



Reversible Airflow Obstruction in Lymphangioleiomyomatosis

Angelo M. Taveira-DaSilva, MD, PhD; Wendy K. Steagall, PhD;
Antoinette Rabel, CRNP; Olanda Hathaway, CRNP; Sergio Harari, MD;
Roberto Cassandro, MD; Mario Stylianou, PhD; and Joel Moss, MD, PhD

Background: We previously reported that approximately one-fourth of patients with lymphangioleiomyomatosis (LAM) may respond to therapy with bronchodilators. However, the validity of those observations has been questioned. The aims of the present study were to determine the prevalence of reversible airflow obstruction in patients with LAM and to identify associated clinical and physiologic parameters.

Methods: First, the clinical and physiologic characteristics of 235 patients were analyzed to determine the frequency of the response to albuterol during a total of 2,307 visits. Second, we prospectively evaluated the response to albuterol (2.5 mg) and ipratropium (500 μ g) in 130 patients, and correlated their responses with their clinical and physiologic characteristics.

Results: In the retrospective study, 51% of the patients responded at least once to bronchodilators; of these, 12% responded $\geq 50\%$ of the time. A higher frequency of positive bronchodilator responses was associated with greater rates of decline in FEV₁ and diffusing capacity of the lung for carbon monoxide (DLCO). In the prospective study, 39 patients (30%) responded to bronchodilators, including 12 to ipratropium, 9 to albuterol, and 18 to both. The prevalence of asthma and smoking in the 39 responders was not different from that seen in the 91 nonresponders. Patients who responded to ipratropium, albuterol, or both had significantly ($p < 0.02$) lower FEV₁ and DLCO, and a greater rate of FEV₁ decline ($p = 0.044$) and DLCO decline ($p = 0.039$) than patients who did not respond to these bronchodilators. After adjusting for FEV₁/FVC ratio, DLCO decline also was greater in responders than in nonresponders ($p = 0.009$).

Conclusions: Patients with LAM may have partially reversible airflow obstruction. A positive response to bronchodilators is associated with an accelerated rate of decline in pulmonary function. (CHEST 2009; 136:1596–1603)

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; LAM = lymphangioleiomyomatosis; NIH = National Institutes of Health; RV = residual volume; TLC = total lung capacity

Lymphangioleiomyomatosis (LAM) is a multisystem disease that predominantly affects women. It is characterized by the proliferation of abnormal smooth muscle-like cells (LAM cells) that lead to the

formation of lung cysts, fluid-filled cystic structures in the axial lymphatics (eg, lymphangioleiomyomas), and abdominal tumors (eg, angiomyolipomas),^{1–5} which occur sporadically or in association with tuberous sclerosis complex.^{6–8} Pulmonary function tests show reduced FEV₁ and diffusing capacity of the lung for carbon monoxide (DLCO).⁵

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Affiliations: From the Translational Medicine Branch (Drs. Taveira-DaSilva, Steagall, and Moss, Ms. Rabel, and Ms. Hathaway) and the Office of Biostatistics Research (Dr. Stylianou), National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; and Unità di Pneumologia e Terapia Semi-Intensiva Respiratoria (Drs. Harari and Cassandro), Servizio di Fisiopatologia Respiratoria ed Emodinamica Polmonare, Ospedale San Giuseppe, Milan, Italy.

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Correspondence to: Angelo M. Taveira-DaSilva, MD, PhD, Translational Medicine Branch, NHLBI, NIH, Building 10, Room 6D05, MSC 1590, Bethesda, MD 20892-1590; e-mail: dasilvaa@nhlbi.nih.gov

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We previously reported⁹ that one-fourth of 143 patients with LAM frequently exhibited a positive response to β -adrenergic bronchodilators, which was associated with more severe airflow obstruction and greater rate of decline in expiratory flow. A subsequent smaller study by Yen et al,¹⁰ however, concluded that reversible airflow obstruction is very rare in LAM patients, which prompted us to revisit this matter. In addition, we questioned whether the type of bronchodilator used could affect the frequency of a positive response. To address these issues, we first expanded our retrospective analysis⁹ to 235 patients. Then, we conducted a prospective study in 130 patients to determine the prevalence of positive responses to both β -adrenergic and anticholinergic agents. The primary aim of this study was to determine the frequency and the factors associated with a positive response to these two families of bronchodilators.

MATERIALS AND METHODS

Study Populations

For the retrospective analysis, the population comprised 235 patients with LAM who had at least five visits to the National Institutes of Health (NIH) [National Heart, Lung, and Blood Institute Protocol 95-H-0186]. For the prospective study, the population consisted of 106 patients participating in the same protocol at NIH (Bethesda, MD) and 24 patients who were followed up at the Ospedale San Giuseppe (Milan, Italy). Physiologic data from 21 of the 106 NIH patients participating in the prospective study were reported previously.⁹ The study was approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute, NIH; Office of Human Subjects Research, NIH; and Ospedale San Giuseppe, which had a Federal-Wide Assurance with the US Office of Human Research Protections. Written consent was obtained from all patients.

Study Design

Pulmonary function tests were performed according to American Thoracic Society/European Respiratory Society standards.^{11,12} On day 1 of the prospective study, flow rates (Master Screen PFT; Erich Jaeger; Wuerzburg, Germany) for the patients were measured before and after nebulization with 2.5 mg of albuterol (or ipratropium). On the following day (day 2) and at the same time of day, flow rates were measured before and after nebulization of 500 μ g of ipratropium (or albuterol). The order of drug testing was random. Patients abstained from using inhaled bronchodilators and corticosteroids for 12 h prior to testing. A positive response to bronchodilators consisted of an increase in FVC or FEV₁ of $\geq 12\%$ over the baseline and of at least 200 mL.¹³ Because the diagnosis of asthma may be difficult to establish in a patient with airflow obstruction caused by LAM, we relied on a history of asthma present during childhood or adolescence prior to the onset of LAM to determine whether a patient could have coexisting asthma.

Chest Roentgenograms and CT Scans

The severity of lung disease was graded by CT scans, as previously described.¹⁴

Statistical Analysis

The yearly rate of change in percent predicted FEV₁ and DLCO was estimated as previously reported.¹⁵ Univariate and multivariate regression analyses were performed to identify factors related to the pulmonary function rate of decline.¹⁵ Analysis of variance and regression methods were used to compare lung function, lung involvement by CT scan, bronchodilator response, and functional decline. The bronchodilator response was considered both as a continuous measurement and as a categorical variable (never, response in $< 50\%$ of visits, or response in $\geq 50\%$ of the visits).

To identify the factors associated with a response to bronchodilators in the prospective study, we analyzed the data using the following response variables: response to albuterol; response to ipratropium; response to any bronchodilator (binary outcome); and response to the number of bronchodilators (three-category response, 0, 1, or 2). The explanatory variables considered were as follows: age; various pulmonary function tests, including FEV₁, DLCO, and FEV₁/FVC ratio; the number of years of previous follow-up; and the yearly rate of change for FEV₁ and DLCO. For each response variable, we identified all explanatory variables that were associated with the response at the 0.10 significance level in a univariate analysis using a *t* test or a trend test (Jonckheere-Terpstra test) for the three-category response variable; these variables then were considered for inclusion in a multivariate logistic regression. All tests were two sided. The data are reported as the mean \pm SEM.

RESULTS

Retrospective Study

Age and pulmonary function data of the population are listed in Table 1. Of the study population, 211 were white, 13 were African American, 9 were Asian, and 2 were Hispanic. The number of visits per

Table 1—Age, Lung Function, and Yearly Change in FEV₁ and DLCO in 235 Patients With LAM

Variables	Values
Age, yr	50.4 \pm 0.6 (25 to 82)
Visits, No.	9.8 \pm 0.3 (5 to 22)
TLC, % predicted	93.0 \pm 1.0 (56 to 141)
FRC, % predicted	95.7 \pm 1.2 (28 to 144)
RV, % predicted	99.2 \pm 1.9 (27 to 241)
RV/TLC ratio, %	36.1 \pm 0.5 (10 to 68)
FVC, % predicted	89.7 \pm 1.1 (44 to 133)
FEV ₁ , % predicted	78.3 \pm 1.5 (26 to 132)
FEV ₁ /FVC, %	67 \pm 1 (21 to 94)
DLCO, % predicted	76.1 \pm 1.6 (26 to 139)
Change in FEV ₁ /yr, mL	-83.1 \pm 5.9 (-684 to 154)
Change in FEV ₁ /yr, %	-2.4 \pm 0.2 (-28 to 6)
Change in DLCO/yr, mL/min/mm Hg	-0.71 \pm 4.7 (-7.3 to 0.9)
Change in DLCO/yr, %	-3.0 \pm 0.2 (-31 to 5)

Values are presented as the mean \pm SEM (range). FRC = functional residual capacity.

Table 2—Mean Pulmonary Function Values and Yearly Change in FEV₁ and DLCO in 235 Patients With LAM Divided According to Bronchodilator Response

Bronchodilator Response	Never	< 50% of Visits	≥ 50% of Visits
Patients, No.	114	93	28
DLCO, %	82.5 ± 2.2*	70.9 ± 2.6	67.1 ± 4.3
FEV ₁ , %	87.7 ± 2.0*	72.4 ± 2.2*	60.0 ± 3.8*
Change in FEV ₁ /yr, mL	-61.3 ± 5.1*	-90.5 ± 9.3*	-147.1 ± 29.4*
Change in FEV ₁ /yr, %	-1.5 ± 0.2*	-2.8 ± 0.4*	-5.0 ± 1.1*
Change in DLCO/yr, mL/min/mm Hg	0.63 ± 0.07	0.71 ± 0.05	1.03 ± 0.15*
Change in DLCO/yr, %	-2.6 ± 0.3	-3.0 ± 0.3	4.6 ± 0.7*

Values are presented as the mean ± SEM.

*Values are significantly different from the other two groups (analysis of variance).

patient was 9.8 ± 0.3 (range, 5 to 22), for a total of 2,307 visits. The response to a β-adrenergic bronchodilator was tested at all visits.

Bronchodilator Response, Severity of Lung Disease, and Decline in Lung Function

Twenty-eight patients (12%) responded to albuterol at ≥ 50% of the visits, 93 patients (40%) responded < 50% of the time, and 114 patients (48%) never responded (Table 2). Patients who responded to bronchodilators ≥ 50% of the visits had significantly lower FEV₁ (p < 0.01) than those who responded < 50% of the time and those who never responded. Patients who ever responded to bronchodilators had a lower DLCO (p < 0.05) than those who never responded. Further, patients who

responded to bronchodilators at ≥ 50% of the visits had greater rates of FEV₁ decline (p < 0.01) and DLCO decline (p < 0.05) than those in the other two groups (Table 2). Conversely, those who never responded had better lung function and slower rates of functional decline. We found a significant relationship between the percentage of positive responses to albuterol and the yearly rate of change in FEV₁ (r = 0.368; p < 0.0001) and DLCO (r = 0.209; p < 0.001) [Fig 1, 2].

Decline in Lung Function and Use of Bronchodilators and Corticosteroids

Of the 235 patients studied, 115 used β-adrenergic or anticholinergic bronchodilators regularly; 59 of the 115 patients also used inhaled corticosteroids.

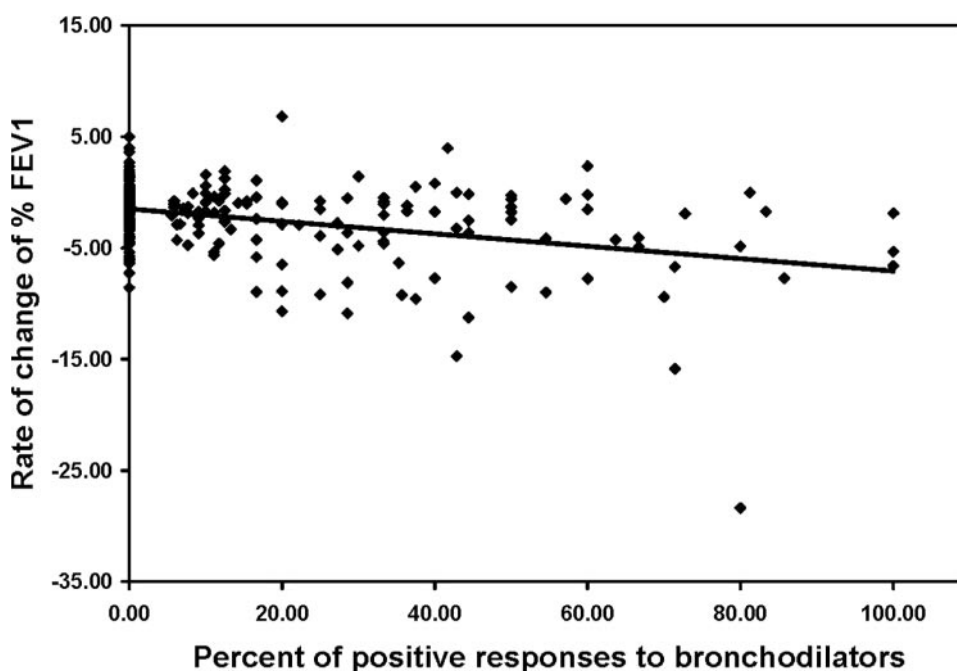


FIGURE 1. Relationship between the percentage of positive responses to bronchodilators and the yearly rate of change in percent predicted FEV₁ (r = 0.368; p < 0.0001).

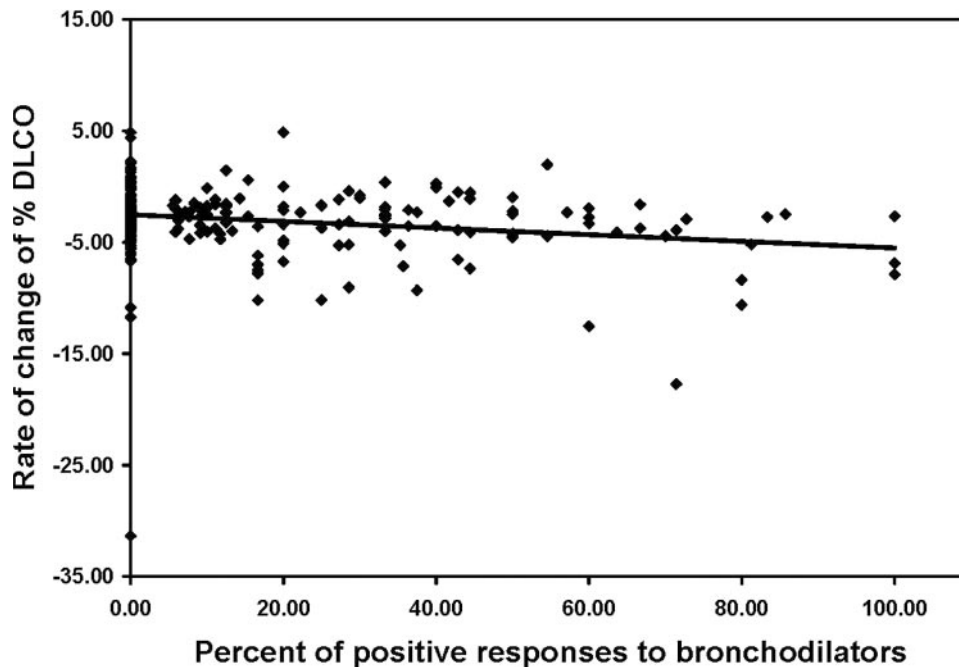


FIGURE 2. Relationship between the percentage of positive responses to bronchodilators and the yearly rate of change in percent predicted DLCO ($r = 0.209$; $p < 0.001$).

Patients who were treated with bronchodilators had lower FEV₁ ($p < 0.001$) and DLCO ($p < 0.001$), and greater rates of FEV₁ decline ($p = 0.02$) and DLCO decline ($p = 0.012$) than those who were not treated with bronchodilators. In addition, they were more likely to have a positive bronchodilator response than those who did not use bronchodilators. This finding could be due to the tendency of physicians to prescribe these agents to patients with poor function and positive bronchodilator response. However, other factors may explain the greater rates of decline in lung function seen with patients who are receiving therapy with bronchodilators. Because within the three bronchodilator response categories (*ie*, never, $< 50\%$, and $\geq 50\%$) no significant differences in the rates of decline of FEV₁ and DLCO were found between those who used bronchodilators and those who did not, it appears that lung function decline is not worsened or improved by the use of bronchodilators.

Factors Affecting the Rate of Decline in Lung Function

A greater rate of FEV₁ decline was associated with more lung involvement by CT scan, more frequent bronchodilator response (continuous measure), lower FEV₁ and DLCO, younger age, and larger cysts. The rate of decline of DLCO was significantly associated with bronchodilator response and age ($p = 0.022$). These variables, along with an interac-

tion term of CT scan grade and bronchodilator response, were included in a multivariate analysis ($n = 220$). The interaction term was statistically significant ($p < 0.05$); therefore, we presented the data in Table 3 by CT scan grade. As shown in Table 3, bronchodilator response ($p < 0.001$), age ($p = 0.007$), and cyst size ($p = 0.046$) were found to be significant predictors of the rate of decline of FEV₁ in those patients in CT scan grade I ($n = 101$). Bronchodilator response ($p = 0.003$) and initial DLCO ($p = 0.04$) were significant predictors of DLCO decline in these patients (Table 3). Bronchodilator response also was a significant predictor of FEV₁ decline ($p = 0.002$) in patients in CT scan grade II ($n = 52$). In patients in CT scan grade III ($n = 67$), bronchodilator response was not a predictor of FEV₁ or DLCO decline.

Prospective Study

Age and pulmonary function data are shown in Table 4. Of the 130 patients, 118 were white, 4 were African American, 6 were Asian, and 2 were Hispanic. The diagnosis of LAM was made from a lung biopsy specimen ($n = 72$) or CT scan ($n = 58$) a mean time of 6.1 ± 0.4 years prior to testing. The Italian cohort was significantly younger than the NIH cohort (38.2 ± 1.9 vs 46.6 ± 0.8 years, respectively; $p < 0.0001$) and had significantly lower FEV₁ ($59.4\% \pm 5.1\%$ predicted vs $74.4\% \pm 2.5\%$ predicted, respectively; $p = 0.010$) and DLCO ($53.0\% \pm 4.9\%$

Table 3—Significant Predictors of Rates of Decline in FEV₁ and DLCO According to CT Scan Grade of Disease Severity

Predictors	Rate of Decline in FEV ₁			Rate of Decline in DLCO		
	Grade I	Grade II	Grade III	Grade I	Grade II	Grade III
BDR	0.061 (< 0.001)	0.068 (0.002)		0.050 (0.003)	-0.070 (< 0.001)	
Age	-0.094 (0.007)		-1.640 (< 0.001)			-0.090 (0.002)
Initial FEV ₁			0.041 (0.009)		0.059 (0.005)	
Initial DLCO				0.030 (0.041)		
Cyst size	1.960 (0.046)					

Values are the parameter estimates (p value) for significant predictors ($p \leq 0.05$) of FEV₁ and DLCO decline in the regression model. Within each column, the reported values are adjusted for the significant variable shown in that column. BDR = positive bronchodilator response (a continuous measure of the percentage response over all visits).

predicted vs $67.8\% \pm 2.3\%$ predicted, respectively; $p = 0.02$). Disease duration also was shorter, but the difference was not statistically significant (5.8 ± 0.9 years vs 7.5 ± 0.5 years, respectively; $p = 0.103$).

Response to Bronchodilators

Thirty-nine patients (30%) responded at least once to bronchodilators as follows: 9 patients responded to albuterol; 12 patients responded to ipratropium; and 18 patients responded to both. Ninety-one patients were nonresponders. In 21 of the 39 responders, we had prior data regarding their response to albuterol that showed that only 2 responders had not exhibited prior positive responses to albuterol. Conversely, in the 48 of the 91 nonresponders in whom the results of prior responses to albuterol were available, only 4 were found to have had positive albuterol responses.

Because the Italian patients were younger, had more advanced disease, and had a shorter duration of their conditions, we evaluated the frequency of bronchodilator response in this cohort. We found that 9 of the 24 patients (37.5%) responded to at least one of the two bronchodilators, 5 patients responded to both, 1 patient responded only to albuterol, and 3 patients responded only to ipratro-

pium. The rates of FEV₁ and DLCO decline for these patients were not available.

Coexistence of Asthma, Cigarette Smoking, and Use of Bronchodilators and Corticosteroids

Among the 39 responders, 2 had a history of asthma, 14 had a history of allergies, and 8 were ex-smokers. Among the 91 nonresponders, 5 had a history of asthma, 36 had a history of allergies, and 23 had a positive history for smoking. Forty-eight of the 130 patients, of whom 22 were responders, used bronchodilators regularly; 24 of the 48 patients also used steroids. Patients who used bronchodilators had lower FEV₁ than those who did not ($64.2\% \pm 3.9\%$ predicted vs $82.1\% \pm 3.5\%$ predicted; $p = 0.0008$) as well as lower DLCO ($61.2\% \pm 3.5\%$ predicted vs $72.4\% \pm 3.4\%$ predicted; $p = 0.024$). The rates of lung function decline were available in 93 of the 130 patients. As in the case of the retrospective study, there was no statistically significant difference between bronchodilator users ($n = 44$) and nonusers ($n = 49$) in the rates of FEV₁ decline ($2.5\% \pm 0.8\%$ predicted vs $2.7\% \pm 0.4\%$ predicted, respectively; $p = 0.77$) and DLCO decline ($3.7\% \pm 1.1\%$ predicted vs $4.7\% \pm 0.9\%$ predicted, respectively; $p = 0.47$).

Response to Bronchodilators, Severity of Disease, and Rate of Functional Decline

Responders had lower FEV₁ and DLCO, and larger residual volume (RV) than nonresponders (Fig 3). We found that in the 93 patients in whom longitudinal data spanning a mean duration of 3.4 ± 0.3 years were available, the rate of FEV₁ decline was significantly greater in the 31 responders than in the 62 nonresponders ($4.0\% \pm 0.9\%$ predicted vs $1.9\% \pm 0.3\%$ predicted, respectively; $p = 0.044$). The decline in DLCO also was significantly greater in responders than in nonresponders ($6.9\% \pm 1.8\%$ predicted vs $2.8\% \pm 0.5\%$ predicted, respectively; $p = 0.039$). Univariate analyses showed that a re-

Table 4—Pulmonary Function Data in 130 Patients With LAM

Variables	Values
Age, yr	45.1 \pm 0.8
TLC, L	4.86 \pm 0.08 (95.0 \pm 1.4)
FRC, L	2.76 \pm 0.06 (99.0 \pm 2.1)
RV, L	1.89 \pm 0.06 (110.3 \pm 3.3)
RV/TLC ratio, %	38.4 \pm 0.9
FVC, L	2.98 \pm 0.06 (87.4 \pm 1.6)
FEV ₁ , L	1.90 \pm 0.06 (71.6 \pm 2.2)
FEV ₁ /FVC ratio, %	63.0 \pm 1.4
DLCO, mL/min/mm Hg	14.0 \pm 0.4 (65.1 \pm 2.1)

Data are presented as the mean \pm SEM (% predicted).

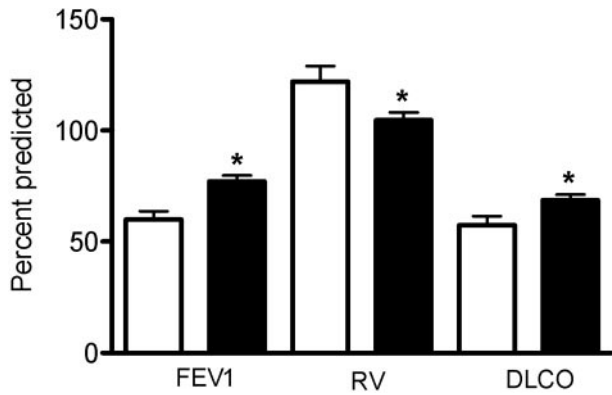


FIGURE 3. Prospective study: percent predicted FEV₁, RV, and DLCO in patients who showed a positive response to at least one of two bronchodilators (white bars) and those who had no response (black bars). Responders had lower FEV₁ and DLCO, and higher RV than nonresponders. * = $p < 0.05$.

ponse to albuterol was associated with a greater rate of decline in percent predicted FEV₁ ($p = 0.047$) and DLCO ($p = 0.034$). A positive response to ipratropium was associated only with the initial percent predicted FEV₁ ($p < 0.001$). A positive response to either bronchodilator was associated with a lower percent predicted FEV₁ ($p = 0.0003$) and DLCO ($p = 0.016$), and greater rates of decline in percent predicted FEV₁ ($p = 0.041$) and DLCO ($p = 0.043$). Multivariate analysis showed that after adjusting for FEV₁/FVC ratio, a response to albuterol, but not to ipratropium, was associated with a greater rate of decline in percent predicted DLCO ($p = 0.004$). Similarly, a response to either of the bronchodilators was associated with a greater decline in percent predicted DLCO ($p = 0.009$).

A trend analysis showed that the rate of decline in either FEV₁ or DLCO is associated with whether a patient was responding to zero, one, or two bronchodilators. A trend for greater rate of decline in FEV₁ and DLCO is associated with a positive bronchodilator response. Younger patients with a greater rate of decline in FEV₁ ($p = 0.018$) and DLCO ($p = 0.007$) were more likely to respond to both bronchodilators (Fig 4). Multivariate analysis showed that FEV₁/FVC ratio ($p < 0.0001$) and age ($p = 0.005$) were the only significant predictors of a bronchodilator response.

DISCUSSION

Our retrospective analysis showed that a greater frequency of a positive bronchodilator response to β -adrenergic bronchodilators was associated with worse lung function and a greater rate of decline in FEV₁ and DLCO. Although patients with worse lung function were more likely to be treated with bron-

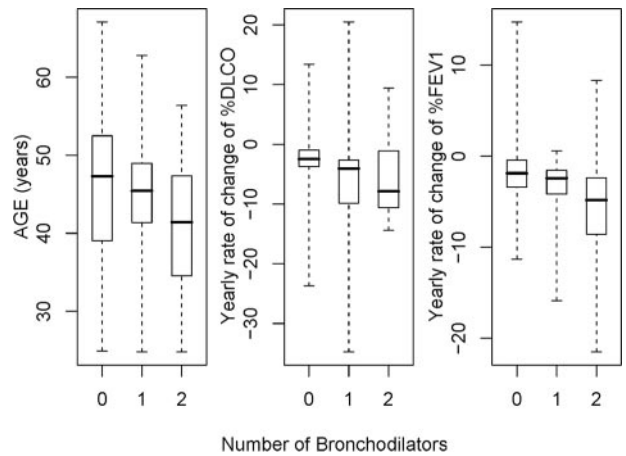


FIGURE 4. Prospective study: median and interquartile range for age and yearly changes in DLCO and FEV₁ according to the response to bronchodilators. The upper and lower limits of the box represent the 75th and 25th percentiles, and the line inside the box represents the median. The upper and lower ends of the "whiskers" represent the 95th and 5th percentiles. Age is based on the whole sample, but the yearly rate of change of percent predicted DLCO and FEV₁ is based only on the NIH patients.

chodilators, we found no evidence that the use of these agents changed the rate of decline in lung function.

The prospective study confirmed that responders to bronchodilators have greater rates of FEV₁ and DLCO decline. Further, a positive response to bronchodilators was a predictor of decline in DLCO after adjusting for FEV₁/FVC ratio. This finding differs from those reported in our previous study⁹ in which we found a relationship between a positive bronchodilator response to albuterol, the predominance of LAM cell proliferation, and an accelerated decline in FEV₁ but not in DLCO. However, the fact that a response to bronchodilators is now shown to be associated with a greater rate of DLCO decline is not surprising. Cyst formation in LAM patients is related to the proliferation of LAM cells and their production of toxic products¹⁶⁻¹⁹; consequently, a greater decline in DLCO caused by new cyst formation would be anticipated. Indeed, LAM cells are clustered in nodules that line the cysts.²⁰ Within the LAM nodules, regions of the basement membrane, and particularly the elastic fibers and collagen fibrils, are disrupted, which could lead to lung tissue destruction and impairment of gas exchange.¹⁶⁻¹⁹

The pathophysiology of airflow obstruction in LAM patients has yet to be fully characterized. The old model²¹ postulated that airflow obstruction was due to the loss of support of small airways, with resultant collapse during expiratory flow. An excess of airway mural smooth muscle was not considered as important. However, changes in lung elastic recoil

do not appear to be an important mechanism of airflow obstruction in LAM.²² Instead, decreased expiratory flow results from an increase in airways resistance caused by the proliferation of LAM cells surrounding the airways. In agreement,⁹ the proportion of positive responses to β -adrenergic bronchodilators was found to be greater in patients whose lung biopsy specimens showed a predominantly proliferative pattern of LAM lesions. Further, although airways inflammation (*ie*, bronchiolitis) was found in airways surrounded by heavy infiltrates of LAM cells,⁹ there was no pathologic evidence of bronchial asthma, smooth-muscle hypertrophy, or any other condition that could be associated with airways disease. One must conclude that airflow obstruction in patients with LAM is related to LAM cell proliferation. Some evidence in favor of this interpretation is found in the report by Bissler et al,²³ who showed that sirolimus improves flow rates and airtrapping in patients with LAM. This effect occurred without any changes in total lung capacity (TLC), DLCO, or CT scan volume of lung cysts, suggesting that the number of LAM cells surrounding the airways was diminished by sirolimus therapy and this effect improved airflow. Alternatively, LAM lung nodules, which are infiltrated by mast cells and contain mast cell mediators,²⁴ could secrete compounds that enhance airway reactivity.

The different frequency of response to β -adrenergic and anticholinergic agents observed in this study could be due to a preferential response to one family of bronchodilators or caused by spontaneous daily variations in the grade of airflow obstruction. It is also possible that those patients who were using bronchodilators and corticosteroids with metered-dose inhalers may have become desensitized to the effects of either family of bronchodilators, and withholding these drugs for 12 h prior to testing may not have been sufficient to eliminate the effect of these therapies. We have not studied the potential roles of neural pathways in determining the bronchodilator response. Contrasting with the adrenergic agents, the bronchodilator effects of anticholinergic agents may favor the large airways rather than the small airways.²⁵ Regardless of the site of action of bronchodilators, as in other lung diseases,²⁶ some patients with LAM may respond more favorably to one or the other category of drugs.

Our finding that patients who respond to bronchodilators appear to have a greater rate of decline in FEV₁ and DLCO needs to be interpreted with caution. Indeed, the possibility that the associations of a positive bronchodilator response, more severe lung disease, and a greater rate of functional decline may be due to a positive response to bronchodilators is more likely to be observed in patients with more

severe airflow limitation who progressed more quickly cannot be excluded. However, in our retrospective study, we found no difference in disease duration between those who responded to bronchodilators during $\geq 50\%$ of the visits (12.9 ± 1.2 years), those who never responded (11.7 ± 0.6 years), and those who responded during $< 50\%$ of the visits (14.5 ± 0.8 years).

The possibility that our studies may underestimate the prevalence of airflow obstruction reversibility in LAM also cannot be discounted. Indeed, the concept that patients with airflow obstruction who show a positive response to bronchodilators at one testing do so consistently is not supported by the literature, even in patients with asthma. Guyatt et al²⁷ found that in patients with chronic airflow obstruction, the reproducibility of short-term change in FEV₁ over three repetitions was poor. Others²⁸ have shown that changes in FEV₁ (or FVC) of $\geq 12\%$ and 200 mL over baseline, as recommended by American Thoracic Society/European Respiratory Society criteria,¹³ may actually underestimate the prevalence of a positive response. Indeed, some^{29,30} have suggested that the criteria for determining a positive response to bronchodilators be changed. Patients with an FEV₁ < 1.5 L may not ever reach the 200-mL increase in FEV₁, and those with an FEV₁ of > 3 L may not reach the 12% increase mark.³⁰ In fact, the short-term bronchodilator response may have limited value in separating patients with asthma from those with COPD.³¹

From our study, we conclude that a significant number of patients with LAM have partially reversible airflow obstruction, which may predict a more rapid decline in function. Although we found no evidence that bronchodilator use changes the rate of decline in lung function, treatment with bronchodilators probably should be undertaken in patients with LAM who have evidence of airflow obstruction. Furthermore, as lung function deteriorates, patients may show a positive response to bronchodilators. Therefore, it is important to monitor lung function not only to evaluate disease progression and the response to bronchodilators, but also to optimize therapy. In this regard, it is also important to test the effectiveness of different families of bronchodilators.

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organized the data for the Italian patients. Dr. Stylianou wrote the Statistical Analysis section and executed the statistical analysis of all data.

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