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Assessment of small airway dysfunction by impulse oscillometry (IOS) in COPD and IPF patients

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Abstract. – OBJECTIVE: Small airway dysfunction is a pathological component of chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), and impulse oscillometry is an easy-to-administer, effort-independent non-invasive test reflecting small airway dysfunction. We aimed to compare the impulse oscillometry (IOS) measurements between COPD and IPF patients and investigate their correlation with severity of both diseases and other conventional parameters.

PATIENTS AND METHODS: This was a prospective, longitudinal study. We longitudinally evaluated the baseline demographic characteristics, COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scale, Pulmonary Function Test (PFT), Carbon Monoxide Diffusing Capacity (DLCO), Hemogram and Impulse Oscillometry measurements of the patients diagnosed with COPD and IPF.

RESULTS: The study included 60 IPF patients and 48 COPD patients. The CAT and mMRC scores were higher in COPD patients. The majority of COPD patients were classified into Category B (46%), while 68% of IPF patients had Stage 1 GAP. The mean FEF 25-75%, which is typically considered to reflect small airway disease, was 93% in IPF patients, while it was significantly lower in COPD patients (29%). Impulse oscillometry measurements were consistent with spirometry parameters. IOS resistance and reactance values were significantly higher in COPD patients than in IPF patients.

CONCLUSIONS: IOS is advantageous in COPD and IPF patients who cannot exhale due to severe dyspnea, as it is easy to administer and reflects small airway resistance better. Diagnosis of small airway dysfunction may be beneficial in the management of patients with IPF and COPD.

Key Words:
Impulse oscillometry, Small airway disease, Resistance, COPD, IPF.

Introduction

Small airways are defined as those with a diameter of less than 2 mm and are called the silent zone of the lung. It is proposed that the pathology of small airways occurs before the appearance of symptoms or abnormal spirometry[1]. With appreciation of the importance of small airways, there has been a remarkable increase in publications on small airways since 2010. Although small airways dysfunction in asthma has been well described, the involvement of small airways in chronic obstructive pulmonary disease (COPD), an obstructive disease, and particularly in interstitial lung disease with a restrictive pattern, has been understudied[1-3].

While it has been suggested that the small airway involvement in COPD is one of the three main components, along with chronic bronchitis and emphysema, it is still not established adequately. However, symptom burden is believed to be higher in COPD patients with a small airway pathology[1,2,4].

In idiopathic pulmonary fibrosis (IPF), small airway dysfunction associated with loss of terminal bronchioles is also a pathological component of IPF. The detection of small airway disease can also guide bronchodilator use in IPF patients[5-6].

Impulse Oscillometry (IOS) is a non-invasive method that can measure airway resistance during spontaneous respiration regardless of the effort, and it is more sensitive than spirometry in detecting small airway dysfunction, and it is useful in adults and children with shortness of breath and severe coughing who cannot perform effort dependent exhalation[7-8]. Although there is an increasing interest in IOS, it is still

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not used as widely as spirometry. Several studies[7] indicated that IOS may be advantageous over spirometry as it requires minimum patient effort, and it provides rapid, easy, and reproducible measurements.

The detection of small airway pathology in COPD and IPF patients may be a guide in early diagnosis, differentiation, and treatment of the disease. We lack information about the relationship between small airway involvement and severity of the disease and its correlation with the impulse oscillometry measurements and other conventional parameters. The present study aimed to investigate the small airway involvement measured by impulse oscillometry in COPD, an obstructive disease and IPF, a restrictive disease, and the correlation of IOS measurements with the severity of both diseases and other conventional parameters.

Patients and Methods

It was a prospective cross-sectional study that was carried out between July 1, 2021, and July 1, 2022, at Chest Diseases and Thoracic Surgery Training and Research Hospital. The study protocol was approved by the institutional Ethics Committee (date of approval/No: 03.06.2021/111). A consent form was obtained from all patients who accepted to participate in the study. For these patients who were followed with a diagnosis of COPD and IPD, demographic data such as age, sex, concomitant diseases, body mass index (BMI), smoking history, COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scale, Pulmonary Function Test (PFT), Carbon Monoxide Diffusing Capacity (DLCO), Hemogram and Impulse Oscillometry measurements were recorded at presentation, and cross-sectionally evaluated.

Patients

The inclusion criteria were as follows:

1. ≥ 40 years of age
2. Patients diagnosed with COPD in accordance with the 2021 GOLD guidelines[9].
3. Patients diagnosed with IPF according to the 2018 ATS/ERS/JRS/ALAT guideline[10].

The following patients were excluded:

1. Those diagnosed with combined pulmonary fibrosis and emphysema[11]
2. Those diagnosed with asthma[12].
3. Those experiencing COPD attacks [9].
4. Those with IPF exacerbation[13].

Measurements and Definitions

Chronic Obstructive Pulmonary Disease (COPD)

Patients who have a clinical history of risk factors such as smoking, complaints of persistent dyspnea, chronic cough, sputum production, obstruction determined by PFT, $FEV_1/FVC < 70\%$ and diagnosed with COPD by a pulmonologist[9].

Idiopathic Pulmonary Fibrosis (IPF)

An interstitial lung disease primarily occurring in advanced age, mostly characterized with complaints of dyspnea and cough, with a chronic and progressive course, radiological or histopathological appearance of usual interstitial pneumonia pattern (UIP), excluding pulmonary fibrosis and other potential causes, and having functionally restrictive pattern[10].

Modified Medical Research Council (mMRC) Scale[9]

Stage 0: Dyspnea only with strenous exercise.

Stage 1: Dyspnea when hurrying or walking up a slight hill.

Stage 2: I walk slower than people of my age because of dyspnea or I have to stop for breath when walking at my pace.

Stage 3: I stop for breath after walking 100 m or after a few minutes.

Stage 4: I cannot leave house due to dyspnea or I am breathless when dressing/undressing.

COPD Assessment Test (CAT)[9]

It is an 8-item test that measures deterioration in health in COPD, assessing cough, sputum, dyspnea, activities, sleep quality and energy level, with 10 being the cutoff score for discrimination.

Scores range from 0 to 40:

≥10 – Symptomatic, poor health status;

≥20 – Too symptomatic.

COPD Categories A-B-C-D9

"Category A": Low Risk, Less Symptoms – 0-1 exacerbation /year CAT<10 or mMRC 0-1.

"Category B": Low Risk, More Symptoms – 0-1 exacerbation /year, CAT ≥10 or mMRC≥2.

"Category C": High Risk, Less Symptoms – ≥2 exacerbations /year or ≥1 exacerbations leading to hospital admission, CAT<10 or mMRC 0-1.

"Category D": High Risk, More Symptoms – ≥2 exacerbations /year or ≥1 exacerbations leading to hospital admission, CAT ≥10 or mMRC ≥2.

GAP (Gender-Age-Physiology) Index[14]

It is a simple screening method to determine the average risk of mortality of patients with IPF. Three stages (stages I, II, and III) were identified based on the GAP index with a1-year mortality of 6%, 16%, and 39%, respectively.

Spirometry (Pulmonary Function Test) Values

FEF25-75 Forced expiratory flow between 25 and 75%.

FEV_1 Forced expiratory volume in 1 second.

FVC (Forced Vital Capacity)

It is the total amount of air exhaled during a maximal forced expiration effort following a rapid and deep inhalation.

FEV_1 (Forced Expiratory Volume in One Second)

It is the total amount of air expelled in the first second of a forced and rapid expiration following a rapid and deep inhalation. Its measurement depends on patient effort and requires cooperation. It reflects large airways in millimeters[1,4]. It is reduced in airway obstruction and in the presence of restrictive respiratory dysfunction due to decreased FVC. It is the most widely used parameter in evaluation and staging of airway obstruction because of its ease of measurement and low variability.

FEV_1/FVC

It is a parameter used to determine the presence of airway obstruction. A FEV_1/FVC <70% indicates presence of airway obstruction in COPD.

$FEF_{25\%-75\%}$

It represents the average flow at 25% and 75% of the FVC maneuver (middle half of FVC), regarded as a parameter reflecting the small airway better than FEV_1. In early obstructive disease, there may be a reduction in $FEF_{25\%-75\%}$ while FEV_1 and FVC are normal. However, it has some shortcomings as being affected by age, smoking, and having a wide normal range and low repeatability[15].

IOS (Impulse Oscillometry)

Specified IOS parameters for analysis included[7,8,16]:

R5: Resistance at 5 Hz;

R20: Resistance at 20 Hz;

R5-R20: Heterogeneity of resistance;

X5: Reactance at 5 Hz;

AX: Area under reactance curve between 5 Hz and resonant frequency;

Fres: Resonant Frequency.

IOS was performed seated using a noseclip and a mouthpiece that stabilized the tongue position and the cheeks supported. Impulses were delivered for 20 s during tidal breathing. A minimum of three maneuvers were performed and data were recorded. Impulse oscillometry (IOS) measures the respiratory system response to the flow of sound waves at a specific frequency[7].

Higher frequency waves travel shorter distances typically reflecting larger airways. Thus, the resistance at 20 Hz (R20) represents proximal resistance. Lower frequency waves travel further reaching the smaller airways <2 mm in diameter after the eighth generation. Hence the resistance at 5 Hz (R5) represents the total lung resistance. COPD and asthma will increase total resistance (R5) to a relatively greater degree than proximal resistance (R20). This is known as a frequency dependent change or heterogeneity of resistance evident as raised peripheral resistance (R5-R20). It was shown that R5-R20 was significantly more sensitive to small airway constriction than most other frequency choices. Reactance can be considered as the out of phase component of respiratory impedance (with flow, but not volume), reflecting the balance between inertial and elastic properties of distensible airways. Typically, this is measured at 5 Hz (X5) or as the area under the reactance curve (AX) between 5 Hz and the resonant frequency (Fres). Fres represents the point at which opposing inertial and capacitive components cancel each other out. AX represents low frequency reactance in smaller airways where elastance exceeds inertance, with increased values reflecting reduced lung compliance and stiffer lungs. AX is strongly correlated with the R5-R20 value[7,8,16]. Until now, no standards have been set for IOS that could be published and adopted as recommendations worldwide[7,8,16].

Statistical Analysis

The descriptive statistics of patient characteristics measured are shown in tables as mean, standard deviation (SD), quartiles (25^{th}, median, 75^{th}), number and % frequencies. The conformity of numerical variables to normal distribution was analyzed using Shapiro-Wilk test. The relationship between the categorical characteristics and the COPD and IPD groups was analyzed using the Pearson Chi-Square test. Furthermore, Mann-Whitney U test was used to compare the two disease groups for numerical characteristics. The associations among the numerical characteristics were analyzed using the Spearman Rank

Table I. Demographic Characteristics of IPF and COPD Patient Groups.

		IPF		COPD		
		n	%	n	%	p*
Sex	M	44	50.0	44	50.0	**0.015**
	F	16	80.0	4	20.0	
Smoking	0	12	100.0	0	0.0	**0.004**
	1	10	55.6	8	44.4	
	2	38	48.7	40	51.3	
Concomitant Disease	No	11	52.4	10	47.6	0.744
	Yes	49	56.3	38	43.7	
Hypertension	No	38	55.1	31	44.9	0.893
	Yes	22	56.4	17	43.6	
Diabetes Mellitus	No	42	52.5	38	47.5	0.280
	Yes	18	64.3	10	35.7	
Coronary Artery Disease	No	41	53.2	36	46.8	0.447
	Yes	19	61.3	12	38.7	
Chronic Heart Failure	No	58	56.3	45	43.7	0.474
	Yes	2	40.0	3	60.0	
Rhythm Disorder	No	57	55.9	45	44.1	0.778
	Yes	3	50.0	3	50.0	
Gastrointestinal Disorder	No	50	52.1	46	47.9	**0.040**
	Yes	10	83.3	2	16.7	
Hyperlipidemia	No	55	53.9	47	46.1	0.159
	Yes	5	83.3	1	16.7	
Psychiatric Disease	No	57	54.3	48	45.7	0.198
	Yes	2	100.0	0	0.0	
Bronchiectasis	No	59	57.3	44	42.7	0.169
	Yes	1	20.0	4	80.0	
Malignity	No	59	57.8	43	42.2	**0.049**
	Yes	1	16.7	5	83.3	
GAP_Stage	I	41	68.3			
	II	16	26.7			
	III	3	5.0			
Gold Category	A			7	14.6	
	B			22	45.8	
	C			0	0.0	
	D			19	39.6	

*: Pearson Chi-square test.

correlation analysis. The statistical significance level was set at $p<0.05$. For calculations, SPSS (version 23) software program (IBM Corp., Armonk, NY, USA) was used.

Results

The study included a total of 108 patients, 60 with IF and 48 with COPD.

The demographic characteristics of the patients (Table I) showed that male sex was dominant in both IPF and COPD groups; and female patients were relatively more in the IPF group than in the COPD group (26% *vs*. 8%, respectively). All COPD patients had a history of smoking, and pack/year smoking was greater in COPD than in IPF. An analysis of concomitant diseases showed that gastrointestinal complaints were significantly higher in the IPF group (16%) compared to the COPD group (4%). Malignity was higher in COPD group than in IPF group, and no other significant difference was observed in concomitant diseases between the groups.

A comparison between IPF and COPD groups for numerical measurements is shown in Table II. The mean age of IPF and COPD patients was similar (66 years). The CAT and mMRC scores were significantly higher in COPD patients. The mean GAP index score was 2.68 in IPF patients. Of 60 IPF patients, 41 (68%) had Stage 1 GAP, and 16 (27%) Stage 2 GAP. According to the GOLD ABCD classification, majority of COPD patients were classified into Categories B (46%) and D (40%). The mean BMI was 28 in IPF patients while it was statistically lower in COPD patients (26). Analysis of hemogram values showed that lymphocytes, eosinophils, and monocytes were

Table II. Comparison of IPF and COPD groups for numerical measurements.

	Diagnosis	N	Mean	SD	Percentiles 25th	Median	75th	p*
Age	IPF	60	65.90	8.57	60.25	66.00	71.75	0.426
	COPD	48	66.83	8.78	62.25	66.00	73.00	
CAT score	IPF	60	10.87	5.44	7.00	10.00	14.00	**0.002**
	COPD	48	14.94	7.16	8.25	15.00	20.00	
mMRC	IPF	60	1.70	.79	1.00	2.00	2.00	**0.048**
	COPD	48	2.00	.88	1.00	2.00	3.00	
GAP INDEX	IPF	60	2.68	1.57	1.00	3.00	4.00	---
PCKS/YEAR	IPF	48	39.17	24.57	30.00	40.00	45.00	**0.023**
	COPD	48	44.50	16.41	40.00	42.50	50.00	
Height	IPF	60	167.67	8.80	165.00	170.00	172.00	0.884
	COPD	48	168.81	7.71	165.00	168.00	174.00	
Weight	IPF	60	78.63	11.95	70.00	76.50	87.75	**0.030**
	COPD	48	73.90	17.06	60.50	70.00	85.00	
BMI	IPF	60	28.08	4.22	25.00	28.00	31.00	**0.004**
	COPD	48	25.74	5.39	22.25	24.00	28.75	
WBC	IPF	60	8839.8	1894.0	7327.5	8645.0	10352.5	0.336
	COPD	48	9845.8	4323.4	7160.0	9435.0	10895.0	
Hemoglobin	IPF	60	13.63	1.56	12.60	13.75	14.80	0.863
	COPD	48	13.47	1.98	12.63	13.65	14.80	
RBC	IPF	60	4.65	.56	4.33	4.66	4.98	0.075
	COPD	48	4.80	.66	4.52	4.87	5.34	
PLT	IPF	60	253100.0	65547.2	210000.0	240500.0	290500.0	0.422
	COPD	48	266354.2	82070.4	208250.0	268500.0	306000.0	
MPV	IPF	60	9.70	.98	9.00	9.40	10.50	0.178
	COPD	48	9.86	1.01	9.20	9.70	10.68	
Lymphocytes, n	IPF	60	2356.50	958.60	1727.50	2430.00	2920.00	**0.001**
	COPD	48	1647.29	957.49	815.00	1545.00	2165.00	
Lymphocytes, %	IPF	60	27.12	9.77	21.55	27.30	35.33	**0.001**
	COPD	48	18.67	10.33	9.38	16.25	28.70	
EOSINOPHILS, n	IPF	60	211.51	175.56	92.50	160.00	287.50	**0.028**
	COPD	48	147.92	153.55	10.00	100.00	232.50	
Eosinophils, %	IPF	60	2.54	1.83	1.25	2.10	3.58	**0.005**
	COPD	48	1.58	1.54	.10	1.20	2.58	
MONOCYTES, n	IPF	60	706.67	200.45	592.50	705.00	840.00	0.843
	COPD	48	697.92	368.37	550.00	665.00	917.50	
Monocytes, %	IPF	60	8.30	1.93	7.13	8.30	9.48	**0.019**
	COPD	48	7.19	3.40	5.60	7.35	9.35	
Neutrophils, n	IPF	60	6419.42	8614.93	4322.50	5175.00	6707.50	**0.003**
	COPD	48	7159.17	4050.74	5307.50	6525.00	8137.50	
Neutrophils, %	IPF	60	61.17	10.61	53.73	61.95	68.53	**0.001**
	COPD	48	72.08	13.25	60.38	71.30	82.68	
NLR	IPF	60	2.91	2.43	1.50	2.26	3.10	**0.001**
	COPD	48	6.56	6.05	2.12	4.65	9.26	
FVC L	IPF	60	2.85	.87	2.14	2.84	3.58	**0.048**
	COPD	48	3.00	3.80	1.88	2.25	3.22	
FVC, %	IPF	60	8.57	18.83	67.25	79.00	92.00	**0.001**
	COPD	48	64.46	22.84	48.25	58.50	88.75	
FEV_1 L	IPF	60	2.35	.66	1.85	2.35	2.91	**0.001**
	COPD	48	1.54	.74	.87	1.38	2.18	
FEV_1, %	IPF	60	87.52	18.73	73.75	86.00	94.00	**0.001**
	COPD	48	49.79	22.98	31.25	47.50	74.50	
FEV_1/FVC	IPF	60	89.60	14.06	80.03	86.55	93.02	**0.001**
	COPD	48	63.08	15.06	54.16	61.46	71.75	
FEF 25/75	IPF	60	4.76	14.12	2.09	2.89	3.80	**0.001**
	COPD	48	2.21	7.68	.45	.75	1.83	
FEF 25%/75%	IPF	60	93.48	38.76	68.00	98.00	113.00	**0.001**
	COPD	48	28.70	22.23	12.25	19.00	44.50	
DLCO	IPF	58	5.11	2.04	3.53	5.00	6.18	0.720
	COPD	41	5.34	2.34	3.23	5.27	7.59	

Table continued

Table II *(Continued)*. Comparison of IPF and COPD groups for numerical measurements.

	Diagnosis	N	Mean	SD	Percentiles 25th	Median	75th	p*
DLCO, %	IPF	58	58.84	19.91	43.75	56.00	71.25	0.952
	COPD	41	59.95	26.02	39.50	56.00	75.00	
KCO	IPF	58	1.15	.42	.94	1.10	1.31	0.317
	COPD	40	3.50	15.65	.76	1.05	1.29	
KCO, %	IPF	58	82.00	22.67	69.00	80.00	91.00	0.402
	COPD	40	75.71	32.50	49.25	77.00	98.75	
R5	IPF	60	.37	.17	.25	.33	.46	**0.004**
	COPD	48	.53	.33	.32	.45	.72	
Resonant frequency (Fres)	IPF	60	17.55	5.15	14.83	17.28	19.13	**0.001**
	COPD	48	22.40	6.58	18.21	21.33	26.33	
R20	IPF	60	.25	.10	.19	.24	.29	**0.035**
	COPD	48	.34	.25	.20	.28	.35	
AX	IPF	60	.84	.94	.26	.57	1.12	**0.001**
	KOAH	48	2.62	2.90	.55	1.84	3.71	
R5-20, %	IPF	60	44.86	25.98	24.21	43.50	64.59	**0.022**
	COPD	48	70.17	51.24	31.26	52.47	103.31	
R5-20	IPF	60	.12	.10	.05	.11	.20	**0.003**
	COPD	48	.25	.23	.07	.18	.36	
X5	IPF	60	-.08	.07	-.12	-.08	-.04	**0.002**
	COPD	48	-.17	.23	-.26	-.14	-.06	

*: Mann-Whitney U test.

lower in COPD patients than in IPF patients, but the number and percentage of neutrophils were higher. The neutrophil/lymphocyte ratio (NLR) was significantly higher in COPD than in IPF (6.56 *vs*. 2.91, respectively). The mean FVC L was lower in IPF. The FEV_1 L (1.54) and FEV_1% (49.8%) were significantly lower in COPD patients compared to FEV_1 L (2.35) and FEV_1% (87.5%) in IPF patients. The FEV_1/FVC was 89.6% in IFP while the mean FEV_1/FVC was significantly lower in COPD (63%). Typically regarded to reflect small airway obstruction, the mean FEF 25/75% was 93.5% in IPF patients while it was significantly lower in COPD patients (28.7%). The parameters measured by IOS significantly differed between IPF and COPD patients. The resistance values were significantly higher in COPD patients compared to IPF patients. The mean R5 was 0.53 in COPD patients *vs.* 0.37 in IFP patients (p=0.004); the mean R20 was 0.34 *vs.* 0.25 (p=0.035), respectively; the mean R5-20 was 0.25 *vs.* 0.12 (p=0.003), respectively; and the mean R5-20% was 70.17% *vs.* 44.86% (p=0.02), respectively. Reactance values were significantly lower in IPF patients compared to COPD patients. The mean X5 was -0.08 in IPF patients *vs.* -0.17 in COPD patients (p=0.002); the mean AX was 0.84 in IFP patients *vs.* 2.62 in COPD patients (p=0.001); and the mean Fres was 17.55 in IFP patients *vs.* 22.40 in COPD patients (p=0.001) (Table II).

Table III shows the associations between the RFT parameters and IOS measurements and the mMRC, CAT score, GAP score and GOLD stages in IPF and COPD patients.

In the IPF group, there was a significant negative correlation between the FVC% and FEV_1% values and the mMRC score, CAT score and GAP index. A significant negative correlation was found between the DLCO% and KCO values and the CAT score and GAP index.

An analysis of the patients with and without small airway obstruction (SAO) by FEF 25/75% in both IPF and COPD groups showed that CAT score, mMRC score and GAP index were similar in IPF patients while the distribution of CAT score, mMRC score and GOLD stage were similar in COPD patients. This result indicates that SAO status determined by FEF 25/75% in both groups was not associated with scores showing the grade/severity of disease.

In IPF, a significant positive correlation was found between the resistance values R5 and R5-20% measured by IOS and the mMRC dyspnea scale only, and between Fres and mMRC and GAP.

Based on this, we can suggest that among IOS measurements, only the GAP index has a significant positive relationship with Fres. In COPD, only Fres and AX have a significant positive correlation with the GOLD stage. In addition, there

Table III. The associations between the PFT parameters and IOS measurements and the mMRC, CAT score, GAP stage and GOLD stage.

		MMRC			CAT SCORE			GAP INDEX			Gold Stage		
Diagnosis		**N**	**r**	***p****	**N**	**r**	***p****	**N**	**r**	***p****	**N**	**r**	***p****
IPF	FVC, L	60	-.377	.003	60	-.350	.006	60	-.149	.256			
	FVC, %	60	-.465	.000	60	-.411	.001	60	-.517	.001			
	FEV_1, L	60	-.398	.002	60	-.353	.006	60	-.180	.169			
	FEV_1, %	60	-.414	.001	60	-.342	.008	60	-.389	.002			
	FEV_1/FVC	60	.121	.358	60	.108	.412	60	.247	.050			
	FEF 25/75, L	60	-.122	.352	60	-.071	.591	60	-.023	.862			
	FEF 25/75, %	60	-.078	.552	60	.018	.890	60	.150	.251			
	DLCO	58	-.229	.084	58	-.249	.060	58	-.367	.005			
	DLCO, %	58	-.244	.065	58	-.293	.026	58	-.491	.000			
	KCO	58	-.162	.224	58	-.255	.050	58	-.398	.002			
	KCO, %	58	-.214	.107	58	-.302	.021	58	-.217	.102			
	R5	60	.250	.050	60	.051	.699	60	.022	.865			
	Fres	60	.325	.011	60	.130	.321	60	.252	.050			
	R20	60	.179	.172	60	.020	.880	60	-.019	.885			
	AX	60	.221	.090	60	.028	.832	60	.050	.707			
	R5-20, %	60	.275	.034	60	.065	.619	60	.164	.211			
	R5-20	60	.221	.089	60	-.002	.985	60	.035	.791			
	X5	60	-.204	.118	60	-.065	.622	60	-.006	.964			
COPD	FVC, L	48	-.428	.002	48	-.369	.010				48	-.572	.001
	FVC, %	48	-.421	.003	48	-.281	.050				48	-.528	.001
	FEV_1, L	48	-.497	.000	48	-.417	.003				48	-.493	.001
	FEV_1, %	48	-.476	.001	48	-.394	.006				48	-.540	.001
	FEV_1/FVC	48	-.352	.014	48	-.431	.002				48	-.276	.057
	FEF 25/75, L	48	-.286	.049	48	-.273	.060				48	-.303	.037
	FEF 25/75, %	48	-.366	.010	48	-.326	.024				48	-.340	.018
	DLCO	41	-.366	.019	41	-.224	.160				41	-.265	.094
	DLCO, %	41	-.253	.110	41	-.101	.531				41	-.265	.094
	KCO	40	-.169	.298	40	-.075	.646				40	-.239	.137
	KCO, %	40	-.080	.623	40	.009	.954				40	-.059	.719
	R5	48	.421	.003	48	.244	.095				48	.268	.066
	Fres	48	.498	.000	48	.296	.041				48	.346	.016
	R20	48	.292	.044	48	.123	.407				48	.140	.344
	AX	48	.511	.000	48	.388	.006				48	.457	.001
	R5-20, %	48	.356	.013	48	.299	.039				48	.259	.076
	R5-20	48	.338	.019	48	.164	.266				48	.229	.118
	X5	48	-.072	.627	48	-.069	.643				48	-.044	.765

*: Spearman Rank correlation analysis.

was a positive relationship, with a trend for statistical significance ($p<0.10$), between the resistance values R5 and R5-20% and the GOLD stage.

The correlation between the values measured by Impulse Oscillometry reflecting the small airway involvement and the conventional measurements (PFT) in IPF and COPD patients is shown in Table IV. For example, a significant negative correlation was observed between FVC L and the R5, Fres, R20, AX, R5-20% and R5-20 values in IPF patients, while no significant relationship was found with X5. In COPD patients, there was a significant negative correlation between FVC L and R5, Fres, AX, R5-20% and R5-20 while a significant positive correlation was found with X5. Overall, there are meaningful correlation between the IOS and PFT measurements as well as some small differences in both IPF and COPD patients.

Discussion

The present study compared the small airway involvement assessed by IOS with laboratory and disease-related prognostic factors in IPF and COPD patients. We found that the values measured by impulse oscillometry are consistent with PFT results, and even more sensitive in demonstrating small airway resistance. Use of IOS may be beneficial, particularly in patients who cannot

Table IV. Relationship between IOS and PFT measurements in IPF and COPD patients.

		Diagnosis													
		IPF							COPD						
		R5	Fres.	R20	AX	R5-20%	R5-20	X5	R5	Fres.	R20	AX	R5-20%	R5-20	X5
FVC, L	r	**-.375**	**-.411**	**-.289**	**-.366**	**-.292**	**-.453**	.098	**-.345**	**-.365**	**-.198**	**-.506**	**-.362**	**-.396**	**.282**
	*p**	**.003**	**.001**	**.025**	**.004**	**.024**	**.000**	.456	**.016**	**.011**	**.176**	**.000**	**.011**	**.005**	**.050**
	N	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**48**	**48**	48	**48**	**48**	**48**	**48**
FVC,	r	-.133	**-.449**	-.065	-.120	**-.254**	**-.245**	-.050	-.168	**-.399**	-.068	**-.309**	**-.295**	-.246	-.016
	p	.310	**.000**	.624	.360	**.050**	**.050**	.706	.255	**.005**	.644	**.032**	**.042**	.092	.914
	N	60	**60**	60	60	**60**	**60**	60	48	**48**	48	**48**	**48**	48	48
FEV_1, L	r	**-.426**	**-.442**	**-.349**	**-.431**	**-.318**	**-.475**	.193	**-.436**	**-.555**	-.227	**-.541**	**-.510**	**-.476**	**.281**
	p	**.001**	**.000**	**.006**	**.001**	**.013**	**.000**	.139	**.002**	**.000**	.121	**.000**	**.000**	**.001**	**.050**
	N	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**48**	**48**	48	**48**	**48**	**48**	**48**
FEV_1,	r	-.200	**-.472**	-.122	-.205	**-.296**	**-.304**	.066	-.211	**-.476**	-.047	**-.303**	**-.358**	-.252	.093
	p	.125	**.000**	.352	.117	**.022**	**.018**	.616	.150	**.001**	.752	**.036**	**.013**	.084	.531
	N	**60**	60	60	60	**60**	**60**	60	48	**48**	48	**48**	**48**	48	48
FEV_1/FVC	r	-.073	.190	-.144	-.077	.069	.045	**.274**	-.123	**-.333**	.008	-.138	-.202	-.050	.157
	p	.578	.146	.272	.559	.600	.733	**.034**	.404	**.021**	.959	.351	.170	.734	.287
	N	60	60	60	60	60	60	**60**	48	**48**	48	48	48	48	48
FEF 25/75, L	r	**-.378**	**-.278**	**-.316**	**-.437**	**-.308**	**-.385**	**.360**	**-.333**	**-.352**	-.179	**-.339**	**-.325**	**-.296**	.111
	p	**.003**	**.032**	**.014**	**.000**	**.017**	**.002**	**.005**	**.021**	**.014**	.223	**.018**	**.024**	**.041**	.453
	N	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**48**	**48**	48	**48**	**48**	**48**	48
FEF 25/75, %	r	**-.380**	**-.282**	**-.324**	**-.410**	**-.314**	**-.393**	**.382**	-.264	**-.523**	-.106	**-.289**	**-.393**	**-.280**	.102
	p	**.003**	**.029**	**.012**	**.001**	**.015**	**.002**	**.003**	.070	**.000**	.472	**.047**	**.006**	**.050**	.492
	N	**60**	**60**	**60**	**60**	**60**	**60**	**60**	48	**48**	48	**48**	**48**	**48**	48
DLCO	r	-.201	**-.295**	-.070	**-.272**	**-.385**	**-.309**	.242	-.394	-.189	-.245	-.386	-.241	**-.304**	.259
	p	.131	**.025**	.599	**.039**	**.003**	**.018**	.067	.011	.237	.122	**.013**	.129	**.050**	.102
	N	58	**58**	58	**58**	**58**	**58**	58	**41**	41	41	**41**	41	**41**	41
DLCO, %	r	-.237	**-.323**	-.119	**-.274**	**-.355**	**-.274**	.192	**-.416**	-.159	**-.314**	**-.350**	-.256	-.276	.211
	p	.073	**.013**	.375	**.037**	**.006**	**.037**	.148	**.007**	.321	**.046**	**.025**	.106	.081	.186
	N	58	**58**	58	58	**58**	**58**	**58**	**41**	41	**41**	**41**	41	41	41
KCO	r	-.063	-.206	-.009	-.112	-.135	-.158	.015	-.004	-.016	.071	-.018	-.060	.094	.080
	p	.636	.120	.947	.401	.311	.237	.912	.983	.921	.662	.914	.715	.566	.622
	N	58	58	58	58	58	58	58	40	40	40	40	40	40	40
KCO, %	r	-.156	**-.329**	-.053	**-.254**	**-.289**	**-.336**	,179	.096	.118	.122	.147	.078	.206	-.030
	p	.242	**.012**	.691	**.050**	**.028**	**.010**	,178	.556	.467	.452	.366	.630	.203	.852
	N	58	**58**	58	**58**	**58**	**58**	58	40	40	40	40	40	40	40

*: Spearman Rank correlation analysis.

perform effort dependent exhalation due to severe dyspnea or cough. It seems that COPD patients had a higher rate of peripheral airway dysfunction compared to IPF patients based on the analysis of resistance and reactance assessments.

IOS in IPF

It is known that IPF primarily involves the interstitium and the alveolar regions; however, recent data suggest that it also affects the airways[17]. The pathogenesis of IPF includes reduced lung compliance and lung volumes, impaired pulmonary gas exchange, reduced diffusion capacity and increased pulmonary hemodynamics[5]. The resulting effort dyspnea is the most prominent symptom in IPF patients, and symptom scores such as CAD can also be used in IPF[5]. FVC is a key measure of disease severity in IPF. However, one in ten patients with IPF has reversible airflow obstruction[18]. In a study by Verleden et al[6] who evaluated IPF patients with multi-detector CT, microCT and histology, IPF patients had a 60% reduction in terminal bronchioles, particularly in minimal fibrosis regions compared to a healthy group. They have postulated that small airway disease is a component of IPF, and it could become a potential therapeutic target in IPF[6].

In our study, FEV_1/FVC was 90% in IPF patients while it was significantly lower in COPD, with a mean FEV_1/FVC of 63%. The mean FEF 25/75% was 94% in IPF patients, and it was significantly lower in COPD patients (29%). We observed that FEV_1/FVC is a valid and effective measure in differentiation of obstructive and re-

strictive diseases. When the FEF25/75%, typically assessing the small airway involvement is considered, it was significantly higher in COPD patients than in IPF. Noord et al[19] reported that the changes in resistance and reactance are not specific to restrictive lung diseases, and they cannot be explained only by increased resistance in lung tissue and reduced lung compliance, and similar changes are also observed in obstructive lung diseases. Thus, they claimed that IOS cannot differentiate between obstructive and restrictive lung diseases[19].

Likewise, we also found that the IOS values in IPF were similar to those in COPD, with increased resistance (R) and reduced reactance (X). However, the impact was not as clear as in COPD.

In a study by Hu et al[5] with 63 IPF patients, the mean IOS values were as follows; R5-20, 0.08; X5, 0.15; AX, 0.69; and Fres, 17.5, which were similar to our results; R5-20, 0.12; X5, -0.8; AX, 0.84; and Fres, 16.

Subsequent studies reported that X5 could be the most useful parameter, and the inspiratory-expiratory variability was different than in COPD[7]. It was shown that X5 value increased in exhalation in IPF, but decreased in COPD, and again in IPF, X5 was inversely correlated with VC and DLCO. In a study comparing the patients with combined pulmonary fibrosis emphysema (CPFE) with IPF and COPD patients, X5, which reflects expiratory flow limitation, was significantly higher in exhalation in CPFE than in IPF, and lower than in COPD, and thus they concluded that both emphysema and fibrosis affect pulmonary functions[20]. In our study, the mean X5 was -0.08 and -0.17 in IPF and COPD patients, respectively (p<0.05).

In the study by Hu et al[5], on small airways in IPF, IOS parameters R5-R20, X5 and Fres showed no correlation with lung function parameters and symptom scores. Among IOS parameters, only AX was correlated with FEV_1% ve FEF25/75 and SGRQ. They also showed no correlation between FVC%, FEV_1% and FEF25-75% and SGRQ score or CAT score and found that DLCO was correlated with SGRQ[5]. In our study, an analysis of the correlation between IOS measurements and other parameters showed that there was only a significant positive correlation between the resistance R5 as measured by IOS and mMRC dyspnea scale, and between Fres and mMRC and GAP in IPF. Based on this, we can postulate that there is no correlation between the GAP index, indicating the severity of IPF disease and the IOS parameters, except for Fres.

IOS in COPD

In COPD, it is suggested that the early pathological change is a respiratory bronchiolitis that occurs in small airways, and it can be typically reflected by FEF 25/75 in spirometry. However, they had a weak association as shown by some studies[16]. ECLIPSE study[16] showed no significant relationship between the presence of small airway disease and the R5-20 and FEF 25/75 values. A study by Su et al[3] which evaluated the small airways by endobronchial optical coherence tomography (EB-OCT) reported that the especially morphological changes in small airways shown in early COPD were compatible with IOS parameters.

In obstructive airway diseases, particularly R5-R20 and Fres were found to be correlated with airflow limitation[3]. As the disease advances, IOS values worsen[7]. The ECLIPSE cohort study represents a large data set where IOS was evaluated in 2,054 COPD patients. This study showed that R5-R20 increased as the severity of disease increased and was significantly higher compared to the healthy subjects[16]. The mean R5-20 was 0.15, 0.20, 0.24 and 0.07 in GOLD stages 2, 3, and 4, and the control groups, respectively, which suggests that small airways are responsible for increased pulmonary resistance rather than large airways. In our study, among IOS parameters, only Fres and AX showed a significant positive relationship with GOLD stages A, B, and D, which indicate severity of disease for COPD. Additionally, a positive relationship, with a trend for statistical significance (p<0.10), was observed between the R5 and R5-20% values and the GOLD stage.

Although there are no defined reference values for COPD, pragmatic IOS cut offs were proposed for R5> 0.5 kPa/L/s, R5-20 > 0.10 kPa/L/s, AX > 1.0 kPa/L as being pathologically abnormal[8]. In the ECLIPSE cohort, the mean IOS values were R5, 0.49; R20, 0.30; R5-20, 0.06; x5, -0.09; AX, 0.34; and FRES, 12.1 in COPD patients[16], and in our study these values also increased as follows: R5, 0.53; R20, 0.34; r5-20, 0.25; x5, -0.17; AX, 2.62; and FRES, 22.4.

Many studies[21,22] showed a significant correlation between oscillometry and spirometry parameters in patients with COPD. In a study comparing spirometry with ISO in 25 COPD patients, Mousa and Kamal[21] showed that there was a significant correlation between FEV_1/FVC, FVC, FEV_1%, MEF75%, MEF75-85% and R5% (negative) and X5 (positive), and a negative correlation between R20% and FEV_1/FVC only. Based on these results, they concluded that spirometry was better in displaying larger airway

dysfunction, and IOS is more sensitive in detection of small airway obstruction than spirometry. In our study, an analysis of IOS values show that there was no correlation between the R20 value, mainly reflecting the large airways, and the PFT results or DLCO, and X5 had no strong correlation as in other IOS parameters. R5-20%, assumed to reflect the small airway pathology most distinctively was also the strongest parameter in our study, showing a negative correlation with FVC L, FEV_1% and FEF25/75. AX and Fres also showed significant negative correlation with FVC L, FVC%, FEV_1 L, FEV_1% and FEF25/75.

It is widely accepted that IOS measurements can provide information about the quality of life and dyspnea, and in a study by Haruna et al[22] with 65 COPD patients, R5-R20 and X5 were shown to be the two parameters having the strongest correlation with SGRQ and mMRC scores. However, Anderson and Lipworth[23] found no correlation between mMRC dyspnea scale and IOS. In our study, Fres, AX, and R5-20% were significantly correlated with both mMRC and CAT scores. While R5 and R20 were correlated with mMRC, X5 had no correlation with mMRC dyspnea score and CAT quality of life questionnaire. Frantz et al[24] also reported that the symptoms in COPD patients, in the absence of confirmation by spirometry according to GOLD criteria, were highly correlated with parameters measured by IOS, and thus IOS may have a potential to detect COPD earlier than spirometry.

Strengths

The fact that it was conducted in a major pulmonology hospital with many COPD and IPF patients and that PFT and IOS measurements were carried out by the same team contribute to the strength and reliability of the study.

Limitations

The limitation of the study is that it was carried out in a single center with a restricted number of patients, and IOS measurements still lack standard reference values for COPD and IPF.

Conclusions

IOS is very useful in COPD and IPF patients who cannot exhale due to shortness of breath and severe coughing as it is non-invasive, easy-to-administer and effort independent. IOS measurements, mainly R5-20% which reflects the small airway resistance, are compatible, and even more sensitive than PFT in detection of small airway dysfunction. Although they are correlated with dyspnea, quality of life, weight, and prognosis of the patient, the IOS measurements in COPD are higher than in IPF, which suggests that small airway resistance is more pronounced. We believe that use of IOS, which is limited and mainly used in clinical studies, in patients who are unable to perform spirometry or combined routine use with PFT may be beneficial in diagnosis, follow-up and management of COPD and IPF patients with small airway dysfunction. There is a need for large cohort studies to obtain data on the clinical use of IOS in COPD and IPF and determine its reference values and management of the disease.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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None.

Availability of Data and Materials

The data presented in this study are available upon request from the corresponding author.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and approved by University of Health Sciences, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (date of approval/No: 03.06.2021/111).

Informed Consent

A consent form was obtained from all patients who accepted to participate in the study.

Authors' Contributions

Conception and design: Dildar Duman, Ömer Faruk Taştı, Fatma Merve Tepetam. Material preparation and data collection: Dildar Duman, Ömer Faruk Taştı. Statistical analyses: Dildar Duman, Fatma Merve Tepetam. Manuscript preparation and writing: Dildar Duman, Ömer Faruk Taştı, Fatma Merve Tepetam. All authors reviewed and approved the final manuscript.

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References

1) Hogg JC, Paré PD, Hackett TL. The Contribution of Small Airway Obstruction to the Pathogenesis of Chronic Obstructive Pulmonary Disease. Physiol Rev 2017; 97: 529-552.
2) Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, Papi A, Van der Molen T, Rabe KF, Siddiqui S, Singh D, Nicolini G, Kraft M; ATLANTIS study group. Exploring the relevanc and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med 2019; 7: 402-416.
3) Su ZQ, Guan WJ, Li SY, Ding M, Chen Y, Jiang M, Chen XB, Zhong CH, Tang CL, Zhong NS. Significances of spirometry and impulse oscillometry for detecting small airway disorders assessed with endobronchial optical coherence tomography in COPD. Int J Chron Obstruct Pulmon Dis 2018; 13: 3031-3044.
4) Bonini M, Usmani OS. The role of the small airways in the pathophysiology of asthma and chronic obstructive pulmonary disease. Ther Adv Respir Dis 2015; 9: 281-293.
5) Hu PW, Ko HK, Su KC, Feng JY, Su WJ, Hsiao YH, Perng DW. Functional parameters of small airways can guide bronchodilator use in idiopathic pulmonary fibrosis. Sci Rep 2020; 10: 18633.
6) Verleden SE, Tanabe N, McDonough JE, Vasilescu DM, Xu F, Wuyts WA, Piloni D, De Sadeleer L, Willems S, Mai C, Hostens J, Cooper JD, Verbeken EK, Verschakelen J, Galban CJ, Van Raemdonck DE, Colby TV, Decramer M, Verleden GM, Kaminski N, Hackett TL, Vanaudenaerde BM, Hogg JC. Small airways pathology in idiopathic pulmonary fibrosis: a retrospective cohort study. Lancet Respir Med 2020; 8: 573-584.
7) Bednarek M, Grabicki M, Piorunek T, Batura-Gabryel H. Current place of impulse oscillometry in the assessment of pulmonary diseases. Respir Med 2020; 170: 105952.
8) Lipworth BJ, Jabbal S. What can we learn about COPD from impulse oscillometry? Respir Med 2018; 139: 106-109.
9) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Report. 2021. Available from: www.goldcopd. org.
10) Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, Kreuter M, Lynch DA, Maher TM, Martinez FJ, Molina-Molina M, Myers JL, Nicholson AG, Ryerson CJ, Strek ME, Troy LK, Wijsenbeek M, Mammen MJ, Hossain T, Bissell BD, Herman DD, Hon SM, Kheir F, Khor YH, Macrea M, Antoniou KM, Bouros D, Buendia-Roldan I, Caro F, Crestani B, Ho L, Morisset J, Olson AL, Podolanczuk A, Poletti V, Selman M, Ewing T, Jones S, Knight SL, Ghazipura M, Wilson KC. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2022; 205: 18-47.
11) Cottin V, Selman M, Inoue Y, Wong AW, Corte TJ, Flaherty KR, Han MK, Jacob J, Johannson KA, Kitaichi M, Lee JS, Agusti A, Antoniou KM, Bianchi P, Caro F, Florenzano M, Galvin L, Iwasawa T, Martinez FJ, Morgan RL, Myers JL, Nicholson AG, Occhipinti M, Poletti V, Salisbury ML, Sin DD, Sverzellati N, Tonia T, Valenzuela C, Ryerson CJ, Wells AU. Syndrome of Combined Pulmonary Fibrosis and Emphysema: An Official ATS/ERS/JRS/ALAT Research Statement. Am J Respir Crit Care Med 2022; 206: 7-41.
12) Global Initiative for Asthma. Global strategy for Astma management and Prevention, 2021. Report 2021. Available from: www.ginasthma. org.
13) Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, Lee JS, Maher TM, Wells AU, Antoniou KM, Behr J, Brown KK, Cottin V, Flaherty KR, Fukuoka J, Hansell DM, Johkoh T, Kaminski N, Kim DS, Kolb M, Lynch DA, Myers JL, Raghu G, Richeldi L, Taniguchi H, Martinez FJ. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med 2016; 194: 265-275.
14) Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE Jr, Collard HR. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012; 156: 684-91.
15) Ulubay G, Dilektaşlı AG, Börekçi Ş, Yıldız Ö, Kıyan E, Gemicioğlu B, Saryal S. Turkish Thoracic Society Consensus Report: Interpretation of Spirometry. Turk Thorac J 2019; 20: 69-89.
16) Crim C, Celli B, Edwards LD, Wouters E, Coxson HO, Tal-Singer R, Calverley PM; ECLIPSE investigators. Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results. Respir Med 2011; 105: 1069-1078.
17) Plantier L, Cazes A, Dinh-Xuan AT, Bancal C, Marchand-Adam S, Restani B. Physiology of the lung in idiopathic pulmonary fibrosis. Eur Respir Rev 2018; 27: 170062.
18) Assayag D, Vittinghoff E, Ryerson CJ, Cocconcelli E, Tonelli R, Hu X, Elicker BM, Golden JA, Jones KD, King TE Jr, Koth LL, Lee JS, Ley B, Shum AK, Wolters PJ, Ryu JH, Collard HR. The effect of bronchodilators on forced vital capacity measurement in patients with idiopathic pulmonary fibrosis. Respir Med 2015; 109: 1058-1062.
19) Van Noord JA, Clément J, Cauberghs M, Mertens I, Van de Woestijne KP, Demedts M. Total respiratory resistance and reactance in patients with diffuse interstitial lung disease. Eur Respir J 1989; 2: 846-852.
20) Mori K, Shirai T, Mikamo M, Shishido Y, Akita T, Morita S, Asada K, Fujii M, Hozumi H, Suda T, Chida K. Respiratory mechanics measured by forced oscillation technique in combined pulmonary fi-

brosis and emphysema. Respir Physiol Neurobiol 2013; 185: 235-240.

21) Mousa H, Kamal E. Impulse oscillation system versus spirometry in assessment of obstructive airway diseases, Egypt. J Chest Dis Tuberc 2018; 67: 106.

22) Haruna A, Oga T, Muro S, Ohara T, Sato S, Marumo S, Kinose D, Terada K, Nishioka M, Ogawa E, Hoshino Y, Hirai T, Chin K, Mishima M. Relationship between peripheral airway function and patient-reported outcomes in COPD: a cross-sectional study. BMC Pulm Med 2010; 10:10.

23) Anderson WJ, Lipworth BJ. Relationships between impulse oscillometry, spirometry and dyspnoea in COPD. J R Coll Physicians Edinb 2012; 42: 111-115.

24) Frantz S, Nihlén U, Dencker M, Engström G, Löfdahl CG, Wollmer P. Impulse oscillometry may be of value in detecting early manifestations of COPD. Respir Med 2012; 106: 1116-1123.