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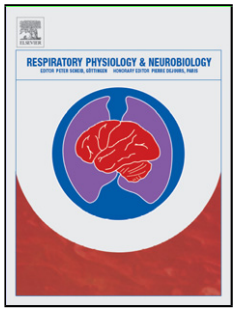

Respiratory reactance in forced oscillation technique reflects disease stage and predicts lung physiology deterioration in idiopathic pulmonary fibrosis

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Research article

Respiratory reactance in forced oscillation technique reflects disease stage and predicts lung physiology deterioration in idiopathic pulmonary fibrosis

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Highlights

- ・Pulmonary function test requires patients' effort in idiopathic pulmonary fibrosis
- ・Forced oscillation technique can be noninvasively performed during normal breathing
- ・Results of forced oscillation technique and pulmonary function test were correlated
- ・Respiratory reactance predicted subsequent lung capacity deterioration
- ・Respiratory reactance reflects disease severity in idiopathic pulmonary fibrosis

Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease. Although pulmonary function test (PFT) is useful for evaluating the progression of IPF, obtaining adequate results in advanced cases can be challenging. Conversely, the forced oscillation technique (FOT) can be noninvasively performed, even in patients with severely deteriorated lung function. In this study, the usefulness of FOT for the evaluation of IPF disease status was investigated.

Methods: We analyzed the PFT and FOT data of 97 patients with IPF.

Results: The respiratory reactance (Xrs) components of FOT, especially in the inspiratory phase, correlated with the PFT values. Patients with advanced disease had significantly lower reactance at 5 Hz (X5), higher resonant frequency (Fres) and low-frequency reactance area (ALX). The longitudinal deterioration of Xrs was also observed. Moreover, X5 in the inspiratory phase predicted subsequent lung capacity

deterioration.

Conclusion: The Xrs components of FOT, especially in the inspiratory phase, reflected restrictive ventilatory impairment and disease severity in patients with IPF.

Keywords: Forced oscillation technique, Lung physiology, Interstitial lung disease, Idiopathic pulmonary fibrosis, GAP model, Respiratory reactance

1. Introduction

Interstitial lung disease (ILD) is a generic term for diseases that present with inflammation and fibrosis in the alveolar septum, causing restrictive ventilatory impairment (American Thoracic Society et al., 2002). Idiopathic pulmonary fibrosis (IPF) is the most common phenotype of ILD and has a chronic progressive course with poor prognosis (Raghu et al., 2011). In patients with IPF, the pulmonary function test (PFT) variables, including vital capacity (VC), forced vital capacity (FVC), and diffusing capacity of the lung for carbon monoxide (DLCO), have been associated with prognosis (Martinez and Flaherry, 2006). The gender, age, and physiologic (GAP) disease staging model, which is scored by gender, age, FVC percent predicted (%FVC) and DLCO percent predicted (%DLCO), has been widely used for the prognostication of patients with IPF (Ley B et al., 2012). Although PFT is important in IPF management, it requires breathing effort from patients and sometimes cannot be successfully performed, owing to severely deteriorated lung capacity or advanced age.

The forced oscillation technique (FOT) applies the pulse or artificial noise vibration that is electrically generated in the air to the intraoral direction of the subject and measures the returning airflow and intraoral pressure. This device enables quantitative evaluation of the mechanical factors, such as viscous resistance due to friction and elasticity or inertia of the airway and air, which prevent ventilation (Oostveen E et al., 2003). Moreover, FOT allows noninvasive measurement of respiratory resistance and reactance during normal breathing, even in patients with severely impaired lung function.

Respiratory impedance (Zrs), which is measured during FOT, can be divided into respiratory resistance (Rrs) and reactance (Xrs), according to the following equation:

$$Zrs^2 = Rrs^2 + Xrs^2$$

Rrs was reported to reflect airway caliber, whereas Xrs was considered to indicate the elasticity and inertia of the respiratory system (Shirai and Kurosawa, 2016).

FOT has been widely used for the evaluation of disease status and drug efficacy in obstructive pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) and bronchial asthma, and many studies have confirmed its usefulness (Dellaca RL et al., 2004; Paredi P et al., 2010; Shirai T et al., 2013; Mikamo M et al., 2013). On the other hand, only few reports have shown the usefulness of FOT in ILD (van Noord JA et al., 1989; Sugiyama A et al., 2013; Fujii M et al., 2015). Moreover, to the best of our knowledge, there have been no reports that focused on the use of FOT in IPF.

In this study, the usefulness of FOT was evaluated by investigating the relationship between PFT and FOT results, the differences in FOT values according to disease stage, and the longitudinal change in FOT values in patients with IPF.

2. Material and methods

2.1. Subjects

A total of 113 patients with IPF and who have undergone PFT and FOT at the Sapporo Medical University Hospital from March 2012 to March 2017 were retrospectively investigated. IPF was diagnosed by a committee that comprised three ILD specialists, based on the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement (Raghu G et al., 2011). Patients who had lung cancer and/or those who underwent lung resection were excluded. Patients with combined pulmonary fibrosis and emphysema,

which was diagnosed according to the criteria by Cottin et al. (Cottin V et al., 2005), were also excluded from the study. A total of 97 patients with IPF were finally included in this study. This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of the Sapporo Medical University Hospital (approval number 282-236; ref. April 13, 2017).

2.2. Measurement of respiratory impedance and PFT

Respiratory impedance was measured with a broadband FOT using MostGraph-01 (Chest M.I. Co., Ltd, Japan) and met the standard recommendations (Oostveen E et al., 2003). Impulse oscillatory signals that were generated by a loud speaker were applied to the respiratory system through the mouthpiece during tidal breathing for approximately 30 seconds. During the measurements, the subjects supported their cheeks to reduce upper airway shunting and were asked to wear a nose clip to avoid air leaks while sitting with their neck in a comfortable neutral posture. In this study, we measured and analyzed Rrs at 5 Hz (R5) and 20 Hz (R20), the difference between R5 and R20 (R5–R20), Xrs at 5Hz (X5), resonant frequency (Fres), and low-frequency reactance area (ALX). Oscillatory indices were expressed as the mean value during a respiratory cycle (whole breath), expiratory phase (Ex), inspiratory phase (In), and difference between expiratory and inspiratory phases (Δ).

VC, FVC, forced expiratory volume in one second (FEV1), and DLCO were measured using CHESTAC-8900 (Chest M.I. Co., Ltd, Japan), according to recommendations (Miller et al., 2005). FOT and PFT were performed on the same day, and FOT measurements were performed before PFT.

2.3. Relationship between the measured values of PFT and FOT

Correlation between the PFT and FOT values was investigated using the Spearman's rank correlation coefficient. For patients who underwent several PFT and FOT evaluations, the initial measurement was used.

2.4. PFT and FOT values according to IPF disease severity

Based on the GAP disease stage (Ley B et al., 2012), patients with IPF were classified in two groups: GAP stage I (n = 47) and GAP stage II/III (n = 50). The PFT and FOT results were compared between the two groups using the Mann–Whitney U test.

2.5. Longitudinal variations of the PFT and FOT values

Next, we assessed the longitudinal variations in PFT and FOT in patients who underwent the evaluations more than twice. The test values at the initial and second measurements were evaluated. Because the interval from the initial to the second measurement differed between cases, patients with a measurement interval of 12 ± 3 months were included in the longitudinal analysis (n = 41). For each patient, the initial PFT and FOT values were compared with the second values using the Wilcoxon signed-rank test.

2.6. Predictive factors of ≥10% FVC decline

Additionally, the predictors of FVC decline after 12 months from when the initial measurements were investigated. Cases in which the interval between the initial and second measurements of PFT and FOT was 12 ± 3 months were included in this analysis (n = 41). Patients were divided into two groups according to the rate of FVC decline (≥10% or <10%) over 12 ± 3 months. FVC decline rate was calculated by the following

formula:

FVC decline rate (%) = (Second value − Initial value)/ Initial value × 100

Logistic regression analyses were performed to identify the predictive factors of ≥10% FVC decline. The variables used in the univariate analysis included age, gender, smoking status, DLCO, %DLCO, and FOT values. The values that had *p* values of <0.20 in the univariate analysis were included in the multivariate analysis.

2.7. Statistical analysis

Statistical analyses were performed using SPSS Statistics software (SPSS Statistics Version 22; IBM, Chicago, IL) and GraphPad Prism v7 software (GraphPad, Inc., San Diego, CA, USA). A *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. The median age of the patients was 72 years [interquartile range (IQR), 67–77 years]; 73 were men and 24 were women. The median values for Brinkman index, body mass index, %FVC, and %DLCO were 700 (IQR, 150–1010), 23.5 (IQR, 21.5–25.9), 86.0 % (IQR, 71.1–98.1%), and 53.4 % (IQR, 43.6–63.0%), respectively.

3.2. Correlations between the PFT and FOT values

The R5 (whole breath, Ex, In); R20 (whole breath, Ex, In); and R5–R20 (whole

breath, In) showed significant negative correlations with the VC, FVC, and FEV1 (Table 2). The X5 (whole breath, Ex, In) showed significant positive correlations with the VC, %VC, FVC, %FVC, and FEV1, whereas the Fres (whole breath, Ex, In) and ALX (whole breath, Ex, In) showed significant negative correlations with the VC, %VC, FVC, %FVC, and FEV1 (Table 2). In particular, the Xrs values in the inspiratory phase demonstrated strong correlations with the VC, %VC, FVC, and %FVC (r = 0.5–0.6, p <0.01) (Figure 1). Additionally, a positive correlation was found between X5 (whole breath, In) and DLCO, and Fres (whole breath, In) and ALX (whole breath, In) were negatively correlated with DLCO.

3.3. Comparison between the PFT and FOT values according to GAP disease stage

On PFT, the VC, %VC, FVC, %FVC, FEV1, DLCO, and %DLCO were significantly lower in the GAP stage II/III than in the GAP stage I group. No significant Rrs difference was found between both groups. Conversely, X5 (whole breath, In) was significantly lower, whereas Fres (whole breath, Ex, In) and ALX (whole breath, In) were significantly higher in the GAP stage II/III than in the GAP stage I group (Table 3).

3.4. Comparison between the initial and second values of PFT and FOT

Among the patients included in the longitudinal analysis, the median duration of the initial and second measurements was 12 months (range, 11–15 months; IQR, 11–13 months). In the longitudinal analysis, VC, %VC, FVC, %FVC, FEV1, DLCO, and %DLCO significantly decreased, whereas FEV1/FVC significantly increased (Table 4). Although no significant change was observed in the Rrs during the clinical course, X5 (whole breath, In) significantly decreased, whereas Fres (whole breath, Ex, In) and

ALX (whole breath, Ex, In) significantly increased.

3.5. Predictive factors of FVC decline over 12 months

On univariate analysis, the Xrs values in the inspiratory phase were significantly associated with ≥10% FVC decline over 12 ± 3 months (p <0.05) (Table 5). Because almost all Xrs indices had p values of <0.20 and were found to be strongly correlated (r = 0.8–0.9), X5 (In) was included in the multivariate analysis as the representative index of Xrs. The multivariate analysis revealed that low X5 (In) was significantly associated with ≥10% FVC decline over 12 ± 3 months [odds ratio (OR) 0.137, 95% CI 0.021–0.875, p = 0.036) (Table 6).

4. Discussion

IPF is a chronic progressive disease of unknown etiology and has a poor prognosis (Natsuizaka et al., 2014). The PFT variables VC, FVC, and DLCO have been used to evaluate disease status (Travis et al., 2013) and were reported to predict the prognosis of patients with IPF (Martinez and Flaherry, 2006). However, some patients with advanced disease have difficultly performing PFT, which requires effort and a certain amount of VC to measure DLCO. Therefore, appropriate results cannot be obtained occasionally. On the other hand, FOT can be noninvasively performed during normal breathing, even in advanced cases.

In this study, the PFT and Xrs on FOT values were strongly correlated, particularly when Xrs was measured in the inspiratory phase. Moreover, the Xrs values predicted ≥10% FVC decline over 12 months after performing FOT. Due to the short observation period of the current study, it was not possible to assess whether Xrs itself

predicted the prognosis of patients with IPF. Nevertheless, ≥10% FVC decline has been reported to predict mortality in patients with IPF (Du Bois et al., 2011; Richeldi et al., 2012) and has been used as the primary endpoint in a pirfenidone clinical trial (King et al., 2014). Therefore, Xrs values, especially in the inspiratory phase, may be used as a PFT substitute to predict disease progression and the prognosis of patients with IPF.

The usefulness of FOT to evaluate the disease status in patients with IPF was also examined in the present study. Sugiyama et al. (2013) evaluated the differences in FOT values between healthy volunteers and patients with ILD, bronchial asthma, and COPD; they reported that patients with ILD showed lower X5 and higher Fres and ALX, compared with those in the healthy controls. In this study, comparison between GAP stage I and stage II/III revealed that X5 decreased and Fres and ALX increased as the disease stage progressed. Moreover, these values deteriorated in the longitudinal analysis. For the Xrs, three indices are mainly used: X5, which is Xrs at 5 Hz; Fres, which is the resonant frequency at point 0; and ALX, which is the low-frequency area (integral from X5 to Fres). These indices were reported to reflect lung parenchymal and airway abnormalities. X5 is considered the reciprocal of lung compliance, and its value becomes more negative when the lung tissue has reduced compliance (Sugiyama et al., 2013). In addition, Fres reflects progression of lung fibrosis and increase in lung elastic recoil in ILD (Shirai and Kurosawa, 2016). According to these reports, X5 decrease, Fres increase, and ALX increase may be considered to indicate the progression of lung fibrosis in IPF.

In this study, patients with IPF were classified in two groups according to the GAP model. Ley et al. (2012) proposed the GAP model, which is scored by gender, age, and lung physiology (%FVC and %DLCO), to discriminate prognosis of patients with IPF. In this model, patients are classified into three stages of disease severity, and

treatment is proposed according to the disease stage. In GAP stage I, patients may not require immediate enlisting for lung transplantation because of the low risk for one-year mortality. However, physicians should consider enlisting patients in GAP stage II/III for lung transplantation. Therefore, in this study, the differences in FOT results according to disease severity were assessed after classifying patients with IPF into GAP stage I or stage II/III.

The usefulness of FOT has been comprehensively investigated in obstructive airway diseases, such as bronchial asthma or COPD. The Rrs in FOT, especially in the expiratory phase, was reported to reflect the disease status of obstructive airway diseases (Ohishi et al., 2011). Conversely, Xrs was believed to be more important for the assessment of ILD pathophysiology, as the current study demonstrated. Fujii et al. (2015) found that Fres in the inspiratory phase correlated with the FVC, FEV1, DLCO, and fibrosis score in ILD. Sugiyama et al. (2013) reported that the presence of ILD was associated with ΔX5 and that ΔX5 was negatively correlated with VC and DLCO. Although several reports have focused on ILD, patients with ILD are considered to have small airway disease in varying degrees, depending on the ILD disease type (Fulmer and Roberts, 1980). Therefore, this study included only patients who were strictly diagnosed as IPF.

This study had some limitations. First, the reference values for MostGraph have not been established; therefore, the parameters of MostGraph cannot be evaluated using percent predicted values. Second, the number of patients who underwent multiple measurements was relatively small. Finally, there are FOT equipments other than MostGraph used in this study [e.g., Master Screen IOS (Eric Jaeger, Germany)], and slight differences in measured values depending on devices are reported. It is unclear whether results of this study could be also applied to other devices.

5. Conclusions

The FOT Xrs values, especially in the inspiratory phase, were useful in evaluating disease progression in IPF. Even in patients with advanced disease and who have difficulty performing PFT, FOT may be performed to noninvasively evaluate disease status and predict lung capacity decline. Further prospective studies are required to validate the use of Xrs for predicting the prognosis of patients with IPF.

Declarations of Competing Interest

None

Acknowledgments

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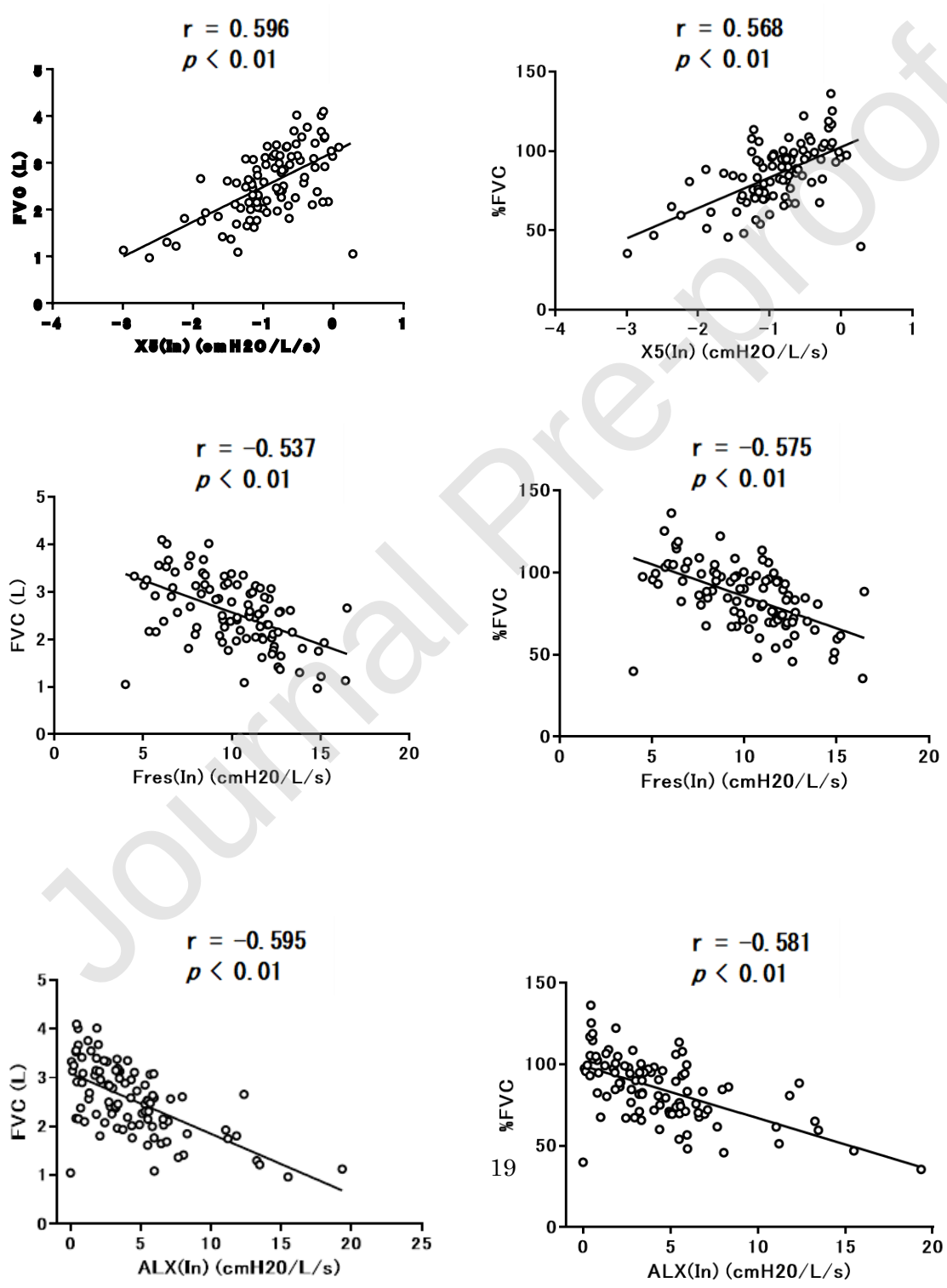
Figure Legends

Figure 1. Correlation between FVC/%FVC and Xrs in the inspiratory phase.

X5 (In) has significant positive correlations with FVC and %FVC. Fres (In) and ALX (In) have significant negative correlations with FVC and %FVC.



ALX (In), low-frequency reactance area in the inspiratory phase; Fres (In), resonant frequency in the inspiratory phase; FVC, forced vital capacity; %FVC, forced vital capacity % predicted; Xrs, respiratory system reactance; X5 (In), respiratory system reactance at 5Hz in the inspiratory phase.

Tables

Table 1. Baseline characteristics, pulmonary function tests, and the FOT parameters

	IPF (n = 97)
Age	72 (67–77)
Sex Men/Women	73 / 24
Body mass index	23.5 (21.5–25.9)
Smoking Current or former/never	78 / 19
Brinkman index	700 (150–1010)
VC (L)	2.58 (2.12–3.18)
%VC	87.6 (74.6–99.7)
FVC (L)	2.54 (2.04–3.12)
%FVC	86.0 (71.1–98.1)
FEV1 (L)	2.09 (1.74–2.45)
FEV1/FVC (%)	83.1 (78.3–88.0)
$ DLCO (mL/min/mmHg)	10.8 (8.99–14.1)
$ %DLCO	53.4 (43.6–63.0)
R5 ($cmH_2O/L/s$)	
Whole breath	2.86 (2.35–3.72)
Ex	3.20 (2.61–4.08)
In	2.69 (2.11–3.25)
ΔR5	0.46 (0.18–0.92)
R20 ($cmH_2O/L/s$)	
Whole breath	2.17 (1.82–2.78)
Ex	2.22 (1.82–2.92)
In	2.05 (1.74–2.62)

ΔR20	0.17 (−0.08–0.51)
R5–R20 ($cmH_2O/L/s$)	
Whole breath	0.69 (0.40–0.97)
Ex	0.86 (0.45–1.18)
In	0.49 (0.32–0.78)
ΔR5–R20	0.29 (0.12–0.53)
X5 ($cmH_2O/L/s$)	
Whole breath	−0.96 (−1.17–−0.48)
Ex	−0.97 (−1.28–−0.42)
In	−0.83 (−1.19–−0.53)
ΔX5	0.04 (−0.17–0.18)
Fres (Hz)	
Whole breath	10.4 (7.89–12.2)
Ex	10.1 (7.27–12.3)
In	10.3 (8.16–12.0)
ΔFres	−0.30 (−1.14–0.75)
ALX ($cmH_2O/L/s$)	
Whole breath	3.90 (1.72–5.81)
Ex	4.02 (1.34–6.11)
In	3.52 (1.85–5.75)
ΔALX	−0.28 (−0.77–1.03)

Data are presented as median (IQR).

p values were calculated using the Chi square test or Mann–Whitney U test.

[$]DLCO was measured in 84 cases.

ALX, low-frequency reactance area; Δ, difference between expiratory and inspiratory phases; DLCO, diffusing capacity of the lung for carbon monoxide; Ex, expiratory phase; FEV1, forced expiratory volume in one second; FOT, forced oscillation technique; Fres, resonant frequency;

FVC, forced vital capacity; In, inspiratory phase; IPF, idiopathic pulmonary fibrosis; Rrs, respiratory system resistance; R5, Rrs at 5 Hz; R20, Rrs at 20 Hz; R5–R20, difference between R5 and R20; VC, vital capacity; Xrs, respiratory system reactance; X5, reactance at 5 Hz.

Table 2. Correlations between the values of PFT and FOT in patients with IPF

	VC	%VC	FVC	%FVC	FEV1	FEV1/FVC	$ DLCO	$ %DLCO
R5 Whole breath	−0.358*	−0.065	−0.365*	−0.085	−0.500*	−0.223#	−0.089	0.066
R5 Ex	−0.324*	−0.041	−0.333*	−0.060	−0.475*	−0.235#	−0.052	0.098
R5 In	−0.354*	−0.052	−0.358*	−0.071	−0.472*	−0.195	−0.130	0.024
ΔR5	−0.126	0.013	−0.133	0.004	−0.260#	−0.205#	0.008	0.082
R20 Whole breath	−0.359*	−0.058	−0.362*	−0.075	−0.492*	−0.246#	−0.085	0.049
R20 Ex	−0.335*	−0.024	−0.342*	−0.045	−0.483*	−0.271*	−0.076	0.067
R20 In	−0.301*	−0.018	−0.300*	−0.036	−0.411*	−0.230#	−0.093	0.020
ΔR20	−0.184	−0.035	−0.198	−0.049	−0.305*	−0.177	−0.007	0.093
R5–R20 Whole breath	−0.244#	−0.113	−0.255#	−0.131	−0.331*	−0.047	−0.057	0.069
R5–R20 Ex	−0.161	−0.042	−0.171	−0.064	−0.247#	−0.052	−0.036	0.068
R5–R20 In	−0.321*	−0.181	−0.330*	−0.191	−0.386*	−0.017	−0.142	−0.006
ΔR5–R20	0.055	0.144	0.060	0.149	−0.035	−0.183	0.019	0.040
	VC	%VC	FVC	%FVC	FEV1	FEV1/FVC	$ DLCO	$ %DLCO
X5 Whole breath	0.556*	0.533*	0.536*	0.509*	0.514*	−0.241#	0.297*	0.197
X5 Ex	0.449*	0.416*	0.434*	0.399*	0.459*	−0.107	0.208	0.122

X5 In	0.613*	0.596*	0.596*	0.568*	0.532*	−0.347*	0.350*	0.242#
ΔX5	−0.048	−0.072	−0.052	−0.070	0.063	0.271*	−0.084	−0.101
Fres Whole breath	−0.494*	−0.526*	−0.477*	−0.498*	−0.433*	0.273*	−0.256#	−0.148
Fres Ex	−0.403*	−0.435*	−0.384*	−0.407*	−0.375*	0.171	−0.173	−0.081
Fres In	−0.552*	−0.607*	−0.537*	−0.575*	−0.462*	0.366*	−0.317*	−0.207
ΔFres	0.051	0.088	0.069	0.104	−0.032	−0.284*	0.093	0.108
ALX Whole breath	−0.543*	−0.533*	−0.525*	−0.510*	−0.501*	0.251#	−0.284*	−0.181
ALX Ex	−0.441*	−0.424*	−0.424*	−0.405*	−0.440*	0.127	−0.201	−0.116
ALX In	−0.612*	−0.611*	−0.595*	−0.581*	−0.526*	0.360*	−0.354*	−0.244#
ΔALX	0.168	0.196	0.170	0.190	0.030	−0.387*	0.144	0.144

Values are presented as correlation coefficients.

*p value <0.01, # p value <0.05.

$DLCO was measured in 84 cases.

ALX, low-frequency reactance area; Δ, difference between expiratory and inspiratory phases; DLCO, diffusing capacity of the lung for carbon monoxide; Ex, expiratory phase; FEV1, forced expiratory volume in one second; FOT, forced oscillation technique; Fres, resonant frequency; FVC, forced vital capacity; In, inspiratory phase; IPF, idiopathic pulmonary fibrosis; PFT, pulmonary function test; Rrs, respiratory system resistance; R5, Rrs at 5 Hz; R20, Rrs at 20 Hz; R5–R20, difference between R5 and R20; VC, vital capacity; Xrs, respiratory system reactance; X5, reactance at 5 Hz.

Table 3. Comparison of the values of PFT and FOT according to the GAP disease stage

	GAP stage I (n = 47)	GAP stage II/III (n = 50)	*p* value
VC (L)	2.88 (2.49–3.35)	2.35 (2.00–2.85)	<0.001
%VC	96.5 (87.2–108.5)	74.7 (67.2–90.4)	<0.001
FVC (L)	2.90 (2.41–3.33)	2.23 (1.89–2.84)	<0.001
%FVC	95.1 (84.6–104.8)	71.2 (64.2–90.8)	<0.001
FEV1 (L)	2.32 (1.90–2.64)	1.93 (1.53–2.26)	0.001
FEV1 / FVC (%)	81.5 (77.5–85.1)	84.1 (80.8–89.4)	0.041
$ DLCO (mL/min/mmHg)	12.9 (10.3–16.5)	9.36 (7.28–10.9)	<0.001
$ %DLCO	61.1 (53.3–71.3)	45.3 (35.3–52.2)	<0.001
R5 (cmH_2O/L/s)			
Whole breath	2.93 (2.31–4.02)	2.79 (2.46–3.42)	0.532
Ex	3.24 (2.62–4.50)	2.87 (2.58–3.86)	0.402
In	2.73 (2.01–3.61)	2.64 (2.14–3.08)	0.528
ΔR5	0.49 (0.18–1.09)	0.42 (0.17–0.87)	0.495
R20 (cmH_2O/L/s)			
Whole breath	2.26 (1.79–2.95)	2.16 (1.84–2.65)	0.636
Ex	2.34 (1.81–3.10)	2.14 (1.86–2.89)	0.537
In	2.19 (1.70–2.78)	2.02 (1.79–2.34)	0.457
ΔR20	0.13 (−0.08–0.50)	0.19 (−0.07–0.51)	0.905
R5–R20 (cmH_2O/L/s)			
Whole breath	0.67 (0.35–1.04)	0.72 (0.42–0.94)	0.707
Ex	0.88 (0.44–1.24)	0.84 (0.44–1.06)	0.410
In	0.47 (0.30–0.84)	0.53 (0.35–0.75)	0.634
ΔR5–R20	0.32 (0.13–0.69)	0.25 (0.03–0.44)	0.082
X5 (cmH_2O/L/s)			
Whole breath	−0.82 (−1.02–−0.35)	−1.13 (−1.39–−0.62)	0.009

Ex	−0.79 (−1.18–−0.34)	−1.08 (−1.49–−0.53)	0.082
In	−0.73 (−1.08–−0.37)	−1.08 (−1.33–−0.73)	0.005
ΔX5	0.03 (−0.33–0.18)	0.05 (−0.11–0.18)	0.593
Fres (Hz)			
Whole breath	9.24 (7.23–11.2)	11.6 (8.97–12.7)	0.007
Ex	9.61 (6.86–11.7)	11.6 (8.47–13.2)	0.038
In	9.50 (6.94–11.0)	11.6 (9.43–12.6)	0.001
ΔFres	−0.46 (−1.13–0.98)	−0.28 (−1.28–0.25)	0.400
ALX ($cmH_2O/L/s$)			
Whole breath	3.20 (1.23–4.71)	5.31 (2.58–7.14)	0.009
Ex	3.16 (1.06–5.37)	5.01 (1.94–7.70)	0.065
In	2.84 (1.25–4.55)	5.21 (2.76–6.60)	0.003
ΔALX	−0.25 (−0.81–2.15)	−0.33 (−0.78–0.60)	0.354

Data are presented as median (IQR).

p values were calculated using the Mann–Whitney U test.

[$]DLCO was measured in 37 cases in GAP stage II/ III.

ALX, low-frequency reactance area; Δ, difference between expiratory and inspiratory phases; DLCO, diffusing capacity of the lung for carbon monoxide; Ex, expiratory phase; FEV1, forced expiratory volume in one second; FOT, forced oscillation technique; Fres, resonant frequency; FVC, forced vital capacity; GAP, gender, age, and physiologic variables; In, inspiratory phase; IPF, idiopathic pulmonary fibrosis; PFT, pulmonary function test; Rrs, respiratory system resistance; R5, Rrs at 5 Hz; R20, Rrs at 20 Hz; R5–R20, difference between R5 and R20; VC, vital capacity; Xrs, respiratory system reactance; X5, reactance at 5 Hz.

Table 4. Comparison of the initial and second measurement values of PFT and FOT in IPF patients (n = 41)

	Initial values	Second values	*p* value
VC (L)	2.73 (2.12–3.29)	2.52 (1.92–3.15)	<0.001
%VC	90.9 (75.8–104.0)	86.7 (71.7–101.7)	<0.001
FVC (L)	2.79 (2.04–3.29)	2.45 (1.85–3.11)	<0.001
%FVC	90.5 (75.4–101.5)	85.5 (71.4–100.5)	<0.001
FEV1 (L)	2.29 (1.77–2.49)	2.00 (1.63–2.48)	0.005
FEV1 / FVC (%)	81.8 (76.8–84.7)	83.8 (77.4–88.3)	0.020
$ DLCO (mL/min/mmHg)	11.0 (9.05–14.8)	10.8 (7.74–13.8)	0.001
$ %DLCO	53.6 (44.6–67.2)	53.8 (38.2–65.3)	0.006
R5 ($cmH_2O/L/s$)			
Whole breath	2.98 (2.30–3.75)	3.19 (2.41–3.70)	0.871
Ex	3.20 (2.62–4.25)	3.30 (2.48–4.16)	0.938
In	2.70 (2.03–3.18)	2.82 (2.18–3.48)	0.707
ΔR5	0.46 (0.20–1.07)	0.52 (0.14–1.07)	0.555
R20 ($cmH_2O/L/s$)			
Whole breath	2.16 (1.80–3.09)	2.10 (1.87–2.75)	0.559
Ex	2.22 (1.82–3.14)	2.30 (1.82–2.95)	0.746
In	2.03 (1.71–2.66)	2.08 (1.67–2.72)	0.659
ΔR20	0.12 (−0.07–0.60)	0.25 (−0.07–0.57)	0.783
R5–R20 ($cmH_2O/L/s$)			
Whole breath	0.68 (0.35–0.97)	0.80 (0.55–1.15)	0.403
Ex	0.86 (0.43–1.08)	1.00 (0.57–1.38)	0.513
In	0.49 (0.32–0.86)	0.67 (0.42–0.81)	0.361
ΔR5–R20	0.26 (0.12–0.52)	0.31 (0.10–0.57)	0.953
X5 ($cmH_2O/L/s$)			
Whole breath	−0.82 (−1.09–−0.29)	−0.92 (−1.43–−0.47)	0.005
Ex	−0.71 (−1.11–−0.25)	−0.87 (−1.46–−0.38)	0.061

In	−0.74 (−1.12–−0.36)	−0.80 (−1.42–−0.55)	<0.001
ΔX5	0.10 (−0.17–0.24)	0.14 (−0.41–0.27)	0.707
Fres (Hz)			
Whole breath	9.67 (6.43–11.3)	10.4 (7.93–13.2)	<0.001
Ex	9.48 (6.44–11.5)	10.2 (7.41–13.1)	0.001
In	9.80 (7.18–11.5)	10.5 (8.40–12.9)	<0.001
ΔFres	−0.79 (−1.35–0.58)	−0.35 (−1.55–1.11)	0.492
ALX ($cmH_2O/L/s$)			
Whole breath	3.28 (1.00–5.10)	3.99 (1.62–7.45)	0.001
Ex	2.78 (0.79–5.12)	3.46 (1.23–7.76)	0.008
In	3.01 (1.14–5.31)	3.61 (1.97–7.75)	<0.001
ΔALX	−0.36 (−1.16–0.64)	−0.58 (−1.53–1.75)	0.425

Data are presented as median (IQR).

p values were calculated using the Wilcoxon signed-rank test.

[$]DLCO was measured in 36 cases.

ALX, low-frequency reactance area; Δ, difference between expiratory and inspiratory phases; DLCO, diffusing capacity of the lung for carbon monoxide; Ex, expiratory phase; FEV1, forced expiratory volume in one second; FOT, forced oscillation technique; Fres, resonant frequency; FVC, forced vital capacity; GAP, gender, age, and physiologic variables; In, inspiratory phase; IPF, idiopathic pulmonary fibrosis; PFT, pulmonary function test; Rrs, respiratory system resistance; R5, Rrs at 5 Hz; R20, Rrs at 20 Hz; R5–R20, difference between R5 and R20; VC, vital capacity; Xrs, respiratory system reactance; X5, reactance at 5 Hz.

Table 5. Univariate logistic regression analysis of the factors that predicted 10% or more decline in FVC within 12 months

	Odds ratio	95% CI	*p* value
Age	1.045	0.946–1.560	0.386
Sex	2.610	0.475–14.25	0.270
Smoking	1.370	0.238–7.883	0.725
DLCO	0.858	0.674–1.092	0.213
%DLCO	0.968	0.917–1.022	0.243
R5 Whole breath	1.073	0.544–2.115	0.840
R5 Ex	1.084	0.613–1.916	0.782
R5 In	0.690	0.314–1.514	0.354
ΔR5	1.930	0.734–5.072	0.182*
R20 Whole breath	0.847	0.343–2.094	0.719
R20 Ex	0.849	0.379–1.899	0.690
R20 In	0.423	0.137–1.306	0.135*
ΔR20	2.431	0.475–12.45	0.287
R5–R20 Whole breath	1.891	0.548–6.527	0.314
R5–R20 Ex	1.499	0.541–4.159	0.436
R5–R20 In	2.580	0.577–11.54	0.215
ΔR5–R20	0.676	0.072–6.381	0.732
X5 Whole breath	0.411	0.166–1.016	0.054*
X5 Ex	0.566	0.289–1.110	0.098*
X5 In	0.271	0.079–0.936	0.039*
ΔX5	0.799	0.278–2.294	0.676
Fres Whole breath	1.296	0.995–1.687	0.055*
Fres Ex	1.198	0.962–1.493	0.107*
Fres In	1.395	1.029–1.891	0.032*
ΔFres	0.851	0.523–1.387	0.518
ALX Whole breath	1.146	0.992–1.325	0.065*
ALX Ex	1.085	0.975–1.208	0.135*

ALX In	1.240	1.005–1.5029	0.044*
ΔALX	1.007	0.849–1.196	0.933

*p value <0.20.

ALX, low-frequency reactance area; CI, confidence interval; Δ, difference between expiratory and inspiratory phases; DLCO, diffusing capacity of the lung for carbon monoxide; Ex, expiratory phase; Fres, resonant frequency; FVC, forced vital capacity; In, inspiratory phase; Rrs, respiratory system resistance; R5, Rrs at 5 Hz; R20, Rrs at 20 Hz; R5–R20, difference between R5 and R20; Xrs, respiratory system reactance; X5, reactance at 5 Hz.

Table 6. Multivariate logistic regression analysis of the factors that predicted 10% or more decline in FVC within 12 months

	Odds ratio	95% CI	*p* value
ΔR5	1.336	0.351–5.092	0.671
R20 In	0.218	0.042–1.117	0.068
X5 In	0.137	0.021–0.875	0.036*

*p value <0.05.

CI, confidence interval; Δ, difference between expiratory and inspiratory phases; FVC, forced vital capacity; In, inspiratory phase; R5, respiratory system resistance at 5 Hz; R20, respiratory system resistance at 20 Hz; X5, respiratory system reactance at 5 Hz.