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Sensory consequences of critical inspiratory constraints during exercise in pulmonary arterial hypertension

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ABSTRACT

We aimed to assess detailed ventilatory and sensory responses to exercise contrasting subjects with and without PAH.

20 non-smoking patients with PAH (37.5 ± 12.1 ys; $FEV_1/FVC = 0.77 \pm 0.04$; mPAP by heart catheterization = 50.6 ± 18.1 mmHg) and 10 matched controls performed cycling cardiopulmonary exercise test with serial assessments of dyspnea, airway occlusion pressure during the first 0.1 s (P0.1) of tidal volume and inspiratory capacity (IC).

Patients showed lower spirometric variables compared to controls. Dyspnea and ventilation (V_E) were significantly higher in patients for a given work rate. Dyspnea persisted more intense in patients even when expressed as a function of V_E. Lower IC at rest (in non-hyperinflators; n = 10) or exercise-induced reduction in IC (in hyperinflators) predisposed patients to achieve earlier and at lower workloads a critical inspiratory reserve volume (IRV). At this point, there was a sudden rise in P0.1 and dyspnea perception.

Attainment of a critical IRV at premature workloads leads to neuromechanical dissociation with an abrupt increment in exertional dyspnea.

1. Introduction

Pulmonary arterial hypertension (PAH) is a devastating disease characterized by remodeling of pulmonary vasculature leading to main complaints of exercise intolerance and dyspnea. The classic pathophysiological mechanism underlying exertional intolerance is the abnormal pulmonary vascular distention and recruitment to accommodate the increasing cardiac output demand of exercise (Simonneau et al., 2013). As corollary, reduced aerobic capacity (peak oxygen uptake; VO_2), ventilatory inefficiency (high minute ventilation/carbon dioxide output; V_E/VCO_2) and variable degrees of O_2 desaturation are the typical findings observed in clinical exercise testing with variable combinations of leg effort and dyspnea as the limiting symptoms (O'Donnell et al., 2017).

On average, increased dyspnea perception at relatively low levels of exercise is commensurate with the exaggerated increases in ventilation, indicating increased neural drive as potential explanation for the higher dyspnea perception (O'Donnell et al., 2017). Although the relatively preserved resting lung function is presumptive of unaltered ventilatory mechanics during exercise, it has been increasingly reported that a significant proportion of patients with PAH present abnormal dynamic ventilatory mechanics that may contribute to exercise dyspnea (Laveneziana et al., 2013; Richter et al., 2013; Laveneziana et al., 2015). Recent advances in our current understanding of respiratory pathophysiology highlight the relevance of operational lung volumes measurements to assess ventilatory mechanics during exercise (O'Donnell et al., 2017; Casaburi and Rennard, 2015). The combination of rising tidal volume (V_T) as exercise intensity increases without contemporaneously increment in inspiratory capacity (IC), or even its decrement, brings the end-inspiratory lung volume (EILV) close to total lung capacity (TLC), i.e., the maximum lung volume that can be inhaled. When the difference between TLC and EILV shrinks to a critical value, in the face of increasing exercise respiratory drive, dyspnea rises. Independently of disease pathophysiology, the intensity of dyspnea during standardized progressive exercise enhances in association with increasing inspiratory effort when the mechanical response to V_T expansion is blunted due to inspiratory constraint (Faisal et al., 2016).

Our main objective, therefore, was to investigate the relevance of critical inspiratory reserve volume (IRV) achievement on the magnitude of dyspnea perception during exercise in PAH patients compared to

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Table 1
Characteristics of studied participants.

	PAH (n = 20)	Control (n = 10)
Gender, M/F	3/17	2/8
Age, yrs	37.5 ± 12.1	37.2 ± 12.9
BMI, kg/m^2	24.6 (18.5 – 32.0)	22.9 (20.3 – 33.7)
NYHA Functional Class, n (%)		
I	10 (50)	10 (100)*
II	9 (45)	0 (0)*
III	1 (5)	0 (0)
IV	0 (0)	0 (0)
Modified MRC dyspnea scale, n (%)		
0	1 (5)	10 (100)*
1	12 (60)	0 (0)*
2	6 (30)	0 (0)
3	1 (5)	0 (0)
4	0 (0)	0 (0)
Medication, n (%)		
Calcium channel blocker	3 (15)	0 (0)
Phosphodiesterase type 5 inhibitors	17 (85)	0 (0)*
Endothelin receptor antagonists	7 (35)	0 (0)*
Diuretics	10 (50)	0 (0)*
Digoxin	4 (20)	0 (0)
Pulmonary Function		
FEV_1, l (% pred)	2.52 ± 0.55 (85 ± 10)	3.24 ± 0.78* (101 ± 7)*
FVC, l (% pred)	3.28 ± 0.76 (92 ± 9)	3.92 ± 0.90 (101 ± 6)*
FEV_1/FVC, %	77.0 ± 4.4	82.6 ± 5.5*
$FEF_{25-75\%}$, l/s (% pred)	2.23 ± 0.63 (72 ± 21)	3.41 ± 1.16* (102 ± 23)*
TLC, l (% pred)	5.20 ± 0.99 (105 ± 10)	5.96 ± 1.18 (109 ± 6)
FRC, l (% pred)	2.71 ± 0.60 (101 ± 17)	3.01 ± 0.66 (104 ± 17)
RV, l (% pred)	1.82 ± 0.39 (126 ± 25)	1.90 ± 0.46 (119 ± 22)
RV/TLC, (%)	35 ± 5	32 ± 6
DL_{CO}, % pred	63 ± 17	–
MIP, cmH_20 (% pred)	−92 ± 23 (95 ± 20)	−112 ± 26* (113 ± 23)*
MEP, cmH_20 (% pred)	98 (69 – 210) (108 ± 18)	128 (95 – 170)* (126 ± 16)*
Pulmonary Haemodynamics		
PASP, mmHg	78.9 ± 29. 0	–
PADP, mmHg	35.2 ± 14.8	–
MPAP, mmHg	50.6 ± 18.1	–
PAOP, mmHg	7.8 ± 2.3	–
CO, l/min	5.0 ± 1.5	
CI, l/min/m^2	3.1 ± 0.9	–
PVR, dyn·s·cm^{-5}	748 ± 360	–
PVR, Wood units	9.4 ± 4.5	–
RAP, mmHg	7.6 ± 5.7	–

Values are presented as mean ± SD or median (range).
Definition of abbreviations: BMI = body mass index; CI = cardiac index; CO = cardiac output; DL_{CO}= diffusing capacity for carbon monoxide; $FEF_{25-75\%}$= forced expiratory flow between 25 and 75 percent of FVC; FEV_1= forced expired volume in first second; FRC = functional residual capacity; FVC = forced vital capacity; IC = inspiratory capacity; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; mMRC = modified Medical Research Council; MPAP = mean pulmonary artery pressure; NYHA = New York Heart Association; PADP = pulmonary artery diastolic pressure; PAH = pulmonary arterial hypertension; PAOP = pulmonary artery occlusion pressure; PASP = pulmonary artery systolic pressure; % pred = percent of predicted; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = reserve volume; TLC = total lung capacity.
* $P < 0.05$.

matched controls. Serial measurements of IC and mouth occlusion pressure during the beginning of tidal breathing were performed to track respiratory mechanics and inspiratory muscle effort, respectively. Considering inspiratory muscle weakness as a common finding in PAH

Table 2
Physiologic and sensory responses to ramp, progressive Cardiopulmonary Exercise Testing.

	PAH (n = 20)	Control (n = 10)
Peak exercise		
Work rate, watts	55 (35 – 110)	135 (105 – 230)*
$\dot{V}_{O2}$, l/min (% pred)	0.96 (0.66 – 1.92) (63 (31 – 121))	1.82 (1.11 – 3.18)* (106 (89 – 134))*
$\dot{V}_{O2}$, ml/kg/min	15.3 (11.2 – 24.7)	26.9 (17.2 – 38.3)*
Heart rate, beats/min (% pred)	143 ± 24 (78 ± 12)	160 ± 18 (88 ± 9)*
O_2 pulse, mL/beat	6.8 (4.6 – 13.4)	10.9 (6.8 – 19.4)*
$\Delta\dot{V}_{O2}/\Delta W$, ml/min/watts	9.6 ± 3.0	10.3 ± 1.4
$\dot{V}E$, l/min	47.5 ± 12.2	57.6 ± 13.9
$\dot{V}E$/eMVV, %	52 ± 13	48 ± 10
*F*b, breaths/min	31 ± 6	28 ± 5
V_T, l	1.54 (0.97 – 2.89)	1.90 (1.30 – 3.31)*
V_T/IC, %	70 ± 12	73 ± 7
IC, l	2.20 (1.50 – 3.43)	2.90 (2.00 – 4.53)*
IRV, l	0.64 ± 0.28	0.76 ± 0.25
EILV, l	4.57 ± 1.02	5.19 ± 1.02
EILV/TLC, %	88 ± 5	87 ± 3
EELV,l	3.01 ± 0.71	3.08 ± 0.5
$\dot{V}E/\dot{V}CO_2$	46.0 ± 9.0	28.2 ± 4.7*
$\Delta\dot{V}E/\Delta\dot{V}CO_2$ slope	42.5 ± 11.6	23.6 ± 3.8*
$P_{ET}CO_2$, mmHg	25.6 ± 5.5	39.7 ± 6.7*
SpO_2, %	95 (71-99)	98 (96-100)
Dyspnea, Borg units	5 (1 – 10)	3 (1-7)*
Leg discomfort, Borg units	4 (2 – 10)	8 (2 – 10)
Anaerobic Threshold		
$\dot{V}_{O2}$, l/min (% pred)	0.69 ± 0.29 (41 ± 13)	1.20 ± 0.46* (71 ± 19)*
$\dot{V}E/\dot{V}CO_2$	42.2 ± 7.3	26.4 ± 4.9*
$\dot{V}E/\dot{V}O_2$	39.4 ± 6.9	23.4 ± 4.7*

Values are mean ± SD or median (range).
Definition of abbreviations: Δ= peak-rest change; EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; eMVV = estimated maximum voluntary ventilation; *F*b = breathing frequency; IC = inspiratory capacity; IRV = inspiratory reserve volume; O_2 pulse = oxygen pulse; % pred = percent of predicted; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide; SpO_2= arterial O_2 saturation by pulse oximetry; TLC = total lung capacity; $\dot{V}CO_2$= carbon dioxide output; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$= oxygen uptake; V_T= tidal volume.
* $P < 0.05$.

(Meyer et al., 2005; Marra et al., 2015), and potentially related to dyspnea perception (Society ATS/ERS, 2002), maximal inspiratory strength were also measured before and immediately post-exercise. We anticipate that dyspnea ratings would be higher as a function of both work rate and ventilation if dynamic mechanical constraints actually play an important role in these patients (Neder et al., 2018).

2. Methods

2.1. Study design

This cross-sectional study was conducted in accordance with the last amendment of the Declaration of Helsinki for medical research involving human subjects and approved by our institutional Ethics Committee (HCPA Nº 13-0505).

Clinical information and diagnostic tests to fulfill inclusion criteria were obtained from medical records. Echocardiography and right heart catheterization were performed within 6 months from study inclusion. The experimental part of the study was conducted in a single visit. Participants initially carried out resting spirometry, lung volume measurements by whole-body plethysmography and lung diffusion capacity for carbon monoxide (D_LCO). Thereafter, an individually tailored symptom-limited incremental cycling cardiopulmonary exercise test (CPET) with serial measurements of airway occlusion pressure during the first 100 ms of the V_T (P0.1) and IC was performed (in this order).

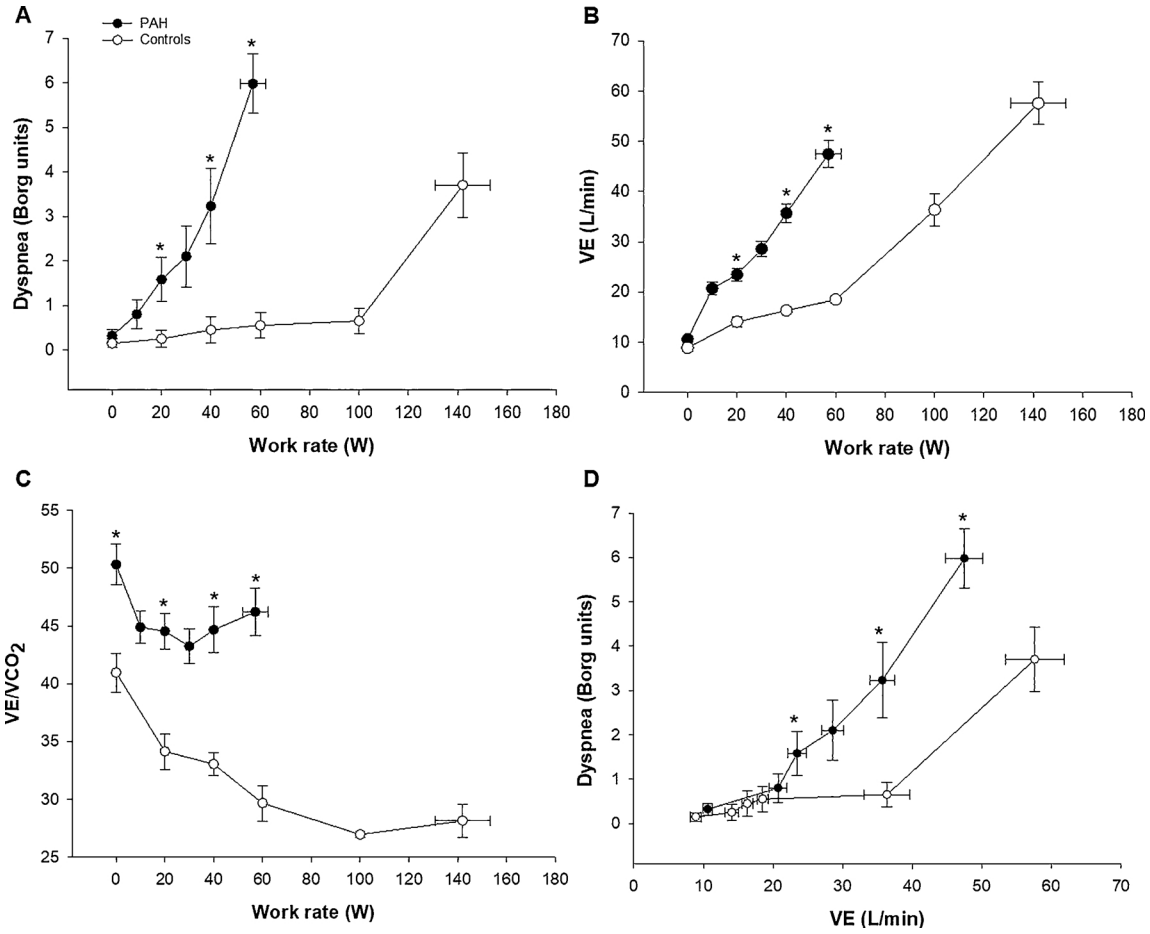

Fig. 1. Dyspnea (A), minute-ventilation (B) and ventilatory equivalent for carbon dioxide output (C) as a function of work rate increment in patients with pulmonary arterial hypertension (PAH) and matched controls. Panel D displays dyspnea for a given ventilation in each group.
Data are presented as mean ± SE.
*p < 0.05 for PAH versus controls in a given moment.

Mouth occlusion maximal inspiratory pressures (MIP) were measured before and immediately post-exercise cessation. Subjects were asked to avoid caffeine-containing beverages and alcohol and heavy meals at least 4–6 h prior to testing, as well as strenuous physical exertion for at least 12 h before the experimental visit schedule. Chronic medications in use were not interrupted.

2.2. Subjects

We prospectively enrolled 20 patients with PAH according to currently accepted international guideline (Simonneau et al., 2013) and 10 healthy matched controls. Resting mean pulmonary arterial pressure ≥25mmHg and pulmonary occlusion arterial pressure ≤15mmHg by heart catheterization were key inclusion criteria for patients. Before entering into the study, patients were required to be clinically stable (no hospitalization, clinical worsening, history of syncope and/or generalized edema) without any change in prescribed medications for PAH treatment in the last 3 months before enrolment.

Resting hypoxemia by pulse oximetry (SpO_2) < 90%, other cardiac, neurologic or orthopedic disorder that could potentially affect exercise performance, asthma, heavy current or former smoking habit (> 10 pack-years) or non-reversible airflow obstruction (forced expiratory volume in the first second (FEV_1)/forced vital capacity (FVC) < 0.7 post-bronchodilator) were exclusion criteria.

2.3. Procedures

Pulmonary function tests were performed with an automated system (Jaeger®, Wüerzburg, Germany) in accordance with international standards. MIP was measured in sitting position from the residual volume using a pressure transducer (MVD-300®, Globalmed, Porto Alegre, Brazil). At least 3 measurements were performed and the highest values (peak values) were recorded with a difference lower than 10% between the three highest values. Maximum voluntary ventilation was estimated (eMVV) as FEV_1 x 37.5.

CPET was conducted on an electronically-braked cycle ergometer (Corival®, Lode, Groningen, Netherlands) using a ramp incremental protocol. After 5 min of rest and 2 min of freewheel, the load was increased 5–10 W/min for patients and 15–20 W/min for controls until exhaustion. Standard metabolic and ventilatory variables were obtained breath-by-breath and summarized each 20 s (Vmax Encore®, CareFusion, Yorba Linda, USA). Dynamic operating lung volumes were calculated from TLC at rest and IC maneuvers obtained every 2 min (Guenette et al., 2013).

Before each IC maneuver, P0.1 was obtained with an in-house developed system that occluded the mouth during the first 100 ms during tidal breathing (Whitelaw et al., 1975) and digitized the measured pressure at 100 Hz using a 10 bits analog-to-digital converter. P0.1 was expressed as a percentage of MIP (P0.1/MIP) in order to normalize for individual differences in inspiratory muscle strength (Peterson et al., 1981). Dynamic hyperinflation (DH) was defined as a reduction in IC > 150 ml from rest to peak exercise (Guenette et al., 2012). Dyspnea

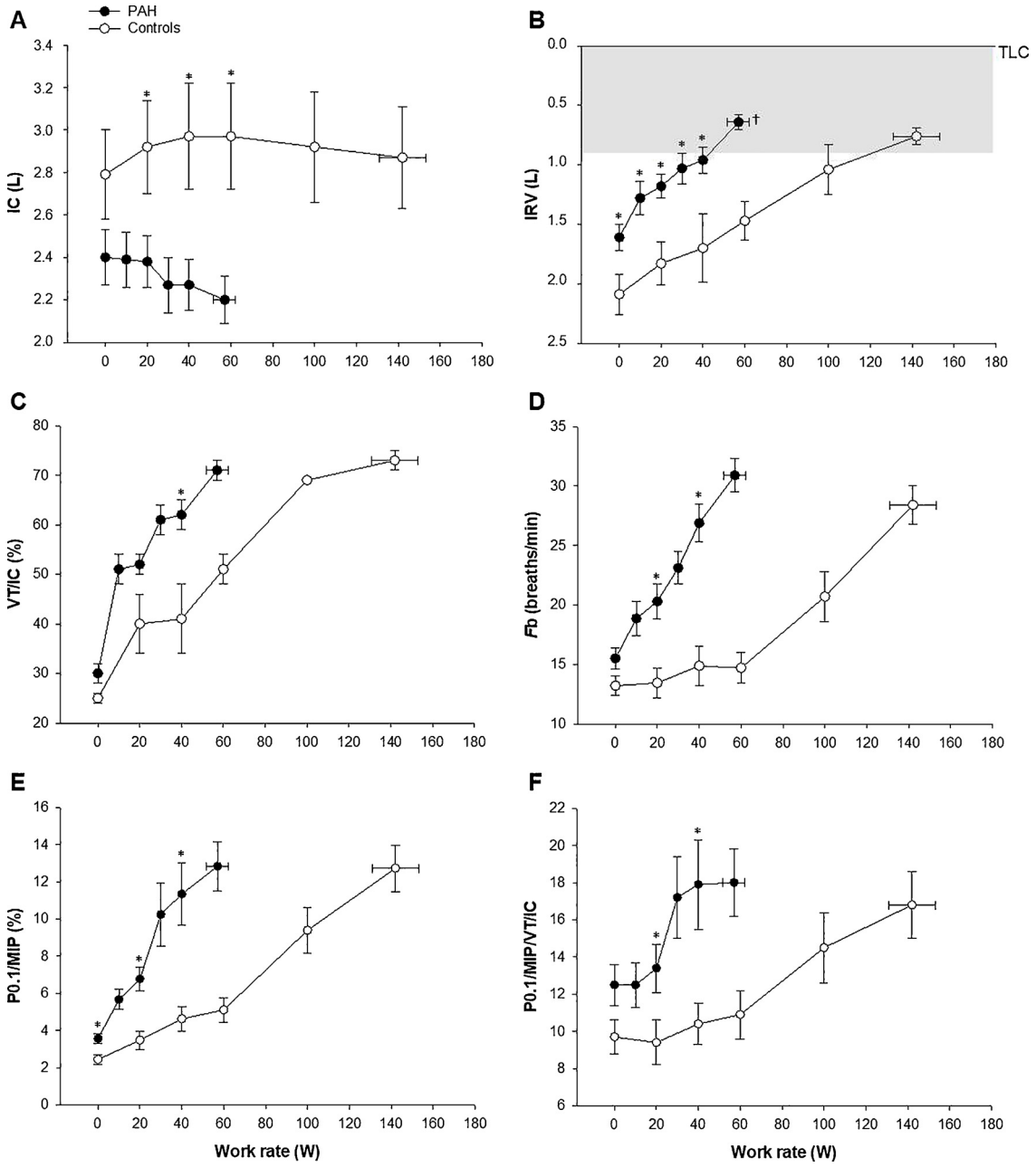

Fig. 2. Operating lung volumes (Panels A–B), breathing pattern (Panels C–D) and inspiratory effort (Panels E–F) in response to progressive incremental work rate in patients with pulmonary arterial hypertension (PAH) and matched controls. The shaded area in Panel B represents the critical exercise IRV where an inflection in dyspnea perception and inspiratory effort are observed.
Data are presented as mean ± SE.
Definition of abbreviations: *Fb* = breathing frequency; IC = inspiratory capacity; IRV = inspiratory reserve volume; MIP = maximal inspiratory pressure; P0.1 = airway occlusion pressure during the first 0.1 s of tidal volume; V_T = tidal volume.
*$p < 0.05$ for PAH versus controls in a given moment.

intensity was assessed with the modified 10-point Borg scale (Borg, 1982) every minute, before the IC maneuvers when appropriate. Immediately after exercise interruption, the participant was moved from the ergometer to a nearby chair for measurement of post-exercise MIP.

2.4. Statistical analyses

Independent t-Test, Mann–Whitney U or $\chi 2$ tests were used to compare groups, as appropriate. Association between selected continuous variables was investigated by Pearson's product-moment correlation test. Generalizing estimating equations were used to compare operating lung volumes, dyspnea intensity and ventilatory parameters at rest and during iso-work rates. A $p < 0.05$ level of significance was considered for all analyses. Data were analyzed using a statistical software package (SPSS®; V20.0, Chicago, IL).

3. Results

3.1. General characteristics

PAH and control groups showed similar gender frequency, age, and body mass index. Albeit with mean values inside the predicted normal

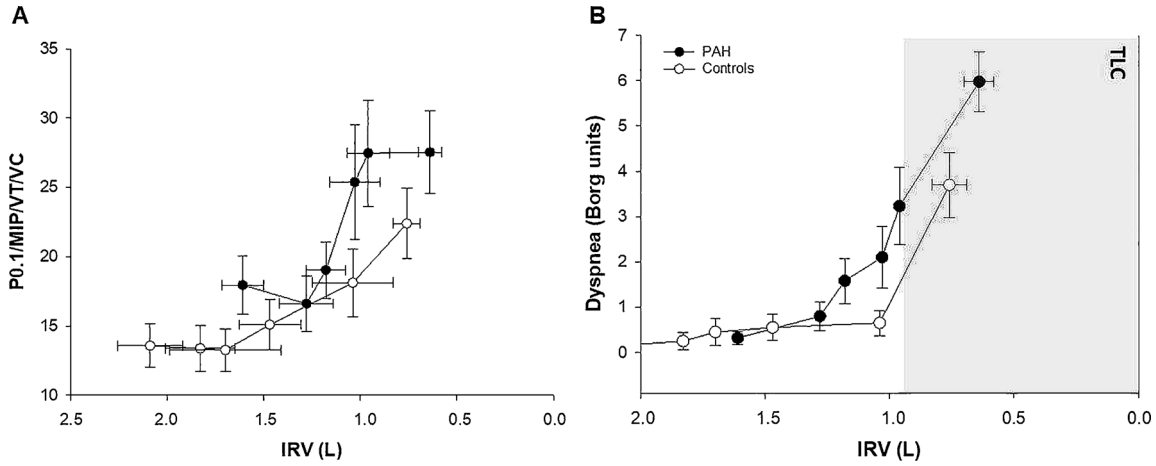

Fig. 3. Mouth occlusion pressure during the first 0.1 s of tidal volume (P0.1) adjusted for maximal inspiratory pressure (MIP) and volume displacement (A), and dyspnea perception (B) expressed as a function of inspiratory reserve volume (IRV) during incremental exercise in patients with pulmonary arterial hypertension (PAH) and matched controls. Observe that after a critical IRV (shaded area) there is an inflection rise in the inspiratory effort and dyspnea perception in both groups. Data are presented as mean ± SE.
Definition of abbreviations: TLC = total lung capacity; VC = vital capacity; V_T = tidal volume.

range, FEV_1, FVC, mid-expiratory flows, FEV_1/FVC ratio were significantly lower in patients (Table 1). PAH patients also had lower MIP (Table 1), but there was no significant decrement immediately post-exercise (from -92 ± 23 to -94 ± 21 mmHg; p = 0.548). There was no relationship between MIP and exercise dyspnea. Exercise-induced changes in MIP was also not related to exercise dyspnea (p > 0.05).

The distribution according to the specific PAH etiology was 8 (40%) idiopathic patients, 8 (40%) HIV, 2 (10%) congenital heart disease, 1 (5%) porto-pulmonary, and 1 (5%) secondary to systemic sclerosis. PAH-specific pharmacotherapy and baseline pulmonary hemodynamics by right heart catheterization are described in Table 1.

3.2. Peak exercise responses

As expected, patients presented a mixed pattern of oxygen delivery/utilization plus pulmonary gas exchange impairment response to exercise (Neder et al., 2018) (Table 2). Of note, 10/20 patients presented DH (IC reduction > 150 ml) during exercise while just one in controls. The proportion of patients stopping due to dyspnea ≥ leg effort was higher in the PAH group (12/20 (60%) vs 3/10 (30%); p = 0.121).

3.3. Dynamic responses to exercise

Dyspnea intensity was significantly higher in patients for a given work rate (Fig. 1-Panel A). Despite a consistent higher submaximal V_E and V_E/VCO_2 in PAH (Fig. 1-Panels B–C), dyspnea persisted more intense in patients even when expressed as function of V_E (Fig. 1-Panel D). An exercise-induced reduction in IC, starting from a tendency to lower values at rest (Fig. 2-Panel A), predisposed patients to achieve earlier and at lower workloads a critical IRV (Fig. 2-Panel B). Consequently, higher V_T/IC relationships (Fig. 2-Panel C), a more tachypneic breathing pattern (Fig. 2-Panel D), and higher indices of inspiratory effort (Fig. 2-Panels E–F) were observed in patients during exercise. When IRV reaches critical values (around 1 l in the present sample), a noticeable inflection response is observed in inspiratory effort (adjusted to V_T expansion) and dyspnea perception in both groups (Fig. 3).

When comparing only PAH patients according to the presence or absence of dynamic IC reduction (Fig. 4-Panel A), both hyperinflators and nonhyperinflator presented similar levels of ventilation, tidal volume expansion and dyspnea perception throughout exercise (Fig. 4-Panels B–D). Both groups also presented a similar V_T increment even when expressed as function of V_E (Fig. 4-Panel E). Moreover, a sudden rise in dyspnea perception was observed in PAH groups at a similar point where V_T increment tended to a plateau, which was lower compared to controls (Fig. 4-Panel F). Finally, no significant deference was observed between these groups in resting lung function parameters (% of predicted) or pulmonary haemodynamics (Table 3).

4. Discussion

The present study substantiates the role of abnormal "qualitative" ventilatory responses (abnormal respiratory mechanics) in addition to the expected abnormal "quantitative" ventilatory responses (excessive exercise ventilation: ↑ V_E/VCO_2 relationship) contributing to higher exercise dyspnea perception in PAH subjects. The main finding of the present study lies in the observation that the achievement of a critical IRV during exercise is a key physiological mechanism leading to an abrupt rise in the inspiratory effort and dyspnea perception in these patients. The observed decline in IC and IRV during exercise in patients with PAH happens independently of dynamic inspiratory strength decrement during IC maneuvers (Laveneziana et al., 2015), confirming the reliability of this approach to assess exercise respiratory mechanics in this population.

Albeit our patients presented resting pulmonary function within the normal range (Table 1), FEV_1, FVC, FEV_1/FVC, and mid-expiratory flows were lower compared to controls, corroborating previous findings of mild ventilatory defects (Meyer et al., 2002; Sun et al., 2003). Right ventricle hypertrophy and main pulmonary arteries dilation, associated with loss of compliance of the smaller arteries, may be important factors causing lung restriction (Sun et al., 2003). Signs of obstructive pattern may be noted as a function of the intimate contact of the airway with the pulmonary vasculature, by either direct compression or a mediator (Meyer et al., 2002). It is known, for example, that endothelin-1 has the potential to cause bronchospasm and mucous secretion (Martin et al., 2000). Regardless of the precise cause(s), starting exercise from lower IC (Fig. 2-Panel A) in the presence of relatively mild airflow obstruction (↓FEV_1/FVC; ↓mid-expiratory flow) may explain the impaired exercise ventilatory mechanics observed.

In PAH group, V_E was higher at any given submaximal exercise intensity (Fig. 1-Panel B) and obvious ventilatory inefficiency was noted (Fig. 1-Panel C). These findings are in accordance with published literature (O'Donnell et al., 2017) reflecting the increased dead space (V_D/V_T) ventilation due to the reduced perfusion of well-ventilated alveoli (V/Q mismatch), a rapid shallow breathing pattern (Fig. 2-Panel D), and enhanced chemostimulation (Weatherald et al., 2017). Excessive V_E for a given work rate represents an important cause for

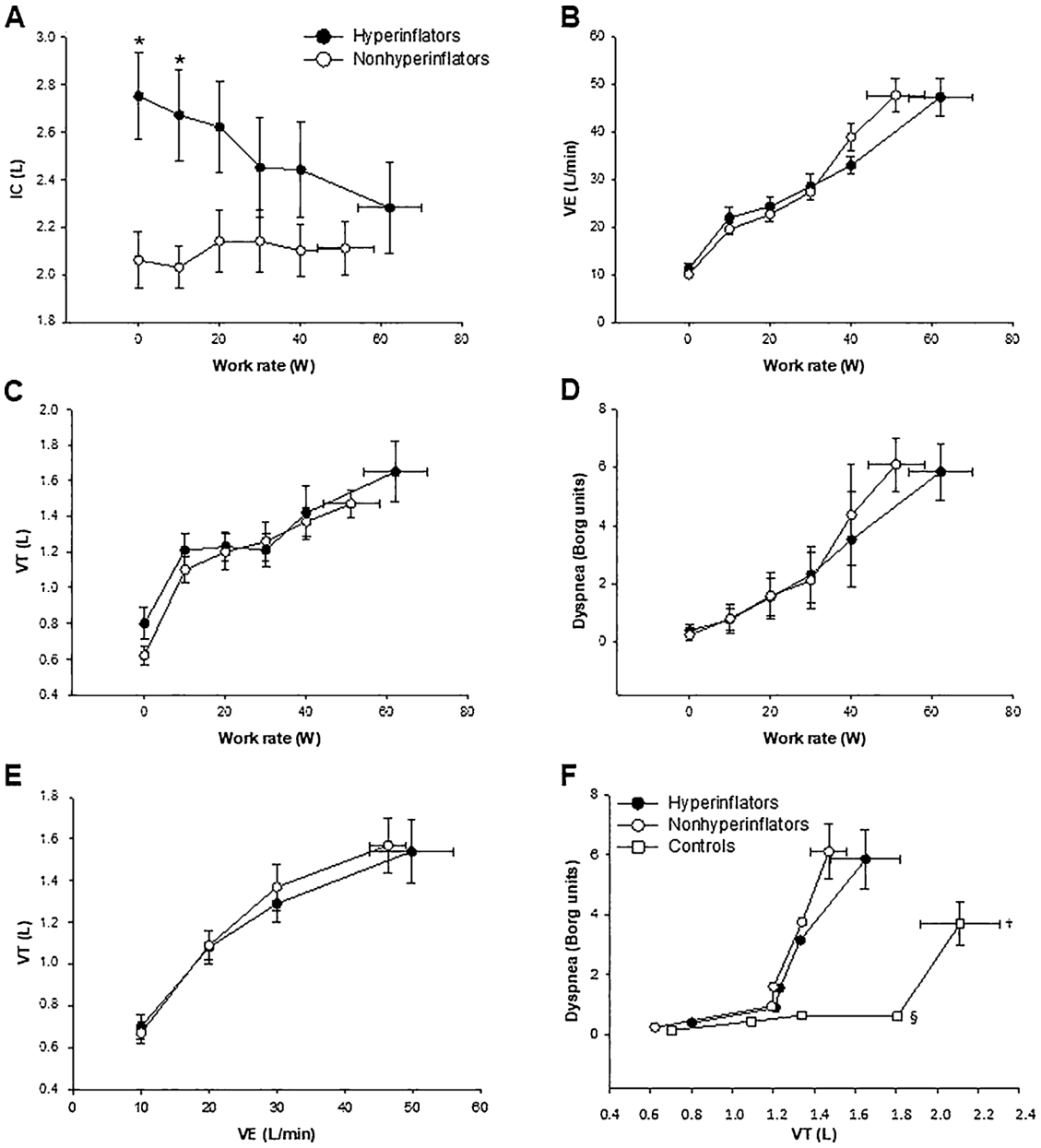

Fig. 4. Inspiratory capacity (IC) (A), minute-ventilation (B), tidal volume (V_T) (C) and dyspnea perception (D) in response to increasing work rate contrasting PAH patients with (hyperinflators) and without (nonhyperinflators) exercise-induced IC reduction. Panel E expresses V_T increment as a function of minute-ventilation and Panel F the evolution of dyspnea versus V_T expansion. Observe a clear inflection point in dyspnea perception after a plateau in V_T increment, which happens at significantly lower values in patients.
Data are presented as mean ± SE values.
*$p < 0.05$ at isowork.
† $p < 0.05$ between nonhyperinflators and controls (at peak)
§ $p < 0.05$ between both PAH groups and controls (at inflection point).

increased dyspnea *per se*. It potentially explains the less marked inflection in dyspnea perception as work rate progresses compared to controls (Fig. 1- Panel A). The higher dyspnea even adjusted for a same level of V_E (Fig. 1-Panel D) reinforces the presence of additional mechanism(s) underlying the increased exercise dyspnea complaint of these patients, especially after 40 W (˜30 l) when critical inspiratory constraint ensues.

Previous works linked increased dyspnea perception with the presence of DH in a substantial proportion of PAH patients (˜50–60%) (Laveneziana et al., 2013; Richter et al., 2013; Laveneziana et al., 2015). Data from COPD population (Guenette et al., 2012; O'Donnell et al., 2012) taught us that resting IC is as or more important than DH to explain exercise dyspnea due to altered respiratory mechanics. Actually, critical dynamic constraint to V_T expansion as indicated by premature encroachment of EILV on TLC, i.e. the attainment of a critically reduced IRV, seems to represent a paramount mechanism of exercise dyspnea. When V_T during exercise reaches approximately 75% of the prevailing IC (or IRV reaches 5–10% of the TLC or < 0.5-1 l), there is a plateau in the V_T/minute-ventilation relationship, which marks the onset of a rising disparity between increasing central neural drive and the mechanical constraint of the respiratory system, where dyspnea rises steeply to intolerable levels (Guenette et al., 2013; Langer et al., 2014). Interestingly, it seems that, regardless of the underlying pathophysiology, exercise dyspnea fundamentally reflects an imbalance

Table 3
Characteristics of PAH participants according to the presence of dynamic hyperinflation during exercise.

	Nonhyperinflators (n = 10)	Hyperinflators (n = 10)
Gender, M/F	0/10	3/7
Age, yrs	38.5 ± 15.1	36.5 ± 8.9
BMI, kg/m^2	23.0 ± 4.46	25.7 ± 4.6
Pulmonary Function		
FEV_1, l (% pred)	2.38 (1.63 – 3.02) (87 ± 13)	2.49 (2.12 – 3.84) (83 ± 5)
FVC, l (% pred)	3.02 ± 0.56 (92 ± 13)	3.55 ± 0.87 (92 ± 5)
FEV_1/FVC, %	79 ± 5	75 ± 4
$FEF_{25-75\%}$, l/s (% pred)	2.28 ± 0.68 (79 ± 23)	2.18 ± 0.61 (65 ± 18)
TLC, l (% pred)	4.83 ± 0.79 (105 ± 11)	5.58 ± 1.07 (105 ± 10)
FRC,l (% pred)	2.68 ± 0.60 (104 ± 18)	2.73 ± 0.62 (99 ± 16)
RV, l (% pred)	1.75 ± 0.30 (124 ± 21)	1.89 ± 0.47 (127 ± 30)
RV/TLC, (%)	36 ± 3	34 ± 6
DL_{CO}, % pred	58 ± 18	68 ± 15
MIP, cmH_20 (% pred)	80 ± 18 (88 ± 21)	104 ± 22* (102 ± 17)
MEP, cmH_20 (% pred)	93 ± 15 (105 ± 18)	118 ± 39 (110 ± 19)
Pulmonary Haemodynamics		
PASP, mmHg	76.7 ± 33.0	81.4 ± 25.7
PADP, mmHg	33.6 ± 17.7	37.0 ± 11.4
MPAP, mmHg	49.3 ± 22.2	51.9 ± 14.1
PAOP, mmHg	7.3 ± 2.5	8.4 ± 2.1
CO, l/min	4.7 ± 1.6	5.3 ± 1.5
CI, l/min/m^2	3.1 ± 1.1	3.1 ± 0.7
PVR, dyn·s·cm^{-5}	812 ± 463	684.3 ± 224
PVR, Wood units	10.2 ± 5.8	8.5 ± 2.8
RAP, mmHg	10.0 ± 6.6	4.9 ± 3.1

Values are presented as mean ± SD or median (range).
Definition of abbreviations: BMI = body mass index; CI = cardiac index; CO = cardiac output; DL_{CO} = diffusing capacity for carbon monoxide; $FEF_{25-75\%}$ = forced expiratory flow between 25 and 75 percent of FVC; FEV_1 = forced expired volume in first second; FRC = functional residual capacity; FVC = forced vital capacity; IC = inspiratory capacity; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure; MPAP = mean pulmonary artery pressure; PADP = pulmonary artery diastolic pressure; PAH = pulmonary arterial hypertension; PAOP = pulmonary artery occlusion pressure; PASP = pulmonary artery systolic pressure; % pred = percent of predicted; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = reserve volume; TLC = total lung capacity.
* $P < 0.05$.

between the increased demand to breathe and the inability to meet that demand (Faisal et al., 2016). Albeit previous works (Laveneziana et al., 2013; Richter et al., 2013; Laveneziana et al., 2015) investigating exercise respiratory mechanics in PAH indeed showed DH influencing exercise dyspnea, the present study advances the knowledge specifically demonstrating that the above-mentioned common mechanism of exercise dyspnea (Faisal et al., 2016) also seems valid for patients with PAH. At the work rate where IRV reached approximately 1 l (Fig. 2-Panel B), V_T attained a high proportion of the prevailing IC (Fig. 2-Panel C) and there was an abrupt rise in the inspiratory effort adjusted for the V_T expansion (neuromechanical dissociation) (Fig. 2-Panel F). Accordingly, dyspnea starts to rise steeply to intense levels at this work load (Fig. 1-Panel A). This critical IRV seems to be a little higher (~1 l) in historic comparison with other chronic lung diseases (COPD and fibrosing interstitial lung disease; ILD) (~0.50–0.75 l) and similar to healthy controls (Faisal et al., 2016). Abnormal resting pulmonary function (mechanics) seems to be the clear difference between these groups (COPD&ILD *vs* PAH&controls) that may explain this finding, which deserves to be confirmed and potential mechanisms further explored in future studies.

As mentioned above, we speculate that lower IC and mid-expiratory flows predispose PAH patients to abnormal ventilatory mechanics during exercise. IC measurements provide an estimate of the inspiratory reserve volume available for exercise, delaying a critical limitation in tidal volume expansion. However, the presence of DH was not associated with increased exertional dyspnea ratings in PAH (Fig. 4-Panel D). In fact, a lower IC at rest or a significant reduction in IC during exercise (Fig. 4-Panel A) can, in isolation or in combination, predispose to earlier critical IRV with premature neuromechanical dissociation (Guenette et al., 2012). Accordingly, similar breathing pattern (Fig. 4-Panels B–C) and a sudden rise in dyspnea perception after a critical constraint to V_T expansion was observed in PAH regardless of the presence of DH (Fig. 4-Panels F).

The present study has some methodological limitations, particularly the heterogeneous etiology of PAH, the small sample size and the use of P0.1 as a surrogate for respiratory neural drive estimation. The first two limitations are inherent of the low frequency of the disease in the general population plus the relative complexity of the physiological evaluations performed. These limitations could be worsened when the sample was further reduced by splitting the PAH group according to the presence or absence of dynamic hyperinflation: the small size of this convenience sample may preclude the detection of some subtle differences to explain this behavior. Future studies concomitantly measuring esophageal pressure and diaphragm electromyography during exercise would be ideal to confirm our findings and interpretation in respect to the inspiratory neural drive and neuromechanical dissociation. Finally, interventional studies (enhancing negative hydric balance, pulmonary vasodilation and/or bronchodilation) linking improved respiratory mechanics with better clinical outcomes are required for translational application of the current findings.

Concluding, on the top of excessive exercise ventilation, typical of patients with abnormal O_2 delivery/utilization, earlier achievement of a critical IRV during exercise leads to neuromechanical dissociation with an inflection rise in dyspnea perception toward intolerable levels. Inspiratory muscle weakness or reduction in MIP was not related to exercise dyspnea.

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Conflict of interest

The authors report no relationships that could be interpreted as a conflict of interest.

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