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Clinical Outcomes of Male Subjects With Moderate COPD Based on Maximum Mid-Expiratory Flow

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BACKGROUND: Although FEV_1 and FEV_1/FVC are accepted as standard parameters in treatment follow-up, these parameters have a limited ability to predict clinical outcomes in patients with COPD. However, small airways dysfunction, which is determined by maximum mid-expiratory flow, is variable in the same stage of patients with COPD, even if their FEV_1 and FEV_1/FVC are similar. The aim of this study was to compare pulmonary function, the severity of perceived dyspnea, the severity of fatigue, physical activity level, and health-related quality of life based on the severity of small airways dysfunction in male subjects with moderate COPD. METHODS: The study consisted of 96 subjects with moderate COPD. Pulmonary function tests, the distance achieved on the 6-min walk test, the modified Medical Research Council Dyspnea Scale, the International Physical Activity Questionnaire - short form, the Fatigue Severity Scale, the St George Respiratory Questionnaire, and Short Form 36 questionnaire were evaluated in all subjects. After calculating the mean percent of predicted maximum mid-expiratory flow for the entire sample, subjects were divided into 2 groups: below average (Group 1, $n = 54$ subjects) and above average (Group 2, $n = 42$ subjects). RESULTS: There were no differences between the groups in age, body mass index, cigarette consumption, percent of predicted FEV_1, and FEV_1/FVC ($P = .55$, .61, .19, .09, and .15, respectively). Scores from the Fatigue Severity Scale and the modified Medical Research Council dyspnea scale were significantly higher in Group 1 ($P = .003$ and $P = .002$, respectively); in addition, results from the 6-min walk test and the International Physical Activity Questionnaire - short form scores were significantly lower ($P = .001$ and $P < .001$, respectively). CONCLUSIONS: Increased small airways dysfunction led to increased perception of dyspnea and fatigue, as well as poor exercise capacity and health-related quality of life in male subjects with COPD. We suggest that it may be useful to consider the maximum mid-expiratory flow in addition to FEV_1 and FEV_1/FVC in the treatment and follow-up of male patients with moderate COPD. *Key words: COPD; maximum mid-expiratory flow; airway obstruction; pulmonary disease; chronic obstructive*. [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

COPD is a disease characterized by irreversible air-flow obstruction due to increased airway resistance and destruction of lung tissue. It affects both the large and small airways.[1,2] FEV_1/FVC indicates the presence of air-flow obstruction and is used to diagnose COPD, and FEV_1 is used as an indicator of disease severity.[1] However, these parameters often indicate the condition of large airways, and there is an increasing opinion that they are insufficient to determine clinical effects in patients with COPD, especially in the early stages of the disease.[3,4] Although FEV_1

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and FEV_1/FVC are objective and accepted parameters in treatment follow-up, many studies have shown that these values have a limited ability to predict clinical outcomes such as exercise capacity and health-related quality of life (HRQOL).[5-7] Therefore, small airways dysfunction has recently come into prominence in the literature.[8]

Small airways dysfunction is determined by the physiological parameter known as the maximum mid-expiratory flow.[9] Small airways contribute little to air-flow resistance in healthy individuals, but in patients with COPD, the small airways are the primary source of air-flow resistance.[10,11] Moreover, the small airways are the key areas of air-flow obstruction in patients with COPD, and small airways dysfunction is considered a functional characteristic of the disease.[12] The damage in these areas is thought to worsen the clinical course of the disease.[13] Dysfunction of the small airways precedes the development of emphysema or abnormal pulmonary function in the early stages of the pathology.[2,14] This is important because emphysema is associated with a subsequent decline in FEV_1, an important predictor of mortality in patients with COPD, and may be present even with normal spirometry.[8]

Several studies suggest that the clinical findings of COPD vary by gender.[15,16] Laviolette et al[15] reported that the disease has different effects between genders. Compared to men with the same degree of obstruction, lung function, and volumes, women have more reactive airways, report more dyspnea, and score worse in quality-of-life questionnaires.[16] Therefore, including only one gender in COPD studies using questionnaires as evaluation methods may give more objective findings. The aim of this study was to compare pulmonary function, the severity of perceived dyspnea, the severity of fatigue, physical activity level, and HRQOL based on the severity of small airways dysfunction in male subjects with COPD.

QUICK LOOK

Current knowledge

FEV_1/FVC indicates the presence of air-flow obstruction and is used to diagnose COPD, and FEV_1 is used as an indicator of disease severity. There is increasing evidence that these are insufficient to determine clinical effects in patients with COPD, especially in early disease stages. In addition, small airways dysfunction, which is identified with maximum mid-expiratory flow, precedes the development of emphysema or abnormal pulmonary functions in the early stages of the disease. The maximum mid-expiratory flow has been proposed as an alternative to monitor the clinical course in male patients with moderate COPD.

What this paper contributes to our knowledge

In male subjects with moderate COPD, increased small airways dysfunction was associated with a higher perception of dyspnea and fatigue, as well as poor exercise capacity and worsening health status, despite similar FEV_1 and FEV_1/FVC. Maximum mid-expiratory flow may be useful in addition to FEV_1 and FEV_1/FVC in the treatment and follow-up of male patients with moderate COPD. Moreover, it may be used to provide information about the clinical course and early pulmonary rehabilitation gains of male patients with moderate COPD.

Methods

Subjects

Outpatients with COPD ($n = 126$) admitted to the Department of Chest Diseases at Dokuz Eylül University Hospital in Izmir, Turkey, between May 2019 and January 2020 were invited to the study by telephone. Fifteen did not accept, 11 were excluded, and 4 did not complete all assessments. The study included male subjects diagnosed with moderate COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[1] All subjects regularly received bronchodilators in the form of long-acting β_2-agonists or long-acting antimuscarinics. Subjects were regarded as adherent with their medications upon their subjective statement. The exclusion criteria were any COPD exacerbation in the previous 3 months, any change in medication during the previous month, any other pulmonary disease, any systemic inflammatory disease, cancer, stroke, severe ischemic heart disease, severe kidney dysfunction, or psychological or physical difficulties that might interfere with the assessments. A total of 96 male subjects were included in this study. The flow chart of the study is shown in Figure 1.

Assessments

After the demographic and clinical features of the subjects were recorded, the following parameters were evaluated. Pulmonary function tests performed with the MIR miniSpir (Medical International Research, Rome, Italy) with standardized methods based on American Thoracic Society/European Respiratory Society criteria by a single technician.[17] The maneuvers were performed 3 times, with all subjects seated and wearing nose clips. The highest values were taken into consideration, and the FEV_1, FVC, and maximum mid-expiratory flow were presented as the percentage of predicted values. The modified Medical Research Council dyspnea scale (mMRC), which consists of 5 items with scores ranging from 0 to 4, was used in determining the severity of subjects' dyspnea. Current

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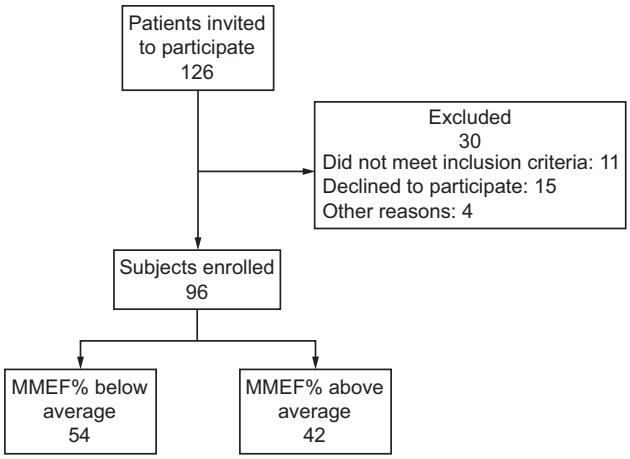

Fig. 1. Flow chart. MMEF = maximum mid-expiratory flow.

guidelines advocate using this scale to assess the severity of perceived dyspnea related to physical activity. A high score indicates a high severity of perceived dyspnea.[1,18] We assessed exercise capacity with a 6-min walk test, which measures the longest distance individuals can walk in a straight corridor in 6 min (ie, 6MWD). The test was performed in a straight, flat hallway 30 m long, according to the American Thoracic Society guidelines.[19] The severity of perceived dyspnea, heart rate, peripheral oxygen saturation, and blood pressure were measured before the start of the test and at the end of the test. The subjects were instructed to walk for 6 min, and the maximum walking distances were recorded.[19]

Physical activity levels of the subjects were determined with the International Physical Activity Questionnaire - short form (IPAQ-SF). It is a standardized self-report measure that generates a total score regarding the duration and frequency of physical activities over the last 7 d and measures the physical activity level related to different types of activities (walking and physical activities with moderate or vigorous intensity). The total score is expressed as a "metabolic equivalent of the task (min/week)."[20] The severity of fatigue was measured with the Fatigue Severity Scale (FSS), which is brief, easy to administer, reliable, and valid. It is a 9-item questionnaire that assesses fatigue in daily life, with items scoring between 1 and 7, with low total scores indicating less severe fatigue.[21] Disease-specific HRQOL was measured with the St George Respiratory Questionnaire, which is a standardized, self-administered questionnaire consisting of 3 categories: symptoms (8 questions), activity (16 questions), and impact (26 questions). In addition, the total score can be calculated from all categories. Scores range from 0 to 100 for all categories, and low scores indicate poor health.[22] The overall HRQOL was measured with the Medical Outcomes Study Short Form 36 (SF-36) questionnaire, which has 8 sub-parameters: physical functioning, physical role functioning, bodily pain, social role functioning, emotional role functioning, mental health, vitality, and general health perceptions. The scores of sub-parameters range from 0 to 100, and low scores indicate worse HRQOL.[23]

Subjects who consented to participate in the study were scheduled to make an appointment at the out-patient clinic. All assessments were performed in a standardized order (ie, demographic and clinical characteristics, questionnaires, mMRC, pulmonary function tests, and 6MWD test) in the morning (ie, between 9:00 AM and 11:00 AM) at one appointment. This cross-sectional study was approved by the Dokuz Eylül University Hospital Ethics Committee, and all subjects provided written informed consent.

Statistical Analysis

Data were expressed as mean ± SD. After calculating the mean percent of predicted maximum mid-expiratory flow for the entire sample, subjects were divided into 2 groups: below average (Group 1, $n = 54$ subjects) and above average (Group 2, $n = 42$ subjects). The differences between Group 1 and Group 2 were analyzed with a Student t test or chi-square test as appropriate. [24] In addition, a partial correlation analysis was performed to investigate the relationship between percent of predicted maximum mid-expiratory flow and other parameters. The significantly correlated parameters that changed significantly between the groups were entered into a multiple regression analysis using percent of predicted maximum mid-expiratory flow as the independent variable with the other pulmonary function parameters and the mMRC, IPAQ-SF, 6MWD, and FSS as dependent variables. Multicollinearity was checked by performing an interaction test. Consequently, if an independent variable displayed a variation inflation factor value > 5, it was considered to be highly correlated, and was thus removed from the model. SPSS 21.0 (SPSS, Chicago, Illinois) was used for the statistical analysis. For all statistical analyses, $P < .05$ indicated statistical significance.[24]

Results

The study consisted of 96 male subjects with moderate COPD. Subjects' demographic and clinical features are presented in Table 1. The mean age of the study sample was 62.3 ± 6.2 y, and the mean percent of predicted maximum mid-expiratory flow was 43.02 ± 9.01. None of the subjects were current smokers. In addition, the mean percent of predicted maximum mid-expiratory flow was 36.63 ± 4.59 in Group 1 and 51.24 ± 6.16 in Group 2 ($P < .001$). The mean FEV_1 percent of predicted was 62.31 ± 4.16 in Group 1 and 63.77 ± 4.04 in Group 2 ($P = .09$). The mean FEV_1/FVC was 66.20 ± 11.23 in Group 1 and 68.92 ± 4.87 in Group 2 ($P = .15$). There were no statistical

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Table 1. Demographic and Clinical Characteristics of Subjects

Parameters	Subjects
Age, y	62.3 ± 6.2
Height, m	1.71 ± .08
Weight, kg	79.42 ± 15.92
Body mass index, kg/m^2	27.23 ± 5.07
Comorbidities, *n* (%)	
Hypertension	26 (27.1)
Diabetes mellitus	17 (17.8)
Other	11 (11.5)
Cigarette consumption, pack-years	38.23 ± 21.63
Cigarette cessation, y	5.5 ± 1.8
mMRC score	1.64 ± 1.17
Distance on 6-min walk test, m	438.53 ± 91.25
IPAQ-SF score, MET-min/wk	756.72 ± 616.78
Fatigue Severity Scale score	37.98 ± 13.99
FEV_1, % predicted	62.95 ± 4.15
FVC, % predicted	83.40 ± 4.66
FEV_1/FVC, %	67.39 ± 9.08
Maximum mid-expiratory flow, % predicted	43.02 ± 9.01

Data are presented as mean ± SD or *n* (%). $N = 96$ subjects.
mMRC = modified Medical Research Council dyspnea scale
IPAQ-SF = International Physical Activity Questionnaire-Short Form
MET = metabolic equivalent of the task

differences between the groups in terms of age ($P = .55$), body mass index ($P = .61$), comorbidities (hypertension: $P = .22$; diabetes mellitus: $P = .81$; other: $P = .60$), cigarette consumption ($P = .19$), cigarette cessation ($P = .69$), FEV_1 percent of predicted ($P = .09$), FVC percentage ($P = .11$), and FEV_1/FVC ($P = .15$) (Table 2). FSS and mMRC scores were significantly higher in Group 1 ($P = .003$ and $P = .002$, respectively), and 6MWD and IPAQ-SF scores were significantly lower ($P = .001$ and $P < .001$, respectively) (Table 2). All parameters on the St George Respiratory Questionnaire were statistically higher (symptoms: $P = .002$; activity: $P = .001$; impact: $P = .004$; total: $P = .001$); in addition, some of the SF-36 sub-parameters were statistically lower in Group 1 (physical functioning: $P = .006$; role-physical: $P = .02$; general health: $P = .04$; vitality: $P = .02$) (Table 2).

The results of the multiple linear regression analysis for of mMRC, IPAQ-SF, 6MWD, and FSS are presented in Table 3. All models with dependent variables mMRC (Adj $R^2 = 0.53$, $P < .001$), IPAQ-SF (Adj $R^2 = 0.31$, $P < .001$), 6MWD (Adj $R^2 = 0.32$, $P < .001$) and FSS (Adj $R^2 = 0.19$, $P < .001$) were significant.

Discussion

The main finding of this study was that increased small airways dysfunction caused significantly lower exercise capacity and physical activity level, higher perceived dyspnea severity and fatigue severity, and worse health conditions. Moreover, all these parameters were significantly associated with the degree of small airways obstruction reflected by maximum mid-expiratory flow. In the early stages of COPD, understanding the effects of small airways dysfunction on disease progression may provide better management of the disease.[25] Despite the pathophysiological importance of maximum mid-expiratory flow in COPD, there is a poor understanding of its contribution to clinical outcomes such as exercise capacity, dyspnea perception, and HRQOL.[10] Small airways dysfunction occurs before the development of emphysema, supporting the argument that maximum mid-expiratory flow is more sensitive in the early stages of the disease.[2,14] Although percent of predicted maximum mid-expiratory flow shows a high correlation with FEV_1/FVC, it was found to decrease more steeply than FEV_1/FVC at mild obstruction levels.[26] It has been proven that some patients who suffer from clinical symptoms of COPD but have normal FEV_1/FVC and FEV_1 (ie, an at-risk group) had significantly lower percent of predicted maximum mid-expiratory flow than healthy subjects.[27,28] Stockley et al[8] reported that a reduction in maximum mid-expiratory flow was associated with impaired health status and a more rapid decline of FEV_1 in subjects with alpha-1 antitrypsin disease. However, the role of small airways on clinical outcomes in COPD is not yet fully understood.[10] Our results suggest that, in patients with moderate COPD, percent of predicted maximum mid-expiratory flow below a certain level indicates severe involvement of the small airways. Further studies should be conducted in subjects with mild COPD to shed more light on this issue. In addition, although these values are related in both groups in this study, differences were noted within groups in exercise capacity, dyspnea, fatigue, and HRQOL values.

Dyspnea is the major symptom that reduces HRQOL and exercise capacity and increases disease severity in patients with COPD.[1] In one study, Lopes and Mafort[25] assessed the correlation between small airways dysfunction and the severity of dyspnea, exercise capacity, and health condition in subjects with COPD. They reported significant relationships between small airways dysfunction and the 6MWD, mMRC, and COPD Assessment Test scores. Furthermore, they found that small airways dysfunction was an independent predictor of 6MWD, mMRC and COPD Assessment Test scores.[25] Haruna et al[29] reported significant correlations between small airways dysfunction and HRQOL and perceived dyspnea. Similarly, we noted that dyspnea was significantly higher in subjects with increased small airways dysfunction, and exercise capacity and physical activity level were significantly lower. Moreover, we observed that percent of predicted maximum mid-expiratory flow significantly affects dyspnea, exercise capacity, and physical activity level in male subjects with moderate COPD.

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Table 2. Comparison of Group 1 and Group 2

Parameters	Group 1	Group 2	*P*
Age, y	62.6 ± 5.4	61.8 ± 7.1	.55
Height, m	1.70 ± .08	1.72 ± .07	.29
Weight, kg	78.02 ± 16.86	81.21 ± 14.62	.33
Body mass index, kg/m^2	26.98 ± 5.55	27.52 ± 4.44	.61
Comorbidities			
Hypertension	12 (22.2)	14 (33.3)	.22
Diabetes mellitus	10 (18.5)	7 (16.7)	. 81
Other	7 (12.9)	4 (9.5)	.60
Cigarette consumption, pack-years	40.8 ± 21.5	34.9 ± 21.6	.19
Cigarette cessation, years	5.4 ± 1.6	5.6 ± 2.0	.69
mMRC score	1.96 ± 1.18	1.21 ± 1.03	.002
Distance on 6-min walk test, m	411.91 ± 78.49	472.86 ± 95.87	.001
IPAQ-SF score, MET-min/wk	542.18 ± 463.18	1032.57 ± 682.31	< .001
Fatigue Severity Scale score	41.63 ± 13.37	33.29 ± 13.51	.003
FEV_1, % predicted	62.31 ± 4.16	63.77 ± 4.04	.09
FVC, % predicted	82.76 ± 5.21	84.21 ± 3.74	.11
FEV_1/FVC, %	66.20 ± 11.23	68.92 ± 4.87	.15
Maximum mid-expiratory flow, % predicted	36.63 ± 4.59	51.24 ± 6.16	< .001
St George Respiratory Questionnaire			
Symptoms	46.76 ± 18.92	32.31 ± 26.23	.002
Activity	60.31 ± 24.47	39.11 ± 33.23	.001
Impact	35.38 ± 23.14	21.29 ± 23.59	.004
Total	44.09 ± 21.03	28.24 ± 25.88	.001
Short Form-36			
Physical functioning	38.57 ± 12.21	46.14 ± 14.16	.006
Role-physical	40.41 ± 13.83	47.01 ± 13.42	.02
Bodily pain	47.93 ± 11.94	48.66 ± 12.37	.77
General health	40.75 ± 14.74	46.20 ± 9.84	.04
Vitality	47.75 ± 12.27	53.85 ± 13.55	.02
Social functioning	42.09 ± 16.68	42.96 ± 12.18	.78
Role-emotional	46.70 ± 13.05	47.13 ± 13.30	.87
Mental health	49.08 ± 11.67	50.92 ± 8.78	.38

Data are presented as mean ± SD or *n* (%). Group 1: $n = 54$ subjects; Group 2: $n = 42$ subjects.
mMRC = modified Medical Research Council dyspnea scale
6MWD = 6-min walk distance
IPAQ-SF = International Physical Activity Questionnaire-Short Form
MET = metabolic equivalent of the task

The disease-specific quality of life (measured with the St George Respiratory Questionnaire) and overall quality of life (measured with the SF-36) were also significantly more affected in subjects with increased small airways dysfunction. Furthermore, there were relationships between the degree of small airways obstruction and exercise capacity, physical activity level, and perceived dyspnea.

There appear to be no studies that identify the relationship between small airways dysfunction and fatigue in patients with COPD. Fatigue is a symptom that is defined as an important problem secondary to dyspnea in patients with COPD. In fact, a strong positive relationship has been shown between fatigue and dyspnea.[30] Breslin et al[31] reported that, despite its high association with dyspnea, fatigue is an independent symptom that reduces quality of life and exercise capacity in patients with COPD. We noted that the severity of perceived fatigue was significantly higher in subjects with increased small airways dysfunction, and that there was also a relationship between the degree of small airways obstruction and the severity of fatigue. Moreover, we noted that percent of predicted maximum mid-expiratory flow significantly affects the severity of fatigue in male subjects with moderate COPD. This supports the argument that small airways dysfunction directly affects the severity of fatigue.

There are proven gender differences in the phenotypic expression and clinical effects of COPD.[15,16] In addition, gender influences responses regarding subjective symptoms in questionnaires, which are the most commonly used assessment tools.[16] In this study, all subjects were male,

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Table 3. Multiple Regression Analysis of 4 Assessment Tools

	B	Standard Error B	β	P	Variation Inflation Factor
Dependent variable: modified Medical Research Council dyspnea scale*					
Constant	15.70	1.89	NA	< .001	
FEV_1, % predicted	–0.04	0.02	–0.16	.05	1.21
FVC, % predicted	–0.12	0.02	–0.47	< .001	1.63
Maximum mid-expiratory flow, % predicted	–0.03	0.01	–0.26	.006	1.70
Dependent variable: International Physical Activity Questionnaire-Short Form†					
Constant	–2,505.43	1,198.88	NA	.04	
FEV_1, % predicted	13.43	13.92	0.09	.34	1.21
FVC, % predicted	12.28	14.40	0.09	.39	1.63
Maximum mid-expiratory flow, % predicted	32.37	7.59	0.47	< .001	1.70
Dependent variable: distance on 6-min walk test‡					
Constant	–291.14	175.96	NA	.10	
FEV_1, % predicted	2.02	2.04	0.09	.33	1.21
FVC, % predicted	5.55	2.11	0.28	.01	1.63
Maximum mid-expiratory flow, % predicted	3.25	1.11	0.32	.004	1.70
Dependent variable: Fatigue Severity Scale§					
Constant	118.28	29.56	NA	< .001	
FEV_1, % predicted	–0.61	0.34	–0.18	.08	1.21
FVC, % predicted	–0.27	0.36	–0.09	.46	1.63
Maximum mid-expiratory flow, % predicted	–0.46	0.19	–0.30	.02	1.70

* Adjusted $R^2 = 0.53$, $P < .001$.
† Adjusted $R^2 = 0.31$, $P < .001$.
‡ Adjusted $R^2 = 0.32$, $P < .001$.
§ Adjusted $R^2 = 0.19$, $P < .001$.
NA = not applicable

and there was no statistical difference between the groups in terms of demographic and clinical features. This facilitated the analysis and interpretation of the data. However, our study has some potential limitations. First, the study population consisted only of subjects with moderate COPD and did not include subjects at different stages of the disease. Second, although there were 2 significantly different groups in terms of percent of predicted maximum mid-expiratory flow, the lower limit of percent of predicted maximum mid-expiratory flow is considered to be 60% of the predicted value of maximum mid-expiratory flow. It was interesting that all subjects in our study population were below this limit, in terms of the results obtained. Consequently, our results may not reflect all patients with COPD.

Conclusions

Increased small airways dysfunction in male subjects with moderate COPD led to a higher perception of dyspnea and fatigue, as well as poor exercise capacity and worsening health status. We suggest that it may be useful to consider the maximum mid-expiratory flow in addition to FEV_1 and FEV_1/FVC in the treatment and follow-up of male patients with moderate COPD. Clinicians should include such patients with reduced maximum mid-expiratory flow in early pulmonary rehabilitation, especially in terms of the clinical course of the disease. They should also consider measuring maximum mid-expiratory flow in routine pulmonary function tests to have an idea of the clinical course of patients and gains in early pulmonary rehabilitation. Further studies are needed to evaluate small airways dysfunction in patients with COPD in terms of clinical outcomes.

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