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Contribution of small airway disease to dynamic hyperinflation in patients with chronic obstructive pulmonary disease

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Abstract

Lung hyperinflation is a treatable trait in chronic obstructive pulmonary disease (COPD) that can often only be detected on exertion. Air trapping in these patients results from the premature closure of the small airways. This study aimed to assess the association between small airway disease (SAD) and dynamic hyperinflation (DH) induced by the Glittre-daily life activities test (TGlittre) in COPD patients. This is a cross-sectional study in which 54 patients with COPD underwent TGlittre coupled with dynamic ventilation measurements. They also underwent the COPD Assessment Test (CAT) questionnaire, the St. George's Respiratory Questionnaire (SGRQ), spirometry, and respiratory oscillometry (RO). In the TGlittre, 30 (55.6%) participants presented DH (DH group), while 24 (44.4%) did not (NDH group). When comparing these two groups, we observed no statistical difference concerning the CAT score, SGRQ score, and spirometric parameters. Respectively, 27 (90%) and 9 (37.5%) participants in the DH and NDH groups presented changes in the RO, with the DH group showing higher values in the reactance area [Ax, 24.7 (17-46) vs. 6.1 (4-9) cm H2O/L/s, $p<0.0001$] and resonance frequency [Fres, (8 (4.3-17.9) vs. 2.8 (2.3-4.7) Hz, $p<0.0001$]. DH correlated significantly with Fres ($rs=-0.604$, $p<0.0001$), Ax ($rs=-0.652$, $p<0.0001$), and several domains of the SGRQ and CAT scores. In the multivariate regression analysis, Fres and Ax explained 49% of the variability in DH. In conclusion, our results show that patients with COPD and DH have more altered RO. In these patients, the more pronounced the DH, the worse the RO parameters, the greater the symptom impact, and the more deteriorated the quality of life. Furthermore, SAD is a significant predictor of DH in this patient population.

Key words: chronic obstructive pulmonary disease, exercise, respiratory function test, small airway disease.

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Introduction

In addition to airflow limitation, in recent years, chronic obstructive pulmonary disease (COPD) has been recognized as a condition with multiple pulmonary and extrapulmonary pathophysiological mechanisms that contribute to the disease burden [1,2]. In patients with COPD, lung hyperinflation (LH) is a common clinical feature that results from a combination of reduced elastic lung recoil and expiratory flow limitation (EFL) [2]. EFL is exacerbated on exertion by damaged airways that collapse under modest intrathoracic pressures [3]. Furthermore, LH is an important determinant of morbidity and mortality in COPD and is partially independent of the degree of EFL [4,5].

In COPD, LH is a broad phenotype with typical pulmonary features including specific symptoms, marked comorbidities, differentiated extrapulmonary manifestations, and different disease trajectories [6,7]. LH is regarded as a treatable trait for which diagnostic criteria and specific interventions are available [2]. In COPD, dynamic hyperinflation (DH) is a major contributor to EFL and is defined as a temporary increase in end-expiratory volume when ventilation is increased, resulting in a discrepancy between the time required for the lungs to empty during expiration and the time available between two consecutive inspiratory efforts [6]. Although DH mitigates EFL and preserves the neuromechanical coupling of the respiratory system, it compromises mechanical efficiency, evokes tidal volume constraint, and increases the work of breathing [3]. Inspiratory capacity (IC) maneuvers during exercise provide valuable information on ventilatory constraints and, therefore, a decline in IC during exercise is an indication of the presence of DH [8].

Although the small airways account for less than 10% of the total airflow resistance in normal lungs, they become the main site of EFL in COPD [2]. Residual volume in these patients is increased not only due to reduced elastic recoil and EFL at low lung volume but also because of premature closure of the small airways during expiration [2]. This phenomenon is already observed even in COPD

patients with mild airflow limitations [3,9]. In patients with COPD, small airway disease (SAD) is one of the main contributors to EFL because the small airways become excessively compressed due to the destruction of the supporting alveolar attachments [10]. In these patients, the loss of small airway support can deteriorate during exertion and contribute to worsening EFL and be an important determinant of DH [11]. Inflammation and structural damage to the small airways precede a marked decrease in EFL, leading to air trapping even early in the course of the disease [12].

One of the exercise tests proposed to assess patients with COPD is the Glittre-daily life activities (ADL) test (TGlittre), which assesses a set of common daily life tasks, such as sitting and standing, going up and down steps, and moving objects from shelves at different heights [13]. In addition to being an easy-to-administer and reliable test [14], the TGlittre has excellent test-retest reliability for assessing functional exercise capacity in patients with COPD (ρ=0.93, $p<0.001$) [13]. Compared with the 6-minute walk test (6MWT), the TGlittre better simulates the situations experienced in ADLs and therefore more accurately measures the burden experienced by patients with COPD [15]. There is a relationship between time to complete the TGlittre and stage of COPD, reported activity limitations, degree of dyspnea during ADLs, and hospitalization rate [13,16-18]. Although the TGlittre is a submaximal test, patients with COPD, when performing the TGlittre, have pulmonary ventilation and oxygen uptake values close to the peak values measured in the cardiopulmonary exercise test (CPET) [19]. As the degree of airflow obstruction progresses, patients with COPD have significantly lower ventilatory reserve to perform the Glittre ADL test [20], which can lead to DH [17]. Furthermore, COPD patients who reported ADL limitation took longer to complete the TGlittre and had a lower oxygen pulse on CPET than those without ADL limitation [21].

There is growing evidence suggesting that LH is not just an isolated feature in COPD, but rather part of a distinct clinical phenotype that may warrant a more integrated treatment [2]. Therefore, reducing LH has become an important target in the treatment of COPD in recent decades, since DH is a treatable trait in COPD. Thus, advances in the diagnosis of LH have become crucial. In this sense, it is increasingly evident that, although the degree of EFL and LH has a certain correlation, many patients present distinct hyperinflation without severe EFL [1]. Since DH is an important contributor to exercise limitation that impacts ADLs [22], we hypothesized that SAD is a contributor to DH in patients with COPD during TGlittre. Thus, the present study aimed to evaluate the association between SAD and TGlittre-induced DH in patients with COPD.

Materials and Methods

Study design, participants and ethics

Between January and August 2024, we conducted a cross-sectional study with COPD patients aged ≥18 years treated at the Piquet Carneiro University Policlinic, State University of Rio de Janeiro, Rio de Janeiro, Brazil. COPD was diagnosed based on clinical manifestations, self-reported smoking history, and the presence of EFL defined as post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio <70% [23]. Based on post-bronchodilator FEV_1, we adopted the cut-off points for the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades and severity of airflow obstruction in COPD [23]. We adopted the following exclusion criteria: presence of severe cardiovascular disease; evidence of malignancy or severe renal or hepatic dysfunction; upper or lower limb dysfunction that could impair the performance of the TGlittre; and inability to perform the TGlittre.

The study was approved by the Research Ethics Committee of the Centro Universitário Augusto Motta (UNISUAM), Rio de Janeiro, Brazil, under protocol number CAAE-76445923.3.0000.5235, and all participants provided written informed consent. All study participants signed an informed consent form, following the Declaration of Helsinki.

Measurements

The COPD Assessment Test (CAT) questionnaire was used to quantify the impact of COPD symptoms on participants' health. This questionnaire consists of eight questions related to cough, phlegm, chest tightness, breathlessness, activity limitation, confidence leaving home, sleep, and energy. Participants select only one response for each question, with a score ranging from zero to five. The results vary according to the range of scores obtained and are classified in relation to clinical impact as follows: 6-10 points, mild; 11-20, moderate; 21-30, severe; and 31-40, very severe [24].

Quality of life (QoL) was assessed using the St George's Respiratory Questionnaire (SGRQ), which was previously validated and adapted for the Brazilian population [25]. This instrument covers aspects in three domains (symptoms, activity, and impacts). The answers are translated into points, which, once added up, can infer an altered QoL in a given domain. A value has been determined for each domain which can vary between 0 and 100%. Values below 10% are considered normal; 11-25%, mild impact on QoL; 26-45%, moderate impact on QoL; 46-75%, severe impact on QoL; and 76-100%, very severe impact on QoL [26].

We performed spirometry using Vitatrace VT 130 SL equipment (Codax Ltda, Rio de Janeiro, Brazil), following previous standards [27]. We used equations with Brazilian predicted values to interpret spirometry [28]. To assess SAD, we performed respiratory oscillometry (RO) using Quark i2m equipment (Cosmed, Rome, Italy), following previous standardizations [29]. We assessed the following resistive and reactive parameters: respiratory system resistance at 5 Hz (R5) and 20 Hz (R20); mean resistance between 5-20 Hz; heterogeneity of resistance between 5-20 Hz (R5-R20); resonance frequency (Fres); respiratory system reactance at 5 Hz (X5) and 20 Hz (X20); and reactance area (Ax). A Fres value of >12 Hz and an Ax value of ≥8.66 cm H_2O/L/s were considered abnormal [30,31].

Participants underwent an assessment of their functional capacity on exertion using the TGlittre, following previous standards [13]. The time spent performing the TGlittre was recorded, and the values were compared to the Brazilian predictions of Reis *et al*. [32]. Pulmonary ventilation measurements were incorporated into the TGlittre using the Spiropalm® portable device (Spiropalm 6MWT, Cosmed, Rome, Italy). With the participant seated on the chair before the beginning of the test, a silicone face mask was attached to his/her face. Before and at the end of the TGlittre, IC was measured, and a decrease of ≥100 mL (ΔIC) during exertion was defined as DH [33]. In addition to IC, other dynamic ventilatory responses were measured, including minute ventilation (VE) and breathing reserve (BR). BR indicates how closely VE approaches maximal ventilation during exertion and was calculated as the difference between maximal voluntary ventilation (MVV) and VE_{peak} ([MVV-VE_{peak}]/MVV) [33]. In this study, BR<30% was considered severe ventilatory limitation on exertion [34]. MVV was determined by the device as FEV_1 times 40. Spiropalm® also provided heart rate (HR) and peripheral oxygen saturation (SpO_2) [33].

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Statistical analysis

The statistical analysis was processed using SPSS statistical software version 26 (IBM Corp., Armonk, NY, USA). The normality of the data distribution was verified using the Shapiro-Wilk test and graphical analysis of the histograms. The comparison of variables between participants who underwent DH (DH group) and those who did not (NDH group) at the end of the TGlittre was analyzed by the Student's *t*-test for independent samples or the Mann-Whitney test for numerical data and by the chi-square ($\chi 2$) or Fisher's exact test for categorical data. The association with TGlittre time (% predicted) or ΔIC (L) was analyzed using Spearman's correlation coefficient for numerical variables and by Student's *t*-test for independent samples or one-way analysis of variance for categorical variables. For exploratory purposes only, we applied the multivariate analysis using multiple linear regression (MLR) to identify the independent variables that explained the variability of TGlittre time and ΔIC. The process we adopted to select variables was stepwise forward, at a 5% level, which selects the smallest subgroup of independent variables that best explains the dependent variable (TGlittre time or ΔIC). We adopted a 5% significance level.

Results

Characteristics of the participants

Of the 56 patients with COPD eligible for the study, two were excluded because they had interrupted TGlittre due to severe dyspnea. Thus, the sample consisted of 54 participants (30 women and 24

Table 1. Comparisons of clinical data, chronic obstructive pulmonary disease severity, symptom impact, quality of life, and exercise functional capacity between patients with and without dynamic hyperinflation.

Variable	Total sample	DH group	NDH group	p
Clinical data				
Female/male ratio	30/24	17/13	13/11	0.85
Age (years)	67.4±7.4	67.4±7.2	67.3±7.9	0.96
BMI (kg/m²)	25.6±5.1	25.8±4.8	25.3±5.6	0.76
Smoking load (pack-years)	48.5 (23-80)	50.5 (28-68)	46 (21-81)	0.73
Hypertension (%)	31 (57.4)	16 (53.3)	15 (62.5)	0.50
Diabetes (%)	13 (24.1)	9 (30)	4 (16.7)	0.25
COPD severity				
GOLD 1 (%)	9 (16.7)	5 (16.7)	4 (16.7)	0.76
GOLD 2 (%)	17 (31.5)	8 (26.7)	9 (37.5)	
GOLD ¾ (%)	28 (51.9)	17 (56.7)	11 (45.8)	
CAT score				
CAT cough score	3 (2-4)	3 (3-4.8)	2.5 (1-4)	0.081
CAT phlegm score	2.5 (1-4)	3 (0.8-4.3)	2 (1-3.8)	0.94
CAT chest tightness score	2 (0-3)	2 (0-3)	1.5 (0-3)	0.72
CAT breathlessness score	4 (3–5)	5 (3.3-5)	4 (3-5)	0.17
CAT activity limitation score	3 (1.8-5)	3 (2-5)	3 (0.8-5)	0.80
CAT confidence leaving home score	0.5 (0-4)	1.5 (0-3.8)	0 (0-4)	0.30
CAT sleep score	3 (1-4)	3 (1.3-4)	3 (0.8-4)	0.60
CAT energy score	3 (1.8-4)	3 (2-4)	3 (1-4)	0.60
CAT sum score	20.8±8.8	22.3±8.6	19.6±8.9	0.28
SGRQ score				
SGRQ symptom score	54.8±19	59.1±18.4	51.4±19.1	0.14
SGRQ activity score	65.3±24.5	68.2±21.3	63±26.9	0.44
SGRQ impact score	41.5±20	47.4±17	36.9±21.2	0.053
SGRQ total score	51.1±19.2	55.7±16.8	47.3±20.5	0.11
Glittre-ADL test				
Total time (min)	5.7±1.2	5.9±1.4	5.6±1	0.52
Total time (% predicted)	142±29	145±35	139±23	0.50
Basal SpO_2 (%)	96 (94-97)	95 (94-97)	97 (94-97)	0.47
End-of-test SpO_2 (%)	95 (95-97)	95 (94-97)	96 (95-97)	0.41
Basal HR (pulse/min)	82.6±18.7	88.6±18.7	77.3±18.4	0.20
End-of-test HR (pulse/min)	89.3±18.9	98.1±15.9	82.3±18.9	0.08
Resting VE (L/min)	12.1 (9-15)	10.4 (10-15)	14 (8-16)	0.80
VE_{peak} (L/min)	19.8 (13-27)	19.5 (13-26)	21.6 (14-32)	0.47
BR (%)	64.9 (46-73)	60.8 (44-70)	69.1 (48-75)	0.12
Basal IC (L)	1.64±0.69	1.77±0.67	1.48±0.69	0.12
End-of-test IC (L)	1.52±0.68	1.39±0.63	1.69±0.72	0.11
ΔIC (L)	-0.12±0.39	-0.38±0.28	0.21±0.23	NA
ΔIC (%)	-3.97±27.6	-21.5±13.8	18±24.8	NA

DH group, patients with dynamic hyperinflation; NDH, patients without dynamic hyperinflation; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, chronic obstructive pulmonary disease Assessment Test; SGRQ, St George's Respiratory Questionnaire; SpO_2, peripheral oxygen saturation; HR, heart rate; VE, minute ventilation; BR, breathing reserve; IC, inspiratory capacity; NA, not applicable. Data represent mean ± standard deviation, median (interquartile range) or number (percentage).

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men), with a mean age of 67.4±7.4 years. The smoking load was 48.5 (23-80) pack-years. According to GOLD grades, 9 (16.7%), 17 (31.5%) and 28 (51.9%) participants were GOLD 1, GOLD 2 and GOLD 3/4, respectively. According to the CAT questionnaire, 28 (51.9%) participants were classified as mild/moderate and 26 (48.1%) as severe/very severe (Table 1).

Comparison of clinical data, quality of life and functional exercise capacity according to dynamic hyperinflation

In the TGlittre, 30 (55.6%) participants showed DH at the end of the test, while 24 (44.4%) did not. When these two groups were compared, no statistical differences were observed regarding gender, age, body mass index, smoking load, and comorbidities. The two groups also showed no significant differences regarding GOLD COPD severity, the CAT score, and the SGRQ score. Although participants in the DH group took longer to complete the TGlittre tasks, there was no statistical difference between the two groups (145±35 *vs*. 139±23 % predicted, p=0.50). It should be noted that both groups took longer to perform the TGlittre tasks when compared to the Brazilian predicted values [32]. The two groups did not differ concerning SpO_2, HR variability, ventilatory demand, and BR. Table 1 shows the comparison of clinical data, COPD severity, symptom impact, QoL, and functional exercise capacity between patients with and without DH.

Comparison of pulmonary function tests according to dynamic hyperinflation

The DH and NDH groups showed no significant differences in spirometric parameters. Although the median values of FEV_1 [(46.8 (34-67) *vs*. 50.6 (37-66)] and forced expiratory flow during the middle half of the FVC maneuver [($FEF_{25-75\%}$, 16.7 (11-35) *vs*. 22.7 (15-35) % predicted] were lower in the DH group, there were no significant differences between them (p=0.72 and p=0.42, respectively). RO was altered in 27 (90%) participants in the DH group and only in 9 (37.5%) in the NDH group (p<0.0001). The median values for Fres [(8 (4.3-17.9) *vs*. 2.8 (2.3-4.7) Hz] and Ax [(24.7 (17-46) *vs*. 6.1 (4-9) cm H_2O/L/s] were higher in the DH group, with significant differences between them (p<0.0001 for both variables). Table 2 shows the comparison of pulmonary function test (PFT) results between participants with and without DH.

Correlations between functional exercise capacity and other study variables

There was a significant correlation between TGlittre time (% predicted) and CAT phlegm score (r_s=0.431, p=0.001), CAT breathlessness score (r_s=0.276, p=0.043), CAT confidence leaving home score (r_s=0. 277, p=0.042), CAT sum score (r_s=0.345, p=0.010), SGRQ activity score (r_s=0.357, p=0.008), SGRQ impact score (r_s=0.355, p=0.008), and SGRQ total score (r_s=0.353, p=0.008). Concerning PFTs, TGlittre time (% predicted) showed a significant correlation with FVC (r_s=-0.310, p=0.022) and FEV_1 (r_s=-0.342, p=0.011). Regarding the variables collected during the test itself, TGlittre time showed significant correlation with VE_{peak} (r_s=-0.588, p<0.0001), basel IC (r_s=-0.533, p<0.0001) and end-of-test IC (r_s=-0.486, p=0.0002). The subgroup with CAT >20 showed a higher TGlittre time than the subgroup with CAT ≤20 (151±20 *vs*. 133±26 % predicted, p=0.024). Table 3 shows Spearman's correlation coefficients for TGlittre time with clinical data, symptom impact, QoL, PFTs, and functional exercise capacity.

Correlations between dynamic hyperinflation and other study variables

The ΔIC (L) presented significant correlation with CAT cough score (r_s=-0.259, p=0.032), CAT breathlessness score (r_s=-0.273, p=0.046), SGRQ symptom score (r_s=-0.413, p=0.002), SGRQ impact score (r_s=-0.411, p=0.002), and SGRQ total score (r_s=-0.386, p=0.004). Concerning PFTs, there was a significant correlation between ΔIC and Fres (r_s=-0.604, p<0.0001) and Ax (r_s=-0.652, p<0.0001). For the variables collected during the test itself, ΔIC (L) showed a significant correlation with basal HR (r_s=-0.576, p=0.009) and BR (r_s=0.301, p=0.044). The subgroup with abnormal RO showed lower ΔIC than the subgroup with normal RO (-0.26±0.34 *vs*. 0.16±0.35 L, p<0.0001), while the subgroup with CAT >20 showed lower ΔIC than the subgroup with CAT ≤20 (-0.22±0.44 *vs*. -0.01±0.30 L, p=0.024). Table 3 and Figure 1 show Spearman's correlation coefficients for TGlittre time and DH with clinical data, symptom impact, QoL, PFTs, and functional exercise capacity.

Table 2. Comparison of pulmonary function test results between patients with and without dynamic hyperinflation.

Variable	Total sample	DH group	NDH group	p
Spirometry				
FVC (% predicted)	72.3 (62-87)	70.9 (60-87)	72.3 (65-87)	0.58
FEV_1 (% predicted)	49.5 (35-67)	46.8 (34-67)	50.6 (37-66)	0.72
FEV_1/FVC (%)	55.6 (48-66)	54.2 (45-63)	61 (49-66)	0.36
$FEF_{25-75\%}$ (% predicted)	20.5 (13-35)	16.7 (1-35)	22.7 (15-35)	0.42
Respiratory oscillometry				
Rm (cm H_2O/L/s)	6.4 (4.7-8.8)	6.4 (4.7-8.8)	6 (4.9-9.3)	0.78
R5 (cm H_2O/L/s)	7.4 (4.9-10.5)	7.9 (5.5-10.2)	7.3 (4-10.7)	0.90
R20 (cm H_2O/L/s)	5.5 (4.2-8)	5.5 (4.5-8.3)	5.4 (3.9-7.9)	0.46
R5–R20 (cm H_2O/L/s)	2 (0.2-3.9)	2 (0.2-4.7)	1.9 (0.1-3.8)	0.90
Fres (Hz)	4.6 (2.7-12.7)	8 (4.3-17.9)	2.8 (2.3-4.7)	<0.0001
X5 (cm H_2O/L/s)	-4.2 (-9.9 - -2.7)	-4.8 (-9 - -3)	-4 (-11 - -3)	0.98
X20 (cm H_2O/L/s)	-1.5 (-3.6-0.34)	-1.5 (-3.6 - -0.62)	-1.3 (-4.1 - -0.22	0.73
Ax (cm H_2O/L/s)	16.5 (6.3-32.8)	24.7 (17-46)	6.1 (4-9)	<0.0001

DH group, patients without dynamic hyperinflation; NDH, patients with dynamic hyperinflation; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; $FEF_{25-75\%}$, forced expiratory flow during the middle half of the FVC maneuver, Rm, mean resistance between 5-20 Hz; R5, respiratory system resistance at 5 Hz; R20, respiratory system resistance at 20 Hz; R5-R20, heterogeneity of resistance between 5-20 Hz; Fres, resonance frequency; X5, respiratory system reactance at 5 Hz; R20, respiratory system reactance at 20 Hz; Ax, reactance area. Data represent median (interquartile range). The values in bold refer to significant differences.

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Table 3. Spearman correlation coefficients for Glittre-daily life activities test time and for dynamic hypersufflation with clinical data, symptom impact, quality of life, pulmonary function test, and exercise functional capacity.

Variable	TGlittre time (% predicted)		ΔIC (L)	
	r_s	p	r_s	p
Age	0.070	0.61	-0.129	0.35
BMI	0.136	0.33	-0.044	0.75
Smoking load	0.108	0.44	-0.124	0.37
CAT cough score	0.147	0.29	-0.292	**0.032**
CAT phlegm score	0.431	**0.001**	-0.077	0.58
CAT chest tightness score	0.190	0.17	-0.106	0.44
CAT breathlessness score	0.276	**0.043**	-0.273	**0.046**
CAT activity limitation score	0.160	0.25	-0.217	0.11
CAT confidence leaving home score	0.277	**0.042**	-0.242	0.077
CAT sleep score	0.058	0.68	-0.262	0.056
CAT energy score	0.065	0.64	-0.142	0.30
CAT sum score	0.345	**0.010**	-0.266	**0.052**
SGRQ symptom score	0.245	0.074	-0.413	**0.002**
SGRQ activity score	0.357	**0.008**	-0.243	0.076
SGRQ impact score	0.355	**0.008**	-0.411	**0.002**
SGRQ total score	0.353	**0.008**	-0.386	**0.004**
FVC	-0.310	**0.022**	0.092	0.51
FEV_1	-0.342	**0.011**	0.047	0.73
FEV_1/FVC	-0.128	0.36	0.137	0.32
$FEF_{25-75\%}$	-0.257	0.060	0.164	0.24
Rm	0.002	0.99	-0.102	0.47
R5	0.048	0.73	-0.077	0.58
R20	0.022	0.88	-0.144	0.31
R5-R20	0.026	0.86	-0.041	0.77
Fres	0.157	0.26	-0.604	**<0.0001**
X5	-0.034	0.81	0.104	0.46
X20	-0.076	0.59	0.010	0.94
Ax	0.073	0.60	-0.652	**<0.0001**
Total time (min)	NA	NA	-0.075	0.59
Total time (% predicted)	NA	NA	-0.056	0.69
Basal SpO_2	-0.361	0.070	0.203	0.32
End-of-test SpO_2	-0.342	0.087	0.126	0.54
Basal HR	0.257	0.29	-0.576	**0.009**
End-of-test HR	0.135	0.59	-0.439	0.055
Resting VE	-0.313	0.086	0.090	0.63
VE_{peak}	-0.588	**<0.0001**	0.210	0.25
BR	-0.222	0.14	0.301	**0.044**
Basal IC	-0.533	**<0.0001**	NA	NA
End-of-test IC	-0.486	**0.0002**	NA	NA
ΔIC (L)	0.056	0.69	NA	NA
ΔIC (%)	0.022	0.87	NA	NA

IC, inspiratory capacity; BMI, body mass index; CAT, COPD Assessment Test; SGRQ, St George's Respiratory Questionnaire; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; $FEF_{25-75\%}$, forced expiratory flow during the middle half of the FVC maneuver, Rm, mean resistance between 5-20 Hz; R5, respiratory system resistance at 5 Hz; R20, respiratory system resistance at 20 Hz; R5-R20, heterogeneity of resistance between 5-20 Hz; Fres, resonance frequency; X5, respiratory system reactance at 5 Hz; R20, respiratory system reactance at 20 Hz; Ax, reactance area; SpO_2, peripheral oxygen saturation; HR, heart rate; VE, minute ventilation; BR, breathing reserve; NA, not applicable. The values in bold refer to significant differences.

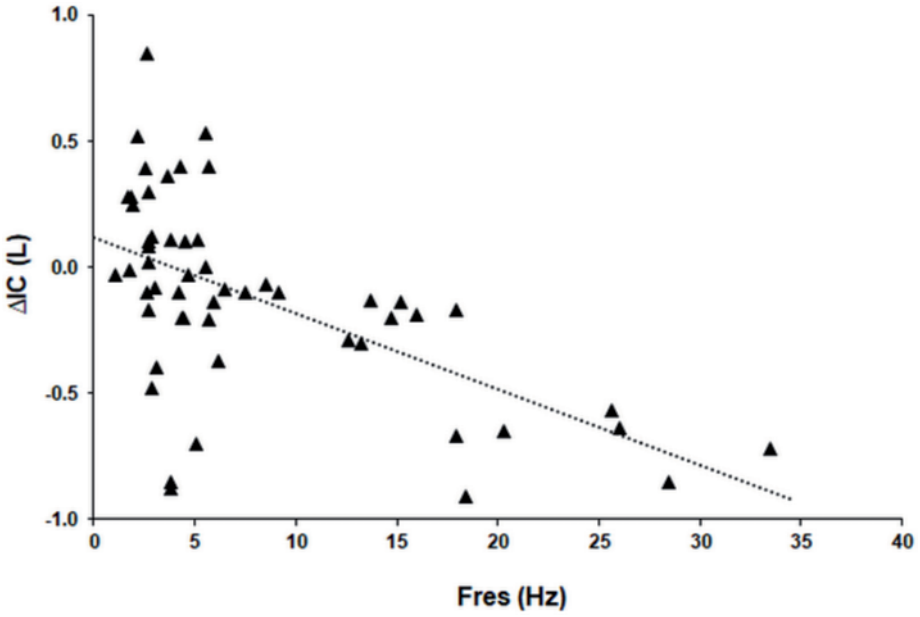


Figure 1. Relationships of the relative delta of the inspiratory capacity (ΔIC) with resonance frequency (Fres) (r_s=-0.604, p<0.0001).

Multiple linear regression

Table 4 shows the MLRs for TGlittre time (% predicted) and ΔIC (L). In the MLR for TGlittre time, FEV_1 was the only independently predictive variable, explaining 10% of its variability. In the MLR for ΔIC, Fres and Ax were the only independently predictive variables, explaining 49% of its variability.

Discussion

The main findings of this study were that DH occurs in more than half of these patients when they are subjected to a submaximal exercise test. Having or not having DH is unrelated to COPD severity, symptom impact, QoL, and performance during TGlittre in this patient population. Unlike spirometry, RO can distinguish patients with and without DH. Both DH and TGlittre time correlate with symptom impact, QoL, and lung function. While spirometry weakly explains TGlittre performance in COPD patients, SAD strongly explains DH in this patient population. To our knowledge, this is the first study to evaluate the real contribution of SAD in triggering DH in patients with COPD using TGlittre.

In COPD, a series of pulmonary and systemic manifestations have a negative impact on exercise capacity [35]. In this sense, we used TGlittre to assess functional capacity on exertion, since it is a more comprehensive test than the 6MWT, as it involves activities of the upper limbs incorporated into ADLs [13]. As in other studies [13,36], we observed poor performance in these patients during the TGlittre. In our study, TGlittre time correlated with the symptom impact as assessed by the CAT score, QoL as measured by the SGRQ, and resting lung function. It is worth noting that the only variable that explains TGlittre time in our MLR was FEV_1, although the association was weak. This result is consistent with the study by Gulart *et al*. [36], which showed that the lung function variable that best predicts TGlittre performance is FEV_1. This corroborates, at least in part, the use of FEV_1 by the GOLD document in the assessment of COPD severity. Of note, MLR is an important statistical method for testing relationships between variables and quantifying the direction and strength of the association [37]. It is advisable to have an adequate sample size when applying MLR, with at least 10

Table 4. Multivariate linear regression models for Glittre-daily life activities test time and delta inspiratory capacity using clinical data and pulmonary function test results.

Variables	β	SEB	p-value	R	Adjusted R^2
TGlittre time (% predicted)					
Constant	159.6	9.34	<0.0001		
FEV_1	-0.328	0.158	0.043	0.28	0.10
ΔIC (L)					
Constant	0.269	0.068	0.0002		
Fres	-0.028	0.005	<0.0001	0.59	0.33
Ax	-0.007	0.002	0.0001	0.72	0.49

β, regression coefficient; SEB, standard error of the regression coefficient; R, cumulative correlation coefficient; R^2, cumulative adjusted coefficient of determination; FEV_1, forced expiratory volume in 1 s; Fres, resonance frequency; Ax, reactance area.

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cases recommended for each independent variable included in the model, which was not an assumption met in our study [38]. However, our MLR was developed for exploratory purposes, where the degree of fit of the variables is not as precise as in predictive models, where the degree of fit should be optimal [38].

The assessment of DH is crucial to understanding exercise tolerance and response to therapy in COPD [2]. Almost 60% of our patients developed DH at the end of TGlittre. Using the 6MWT and ΔIC to elucidate the physiological factors responsible for the development of DH in patients with COPD, Chen *et al*. [11] observed that DH was present in 66.7% of patients. Interestingly, DH has been described even in patients with mild stages of COPD [39], which is in line with our findings, which revealed no significant differences in COPD severity, symptom impact, QoL, and performance during TGlittre when the DH and NDH groups were compared. In line with our results, Augustin *et al.* [1] observed that 14% of their patients with stable COPD had LH without significant EFL. Thus, although most COPD patients present an interrelationship between EFL, LH, and emphysema, these data imply that the presence of LH does not always mean the coexistence of significant EFL.

The EFL that occurs in COPD is the result of chronic inflammation whose physiological basis is both increased resistance in small airways and loss of alveolar units [40]. In this sense, we used RO, whose fundamental characteristic is its accuracy in detecting SAD [41]. Interestingly, we observed that when patients were separated into hyperinflators and non-hyperinflators, the parameters provided by RO were the only ones capable of differentiating the two groups. Chen *et al*. [11] observed that the 6-minute walking distance and spirometric parameters did not differ significantly between hyperinflators and non-hyperinflators, which shows the importance of assessing the small airways. Using the forced oscillation technique (FOT), Teixeira *et al.* [42] observed correlations between several FOT parameters and TGlittre time, particularly in the emphysema phenotype. Of note, another study found that at peak exercise performed by CPET, there were moderate to strong associations between RO variables and IC, and between RO variables and concavity in the expiratory limb of the flow-volume curve measured during exertion [3].

SAD may be an important mechanism contributing to DH, potentially worsening DH when respiratory demand increases during exercise and creating a sensation of dyspnea as the work of breathing intensifies [43]. We observed that SAD strongly explains DH in patients with COPD. Along the same lines, Chen *et al*. [11] observed that forced expiratory flow after exhaling 50% of FVC was the only predictor of ΔIC assessed during 6MWT. In addition to RO being more sensitive than spirometry for monitoring EFL, it predicts poor exercise tolerance in patients with moderate/severe COPD [43]. An imaging study using parametric response mapping to assess air trapping resulting from SAD showed that this is also the dominant cause of hyperinflation in mild/moderate COPD [44]. From a practical perspective, the availability of inhaled drugs containing extrafine particles has the potential to treat SAD and, as a consequence, improve DH in patients with COPD, which further supports the notion of a treatable trait for DH [45].

Reduced IC and consequent DH are fundamental ventilatory mechanisms that significantly contribute to the limitation in performing ADLs and, consequently, impact QoL [32]. Although we did not observe differences between the DH and NDH groups for the SGRQ score and the CAT score, we did observe significant correlations between several domains of these questionnaires and DH. Interestingly, Chen *et al.* [11] found that SGRQ scores did not differ significantly between hyperinflators and non-hyperinflators using the 6MWT and ΔIC in COPD patients. However, these authors did not evaluate correlation analyses. Exploring the effects of DH on exercise capacity and QoL in patients with COPD, Zhao *et al*. [46] showed that patients with severe DH during CPET tended to have higher CAT scores. Similar to our results, these authors observed that the occurrence and severity of DH had no association with baseline lung function assessed by spirometry.

We should point out some limitations of this study. Firstly, the sample was relatively small, and the study was cross-sectional, which does not allow us to establish a cause-and-effect relationship. Secondly, we did not assess static LH, for example using body plethysmography, which could help in understanding the physiological mechanisms involved in DH in patients with COPD. In particular, the residual volume/total lung capacity ratio (RV/TLC percentage, Motley index) could be quite useful, as it correlates with the frequent exacerbator phenotype in COPD patients [47]. Thirdly, CPET has been used to show DH in patients with COPD; however, CPET is often impractical because it requires specialized equipment and trained technicians. Finally, the RO technique during exercise may assist in the clinical assessment of dynamic airway function in COPD patients [3], although we do not yet have this technical apparatus. Despite the limitations, our findings could serve as a starting point for randomized controlled studies evaluating the role of incorporating RO and TGlittre coupled with dynamic ventilation measurements in the monitoring and assessment of the therapeutic response of patients with COPD.

Conclusions

Patients with COPD who undergo DH during TGlittre present more alterations in RO. In these patients, the more pronounced the DH, the worse the RO parameters, the greater the symptom impact, and the more deteriorated the QoL. Furthermore, SAD is a significant predictor of DH in this patient population. Although these results are promising, further studies are needed to demonstrate whether interventions to improve small airway function can reduce DH in patients with COPD.

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