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Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome

Original article

Authors : Vincent Cottin, [1*], Jérome Le Pavec [2*], Grégoire Prévot [3], Hervé Mal [4], Marc Humbert [2], Gérald Simonneau [2], Jean-François Cordier MD [1], and the GERMOP [5]

[1] 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 ; France

[2] 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 ; France

[3] Service de pneumologie, Hôpital Larrey, Toulouse

[4] CHU Bichat, Paris, France

[5] Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires

* contributed equally

Correspondence: Jean-François Cordier, Hôpital Louis Pradel, 69677 Lyon (Bron) Cedex, France. Tel: (33) 472 357 652, Fax: (33) 472 357 653. e-mail: jean-francois.cordier@chu-lyon.fr

Other collaborators : A Berezné (Paris, France), D. Coëtmeur (St-Brieuc), I. Danner-Boucher (Nantes), D. Funke (Bern, Switzerland), D. Israel-Biet (Paris, France), E. Marchand (Yvoir, Belgium), and L. Mouthon (Paris, France).

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Abstract

Objective. To describe the hemodynamic and survival characteristics of patients with pulmonary hypertension in the recently individualized syndrome of combined pulmonary fibrosis and emphysema.

Methods. A retrospective multicenter 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 catheterization.

Results. Dyspnea was functional class II in 15%, III in 55%, and IV in 30%. Six minute walk distance was 244 ± 126 m. Forced vital capacity was 86 ± 18%, forced expiratory volume in one second 78 ± 19%, and carbon monoxide diffusion transfer coefficient 28 ± 16% of predicted. Room air PaO2 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 $dyn.s.cm^{-5}$. One year survival was 60%. Higher pulmonary vascular resistance, higher heart rate, lower cardiac index, and lower carbon monoxide diffusion transfer, were associated with shorter survival.

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

(word count, 200)

Keywords : Pulmonary hypertension ; pulmonary fibrosis ; chronic obstructive pulmonary disease ; emphysema ; disproportionate ; tobacco smoking

Introduction (422 words)

Idiopathic pulmonary fibrosis (IPF) is a severe chronic disease of unknown etiology, with a median survival of three years. 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 chest tomography (HRCT) of the chest in a homogenous group of 61 patients, further characterised by severe dyspnea on exertion, subnormal spirometry, severe impairment of gas exchange, and a median survival of 6.1 years [5]. CPFE is likely 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 (PH) [8, 9], with 31% to 46% of patients with mean pulmonary arterial pressure (PAP) > 25 mmHg at right-sided heart catheterization (RHC) at evaluation for lung transplantation [9-12], and 86% at the time of transplantation [13]. Similarly, the prevalence of PH (defined by mean PAP > 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 PH has been demonstrated both in IPF [9, 10, 17] and COPD [18].

Two studies have reported that PH 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 PH is much higher in CPFE than in IPF without emphysema (odds ratio: 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 PH and not only by the presence of associated emphysema [19]}. Indeed, PH is associated with an increased risk of death in CPFE (hazard ratio: 4.03), with 5-year probability of survival of 25% in patients with

PH at echocardiography as compared to 75% in those without PH at diagnosis [5]. The syndrome of CPFE has been included in the update clinical classification of etiology of PH in the category (3.3) of lung disease characterized by a mixed obstructive and restrictive pattern [20]. However, PH was only evaluated by echocardiography in both studies [5, 19], and hemodynamic analysis is not yet available in CPFE. Thus, the objective of the present study was to describe the hemodynamic characteristics and their relation to survival in patients with CPFE and precapillary PH demonstrated by RHC.

Patients and methods

Study design

This retrospective multicenter study was conducted by the French Reference center for rare pulmonary diseases (coordinator, JFC), the French Reference center for PH (coordinator, GS), 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 PH using echocardiography. RHC was performed at the discretion of the physician in case of suspected severe PH. Only cases with precapillary PH 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 (VC, JFC) 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 ATS/ERS 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 $P(A-a)O_2$, decreased PaO_2 with rest or exercise, or decreased DLco); 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 years, insidious onset of otherwise unexplained dyspnea 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 (less than 1-mm) or no wall.

3. Precapillary PH defined by mean PAP > 25 mmHg at rest, with pulmonary arterial wedge pressure (PAWP) < 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 PH due to left heart disease and chronic thromboembolic PH were excluded.

Investigations

We reviewed the medical records to collect information using a standardized form. Six-minute walk test 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, six-minute walk test, pulmonary function, echocardiography) were obtained at the time of the RHC. In the absence of guidelines on the treatment of PH associated with parenchymal pulmonary diseases, treatment was left at the discretion of the physician, including oral anticoagulation, diuretics, oxygen as needed, and possible PH-specific therapy initiated after the RHC.

Statistical Analysis

Microsoft Excel 2003 and SPSS 16.0 (SPSS, Inc., Chicago, IL) were used for data analysis. All values were expressed as mean ± standard deviation (SD). Two-tailed p values less than 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 hemodynamic evaluation demonstrating PH to the endpoints of death or censoring. All-cause mortality was used in survival statistics. Transplanted subjects were censored at the time of transplantation. Alive patients were censored at the date of the last visit. Comparisons of survival were performed using the Log-Rank test. The relation 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, 2 females), with a mean age of 68.2 ± 8.9 yrs. Three patients were 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 1 were current or ex-smokers. One patient was exposed to agrochemical compounds. Thirteen patients (32%) had a history of atherosclerotic coronary artery disease and 3 (7%) of peripheral artery disease.

Baseline demographic and clinical data are shown in table 1. Six patients (15%) had chronic bronchitis. Eleven patients (27%) had clinical signs of right heart failure, 2 (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 6 cases demonstrated a pattern of usual interstitial pneumonia and emphysema in all cases. The serum level of alpha1-antitrypsin measured in 14 cases was normal.

Functional evaluation and hemodynamics

NYHA functional class was III or IV in 85% of the patients. Six-minute-walk distance (6MWD) was 244 ± 126 m.

The mean delay between the diagnosis of CPFE and the RHC demonstrating PH was 16 ± 25 months, and the mean delay between the first respiratory symptoms and the diagnosis of PH was 53 ± 66 months. Results of RHC are presented in table 2. Six-minute walk distance

was 314 ± 153 m in patients with NYHA functional class II, 255 ± 126 m in class III, and 180 ± 91 m in class IV. Hemodynamic measurements showed a mean PAP of 40 ± 9 mmHg, and PVR of 521 ± 205 dyn.s.cm^{-5}. Mean PAP, cardiac index and PVR did not significantly correlate with FVC, DLco, or Kco.

In 27 patients (68%), the mean PAP was greater than 35 mmHg (and greater than 40 mmHg in 48%), with a mean PAP 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 PAP was 67 ± 15 mmHg (20-100; n=36) and was 35 mmHg or higher in 97% of patients. Pericardial effusion was not reported. B-type natriuretic peptide level available in 14 patients was 340 ± 298 pg/mL (normal < 100).

Mean values of lung volumes were within normal limits, contrasting with severely impaired gas exchange (mean Kco was 28 ± 16% of predicted) (Table 1).

Outcome and survival analysis

Patients were followed for a median of 8 ± 8 months (range, 1-34). Treatment of PH, pulmonary fibrosis, and emphysema, are shown on table 3. Ninety two percent of the patients received long-term oxygen therapy. Twenty four patients (60%) received first line therapy of PH with sildenafil, bosentan, or inhaled iloprost after RHC and were evaluated after 3 to 6 months. No statistically significant effect of treatment was observed regarding NHYA class, 6-minute-walk distance, or estimation of systolic PAP at echocardiography.

At the end of the follow-up period, 6 patients (15%) had developed acute right heart failure, 14 had died (35%), none had been lost to follow-up, and 4 had been transplanted

(10%). The overall survival rate at one year was 60 ± 10% (Figure 1). Death was due to hypoxemia and chronic respiratory failure due to PH and CPFE in 10 cases, to cancer in 3 patients (lung, n=2; throat, n=1), and to septic shock in 1 patient. A higher survival rate was observed in patients with DLco higher than the median value of 22% of predicted than in those with lower DLco) (estimated one-year 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} (one-year 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/m² (one-year survival of 79.1 ± 13.8 % versus 45.8 ± 14.2 %, p=0.044). Ten of 20 patients with cardiac index lower than 2.4 L/min/m² died, as compared to 2 of the 20 patients with a cardiac index higher than 2.4 L/min/m² (p=0.01). The median survival in patients with cardiac index lower than 2.4 L/min/m² was only 7.5 months (95% CI: 1.2 – 13.9), and the median survival in patients with PVR higher than 485 dyn.s.cm^{-5} was 6.6 months (95% CI: 5.2 – 8.0). Non-significant trends for higher survival rate were observed in patients with higher transfer coefficient, lower mean PAP, higher 6MWD, and NYHA class II or III.

The results of the univariate analysis relating survival time to clinical, functional, and hemodynamic characteristics measured at baseline in the overall population are shown in Table 4. High mean PAP, high PVR, high heart rate, and low carbon monoxide diffusion capacity, 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 carbon monoxide diffusion coefficient, and lower cardiac index. Similar results were obtained when selected numerical variables (mean PAP, cardiac index, PVR) were treated as non-linear and separated into two categories or into 4 quartiles (data not shown). No significant effect of therapy was observed in patients who received medical treatment for PH as compared to conventional therapy alone.

Discussion

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

CPFE is a distinct syndrome contrasting with both solitary IPF and emphysema by relatively preserved lung volumes and airflow measurements, respectively [4]. It is associated with a poor outcome related to the high prevalence of PH, a characteristic feature in the natural history of the CPFE syndrome [5, 19]. In this study, we showed that (1) PH was demonstrated at RHC with a mean delay of only 16 months after the diagnosis of CPFE at HRCT scan; (2) patients had severe dyspnea (with functional class III or IV in 85%), and severe exercise limitation (with a mean 6MWD of 244 ± 126 m), despite subnormal spirometry and moderately severe hemodynamic parameters; (3) PH in CPFE was associated with a dismal prognosis, with a one-year 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 3 patients were included in both studies. This reproductibility 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, TLC, and FEV1, were normal, contrasting with severely impaired diffusion capacity of the lung, with mean values of DLco and Kco of only 24% and 28% of predicted, respectively, and severe hypoxemia in 92% of the patients. The severe impairment of diffusion capacity likely represents the additive or synergistic effects of emphysema, fibrosis, and of the pulmonary vascular disease, and is one of the hallmarks of the CPFE syndrome [27]. Most patients with CPFE syndrome were males, as previously shown [5, 19].PH 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 precapillary PH confirmed at RHC were included in this study, we could not evaluate further the proportion of CPFE patients with PH or the proportion of patients with post-capillary PH. Selection bias toward 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 PH [29, 30]. The present study is the first to report on hemodynamic evaluation in CPFE patients with precapillary PH confirmed by RHC, the gold standard for the diagnosis of PH, thus allowing prognostic analysis according to hemodynamic parameters. The delay in diagnosing PH in patients with CPFE seemed to be mostly related to the natural history of disease, with PH 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 PH and CPFE had a dismal prognosis, with a 60% probability of survival at one year from the diagnosis of PH, comparable to the probability of survival at one year of 72% in patients with IPF and associated PH at RHC [10]. The reported median survival from the diagnosis is ~3 years in IPF [31], and 6 years 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 PH at echocardiography in CPFE [5, 19].In contrast, the survival was 36% at 5 years in patients with COPD and PH (mean PAP > 25 mmHg) at onset of long-term oxygen therapy (GOLD IV) [18].The one-year survival of incident cases of pulmonary arterial hypertension in the national French registry was 88%, although with worse hemodynamic profile than that of the present cohort (with higher PVR index of 1640 dyn.s.cm^{-5}.m^{-2} and similar cardiac index of 2.5 L.min^{-1}.m^{-2}) [32]. Thus, CPFE with associated PH is a most

severe condition with especially poor prognosis, worse than that of solitary COPD with associated precapillary PH, and somewhat comparable to that of IPF with precapillary PH.

PH occurring in the context of chronic parenchymal lung disease is usually mild or moderate (i.e. with mean PAP less than 35-40 mmHg). Recently, attention has focused on a subgroup of COPD patients, with severe "out-of-proportion" precapillary PH despite long-term oxygen therapy [14, 15, 33], arbitrarily defined by mean PAP > 35-40 mmHg [14]. These patients are prone to right heart failure and may share similarities with idiopathic pulmonary arterial hypertension [16]. Interestingly, 68% of the patients included in the present study had PH that was disproportionate to the underlying parenchymal lung disease, with mean PAP higher than 35 mmHg. The mean value of FVC was 86% of predicted in CPFE (compared to 49% of predicted in patients with IPF and associated PH [10]), and the mean value of FEV1 was 78% (compared to 55% in patients with COPD and disproportionate PH [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 PH, 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 PH therapy in this condition. No significant effect of treatment was found on survival. However, this result must be interpreted with caution due to the retrospective design, heterogeneity of treatment, and lack of systematic hemodynamic assessment of the effect of treatment. Whether patients with CPFE and out-of-proportion precapillary PH 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 PH associated with parenchymal pulmonary disease have been little evaluated. The present study identified high PVR, low cardiac index, and low carbon monoxide diffusion capacity as significant predictors of a worse prognosis. Several hemodynamic 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 PH. 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, especially 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 proper evaluation of efficacy of treatment, which will require specific studies. However, cases of CPFE syndrome were prospectively identified by participating centers; data regarding hemodynamic 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 due 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 be followed-up longer.

In conclusion, PH may appear with 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 hemodynamic parameters, with a one-year survival of 60% from the diagnosis of PH.

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Table 1. Characteristics, clinical manifestations, and pulmonary function tests at diagnosis in patients with CPFE syndrome.

Variables	Number (%) or mean values ± SD (range)
Sex, male - female	38 - 2
Age, years	68.2 ± 8.9 yrs (47.7-82.2)
Current – ex – never smokers	2 – 37 – 1
Pack-years smoking	46 ± 23 (17-120)
NYHA class I	0
NYHA class II	6 (15%)
NYHA class III	22 (55%)
NYHA class IV	12 (30%)
6-min walk distance, m	244 ± 126 (78-689)
6-min walk test, SpO2 at end of test	77 ± 10 (62-96)
6-min walk test, SpO2 decrease during test	-15 ± 8 (-30- -1)
FVC, % predicted	86 ± 18 (46-116)
FEV_1, % predicted	78 ± 19 (38-114)
FEV_1/FVC, %	75 ± 18 (29-107)
TLC, % predicted	84 ± 23 (47-139)
RV, % predicted	87 ± 47 (41-219)
DLco, % predicted	24 ± 14 (3-52)
Kco, % predicted	28 ± 16 (4-68)
PaO_2 at rest, kPa	7.5 ± 1.6 (5.2-11.7)
PaO_2 at rest, mmHg	56.2 ± 12.0 (39-84)
$PaCO_2$ at rest, kPa	4.7 ± 0.6 (3.3-5.9)
$PaCO_2$ at rest, mmHg	35.2 ± 4.5 (25-44)

FEV1, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLco, single-breath diffusing capacity of the lung for carbon monoxide; Kco, single breath transfer factor of the lung for carbon monoxide; NYHA, New York Heart Association; RV, residual volume; SpO2, peripheral oxygen saturation;

Table 2. Hemodynamic data at the time of diagnosis of pulmonary hypertension in patients with CPFE syndrome.

Variables	mean ± SD (range)
HR, beats.min^{-1}	78 ± 15 (50-112)
RAP, mmHg	7 ± 4 (0-18)
mPAP, mmHg	40 ± 9 (24-56)
dPAP, mmHg	26 ± 6 (15-40)
sPAP, mmHg	64 ± 14 (39-90)
PAWP, 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)
SvO2, %	65 ± 9 (47-86)

CI, cardiac index; CO, cardiac output; HR, heart rate; d/m/sPAP, diastolic/mean/systolic pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RAP, right atrial pressure; SvO2, venous oxygen saturation.

Table 3. Treatment in 40 patients with CPFE syndrome and precapillary pulmonary hypertension.

	Number of patients (%)
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-acetyl-cysteine	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%)

Table 4. Univariate analysis relating survival to selected baseline variables.

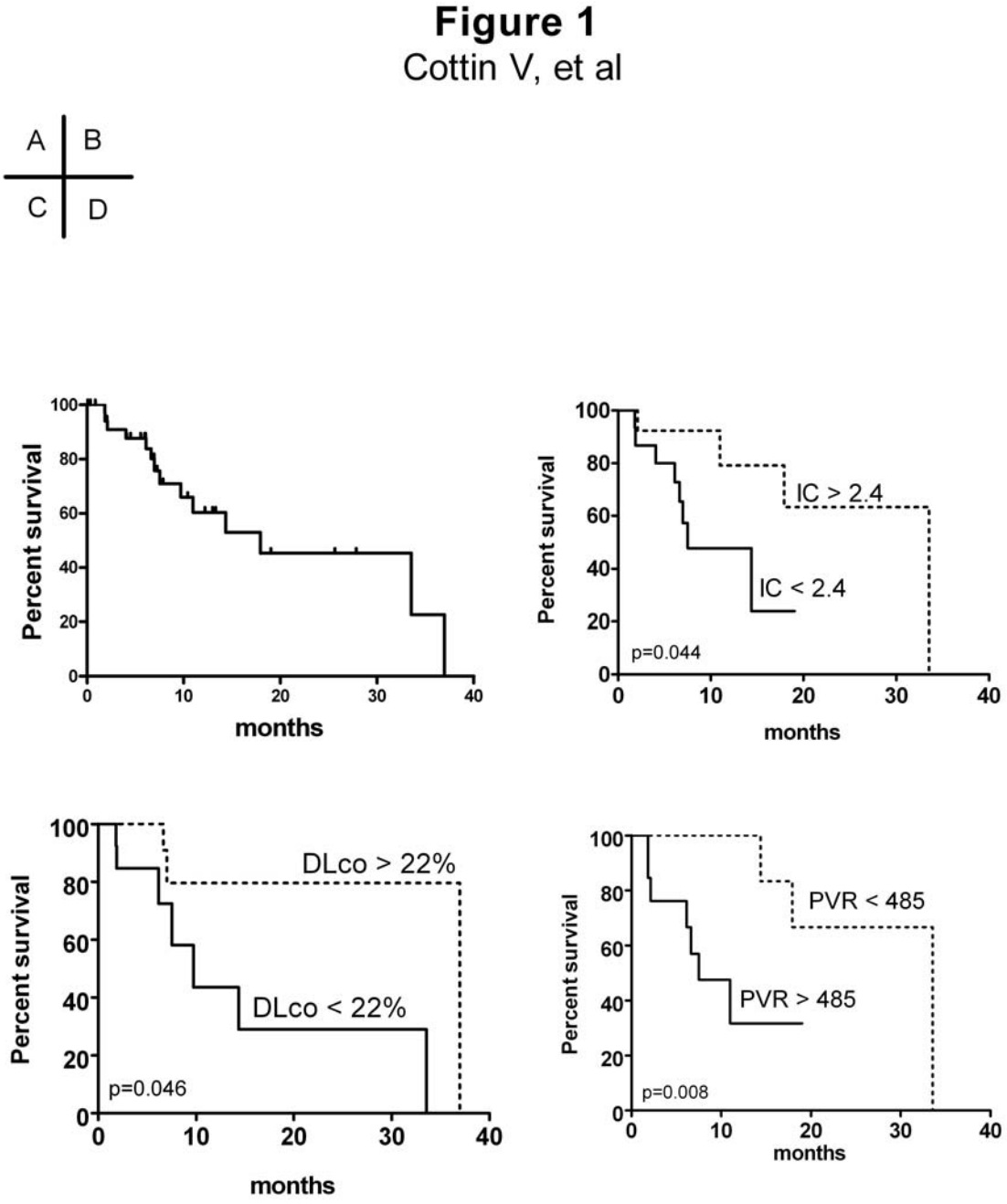
Variables	Hazard ratio *	95% confidence interval	*p* value
Age, yr	1.04	0.97-1.11	0.297
NYHA class (II – III : IV)	2.25	0.86-5.87	0.096
DLCO, % predicted	0.93	0.87-1.00	0.049
Kco, % predicted	0.94	0.88-1.01	0.071
PaO2, kPa	0.80	0.35-1.84	0.604
6MWD, m	0.99	0.99-1.00	0.157
SaO2 6MWD, %	0.97	0.91-1.04	0.444
Heart rate, $beats.min^{-1}$	1.07	1.01-1.12	0.010
RAP, mmHg	0.99	0.84-1.17	0.904
mPAP, 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
SvO2, %	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

CI, cardiac index; CO, cardiac output; HR, heart rate; NYHA, New York Heart Association mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; 6MWD, 6-minute-walk distance; SvO2, venous oxygen saturation.

Figure legends

Figure 1. Survival in patients with combined pulmonary fibrosis and emphysema and associated pulmonary hypertension using Kaplan Meier estimates in the overall population (A) and according to cardiac index (B), transfer factor (C), and pulmonary vascular resistance (D). Transplanted patients were censored at the time of transplantation. Median value of cardiac index was 2.4 $L.min^{-1}.m^{-2}$.



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