Low initial KCO predicts rapid FEV₁ decline in pulmonary lymphangioleiomyomatosis

Romain Lazor, Dominique Valeyre, Jacques Lacronique, Benoît Wallaert, Thierry Urban, Jean-François Cordier, The Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM''O''P)

Division de Pneumologie, Hôpitaux Universitaires, 24, rue Micheli-du-Crest, 1211 Genève 14, Switzerland
Service de Pneumologie, Hôpital Avicenne, Bobigny 93000, France
Service de Pneumologie, Groupe Hospitalier Cochin, Paris 75679, France
Département de Pneumologie, Hôpital Albert Calmette, Lille 59037, France
Service de Pneumologie, Centre Hospitalier Universitaire, Angers 49033, France
Service de Pneumologie, Hôpital Cardiovasculaire et Pneumologique, Lyon Cedex 03 69394, France

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Summary Pulmonary lymphangioleiomyomatosis (LAM) is a rare interstitial disorder affecting exclusively women, and leading to progressive deterioration of lung function. The disease course is highly variable from one patient to another, but no clinical predictor of rapid disease progression is currently available. To identify clinical variables, which could detect patients at risk for rapid lung function decline, we searched for correlations between the rate of forced expiratory volume in 1 s (FEV₁) decline and clinical features at diagnosis in a retrospective series of 31 cases of LAM followed for ≥ 1 yr. The mean FEV₁ decline was 106 ± 143 ml/yr or 3.4 ± 4.6% predicted FEV₁/yr. Among clinical features at diagnosis, only initial values of carbon monoxide transfer factor (TLCO, P = 0.006) and carbon monoxide transfer coefficient (KCO, P = 0.0001) were significantly correlated with the rate of FEV₁ decline. Lung volumes and FEV₁/FVC ratio at diagnosis were not predictive of rapid decline. No effect of previous smoking, contraceptive use or pregnancy on FEV₁ decline could be detected. We conclude that low TLCO and KCO at the time of diagnosis are the best clinical predictors of rapid FEV₁ decline in patients with LAM.

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Lymphangioleiomyomatosis (LAM) is a rare disorder of unknown cause affecting exclusively women, characterised by abnormal proliferation of nonmalignant smooth muscle cells (LAM cells). In the lung, LAM cells proliferation in the walls of bronchi, blood vessels and lymphatics leads to cystic destruction of the lung parenchyma characterised by an obstructive ventilatory defect, lung hyperinflation, recurrent pneumothorax, and eventually progressive respiratory insufficiency. Other manifestations include enlarged thoracoabdominal lymph nodes, lymphangiectasis, chylothorax, chylous ascites, and renal angiomyolipomas. The disease usually appears during childbearing age.
Although retrospective analyses suggested that progesterone might be beneficial in some cases, no effective treatment has been established. The natural course of pulmonary LAM is highly variable from one patient to another. Some remain stable for years and even decades with only mild ventilatory impairment, whereas others experience rapid disease progression leading to lung transplantation or death within a few years after disease onset. Besides a histological score predicting survival, no tools are currently available to detect patients at risk of rapid disease progression. The objective of the present study was to identify clinical factors associated with rapid lung function decline in patients with LAM, in order to predict unfavourable outcome at the time of diagnosis. Such predictors could be especially of interest to select patients for therapeutic trials using lung function decline as the main variable, since the effect of an experimental treatment would be easier to detect in patients with rapid deterioration of lung function than in those with stable disease.

Methods

Case recruitment and data collection

This study was undertaken by the Groupe d’Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P), a French group dedicated to the study of "orphan" pulmonary diseases, including LAM. In December 1996, a detailed questionnaire was sent to physicians who had reported cases of LAM to the GERM"O"P registry. Questionnaires were answered by a review of the medical records. In October 1999, following completion of our two previous studies, physicians were asked to update information on their LAM patients, especially lung function tests, occurrence of lung transplantation, and survival. New cases were also included. This second data collection ended in April 2000.

Selection of cases

Cases meeting the two following criteria were eligible for inclusion:

1. Diagnosis of pulmonary LAM, based on:
   (a) characteristic pathological features at lung biopsy or
   (b) typical cystic appearance on chest computed tomography (CT) and at least one of the following: characteristic pathological findings on lymph node biopsy; typical angiomyolipoma of the kidney at imaging and/or histology; chylous ascites with abdominal lymphadenopathy at imaging; or abdominal lymphangiectasis at lymphangiogram.

2. Complete pulmonary function testing performed in stable condition at diagnosis, and \( \geq 2 \) forced expiratory volume in 1 s (FEV\(_1\)) measurements performed in stable condition at least 1 yr apart.

Complete pulmonary function tests included FEV\(_1\), forced vital capacity (FVC), FEV\(_1\)/FVC, total lung capacity (TLC), residual volume (RV), single breath carbon monoxide transfer factor (TLCO) and coefficient (KCO), and arterial blood gases. All lung function tests performed during pleural events such as pneumothorax or chylothorax, and \( \leq 2 \) months after thoracotomy or thoracoscopy, were discarded. Lung function tests performed after lung transplantation were of course not included in this analysis.

Determination of the rate of FEV\(_1\) decline

For each patient, the rate of FEV\(_1\) decline over time (\( \Delta FEV_1 \)) was determined as the slope of the linear regression, both in percentage of predicted value per year (\% pred/yr) and in ml/yr. FEV\(_1\) gain over time resulted in a positive \( \Delta FEV_1 \) value, and FEV\(_1\) loss in a negative \( \Delta FEV_1 \) value. Since the response to beta-2-agonists was not systematically available, only pre-bronchodilator measurements were used.

Data analysis

The main independent variable was \( \Delta FEV_1 \) expressed in \% pred/yr. This unit was preferred to ml/yr, because it corrects for morphometric variations among subjects. The following items were examined in the search for a correlation with \( \Delta FEV_1 \): history of smoking, contraceptive use, pregnancy, age at first symptoms, clinical features at diagnosis (dyspnoea, pneumothorax, chylous effusions, lymphadenopathy, and angiomyolipoma), initial lung function tests, hormonal treatment, and outcome. To detect a selection bias, we searched for correlations between \( \Delta FEV_1 \) and, respectively, year of first symptoms, year of diagnosis, duration of lung function follow-up, and number of FEV\(_1\) measurements. Correlation between \( \Delta FEV_1 \) and continuous variables were analysed by linear regression and by Spearman’s rank correlation coefficient. For binary variables, the cases were separated into two groups according to the
presence or absence of the studied feature, and \( \Delta \text{FEV}_1 \) was compared between groups with the unpaired \( t \)-test and the Mann–Whitney test. All data were expressed as mean ± standard deviation. Because of multiplicity, only \( P \) values < 0.01 were considered significant.

**Results**

**Study population**

Thirty-one cases of pulmonary LAM meeting inclusion criteria were available. Twenty-nine have been previously reported by our group,\(^4\,\!^{10} \) and 20 of them were updated for the present study. Two were new cases. Diagnoses were made between 1980 and 1998. Diagnostic criteria were met by lung biopsy in 26 cases (84%) and by typical chest CT scan with one or more additional criteria in the remaining five cases (16%). The clinical characteristics of the study population are presented in Table 1, and the initial lung function tests are summarised in Table 2. The most frequent abnormality was reduced TLCO. An obstructive ventilatory defect (FEV\(_1/\text{FVC}<70\%\)) was present in half of the cases. No patients had respiratory insufficiency at the time of diagnosis.

Treatment modalities are summarised in Table 3. Twenty-eight patients (90%) received at least one hormonal treatment during disease course. Two or more treatments were used in 12 (39%). Patients who received progestatives at some point during disease course \((n = 20)\) had a nonsignificant trend for lower initial TLCO and KCO as compared to those who did not receive this therapy \((n = 11)\), but the two groups were otherwise similar for all characteristics (data not shown). Likewise, no significant difference was found between patients who received antiestrogens \((n = 10)\) as compared to those who did not \((n = 21)\), and between patients who were treated with luteinising-hormone-releasing hormone (LHRH) agonists \((n = 12)\), as compared to those who were not \((n = 19, \text{data not shown})\).

Three patients eventually underwent lung transplantation. Four patients died, either from pulmonary LAM \((n = 2)\) or from complications of lung transplantation \((n = 2)\).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected clinical characteristics at diagnosis in 31 cases of LAM.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first symptoms (yr)</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>38 ± 9</td>
</tr>
<tr>
<td>History of smoking (%)</td>
<td>37</td>
</tr>
<tr>
<td>History of contraceptive use (%)</td>
<td>33</td>
</tr>
<tr>
<td>History of pregnancy (%)</td>
<td>70</td>
</tr>
<tr>
<td>History of menopause (%)</td>
<td>4</td>
</tr>
<tr>
<td>Pneumothorax (%)</td>
<td>55</td>
</tr>
<tr>
<td>Chyloous effusion (%)</td>
<td>19</td>
</tr>
<tr>
<td>Angiomyolipoma (%)</td>
<td>37</td>
</tr>
<tr>
<td>Typical chest CT scan (%)</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Initial lung function tests in 31 cases of LAM.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of abnormal values</td>
<td>Mean values</td>
</tr>
<tr>
<td>Criterion</td>
<td>% of cases</td>
</tr>
<tr>
<td>FEV(_1) (% pred)</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>FEV(_1/\text{FVC}) (%)</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>TLC (% pred)</td>
<td>&gt; 120</td>
</tr>
<tr>
<td>RV (% pred)</td>
<td>&gt; 120</td>
</tr>
<tr>
<td>TLCO (% pred)</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>KCO (% pred)</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>PaO(_2) (mmHg)</td>
<td>&lt; 75</td>
</tr>
<tr>
<td>PaCO(_2) (mmHg)</td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

FEV\(_1\): forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; TLCO: carbon monoxide transfer factor; KCO: carbon monoxide transfer coefficient. \( n = 31 \) for all variables except PaO\(_2\) and PaCO\(_2\) \((n = 26)\).
The characteristics of ΔFEV₁ in the whole study population are presented in Table 4. The standard error of the 31 individual ΔFEV₁ regression lines averaged 1.4% pred/yr, thus reflecting good linearity of the relationship in each case. The mean ΔFEV₁ in the whole study population was −106 ml/yr or −3.4% pred/yr (range: −439 to +139 ml/yr and −13.9 to +5.6% pred/yr). The average duration of lung function follow-up was 4.8 yr. In search of a recruitment bias, ΔFEV₁ was plotted against, respectively, year of first symptoms, year of diagnosis, duration of lung function follow-up, or number of FEV₁ measurements, but no correlation was found (data not shown).

Correlation between ΔFEV₁ and continuous variables

A significant correlation was found between ΔFEV₁ and, respectively, initial KCO (r = 0.64, P = 0.0001) and initial TLCO (r = 0.46, P = 0.006) by linear regression. The correlation coefficient was higher for KCO than for TLCO. Lower initial TLCO and KCO at the time of diagnosis correlated with more negative ΔFEV₁ as compared to patients who did not receive such therapy, although the difference did not reach statistical significance. Patients who received LHHR agonists also had a nonsignificant trend for more negative ΔFEV₁ as compared to patients who did not receive this treatment. The five patients who either required lung transplantation or died tended to have a more negative ΔFEV₁ compared to the others, although the difference did not reach statistical significance.

Correlation between ΔFEV₁ and binary variables

In this analysis, the study population was divided into two groups according to the presence or absence of a given clinical feature, and ΔFEV₁ was compared between groups by the unpaired t-test. The same procedure was repeated for all binary variables. No difference in mean ΔFEV₁ was found between groups according to history of smoking, pregnancy, and oral contraceptive use. Similarly, the presence of pneumothorax, chylos effusion, or angiomyolipoma at diagnosis was not associated with increased ΔFEV₁. Repeating these analyses with nonparametric statistics led to the same conclusions. Patients who received progesterative treatment at some point during disease course tended to have a more negative ΔFEV₁ as compared to patients who did not receive such therapy, although the difference did not reach statistical significance.

Discussion

The main finding of the present study is that low KCO and TLCO at the time of diagnosis correlated with rapid FEV₁ decline in patients with LAM, whereas all other spirometric and clinical variables at diagnosis were not predictive of rapid FEV₁ decline.

Reduced initial TLCO has been previously shown to correlate with rapid FEV₁ decline in smokers, greater deterioration of gas exchange in idiopathic pulmonary fibrosis, and poorer survival in COPD. In LAM, cross-sectional analyses showed that TLCO correlates with disease severity at imaging, a positive response to bronchodilators, and a histological score of parenchymal involvement, which in turn predicted survival. Taken together, these two studies suggest that a relationship exists between initial TLCO and progression in LAM. Our data are consistent with these observations. Although our findings are insufficient to allow an accurate quantitative prediction of FEV₁ decline in LAM, they could be useful to identify patients at risk for rapid deterioration of lung function, in spite of initially preserved lung volumes. Therefore, complete pulmonary function tests including TLCO and KCO should be performed in all cases of LAM at the time of diagnosis.

We did not find any correlation between FEV₁ decline and initial FEV₁ or other spirometric variables at diagnosis. Interestingly, the mean values of initial FEV₁ and initial KCO were very similar (65% and 72% of predicted, respectively), as were the percentage of abnormal values for these two variables (58% and 65% of cases below 80% of predicted, respectively). These similarities contrasted with the fact that initial KCO was strongly correlated with ΔFEV₁, whereas initial FEV₁ was not. These data confirm previous observations and
suggest that abnormal lung volumes or an obstructive ventilatory defect at the time of diagnosis are not necessarily associated with more rapid deterioration of lung function in LAM.

How the gas exchange abnormalities and, respectively, obstructive ventilatory defect evolve over time in the natural course of LAM is not precisely known at the present time. They might start to decline at different time points and evolve at different rates, so that KCO could be an earlier and more sensitive marker of disease progression than spirometry. Studying KCO decline in LAM would be of great interest, but we could not address this issue in the present study due to the lack of follow-up data. Whether low initial KCO correlates with survival needs to be addressed in a larger population.

No clear relationship has been demonstrated so far between smoking, pregnancy, or contraceptive use and the development or rate of progression of pulmonary LAM. Likewise, we could not detect an influence of these characteristics on FEV₁ decline in the present study. However, a weak correlation could have been missed due to small sample size.

Whether hormonal treatment has any therapeutic effect on lung function in LAM remains controversial. In the only study, which retrospectively addressed this issue, a favourable effect of progesterone on FEV₁ decline was observed in a subgroup, but this did not reach statistical significance in the whole study population. Should progesterone have any therapeutic effect, one would expect treated patients to have a milder FEV₁ decline. In contrast, a trend for the opposite was observed in the present study, both for progesterone and for LHRH agonists. No selection bias was found in our study population by comparing patients who received either one of these treatments with those who did not. Therefore, the most likely explanation for this nonsignificant trend is that rapidly deteriorating patients were more prone to be treated, in an attempt to minimise the worsening of their lung function. Because of great intraindividual variations of treatment over time in most cases, a detailed analysis of the effect of a given treatment on the rate of FEV₁ decline could not be performed in this study.

Only two studies have previously analysed FEV₁ decline in LAM. The mean rate of FEV₁ decline in our population was 106 ml/yr, which is very similar to the findings of these two previous studies. This confirms that, on average, there is accelerated FEV₁ decline in LAM. In comparison, FEV₁ declines approximately by 30 ml/yr in non- or former smokers, and 60 ml/yr in active smokers. Similarly to previous series, there was a wide interindividual variation of ΔFEV₁ in our population. These concordant data from several LAM populations suggest that this heterogeneity in FEV₁ decline truly reflects the variable nature of the disease course from one patient to another.

Despite the retrospective nature of our study and the small number of cases, we could not detect any significant selection bias which could have altered our findings. We searched for correlations between ΔFEV₁ and, respectively, year of first symptoms, year of diagnosis, FEV₁ follow-up duration, or the number of FEV₁ measurements. No such relationship was found, suggesting that our study population has not been biased by underreporting of older cases with unfavourable outcome, or selection of long survivors with stable disease and long follow-up. We used only baseline FEV₁ measurements without beta-2-agonists, since response to bronchodilators was not systematically available. Although a mild effect of beta-2-agonists on obstructive ventilatory impairment has been reported in a minority of patients with LAM, there are no data suggesting that such therapy may modify the natural course of the disease. We therefore believe that our ΔFEV₁ calculation would not have been affected by using post-bronchodilator FEV₁ measurements instead of pre-bronchodilator values. Finally, we believe that hormonal treatments did not bias our findings, for the following reasons. First, no treatment has proved its efficacy in LAM at the present time. Secondly, no significant difference was found between the various treatment subgroups. Thirdly, patients who received a treatment intended to improve their lung function did not disclose a milder FEV₁ decline but a trend for the opposite was even observed.

In summary, this study shows that lower TLCO and KCO at the time of diagnosis were strongly correlated with more rapid FEV₁ decline in pulmonary LAM. These data may prove useful to identify patients at risk for rapid deterioration of lung function, in spite of apparently preserved lung volumes at diagnosis. These data could also help to select patients for future therapeutic trials using the rate of FEV₁ decline as the main outcome variable. Hence, the effect of an experimental treatment on this variable would be easier to detect in patients with rapid deterioration than in those with stable disease.

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