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Original Article

Use of Impulse Oscillometry in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

OBJECTIVE: Although spirometry is a standard diagnostic tool for obstructive lung diseases, it is rarely performed, and the quality of basic spirometry is low in many countries. The impulse oscillometry system (IOS) is a non-invasive method that requires minimal patient cooperation and, therefore, can be performed even in the pediatric population. It has been also suggested that IOS may help to clarify the relationship between small airway disease and the underlying mechanisms of chronic obstructive pulmonary disease (COPD). The primary objective of the study was to compare IOS parameters in COPD patients with those in healthy individuals. Our secondary objective was to determine the relationship between IOS parameters and standard pulmonary function tests (PFTs). Our hypothesis was that airway resistance detected by IOS would be higher in COPD patients than in controls. Hence, IOS would provide findings comparable to and correlated with those of standardized PFTs for small airway obstruction.

MATERIAL AND METHODS: A total of 104 subjects (62 patients with COPD and 42 healthy non-smoking individuals) were included in the study. All subjects underwent spirometry, diffusing capacity for carbon monoxide (DLCO), lung-volume measurements, and IOS.

RESULTS: COPD patients showed significant decreases in forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, FEF 25–75, and DLCOadj, and significant increases in residual volume (RV) and total lung capacity (TLC) compared with the control group. In terms of IOS parameters, R5%, Z5%, Fres, and R5–R20/R5% values were significantly higher in the COPD group ($P = 0.029$, $P = 0.022$, $P = 0.009$, $P = 0.004$, respectively). The reactance area (AX) value, defined as the AX, was also significantly increased in the COPD group ($P = 0.004$). The correlation between FEF 25–75% (L/s) and R5–R20 was moderate and negative ($r = -0.491$, $P < 0.001$). A weak correlation ($r = 0.240$, $P = 0.017$) was also found between the RV/TLC ratio and R5–R20.

CONCLUSION: This study showed that airway resistance was increased in the COPD group and that IOS parameters were associated with measures of small-airway function in standard PFTs. IOS can be used as a non-invasive, patient-friendly method that complements PFTs by providing a comprehensive assessment of COPD pathology and pathophysiological changes and detecting changes in symptomatic patients.

KEYWORDS: Impulse oscillometry, chronic obstructive pulmonary disease, impedance

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable chronic inflammatory disease characterized by airflow limitation and respiratory symptoms resulting from airway and/or alveolar destruction.[1,2] It results from an inflammatory process initiated by harmful gases and particles and by developmental host factors. COPD affects millions of people worldwide and is a major cause of morbidity and mortality.[3]

Pulmonary function tests (PFT) should be performed in patients with dyspnea, chronic cough and/or mucus production, a history of exposure to various particles, or risk factors for COPD. Spirometry is the most objective and best-standardized method for demonstrating airflow limitation; it is simple and reproducible.[2]

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Impulse oscillometry system (IOS) is a variant of the forced oscillation technique and is an easy, non-invasive method for assessing lung function. It can be easily used with young children and older adults, since the procedure does not require patient cooperation. Moreover, it provides more detailed information than spirometry, allowing it to detect differences between central and peripheral airways, as well as early changes in small airways. The oscillations are applied at a fixed square-wave frequency of 5 Hz, from which all other frequencies of interest are derived; these are typically multiples of 5 Hz (5 to 35 Hz) and last between 30 and 40 ms each.[4] Low-frequency waves (5 Hz) reach the periphery of the lungs, whereas high-frequency waves (20 Hz) reach the upper airways.[4] In IOS, impedance (Z) represents the opposition to oscillatory airflow in the respiratory system and reflects the combined resistive and reactive components. The two main components of impedance are resistance (R) and reactance (X). These are measured in the frequency range 5–20 Hz and are named according to these frequencies. For example, R and X measured at 5 Hz are denoted R5 and X5. These values are recorded simultaneously with each breath during the measurement. By measuring resistance and reactance, IOS may better assess distal airway pathology, a key component of COPD.[5,6] Since IOS is a non-invasive method that requires minimal active participation by the patient, it can also be used routinely for the diagnosis and follow-up of COPD.[7] In theory, the elastic properties of the lung are reflected in low-frequency reactance, which corresponds to the distal airways.[8] Studies have shown that IOS can be used to evaluate respiratory system impedance, assess lung heterogeneity at low frequencies, detect airway resistance earlier than spirometry in symptomatic patients, and define different subgroups of COPD patients.[9] In addition to these data, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 states that IOS may help to better understand the relationships between small airway disease and the underlying disease mechanisms of COPD, such as clinically significant symptoms.[9] IOS can be used to complement spirometry for this purpose. In addition, IOS is thought to be valuable for detecting individuals with pathological airway changes (small airway disease) typical of COPD.[10] With these considerations in mind, we hypothesized that parameters derived from IOS that reflect small airway dysfunction –particularly the reactance area (AX) and indices representing the relative contribution of peripheral airway resistance (R5–R20/R5)– would be more sensitive indicators of COPD-related pathophysiology than absolute resistance values alone. Therefore, IOS can provide complementary information to standard PFTs in the assessment of small airway involvement in COPD. The aim of this study was to compare IOS parameters in patients with stable COPD and healthy individuals, to examine the relationship between spirometry parameters, and to evaluate whether IOS parameters reflecting small airway dysfunction, particularly AX and R5–R20/R5 values, differ between the two groups. A secondary aim was to investigate the relationship between these IOS parameters and traditional pulmonary function indices [including FEF 25–75 and residual volume (RV)/total lung capacity (TLC)] associated with small airway obstruction and air trapping. Our hypothesis is that relative and reactance-based IOS indices will show stronger associations with small airway dysfunction than absolute resistance measurements.

Main Points

- One of the main points of this article is to demonstrate changes in chronic obstructive pulmonary disease (COPD) patients by performing impulse oscillometry system (IOS) testing on healthy adults and patients diagnosed with COPD.
- Another key point is the correlation between standard spirometry and IOS.

MATERIAL AND METHODS

Our study is a cross-sectional case-control study. Patients aged 40 and older who presented to the Department of Pulmonology Outpatient Clinic of Gazi University Hospital, Health Research and Application Center between October 2020 and September 2021 were included in the study. An informed consent form was obtained from all participants. Ethics committee approval was obtained from the Gazi University Faculty of Medicine Clinical Research Ethics Committee with the decision numbered 533 and dated 07.09.2020.

Inclusion Criteria

Two groups of patients were enrolled in the study.

COPD Group

- Patients aged 40 and over,
- Patients with stable COPD diagnosed with GOLD spirometric criteria,[1]
- Patients with no other pulmonary pathology,
- COPD patients who applied for routine outpatient controls and were requested a PFT.

Control Group

- Those aged 40 and over,
- Healthy, non-active smoking volunteers.

Smokers were defined as follows:[11]

- Smoking at least one cigarette per week for at least 6 months,
- Smoking at least 100 cigarettes in a lifetime.

Individuals who smoked and quit within the last 15 years were classified as ex-smokers.

Those who have smoked previously but have quit, and those who have not smoked in the last 15 years, were included in the non-smokers group.

Exclusion Criteria

- Patients with any pulmonary disease,
- The subjects who have coronavirus disease-2019 (COVID-19) positive test results,
- Those who did not agree to participate in the research.

Study Design

Demographic characteristics of the patients (age, sex, smoking history, occupation), current complaints (cough, phlegm, shortness of breath, hemoptysis, chest pain), history of pulmonary disease, current pulmonary diseases, and comorbidities were assessed and recorded. The cases were evaluated with symptoms, physical examination and spirometry measurements [forced expiratory volume in 1 second (FEV_1) (L and %), forced vital capacity (L and %), FEV_1/FVC (%), peak expiratory flow-(PEF) (%), forced expiratory flow (FEF) 25-75 (L/s)], GOLD stage and GOLD spirometric grade for patients with a diagnosis of COPD, lung volumes [TLC (L and %) if measured, functional residual capacity (FRC) (L and %), expiratory residual volume (ERV) (L and %), RV (L and %) and the ratio of RV to TLC (%)] and diffusing capacity for carbon monoxide (DLCO) hemoglobin adjusted (%) test results.

IOS measurement results were recorded as R5 [kPa/(L/s) and %], X5 [kPa/(L/s) and %], AX (kPa/L), R20 [kPa/(L/s) and %], X20 [kPa/(L/s) and %], Z5 [kPa/(L/s) and %] and R5–R20.

Spirometric Maneuvers

Spirometry was performed using the MasterScreen (CareFusion, Germany) instrument. All tests were performed consecutively on the same day, with the patient resting; the patient had rested for at least 1 hour and had not smoked. The patient rested for one hour before undergoing IOS. The FVC maneuver was performed by an experienced technician with the patient seated upright and the nose clipped. The best of the 3 measurements in which patients took a deep inspiration followed by a forced expiration was considered. The largest observed FVC and largest FEV_1 of all acceptable values, were reported, even if they did not come from the same maneuver.[12] In the report, prebronchodilator FEV_1 (L and %), FVC (L and %), FEV_1/FVC (%), PEF (%), and FEF 25–75 (L/s) values were recorded.

The single-breath-hold technique was used to measure DLCO. Hemoglobin values (g/dL) were recorded prior to measurements. The DLCO single-breath maneuver begins with several cycles of tidal breathing followed by a full exhalation to near RV. The patient then rapidly inhales the test gas mixture to full lung capacity and holds their breath for approximately ten seconds. Following the breath-hold, the patient exhales completely and rapidly; the first portion of exhaled gas is expelled, and an alveolar sample is then collected. DLCO is then calculated from the concentrations of carbon monoxide and tracer gas in the sample. Following DLCO measurement by the single-breath-hold method, lung volumes were measured by nitrogen washout using the same device. Measured TLC (L and %), FRC (L and %), ERV (L and %), RV (L and %), and the ratio of RV to TLC (%) were recorded. When clinically feasible, lung volume measurements were obtained using the nitrogen washout method; they were not available for all participants, reflecting real-life clinical practice during the COVID-19 period.

Patients who underwent PFT were subsequently assessed using the Masterscreen IOS (CareFusion, Germany, 2016). For spirometric measurements using IOS, the device was calibrated each morning before measurements. Three acceptable measurements were made for each patient, and the average of the three acceptable R measurements across all frequencies was recorded. During the test, the patients were kept in a sitting position with their heads upright. While seated in this position, patients were asked to hold the disposable mouthpiece between their teeth and to close their lips tightly around it. The patient was asked to support both cheeks to prevent swelling of the upper airway shunt. While the patient maintains relaxed breathing, the device delivers small pressure impulses into the airway. No forced or deep breaths are required. The system then analyzes the resulting pressure–flow oscillations during tidal breathing to measure respiratory resistance and reactance across a range of frequencies.

The study was conducted during the COVID-19 pandemic, a period in which PFT was subject to significant restrictions. Therefore, spirometry and IOS were performed only in patients with documented negative severe acute respiratory syndrome-coronavirus-2 test results. To minimize procedure duration and potential aerosol exposure, measurements were limited to pre-bronchodilator assessments; post-bronchodilator testing could not be routinely performed.

Statistical Analysis

We reported descriptive statistics as mean and standard deviation for continuous variables with a normal distribution, and as median, minimum, and maximum values for continuous variables with a non-normal distribution. Frequencies and percentages were used to describe categorical variables. To determine the normality of continuous variables, the Shapiro-Wilk test results and the histograms, box plots, and Q-Q plots were evaluated. Based on the assumption of normal distributions, two independent groups (study groups) were compared using either the independent-samples t-test or the Mann-Whitney U test. For categorical variables, differences between groups were examined using the chi-square test or Fisher's exact test. The relationship between continuous variables was evaluated using Spearman's rank correlation coefficient because the assumption of normality was not met. To evaluate diagnostic accuracy, receiver operating characteristic curve analysis was performed. *P* values of 0.05 or lower were considered statistically significant. Statistical analyses were performed using IBM SPSS version 23.

Given the real-world and pandemic-related constraints of the study, no a priori power analysis was performed. The study was therefore designed as an exploratory and hypothesis-generating investigation.

RESULTS

A total of 104 patients aged 40 years and older who presented to the Pulmonology department outpatient clinic between October 2020 and September 2021 were included in the study. The COPD group included 62 patients aged 40 and over who were diagnosed with stable COPD and were attending routine outpatient clinic follow-up visits. In the control group, 42 healthy, non-smoking patients aged 40 years and over were included. Table 1 summarizes the demographic characteristics and pulmonary complaints in the two groups.

When the patients' spirometry and DLCO measurements were examined, all spirometric parameters and DLCO values were lower in the COPD group. RV (L) and RV/TLC% values were increased in the COPD group. These differences were found to be statistically significant. Comparisons of spirometry and DLCO values between the groups are presented in Tables 2 and 3.

While the patients' IOS values were examined, resistance was calculated using pressure waves at different frequencies (5-20 Hz) [R5 kPa/(L/s), R5%, R20 kPa/(L/s), R20%, R5-20 kPa/(L/s)]. A significant difference was observed in R5% values between the COPD and control groups ($P = 0.029$). The median R5 value, which provides information about the resistance of the entire respiratory system, was 0.59 kPa/(L/s) (184%) in the COPD group and 0.52 kPa/(L/s) (172%) in the control group. When the R20 values, which provide information about the large airways were examined, they were 0.36 kPa/(L/s) (133.5%) in the COPD group and 0.4 kPa/(L/s) (133%) in the control group. No significant difference was observed between R20 values ($P = 0.782$). When the R5–R20 results were examined, no significant difference was found between the groups. No statistically significant difference was found ($P = 0.079$).

Reactance was calculated using pressure waves at different frequencies (5–20 Hz): X5 kPa/(L/s), X5%, X20 kPa/(L/s), and X20%. The X5 value, which is expected to decrease in distal airway obstruction, was significantly lower in the COPD group than in the control group ($P < 0.009$). Similarly, the X20 value, which is expected to decline more slowly than X5 in distal airway obstruction, decreased significantly in the COPD group compared with the control group ($P < 0.014$).

Impedance (Z) was calculated using pressure waves at a frequency of 5 Hz in two ways: Z5 [kPa/(L/s)] and Z5%. Although no significant difference was observed between the groups for Z5 kPa/(L/s) —the sum of the forces required to propagate the pressure wave applied to the respiratory system— a significant difference was observed for Z5% values, which were higher in the COPD group ($P = 0.200$ and 0.022, respectively). The reactance area (AX) value, was significantly higher in the

Table 1. Comparative demographic characteristics of patient groups

	COPD group (n = 62)	Control group (n = 42)	Test statistic	*P* value
Age (years)	63.5 (40–80)	56.5 (40–72)	2.699	**0.007**
Sex				
Female	9 (14.52)	19 (45.24)	12.012	**0.001**
Male	53 (85.48)	23 (54.76)		
Height (cm)	166 (146–182)	162.5 (143–185)	1.114	0.265
Weight (kilograms)	76.5 (42–133)	80.5 (36–120)	1.286	0.198
BMI	28.13±5.93	30.10±5.34	1.721	0.088
Smoking history				
Non-smoker	5 (8.06)	31 (73.81)	54.010	**<0.001**
Ex-smoker	26 (41.94)	11 (26.19)		
Active smoker	31 (50.00)	0		
Pack year	38 (2–135)	12 (2–35)	4.017	**<0.001**
Symptoms				
Active				
Pulmonary	56 (90.32)	0 (0)	82.194	**<0.001**
Complaints	23 (37.10)	1 (2.38)	16.999	**<0.001**
Cough	23 (37.10)	0 (0)	20.005	**<0.001**
Phlegm	0 (0)	0 (0)	NA	NA
Hemoptysis	3 (4.84)	0 (0)	NA	0.271
Chest pain	55 (88.71)	1 (2.38)	75.085	**<0.001**
Shortness of breath	56 (90.32)	0 (0)	82.194	**<0.001**
mMRC				
Scale				
0	1 (1.82)		NA	NA
1	12 (21.82)			
2	27 (49.09)			
3	13 (23.64)			
4	2 (3.64)			

Descriptive statistics are given as median (minimum–maximum) or mean ± standard deviation
COPD: chronic obstructive pulmonary disease, BMI: body mass index, mMRC: modified Medical Research Council, NA: not applicable

Table 2. Comparison of spirometric values by patient groups

	COPD group (n = 62)	Control group (n = 42)	Test statistic	*P* value
FEV_1 (L)	1.52 (0.38–3.69)	2.86 (1.62–5.23)	6.238	**<0.001**
FEV_1 (%)	62.02±23.84	108.14±16.97	11.524	**<0.001**
FVC (L)	2.79 (0.83–5.20)	3.53 (1.94–5.03)	3.124	**0.002**
FVC (%)	81.03±23.80	108.83±17.38	6.486	**<0.001**
FEV_1/FVC (%)	62 (27–70)	81 (72.5–96)	8.632	**<0.001**
PEF (L)	4.31 (1.26–11.7)	6.64 (3.49–10.63)	4.790	**<0.001**
PEF (%)	59 (17–143)	101 (68–137)	6.411	**<0.001**
FEF 25 (L)	2.3 (0.44–8.05)	6.14 (3.34–10.38)	6.593	**<0.001**
FEF 25 (%)	36.5 (8–116)	105 (67–140)	7.633	**<0.001**
FEF 50 (L)	1.1 (0.15–3.73)	3.8 (1.85–6.54)	8.023	**<0.001**
FEF 50 (%)	28 (3–90)	92 (58–154)	8.302	**<0.001**
FEF 75 (L)	0.35 (0.14–1.52)	1.12 (0.52–2.16)	7.450	**<0.001**
FEF 75 (%)	28 (4–102)	69.5 (40–141)	7.467	**<0.001**
FEF 25–75(L)	0.80 (0.17–3.19)	2.89 (1.31–4.88)	8.083	**<0.001**
FEF 25–75 (%)	27 (5–94)	89 (51–138)	8.241	**<0.001**

Descriptive statistics are given as median (minimum–maximum) or mean ± standard deviation
COPD: chronic obstructive pulmonary disease, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, FEF: forced expiratory flow

Table 3. Comparison of DLCO measurement results by groups

	COPD group (n = 62)	Control group (n = 42)	Test statistic	*P* value
DLCO (%)	71.316±24.575	100.927±18.227	6.528	**<0.001**
TLC (L)	4.935±1.317	4.936±1.018	0.015	0.988
TLC (%)	82.632±16.802	90.293±13.950	2.386	0.019
FRC (L)	3.14 (1.42–6.1)	2.99 (1.06–26.2)	1.412	0.158
FRC (%)	98 (45–181)	97 (60–140)	0.187	0.851
ERV (L)	0.80 (0.01–2.35)	0.85 (0.03–2.67)	0.709	0.478
ERV (%)	83 (1–284)	97 (4–236)	0.699	0.485
RV (L)	2.18 (1.12–4.51)	1.91 (1.2–3.02)	3.104	**0.002**
RV (%)	100 (54–195)	94 (73–154)	1.192	0.233
RV/TLC (%)	48 (27–71)	37 (27–55)	4.091	**<0.001**

Descriptive statistics are given as median (minimum–maximum)or mean ± standard deviation
DLCO: carbon monoxide, COPD: chronic obstructive pulmonary disease, TLC: total lung capacity, FRC: functional residual capacity, ERV: expiratory residual volume, RV: residual volume,

COPD patient group ($P < 0.004$). When the Fres values of other parameters measured with the IOS were compared, a significant difference was observed, with higher Fres values in the COPD group ($P < 0.009$). All results of the IOS measurements, along with comparisons between the groups, are presented in Table 4. Under physiological conditions, peripheral airway resistance is known to constitute approximately 10–30% of total respiratory resistance.[13] In obstructive diseases with peripheral airway obstruction, peripheral resistance contributes a significantly greater proportion of total resistance. Based on this, the (R5–R20)/R5 ratio was examined and found to be 36.3% in the COPD group and 28.4% in the control group ($P = 0.004$). A comparison of the R5–R20/R5 ratios is shown in Table 4.

To examine the relationship between the severity of obstruction and oscillometric parameters in patients with COPD, GOLD grades 2 and 3 were compared. Because each of the GOLD grade 1 and GOLD grade 4 groups contained only one patient, these groups were excluded from the analysis. No significant differences were observed between the groups in the values of R5 [kPa/(L/s)], indicating total airway resistance, and R5–R20 [kPa/(L/s)], indicating ventilation heterogeneity. Similarly, no significant difference was observed between the groups in the values of X5 kPa/(L/s), X20 kPa/(L/s), and Z5 kPa/(L/s), the latter of which represents the sum of the forces required to move the pressure wave in the respiratory system. Only the AX kPa/L value increased as obstruction severity increased, and this increase was significant ($P = 0.032$). Table 5 shows a comparison of IOS results across spirometric GOLD grades.

Correlation

We examined the correlation between the spirometry measurement FEF 25–75, which indicates small airway obstruction, and the IOS measurement R5–R20. A moderate negative correlation was observed between FEF 25–75% and R5–R20 (Spearman correlation coefficient r = -0.49, $P < 0.001$; Figure 1). When the correlation between the RV/TLC ratio, an

Table 4. Comparison of IOS measurement results by groups

	COPD group (n = 62)	Control group (n = 42)	Test statistic	*P* value
R5 [kPa/(L/s)]	0.59 (0.24–1.29)	0.52 (0.28–0.99)	1.165	0.244
R5 (%)	184 (79–406)	172 (92–252)	2.185	**0.029**
R20 [kPa/(L/s)]	0.36 (0.2–0.68)	0.4 (0.25–0.63)	0.551	0.582
R20 (%)	133.5 (65–257)	132.5 (80–198)	0.391	0.696
R5–R20	0.18 (0.03–0.82)	0.13 (0.02–0.51)	1.754	0.079
X5 [kPa/(L/s)]	-0.17 (-0.7–0.21)	-0.12 (-0.33–0.42)	2.613	**0.009**
X5 (%)	656 (-2996–6443)	277 (-7432–5129)	3.707	**<0.001**
X20 [kPa/(L/s)]	-0.02 (-0.24–0.11)	0 (-0.11–0.07)	2.459	**0.014**
X20 (%)	-58.5 (-4492–729)	-5.5 (-2122–5675)	1.729	0.084
AX (kPa/L)	1.77 (0.14–8.52)	0.87 (0.19–4.22)	2.879	**0.004**
Z5 [kPa/(L/s)]	0.62 (0.24–1.39)	0.54 (0.29–1.03)	1.282	0.2
Z5 (%)	197 (82–474)	175 (93–268)	2.299	**0.022**
Fres	24.03 (9.97–39.54)	19.94 (12.96–34.6)	2.607	**0.009**
R5–R20/R5 (%)	36.311±16.015	28.462±11.255	2.921	**0.004**

Descriptive statistics are given as median (minimum–maximum) or mean ± standard deviation
COPD: chronic obstructive pulmonary disease, AX: reactance area

Table 5. Comparison of IOS results by spirometric GOLD grade

	GOLD grade 2 (n = 50)	GOLD grade 3 (n = 10)	Test statistic	*P* value
R5 [kPa/(L/s)]	0.57 (0.29–1.29)	0.77 (0.39–1.24)	1.413	0.158
R5 (%)	173.5 (95–406)	263 (127–406)	1.666	0.096
R20 [kPa/(L/s)]	0.37 (0.21–0.68)	0.37 (0.22–0.55)	0.010	0.992
R20 (%)	132.5 (65–257)	144 (85–207)	0.436	0.663
R5–R20 [kPa/(L/s)]	0.17 (0.03–0.82)	0.35 (0.04–0.76)	1.330	0.183
R5–R20/R5 (%)	32.19 (6.25–67.44)	49.07 (25.64–65.52)	1.908	0.056
X5 [kPa/(L/s)]	-0.15 (-0.62–0.21)	-0.19 (-0.7– -0.12)	1.953	0.051
X5 (%)	656 (–2996–6443)	1035.5 (527–5255)	1.533	0.125
X20 [kPa/(L/s)]	–0.02 (–0.24–0.01)	-0.09 (-0.24–0.04)	1.520	0.129
X20 (%)	–39.5 (–4492–729)	-166.5 (-792–95)	1.210	0.226
AX (kPa/L)	1.59 (0.14–8.12)	4.39 (0.77–8.52)	2.151	**0.032**
Z5 [kPa/(L/s)]	0.61 (0.30–1.39)	0.81 (0.32–1.35)	0.903	0.367
Z5 (%)	186 (98–421)	275 (104–474)	1.240	0.215
Fres	23.65 (9.97–39.54)	29.09 (15.22–36.28)	1.230	0.219

Descriptive statistics are given as median (minimum–maximum) or mean ± standard deviation
IOS: impulse oscillometry system, GOLD: Global Initiative for Chronic Obstructive Lung Disease, AX: reactance area

indicator of air trapping, and R5–R20 was examined, a weak association was observed (Spearman correlation coefficient r = 0.24, *P* = 0.017) (Figure 2).

DISCUSSION

Current COPD guidelines recommend using spirometry to assess airflow limitation along with symptoms and exacerbation history.[1] Spirometry is the most widely used PFT. However, spirometry may fail to detect early changes in respiratory function. Some studies have shown that IOS parameters can reflect pathological changes such as airway obstruction, air trapping, and decreased compliance in COPD patients to a certain extent, as with traditional PFT parameters.[14,15] For this reason, IOS can be used as a non-invasive, patient-friendly method that complements PFTs, provides a comprehensive assessment of COPD pathology and associated pathophysiological changes, and detects early changes in symptomatic patients. Therefore, IOS has emerged as a complementary approach to traditional PFTs.[4] IOS is performed during normal breathing for approximately 30–40 seconds and is more physiological than spirometry because it does not require extra effort. It provides more detailed information than spirometry and should be considered a complement to it for comprehensive assessment of pulmonary function. We conducted this study to compare IOS parameters between patients with COPD and healthy individuals.

In our study, the non-smoking COPD group differed significantly from the control group in R5% oscillometric values. However, no significant difference was observed between R20 and R5–R20 values for the two groups. Other significant IOS parameters

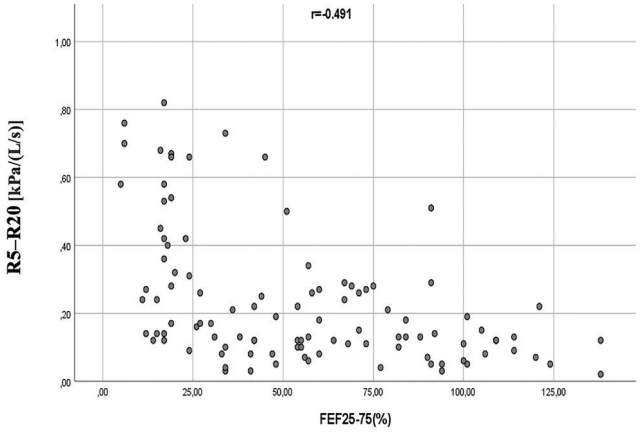

Figure 1. Spearman's correlation analysis between FEF 25–75% and R5–R20 [kPa/(L/s)]

FEF: forced expiratory flow

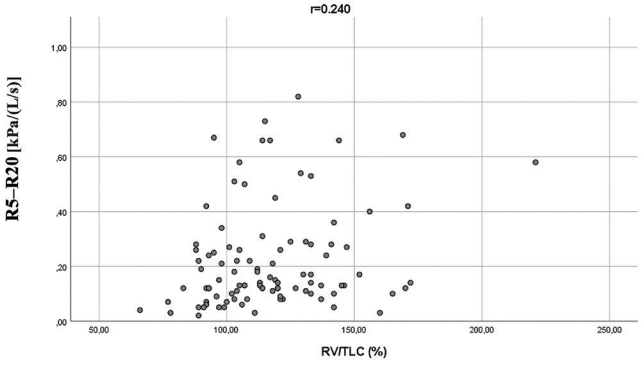

Figure 2. Spearman's correlation analysis between RV/TLC and R5–R20 [kPa/(L/s)]

RV/TLC: residual volume/total lung capacity

included X5 [kPa/(L/s)], X5 (%), X20 [kPa/(L/s)], AX (kPa/L), Z5 (%), Fres, and R5–R20/R5 (%). The results for the control and COPD groups in our study are similar to those reported in the ECLIPSE study by Crim et al.[14] The ECLIPSE study reported that the oscillometric parameter values in the COPD group were significantly different from those in both healthy smokers and healthy non-smokers.

Potentially, the most important application area of IOS is the assessment and control of peripheral airways. In 2007, Oppenheimer et al.[16] reported that IOS allows assessment of peripheral airways in a manner similar to dynamic compliance. In our study, the median value of R5–R20, a sensitive index of small airway obstruction, was found to be 0.13 kPa/(L/s) in the control group and 0.18 kPa/(L/s) in the COPD group. This difference was not statistically significant. In a study by Tomalak et al.[17], the median R5–R20 in the non-obstructed group was 0.13 kPa/(L/s) [range, 0.01 to 0.72 kPa/(L/s)], whereas in the obstructed group it was 0.32 kPa/(L/s) [range, 0.01 to 1.07 kPa/(L/s)]. Although the absolute values in our study were similar those in literature, no significant difference was observed between the control group and the COPD group. Although R5–R20 is frequently used as an indicator of small airway resistance, it is influenced by multiple physiological factors, including lung volume, age, and ventilation heterogeneity. In cross-sectional studies, absolute R5–R20 values may therefore lack the sensitivity to discriminate between groups with varying degrees of small airway involvement. In our study, the age difference between the two groups may explain this finding. The median age was 56.5 years in the control group and 63.5 years in the COPD group. One of the limitations of this study is our inability to control for age-related factors. Age and sex are known to influence respiratory mechanics and IOS measurements. In this study, the COPD group was older and predominantly male compared with the control group, which is consistent with the epidemiological characteristics of COPD. Although this imbalance may have contributed to differences in IOS parameters, performing formal multivariable adjustment would have led to both a substantial reduction in sample size and the introduction of potential selection bias. Therefore, the results should be interpreted as associations rather than causal effects.

Under physiological conditions, peripheral airway resistance accounts for approximately 10-30% of total respiratory resistance.[13] In obstructive diseases with obstruction in the peripheral airways, peripheral and total airway resistance are markedly increased. In our analysis, the R5–R20/R5 ratio was 28.4% in the control group, 36.3% in the COPD group, 32% in the GOLD 2 group, and 49% in the GOLD 3 group. In an analysis by Tomalak et al.[17], the R5–R20/R5 ratio was 33% in the group without airway obstruction and 50.7% in the group with airway obstruction.

In the present study, the absence of a statistically significant difference in absolute R5–R20 between COPD patients and controls does not contradict the presence of peripheral airway dysfunction. Instead, the significantly higher R5–R20/R5 ratio suggests a relatively greater contribution of peripheral airway resistance to total respiratory resistance in COPD. This proportional index may better capture the pathophysiological heterogeneity of COPD than absolute resistance values alone.

In the ECLIPSE study, the AX value was found to be 0.38 kPa/L in the non-smoking control group, 0.34 kPa/L in the smoker group without obstruction, and 1.99 kPa/L in the COPD group.[14] As the severity of obstruction increased from GOLD 2 to GOLD 4, the AX values were 1.37 kPa/L, 2.25 kPa/L, and 3.23 kPa/L, respectively. In our study, the AX values were 0.87 kPa/L in the non-smoking control group, 1.77 kPa/L in the COPD group, and 1.59 kPa/L and 4.39 kPa/L in the GOLD 2 and GOLD 3 groups, respectively. In our study, a significant difference in the AX value was observed between the two groups. Although the patient population in our study was smaller than in the ECLIPSE study, the AX values were similar. In a study by Wei et al.[15] of 215 patients, values for GOLD grades 1–4 were 0.66 kPa/L, 1.43 kPa/L, 2.07 kPa/L, and 2.5 kPa/L, respectively. Reactance-based parameters, particularly AX, are thought to reflect abnormalities in distal airway compliance and lung elastic properties. The significant increase in AX observed in the COPD group and its association with disease severity support the notion that reactance-based IOS indices may be more sensitive markers of small airway dysfunction in COPD than resistance-based parameters alone.

In the study conducted by Wei et al.[15], IOS resistance parameters Z5%, R5 kPa/L/s, R5%, R5–R20 kPa/L/s, and R5–R20/R5% showed a gradual increase with increasing GOLD grade, while no such increase was observed for R20 kPa/L/s and R20%. This suggests that the increase in total resistance was solely attributable to increased resistance in the peripheral airways. In our study, although a gradual increase in the absolute values of R5% and R5 kPa/L/s, Z5 kPa/L/s and Z5%, R5–R20 kPa/L/s, and R5–R20/R5% with increasing GOLD grade was observed, these increases were not statistically significant. In the study by Wei et al.[15], the reactance indices X5 kPa/L/s, Fres, and AX, reflecting peripheral airways, lung tissue, and thoracic elastic resistance, showed a gradual change with increasing GOLD grade. Kanda et al.[18] reported significantly more negative X5 values, reflecting small airway collapse, in COPD patients with severe pulmonary dysfunction.

Our results indicate that although total airway resistance was higher in the COPD group, no significant difference was found in R5–R20 values, which reflect small-airway resistance. A significant difference was found between the R5–R20/R5 (%) and AX (kPa/L) values. This may be related to differences in age and demographic characteristics between the two groups, suggesting that these parameters may be more sensitive. In our study, consistent with the literature, X5 (kPa/L/s), Fres, and AX values were higher in GOLD grade 3 than in grade 2. A significant difference in AX values was found between GOLD grades 2 and 3. However, because the number of patients in GOLD grades 1 and 4 was 1, only GOLD grades 2 and 3 were compared. Although the lack of uniform GOLD grades might be a limitation, the aim of the study was not to re-evaluate COPD diagnoses determined according to GOLD criteria but to investigate the relationship between IOS parameters and markers of small airway dysfunction in a real-world clinical setting.

Studies have shown a good correlation between IOS parameters and conventional lung function parameters in elderly patients.[19-21] As an alternative, IOS offers the advantage of ease of use. Wei et al.[15] observed moderate negative correlations between FEV_1% and Z5%, R5–R20, R5–R20/R5%, Fres, and AX (Spearman correlation coefficients r = 0.435, 0.425, 0.474, 0.5, and 0.521, respectively, $P < 0.001$). They also found moderate negative correlations between FEF 75–25% and %Z5, R5–R20, %R5–R20/R5, Fres and AX, reflecting small airway dysfunction (Spearman correlation coefficients r = 0.439, 0.452, 0.489, 0.510, and 0.540, respectively, $P < 0.001$). In our study, we observed a moderate negative correlation between R5–R20 and FEF 75–25% (Spearman correlation coefficient r = -0.49, $P < 0.001$), consistent with the findings of Wei et al.[15] found a weak correlation between RV/TLC and R5–R20 with r = 0.346, and we also found a weak correlation with r = 0.240 in our study ($P = 0.017$).

Study Limitations

IOS may have technical limitations. IOS-derived indices, as in the ECLIPSE study, have been compared with spirometry, and a lack of reference values obtained from healthy non-smokers has been reported.[14] According to this study, IOS can assess lung heterogeneity at lower oscillation frequencies and be used not only to monitor spirometric changes but also to identify subgroups of COPD patients.

The main limitation of this study is that it is a single-center study. A multicenter study could be designed to improve population representativeness. The age and gender distributions between groups were not equal. One major limitation of this study is that it was conducted during the COVID-19 pandemic. The absence of post-bronchodilator spirometry and lung volume measurements represents a significant limitation of this study. This situation was primarily related to the COVID-19 pandemic; during this period, lung function testing was restricted, and procedures were modified to reduce aerosol generation and patient exposure. As a result, all measurements were obtained under baseline conditions. Recruitment of a larger number of subjects because of the COVID-19 pandemic. The lack of prior power calculations and the relatively small sample size reflect the exploratory nature of the study. The distribution of GOLD grades was uneven, limiting the interpretation of subgroup analyses based on disease severity. These limitations should be considered when interpreting the results and underscore the need for larger prospective studies.

CONCLUSION

Although spirometry is the GOLD standard method for diagnosing COPD, its application can be challenging. IOS can be used in addition to spirometry, or in patients who are unable to perform spirometry. IOS provides complementary information regarding respiratory mechanics, particularly in relation to small airway dysfunction. In this study, reactance-based and relative IOS parameters, especially AX (kPa/L) and R5–R20/R5 (%), were more consistently associated with established markers of small airway involvement than absolute resistance measures alone. Total airway resistance was higher in the control group. Among the standard PFT parameters, FEF 25–75 and RV/TLC ratio were correlated with R5–R20; among the IOS parameters, R5–R20 was correlated with FEF 25–75 and RV/TLC ratio.

Given the cross-sectional design and methodological limitations, IOS should be regarded as an adjunct rather than a substitute for conventional PFT. Prospective studies with standardized post-bronchodilator measurements and larger sample sizes are warranted to further define the clinical utility of IOS in COPD.

Although IOS has been used since the 1970s, this test is still not widely adopted in clinical practice. Consistent with results in the literature, we highlight the use of IOS. IOS is an effortless, non-invasive method and is as effective as spirometry.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Gazi University Faculty of Medicine Clinical Research Ethics Committee with the decision numbered 533 and dated 07.09.2020.

Informed Consent: An informed consent form was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Ö.Ş., Concept: N.K., Design: N.K., Data Collection or Processing: B.Ö.Ş., Analysis or Interpretation: B.Ö.Ş., N.K., Literature Search: B.Ö.Ş., N.K., Writing: B.Ö.Ş., N.K.

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