Annual changes in pulmonary function in combined pulmonary fibrosis and emphysema: over a 5-year follow-up

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Abstract

Background: Combined pulmonary fibrosis and emphysema (CPFE) is a unique disorder that has been previously described, and the distinct features of CPFE in comparison with chronic obstructive pulmonary disease (COPD) have been reported. However, the yearly dynamics of pulmonary function parameters in CPFE patients compared with those in COPD patients have not yet been reported.

Methods: We retrospectively enrolled patients with CPFE and COPD who had undergone pulmonary function tests more than five times during a follow-up period of more than five years. The baseline clinical characteristics and the annual changes in pulmonary function during the follow-up period in 16 stable CPFE patients were compared with those in 19 stable COPD patients. Annual changes in pulmonary function were estimated from linear regressions, with assumptions for time-dependency and linearity. We analyzed the time-dependent fluctuations in pulmonary function for the two disorders.

Results: Annual decreases in VC and FVC in the CPFE group were significantly higher than those in the COPD group. Annual decrease in FEV_1/FVC in the COPD group was significantly higher than in the CPFE group. During the

follow-up period, FEV_1/FVC in the CPFE group appeared to improve because of annual decrease in FVC. Annual decreases in DLco and DLco/VA in the CPFE group were significantly higher than those in the COPD group.

Conclusion: This is the first report showing the yearly dynamics of pulmonary function parameters in CPFE patients compared with those in COPD patients during a follow-up period of more than five years. This study revealed that the physiologic consequences of CPFE including the rate of progression of pulmonary function impairment were different from those of COPD.

Key words: CPFE, COPD, pulmonary function, annual changes

Running title: Annual changes in pulmonary function in CPFE

Introduction

There is increasing clinical recognition of the coexistence of emphysema and pulmonary fibrosis in individual patients, resulting in a clinical syndrome known as combined pulmonary fibrosis and emphysema (CPFE). CPFE is a unique disorder that has been described in several case series [1-5], and the distinct features of CPFE in comparison with chronic obstructive pulmonary disease (COPD) [3] and idiopathic pulmonary fibrosis (IPF) [5-7] have been reported. CPFE was characterized by subnormal spirometry (mild airflow limitation and mild lung hyperinflation), severe impairment of gas exchange and desaturation during exercise. The relatively normal lung volumes in CPFE are usually attributed to the counterbalancing effects of the restrictive defect of pulmonary fibrosis and the propensity for hyperinflation seen in emphysema.[8] The decrease in diffusing capacity of lung for carbon monoxide (DLco) was more advanced in CPFE patients than in COPD or IPF-alone patients. This phenomenon was likely due to the additive effects of emphysema and fibrosis in that both disorders reduce diffusing capacity. Therefore, the physiologic consequences of CPFE were different from those of COPD. However, the yearly dynamics of pulmonary function parameters in CPFE patients compared with those in COPD patients

have not yet been reported. Akagi et al. have investigated the yearly dynamics of pulmonary function parameters in CPFE patients compared with those in IPF-alone patients, and reported that the annual decrease in diffusion capacity was significantly lower in CPFE patients than in IPF-alone patients.[6] We retrospectively enrolled CPFE and COPD patients who had undergone pulmonary function tests more than five times during a follow-up period of more than five years, and analyzed the time-dependent fluctuations in pulmonary function in CPFE patients.

Methods

Subjects

This study details the retrospective analysis of 16 stable CPFE patients with concurrent emphysema and idiopathic diffuse parenchymal lung disease with fibrosis based on chest CT.[9-10] These outpatients were first seen at Shinshu University Hospital between April 2004 and December 2007, and were then followed up with over the next five or more years. Exclusion criteria included the presence of connective tissue disease and any other interstitial lung disease, such as drug-induced interstitial lung disease, pneumoconiosis, hypersensitivity pneumonitis, sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis and eosinophilic pneumonia. Nineteen stable COPD patients, who were first seen at Shinshu University Hospital between April 2004 and December 2007, and were then followed up with over the next five or more years, were recruited. The diagnosis of COPD was based on the clinical history and symptoms, including dyspnea while exercising and pulmonary function characterized by irreversible airflow limitation ($FEV_1/FVC < 70\%$ after inhalation of a β_2-agonist) in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[11] The baseline clinical characteristics and the annual change

in pulmonary function during the follow-up period in CPFE patients were compared with those in stable COPD patients. Stable patients were defined as those who had not suffered from respiratory tract infections or an exacerbation of COPD or pulmonary fibrosis during the preceding three months.

A total of 20 consecutive CPFE patients were seen at our hospital and followed up for five or more years. However, one patient who underwent a surgical lung biopsy and three patients who underwent lobectomy as a result of lung cancer were excluded from this study, since the procedure may influence pulmonary function. In total, 16 patients were included in the CPFE group. On the other hand, a total of 40 consecutive COPD patients were seen at our hospital and followed up for five or more years. However, nine COPD patients with "absence of emphysema, with little emphysema phenotype [12-13]" were excluded from this study, because our imaging criteria of COPD and CPFE included the percentage ratio of low attenuation area (%LAA) ≥25% on chest HRCT.[3] Six COPD patients who had any history of asthma or asthmatic symptoms, three patients who underwent lobectomy as a result of lung cancer and three patients who underwent lung volume reduction surgery for COPD were excluded from this study. In total, 19 patients were included in the COPD

group. This study was approved by the institutional Human Ethics Committee.

Evaluation of emphysema and diffuse parenchymal lung disease with significant pulmonary fibrosis on chest HRCT

Emphysema and diffuse parenchymal lung disease with significant pulmonary fibrosis were evaluated using chest HRCT as described previously.[12-13] Briefly, emphysema was scored visually in bilateral upper, middle and lower lung fields according to the methods of Goddard et al..[9] The score in each of the 6 dimensions was calculated according to %LAA in each lung field as follows: score 0, %LAA<5%; score 1, 5%≤%LAA<25%; score 2, 25%≤%LAA<50%; score 3, 50%≤%LAA<75%; score 4, 75%≤%LAA. The severity of emphysema was graded in accordance with the sum of the scores at the 6 dimensions as follows: Grade 0, total score=0; Grade 1, total scores=1-6; Grade 2, total scores=7-12; Grade 3, total scores=13-18; Grade 4, total scores=19-24. The presence of diffuse parenchymal lung disease with significant pulmonary fibrosis on HRCT, defined as thick-walled bulla, honeycombing, reticular opacities, ground-glass opacities, consolidation, traction bronchiectasis, peribronchovascular interstitial thickening and

architectural distortion, were evaluated as described previously.[3] CT images were analyzed independently by two pulmonologists (Y.K. and K.F.) with no knowledge of the patients' clinical information. CPFE patients were characterized by the coexistence of significant emphysema (Grade 2 or more, %LAA≥25%) and diffuse parenchymal lung disease with significant pulmonary fibrosis. COPD patients were characterized by the presence of significant emphysema (Grade 2 or more, %LAA≥25%) without any significant pulmonary fibrosis.

Pulmonary function tests

Both spirometry and the measurement of DLco and DLco corrected for alveolar volume (DLco/VA) were performed using a pulmonary function testing system (Chestac-55V; Chest Co. Ltd.). The functional residual capacity (FRC) was measured using a Body Box (Medgraphic, Ann Harbor, MI), after which the subjects immediately inspired to total lung capacity (TLC) and maximally expired to residual volume (RV), thus allowing for calculation of lung volumes and of RV/TLC. The pulmonary function tests were performed by two special technicians according to the American Thoracic Society criteria. Two or three

tests were repeated to guarantee repeatability.

Pulmonary function tests were repeated during the course of the study. Baseline pulmonary function was estimated from the first tests conducted at our hospital. To estimate the annual change in pulmonary function, we used data from patients who had undergone pulmonary function tests more than five times during a follow-up period of more than five years. Annual changes in pulmonary function were estimated from linear regressions, with assumptions for time-dependency and linearity.

Data analysis

The values shown in the text, figures and tables represent means ± standard error of the mean (SEM). The baseline values and changes per year in the parameters of pulmonary function in the CPFE and COPD groups were compared using unpaired t-test. Categorical variables such as gender, age, smoking status, and medication for COPD were evaluated using Fisher's exact test. All statistical analyses were performed using a Windows-compatible software (Stat Flex version 5.0; Artech, Osaka, Japan). A value of $P<0.05$ was considered to be significant for the results of all statistical analyses.

Results

Baseline clinical characteristics and pulmonary function of the CPFE and COPD groups are shown in **Table 1**. There were no significant differences in percent predicted vital capacity (VC) and percent predicted forced vital capacity (FVC) between the COPD and CPFE groups. Forced expiratory volume in one second (FEV_1), percent predicted FEV_1 and FEV_1/FVC were significantly higher in the CPFE group. Percent predicted FRC, percent predicted RV, percent predicted TLC and RV/TLC were significantly lower in the CPFE group. There were no significant differences in percent predicted DLco and percent predicted DLco/V_A, although percent predicted DLco tended to be lower in the CPFE group.

There was no significant difference in the average follow-up period after the first visit between the two groups **(Table 2)**. One patient in each group was a current smoker, all other patients were former smokers. The number of patients who had received any medication for COPD was significant smaller in the CPFE group. None of the patients from either group had received oral steroids or immunosuppressants treatment.

Annual changes in pulmonary function are shown in **Table 3.** Changes in VC,

FVC, FEV_1/FVC, DLco and DLco/VA observed during the follow-up period in all patients are presented in **Figure 1-5**. Annual decreases in VC and FVC in the CPFE group were significantly higher than those in the COPD group **(Table 3, Figure 1-2)**. There were no significant differences in annual decrease in FEV_1 and percent predicted FEV_1 between the two groups. Annual decrease in FEV_1/FVC in the COPD group was significantly higher than that in the CPFE group **(Table 3, Figure 3)**. FEV_1/FVC in the CPFE group appeared to improve during the follow-up period because of annual decrease in FVC. Annual decreases in DLco and DLco/VA in the CPFE group were significantly higher than those in the COPD group **(Table 3, Figure 4-5)**.

Discussion

This study is the first to compare the yearly dynamics of pulmonary function parameters in CPFE patients with those in COPD patients. This study revealed that airflow limitation represented as FEV_1/FVC appeared to improve during the follow-up period of more than five years in CPFE patients because of the annual decrease in FVC. The annual decreases in DLco and DLco/VA were significantly higher in the CPFE group provably due to the additive effects of emphysema and fibrosis, in that both reduce diffusing capacity. These findings suggest that the physiologic consequences of CPFE including the rate of progression of pulmonary function impairment were different from those of COPD. There was no significant difference between the two groups in the annual change in FEV_1, which is the parameter most commonly used to assess the course of COPD [14] and to predict future changes in pulmonary function and survival in COPD.[15]

Akagi et al. reported that ventilatory and gas-exchange deterioration during the course of IPF became mild when emphysema was coexistent.[6] This study has demonstrated that the annual decreases in VC, FVC, DLco and DLco/VA were more advanced in CPFE patients than in COPD patients. However, there is a potential problem with the differences in imaging criteria between these two

studies. We based a clinical diagnosis of CPFE on the imaging criteria for CPFE as described by Cottin et al.[1], which included idiopathic interstitial pneumonias other than IPF. CPFE patients in this study also had the presence of significant emphysema (Grade 2 or more, %LAA≥25%). Therefore, one possibility is that CPFE patients in this study may have been in a different phase and/or a different disease state compared with those in the previous report described by Akagi et al..[6] Standard clinical diagnostic criteria for CPFE needed to be established, particularly for imaging, even though the imaging findings and pathology in CPFE patients are heterogeneous.[2]

Previous studies have investigated the predictors of mortality for CPFE in pulmonary function parameters. Schmidt et al. reported that longitudinal decline in FEV_1 over 12 months was more predictive of mortality in CPFE patients than the other pulmonary function parameters.[16] Kishaba et al. reported that a value of more than 1.2 for the ratio of percent predicted FEV_1 to percent predicted FVC was an independent predictor of mortality in CPFE patients.[17] Mejía et al. reported that the Cox regression model showed that a FVC less than 50% predicted was one of the most important variables associated with mortality in patients with IPF and emphysema.[18] In contrast, longitudinal changes in FVC

and DLco have been shown to have prognostic value in IPF.[19-22] Therefore, it may be helpful to measure the longitudinal changes in FVC and DLco as a prognostic predictor in CPFE as well as IPF. In addition, pulmonary function parameters with large longitudinal changes such as VC, FVC, DLco and DLco/VA may be shown to have prognostic values in CPFE. Further studies to elucidate the roles of ventilation and gas-exchange impairments as prognostic factors are needed in CPFE.

There were several limitations in this study. First, this was a single-centre, uncontrolled design retrospective study. Additional prospective studies with large sample sizes are warranted to confirm our results. Second, the assessment of emphysema was done by a visual scoring method, rather than by using a software-based quantification of emphysema. However, the reproducibility of visual scoring had been demonstrated in our previous report.[13] Third, we did not measure the exact areas of fibrosis. Forth, the differences in pharmacotherapy between CPFE and COPD groups may influence the results. The number of patients who had received any medication for COPD was significant larger in the COPD groups. For this reason, the values of the pulmonary function parameters may have varied widely during the follow-up period especially in the COPD

patients. Fifth, we could not evaluate the detailed pathology of our CPFE patients, because patients who underwent a surgical lung biopsy were excluded from the study, since the procedure influences pulmonary functions. Sixth, a linear regression analysis was employed to analyze longitudinal changes in the pulmonary function, based on previous reports describing longitudinal changes in pulmonary function.[6,23-24] Therefore, a mixed-effects analysis was not employed in this study. However a linear regression analysis may not be a reasonable assumption in some cases according to the figures, which may also have affected the results. In addition, the unpaired t-test may not appropriate for the statistical analysis of annual changes in the pulmonary function due to the small sample size. Therefore, further studies with larger sample sizes are needed to confirm our results. Seventh, one potential problem with this study is generalizability. Patients who underwent a lobectomy as a result of lung cancer were excluded from this study, since the procedure may influence pulmonary function. Therefore, a selection bias may exist, because the prevalence of lung cancer may be high in CPFE patients.[3,25] This study details the retrospective analysis of stable CPFE and COPD patients who had been followed up for more than five years. Therefore, patients with an advanced disease who died during

the course of CPFE were not included in this study. In fact, there was no significant difference in DLco between the COPD and CPFE groups in this study, even though several previous reports have documented a significant decrease in DLco in CPFE patients.[1-5] This discrepancy between previous findings and those from this study may suggest that the proportion of patients with a mild disease was relative large in this study.

In conclusion, this is the first report showing the yearly dynamics of pulmonary function parameters in CPFE patients compared with those in COPD patients during a follow-up period of more than five years. The annual decreases in DLco and DLco/VA were significantly higher in CPFE patients. Airflow limitation represented as FEV_1/FVC appeared to improve during the course of CPFE because of the annual decrease in FVC. This study revealed that the physiologic consequences of CPFE including the rate of progression of pulmonary function impairment were different from those of COPD.

References

1. Cottin V, Nunes H, Brillet PY, Delaval P, Devouassoux G, Tillie-Leblond I, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005; 26: 586-93.

2. Jankowich MD, Polsky M, Klein M, Rounds S. Heterogeneity in combined pulmonary fibrosis and emphysema. Respiration 2008; 75: 411-7.

3. Kitaguchi Y, Fujimoto K, Hanaoka M, Kawakami S, Honda T, Kubo K. Clinical characteristics of combined pulmonary fibrosis and emphysema. Respirology 2010; 15: 265-71.

4. Grubstein A, Bendayan D, Schactman I, Cohen M, Shitrit D, Kramer MR. Concomitant upper-lobe bullous emphysema, lower-lobe interstitial fibrosis and pulmonary hypertension in heavy smokers: report of eight cases and review of the literature. Respir Med 2005; 99: 948-54.

5. Mura M, Zompatori M, Pacilli AM, Fasano L, Schiavina M, Fabbri M. The presence of emphysema further impairs physiologic function in patients with idiopathic pulmonary fibrosis. Respir Care 2006; 51: 257-65.

6. Akagi T, Matsumoto T, Harada T, Tanaka M, Kuraki T, Fujita M, et al. Coexistent emphysema delays the decrease of vital capacity in idiopathic

pulmonary fibrosis. Respir Med 2009; 103: 1209-15.

7. Kurashima K, Takayanagi N, Tsuchiya N, Kanauchi T, Ueda M, Hoshi T, et al. The effect of emphysema on lung function and survival in patients with idiopathic pulmonary fibrosis. Respirology 2010; 15: 843-8.

8. Jankowich MD, Rounds SI. Combined pulmonary fibrosis and emphysema syndrome: a review. Chest 2012; 141: 222-31.

9. Goddard PR, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. Clin Radiol 1982; 33: 379-87.

10. Gotway MB, Freemer MM, King TE Jr. Challenges in pulmonary fibrosis. 1: Use of high resolution CT scanning of the lung for the evaluation of patients with idiopathic interstitial pneumonias. Thorax 2007; 62: 546-53.

11. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO workshop report. Bethesda, National Heart, Lung and Blood Institute, April 2001; Revised 2011, see also→http://www.goldcopd.com.

12. Kitaguchi Y, Fujimoto K, Kubo K, Honda T. Characteristics of COPD phenotypes classified according to the findings of HRCT. Respir Med 2006; 100: 1742-52.

13. Fujimoto K, Kitaguchi Y, Kubo K, Honda T. Clinical analysis of chronic obstructive pulmonary disease phenotypes classified using high-resolution computed tomography. Respirology 2006; 11: 731-40.

14. Wise RA. The value of forced expiratory volume in 1 second decline in the assessment of chronic obstructive pulmonary disease progression. Am J Med 2006; 119: 4-11.

15. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. A 15-year follow-up study. Am Rev Respir Dis 1979; 119: 895-902.

16. Schmidt SL, Nambiar AM, Tayob N, Sundaram B, Han MK, Gross BH, et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. Eur Respir J 2011; 38: 176-83.

17. Kishaba T, Shimaoka Y, Fukuyama H, Yoshida K, Tanaka M, Yamashiro S, et al. A cohort study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema. BMJ Open 2012; 2: e000988.

18. Mejía M, Carrillo G, Rojas-Serrano J, Estrada A, Suárez T, Alonso D, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009; 136: 10-5.

19. Schwartz DA, Helmers RA, Galvin JR, Van Fossen DS, Frees KL, Dayton CS, et al. Determinants of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994; 149: 450-4.

20. Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003; 168: 543-8.

21. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003; 168: 538-42.

22. Flaherty KR, Andrei AC, Murray S, Fraley C, Colby TV, Travis WD, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 2006; 174: 803-9.

23, Wang ML, Avashia BH, Petsonk EL. Interpreting periodic lung function tests in individuals: the relationship between 1- to 5-year and long-term FEV1 changes. Chest 2006; 130: 493-9.

24, Omori H, Nonami Y, Morimoto Y. Effect of smoking on FEV decline in a cross-sectional and longitudinal study of a large cohort of Japanese males. Respirology 2005; 10: 464-9.

25. Usui K, Tanai C, Tanaka Y, Noda H, Ishihara T. The prevalence of pulmonary fibrosis combined with emphysema in patients with lung cancer. Respirology 2011; 16: 326-31.

Legends

Figure 1

(a)(b) Changes in vital capacity (VC) observed during the follow-up period in all CPFE and COPD patients

(c) Change per year in VC in the CPFE and COPD groups

Annual decrease in VC in the CPFE group was significantly higher than in the COPD group ($p<0.05$).

Figure 2

(a)(b) Changes in forced vital capacity (FVC) observed during the follow-up period in all CPFE and COPD patients

(c) Change per year in FVC in the CPFE and COPD groups

Annual decrease in FVC in the CPFE group was significantly higher than in the COPD group ($p<0.05$).

Figure 3

(a)(b) Changes in forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) observed during the follow-up period in all CPFE and

COPD patients

(c) Change per year in FEV1/FVC in the CPFE and COPD groups

Annual decrease in FEV_1/FVC in the COPD group was significantly higher than that in the CPFE group ($p<0.05$).

Figure 4

(a)(b) Changes in diffusing capacity of lung for carbon monoxide (DLco) observed during the follow-up period in all CPFE and COPD patients

(c) Change per year in DLco in the CPFE and COPD groups

Annual decrease in DLco in the CPFE group were significantly higher than those in the COPD group ($p<0.01$).

Figure 5

(a)(b) Changes in diffusing capacity of lung for carbon monoxide corrected for alveolar volume (DLco/VA) observed during the follow-up period in all CPFE and COPD patients

(c) Change per year in DLco/VA in the CPFE and COPD groups

Annual decrease in DLco/VA in the CPFE group were significantly higher than

those in the COPD group ($p<0.01$).

Table 1. Baseline clinical characteristics and pulmonary function in the CPFE and COPD groups

Values are the number (%) or the means±SEM. $^{\dagger}p<0.05$ and $^{\dagger\dagger}p<0.01$ vs. COPD

Definition of abbreviations: CPFE, combined pulmonary fibrosis and emphysema; COPD, chronic obstructive pulmonary disease; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity of lung for carbon monoxide; DLco/VA, diffusing capacity of lung for carbon monoxide corrected for alveolar volume

Table 2. Clinical characteristics during the follow-up period in the CPFE and COPD groups

Values are the number (%) or the means±SEM. $^{\dagger}p<0.05$ and $^{\dagger\dagger}p<0.01$ vs. COPD

Definition of abbreviations: CPFE, combined pulmonary fibrosis and emphysema; COPD, chronic obstructive pulmonary disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2-agonist; ICS, inhaled corticosteroid

* Subjects were described as continuous, intermittent, or former smokers, depending of the smoking status during the follow-up period.

** Numbers denote the number of subjects with more than 50% of usage during the follow-up period

Table 3. Annual changes in pulmonary function in the CPFE and COPD groups

Values are the means±SEM. $^{\dagger}p<0.05$ and $^{\dagger\dagger}p<0.01$ vs. COPD

Definition of abbreviations: CPFE, combined pulmonary fibrosis and emphysema; COPD, chronic obstructive pulmonary disease; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity of lung for carbon monoxide; DLco/VA, diffusing capacity of lung for carbon monoxide corrected for alveolar volume

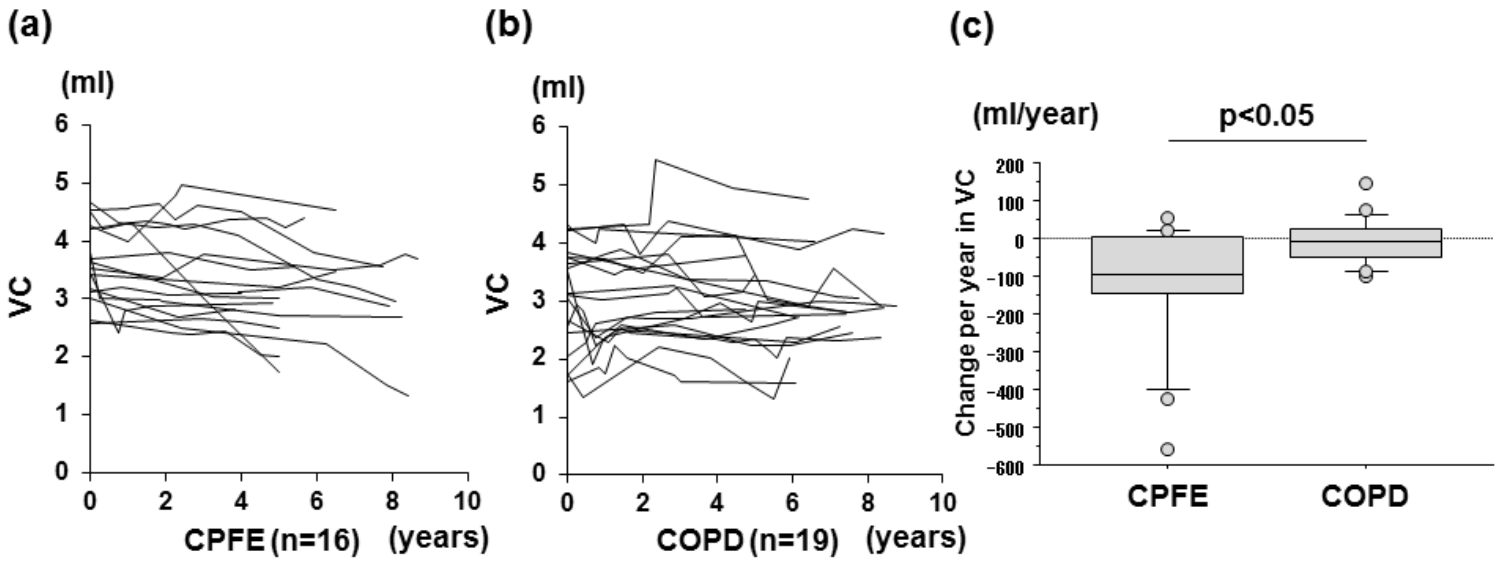
(a)
(ml)
VC
CPFE (n=16)
(years)
(b)
(ml)
VC
COPD (n=19)
(years)
(c)
(ml/year)
p<0.05
Change per year in VC
CPFE
COPD

Figure 1.

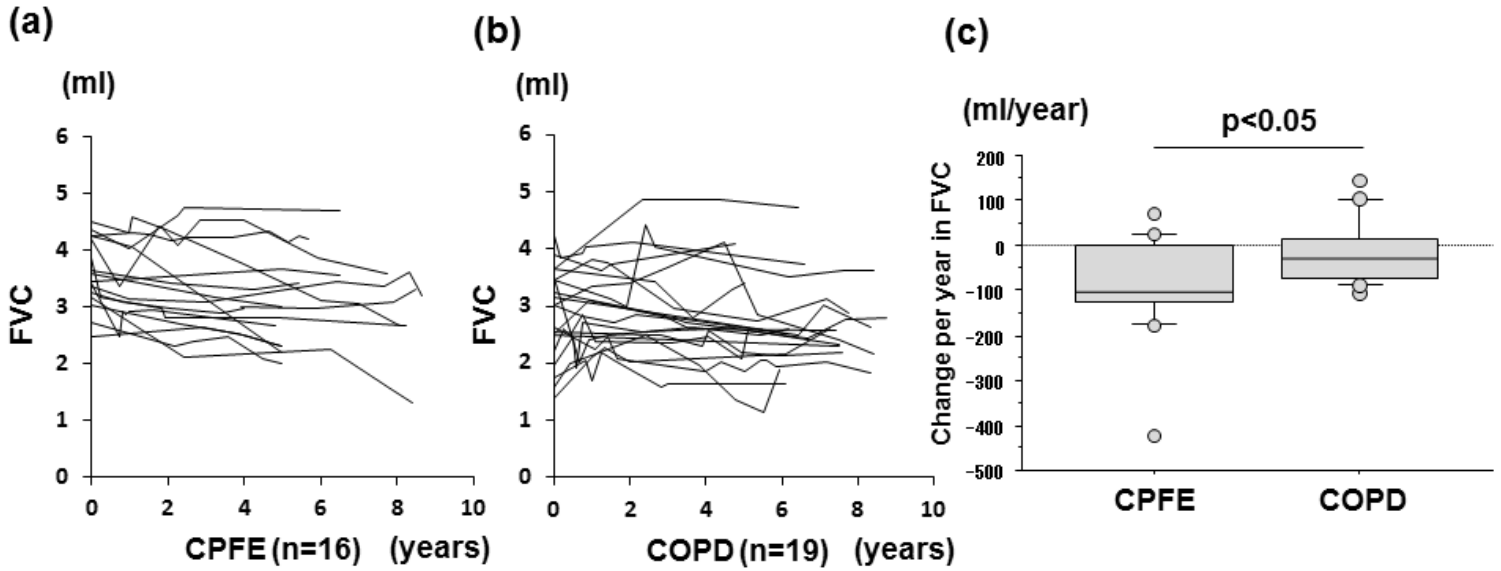
(a)
(ml)
FVC
CPFE (n=16)
(years)
(b)
(ml)
FVC
COPD (n=19)
(years)
(c)
(ml/year)
p<0.05
Change per year in FVC
CPFE
COPD

Figure 2.

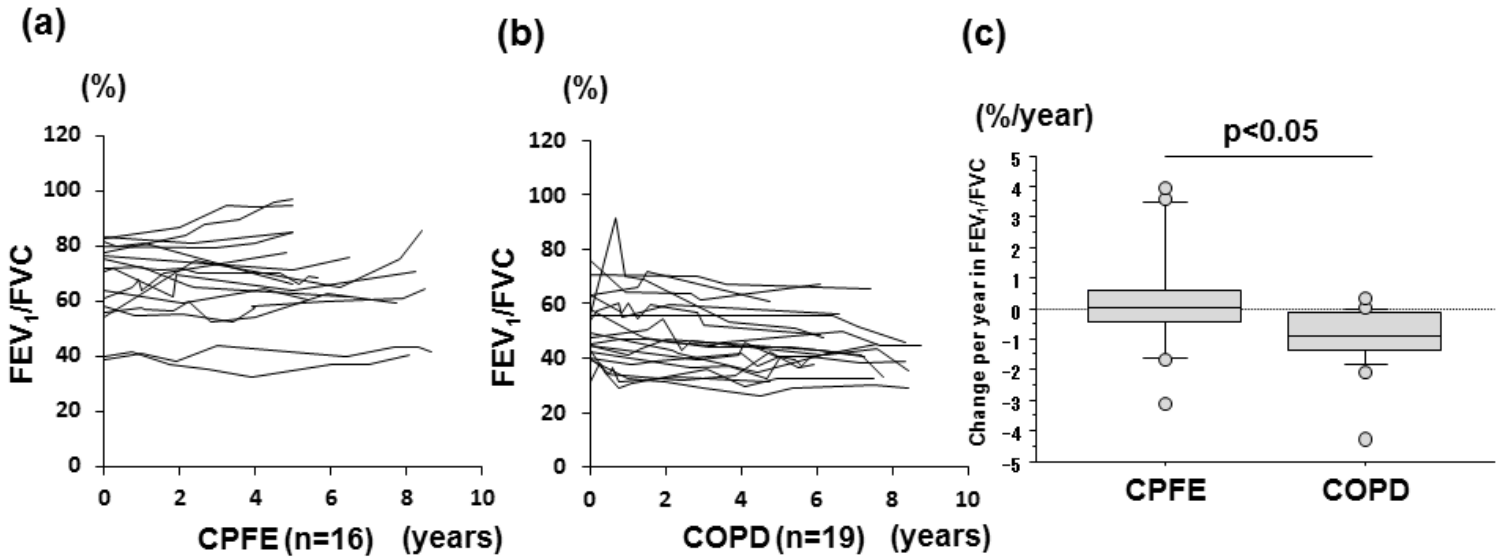
(a)
(%)
FEV1/FVC
120
100
80
60
40
20
0
0
2
4
6
8
10
CPFE (n=16) (years)
(b)
(%)
FEV1/FVC
120
100
80
60
40
20
0
0
2
4
6
8
10
COPD (n=19) (years)
(c)
(%/year)
p<0.05
Change per year in FEV1/FVC
5
4
3
2
1
0
-1
-2
-3
-4
-5
CPFE
COPD

Figure 3.

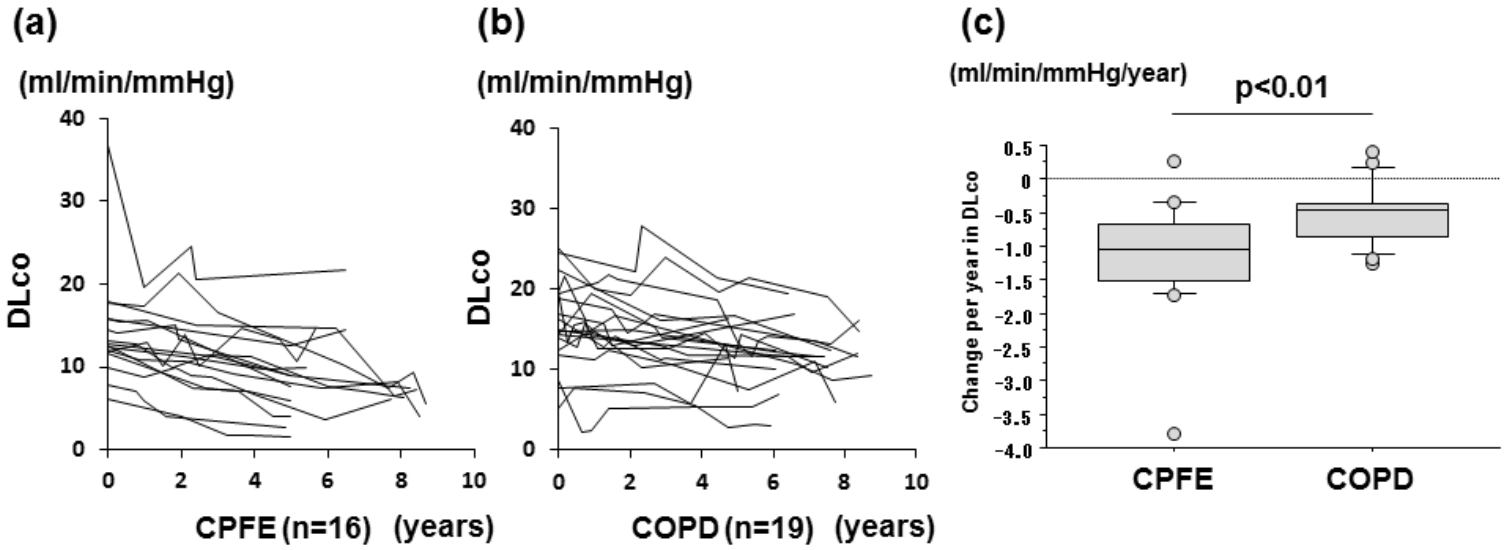
(a)
(ml/min/mmHg)
DLco
40
30
20
10
0
0
2
4
6
8
10
CPFE (n=16) (years)
(b)
(ml/min/mmHg)
DLco
40
30
20
10
0
0
2
4
6
8
10
COPD (n=19) (years)
(c)
(ml/min/mmHg/year)
p<0.01
Change per year in DLco
0.5
0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
CPFE
COPD

Figure 4.

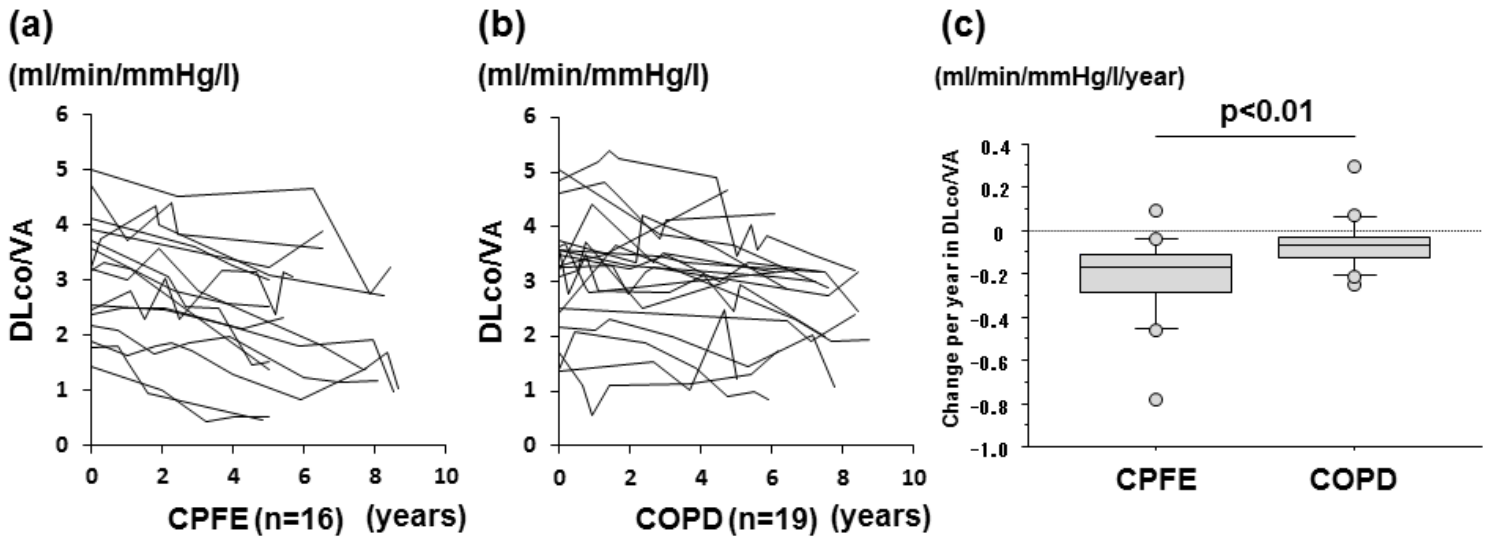
(a)
(ml/min/mmHg/l)
DLco/VA
CPFE (n=16) (years)
(b)
(ml/min/mmHg/l)
DLco/VA
COPD (n=19) (years)
(c)
(ml/min/mmHg/l/year)
p<0.01
Change per year in DLco/VA
CPFE
COPD

Figure 5.

Table 1. Baseline clinical characteristics and pulmonary function in the CPFE and COPD groups

	CPFE (n=16)	COPD (n=19)
Gender(Male/Female)	16/0	19/2
Age at first visit, yr	66.8±1.8	67.7±1.1
Body Mass Index, kg/m^2	22.9±0.7	21.5±0.7
Smoking index, pack-years	67.9±5.3	57.6±5.5
VC, % predicted	97.0±4.6	88.5±4.8
FVC, % predicted	98.1±4.5	85.6±4.8
FEV_1, L	2.37±0.16 ††	1.48±0.14
FEV_1, % predicted	81.4±6.0 ††	54.2±4.6
FEV_1/FVC, %	67.6±3.5 ††	49.6±2.5
FRC, % predicted	103.7±6.1 ††	142.1±9.6
RV, % predicted	141.2±12.4 ††	221.2±12.9
TLC, % predicted	112.2±6.0 †	133.0±5.0
RV/TLC, %	42.2±2.9 ††	53.8±2.3
DLco, % predicted	56.7±6.2	64.9±4.9
DLco/V_A, % predicted	66.9±5.8	70.9±5.3

Table 2. Clinical characteristics during the follow-up period in the CPFE and COPD groups

	CPFE (n=16)	COPD (n=19)
Follow-up period, years	6.47±0.38	6.92±0.30
Smoking status*		
Continuous smoker, n(%)	1(6.3)	1(5.3)
Intermittent smoker, n(%)	0(0)	0(0)
Former smoker, n(%)	15(93.8)	18(94.7)
Medication for COPD**		
Any medication, n(%)	7(43.8) ††	19(100)
LAMA, n(%)	4(25.0) ††	15(78.9)
LABA, n(%)	3(18.8) ††	13(68.4)
ICS, n(%)	1(6.3)	5(26.3)
Theophyllline, n(%)	3(18.8) †	11(57.9)

Table 3. Annual changes in pulmonary function in the CPFE and COPD groups

	CPFE (n=16)	COPD (n=19)
VC, ml/year	-113.5±41.3 †	-11.0±13.9
FVC, ml/year	-88.2±28.5 †	-15.6±16.6
FEV_1, ml/year	-57.7±26.7	-34.8±8.8
FEV_1, % predicted/year	-0.98±0.91	-0.76±0.34
FEV_1/FVC, %/year	0.31±0.45 †	-0.94±0.24
FRC, ml/year	-20.9±29.2	-57.3±20.8
RV, ml/year	9.5±36.1	-41.0±22.8
TLC, ml/year	-93.7±37.4	-61.3±16.4
DLco, ml/min/mmHg/year	-1.15±0.22 ††	-0.51±0.10
DLco/V_A, ml/min/mmHg/l/year	-0.22±0.05 ††	-0.06±0.03