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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Research Article

Basal Computation of Emphysema Severity Index (ESI) in COPD Patients is Not Affected by Bronchodilation

Roberto W Dal Negro[1]*, Turco P[1], Povero M[2] and Pistolesi M[3]

[1]*National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology - CESFAR, Verona, Italy*

[2]*AdRes Health Economics and Outcome Research, Turin, Italy*

[3]*Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Italy*

***Corresponding Author:** Roberto W Dal Negro, National Center for Respiratory Pharmacoeconomics and Pharmacoepidemiology, Verona, Italy.

Received: January 28, 2025; **Published:** March 05, 2025

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a complex pathological respiratory condition characterized by a range of heterogeneous disorders that variably affect the airways and/or lung parenchyma, with significant morbidity, mortality and socio-economic impact. This underlying heterogeneity results in distinct clinical phenotypes that are rarely investigated in routine clinical practice using standard spirometric parameters. The Emphysema Severity Index (ESI) is a lung function parameter recently developed to evaluate the presence and severity of the emphysema component in COPD patients using standard spirometry. ESI is derived from a biomechanical model of the airways, which analyzes the shape of the descending slope of the maximal expiratory flow-volume (MEFV) curve. The consistency of ESI following bronchodilation has not yet been examined. This study aimed to evaluate the effect of bronchodilation on ESI computation in COPD patients.

Methods: Parameters such as FEV_1, FVC, FEV_1/FVC, RV, TLC, RV/TLC, PEF, MEF (75%, 50%, 25%), and ESI were measured before and 30 minutes after inhalation of 400 mcg of salbutamol in COPD patients, and the results were compared.

Results: A total of 51 COPD patients (31 males [60.8%], mean age 70.4 ± 12.2 years, mean BMI 25.6 ± 4.7) were automatically and anonymously selected from the database based on inclusion and exclusion criteria. All parameters reflecting parenchymal involvement, including RV, TLC, Motley index, and ESI in particular, remained completely unchanged following bronchodilation.

Conclusion: Bronchodilation does not significantly impact the computation of ESI in COPD patients.

Keywords: *COPD; Emphysema; Airway Obstruction; Bronchodilation; ESI*

Introduction

COPD has long been defined as the presence of a not fully reversible airflow limitation (i.e. FEV_1/FVC < 0.7 after bronchodilation) as measured by spirometry. However, COPD patients may exhibit varying degrees of partial reversibility, largely depending on their clinical phenotype. Patients with the emphysema phenotype typically demonstrate a lower degree of reversibility compared to those with the chronic bronchitis phenotype [1,2].

The Emphysema Severity Index (ESI) is a novel parameter recently developed to detect the presence and severity of the emphysema component in COPD patients using standard spirometry. ESI is derived from a biomechanical model of the airways, analyzing the shape of the descending slope of the maximal expiratory flow-volume (MEFV) curve through specific parameters obtained from spirometry. This process produces a numerical value that is highly correlated with the extent of emphysema quantified by CT metrics [3]. Conversely, ESI does not correlate with CT metrics of airway disease, enabling differentiation between the contributions of parenchymal destruction (emphysema) and/or conductive airway disease (chronic bronchitis, small airway disease) to lung function impairment assessed by spirometry [4].

ESI has already been validated in a large population of smokers and COPD patients who underwent inspiratory-expiratory CT scans and spirometry on the same day [5]. Furthermore, a national multicenter study demonstrated that ESI could aid in phenotyping COPD patients in clinical settings [6].

Aim of the Study

The aim of the present study was to investigate whether the partial reversibility observed after bronchodilation in COPD patients could affect the morphology of the spirometric MEFV curve, potentially leading to significant changes in ESI stability.

Methods

Spirometry tests performed before and 30 minutes after bronchodilation (following administration of 400 mcg of salbutamol) in COPD patients during November 2024 were retrospectively and anonymously collected from the institutional ISO-certified database. The dataset included smoking history (expressed in pack-years) and the extent of CT scan damage (reported as % parenchymal emphysema component). Inclusion criteria included COPD patients aged ≥ 40 years of either genders, who were either non-smokers or former smokers, in a stable clinical condition, and had not used systemic steroids in the preceding eight weeks. Exclusion criteria were: a) Patients aged < 40 years; b) presence of bronchial asthma or asthma COPD overlap (ACO); c) physical limitations and/or cognitive impairments preventing the performance of lung function tests; d) COPD patients in unstable clinical conditions or who had used systemic steroids in the past eight weeks; e) patients with a forced expiratory volume in 1 second (FEV_1) reversibility ≥ 12% from baseline after administration of 400 mcg of salbutamol. In addition to age, gender, and BMI, the following lung function parameters were collected for all included patients**:** Forced expiratory volume in 1 second (FEV_1) (% predicted), Forced vital capacity (FVC) (% predicted), FEV_1/FVC ratio (%), Residual volume (RV) (L), Total lung capacity (TLC) (L), Motley Index (RV/TLC, %), Peak expiratory flow (PEF) (L), Maximal expiratory flow at 75%, 50%, and 25% of FVC (MEF75, MEF50, MEF25, L). All lung function parameters were obtained using a Plethysmography Platinum DX Elite system (MedGraphics, Saint Paul, MN, USA) and expressed in liters (L), except for FEV_1/FVC and the Motley Index, which were reported as percentages (%). The Emphysema Severity Index (ESI) was calculated by inputting the absolute values of PEF, FEF25, FEF50, FEF75, and FVC from standard spirometry into dedicated software designed to mathematically represent the expiratory downslope of the flow-volume curve morphology for each individual. The calculation is independent of age, sex, ethnicity, or anthropometric characteristics because it depends directly from the shape of the MEFV curve of each patient. The mathematical model generates a numerical output ranging from 0 to 10, classifying each patient based on the presence and severity of emphysema [3,4]. A detailed theoretical description of the biomechanical model has been previously published [3].

Statistics

Categorical variables were expressed as counts and percentages, continuous variables were summarized using the mean and standard deviation (SD). Difference in each parameter before and after bronchodilation was evaluated using a generalized estimating equation (GEE) model [7] (gamma family, identity as link function). The variation before and after bronchodilation on the outcomes were expressed in terms of adjusted mean difference (AMD) and 95% confidence interval (CI). All models were adjusted by age, gender, BMI, CT scan damage, and smoke consumption by including the variables as covariates in the GEE models.

Statistical analysis was performed using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

Data were collected from 51 COPD patients via anonimous boolean selectiom from the institutional data base. Around two third of the cohort were males (n = 31, 60.8%). Mean age was 70.4 years (SD 12.2), and mean BMI was 25.6 kg/m^2 (SD 4.7). Moreover, CT scan damage was about 12.9% (SD 10.7) and mean smoke consumption was 22.2 pack/year (SD 25.8) (Table 1).

n	51
Mean year (SD)	70.39 (12.16)
Male (%)	31 (60.8%)
Mean BMI (SD)	25.56 (4.74)
CT scan (%)	12.90 (10.74)
Pack/year	22.18 (25.75)

Table 1: *Baseline characteristics.*

Mean basal values ± SD obtained in basal condition and after bronchodilation for all parameters are reported in table 2 together with the corresponding mean differences and p-values for their comparisons. Generally, lung fuction parameters did not change after bronchodilation. Only FVC, MEF75, MEF50, MEF25 were slightly higher after bronchdilation even if such increase was clinically negligible (Table 2).

Variable	Pre-dilation	Post-dilation	AMD	p-value
FEV_1	63.16 (16.15)	65.04 (16.44)	1.71 (-0.18 to 3.60)	0.075
FEV_1/FVC	77.10 (11.99)	75.57 (13.10)	-1.55 (-3.13 to 0.03)	0.055
RV (L)	2.75 (0.83)	2.67 (0.84)	-0.08 (-0.23 to 0.07)	0.289
TLC (L)	5.76 (1.50)	5.58 (1.44)	-0.17 (-0.35 to 0.02)	0.077
Motley index	48.76 (11.52)	48.02 (11.47)	-1.27 (-3.32 to 0.79)	0.228
ESI	2.01 (1.57)	1.82 (1.40)	-0.08 (-0.22 to 0.07)	0.286
PEF	4.69 (2.03)	4.80 (2.06)	0.12 (-0.12 to 0.37)	0.323
FVC	2.61 (1.19)	2.68 (1.18)	0.08 (0.03 to 0.13)	0.003
V75	3.17 (1.81)	3.45 (1.87)	0.25 (0.16 to 0.34)	<0.001
V50	1.43 (0.91)	1.60 (0.95)	0.13 (0.06 to 0.20)	<0.001
V25	0.49 (0.29)	0.59 (0.36)	0.10 (0.04 to 0.16)	0.001

Table 2: *Mean values and (SD) for each parameter in baseline and corresponding changes after bronchodilation.*

AMD: Adjusted Mean Difference (Adjusted for age, sex, BMI CT scan, and pack/year).

The correlation matrix of variations pre and post bronchodilation is reported in table 3. Almost all parameters seemed to be not correlated. A positive correlation was found only between variation in TLC and RV (Table 3 and figure 1) and between variation in Motley index and RV (Table 3 and figure 2) (0.504 $p < 0.01$ and 0.616 $p < 0.001$, respectively).

FEV1					
-0.031	**FEV1/ FVC**				
-0.127	0.207	**RV**			
-0.142	0.103	0.504 **	**TLC**		
-0.127	0.125	0.616 ***	0.358	**Motley index**	
0.019	-0.053	0.257	0.192	0.113	**ESI**

Table 3: *Correlation matrix of variations pre- and post-dilation.*

*°p<0.1, *p<0.05; **p<0.01; ***p<0.001.*

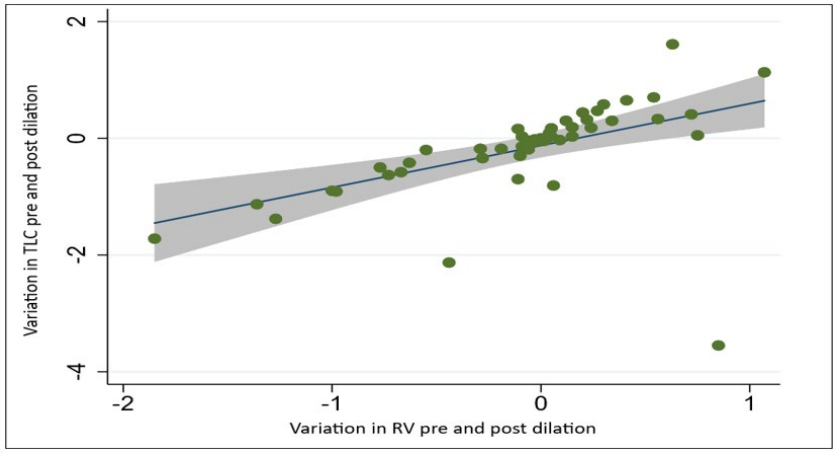

Figure 1: *Linear regression between pre-post dilation values for RV and TLC.*

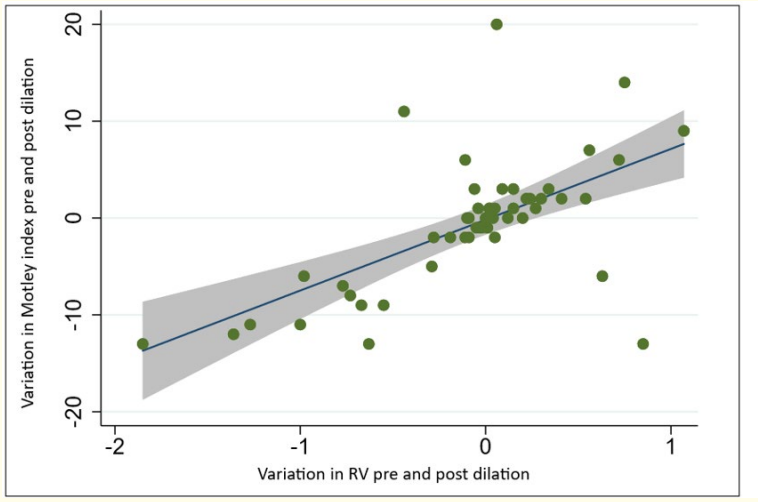

Figure 2: *Linear regression between pre-post dilation values for RV and Motley index.*

Finally, the effect of baseline characteristics on mean values for each lung function parameter before and after bronchodilation, and for the corresponding mean variations is reported in table S1. Age and gender affected almost all parameters (except FEV1), while BMI was associated with ESI only. CT scan damage affected FEV1 and ESI, while smoke consumption influenced RV and TLC. The influence of these parameters proved similar for mean values before or after bronchodilation and for the corresponding mean variations.

Variable	**Pre-dilation**		**Post-dilation**		**Post vs. pre dilation**	
FEV_1	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Age (years)	-0.06 (-0.50 to 0.37)	0.775	-0.10 (-0.53 to 0.33)	0.643	-0.08 (-0.53 to 0.38)	0.746
Male vs. female	0.53 (-9.18 to 10.25)	0.914	-1.21 (-11.29 to 8.86)	0.813	0.02 (-8.82 to 8.85)	0.997
BMI (kg/m^2)	0.0 (-1.08 to 1.08)	0.995	0.07 (-0.91 to 1.06)	0.884	0.03 (-0.91 to 0.96)	0.956
CT scan (%)	-0.80 (-1.29 to -0.31)	0.001	-0.84 (-1.32 to -0.36)	0.001	-0.81 (-1.24 to -0.38)	<0.001
Pack /year	0.04 (-0.11 to 0.20)	0.590	0.03 (-0.13 to 0.19)	0.720	0.04 (-0.13 to 0.21)	0.643
Post vs. pre dilation	NA	NA	NA	NA	1.71 (-0.18 to 3.60)	0.075
FEV_1/FVC	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Age (years)	-0.39 (-0.65 to -0.13)	0.003	-0.38 (-0.64 to -0.12)	0.004	-0.39 (-0.64 to -0.13)	0.003
Male vs. female	2.60 (-2.80 to 8.0)	0.345	1.11 (-4.97 to 7.18)	0.721	1.75 (-3.71 to 7.21)	0.530
BMI (kg/m^2)	0.15 (-0.43 to 0.72)	0.617	0.08 (-0.52 to 0.67)	0.799	0.11 (-0.53 to 0.74)	0.740
CT scan (%)	-0.14 (-0.40 to 0.13)	0.325	-0.24 (-0.58 to 0.09)	0.157	-0.20 (-0.50 to 0.10)	0.194
Pack /year	-0.06 (-0.17 to 0.05)	0.265	-0.02 (-0.15 to 0.11)	0.793	-0.04 (-0.16 to 0.09)	0.565
Post vs. pre dilation	NA	NA	NA	NA	-1.55 (-3.13 to 0.03)	0.055
RV (L)	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Age (years)	0.02 (0.0 to 0.03)	0.029	0.02 (0.01 to 0.04)	0.005	0.02 (0.0 to 0.03)	0.017
Male vs. female	0.37 (0.03 to 0.71)	0.033	0.52 (0.16 to 0.87)	0.004	0.45 (0.11 to 0.79)	0.010
BMI (kg/m^2)	-0.03 (-0.06 to 0.01)	0.188	-0.01 (-0.05 to 0.03)	0.695	-0.02 (-0.06 to 0.02)	0.417
CT scan (%)	0.0 (-0.03 to 0.03)	0.882	0.0 (-0.03 to 0.02)	0.871	0.0 (-0.03 to 0.03)	0.981
Pack /year	0.01 (0.01 to 0.02)	0.001	0.01 (0.0 to 0.02)	0.002	0.01 (0.0 to 0.02)	0.003
Post vs. pre dilation	NA	NA	NA	NA	-0.08 (-0.23 to 0.07)	0.289
TLC (L)	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Age (years)	-0.01 (-0.03 to 0.01)	0.191	-0.01 (-0.03 to 0.01)	0.319	-0.01 (-0.03 to 0.01)	0.225
Male vs. female	1.77 (1.18 to 2.37)	<0.001	1.74 (1.17 to 2.32)	<0.001	1.76 (1.21 to 2.30)	<0.001
BMI (kg/m^2)	-0.04 (-0.09 to 0.01)	0.132	-0.04 (-0.09 to 0.01)	0.111	-0.04 (-0.08 to 0.0)	0.079
CT scan (%)	-0.01 (-0.05 to 0.03)	0.547	0.0 (-0.03 to 0.03)	0.907	-0.01 (-0.04 to 0.03)	0.734
Pack /year	0.02 (0.01 to 0.03)	0.001	0.02 (0.01 to 0.03)	<0.001	0.02 (0.01 to 0.03)	0.002
Post vs. pre dilation	NA	NA	NA	NA	-0.17 (-0.35 to 0.02)	0.077
Motley index	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Age (years)	0.36 (0.15 to 0.57)	0.001	0.54 (0.36 to 0.73)	<0.001	0.46 (0.24 to 0.68)	<0.001
Male vs. female	-8.80 (-14.02 to -3.59)	0.001	-7.07 (-11.47 to -2.66)	0.002	-7.88 (-12.29 to -3.47)	<0.001
BMI (kg/m^2)	0.0 (-0.54 to 0.55)	0.987	0.36 (-0.11 to 0.82)	0.133	0.19 (-0.32 to 0.71)	0.460
CT scan (%)	0.10 (-0.27 to 0.47)	0.588	0.02 (-0.29 to 0.34)	0.884	0.05 (-0.26 to 0.36)	0.736
Pack /year	0.10 (-0.02 to 0.21)	0.102	0.04 (-0.06 to 0.14)	0.404	0.07 (-0.03 to 0.17)	0.180

Post vs. pre dilation	NA	NA	NA	NA	-1.27 (-3.32 to 0.79)	0.228
ESI	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Age (years)	0.01 (-0.02 to 0.05)	0.411	0.01 (-0.01 to 0.03)	0.250	0.01 (-0.01 to 0.03)	0.261
Male vs. female	0.53 (0.04 to 1.01)	0.033	0.34 (-0.38 to 1.06)	0.350	0.43 (0.0 to 0.86)	0.052
BMI (kg/m^2)	-0.06 (-0.10 to -0.02)	0.003	-0.05 (-0.13 to 0.02)	0.146	-0.05 (-0.10 to -0.01)	0.011
CT scan (%)	0.06 (0.03 to 0.09)	<0.001	0.05 (0.02 to 0.08)	0.001	0.06 (0.03 to 0.08)	<0.001
Pack /year	0.0 (0.0 to 0.01)	0.465	0.0 (0.0 to 0.01)	0.263	0.0 (0.0 to 0.01)	0.334
Post vs. pre dilation	NA	NA	NA	NA	-0.08 (-0.22 to 0.07)	0.286

Table S1: *Linear regression between each patient's characteristic and (1) value of each variable pre-dilation; (2) value of each variable post-dilation, and (3) value of the variation in each variable pre- and post-dilation.*

Discussion

The identification of the prevailing phenotype of COPD, whether inflammatory narrowing of the conductive airways or parenchymal destruction (emphysema) [8-17], holds significant clinical and strategic importance [18,19].

Compared to patients with predominant chronic conductive airway obstruction, those with a prevailing emphysema phenotype exhibit a distinct morphology in their maximal expiratory flow/volume (MEFV) curve. CT densitometric changes are more accurately reflected by diffusing capacity and hyperinflation measurements (e.g. RV, TLC, Motley index) in more severely affected patients, while airflow obstruction measurements are more indicative in less severely affected patients [20].

Various pathophysiological mechanisms may contribute to the characteristic "kink" in the descending limb of the MEFV curve observed in patients with varying degrees of emphysema [3]. This peculiar morphological change is thought to result from the sudden narrowing or closure of small airways, which depends on the sharp decrease in lung elastic recoil and reduced thoracic gas compression at high-to-mid lung volumes. Reduced gas compression has been shown to be more pronounced in patients with emphysema than in those with chronic bronchitis [21]. Additionally, early airway collapse during forced expiration may arise from the loss of alveolar wall tethering of small airways in emphysema patients.

As the ESI value reflects these pathophysiological events and the resulting changes in the MEFV curve shape, its quantitative expression correlates with the contribution of emphysema to airway obstruction, as measured by spirometry. Consequently, changes in the descending limb of the MEFV curve following bronchodilation may differ between the two main COPD phenotypes, with a relatively greater extent of partial reversibility observed when conductive airway obstruction predominates.

Furthermore, ESI estimates of emphysema's contribution to airway obstruction have been shown to correlate with the presence and severity of emphysema, as assessed through inspiratory-expiratory CT metrics, CT co-registration analysis, and computational unsupervised CT-based radiomics in COPD patients [3,4].

Data from the present study demonstrate for the first time to our best knowledge that ESI values remain stable and are not significantly affected by bronchodilation in COPD patients with emphysema components. While most input variables for the algorithm computing ESI, except for PEF, change significantly after bronchodilation, the ESI value itself does not show significant variation. This stability may be attributed to ESI's ability to reflect the shape of the MEFV curve, regardless of changes in flow and volume induced by bronchodilation.

Unlike other parameters that are also unaffected by bronchodilation (e.g. RV, TLC, Motley index), ESI does not require time-consuming or expensive equipment. It can be easily obtained using standard spirometry, making it suitable for routine clinical practice, even in outpatient settings [6].

Limitation of the Study

The present study has some limitations: a) the sample size is limited; b) it is a single-center study, requiring validation through multicenter studies. Strengths include: a) careful patient selection. b) the original study design, previously unexplored. c) the use of comprehensive spirometric parameters to investigate COPD phenotypes in both baseline and post-bronchodilation conditions.

Conclusion

COPD is a respiratory condition characterized by heterogeneous involvement of the airways and lung parenchyma, with variable impairment depending of the mechanisms and sites of tissue injury.

Patients with the emphysema phenotype generally exhibit a lower degree of reversibility compared to those with airflow limitation due to the chronic bronchitis phenotype. However, more specific lung function parameters beyond FEV_1 and FEV_1/FVC should be utilized to distinguish these clinical phenotypes. Unfortunately, due to technological limitations, cost, and time constraints, these clinical phenotypes are not routinely investigated in practice.

Reliable lung function parameters that are stable, easily obtainable, time-efficient, and low-cost play a crucial role in advancing a precision medicine approach to COPD diagnosis and treatment. ESI fulfills these requirements, reflecting the partial bronchodilation observed in varying degrees of COPD patients.

Unlike parameters derived from plethysmographic measurements, ESI can be obtained using standard spirometry. It is independent of factors such as sex, age, anthropometric measurements, or ethnicity, as it directly reflects the shape of the descending portion of the MEFV curve for each individual undergoing spirometry.

Authors Contributions

Authors equally contributed to the study: [1]DNRW planned the study and wrote the manuscript; [1]PT and [2]PM contributed to the manuscript; [4]MP carried out the statistical calculations. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of Interest

The authors declare no conflict of interest in the present investigation.

Ethics Approval

The project and the study design were approved by the Ethical and Scientific Commission of Research and Clinical Government in the session of September 9, 2024 (cod. # ESI-3/2024).

Consent for Publication

Not applicable.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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Volume 14 Issue 3 March 2025