Respiratory Impedance is Associated with Ventilation and Diffusing Capacity in Patients with Idiopathic Pulmonary Fibrosis Combined with Emphysema

Yuji Yamamoto, Haruhiko Hirata, Takayuki Shiroyama, Tomoki Kuge, Kinnosuke Matsumoto, Midori Yoneda, Makoto Yamamoto, Yujiro Naito, Yasuhiro Suga, Kiyoharu Fukushima, Kotaro Miyake, Shohei Koyama, Kota Iwahori, Izumi Nagatomo, Yoshito Takeda, Atsushi Kumanogoh

1Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan; 2Department of Immunopathology, WPI, Immunology Frontier Research Center (iFReC), Osaka University, Suita, Osaka, Japan; 3Integrated Frontier Research for Medical Science Division, Institute for Open and Transdisciplinary Research Initiatives (OTRI), Osaka University, Suita, Osaka, Japan; 4Center for Infectious Diseases for Education and Research (CiDER), Osaka University, Suita, Osaka, Japan

Correspondence: Yuji Yamamoto, Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka, 565-0871, Japan, Tel +81 6-36879-3833, Fax +81 6-6879-3839, Email cyyamamoto1110@gmail.com

Purpose: Pulmonary fibrosis and emphysema result in relatively maintained ventilation and reduced diffusing capacity. This pulmonary functional impairment complicates the evaluation of pulmonary function in patients with combined pulmonary fibrosis and emphysema (CPFE). Therefore, a single and easy-to-use pulmonary function index to evaluate patients with CPFE warrants further studies. Respiratory impedance can easily be provided by oscillometry and might be a candidate index to evaluate pulmonary function in patients with CPFE. As a preliminary study to assess the utility of respiratory impedance, we investigated the associations of physiological indices, including respiratory impedance, in patients with idiopathic pulmonary fibrosis (IPF) with and without emphysema.

Patients and Methods: This retrospective study evaluated patients with IPF who did and did not satisfy the diagnostic criteria of CPFE. All patients underwent oscillometry, spirometry, and diffusing capacity for carbon monoxide (DLCO). Correlations of the obtained physiological indices were analyzed.

Results: In total, 47 patients were included (18 and 29 patients with CPFE and IPF, respectively). Respiratory reactance (Xrs) at 5 Hz (X5) in the inspiratory phase was associated with forced vital capacity (FVC) % predicted in patients with CPFE (rS = 0.576, P = 0.012) and IPF (rS = 0.539, P = 0.003). Inspiratory X5 positively correlated with DLCO % predicted only in patients CPFE (rS = 0.637, P = 0.004).

Conclusion: Emphysema might associate Xrs with ventilation and diffusing capacity in patients with IPF and emphysema. Given the multiple correlations of Xrs with FVC and DLCO, this study warrants further studies to verify the utility of oscillometry in a large-scale study for patients with CPFE.

Keywords: chronic obstructive pulmonary disease, forced oscillation technique, gas exchange, idiopathic pulmonary fibrosis, ventilation

Introduction

Combined pulmonary fibrosis and emphysema (CPFE) was first defined as an interstitial lung disease (ILD) that is attributed to idiopathic pulmonary fibrosis (IPF) and emphysema, and the definition now covers other idiopathic ILDs in combination with emphysema. Pulmonary fibrosis reduces the lung volume and leads to restrictive ventilatory defects in patients with ILD. The restrictive ventilatory defect due to pulmonary fibrosis, commonly evaluated by forced vital
capacity (FVC), is associated with the reduction in lung compliance: the change in lung volumes divided by the change in transpulmonary pressure.\textsuperscript{3–5} In contrast, emphysema increases lung compliance and ameliorates the restrictive ventilatory defect.\textsuperscript{6} Accordingly, pulmonary fibrosis and emphysema balance each other and result in a relatively normal FVC in patients with CPFE.

A balance between pulmonary fibrosis and emphysema is also observed during expiration in patients with CPFE. Emphysema induces airflow obstruction, which is evaluated by forced expiration volume in 1 s (FEV\textsubscript{1})/FVC; whilst, pulmonary fibrosis increases FEV\textsubscript{1}/FVC and protects patients with ILD against airflow obstruction.\textsuperscript{3,7} Consequently, FEV\textsubscript{1}/FVC in patients with CPFE is generally within the normal range.\textsuperscript{2}

Despite the relatively maintained ventilation, patients with CPFE sometimes present with severely impaired diffusing capacity for carbon monoxide (D\textsubscript{LCO}): the physiological index that reflects gas exchange in the lungs and is theoretically associated with alveolar volume (V\textsubscript{A}).\textsuperscript{8,9} Various changes in pulmonary function indices contribute to the difficult evaluation of pulmonary function and disease severity using a single physiological index; thus, a previous study showed a useful combination of multiple physiological indices for predicting mortality specifically in patients with CPFE.\textsuperscript{10}

However, performing multiple pulmonary function tests is sometimes time-consuming for the routine follow-up in clinical practice; therefore, exploring an easy-to-use, single pulmonary function test that reflects both ventilation and diffusing capacity is warranted in patients with CPFE.

Oscillometry provides respiratory impedance with broadband frequency by analyzing the mechanical waves superimposed on respiratory maneuvers.\textsuperscript{11} Since oscillometry is measured at rest with minimal respiratory effort, it is less time-consuming and technically easier than spirometry.\textsuperscript{12} Respiratory impedance represents the mechanical properties of the respiratory system and is comprised of respiratory resistance (Rrs) and respiratory reactance (Xrs).\textsuperscript{11} Xrs reflects the dynamic elastance (a reciprocal of lung compliance) and inertia of the respiratory system.\textsuperscript{13} In contrast to the counterbalance of pulmonary fibrosis and emphysema in ventilation, Xrs becomes more negative in patients with IPF and chronic obstructive pulmonary disease (COPD).\textsuperscript{14,15} Therefore, we hypothesized that Xrs is a candidate parameter to monitor the pulmonary functional impairment in patients with CPFE. Given the effortless maneuver of oscillometry, Xrs might be suitable for the routine follow-up of pulmonary function.

As a preliminary study for validating our hypothesis, we aimed to assess the associations of the physiological indices, including respiratory impedance, in patients with IPF who were and were not diagnosed with CPFE.

Materials and Methods
Study Design
This retrospective observational study was conducted at Osaka University Hospital (a 1086-bed National University Hospital in Osaka, Japan). As described later, patients with IPF who did and did not satisfy the diagnostic criteria of CPFE underwent pulmonary function tests, including oscillometry, spirometry, and diffusing capacity. Correlations of the physiological indices were analyzed.

This study followed the Ethical Guidelines of the Japan Ministries of Health and Labor for Medical and Health Research Involving Human Subjects and the Declaration of Helsinki. The Institutional Review Board of Osaka University Hospital approved the study protocol (approval number: 21,342). An opt-out system was applied to obtain patients’ informed consent for this retrospective study, which provided patients the opportunity to decline participation in the study.

Patients
All screened patients were adult patients (age ≥20 years old) who were diagnosed with IPF or CPFE with usual interstitial pneumonia (UIP) pattern at Osaka University Hospital between January 1st, 2015 and December 31st, 2017. To accurately evaluate the effect of pulmonary fibrosis and emphysema on pulmonary function, patients with coexisting tumors in the lungs, thorax, and airways, heart diseases, or cerebral diseases were excluded, as well as those who received thoracic surgery and satisfied the diagnostic criteria of asthma (ie, (1) respiratory symptoms, including wheeze, dyspnea, chest tightness, and cough; and (2) confirmed variable airflow obstruction: the increase in FEV\textsubscript{1} of
Only patients who underwent the pulmonary function tests and high-resolution computed tomography (HRCT) imaging were included.

Data Collection
Clinical, physiological, and radiological data were collected from individual case review. Baseline data were obtained at the time of initial diagnosis. Clinical characteristics included age, sex, height, weight, body mass index (BMI), smoking status, modified Medical Research Council (mMRC) dyspnea scale, and medications. Each patient underwent oscillometry, spirometry, and D\textsubscript{LCO} in this listed order on the same day. Short-acting $\beta_2$-agonists were not used for at least 12 h before tests in all patients. Long-acting antimuscarinic agents and long-acting $\beta_2$-agonists were continued before pulmonary function tests. All patients underwent these examinations described above without exacerbation of interstitial pneumonia for at least three months.

HRCT Imaging and Diagnosis
Chest HRCT scans were conducted with 1 mm section thickness. The HRCT images were reviewed independently by two pulmonologists and one radiologist. Patients were diagnosed with IPF in combination with HRCT imaging and surgical lung biopsy (SLB; if applicable) according to the international guideline. Among the patients with IPF, those who satisfied the criteria were diagnosed with CPFE. As described elsewhere, CPFE was identified based on the two HRCT findings: (1) emphysema and/or multiple bullae with upper zone predominance; and (2) ILD with significant pulmonary fibrosis.

Oscillometry
Oscillometry was performed at rest according to the recommendations of the European Respiratory Society (ERS) (Mostgraph-01; Chest M.I. Co., Ltd., Tokyo, Japan). Respiratory impedance included the mean values of respiratory phases and the within-breath changes (the differences between the inspiratory and expiratory mean values, $\Delta$). $Rrs$ represents the sum of airway resistance and viscous resistance of the lung and thoracic tissue. $Rrs$ is primarily associated with airway diameter; narrower and longer airways have higher resistance due to greater frictional pressure loss during air flow. As indicators of the frequency dependence of $Rrs$, $Rrs$ at 5 Hz ($R5$), $Rrs$ at 20 Hz ($R20$), and the difference between $R5$ and $R20$ ($R5–R20$) were adopted.

$Xrs$ represents pressure changes that are out of phase with flow, but in phase with volume changes. Elastance includes the compressibility of gas in the airways and alveoli and causes $Xrs$ to be negative. Inertia is an index of pressure losses mostly due to the acceleration of the gas column in the central airways and causes $Xrs$ to be positive. As indicators of $Xrs$, $Xrs$ at 5 Hz ($X5$), resonant frequency (Fres), and low-frequency reactance area at 5 Hz (AX) were calculated. Fres indicates the point at which $Xrs$ crosses zero and the elastance and inertia balance each other, and AX is defined as the integral of $X5$ to Fres.

Spirometry
All patients underwent spirometry using the Autospirometer S21 (Minato Medical Science Co., Ltd., Osaka, Japan) according to the recommendations of the American Thoracic Society (ATS) and ERS. Functional residual capacity and closing capacity were measured using multiple-breath and single-breath nitrogen washouts, respectively. Predicted FVC and FEV\textsubscript{1} and the lower limits of normal of a normally distributed set of values of FEV\textsubscript{1}/FVC for a population of non-smoking, normal individuals were calculated according to the formula for Japanese patients developed by the Japanese Respiratory Society. Predicted closing volume (CV)/vital capacity (VC) was calculated using the formulas developed by Buist et al.

Diffusing Capacity
$D_{LCO}$ and $D_{LCO}/V\textsubscript{A}$ were measured using the Autospirometer S21 (Minato Medical Science Co., Ltd., Osaka, Japan) and a single-breathing method according to the recommendations of the ERS and ATS standard criteria. $D_{LCO}$ values were
adjusted using hemoglobin levels when possible. Predicted $D_LCO$ and $D_LCO/V_A$ values were calculated according to the formula developed by Burrows et al.\textsuperscript{23}

**Statistical Analysis**

All statistical analyses were performed using R version 4.1.1. Mann–Whitney $U$-test and Fisher’s exact tests were used to compare patient characteristics and laboratory data between patients with IPF and CPFE. Spearman’s rank correlation coefficient ($r_S$) assessed the correlations between the different types of pulmonary functional data. For all analyses, a $P$-value $<0.05$ was considered statistically significant. All $P$ values were two-sided.

**Results**

**Baseline Characteristics**

This study included 47 Japanese patients with either CPFE ($n=18$) or IPF ($n=29$; \textbf{Figure 1}). The baseline characteristics are shown in Table 1. Among the patients, 13/47 (27.7\%) were diagnosed with UIP pattern in combination with HRCT and SLB findings. There was no significant difference in the patient ratio receiving SLB (22.2\% in CPFE and 31.0\% in IPF, respectively, $P=0.739$). The group of patients with CPFE showed a larger proportion of males (94.4\% in CPFE and 65.5\%, respectively, $P=0.033$), had a higher smoking rate ($P=0.037$), and higher smoking amount ($P<0.001$) than those with IPF. There were no significant differences in treatments administered to patients with CPFE and IPF (all $P>0.05$). No patient received inhaled corticosteroids.

The pathophysiological indices are summarized in Tables 2 and 3. Spirometry did not show differences in parameters reflecting restrictive ventilatory defects, such as VC and FVC (all $P>0.05$). However, patients with CPFE had smaller $FEV_1/FVC$ and greater CV and CV/VC (all $P<0.05$), indicative of more severe airway closure. Additionally, $D_LCO/V_A$ was smaller in patients with CPFE ($P=0.009$). Despite having no significance due to the small sample sizes, $X5$ was less negative in patients with CPFE than in those with IPF (Table 3).

**Correlations of Respiratory Impedance with Ventilation and Diffusing Capacity**

We assessed the correlations of $X5$ with other pathophysiological indices in patients with CPFE. Inspiratory $X5$ was positively associated with FVC % predicted in patients with CPFE and IPF (CPFE, $r_S=0.576$, $P=0.012$; and IPF,
Regarding the association between X5 and diffusing capacity, inspiratory X5 was positively associated with $D_{LCO}$ % predicted ($r_s=0.637, P=0.004$) and $D_{LCO}/V_A$ % predicted ($r_s=0.525, P=0.025$) in patients with CPFE but not in those with IPF (all $P>0.05$; Figure 3).
Correlations Between Ventilation and Diffusing Capacity
We investigated the difference in correlations between restrictive ventilatory defects and diffusing capacity among patients with CPFE and IPF (Figure 4). Both DLco % predicted and DLco/Va % predicted were positively associated with FVC % predicted in patients with CPFE (DLco % predicted, r_S=0.740, P<0.001; and DLco/Va % predicted, r_S=0.478, P=0.047). Neither DLco % predicted nor DLco/Va % predicted was associated with FVC % predicted in patients with IPF (all P>0.05).

Correlations of Airway Closure with Respiratory Impedance
Based on the differences in CV and CV/VC between patients with CPFE and IPF (Table 2), we assessed the correlations of airway closure with ventilation and X5. CV/VC was positively associated with FVC % predicted (r_S=0.394, P=0.034) and expiratory X5 (r_S=0.530, P=0.003) only in patients with IPF (Figure 5). CV and CV/VC were not associated with ΔX5 in patients with IPF (all P>0.05). Regarding patients with CPFE, expiratory X5 correlated with neither CV nor CV/VC (all P>0.05); however, ΔX5 was positively associated with CV (r_S=0.593, P=0.010; Supplementary Figure 1).

Table 3 Oscillometry in Patients with and without Emphysema (n = 47)

| Parameter | IPF (n = 29) | CPFE (n = 18) | P-value |
|-----------|--------------|--------------|---------|
| R5, cmH2O/L/s | | | |
| Expiratory | 3.08 (2.63–4.28) | 2.80 (2.38–3.26) | 0.128 |
| Inspiratory | 2.53 (2.06–3.12) | 2.40 (2.03–2.78) | 0.477 |
| Average | 2.80 (2.31–3.90) | 2.63 (2.20–3.18) | 0.299 |
| R20, cmH2O/L/s | | | |
| Expiratory | 2.43 (1.90–3.27) | 2.14 (1.86–2.44) | 0.168 |
| Inspiratory | 1.97 (1.52–2.62) | 1.84 (1.57–2.14) | 0.352 |
| Average | 2.19 (1.73–2.92) | 1.97 (1.73–2.37) | 0.246 |
| R5-R20, cmH2O/L/s | | | |
| Expiratory | 0.81 (0.53–1.02) | 0.76 (0.49–0.93) | 0.511 |
| Inspiratory | 0.50 (0.24–0.69) | 0.55 (0.31–0.71) | 0.827 |
| Average | 0.65 (0.40–0.90) | 0.65 (0.49–0.77) | 0.718 |
| X5, cmH2O/L/s | | | |
| Expiratory | −0.76 (−1.05–0.57) | −0.61 (−0.95–0.46) | 0.375 |
| Inspiratory | −0.92 (−1.40–0.68) | −0.72 (−0.96−0.55) | 0.050 |
| Average | −0.95 (−1.23–0.63) | −0.70 (−0.91–0.59) | 0.143 |
| Δ | −0.28 (−0.41–0.08) | −0.13 (−0.42–0.11) | 0.370 |
| Fres, Hz | | | |
| Expiratory | 10.53 (8.81–12.65) | 9.33 (8.11–12.90) | 0.657 |
| Inspiratory | 11.67 (9.44–12.67) | 10.08 (9.37–11.96) | 0.336 |
| Average | 10.95 (9.15–13.11) | 10.17 (9.10–12.03) | 0.519 |
| Δ | 1.18 (0.12–1.85) | 1.40 (−1.26–2.20) | 0.641 |
| AX, cmH2O/L/s × Hz | | | |
| Expiratory | 3.14 (2.01–5.46) | 2.43 (1.56–4.78) | 0.416 |
| Inspiratory | 4.61 (2.54–6.83) | 3.00 (2.10–4.44) | 0.078 |
| Average | 4.23 (2.41–6.43) | 3.04 (2.20–4.52) | 0.251 |
| Δ | 1.12 (0.22–2.59) | 0.57 (−1.01–2.61) | 0.491 |

Note: Data are median (interquartile range).
Abbreviations: AX, low-frequency reactance area; CPFE, combined pulmonary fibrosis and emphysema; Δ, a within-breath change in each parameter; Fres, resonant frequency; IPF, idiopathic pulmonary fibrosis; R5 and R20, respiratory resistance at 5 and 20 Hz, respectively; X5, respiratory reactance at 5 Hz.
**Discussion**

This preliminary study first assessed the association of Xrs with ventilation and diffusing capacity in patients with CPFE and highlighted two major findings. First, X5 was positively associated with \( D_{LCO} \) % predicted and \( D_{LCO}/V_A \) % predicted only in patients with CPFE; therefore, emphysema might have independently associated X5 with diffusing capacity. Second, the associations of airway closure with ventilation and diffusing capacity were observed only in patients with IPF; therefore, emphysema might have hindered the correlations of these pulmonary function indices in patients with CPFE. Our findings demonstrated that Xrs might show the utility for predicting diffusing capacity in patients with CPFE.
Pulmonary functional impairment due to pulmonary fibrosis has previously been described in patients with IPF.\textsuperscript{3,14,24,25} Pulmonary fibrosis increases elastic recoil and makes Xrs more negative.\textsuperscript{3,14} Since elastance is a reciprocal of compliance, the fibrotic lungs do not retain their compliance.\textsuperscript{3} The reduction in lung compliance typically appears before the onset of restrictive ventilatory defects; thus, the lungs with an early stage of IPF show normal FVC but abnormal Xrs.\textsuperscript{25} Progressive fibrosis eventually decreases lung compliance and volume and strongly associates inspiratory Xrs and FVC % predicted.\textsuperscript{14,24}

Emphysema in combination with pulmonary fibrosis complicates the respiratory physiology in patients with CPFE. Patients with IPF sometimes have a smoking history, and therefore 6–67% of them present with emphysema.\textsuperscript{26}

Figure 4 Correlations between FVC and diffusing capacity in patients with CPFE and IPF (n=18 and n=29, respectively). (A) A scatter plot between FVC % predicted and $D_{LCO}$ % predicted. (B) A scatter plot between FVC % predicted and $D_{LCO}/V_{A}$ % predicted. $D_{LCO}$ % predicted and $D_{LCO}/V_{A}$ % predicted were positively associated with FVC % predicted only in patients with CPFE.

**Abbreviations:** CPFE, combined pulmonary fibrosis and emphysema; $D_{LCO}$, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; $r_S$, Spearman’s rank correlation coefficient; $V_{A}$, alveolar volume.

Figure 5 Correlations between CV/VC, FVC, and expiratory X$_5$ in patients with CPFE and IPF (n=18 and n=29, respectively). (A) A scatter plot between CV/VC and FVC % predicted. (B) A scatter plot between CV/VC and expiratory X$_5$. CV/VC correlated with expiratory X$_5$ and FVC % predicted only in patients with IPF.

**Abbreviations:** CPFE, combined pulmonary fibrosis and emphysema; CV/VC, closing volume/vital capacity; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; $r_S$, Spearman’s rank correlation coefficient; X$_5$, respiratory reactance at 5 Hz.

https://doi.org/10.2147/COPD.S368162

DovePress
Emphysema decreases lung elastic recoil and subsequently causes lung hyperinflation. Reduction in lung elastic recoil theoretically makes Xrs less negative in healthy subjects, but emphysema eventually makes Xrs more negative due to airflow obstruction in patients with COPD. These above-mentioned interactions of pulmonary fibrosis and emphysema have obscured the utility of respiratory impedance for monitoring ventilation in patients with CPFE. New information obtained from this study suggests that inspiratory X5 might be useful for predicting restrictive ventilatory defects in patients with CPFE (Figure 2). Given that airway closure in patients with CPFE was milder than in healthy subjects (Table 2), the effect of decreased airflow on X5 might have been limited; therefore, the associations of X5 with FVC might have been based on the changes in lung elastic recoil due to pulmonary fibrosis and emphysema.

Pulmonary fibrosis causes abnormalities in the alveolar-capillary membrane and lung vasculature. The fibrotic lungs are accompanied by isolated thickening of the smooth muscle layer and proliferative intima lesions in pulmonary arteries and by complete occlusion of the vessel due to scar tissue and plexiform lesions. Consequently, both oxygen diffusion limitation and alveolar ventilation-perfusion mismatch reduce DLCO/V_A in patients with IPF. Based on the mechanism, patients with mild IPF sometimes have a gas exchange deficiency under the maintained ventilation.

Emphysema induces the similar abnormalities in the alveolar-capillary membrane and lung vasculature. In patients with COPD, diminution and narrowing of the pulmonary vessels worsen the severity of pulmonary hypertension. Furthermore, cigarettes induce vascular injury and pulmonary vascular remodeling, thereby thickening the alveolar-capillary membrane. These smoking-related abnormalities impair gas exchange in patients with CPFE; emphysema presented in the fibrotic lungs independently reduces DLCO alongside preserved FVC. Accordingly, patients with CPFE have more marked reductions in DLCO than those with IPF.

These preceding studies indicate that ventilation and gas exchange do not necessarily present with the same fluctuations and contribute to the difficult evaluation of pulmonary function using a single physiological index in patients with CPFE; therefore, a composite physiologic index, the combination of % predicted FVC, FEV_1, and DLCO, is useful to monitor patients with CPFE. Given the complicated procedure of performing multiple pulmonary function tests for routine clinical practice, a single physiologic index reflecting both ventilation and diffusing capacity can be useful for monitoring the respiratory conditions in patients with CPFE.

This study demonstrated that X5 was associated with diffusing capacity and FVC % predicted only in patients with CPFE (Figures 2 and 3); however, diffusing capacity was not associated with X5 or FVC % predicted in patients with IPF (Figures 3 and 4). The results suggest that emphysema-related abnormalities independently might have affected the association of gas exchange with Xrs and ventilation in CPFE. Since the lung volume is associated with DLCO that is calculated by multiplying VA and DLCO/V_A, the increased lung volume due to emphysema might have contributed to the correlations between X5 and diffusing capacity. This study highlights the utility of Xrs as a physiological index to predict both ventilation and gas exchange specifically in patients with CPFE. Given the effortless measurement of oscillometry, Xrs might be a complementary physiological index in the daily clinical practice of CPFE.

The normal FEV_1 seen in some patients with CPFE can also be explained by the counterbalance between increased traction bronchiectasis due to pulmonary fibrosis and expiratory airway closure due to emphysema. Our previous study showed that traction bronchiectasis evaluated on HRCT was associated with Xrs rather than Rrs, which implies that peribronchial fibrosis progresses traction bronchiectasis and increases airway elastance. Contrarily, emphysema makes Xrs more negative due to airflow obstruction but induces lung hyperinflation by reducing elastic recoil of the lungs. These countereffects of pulmonary fibrosis and emphysema were hypothesized to inhibit the association between Xrs and CV/VC. In fact, our findings first demonstrated that airway closure was not associated with expiratory X5 specifically in patients with CPFE (Figure 5). However, our study first showed that ΔX5 was associated with CV in patients with CPFE. Given that ΔXrs is associated with expiratory flow limitation in patients with COPD, the change in ΔX5 might have reflected the emphysema-related airway closure in patients with CPFE. Although the baseline Xrs might not be suitable for evaluating airway abnormalities, ΔXrs might detect emphysema-related airway abnormalities in patients with CPFE.

This study had some limitations. First, this was a single-center retrospective study and might have been affected by selection bias, especially on the diagnosis of CPFE. This bias is primarily based on the difficulty of definite differential diagnosis of CPFE from IPF. Second, this study did not assess the association of radiographic findings with respiratory impedance, ventilation, and gas exchange. Further research should assess whether the distribution and amount of pulmonary...
fibrosis and emphysema affect pulmonary function tests. Third, this study did not evaluate the lung vasculature and perfusion. Further investigations should describe the effect of ventilation-perfusion mismatch on gas exchange in patients with CPFE. Fourth, because ILDs other than IPF sometimes have different pulmonary fibrosis progression and complication profiles, we focused on patients with IPF combined with emphysema. Further comprehensive research targeting entire patients with CPFE is needed. Finally, this is a preliminary study assessing the correlations of respiratory impedance with other physiological indices in CPFE; thus, we did not calculate the necessary sample sizes. Consequently, we did not correct multiple correlations using multivariate analysis due to the lack of statistical power.

Conclusion
This study evaluated respiratory impedance, ventilation, and gas exchange in patients with CPFE. Emphysema might associate Xrs with FVC and diffusing capacity and enable Xrs to provide complementary information about ventilation and gas exchange in patients with CPFE. Emphysema can inhibit the association between airway closure and Xrs in patients with CPFE; hence, the baseline Xrs might not appropriately monitor airway abnormalities. However, ΔXrs might reflect emphysema-related airway closure in patients with CPFE. Further large-scale studies are warranted to assess the utility of respiratory impedance in the clinical practice of CPFE.

Data Sharing Statement
All data generated or analyzed during this study are included in this published article.

Funding
This study was supported in part by the Center of Innovation program (COISTREAM) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (to A. Kumanogoh); the Japan Society for the Promotion of Science (JSPS) KAKENHI (JP18H05282 to A. Kumanogoh); the Japan Agency for Medical Research and Development (AMED) (J210705582, J200705023, J200705710, J200705049, JP18cm016335 and JP18cm059042 to A. Kumanogoh); a grant from the Kansai Economic Federation (KANKEIREN); Grants from the Mitsubishi Foundation (to A. Kumanogoh); and JST SPRING (JPMJSP2138 to Y. Yamamoto). The research was designed, conducted, analyzed, and interpreted by the authors entirely independently of the funding sources.

Disclosure
The authors report no conflicts of interest in this work.

References
1. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005;26(4):586–593. doi:10.1183/09031936.05.0021005
2. Jankowich MD, Rounds SIS. Combined pulmonary fibrosis and emphysema syndrome. Chest. 2012;141(1):222–231. doi:10.1378/chest.11-1062
3. 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(147):170062. doi:10.1183/16000617.0062-2017
4. Orenes JB, Kazerooni EA, Martinez FJ, et al. The sensitivity of high-resolution CT in detecting idiopathic pulmonary fibrosis proved by open lung biopsy. A prospective study. Chest. 1995;108(1):109–115. doi:10.1378/chest.108.1.109
5. du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med. 2011;184(12):1382–1389. doi:10.1164/rccm.201105-0840OC
6. Amariei DE, Dodia N, Deepak J, et al. Combined pulmonary fibrosis and emphysema: pulmonary function testing and a pathophysiology perspective. Medicina. 2019;55(9):580. doi:10.3390/medicina55090580
7. Pastre J, Plantier L, Planes C, et al. Different KCO and VA combinations exist for the same DLCO value in patients with diffuse parenchymal lung diseases. BMC Pulm Med. 2015;15(1):100. doi:10.1186/s12890-015-0084-1
8. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest. 2013;144(1):234–240. doi:10.1378/chest.12-2403
9. Kaminsky DA, Whitman T, Callas PW. DLCO versus DLCO/VA as predictors of pulmonary gas exchange. Respir Med. 2007;101(5):989–994. doi:10.1016/j.rmed.2006.09.003
10. Schmidt SL, Namibiar AM, Tayob N, et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. Eur Respir J. 2011;38(1):176–183. doi:10.1183/09031936.0014010
11. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2005;22(6):1026–1041. doi:10.1183/09031936.00080403
12. Horsley A, Siddiqui S. Putting lung function and physiology into perspective: cystic fibrosis in adults. *Respirology*. 2015;20(1):33–45. doi:10.1111/resp.12382

13. King GG, Bates J, Berger KI, et al. Technical standards for respiratory oscillometry. *Eur Respir J*. 2020;55(2):1900753. doi:10.1183/13993003.00733-2019

14. Yamamoto Y, Miki K, Tsuji K, et al. Oscillometry and computed tomography findings in patients with idiopathic pulmonary fibrosis. *ERJ Open Res*. 2020;6(4):00391–0020. doi:10.1183/23123454.00391-2020

15. DellaCà RL, Santus P, Aliverti A, et al. Detection of expiratory flow limitation in COPD using the forced oscillation technique. *Eur Respir J*. 2004;23(2):232–240. doi:10.1183/09031936.04.00046804

16. Global Initiative for Asthma. Global strategy for asthma management and prevention; 2021. Available from: https://ginasthma.org/. Accessed May 25, 2021.

17. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44–e68. doi:10.1164/rrc.201807-1255ST

18. Shirai T, Kurosawa H. Clinical application of the forced oscillation technique. *Intern Med*. 2016;55(6):559–566. doi:10.2169/internalmedicine.55.55876

19. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338. doi:10.1183/09031936.05.00034805

20. Kubota M, Kobayashi H, Quanjer PH, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. *Respir Investig*. 2014;52(4):242–250. doi:10.1016/j.resinv.2014.03.003

21. Buist AS, Ross BB. Predicted values for closing volumes using a modified single breath nitrogen test | American review of respiratory disease. *Am Rev Respir Dis*. 1973;107:574–572. doi:10.1164/arrd.1973.107.5.744

22. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. 2017;49(1):1600016. doi:10.1183/13993003.00016-2016

23. Burrows B, Kaslik JE, Niden AH, Barclay WR. Clinical usefulness of the single-breath pulmonary diffusing capacity test. *Am Rev Respir Dis*. 1961;84(6):789–806. doi:10.1164/arrd.1961.84.6.789

24. 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. doi:10.1016/j.resp.2020.103386

25. Zielonka TM, Demkow U, Radzikowska E, et al. Angiogenic activity of sera from interstitial lung disease patients in relation to pulmonary function. *Eur J Med Res*. 2010;15(Suppl 2):229–234. doi:10.1186/2047-783x-15-2-229

26. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J*. 2014;46(4):1113–1130. doi:10.1183/13993003.02316-2014

27. Gagnon P, Guenette JA, Langer D, et al. Pathogenesis of hyperinflation in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2014;9:187–201. doi:10.2147/COPD.S38934

28. Akita T, Shirai T, Mori K, et al. Association of the forced oscillation technique with negative expiratory pressure in COPD. *Respir Physiol Neurobiol*. 2016;220:62–68. doi:10.1016/j.resp.2015.09.002

29. Farkas L, Gauldie J, Voelkel NF, Kolb M. Pulmonary hypertension and idiopathic pulmonary fibrosis: a tale of angiogenesis, apoptosis, and growth factors. *Am J Respir Cell Mol Biol*. 2011;45(1):1–15. doi:10.1165/rcmb.2010-0363TR

30. Agustí AGN, Roca J, Gea J, Wagner PD, Xaubet A, Rodriguez-Roisin R. Mechanisms of gas-exchange impairment in idiopathic pulmonary fibrosis. *Eur Respir Physiol Neurobiol*. 1991;220:62–68. doi:10.1016/j.resp.2014.02.035

31. Cortes-Telles A, Forkert L, O'Donnell DE, Morán-Mendoza O. Idiopathic pulmonary fibrosis: new insights to functional characteristics at diagnosis. *Can Respir J*. 2014;21(3):e55–e60. doi:10.1155/2014/825606

32. Sakao S, Voelkel NF, Tatsumi K. The vascular bed in COPD: pulmonary hypertension and pulmonary vascular alterations. *Eur Respir Rev*. 2014;23(133):350–355. doi:10.1183/09059180.0007913

33. Matsuoka S, Washko GR, Yamashiro T, et al. Pulmonary hypertension and computed tomography measurement of small pulmonary vessels in severe emphysema. *Am J Respir Crit Care Med*. 2010;181(3):218–225. doi:10.1164/rrc.200908-1189OC

34. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Functional and prognostic effects when emphysema complicates idiopathic pulmonary fibrosis. *Eur Respir J*. 2015;50(1):1700379. doi:10.1183/13993003.00379-2017

35. Balasubramanian A, MacIntyre NR, Henderson RJ, et al. Diffusing capacity of carbon monoxide in assessment of COPD. *Chest*. 2019;156(6):1111–1119. doi:10.1016/j.chest.2019.06.035

36. Wells AU, King AD, Rubens MB, Cramer D, du Bois RM, Hansell DM. Lone cryptogenic fibrosing alveolitis: a functional-morphologic correlation based on extent of disease on thin-section computed tomography. *Am J Respir Crit Care Med*. 1997;155(4):1367–1375. doi:10.1164/ajcc.155.4.9105081

37. Sham H, Krumer FJ, Versprille A. Effect of lung volume and positional changes on pulmonary diffusing capacity and its components. *J Appl Physiol*. 1991;71(4):1477–1488. doi:10.1152/jappl.1991.71.4.1477

38. Dellacà RL, Duffy N, Pompilio PP, et al. Expiratory flow limitation detected by forced oscillation and negative expiratory pressure. *Eur Respir J*. 2007;29(2):363–374. doi:10.1183/09031936.00038006

39. Suh ES, Pompilio P, Mandal S, et al. Autotitrating external positive end-expiratory airway pressure to abolish expiratory flow limitation during tidal breathing in patients with severe COPD: a physiological study. *Eur Respir J*. 2020;56(3):1902234. doi:10.1183/13993003.02234-2019
