

# Role of inspiratory capacity on dyspnea evaluation in COPD with or without emphysematous lesions: a pilot study

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**Background:** Since forced expiratory volume in 1 second (FEV<sub>1</sub>) shows a weak correlation with patients' symptoms in COPD, some volume parameters may better reflect the change in dyspnea symptoms after treatment. In this article, we investigated the role of inspiratory capacity (IC) on dyspnea evaluation among COPD patients with or without emphysematous lesions.

**Methods:** In this prospective study, 124 patients with stable COPD were recruited. During the baseline visit, patients performed pulmonary function tests and dyspnea evaluation using the modified Medical Research Council (mMRC) scale. Partial patients underwent quantitative computerized tomography scans under physicians' recommendations, and emphysematous changes were assessed using the emphysema index (EI; low attenuation area [LAA]% -950). These subjects were then divided into the emphysema-predominant group (LAA% -950 ≥ 9.9%) and the non-emphysema-predominant group (LAA% -950 < 9.9%). After treatment for ~1 month, subjects returned for reevaluation of both pulmonary function parameters and dyspnea severity. Correlation analysis between the change in IC ( $\Delta$ IC) and dyspnea ( $\Delta$ mMRC) was performed.

**Results:** Correlation analysis revealed that  $\Delta$ IC was negatively correlated with  $\Delta$ mMRC (correlation coefficient [cc], -0.490,  $P < 0.001$ ) in the total study population, which was stronger than that between  $\Delta$ FEV<sub>1</sub> and  $\Delta$ mMRC (cc, -0.305,  $P = 0.001$ ). Patients with absolute  $\Delta$ mMRC > 1 were more likely to exhibit a marked increase in IC ( $\geq 300$  mL) than those with absolute  $\Delta$ mMRC  $\leq 1$  (74.36% versus 35.29%; odds ratio [OR], 5.317;  $P < 0.001$ ). In the emphysema-predominant group, only  $\Delta$ IC strongly correlated with  $\Delta$ mMRC (cc, -0.459,  $P = 0.005$ ), while  $\Delta$ FEV<sub>1</sub> did not ( $P > 0.05$ ).

**Conclusion:** IC could serve as an effective complement to FEV<sub>1</sub> in COPD patients undergoing dyspnea evaluation after treatment. For COPD patients with predominant emphysematous lesions, an increase in IC is particularly more suitable for explaining dyspnea relief than FEV<sub>1</sub>.

**Keywords:** IC, COPD, mMRC score, quantitative computerized tomography, emphysema index

## Introduction

COPD, as a common preventable and treatable disease, is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by a significant exposure to noxious particles or gases.<sup>1</sup> For patients with COPD, precise evaluation of symptom severity and treatment efficacy is closely linked to the patient's confidence in the treatment and physicians' considerations for further therapy options.<sup>2-4</sup>

Dyspnea, the hallmark complaint of patients with COPD, correlates with exercise intolerance and declining life quality.<sup>5</sup> Persistent activity-related dyspnea often obliges

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patients to adopt a sedentary lifestyle, which further erodes the perceived quality of life. Frequent exacerbation of dyspnea, on the other hand, which forces patients to seek help from physicians and hospitals, is an independent predictor of a poor prognosis.<sup>6</sup> Therefore, dyspnea relief and precise assessment play crucial roles in daily management of stable COPD patients.

A simple measure of dyspnea severity by the modified Medical Research Council (mMRC) scale is considered an adequate and convenient tool for daily assessment of COPD patients, which is well related to patients' health status<sup>7</sup> and future mortality risk.<sup>8,9</sup> In addition, the mMRC score has been shown to have good correlation with declining lung function and other evaluation systems, such as the Chronic Respiratory Disease Questionnaire (CRQ) and the St George's Respiratory Questionnaire (SGRQ) in a previous longitudinal study.<sup>10</sup>

Historically, forced expiratory volume in 1 second ( $FEV_1$ ) has been the "gold standard" for diagnosis and severity assessment of airflow limitation. However, some issues with its efficacy have remained, namely, that some patients with severe airflow limitation conduct nearly normal daily activities, and  $FEV_1$  sometimes shows no obvious improvement despite dyspnea being significantly alleviated. This coincides with the statement from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) that  $FEV_1$  shows quite a weak correlation with symptom severity in COPD patients.<sup>1</sup> Therefore, in this article, we have focused on other objective parameters that might be well correlated with subjective dyspnea evaluation and then might serve as a complement to  $FEV_1$  for more precise assessment of COPD.

In this work, we verified the efficiency of the volume parameter inspiratory capacity (IC) to evaluate dyspnea relief for ~1 month. This composite parameter may indirectly reflect the severity of lung hyperinflation, which represents the fundamental origin of dyspnea development.<sup>10,11</sup>

As a heterogenic disease, airflow limitation in COPD develops as a co-effect of both airway narrowing and destruction of lung elastic recoil, and the latter may display more severe gas trapping during hard expiration. Quantitative computerized tomography (QCT) provides a new approach for COPD subtyping by calculating the emphysema index (EI), which is the percentage of voxels with low attenuation, ie,  $<-950$  Hounsfield units (Hu).<sup>12</sup> Patients with or without marked emphysematous lesions may display distinct clinical characteristics and treatment responses. A study showed that QCT measures of emphysema were more likely to be associated with dyspnea severity, while complaints such as

coughing and phlegm might relate to airway disease.<sup>13</sup> This proposed a question of whether emphysematous changes may influence the application value of IC during dyspnea relief.

The aims of this study were to investigate the role of IC when evaluating dyspnea relief among total COPD subjects and then to compare the possible, different applications of IC in patients with different emphysematous phenotypes.

## Methods

### Subject population

Subjects eligible for inclusion in this prospective clinical study were patients aged  $>40$  years who were diagnosed with COPD. All the subjects were in a stable state, with no exacerbation history for the recent 6 weeks prior to their entry into the study. All the subjects were enrolled between January 2015 and May 2017 in Qilu Hospital, Shandong University, People's Republic of China. Subjects with a definite diagnosis of asthma or interstitial lung disease were excluded from the present study. Other exclusion criteria included thoracic pleural disease, bronchiectasis, or a computerized tomography (CT) mass with a diameter  $>3$  cm.

This research was approved by the Human Research Ethics Committees of Qilu Hospital, Shandong University, People's Republic of China (No 2015091). The study information was provided to subjects verbally prior to enrollment, and then informed consent was obtained in writing from each subject.

### Study design

During baseline registration, individual information and medical history were collected. Dyspnea severity was evaluated through the mMRC scale. Pulmonary function tests were performed and interpreted for all subjects by experienced technicians, according to the requests of the American Thoracic Society/European Respiratory Society (ATS/ERS) statement.<sup>14</sup> Subjects with the following conditions were recommended by the respiratory physicians to complete QCT scans: 1) subjects who did not complete any imaging examination, such as chest X-rays or chest CT scans, prior to the enrollment and 2) subjects whose symptom evaluation did not match the pulmonary function impairment under a physician's consideration, especially for those with a slight activity-related dyspnea but with a severe decline in  $FEV_1$ . The necessity and benefits of the QCT check were explained to the patients before the check. After QCT scanning, the EI was calculated as the percentage of lung voxels with a CT attenuation value  $\leq -950$  Hu (low attenuation area [LAA]%  $-950$ ). According to the adopted cutoff value of 9.9%,<sup>15</sup> subjects were further divided into an emphysema-predominant group

(LAA%  $-950 \geq 9.9\%$ ) and a non-emphysema-predominant group (LAA%  $-950 < 9.9\%$ ).

We offered no medical intervention with household treatments, which was directed by physicians after baseline enrollment. Conventional treatments included inhaled bronchodilators, such as a long-acting  $\beta_2$  receptor agonist (LABA; eg, formoterol and salmeterol), a long-acting muscarinic antagonist (LAMA; eg, tiotropium bromide), and an inhaled corticosteroid (ICS; eg, budesonide), as well as systemic medicines, including theophylline. No systematic corticosteroids or antibiotics were given to these patients. Regular phonic follow-ups were made to supervise the patients' compliance to treatment. After ~1 month, patients were called in for reexamination. Pulmonary function tests were conducted, while dyspnea severity was assessed by investigators who coordinated follow-up and were blind to previous assessment results and CT phenotypes.

Patients who experienced exacerbation, missed to follow-up, or changed the initial therapy for personal reasons during the treatment were eliminated from this study.

### Assessment of dyspnea severity

Patients in this study were questioned regarding their degree of dyspnea symptoms by utilizing the mMRC dyspnea scale. The baseline and second tests were performed by different investigators, avoiding any implicating words during the investigation. The dyspnea severity was then scored on a scale from 0 to 4. According to the change in the mMRC score after treatment, subjects in this study were divided into a dyspnea obvious-remission group (absolute value of  $\Delta$ mMRC score  $> 1$ ) and a non-remission group (absolute value of  $\Delta$ mMRC score  $\leq 1$ ).

### Pulmonary function tests

Pulmonary function tests were performed by experienced technicians at the baseline and second visits. Parameters were measured with instruments, including a spirometer and a diffusion device (MasterScreen; Jaeger, Wurzburg, Germany). The observed parameters included IC,  $FEV_1$ , vital capacity (VC), forced vital capacity (FVC), total lung capacity (TLC), residual volume (RV), diffusing capacity of the lungs for carbon monoxide (DLCO), and diffusing capacity divided by the alveolar volume (DLCO/VA). Changes in parameters were calculated and presented as the  $\Delta$  parameter.

### QCT scan

Subjects who followed the recommendation of the physicians underwent chest CT scans performed at full inspiration stage.

The scan was conducted with a 64-multidetector helical CT scanner (Philips Brilliance, Amsterdam, the Netherlands). Tube voltage of the scanner was 120 kV, and tube current was varied by automatic regulation in the range of 20–500 mA. Exposure time was 0.5 seconds, and image reconstruction was built in 1 mm – thick slices using a standard algorithm. LAAs were analyzed using a Airway Inspector CT Slicer software (Surgical Planning Laboratory at Brigham and Women's Hospital, Boston, MA, USA). EI was calculated as the percentage of lung voxels with a CT attenuation value  $\leq -950$  Hu, presented as LAA%  $-950$ . Based on the EI value, these subjects were then divided into an emphysema-predominant group (LAA%  $-950 \geq 9.9\%$ ) and a non-emphysema-predominant group (LAA%  $-950 < 9.9\%$ ).

### Statistical analysis

Data in this study were analyzed with SPSS 19.0 software (IBM Corporation, Armonk, NY, USA). Quantitative variables were presented as mean  $\pm$  standard deviation (SD), and categorical variables were mainly shown as percentages (%). A paired *t*-test was utilized for comparison of clinical characteristics of subjects between the baseline and second visits. An independent sample *t*-test was applied on quantitative variables between the obvious-remission and non-remission groups and between the emphysema-predominant and non-emphysema-predominant groups. Categorical variables were analyzed via a chi-squared test. Correlations were verified by Pearson correlation coefficient (cc) analysis, while odds ratio (OR) and model fitting were calculated using a regression model. A *P*-value of  $< 0.05$  was considered as statistically different.

## Results

### Subject characteristics at baseline and second visits

A total of 124 stable COPD patients were enrolled in this study. The median interval between the first and second visits was 30.5 days. Mean age of these subjects was  $62.08 \pm 8.36$  years. Mean IC pretreatment was  $2.08 \pm 0.63$  L, which increased by ~300 mL after the treatment period. Apart from this,  $FEV_1$  and mMRC scores also changed significantly ( $P < 0.001$ ). Comparison of subjects' clinical characteristics between the baseline and second visits is shown in Table 1.

### Association between the changes in mMRC scores and the changes in IC and $FEV_1$

Correlation analysis between the changes in mMRC scores and the changes in lung function parameters showed that

**Table 1** Subjects' clinical characteristics at baseline and second visits

Characteristics	Baseline visit	Second visit	P-value
Case	124		
Age, years	62.08±8.36		NA
Sex, male/female	96/28		NA
Smoking history, pack-years	25.03±24.21		NA
BMI, kg/m <sup>2</sup>	24.64±3.33		NA
GOLD			
I	11		
II	47		
III	47		
IV	19		
CT-EI			
LAA% -950, %	12.79±11.49		NA
mMRC scores	1.98±0.86	0.78±0.75	<0.001 <sup>a</sup>
Pulmonary function			
IC, L	2.08±0.63	2.41±0.65	<0.001 <sup>a</sup>
VC, L	2.88±0.79	3.27±0.80	<0.001 <sup>a</sup>
FVC, L	2.70±0.76	3.04±0.78	<0.001 <sup>a</sup>
FEV <sub>1</sub> , L	1.33±0.57	1.62±0.64	<0.001 <sup>a</sup>
FEV <sub>1</sub> %pred, %	50.09±18.83		
FEV <sub>1</sub> /FVC, %	48.56±10.84	52.89±12.87	<0.001 <sup>a</sup>
FEV <sub>1</sub> /VC, %	45.57±10.61	49.21±12.96	<0.001 <sup>a</sup>
TLC, L	5.24±1.02	5.53±0.95	0.002 <sup>a</sup>
RV/TLC, %	44.31±9.35	40.38±8.15	0.004 <sup>a</sup>
DLCO, mL/mmHg/min	7.60±4.75	8.11±4.84	0.002 <sup>a</sup>
Changes in IC and FEV <sub>1</sub>			
ΔIC, L		0.33±0.40	NA
ΔFEV <sub>1</sub> , L		0.29±0.35	NA

**Notes:** Data are presented as mean ± SD. <sup>a</sup>Analysis with paired t-test.

**Abbreviations:** NA, not applicable; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CT, computerized tomography; EI, emphysema index; LAA% -950, percentage of low attenuation areas less than -950 Hu; mMRC, modified Medical Research Council; IC, inspiratory capacity; VC, vital capacity; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of the lungs for carbon monoxide; ΔIC, increases in inspiratory capacity; ΔFEV<sub>1</sub>, increases in forced expiratory volume in 1 second; SD, standard deviation; CT, computed tomography; Hu, Hounsfield units.

ΔIC was negatively correlated with the ΔmMRC score (cc, -0.490,  $P < 0.001$ ). Although still significant, this association was weaker between ΔFEV<sub>1</sub> and ΔmMRC (cc, -0.305,  $P = 0.001$ ). Detailed correlation analysis is shown in Table 2.

## Comparison of clinical characteristics between subjects with dyspnea obvious remission and non-remission

According to the changes in mMRC scores after treatment, subjects were divided into a dyspnea obvious-remission group (absolute value of ΔmMRC >1) and a non-remission group (absolute value of ΔmMRC ≤1). Comparison of the clinical characteristics between the two subgroups showed no significant difference between GOLD grades and

**Table 2** Correlation analysis of ΔmMRC scores and changes in pulmonary function parameters

Parameters	ccs <sup>a</sup> of ΔmMRC score	P-value
ΔIC	-0.490	<0.001
ΔVC	-0.417	<0.001
ΔFVC	-0.393	<0.001
ΔFEV <sub>1</sub>	-0.305	0.001
ΔRV/TLC	0.420	0.004
ΔTLC	-0.317	0.034
ΔDLCO	-0.185	0.235

**Note:** <sup>a</sup>Analysis with Pearson's correlation test.

**Abbreviations:** ΔmMRC scores, decline in the modified Medical Research Council scores; ccs, correlation coefficients; ΔIC, increases in inspiratory capacity; ΔVC, increases in vital capacity; ΔFVC, increases in forced vital capacity; ΔFEV<sub>1</sub>, increases in forced expiratory volume in 1 second; ΔRV/TLC, increases in the ratio of RV to TLC; ΔTLC, increases in total lung capacity; ΔDLCO, increases in diffusing capacity of the lungs for carbon monoxide; RV, residual volume; TLC, total lung capacity.

emphysema subtypes ( $P > 0.05$ ). However, subjects in the obvious-remission group showed a significant increase in IC and FEV<sub>1</sub> compared to those in the non-remission group ( $P < 0.001$ ; Table 3). Since both IC and FEV<sub>1</sub> increased by ~300 mL after treatment, we further set 300 mL as a cutoff value for grouping. A higher percentage of subjects in the obvious-remission group showed a significant increase in IC (ΔIC ≥300 mL) compared to the non-remission group (74.36% versus 35.29%; OR, 5.317; 95% CI, 2.28–12.38;  $P < 0.001$ ). Moreover, more subjects in the obvious-remission group showed a significant increase in IC (ΔIC ≥300 mL) than an increase in FEV<sub>1</sub> (ΔFEV<sub>1</sub> ≥300 mL; 74.36% versus 51.28%).

**Table 3** Comparison of characteristics between subjects of the obvious-remission group and the non-remission group

Characteristics	Obvious-remission group	Non-remission group	P-value
Case	39	85	
Absolute value of ΔmMRC	2.15±0.37	0.75±0.46	<0.001 <sup>a</sup>
LAA% -950, %	13.32±8.47	12.59±12.49	0.817 <sup>a</sup>
ΔIC, L	0.54±0.37	0.23±0.38	<0.001 <sup>a</sup>
ΔFEV <sub>1</sub> , L	0.42±0.39	0.23±0.32	0.01 <sup>a</sup>
Emphysema predominant, %	63.16	47.06	0.176 <sup>b</sup>
Significant change in IC (ΔIC ≥300 mL), %	74.36	35.29	≤0.001 <sup>b</sup>
Significant change in FEV <sub>1</sub> (ΔFEV <sub>1</sub> ≥300 mL), %	51.28	32.94	0.041 <sup>b</sup>

**Notes:** Data are presented as mean ± SD. <sup>a</sup>Analysis with paired t-test. <sup>b</sup>Analysis with chi-squared test.

**Abbreviations:** ΔmMRC scores, decline in the modified Medical Research Council scores; LAA% -950, percentage of low attenuation areas less than -950 Hu; ΔIC, increases in inspiratory capacity; ΔFEV<sub>1</sub>, increases in forced expiratory volume in 1 second; IC, inspiratory capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second; SD, standard deviation; CT, computed tomography; Hu, Hounsfield units.

**Table 4** Comparison of characteristics between the emphysema-predominant group and the non-emphysema-predominant group

Characteristics	Emphysema-predominant group	Non-emphysema-predominant group	P-value
Case	36	34	
Sex, male/female	33/3	24/10	0.023 <sup>a</sup>
Age, years	64.33±6.88	61.03±9.57	0.100 <sup>b</sup>
Smoking history, pack-years	29.32±26.13	19.79±19.08	0.088 <sup>b</sup>
BMI, kg/m <sup>2</sup>	23.69±3.06	25.37±2.86	0.020 <sup>b</sup>
LAA% -950, %	21.10±10.28	3.99±2.94	<0.001 <sup>b</sup>
mMRC score	2.39±0.77	1.68±0.73	<0.001 <sup>b</sup>
IC, L	2.01±0.68	2.18±0.62	0.283 <sup>b</sup>
FEV <sub>1</sub> , L	1.27±0.53	1.48±0.63	0.131 <sup>b</sup>
FEV <sub>1</sub> %pred, %	46.92±19.71	56.33±17.11	0.037
FEV <sub>1</sub> /FVC, %	45.78±10.60	53.37±10.69	0.004 <sup>b</sup>
FVC, L	2.71±0.65	2.75±0.91	0.807 <sup>b</sup>
DLCO, mL/mmHg/min	6.90±4.10	8.40±5.41	0.324 <sup>b</sup>

**Notes:** Data are presented as mean ± SD. <sup>a</sup>Analysis with chi-squared test. <sup>b</sup>Analysis with independent-sample t-test.

**Abbreviations:** BMI, body mass index; LAA% -950, percentage of low attenuation areas less than -950 Hu; mMRC, modified Medical Research Council; IC, inspiratory capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; SD, standard deviation; CT, computed tomography; Hu, Hounsfield units.

## Comparison of characteristics between the emphysema-predominant group and the non-emphysema-predominant group

According to the value of LAA% -950, 70 COPD subjects who performed QCT scans were divided into an emphysema-predominant group (LAA% -950 ≥ 9.9%, n=36) and a non-emphysema-predominant group (LAA% -950 < 9.9%, n=34), as previously described. Subjects in the emphysema-predominant group show a higher mMRC score (2.39±0.77 versus 1.68±0.73,  $P < 0.001$ ) and a higher EI (21.10±10.08 versus 3.99±2.94,  $P < 0.001$ ). Comparisons of clinical characteristics of the two groups are shown in Table 4.

## Role of IC and FEV<sub>1</sub> applied to dyspnea evaluation in different COPD emphysematous phenotypes

In this study, we investigated the role of IC and FEV<sub>1</sub> dyspnea evaluation in different COPD subtypes. As shown in Table 5, ΔIC was negatively correlated with ΔmMRC scores in the non-emphysema-predominant group (cc, -0.465,  $P = 0.006$ ), while cc of ΔFEV<sub>1</sub> and ΔmMRC scores was -0.335 ( $P = 0.053$ ). In the emphysema-predominant group, only ΔIC was negatively correlated with ΔmMRC scores (cc, -0.459,  $P = 0.005$ ), while ΔFEV<sub>1</sub> was not ( $P = 0.723$ ). Further logistic

**Table 5** Correlation analysis of ΔIC and ΔFEV<sub>1</sub> with ΔmMRC in the emphysema-predominant group and the non-emphysema-predominant group

Parameters	Emphysema-predominant group		Non-emphysema-predominant group	
	cc <sup>a</sup>	P-value	cc <sup>a</sup>	P-value
ΔIC and ΔmMRC	-0.459	0.005	-0.465	0.006
ΔFEV <sub>1</sub> and ΔmMRC	-0.061	0.723	-0.335	0.053

**Note:** <sup>a</sup>Analysis with Pearson's correlation test.

**Abbreviations:** ΔIC, increases in inspiratory capacity; ΔFEV<sub>1</sub>, increases in forced expiratory volume in 1 second; ΔmMRC, decline in the modified Medical Research Council scores; cc, correlation coefficient.

regression model was utilized to analyze the relationship between dyspnea outcomes and improvements in IC and FEV<sub>1</sub> in two groups separately. In the emphysema-predominant group, only ΔIC predicted the degree of dyspnea relief ( $R = 0.459$ ,  $P = 0.005$ ), while FEV<sub>1</sub> did not ( $P > 0.05$ ). For the non-emphysema-predominant group, no effective logistic regression model to predict the changes in mMRC scores was built in terms of ΔIC and ΔFEV<sub>1</sub> ( $P > 0.05$ ). However, a regression analysis revealed that subjects with a significant increase in IC (ΔIC ≥ 300 mL) tended to achieve obvious dyspnea relief (absolute ΔmMRC > 1; OR, 10.20; 95% CI, 1.07–97.41;  $P = 0.021$ ). Apart from this, the significant increase in FEV<sub>1</sub> (ΔFEV<sub>1</sub> ≥ 400 mL) may also predict dyspnea relief to some degree in the non-emphysema-predominant group (OR, 7.14; 95% CI, 1.12–45.52;  $P = 0.025$ ). Results of regression analysis are shown in Table 6.

## Discussion

The increase in IC showed a better correlation with the decline in mMRC scores than FEV<sub>1</sub> did in the total COPD population. Moreover, patients with obvious dyspnea relief tended to display a significant IC increase compared to

**Table 6** Regression analysis for dyspnea remission in terms of ΔIC and ΔFEV<sub>1</sub>

Variable	OR <sup>a</sup>	95% CI	P-value
Emphysema-predominant group (remission, absolute ΔmMRC ≥ 1)			
ΔIC ≥ 300 mL	2.29	1.54–3.39	0.034
ΔFEV <sub>1</sub> ≥ 300 mL	1.39	1.12–1.73	0.221
Non-emphysema-predominant group (obvious remission, absolute ΔmMRC > 1)			
ΔIC ≥ 300 mL	10.20	1.07–97.41	0.044
ΔFEV <sub>1</sub> ≥ 300 mL	3.64	0.60–22.23	0.162
ΔFEV <sub>1</sub> ≥ 400 mL	7.143	1.12–45.52	0.037

**Note:** <sup>a</sup>Analysis of bivariate logistic regression.

**Abbreviations:** ΔIC, increases in inspiratory capacity; ΔFEV<sub>1</sub>, increases in forced expiratory volume in 1 second; OR, odds ratio; CI, confidence interval; ΔmMRC, decline in the modified Medical Research Council scores.

patients whose symptoms showed hardly any improvement. As to the different COPD emphysematous phenotypes, increases in both IC and FEV<sub>1</sub> might negatively correlate with the decline in mMRC scores in the non-emphysema-predominant group. However, only the increase in IC could be used to specifically assess the relief of dyspnea in patients with predominant emphysematous lesions.

We tried to elucidate two points in this study. The first is that the volume parameter IC may serve as an effective complement to FEV<sub>1</sub> in dyspnea evaluation during COPD daily management and assessment. As is known, FEV<sub>1</sub> is widely used as a major criterion for judging and grading the severity of the expiratory flow limitation (EFL) in COPD patients.<sup>1</sup> Despite the close correlation between the progressive decline in FEV<sub>1</sub> and the mortality of patients, a number of studies<sup>5,16,17</sup> have demonstrated rather weak correlations between FEV<sub>1</sub> and symptom severity, especially for exertional dyspnea and exercise intolerance. In this study, a relatively weaker correlation was shown between an increase in FEV<sub>1</sub> and a decline in mMRC score. This may be partially explained by the fact that the subjects selected in this study were distributed from GOLD I to IV, and the higher proportion of subjects with severe airflow limitation (GOLD IV) may have brought about this unexpected cc.

To explore the mechanism, the dyspnea symptom of COPD patients mainly results from the uncoupling between limited tidal volume (VT) expansion and increasing ventilation demand during exercise.<sup>18</sup> This uncoupling is one of the intuitive manifestations of the EFL, and the latter represents the principal function disorder of COPD.<sup>19</sup> The underlying pathogenesis is that EFL further promotes the development of dynamic hyperinflation (DH). DH forces patients to breathe at a high end-expiratory lung volume level, which is affected by both a faint breathing drive (mainly by recoil destruction) and airway construction (mainly by airway remodeling).<sup>16</sup> During exercise, VT expansion is greatly restricted and thus reaches an inflection point or plateau earlier than in healthy subjects. To interpret the uncoupling during dyspnea development, it is key to find a parameter that fully reflects the change in DH. Since DH has more volume expansion than flow disorder, IC showed more advantages over FEV<sub>1</sub> in terms of dyspnea evaluation. Compared to volume parameters, such as TLC and RV, obtained by a single-breath diffusion test or body plethysmograph, the measurement of IC can be obtained through a spirometer, which is simpler, is cost-effective, and has a low demand for technical requirements and patient cooperation. This means, for primary hospitals or clinics, simple detection of IC may

well explain the obvious improvement in dyspnea symptoms of patients after treatment, despite almost no change in FEV<sub>1</sub> in some instances.

Several previous studies have focused on the application of IC during clinical practice. Manriquez et al<sup>20</sup> compared the proportion of 50 stable COPD patients whose FEV<sub>1</sub> and IC improved by >10% after inhaling 200 mg of salbutamol. In a display of transient efficacy, only 13 patients (26%) showed FEV<sub>1</sub> improvement in excess of 10%, while 40 patients (80%) displayed an obvious IC increase. Ramon et al<sup>21</sup> investigated the relationship between the ratio of IC to TLC and the decline in exercise capacity among COPD patients and suggested that patients with a lower IC/TLC ratio had a greater decline in 6-minute walk distance (6MWD) decline. In the present study, no significant correlation was found between  $\Delta$ IC/TLC and declining mMRC scores; one possible reason for this may be that the volume measurements in this study were mainly obtained through diffusion tests of one single breath. This method might sometimes severely underestimate the actual lung volume, thus affecting the correlation analysis results.

The second point we wanted to elucidate is that the increase in IC may be particularly more suitable for interpreting dyspnea relief in COPD patients with an emphysema-predominant CT indication. As a heterogenic disease, patients of different COPD subtypes may display distinct clinical characteristics and therapeutic responses.<sup>22–24</sup> COPD heterogeneity depends mostly on different pathological and physiological impairments, such as airway remodeling, emphysematous lung destruction, or some other specific features.

Since QCT is a promising technique for the diagnosis and severity assessment of COPD, different CT phenotypes may exhibit distinct characteristics and bronchodilator responses. Hersh et al<sup>25</sup> compared clinical features between emphysema-predominant COPD and non-emphysematous COPD in a multicenter clinical study. It showed that patients in the emphysema-predominant group underwent more severe airflow obstruction, greater exercise limitation, and reduced quality of life, while non-emphysematous patients were more frequent to be diagnosed with diabetes. Moreover, CT quantitative analysis showed a strong correlation with COPD candidate gene in which CTGA diplotype was closely associated with emphysematous phenotype.<sup>26</sup> In this study, we divided the subjects according to emphysema severity.<sup>27,28</sup> The measure of emphysema, executed by calculating the percentage of voxels with the CT attenuation value  $\leq -950$  Hu, exhibits a good correlation with visual

emphysema assessment and pathologic morphology.<sup>29–31</sup> Our previous study<sup>15</sup> showed that the measure of EI (LAA%–950) among normal subjects was  $2.79\% \pm 2.37\%$ , and LAA%–950 exceeding 9.9% may suggest evidence of obvious emphysema. Fewer studies have focused on the role of IC in the evaluation of dyspnea relief in different COPD subtypes.

In patients with no obvious change in emphysema, increase in both IC and FEV<sub>1</sub> may be possible to explain the relief of dyspnea, and the role of FEV<sub>1</sub> is doubted. This may depend on the fact that airway obstruction may be dominant rather than severe recoil destruction among these patients. The decline in FEV<sub>1</sub> represents the severity of airflow limitation, and the detection of it may be affected by both emphysema severity and airway obstruction. However, for patients of the emphysema-predominant subtype, airflow limitation develops mainly on the basis of parenchyma destruction. This pathogenic change thus results in severe hyperinflation and air trapping. Therefore, volume changes may be more sensitive and could reliably reflect the relief of dyspnea symptoms. This point is also verified by regression model that a significant increase in IC may predict the remission of activity-related dyspnea. Taken together with factors including age, sex, nutrition status, smoking history, and pulmonary function parameters, an increase in IC alone may serve as a linear predictor for the degree of dyspnea relief.

## Limitations

There are several limitations in this study. First, as a single-center pilot study, the limited cohort size may affect the correlation analysis results, despite the association between IC and dyspnea showed in this article. The limited cohort size also affected the efficacy of regression model for predicting dyspnea remission in terms of  $\Delta$ IC and FEV<sub>1</sub>. Therefore, an enlarged cohort study was necessary to better elucidate the conclusions. Second, mMRC scores were utilized as the only measure of symptom evaluation in this study. Different investigators, who were blinded to the previous evaluating scores, assessed the severity of dyspnea during the baseline and second visits. However, different questioning methods may still affect the accuracy of mMRC scores. For further study, a more comprehensive evaluation system, such as COPD Assessment Test (CAT) or SGRQ, needs to be used. Finally, lung volume measures in this study were mainly obtained via diffusion tests of one single breath; this may somewhat underestimate the actual lung volume values and changes. IC is a composite parameter that is easily interfered by breathing patterns during the check. Despite strict quality control, a larger sample size may be helpful to improve

accuracy. Besides, a study focusing on volume changes determined by body plethysmography is also needed.

## Conclusion

IC could serve as an effective complement to FEV<sub>1</sub> in COPD patients for dyspnea evaluation during a stable period of treatment. For COPD patients with predominant emphysematous lesions, an increase in IC is particularly more suitable for explaining dyspnea relief than that in FEV<sub>1</sub>.

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## Disclosure

The authors report that no potential conflicts of interest exist with any companies or organizations whose products or services are discussed in this article.

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