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Correlation between Pulmonary Fibrosis and the Lung Pressure-Volume Curve

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Abstract. The severity of pulmonary fibrosis is the main prognostic factor for survival of patients with interstitial lung diseases (ILD). Unfortunately, lung biopsy, which is the best method to assess fibrosis quantitatively, is done only once during the evolution of the disease. In this study we analyzed the relationship between the degree of fibrosis and the exponential constant k, derived from the lung pressure-volume curve (LPVC) in 33 patients with chronic ILD, 19 with pigeon breeder's disease (PBD), and 14 with idiopathic pulmonary fibrosis (IPF). Pulmonary function tests, including the LPVC, were obtained before biopsy. A semiquantitative histologic assessment of the severity of fibrosis was performed on lung tissues. All patients showed a decrease of total lung capacity, residual volume, compliance, and Pao_2. The mean value of the constant k was 0.08 ± 0.06. When expressed as a percent of normal values, 25 patients exhibited values of k lower than 70% of predicted; of the remaining 8 patients whose values were above 70% of predicted, 7 had PBD and only one IPF. On morphologic analysis, 19 patients displayed more than 50% fibrosis. No significant correlations were found between the extent of the lesion or severity of lung fibrosis and the conventional pulmonary function tests. By contrast, a moderate but significant correlation was found between k and the severity of lung fibrosis ($r = -0.38$, $p < 0.05$). These findings show that the shape of the LPVC, represented by the constant k, predicts the degree of lung fibrosis and could be useful in the clinical assessment and follow-up of patients with ILD.

Key Words: Fibrosis—Lung fibrosis—Lung compliance—Pressure-volume curve.

Introduction

Pulmonary fibrosis is a consequence of a wide and heterogeneous group of interstitial lung disease(s) (ILD) that are characterized by a diffuse, nonuniform inflammation

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affecting interstitial and alveolar compartments of the lung [8]. Progression of ILD depends on a complex series of events involving inflammation, fibroblast proliferation, and fibrosis. Since the accumulation of collagen inexorably destroys lung architecture, it is believed that, independently of ILD etiology, the severity of histologically determined pulmonary fibrosis is the main prognostic factor for the survival of these patients [1, 22, 25, 28]. Because lung biopsy is done only once during the evolution of the disease, a variety of noninvasive techniques has been proposed to evaluate the severity of lung involvement and the degree of fibrosis in these diseases [10, 17, 20, 29, 31]. None of these tests has been shown to predict accurately the extent of pulmonary fibrosis and therefore the potential for response to therapy.

We have shown recently that a low value of the exponential constant k derived from the lung pressure-volume curve is associated with a worse prognosis in a group of patients with hypersensitivity pneumonitis (HP) [24]. We hypothesized that k would be predictive of the severity and extent of pulmonary fibrosis in ILD, probably the best prognostic indicator in these pathologic conditions. To test this hypothesis we measured prospectively a variety of lung function tests, including the exponential constant k, in a group of patients who had ILD of idiopathic origin or related to inhalation of avian antigens [26] and quantified the severity and extent of pulmonary fibrosis on open lung biopsy. Our results show that, of the lung function tests, k best predicts the degree of pulmonary fibrosis.

Patients and Methods

Patients

Thirty-three consecutive patients with chronic ILD were studied. Nineteen had HP induced by avian antigen (pigeon breeder's disease, PBD), and 14 had idiopathic pulmonary fibrosis (IPF). Criteria for the diagnosis of HP were the same as have been described elsewhere [24] and included: (1) exposure to avian antigens preceding symptoms; (2) dyspnea at rest worsening with exercise; (3) bilateral crackles on auscultation; (4) a predominantly restrictive pattern on pulmonary function tests; (5) hypoxemia at rest worsening with exercise; (6) specific serum antibodies detected by enzyme-linked immunosorbent assay and (7) lung biopsy (performed in all patients) with histopathologic changes characteristic of HP. The large majority (17 out of 19) were female patients who kept a few pigeons at home. The diagnosis of IPF was made in 14 patients (8 female, 6 male) using the same clinical, radiologic, and functional criteria as for HP, but the patients had neither antecedent exposure to birds nor circulating antibodies against avian antigens. In addition, pulmonary biopsy done in all of these patients showed the characteristic histopathologic abnormalities described for IPF and lacked granulomas, vasculitis, microorganisms, and inorganic material by polarized light microscopy [6].

Pulmonary Function Tests

Spirometry was performed using electronic integration of a pneumotachometer signal (Erich Jaeger Gmb H & CoKG, Wurzburg, Federal Republic of Germany). Three acceptable forced vital capacity (FVC) maneuvers were obtained from each patient, and the best forced expired volume in 1 s (FEV_1) and FVC were chosen. Total lung capacity (TLC) and residual volume (RV) were derived from functional residual capacity (FRC), which was measured in a constant volume plethysmograph (Jaeger Bodytest, Erick Jaeger Gmb H & CoKG) according to the technique of DuBois et al. [7]. Spirometric measurements and the subdivisions of lung volume were expressed as percent of predicted using the reference equations of Quanjer et al. [23].

Measurements of the lung pressure-volume curve (LPVC) relationship were made as described previously [24]. Transpulmonary pressure was measured using an esophageal balloon and a pressure transducer according to the technique of Milic Emili and co-workers [19]. Volume was measured using electrical integration of the flow signal derived from the pneumotachometer in the Jaeger plethysmograph. The esophageal balloon was 10 cm in length and was coupled to PE-90 polyethylene tubing. Multiple side holes were made in the catheter within the balloon, and the balloon catheter was initially inserted into the stomach as assessed by the development of positive pressures during inspiration. The balloon was then withdrawn slowly until the first negative pressure swings were documented during inspiration and then was withdrawn a further 10 cm from the gastroesophageal junction. The volume of air in the balloon was kept constant at 0.5 ml. A constant volume history was assured by having the patients breathing normally and then inspiring to TLC three times. Static transpulmonary pressure at TLC was recorded with the glottis open while the patient maintained a maximal inspiration for 2–3 s. The patients then expired slowly to RV through an orifice that was occluded every 0.5 s (6–12 static pressure volume points/curve). The pressure and volume points were recorded on an X-Y recorder (Hewlett-Packard), and at least three satisfactory and reproducible curves were obtained from each patient.

Static compliance (Cst) was measured as the change in volume per unit pressure change between FRC and FRC + 0.5 liter on the static deflation volume-pressure curve. Maximal transpulmonary pressure ($P_L$max) was measured at TLC and expressed in cm H_2O. Transpulmonary pressure at 90% of TLC (P_L90) was also determined.

The pressure-volume data above FRC were fitted to the exponential equation $V = A - Be^{-kp}$ using a least squares iterative computation [4]. V is lung volume above FRC; A is the asymptote, a hypothetical lung volume usually above TLC where the LPVC plateau, that is, compliance, is zero; B is the volume below A at which the pressure is 0; P is transpulmonary pressure (cmH_2O); and k is the exponential constant (cmH_2O^{-1}), which describes the shape of the curve and is related to specific compliance. At any point of the LPVC, the compliance (slope) becomes $k(A - V)$. The exponential constant k was expressed as percent predicted according to the equations of Colebatch et al. [3].

Pulmonary diffusing capacity for carbon monoxide (DL_{CO}) was measured by the single breath technique and was expressed as percentage of predicted values according to Quanjer [23]. Arterial oxygen tension (Pa_{O_2}) and arterial carbon dioxide tension (Pa_{CO_2}) were also recorded.

Morphologic Evaluation

All lung samples were taken by open lung biopsy, usually 1 week after hospital admission. None of the patients had been treated with steroids or immunosuppressive drugs at the time of biopsy or before. Lung biopsy tissue was obtained from two different sites generally from the right lung guided by the images of fibrosis on chest X-rays and CT scan when available.

The morphologic observations were made by a pathologist (MG) blinded to the results of the pulmonary function tests. The degree of pulmonary fibrosis was assessed on the lung biopsy using a semiquantitative grading scheme that has been described elsewhere [22]. The grading scheme is based on the severity of three histologic features. (1) The extent of the lesion represents the percentage of the lung biopsy involved with either inflammation or fibrosis or both. A biopsy can have 11 possible scores from 0 to 100% for the extent of the lesion (100% when the whole surface of the biopsy is abnormal). (2) The percentage of fibrosis represents the part of the abnormal lung where there is an increased deposition of collagen. This variable is expressed on an 11-point scale between 0 and 100% (100% when the entire involved area is characterized by collagen deposition). (3) Third is the percentage of inflammation occupying the rest of the affected area of the lung sample. This is also expressed on an 11-point scale between 0 and 100% (100% when the entire involved area is characterized by an inflammatory process). Thus, for example, a lung specimen could have an 80% extent of lesion and in this affected area, 40% fibrosis and 60% inflammation. The assessment was done on the histologic slides scanned completely in zigzag fashion, first at 32 and then at 125× magnification. In all cases at least four slides, two stained with Masson's trichrome and two with hematoxylin-eosin, were analyzed. Reproducibility of the pathologist for the extent of the lesion and severity of inflammation and fibrosis have been reported previously [22].

Table 1. Functional and morphologic characteristics of the patients

	Mean	Range
Age	47 ± 15	17–78
FVC (% predicted)	57 ± 20	31–99
TLC (% predicted)	70 ± 18	34–118
FEV_1/FVC	88 ± 7	82–97
Pao_2 (mmHg)	51 ± 8	37–70
$Paco_2$ (mmHg)	32 ± 5	22–44
DL_{CO} (% predicted)	54 ± 16	13–79
P_L 90 (cmH_2O)	26 ± 13	13–65
P_L max (cmH_2O)	60 ± 25	18–118
k (% predicted)	56 ± 27	15–103
Cst (liters/cmH_2O)	0.114 ± 0.1	0.013–0.5
Extent of the lesion (%)	67 ± 23	20–100
Percent of fibrosis	47 ± 23	20–90

Data Analysis

The majority of the lung function tests, including *k*, were distributed normally. However, the histologic variables were not. These variables were transformed by expressing them as logarithmic values to allow linear correlation. To test the hypotheses we performed linear least squares regression analysis using the histologic scores (extent of abnormal lung and severity of fibrosis) as the dependent variables and the tests of lung function (FVC, TLC, compliance, DL_{CO}, and *k*) as the independent variables.

Results

Thirty-three patients were included in this study: 19 had a diagnosis of PBD (nonsmokers); and 14 had IPF (three smokers). The mean time of exposure to avian antigens in the patients with HP was 50 ± 72 months (range, 1–240 months). Most of these patients had been exposed to pigeons (17 out of 19), although some also had other birds such as parakeets ($n = 6$), chickens ($n = 12$), and canaries ($n = 4$). The mean time of disease ranged from 1 to 23 months for PBD patients and from 6 to 28 months for IPF patients. Table 1 shows the pulmonary function tests as well as the measurements obtained from the analysis of the pressure-volume curve, and the morphologic assessment of fibrosis in the lung tissue.

Lung Function Tests

The patients showed a restrictive pattern of pulmonary function characterized by a decrease of TLC and RV. FVC and FEV_1 were also decreased, whereas the mean FEV_1/FVC ratio was normal or supranormal. Likewise, abnormal gas exchange as evidenced by hypoxemia at rest, which worsened with exercise, was generally observed. When measured, decreased levels of DL_{CO} were also found ($n = 20$).

Lung Pressure-Volume Curve

Compliance varied from 0.013 to 0.50 liters/cmH_2O with only five patients exhibiting values within the normal range, four of them with a diagnosis of PBD. When volume was expressed as percent of predicted all the patients showed a pressure-volume curve shifted down and to the right. Likewise, the $P_L$max) was increased markedly, with a mean of 60 ± 25 cmH_2O; normal values in this age group ranged between 20 and 45 cmH_2O [26]. The mean value of the constant k obtained from the exponential analysis of the pressure-volume curve was 0.08 ± 0.06. When expressed as percent of normal values, according to the equations of Colebatch and co-workers [3], 25 patients showed values of k lower than 70% of predicted; of the remaining 8 patients whose values were above 70% predicted, 7 had a diagnosis of HP and only 1 a diagnosis of IPF. Taken together these results indicate that the patients had moderate to severe pulmonary restriction with increased lung recoil.

Morphologic Assessment

All patients showed histologic features of either HP or IPF. In HP, tissue samples showed diffuse interstitial inflammation of mononuclear predominance, mainly lymphocytes, and frequent multinucleated giant cells in terminal and respiratory bronchioles as well as in the alveolar spaces. Small and loosely arranged granulomas were observed in the interstitium, and there were no changes suggestive of infection or of any other ILD. In IPF, morphologic changes included patchy alveolar septal fibrosis and interstitial inflammation consisting mostly of mononuclear cells but also of neutrophils and eosinophils; a variable macrophage accumulation was observed in the air spaces as well as cuboidalization of the alveolar epithelium. Biopsies lacked granulomas, vasculitis, microorganisms, and inorganic material by polarized light microscopy.

There was a variable extent of the lesion as well as of the severity of fibrosis (Table 1). Nineteen patients showed a score for the severity of fibrosis of more than 50%, and 14 had a score of less than 50%.

Correlations of the Pulmonary Function Tests and Morphology

No statistically significant correlations were found between the extent of abnormal lung or the severity of pulmonary fibrosis and the standard functional tests, or with some parameters derived from pressure-volume curve such as lung compliance, $P_L$max, or P_L90, expressed either as a percent of predicted or as raw values (Table 2). However, when k was expressed as a percent of predicted (for age) a moderate but statistically significant correlation was found with the severity of lung fibrosis ($r = -0.38$, $p < 0.05$) (Table 2 and Fig. 1). Furthermore, 16 out of 19 patients with more than 50% of fibrosis showed a low k (<2 S.D. of normal), whereas all patients having a normal k showed 50% or less fibrosis ($p = 0.004$).

When patients were separated by diagnosis, the same trend was observed. As can be seen in Table 3, PBD patients showed an average of 35% fibrosis with 59% of k, whereas IPF patients displayed a significantly higher degree of fibrosis with a lower k.

Table 2. Coefficient of correlation between functional parameters and severity of degree of pulmonary fibrosis

Parameter	Fibrosis $(r)^a$
FVC (% predicted)	0.25
TLC (% predicted)	0.18
Cst	0.12
P_L 90	0.03
k (% predicted)	-0.38^b
DL_{CO}	0.03
Pao_2	0.04
$Paco_2$	0.03

[a] Pearson correlation coefficient.
[b] $p < 0.05$.

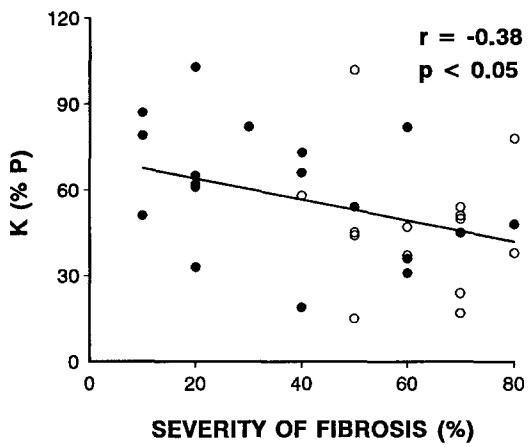

Fig. 1. Relationship between severity of fibrosis and the constant k. The exponential constant, which describes the shape of the LPVC displayed a moderate but significant correlation with the percentage of histologic lung fibrosis. *Closed circles,* PBD patients; *open circles,* IPF patients.

Discussion

Interstitial and intralveolar fibrosis is a final common denominator for many ILD patients, whatever their etiology. The mechanisms responsible for the progression of the disease are not completely understood, but they include the characteristics of the initial injury, the epithelial damage and loss of permeability barrier, the inflammatory process, fibroblast proliferation, and matrix remodeling and deposit. However, since exaggerated interstitial collagen deposition destroys lung parenchyma irreversibly, the severity of the fibrous thickening of alveolar walls is considered the main predictor of mortality in fibrosing diseases of the lung [1, 22, 25, 28]. An open lung biopsy is feasible only once during the course of the disease, and therefore noninvasive clinical and functional monitors are needed for the follow-up of these patients. These putative

Table 3. Pulmonary fibrosis and k in patients with pigeon breeder's disease (PBD) and idiopathic pulmonary fibrosis (IPF)

	PBD (n == 19)	IPF (n == 14)	p
Percent of fibrosis	35 ± 22	62 ± 12	0.001
K (% predicted)	59 ± 21	45 ± 23	0.14

monitors should be validated in relation to the morphologic degree of lung inflammation and fibrosis.

Several tests for predicting the underlying pathology and the eventual outcome have been proposed. The cell profile in the bronchoalveolar lavage (BAL) appears to be useful in some ILD. Specifically in IPF, increased BAL lymphocytes correlate with a cellular interstitial pneumonitis as opposed to advanced fibrosis [30]. By contrast, excess neutrophils or eosinophils have been associated with disease progression [14]. However, there are few published data to substantiate these correlations. More recently, McCormac et al. [18] have found that the surfactant protein A/total phospholipid ratio in BAL fluid predicts survival in IPF. Likewise, a high resolution, thin cut CT scan is potentially useful in staging ILD, and there is preliminary evidence that a ground glass pattern strongly suggest an inflammatory process, whereas reticular changes and honeycomb cysts indicate fibrotic changes [21].

Studies of the relationships between morphologic and physiologic data have given contradictory results. Some authors have suggested that certain functional tests predict morphologic abnormalities, whereas others have shown that the same tests are not correlated with the pathology [2, 9, 13]. For example, Fulmer et al. [9] have reported that lung volumes and diffusing capacity are poor monitors of the degree of fibrosis, whereas Chinet et al. [2] found good correlation among lung volumes, DL_{CO}, and severity of pulmonary fibrosis. Likewise, Green and co-workers [13] have observed good correlations between pulmonary fibrosis and lung volumes but not between fibrosis and DL_{CO}.

It has been proposed that exercise-induced changes in Pao_2, normalized for change in oxygen consumption, provide a sensitive and objective method of following the temporal changes in the fibrotic process [6]. However, this assumption has not been clearly demonstrated [12].

In the present study, the classical restrictive pattern described in ILD was observed. Patients exhibited decreased lung volumes, normal or supranormal volume-corrected airflow, reduced compliance with an increased $P_L$max; and resting hypoxemia that worsened with exercise. However, none of these parameters individually, including exercise blood gases, correlated with the semiquantitative histologic assessment of fibrosis.

It has been suggested that of all respiratory functional parameters, those derived from the static deflation pressure-volume curve should be the best predictors of the degree of pulmonary fibrosis [9, 16]. Theoretically, lung compliance can be decreased by inflammation, which reduces lung volume by replacing gas volume with cells and fluid, or by fibrosis, which diminishes lung volumes by destroying the alveolocapillary

units and altering lung architecture. To help differentiate the pathologic situations, an exponential modeling of static lung compliance has been proposed. This model is an approach to the problem of volume dependence of compliance and offers a volume-corrected compliance. In this model, k is a constant that describes the curvature of the pressure-volume curve.

Gibson and Pride [11] have suggested that the shape of the pressure-volume curve, as reflected in the constant k, can indicate increased stiffness of the functioning alveoli by fibrosis rather than a simple decrease of the alveolar volume. Our findings support this hypothesis since we observed that the greater the severity of lung fibrosis, the lower the k expressed as percent of predicted for age. Most of the patients with k values within the normal range displayed a semiquantitative score of less than 50% for fibrosis, whereas patients having a low k (<2 S.D. of normal) had more than 50% fibrosis. Although significant, the correlation between k and fibrosis was low, indicating that only a relatively small percentage of the variation in k could be explained by the degree of fibrosis. Nonuniformity of lung damage [5, 15] and the variability in human assessment of pathology and lung function are some of the reasons for relatively poor correlation regularly found between lung structure and function.

In summary, lung volumes, flows, and static compliance did not correlate with the degree of pulmonary fibrosis in our study. By contrast, the shape of the LPVC expressed by the exponential constant k exhibits a moderate correlation with the severity of the lung fibrosis, the best known predictor of prognosis in progressive ILD such as IPF. This test might provide useful information in the clinical evaluation of patients with ILD.

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