Cross-Sectional Assessment of the Relationships between Dyspnea Domains and Lung Function in Diffuse Parenchymal Lung Disease

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Key Words

Dyspnea · Interstitial lung disease · Lung diffusion for carbon monoxide · Mouth occlusion pressure · Ventilatory capacity · Ventilatory demand

Abstract

Background: Activity-related dyspnea is the main contributor to the altered quality of life in diffuse parenchymal lung diseases (DPLD). Instruments pertaining to dyspnea are classified as pertaining to domains of sensory-perceptual experience, affective distress or symptom/disease impact; whether these domains are equally related to lung function impairments remains to be established. **Objectives:** They were to assess the relationships between two domains of dyspnea (sensory-perceptual experience and symptom impact) and pulmonary function tests according to their evaluation of ventilatory demand, capacity and drive in patients suffering from DPLD. **Methods:** Fifty patients were prospectively enrolled (median age, 58 years; 25 women) and underwent spirometry, body plethysmography, measurements of lung diffusion for carbon monoxide (DLCO) and nitric oxide, maximal airway pressures (capacity and demand assessments), mouth occlusion pressure at 0.1 s ($P_{0.1}$: respiratory drive assessment) and a 6-min walk test with Borg score assessment (dyspnea:

sensory domain). The impact domain of dyspnea was evaluated using the baseline dyspnea index. **Results:** The sensory domain of dyspnea was linked to demand (CO transfer coefficient, kCO) only, while the impact domain was independently linked to demand and capacity (kCO and forced vital capacity, respectively). Among resting pulmonary function tests, both $P_{0.1}$ and DLCO allowed the assessment of these two domains of dyspnea. **Conclusions:** In DPLD, the sensory-perceptual domain of dyspnea is mainly linked to alterations in ventilatory demand while the impact domain is related to both demand and capacity. DLCO that assesses both demand and capacity and $P_{0.1}$ were the strongest correlates of dyspnea.

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Introduction

Activity-related dyspnea is the main contributor to the altered quality of life of patients suffering from diffuse parenchymal lung diseases (DPLD) [1–4]. As a consequence, dyspnea constitutes a major end-point of therapeutic trials [2] as well as routine follow-up [5]. A recent official American Thoracic Society statement proposed that instruments pertaining to dyspnea should be classified as pertaining to domains of sensory-perceptual experience,

affective distress or symptom/disease impact or burden [6]. The respective relationships between the degree of impairment in lung function and these different dyspnea domains remain to be established. In routine clinical practice, dyspnea evaluation often relies on the use of questionnaires of disease impact as Medical Research Council (MRC) scale, which is based on the recall of the level of activity associated with (or limited by) dyspnea sensory-perceptual experience. We and others have demonstrated that the relationship between dyspnea evaluated by the MRC scale and the degree of lung function impairment evaluated by vital capacity is weak [7, 8]. In clinical trials, activity-related dyspnea is often recorded at the end of a 6-min walk test (6MWT), but to the best of our knowledge, the relationship between this assessment of dyspnea and lung function has not been determined, which is an important issue since both are parameters and major end-points of clinical trials [1, 2].

Respiratory diseases, such as DPLD, are characterized by both increased ventilatory demand and altered ventilatory capacity that are present in varying degrees [6], and both would be affected in activity-related dyspnea. Consequently, our objectives were to assess the relationships between two different domains of dyspnea (sensory-perceptual experience and symptom impact) and pulmonary function tests based on the evaluation of ventilatory demand, capacity and drive in patients suffering from DPLD. We hypothesized that sensory-perceptual and impact domains of dyspnea would exhibit different relationships with lung function.

Patients and Methods

Design

This is a cross-sectional observational study conducted in a university hospital with a referral center for DPLD. Reporting is in accordance with STROBE Statement (<http://www.strobe-statement.org/>). Since a specific question was the assessment of ventilatory demand, we first needed to assess which respiratory function parameters were linked to the main pathophysiological determinant of demand [ratio of physiological dead space (VD)/tidal volume (VT)] in patients with DPLD.

Patients

Consecutive patients with DPLD referred for lung function testing were prospectively enrolled between April and July 2011, and between October and November 2011 (additional experiment). The diagnosis of DPLD was made according to current criteria [9]. Patients were not included if they had other unstable medical conditions that could cause or contribute to breathlessness or a severe psychiatric condition. The study was approved by the Ethics Committee of Ile de France VI (2011-A00388-33) and the patients gave written informed consent prior to participating.

Methods

Physiological VD/VT Ratio. Capnography and airflow measurements during tidal breathing, digitized using the MP-100 system (Biopac Systems Inc., Santa Barbara, Calif., USA), allowed the measurement of fractional expired carbon dioxide and VT while fractional arterial CO₂ was obtained from arterial blood gas. The physiological VD/VT ratio was calculated using the modified Bohr-Enghoff equation [10].

Dyspnea Assessment: 6MWT. Different domains of dyspnea were evaluated: the symptom impact (disability) using the MRC scale and the baseline dyspnea index (BDI), as described previously [8], and the sensory-perceptual experience while walking by rating dyspnea intensity using the CR-10 Borg scale (Borg scale with maximum set at 10, before and immediately after a 6-MWT [11]). The 6MWT was performed according to recommendations of the American Thoracic Society [11], and reported as distance (in m) and as percent of predicted distance [12]. Arterial saturation was assessed by pulse oximetry (SpO₂) each minute. Desaturation was defined as a decrease in SpO₂ of at least 4% on two successive measures [13].

Lung Function Tests. Routine resting lung function testing (MasterScreen, Jaeger, CareFusion, San Diego, Calif., USA) included spirometry, body plethysmography, and lung diffusion of carbon monoxide (DLCO) and of nitric oxide (DLNO), allowing the calculation of capillary blood volume available for gas exchange (VC) and membrane conductance for CO (membrane diffusion capacity for CO, DMCO), maximal inspiratory and expiratory airway pressures and mouth occlusion pressure at 0.1 s (P_{0.1}). Arterial blood gases were analyzed (ABL 520; Radiometer; Copenhagen, Denmark). Parameters were expressed as the percentage of theoretical values [14–17]. The theoretical value of P_{0.1} was 0.02/7*weight.

Statistical Analyses

Values were expressed as means ± SD or medians and interquartile ranges [25th and 75th percentiles]. Between-group comparisons were conducted using the Mann-Whitney U test (continuous variables) or χ^2 test (qualitative variables with Fisher's correction when necessary). Correlations were evaluated using Spearman's rank correlation coefficient. Multivariate linear analyses (with log-transformed values for nonnormally distributed variables) were performed using a backward selection method, and we limited the number of variables to 5 (1 variable per 10 patients) and 3 in the additional experiment [18, 19]. Due to the exploratory design of the study, no correction for multiplicity of testing was done [20]. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using Statview 5.0 software (SAS Institute, Berkeley, Calif., USA).

Results

A schematic representation of the pulmonary function tests assessing ventilatory demand, capacity and drive is shown in figure 1.

Population Characteristics

The characteristics of the 50 enrolled patients are presented in table 1.

Fig. 1. Schematic representation of the model of dyspnea [6]. The upper schema describes the physiological condition in which ventilatory demand and capacity are at equilibrium (balance). $\dot{V}_E$ = Minute ventilation; $\dot{V}_{CO_2}$ = CO_2 production; $phVD/VT$ = physiological VD/VT ratio; RR = respiratory rate; C = compliance of the respiratory system; ΔP_m = pressure drop related to muscular effort; R = resistance of the respiratory system; $\dot{V}$ = flow; ABG = arterial blood gases. Equation of the capacity has been obtained by rearrangement of the simplest equation for respiratory motion ($\Delta P_m = \dot{V}R + VT/C$). On exercise, in the presence of increased ventilatory demand or impaired capacity in chronic lung diseases (lower schema), the restoration of the balance for homeostasis purpose is obtained by increasing respiratory drive and the resulting increase in ventilation (when demand is increased with increased afferent output to respiratory centers, secondary increase in effort) or primary increase in respiratory muscle effort (reduced afferent feedback for a given efferent output when capacity is altered). A new balance state is observed but at the cost of increased drive and resulting sensation, i.e. dyspnea. FEV_1 = Forced expiratory volume in 1 s.

(Footnote to Table 1.)

Values are means $\pm$ SD or medians (interquartile ranges).

The p value is related to the comparison of patients with or without restrictive defect (defined by TLC below the lower limit of normal). VC/VA , $p = 0.24$; $DMCO/VA$, $p = 0.78$, $P_{0.1}/MIP$, $p = 0.49$. $FEF_{25-75\%}$ = Forced expiratory flow at 25–75% of the pulmonary volume; FEV_1 = forced expiratory volume in 1 s; FRC = functional residual capacity; MIP/MEP = maximal inspiratory and expiratory airway pressure; RV = residual volume; sR_{aw} = specific R_{aw} .

¹ Two patients did not have the 6MWT due to orthopedic problems at the time of the test.

Table 1. Clinical and functional characteristics of the patients

Characteristics	Whole population (n = 50)
Gender, female/male	25/25
Age, years	59 $\pm$ 15
Body mass index, kg/m ²	25.4 $\pm$ 3.8
Smoking history	
Never smokers, n	22
Former smokers, n	28
Dyspnea scales	
BDI	7.0 (5.0–11.0)
MRC grade	3.0 (2.0–3.0)
6MWT, n tested ¹	48
Borg score before 6MWT	0.0 (0.0–0.0)
Borg score after 6MWT	3.0 (1.0–5.0)
Distance, m	501 (422–564)
Distance, % of predicted	116 (97–134)
Desaturation, n	22
Spirometry	
FEV_1 , liters	2.03 (1.44–2.53)
FEV_1 , % of predicted	70 (59–81)
FVC, liters	2.55 (1.85–3.17)
FVC, % of predicted	70 (56–79)
FEV_1/FVC	0.84 (0.78–0.86)
$FEF_{25-75\%}$, l·s ⁻¹	2.14 (1.52–2.78)
$FEF_{25-75\%}$, % of predicted	84 (62–115)
Body plethysmography	
TLC, liters	4.12 (3.47–4.83)
TLC, % of predicted	73 (59–86)
FRC, liters	2.55 (2.14–2.88)
FRC, % of predicted	79 (66–91)
RV, liters	1.69 (1.35–1.91)
RV, % of predicted	79 (65–94)
R_{aw} , kPa·s·l ⁻¹	0.24 (0.18–0.29)
sR_{aw} , kPa·s	0.62 (0.46–0.84)
Arterial blood gas, n tested	45
PaO_2 , mm Hg	81 (71–91)
$PaCO_2$, mm Hg	38.4 (36.2–41.0)
Lung diffusion, n tested	48
kCO , mmol/min/kPa	1.07 (0.87–1.28)
kCO , % of predicted	74 (62–84)
VA, liters	3.50 (2.70–4.01)
VA, % of predicted	61 (51–70)
DLCO, mmol/min/kPa/l	3.65 (2.65–4.92)
DLCO, % of predicted	45 (33–56)
VC, ml	31 (21–43)
DMCO, mmol/min/kPa/l	8.69 (6.01–10.98)
Maximal static pressures	
MIP, kPa	5.89 (4.67–8.06)
MIP, % of predicted	80 (61–116)
MEP, kPa	6.85 (5.51–8.93)
MEP, % of predicted	73 (45–83)
Respiratory drive	
$P_{0.1}$, kPa	0.23 (0.18–0.32)
$P_{0.1}$, % of predicted	118 (79–192)
$P_{0.1}/MIP$	0.041 (0.022–0.071)
Physiological VD/VT	0.42 (0.35–0.51)

Table 2. Univariate analyses between BDI and pulmonary function parameters characterizing ventilatory demand and capacity

	BDI: impact domain of dyspnea		Borg score after 6MWT: sensory/perceptual domain	
	ρ value	p value	ρ value	p value
Ventilatory demand				
Physiological VD/VT ratio	-0.12	0.39	0.26	0.11
PaCO ₂ (mm Hg)	-0.10	0.51	-0.05	0.70
PaO ₂ (mm Hg)	0.45	0.003	-0.51	<0.001
kCO (% of predicted)	0.38	0.011	-0.43	0.003
VC/VA	0.36	0.017	-0.41	0.004
DMCO/VA (mmol/min/kPa/l)	0.23	0.13	-0.37	0.011
Ventilatory capacity				
TLC (% of predicted)	0.44	0.002	-0.22	0.11
VA (% of predicted)	0.46	0.002	-0.28	0.051
FRC (% of predicted)	0.40	0.005	-0.21	0.12
FVC (% of predicted)	0.44	0.002	-0.20	0.15
FEV ₁ (% of predicted)	0.48	<0.001	-0.18	0.19
R _{aw} (kPa·s·l ⁻¹)	-0.35	0.012	0.12	0.44
MIP (% of predicted)	-0.18	0.21	0.03	0.88
MEP (% of predicted)	0.21	0.13	-0.23	0.10
Ventilatory drive				
P _{0.1} (% of predicted)	-0.65	<0.001	0.39	0.009
P _{0.1} /MIP	-0.55	<0.001	0.39	0.008

For abbreviations, see legend to table 1.

DPLD was classified into 4 categories [9]: (1) DPLD of known association (e.g., drugs, $n = 1$, connective tissue diseases, $n = 16$, and environmental/occupational exposure, $n = 1$), (2) granulomatous DPLD (sarcoidosis, $n = 8$), (3) rare DPLD (eosinophilic pneumonia, $n = 1$) and (4) fibrosing idiopathic interstitial pneumonitis ($n = 23$). Nineteen patients received systemic steroid treatment (median 24 mg, range 5–60 mg).

Exercise capacity (6MWT distance expressed as % of predicted) correlated with forced vital capacity (FVC; $\rho = 0.41$, $p = 0.005$) and DLCO ($\rho = 0.40$, $p = 0.006$), both expressed as % of predicted. Exercise capacity correlated more closely with the impact domain of dyspnea (MRC: $\rho = -0.58$, $p < 0.0001$; BDI: $\rho = 0.64$, $p < 0.0001$) than with its sensory-perceptual domain (Borg: $\rho = -0.36$, $p = 0.013$).

Routine Functional Parameters Linked to Resting Ventilatory Demand

A significant relationship between the physiological VD/VT ratio and both CO transfer coefficient (kCO; % of predicted; $\rho = -0.30$, $p = 0.049$), VC/alveolar volume (VA; $\rho = -0.35$, $p = 0.025$) and DMCO/VA ($\rho = -0.37$, $p = 0.020$) were found, showing that several DLCO parameters are linked to resting ventilatory demand.

Correlations between the Different Methods of Dyspnea Assessment

The two measures of dyspnea impact were highly correlated ($\rho = -0.89$, $p < 0.001$) and can be considered as equivalent. The BDI was used for subsequent analyses. Dyspnea sensory-perceptual experience evaluated using the Borg scale at the end of the 6MWT was correlated (both $p < 0.001$) with the measures of impact domain of dyspnea: MRC scale ($\rho = 0.71$) and BDI ($\rho = -0.67$).

Relationships between Resting Functional Parameters and Dyspnea Domains

The univariate analyses used to assess these relationships are described in table 2 demonstrating that the sensory-perceptual domain of dyspnea after 6MWT was closely associated with resting ventilatory demand, while the impact domain of dyspnea was associated with both ventilatory demand and capacity. The main results of the univariate analyses are summarized in figure 2.

A multivariate analysis was conducted with BDI score as the dependent variable and 4 variables that assess demand (arterial oxygen tension, PaO₂ and kCO) or capacity (FVC and airway resistance, R_{aw}) as independent variables. This analysis showed that both kCO and FVC were

Fig. 2. Schematic representation of the main results of univariate analyses. The sensory domain of exertional dyspnea is linked to ventilatory demand only, while the impact domain of dyspnea is linked to both demand and capacity.

independently associated with BDI (coefficient: 0.40, $p = 0.017$, and coefficient: 0.29, $p = 0.038$, respectively; p value of the model = 0.002, $r^2 = 0.37$), demonstrating the independent association of ventilatory demand and capacity with the impact domain of dyspnea.

As DLCO is calculated by multiplying kCO by VA, we evaluated its relationship with dyspnea domains. There was a significant relationship between DLCO % of predicted and both BDI and Borg score after 6MWT (fig. 3).

Respiratory drive ($P_{0.1}$) was correlated (relationships between % predicted values to avoid confounding effect of anthropometrics) with parameters characterizing ventilatory capacity: lung volumes (total lung capacity, TLC: $\rho = -0.46$, $p = 0.001$) and airway caliber (R_{aw} : $\rho = 0.53$, $p < 0.001$). There was no relationship with maximum airway pressures. Predicted $P_{0.1}$ was also correlated with parameters characterizing ventilatory demand, as kCO % of predicted ($\rho = -0.34$, $p = 0.020$) and PaO_2 ($\rho = -0.42$, $p = 0.005$).

Additional Experiment

The sensory-perceptual experience is what breathing feels like to the patient, it can also be assessed by descriptors of specific sensations [6]; furthermore, von Leupoldt et al. [21] have shown that sensory and affective aspects of perceived dyspnea differentially influence the global measure of dyspnea determined by the Borg scale. Therefore, an additional experiment was conducted with the first 25 patients seen for their follow-up visit 6 months

Fig. 3. Relationships between DLCO and dyspnea domains. **a** Relationship between DLCO (% of predicted) and dyspnea (BDI: impact domain of dyspnea): $\rho = 0.55$, $p = 0.0002$. **b** Relationship between DLCO (% of predicted) and dyspnea (Borg score after 6MWT: sensory domain of dyspnea): $\rho = -0.42$, $p < 0.003$.

later in order to better describe this domain of dyspnea while walking. At the end of the 6MWT, the patients were instructed to rate their overall dyspnea first, then the sensory domain and affective dimension of dyspnea was explained (descriptors of work/effort and air hunger, and distress and anxiety associated with dyspnea, respectively) and quantified (Borg CR-10 scale), as previously done by other investigators [21–23]. Relationships with ventilatory demand and capacity obtained on the same day were also assessed.

The results of this additional experiment are summarized in table 3, which shows that the Borg score at the end of the 6MWT (overall assessment of dyspnea) was linked to effort and air hunger sensations and to the af-

Table 3. Relationships between dyspnea domains and pulmonary function in the additional experiment conducted in 25/50 patients: Spearman rank test, ρ value and p value

	Sensory-perceptual domain of dyspnea		Affective domain	Ventilatory capacity		Ventilatory demand	
	Borg score (effort)	Borg score (air hunger)	Borg score	FEV ₁ (% predicted)	FVC (% predicted)	DLCO (% predicted)	kCO (% predicted)
Overall dyspnea	0.65	0.74	0.56	-0.27	-0.31	-0.46	-0.54
Borg score	0.0018	0.0003	0.0056	0.187	0.132	0.0178	0.0086

The overall assessment of dyspnea is obtained using Borg score quantification at the end of the 6MWT, the median (25th–75th percentiles) value of this score was 4.0 (3.0–5.0) [the affective dimension of dyspnea was rated 3.0 (0.75–5.0)]. DLCO assesses both demand and capacity. For abbreviations, see legend to table 1.

factive dimension of dyspnea. The Borg scores related to the sensation of air hunger (sensory domain of dyspnea) and to the affective domain of dyspnea were closely correlated ($\rho = 0.84$, $p < 0.0001$).

Discussion

This cross-sectional physiological study demonstrated that the sensory-perceptual domain of dyspnea after the 6MWT of patients suffering from DPLD is linked to the resting ventilatory demand only, while the impact domain of dyspnea is linked to both resting ventilatory demand and capacity. Among usual resting pulmonary function tests, DLCO allows an optimal assessment of these two domains of dyspnea in DPLD.

The pathophysiology of DPLD is multifactorial, including interstitial, bronchiolar and vascular injuries [9], and one may hypothesize that both increased ventilatory demand and altered ventilatory mechanics are present at varying degrees [6]. Ventilatory demand depends on CO₂ production, the arterial carbon dioxide tension (PaCO₂) set point and wasted ventilation (VD/VT ratio) while ventilatory mechanics, or capacity, rely on the impedance of the respiratory system (including elastance and resistance) and the muscle force required to allow ventilation [24]. While exercising, as the demand for ventilation exceeds the capacity (impaired in DPLD) to provide it, a state of imbalance develops between the motor drive to breathe (evaluated by $P_{0.1}$ in our study), as sensed via corollary discharge, and afferent feedback from mechanoreceptors of the respiratory system [6]. This becomes increasingly unpleasant and distressing

(dyspnea increases). This sensory-perceptual experience of dyspnea was quantified at 6MWT using the Borg score in our study. The additional experiment further showed that two sensations of this sensory-perceptual experience, namely inspiratory effort and air hunger, independently contributed to the Borg score. Accordingly, O'Donnell et al. [25] have shown that patients with interstitial lung diseases depict distinctive qualitative perceptions of inspiratory difficulty, unsatisfied inspiratory effort (including the feeling of a need for more air) and rapidity of breathing. The air hunger sensation was closely associated with the affective domain of dyspnea in our experiment. Banzett et al. [26] have demonstrated that maximal respiratory work is less unpleasant than moderately intense air hunger in a brief test in healthy subjects and that unpleasantness of dyspnea can vary independently from perceived intensity. These unpleasant sensations will also affect daily activities, which can be assessed by the impact domain of dyspnea (assessed by MRC scale or BDI) [6]. Why the sensory-perceptual experience of dyspnea was not linked to ventilatory capacity remains open to discussion. We hypothesize that the less stressful work/effort sensation related to capacity may have dampened the relationship with the Borg score.

To the best of our knowledge, this is the first study to address the relationship between respiratory drive and dyspnea in DPLD. It has been shown that ventilatory and drive parameters increased in interstitial lung diseases as a function of elastic load [27]. It has to be stated that $P_{0.1}$ is a crude assessment of respiratory drive. $P_{0.1}$ is the pressure generated in the first 100 ms of inspiration against an occluded airway. Its timing is such that it is not influenced by the conscious response to occlusion, and as an

index of ventilatory drive, it has the advantage over ventilation of being independent of the mechanical properties of the lung [28]. It is, however, dependent on the contractile state and function of the respiratory muscles and consequently on the lung volume at which it is measured. Finally, $P_{0.1}$, due to its proximal and integrative nature, was linked to dyspnea.

The dual origin of dyspnea (demand and capacity) explains why DLCO was the most highly correlated with dyspnea among routine pulmonary function tests, as previously observed in DPLD and chronic obstructive lung disease [7, 29, 30]. To our best knowledge, the first demonstration of the statistical relationship between DLCO and dyspnea (BDI and MRC score) in interstitial lung diseases was made by Mahler et al. [29], while ventilatory capacity (TLC and FVC) did not correlate with dyspnea. DLCO is calculated by multiplying kCO and VA, the former being linked to demand (increased physiological VD/VT ratio), as previously shown in patients with chronic obstructive lung disease [31], and the latter to capacity (restrictive defect). We previously established in patients with chronic obstructive lung disease that both resting and peak exercise physiological VD/VT ratios were linked to DLCO [31], further justifying the only evaluation of ventilatory demand at rest in this study. Obviously, kCO is a crude surrogate marker of demand, but available in most lung function testing laboratories. Histological patterns may include some degree of bronchiolar and vascular injury. Our results suggest that the vascular disease observed in DPLD (quantified by VC/VA) is an important contributor to dyspnea, which is an original finding.

Overall, the correlations between dyspnea and resting pulmonary function are modest in our study, and that more than half of variance in dyspnea is not explained. First, pulmonary function tests were obtained at rest, which is an inherent limitation, but these tests are those commonly performed in routine practice and even in therapeutic trials. Second, the level of variance in dyspnea explained by these resting function tests is in agreement with those observed in other studies in DPLD [7, 8, 32]. Third, even when evaluating the correlates of dyspnea with ventilatory mechanics on exercise, the explained variance in dyspnea remains modest [25].

Our cross-sectional physiological study has inherent limitations. First, our conclusions are based on correlative analyses that do not imply causality. Our patients were suffering from various causes of DPLD and our results may not apply to all causes separately. However, this

nonselective design was warranted since we wanted to assess the multidimensional aspects of DPLD, and we first verified that we were able to reproduce the results of other studies (as the relationship between FVC and performance for instance [25]). The number of patients included was restricted, but all were characterized using a large panel of routine function tests, even if nonvolitional tests for muscle strength assessment were not applied. Finally, pulmonary function was evaluated at rest only, and our results may not be generalizable to patients with other pulmonary conditions obviously.

The practical consequences are twofold. First, DLCO is a test that is related to both impact and sensory domains of dyspnea. Since activity-related dyspnea is the main complaint in DPLD, DLCO measurement should be performed routinely. Second, our study emphasizes that dyspnea quantification at the end of the 6MWT should not be considered as a 'better' assessment than dyspnea obtained by recall since both are clearly different: belonging to different domains and linked to different features of pulmonary function; rather dyspnea assessment should be based on judgments about which measurement domains are of theoretical interest and relevant to study aims.

In conclusion, in DPLD, the sensory-perceptual domain of dyspnea is mainly linked to alterations in ventilatory demand assessed by kCO measurement, while the impact domain of dyspnea is related to both ventilatory demand and capacity, assessed by DLCO measurement.

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