ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original article

Oscillometry and Computed Tomography Findings in Patients with Idiopathic Pulmonary Fibrosis

Yuji Yamamoto, Keisuke Miki, Kazuyuki Tsujino, Tomoki Kuge, Fukuko Okabe, Takahiro Kawasaki, Takanori Matsuki, Hiroyuki Kagawa, Mari Miki, Hiroshi Kida

Please cite this article as: Yamamoto Y, Miki K, Tsujino K, *et al*. Oscillometry and Computed Tomography Findings in Patients with Idiopathic Pulmonary Fibrosis. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00391-2020).

Oscillometry and Computed Tomography Findings in Patients with Idiopathic Pulmonary Fibrosis

Yuji Yamamoto*, M.D., Keisuke Miki, M.D., Ph.D., Kazuyuki Tsujino, M.D., Ph.D., Tomoki Kuge, M.D., Fukuko Okabe, M.D., Takahiro Kawasaki, M.D., Takanori Matsuki, M.D., Hiroyuki Kagawa, M.D., Mari Miki, M.D., Ph.D., Hiroshi Kida, M.D., Ph.D.

Department of Respiratory Medicine, National Hospital Organization Osaka Toneyama Medical Center, Toyonaka, Japan

***Corresponding author:** Yuji Yamamoto, M.D., Department of Respiratory Medicine, National Hospital Organization Osaka Toneyama Medical Center, Address: 5-1-1 Toneyama, Toyonaka, Osaka 560-8552, Japan. Phone: +81-6-6853-2001, Fax: +81-6-6853-3127, E-mail: cyyamamoto1110@gmail.com

Take-home message: Respiratory reactance measured by oscillometry correlated with fibrosis-related computed tomography findings in idiopathic pulmonary fibrosis (IPF). Respiratory resistance was independent of traction bronchiectasis and airflow obstruction in IPF.

Running head: Oscillometry and CT findings in IPF

Key words: respiratory impedance, forced oscillation technique, physiology, pulmonary ventilation, radiology

Total word count for the body of the manuscript: 2,877 words

Abstract

Although the utility of oscillometry for predicting disease severity in idiopathic pulmonary fibrosis (IPF) had been researched, little has been reported on the mechanism of why respiratory impedance reflects the disease severity. In addition, traction bronchiectasis has been considered to reduce respiratory resistance and correlate negatively with airflow obstruction, but this hypothesis has not been validated. The present study aimed to investigate the correlations between oscillometric parameters and fibrosis-related lung abnormalities in IPF and to assess the utility of oscillometry as a surrogate marker for traction bronchiectasis and airflow obstruction.

Eighty Japanese patients with IPF underwent high-resolution computed tomography (HRCT), spirometry, and oscillometry and were retrospectively investigated. Fibrosis-related HRCT findings were scored regarding airspace consolidation, honeycombing, architectural distortion, traction bronchiectasis, and fibrosis. Correlations between the HRCT scores, spirometric parameters, and oscillometric parameters were analyzed.

Respiratory reactance correlated positively with all fibrosis-related HRCT scores. Vital capacity and forced vital capacity (FVC) correlated negatively with oscillometric parameters and HRCT scores, reflecting the severity of restrictive ventilatory deficiency. Respiratory resistance was not related to any of the HRCT scores or forced expiration volume in 1 s/FVC.

However, forced expiration volume in 1 s/FVC correlated positively with HRCT scores, which showed that airflow obstruction became milder as the disease progressed.

In conclusion, respiratory reactance reflects fibrosis and restrictive ventilatory deficiency in IPF. Moreover, respiratory resistance is independent of traction bronchiectasis and airflow obstruction in patients with IPF, which implies that respiratory resistance might reflect different properties of the airways.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause with a poor prognosis [1–3]. Since the clinical course of individual patients with IPF varies [4], many studies have been reported regarding developing clinical, physiological, and radiological markers to evaluate the clinical conditions and prognosis of patients with IPF [5–17]. As radiological and physiological markers, fibrosis-related high-resolution computed tomography (HRCT) findings and pulmonary function tests are used for predicting the prognosis of patients with IPF [10, 11, 13, 16, 17]. Notably, forced vital capacity (FVC), which reflects restrictive ventilatory deficiency, has been used as a surrogate marker for prognosis [13]. Restrictive ventilatory deficiency in IPF is primarily attributed to reduction of lung compliance [16]. Although the measurement requires placement of an esophageal pressure probe to obtain transpulmonary pressure, lung compliance is useful for early IPF diagnosis because it is markedly reduced even in patients without abnormal HRCT findings [16, 18].

In addition to these markers, studies for evaluating patients with IPF using oscillometry, also called the forced oscillation technique, have been reported [14, 15]. Oscillometry, which involves measurements of within-breath changes in respiratory impedance, measures respiratory resistance (Rrs) and respiratory reactance (Xrs). Rrs represents the sum of

the airway resistance and viscous resistance of lung and thoracic tissue [19], whereas Xrs reflects the dynamic elastance and inertia of the respiratory system [20]. Measuring respiratory impedance using oscillometry is less time-consuming and is technically easier to perform than spirometry because it is measured at rest with minimal respiratory effort [21, 22].

Regarding the utility of oscillometry as a physiological marker in IPF, respiratory reactance correlated with FVC and was useful as a surrogate marker for prognosis in IPF [14]. However, oscillometry and spirometry do not necessarily reflect the same physiological conditions of the respiratory tract system [23], and little has been reported on the mechanism of why respiratory reactance reflects the disease severity. In particular, no studies have validated the correlation of respiratory impedance with the degree of fibrosis and lung compliance in patients with IPF. Since respiratory reactance correlates with lung compliance theoretically [24], we hypothesized that respiratory reactance reflects the degree of fibrosis and might be useful for early diagnosis in IPF.

Apart from the correlation between respiratory reactance and fibrosis, patients with IPF sometimes show traction bronchiectasis and increased forced expiratory volume in 1 s (FEV_1)/FVC [16]. Given that airway resistance is affected by the diameter of the airways [25], we hypothesized that traction bronchiectasis reduces respiratory resistance, allows more air to pass out of the lungs, and correlates negatively with airflow obstruction in patients with IPF.

The objectives of the present study regarding IPF were as follows: (1) to investigate the correlation of oscillometric parameters with fibrosis-related lung abnormalities and (2) to assess the utility of oscillometry as a surrogate marker of traction bronchiectasis and airflow obstruction.

Methods

Patients

All 343 Japanese patients with interstitial pneumonia who attended clinics at the National Hospital Organization Osaka Toneyama Medical Center between 2013 and 2019 were screened in this study. Patients were excluded if they had secondary interstitial pneumonia, as well as patients who did not undergo spirometry, oscillometry, or HRCT. The usual interstitial pneumonia (UIP) diagnosis was based on the presence of UIP pattern on HRCT not subjected to surgical lung biopsy or specific combinations of HRCT findings and surgical lung biopsy patterns [26]. Patients with combined pulmonary fibrosis and emphysema (CPFE) or with FEV_1/FVC of less than 70% (i.e. suspected of having chronic obstructive pulmonary disease) were also excluded. The diagnosis of CPFE was based on the criteria developed by Cottin et al [27]. Patients were excluded if they had malignancy, severe heart diseases, or severe cerebral diseases. Only patients with at least 3 months of convalescence were included. Figure 1 shows the inclusion flowchart. In total, 80 patients qualified for this study and were evaluated using the examinations and analysis described in the following sections.

Study design

Respiratory impedance was measured in all patients using oscillometry. Spirometry and

oscillometry were performed on the same day. Oscillometry was performed at first, and thereafter, spirometry was measured. Short-acting β_2-agonists were not used for at least 12 h before tests in all patients. Chest HRCT scans were performed within three months from the measurement of oscillometry and spirometry, and patients were stable until the completion of these measurements. Treatment for IPF was not changed at least one month before the initial data measurement to the completion of all data measurements. The HRCT findings were quantified by calculating HRCT scores described in the latter section. Correlations between the HRCT scores, respiratory impedance, and spirometric parameters were analyzed regarding the total patients included in this study. The Institutional Review Board of the National Hospital Organization Osaka Toneyama Medical Center approved the study protocols and chose an opt-out system for obtaining patients' informed consent (approval number: TNH-R-2020005).

Measurement of respiratory impedance using oscillometry

Respiratory impedance was measured at rest with broadband oscillometry using a commercially available device (Mostgraph-01; Chest M.I. Co., Ltd, Tokyo, Japan). Oscillometry was performed according to the recommendations of the European Respiratory Society [28]. Whole-breath respiratory impedance was measured, and the average data of each oscillometric parameter were used. As indicators of the frequency dependence of Rrs, Rrs at 5 and 20 Hz (R5

and R20, respectively) and the difference between these (R5−R20) were used. In addition, Xrs at 5Hz (X5), resonant frequency (Fres), and low-frequency reactance area (ALX) were measured as indicators of respiratory reactance. Fres indicates the point at which Xrs crosses zero and elasticity and inertia balance each other, and ALX is defined as the integral of X5 to Fres [23]. Predicted respiratory impedance values were calculated according to the formula developed by Oostveen et al [29].

Spirometry

All patients underwent spirometry using the CHESTAC 8800 spirometer (Chest M.I., Inc.) according to the recommendations of the American Thoracic Society and the European Respiratory Society [30]. Predicted FVC and FEV_1 were calculated according to the formula for Japanese patients developed by the Japanese Respiratory Society [31].

HRCT scores

Chest HRCT scans were conducted with 1 mm section thickness. HRCT images were reviewed independently by two pulmonologists trained in HRCT scoring, and average HRCT scores were adopted. The presence, extent, and distribution of HRCT findings were evaluated based on the presence of airspace consolidation, honeycombing, architectural distortion, traction

bronchiectasis, and fibrosis, because these lung abnormalities reportedly correlate with the prognosis of patients with IPF [11].

The HRCT scores were evaluated based on the definition of HRCT findings and the scores developed by Sumikawa et al [11] (supplementary tables 1 and 2). The observers evaluated the extent of all radiological abnormalities that were present in both lungs to determine the percentage of lung parenchyma occupied by the disease. The lungs were divided into six zones (upper, middle, and lower on both sides), and each zone was evaluated separately. The upper lung zone was defined as the area of the lung above the level of the tracheal carina, the lower lung zone was defined as the area of the lung below the level of the inferior pulmonary vein, and the middle lung zone was defined as the area of the lung between the upper and lower zones [11]. When abnormal HRCT findings were present, the extent of lung involvement was evaluated visually and independently for each of the six lung zones. The airspace consolidation and honeycombing scores were based on the percentage of the lung parenchyma with these abnormalities and were estimated to the nearest 5% of parenchymal involvement. The overall percentage of lung involvement was calculated by averaging the six lung zones. The extent of architectural distortion, traction bronchiectasis, and interstitial fibrosis was quantified by adding the HRCT scores of the six lung zones (supplementary table 2).

Statistical analysis

Spearman's rank correlation coefficient (r_S) was used for bivariate correlation analysis between HRCT scores and parameters of oscillometry and spirometry. Univariate and multivariate analyses were used for interaction analyses. For all analyses, p values less than 0.05 were considered statistically significant. Furthermore, all statistical analyses were performed using EZR version 1.38 (based on R version 3.5.2 and R commander Version 2.5-1; Jichi Medical University Saitama Medical Center, Saitama, Japan) [32].

Results

Baseline characteristics

Among the 80 patients included in the present study, 6 patients were diagnosed by a combination of surgical biopsy and HRCT findings, and 74 patients without pathology were diagnosed with UIP on HRCT. Table 1 summarizes the patients' baseline characteristics. Many of the patients had been treated with pirfenidone (800–1,800 mg daily), nintedanib (200–300 mg daily), inhaled N-acetylcysteine (350 mg diluted with saline to a total volume of 10mL, twice a day), and/or oral corticosteroids (2–10 mg daily). No treatment for IPF affected oscillometric parameters (supplementary table 3). Moreover, multivariate analysis showed that age and body mass index did not affect any oscillometric parameters (all p values >0.05). Table 2 lists the results of the HRCT scores, oscillometric parameters, and spirometric parameters. The average FEV_1/FVC was higher than the predicted FEV_1/FVC of healthy subjects (men, 76.7%; and women, 76.8%) [31].

Correlations of respiratory impedance with spirometry

Oscillometric parameters variously correlated with spirometric parameters in patients with IPF (table 3). All oscillometric parameters correlated with vital capacity (VC), FVC, and FEV_1. Of note, respiratory reactance strongly correlated with VC and FVC, but FEV_1 correlated with both

respiratory resistance and reactance almost equally (tables 3 and 4). FEV_1/FVC was increased as Fres and ALX became higher and X5 became more negative (table 3), but no correlations were observed between FEV_1/FVC and respiratory resistance (figure 2 and supplementary table 4). The results showed that airflow obstruction became milder as respiratory reactance was increased, and that respiratory resistance did not correlate with airflow obstruction.

Regarding subdivisions of VC, respiratory reactance correlated both with inspiratory reserve volume (IRV) and expiratory reserve volume (ERV). However, respiratory resistance correlated only with ERV (table 3 and figure 3). Both respiratory reactance and resistance correlated with tidal volume, but no oscillometric parameters were related to tidal volume with clinical significance (table 4). Based on the results described above, respiratory reactance correlated with VC stronger than respiratory resistance, and respiratory resistance correlated with spirometric parameters that were related to forced expiration.

Correlations of HRCT scores with respiratory impedance and spirometry

Respiratory reactance significantly correlated with all HRCT scores, but respiratory resistance did not correlate with any of the scores (table 5). Even traction bronchiectasis score did not correlate with respiratory resistance. The HRCT scores became more severe as Fres and ALX became higher and X5 became more negative. The results showed that only respiratory

reactance correlated positively with fibrosis-related HRCT findings in the lungs of IPF patients.

Consistent with the correlation of oscillometric parameters with the HRCT scores, VC, FVC, and FEV_1 correlated negatively with the HRCT scores. Meanwhile, FEV_1/FVC correlated positively with all HRCT scores (table 5). This showed that restrictive ventilatory deficiency became more severe and airflow obstruction became milder as fibrosis-related lung abnormalities progressed in patients with IPF. Regarding subdivisions of VC, IRV correlated with all HRCT scores, but ERV was not related to any of the scores. These data showed that fibrosis-related lung abnormalities correlated not with forced expiration but rather forced inspiration in patients with IPF.

Discussion

The present study highlights two major findings regarding the utility of oscillometry in IPF: (1) respiratory reactance correlates positively with fibrosis-related lung abnormalities in patients with IPF, and (2) respiratory resistance can be independent of traction bronchiectasis and airflow obstruction in patients with IPF. To the best of our knowledge, this is the largest study to date that assessed the correlation of HRCT findings with oscillometry in patients with IPF.

Respiratory reactance correlates positively with lung fibrosis-related HRCT findings in patients with IPF. In patients with IPF, FVC is a reliable measurement that reflects the clinical conditions [13]. Respiratory reactance correlated positively with FVC and was useful for evaluating disease progression [14]. However, no studies have thoroughly reported the mechanism of how respiratory reactance correlates with FVC. Therefore, the present study investigated the mechanism by analyzing the correlations between HRCT scores, spirometry, and oscillometry.

In patients with IPF, reduction of lung compliance tightly correlates with lung fibrosis and occurs in patients with an early stage of IPF [16, 18]. This leads to restrictive ventilatory deficiency and is reflected in the decrease in FVC [16]. Even IPF patients without restrictive ventilatory deficiency have reduction of lung compliance [33]. Lung compliance was considered to correlate with respiratory reactance theoretically [24], but earlier studies failed to show the

correlation of lung compliance with respiratory impedance in a small number of patients with IPF [34, 35]. The present study first showed that respiratory reactance correlated with fibrosis-related lung abnormalities in patients with IPF (table 5). Given that respiratory reactance also correlated with FVC that reflects lung compliance and predicts the disease severity in patients IPF [13], respiratory reactance might correlate with lung compliance in patients with IPF. Lung compliance is useful for early diagnosis of IPF because it is markedly reduced even in IPF patients without abnormal HRCT findings [16, 18]. Therefore, assessing the utility of respiratory reactance as a substitute for lung compliance might be useful for early and effortlessly diagnosing IPF patients without abnormal HRCT findings because the measurement of lung compliance requires an invasive technique for patients compared with that of oscillometry [16, 21, 22]. Thus, further studies are necessary to validate this hypothesis and the utility of respiratory reactance.

FEV_1/FVC and respiratory resistance can be independent in patients with IPF. Since the progressive increase in elastic recoil occurs with worsening pulmonary fibrosis, FEV_1/FVC increases as lung compliance is reduced in IPF [36]. Apart from lung fibrosis and restriction, IPF is understood to primarily involve the alveolar regions, but some previous studies have suggested the involvement of the airways [16, 37–39]. Airway epithelial cells proliferate and differentiate with increased numbers of bronchioles in patients with IPF [37–39], and airway

dilation occurs as part of the disease process [16]. Therefore, FEV_1/FVC of patients with IPF is higher than that of healthy subjects, which shows that airflow obstruction becomes milder in IPF [40]. Hence, respiratory resistance, which is obtained theoretically by dividing respiratory pressure by respiratory airflow, has been considered to decline in IPF [16]. From these observations, both respiratory reactance and resistance were hypothesized to correlate with FEV_1/FVC. In fact, the results of this study showed the correlation of FEV_1/FVC with respiratory reactance (table 3). However, the present study showed no correlations between respiratory resistance and FEV_1/FVC (table 3 and figure 2) and between traction bronchiectasis and respiratory resistance (table 5). These results implied that respiratory resistance and FEV_1/FVC reflected different properties of the airways in IPF. The change of FEV_1/FVC might have been attributed to fibrosis-related structural abnormalities of the lungs (table 5). However, given that respiratory resistance correlated with ERV but not with fibrosis-related structural abnormalities in the lung (table 5 and figure 3), other mechanisms related to forced expiration might have increased respiratory resistance.

Two possible hypotheses for the mechanism can be explained. First, reduced airway distensibility might increase respiratory resistance during forced expiration. Proximal airways of healthy subjects can expand and decrease airway pressure during forced expiration, but patients with IPF fail to reduce airway pressure because the proximal airways show reduced

distensibility [41]. Hence, respiratory resistance might be higher only during forced expiration as the airway distensibility declines. Second, lung surfactant abnormalities might affect respiratory resistance. IPF induces lung surfactant abnormalities and subsequently decreases surface activity of the airways [42]. Reduced surface activity of the airways leads to increased airway resistance and lung compliance [16, 43]. Thus, increased respiratory resistance as a result of reduced surface activity might affect impaired force expiration of IPF. Further investigations are necessary to verify these hypotheses.

The present study had some limitations. First, it was a single-center retrospective study, and some selection bias might have affected the findings. Second, the present study included only patients with IPF; thus, whether the results can be applicable to patients with CPFE remains unknown. Third, this study did not include healthy subjects, and whether the results are specifically applicable to patients with IPF remains unknown. Finally, this study did not mention the correlation of within-breath changes of oscillometric parameters with spirometric parameters and HRCT findings to generalize the results because oscillometric devices do not necessarily measure inspiratory and expiratory oscillometric parameters separately. Respiratory impedance reportedly changes between inspiratory and expiratory phases in IPF and chronic obstructive pulmonary disease [14, 21]. In particular, inspiratory oscillometric parameters correlated with spirometric parameters in IPF [14]. Therefore, further studies to investigate the

utility of inspiratory and expiratory oscillometric parameters are needed in patients with IPF and CPFE.

In conclusion, the present study assessed the correlation of respiratory impedance with fibrosis and traction bronchiectasis in IPF. Respiratory reactance correlates with fibrosis-related HRCT findings. The utility of respiratory reactance should be investigated for early diagnosis of IPF without abnormal HRCT findings because respiratory reactance might be a substitute for lung compliance. Respiratory resistance can be independent of traction bronchiectasis and airflow obstruction in patients with IPF because respiratory resistance might show different properties of the airways. This study provides a theoretical foundation of the utility of oscillometry in IPF.

Acknowledgements: The authors would like to thank Ms. S. Ito, Ms. S. Sakaguchi, and Mr. T. Uenishi for their help with spirometry and oscillometry measurements.

Footnotes: This article has supplementary material available from openres.ersjournals.com

Availability of data and materials: All data generated or analyzed during this study are included in this published article and its supplementary information files.

Author contributions: Y.Y. contributed to the conceptualization and design of the study, data collection and analysis, and wrote the manuscript. K.M. and K.T. contributed to the design of the study and supervised the manuscript. T.K. and F.O. contributed to the conceptualization of the study. T.K., T.M., H.K., and M.M. cared for all patients and contributed to data analyses. H.K. contributed to supervision of the manuscript. All the authors reviewed and approved the submission of the final manuscript.

Funding sources: The authors received no specific funding for the present study.

Conflict of interest: The authors declare no conflicts of interest in association with the present study.

References

1. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am. J. Respir. Crit. Care Med.* 2000; 161: 646–664.

2. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, Offord KP. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 1998; 157: 199–203.

3. Flaherty KR, Toews GB, Travis WD, Colby TV, Kazerooni EA, Gross BH, Jain A, Strawderman RL, Paine R, Flint A, Lynch JP, Martinez FJ. Clinical significance of histological classification of idiopathic interstitial pneumonia. *Eur. Respir. J.* 2002; 19: 275–283.

4. Ley B, Collard HR, King TE. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 2011; 183: 431–440.

5. King TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am. J. Respir. Crit. Care Med.* 2001; 164: 1171–1181.

6. Wells AU, Desai SR, Rubens MB, Goh NSL, Cramer D, Nicholson AG, Colby TV, du Bois RM, Hansell DM. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *Am. J. Respir. Crit. Care Med.* 2003; 167: 962–969.

7. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Raghu G, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 2011; 184: 459–466.

8. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE, Collard HR. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann. Intern. Med.* 2012; 156: 684–691.

9. Kim ES, Choi SM, Lee J, Park YS, Lee CH, Yim JJ, Yoo CG, Kim YW, Han SK, Lee SM. Validation of the GAP score in Korean patients with idiopathic pulmonary fibrosis. *Chest* 2015; 147: 430–437.

10. Oda K, Ishimoto H, Yatera K, Naito K, Ogoshi T, Yamasaki K, Imanaga T, Tsuda T, Nakao H, Kawanami T, Mukae H. High-resolution CT scoring system-based grading scale predicts the clinical outcomes in patients with idiopathic pulmonary fibrosis. *Respir. Res.* 2014; 15: 10.

11. Sumikawa H, Johkoh T, Colby TV, Ichikado K, Suga M, Taniguchi H, Kondoh Y, Ogura T, Arakawa H, Fujimoto K, Inoue A, Mihara N, Honda O, Tomiyama N, Nakamura H, Müller NL. Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. *Am. J. Respir. Crit. Care Med.* 2008; 177: 433–439.

12. Robbie H, Daccord C, Chua F, Devaraj A. Evaluating disease severity in idiopathic pulmonary fibrosis. *Eur Respir Rev* 2017; 26.

13. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, King TE, Lancaster L, Noble PW, Sahn SA, Thomeer M, Valeyre D, Wells AU. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am. J. Respir. Crit. Care Med.* 2011; 184: 1382–1389.

14. Mori Y, Nishikiori H, Chiba H, Yamada G, Kuronuma K, Takahashi H. Respiratory reactance in forced oscillation technique reflects disease stage and predicts lung physiology deterioration in idiopathic pulmonary fibrosis. *Respir Physiol Neurobiol* 2020; 275: 103386.

15. Mikamo M, Fujisawa T, Oyama Y, Kono M, Enomoto N, Nakamura Y, Inui N, Sumikawa H, Johkoh T, Suda T. Clinical Significance of Forced Oscillation Technique for Evaluation of Small Airway Disease in Interstitial Lung Diseases. *Lung* 2016; 194: 975–983.

16. Plantier L, Cazes A, Dinh-Xuan AT, Bancal C, Marchand-Adam S, Crestani B. Physiology of the lung in idiopathic pulmonary fibrosis. *Eur Respir Rev* 2018; 27.

17. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; 246: 697–722.

18. Orens JB, Kazerooni EA, Martinez FJ, Curtis JL, Gross BH, Flint A, Lynch JP. The sensitivity of high-resolution CT in detecting idiopathic pulmonary fibrosis proved by open lung biopsy. A prospective study. *Chest* 1995; 108: 109–115.

19. Oostveen E, MacLeod D, Lorino H, Farré R, Hantos Z, Desager K, Marchal F, ERS Task Force on Respiratory Impedance Measurements. The forced oscillation technique in

clinical practice: methodology, recommendations and future developments. *Eur. Respir. J.* 2003; 22: 1026–1041.

20. Tse HN, Tseng CZS, Wong KY, Yee KS, Ng LY. Accuracy of forced oscillation technique to assess lung function in geriatric COPD population. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1105–1118.

21. Kubota M, Shirai G, Nakamori T, Kokubo K, Masuda N, Kobayashi H. Low frequency oscillometry parameters in COPD patients are less variable during inspiration than during expiration. *Respir Physiol Neurobiol* 2009; 166: 73–79.

22. Horsley A, Siddiqui S. Putting lung function and physiology into perspective: cystic fibrosis in adults. *Respirology* 2015; 20: 33–45.

23. Shirai T, Kurosawa H. Clinical Application of the Forced Oscillation Technique. *Intern. Med.* 2016; 55: 559–566.

24. Nagels J, Làndsér FJ, van der Linden L, Clément J, Van de Woestijne KP. Mechanical properties of lungs and chest wall during spontaneous breathing. *J Appl Physiol Respir Environ Exerc Physiol* 1980; 49: 408–416.

25. Kaminsky DA. What Does Airway Resistance Tell Us About Lung Function? *Respiratory Care* 2012; 57: 85–99.

26. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendía-Roldán I, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am. J. Respir. Crit. Care Med.* 2018; 198: e44–e68.

27. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, Israel-Biet D, Court-Fortune I, Valeyre D, Cordier J-F, Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires (GERM O P). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur. Respir. J.* 2005; 26: 586–593.

28. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, Farré R, Hall GL, Ioan I, Irvin CG, Kaczka DW, Kaminsky DA, Kurosawa H, Lombardi E, Maksym GN, Marchal F, Oppenheimer BW, Simpson SJ, Thamrin C, van den Berge M, Oostveen E.

Technical standards for respiratory oscillometry. *Eur Respir J* 2020; 55: 1900753.

29. Oostveen E, Boda K, van der Grinten CPM, James AL, Young S, Nieland H, Hantos Z. Respiratory impedance in healthy subjects: baseline values and bronchodilator response. *Eur Respir J* 2013; 42: 1513–1523.

30. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force. Standardisation of spirometry. *Eur. Respir. J.* 2005; 26: 319–338.

31. Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M, Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. *Respir Investig* 2014; 52: 242–250.

32. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant.* 2013; 48: 452–458.

33. Zielonka TM, Demkow U, Radzikowska E, Bialas B, Filewska M, Zycinska K, Obrowski MH, Kowalski J, Wardyn KA, Skopinska-Rozewska E. Angiogenic activity of sera from interstitial lung disease patients in relation to pulmonary function. *Eur. J. Med. Res.* 2010; 15 Suppl 2: 229–234.

34. van Noord JA, Clément J, Cauberghs M, Mertens I, Van de Woestijne KP, Demedts M. Total respiratory resistance and reactance in patients with diffuse interstitial lung disease. *Eur. Respir. J.* 1989; 2: 846–852.

35. Takeichi N, Yamazaki H, Fujimoto K. Comparison of impedance measured by the forced oscillation technique and pulmonary functions, including static lung compliance, in obstructive and interstitial lung disease. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 1109–1118.

36. Cortes-Telles A, Forkert L, O'Donnell DE, Morán-Mendoza O. Idiopathic Pulmonary Fibrosis: New Insights to Functional Characteristics at Diagnosis. *Canadian Respiratory Journal* 2014; 21: e55–e60.

37. Vuorinen K, Ohlmeier S, Leppäranta O, Salmenkivi K, Myllärniemi M, Kinnula VL. Peroxiredoxin II Expression and Its Association With Oxidative Stress and Cell

Proliferation in Human Idiopathic Pulmonary Fibrosis. *J Histochem Cytochem* 2008; 56: 951–959.

38. Plantier L, Debray MP, Estellat C, Flamant M, Roy C, Bancal C, Borie R, Israël-Biet D, Mal H, Crestani B, Delclaux C. Increased volume of conducting airways in idiopathic pulmonary fibrosis is independent of disease severity: a volumetric capnography study. *J Breath Res* 2016; 10: 016005.

39. Chilosi M, Poletti V, Murer B, Lestani M, Cancellieri A, Montagna L, Piccoli P, Cangi G, Semenzato G, Doglioni C. Abnormal re-epithelialization and lung remodeling in idiopathic pulmonary fibrosis: the role of deltaN-p63. *Lab. Invest.* 2002; 82: 1335–1345.

40. Pastre J, Plantier L, Planes C, Borie R, Nunes H, Delclaux C, Israël-Biet D. Different KCO and VA combinations exist for the same DLCO value in patients with diffuse parenchymal lung diseases. *BMC Pulm Med* 2015; 15: 100.

41. Baier H, Zarzecki S, Wanner A. Influence of lung inflation on the cross-sectional area of central airways in normals and in patients with lung disease. *Respiration* 1981; 41: 145–154.

42. Günther A, Schmidt R, Nix F, Yabut-Perez M, Guth C, Rosseau S, Siebert C, Grimminger F, Morr H, Velcovsky HG, Seeger W. Surfactant abnormalities in idiopathic pulmonary fibrosis, hypersensitivity pneumonitis and sarcoidosis. *Eur. Respir. J.* 1999; 14: 565–573.

43. Enhorning G, Yarussi A, Rao P, Vargas I. Increased airway resistance due to surfactant dysfunction can be alleviated with aerosol surfactant. *Can. J. Physiol. Pharmacol.* 1996; 74: 687–691.

Figure legends

Figure 1. Patient inclusion flowchart.

AE, acute exacerbation; CPFE, combined pulmonary fibrosis and emphysema; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; NHO, National Hospital Organization; pulmonary function test; UIP, usual interstitial pneumonia.

Figure 2. Spearman's rank correlation coefficient for respiratory resistance and FEV_1/FVC (n = 80).

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NS, not significant; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; r_S, Spearman's rank correlation coefficient.

Figure 3. Spearman's rank correlation coefficient for respiratory resistance with inspiratory and expiratory reserve volume (n = 80).

** indicates $p < 0.01$, as measured by Spearman's rank correlation coefficient; ERV, expiratory reserve volume; IRV, inspiratory reserve volume; NS, not significant; r_S, Spearman's rank correlation coefficient; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively.

Table 1. Patients' baseline characteristics (n = 80)

Parameter		
Age, y	74.2 ± 7.8	50 – 88
Sex, male/female, n	51/29	
Height, cm	159.2 ± 9.5	130.0 – 178.2
Weight, kg	55.8 ± 13.9	27.6 – 97.5
BMI, kg m^{-2}	21.8 ± 3.9	13.2 – 31.6
Smoking, pack-years	27 ± 26	0 – 135
mMRC dyspnea scale, n 0/1/2/3/4	28/21/12/11/8	
LDH, U/L	220 ± 37	156 – 356
KL-6, U/mL	1002 ± 647	222 – 4348
Medications		
Pirfenidone, n (%)	21 (26.3)	
Inhaled N-acetylcysteine, n (%)	16 (20.0)	
Nintedanib, n (%)	9 (11.3)	
Oral corticosteroids, n (%)	6 (7.5)	

Data are presented as mean ± SD and minimum and maximum values, unless otherwise stated.

BMI, body mass index; LDH, lactate dehydrogenase; mMRC, modified Medical Research Council; SD, standard deviation.

Table 2. Results of spirometry, oscillometry, and high-resolution computed tomography scores (n = 80)

Parameter		
Spirometry		
FEV_1, L	2.05 ± 0.62	0.76 – 3.33
FEV_1, % predicted	88.9 ± 16.8	54.1 – 142.3
FEV_1/FVC, %	85.0 ± 7.3	71.3 – 100.0
VC, L	2.45 ± 0.83	0.79 – 4.15
FVC, L	2.46 ± 0.83	0.76 – 4.14
FVC, % predicted	83.3 ± 18.0	41.5 – 127.1
IC, L	1.60 ± 0.60	0.47 – 3.12
IRV, L	0.74 ± 0.42	0.08 – 2.40
ERV, L	0.85 ± 0.37	0.19 – 2.00
TV, L	0.86 ± 0.36	0.28 – 1.82
Oscillometry		
R5, cmH_2O/L/s	3.14 ± 1.04	1.21 – 5.96
R5, % predicted	153.7 ± 56.5	39.0 – 388.1
R20, cmH_2O/L/s	2.39 ± 0.77	1.10 – 4.32
R20, % predicted	92.6 ± 29.4	32.9 – 196.8
R5-R20, cmH_2O/L/s	0.75 ± 0.37	0.05 – 1.99
X5, cmH_2O/L/s	−1.24 ± 0.76	-3.04 – 0.00
X5, % predicted	94.5 ± 56.2	0.0 – 246.4
Fres, Hz	12.11 ± 3.34	4.30 – 20.89
Fres, % predicted	102.4 ± 30.3	36.0 – 184.2
ALX, cmH_2O/L/s × Hz	6.99 ± 5.69	0.04 – 24.66
ALX, % predicted	232.8 ± 197.3	1.1 – 857.9
HRCT scores		
Airspace consolidation	1.9 ± 2.7	0.0 – 11.7
Honeycombing	10.8 ± 11.9	0.0 – 55.8
Architectural distortion	1.4 ± 1.7	0 – 6
Traction bronchiectasis	6.7 ± 4.4	0 – 18
Interstitial fibrosis	18.8 ± 4.8	7 – 24

Data are presented as mean ± SD and as the minimum and maximum values, unless otherwise stated. ALX, low-frequency reactance area; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IC, inspiratory capacity; IRV, inspiratory reserve volume; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; SD, standard deviation; TV, tidal volume; VC, vital capacity; X5, respiratory system reactance at 5 Hz.

Table 3. Results of Spearman's rank correlation coefficient for parameters of oscillometry and spirometry (n = 80)

Parameter	R5		R20		R5-R20		X5		Fres		ALX	
VC	−0.465	**	−0.437	**	−0.304	**	0.517	**	−0.562	**	−0.523	**
FVC	−0.450	**	−0.423	**	−0.291	**	0.506	**	−0.541	**	−0.509	**
FEV_1	−0.485	**	−0.468	**	−0.306	**	0.497	**	−0.530	**	−0.497	**
FEV_1/FVC	0.092	NS	0.041	NS	0.063	NS	−0.250	*	0.286	*	0.261	*
IC	−0.154	NS	−0.331	**	−0.127	NS	0.444	**	−0.504	**	−0.454	**
IRV	−0.144	NS	−0.128	NS	−0.076	NS	0.422	**	−0.530	**	−0.445	**
ERV	−0.551	**	−0.479	**	−0.474	**	0.406	**	−0.414	**	−0.403	**
TV	−0.355	**	−0.377	**	−0.176	NS	0.272	*	−0.232	*	−0.265	*

* indicates $p < 0.05$, ** indicates $p < 0.01$, as measured by Spearman's rank correlation coefficient; ALX, low-frequency reactance area; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; NS, not significant; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; TV, tidal volume; VC, vital capacity; X5, respiratory system reactance at 5 Hz.

Table 4. Results of univariate analysis for parameters of oscillometry and spirometry (n = 80)

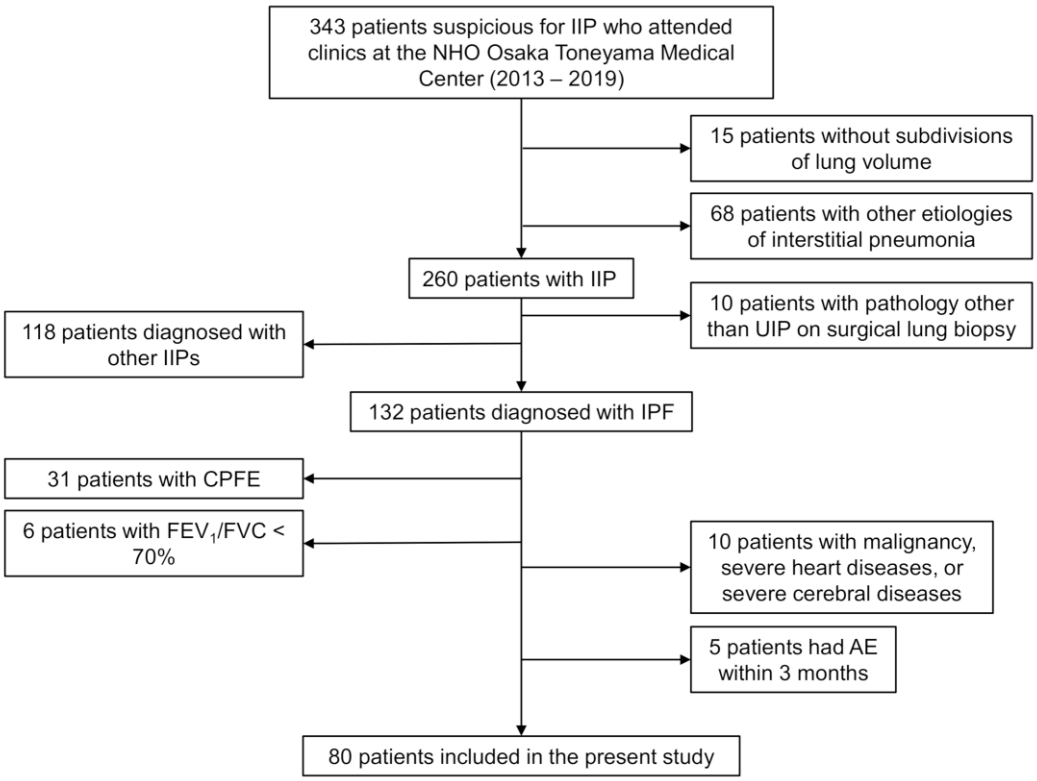
Parameter	R5			R20			R5-R20			X5			Fres			ALX		
	std β	Adjusted R^2		std β	Adjusted R^2		std β	Adjusted R^2		std β	Adjusted R^2		std β	Adjusted R^2		std β	Adjusted R^2	
VC	−0.437	0.181	**	−0.445	0.188	**	−0.309	0.084	**	0.467	0.208	**	−0.520	0.262	**	−0.439	0.183	**
FVC	−0.418	0.164	**	−0.425	0.170	**	−0.295	0.075	*	0.459	0.201	**	−0.501	0.241	**	−0.426	0.171	**
FEV_1	−0.449	0.192	**	−0.459	0.201	**	−0.313	0.087	**	0.461	0.202	**	−0.493	0.233	**	−0.427	0.172	**
FEV_1/FVC	0.072	−0.008	NS	0.076	−0.007	NS	0.041	−0.011	NS	−0.190	0.024	NS	0.271	0.062	*	0.031	0.019	NS
IC	−0.290	0.072	**	−0.219	0.037	*	−0.168	0.006	NS	0.418	0.164	**	−0.480	0.221	**	−0.380	0.134	**
IRV	−0.135	0.005	NS	−0.149	−0.010	NS	−0.069	−0.008	NS	0.344	0.087	**	−0.450	0.192	**	−0.323	0.093	**
ERV	−0.505	0.245	**	−0.486	0.226	**	−0.415	0.162	**	0.366	0.123	**	−0.384	0.136	**	−0.365	0.122	**
TV	−0.324	0.093	**	−0.344	0.107	*	−0.199	0.028	NS	0.291	0.073	*	−0.272	0.062	*	−0.254	0.053	*

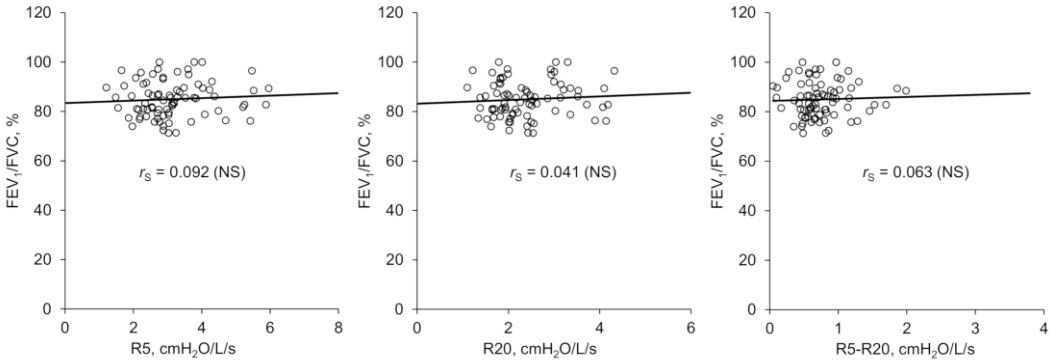
* indicates $p < 0.05$, ** indicates < 0.01, as measured by univariate analysis; ALX, low-frequency reactance area; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; NS, not significant; R^2, R-squared; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; std β, standardized regression coefficient; TV, tidal volume; VC, vital capacity; X5, respiratory system reactance at 5 Hz.

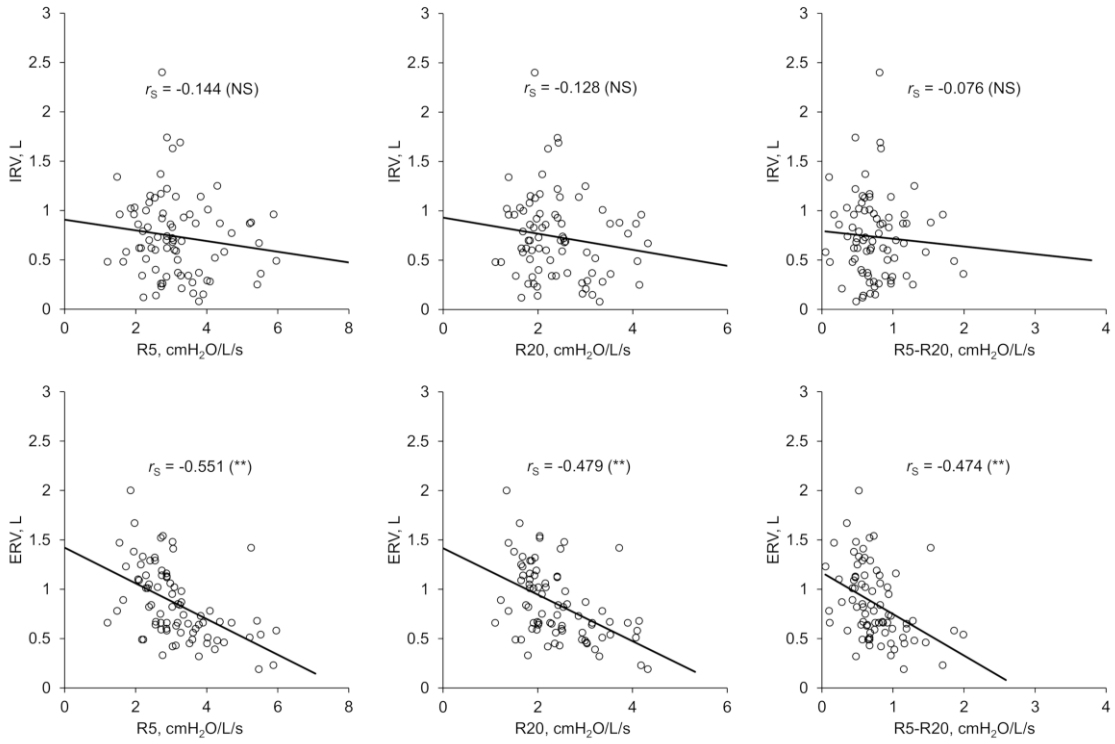
Table 5. Results of Spearman's rank correlation coefficient for high-resolution computed tomography scores, oscillometry, and spirometry (n = 80)

Parameter	Airspace consolidation		Honeycombing		Architectural distortion		Traction bronchiectasis		Interstitial fibrosis	
Oscillometry										
R5	0.005	NS	−0.080	NS	−0.041	NS	−0.072	NS	−0.119	NS
R20	−0.057	NS	−0.114	NS	−0.059	NS	−0.092	NS	−0.153	NS
R5-R20	0.065	NS	−0.078	NS	−0.008	NS	−0.048	NS	−0.096	NS
X5	−0.375	**	−0.264	**	−0.345	**	−0.297	**	−0.206	NS
Fres	0.435	**	0.296	**	0.396	**	0.348	**	0.236	*
ALX	0.396	**	0.285	**	0.366	**	0.324	**	0.222	*
Spirometry										
VC	−0.386	**	−0.271	**	−0.393	**	−0.373	**	−0.181	NS
FVC	−0.406	**	−0.259	**	−0.386	**	−0.371	**	−0.159	NS
FEV_1	−0.350	**	−0.181	NS	−0.329	**	−0.301	**	−0.100	NS
FEV_1/FVC	0.438	**	0.413	**	0.459	**	0.436	**	0.293	**
IC	−0.421	**	−0.301	**	−0.415	**	−0.431	**	−0.199	*
IRV	−0.492	**	−0.367	**	−0.465	**	−0.496	**	−0.297	**
ERV	−0.181	NS	−0.074	NS	−0.172	NS	−0.124	NS	−0.031	NS
TV	−0.121	NS	−0.068	NS	−0.142	NS	−0.196	NS	0.013	NS

* indicates $p < 0.05$, ** indicates $p < 0.01$, as measured by Spearman's rank correlation coefficient; ALX, low-frequency reactance area; ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; Fres, resonant frequency; FVC, forced vital capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; NS, not significant; R5 and R20, respiratory system resistance at 5 and 20 Hz, respectively; TV, tidal volume; VC, vital capacity; X5, respiratory system reactance at 5 Hz.


343 patients suspicious for IIP who attended clinics at the NHO Osaka Toneyama Medical Center (2013 – 2019)
15 patients without subdivisions of lung volume
68 patients with other etiologies of interstitial pneumonia
260 patients with IIP
10 patients with pathology other than UIP on surgical lung biopsy
118 patients diagnosed with other IIPs
132 patients diagnosed with IPF
31 patients with CPFE
6 patients with FEV1/FVC < 70%
10 patients with malignancy, severe heart diseases, or severe cerebral diseases
5 patients had AE within 3 months
80 patients included in the present study


120
100
80
60
40
20
0
FEV1/FVC, %
rS = 0.092 (NS)
0
2
4
6
8
R5, cmH2O/L/s
rS = 0.041 (NS)
R20, cmH2O/L/s
rS = 0.063 (NS)
1
3
R5-R20, cmH2O/L/s


IRV, L
r_S = -0.144 (NS)
R5, cmH2O/L/s
IRV, L
r_S = -0.128 (NS)
R20, cmH2O/L/s
IRV, L
r_S = -0.076 (NS)
R5-R20, cmH2O/L/s
ERV, L
r_S = -0.551 (**)
R5, cmH2O/L/s
ERV, L
r_S = -0.479 (**)
R20, cmH2O/L/s
ERV, L
r_S = -0.474 (**)
R5-R20, cmH2O/L/s

Online supplement

Oscillometry and Computed Tomography Findings in Patients with Idiopathic Pulmonary Fibrosis

Yuji Yamamoto*, M.D., Keisuke Miki, M.D., Ph.D., Kazuyuki Tsujino, M.D., Ph.D., Tomoki Kuge, M.D., Fukuko Okabe, M.D., Takahiro Kawasaki, M.D., Takanori Matsuki, M.D., Hiroyuki Kagawa, M.D., Mari Miki, M.D., Ph.D., Hiroshi Kida, M.D., Ph.D.

Department of Respiratory Medicine, National Hospital Organization Osaka Toneyama Medical Center, Toyonaka, Japan

***Corresponding author:** Yuji Yamamoto, M.D., Department of Respiratory Medicine, National Hospital Organization Osaka Toneyama Medical Center, Address: 5-1-1 Toneyama, Toyonaka, Osaka, 560-8552, Japan. Phone: +81-6-6853-2001, Fax: +81-6-6853-3127, E-mail: cyyamamoto1110@gmail.com

Supplementary table 1. Definition of high-resolution computed tomography findings

HRCT finding	Definition
Airspace consolidation	Homogeneous increase in pulmonary parenchymal attenuation that obscured the underlying vessels
Honeycombing	Clustered cystic airspaces from several mm to 1 cm in size with well-defined and thick walls were seen in the subpleural regions
Architectural distortion	Abnormal displacement of bronchi, pulmonary vessels, interlobar fissures, or interlobular septa
Traction bronchiectasis	Irregular bronchial dilatation within or around areas with parenchymal abnormality

HRCT, high-resolution computed tomography.

Supplementary table 2. High-resolution computed tomography scores

Score	0	1	2	3	4
Architectural distortion	Absent	Present			
Traction bronchiectasis	Absent	Bronchial dilatation involving bronchi distal to the fifth generation	Bronchial dilatation involving bronchi distal to the fourth generation	Bronchial dilatation involving bronchi proximal to the third generation bronchi	
Interstitial fibrosis	Absent	Ground-glass attenuation without reticulation	Ground-glass and fine reticular opacity	Reticular opacity and microcysts < 3 mm	Coarse reticular opacity and large cysts > 3 mm

Supplementary table 3. Results of multivariate analyses assessing interactions between treatment for idiopathic pulmonary fibrosis and oscillometric parameters (n = 80)

Parameter	Pirfenidone		Inhaled N-acetylcysteine		Nintedanib		Oral corticosteroids	
	std β	p value	std β	p value	std β	p value	std β	p value
R5	–0.111	0.350	0.137	0.246	–0.073	0.535	–0.103	0.372
R20	–0.114	0.331	0.136	0.245	–0.101	0.385	–0.157	0.171
R5-R20	–0.075	0.531	0.104	0.384	0.005	0.968	0.036	0.760
X5	–0.040	0.742	–0.076	0.524	0.019	0.876	0.010	0.935
Fres	0.139	0.247	0.024	0.841	0.038	0.745	0.091	0.435
ALX	0.075	0.531	0.033	0.783	–0.035	0.771	–0.023	0.843

ALX, low-frequency reactance area; Fres, resonant frequency; R5 and R20, respiratory system resistance at 5 and 20Hz, respectively; std β, standardized partial regression coefficient; X5, respiratory system reactance at 5Hz.

Supplementary table 4. Results of multivariate analysis assessing interactions between forced expiration volume in 1s/forced vital capacity and oscillometric parameters (n = 80)

Parameter	std β	p value
R5	0.198	0.324
R20	indeterminate	indeterminate
R5-R20	–0.259	0.229
X5	–0.246	0.598
Fres	0.533	0.021
ALX	–0.470	0.369

ALX, low-frequency reactance area; Fres, resonant frequency; R5 and R20, respiratory system resistance at 5 and 20Hz, respectively; std β, standardized partial regression coefficient; X5, respiratory system reactance at 5Hz.