.

of greater ventilatory requirements, secondary to a variable combination of pulmonary gas-exchange abnormalities and early anaerobic threshold, as previously discussed. In the context of current neurophysiological constructs of the origins of dyspnea (46–49), we posit that increased efferent electrical activation from medullary and cortical centers in the brain, descending to the diaphragm, is relayed (central corollary discharge) to the somatosensory cortex and perceived as greater breathing effort or discomfort. However, the potential modulating influences on respiratory sensation of ascending afferent inputs from the respiratory, cardiocirculatory, and peripheral locomotor muscles during exercise could not be quantified in the current study and may be important.

Limitations

The current study had a small heterogeneous sample size, recruited from specialized Respirology and PH clinics. Therefore, the results may not be applicable to all patients with post-PE syndrome.

Our groups were not matched for habitual physical activity level and the control group was relatively fit ($\dot{V}O_{2peak}$ = 124% predicted), which limits between-group comparisons at peak exercise. For this reason, we were careful to undertake all neurophysiological and sensory comparisons at standardized submaximal work rates using the same exercise protocol.

Seven post-PE participants had previous smoking history, which may confound results of the study. However, there were no observed differences in key parameters (i.e., resting K_{CO}, nadir $\dot{V}E/\dot{V}CO_2$, exercise EMGdi, or $\dot{V}O_{2peak}$) between ever- and never-smokers within the sample.

Capillary P_{CO_2} was used as an estimate of arterial P_{CO_2} on the basis that previous studies have shown that arterialized capillary blood gas samples from the earlobe provide an accurate assessment of arterial CO_2 and can be reliably used in healthy individuals and patients with cardiorespiratory disease (50, 51). Arterialized blood gas data were unavailable in the control group, therefore, limiting our interpretation of the Pc_{CO_2} and V_D/V_T data in the post-PE group. We obtained EMG measurements of the crural diaphragm and cannot comment on concomitant electrical activation of the costal diaphragm and/or accessory muscles to support ventilation during exercise. The strengths and limitations of the EMGdi technique have been comprehensively reviewed in recent publications by our group (6, 52).

Conclusions

This study is the first to show a consistent and direct association between increased inspiratory neural drive and increased exertional dyspnea intensity in patients with post-PE syndrome without PH, when compared with age-, sex-, and BMI-matched controls. Moreover, compensatory increases in inspiratory neural drive to maintain arterial blood gas homeostasis in the setting of worse ventilatory efficiency came at the expense of greater breathing discomfort and exercise intolerance.

This study provides a sound physiological rationale for measurements of resting K_{CO}, and $\dot{V}E/\dot{V}CO_2$ nadir and mean inspiratory flow rates (V_T/T_I) during exercise, in patients with remote PE who present with persistent dyspnea and exercise limitation. The results suggest that in many patients with post-PE syndrome, with chronic activity-related dyspnea, the negative physiological effects of deconditioning may be important and merit referral for pulmonary rehabilitation. Finally, our results set the stage for new studies to examine the nature of pulmonary vascular injury and resultant pulmonary gas-exchange disturbances from remote thrombotic occlusion.

DATA AVAILABILITY

Data will be made available upon reasonable request.

GRANTS

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DISCLAIMERS

K. M. Milne, D. E. O'Donnell, and D. B. Phillips had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

DISCLOSURES

D. E. O'Donnell has served on speaker bureaus, consultation panels, and advisory boards for AstraZeneca and Boehringer

Ingelheim. No personal fees were received by D. E. O'Donnell from the listed commercial agencies outside the submitted work. The funders had no role in study design, data collection and analysis, or preparation of the manuscript. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

K.M.M., D.E.O., and D.B.P. conceived and designed research; K.M.M., M.D.J., R.M.S., S.G.V., and D.B.P. performed experiments; K.M.M., M.D.J., R.M.S., N.S., C.L.D., J.P.d.-T., A.J., and D.B.P. analyzed data; K.M.M., N.S., C.L.D., J.P.d.-T., K.d.W., A.J., D.E.O., and D.B.P. interpreted results of experiments; M.D.J., R.M.S., and D.B.P. prepared figures; K.M.M., M.D.J., D.E.O., and D.B.P. drafted manuscript; K.M.M., M.D.J., R.M.S., S.G.V., N.S., C.L.D., J.P.d.-T., K.d.W., A.J., J.A.N., D.E.O., and D.B.P. edited and revised manuscript; K.M.M., M.D.J., R.M.S., S.G.V., N.S., C.L.D., J.P.d.-T., K.d.W., A.J., J.A.N., D.E.O., and D.B.P. approved final version of manuscript.

REFERENCES

1. **Klok FA**, **van Kralingen KW**, **van Dijk AP**, **Heyning FH**, **Vliegen HW**, **Huisman MV.** Prevalence and potential determinants of exertional dyspnea after acute pulmonary embolism. *Respir Med* 104: 1744–1749, 2010. doi:10.1016/j.rmed.2010.06.006.
2. **Kahn SR**, **Akaberi A**, **Granton JT**, **Anderson DR**, **Wells PS**, **Rodger MA**, **Solymoss S**, **Kovacs MJ**, **Rudski L**, **Shimony A**, **Dennie C**, **Rush C**, **Hernandez P**, **Aaron SD**, **Hirsch AM.** Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE Cohort Study. *Am J Med* 130: 990.e999–990.e921, 2017. doi:10.1016/j.amjmed.2017.03.033.
3. **Kahn SR**, **Hirsch AM**, **Akaberi A**, **Hernandez P**, **Anderson DR**, **Wells PS**, **Rodger MA**, **Solymoss S**, **Kovacs MJ**, **Rudski L**, **Shimony A**, **Dennie C**, **Rush C**, **Geerts WH**, **Aaron SD**, **Granton JT.** Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE Prospective Cohort Study. *Chest* 151: 1058–1068, 2017. doi:10.1016/j.chest.2016.11.030.
4. **Pugliese SC**, **Kawut SM.** The post-pulmonary embolism syndrome: real or ruse? *Ann Am Thorac Soc* 16: 811–814, 2019. doi:10.1513/AnnalsATS.201901-061PS.
5. **Simonneau G**, **Montani D**, **Celermajer DS**, **Denton CP**, **Gatzoulis MA**, **Krowka M**, **Williams PG**, **Souza R.** Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 53: 1801913, 2019. doi:10.1183/13993003.01913-2018.
6. **James MD**, **Phillips DB**, **Vincent SG**, **Abdallah SJ**, **Donovan AA**, **de-Torres JP**, **Neder JA**, **Smith BM**, **Jensen D**, **O'Donnell DE.** Exertional dyspnoea in patients with mild-to-severe Chronic Obstructive Pulmonary Disease (COPD): neuromechanical mechanisms. *J Physiol* 18: 4227–4245, 2022. doi:10.1113/JP283252.
7. **Faisal A**, **Alghamdi BJ**, **Ciavaglia CE**, **Elbehairy AF**, **Webb KA**, **Ora J**, **Neder JA**, **O'Donnell DE.** Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. *Am J Respir Crit Care Med* 193: 299–309, 2016. doi:10.1164/rccm.201504-0841OC.
8. **Jolley CJ**, **Luo YM**, **Steier J**, **Rafferty GF**, **Polkey MI**, **Moxham J.** Neural respiratory drive and breathlessness in COPD. *Eur Resp J* 45: 355–364, 2014. doi:10.1183/09031936.00063014.
9. **Claeys M**, **Claessen G**, **La Gerche A**, **Petit T**, **Belge C**, **Meyns B**, **Bogaert J**, **Willems R**, **Claus P**, **Delcroix M.** Impaired cardiac reserve and abnormal vascular load limit exercise capacity in chronic thromboembolic disease. *JACC Cardiovasc Imaging* 12: 1444–1456, 2019. doi:10.1016/j.jcmg.2018.07.021.
10. **McCabe C**, **Deboeck G**, **Harvey I**, **Ross RM**, **Gopalan D**, **Screaton N**, **Pepke-Zaba J.** Inefficient exercise gas exchange identifies pulmonary hypertension in chronic thromboembolic obstruction following pulmonary embolism. *Thromb Res* 132: 659–665, 2013. doi:10.1016/j.thromres.2013.09.032.
11. **Fernandes TM**, **Alotaibi M**, **Strozza DM**, **Stringer WW**, **Porszasz J**, **Faulkner GG**, **Castro CF**, **Tran DA**, **Morris TA.** Dyspnea postpulmonary embolism from physiological dead space proportion and stroke volume defects during exercise. *Chest* 157: 936–944, 2020. doi:10.1016/j.chest.2019.10.047.
12. **Farina S**, **Bruno N**, **Agalbato C**, **Contini M**, **Cassandro R**, **Elia D**, **Harari S**, **Agostoni P.** Physiological insights of exercise hyperventilation in arterial and chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 259: 178–182, 2018. doi:10.1016/j.ijcard.2017.11.023.
13. **Robertson HT.** Dead space: the physiology of wasted ventilation. *Eur Respir J* 45: 1704–1716, 2015 [Erratum in *Eur Respir J* 46(4):1226, 2015]. doi:10.1183/09031936.00137614.
14. **Madani M**, **Ogo T**, **Simonneau G.** The changing landscape of chronic thromboembolic pulmonary hypertension management. *Eur Respir Rev* 26: 170105, 2017. doi:10.1183/16000617.0105-2017.
15. **Galiè N**, **Humbert M**, **Vachiery JL**, **Gibbs S**, **Lang I**, **Torbicki A**, **Simonneau G**, **Peacock A**, **Vonk Noordegraaf A**, **Beghetti M**, **Ghofrani A**, **Gomez Sanchez MA**, **Hansmann G**, **Klepetko W**, **Lancellotti P**, **Matucci M**, **McDonagh T**, **Pierard LA**, **Trindade PT**, **Zompatori M**, **Hoeper M.** 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 37: 67–119, 2016. doi:10.1093/eurheartj/ehv317.
16. **Mahler DA**, **Weinberg DH**, **Wells CK**, **Feinstein AR.** The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 85: 751–758, 1984. doi:10.1378/chest.85.6.751.
17. **Macintyre N**, **Crapo RO**, **Viegi G**, **Johnson DC**, **van der Grinten CP**, **Brusasco V**, **Burgos F**, **Casaburi R**, **Coates A**, **Enright P**, **Gustafsson P**, **Hankinson J**, **Jensen R**, **McKay R**, **Miller MR**, **Navajas D**, **Pedersen OF**, **Pellegrino R**, **Wanger J.** Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 26: 720–735, 2005. doi:10.1183/09031936.05.00034905.
18. **Wanger J**, **Clausen JL**, **Coates A**, **Pedersen OF**, **Brusasco V**, **Burgos F**, **Casaburi R**, **Crapo R**, **Enright P**, **van der Grinten CP**, **Gustafsson P**, **Hankinson J**, **Jensen R**, **Johnson D**, **Macintyre N**, **McKay R**, **Miller MR**, **Navajas D**, **Pellegrino R**, **Viegi G.** Standardisation of the measurement of lung volumes. *Eur Respir J* 26: 511–522, 2005. doi:10.1183/09031936.05.00035005.
19. **Miller MR**, **Hankinson J**, **Brusasco V**, **Burgos F**, **Casaburi R**, **Coates A**, **Crapo R**, **Enright P**, **van der Grinten CP**, **Gustafsson P**, **Jensen R**, **Johnson DC**, **MacIntyre N**, **McKay R**, **Navajas D**, **Pedersen OF**, **Pellegrino R**, **Viegi G**, **Wanger J**, **ATS/ERS Task Force.** Standardisation of spirometry. *Eur Respir J* 26: 319–338, 2005. doi:10.1183/09031936.05.00034805.
20. **Quanjer PH**, **Stanojevic S**, **Cole TJ**, **Baur X**, **Hall GL**, **Culver BH**, **Enright PL**, **Hankinson JL**, **Ip MS**, **Zheng J**, **Stocks J**; **ERS Global Lung Function Initiative.** Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 40: 1324–1343, 2012. doi:10.1183/09031936.00080312.
21. **Hall GL**, **Filipow N**, **Ruppel G**, **Okitika T**, **Thompson B**, **Kirkby J**, **Steenbruggen I**, **Cooper BG**, **Stanojevic S**; **contributing GLI Network members.** Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry. *Eur Respir J* 57: 2000289, 2021. doi:10.1183/13993003.00289-2020.
22. **Stanojevic S**, **Graham BL**, **Cooper BG**, **Thompson BR**, **Carter KW**, **Francis RW**, **Hall GL**; **Global Lung Function Initiative TLCO working group.** Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J* 50: 1700010, 2017. doi:10.1183/13993003.00010-2017.
23. **Stickland MK**, **Neder JA**, **Guenette JA**, **O'Donnell DE**, **Jensen D.** Using cardiopulmonary exercise testing to understand dyspnea and exercise intolerance in respiratory disease. *Chest* 161: 1505–1516, 2022. doi:10.1016/j.chest.2022.01.021.
24. **Lewthwaite H**, **Benedetti A**, **Stickland MK**, **Bourbeau J**, **Guenette JA**, **Maltais F**, **Marciniuk DD**, **O'Donnell DE**, **Smith BM**, **Tan WC**, **Jensen D**; **CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network.** Normative peak cardiopulmonary exercise test responses in canadian adults aged ≥40 years. *Chest* 158: 2532–2545, 2020. doi:10.1016/j.chest.2020.06.074.
25. **Borg GAV.** Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14: 377–381, 1982.

26. **Ciavaglia CE**, **Guenette JA**, **Langer D**, **Webb KA**, **Alberto Neder J**, **O'Donnell DE.** Differences in respiratory muscle activity during cycling and walking do not influence dyspnea perception in obese patients with COPD. *J Appl Physiol (1985)* 117: 1292–1301, 2014. doi:10.1152/japplphysiol.00502.2014.
27. **Jensen D**, **O'Donnell DE**, **Li R**, **Luo YM.** Effects of dead space loading on neuro-muscular and neuro-ventilatory coupling of the respiratory system during exercise in healthy adults: implications for dyspnea and exercise tolerance. *Respir Physiol Neurobiol* 179: 219–226, 2011. doi:10.1016/j.resp.2011.08.009.
28. **Domnik NJ**, **Phillips DB**, **James MD**, **Ayoo GA**, **Taylor SM**, **Scheeren RE**, **Di Luch AT**, **Milne KM**, **Vincent SG**, **Elbehairy AF**, **Crinion SJ**, **Driver HS**, **Neder JA**, **O'Donnell DE.** Compensatory responses to increased mechanical abnormalities in COPD during sleep. *Eur J Appl Physiol* 122: 663–676, 2022. doi:10.1007/s00421-021-04869-0.
29. **Elbehairy AF**, **Guenette JA**, **Faisal A**, **Ciavaglia CE**, **Webb KA**, **Jensen D**, **Ramsook AH**, **Neder JA**, **O'Donnell DE**; **Canadian Respiratory Research Network (CRRN).** Mechanisms of exertional dyspnoea in symptomatic smokers without COPD. *Eur Respir J* 48: 694–705, 2016. doi:10.1183/13993003.00077-2016.
30. **Elbehairy AF**, **Webb KA**, **Laveneziana P**, **Domnik NJ**, **Neder JA**, **O'Donnell DE**; **Canadian Respiratory Research Network (CRRN).** Acute bronchodilator therapy does not reduce wasted ventilation during exercise in COPD. *Respir Physiol Neurobiol* 252-253: 64–71, 2018. doi:10.1016/j.resp.2018.03.012.
31. **Phillips DB**, **Domnik NJ**, **Elbehairy AF**, **Preston ME**, **Milne KM**, **James MD**, **Vincent SG**, **Ibrahim-Masthan M**, **Neder JA**, **O'Donnell DE**; **Canada Respiratory Research Network (CRRN).** Elevated exercise ventilation in mild COPD is not linked to enhanced central chemosensitivity. *Respir Physiol Neurobiol* 284: 103571, 2021. doi:10.1016/j.resp.2020.103571.
32. **Enghoff H.** Volumen inefficax. Bemerkungen zur frage des schadlichen raumes. *Uppsala Lakarefoeren Fohr* 44: 191–218, 1938.
33. **Gläser S**, **Ittermann T**, **Koch B**, **Schäper C**, **Felix SB**, **Völzke H**, **Könemann R**, **Ewert R**, **Hansen JE.** Influence of smoking and obesity on alveolar-arterial gas pressure differences and dead space ventilation at rest and peak exercise in healthy men and women. *Respir Med* 107: 919–926, 2013. doi:10.1016/j.rmed.2013.02.013.
34. **Ries AL.** Minimally clinically important difference for the UCSD shortness of breath questionnaire, Borg scale, and visual analog scale. *COPD* 2: 105–110, 2005. doi:10.1081/copd-200050655.
35. **Beaver WL**, **Wasserman K**, **Whipp BJ.** A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol (1985)* 60: 2020–2027, 1986. doi:10.1152/jappl.1986.60.6.2020.
36. **Balady GJ**, **Arena R**, **Sietsema K**, **Myers J**, **Coke L**, **Fletcher GF**, **Forman D**, **Franklin B**, **Guazzi M**, **Gulati M**, **Keteyian SJ**, **Lavie CJ**, **Macko R**, **Mancini D**, **Milani RV**; **Interdisciplinary Council on Quality of Care and Outcomes Research.** Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 122: 191–225, 2010. doi:10.1161/CIR.0b013e3181e52e69.
37. **Sue DY**, **Wasserman K**, **Moricca RB**, **Casaburi R.** Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. *Chest* 94: 931–938, 1988. doi:10.1378/chest.94.5.931.
38. **Schneider DA**, **Phillips SE**, **Stoffolano S.** The simplified V-slope method of detecting the gas exchange threshold. *Med Sci Sports Exerc* 25: 1180–1184, 1993.
39. **Phillips DB**, **Elbehairy AF**, **James MD**, **Vincent SG**, **Milne KM**, **de-Torres JP**, **Neder JA**, **Kirby M**, **Jensen D**, **Stickland MK**, **Guenette JA**, **Smith BM**, **Aaron SD**, **Tan WC**, **Bourbeau J**, **O'Donnell DE**; **CanCOLD Collaborative Research Group and the Canadian Respiratory Research Network (CRRN).** Impaired ventilatory efficiency, dyspnea and exercise intolerance in chronic obstructive pulmonary disease: results from the CanCOLD study. *Am J Respir Crit Care Med* 205: 1391–1402, 2022. doi:10.1164/rccm.202109-2171OC.
40. **Neder JA**, **Alharbi A**, **Berton DC**, **Alencar MC**, **Arbex FF**, **Hirai DM**, **Webb KA**, **O'Donnell DE.** Ventilatory inefficiency adds to lung function in predicting mortality in COPD. *J COPD* 13: 416–424, 2016. doi:10.3109/15412555.2016.1158801.
41. **Myers J**, **Arena R**, **Oliveira RB**, **Bensimhon D**, **Hsu L**, **Chase P**, **Guazzi M**, **Brubaker P**, **Moore B**, **Kitzman D**, **Peberdy MA.** The lowest VE/VCO_2 ratio during exercise as a predictor of outcomes in patients with heart failure. *J Card Fail* 15: 756–762, 2009. doi:10.1016/j.cardfail.2009.05.012.
42. **Poon CS.** Potentiation of exercise ventilatory response by airway CO_2 and dead space loading. *J Appl Physiol (1985)* 73: 591–595, 1992. doi:10.1152/jappl.1992.73.2.591.
43. **Villafranca C**, **Borzone G**, **Leiva A**, **Lisboa C.** Effect of inspiratory muscle training with an intermediate load on inspiratory power output in COPD. *Eur Respir J* 11: 28–33, 1998. doi:10.1183/09031936.98.11010028.
44. **O'Donnell DE**, **James MD**, **Milne KM**, **Neder JA.** The pathophysiology of dyspnea and exercise intolerance in chronic obstructive pulmonary disease. *Clin Chest Med* 40: 343–366, 2019. doi:10.1016/j.ccm.2019.02.007.
45. **Younes M**, **Kivinen G.** Respiratory mechanics and breathing pattern during and following maximal exercise. *J Appl Physiol Respir Environ Exerc Physiol* 57: 1773–1782, 1984. doi:10.1152/jappl.1984.57.6.1773.
46. **Eldridge FL**, **Millhorn DE**, **Waldrop TG.** Exercise hyperpnea and locomotion: parallel activation from the hypothalamus. *Science* 211: 844–846, 1981. doi:10.1126/science.7466362.
47. **Chen Z**, **Eldridge FL**, **Wagner PG.** Respiratory-associated rhythmic firing of midbrain neurones in cats: relation to level of respiratory drive. *J Physiol* 437: 305–325, 1991. doi:10.1113/jphysiol.1991.sp018597.
48. **Chen Z**, **Eldridge FL**, **Wagner PG.** Respiratory associated thalamic activity is related to level of respiratory drive. *Resp Physiol* 90: 99–113, 1992. doi:10.1016/0034-5687(92)90137-I.
49. **Banzett RB**, **Lansing RW**, **Binks AP.** Air hunger: a primal sensation and a primary element of dyspnea. *Compr Physiol* 11: 1449–1483, 2021. doi:10.1002/cphy.c200001.
50. **Zavorsky GS**, **Cao J**, **Mayo NE**, **Gabbay R**, **Murias JM.** Arterial versus capillary blood gases: a meta-analysis. *Respir Physiol Neurobiol* 155: 268–279, 2007. doi:10.1016/j.resp.2006.07.002.
51. **Murphy R**, **Thethy S**, **Raby S**, **Beckley J**, **Terrace J**, **Fiddler C**, **Craig M**, **Robertson C.** Capillary blood gases in acute exacerbations of COPD. *Respir Med* 100: 682–686, 2006. doi:10.1016/j.rmed.2005.08.007.
52. **Domnik NJ**, **O'Donnell DE.** Reply to Hudson and Catcheside's "Estimating inspiratory neural drive and the wakefulness drive to breathe". *Eur J Appl Physiol* 122: 2147–2149, 2022. doi:10.1007/s00421-022-04986-4.