

# The Presence of Emphysema Further Impairs Physiologic Function in Patients With Idiopathic Pulmonary Fibrosis

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**BACKGROUND:** Emphysema, especially in the upper lobes, is frequently observed in association with idiopathic pulmonary fibrosis (IPF). However, the combination of emphysema plus IPF has received little attention. **OBJECTIVE:** To investigate the additional functional impairment from emphysema in IPF patients. **METHODS:** Twenty-one patients (mean age 66 y, 20 men) (Group I) who had both IPF (mean 35% of total lung volume) and emphysema (mean 14% of total lung volume) were compared to a group of 21 subjects who had IPF but no emphysema (Group II). The groups were matched for (among other criteria) the total extent of disease. Pulmonary function tests, Medical Research Council dyspnea score, 6-min walk test, and radiographic extents of both IPF and emphysema were obtained for each patient. The Composite Physiologic Index was calculated. In the total population ( $n = 42$ ), the independent contributions of IPF and emphysema to several physiologic variables were investigated by using stepwise multiple regression analysis. **RESULTS:** Despite the limited extent of emphysema, Groups I and II had similar physiologic impairment. Only residual volume and total lung capacity were significantly higher in Group I. According to stepwise multiple regression analysis, the extent of IPF and either the presence or the extent of emphysema in the total population were independent and significant predictors of dyspnea score, 6-min walk test,  $P_{aO_2}$ , forced expiratory volume in the first second ( $FEV_1$ ), forced vital capacity (FVC),  $FEV_1/FVC$ , the diffusing capacity of the lung for carbon monoxide, carbon monoxide diffusing capacity adjusted for alveolar volume (gas-transfer coefficient), and residual volume. The Composite Physiologic Index was closely related to the extent of IPF ( $r = 0.65$ ,  $p < 0.0001$ ) and to the dyspnea score ( $\rho = 0.59$ ,  $p < 0.0001$ ). **CONCLUSIONS:** In former smokers with IPF, the presence and the extent of emphysema have a profound influence on physiologic function in terms of both further impairment and confounding effects. *Key words:* idiopathic pulmonary fibrosis, emphysema, cigarette smoking, dyspnea, composite physiologic index. [Respir Care 2006;51(3):257–265. © 2006 Daedalus Enterprises]

## Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic pulmonary disease associated with alveolitis of unknown etiology, progressive fibrotic course, and poor prognosis after 3–5 years since diagnosis.<sup>1–3</sup> Smoking has been identified as a risk

factor for IPF,<sup>4</sup> and emphysema has been reported in association with IPF, especially in the upper lobes.<sup>5,6</sup> In the assessment of patients with combined IPF and emphysema, pulmonary function test (PFT) results can be misleading. Lung volumes may be preserved while forced expired volume in

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the first second (FEV<sub>1</sub>) and the ratio of FEV<sub>1</sub> to forced vital capacity (FVC) may be similar to those of normal subjects, because the supervening fibrosis prevents the early airway closure seen in emphysema, with the result that emphysematous areas, including bullae, ventilate normally.<sup>7</sup> Despite their apparently more favorable functional presentation, subjects with combined IPF and emphysema have a prognosis similar to that of patients without emphysema, which suggests that the dominant prognostic factor is the lung fibrosis.<sup>8</sup>

The *composite physiologic index* (CPI) was designed to quantify the functional defect ascribable to pulmonary fibrosis while excluding that attributable to emphysema.<sup>5</sup> The CPI is derived using high-resolution computed tomography (HRCT) and the percent-of-predicted values of FEV<sub>1</sub>, FVC, and diffusing capacity of the lung for carbon monoxide (D<sub>LCO</sub>). The CPI predicts mortality more accurately than PFT alone, even in patients without emphysema.<sup>5</sup>

Combined IPF and emphysema is a condition that has received little attention; the impact of emphysema on symptoms, physiologic function, and exercise capacity of patients affected by IPF remains to be established. The aim of this study was to investigate the additional functional impairment from emphysema in patients with IPF. We compared matched populations of IPF patients with and without emphysema, conducted multiple regression analysis of the relative contribution of each disease to the functional impairment, and investigated the correlations between CPI, disease extent, and exertional dyspnea.

## Methods

### Patients

The subjects were recruited sequentially from the respiratory out-patient clinic, over a period of 36 months (June 2000 to June 2003). Twenty-one white patients (20 males) with clinical and radiographic features of both IPF and emphysema were included in Group I. It should be noted that both IPF<sup>4</sup> and emphysema<sup>9</sup> are conditions more frequently observed in men. The diagnosis of IPF was based on the following criteria:

- Insidious onset of otherwise unexplained dyspnea on exertion
- Persistent crackles at auscultation
- Evidence of pulmonary fibrosis on HRCT, consisting of reticular abnormalities, honeycomb pattern, and traction bronchiectasis, with minimal ground-glass opacities and a prevalent bibasilar and peripheral distribution, in the absence of atypical features for IPF, such as peribronchovascular nodules, micronodules, isolated cysts, and consolidation
- Abnormal PFT values, including evidence of lung restriction or decreased D<sub>LCO</sub>, in the absence of other causes of pulmonary fibrosis
- Duration of illness > 3 months<sup>3,4</sup>

The presence of collagen vascular diseases was excluded in all patients, using detailed history, clinical examination, and serum tests for anti-neutrophil cytoplasmic antibody (ANCA) P-ANCA, C-ANCA, extractable nuclear antigens (ENA), anti-nucleus antibodies, anti-mitochondrion antibodies, anti-DNA antibodies, rheumatoid factor, angiotensin-converting enzyme, and cryoglobulins. Drug toxicities and environmental exposures were excluded in all cases. Patients with a predominant ground glass pattern on CT scan were excluded from the study. When typical radiographic features are present in association with a compatible clinical picture, the diagnosis of IPF is correct in more than 90% of cases.<sup>10–12</sup> Four patients had the diagnosis of IPF/usual interstitial pneumonia, confirmed via biopsy obtained during video-assisted thoracoscopy. Six more subjects underwent transbronchial biopsy, and had no features incompatible with the diagnosis of IPF.

All patients in Group I presented coexisting evidence of emphysema ( $\geq 5\%$  of total lung volume) on HRCT scan. At the time of the study, 9 of the patients were being treated with corticosteroids, according to the following protocol: prednisolone 0.5 mg/kg/d orally for 4 wk, followed by 0.25 mg/kg/d for 8 wk, followed by 0.125 mg/kg/d for 4–12 wk. Nine subjects were on long-term oxygen therapy.

Group II consisted of 21 more IPF patients (5 confirmed via video-assisted thoracoscopy), who had no evidence of emphysema, and were matched with Group I for age, sex, race, body mass index, treatment methods, and radiographic extent of total disease (Table 1). Therefore, the Group I individuals had both IPF and emphysema, while the Group II individuals had only IPF, though the total extent of disease in the 2 groups was the same.

All the patients were in a stable clinical and functional state, receiving their usual medications, without clinical, radiographic, or electrocardiographic signs of heart failure, pulmonary hypertension, or acute inflammation. Informed consent for the HRCT scan was obtained from all patients. All investigations were conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.<sup>13</sup>

### Study Design

The extent of emphysema was visually scored, excluding the eventual amount of emphysema associated with honeycombing.<sup>14</sup> We compared the groups' pulmonary function data, dyspnea scores, and exercise capacity. Stepwise multiple regression analysis was then performed on the whole study population ( $n = 42$ ) to examine in separate models whether the presence/absence of emphysema or the extent of

Table 1. Patients Characteristics

Variable	Total Population ( <i>n</i> = 42)	Group I (IPF + emphysema) ( <i>n</i> = 21)	Group II (IPF alone) ( <i>n</i> = 21)
Male/Female ( <i>n</i> )	40/2	20/1	20/1
Age (mean ± SD y)	66 ± 10 (range 43–83)	66 ± 10 (range 43–83)	66 ± 9 (range 50–77)
Body mass index (mean ± SD kg/m <sup>2</sup> )	27 ± 5	26 ± 6	27 ± 4
Smoking (ever/never)	34/8	21/0	13/8
Pack-years (mean ± SD)	19 ± 16	25 ± 15	14 ± 15
Extent of fibrosis (mean ± SD % of total lung volume)*	42 ± 13 (range 22–70)	36 ± 12 (range 22–65)	48 ± 10 (range 30–70)
Extent of emphysema (mean ± SD % of total lung volume)†	7 ± 10 (range 0–40)	14 ± 10 (range 5–40)	0
Total extent of disease (mean ± SD % of total lung volume with IPF + emphysema)	49 ± 12 (range 30–70)	49 ± 12 (range 32–70)	48 ± 10 (range 30–70)
Corticosteroid therapy (yes/no)	18/24	9/12	9/12
Long-term oxygen therapy (yes/no)	17/25	9/12	8/13

\*Extent of fibrosis on high-resolution computed tomography scan

†Extent of emphysema on high-resolution computed tomography scan

emphysema improved equation explanatory power of physiologic variables. In this mixed population, in which half the patients had coexisting emphysema, to confirm the adjustment power of CPI we calculated the correlation coefficients between CPI and physiologic variables.

### Dyspnea Evaluation

The severity of chronic dyspnea, defined as “the unpleasant sensation of labored or difficult breathing,” was rated according to the United Kingdom Medical Research Council (MRC) modified dyspnea scale,<sup>15,16</sup> which ranges from 0 (not troubled by dyspnea) to 5 (dyspnea with minimal effort).

### Pulmonary Function Tests

PFTs were performed according to American Thoracic Society guidelines.<sup>17</sup> With each patient we recorded  $P_{aO_2}$ , alveolar-arterial oxygen difference ( $P_{A-aO_2}$ ) (Radiometer ABL 520 gas analyzer, Diamond Diagnostic, Holliston, Massachusetts), FVC, FEV<sub>1</sub>, inspiratory capacity, forced expiratory flow between 25% and 75% of the FVC (FEF<sub>25–75</sub>) (Transflow 544 pneumotachograph, Morgan Scientific, Haverhill, Massachusetts),  $D_{LCO}$ , and gas-transfer coefficient (single-breath method, with the values corrected for the present hemoglobin values), residual volume, and total lung capacity (TLC). We used the European Coal and Steel Community’s predicted values for spirometry,  $D_{LCO}$ , gas-transfer coefficient, and lung volumes.<sup>18</sup>

The CPI was obtained with the following equation:<sup>5</sup>

$$\text{CPI} = 91 - (0.65 \times D_{LCO} \% \text{ of predicted}) - (0.53 \times \text{FVC} \% \text{ of predicted}) + (0.34 \times \text{FEV}_1 \% \text{ of predicted})$$

### Computed Tomography Scans

HRCT (LightSpeed, General Electric, Milwaukee, Wisconsin) was performed with a single breath-hold, in the prone position, to avoid the interpretative problems related to gravitational density,<sup>19</sup> without intravenous injection of contrast material, and using a filter for the osseous tissue. We took 1-mm sections, with a 1-s scan time, and an interval of 10 mm in the apex-base scans, including both lungs in the field of view.

Emphysema was defined as permeative destruction, without visible walls and without uniform distribution.<sup>20</sup> The visual scoring of IPF and emphysema were separately performed according to the methods previously described for IPF<sup>21,22</sup> and emphysema.<sup>14</sup> The evaluation was based on a 5-point scale (0 = absence of lesions, 1, 2, 3, 4 = extent of lesions, respectively, < 25%, 25–50%, 50–75%, > 75%) (Fig. 1). The scores assigned for each scan and each hemithorax were summed, and a final value, expressed as a pixel-index, were obtained with the following formula:

$$\text{real score} \times 100 / \text{maximum predicted value}$$

(equivalent to 8 times the number of scans performed)

The extent of fibrosis, expressed as a percentage of the total lung volume with a 5% approximation, was separately calculated by 2 experienced radiologists who had no knowledge of the clinical and functional findings. The final score was obtained as a mean of the 2 observations; the standard deviation was 8%.

### Six-Minute Walk Test

The 6-min walk test (6-MWT) was performed according to American Thoracic Society recommendations, along a flat,

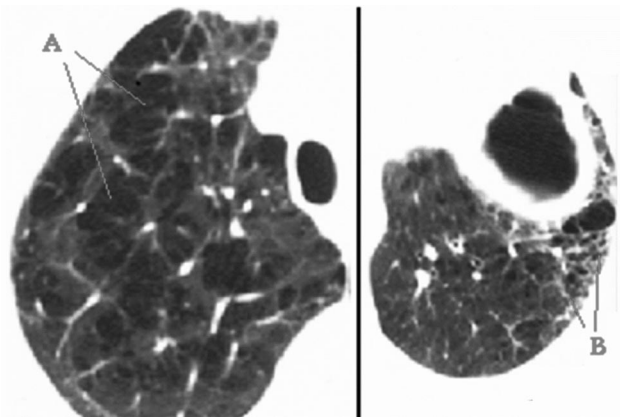


Fig. 1. Left: High-resolution computed tomogram (HRCT) of the upper lobes (left) of this patient demonstrates severe emphysema (A: grade 3). Right: HRCT of the lower lobes (right) demonstrates honeycombing (B: grade 2).

indoor corridor, with continuous pulse-oximetry monitoring of arterial oxygen saturation, heart rate, and breathing frequency.<sup>23,24</sup> During the 6-MWT, patients who used long-term oxygen therapy used the same inspired oxygen concentration they normally used during their daily activities.<sup>23</sup>

### Statistical Analysis

PFT values were compared using Student's *t* test for independent variables. Stepwise multiple regression analysis was then performed to determine if the radiographic extent of IPF and emphysema were significant and independent contributors to dyspnea, 6-MWT, and functional (dependent) variables. Because the MRC dyspnea score uses a 5-point scale, we used the multinomial logistic regression. Each independent variable was entered in sequence (in the following order: extent of fibrosis, extent of emphysema, age, body mass index, and smoking history), and the value of each independent variable was assessed. If adding the variable contributed to the model, then it was retained, but all other variables in the model were retested to see if they were still contributing to the success of the model. If they no longer contributed significantly, they were removed. Twenty-five combinations were tested in each model to determine the final variables to be included. Several assumptions were verified before running the regression models:

1. The variables were normally distributed (no skewing on formal testing for skewing), with the exception of  $P_{A-aO_2}$ ,  $P_{aCO_2}$ , inspiratory capacity, and TLC, which were excluded from the analysis.
2. The correlations between independent and dependent variables were linear. Linearity was assessed by graphing the data, which did not show a distinct curvature in any relationship.
3. There was no high collinearity between the independent variables (all correlation coefficients between the in-

dependent variables were below 0.3). The absence of multicollinearity was further confirmed by the low ( $< 1$ ) standard errors of T ratios\* in all models.

The ratio between the number of observations and the independent variables was kept above 10:1; therefore, the sample size allowed us to use up to 4 independent variables. The best models in term of overall variance ( $r^2$ ) are shown in each case.

The correlation between dyspnea score and other variables was examined using the Spearman rank correlation coefficient ( $\rho$ ), because the MRC dyspnea score is an ordinal categorical variable. The correlations between HRCT fibrosis score and other variables were examined using the 2-tailed Pearson's correlation coefficient ( $r$ ). The correlations between extent of emphysema and other variables were examined with Pearson's correlation coefficient in Group I and with the Spearman rank correlation coefficient in the whole population, because in the whole population half the data points had zero values for the extent of emphysema. Differences were considered statistically significant when  $p < 0.05$ . Calculations were made with statistical software (JMP, SAS Institute, Cary, North Carolina).

### Results

Functional findings for the whole study population and for the 2 groups are shown in Table 2. Group I was affected by an apparently mild mixed restrictive-obstructive lung-function pattern and moderate gas-exchange impairment. Lung volumes were found to be higher than usual for a restrictive disorder. The 6-MWT averaged 258 m. The MRC dyspnea score averaged 3.1.

In comparison with a matched population of IPF subjects affected by the same total extent of disease, but without emphysema (Group II), patients with combined IPF and emphysema (Group I) showed significantly higher residual volume and TLC (see Table 2). In addition, Group I had lower 6-MWT,  $P_{aO_2}$ ,  $P_{A-aO_2}$ ,  $FEV_1/FVC$ , and  $FEF_{25-75}$  (see Table 2).

According to stepwise multiple regression analysis of the whole population ( $n = 42$ ), the extent of emphysema improved equation explanatory power of several physiologic variables. As shown in Table 3, the extent of IPF and emphysema were independent contributors to MRC dyspnea score, 6-MWT,  $P_{aO_2}$ ,  $FEV_1$ , FVC,  $FEV_1/FVC$ , gas-transfer coefficient, and residual volume.  $D_{LCO}$  was also predicted by both the extent of fibrosis and emphysema ( $r^2 = 0.41$ ). In regard to 6-MWT,  $P_{aO_2}$ , and  $FEV_1/FVC$ , the predictive power of the extent of emphysema was superior to that of the IPF extent (see Table 3). However, it should be noted that the multi-variable models explaining MRC dyspnea score and

\* The T ratio is the parameter estimate divided by its standard error.

Table 2. Comparison of Pulmonary Function Indices\*

	Total population (n = 42)	Group I (IPF + Emphysema) (n = 21)	Group II (IPF alone) (n = 21)	p
MRC dyspnea score	2.8 ± 1.4	3.1 ± 1.5	2.9 ± 1.3	> 0.05
6-MWT (m)	297 ± 120	258 ± 104	322 ± 126	> 0.05
P <sub>aO<sub>2</sub></sub> (mm Hg)	73 ± 14	70 ± 14	75 ± 13	> 0.05
P <sub>aCO<sub>2</sub></sub> (mm Hg)	42 ± 6	40 ± 7	43 ± 4	> 0.05
P <sub>A-aO<sub>2</sub></sub> (mm Hg)	38 ± 29	44 ± 34	34 ± 25	> 0.05
FVC (% of predicted)	73 ± 21	77 ± 20	70 ± 22	> 0.05
FEV <sub>1</sub> (% of predicted)	77 ± 28	76 ± 31	77 ± 26	> 0.05
FEV <sub>1</sub> /FVC	79 ± 14	74 ± 18	83 ± 7	> 0.05
FEF <sub>25-75</sub> (% of predicted)	78 ± 42	64 ± 42	88 ± 39	> 0.05
D <sub>LCO</sub> (% of predicted mL/min/mm Hg)	49 ± 22	48 ± 26	49 ± 18	> 0.05
K <sub>CO</sub> (% of predicted)	61 ± 27	60 ± 25	62 ± 26	> 0.05
CPI	44 ± 16	39 ± 16	48 ± 16	> 0.05
RV (% of predicted)	90 ± 43	111 ± 49	73 ± 29	0.023
TLC (% of predicted)	82 ± 24	95 ± 25	71 ± 18	0.009

\*Calculated with Student's *t* test for independent variables

MRC = Medical Research Council of the United Kingdom

6-MWT = 6-min walk test

P<sub>A-aO<sub>2</sub></sub> = alveolar-arterial oxygen difference

FVC = forced vital capacity

FEV<sub>1</sub> = forced expired volume in the first second

FEF<sub>25-75</sub> = forced expiratory flow between 25% and 75% of FVC

D<sub>LCO</sub> = diffusing capacity of the lung for carbon monoxide

K<sub>CO</sub> = carbon monoxide diffusing capacity adjusted for alveolar volume (gas-transfer coefficient)

CPI = Composite Physiologic Index

RV = residual volume, measured via plethysmography

TLC = total lung capacity, measured via plethysmography

6-MWT were characterized by a low variance ( $r^2$ ), and the differences did not reach statistical significance.

Confirming these results, in Group I alone, the radiographic extent of emphysema was significantly correlated with P<sub>aO<sub>2</sub></sub> ( $r = -0.47$ ,  $p = 0.037$ ) and FEV<sub>1</sub>/FVC ( $r = -0.66$ ,  $p = 0.010$ ) (Fig. 2).

We hypothesized that most of the functional impact of emphysema can be captured simply by factoring in whether emphysema is present or absent. To test this hypothesis, we used stepwise multiple regression analysis on the whole population, considering the presence/absence of emphysema as an independent variable. In comparison with the analysis that included emphysema coded as 0 or the actual extent, the predictive power of the equations and the F ratio\* of emphysema (coded as 0/1) resulted lower in regard to all the physiologic variables considered (data not shown), although the presence of emphysema still contributed to all the dependent variables considered.

In this mixed population of IPF patients with and without emphysema, the CPI was highly correlated to the extent of fibrosis, showing the best correlation coefficient

among the variables considered ( $r = 0.65$ ,  $p < 0.0001$ ) (Table 4 and Fig. 3A). In the whole population, the extent of emphysema was significantly correlated only to FEV<sub>1</sub>/FVC (see Table 4). The MRC dyspnea score was correlated to several pulmonary function indices. Among all the variables considered, the CPI was the best predictor of MRC dyspnea score ( $\rho = 0.59$ ,  $p < 0.0001$ ) (see Table 4 and Fig. 3B), and it correlated with dyspnea even better than the stepwise model ( $\rho^2 = 0.34$  vs  $r^2 = 0.17$ ).

## Discussion

The main finding of the present study is that, in former smokers with IPF, the presence of emphysema, even when limited in extent (mean 14% of total lung volume), is an independent and significant contributor to functional impairment and exertional dyspnea. Patients with IPF and emphysema also presented a similar physiologic impairment, in terms of exertional dyspnea, gas exchange, exercise, and ventilatory capacity, to a matched group of individuals with the same total extent of disease but affected by IPF alone. In this mixed population of subjects with IPF and concomitant emphysema, the CPI was confirmed to be closely related to the extent of fibrosis, and CPI was the best predictor of dyspnea.

\* The F ratio is the regression (model) mean square divided by the error mean square.

# COMBINED IDIOPATHIC PULMONARY FIBROSIS AND EMPHYSEMA

Table 3. Independent Contributions of the Extent of Fibrosis and Emphysema to Physiologic Impairment in the Whole Population\*

Variable Covariables	Cumulative $r^2$	Regression Coefficient†	SE
<b>MRC Dyspnea Score</b>			
Fibrosis	0.07	0.39	0.01
Emphysema	0.17	0.36	0.03
F ratio = 3.0			
p = 0.063			
<b>6-Min Walk Test</b>			
Emphysema	0.09	-1.58	0.45
Fibrosis	0.27	-0.93	0.68
F ratio = 3.1			
p = 0.071			
<b>P<sub>aO<sub>2</sub></sub></b>			
Emphysema	0.19	-0.89	0.27
Fibrosis	0.32	-0.39	0.16
Body mass index	0.40	-0.74	0.43
F ratio = 4.7			
p = 0.012			
<b>FEV<sub>1</sub></b>			
Fibrosis	0.25	-1.18	0.37
Emphysema	0.37	-1.74	0.69
Pack years	0.44	0.60	0.36
F ratio = 5.5			
p = 0.006			
<b>FVC</b>			
Fibrosis	0.39	-1.11	0.28
Pack years	0.45	0.61	0.27
Emphysema	0.54	-1.02	0.52
F ratio = 8.1			
p = 0.0009			
<b>FEV<sub>1</sub>/FVC</b>			
Emphysema	0.37	-1.21	0.25
Fibrosis	0.53	-0.39	0.14
F ratio = 12.5			
p = 0.0002			
<b>K<sub>CO</sub></b>			
Fibrosis	0.26	-0.06	0.01
Emphysema	0.55	-0.08	0.02
Age	0.61	-0.02	0.01
F ratio = 10.2			
p = 0.0003			
<b>RV</b>			
Fibrosis	0.27	-1.75	0.76
Emphysema	0.35	1.87	0.89
Age	0.41	-1.05	0.83
F ratio = 3.9			
p = 0.028			

\*n = 42. Significant independent predictors of Medical Research Council (MRC) dyspnea score and physiologic variables were selected by stepwise multiple regression analysis.

†Regression coefficient variable estimates

SE = standard error

F ratio = regression (model) mean square divided by the error mean square

FEV<sub>1</sub> = forced expiratory volume in the first second

FVC = forced vital capacity

K<sub>CO</sub> = carbon monoxide diffusing capacity adjusted for alveolar volume (gas-transfer coefficient)

RV = residual volume

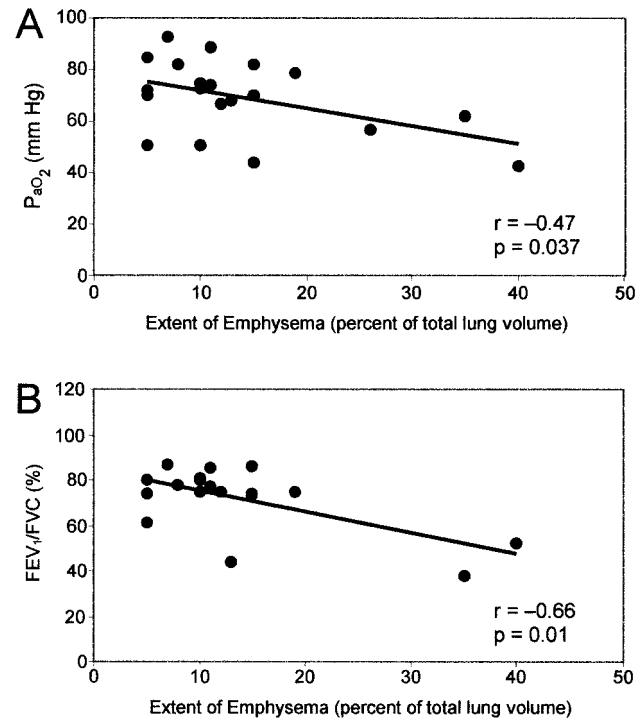


Fig. 2. A: Relationship between extent of emphysema (percent of total lung volume) and P<sub>aO<sub>2</sub></sub> in Group I (n = 21). The Pearson correlation coefficient (r) is -0.47. B: Relationship between extent of emphysema (percent of total lung volume) and the ratio of forced expiratory volume in the first second (FEV<sub>1</sub>) to forced vital capacity (FVC) in Group I (n = 21). The Pearson correlation coefficient (r) is -0.66.

In combined IPF and emphysema the independent contribution of each disease to functional impairment has received little attention. In our experience, and in accordance with previous studies,<sup>5,24</sup> the extent of emphysema is usually more limited than the extent of fibrosis. However, our comparison of matched patient groups revealed that having half the total lung volume with the combined disease (IPF plus emphysema) is as physiologically impairing as having half the total lung volume with IPF alone. Therefore, the presence of emphysema caused a similar impairment of diffusing capacity and gas exchange, which are two of the main features of functional impairment in lung fibrosis<sup>4</sup> and contribute to dyspnea and exercise incapacity. As expected, lung volumes were significantly higher in the patients who had the combined disease.

In addition, stepwise multiple regression analysis identified both the radiographic extent of emphysema and the extent of IPF as significant independent contributors to several functional variables. These findings may be explained by the worse ventilation-perfusion mismatching due to the presence of concomitant emphysema, which can also explain the presence of a significant correlation with P<sub>aO<sub>2</sub></sub> in Group I.

Although emphysema improved equation explanatory power, the predictive power of the stepwise models of

Table 4. Summary of Univariate Analysis of the Whole Population\*

Variable	Correlation With Fibrosis, Emphysema, and Dyspnea Score		
	Extent of Fibrosis (r) <sup>†</sup>	Extent of Emphysema (rho) <sup>‡</sup>	MRC Dyspnea Score (rho) <sup>‡</sup>
MRC score	0.28	0.31	NA
6-MWT	-0.08	-0.28	-0.25
P <sub>a</sub> O <sub>2</sub>	-0.07	-0.38	-0.34
P <sub>a</sub> CO <sub>2</sub>	0.14	0.31	0.30
P <sub>A-a</sub> O <sub>2</sub>	0.32	0.24	0.50, p = 0.0011
FVC	-0.53, p = 0.0007	-0.04	-0.42, p = 0.008
FEV <sub>1</sub>	-0.49, p = 0.001	-0.10	-0.36
FEV <sub>1</sub> /FVC	-0.24	-0.51, p = 0.004	-0.20
FEF <sub>25-75</sub>	-0.12	-0.33	-0.35
D <sub>L</sub> CO	-0.55, p = 0.0006	-0.23	-0.50, p = 0.0011
K <sub>CO</sub>	-0.49, p = 0.001	-0.20	-0.48, p = 0.0013
CPI	0.65, p < 0.0001	-0.037	0.59, p < 0.0001
RV	-0.51, p = 0.0009	0.34	0.16
TLC	-0.62, p = 0.0003	0.37	0.11

\*n = 42

<sup>†</sup>Pearson correlation coefficient<sup>‡</sup>Spearman rank correlation coefficient

MRC = Medical Research Council of the United Kingdom

NA = not applicable

6-MWT = 6-min walk test

P<sub>A-a</sub>O<sub>2</sub> = alveolar-arterial oxygen difference

FVC = forced vital capacity

FEV<sub>1</sub> = forced expired volume in the first secondFEF<sub>25-75</sub> = forced expiratory flow between 25% and 75% of FVCD<sub>L</sub>CO = diffusing capacity of the lung for carbon monoxideK<sub>CO</sub> = carbon monoxide diffusing capacity adjusted for alveolar volume (gas transfer coefficient)

CPI = Composite Physiologic Index

RV = residual volume

TLC = total lung capacity

dyspnea score and 6-MWT was low. Exertional dyspnea and exercise capacity in this condition are probably multifactorial, being related to gas exchange and ventilatory impairments, increased dead-space ventilation, peripheral muscle dysfunction, and increased elastic inspiratory load,<sup>25,26</sup> and are thus difficult to predict in IPF.

Emphysema also has substantial confounding effects on the functional assessment,<sup>8,25</sup> which was confirmed in this study by the significant correlations with P<sub>a</sub>O<sub>2</sub> and FEV<sub>1</sub>/FVC and the finding of higher-than-usual lung volumes. We therefore investigated the usefulness of the CPI in the clinical evaluation at presentation. Considering the whole population, the correlation between CPI and the extent of fibrosis was highly significant. The CPI was also the best predictor of dyspnea, which is a previously unexplored aspect of this new variable.

In a study of 54 patients with IPF, including 14 subjects with concurrent emphysema, Wells et al found, using multivariate analysis, that the presence of emphysema had profound effects on functional measures.<sup>25</sup> However, in that study the relationship between PFT values and the extent of emphysema was not studied and dyspnea scores were not considered. In accordance with that study, our

results suggest that emphysema profoundly influences functional-morphologic relationships in IPF.

Doherty and co-workers observed that conserved lung volumes in former smokers affected by IPF is a frequent finding, although in their study the CT scan documented the presence of concomitant emphysema only in 9 of 21 patients.<sup>8</sup> In that study, no evidence suggested that the concomitant emphysema was the result of more extensive fibrosis, so that emphysema due to smoking can explain the lung-volume preservation.<sup>8</sup>

The present study has several clinical implications. First, cigarette smoke is the main cause of emphysema<sup>26</sup> and it may be possible that the finding of combined emphysema plus IPF in former smokers is coincidental. However, case-control studies have demonstrated that in ever-smokers, cigarette smoking is a risk factor for IPF, with the odds ratio ranging from 1.6 to 2.9.<sup>4</sup> Given the high incidence of emphysema in the upper lobes and fibrosis in the lower lobes in our population of IPF patients (21 of 64 subjects), we argue that smoking can indeed induce both processes in the same patient, as has been observed in pathology studies.<sup>27</sup> It has been suggested that air-space enlargement

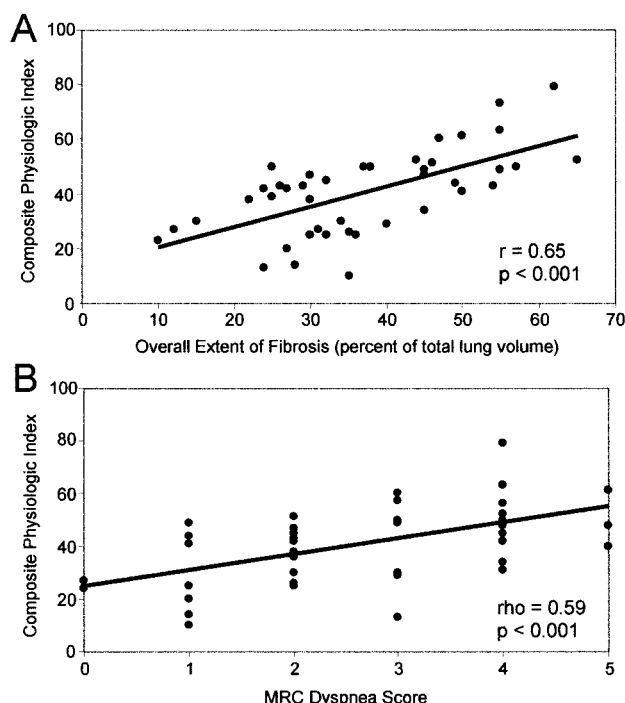


Fig. 3. A: Relationship between overall extent of fibrosis (percent of total lung volume) and the Composite Physiologic Index in the whole population ( $n = 42$ ). The Pearson correlation coefficient ( $r$ ) is 0.65. B: Relationship between Medical Research Council (MRC) dyspnea score and CPI in the whole population ( $n = 42$ ). The Spearman rank correlation coefficient ( $\rho$ ) is 0.59.

and emphysema are a stereotypical response of the lung to a wide variety of insults,<sup>28</sup> perhaps including the altered balance between injury and repair of lung epithelium, with myofibroblast differentiation, which characterize the pathogenesis of IPF.<sup>29</sup> In the combined disorder, the emphysema is localized in the upper lobes, which present a higher ventilation-perfusion ratio and may therefore be more sensitive to the insults of the irritating agents in cigarette smoke.<sup>30</sup> It remains to be explained why IPF usually starts in the subpleural areas of the lower lobes.<sup>3,4</sup>

Second, the American Thoracic Society/European Respiratory Society consensus document on the diagnosis and treatment of IPF states that a favorable (or improved) response to therapy is defined by a  $\geq 10\%$  increase in TLC.<sup>4</sup> Because emphysema may not be a stable disease, even after quitting smoking,<sup>26</sup> we argue that prudence may be required when evaluating PFT values during follow-up of patients affected by combined IPF and emphysema. However, long-term follow-up was not included in the present study, and future studies on the clinical course of combined IPF and emphysema may better explore this problem. These implications point to the possible role of CPI as a predictor of the combined disorder, which can rule out the functional defect attributable to emphysema.<sup>5</sup>

Third, in patients with IPF referred for lung transplantation, the HRCT fibrosis score is the best independent predictor of survival.<sup>31</sup> Because additional functional impairment comes from concomitant emphysema, in those subjects affected by combined disease the extent of emphysema should also be taken into account. Given the confounding effects of the 2 concomitant conditions and their independent contribution to several physiologic variables, it is likely that the best method to follow these patients and predict survival is to combine PFTs,<sup>5</sup> 6-MWT,<sup>32</sup> and HRCT score.<sup>33</sup> Again, further long-term follow-up studies focused on this particular condition are needed.

Finally, although long-term therapy was not addressed in this study, based on our results we hypothesize that selected patients with considerable extent of emphysema, identified via CT scan and PFT values, might benefit from bronchodilator therapy or pulmonary rehabilitation to improve exercise capacity and symptoms.

Some methodological limitations of the present study should be recognized. First, in general, the use of multiple statistical comparisons increases the risk of finding statistically significant differences by chance. Second, variable-selection algorithms in current statistics software programs, such as conventional stepwise regression, can easily lead to invalid estimates and tests of effect.<sup>34</sup> However, a large number of assumptions (including normal distribution of variables, linearity of correlations, and absence of high collinearity among independent variables) were verified before running the models. In addition, the number of independent variables used was carefully limited, based on the number of observations. Third, given the relatively small number of patients included in the present study and the consequent lack of statistical power, further studies are needed to support our findings.

## Conclusions

In former smokers with IPF, the presence and the extent of emphysema significantly influence physiologic function, in terms of both further impairment and confounding effects. In the presence of concomitant emphysema, when considering the response to therapy, prudence is therefore required in the evaluation of the functional results, and a multidisciplinary approach is probably required to adequately manage these patients.

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