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Combined Pulmonary Fibrosis and Emphysema Alters Physiology but Has Similar Mortality to Pulmonary Fibrosis Without Emphysema

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Abstract

Studies have described individuals with combined pulmonary fibrosis and emphysema (CPFE), with preserved lung volumes, significant reductions in gas exchange, and high prevalence of pulmonary hypertension. While physiologic changes in CPFE are well documented, there is little mortality data in the CPFE population compared to appropriate controls. A study was performed to determine the features and outcomes of a group of individuals with imaging and/or pathologic evidence of CPFE to determine if individuals with combined pulmonary fibrosis and emphysema have different features and survival than individuals with pulmonary fibrosis alone. We conducted a retrospective study at a Veterans Affairs Medical Center. Included in the study were individuals hospitalized over a 5-year period who were given a clinical diagnosis of pulmonary fibrosis. Individuals with confirmed imaging or pathologic evidence of pulmonary fibrosis were divided into a study group with concomitant emphysema (CPFE group, $n = 20$) and a control group without emphysema (isolated pulmonary fibrosis (PF) group, $n = 24$). The CPFE group, all current or former cigarette smokers, had significantly larger lung volumes, more expiratory airflow obstruction, and worse gas exchange than the isolated pulmonary fibrosis group. Mortality did not differ between the groups. Combined pulmonary fibrosis and emphysema results in unique physiologic features but no difference in survival compared with a group with pulmonary fibrosis alone.

Keywords

Combined pulmonary fibrosis and emphysema; Idiopathic pulmonary fibrosis; Emphysema

Introduction

While traditionally regarded as separate disease states, imaging studies have demonstrated that emphysema and pulmonary fibrosis can coexist in individuals [1], an entity termed “combined pulmonary fibrosis and emphysema” (CPFE) [2]. There is increasing interest in this phenotype since individuals with CPFE have been reported to have elevated rates of pulmonary hypertension and possibly higher mortality when compared with subjects with idiopathic pulmonary fibrosis alone [2,3]. Therefore, it has been suggested that these individuals represent an entirely separate disease state that would merit individualized treatment [4]. No consensus definition of CPFE exists, and a recent study of selected individuals with emphysema in the setting of established idiopathic pulmonary fibrosis did not precisely reflect the previously described characteristics of individuals with CPFE seen in other studies, such as relative lung volume preservation [3]. Indeed, the radiologic and pathologic presentation of individuals with CPFE may be heterogeneous [5]. Therefore, further data on outcomes in CPFE, particularly when compared with appropriate controls with pulmonary fibrosis, would be desirable.

We hypothesized that emphysema would be common in hospitalized veterans with the clinical diagnosis of pulmonary fibrosis. We further hypothesized that subjects with CPFE would have unique clinical features compared to subjects with interstitial pulmonary fibrosis alone, and that the advanced structural lung disease present in individuals with CPFE would result in worsened survival compared to a group with pulmonary fibrosis only. We retrospectively assessed the characteristics and outcomes of a group of individuals with imaging and/or pathologic evidence of CPFE compared to a control group with evidence of isolated interstitial pulmonary fibrosis without concomitant emphysema.

Methods

Study Design

A retrospective, single-center clinical study was conducted to establish the prevalence and characteristics of veterans with CPFE compared to veterans with isolated pulmonary fibrosis without emphysema. This study had the full approval of the Institutional Review Board of the Providence VA Medical Center.

Study Population and Definition of CPFE Used for Study

We identified all consecutive individuals hospitalized at the Providence VA Medical Center over a 5-year study period from 1 April 2003 to 1 April 2008 with an ICD-9 diagnosis potentially related to pulmonary fibrosis, including ICD-9 515 (“Post-inflammatory pulmonary fibrosis”), 516.3 (“Idiopathic fibrosing alveolitis”; “Hamman-Rich syndrome”), 516.8 (“Pulmonary fibrosis”), and 466.19 (“Respiratory bronchiolitis”). Respiratory bronchiolitis was included for completeness as we felt patients with smoking-related interstitial lung disease could potentially be categorized under this diagnostic code. Seventy-nine patients were identified by a systematic search of the medical center’s database for all consecutive patients discharged from the Providence VA Medical Center during the given date range after an inpatient admission who were given one of the above ICD-9 diagnoses on discharge. We included patients with either a primary or a secondary diagnosis of pulmonary fibrosis at the time of discharge (i.e., pulmonary fibrosis could have been the primary clinical diagnosis for hospitalization or a secondary clinical diagnosis noted during hospitalization).

We then reviewed imaging and pathologic data of all potential subjects. All subjects had a CT scan (conventional or high-resolution) with reported fibrosis, honeycombing, or interlobular thickening on radiology interpretation or evidence of interstitial pulmonary fibrosis on pathologic examination of a lung specimen. Histologic evidence of usual interstitial pneumonia

was not a requirement for pathologic evidence of pulmonary fibrosis, but the pathologic specimen had to have a prominence of interstitial fibrosis as a main finding. Subjects with nonspecific ground-glass changes only on CT scan were not included unless they also had a lung specimen available for pathologic examination with findings compatible with interstitial pulmonary fibrosis. We excluded 35 subjects without CT imaging or pathologic data to support the clinical diagnosis of pulmonary fibrosis, yielding 44 subjects for inclusion in the study to be categorized as either having CPFE or isolated interstitial pulmonary fibrosis (see Fig. 1 for a flow diagram of subject selection and exclusion).

To be defined as having CPFE, subjects must have had evidence of emphysema or bullous disease on CT scan (conventional or high-resolution) report or on lung pathology report. Subjects categorized as having isolated interstitial pulmonary fibrosis did not have reported imaging or pathologic evidence of emphysema. Subjects were thereby categorized into CPFE ($n = 20$) and isolated interstitial pulmonary fibrosis (PF) groups ($n = 24$), yielding the final study subject groups. Nine CPFE patients had been categorized under the ICD-9 code 515 ("Post-inflammatory pulmonary fibrosis") alone, 10 under ICD-9 code 515 and either 516.3 ("Idiopathic fibrosing alveolitis"; "Hamman-Rich syndrome") or 516.8 ("Pulmonary fibrosis"), and 1 under 516.8 alone. Six of the PF controls had been categorized under the 515 code alone, 1 under 516.3 alone, and 17 under 515 and either 516.3 and/or 516.8. No subjects or controls had been categorized under 466.19 ("Respiratory bronchiolitis").

Nine of the 20 subjects with CPFE in this study were included in our prior case series of ten individuals with CPFE [5].

Data Review

Available demographic, clinical, pulmonary function test (PFT), echocardiography, and pathology data present in the electronic medical records were recorded for the subjects with CPFE and the control subjects with isolated interstitial pulmonary fibrosis without emphysema by one of the authors (MJ). The period for which data was reviewed and collected encompassed the entire 5-year study period from 1 April 2003 to 1 April 2008. Vital status was assessed until 1 April 2008, with patients alive at the end of this study period considered alive for purposes of data analysis.

Pulmonary Function Testing—All pulmonary function tests (PFTs) were performed on equipment calibrated according to American Thoracic Society standards. The first available PFT for each subject done for clinical purposes before or during the study period for investigation of the subject's respiratory condition was used for analysis of pulmonary function data. Post-bronchodilator FEV₁ percent predicted was recorded preferentially if available. All lung volumes were done by helium dilution during that time period. The diffusion capacity for carbon monoxide was performed using the single-breath method.

Echocardiograms—All echocardiograms were transthoracic studies. The first echocardiogram performed during or up to 5 years before the study period was used for the baseline echocardiogram data. Data were abstracted from clinical echocardiogram reports in the electronic medical records. If subjects had follow-up echocardiograms, significant changes were noted and recorded. An estimated pulmonary artery pressure of 40 mmHg or greater was considered diagnostic of pulmonary hypertension on the baseline or follow-up echocardiogram.

Statistical Analysis

Data are presented as mean $\pm$ standard deviation or ratios with percentages as appropriate. Descriptive statistical analysis of each group was followed by intragroup comparisons using

Fisher's exact test for categorical variables or unpaired *t* test (for normally distributed variables) or Wilcoxon rank sum test (for non-normally distributed variables) for continuous variables. Kaplan–Meier survival curves were drawn for each group for the 60-month study period to assess survival differences between groups. Statistical analysis was performed using Microsoft Office Excel 2007 (Microsoft Corp., Redmond, WA) and Stat-View version 5.0.1 software (SAS Institute Inc., Cary, NC), and $p < 0.05$ was considered significant.

Results

The baseline characteristics of the groups with CPFE and isolated pulmonary fibrosis are listed in Table 1. Subjects with CPFE tended to be younger and more likely to have smoked cigarettes. The predominance of males reflects the patient population of the VA health-care system.

Examples of the imaging characteristics of six subjects with CPFE are presented in Fig. 2. Pleural plaque was reported on CT in 4/20 subjects in the CPFE group and in 3/24 subjects in the PF group, with an additional subject in the PF group having a small pleural plaque present on autopsy. Imaging demonstrated centrilobular emphysema in 10/20 CPFE patients, paraseptal emphysema in 5/20 CPFE patients, and bullous changes in 11/20 CPFE patients (patients may have exhibited more than one type of emphysema).

Table 2 lists the pulmonary function data for subjects for whom pulmonary function data were available. One subject in the CPFE group did not have PFTs done because of dementia. Two subjects in the PF group did not have PFTs done due to dementia, one because of multiple sclerosis, and two for unclear reasons. CPFE subjects had significantly higher forced vital capacity, a lower FEV₁/FVC ratio, higher total lung capacity, and lower diffusion capacity than did subjects in the PF group. The CPFE group had a mean FEV₁/FVC ratio that was consistent with airway obstruction.

The echocardiography data of subjects for whom echocardiography had been performed are listed in Table 3. Left ventricular (LV) ejection fraction was lower in the PF group. Diastolic dysfunction as assessed by transmitral e/a reversal was common in both groups. Pulmonary hypertension was not more frequent in the CPFE group, though recorded pulmonary artery pressures tended to be higher, and there tended to be more right ventricular dilation in the CPFE group. One subject in the CPFE group, who had not had pulmonary hypertension diagnosed by echocardiogram, underwent right heart catheterization revealing a mean pulmonary artery pressure of 39 mmHg, which is diagnostic of mild to moderate pulmonary hypertension.

Lung biopsy or resection was performed on five subjects in the CPFE group before or during the study period. Four subjects in the PF group underwent lung biopsy or examination of the lungs at autopsy during the study period. Of the subjects in the CPFE group, one had a transbronchial biopsy showing interstitial fibrosis, two had extensive interstitial fibrosis with intra-alveolar macrophage accumulation, one had evidence of centriacinar emphysema and usual interstitial pneumonia without evidence of asbestos bodies, and one had a right-upper-lobe resection demonstrating squamous cell carcinoma and emphysema. Of the subjects in the PF group, two had biopsies demonstrating usual interstitial pneumonia, one had a biopsy at an outside institution that was reported to be consistent with idiopathic pulmonary fibrosis (presumably therefore demonstrating usual interstitial pneumonia), and one had diffuse alveolar damage at autopsy with acute and organizing pneumonia and a small pleural plaque.

Prescribed pharmacologic or respiratory treatments during the study period are listed in Table 4. Inhaled steroids and long-acting β agonists were prescribed more frequently for members of the CPFE group. There were no clear differences between the two groups with respect to prescription of acute or chronic steroids, nonsteroidal immunosuppressants, or N-

acetylcysteine. Oxygen flow rates, if oxygen had been prescribed, were relatively high in both groups.

The morbidity and mortality rates for the subjects at the end of the 5-year study period are listed in Table 5. Mortality at the end of the 5-year study period was considerable in both groups. Kaplan–Meier survival curves for the two groups are displayed in Fig. 3. There was no significant difference between the groups with regard to hospitalization for respiratory causes or mortality, though patients in the isolated interstitial pulmonary fibrosis group tended to have undergone a period of mechanical ventilation more often than individuals in the CPFE group.

Discussion

There is increasing interest in the advanced lung disease syndrome known as CPFE. Published reports include a number of case series of CPFE patients and, more recently, studies comparing subjects with established idiopathic pulmonary fibrosis with emphysema to subjects with idiopathic pulmonary fibrosis without emphysema [2,3,5–7]. The natural history of CPFE, in contrast to that of pulmonary fibrosis alone, remains to be determined; whether the presence of emphysema results in worsened survival in pulmonary fibrosis patients is unclear.

In our current study, we found that the pulmonary physiologic findings were consistent with those previously reported, with relative preservation of lung volumes and severely reduced gas exchange in subjects with CPFE compared to those with isolated pulmonary fibrosis. In contrast to the findings of the study by Mejía et al. [3] of patients with idiopathic pulmonary fibrosis and emphysema but in agreement with the results of a study by Akagi et al. [7], we did not find a higher mortality rate in subjects with CPFE at the end of the 5-year study period, although mortality was significant in both groups. Also in contrast with Mejía et al., our study population with CPFE had more of an obstructive pattern of expiratory airflow limitation and larger lung volumes, as is typical in CPFE patients [2,3,7]. Because Mejía et al.'s patients were selected from a group with established idiopathic pulmonary fibrosis (IPF), their patients may not reflect the broader population of individuals with CPFE, in whom usual interstitial pneumonia (UIP)/IPF may not be the underlying disease state resulting in pulmonary fibrosis. We believe that CPFE is a lung disease phenotype resulting from cigarette smoke exposure, as has been uniformly reported in prior series of CPFE patients, and not a result of the coincidental occurrence of emphysema in the presence of IPF.

Our study group of CPFE patients encompassed a group of subjects with a clinical phenotype related to cigarette smoking characterized by imaging evidence of emphysema plus fibrosis, airflow limitation, preserved lung volumes, and depressed gas exchange. Not all of these patients had pathology consistent with usual interstitial pneumonia, suggesting that CPFE does not occur only in the subset of individuals with idiopathic pulmonary fibrosis and coincident emphysema. Given that a combination of emphysema and pulmonary fibrosis was relatively common in the hospitalized individuals that we studied, a standard case definition for CPFE should be developed since the condition does not appear to be rare. We agree with Cottin and Cordier [4] that a case definition of CPFE should rely primarily on computed tomographic imaging evidence of emphysema and pulmonary fibrosis occurring in the same individual, but should not be limited to individuals with a single established pathologic pattern of pulmonary fibrosis such as usual interstitial pneumonia. We suggest, as did Cottin and Cordier, that CPFE may represent a syndrome, as opposed to a specific disease state, that occurs in current or former smokers and has a common clinical presentation and common diagnostic findings but possibly divergent underlying histopathology. Our study group undoubtedly included individuals not just with usual interstitial pneumonia but also with smoking-related interstitial lung disease and possibly asbestos-related fibrosis (given the frequency of asbestos exposure

in our population, which included naval veterans); our control group was also likely somewhat heterogeneous with regard to causes of pulmonary fibrosis. However, despite this pathological heterogeneity, our CPFE study group had relatively uniform findings of severely depressed gas exchange, airflow obstruction, preserved lung volumes, and a prominence of right heart disease (though differences in estimated pulmonary artery pressures were not statistically significant between groups), similar to that reported in prior studies of CPFE [2,6,8]. On the other hand, our control group of patients with isolated interstitial pulmonary fibrosis had the more typical features of restrictive lung disease with less severely decreased gas exchange.

The growing number of published reports of CPFE demonstrates that fibrosis and emphysema are clearly not mutually exclusive clinical entities. Indeed, in an animal model, emphysema and pulmonary fibrosis may occur due to divergent responses to a common lung injury [9]. Furthermore, evidence of increased lung collagen content is present in individuals with emphysema, suggesting that the connective tissue remodeling occurring in the emphysematous lung includes fibrotic changes [10]. The repertoire of responses of the lung to chronic injury may be relatively limited and stereotyped, so the coincidental findings of pulmonary fibrosis and emphysema in an individual should not be surprising. Indeed, in CT-based imaging studies, the presence of emphysema is relatively common in individuals with pulmonary fibrosis, being seen in about 30% of cases [3,8]. In our subjects, emphysema was present in 45% of the patients with pulmonary fibrosis, which may reflect the high prevalence of cigarette use in the veteran population. The clinical syndrome of CPFE may occur in susceptible individuals chronically exposed to cigarette smoke and possibly other inhaled substances such as mineral dusts, with resultant lung injury and remodeling encompassing both emphysema and fibrotic changes.

The clinical course of individuals with CPFE may not be parallel to that of individuals with idiopathic pulmonary fibrosis. In a study by King et al. [11], smokers with pulmonary fibrosis had an improved survival compared with nonsmokers. This improved survival in smokers with pulmonary fibrosis has been theorized to be due to a healthy smoker effect [12]. In King et al.'s study, smokers with pulmonary fibrosis had relatively preserved lung volumes and greater impairment in gas exchange, when adjusted for alveolar volume, compared with nonsmokers with pulmonary fibrosis [11]. We speculate that this group of smokers with pulmonary fibrosis included individuals with CPFE. In Akagi et al.'s recent study [7], there was a trend toward improved survival in individuals with CPFE compared to controls with pulmonary fibrosis alone.

In our own study, subjects with CPFE did not have worse survival than the PF group. Although gas exchange is more severely reduced in individuals with CPFE, in our study vital capacity was better preserved in these individuals; changes in vital capacity have been better predictors of survival in idiopathic pulmonary fibrosis than diffusing capacity [13]. However, the underlying reason that survival was not adversely altered in subjects with emphysema accompanying pulmonary fibrosis versus control subjects with pulmonary fibrosis alone is not clear.

To better delineate the prognosis and natural history related to CPFE, we agree with Cottin and Cordier [4] who suggest that it may be important to distinguish individuals with CPFE from individuals with idiopathic pulmonary fibrosis in future clinical studies. Future clinical studies of individuals with pulmonary fibrosis should be careful to delineate whether emphysema is concomitant. A prospectively defined subgroup of individuals with concomitant emphysema and fibrosis in future treatment and outcome studies on pulmonary fibrosis would be beneficial in attempting to answer the question of whether the definable clinical and pulmonary function characteristics seen in CPFE translate to unique outcomes meriting individualized treatment goals. Consensus regarding a case definition of CPFE is also needed for future research.

We discourage any future case definition for CPFE from requiring a specific pattern of histopathologic changes such as usual interstitial pneumonia on biopsy because pathology in CPFE may encompass forms of idiopathic pneumonia, including nonspecific interstitial pneumonitis, tobacco-related interstitial lung disease, or indeed other unclassifiable fibrotic lung disease [14–16]. The requirement of a specific histopathologic pattern on idiopathic pneumonia may inappropriately limit study of patients with CPFE to a subset of the actual number of individuals affected by this syndrome and may thereby distort future study of causes and outcomes. A diagnosis of CPFE should rely on the combination of typical clinical features, imaging, and congruent histopathologic findings.

One intriguing feature seen in our study population as a whole was an elevated prevalence of left ventricular diastolic dysfunction on echocardiography. This was noted in 17/36 (47%) of the CPFE subjects and isolated interstitial pulmonary fibrosis subjects on either baseline or follow-up echocardiography. In a recent study, left ventricular diastolic dysfunction was universal in a group of individuals with idiopathic pulmonary fibrosis [17]. Diastolic dysfunction also appears to be a feature of individuals with more heterogeneous causes of pulmonary fibrosis, as included in our study population.

The limitations of the present study include its retrospective nature, with dependence on data derived from tests ordered for clinical indications. Not all subjects underwent pulmonary function or echocardiographic examination, and in some cases studies had been done before the period during which the hospitalization occurred. More subjects might have been found to have pulmonary hypertension if greater numbers of right heart catheterizations had been performed, as seen in the one subject with CPFE who underwent right heart catheterization which confirmed the presence of pulmonary hypertension. Right heart catheterization remains the gold standard for the diagnosis of pulmonary hypertension, with echocardiography having significant limitations, especially in the setting of lung disease. We cannot conclude on the basis of this limited study that pulmonary hypertension is more or less common in individuals with CPFE than in those with isolated pulmonary fibrosis. However, we believe that had more subjects been included in our study, we likely would have seen a statistically significant difference in right ventricular dilation and possibly estimated pulmonary arterial pressures between the groups, given the trends in our data. Indeed, the most recent updated clinical classification of pulmonary hypertension includes “Other pulmonary diseases with mixed restrictive and obstructive pattern” because of increased prevalence of pulmonary hypertension in these patients [18]. Given the lack of specific approved therapeutic modalities, aside from supplemental oxygen therapy, available for the treatment of pulmonary hypertension in the setting of hypoxemia or lung disease, it is understandable that more subjects were not referred for clinical investigation to determine whether pulmonary hypertension was present.

Another limitation of our study is that lung volumes were determined using the helium dilution method, which could underestimate lung volumes in subjects with emphysema, thereby diminishing the apparent differences between groups. However, a recent study suggests that body plethysmography actually overestimates lung volumes in individuals with airway obstruction compared with a volumetric CT, with which helium dilution volumes were well correlated [19]. Despite these limitations, our study group was reasonably well characterized for such a retrospective study and ultimately represented a cohort with typical features of CPFE. The incomplete availability of pathologic results for patients in the study and control groups is unfortunate, but patients with advanced lung disease may not be appropriate candidates for biopsy. Further studies involving larger cohorts with available pathology would aid in characterizing the frequency of specific pathologic findings in CPFE. For such a relatively uncommon entity, a common patient registry may be beneficial in collecting such data prospectively.

The goal of our study was to assess the clinical and pulmonary function characteristics of a group of subjects with combined pulmonary fibrosis and emphysema compared to a group with isolated pulmonary fibrosis. A further limitation of our study was a lack of a quantitative radiographic scoring system to assess the extent of emphysema and fibrosis in our subjects. Such quantitative assessment techniques, e.g., for emphysema, are technically challenging, require specialized scanning features, and are not universally accepted for clinical use [20]. Quantitative imaging assessments were therefore beyond the scope of the current study. The consistency of clinical results in patients with CPFE identified on the basis of routine clinical radiographic studies compared with the features noted in such patients in prior studies confirms that such quantitative assessments are not necessary for routine clinical assessment and diagnosis of combined pulmonary fibrosis and emphysema. In future studies we plan to use quantitative imaging assessment in subjects with combined pulmonary fibrosis and emphysema to assess whether such imaging features provide additional prognostic or physiologic information.

In summary, we describe a group of individuals with combined pulmonary fibrosis and emphysema, all current or former cigarette smokers, who demonstrate typical, identifiable features of classic CPFE, including relative preservation of lung volumes and severely reduced gas exchange in the setting of imaging and/or pathologic evidence of emphysema and pulmonary fibrosis. Future prospective studies should be considered to identify whether the presence of emphysema in individuals with pulmonary fibrosis will result in unique outcomes and treatment goals meriting the formal separation of CPFE from other interstitial lung diseases in future consensus definitions.

Conclusions

Combined pulmonary fibrosis and emphysema, a subject of increasing clinical and research interest, has unique features representative of a clinical syndrome that occurs in susceptible individuals with exposure to cigarette smoke. Our study does not support worsened survival in individuals with CPFE than with pulmonary fibrosis alone. Further definition of the natural history of CPFE is needed.

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Fig. 1.
Flow diagram of subject selection

Fig. 2.

CT features of CPFE. Paired computed tomographic images (**a + b**; **c + d**; **e + f**; **g + h**; **i + j**; and **k + l**) from the upper and lower lung zones of six subjects (designated *patients A–F*) in the CPFE group illustrating areas of emphysema (*thin arrows*), which appeared to be distributed predominantly, though not exclusively, in the upper lobes, with fibrotic changes (*block arrows*) most marked in the lower lobes

Fig. 3. Kaplan–Meier survival curves for CPFE group (study group) and isolated pulmonary fibrosis group (control group). No significant difference in survival was seen between the two groups. Time is in months

Table 1

Baseline characteristics of the subjects

	CPFE group (n = 20)	PF group (n = 24)	p value
Age (as of initial study date)	69 ± 10	75 ± 10	NS
Sex (M/F)	20/0	24/0	
Past cigarette use	20/20 (100%)	19/24 (79%)	0.053 (NS)
Never smokers	0/20 (0%)	3/24 ^a (13%)	NS
Pack years (mean + SD)	57 ± 29	36 ± 29	NS
Baseline BMI (kg/m ²)	28 ± 6	27 ± 5	NS
Asbestos exposure (by history)	8/20 (40%)	5/24 (21%)	NS
Systemic hypertension	17/20 (85%)	15/24 (63%)	NS
Diabetes mellitus	11/20 (55%)	8/24 (33%)	NS
Coronary artery disease	8/20 (40%)	15/24 (63%)	NS
Myocardial infarction	6/20 (30%)	4/24 (17%)	NS
Atrial fibrillation	1/20 (5%)	4/24 (17%)	NS
Venous thromboembolism	2/20 (10%)	2/24 (8%)	NS
Obstructive sleep apnea	3/20 (15%)	4/24 (17%)	NS
Connective tissue disease	1/20 (5%)	0/24 ^b (0%)	NS

CPFE combined pulmonary fibrosis and emphysema, PF isolated pulmonary fibrosis

^aTwo who smoked a pipe only were not classified as having past cigarette use or being never smokers

^bTwo with multiple sclerosis

Table 2

Pulmonary function data

	CPFE group (n = 18)	PF group (n = 19)	p value
FEV ₁ (% pred.)	71 ± 20	67 ± 15	NS
FVC (% pred.)	77 ± 14	62 ± 16	0.006
FEV ₁ /FVC	0.67 ± 0.12	0.78 ± 0.09	0.006
TLC (% pred.)	76 ± 11	66 ± 15	0.032
VC (% pred.)	71 ± 13	62 ± 14	0.051 (NS)
RV (% pred.)	75 ± 24	73 ± 30	NS
RV/TLC	0.37 ± 0.10	0.42 ± 0.11	NS
DLCO (ml/min/mmHg)	7.6 ± 3.0	11.4 ± 4.1	0.003
DLCO (% pred.)	29 ± 11	50 ± 22	0.003
Hemoglobin range (g/dl)	12–16.7	9.1–15.3	

CPFE combined pulmonary fibrosis and emphysema, *PF* isolated pulmonary fibrosis

Table 3

Echocardiographic data

	CPFE group	PF group	<i>p</i> value
LV ejection fraction (%)	59 ± 3 (<i>n</i> = 19)	50 ± 16 (<i>n</i> = 18)	0.013
LV diastolic dysfunction			
Baseline echocardiogram	7/18	8/18	NS
Total on baseline or follow-up echocardiogram	9/18	8/18	NS
LV hypertrophy	2/17	4/16	NS
Wall motion abnormalities	2/18	6/18	NS
Abnormal RV function	5/14	3/13	NS
RV dilation	8/17	2/13	NS
RV hypertrophy	1/17	0/12	NS
Pulmonary hypertension (baseline echocardiogram)	7/18	5/16	NS
Average estimated pulmonary artery pressure if recorded (mmHg)	62 ± 32 (<i>n</i> = 7)	40 ± 10 (<i>n</i> = 8)	NS
Total pulmonary hypertension (by baseline/follow-up echocardiogram or catheterization)	8/19	5/16	NS

CPFE combined pulmonary fibrosis and emphysema, PF isolated pulmonary fibrosis

Table 4

Respiratory and pharmacologic treatments prescribed during the study period

	CPFE group (<i>n</i> = 20)	PF group (<i>n</i> = 24)	<i>p</i> value
Short-acting β agonists	17/20	17/24	NS
Short-acting anticholinergics	16/20	12/24	0.06 (NS)
Inhaled steroids	12/20	6/24	0.031
Long-acting β agonists	12/20	4/24	0.005
Long-acting anticholinergics	2/20	1/24	NS
Acute steroid taper	9/20	9/24	NS
Chronic steroids (>4 weeks duration)	6/20	8/24	NS
Nonsteroid immunosuppressants	3/20	2/24	NS
<i>N</i> -acetyl cysteine	2/20	3/24	NS
Oxygen prescription	16/20	13/24	NS
Mean flow rates (rest/exercise/sleep)	3.3/4.3/3.6 ($\pm$ 1.9/1.8/1.7)	3.0/4.1/3.5 ($\pm$ 1.8/1.7/1.6)	NS/NS/NS
Chronic continuous or bilevel positive airway pressure	2/20	3/24	NS

CPFE combined pulmonary fibrosis and emphysema, PF isolated pulmonary fibrosis

Table 5

Morbidity and mortality for the study period

	CPFE group	PF group	<i>p</i> value
Hospitalization for respiratory causes during study period	15/20	19/24	NS
Lung cancer diagnosis prior to or during study period	3/20 ^a	1/24 ^b	NS
Lung cancer type	2 small-cell; 1 non-small-cell	1 small cell	
Other aerodigestive tract cancers	1 esophageal cancer	2 head and neck cancers	
Number receiving acute invasive mechanical ventilation during study period	0/20	5/24	0.053 (NS)
Number receiving acute noninvasive ventilation during study period	2/20	2/24	NS
Mortality as of 4/1/08 (end of study period)	13/20 (65%)	17/24 (71%)	NS

CPFE combined pulmonary fibrosis and emphysema, *PF* isolated pulmonary fibrosis

^a A fourth subject had a lung mass and cytology “suspicious” for lung cancer

^b A second subject had metastatic carcinoma, suspected lung primary