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EDITORIAL

Combined pulmonary fibrosis and emphysema: a high-pressure situation

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The combination of pulmonary fibrosis and emphysema (CPFE) was first described in 1990 by WIGGINS *et al.* [1]. Subsequent case studies further described what are now recognised as hallmarks of the syndrome: significant dyspnoea, a predilection for the disease among male smokers, normal or near normal lung volumes resulting from the opposing effects of hyperinflation and fibrosis, and a significantly reduced diffusing capacity [2–4]. More recent work has demonstrated that significant pulmonary hypertension is also common in patients with CPFE and associated with shortened survival [5–7]. However, these studies relied on transthoracic echocardiography (TTE) without confirmation by right heart catheterisation (RHC) to diagnose pulmonary hypertension, an approach that may have important limitations [8, 9].

In this issue of the *European Respiratory Journal*, COTTIN *et al.* [10] present the results of a retrospective, multicentre cohort study of patients with CPFE and pulmonary hypertension confirmed by RHC. The study cohort was derived from a population of patients meeting diagnostic criteria for CPFE who were reported to a registry of orphan diseases and who subsequently underwent annual TTE to assess for the development of pulmonary hypertension. Patients were referred for RHC by their treating physicians guided by the TTE results. Those with a mean pulmonary artery pressure ($\bar{P}_{pa}$) >25 mmHg, a pulmonary capillary wedge pressure <15 mmHg and a pulmonary vascular resistance (PVR) >240 dyn·s·cm^{-5} were included in the analysis. The patient cohort had a median follow-up after RHC of 8 months.

This study not only confirms many of the clinical characteristics of CPFE described in prior studies but also provides several new and important insights. First, the mean time from diagnosis with CPFE to diagnosis of pulmonary hypertension was 16 months, suggesting that pulmonary hypertension can occur rapidly after diagnosis. Secondly, patients with pulmonary hypertension had a very poor prognosis with an estimated survival of only 60% at 1 yr. Thirdly, univariate analyses demonstrated a physiologically consistent pattern in which increasing P_{pa}, PVR and heart rate, and lower cardiac index, were significantly associated with a higher risk of death. Finally, lower diffusing capacity of the lung for carbon monoxide was also associated with increased mortality.

This work has several strengths. First, unlike prior studies that required lung volume restriction for study inclusion [7], this study used American Thoracic Society/European Respiratory Society diagnostic criteria for idiopathic pulmonary fibrosis (IPF) that were broadened to include patients with normal lung volumes. These revised criteria increase the generalisability of the study by including a more representative population of CPFE patients and avoid the potential bias associated with selecting only those patients with more advanced fibrosis [11]. Secondly, the use of RHC to measure P_{pa} and PVR provides a more accurate definition of the primary exposure, thereby enhancing the scientific validity of the observed association between pulmonary hypertension and mortality. Finally, the authors were able to assess the impact of separate haemodynamic parameters and clinical variables on long-term survival.

The study also has limitations. The short median follow-up time precluded estimates of long-term survival, including median and 5-yr survival; however, the frequency of events early in follow-up and the high 1-yr mortality are sufficient to illustrate a significant effect of pulmonary hypertension on prognosis. The nonprotocolised decision to perform RHC may have introduced a selection bias if patients with the most significant symptoms or severe disease were chosen to undergo RHC rather than continued noninvasive monitoring. This bias may have overestimated the impact of pulmonary hypertension on survival. Finally, because of the small number of outcomes, the authors were unable to perform a multivariate analysis to control for confounding.

Despite these limitations, this study makes an important contribution to our understanding of CPFE as a clinical entity. However, several mechanistic and clinical questions remain. It is still unclear whether the appearance of both processes is simply the coincidence of two diseases with distinct underlying mechanisms but a common risk factor, or whether there is a shared pathway in certain individuals that results in both fibrosis and emphysema after exposure to cigarette smoke. Animal models have suggested shared mechanisms through which cigarette smoke could lead to both emphysema and IPF [12–14], but these mechanisms have not been substantiated in humans.

Pulmonary hypertension has been shown to be substantially more common and more severe in CPFE than in either IPF or

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emphysema alone. It is possible that the prevalence and severity of pulmonary hypertension is simply an additive effect of two disease processes independently associated with pulmonary hypertension. A more intriguing possibility is that there is a common process in susceptible individuals, perhaps mediated through chronic inflammation induced by cigarette smoke that results in vascular remodelling in addition to fibrosis and emphysema. While animal data suggest a common link is at least theoretically possible [14, 15], there are as yet no human studies defining whether pulmonary hypertension in CPFE is one part of a single biological response or a by-product of two distinct synergistic entities.

In the meantime, does the recognition of emphysema have added clinical significance beyond the diagnosis of IPF alone? Once pulmonary hypertension has developed, both CPFE and IPF have a similarly poor prognosis [7, 16–18] and options for medical therapy are unproven. However, early in the disease course, the recognition of emphysema in patients with IPF has critical implications for monitoring. The prognosis of patients with CPFE is tightly linked to the development of pulmonary hypertension, and clinical surveillance should include regular assessments of pulmonary artery pressures. While TTE is most convenient, the inaccuracy of systolic P_{pa} estimates by echo in patients with advanced lung disease suggests that physicians should have a low threshold to perform RHC in cases where eligibility for, timing of and selection of single *versus* double lung transplantation depend upon an accurate determination of haemodynamics [8, 9, 16, 19].

Additionally, it should be noted that some of the methods commonly used to follow patients with IPF may not be useful in the management of CPFE. For instance, serial spirometry is commonly used as a measure of disease progression in IPF [20]; however, it has been shown that forced vital capacity declines more slowly in patients with CPFE than in those with IPF, despite similarly poor survival in both groups [21]. Repeated measures of lung volumes are therefore unlikely to provide an accurate assessment of disease trajectory and may even provide false assurances of disease stability. In such cases, worsening hypoxaemia may indicate progression of CPFE in the absence of spirometric changes.

Because of these complexities in clinical presentation and monitoring, it has been suggested that patients with CPFE should be excluded from future studies of IPF [11]. Certainly CPFE patients with normal or near normal pulmonary function tests at baseline and a slower average rate of decline in measured lung volumes could distort the results of trials that use changes in spirometry as a marker of disease progression [21]. This is also an important consideration in future studies examining prognostic markers in IPF. Additionally, although patients with CPFE may satisfy all diagnostic criteria for IPF, including the presence of usual interstitial pneumonia pattern on surgical biopsy, it is not known whether CPFE and isolated IPF share a common pathogenetic mechanism. Combining these patients in prospective trials may therefore mask an observable treatment response in either group. Similarly, the impact that CPFE may have had on past observational studies and clinical trials should be examined.

Our understanding of the combination of pulmonary fibrosis and emphysema is still evolving. It is clear, however, that the presence of emphysema in patients with IPF has important implications for survival associated with the development of pulmonary hypertension and important ramifications for disease surveillance. It is also evident that future studies on the mechanism and management of this syndrome are needed. Many questions remain unanswered, and the pressure is building.

STATEMENT OF INTEREST

None declared.

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