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ORIGINAL RESEARCH

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

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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 (D_{LCO}). 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 (r_S=0.576, P=0.012) and IPF (r_S=0.539, P=0.003). Inspiratory X5 positively correlated with D_{LCO} % predicted only in patients CPFE (r_S=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 D_{LCO}, 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,[1] and the definition now covers other idiopathic ILDs in combination with emphysema.[2] 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

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capacity (FVC), is associated with the reduction in lung compliance: the change in lung volumes divided by the change in transpulmonary pressure.[3–5] In contrast, emphysema increases lung compliance and ameliorates the restrictive ventilatory defect.[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_1)/FVC; whilst, pulmonary fibrosis increases FEV_1/FVC and protects patients with ILD against airflow obstruction.[3,7] Consequently, FEV_1/FVC in patients with CPFE is generally within the normal range.[2]

Despite the relatively maintained ventilation, patients with CPFE sometimes present with severely impaired diffusing capacity for carbon monoxide (D_{LCO}): the physiological index that reflects gas exchange in the lungs and is theoretically associated with alveolar volume (V_A).[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.[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.[11] Since oscillometry is measured at rest with minimal respiratory effort, it is less time-consuming and technically easier than spirometry.[12] Respiratory impedance represents the mechanical properties of the respiratory system and is comprised of respiratory resistance (Rrs) and respiratory reactance (Xrs).[11] Xrs reflects the dynamic elastance (a reciprocal of lung compliance) and inertia of the respiratory system.[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).[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_1 of

>12% and >200 mL after the prescription of a bronchodilator).[16] 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_{LCO} in this listed order on the same day. Short-acting β_2-agonists were not used for at least 12 h before tests in all patients. Long-acting antimuscarinic agents and long-acting β_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.[17] 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.[2]

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).[13] Respiratory impedance included the mean values of respiratory phases and the within-breath changes (the differences between the inspiratory and expiratory mean values, Δ). Rrs represents the sum of airway resistance and viscous resistance of the lung and thoracic tissue.[11] Rrs is primarily associated with airway diameter; narrower and longer airways have higher resistance due to greater frictional pressure loss during air flow.[13] 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.[13] Elastance includes the compressibility of gas in the airways and alveoli and causes Xrs to be negative.[13] 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.[13] 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.[18]

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.[19] Functional residual capacity and closing capacity were measured using multiple-breath and single-breath nitrogen washouts, respectively. Predicted FVC and FEV_1 and the lower limits of normal of a normally distributed set of values of FEV_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.[20] Predicted closing volume (CV)/vital capacity (VC) was calculated using the formulas developed by Buist et al.[21]

Diffusing Capacity

D_{LCO} and D_{LCO}/V_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.[22] 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.[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; 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,

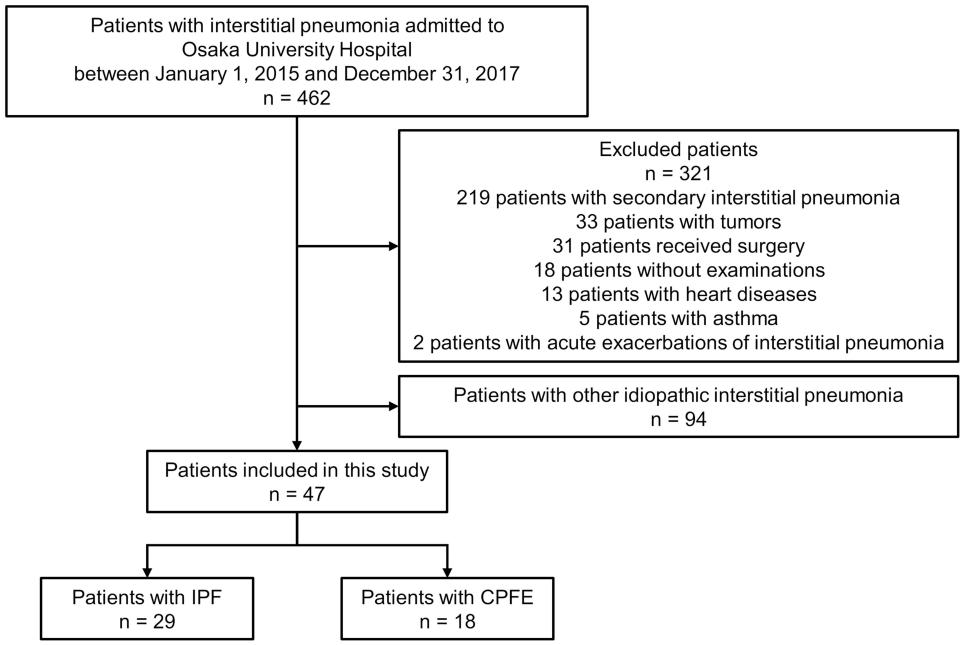

Figure 1 Inclusion flowchart.
Abbreviations: CPFE, combined pulmonary fibrosis with emphysema; IPF, idiopathic pulmonary fibrosis.

Table 1 Baseline Characteristics (n = 47)

Parameter	IPF (n = 29)	CPFE (n = 18)	*P*-value
Age, y	72 (66–76)	75 (70–79)	0.224
Sex, male/female, n	19/10	17/1	0.033
BMI, kg m^{-2}	22.0 (20.5–23.4)	23.2 (21.9–25.5)	0.057
Smokers, n (%)	21 (75.0)	16 (100.0)	0.037
Smoking, pack-years	28 (1–39)	58 (45–81)	<0.001
mMRC dyspnea scale, 0/1/2/3/4, n	11/10/5/1/2	6/7/2/1/2	0.943
LDH, U/L	232 (204–254)	219 (183–243)	0.216
KL-6, U/mL	727 (517–1005)	724 (480–1503)	0.905
Diagnosis, n (%)			
HRCT, n (%)	20 (69.0)	14 (77.8)	0.739
HRCT and SLB, n (%)	9 (31.0)	4 (22.2)	
Treatment			
Nintedanib, n (%)	1 (3.4)	1 (5.6)	>0.999
Pirfenidone, n (%)	6 (20.7)	1 (5.6)	0.225
Prednisolone, n (%)	3 (10.3)	1 (5.6)	>0.999
LAMA, n (%)	1 (3.4)	2 (11.1)	0.549
LABA, n (%)	2 (6.9)	0 (0.0)	0.517

Notes: Data are median (interquartile range) and n (%), unless otherwise stated.
Abbreviations: BMI, body mass index; CPFE, combined pulmonary fibrosis and emphysema; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lugen-6; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; LDH, lactate dehydrogenase; mMRC, modified Medical Research Council; SLB, surgical lung biopsy.

Table 2 Pulmonary Function Tests in Patients with and without Emphysema (n = 47)

Parameter	IPF (n = 29)	CPFE (n = 18)	*P*-value
VC, L	2.27 (1.81–3.02)	2.75 (2.43–3.21)	0.131
FVC, L	2.21 (1.63–2.88)	2.68 (2.33–3.08)	0.078
FVC % predicted, %	72.8 (63.2–83.4)	81.7 (63.7–94.4)	0.244
FEV_1, L	2.07 (1.43–2.51)	2.17 (1.77–2.42)	0.444
FEV_1% predicted, %	82.6 (67.5–92.4)	83.0 (65.8–89.9)	0.835
FEV_1/FVC, %	87.8 (83.9–92.2)	81.9 (73.1–88.6)	0.019
FRC, L	2.21 (1.63–2.81)	2.53 (2.09–3.22)	0.175
RV, L	1.45 (1.11–1.85)	1.65 (1.02–2.06)	0.298
CC, L	1.24 (1.13–1.79)	1.64 (1.40–2.00)	0.126
CV, L	0.31 (0.21–0.56)	0.56 (0.34–1.13)	0.017
CV/VC, %	17.4 (11.4–21.1)	21.2 (18.5–29.6)	0.009
CV/VC % predicted, %	70.6 (43.2–87.8)	80.4 (66.1–111.8)	0.086
D_{LCO},mL/min/mmHg	9.30 (7.93–19.74)	8.06 (6.52–10.37)	0.358
D_{LCO}% predicted, %	60.9 (55.7–78.4)	47.1 (41.0–72.2)	0.074
D_{LCO}/V_A, mL/min/mmHg/L	3.36 (2.51–3.73)	2.29 (2.12–2.64)	0.009
D_{LCO}/V_A % predicted, %	60.9 (55.7–78.4)	47.1 (41.0–72.2)	0.074

Note: Data are median (interquartile range).
Abbreviations: CC, closing capacity; CPFE, combined pulmonary fibrosis and emphysema; CV, closing volume; D_{LCO}, diffusing capacity for carbon monoxide; FEV_1, forced expiration volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; RV, residual volume; V_A, alveolar volume; VC, vital capacity.

r_S=0.539, *P*=0.003; Figure 2). 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).

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

Parameter	IPF (n = 29)	CPFE (n = 18)	*P*-value
R5, cmH_2O/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, cmH_2O/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, cmH_2O/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, cmH_2O/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, cmH_2O/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.

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 D_{LCO} % predicted and D_{LCO}/V_A % predicted were positively associated with FVC % predicted in patients with CPFE (D_{LCO} % predicted, r_S=0.740, P<0.001; and D_{LCO}/V_A % predicted, r_S=0.478, P=0.047). Neither D_{LCO} % predicted nor D_{LCO}/V_A % 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).

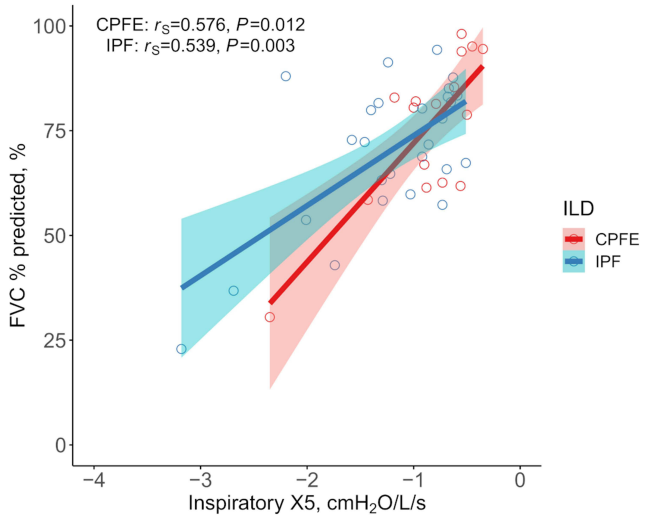

Figure 2 Correlations between FVC and inspiratory X5 in patients with CPFE and IPF (n=18 and n=29, respectively). FVC % predicted was positively associated with inspiratory X5 in both the subgroups.
Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; r_S, Spearman's rank correlation coefficient; X5, respiratory reactance at 5 Hz.

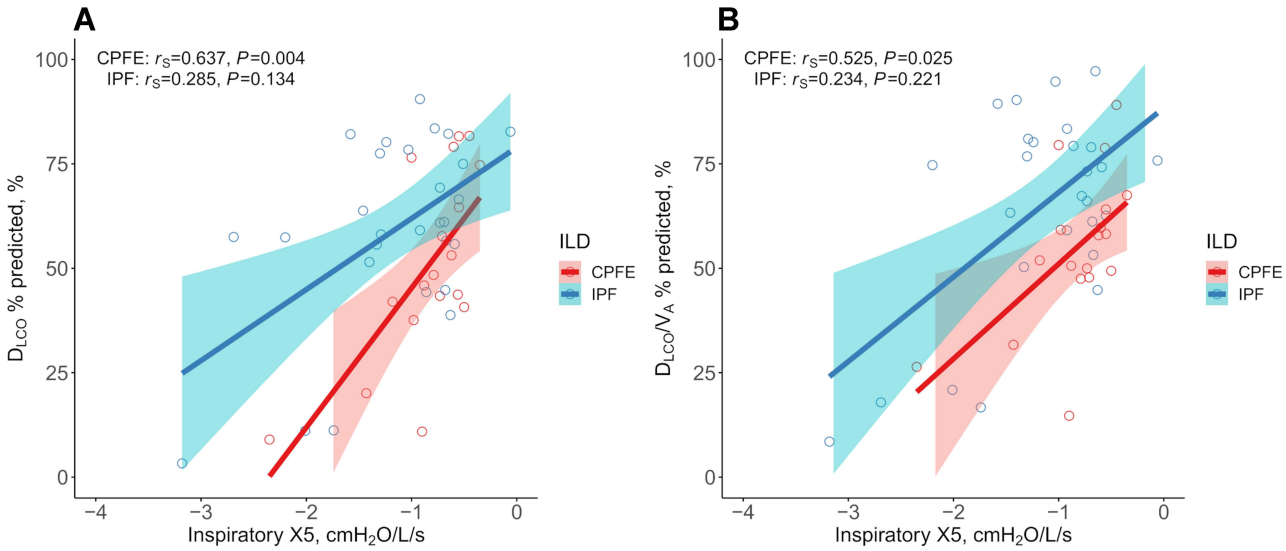

Figure 3 Correlations between inspiratory X5 and diffusing capacity in patients with CPFE and IPF (n=18 and n=29, respectively). (**A**) A scatter plot between inspiratory X5 and D_{LCO} % predicted. (**B**) A scatter plot between inspiratory X5 and D_{LCO}/V_A percent predicted. Inspiratory X5 was positively associated with both D_{LCO} % predicted and D_{LCO}/V_A % predicted only in patients with CPFE.
Abbreviations: CPFE, combined pulmonary fibrosis and emphysema; D_{LCO}, diffusing capacity for carbon monoxide; IPF, idiopathic pulmonary fibrosis; r_S, Spearman's rank correlation coefficient; V_A, alveolar volume; 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.

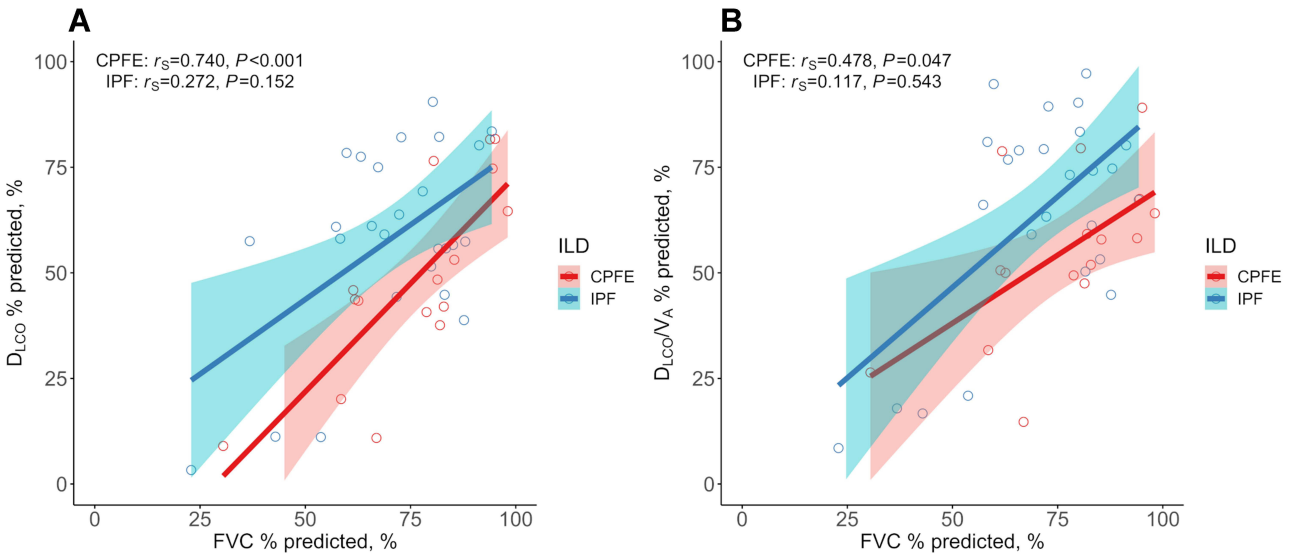

Figure 4 Correlations between FVC and diffusing capacity in patients with CPFE and IPF (n=18 and n=29, respectively). (**A**) A scatter plot between FVC % predicted and D_{LCO} % predicted. (**B**) A scatter plot between FVC % predicted and D_{LCO}/V_A % predicted. D_{LCO} % predicted and D_{LCO}/V_A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

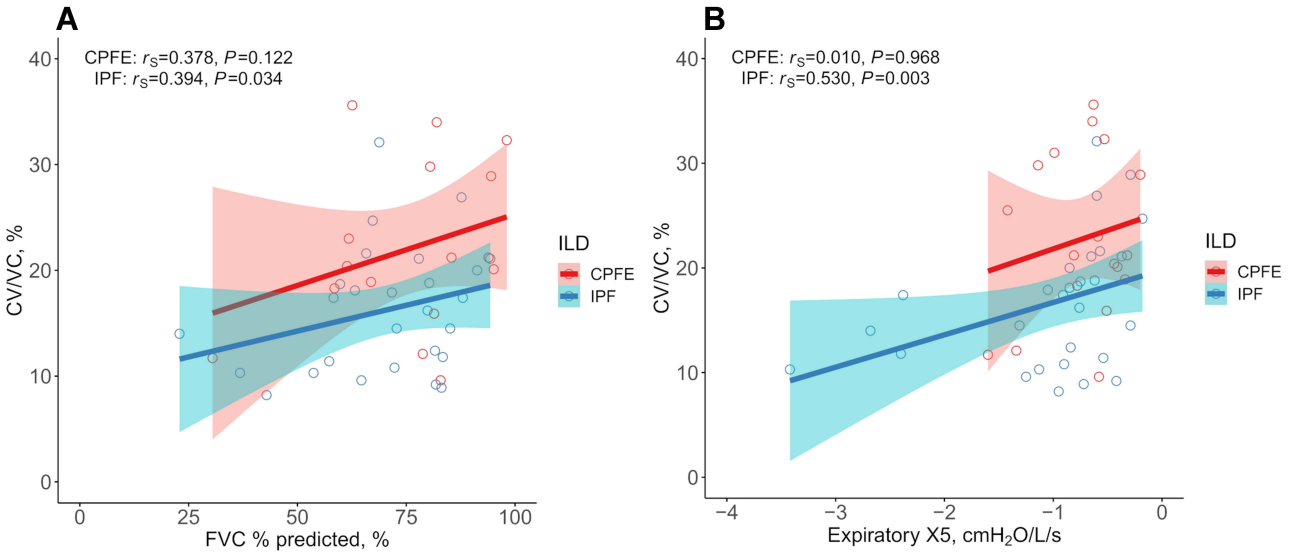

Figure 5 Correlations between CV/VC, FVC, and expiratory X5 in patients with CPFE and IPF (n=18 and n=29, respectively). (**A**) A scatter plot between CV/VC and FVC % predicted. (**B**) A scatter plot between CV/VC and expiratory X5. CV/VC correlated with expiratory X5 and FVC % predicted only in patients 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; X5, respiratory reactance at 5 Hz.

Pulmonary functional impairment due to pulmonary fibrosis has previously been described in patients with IPF.[3,14,24,25] Pulmonary fibrosis increases elastic recoil and makes Xrs more negative.[3,14] Since elastance is a reciprocal of compliance, the fibrotic lungs do not retain their compliance.[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.[25] Progressive fibrosis eventually decreases lung compliance and volume and strongly associates inspiratory Xrs and FVC % predicted.[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.[26]

Emphysema decreases lung elastic recoil and subsequently causes lung hyperinflation.[27] Reduction in lung elastic recoil theoretically makes Xrs less negative in healthy subjects,[13] but emphysema eventually makes Xrs more negative due to airflow obstruction in patients with COPD.[15,27,28] 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.[3] 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.[29] Consequently, both oxygen diffusion limitation and alveolar ventilation-perfusion mismatch reduce D_{LCO}/V_A in patients with IPF.[30] Based on the mechanism, patients with mild IPF sometimes have a gas exchange deficiency under the maintained ventilation.[31]

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.[32,33] Furthermore, cigarettes induce vascular injury and pulmonary vascular remodeling, thereby thickening the alveolar-capillary membrane.[32] These smoking-related abnormalities impair gas exchange in patients with CPFE; emphysema presented in the fibrotic lungs independently reduces D_{LCO} alongside preserved FVC.[34] Accordingly, patients with CPFE have more marked reductions in D_{LCO} than those with IPF.[1,2,8,35]

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 D_{LCO}, is useful to monitor patients with CPFE.[10] Given the complicated procedure of performing multiple pulmonary function tests for routine clinical practice, a single physiological 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 D_{LCO} that is calculated by multiplying V_A and D_{LCO}/V_A,[36,37] 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,[14] 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.[15,27,28,38] 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,[15,39] 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 [1]. 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.

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Disclosure

The authors report no conflicts of interest in this work.

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