Eur Respir J 2010; 35: 105–111
DOI: 10.1183/09031936.00038709
Copyright©ERS Journals Ltd 2010

Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome

V. Cottin*[,f], J. Le Pavec[#,f], G. Prévot[¶], H. Mal[+], M. Humbert[#], G. Simonneau[#], J-F. Cordier* and GERM"O"P[§]

ABSTRACT: This study aims to describe the haemodynamic and survival characteristics of patients with pulmonary hypertension in the recently individualised syndrome of combined pulmonary fibrosis and emphysema.

A retrospective multicentre study was conducted in 40 patients (38 males; age 68±9 yrs; 39 smokers) with combined pulmonary fibrosis and emphysema, and pulmonary hypertension at right heart catheterisation.

Dyspnoea was functional class II in 15%, III in 55% and IV in 30%. 6-min walk distance was 244±126 m. Forced vital capacity was 86±18%, forced expiratory volume in 1 s 78±19%, and carbon monoxide diffusion transfer coefficient 28±16% of predicted. Room air arterial oxygen tension was 7.5±1.6 kPa (56±12 mmHg). Mean pulmonary artery pressure was 40±9 mmHg, cardiac index 2.5±0.7 L·min^{-1}·m^{-2} and pulmonary vascular resistance 521±205 dyn·s·cm^{-5}. 1-yr survival was 60%. Higher pulmonary vascular resistance, higher heart rate, lower cardiac index and lower carbon monoxide diffusion transfer were associated with shorter survival.

Patients with combined pulmonary fibrosis and emphysema syndrome and pulmonary hypertension confirmed by right heart catheterisation have a dismal prognosis despite moderately altered lung volumes and flows and moderately severe haemodynamic parameters.

KEYWORDS: Chronic obstructive pulmonary disease, disproportionate, emphysema, pulmonary fibrosis, pulmonary hypertension, tobacco smoking

AFFILIATIONS
*Hospices civils de Lyon, Hôpital Louis Pradel, Service de pneumologie – Centre de référence des maladies pulmonaires rares, Université de Lyon, Université Lyon I, UCBL-INRA-ENVL-EPHE, UMR754, IFR128, Lyon,
[#]Assistance publique – Hôpitaux de Paris, Hôpital Antoine Béclère, Service de pneumologie et réanimation, Centre de Référence de l'hypertension artérielle pulmonaire, Université Paris sud 11, Clamart,
[¶]Service de pneumologie, Hôpital Larrey, Toulouse,
[+]CHU Bichat, Paris, France.
[§]A list of contributors from the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P) and their affiliations can be found in the Acknowledgements section.
[f]Both authors contributed equally.

CORRESPONDENCE
J-F. Cordier
Hôpital Louis Pradel
69677 Lyon (Bron) Cedex
France
E-mail: jean-francois.cordier@chu-lyon.fr

Received:
March 07 2009
Accepted after revision:
July 18 2009
First published online:
July 30 2009

Idiopathic pulmonary fibrosis (IPF) is a severe chronic disease of unknown aetiology, with a median survival of 3 yrs. In smokers, some emphysema may be associated with IPF [1–3]. We recently individualised the syndrome of combined pulmonary fibrosis and emphysema (CPFE) [4] based on high-resolution computed tomography (HRCT) of the chest in a homogeneous group of 61 patients, further characterised by severe dyspnoea on exertion, subnormal spirometry, severe impairment of gas exchange and a median survival of 6.1 yrs [5]. CPFE is probably related to tobacco smoking, a common risk factor for both emphysema and fibrosis (with odds ratios of up to 3.6 in familial fibrosis) [6, 7].

Patients with advanced IPF have a high prevalence of pulmonary hypertension [8, 9], with 31–46% of patients with mean pulmonary arterial pressure (P_{pa}) >25 mmHg at right-sided heart catheterisation (RHC) at evaluation for lung transplantation [9–12] and 86% at the time of transplantation [13]. Similarly, the prevalence of pulmonary hypertension (defined by mean P_{pa} >20 mmHg) in patients hospitalised for chronic obstructive pulmonary disease (COPD) is ~50% [14], and may be as high as 50–90% in COPD patients evaluated for lung volume reduction surgery or lung transplantation [15, 16]. The pejorative prognostic significance of pulmonary hypertension has been demonstrated in both IPF [9, 10, 17] and COPD [18].

Two studies have reported that pulmonary hypertension is frequent in patients with the CPFE syndrome [5, 19], with 47% of patients with estimated systolic right ventricular pressure ⩾45 mmHg at echocardiography [5]. The risk of developing pulmonary hypertension is much higher in CPFE than in IPF without emphysema

For editorial comments see page 9.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

(OR 19, 95% CI 5.1–68.7) [19]. The prognosis of CPFE is worse than that of IPF without emphysema, an outcome determined by severe pulmonary hypertension and not only by the presence of associated emphysema [19]. Indeed, pulmonary hypertension is associated with an increased risk of death in CPFE (hazard ratio 4.03), with 5-yr probability of survival of 25% in patients with pulmonary hypertension at echocardiography compared with 75% in those without pulmonary hypertension at diagnosis [5]. CPFE syndrome has been included in the updated clinical classification of the aetiology of pulmonary hypertension under the category (3.3) of lung disease characterised by a mixed obstructive and restrictive pattern [20]. However, pulmonary hypertension was evaluated by echocardiography only in both studies [5, 19] as haemodynamic analysis is not yet available for CPFE. Thus, the objective of the present study was to describe the haemodynamic characteristics and their relationship to survival in patients with CPFE and pre-capillary pulmonary hypertension demonstrated by RHC.

PATIENTS AND METHODS

Study design

This retrospective multicentre study was conducted by the French reference centre for rare pulmonary diseases (coordinator, J-F. Cordier), the French reference centre for pulmonary hypertension (coordinator, G. Simonneau) and the Groupe d'Etudes et de Recherche sur les Maladies ''Orphelines'' Pulmonaires (GERM''O''P), a collaborative group dedicated to the study of rare (so-called ''orphan'') pulmonary diseases. Following the previous study [5], all participating physicians of the group were asked to prospectively report all cases of CPFE to the GERM''O''P registry, and were advised to perform at least yearly screening for pulmonary hypertension using echocardiography. RHC was performed at the discretion of the physician in cases of suspected severe pulmonary hypertension. Only cases with pre-capillary pulmonary hypertension confirmed at RHC were included, and clinical data were then collected retrospectively. Data collection ended in December 2008. HRCT scans were reviewed by two of us (V. Cottin and J-F. Cordier) to validate the imaging diagnostic criteria.

According to French legislation, the agreement of an ethics committee and informed consent are not required for retrospective collection of data corresponding to current practice. However, the database was anonymous and complied with the restrictive requirements of the Commission Nationale Informatique et Liberté, the organisation dedicated to privacy, information technology and civil rights in France. This study was approved by our institutional review board.

Inclusion criteria

The following criteria were required for inclusion.

1) Modified American Thoracic Society/European Respiratory Society criteria for the diagnosis of IPF [21], with exclusion of other known causes of interstitial lung disease, such as certain drug toxicities, environmental exposures and connective tissue diseases; impaired gas exchange (increased alveolar–arterial oxygen tension difference, decreased arterial oxygen tension with rest or exercise or decreased diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$)); bibasilar reticular abnormalities with basal and subpleural predominance, traction bronchiectasis and/or honeycombing, and with minimal ground-glass opacities on HRCT scan; transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis; and at least three of the following: age >50 yrs, insidious onset of otherwise unexplained dyspnoea on exertion, duration of illness >3 months, bibasilar inspiratory crackles (dry or ''velcro''-type in quality). As opposed to IPF criteria [21], evidence of restriction (reduced vital capacity) may or may not be present.

2) Presence of conspicuous emphysema (centrilobular and/or paraseptal) on HRCT scan, defined as well-demarcated areas of low attenuation delimitated by a very thin wall (>1 mm) or no wall.

3) Pre-capillary pulmonary hypertension defined by mean P_{pa} >25 mmHg at rest, with pulmonary arterial wedge pressure <15 mmHg and pulmonary vascular resistance (PVR) >240 dyn·s·cm^{-5} at RHC [22, 23].

Patients with connective tissue disease, hypersensitivity pneumonitis, drug-induced lung disease and pneumoconiosis were excluded from this study. Patients with pulmonary arterial hypertension related to portal hypertension, congenital heart disease, HIV infection, anorexigen exposure, and patients with pulmonary hypertension due to left heart disease and chronic thromboembolic pulmonary hypertension were excluded.

Investigations

We reviewed the medical records to collect information using a standardised form. The 6-min walk test (6MWT) and pulmonary function tests were performed according to recommendations [24, 25]. RHC was performed as described [26]. Date of diagnosis was defined as the date of RHC, and all data (symptoms, 6MWT, pulmonary function and echocardiography) were obtained at the time of the RHC. In the absence of guidelines on the treatment of pulmonary hypertension associated with parenchymal pulmonary diseases, treatment was left at the discretion of the physician, and included oral anticoagulation, diuretics, oxygen as needed and possible pulmonary arterial hypertension-specific therapy initiated after the RHC.

Statistical analysis

Microsoft Excel 2003 and SPSS 16.0 (SPSS, Chicago, IL, USA) were used for data analysis. All values were expressed as mean ± SD. Two-tailed p-values <0.05 were considered statistically significant. Estimation of the probability of survival at each time point was performed using the Kaplan–Meier method, from the date of the first haemodynamic evaluation demonstrating pulmonary hypertension, to the end-points of death or censoring. All-cause mortality was used in survival statistics. Transplanted subjects were censored at the time of transplantation. Surviving patients were censored at the date of the last visit. Comparisons of survival were performed using the log rank test. The relationship between survival and selected baseline variables was examined for each variable using univariate analysis of hazard ratios based on the proportional hazards model.

RESULTS

Patient population

The study population included 40 patients (38 males and two females), with a mean±SD age of 68.2±8.9 yrs. Three patients had been included in a previous study [5]. The mean delay between the first respiratory symptoms and the diagnosis of CPFE was 37±66 months. All patients except one were current or ex-smokers. One patient was exposed to agrochemical compounds. 13 patients (32%) had a history of atherosclerotic coronary artery disease and three (7%) of peripheral artery disease.

Baseline demographic and clinical data are shown in table 1. Six patients (15%) had chronic bronchitis. 11 patients (27%) had clinical signs of right heart failure, two (5%) had a history of syncope. Finger clubbing was reported in 23 patients (57%) and basal crackles were present in 34 patients (85%).

Histopathology of the lungs available in six cases demonstrated a pattern of usual interstitial pneumonia and emphysema in all cases. The serum level of α_1-antitrypsin measured in 14 cases was normal.

TABLE 1 Characteristics, clinical manifestations, and pulmonary function tests at diagnosis in patients with combined pulmonary fibrosis and emphysema syndrome

Variables	
Sex male/female n	38/2
Age yrs	68.2±8.9 (47.7–82.2)
Current/ex/never-smokers n	2/37/1
Smoking history pack-yrs	46±23 (17–120)
NYHA class I	0
NYHA class II	6 (15)
NYHA class III	22 (55)
NYHA class IV	12 (30)
6MWD m	244±126 (78–689)
6MWT S_{p,O_2} at end of test	77±10 (62–96)
6MWT S_{p,O_2} decrease during test	-15±8 (-30– -1)
FVC % pred	86±18 (46–116)
FEV_1 % pred	78±19 (38–114)
FEV_1/FVC %	75±18 (29–107)
TLC % pred	84±23 (47–139)
RV % pred	87±47 (41–219)
$D_{L,CO}$ % pred	24±14 (3–52)
K_{CO} % pred	28±16 (4–68)
P_{a,O_2} at rest kPa	7.5±1.6 (5.2–11.7)
P_{a,O_2} at rest mmHg	56.2±12.0 (39–84)
P_{a,CO_2} at rest kPa	4.7±0.6 (3.3–5.9)
P_{a,CO_2} at rest mmHg	35.2±4.5 (25–44)

Data are presented as mean±SD (range) or n (%), unless otherwise stated. NYHA: New York Heart Association; 6MWD: 6-min walk distance; 6MWT: 6-min walk test; S_{p,O_2}: peripheral oxygen saturation; FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; $D_{L,CO}$: single-breath diffusing capacity of the lung for carbon monoxide; K_{CO}: single breath transfer factor of the lung for carbon monoxide; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension.

Functional evaluation and haemodynamics

New York Heart Association (NYHA) functional class was III or IV in 85% of the patients. 6-min walk distance (6MWD) was 244±126 m.

The mean delay between the diagnosis of CPFE and the RHC demonstrating pulmonary hypertension was 16±25 months, and the mean delay between the first respiratory symptoms and the diagnosis of pulmonary hypertension was 53±66 months. Results of RHC are presented in table 2. 6MWD was 314±153 m in patients with NYHA functional class II, 255±126 m in class III and 180±91 m in class IV. Haemodynamic measurements showed a mean P_{pa} of 40±9 mmHg, and PVR of 521±205 dyn.s.cm^{-5}. Mean P_{pa}, cardiac index and PVR did not significantly correlate with forced vital capacity (FVC), $D_{L,CO}$ or transfer factor of the lung for carbon monoxide (K_{CO}).

In 27 patients (68%), the mean P_{pa} was >35 mmHg (and >40 mmHg in 48%), with a mean P_{pa} of 45±6 mmHg, PVR of 603±181 dyn·s·cm^{-5}, cardiac index of 2.5±0.7 L·min^{-1}·m^{-2} and 6MWD of 231±105 m.

Echocardiography showed dilated right cardiac cavities in 77% of cases, with paradoxical movement of the interventricular septum in 32% of the cases. Estimated systolic P_{pa} was 67±15 mmHg (range 20–100; n=36) and was 35 mmHg or higher in 97% of patients. Pericardial effusion was not reported. The B-type natriuretic peptide level available for 14 patients was 340±298 pg·mL^{-1} (normal <100 pg·mL^{-1}).

Mean values of lung volumes were within normal limits, contrasting with severely impaired gas exchange (mean K_{CO} was 28±16% of predicted) (table 1).

Outcome and survival analysis

Patients were followed for a median of 8±8 months (range 1–34 months). Treatment of pulmonary hypertension, pulmonary

TABLE 2 Haemodynamic data at the time of diagnosis of pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome

Variables	
f_C beats·min^{-1}	78±15 (50–112)
P_{ra} mmHg	7±4 (0–18)
Mean P_{pa} mmHg	40±9 (24–56)
Diastolic P_{pa} mmHg	26±6 (15–40)
Systolic P_{pa} mmHg	64±14 (39–90)
P_{paw} mmHg	10±3 (2–14)
CO L·min^{-1}	4.7±1.3 (2.8–7.6)
CI L·min^{-1}·m^{-2}	2.5±0.7 (1.5–4.4)
PVR dyn·s·cm^{-5}	521±205 (240–1040)
PVRi dyn·s·cm^{-5}·m^{-2}	947±401 (360–1912)
S_{V,O_2} %	65±9 (47–86)

Data are presented as mean±SD (range). f_C: cardiac frequency; P_{ra}: right atrial pressure; P_{pa}: pulmonary arterial pressure; P_{paw}: pulmonary arterial wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; PVRi: pulmonary vascular resistance index; S_{V,O_2}: venous oxygen saturation.

fibrosis and emphysema is shown on table 3. 92% of the patients received long-term oxygen therapy. 24 patients (60%) received first-line therapy for pulmonary hypertension with bosentan, sildenafil or inhaled iloprost after RHC and were evaluated after 3–6 months. No statistically significant effect of treatment was observed regarding NHYA class, 6MWD or estimation of systolic P_{pa} at echocardiography.

At the end of the follow-up period, six patients (15%) had developed acute right heart failure, 14 (35%) had died, none had been lost to follow-up and four (10%) had been transplanted. The overall survival rate at 1 yr was 60±10% (fig. 1). Death was due to hypoxaemia and chronic respiratory failure as a result of pulmonary hypertension and CPFE in 10 cases, cancer in three patients (lung, n=2; throat, n=1) and septic shock in one patient. A higher survival rate was observed in patients with $D_{L,CO}$ higher than the median value of 22% pred than in those with lower $D_{L,CO}$ (estimated 1-yr survival of 79.5±13.1% *versus* 43.5±18%; p=0.046); in patients with PVR lower than the median value of 485 dyn·s·cm^{-5} (1-yr estimate of survival of 100% *versus* 47.6±15.1%; p=0.008); and in patients with a cardiac index higher than the median value of 2.4 L·min^{-1}·m^{-2} (1-yr survival of 79.1±13.8% *versus* 45.8±14.2%; p=0.044). 10 of 20 patients with cardiac index <2.4 L·min^{-1}·m^{-2} died, compared with two of the 20 patients with a cardiac index >2.4 L·min^{-1}·m^{-2} (p=0.01). The median survival in patients with cardiac index <2.4 L·min^{-1}·m^{-2} was only 7.5 months (95% CI 1.2–13.9 months), and the median survival in patients with PVR >485 dyn·s·cm^{-5} was 6.6 months (95% CI 5.2–8.0 months). Nonsignificant trends for higher survival rate were observed in patients with higher transfer coefficient, lower mean P_{pa}, higher 6MWD and NYHA class II or III.

The results of the univariate analysis relating survival time to clinical, functional and haemodynamic characteristics measured at baseline in the overall population are shown in table 4. High mean P_{pa}, high PVR, high heart rate and low $D_{L,CO}$ were significantly associated with a poor outcome. In addition, there was a trend for a poor outcome in patients with NYHA functional class IV, lower K_{CO} and lower cardiac index. Similar results were obtained when selected numerical variables (mean P_{pa}, cardiac index and PVR) were treated as nonlinear and separated into two categories or into four quartiles (data not shown). No significant effect of therapy was observed in patients who received medical treatment for pulmonary hypertension compared with conventional therapy alone.

TABLE 3 Treatment in 40 patients with combined pulmonary fibrosis and emphysema syndrome and pre-capillary pulmonary hypertension

Treatment of pulmonary hypertension	
Diuretics	30 (75)
Oral anticoagulant	19 (47)
Bosentan	12 (30)
Sildenafil	11 (27)
Inhaled iloprost	1 (2)
Treatment of pulmonary fibrosis	
Oral corticosteroids	16 (40)
N-acetylcysteine	9 (22)
Azathioprine	4 (10)
Treatment of emphysema	
Inhaled bronchodilators	23 (57)
Inhaled corticosteroids	17 (42)
Long-term oxygen	37 (92)
Pulmonary transplantation	4 (10)

Data are presented as n (%).

DISCUSSION

This is the first study of pulmonary hypertension confirmed by RHC in patients with CPFE.

CPFE is a distinct syndrome contrasting with both solitary IPF and emphysema by demonstrating relatively preserved lung volumes and airflow measurements, respectively [4]. It is associated with a poor outcome related to the high prevalence of pulmonary hypertension, a characteristic feature in the natural history of CPFE syndrome [5, 19]. In this study, we showed that: 1) pulmonary hypertension was demonstrated at RHC with a mean delay of only 16 months after the diagnosis of CPFE at HRCT scan; 2) patients had severe dyspnoea (with 85% in functional class III or IV) and severe exercise limitation (with a mean 6MWD of 244±126 m), despite subnormal spirometry and moderately severe haemodynamic parameters; 3) pulmonary hypertension in CPFE was associated with a dismal prognosis, with a 1-yr survival of only 60%; 4) a lower cardiac index, a lower transfer factor and increased PVR were associated with a shorter survival.

The pulmonary function characteristics of the patients included in the present study were strikingly similar to that of our previous report [5], although only three patients were included in both studies. This reproducibility underscores the clinical relevance of defining the syndrome of CPFE with simple diagnostic criteria, thus justifying our pragmatic approach based on the presence of conspicuous features of both emphysema and fibrosis on HRCT (*e.g.* noticeable without quantification of imaging features). Mean values of FVC, total lung capacity and forced expiratory volume in 1 s (FEV_1) were normal, contrasting with severely impaired diffusion capacity of the lung, with mean values of $D_{L,CO}$ and K_{CO} of only 24% and 28% pred, respectively, and severe hypoxaemia in 92% of the patients. The severe impairment of diffusion capacity probably represents the additive or synergistic effects of emphysema, fibrosis and pulmonary vascular disease, and is one of the hallmarks of CPFE syndrome [27]. Most patients with CPFE syndrome were males, as previously shown [5, 19]. Pulmonary hypertension is present in 47–90% of patients with CPFE, based on echocardiographic measurement of right ventricular systolic pressure, and is associated with an increased risk of death [5, 19]. Since only patients with pre-capillary pulmonary hypertension confirmed at RHC were included in this study, we could not further evaluate the proportion of CPFE patients with pulmonary hypertension or the proportion of patients with post-capillary pulmonary hypertension. Selection bias towards the most severe cases cannot be excluded. However, echocardiography especially lacks specificity and accuracy in patients with advanced lung disease, including COPD [28] and IPF [29, 30], frequently leading to overdiagnosis of pulmonary hypertension [29, 30]. The present study is the first to report on haemodynamic

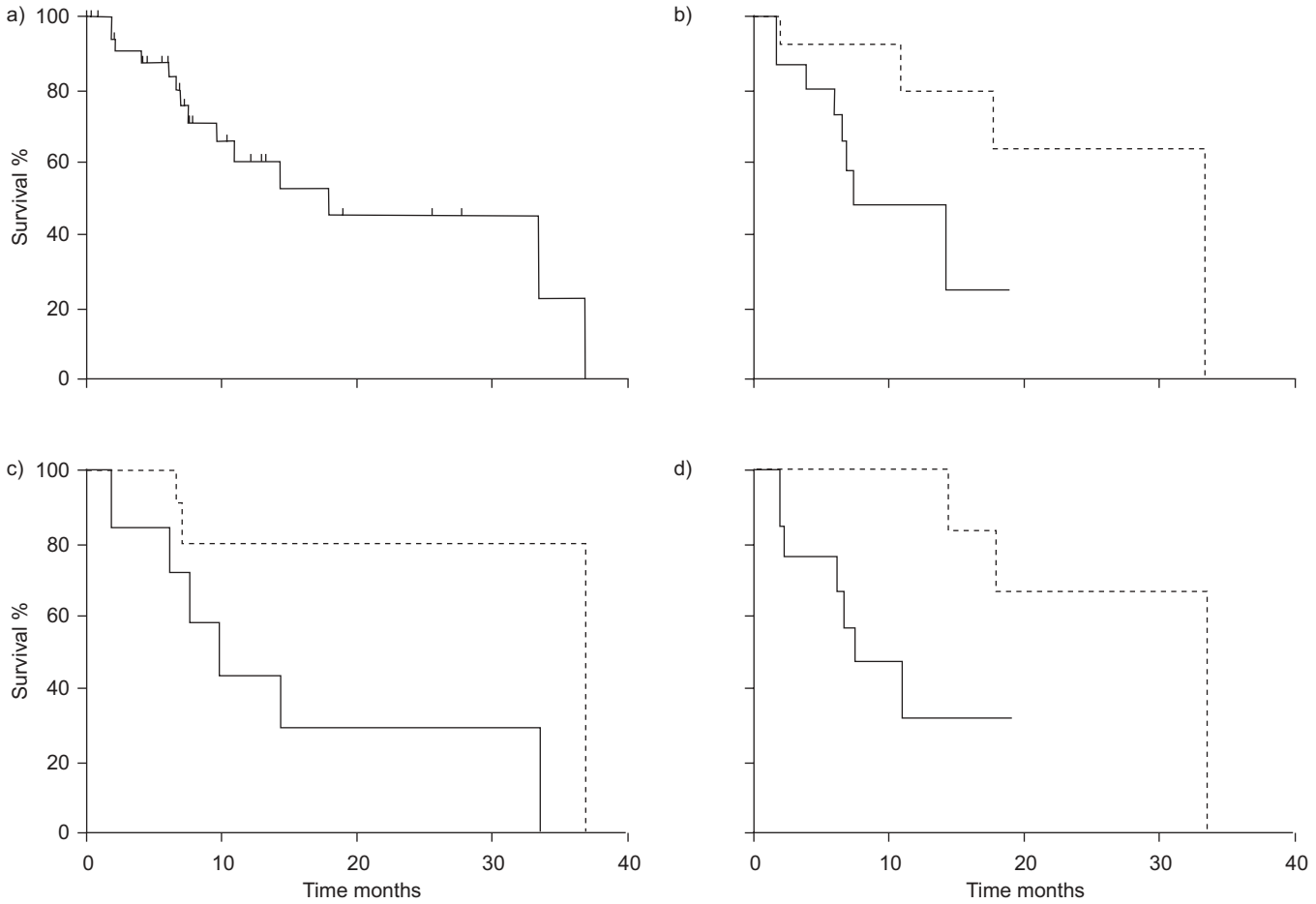

FIGURE 1. Survival in patients with combined pulmonary fibrosis and emphysema and associated pulmonary hypertension using Kaplan–Meier estimates a) in the overall population and according to b) cardiac index (CI) (- - - -: CI >2.4 L·min^{-1}·m^{-2}; ——: CI <2.4 L·min^{-1}·m^{-2}; p=0.044), c) diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) (- - - -: $D_{L,CO}$ >22% predicted; ——: $D_{L,CO}$ <22% pred; p=0.046) and d) pulmonary vascular resistance (PVR) (- - - -: PVR <485 dyn·s·cm^{-5}; ——: PVR >485 dyn·s·cm^{-5}; p=0.008). Transplanted patients were censored at the time of transplantation. Median CI was 2.4 L·min^{-1}·m^{-2}.

evaluation in CPFE patients with pre-capillary pulmonary hypertension confirmed by RHC, the gold standard for the diagnosis of pulmonary hypertension, thus allowing prognostic analysis according to haemodynamic parameters. The delay in diagnosing pulmonary hypertension in patients with CPFE seemed to be mostly related to the natural history of disease, with pulmonary hypertension detected at echocardiography during follow-up; therefore, we perform echocardiography at least once a year in any patient with CPFE.

Although no formal comparison can be made from this retrospective analysis, it is noteworthy that patients with pulmonary hypertension and CPFE had a dismal prognosis, with a 60% probability of survival at 1 yr from the diagnosis of pulmonary hypertension, similar to the probability of survival at 1 yr of 72% in patients with IPF and associated pulmonary hypertension at RHC [10]. The reported median survival from the diagnosis is ~3 yrs in IPF [31] and 6 yrs in one series of CPFE [5, 19]; however, survival from the diagnosis of fibrosis was lower in patients with CPFE than in those with IPF without emphysema when compared within a single institution, mostly due to a higher incidence of pulmonary hypertension at echocardiography in CPFE [5, 19]. In contrast, the survival was 36% at 5 yrs in patients with COPD and pulmonary hypertension (mean P_{pa} >25 mmHg) at onset of long-term oxygen therapy (Global Initiative for Chronic Obstructive Lung Disease IV) [18]. The 1-yr survival of incident cases of pulmonary arterial hypertension in the national French registry was 88%, although with a worse haemodynamic profile than that of the present cohort (with a higher PVR index of 1,640 dyn·s·cm^{-5}·m^{-2} and similar cardiac index of 2.5 L·min^{-1}·m^{-2}) [32]. Thus, CPFE with associated pulmonary hypertension is a most severe condition with especially poor prognosis, worse than that of solitary COPD with associated pre-capillary pulmonary hypertension, and somewhat similar to that of IPF with pre-capillary pulmonary hypertension.

Pulmonary hypertension occurring in the context of chronic parenchymal lung disease is usually mild or moderate (*i.e.* with mean P_{pa} <35–40 mmHg). Recently, attention has focused on a subgroup of COPD patients, with severe ''out-of-proportion'' pre-capillary pulmonary hypertension despite long-term oxygen therapy [14, 15, 33], arbitrarily defined by mean P_{pa} >35–40 mmHg [14]. These patients are prone to right heart failure and may share similarities with those with idiopathic pulmonary

TABLE 4 Univariate analysis relating survival to selected baseline variables

Variables	Hazard ratio	95% CI	p-value
Age yrs	1.04	0.97–1.11	0.297
NYHA class (II–III/IV)	2.25	0.86–5.87	0.096
$D_{L,CO}$ % pred	0.93	0.87–1.00	0.049
K_{CO} % pred	0.94	0.88–1.01	0.071
P_{a,O_2} kPa	0.80	0.35–1.84	0.604
6MWD m	0.99	0.99–1.00	0.157
S_{a,O_2} 6MWD %	0.97	0.91–1.04	0.444
f_C beats·min^{-1}	1.07	1.01–1.12	0.010
P_{ra} mmHg	0.99	0.84–1.17	0.904
Mean P_{pa} mmHg	1.07	1.00–1.14	0.049
CI L·min^{-1}·m^{-2}	0.23	0.05–1.02	0.054
PVR dyn·s·cm^{-5}	1.01	1.00–1.01	0.002
S_{v,O_2} %	1.02	0.95–1.10	0.513
Medical treatment of PH (yes/no)	1.32	0.39–4.93	0.656

A value of hazard ratio >1 indicates an increased risk of death. NYHA: New York Heart Association; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred; % predicted; K_{CO}: transfer factor of the lung for carbon monoxide; P_{a,O_2}: arterial oxygen tension; 6MWD: 6-min walk distance; S_{a,O_2}: arterial oxygen saturation; f_C: cardiac frequency; P_{ra}: right atrial pressure; P_{pa}: pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; S_{v,O_2}: venous oxygen saturation; PH: pulmonary hypertension.

arterial hypertension [16]. Interestingly, 68% of the patients included in the present study had pulmonary hypertension that was disproportionate to the underlying parenchymal lung disease, with mean P_{pa} >35 mmHg. The mean value of FVC was 86% pred in CPFE (compared with 49% pred in patients with IPF and associated pulmonary hypertension [10]), and the mean value of FEV_1 was 78% (compared with 55% in patients with COPD and disproportionate pulmonary hypertension [14]).

Although the efficacy of drugs specifically indicated in pulmonary arterial hypertension has not been demonstrated in patients with pulmonary parenchymal disorders and associated out-of-proportion pulmonary hypertension, a large number of patients from the present study were treated off-label on an individual basis, thereby providing some preliminary information on the efficacy and safety of pulmonary hypertension therapy in this condition. No significant effect of treatment was found on survival. However, this result must be interpreted with caution, owing to the retrospective design, heterogeneity of treatment and lack of systematic haemodynamic assessment of the effect of treatment. Whether patients with CPFE and out-of-proportion pre-capillary pulmonary hypertension may benefit from treatment could be best evaluated in randomised controlled trials, although the feasibility of trials is challenged in such a rare and severe condition. Anyway, careful individual evaluation of patients under treatment should be obtained prospectively. Younger patients should be evaluated early for lung transplantation.

Prognostic factors in pulmonary hypertension associated with parenchymal pulmonary disease have not been extensively evaluated. The present study identified high PVR, low cardiac index and low $D_{L,CO}$ as significant predictors of a worse prognosis. Several haemodynamic factors associated with a shorter survival in pulmonary arterial hypertension were thus also associated with worse prognosis in this group of patients with CPFE and associated pulmonary hypertension. Other factors associated with a shorter survival in pulmonary arterial hypertension, such as NYHA functional class, 6MWD, pericardial effusion, elevated B-type natriuretic peptide levels and elevated right atrial pressure [34] were not significantly associated with survival in the present study, possibly due to insufficient statistical power.

Our study has several limitations, in particular its observational and uncontrolled design, with retrospective collection of data. Our results are subject to selection and treatment bias. Indication for therapy and choice of drug were not uniform among patients, limiting evaluation of the effect of treatment. Data presented here should not be interpreted as a proper evaluation of efficacy of treatment, which will require specific studies. However, cases of CPFE syndrome were prospectively identified by participating centres; data regarding haemodynamic parameters and survival were unlikely to be affected by the study design. Multivariate analysis could not be performed due to the sample size, and possible confounding effects of various variables related to survival time could not be evaluated. Long-term follow-up was not available in all patients owing to recent diagnosis; patients who were censored for short follow-up were not significantly different at baseline than the rest of the group; given the high mortality rate, it is unlikely that different results would have been found had the whole cohort been followed up for a longer period of time.

In conclusion, pulmonary hypertension may appear within a mean of only 16 months after the diagnosis of CPFE syndrome, mostly in patients requiring long-term oxygen therapy. Prognosis is poor, despite moderately severe haemodynamic parameters, with a 1-yr survival of 60% from the diagnosis of pulmonary hypertension.

SUPPORT STATEMENT

Financial support was provided by Hospices Civils de Lyon, Lyon, France ("PHRC regional 2005"; PHRC 2009).

STATEMENT OF INTEREST

A statement of interest for M. Humbert can be found at www.erj.ersjournals.com/misc/statements.dtl

ACKNOWLEDGEMENTS

Contributors from the GERM''O''P group: A Berezné (Paris, France), D. Coëtmeur (St-Brieuc, France), I. Danner-Boucher (Nantes, France), D. Funke (Bern, Switzerland), D. Israel-Biet (Paris, France), E. Marchand (Yvoir, Belgium) and L. Mouthon (Paris, France).

The authors are indebted to all physicians who took care of the patients. We thank S. Zeghmar and A.C. Cadoré (Lyon, France) for data extraction and data entry.

REFERENCES

1 Wiggins J, Strickland B, Turner-Warwick M. Combined cryptogenic fibrosing alveolitis and emphysema: the value of high resolution computed tomography in assessment. *Respir Med* 1990; 84: 365–369.

2 Doherty MJ, Pearson MG, O'Grady EA, *et al.* Cryptogenic fibrosing alveolitis with preserved lung volumes. *Thorax* 1997; 52: 998–1002.
3 Wells AU, King AD, Rubens MB, *et al.* Lone cryptogenic fibrosing alveolitis: a functional-morphologic correlation based on extent of disease on thin-section computed tomography. *Am J Respir Crit Care Med* 1997; 155: 1367–1375.
4 Cottin V, Cordier JF. The syndrome of combined pulmonary fibrosis and emphysema. *Chest* 2009; 136: 1–2.
5 Cottin V, Nunes H, Brillet PY, *et al.* Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J* 2005; 26: 586–593.
6 Rosas IO, Ren P, Avila NA, *et al.* Early interstitial lung disease in familial pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; 176: 698–705.
7 Steele MP, Speer MC, Loyd JE, *et al.* Clinical and pathologic features of familial interstitial pneumonia. *Am J Respir Crit Care Med* 2005; 172: 1146–1152.
8 Nadrous HF, Pellikka PA, Krowka MJ, *et al.* Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Chest* 2005; 128: 2393–2399.
9 Patel NM, Lederer DJ, Borczuk AC, *et al.* Pulmonary hypertension in idiopathic pulmonary fibrosis. *Chest* 2007; 132: 998–1006.
10 Lettieri CJ, Nathan SD, Barnett SD, *et al.* Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006; 129: 746–752.
11 Nathan SD, Shlobin OA, Ahmad S, *et al.* Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. *Chest* 2007; 131: 657–663.
12 Shorr AF, Wainright JL, Cors CS, *et al.* Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. *Eur Respir J* 2007; 30: 715–721.
13 Nathan SD, Shlobin OA, Ahmad S, *et al.* Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Respiration* 2008; 76: 288–294.
14 Chaouat A, Bugnet AS, Kadaoui N, *et al.* Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 172: 189–194.
15 Thabut G, Dauriat G, Stern JB, *et al.* Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* 2005; 127: 1531–1536.
16 Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. *Eur Respir J* 2008; 32: 1371–1385.
17 Hamada K, Nagai S, Tanaka S, *et al.* Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest* 2007; 131: 650–656.
18 Oswald-Mammosser M, Weitzenblum E, Quoix E, *et al.* Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest* 1995; 107: 1193–1198.
19 Mejia M, Carrillo G, Rojas-Serrano J, *et al.* Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. *Chest* 2009; 136: 10–15.
20 Simonneau G, Robbins IM, Beghetti M, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: S43–S54.
21 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002; 165: 277–304.
22 Galie N, Torbicki A, Barst R, *et al.* Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25: 2243–2278.
23 McGoon M, Gutterman D, Steen V, *et al.* Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: 14S–34S.
24 ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
25 Quanjer PH, Tammeling GJ, Cotes JE, *et al.* Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993; 16: 5–40.
26 Sitbon O, Humbert M, Jais X, *et al.* Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111: 3105–3111.
27 Aduen JF, Zisman DA, Mobin SI, *et al.* Retrospective study of pulmonary function tests in patients presenting with isolated reduction in single-breath diffusion capacity: implications for the diagnosis of combined obstructive and restrictive lung disease. *Mayo Clin Proc* 2007; 82: 48–54.
28 Fisher MR, Criner GJ, Fishman AP, *et al.* Estimating pulmonary artery pressures by echocardiography in patients with emphysema. *Eur Respir J* 2007; 30: 914–921.
29 Nathan SD, Shlobin OA, Barnett SD, *et al.* Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. *Respir Med* 2008; 102: 1305–1310.
30 Arcasoy SM, Christie JD, Ferrari VA, *et al.* Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003; 167: 735–740.
31 King TE Jr, Tooze JA, Schwarz MI, *et al.* Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001; 164: 1171–1181.
32 Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a National Registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
33 Treatment of pulmonary hypertension in chronic obstructive pulmonary disease. *In*: Siafakas NM, ed. Management of Chronic Obstructive Pulmonary Disease. *Eur Respir Mon* 2006; 38: 313–324.
34 McLaughlin VV, Presberg KW, Doyle RL, *et al.* Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: 78S–92S.