Intensity and quality of exertional dyspnoea in patients with stable pulmonary hypertension

ON-LINE SUPPLEMENT

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MATERIALS AND METHODS

Indices of Ventilatory Constraint

Operating lung volumes derived from IC maneuvers (end expiratory lung volume “EELV”) were measured at rest, every second minute during exercise and at end-exercise based on the assumption that TLC did not change significantly during the exercise, as previously demonstrated (1). IC was used to track any decrease or increase in EELV [expressed as absolute value] during exercise, as previously described (2-4). Dynamic hyperinflation during exercise was defined as a decrease in IC from rest of more than 150 mL at any time-point during exercise (4). This because it has previously been demonstrated that the 95% confidence interval for the resting IC measurement was ±0.14L in patients with COPD, indicating that reproducibility criteria of within 150 mL are appropriate for testing IC in COPD. Importantly, the 95% confidence interval for peak exercise IC was similar. Based on this definition/criterion PH patients were divided into two groups based on the presence or absence of dynamic hyperinflation: hyperinflators (H, n=17) and non-hyperinflators (NH, n=9), respectively. The erosion of inspiratory reserve volume (IRV) and the ratio of V_T to IC [V_T/IC(%)] were both taken as indices of the mechanical constraint on V_T expansion (2-4). The inflection point of the V_T and V'_E relationship was determined by two different observers (PL, AB) for each subject during CPET by examining individual Hey plots (5): if more than one inflection point was evident, the first was chosen. Tidal flow-volume curves at rest, every 2 minutes during exercise and at peak exercise were constructed for each patient and placed within their respective maximal flow-volume envelopes according to coinciding IC measurements. Maximal flow-volume loops were performed only at rest for this analysis. The presence or absence of flow limitation was then determined by comparing tidal expiratory flows with those of the maximal envelope at isovolume: we looked at the shape and limits of the maximal flow-volume curve in the tidal operating range ($FEF_{50\%}$ and $FEF_{75\%}$), as well as the extent of expiratory flow limitation by evaluating the percentage of V_T that encroached on the maximal flow-volume envelope (15).

Right heart catheterization (RHC)

Right heart catheterization (RHC) with hemodynamic evaluation was performed in the supine position. RHC was performed using the modified Seldinger technique with an 8F sheath inserted in the jugular, basilic or cephalic vein (6). The Swan-Ganz catheter was a 7F, two-lumen, fluid filled and pressure-measuring tipped catheter (Corodyn TD; Braun Medical, Bethlehem, PA, USA). The zero-level reference was determined at mid-thoracic line (6). Patients underwent also exercise hemodynamic evaluation with lower limb cycle ergometry (6). The detailed exercise protocol has been reported previously (7).

Exertional Symptoms Evaluation

Patients rated the intensity of "breathing discomfort" (dyspnoea) at rest, every minute throughout CPET exercise, and at peak CPET exercise using the Borg 0-10 category-ratio scale (3). The Borg 0-10 category-ratio scale was also used for assessing the intensity of "breathing discomfort" (dyspnoea) during the 6MWT (rest and peak) and during the hemodynamic cycle ergometry exercise (rest and peak). During CPET, 6MWT and exercise RHC evaluation with lower limb cycle ergometry, patients were also asked to select the phrase that best described their breathing at the exact moment of the Borg scale evaluation from a previously-described list of three items (2): "My breathing requires more work and effort" (work/effort); "I cannot get enough air in" (unsatisfied inspiration); "My chest feels tight" (chest tightness). Patients were allowed to select multiple phrases if equally applicable. The former two descriptors were collected for primary analyses, while the latter was used as a control symptom that was not expected to be selected very often. We have previously used these descriptors in COPD (2) and asthma patients (8, 9) and ensured that these words exactly described the same perception in both languages (i.e., English and French). Nonetheless, many patients were unable to retrospectively select or understand other descriptive phrases from the proposed questionnaire. This is in line with the limitations of the language of dyspnea (10-12). It cannot be assumed that all individuals share a common understanding of the same descriptors; differences in language, race, culture, and the manner in which concepts or symptoms are held can influence a subject's perception of dyspnoea (10-12). Immediately after each type of exercise (CPET, 6MWT and hemodynamic cycle ergometry exercise), subjects completed the Multidimensional Dyspnea Profile (MDP) focusing on the last 30 s of each type of exercise (13).

MDP data were used to describe the nature of discomfort produced by the stimulus and to determine whether that description changed with exercise modality (13, 14).

The MDP consists of eleven items. One item (A1) assesses the unpleasantness of dyspnoea on a 0-10 visual numerical scale anchored by "neutral" and "unbearable". Five items assess the sensory dimension of dyspnoea (choice of one of several descriptors, 0-10 ordinal rating for each of them). Five items assess the affective dimension of dyspnoea (choice of one of several feelings among anxiety, fear, frustration, depression, anger; 0-10 ordinal rating for each of them). Patients are asked to focus on a period of interest defined by the investigator, in this case the last 30 seconds of the exercise performed. Two domain scores are calculated: "immediate perception" (S) as the sum of A1 intensity and the intensities of the 5 sensory descriptors; "emotional response" (A2) as the sum of the 5 emotional descriptors.

Statistical analysis

Data were expressed as means ±SD for normally distributed variables or medians [25-75 interquartile range] for non-normally distributed variables (Kolmogorov-Smirnov test). For variables with normal distribution, a t-test was used. For non-normally distributed variables, a non-parametric test (Mann-Whitney Rank Test) was used. The threshold for statistical significance was considered to be $p<0.05$.

RESULTS

Seventeen patients were diagnosed with PAH and 9 with CTEPH (Table E1). Ten patients were in New York Heart Association (NYHA) functional class I, nine in functional class II and seven in functional class III. Fourteen patients were already being treated with at least one PAH-targeted medication, two with calcium antagonists, and ten (including 9 newly diagnosed patients) did not receive any treatment. Of note, these latter 10 patients included 9 incident cases of CTEPH and one patient with PAH with ACRVL1 mutation. After the present study, 3 incident CTEPH have undergone thromboendarterectomy and 2 incident CTEPH balloon pulmonary angioplasty. The 4 remaining incident CTEPH patients have been initiated with oral Riociguat. The only patient with PAH presenting with ACRVL1 mutation had very high cardiac output (cardiac index 5 L/min/m2), moderately elevated PVR (4 WU) and was mildly symptomatic (functional class II, with a 6MWD of 490 m). That's why no treatment was started in this patient. Five years after diagnosis, this patient was still untreated, and was in the same clinical and haemodynamic conditions. Of note, among these 10 patients who did not receive any treatment (incl. 9 incident CTEPH patients), 4 were non-hyperinflators and 6 were hyperinflators. This proportion is similar in patients who received a treatment at the time of the study was performed (5 non hyperinflators and 11 hyperinflators; Pearson's Chi-square test with Yates' continuity correction: $p=0.97$). It is therefore unlikely that the inclusion of those patients in the analysis has created a relevant bias.

Physiological group responses to CPET

The physiological and perceptual responses to CPET in PAH and CTEPH are summarized in Table 2 of the main manuscript. Compared with PAH subjects, V'_E was significantly increased at any submaximal WR in all CTEPH patients. V_D/V_T was also greater in CTEPH compared with PAH, both at rest and peak exertion (Table 2 of the manuscript). When compared with PAH subjects, dyspnoea intensity was higher in the CTEPH group at any given WR because of the concomitant higher V'_E. IC decreased in both PAH and CTEPH subjects throughout exercise: on average, rest-to-peak IC change was of 0.21±0.23L in PAH patients and of 0.27±0.27L in CTEPH subjects ($p=0.32$).

Identification of two subgroups of PH patients

Based on rest-to-peak changes in IC, 17 patients (65%: 11 PAH and 6 CTEPH) exhibited DH during exercise (hyperinflator group, IC= -0.36L), whereas the remaining 9 patients (35%: 6 PAH and 3 CTEPH) did not (non-hyperinflator group, IC= +0.01L).

All metabolic and cardio-ventilatory measurements obtained at rest were similar in both groups, as were the patterns of $V'O_2$, V'_E and breathing pattern responses to exercise (iso-WR 1, iso-WR 2 and peak included) except for a greater IC at peak exercise in non-hyperinflators compared with hyperinflators (2.6±0.6L vs 2.0±0.4, p=0.011) and IC, IRV and dyspnoea measurements at the V_T inflection point: IC and IRV were higher and dyspnoea intensity (Borg score) was lower in non-hyperinflators compared with hyperinflators at the V_T inflection point (2.6L and 0.8L and 3.3 a.u. vs 2.1L and 0.5L and 4.4 a.u. respectively, p<0.05) (Figure 1A and 1B in the main manuscript).

To evaluate the contribution of DH to dyspnoea intensity, the dyspnoea/WR and dyspnoea/V'_E slopes were assessed: though the dyspnoea/WR slopes were similar (Figure 1 in the main manuscript), the dyspnoea/V'_E slopes were steeper in hyperinflators than in non-hyperinflators (Figure 1 in the main manuscript). The greater dyspnoea/V'_E steepness seen in hyperinflators was explained by the greater DH (lower IC) observed at iso-V'_E in hyperinflators compared with non-hyperinflators (2.2L vs 2.5L respectively, p=0.042) which explained why dyspnoea intensity was significantly greater (p=0.043) at iso-V'_E in hyperinflators (3.7 Borg units) than in non-hyperinflators (2.3 Borg units) (Figure 1 in the main manuscript).

A RHC at rest and on exercise has been performed within 24 hours of CPET. Cardiac output has been measured at rest and on exercise by thermodilution during RHC. Thus, we were able to draw the mPAP/CO relationship in all patients, then we applied the Poon's correction. There was a difference between hyperinflators and non hyperinflators in term of mPAP/CO slopes (p<0.001 by ANCOVA). Interestingly, non-hyperinflators had a steeper mPAP/CO slope, what it means that non-hyperinflators had a more pronounced increase in mPAP in response to the increase in CO during exercise. In addition, when we analysed the VE/VCO_2 slopes in the two groups (Poon's correction applied), we found that they were different, non-hyperinflators having a steeper slope than hyperinflators (p<0.001, by ANCOVA).

V_T inflection point and dyspnoea descriptors

Regardless of the type of exercise performed (CPET or 6MWT or RHC), the evolution of dyspnoea descriptors profile was identical during the three different types of exercise (Figure E1).

When exploring the reasons for differences in IRV behaviour between hyperinflators and non-hyperinflators at the V_T inflection, we found that V_T and consequently IRV were critically constrained because of a significant decrease in IC (i.e. dynamic lung hyperinflation) only and exclusively in hyperinflators compared with non-hyperinflators (Figure 1 in the main manuscript).

No significant differences in ventilatory and perceptual responses to cycle exercise were observed between hyperinflators and non-hyperinflators at peak exercise (Table 3 in the main manuscript).

The anthropometric characteristics of the two groups were similar in hyperinflators and non-hyperinflators for, respectively, height (167±9 *vs* 167±11 cm, p=0.88), weight (70kg (IQR:62-80) *vs* 69kg (IQR:60-82), p=0.78) and body mass index (BMI, 24.6 kg/m^2 (IQR: 21.3-26.6) *vs* 24.2 kg/m^2 (IQR: 24.0-28.1), p=0.82)and age (47±16 years *vs* 45±18 years, p=0.85).

The two groups were also similar in terms of pulmonary function tests, functional class, six-minute walk distance and haemodynamics. Comparisons of resting IC, FRC, TLC and VC between the two groups were practically identical.

MDP

Although dyspnoea intensity did not differ between hyperinflators and non-hyperinflators at the peak of CPET, 6MWT and RHC (Table 3 in the main manuscript), the dyspnoea/V'_E slopes were steeper in hyperinflators than in non-hyperinflators (Figure 1 in the main manuscript) during CPET (data on V'_E were not obtained during 6MWT or RHC), and dyspnoea intensity was significantly greater ($p<0.05$) at iso-V'_E in hyperinflators (3.7 Borg units) than non-hyperinflators (2.3 Borg units) when adjusted for the same V'_E measured during CPET.

This was also in line with the results from the MDP concerning unpleasantness or discomfort (A1 scale) immediately after CPET (Table 3 in the main manuscript): hyperinflators rated unpleasantness or discomfort higher (8 [7-9]) than non-hyperinflators (5 [0-8]) (p=0.037); among sensory dimension items (Table 3 in the main manuscript), "not enough air, smothering or hunger for air", applied in 65% of hyperinflators responses compared with 11% of non-hyperinflators responses (p=0.025). In the affective domain, the emotion most frequently associated with "not enough air, smothering or hunger for air" was anxiety (4.4 arbitrary units) in hyperinflators compared with non-hyperinflators (2 arbitrary units) during CPET (p=0.025), with no statistical difference between patients with or without hyperinflation in conditions such as 6MWT and RHC. The same pattern of response in terms of sensory and affective dimension/domain was found when MDP was performed immediately after 6MWT and RHC (Table 3 in the main manuscript).

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Table E1: Comparisons of patient characteristics, resting hemodynamic and pulmonary function between PAH and CTEPH patients

	PAH	**CTEPH**	p
Sex Female/Male	11/6	5/4	0.65
Age, *years*	39 ± 11	58 ± 18	0.003
BMI, *kg/m²*	24 ± 4	26 ± 3	0.40
Hyperinflator/non hyperinflator	11/6	6/3	-----
NYHA I/II/III/IV	9/5/3/0	1/4/4/0	0.06
6-MWD, *m*	549 ± 90	446 ± 89	0.01
Haemodynamic			
Right atrial pressure, mmHg	7 ± 3	8 ± 2	0.17
Mean pulmonary artery pressure, mmHg	49 ± 15	48 ± 15	0.87
Pulmonary artery wedge pressure, mmHg	10 ± 3	9 ± 3	0.31
Cardiac output, L/min	6.3 ±1.8	4.9 ± 1.2	0.04
Cardiac index, $L/min/m^2$	3.5 ± 0.8	2.6 ± 0.5	0.004
Pulmonary vascular resistance, Wood units	6 ± 2	9 ± 4	0.97
Mixed venous oxygen saturation, %	70 ± 5	63 ± 10	0.11
Lung function test			
FEV1/VC	82 ± 11	82 ± 6	0.86
FEV1, *% predicted*	92 ± 15	102 ± 23	0.20
TLC, *% predicted*	95 ± 15	93 ± 18	0.75
DLCO, *% predicted*	65 ± 16	66 ± 13	0.84

Results are presented as mean ± SD. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; CTEPH: chronic thrombo-embolic pulmonary hypertension; 6-MWD: six-minute walk distance; FEV_1: forced expiratory volume in one second; VC: vital capacity; TLC: total lung capacity; DLCO: diffusing capacity of the lung for carbon monoxide.

FIGURE LEGENDS

Figure E1: Selection frequency of the three descriptor phrases evaluated during six-minute walking test (6MWT, upper panel) and cycle-ergometry exercise right heart catheterisation (RHC, lower panel) in patients with pulmonary hypertension as whole group (n=26): increased work and effort, unsatisfied inspiration, and chest tightness. Upper panel: data are presented as mean at rest, 2, 4 and 6 minutes of 6MWT; Lower panel: data are presented as mean at rest, at 20W, at 40 W and at peak exercise RHC.

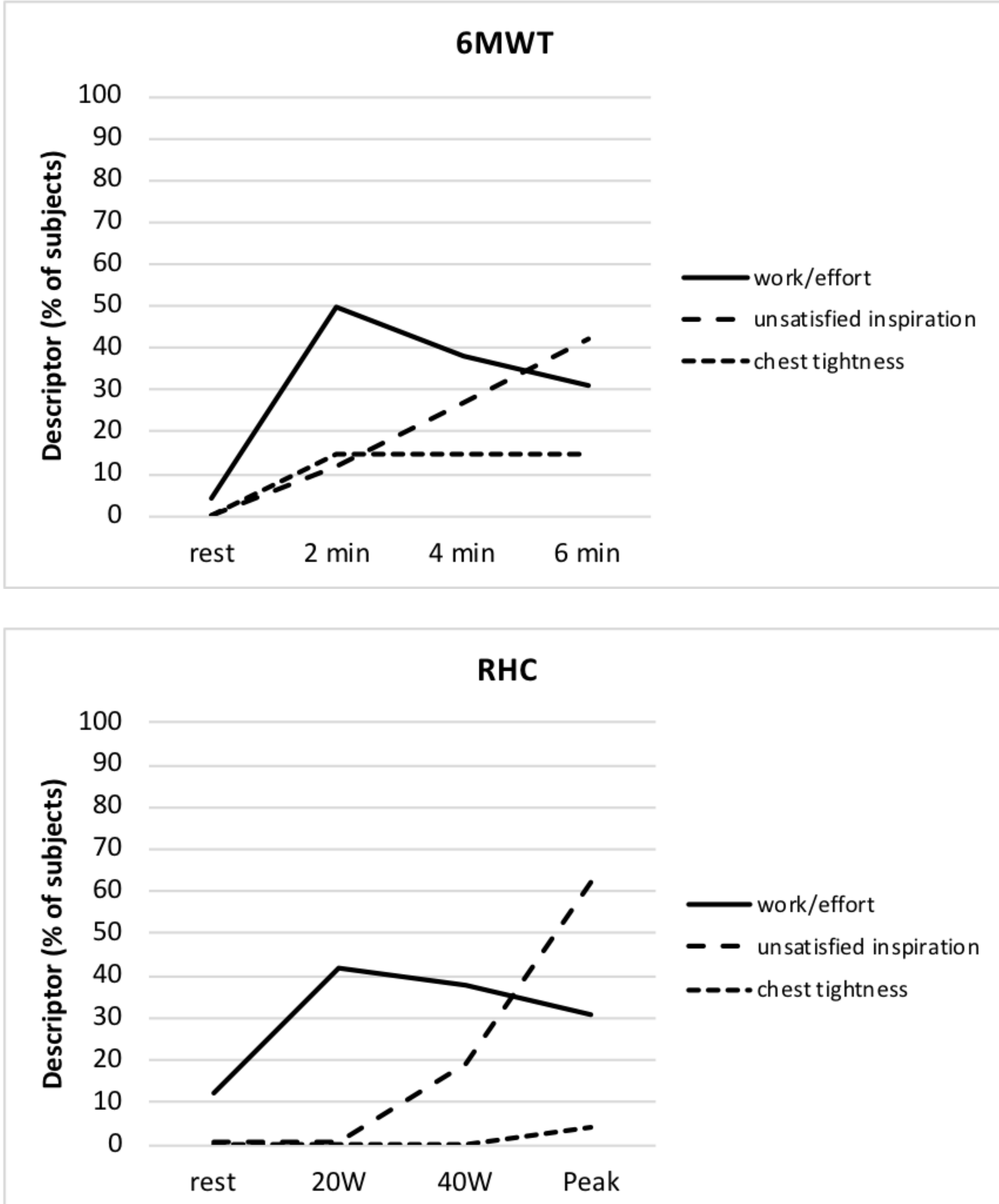
6MWT
Descriptor (% of subjects)
100
90
80
70
60
50
40
30
20
10
0
rest
2 min
4 min
6 min
work/effort
unsatisfied inspiration
chest tightness
RHC
Descriptor (% of subjects)
100
90
80
70
60
50
40
30
20
10
0
rest
20W
40W
Peak
work/effort
unsatisfied inspiration
chest tightness

Figure E1