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Athénaïs Boucly, Capucine Morélot-Panzini, Gilles Garcia, Jason Weatherald, Xavier Jaïs, Laurent Savale, David Montani, Marc Humbert, Thomas Similowski, Olivier Sitbon, Pierantonio Laveneziana

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

Authors:

Athénaïs Boucly[1,2,3], Capucine Morélot-Panzini[4,5], Gilles Garcia[1,3,6], Jason Weatherald[7,8], Xavier Jaïs[1,2,3], Laurent Savale[1,2,3], David Montani[1,2,3], Marc Humbert[1,2,3], Thomas Similowski[4,5], Olivier Sitbon[1,2,3#], Pierantonio Laveneziana[4,9#]

Affiliations:

[1]Univ. Paris-Sud, Faculté de Médecine, Université Paris-Saclay, Le Kremlin-Bicêtre, France; [2]AP-HP, Hôpital Bicêtre, Service de Pneumologie et Soins Intensifs, Le Kremlin-Bicêtre, France; [3]INSERM UMR_S_999, Hôpital Marie Lannelongue, Le Plessis Robinson, France; [4]Sorbonne Université, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, Paris, France; [5]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation, Département R3S, Paris, France; [6]APHP, Hôpital Bicêtre, Service de Physiologie, Le Kremlin-Bicêtre, France; [7]University of Calgary, Department of Medicine, Division of Respirology, Calgary, Alberta, Canada ; [8]Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta ; [9]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service des Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée du Département R3S, F-75013 Paris, France.

Correspondence to: Dr. Pierantonio Laveneziana, Service d'Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée, Département "R3S" (Respiration, Réanimation, Réhabilitation, Sommeil), Pôle PRAGUES, Hôpital Universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), 47-83 Boulevard de l'Hôpital, 75013, Paris, France; Tel: 00 33 (0) 1 42 17 85 84; Fax: 00 33 (0) 1 42 17 85 76; email: pierantonio.laveneziana@aphp.fr

[#]Olivier Sitbon and Pierantonio Laveneziana have equally contributed and are both last authors.

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ABSTRACT

Dynamic hyperinflation is observed during exercise in 60% of patients with clinically stable pulmonary arterial hypertension (PAH) and chronic thrombo-embolic pulmonary hypertension (CTEPH), intensifying exertional dyspnoea.

The impact of dynamic changes in respiratory mechanics during exercise on qualitative dimensions of dyspnoea in these patients has not been evaluated.

Twenty-six patients (PAH n =17; CTEPH n =9) performed an incremental symptom-limited cycle exercise test. Ventilation (V'_E), breathing pattern, operating lung volumes, and dyspnoea intensity were assessed throughout exercise. Dyspnoea quality was serially assessed during exercise using a 3-item questionnaire (dyspnoea descriptors). The inflection point of tidal volume (V_T) relative to V'_E was determined for each incremental test. Changes in inspiratory capacity (IC) during exercise defined two groups of patients: hyperinflators (65%) and non-hyperinflators (35%), respectively. Multidimensional characterisation of dyspnoea was performed after exercise using the Multidimensional Dyspnea Profile (MDP).

In hyperinflators, IC decreased progressively throughout exercise by 0.36L, while remaining stable in non-hyperinflators. The "work/effort" descriptor was most frequently selected throughout exercise in both types of patients (65% of all responses). At the V_T/V'_E inflection, "work/effort" plateaued while "unsatisfied inspiration" descriptors became selected predominantly only in hyperinflators (77% of all responses). In the affective domain, the emotion most frequently associated with dyspnoea was anxiety.

In PH patients who develop hyperinflation during exercise, dyspnoea descriptors referring to unsatisfied inspiration become predominant following the V_T/V'_E inflection. As these descriptors are generally associated with more negative emotional experiences, delaying or preventing the V_T/V'_E inflection may have important implications for symptom management in PH patients.

Keywords: pulmonary hypertension; dyspnoea; dynamic lung hyperinflation; exercise; qualitative descriptors of dyspnoea.

INTRODUCTION

Exertional dyspnoea is the commonest presenting complaint in patients with idiopathic pulmonary arterial hypertension (PAH) and chronic thrombo-embolic pulmonary hypertension (CTEPH) (1-3). Despite considerable research, its origins and underlying mechanisms have not been fully elucidated (1, 3). The symptom progresses inexorably as the disease advances, impoverishing quality of life (1-3). Previous studies have largely focused on the cardiovascular determinants of exertional dyspnoea (4-6). However, mechanical anomalies of respiration, such as dynamic lung hyperinflation (DH), have recently been shown to occur in some PAH and CTEPH patients during exercise (7-9) and are likely to aggravate exertional dyspnoea in these patients (8, 9).

In terms of lung volumes, patients with stable pulmonary hypertension (PH) may either deflate (decrease their end-expiratory lung volume, EELV) or progressively hyperinflate (increase their EELV) during exercise (7-9). This may also occur in patients with asthma (10) and COPD (11, 12). The nature of these exercise-related changes in lung volumes is associated with the terms that patient uses to describe their dyspnoea. Patients who deflate predominantly describe their dyspnoea as increased “work/effort” of breathing at the limit of tolerance during exercise. In those who hyperinflate, both increased “work/effort” of breathing and "unsatisfied inspiration" are reported at the limit of tolerance during exercise (8, 10). It has previously been postulated that the increased intensity of “work/effort” may reflect the conscious appreciation of increased central neural command output (and the concurrent inspiratory muscle contractile effort relative to maximum required) to keep pace with the increasing metabolic and ventilatory demands imposed by exercise (9, 10, 13-16). On the other hand, the growing mismatch between the increase in the central neural command to the ventilatory musculature and the blunted respiratory mechanical and/or muscular response caused by DH and/or critical mechanical constraints of tidal volume (V_T) expansion has been hypothesized to play a part in the neurophysiological basis of the sensation of "unsatisfied inspiration" (9, 10, 13).

It has been shown that during exercise in COPD (11, 16-18) , and more recently in asthma (10), an inflection in the V_T response occurs when inspiratory reserve volume (IRV) becomes critically reduced. This is not always the case in some sedentary (16) and asthmatic (10) subjects in whom this V_T inflection may occur on exertion when IRV is largely preserved. When this inflection in the V_T response is reached at a critical IRV, dyspnoea intensity rises more impressively and quasi-vertically, and "unsatisfied inspiration" becomes the prominent qualitative descriptor. This inflection can easily be detected in healthy sedentary subjects (16), in athletes (19), and in most COPD (11, 16-18) and asthma patients (10) by examining a) the contributions of V_T and respiratory frequency (fR) to the ventilatory response (V'_E) to exercise by plotting V_T as a function of V'_E (V_T/ V'_E relations), and b) analyzing the relationship between the nature of the dyspnoea and the IRV. The practical implication of

this is that the V_T inflection occurring at a critically reduced IRV marks a reproducible mechanical event with important sensory consequences during exercise (10, 11, 16). We hypothesized that the same mechanical and sensory phenomena would occur in PH patients exhibiting exercise-related hyperinflation, regardless of the etiology of their PAH or CTEPH. In contrast, PH patients who do not hyperinflate during exercise would not exhibit similar mechanical and sensory changes but would behave more like healthy subjects (16) or some asthmatics who do not hyperinflate on exertion (10).

Characterizing how patients describe their dyspnoea when they reach the limit of their exercise tolerance is clinically relevant because the different types of dyspnoea have different emotional implications (1, 3). For instance, in the experimental setting, the sensation of “unsatisfied inspiration” is much more unpleasant than the excessive “work/effort” sensation at a given sensory intensity (20). Therapeutic interventions that postpone the moment where PH patients shift from "work/effort" to "unsatisfied inspiration" could thus be of clinical interest.

MATERIALS AND METHODS

Study Design

We studied 26 non-smoking consecutive patients with clinically stable PAH (n=17) and incident CTEPH (n=9) (21), diagnosed according to currently available practice guidelines (22, 23), with a normal body mass index (BMI) and no evidence of obstructive ventilatory defect at resting spirometry (24). This sample size estimation was based on dyspnoea intensity ratings measured previously in our laboratory (8, 9)and the following assumptions: a SD of approximately 1.0 unit, a difference of approximately 1.5 units measured at a standardized work rate during incremental cardiopulmonary cycle exercise testing (CPET), a two-sided test, 80% power, and α=0.05.

Patients were included in the study irrespective of the treatment received, if they had been clinically stable during the 3 preceding months, and if they had been scheduled for CPET within the framework of the standard clinical follow-up at our centre. The study consisted of two consecutive visits. At visit 1, patients performed a six-minute walking test (6MWT) in the morning, and a right heart catheterization at rest, and during recumbent cycle exercise testing in the afternoon (25). At visit 2, patients performed pulmonary function tests followed by incremental cardiopulmonary cycle exercise testing (CPET) (8, 26).

Patients with other diseases than PH were excluded from the study; also subjects with dysfunctional breathing were excluded.

The research was carried out in accordance with the principles outlined in the Declaration of Helsinki. The subjects gave their informed consent to participate, and the study received the ethical committee approval of the Institutional Review Board of the National Centre for Pulmonary Hypertension

(*DYSPNEE HTAP-ID-RCB: 2015-A01826-43*).

Procedures

Pulmonary function tests were performed according to recommended standards (27-29). Measurements were expressed as percentages of predicted normal values (30). Procedures for conducting symptom-limited incremental CPET have been described previously (8, 26). Briefly, symptom-limited incremental CPETs were conducted on an electrically braked cycle ergometer (Ergoline 100P mitBD; Medisoft, Sorinnes, Belgium) with a cardiopulmonary exercise testing system (Ergocard model E, Medisoft, Sorinnes, Belgium). The equipment was calibrated before each test. To ensure safety, oxygen saturation (SpO_2), heart rate (HR), cardiac rhythm and ST-segment changes, and blood pressure (indirect sphygmomanometry) were evaluated at rest and throughout exercise testing. Breath-by-breath cardiopulmonary and metabolic data were collected at baseline and throughout exercise while subjects breathed through a mouthpiece with nasal passages occluded by a nose-clip. All exercise tests consisted of a steady-state resting period of 6 minutes and a 3-min warm-up of unloaded pedaling followed by an incremental test in which the work rate (WR) was increased in 1-minute intervals by increments of 10 watts until the point of symptom-limitation (peak exercise). Patients were instructed to maintain the pedalling rate between 50 and 70 revolutions per minute. Exercise variables were measured and averaged over the last 20 seconds of each minute and at peak exercise. Measurements of arterial partial pressure of CO_2 (PaCO2, Torr) were obtained at rest and at peak exercise only in PAH patients. The physiological dead space-totidal volume ratio (VD/VT) and the gradient between arterial and end-tidal carbon dioxide partial pressure [P(a-ET)CO2] were also calculated (8, 26). The intensity of dyspnoea and of leg discomfort were rated using the modified 10-point Borg scale (31) at rest, every minute during exercise and at peak exercise. Iso-WR and iso-V'_E were defined as the highest equivalent exercise WR and exercise V'_E achieved by all participants during all the tests.

Indices of Ventilatory Constraint

Operating lung volumes derived from IC manoeuvres, such as EELV, were measured at rest, at every second minute during exercise, and at the end of exercise, based on the assumption that TLC did not change significantly during the exercise, as previously demonstrated (8). IC was used to track any decrease or increase in EELV [expressed as an absolute value] during exercise, as previously described (11, 26). Dynamic Hyperinflation during exercise is now clearly defined as a decrease in IC from rest of more than 150 mL at any time-point during exercise (26). A critically low IRV was arbitrarily (although now universally accepted) defined as a reduction in the IRV to a minimum of approximately

0.5L (ranging from 0.4 to 0.6L), as described in COPD (11-13, 16-18). Indices of ventilatory constraint, the extent and the method of assessment of expiratory flow limitation and the inflection point of the V_T and V'_E relationship are described in detail in the on-line supplement.

Right heart catheterisation (RHC)

Right heart catheterisation (RHC) with hemodynamic evaluation was performed at rest and during cycle-ergometry exercise in the supine position as previously described (32). Details are available in the online supplement.

Evaluation of exercise-related symptoms

Patients rated the intensity of "breathing discomfort" (dyspnoea) at rest, every minute throughout CPET, and at peak CPET, using the Borg 0-10 category-ratio scale (31). 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 exercise RHC (rest and peak). At the moment of the Borg scale evaluation during CPET, 6MWT and exercise RHC, patients were also asked to select the phrase that best described their breathing from a list of three items (11): "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 all were equally applicable. The former two descriptors were collected for primary analysis, while the latter was used as a control symptom that was not expected to be selected very often. More details about the dyspnoea descriptors can be found in the on-line supplement. Immediately after each type of exercise (CPET, 6MWT and haemodynamic cycle ergometry exercise), subjects completed the Multidimensional Dyspnea Profile (MDP) focusing on the last 30 s of each type of exercise (33). MDP data were used to describe the nature of discomfort produced by the stimulus and to determine whether that description changed according to exercise modality (33, 34). More details on the MDP are available in the on-line supplement.

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. McNemar's exact test was used to assess the statistical significance of changes of selection frequency of dyspnoea descriptors before and after the V_T inflection. Comparisons between PH-H and PH-NH were performed at rest, at common standardized exercise work-rates (WR)

(20 watts: iso-WR 1; and 40 watts: iso-WR 2), at iso-V'_E, at the V_T inflection and at peak exercise using Friedman Repeated Measures Analysis of Variance on Ranks. Metabolic, cardio-ventilatory, and perceptual responses at iso-V'_E were calculated by linear interpolation between adjacent measurement points for each subject. All statistical procedures were carried out using Intercooled Stata 8.0 for Windows (Stata, College Station, TX) and SPSS 18.0 for Windows (SPSS Inc, Chicago IL, USA). Differences were considered significant when the probability P of a type I error was <0.05.

RESULTS

The patients' characteristics, resting pulmonary function testing and the physiological and perceptual responses to CPET in PAH and CTEPH are summarized in Table 1 and 2. More details are available in the online supplement.

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). The remaining nine patients (35%: 6 PAH and 3 CTEPH) did not (Non-hyperinflators group, IC=+0.01L) ($p<0.001$, Figure 1 and Table 3). Both hyperinflator and non-hyperinflator patients were stable on therapy with satisfactory hemodynamic and clinical status, as demonstrated by cardiac output at rest, right atrial pressure, NYHA functional class, and 6-minute walk distance (Table 3). Patients' characteristics, resting pulmonary function and the physiological and perceptual responses to CPET of the two groups are compared in Table 3 and Table 4.

Hyperinflator group presented with greater dynamic expiratory flow limitation than non-hyperinflator counterpart (at 20 watts: 25±5% vs 5±10%, $p=0.0005$), as suggested by the encroachment of V_T on the maximal expiratory flow-volume envelope (see online supplement for details on methods). The percentage of V_T being expiratory flow-limited was consistently higher in hyperinflator group than non-hyperinflator at any stage of cycle exercise ($p<0.05$). Of interest, a strong correlation was found between expiratory flow limitation and IC at V_T inflection in hyperinflator group ($r= -0.80$, $p=0.04$). More details can be found in the on-line supplement.

V_T inflection and dyspnoea descriptors

A notable inflection in the V_T/V'_E relationship occurred in both hyperinflators and non-hyperinflators patients, regardless of PH etiology. The average exercise WR at the V_T inflection was 66±25W in hyperinflators vs 56±30W in non-hyperinflators ($p=0.19$). The evolution of dyspnoea descriptors during CPET in PH as whole group is shown in Figure 2. At iso-WR 1, 35% of patients (9/26) selected work/effort, 15% (4/26) selected difficult/unsatisfied inspiration, and the remaining 13 patients (50%) did

not select anything. At the V_T inflection, 65% of patients (17/26) selected work/effort, 23% (6/26) selected difficult/unsatisfied inspiration, and one patient selected chest tightness. At peak 19% of patients (5/26) selected work/effort, 77% (20/26) selected difficult/unsatisfied inspiration, and one patient selected chest tightness. Figures 3A and 3B describe the evolution of dyspnoea descriptors during CPET in hyperinflator and non-hyperinflator patients.

When coupling the specific dyspnoea descriptor selection to the response of V_T before, at, and after its inflection on an individual basis, we found a clear and consistent change in the selection of dyspnoea descriptor in hyperinflator patients: these patients reached their V_T inflection at a critically low IRV of 0.53±0.22L compared with the remaining non-hyperinflator patients who reached their V_T inflection at a preserved IRV of 0.81±0.32L (Figure 1). Hyperinflators notably selected work/effort as the most representative qualitative dyspnoea descriptor of their dyspnoea until the V_T inflection, then consistently changed their qualitative dyspnoea descriptor from work/effort to difficult/unsatisfied inspiration (McNemar test, p=0.025) from V_T inflection to peak exercise. In contrast, non-hyperinflators continued to select work/effort throughout exercise, with no change between V_T inflection and peak exercise.

We also observed that the V_T inflection coincided with an inflection in the dyspnoea/IRV relationships in the hyperinflator group. This means that the relation between dyspnoea intensity and IRV was biphasic in the hyperinflator group: reported dyspnoea gradually increased up to 4.4 Borg units until the critical IRV corresponding to the V_T inflection was reached, then impressively and quasi-vertically increased by 3 Borg units to reach the symptom-limited endpoint of exercise (7.2 Borg units) (Figure 1). The relationship between the selection frequency of difficult/unsatisfied inspiration and IRV was also found to be biphasic in the hyperinflator group.

In contrast, in the non-hyperinflator group, dyspnoea increased linearly with time and V'_E up to 3.3 Borg units to reach the V_T inflection, then increased by 3 Borg units from the V_T inflection to peak exercise.

MDP

Results of the MDP (arbitrary units, a.u.) are expressed as medians [25-75 interquartile range]. In the MDP items relating to unpleasantness or discomfort (A1 scale) recorded immediately after CPET (Table 4), hyperinflators rated unpleasantness or discomfort higher (8 a.u. [7-9]) than non-hyperinflators (5 a.u. [0-8]) (p=0.037); 65% of hyperinflators compared with 11% of non-hyperinflators (p=0.025) reported "not enough air, smothering or hunger for air" on the sensory dimension items of the MDP (Table 4). Of note "Not enough air, smothering or hunger for air" was associated with greater anxiety (4.4 a.u., data not shown in Table 4) in the 65% of hyperinflators compared with 11% of non-hyperinflators (2 a.u.) during CPET (p=0.025), with no statistical difference between patients with and without hyperinflation under conditions such as 6MWT and RHC. A similar pattern of sensory and

affective responses was obtained when MDP was administered immediately after 6MWT and RHC (Table 4).

DISCUSSION

The main findings of this study are as follows: *1)* a notable V_T inflection occurred in both hyperinflator and non-hyperinflator patients, regardless of PH etiology; *2)* the attainment of a V_T inflection at a critically low dynamic IRV marks an important mechanical event during exercise in PH patients who hyperinflate and has major sensory consequences. At that moment, dyspnoea intensity escalates sharply and there is a transition in the dominant qualitative descriptor choice from "work/effort" to "unsatisfied inspiration"; *3)* the sense of breathing "work/effort" is the predominant description of respiratory discomfort in PH patients who do not hyperinflate and who still present with a V_T inflection but at a preserved IRV during exercise; 4) the MDP revealed that the sensation of "unsatisfied inspiration" was far more unpleasant than the excessive "work/effort" sensation, and that the emotion most frequently associated with dyspnoea was anxiety; 5) the evolution of the intensity and quality of exertional dyspnoea seems to be independent of the PH etiology and rather reflects the mechanical constraints and operating lung volume evolution on individual basis.

Ventilatory response and constraints

This study is the first to show that a notable inflection in the V_T response occurs during exercise in hyperinflators with stable PH, as happens in healthy unfit subjects (16, 35-38), athletes (19) and in patients with COPD (11, 39) and CHF (40). At this point, the V_T began to plateau with no further significant expansion until the end of exercise. Of note, in non-hyperinflators, the V_T inflection did occur but at a preserved IRV (Table 3). This behavior seems to be crucial to sensory perception. When this inflection occurred while the IRV is preserved, dyspnoea increased linearly with time and V'_E and showed only a modest increase (by 3 Borg units) from the V_T/ V'_E inflection to peak exercise. The sensation of breathing *work/effort* was the dominant dyspnoea descriptor selected throughout exercise (Figure 3B), regardless of type and mode of exercise (CPET, 6MWT and haemodynamic cycle ergometry exercise, Figure E3). This is in line with our previous observations in asthmatic patients (10, 13) and healthy subjects at the termination of exercise (14, 16). This behaviour can be explained as follows: the greater IC observed at the V_T inflection in non-hyperinflators (Figure 1) would have permitted ventilation at lung volumes well below the TLC, thus avoiding a critically low IRV and all the mechanical and sensory consequences associated with it. In these circumstances, it is not surprising that the sense of breathing *work/effort* was the predominant description of respiratory discomfort in non-hyperinflators during exercise.

In contrast, attainment of a critically low dynamic IRV at V_T inflection marked the point where dyspnoea intensity rose more impressively and quasi-vertically and *difficult/unsatisfied inspiration* increased steeply relative to *work/effort* only and exclusively in hyperinflators (Figure 2 and 3A). Before the V_T inflection, dyspnoea intensity rose linearly into the moderate range (Borg rating around 4) and hyperinflators were more likely to select *work/effort* and less likely to select the *difficult/unsatisfied inspiration* descriptor. After the V_T inflection, dyspnoea intensity rose more steeply to intolerable levels (mean Borg rating 7 "very severe" at peak) and *difficult/unsatisfied inspiration* was increasingly selected as the dominant qualitative descriptor (Figure 3A).

The last point to highlight here is why some patients hyperinflated during exercise while others did not. Compared with non-hyperinflators, hyperinflators exhibited a consistent and uniform reduction of the maximal expiratory flow rates over the effort-independent portion of the maximal flow-volume curve ($FEF_{75\%}$), whilst the FEV_1/VC ratio, TLC, and IC were preserved between the two groups (Table 3). Whether these spirometric abnormalities truly reflect peripheral airways obstruction is still debated (8). However, small airway dysfunction has previously been described in PAH (8) and suspected in CTEPH (46); its mechanisms are poorly understood. Regardless of the mechanisms underlying the PH-related small airway dysfunction, the shape and limits of the maximal flow–volume curve in the tidal operating range (showing a reduction of $FEF_{75\%}$) mean that, in our hyperinflator patients (both PAH and CTEPH), the operating V_T was positioned closer to residual volume than normally. As a result, our hyperinflator patients (both PAH and CTEPH) had an increased propensity to expiratory flow limitation. Indeed, although hyperinflator patients (both PAH and CTEPH) did not exhibit evident expiratory flow limitation during resting breathing, they encroached on their maximal expiratory flow reserve relatively early in exercise (at 20W). In fact, from 20W to peak exercise, our hyperinflator patients (both PAH and CTEPH) were no more able to expand V_T by encroaching on the ERV due to the no longer available expiratory flow reserve at that lung volume (expiratory flow limitation was 25±5% in hyperinflators vs 5±10% in non-hyperinflators, p=0.0005). Of note, a strong correlation was found between expiratory flow limitation and IC at V_T inflection in hyperinflator group ($r= -0.80$, $p=0.04$). As a consequence, V_T continued to increase only by encroaching on the IRV, and the IC decreased substantially (DH) in our hyperinflator patients (both PAH and CTEPH), under the condition of increased ventilatory demand. Therefore, even if resting IC is preserved in both PAH (8) and CTEPH (46) (as recently demonstrated by Richter et al in operable CTEPH pre and post pulmonary endarterectomy after excluding pulmonary diseases), its dynamic decrease during exercise may be attributed, at least in part, to the development of expiratory flow limitation, provided that TLC remains stable and respiratory muscle dysfunction does not develop during exercise, as previously ruled out in PAH patients (8, 9).Last but not least, how and to what extent hemodynamics may have influenced dynamic hyperinflation and vice-versa is difficult to

ascertain; non-hyperinflators had a significantly steeper mPAP/CO slope and VE/VCO_2 slopes compared with hyperinflators (Table 3 and the online supplement for more detail), this suggesting (but of course with a word of caution) that dynamic hyperinflation, by increasing intrathoracic pressure and imposing mechanical constraints on V_T expansion, might have mitigated the rise in CO, mPAP and V'_E in hyperinflator patients (both PAH and CTEPH), as recently demonstrated in COPD patients undergoing exercise (47, 48). In addition, a steeper VE/VCO_2 slope (ventilatory inefficency) was recently found to be related to impaired right ventricular diastolic function in PAH (52); whether these recent and intriguing findings may add to the explanations already given for the differences in mPAP/CO steepness observed between non-hyperinflators and hyperinflators PH patients in our study is difficult to say and further studies are needed to shed light upon these mechanisms.

Work/effort and unsatisfied inspiration

It seems that these major qualitative descriptors evolve separately throughout exercise and are strongly influenced by mechanical events such as the V_T inflection in hyperinflators. Before this inflection, the negative mechanical consequences of breathing at a higher lung volume (i.e. DH) may be initially counterbalanced by reduced resistive work which attenuates the rise in the intensity of dyspnoea. The attendant acute mechanical loading early in exercise (up until the V_T inflection) may result in a relatively higher inspiratory effort than normal for a given force generated by the respiratory muscles (11, 41) and the qualitative sensation of “work/effort” may reflect the conscious appreciation of increased central motor command output under these circumstances.

In contrast, as IRV reaches a critical level at the V_T inflection (because of DH), little or no further V_T expansion is possible and dyspnoea intensity then rises steeply to intolerable levels. This blunted V_T displacement occurring as a result of DH in the face of progressive increases in central respiratory drive may be responsible, at least in part, for the perception of *difficult/unsatisfied inspiration* in hyperinflators.

Although the precise mechanisms responsible for the critical reduction in IRV observed in hyperinflators has not been fully elucidated, the significant decrease in IC (i.e. DH) observed in this group appears to be the most plausible contributory factor. Regardless of mechanisms, the reduced IC observed in hyperinflators forces V_T to the upper non-compliant reaches of the respiratory system’s pressure-volume relationship and negatively affects inspiratory muscle performance, which was not the case in non-hyperinflators. This may contribute directly or indirectly to the intensity and quality of dyspnoea in hyperinflators after the V_T inflection (42).

MDP and its clinical relevance

The MDP revealed that the sensation of “unsatisfied inspiration” was far more unpleasant than the excessive “work/effort” sensation, and corroborated the contention that in the affective domain, the emotion most frequently associated with dyspnoea was anxiety. Interestingly, the same pattern of response in terms of sensory and affective dimension/domain was found when the MDP was administered immediately after 6MWT and RHC (Table 4).

Regardless of the mechanisms involved, it is important to emphasize that observing a change in dyspnoea description as the causative stimulus (here, exercise) persists can be clinically relevant. Experiments conducted in healthy subjects have shown that the "unsatisfied inspiration" family of descriptors of dyspnoea ("air hunger", "not enough air", "smothering", "suffocating") is associated with a more negative affect than "work/effort" even when the corresponding sensory intensity is identical (20). Clinical studies based on the MDP suggest that "air hunger" is more often associated with anxiety and fear than "excessive/effort" (34, 43). Therapeutic interventions can relieve dyspnoea by interfering mostly with its affective component (43). In our study, hyperinflators had MDP sub-scores significantly different from non-hyperinflators: hyperinflators rated unpleasantness or discomfort higher than non-hyperinflators (Table 3, p=0.037); among sensory dimension items, "not enough air, smothering or hunger for air", was reported in 65% of hyperinflators’ responses compared with 11% of non-hyperinflators’ responses (p=0.025). The emotion most frequently associated with "not enough air, smothering or hunger for air" was anxiety (4.4 a.u.) in 65% of hyperinflators compared with 11% of non-hyperinflators (2 a.u.) during CPET, with no statistical difference between them under conditions such as 6MWT and RHC.

The multifactorial origin of exertional dyspnoea in pulmonary hypertension

Our results reinforce the previously documented notion that in clinical situations where lung mechanics are not an intuitive candidate to explain dyspnoea, DH-induced constraint of V_T expansion can play a significant role. This seems important from a therapeutic standpoint because it opens up new horizons for research in the “multiaxial” treatment of dyspnoea. Any intervention that improves exertional dyspnoea should be beneficial even when this intervention is not directly related to the principal pathophysiological determinant of the disease (44). This reasoning is supported by the observation that the relationship between dyspnoea intensity and the underlying disease’ abnormalities is not linear, but rather exponential, especially in PH. In other words, when a disease is already responsible for intense dyspnoea, a small additional deterioration directly or indirectly related to the disease (for example, abnormalities of respiratory mechanics) can make dyspnoea intolerable, and there is evidence that improving airway mechanics after acute administration of bronchodilators can ameliorate the condition of patients with chronic heart failure patients (45). It follows, therefore, that a therapeutic

intervention that effectively reduces DH, such as inhaled bronchodilators, should theoretically delay the appearance of the mechanical constraint of V_T expansion and the attendant dyspnoea during physical activity in selected patients with stable PH. An important clinical implication for symptom management in PH patients arises from our study: as the sensation of “unsatisfied inspiration” is more uncomfortable than “work/effort” and was generally associated with more negative emotional experiences such as anxiety in our study, it is fundamental not only to slow down the build-up of dyspnoea (intensity), but also to delay or prevent the moment (the V_T/V'_E inflection point) when the highly anxiogenic "unsatisfied inspiration" occurs. The last point to highlight here is the contention that the evolution of the intensity and quality of exertional dyspnoea seems to be largely independent of PH etiology and rather reflects the mechanical constraints and operating volume history on individual basis.

Limitations

Our primary analysis of the qualitative dimensions of dyspnoea during exercise was confined to two descriptors based on our primary hypothesis on respiratory mechanical constraints during exercise in this population: other descriptors not included here may also be relevant to the complex experience of exertional dyspnoea in stable PH. The relatively small and heterogeneous sample size of the present study means that we must be circumspect in generalizing our findings to the wider PH population. In addition, differences between the sexes in terms of respiratory mechanics and psychological impact might be relevant in the current study. Studies of the physiological mechanisms that also measure oesophageal pressure will be required to further elucidate the respiratory mechanics of exertional dyspnoea in PH patients.

Last but not least, we are aware that the issue as to whether DH is a cause of tachypnea and anxiety or vice-versa is not resolved in this study and should be clearly addressed in future studies. What is clear in our study is that there is absolutely no difference between hyperinflators and non-hyperinflators in terms of respiratory rate: hyperinflators are as much tachypnoeic as non-hyperinflators. Of note, we excluded patients with dysfunctional breathing on purpose. Concerning the link between anxiety, dyspnoea and DH, we can say that in some COPD studies (nothing in PH) dyspnoea is able to elicit or aggravate anxiety, but we know also from other COPD studies that anxiety is able to increase dyspnoea, especially its qualitative dimensions rather than its intensity (49, 50). Finally, COPD studies (nothing in PH) have clearly demonstrated the salutary effects of pulmonary rehabilitation on anxiety, dyspnoea (51) and less consistently on DH (49). It would be interesting to evaluate the effects of anxyolitic treatment on breathing pattern profile and DH and exertional dyspnoea in future studies.

Conclusions

This study demonstrates the importance of constraints on V_T expansion on dyspnoea intensity and quality during exercise in patients with PH, irrespective of etiology. Specifically, the inflection point in V_T relative to V'_E marked the onset of a large increase in dyspnoea intensity and an increase in the selection frequency of unsatisfied inspiration as the predominant dyspnoea descriptor. In the affective domain, the emotion most frequently associated with this dyspnoea descriptor was, clearly, anxiety.

Interventions that reduce ventilatory demand and therefore delay or prevent an inflection in tidal volume relative to ventilation from occurring should reduce dyspnoea intensity and the highly anxiogenic perception of unsatisfied inspiration in this population.

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Table 1: Patient characteristics and resting hemodynamic and pulmonary function

Sex Female/Male, *n*	16/10
Age, *years, median (IQR)*	45 (30 – 52)
BMI, *kg/m^2*	25.7 ± 5.0
Pulmonary hypertension aetiology, *n*	
PAH (idiopathic / heritable / HIV-associated)	17 (10 / 5 / 2)
CTEPH	9
Newly diagnosed cases, *n*	9
Duration of prevalent PH, *years, median (IQR)*	4.4 (1.6 – 9.7)
Haemodynamics, *mean ± SD*	
Right atrial pressure, *mmHg*	7 ± 3
Mean pulmonary artery pressure, *mmHg*	49 ± 14
Pulmonary artery wedge pressure, *mmHg*	9 ± 3
Cardiac output, *L/min*	5.7 ± 1.8
Cardiac index, *L/min/m^2*	3.2 ± 0.9
Pulmonary vascular resistance, *Wood units*	7 ± 3
Mixed venous oxygen saturation, *%*	67 ± 8
PAH-targeted therapy, *n*	
None	10
Calcium channel blockers	2
Oral monotherapy	3
Dual oral combination therapy	3
PDE-5 inhibitor + IV epoprostenol	1
Triple combination therapy with IV epoprostenol	7
NYHA functional class I / II / III / IV, *n*	10 / 9 / 7 / 0
6-MWD, *m, mean ± SD*	517 ± 101
Lung function test *(mean ± SD)*	
FEV_1/VC, *%,*	82 ± 10
FEV_1, *% of predicted*	96 ± 18
TLC, *% of predicted*	94 ± 16
DLCO, *% of predicted*	65 ± 15
KCO, *% of predicted*	76 ± 20
P_aO_2, *mmHg*	80 ± 13
P_aCO_2, *mmHg*	33 ± 4

Results are presented as mean ± SD or median (IQR 25%-75%). IQR: Interquartile range; BMI: body mass index; PAH: pulmonary arterial hypertension; CTEPH: chronic thrombo-embolic pulmonary hypertension; PDE-5: phosphodiesterase type-5; NYHA: New York Heart Association; 6-MWD: six-minute walk distance; FEV1: forced expiratory volume in one second; VC: vital capacity; TLC: total lung capacity; DLCO: diffusing capacity of the lung for carbon monoxide; KCO: carbon monoxide transfer coefficient; P_aO_2, P_aCO_2 : partial pressure of oxygen/carbon dioxide in arterial blood, respectively.

Table 2. Physiological and perceptual responses to cardiopulmonary exercise testing in PAH and CTEPH patients

	Rest		iso-WR 1		iso-WR 2		Peak	
Variables	**PAH**	**CTEPH**	**PAH**	**CTEPH**	**PAH**	**CTEPH**	**PAH**	**CTEPH**
Work rate, watts	/	/	20±0	20±0	40±0	40±0	104±36*	78±27
$V'O_2$, L/min	0.33±0.11	0.34±0.06	0.58±0.13	0.63±0.15	0.78±0.15	0.79±0.14	1.34±0.37 p=0.06	1.07±0.39
$V'CO_2$, L/min	0.28±0.09	0.32±0.08	0.52±0.13	0.57±0.15	0.72±0.13	0.74±0.13	1.58±0.41*	1.19±0.50
V'_E, L/min	15.0±4.2*	24.2±8.7	23.8±6.7*	37.3±8.7	31.6±7.5*	48.8±10.2	75.3±23.2	77.2±13.4
RR, breaths/min	19±4*	22±5	24±7	31±13 p=0.09	25±7*	32±9	41±7	42±10
V_T, L	0.81±0.20 p=0.07	1.14±0.61	1.03±0.29*	1.32±0.42	1.33±0.35*	1.59±0.34	1.85±0.43	1.91±0.59
IC, L	2.4±0.5	2.6±0.6	2.3±0.5	2.4±0.6	2.2±0.4	2.4±0.5	2.2±0.5	2.3±0.7
Dyspnea, Borg units	0.4±0.7	0.3±0.7	0.9±1.1*	2.9±2.0	1.9±1.6*	4.2±2.5	6.7±1.5	7.4±1.7
PaO_2, mmHg	84.1±12.1*	69.9±8.4	/	/	/	/	76.9±15.9*	57.3±11.5
$PaCO_2$, mmHg	31.1±4.1 p=0.06	33.6±5.2	/	/	/	/	31.3±3.4	32.8±13.0
$P(A\text{-}a)O_2$, mmHg	25.9±11.5*	46.0±10.0					45.8±16.9*	62.2±10.6
V_D/V_T	0.43±0.10*	0.57±0.13	/	/	/	/	0.49±0.08*	0.64±0.10

Definition of abbreviations: PAH: pulmonary arterial hypertension; CTEPH: chronic thrombo-embolic pulmonary hypertension; iso-WR 1 = common standardized exercise work-rate (WR) of 20watts; iso-WR 2 = common standardized exercise WR of 40 watts; $V'O_2$ = oxygen uptake; $V'CO_2$ = carbon dioxide production; V'_E= ventilation; RR = respiratory rate; V_T = tidal volume; IC = inspiratory capacity; IRV = inspiratory reserve volume; PaO2 = arterial partial pressure of oxygen; PaCO2 = arterial partial pressure of carbon dioxide; $P(A\text{-}a)O_2$ = the difference between Alveolar and arterial oxygen partial pressure; V_D/V_T = the physiological dead space-to-tidal volume ratio. Values are mean±SD. * $p<0.05$, PAH versus CTEPH at the same measurement point.

Table 3: Comparisons between hyperinflator and non-hyperinflator PH patients

	Hyperinflator n=17	**Non hyperinflator** n=9	**p**
Sex Female/Male	11/6	5/4	0.65
Age, *years*	47 ± 17	42 ± 15	0.4
Pulmonary hypertension etiology, n			0.44
PAH (idiopathic/heritable/HIV)	11 (7/2/2)	6 (3/3/0)	
CTEPH	6	3	
NYHA I/II/III/IV	7/7/3/0	3/2/4/0	0.67
6-MWD, *m*	500 ± 103	538 ± 99	0.37
Haemodynamic			
Right atrial pressure, mmHg	8 ± 3	7 ± 3	0.31
Mean pulmonary artery pressure (mPAP), mmHg	51 ± 13	45 ± 16	0.31
Pulmonary artery wedge pressure, mmHg	10 ± 3	9 ± 2	0.19
Cardiac output (CO), L/min	5.9 ±1.8	5.6 ± 1.7	0.62
Cardiac index, L/min/m^2	3.3 ± 0.8	3.1 ± 0.9	0.57
Pulmonary vascular resistance, Wood units	7.3 ± 2.9	7.1 ± 3.6	0.89
Mixed venous oxygen saturation, %	68 ± 6	65 ± 14	0.49
mPAP/CO slope	5.8 (3.5 - 6.8)	7.9 (4.8 - 9.7)	**p<0.001**
Lung function test			
FEV_1/FVC, *%*	81 ± 9	84 ± 10	0.47
FEV_1, *L*	2.7 ± 0.5	3.1 ± 1.0	0.26
FEV_1, *% predicted*	93 ± 18	101 ± 18	0.20
FVC, *L*	3.6 ± 0.7	3.9 ± 1.1	0.38
FVC, *% predicted*	105 ± 26	103 ± 14	0.67
$FEF_{75\%}$, L/s (% pred)	1.1±0.5 (55±14)	1.8±0.7 (90±20)	0.004
TLC, *L*	5.0 ± 0.7	5.4 ± 1.2	0.30
TLC, *% predicted*	94 ± 17	96 ± 14	0.72
RV, *L*	1.3 ± 0.5	1.4 ± 0.9	0.90
RV, *% predicted*	84 ± 27	81 ± 30	0.88
DLCO, *% predicted*	64 ± 16	68 ± 14	0.54
Work rate peak, *Watts*	94 ± 33	97 ± 41	0.42
Work rate at anaerobic/ventilatory threshold, *Watts*	61 ± 21	57 ± 29	0.32
$V'O_2$ peak, *ml/kg*	16.8 ± 4.4	18.0 ± 4.9	0.54
$V'O_2$ peak, *% predicted*	59 ± 21	55 ± 15	0.57
$V'O_2$ at anaerobic/ventilatory threshold, *ml/kg/min*	13.4 ± 3.1	13.0 ± 3.7	0.77
V'_E at rest, *L/min*	16.3 ± 6.2	21.8 ± 8.7	0.058
V'_E at anaerobic/ventilatory threshold, *L/min*	45 ± 12	46 ± 16	0.87
V'_E at peak, *L/min*	71.9 ± 15.3	83.5± 26.3	0.12
$V'_E/V'CO_2$ slope	52 (41 - 48)	57 (44 - 68)	**p<0.001**
RR at peak, *breaths/min*	42 ± 9	40 ± 7	0.27
V_D/V_T at rest	0.45 ± 0.13	0.52 ± 0.12	0.070
V_D/V_T at peak	0.55 ± 0.08	0.57 ± 0.15	0.36
V_T at rest, *L*	0.8 ± 0.2	1.1 ± 0.6	0.10
V_T at V_T inflection, *L*	1.5 ± 0.4	1.8 ± 0.5	0.11
V_T at peak, *L*	1.7 ± 0.4	2.1 ± 0.6	0.054
IC at rest, *L*	2.4 ± 0.5	2.6 ± 0.6	0.18
IC at V_T inflection, *L*	2.1 ± 0.4	2.6 ± 0.6	**0.018**
IC at peak, *L*	2.0 ± 0.4	2.6 ± 0.6	**0.011**
IRV at rest, *L*	1.6 ± 0.5	1.5 ± 0.5	0.37
IRV at V_T inflection, *L*	0.5 ± 0.2	0.8 ± 0.3	**0.017**
IRV at peak, *L*	0.3 ± 0.3	0.5 ± 0.4	0.07
Dyspnoea, Borg at rest (a.u.)	0.4 ± 0.7	0.3 ± 0.7	0.47
Dyspnoea, Borg at V_T inflection (a.u.)	4.4 ± 1.5	3.3 ± 1.3	**0.036**

Dyspnoea, Borg at peak (a.u.)	7.2 ± 1.6	6.4 ± 1.4	0.11
Respiratory Exchange Ratio (RER) at peak	1.17 ± 0.09	1.14 ± 0.08	0.20

Results are presented as mean ± SD or median (IQR 25%-75%). IQR: Interquartile range. 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; $FEF_{75\%}$: forced expiratory flow at 75% of the FVC; RV: residual volume; TLC: total lung capacity; DLCO: diffusing capacity for carbon monoxide; $V'O_2$: oxygen uptake; $V'CO_2$: carbon dioxide output; V'_E: minute ventilation; RR: respiratory rate; V_D/V_T = the physiological dead space-to-tidal volume ratio; V_T: tidal volume; IC: inspiratory capacity; IRV: inspiratory reserve volume; a.u.: arbitrary units.

Table 4: Comparisons of Multidimensional Dyspnea Profile (MDP) in hyperinflator and non-hyperinflator PH patients

	Hyperinflator n=17	**Non hyperinflator** n=9	**p**
6MWT:			
Borg at 6 minutes	4.7 ± 3.1	5.6 ± 2.8	0.47
MDP:			
A1 Scale:			
Rating from 0 to 10 a.u.:			
Unpleasantness or discomfort	3.8 ± 2.9	4.9 ± 2.9	0.37
% of responses:			
My breathing requires muscle work or effort	22%	22%	0.10
I am not getting enough air or I am smothering or I feel hunger for air	45%	0%	**0.025**
My chest and lungs feel tight or constricted	11%	22%	0.47
My breathing requires mental effort or concentration	0%	11%	0.08
I am breathing a lot	11%	45%	**0.025**
No response	11%	0%	0.08
Score S of MDP	17 ± 16	20 ± 13	0.45
A2 Scales			
Rating from 0 to 10 a.u.:			
Depressed	0 (0-0)	0 (0-0)	0.65
Anxious	0 (0-0)	0 (0-2)	0.29
Frustrated	0 (0-0)	0 (0-0)	0.81
Angry	0 (0-0)	0 (0-0)	0.36
Afraid	0 (0-0)	0 (0-0)	0.52
Other?	0 (0-0)	0 (0-0)	1
Score A2 of MDP	0 (0-0)	2 (0-5)	0.10
CPET:			
Borg at peak	7.2 ± 1.6	6.4 ± 1.4	0.11
MDP:			
A1 Scale:			
Rating from 0 to 10 a.u.:			
Unpleasantness or discomfort	8 (7-9)	5 (0-8)	**0.037**
% of responses:			
My breathing requires muscle work or effort	0%	0%	0.81
I am not getting enough air or I am smothering or I feel hunger for air	65%	11%	**0.025**
My chest and lungs feel tight or constricted	0%	11%	0.08
My breathing requires mental effort or concentration	0%	11%	0.08
I am breathing a lot	29%	56%	**0.037**

No response	6%	11%	0.10
Score S of MDP	29 ± 13	26 ± 12	0.56
A2 Scales			
Rating from 0 to 10 a.u.:			
Depressed	0 (0-0)	0 (0-0)	0.78
Anxious	0 (0-4)	0 (0-2)	0.3
Frustrated	0 (0-2)	0 (0-4)	0.93
Angry	0 (0-0)	0 (0-0)	0.8
Afraid	0 (0-1)	0 (0-0)	0.33
Other?	0 (0-0)	0 (0-0)	1
Score A2 of MDP	3 (0-7)	0 (0-2)	0.35
RHC:			
Borg at peak	7.7 ± 1.9	6.8 ± 1.6	0.11
MDP:			
A1 Scale:			
Rating from 0 to 10 a.u.:			
Unpleasantness or discomfort	6.0 ± 2.8	5.1 ± 1.8	0.43
% of responses:			
My breathing requires muscle work or effort	12%	22%	0.63
I am not getting enough air or I am smothering or I feel hunger for air	47%	22%	**0.040**
My chest and lungs feel tight or constricted	0%	11%	0.80
My breathing requires mental effort or concentration	0%	0%	1
I am breathing a lot	35%	45%	0.43
No response	6%	0%	0.78
Score S of MDP	24 ± 14	21 ± 12	0.71
A2 Scales			
Rating from 0 to 10 a.u.:			
Depressed	0 (0-0)	0 (0-0)	0.61
Anxious	0 (0-4)	0 (0-0)	0.37
Frustrated	0 (0-1)	0 (0-0)	0.65
Angry	0 (0-0)	0 (0-0)	0.82
Afraid	0 (0-3)	0 (0-0)	0.35
Other?	0 (0-0)	0 (0-0)	1
Score A2 of MDP	2 (0-6)	0 (0-0)	0.22

Data are expressed as *mean ± SD or* median (25-75 interquartile range); PH: pulmonary hypertension; a.u.: arbitrary units; 6MWT: six-minute walk test; CPET: cardiopulmonary exercise testing; RHC: right heart catheterisation.

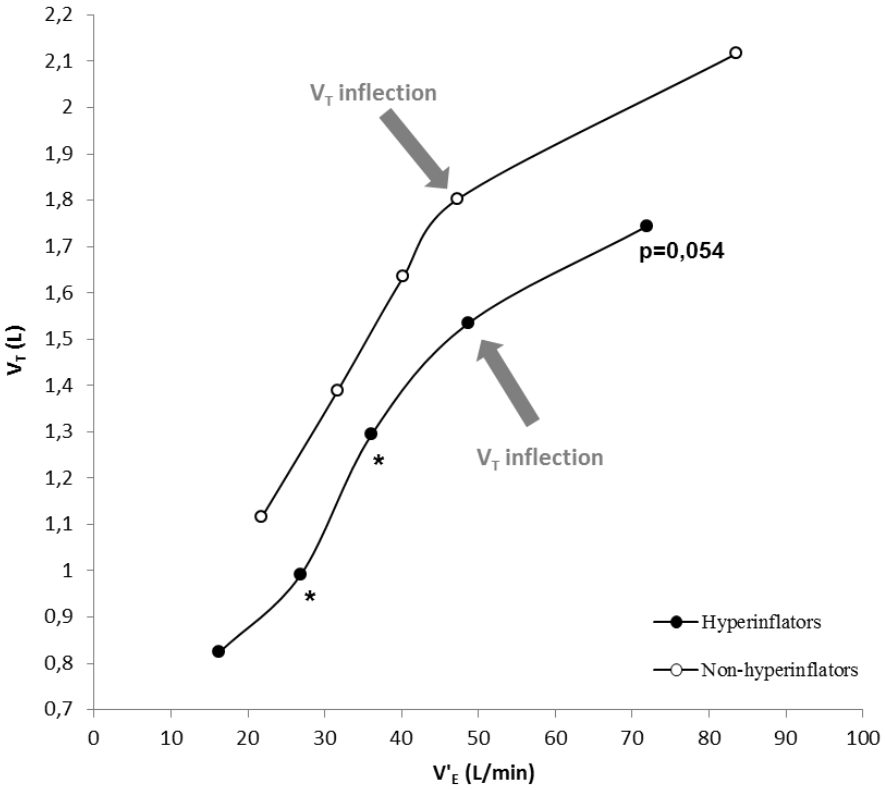
FIGURE LEGENDS

Figure 1A: Evolution (change) in tidal volume (V_T, left panel) and inspiratory reserve volume (IRV, right panel) from rest to peak exercise is shown in response to increasing ventilation (V'_E) during symptom-limited incremental cycle exercise in patients with pulmonary hypertension who hyperinflate (decrease their IC: Hyperinflators) and deflate (increase their IC: Non-hyperinflators). Data are presented as mean at rest, at 20W (iso-WR 1), at 40 W (iso-WR 2), at the V_T inflection point and at peak exercise. *: $p<0.05$ significant difference between groups at a given time-point. Arrows indicate the V_T inflection point in each group. TLC indicates the total lung capacity. Please note that Hyperinflators reached their V_T inflection at a critically low IRV of 0.53L compared with the remaining Non-hyperinflators who reached their V_T inflection at a preserved IRV of 0.81L. Please also note that Hyperinflators reported dyspnoea gradually increased up to 4.4 Borg units until the critical IRV corresponding to the V_T inflection point was reached, then impressively and quasi-vertically increased by 3 Borg units to reach the symptom-limited endpoint of exercise (7.2 Borg units). In contrast, in the Non-hyperinflator group, dyspnoea increased linearly with V'_E up to 3.3 Borg units to reach the V_T inflection point, then increased by 3 Borg units from the V_T inflection point to peak exercise.

Figure 1B: Exertional dyspnoea intensity (Borg score) is shown in response to increasing work rate (watts, left panel) increasing ventilation (V'_E, right panel) and during symptom-limited incremental cycle exercise in patients with pulmonary hypertension who hyperinflate (decrease their IC: Hyperinflators) and deflate (increase their IC: Non-hyperinflators). Data are presented as mean at rest, at 20W (iso-WR 1), at 40W (iso-WR 2) and at peak exercise as for left panel and as mean at rest, at 20W (iso-WR 1), at iso-V'_E and at peak exercise as for right panel. *: $p<0.05$ significant difference between groups at a given time-point. Vertical dotted line indicates iso-V'_E for both groups.

Figure 2: Selection frequency of the three descriptor phrases evaluated during symptom-limited incremental cycle exercise in patients with pulmonary hypertension as whole group (n=26): increased work and effort, unsatisfied inspiration, and chest tightness. Data are presented as mean at rest, at 20W (iso-WR 1), at 40W (iso-WR 2), at the tidal volume (VT) inflection point, after the VT inflection point and at peak exercise.

Figure 3: Selection frequency of the three descriptor phrases evaluated during symptom-limited incremental cycle exercise in patients with pulmonary hypertension (PH) who **A)** deflate (Non-hyperinflators) and **B)** hyperinflate (Hyperinflators) during exercise: increased work and effort, unsatisfied inspiration, and chest tightness. Data are presented as mean at rest, at 20W (iso-WR 1), at 40 W (iso-WR 2), at the tidal volume (VT) inflection point, after the VT inflection point and at peak exercise.


V_T inflection
p=0,054
V_T inflection
*
*
Hyperinflators
Non-hyperinflators
V_T (L)
V'_E (L/min)

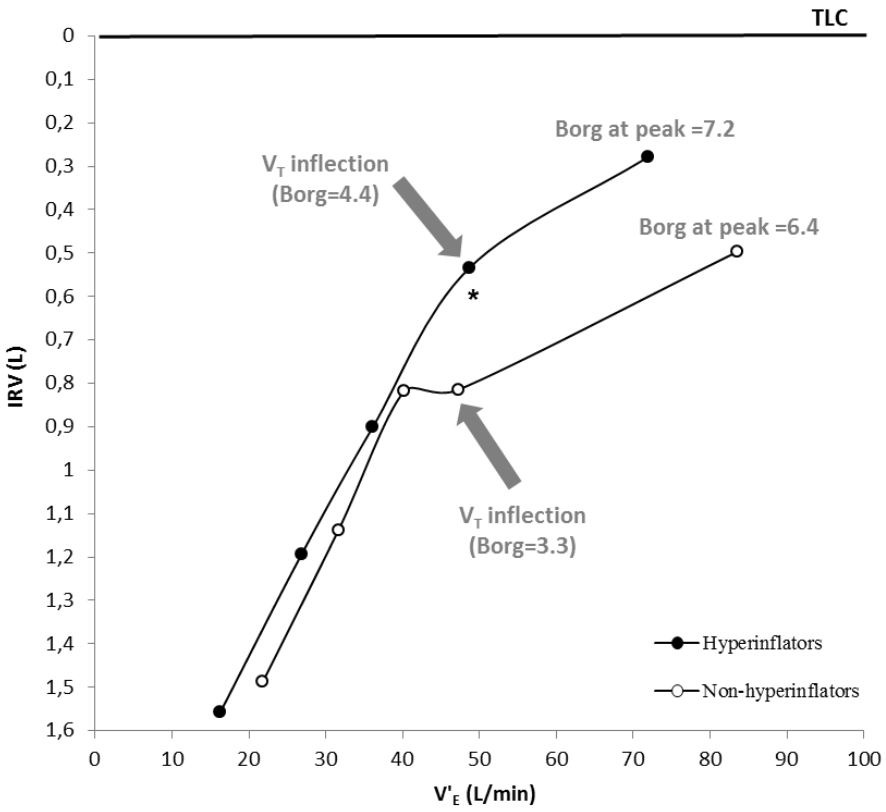
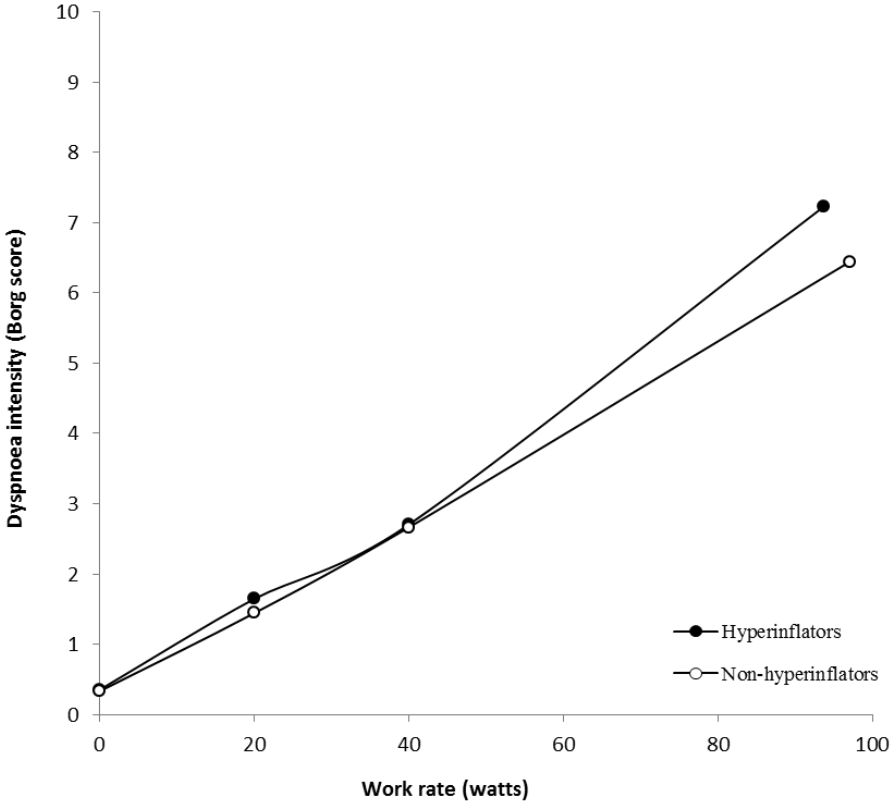

TLC
Borg at peak =7.2
V_T inflection
(Borg=4.4)
Borg at peak =6.4
*
V_T inflection
(Borg=3.3)
Hyperinflators
Non-hyperinflators
IRV (L)
V'_E (L/min)

Figure 1A


Dyspnoea intensity (Borg score)
Work rate (watts)
Hyperinflators
Non-hyperinflators

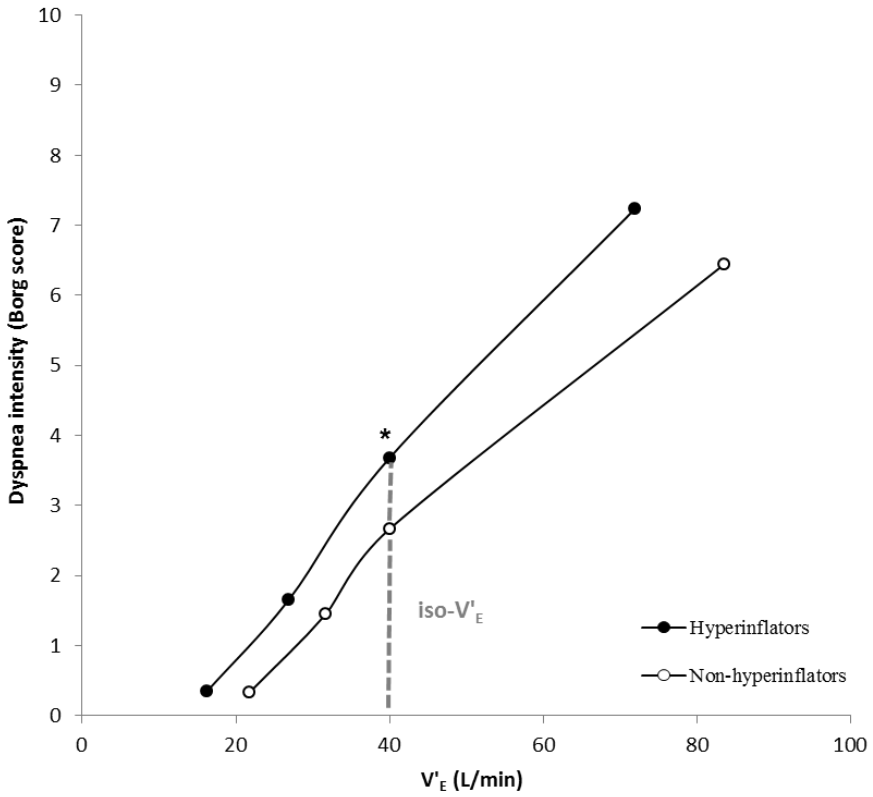

Dyspnea intensity (Borg score)
V'E (L/min)
iso-V'E
*
Hyperinflators
Non-hyperinflators

Figure 1B

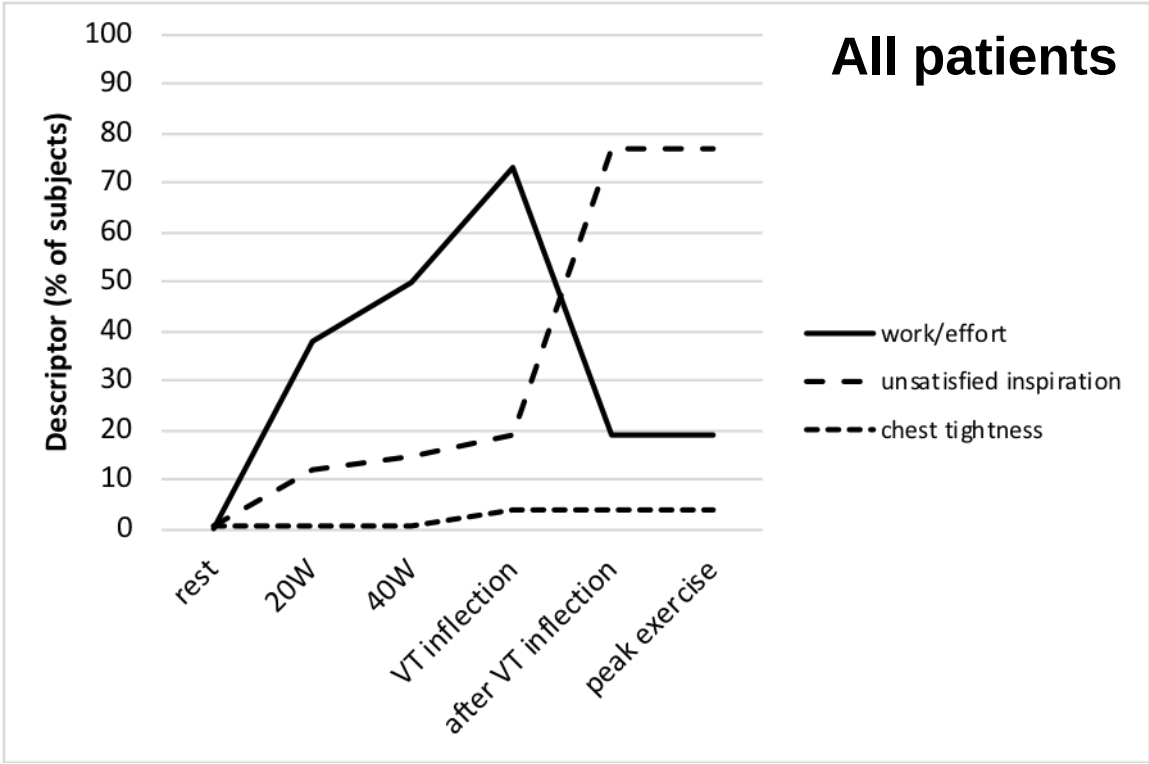

All patients
Descriptor (% of subjects)
100
90
80
70
60
50
40
30
20
10
0
rest
20W
40W
VT inflection
after VT inflection
peak exercise
work/effort
unsatisfied inspiration
chest tightness

Figure 2

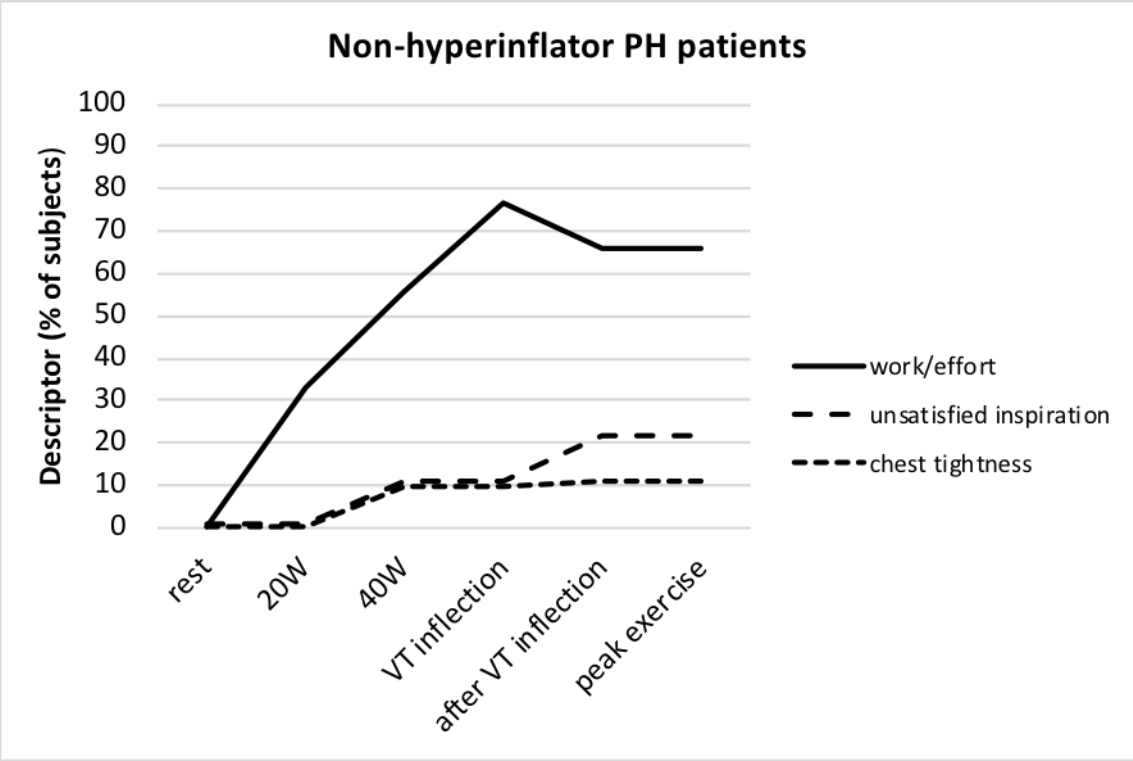

Non-hyperinflator PH patients
Descriptor (% of subjects)
100
90
80
70
60
50
40
30
20
10
0
rest
20W
40W
VT inflection
after VT inflection
peak exercise
work/effort
unsatisfied inspiration
chest tightness

Figure 3A

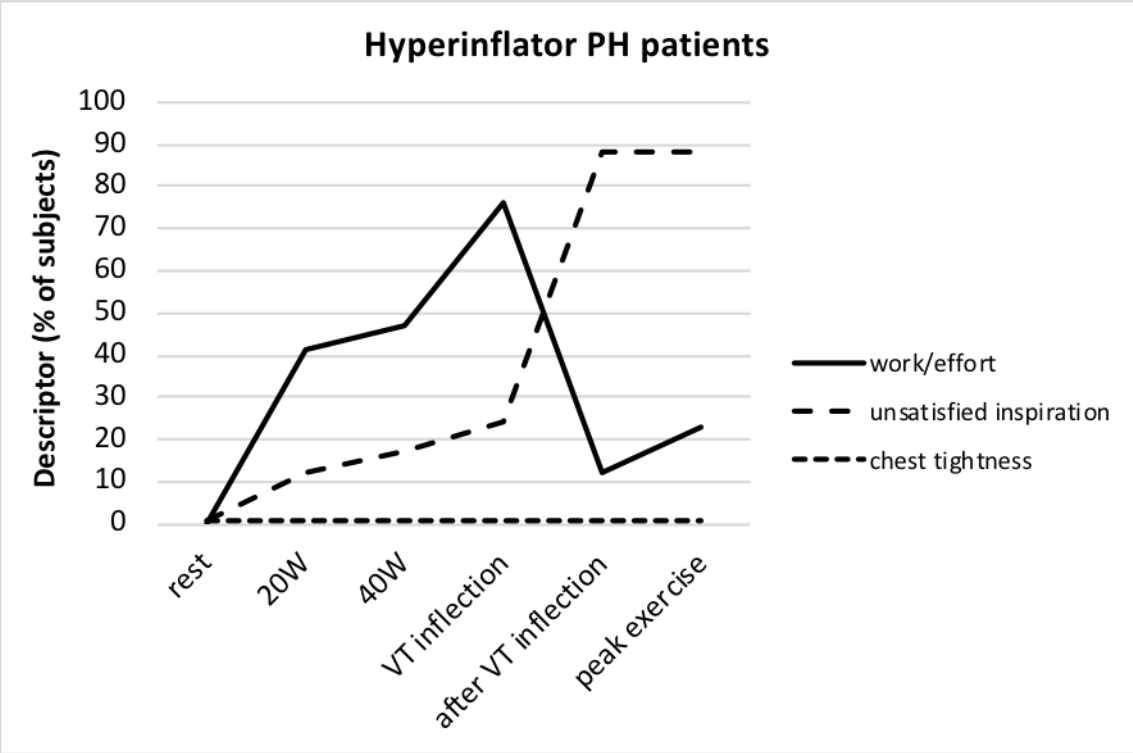

Hyperinflator PH patients
Descriptor (% of subjects)
100
90
80
70
60
50
40
30
20
10
0
rest
20W
40W
VT inflection
after VT inflection
peak exercise
work/effort
unsatisfied inspiration
chest tightness

Figure 3B

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

ON-LINE SUPPLEMENT

Authors:

Athénaïs Boucly[1,2,3], Capucine Morélot-Panzini[4,5], Gilles Garcia[1,3,6], Jason Weatherald[7,8], Xavier Jaïs[1,2,3], Laurent Savale[1,2,3], David Montani[1,2,3], Marc Humbert[1,2,3], Thomas Similowski[4,5], Olivier Sitbon[1,2,3#], Pierantonio Laveneziana[4,9#]

Affiliations:

[1]Univ. Paris-Sud, Faculté de Médecine, Université Paris-Saclay, Le Kremlin-Bicêtre, France; [2]AP-HP, Hôpital Bicêtre, Service de Pneumologie et Soins Intensifs, Le Kremlin-Bicêtre, France; [3]INSERM UMR_S_999, Hôpital Marie Lannelongue, Le Plessis Robinson, France; [4]Sorbonne Université, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, Paris, France; [5]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation, Département R3S, Paris, France; [6]APHP, Hôpital Bicêtre, Service de Physiologie, Le Kremlin-Bicêtre, France; [7]University of Calgary, Department of Medicine, Division of Respirology, Calgary, Alberta, Canada ; [8]Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta ; [9]AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service des Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée du Département R3S, F-75013 Paris, France.

Correspondence to: Dr. Pierantonio Laveneziana, Service d'Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée, Département "R3S" (Respiration, Réanimation, Réhabilitation, Sommeil), Pôle PRAGUES, Hôpital Universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), 47-83 Boulevard de l'Hôpital, 75013, Paris, France; Tel: 00 33 (0) 1 42 17 85 84; Fax: 00 33 (0) 1 42 17 85 76; email: pierantonio.laveneziana@aphp.fr

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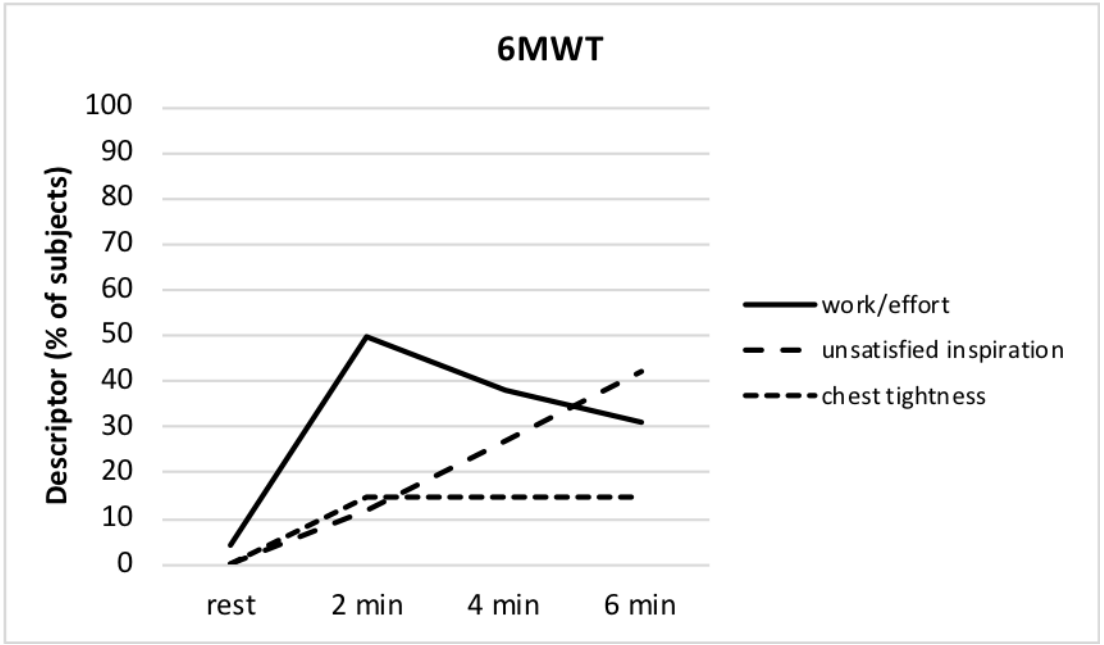
Table E1: Comparisons of patient characteristics, resting hemodynamic and pulmonary function between PAH and CTEPH patients

	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/m²	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

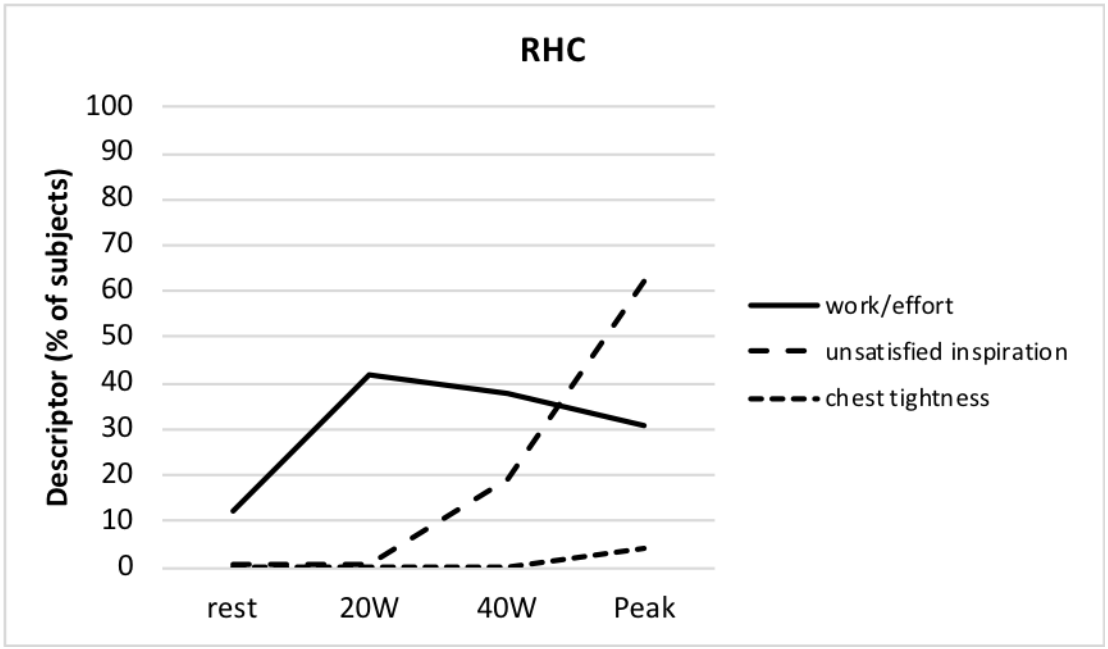

RHC
Descriptor (% of subjects)
100
90
80
70
60
50
40
30
20
10
0
rest
20W
40W
Peak
work/effort
unsatisfied inspiration
chest tightness

Figure E1