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Forced oscillation technique in progressive pulmonary fibrosis in a single-center retrospective study

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The contribution of forced oscillation technique (FOT), also called oscillometry, in diagnosis and follow-up of progressive pulmonary fibrosis (PPF) is not yet established. The aims of this monocentric retrospective study were to compare the FOT profile between patients suffering from PPF and stable non-idiopathic pulmonary fibrosis (IPF) interstitial lung diseases (ILDs), to look for a correlation between oscillometry and conventional function tests currently used for PPF follow-up and functional definition (forced vital capacity (FVC) and diffusing lung capacity (DLCO)) and correlation with ILD severity according to FVC. Compared to non-IPF stable ILDs (n = 96), PPF patients (n = 45) showed lower median resistance at 5Hz (X_{rs5}) values (during inspiratory phase: 0.31 versus -0.39 cmH2O/(L/sec), p = 0.019595). X_{rs5} also showed moderate correlation with FVC and DLCO. Finally, among all ILDs (n = 160), X_{rs5} showed correlation with disease severity according to FVC. These results suggest that, in conjunction with conventional pulmonary function tests, FOT could be an interesting tool to predict progressive course of fibrosing non-IPF ILDs. Its exact contribution to PPF diagnosis and follow-up needs to be determined by a prospective approach.

Keywords Oscillometry, Forced oscillation technique, Pulmonary function tests, Interstitial lung diseases, Progressive pulmonary fibrosis, Idiopathic pulmonary fibrosis

Abbreviations

cHP	Chronic hypersensitivity pneumonitis
CPFE	Combined fibrosis and emphysema
CTD-ILD	Connective tissue disease-associated interstitial lung disease
DLCO	Diffusing lung capacity of carbon monoxide
FEV-1	Forced expired volume in one second
Fres	Resonant frequency
Fsarcoidosis	Fibrosing sarcoidosis
FOT	Forced oscillation technique
FVC	Forced vital capacity
HRCT	High resolution computed tomography
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
PFT	Pulmonary function test
PPF	Progressive pulmonary fibrosis
P	P-value
R	Spearman correlation coefficient
R_{rs}	Resistance
R_{rs5}	Resistance at 5Hz
R_{rs20}	Resistance at 20Hz
X_{rs}	Reactance
X_{rs5}	Reactance at 5Hz
TLC	Total lung capacity
VC	Vital capacity
Z_{rs}	Impedance

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This study focuses on the potential role of forced oscillation technique (FOT), also called oscillometry, in progressive pulmonary fibrosis (PPF). PPF represents a subtype of patients suffering from intersitial lung diseases (ILD) of various etiologies but characterized by a common feature, similar to idiopathic pulmonary fibrosis (IPF), the progression of pulmonary fibrosis, which needs to be identified at an earliest stage in order to propose antifibrotic therapy. PPF was defined by the 2022 ATS/ERS/JRS/ALAT Clinical Practice Guidelines in non-IPF patients independently of the underlying physiological process presenting two of the three following criteria occurring within the last year with no alternative explanation: worsening respiratory symptoms, physiological progression and radiological progression. Physiological evidence of disease progression is defined as the presence of either of the following findings: absolute decline in forced vital capacity (FVC) ≥ 5% predicted or absolute decline in diffusing lung capacity of carbon monoxide (DLCO) (corrected for hemoglobin) of ≥10% predicted[1].

At present, the definition and prognosis of PPF essentially relies on conventional pulmonary function tests (PFTs). Measuring FVC and DLCO can be burdensome for some patients as it requires their cooperation and sufficient breath, thereby reducing reproducibility. FOT represents an innovative alternative because it is a non-invasive, quick, reproductible and convenient method to perform both for operator and patient, avoiding any special breathing maneuver (measured during regular breathing), initially developed for obstructive lung diseases[2–4]. Pressures waves are applied at the mouth through a mouthpiece (with a nose clip in place), surimposing sinusoidal oscillations to spontaneous tidal breathing at different frequencies (in a range of 5 to 40Hz)[4]. Airflows and pressures are measured by a transducer, assessing mechanical properties of the respiratory system, called respiratory system impedance (Z_{rs}). Z_{rs} is not used in clinical practice but represented by its components, respiratory system resistance (R_{rs}) and reactance (X_{rs}), which it is linked to by the equation $Z_{rs}^2 = R_{rs}^2 + X_{rs}^2$ [2–4].

R_{rs} measures airway resistance from the mouth to the small caliber bronchi. R_{rs} at 5Hz (R_{rs5}) captures the total airway resistance while R_{rs} at 20Hz (R_{rs20}) reflects the resistance of the large airways. R_{rs} values are also influenced, to a lesser extent, by the resistance of the pulmonary tissues, the chest wall and the airway heterogeneity[2,4,5].

X_{rs} represents the energy stored and dissipated by the airways, lung tissue and thorax to waves passing through and stretching it. It is composed of inertance, the forces of the moving air column in the conducting airways, and capacitance, the elastic properties of the peripheral parts of the respiratory system. Capacitance dominates at lower frequencies, representing the energy absorbed by the distal airways, parenchyma and chest wall. By convention, capacitance is described by negative values. Thus, if the capacitive energy is impaired by fibrosis or hyperinflation, X_{rs} will be more negative at low oscillation frequencies[2,5].

Values can be reported at a single frequency or over the frequency range of 5-40Hz and its indices are expressed as the mean values of whole-breath data and of each phase as inspiration and expiration.

Oscillometry is a promising tool in the diagnosis, prognosis, and management of ILDs but its clinical application is still less established than in obstructive diseases[2–4]. Current literature data demonstrate that patients with ILD have increased R_{rs}, increased frequency dependence of R_{rs} and more negative X_{rs} values at low frequencies, consistent with increased elastance[2,6–8]. FOT is currently more of a clinical research tool in ILDs and remains difficult to implement in clinical practice. The literature is sparse, focusing mainly on limited cohorts of patients and IPF. Apart from a recent study by *Liang* et al. [9], there are few data comparing ILD with other pulmonary diseases and no standardized cut-offs, making it difficult to accurately interpret results[9]. To the best of our knowledge, no study has looked specifically at the role of FOT in PPF population, despite the fact that conventional PFTs, which are sometimes difficult to perform and less convenient than FOT, play a major role in the early detection of progressive phenotypes among ILD patients and prediction of their evolution.

The aim of this study was to determine whether FOT is a reliable tool to predict the progressive course of fibrosing ILDs by demonstrating that certain values differ between patients with PPFs versus stable non-IPF ILDs. In addition, it was intended to look for a correlation between FOT and PFT values currently used in the follow-up of ILDs and PPF functional definition (FVC and DLCO). Finally, correlation was investigated between ILD severity according to FVC (by dividing patients into 3 severity groups) and FOT values.

Methods

Population

This is a single-center retrospective study. Data were collected retrospectively among patients with fibrosing ILD diagnoses (according to a multidisciplinary discussion among experienced clinical experts in the field of ILDs), evaluated in a tertiary ILD center in the pneumology clinic of CHU Liège between 11th January 2021 and 13th January 2023. The inclusion criteria were a fibrosing ILD diagnosis of any type (established by a multidisciplinary discussion including at least pulmonologists and radiologists with specific expertise in this field) and the availability of at least one conventional PFT and FOT performed during the same visit. There was no exclusion criterion.

IPF and PPF were defined based on the 2022 ATS/ERS/JRS/ALAT guidelines on Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis[1].

Patients with fibrosing ILDs not fulfilling either IPF or PPF definitions were classified as "stable non-IPF patients".

The protocol was approved by the ethics committee of University Hospital of Liège (Comité d'Éthique Hospitalo-Facultaire Universitaire de Liège (707), study refrence: 2022/20). The need to obtain informed consent was waived by the ethics committee of University Hospital of Liège. All methods were performed in accordance with the relevant guidelines and regulations.

FOT analysis

FOT was performed using a Resmon PRO FULL V3 FOT system, software version 21.5.0, following the European Respiratory Society technical standards[10]. Values were assessed at 5Hz, as measurements averaged

over several tidal breaths (whole-breath analysis) and as measurements separately averaged during inspiration and expiration. The percentage of predicted value given by the software was calculated using the prediction equation developed by *Oostveen* et al. [11]. This equation takes into account the age, sex, height and weight of healthy Caucasian subjects aged between 18 and 80 years.

Statistics

For comparison between PPF and stable patients non-IPF ILDs, the unpaired t-test was used for PFT data given the normal distribution of these data, and the Mann–Whitney test for FOT data selected due to the non-normal distribution of these data.

Spearman rank correlation method was used in order to correlate forced expired volume in one second (FEV-1), FVC and DLCO values with FOT values, as it is suitable for non-linear variables. Spearman correlation coefficient is referred to as "r".

All patients were categorized into 3 groups according to their FVC value (≥ 80%, ≥ 60 and < 80% and < 60% of predicted values). FOT values were compared between those groups, using Kruskall Wallis test and Dunn's post hoc test (reflecting the variability in group data distributions).

FOT results are expressed as median (interquartile range) and PFTs an mean ± standard derivation.

P-value < 0.05 was considered to be statically significative.

Statistical analyses were performed using *TIBCO Statistica*, v. 13.5.0, TIBCO Software Inc, Palo Alto, CA, USA and graphs using GraphPad Prism software version 9.0.0 for Windows, GraphPad Software, San Diego, California, USA.

Results

Demographic, treatments and functional characteristics

Among 160 patients with fibrosing ILDs, 21 (13%) had IPF and 139 (87%) had non-IPF ILDs which included 94 (59%) stable ILDs and 45 (28%) PPFs (Fig. 1).

In comparison to stable patients, PPF patients included less non-smoker (46 patients (49%) versus 15 patients (33%), p-value (p) < 0.001) (Table 1).

Non-IPF ILDs included connective tissue disease-associated interstitial lung disease (CTD-ILD; n = 61), fibrosing sarcoidosis (fsarcoidosis; n = 27), idiopathic interstitial pneumonia (IIP; n = 19), combined fibrosis and emphysema (CPFE; n = 3), chronic hypersensitivity pneumonitis (cHP; n = 3) and other ILDs (n = 26). CTD-ILD was the most frequent condition both in PPF and stable patients.

Compared to stable patients, PPF had statistically significantly lower FEV-1 (76 ± 19 versus 85 ± 16, p = 0.005), FVC (74 ± 18 versus 87 ± 16, p < 0.001), total lung capacity (TLC) (77 ± 18 versus 92 ± 20, p = 0.006) and DLCO (53 ± 19 versus 70 ± 22, p < 0.001) values.

FOT value comparison between PPF and stable non-IPF ILDs

In comparison to stable patients, PPFs showed significantly lower median X_{rs} at 5Hz (X_{rs5}) during inspiratory phase (0.31 cmH2O/(L/sec) *versus* -0.39 cmH2O/(L/sec), p = 0.0120) (Table 2).

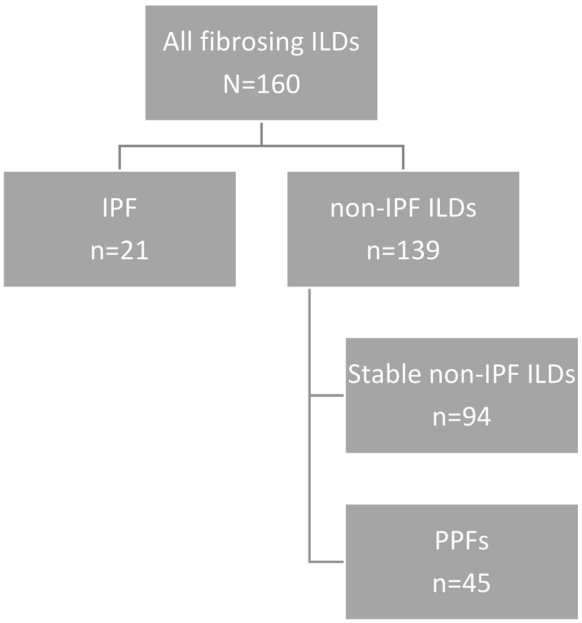

Fig. 1. Flowchart . *ILDs* interstitial lung diseases, *IPF* idiopathic pulmonary fibrosis, *PPFs* progressive pulmonary fibrosis.

	All patients N = 160	Stable non-IPF ILDs n = 94	PPFs n = 45
Demography			
Age (years)	64 (53–72)	62 (50–70)	68 (59–75)
Biological sex (M/F)	96/64	48/46	30/15
BMI (kg/m^2)	27 ± 9.3	28 ± 8.5	26 ± 10.3
Smoking (NS/ES/CS)	61/63/22	46/26/15	15/37/7***
Diagnosis			
CTD-ILD (nb (%))	61 (38.1%)	35 (37.2%)	26 (57.8%)
fsarcoidosis (nb (%))	27 (16.9%)	23 (24.5%)	4 (8.9%)
IIP (nb (%))	19 (11.9%)	13 (13.8%)	6 (13.3%)
CPFE (nb (%))	3 (1.9%)	1 (1.1%)	2 (4.4%)
cHP (nb (%))	3 (1.9%)	2 (2.1%)	1 (2.2%)
Other ILDs	26 (16.3%)	20 (21.3%)	6 (13.3%)
Treatments			
IS (nb (%))	59 (36.9%)	35 (37.2%)	24 (53.3%)
Anti-fibrotic (nb (%))	10 (6.3%)	0(0%)	10 (22.2%)
OCS (nb (%))	58 (36.3%)	32 (34%)	26 (57.8%)
ICS (nb (%))	39 (24,3%)	12 (12.8%)	6 (13.3%)
LABA (nb (%))	34 (21.3%)	18 (19.1%)	10 (22.2%)
LAMA (nb (%))	5 (3%)	5 (5.3%)	1 (2.2%)
SABA/SAMA (nb (%))	18 (11,3%)	7 (7.4%)	5 (11.1%)
Pulmonary functional test			
FEV-1 (%pred)	83 ± 18	85 ± 16	76 ± 19**
FVC (%pred)	82 ± 18	87 ± 16	74 ± 18***
FEV-1/FVC (absolute ratio)	79 ± 7	78 ± 8	80 ± 7*
MEF25-75 (%pred)	97 ± 38	90 ± 33	95 ± 36
TLC (%pred)	86 ± 20	92 ± 20	77 ± 18**
DLCO (%pred)	64 ± 22	70 ± 22	53 ± 19****

Table 1. Baseline characteristics (demography, treatments and PFTs) of all patients and comparison between PPFs and stables non-IPF ILDs. Continuous variables are Age is expressed as median (interquartile ranges). BMI and PFTs are expressed as mean ± standard deviation. * p-value < 0.05; **p-value < 0.01; ***p-value < 0.001; ****p-value < 0.0001 comparing stable non-IPF ILDs to PPF. *cHP* chronic hypersensitivity pneumonitis, *CPFE* combined fibrosis and emphysema, *CS* current smoker, *CTD-ILD* connective tissue disease-associated interstitial lung disease, *DLCO* diffusion lung capacity for carbon monoxide, *ES* ex-smoker, *FEV-1* forced expired volume in 1 s, *fsarcoidosis* fibrosing sarcoidosis, *FVC* forced vital capacity, *IIP* idiopathic interstitial pneumonia, *ILDs* interstitial lung diseases, *ICS* inhaled corticosteroids, *IPF* idiopathic pulmonary fibrosis, *IS* immunosuppressors, *kg/m^2* kilogram per square meter, *LABA* long-acting beta agonists, *LAMA* long-acting muscarinic antagonists, *M/F* male/female, *MEF25-75* mean flow between 25 and 75% of FVC, *NS* non-smoker, *OCS* oral corticosteroids, *PFT* pulmonary function test, *PPF* progressive pulmonary fibrosis, *SABA* short-acting beta agonists, *SAMA* short-acting muscarinic antagonists, *sGaw* specific airway conductance, *TLC* total lung capacity, *%pred* % of predicted value.

Correlation between FOT and pulmonary function tests

As shown in Fig. 2, a correlation was found between certain FOT values and FEV-1, FVC and DLCO values.

FEV-1 values were significantly correlated with R_{rs5} ($p < 0.0001, = 0.0016$ and $= 0.0063$ respectively for inspiratory, expiratory and whole breath values; Spearman correlation coefficient (r) = -0.310, -0.250 and -0.271 respectively for inspiratory, expiratory and whole-breath values) and X_{rs5} ($p < 0.0001$ for inspiratory, expiratory and whole breath values; r = -0.517, -0.483 and -0.533 respectively for inspiratory, expiratory and whole-breath values).

Similarly, FVC values correlated significantly with R_{rs5} ($p < 0.0004$, 0.0064 and 0.0038 respectively for inspiratory, expiratory and whole breath values; r = -0.279, -0.217 and -0.230 respectively for inspiratory, expiratory and whole-breath values) and X_{rs5} ($p < 0.0001$ for inspiratory, expiratory and whole breath values; r = -0.587, -0.507 and -0.564 respectively for inspiratory, expiratory and whole-breath values).

Concerning DLCO values, correlation was found concerning X_{rs5} (inspiratory ($p < 0.0001$, r = -0.330), expiratory ($p = 0.0050$, r = -0.225) and whole-breath ($p = 0.0013$, r = -0.258)) but no correlation was found concerning R_{rs5}.

See supplementary material for correlation table (sTable 1).

	All patients N = 160	Stable non-IPF ILDs n = 139	IPF n = 21
R_{rs5} Inspiratory (cmH2O/(L/sec))	0.38 (-0.35–1.18)	0.33 (-0.28–1.25)	0.41 (-0.64–1.15)
R_{rs5} Inspiratory (%pred)	111 (91–139)	109 (93–142)	112 (84–137)
R_{rs5} Expiratory (cmH2O/(L/sec))	1.01 (0.08–1.75)	0.98 (0.2–1.75)	0.84 (-0.34–1.8)
R_{rs5} Expiratory (%pred)	132 (104–163)	131 (105–161)	126 (93–166)
R_{rs5} Whole breath (cmH2O/(L/sec))	0.71 (0.05–1.57)	0.7 (0.17–1.58)	0.49 (-0.4–1.57)
R_{rs5} Whole breath (%pred)	122 (100–154)	122 (105–155)	115 (89–154)
X_{rs5} Inspiratory (cmH2O/(L/sec))	-0.01 (-1.2–0.8)	0.31 (-0.61–0.99)	-0.39 (-1.42–0.53)*
X_{rs5} Inspiratory (%pred)	100 (73–141)	91 (67–121)	115 (82–149)*
X_{rs5} Expiratory (cmH2O/(L/sec))	-0.1 (-1.96–1.01)	0.24 (-2.17–1.14)	-0.23 (-1.69–0.97)
X_{rs5} Expiratory (%pred)	101 (66–179)	90 (61–182)	106 (67–179)
X_{rs5} Whole breath(cmH2O/(L/sec))	-0.08 (-1.89–0.8)	0.13 (-1.4–1.07)	-0.52 (-2.12–0.78)
X_{rs5} Whole breath (%pred)	103 (71–170)	96 (63–151)	116 (74–170)

Table 2. Comparison of FOT values between non-IPF ILDs and IPFs. Continuous variables are expressed as median (interquartile ranges). *p-value < 0,05 comparing stable ILDs to PPFs. *FOT* forced oscillation technique, *ILD* interstitial lung disease, *PPF* progressive pulmonary fibrosis, R_{rs5} respiratory system resistance at 5Hz, X_{rs5} respiratory system reactance at 5Hz, *cmH2O/(L/sec)* centimeter of water per liter per second

FOT values according to disease severity

All patients (N = 160), were divided into 3 groups according to their FVC value, reflecting disease severity: < 60% (n = 19), between 60 and 80% (n = 52) and ≥ 80% of predicted values (n = 93) and X_{rs5} values were lower according to severity (Table 3 and Fig. 3).

Compared to patients with FVC < 60%, the ones with FVC between 60 and 80% had lower inspiratory X_{rs5} expressed as predicted values (187% *versus* 122% of predicted values, p = 0.0073) and whole-breath X_{rs5} (-2.36 *versus* -0.79 cmH2O/(L/sec), p = 0.0113 and 197% *versus* 128% of predicted values, p = 0.0359).

Likewise, compared to patients with FVC < 60%, the ones with FVC above 80% had lower X_{rs5} values (inspiratory (-2.73 *versus* -0.8 cmH2O/(L/sec), p < 0.0001, 187% *versus* 122% of predicted values, p < 0.0001) expiratory (-2.72 *versus* -0.43 cmH2O/(L/sec), p < 0.0001 and 181% *versus* 114% of predicted values, p < 0.0001) and whole-breath (-2.36 *versus* -0.79 cmH2O/(L/sec), p < 0.0001 and 197% *versus* 128% of predicted values, p < 0.0001).

Again, compared to patients with FVC between 60 and 80%, the ones with FVC ≥ 80% had lower X_{rs5} values (inspiratory (-0.8 *versus* 0.53 cmH2O/(L/sec), p < 0.0001, 122% *versus* 82% of predicted values, p = 0.0002) expiratory (-0.43 *versus* 0.74 cmH2O/(L/sec), p < 0.0001 and 114% *versus* 76% of predicted values, p < 0.0001) and whole-breath (-0.79 *versus* 0.52 cmH2O/(L/sec), p < 0.0001 and 128% *versus* 83% of predicted values, p < 0.0001).

Demographic characteristics and diagnoses according to FVC values are described in sTable 2 (see Supplementary Material).

Of interest, we did not find any significant difference between FOT at baseline and PFT modifications over time (Figure 1 in Supplementary Material).

Discussion

These data show that in a monocentric retrospective cohort of 160 patients with fibrosing ILDs, PFT values correlate moderately with FOT values. Indeed, FEV-1, FVC and DLCO values (expressed as predicted values), commonly used for longitudinal monitoring of ILD patients, correlated moderately with inspiratory, expiratory and whole-breath X_{rs5}. This consistently implies that patients with lower DLCO and FVC values display more impaired lung compliance secondary to lung fibrosis which is known to alternate both lung volume and gas exchange. FEV-1 and FVC values (expressed as predicted values), in addition to being related with X_{rs} values, were also moderately related with inspiratory, expiratory and whole-breath R_{rs5}, indicating higher total airway resistance.

The link between FOT and PFT values has been demonstrated in numerous studies involving patients with obstructive lung diseases (such as chronic obstructive pulmonary disease and asthma). In particular, R_{rs5} and X_{rs5} values have been shown to be related to FEV-1 and FVC values[2,5,12]. There are fewer studies involving patients suffering of ILD but van Noord et al. already showed in 1989 that in these patients, TLC (expressed as absolute value) and vital capacity (VC) (expressed as predicted value) were correlated with mean X_{rs} values and the slopes of X_{rs} and R_{rs} as a function of frequency (8).

Consistent with our findings, some recent studies focusing on IPF, CPFE and ILD patients demonstrated correlation between X_{rs5} and PFT values, in particular DLCO and FVC[12–15]. Mori et al. and Ishikawa et al., both focusing on IPF patients, also showed correlation between VC, FVC and FEV-1[14,16].

Furthermore, *Fuji* et al. demonstrated that inspiratory resonant frequency (Fres) (the frequency where capacitance and inertance make equal and opposite contribution to impedance) was significantly correlated with

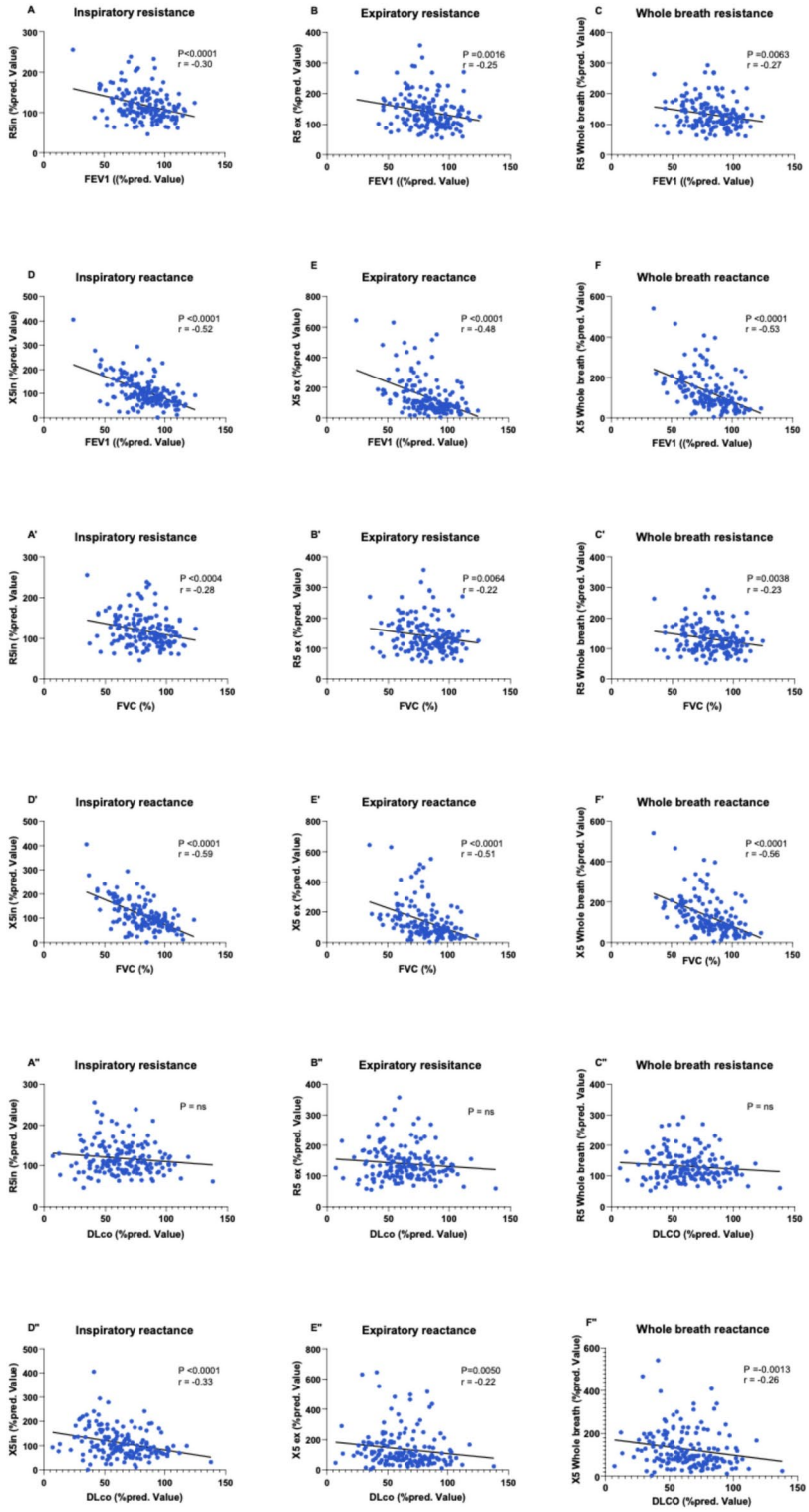

Fig. 2. Spearman rank correlations between FEV-1, FVC and DLCO values and R_{rs5} and X_{rs5} values. *FEV1* forced expired volume in 1 s, *%pred* % of predicted value, *p* p-value, *r* Spearman coefficient, *R5* resistance at 5Hz, *X5* reactance at 5Hz, *in* inspiratory, *ex* expiratory, *ns* non significant.

the *composite physiological index*, which is a score predicting the fibrosis severity on high-resolution computed tomography (HRCT) in patients suffering from IPF[17].

Finally, two studies (focusing on systemic sclerosis and rheumatoid arthritis) found a positive association between reactance and Fres values and interstitial lung abnormalities on HRCT[18,19].

	FVC ≥ 80%pred n = 93	FVC ≥ 60% & < 80%pred n = 52	FVC < 60%pred n = 19
R_{rs5} Inspiratory (cmH2O/(L/sec))	0.21 (-0.42–0.81)	0.73 (0.02–1.42)	1.25 (-0.26–1.73)
R_{rs5} (%pred)	106 (90–126)	122 (101–149)	142 (93–159)
R_{rs5} Expiratory (cmH2O/(L/sec))	0.79 (0.03–1.52)	1.21 (0.25–2.14)	1.58 (0.08–2.19)
R_{rs5} Expiratory (%pred)	124 (101–150)	141 (109–183)	156 (102–183)
R_{rs5} Whole breath (cmH2O/(L/sec))	0.59 (-0.16–1.21)	1.19 (0.14–1.93)	1.57 (-0.15–1.96)
R_{rs5} Whole breath (%pred)	118 (96–140)	134 (103–168)	152 (96–173)
X_{rs5} Inspiratory (cmH2O/(L/sec))	0.53 (-0.12–1.17)	-0.8 (-1.68–0.45)****	-2.73 (-3.22–1.32)++++°
X_{rs5} Inspiratory (%pred)	82 (66–105)	122 (85–158)***	187 (164–212)++++°°
X_{rs5} Expiratory (cmH2O/(L/sec))	0.74 (-0.22–1.3)	-0.43 (-3.1–0.53)****	-2.27 (-3.9–1.39)++++
X_{rs5} Expiratory (%pred)	76 (48–106)	114 (81–224)****	181 (153–249)++++
X_{rs5} Whole breath (cmH2O/(L/sec))	0.52 (-0.11–1.29)	-0.79 (-2.75–0.31)	-2.36 (-3.16–1.85)
X_{rs5} Whole breath (%pred)	83 (57–104)	128 (88–197)****	197 (170–222)++++°

Table 3. FOT values according to FVC values (≥ 80%, ≥ 60 and < 80% and < 60% of predicted values). Continuous variables are expressed as median (interquartile ranges). ***p-value < 0.001; ****p-value < 0.0001 comparing FVC ≥ 80% to FVC between 60 and 80%. ++++p-value < 0.0001 comparing FVC ≥ 80% to FVC < 60%. °p-value < 0,05; °°p-value < 0,01 comparing to FVC < 60% to FVC between 60 and 80%. *%pred* % of predicted value, *FOT* forced oscillation technique, *FVC* forced vital capacityR_{rs5}, respiratory system resistance at 5Hz, X_{rs5} respiratory system reactance at 5Hz; cmH2O/(L/sec), centimeter of water per liter per second. *FVC* forced vital capacity, *%pred* % of predicted value, *R5* resistance at 5Hz, *X5* reactance at 5Hz, *in* inspiratory, *ex* expiratory; *ns* non significant.

When patients in this study were divided into three severity groups based on FVC (< 60%, between 60 and 80% and ≥ 80%, expressed as predicted values), the X_{rs5} values were significantly different between the groups. This means that X_{rs5} is considered to be an accurate predictor of the functional severity of a patient with fibrosing ILD based on FVC. Logically, the more severe the patient is considered to be, the more his pulmonary compliance is impaired. Similarly, *van Noord* et al., divided their cohort of 54 ILD patients according to their TLC value (predicted value above or below 80%) and the more severe group showed decreased X_{rs} values at low frequencies, unlike group displaying TLC values above 80%[6]. A recent study conducted by *Matesanz-Lopez* et al. classified their ILD patients as severe if DLCO and/or FVC value was less than 70% of predicted values and severe patients had more impaired X_{rs5} (inspiratory, expiratory and whole-breath) values than others[15].

In the present study, PPF patients, compared to stable non-IPF patients, showed lower X_{rs5} inspiratory values, meaning that this tool could be interesting in conjunction with standard PFTs (which appear to be superior, comparing Tables 1 and 2) in order to discriminate patients with progressive pattern.

Due to the restricted number of patients with longitudinal data, we did not find any correlation between FOT values and PFT values over follow-up. Several other studies demonstrated correlation between GAP score (prognostic of survival among IPF patients) and oscillometry data[14,20,21]. *Mori* et al. showed that, in IPF patients, X_{rs5} values was significantly associated with ≥ 10% FVC decline over 12 ± 3 months (odds ratio 0.137, 95% CI 0.021–0.875, $p = 0.036$)[14]. Finally, Ishikawa et al. demonstrated that X_{rs} had significant impact on survival among IPF patients[16].

The main limitation of this study is its retrospective, monocentric design, including a restricted number of patients, and therefore reducing its generalizability. A future multicentric, longitudinal and prospective approach is required in order to determine more precisely the predictive, diagnostic and prognostic role of oscillometry in PPF compared with conventional FOT. It should include a large cohort of patients (with a real-life PPF population representative in terms of demography and underlying ILD etiology). This approach would appear to be of great interest given the expected benefit of FOT in clinical practice. Severely ill patients suffering from pulmonary fibrosis may be, in certain cases, unable to perform traditional PFT, either because of an inability to coordinate, understand the instructions or have sufficient breath. The reproducibility of FOT values is also of great concern given the need to define a functional fibrosis progression with precision and without confounding factors.

Another limitation of this study is due to the fact that one single frequency of FOT value (5Hz) is covered, and therefore does not include values such as the resonant frequency and the area of the X_{rs} curve. Plus, despite the growing literature on the subject, FOT measurements still lack standard reference values.

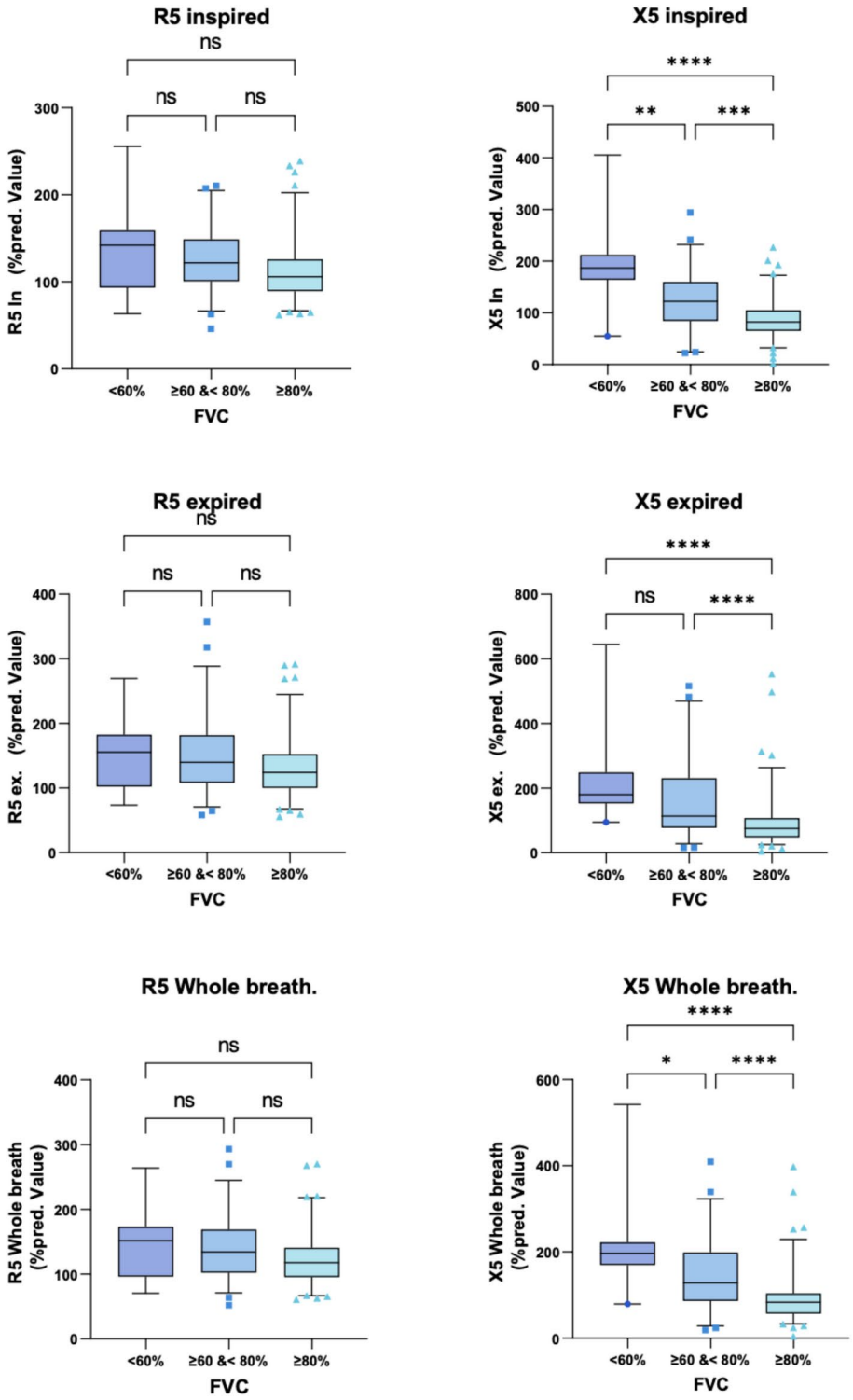

Fig. 3. FOT values according to FVC. * p-value < 0,05; ** p-value < 0,01; ***p-value < 0,001; ****p-value < 0,0001. *FVC* forced vital capacity, *%pred* % of predicted value, *R5* resistance at 5Hz, *X5* reactance at 5Hz, *in* inspiratory, *ex* expiratory, *ns* non significant

Conclusion

In this monocentric retrospective study including a restricted number of patients, the ones with progressive pulmonary fibrosis showed lower median inspiratory reactance at 5Hz, and thus pulmonary compliance, compared to patients with stable non-IPF fibrosing ILDs. FVC and DLCO values correlated moderately with X_{rs5} values and X_{rs5} was more impaired in patients with lower FVC. This implies that, in conjunction with PFTs, FOT which do not rely on patients' collaboration, moderately correlate with severity and progressive phenotype.

The exact contribution of this tool to the diagnosis and follow-up of PPF patients needs to be further determined in a prospective study involving a sufficient number of patients.

Data availability

Datasets can be made accessible if needed by contacting the corresponding author. The content of the manuscript was presented as a poster at European Respiratory Society International Congress in September 2023, in Milan. The title of the poster was "Forced oscillation technique in progressive pulmonary fibrosis".

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Author contributions

A.D and J.G. wrote the main manuscript text. M.H. prepared figures and performed statistical analyses. L.G, H.G. and X.C. participated to data collection. All authors read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The protocol was approved by the ethics committee of University Hospital of Liège (Comité d'Éthique Hospitalo-Facultaire Universitaire de Liège (707), study refrence: 2022/20). The need to obtain informed consent was waived by the ethics committee of University Hospital of Liège. All methods were performed in accordance with the relevant guidelines and regulations.

Additional information

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