

**Review Article**

**Combined pulmonary fibrosis and emphysema (CPFE)**

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**Abstract**

Combined pulmonary fibrosis and emphysema (CPFE) is rare but increasingly recognized condition characterized by simultaneous coexistence of both upper lobe predominant emphysema and diffuse pulmonary fibrosis mainly in lower lobe. Patients with CPFE are usually heavy smokers or former smokers. HRCT has a pivotal role in diagnosis. Pulmonary function test showed relatively preserved lung volumes and reduced diffusing capacity of the lung for carbon monoxide (DLCO). Development of pulmonary hypertension (PH) is largely attributed to morbidity in patients with CPFE which is the principal prognostic factor for this condition. However more studies are needed to establish natural history of the disease & treatment option. In this review, we will discuss the current knowledge of the pathogenesis, clinical characteristics, treatment options and prognostic factors of CPFE.

**Keywords:** Combined pulmonary fibrosis and emphysema (CPFE), pulmonary arterial hypertension (PAH), forced expiratory volume in 1 second (FEV1).

**Introduction:**

Combined pulmonary fibrosis and emphysema (CPFE) is a radiologically defined syndrome characterized by simultaneous coexistence of both upper lobe predominant emphysema and lower lobe pulmonary fibrosis. With the advent of HRCT, the combination of these two conditions has been increasingly described and has been proven to be a prevalent and distinct entity rather than a rare coincidence. Initially the association of Interstitial Pulmonary Fibrosis (IPF) and emphysema was described by Wiggins et al in 1990. But the term CPFE was first used in 2005 by Cottin et al who described a group of patients with CT findings of emphysema in the upper zones and interstitial lung disease (ILD) with pulmonary fibrosis in the lower lobes. In 2005 Grubstein et al. reported an association of fibrosis with emphysema in eight patients, their clinical and functional findings being similar to those of the aforementioned study. The authors also found moderate to severe pulmonary arterial hypertension (PAH) and postulated that smoking is an important factor linking emphysema, pulmonary fibrosis, and pulmonary vascular disease. When CPFE was first described, patients with ILDs other than interstitial pulmonary fibrosis (IPF) were excluded from the study. Later on, CPFE was described in patients with other ILDs, such as connective tissue disease (CTD) associated ILD, as well as in patients with microscopic polyangiitis.

The fact that IPF has the worst prognosis in relation to other chronic lung fibrotic diseases, it is important to establish the interstitial lung disease that constitutes the fibrotic component of CPFE. Patients with CPFE are predominantly male, with a history of heavy tobacco exposure, and usually present with severe breathlessness and cough. Physical examination reveals “Velcro” crackles at the lung bases and digital clubbing. Pulmonary hypertension is a hallmark of the syndrome and determines poor prognosis. Studies have shown that patients with CPFE associated with CTDs (e.g. rheumatoid arthritis and systemic sclerosis) are significantly younger than their idiopathic CPFE counterparts, are predominantly female, and have less DLCO impairment.

**Pathogenesis:**

The exact pathogenetic mechanisms that lead to the development of CPFE has yet to be elucidated. Smoking is believed to play a major role as almost all (about 98%) of CPFE patients are current or former smokers. Tobacco smoke-induced oxidative and nitrate stress in the lungs may amplify inflammation due to reduced histone deacetylase activity that may contribute pathogenetically to both emphysema and fibrosis. Smoking may also contribute to both emphysema and fibrosis by over expression of tumor necrosis factor-α and platelet-derived growth factor-β(PDGF-β). Exposure to agrochemical substances has also been described as risk factor for CPFE. Diaz CleLeon et al. demonstrated evidence of emphysema in 20% of telomerase mutation carriers with idiopathic pulmonary fibrosis(IPF). Cottin et al. reported a dominant mutation 173T in the surfactant protein C gene in a patient with CPFE.

**Lung Function in CPFE:**

In patients with CPFE, spirometry can be normal or show mild abnormalities. They typically present with preserved or slightly reduced lung volumes in relation to the extent of fibrotic changes in the lungs. Forced vital capacity (FVC), FEV1, and Total lung capacity(TLC) values usually within normal limits or slightly reduced. The ratio FEV1/FVC can be normal or reduced (<70%) and is lower compared to patients...
with IPF alone. One possible explanation for normal or subnormal spirometry results despite severe impairment in DLCO is that hyperinflation and greater lung compliance as a result of loss of elasticity in the areas of emphysema can compensate for the losses in volume and lung compliance caused by fibrosis. Another plausible explanation is that fibrosis prevents the early small airway closure observed in patients with emphysema. However, both processes cause damage to the alveolar-capillarv membrane resulting in a disproportionately reduced DLCO.1,7-10 In patients with CPFE, arterial oxygen tension (PaO2) and arterial oxygen saturation (SaO2) at rest, and SaO2 and PaO2 at exercise are significantly decreased.20,21 Hypercapnia is usually not observed.1,22 Patients with fibrosis adopt a rapid/shallow pattern of breathing which increases alveolar ventilation and thus reduces the levels of alveolar and blood pCO2. Exertional dyspnea is the most common presenting symptom in patients with CPFE. on examination, end-inspiratory fine ‘velcro’ crackles mainly in basal regions are the predominant findings and digital clubbing may also be seen in many of these patients.22

Imaging studies in CPFE:

The diagnosis of the CPFE syndrome is based on findings on High-Resolution Computed Tomography (HRCT) of the chest.1 HRCT scans typically show centrilobular or paraseptal emphysema in the upper lobes, as well as reticular opacities, traction bronchiectasis, septal thickening, ground-glass opacities, and honeycombing in the lower lobes. (Figures 1). Although Usual Interstitial Pneumonia (UIP) is the most common CT pattern, some patients have ground-glass opacities that are more extensive than expected for a UIP pattern and are therefore suggestive of nonspecific interstitial pneumonia, Respiratory Bronchiolitis Interstitial Lung Disease (RB-ILD), and even Desquamative Interstitial Pneumonia (DIP).1

Paraseptal emphysema seems to be more common in the CPFE population than in patients with COPD. In the study by Cottin et al.1 it was observed in 93% of patients and was suggested to be a hallmark of CPFE. The increased prevalence of paraseptal emphysema in CPFE was also observed in another study. Furthermore, the presence of paraseptal emphysema has been associated with a higher extent of fibrosis in comparison to centrilobular emphysema.23

The coexistence of emphysema and fibrosis makes the estimation of the extent of fibrosis really difficult. In the transition zone of the emphysematic to the fibrotic areas it is very tricky to make the appropriate distinction. Brillet et al.24 identified three HRCT patterns in 61 patients with CPFE: i) progressive transition (38%) with diffuse emphysema (centrilobular and/or bullous) and zone of transition between bullae and honeycombing, ii) paraseptal emphysema (21%) with predominant subpleural bullae of enlarging size at the bases and iii) separate processes (23%) with independent areas of fibrosis and emphysema.

CPFE and pulmonary hypertension (PH):

The prevalence of PAH is exceedingly high in patients with CPFE, and PAH correlates with worse survival.1,24,25 The prevalence of PAH in CPFE patients varies from 47% to 90%, being considerably higher than that in patients with COPD or IPF alone.26 Transthoracic echocardiography used to measure pulmonary artery pressure (Ppa) is an operator dependent imaging examination. Furthermore, the presence of emphysema can add further difficulties in the accurate estimation of right ventricular systolic pressure (RVSP). Right heart catheterization (RHC) remains the gold standard for the diagnosis of PAH. Cottin et al. retrospectively estimated the prevalence of PAH in 40 CPFE patients with RHC.24 Out of them 27 patients (68%), the mean Ppa was >35 mmHg.

The increased prevalence of PAH in CPFE is probably explained by the coexistence of emphysema and fibrosis. Both cause destruction of the pulmonary vasculature bed and of the lung parenchyma. The destruction of pulmonary vasculature reduces the total cross sectional area. Furthermore, as mentioned CPFE patients are usually hypoxemic due to V/Q mismatching caused by the coexisting emphysema and pulmonary fibrosis. The induced hypoxic pulmonary vasoconstriction is also an important cause of elevated pulmonary arterial pressure. If other pathogenic pathways are implicated, then the development of “out of proportion” PAH remains to be clarified. From a clinical point of view the physician should be vigilant in looking for underlying intermittent nocturnal and exercise induced intermittent hypoxia.27-29

Novel noninvasive methods for the diagnosis and quantification of PAH in CPFE patients have been proposed, including time-resolved Magnetic Resonance Angiography (MRA), which allows anatomic imaging of the pulmonary vasculature and evaluation of hemodynamic parameters. Using this technique, Sergiacomi et al. prospectively studied...
18 CPFE patients using pulmonary arterial mean transit time and time to peak enhancement as surrogate parameters for hemodynamic data (mean pulmonary artery pressure and pulmonary vascular resistance), which were obtained through right heart catheterization performed three days before time-resolved MRA was performed. Pulmonary arterial mean transit time and time to peak enhancement showed good correlation with the invasive parameters.30

Patient Management & Prognosis:

Therapeutic options for patients with CPFE are limited. According to the most recent international guidelines, there are no data on which to make recommendations for treatment of emphysema in the setting of IPF.31 Smoking cessation is an obvious objective. Oxygen therapy is appropriate for the management of hypoxemia. Inhaled bronchodilators are often prescribed. Currently, there are two approved drugs for the treatment of IPF, pirfenidone and nintedanib.32 They slowed disease progression by reducing the annual rate of FVC decline independent of the presence of emphysema at baseline.33 The main concern is whether pirfenidone and nintedanib are efficacious in CPFE, but whether the rate of FVC decline underestimates their efficacy in this specific subgroup.

The presence of emphysema and abnormal pulmonary pathology in patients with CPFE and pulmonary hypertension may be associated with an imbalance in the ventilation / perfusion ratio (V/Q), as hypoxic vasoconstriction is one of the main mechanisms to avoid worsening arterial oxygenation. Vasodilator drugs can worsen hypoxemia by inhibiting this mechanism.34 Specific therapies approved for treating pulmonary arterial hypertension in appropriately designed trials are also necessary to study the effect of these drugs in CPFE patients.35

Patients with CPFE seem to be at greater risk for developing lung cancer. Thus, increased vigilance is required for early detection of such lesions. Management of lung cancer in CPFE patients should follow current guidelines.36 Stem cell therapy is a promising approach for COPD and IPF. Conducting clinical trials of stem cell therapy in CPFE is an intriguing project that could shed further light in the areas of pathogenesis and treatment.37

In IPF patients the follow up and response to therapy are based on the measurement of FVC and DLCO. However, CPFE patients tend to exhibit a delay in the reduction of FVC and DLCO which reduces their utility as surrogate markers for disease progression.37, 38. In addition, a decline in DLCO should be viewed cautiously, as it could be the result of development/progression of pulmonary hypertension which is commonly encountered in CPFE. The annual decrease of the ratio FEV1 / FVC in CPFE seems to be significantly higher compared to IPF.37, 19

In a study by Schimdt et al., mortality in CPFE patient was better predicted by the decline in FEV1, while changes in FVC, DLCO and Composite Physiological Index (CPI) were not predictive at 12 months follow-up and only FVC was predictive at 6 months.39. The prognostic validity of FEV1 increased with increasing severity of emphysema in a dose-dependent fashion. On the other hand, FEV1 had no prognostic role in patients with IPF and with no emphysema.

Conclusion:

CPFE is a recently recognized entity with unique features. It is more frequent (30%) than previously believed and may have a worse prognosis than IPF alone, with PAH being the major determinant of morbidity and mortality. The rate of FEV1 decline is the strongest predictor of mortality.

It is obvious that many aspects of the CPFE syndrome still remain to be explored. Further studies are needed to ascertain the aetiology, morbidity, mortality and management of CPFE, with or without PH, and also to delineate more precisely the boundaries between IPF and patients with CPFE syndrome. Further research is essential to understand etiology, pathophysiology, and management of this distinct clinical entity.

References:


