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Small airway dysfunction predicts excess ventilation and dynamic hyperinflation during exercise in patients with COPD

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Abstract (205 words < 250)

Introduction

Small airway dysfunction (SAD) is a pathophysiological characteristic of chronic obstructive pulmonary disease (COPD). Excess ventilation and dynamic hyperinflation (DH) are two main pathophysiological traits and limiting factors of COPD patients while exercising. We aimed to ascertain whether or not SAD, assessed by the multiple breath nitrogen washout (MBNW), may predict exercise ventilatory inefficiency and DH.

Methods

Fifty stable COPD patients were prospectively studied and underwent MBNW and incremental cardio-pulmonary exercise test (CPET). Indices of conductive (S_{cond}) and acinar (S_{acin}) ventilation heterogeneity as well as minute ventilation/CO_2 production (V_E/VCO_2) linear relationship and the change in inspiratory capacity (IC) were analyzed.

Results

S_{acin} was significantly and directly related to V_E/VCO_2 slope and inversely related to IC change and to peak O_2 uptake ($p< 0.01$ for all correlations). No significant correlation was found between S_{cond} and CPET parameters. The regression equation generated by stepwise multiple regression analysis for the V_E/VCO_2 slope and IC change, as dependent variables, included only S_{acin}, as independent variable. This model accounted for 31% and 36% of the total variance for the V_E/VCO_2 slope and IC change, respectively.

Conclusion

Our study shows the value of the SAD as determinant of the excess ventilation and DH during exercise in patients with stable COPD.

Introduction

Small airway dysfunction (SAD) is a pathophysiological characteristic of chronic obstructive pulmonary disease (COPD) [1] and it has been related to breathlessness and poor quality of life of the patients [2] [3]. SAD can be reliably investigated by the multiple breath nitrogen washout (MBNW) test, which assesses the ventilatory impairment due to structural asymmetry between lung units, thereby defining the subsequent ventilation inhomogeneity [4]. It is of note that MBNW can provide some indices which anatomically situate the airway changes responsible for the ventilation inhomogeneity, and can quantify it [5].

Minute ventilation (V_E) largely relies on the carbon dioxide production (VCO_2) during exercise [6]. Thus, the VE/VCO_2 linear relationship during incremental cardiopulmonary exercise testing (CPET) is considered as a reliable measure of exercise ventilatory efficiency in removing CO_2 produced by the body [7]. Importantly, in patients with COPD the exercise ventilatory efficiency is impaired and high values in V_E/VCO_2 slope can occur [8]. Excess ventilation may underlie the mechanisms of exercise intolerance and exertional breathlessness of these patients [8]. COPD patients can further experience ventilatory constraints during exercise. Notably, these patients while exercising may breathe in before fully exhaling because of the expiratory flow limitation and, for that reason, entrap air within the lungs with each further breath [9]. This phenomenon is well-known as dynamic hyperinflation (DH) and can strongly limit exercise capacity in COPD, playing a relevant role in the breathlessness on exertion [9].

No study has been, so far, specifically addressed to investigate the relationship between the ventilation inhomogeneity of the small airways at rest and ventilatory inefficiency

and DH during exercise in COPD patients. The aim of the present study was, therefore, to evaluate in a cohort of COPD patients the resting ventilation inhomogeneity by means of MBNW, and to ascertain whether or not the MBNW parameters are related to the slope of V_E/VCO_2 linear relationship and to DH, measured as inspiratory capacity (IC) change, during incremental CPET. We hypothesized that in COPD patients, the resting ventilation inhomogeneity of the small airways might strictly relate to ventilatory inefficiency and DH during exercise.

Material and Methods

Subjects

We consecutively enrolled over a period of 12 months between January and December 2019 patients with COPD, diagnosed according to the GOLD criteria [10] and having: (a) smoking history of ≥ 20 pack-years; (b) postbronchodilator Forced Expiratory Volume at 1st second (FEV_1)/ Forced Vital Capacity (FVC) ratio <0.7; (c) a regular treatment over a period of 6 months. We excluded patients with: (a) an exacerbation in the 8 weeks prior to enrolment; (b) patients with another coexistent chronic pulmonary disease; (c) patients with severe comorbidities associated to COPD, such as unstable cardiovascular disease or cancer; (d) patients unable to perform all tests required.

Anthropometric variables (age, sex and body mass index – BMI, in kg/m^2), smoking habit, CAT score (Italian version) [11], history exacerbations and domiciliary medications were recorded. Daily living activity-related dyspnea was assessed by the Italian version of the five-point modified MRC scale [12].

The study protocol was approved by the local Ethics Committee (approval number n. 3027; 22 January 2019). All patients gave their informed consent.

Spirometry and body plethysmography

Spirometry and body plethysmography were performed by using a flow-sensing spirometer and a body plethysmograph (Vmax 22 and 6200; SensorMedics, Yorba Linda, CA, USA). FEV_1, Forced Expiratory Flow at 75% of FVC (FEF_{75}) and FVC

were recorded and expressed as absolute values (liters) and percentage of predicted value (% pred); FEV_1/FVC, expressed as a ratio, was taken as index of airway obstruction.

Thoracic gas volume (TGV) was measured by body plethysmography and total lung capacity (TLC, % pred) was obtained as the sum of TGV and linked IC. IC/TLC, expressed as a ratio, was taken as an index of static hyperinflation of the lung.

Lung transfer factor for carbon monoxide (TLco, % pred) was measured by the single breath method using a mixture of carbon monoxide and methane.

Patients were advised to avoid inhaled bronchodilators 12 h before baseline spirometry and the reversibility test was performed with a second spirometry 15 minutes after inhaled Salbutamol (400 μg).

MBNW testing

MBW testing was performed according to a standard procedure [13]. Briefly, patients, wearing a nose clip, were seated with their lips sealed tightly around the mouthpiece connected to a gas analyzer (EXHALYZER® D, ECO MEDICS AG, Dürnten, Switzerland). They inhaled 100% oxygen from end-expiratory lung volume while breathing with a fixed tidal volume and respiratory rate, helped by a visual breathing pattern feedback, until the nitrogen concentration in the exhaled volume reached 1/40th or 2.5% of the initial concentration of the resident nitrogen in the lungs for three consecutive breaths. Each test lasted about 2 to 10 minutes and was performed at least two times to ensure the reproducibility.

We measured lung clearance index (LCI), considered as an index of global ventilation inhomogeneity, as well as indices of conductive (S_{cond}) and acinar (S_{acin}) ventilation heterogeneity, and ventilated FRC (FRC_{MBNW}). LCI was the ratio between the cumulative expired volume of the inert gas over the FRC_{MBNW}. S_{cond} and S_{acin} (in L^{-1}) were derived from phase III slopes of the nitrogen spirogram and their value increases when ventilation heterogeneity increases [13].

CPET

CPET was performed using a cycloergometer (Corival PB, Lode BV, Groningen, The Netherlands), according to a standardized procedure [14]. The patients were continuously monitored with a 12-lead electrocardiogram (CardioPerfect, Welch Allyn, Delft, The Netherlands) and a pulse oximeter (Pulse Oximeter 8600, Nonin Medical Inc, MPLS, Mn U.S.). The exercise protocol included at first 3 min of rest, then other 3 minutes of unloaded cycling, followed by a progressive increment of 5–15 watts each minute, depending on the anthropometric data and the individual functional impairment. The total exercise time ranged from 8 to 12 minutes. Blood pressure (mm Hg) was measured at 2-min intervals. Stopping criteria included unsustainable dyspnea or muscular fatigue, chest pain, electrocardiogram significant ST-segment depression, a drop in systolic blood pressure or arterial oxygen saturation < 84%.

Breath-by-breath oxygen uptake (VO_2, in L/min), carbon dioxide output (VCO_2, in L/min), tidal volume (V_T, in L) and V_E (in L/min) were recorded during the test (CPX/D; Med Graphics, St. Paul, MN, U.S.A.). Peak work load and peak VO_2 were recorded as the mean value of watts and VO_2 (mL/kg/min) during the last 20 s of the

test. The ventilatory response during exercise was expressed as a linear regression function by plotting V_E against VCO_2 obtained every 10 s, excluding data above the ventilatory compensation point [7], and by measuring the slope (V_E/VCO_2 slope) and y intercept (V_E/VCO_2 intercept). The end-tidal pressure of CO_2 ($PETCO_2$, mm Hg) was recorded as the mean value of $PETCO_2$ during the 3-min rest period (rest $PETCO_2$), during the last 20 s of the test (peak $PETCO_2$), and as the difference between peak and rest $PETCO_2$ ($PETCO_2$ change, mm Hg).

Changes in operational lung volumes were assessed every 2 min during exercise and at peak exercise, taking the IC measured at rest as the baseline (in L). Assuming that TLC remains constant during exercise in COPD patients [15], changes in IC reflect changes in end-expiratory lung volume. ~~Therefore, DH can be defined as a decline in the IC greater than zero [16].~~ DH during exercise can be defined as a decrease in IC from rest of more than 150 mL at any time-point during exercise [16]. Based on this definition, patients were divided into two subgroups in relation to the presence or absence of DH (hyperinflators *vs* non-hyperinflators). The ratio of V_T at peak of exercise over IC ($V_T$peak/IC), as index of ventilatory limitation [7], was also measured.

Dyspnea induced by CPET was measured at the end of the exercise by a 0-100 visual analogue scale (VAS). Dyspnea perception ratings were then divided by the maximal workload (VAS/MW, in mm/watts) for analysis.

Statistical Analysis

The normality of distribution of all variables was assessed by the Shapiro-Wilk test. Data were reported as means ± standard deviation (SD) for the variables with normal

distribution. Relationships between variables were assessed by Pearson correlation coefficient (*r*). A linear regression analysis was performed for those values that showed a significant correlation. Stepwise multiple regression analysis was used to determine the best predictor variables (age, sex, BMI, FEV_1, IC/TLC, TLCO and S_{acin}) for the VE/VCO_2 slope and IC change, as dependent variables. Percentage of total variance in the dependent variable, accounted for by the predictor variables, is expressed as the adjusted square of the multiple correlation coefficient (r^2). A p value <0.05 was considered significant.

Results

We studied 57 consecutive COPD patients (16 females), aged between 51 and 82 years. Seven patients were excluded because not able to successfully perform MBNW. The characteristics of the 50 patients included in the study are shown in Table 1.

At study entry, patients were treated with inhaled steroids (78%), long-acting beta$_2$-agonists (94%) and long-acting muscarinic antagonists (72%); all of them were ex-smokers (66%) or current smokers (24%). Twenty-nine (6 females) out of 50 patients (58%) were affected by arterial hypertension and were on ACE-inhibitors or sartans (44%), Ca-antagonists (18%), beta-blockers (18%) and diuretics (18%).

In all patients, a wide range of airflow obstruction and lung hyperinflation were found, (FEV_1/VC from 28 to 68% and IC/TLC from 23 to 48%, respectively). In regards to MBNW testing, mean LCI, S_{cond} and S_{acin} values were respectively 14.2 ± 3.6, 0.025 ± 0.022 L^{-1} and 0.458 ± 0.179 L^{-1} (Table 1).

All patients underwent the CPET without complications. Peak workload was 84 watts ± 32, while mean peak VO_2 values were 16.2 mL/kg/min ± 4.5 or 63 % pred ± 13. ~~Thirty-eight out of 50 patients (76%) experienced DH~~. Based on the presence of DH (>150 mL decrease in IC at any time-point during exercise), thirty-five out of 50 patients (70%) were considered as hyperinflators. Mean resting and peak IC values were 2.09 L ± 0.48 and 1.77 L ± 0.46, respectively ($p < 0.0001$), and mean IC change value was -0.327 L ± 0.388 (range -0.970 to 0.940 L). Mean V_E/VCO_2 slope and intercept values were respectively 33.4 L ± 6.64 and 4.05 L/min ± 1.86. Mean resting and peak $PETCO_2$ values were 30.1 mm Hg ± 4.6 and 35.8 mm Hg ± 5.8, respectively ($p < 0.0001$), and

mean $PETCO_2$ change value was 5.7 mm Hg ± 3.1 (range 1 to 15 mm Hg). Mean VAS/MW was 1.04 mm/watts ± 0.42 (Table 2).

In all patients, FEF_{75} (% pred) values were significantly and negatively related to LCI (*r=-0.439, p=0.002*), S_{acin} (*r=-0.413, p=0.003*) and V_E/VCO_2 intercept values (*r = -0.352, p = 0.013*). Furthermore, FEF_{75} values were significantly lower in hyperinflators compared to non-hyperinflators (*23% ±18 vs 40% ±30, p = 0.023*).

LCI showed a negative correlation with FEV_1 (*r=-0.529, p=0.0001*), FEV1/FVC (*r = -0.445, p = 0.002*), FVC (*r = - 0.415, p = 0.003*), IC/TLC (*r = - 0.336, p = 0.018*) and TL_{CO} (*r = - 0.301, p = 0.039*), and a positive correlation with TLC (*r = 0.352, p = 0.013*). Furthermore, LCI was significantly and directly related to V_E/VCO_2 intercept (*r = 0.384, p = 0.006*) and $PETCO_2$ change (*r = 0.465, p = 0.001*) and inversely related to IC change (*r = -0.321, p = 0.0019*). Lastly, LCI values were significantly higher in hyperinflators compared to non-hyperinflators (*15 ±3 vs 12 ±3, p = 0.001*).

S_{acin} was negatively related to FEV_1 (*r=-0.433, p=0.0019*), FEV1/FVC (*r = - 0.489, p = 0.0004*), and TL_{CO} (*r = - 0.301, p = 0.039*). Moreover, S_{acin} was significantly and directly related to V_E/VCO_2 slope (*r = 0.592, p = 0.0001*), V_E/VCO_2 intercept (*r = 0.297, p = 0.036*), $V_T$peak/IC (*r = 0.362, p = 0.011*) and VAS/MW (*r = 0.318, p = 0.026*) and inversely related to IC change (*r = -0.570, p = 0.0001*) and to peak VO_2 (*r = -0.388, p = 0.0054*) (Fig 1). S_{acin} values were significantly higher in hyperinflators compared to non-hyperinflators (*0.517 L^{-1} ±0.162 vs 0.305 L^{-1} ±0.115, p < 0.001*). No significant correlation was found, when S_{cond} was related to resting lung function and CPET parameters. No difference was found in S_{cond} values, when hperinflators were compared to non-hyperinflators (*0.027 L^{-1} ±0.025 vs 0.025 L^{-1} ±0.019, p = 0.733*).

The regression equation generated by stepwise multiple regression analysis for the V_E/VCO_2 slope and IC change, as dependent variables, included only S_{acin}, as independent variable. This model accounted for 31% and 36% of the total variance for the V_E/VCO_2 slope and IC change, respectively (Table 3).

Discussion

This prospective study on patients with stable COPD demonstrates that a ventilatory distribution inhomogeneity at rest, as globally measured by means of LCI, is related to V_E/VCO_2 intercept and to DH during a maximal exercise. Importantly, these findings were confirmed and further extended when the ventilation heterogeneity was assessed by the specific index for the acinar district, such as S_{acin}, but not by S_{cond}, the index of the conductive district inhomogeneity. Notably, S_{acin} was significantly and directly related to the ventilatory inefficiency, expressed as V_E/VCO_2 slope, to V_E/VCO_2 intercept and to breathlessness perception on exertion. Furthermore, S_{acin} was strongly related to DH and poor maximal exercise capacity. Finally, and most importantly, S_{acin} was the only independent predictor for V_E/VCO_2 slope and IC change values.

Previous studies [17] [18] [19] on COPD patients demonstrated that resting ventilatory inhomogeneity, assessed by the single-breath nitrogen washout test (SBNW), is one of the main predictors of the reduced exercise capacity, assessed with a maximal exercise test [19], or by the 6-minute walking test [17] [18]. Notably, both Lopes and Mafort [17] and Boeck et al [18] found that ventilatory inhomogeneity at rest can affect the degree of perceived dyspnea and tolerance to exercise, expressed as walking distance. Deus et al [19] also showed that the increase in ventilatory distribution inhomogeneity was significantly related with lower VO_2 peak and lower breathing reserve. Furthermore, compared with healthy controls, patients with GOLD stage I COPD (post-bronchodilator FEV1>80% pred.) showed lung hyperinflation during exercise as well as a greater closing capacity and N2 slope [20]. Our findings by using MBNW to assess ventilatory distribution inhomogeneity and small airway dysfunction in COPD patients, confirm and further expand these previous results.

The ventilatory distribution inhomogeneity can be reliably assessed by both single and multiple breath washout techniques. The advantage of using the multiple breath washout techniques rather than the single breath ones consists of the possibility to anatomically locate the airways impairment in the distal airways or in the conducting airways [4] [5] [21] [22]. In spite of its sensitivity, the SBNW is not specific to peripheral airway pathology and any alteration in the proximal airways can affect phase III slope [20]. Furthermore, the reproducibility of the single breath washout techniques is lower than the multiple breath washout ones [22]. On the other hand, both techniques are not entirely easy to perform [4] [21] [22] and, indeed, in our cohort, 7 out of the 57 patients (12%) failed the MBNW maneuver. Patients who failed the MBNW did not significantly differ in anthropometric, clinical and spirometry characteristics, as compared to patients who successfully performed MBNW (data not shown).

This study provided the first evidence that in COPD patients, S_{acin}, a marker of small airway dysfunction, can independently predict two main pathophysiological traits of COPD patients while exercising, such as the excess ventilation and DH. Elevated values in V_E/VCO_2 slope can reflect a ventilation in excess to the metabolic stress and point out ventilatory inefficiency if the excess ventilation stems from an increase in dead space, since the minute ventilation is the sum of alveolar and dead space ventilation. Increase in ventilation-perfusion heterogeneity causes inefficient gas exchange and conduces to abnormal V_E/VCO_2 slope, as it may be found in COPD. DH represents the main ventilatory limit to exercise in COPD, since progressively restricts the inspiratory capacity and, consequently, the minute ventilation can increase only by increasing the respiratory rate, thereby inducing a further hyperinflation in a vicious circle with serious

mechanical and sensory consequences [9]. It is worthy of note that DH was found to be related with a poor cardiovascular response to exercise in COPD patients [23].

The findings of the present study further support the view concerning the crucial involvement of the small airways dysfunction in the pathogenesis of COPD, and its impact on patients. There is rising acknowledgment that increased resistance in the small airways plays a key role in airflow limitation in COPD, even greater than the decrease in elastic recoil caused by the structural changes of emphysema. In a large cohort of COPD patients, severity of emphysema varied widely even in patients with the same stage of COPD and there was no correlation between the extent of emphysema and the degree of airflow limitation [24]. On the other hand, Hogg et al [1] in their seminal study showed that in patients with COPD, pulmonary function was strictly related to both wall area and degree of luminal patency of the small airways. Furthermore, the role of small airways is far more important than the one of the large airways in determining airflow limitation. In COPD patients, a study based on three-dimensional computed tomography showed that airflow limitation is more closely related to the dimensions of the distal airways than the proximal airways [25].

This study has some limitations. Firstly, our cohort of patients has a male predominance (72%) and our results may not be fully applicable to female patients. However, the predominance of male gender in our study is in agreement with the epidemiology of the disease. In addition, in this non-invasive study, excess ventilation during exercise was based only on the V_E/VCO_2 value without a measure of the dead space. We did not perform arterial blood gas analysis during exercise and, accordingly, we cannot confirm or exclude that excess ventilation is a consequence of an increased ventilatory drive or of a high dead space ventilation. However, there is a body of evidence [26] which

clearly supports the hypothesis of an increase in dead space as the most likely determining factor for high values of V_E/VCO_2 in patients with COPD.

In conclusion, our study demonstrates the value of the small airways dysfunction as a determinant of the excess ventilation and DH during exercise in patients with stable COPD and without serious cardiovascular comorbidities. Further studies are required to demonstrate whether a therapy aimed at treating small airway dysfunction in COPD may or may not affect exercise capacity in these patients.

Contributions

RP and AC contributed to conception and design of the work. AM, RP, PT, AFa, AFr contributed to acquisition, analysis or interpretation of data for the work. AM, RP, MA, VA, GP, AC, contributed to drafting the article or revising it critically for important intellectual content. AC: Final approval of the version.

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Table 1. Anthropometric, clinical and lung function characteristics of 50 COPD patients (14 females).

Age (years)	67 ± 8	(51–82)
BMI (kg/m^2)	26 ± 3	(17–33)
CAT (0-40)	11 [7-15]	(4–26)
MRC (0-4)	1 [1-1]	(0-3)
TLC (% pred)	120 ± 17	(80–154)
FVC (% pred)	90 ± 19	(55-134)
FEV_1 (% pred)	54 ± 19	(26-106)
FEV_1/FVC (%)	47 ± 11	(28-68)
FEF_{75} (% pred)	28 ± 23	(7-106)
IC/TLC (%)	32 ± 8	(18–48)
TL_{CO} (% pred)	58 ± 20	(21–123)
LCI	14 ± 4	(8–25)
S_{cond} (L^{-1})	0.025 ± 0.022	(0–0.112)
S_{acin} (L^{-1})	0.458 ± 0.179	(0–0.847)

Values are expressed as mean ± SD or median [25th – 75th percentile] and (range)

Table 2. Exercise characteristics of 50 COPD patients (14 females).

Peak VO_2 (mL/kg/min)	16.2 ± 4.5	(8.9 – 27.1)
Peak VO_2 (% pred)	63 ± 18	(27 – 114)
Peak Workload (watts)	84 ± 32	(33 – 160)
V_E (L/min)	43.7 ± 14.8	(20.2 – 79.0)
IC rest (L)	2.09 ± 0.48	(1.13 – 3.20)
IC peak (L)	1.77 ± 0.46	(0.95 – 2.83)
IC change (L)	-0.327 ± 0.388	(-0.970 – 0.940)
$V_T$peak (L)	1.37 ± 0.36	(0.79-2.20)
$V_T$peak/IC	0.78 ± 0.10	(0.55-1.00)
V_E/VCO_2 slope (L)	33.4 ± 6.7	(23.0 – 46.0)
V_E/VCO_2 intercept (L/min)	4.05 ± 1.9	(1.15 – 8.60)
$PETCO_2$ rest (mm Hg)	30.1 ± 4.6	(21.0 – 40.0)
$PETCO_2$ peak (mm Hg)	35.8 ± 5.8	(26.0 – 50.0)
$PETCO_2$ change (mm Hg)	5.7 ± 3.2	(1.0 – 15.0)
VAS/MW (mm/watt)	1.04 ± 0.42	(0.45 – 2.73)

Values are expressed as mean ± SD and (range)

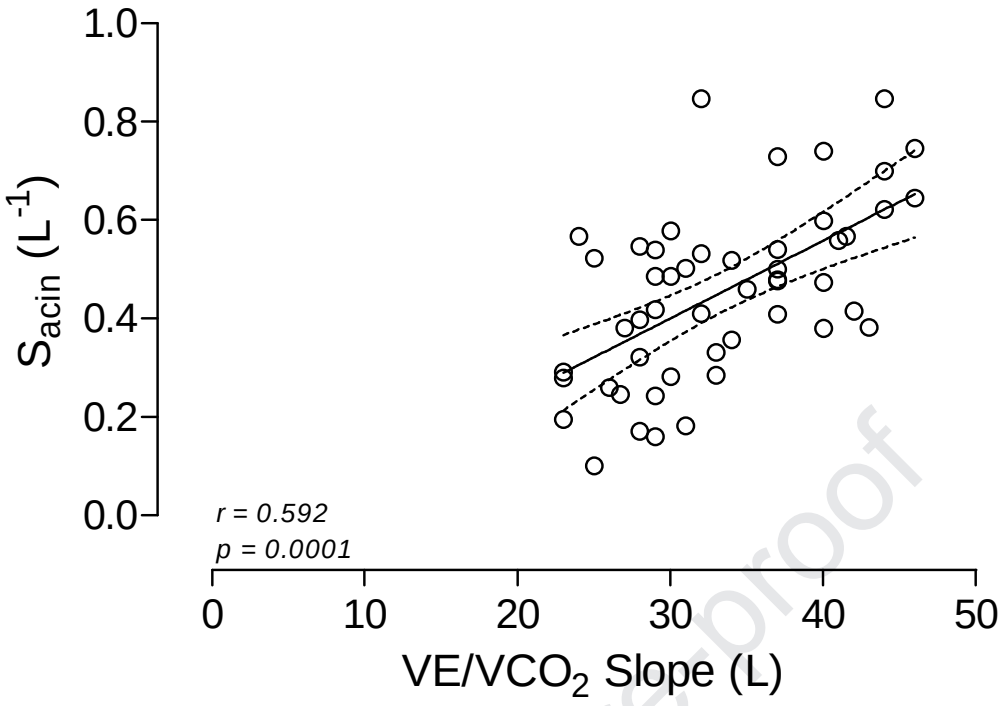
Table 3. Predicting models for V_E/VCO_2 slope and IC change by stepwise multiple regression analysis

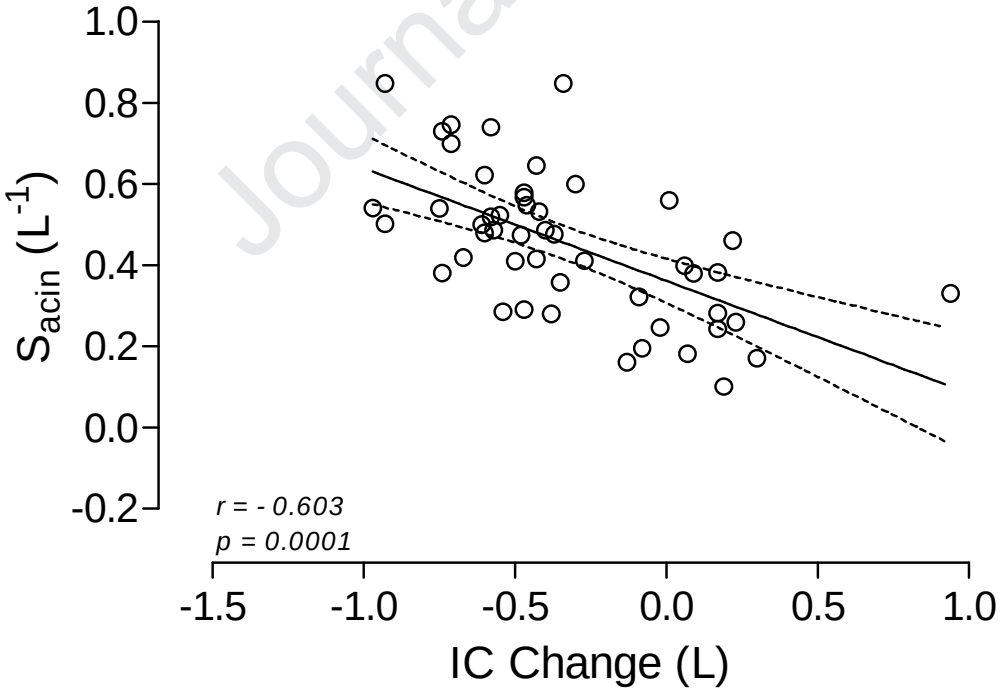
	Coefficient	**Standard Error**	***p***	**95% Confidence Intervals**	
VE/VCO_2 slope (L)					
S_{acin}	20.873	4.490	0.000	11.829	29.917
Constant	23.929	2.197	0.000	19.503	28.354
(r^2=*0.309*)					
IC change (L)					
S_{acin}	-1.328	0.261	0.000	-1.853	-0.802
Constant	0.284	0.127	0.030	0.028	0.540
(r^2=*0.357*)					

For every model, the following were tested as predictors: age, sex, BMI, FEV_1, IC/TLC, TL_{CO} and S_{acin}

Legend for figure

Figure 1. Relationship between S_{acin} and V_E/VCO_2 slope (*upper panel*) and IC change (*lower panel*) in 50 COPD patients. The linear regression line is superimposed, surrounded with the 95% confidence interval lines for the regression line.





Highlights

- The two main pathophysiological traits of COPD patients while exercising are the excess ventilation and dynamic hyperinflation.
- This study provided the first evidence that in COPD patients, S_{acin}, a marker of small airway dysfunction, can independently predict excess ventilation and dynamic hyperinflation.
- The findings of the present study further support the view concerning the crucial involvement of the small airways dysfunction in the pathogenesis of COPD and its impact on functional status of the patients.

Contributions

Roberta Pisi and Alfredo Chetta contributed to conception and design of the work. Alessandra Manco, Roberta Pisi, Panagiota Tzani, Alberto Fantin, Annalisa Frizzelli contributed to acquisition, analysis or interpretation of data for the work. Alessandra Manco, Roberta Pisi, Marina Aiello, Veronica Alfieri, Giuseppina Bertorelli, Alfredo Chetta contributed to drafting the article or revising it critically for important intellectual content. Alfredo Chetta: Final approval of the version.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: