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REVIEW

The impact of emphysema in pulmonary fibrosis

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ABSTRACT: Several groups have described a syndrome in which idiopathic pulmonary fibrosis (IPF) coexists with pulmonary emphysema. This comes as no surprise since both diseases are associated with a history of exposure to cigarette smoke. The syndrome of combined pulmonary fibrosis and emphysema (CPFE) is characterised by upper lobe emphysema and lower lobe fibrosis. Physiological testing of these patients reveals preserved lung volume indices contrasted by markedly impaired diffusion capacity. The incidence of CPFE remains unknown but several case series suggest that this subgroup may comprise up to 35% of patients with IPF. CPFE is a strong determinant of associated pulmonary hypertension (PH). In addition, CPFE has major effects on measures of physiological function, exercise capacity and prognosis, and may affect the results of pulmonary fibrosis trials. Further studies are needed to ascertain the aetiology, morbidity, mortality and management of the CPFE syndrome, with or without PH, and to evaluate novel therapeutic options in CPFE.

KEYWORDS: Combined pulmonary fibrosis and emphysema, emphysema, idiopathic pulmonary fibrosis, pulmonary hypertension

Pulmonary emphysema and the idiopathic interstitial pneumonias, of which idiopathic pulmonary fibrosis (IPF) is the most frequent, are entities defined by distinct clinical, functional, radiological and pathological characteristics. Having traditionally been considered as separate disorders, recent studies suggest that the diseases are more commonly associated than previously considered [1]. Indeed, several groups have described series of combined pulmonary fibrosis and emphysema (CPFE) [1–4], with upper lobe emphysema and pulmonary fibrosis of the lower lungs [5]. Initially reported to be coincidental and not comprehensively described [6], CPFE has been proposed as a distinct syndrome [3, 7, 8].

DISEASE CHARACTERISTICS

CPFE is most often observed in males (mean age of 65 years) who are tobacco smokers or ex-smokers of >40 pack-years [9, 10]. CPFE has a poor prognosis, with a 5-year survival of 55% [4]. CPFE may be found in patients presenting with lung cancer, and cancer may develop in patients followed for CPFE, probably reflecting similarities in the susceptibility to chronic smoking-induced inflammation and carcinogenesis [11, 12].

The syndrome of CPFE results from the association of distinct features and symptoms, that include severe dyspnoea, unexpected subnormal spirometry findings, severely impaired transfer capacity for carbon monoxide, hypoxaemia at exercise, and characteristic imaging features [8, 13–15]. Basal crackles are heard on auscultation (table 1) [4, 9]. Severe impairment in gas exchange often parallels significant exercise limitation and contrasts with the relative lack of clinical manifestation at rest.

The symptoms and morbidity in patients with CPFE are largely attributable to the development of severe precapillary pulmonary hypertension (PH) [16, 17]. The risk of the development of PH is elevated (about 50%) and is higher in patients with CPFE than either IPF or emphysema alone, and its onset heralds a poor prognosis and increased mortality [4, 18]. In one cohort of 110 patients, 31 (28%) patients with CPFE had a higher mortality than IPF patients without emphysema (median survival time of 25 *versus* 34 months, p=0.01) [16]. However, adjusting for disease severity is difficult in CPFE.

PATHOLOGY AND PATHOGENESIS

It is unclear whether emphysematous and fibrotic lesions progress independently or if one is the

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TABLE 1 Characteristics and clinical manifestations at diagnosis in 61 patients with combined pulmonary fibrosis and emphysema

Patient characteristics	
Sex	
Male	60
Female	1
Age years	65.2±10.2 (36–84)
Body mass index kg·m^{-2}	26±3 (19–32)
Smoking status	
Current smoker	19
Ex-smoker	42
Never-smoker	0
Pack-years smoking	46±27 (5–120)
Current smokers	57±27 (8–120)
Ex-smokers	41±25 (5–110)
Asthenia	14 (23)
NYHA grade of dyspnoea	
Grade 1	10 (16)
Grade 2	23 (38)
Grade 3	23 (38)
Grade 4	5 (8)
Cough	29 (48)
Sputum production	22 (36)
Chest pain	10 (17)
Finger clubbing	26 (43)
Basal crackles	53 (87)
Wheezes	8 (13)

Data are presented as n, mean±SD (range) or n (%). NYHA: New York Heart Association. Reproduced from [4].

result of the development of the other [5]. In most cases, CPFE occurs as the development of fibrosis superimposed on a known history of emphysema that may modify its progression. Conversely, it has also been suggested that the presence of pulmonary emphysema modifies the outcome of patients with IPF [5]. Thus, CPFE deserves to be termed a ''syndrome'' because of the association of symptoms and clinical manifestations, each with a probability of being present increased by the presence of the others [8]. CPFE also warrants inclusion as a distinct pulmonary manifestation within the spectrum of connective tissue disease-associated lung diseases, such as rheumatoid arthritis and systemic sclerosis [19].

Although tobacco smoking has been identified as a major cause, the exact pathophysiology of the CPFE syndrome is unclear [20, 21]. Possible additional risk factors have been identified, such as exposure to agrochemical compounds [22]. It is also recognised that overexpression of tumour necrosis factor-α and platelet-derived growth factor-β in mouse lungs produces airspace dilatation and fibrosis [23, 24]. Individual genetic backgrounds may also predispose to the development of CPFE. A polymorphism in the promoter of the matrix metalloproteinase-1 gene, for example, has been identified in smokers [25], and it is conceivable that such pathway might be dysregulated in patients with CPFE. A heterozygous mutation in *SFTPC* (the gene encoding surfactant protein C) has been reported in a nonsmoking young female with CPFE [26]. In addition, both fibrosis and emphysema are associated with shorter telomeres [27, 28], and smokers also have shorter telomeres as compared with nonsmokers [29].

CLINICAL FEATURES

The quantification and interpretation of disease severity using pulmonary function tests in patients with IPF is often confounded by coexistent emphysema and results in a spurious preservation of lung volume and depression of gas transfer [30, 31]. However, although pulmonary function tests usually show respiratory volumes and flows that are normal or subnormal, diffusing capacity of the lung for carbon monoxide (D_{LCO}) is substantially reduced and exercise hypoxaemia is common (table 2). Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), arterial oxygen tension (P_{aO_2}) and arterial oxygen saturation (S_{aO_2}) at rest, and S_{aO_2} and P_{aO_2} at exercise are significantly decreased in patients with CPFE [4, 14, 32].

The composite physiological index is a measure derived to capture the effect of emphysema on IPF by fitting pulmonary function tests against disease extent on computed tomography [33, 34]. This index is simple to calculate (based on % predicted D_{LCO}, FVC and FEV_1), and has been shown to reflect the extent of disease more accurately than single physiological indices and is also a powerful predictor of mortality (fig. 1) [35].

RADIOLOGICAL FEATURES

The diagnosis of the CPFE syndrome is based on findings on high-resolution computed tomography (HRCT) of the chest [4, 5]. Although emphysema may modify the HRCT appearance of fibrosis [36], the characteristic imaging features of CPFE (table 3) include radiological evidence of emphysema in the upper zones (*i.e.* centrilobular and/or paraseptal emphysema in 90% of cases [26]), and diffuse infiltrating fibrosing lung disease at the bases (subpleural reticular opacities, honeycomb images and traction bronchiectasis), with more frequent ground-glass opacities than in IPF. However, patients with CPFE show a high HRCT fibrotic score ($p=0.015$) [13, 14, 37].

PATIENT MANAGEMENT

Therapeutic options for patients with CPFE are limited and may require treatment for both IPF and emphysema. 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 [38]. Smoking cessation is an obvious objective. Oxygen therapy is appropriate for the management of hypoxaemia. Inhaled bronchodilators are often prescribed.

Treatment with immunomodulator therapy, similar to that used for treating IPF, *e.g.* *N*-acetylcysteine or novel agents such as pirfenidone, has been considered, although no studies have been published to date on this issue. Triple combination therapy with corticosteroids and *N*-acetylcysteine, with or without azathioprine, is discouraged if a diagnosis of IPF is made. However, it must be considered that the inclusion of patients with CPFE syndrome in IPF clinical trials may lead to spurious under-evaluation of the effect of treatment in IPF patients [8].

The possibility of using specific therapies approved for treating pulmonary arterial hypertension (*i.e.* endothelin-1 receptor antagonists, prostanoids or phosphodiesterase type

TABLE 2 Pulmonary function tests in 61 patients with combined pulmonary fibrosis and emphysema

Test	Patients tested n	
FVC % pred	61	90±18 (47–125)
FEV_1 % pred	61	80±21 (33–123)
Post-bronchodilator improvement in FEV_1 L	36	0.06±0.13 (-0.35–0.3)
FEV_1/FVC %	61	69±13 (30–94)
$FEF_{25–75\%}$ % pred	57	51±26 (15–118)
TLC % pred	56	88±17 (44–132)
RV % pred	56	90±32 (35–188)
D_{LCO} % pred	57	37±16 (10–80)
K_{CO} % pred	57	46±19 (8–84)
P_{aO_2} at rest (surpine position) kPa	61	8.4±1.9 (4.6–13.3)
P_{aCO_2} at rest (surpine position) kPa	61	4.9±0.7 (3.0–7.3)
Alveolar–arterial P_{aO_2} difference (room air) kPa	61	5.5±2.1 (0.1–11.7)
P_{aO_2} at exercise–P_{aO_2} at rest (surpine position) kPa	22	-1.5±1.6 (-4.4–1.7)
6-min walking distance m	23	336±139 (50–548)
Decrease in S_{pO_2} during 6-min walk test %	23	-8.9±5.7 (-20–0)

Data are presented as mean±SD (range), unless otherwise stated. FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75\%}$: mean forced expiratory flow between 25% and 75% of FVC; TLC: total lung capacity; RV: residual volume; D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry. Reproduced from [4].

5 inhibitors) in appropriately designed trials are also necessary to study the effect of these drugs in these patients [18, 39, 40]. It is important to point out, however, that 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 hypoxaemia by inhibiting this mechanism [39–41].

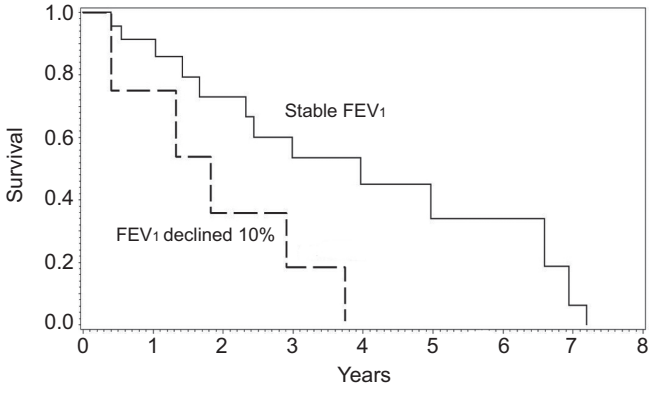

FIGURE 1. Cox model survival estimates for relevant 12-month longitudinal changes in pulmonary function tests in patients with combined idiopathic pulmonary fibrosis and moderate/severe emphysema. A relative decline in forced expiratory volume in 1 s (FEV_1) of >10% predicted *versus* <10% is shown. Physiological cut-off points were chosen based on prior literature and the best prognostic fit according to index of concordance. All Cox models are adjusted for the baseline average pulmonary function test, average age at diagnosis of 62 years, male sex and positive smoking history. Reproduced from [35].

DISCUSSION

CPFE is a distinct but under-recognised and common syndrome with a characteristic presentation. It is more frequent (30%) than previously believed and may have a worse prognosis than IPF alone, with PH being the major determinant of morbidity and mortality. It is clear that many aspects of the CPFE syndrome remain to be explored. Further studies are needed to ascertain the aetiology, morbidity, mortality and management of CPFE, with or without PH, and to delineate more precisely the boundaries between IPF and patients with CPFE syndrome. In particular, studies are required to determine the following aspects of CPFE: 1) the pathophysiological mechanisms of CPFE, including risk factors other than smoking; 2) definition, classification and staging of CPFE, *e.g.* boundaries between IPF and the CPFE syndrome;

TABLE 3 Imaging features of combined pulmonary fibrosis and emphysema

Feature	
Emphysema	100
Centrolobular	97
Paraseptal	93
Bullae	54
Fibrosis	100
Honeycombing	95
Reticulation	87
Traction bronchiectasis	69
Ground-glass opacities	66
Consolidation	15

Data are presented as %. Reproduced with modification from [4].

3) identification and relevance of different CPFE phenotypes; 4) validation of robust and specific outcome measures; and 5) development of therapeutic options in CPFE.

STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at err.ersjournals.com

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