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Pulmonary Artery Pressure in Lymphangioleiomyomatosis:

An Echocardiographic Study

Angelo M. Taveira-DaSilva, MD, PhD, Olanda M. Hathaway, CRNP, Vandana Sachdev, MD, Yukitaka Shizukuda, MD, PhD[†], Charles W. Birdsall, RDCS, and Joel Moss, MD, PhD
Pulmonary-Critical Care Medicine Branch (Drs. Taveira-DaSilva and Moss, and Ms. Hathaway) and Cardiovascular Branch (Drs. Sachdev and Shizukuda, and Mr. Birdsall), National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD.

Abstract

Background—Exercise-induced hypoxemia is frequent in patients with lymphangioleiomyomatosis (LAM) and could be associated with pulmonary hypertension. The aims of this study were to determine the prevalence of pulmonary hypertension in patients with LAM, to identify physiologic parameters associated with its occurrence, and to evaluate the effect of oxygen on response to exercise.

Methods—Studies were performed in 120 patients. Complete data, including exercise echocardiography, pulmonary function testing, and standard cardiopulmonary exercise testing, were obtained in 95 patients.

Results—Resting pulmonary artery pressure (PAP) was 26 ± 0.7 mm Hg (mean $\pm$ SEM). Eight patients had pulmonary hypertension (43 ± 3 mm Hg), and two patients had right ventricular dilatation. Ninety-five patients exercised (room air, $n = 64$; oxygen, $n = 31$) to a power of 58 ± 2 W (49% of predicted) and an estimated peak oxygen uptake of 938 ± 30 mL/min (56% of predicted). Sixty-one patients had a decline in arterial oxygen saturation (SaO_2) $> 3\%$, and 56 patients had an elevation in PAP > 40 mm Hg. Peak exercise PAP was negatively correlated with exercise SaO_2 ($p = 0.0005$). Multivariate analysis showed that exercise SaO_2 was the best predictor of exercise PAP ($p = 0.012$).

Conclusions—Although resting pulmonary hypertension is rare in patients with LAM, a rise in PAP at low exercise levels occurs frequently, in part related to exercise-induced hypoxemia. Optimization of oxygen administration during activities of daily living should be undertaken in patients with LAM to prevent hypoxemia and exercise-induced pulmonary hypertension.

Keywords

exercise; hypoxemia; pulmonary function tests; pulmonary hypertension

Lymphangioleiomyomatosis (LAM), a multisystem disorder affecting primarily women, is characterized by cystic lung destruction, lymphatic abnormalities, and abdominal tumors (*eg*, angiomyolipomas [AML]).^{1–6} A hallmark of the disease is the proliferation of abnormal-

Correspondence to: Angelo M. Taveira-DaSilva, MD, PhD, Pulmonary-Critical Care Medicine Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room 6D05, MSC 1590, Bethesda, MD 20892-1590; dasilvaa@nhlbi.nih.gov.

[†]Dr. Shizukuda is currently at the Division of Cardiovascular Diseases, University Hospital, University of Cincinnati Medical Center, Cincinnati, OH.

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appearing smooth-muscle-like cells (LAM cells) in the lung, along axial lymphatics in the thorax and abdomen, and in AML. The proliferation of LAM cells leads to the formation of thin-walled cysts in the lungs, fluid-filled cystic structures in the axial lymphatics (*ie*, lymphangioleiomyomas), and kidney AML that are characterized by abnormal smooth muscle cells and adipose tissue intermixed with incompletely developed vascular structures.⁷

The most common pulmonary function abnormalities in patients with LAM are impairment of gas exchange, with a decrease in the diffusing capacity of the lung for carbon monoxide (D_{LCO}), and airflow obstruction, producing a decline in FEV_1 .^{6,8,9} D_{LCO} correlates well with histologic scores of disease severity, a predictor of time to transplantation or death,^{9,10} and is the single best lung function predictor of peak oxygen uptake ($\dot{V}_{O_2 \text{ max}}$) and exercise-induced hypoxemia.⁹ Exercise-induced hypoxemia, however, may occur in patients with near-normal D_{LCO} .⁹ Since exercise-induced hypoxemia is common in LAM, we hypothesized that LAM patients may have hypoxic pulmonary vascular vasoconstriction during exercise and pulmonary hypertension may develop. This could occur during activities of daily living and, by its recurrence, lead to pulmonary vascular remodeling, right ventricular hypertension, and right ventricular failure. The aims of this study were as follows: (1) to determine the prevalence of pulmonary hypertension in patients with LAM, and characterize pulmonary artery pressure (PAP) responses to exercise; (2) to identify physiologic parameters that could be potential predictors of an abnormal pulmonary vascular response; and (3) to determine whether oxygen therapy during exercise prevents hypoxemia and exercise-induced pulmonary hypertension.

Materials and Methods

Study Population

The study population consisted of 120 subjects selected from a large cohort of LAM patients referred to the National Institutes of Health since 1995 for participation in a natural history study (National Heart, Lung, and Blood Institute protocol 95-H-0186). The study was approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute, and written consent was obtained from all subjects. Patients who had undergone kidney or lung transplantation were excluded from the study. Subjects were selected according to their availability to perform stress echocardiography on preset dates and times assigned to the study by the echocardiography laboratory. In general, two patients were studied every week.

Stress Echocardiography

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography.¹¹ Tricuspid regurgitation (TR) was assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views.¹² Continuous-wave Doppler echocardiographic sampling of the peak regurgitant jet velocity was used to estimate the right ventricular-to-right atrial systolic pressure gradient with the use of the modified Bernoulli equation ($4 \times [\text{TR jet velocity}]^2$).^{12–15} Resting pulmonary hypertension was defined as a systolic PAP > 35 mm Hg.¹⁴ After resting echocardiographic measurements, patients exercised on a recumbent ergocycle, using an incremental protocol whereby the work rate was increased by 15 W every 3 min. At each stage of the exercise test, heart rate, BP, pulse arterial oxygen saturation (SpO_2), and PAP were measured. Patients who used supplemental oxygen during physical activities were administered nasal oxygen during the test. Oxygen flow was adjusted with the objective of maintaining $SpO_2 > 90\%$. Patients who did not use supplemental oxygen during physical activities exercised on room air. The test was discontinued if patients complained of severe leg muscle fatigue, severe dyspnea, or if SpO_2 fell to < 85%.

Pulmonary Function Testing

Lung volumes, flow rates, and D_{LCO} were measured (Master Screen PFT; Erich Jaeger; Wuerzburg, Germany) according to American Thoracic Society standards.^{16–18}

Cardiopulmonary Exercise Testing

Standard incremental cardiopulmonary exercise tests (CPETs) were performed on a bicycle ergometer ($\dot{V}_{max}$ 229 Cardiopulmonary Exercise System; SensorMedics; Yorba Linda, CA), as previously described.⁹ A decline in SaO_2 at peak exercise $> 3\%$ was considered abnormal.⁹

Statistical Methods

To identify functional parameters associated with an elevated systolic PAP, we ran univariate regression analyses between PAP and pulmonary function tests, CPET variables, and SaO_2 at rest and at peak exercise. Then, using a stepwise procedure, we ran a multiple regression analysis with PAP as the dependent variable and all the independent variables found to be statistically significant at a 0.10 level in the univariate regression analysis. The level of significance was set at $p < 0.05$. Student t test was employed for comparisons between groups of patients. All reported p values are two sided. Data are shown as mean $\pm$ SEM.

Results

Pulmonary Function and Resting Echocardiography

Age, pulmonary function testing results, and resting Pao_2 values are shown in Table 1. FEV_1 , D_{LCO} , and resting Pao_2 were decreased compared to normal values. Forty of the 120 patients used oxygen regularly during physical exercise. The remaining 80 patients had never used oxygen. In 16 of the 120 patients, PAP could not be estimated. Mean resting TR jet velocity and systolic PAP for the remaining patients were 2.2 ± 0.03 m/s and 26.0 ± 0.7 mm Hg (range, 14 to 62 mm Hg), respectively. Eight patients had pulmonary hypertension at rest (mean systolic PAP, 43 ± 3 mm Hg), three patients had right atrial enlargement, and two patients had a dilated right ventricle. Left ventricular function was normal in all patients except two, in whom the ejection fraction was decreased.

Stress Echocardiography

Two patients were unable to exercise because of severe dyspnea. In seven patients, PAP could not be estimated. Complete data were available in 95 patients. CPET and stress echocardiography data are summarized in Tables 2, 3. The average duration of CPET, excluding warm-up and recovery, was 6.0 ± 0.2 min. Fourteen of the 95 patients failed to reach anaerobic threshold. The main reasons for exercise limitation were leg fatigue (40%), dyspnea (36%), a combination of leg fatigue and dyspnea (11%), and severe hypoxemia (7%).

During stress echocardiography, patients exercised to a power of 58 ± 2.5 W ($49 \pm 2.3\%$ of predicted). Sixty-four patients exercised while breathing room air, and 31 exercised while receiving supplemental oxygen (average oxygen flow, 4.8 ± 0.4 L/min). Sixty-one of the 95 patients (room air, $n = 31$; oxygen, $n = 30$) had a decline in SaO_2 during exercise $> 3\%$.⁹ PAP increased from 25.0 ± 0.6 to 40.5 ± 1.1 mm Hg (peak TR jet velocity, 2.98 ± 0.05 m/s). In 56 patients (room air, $n = 34$; oxygen, $n = 22$), peak exercise PAP reached values > 40 mm Hg.^{19–21} Peak exercise PAP was negatively correlated ($p = 0.0005$) with peak exercise SaO_2 (Fig 1). Multivariate analysis showed that SaO_2 at peak exercise had the best correlation with the peak exercise PAP ($p = 0.012$). FEV_1 ($p = 0.005$) and D_{LCO} ($p < 0.0001$) were significantly correlated with peak exercise SaO_2 . D_{LCO} was the best predictor of peak exercise SaO_2 ($p = 0.001$). There was a trend for a negative correlation between D_{LCO} and peak exercise systolic

PAP, but this relationship did not reach statistical significance ($p = 0.11$). There was no significant association between a positive history of hemoptysis ($n = 28$) and higher resting or exercise systolic PAP.

Supplemental Oxygen and Exercise PAP

Thirty-one of the 64 patients (48%) who exercised on room air had a decline in SaO_2 . Thirty of the 31 patients who exercised on oxygen had a decline in SaO_2 . Patients in whom supplemental oxygen was administered during exercise had more severe disease than those who were exercised while breathing room air (Table 4). Despite the administration of supplemental oxygen, their exercise SaO_2 and estimated $\dot{V}O_{2\max}^{22,23}$ during stress echocardiography ($47.6 \pm 1.6\%$ of predicted) were significantly lower than those of the patients who exercised on room air (Table 4). There was no difference in resting systolic PAP between the two groups of patients, but systolic PAP at peak exercise in patients who exercised on supplemental oxygen (44.0 ± 2.3 mm Hg) was significantly higher ($p = 0.044$) than that of patients who exercised on room air (38.8 ± 1.3 mm Hg).

Discussion

In this study, we found that resting pulmonary hypertension is relatively uncommon in patients with LAM. It occurred in $< 10\%$ of 95 LAM patients, of which approximately one third were using supplemental oxygen therapy. Yet, more than half of the patients had elevations in systolic PAP during exercise above the levels usually observed in normal subjects.^{19–21} This rise in PAP was in part associated with the development of hypoxemia, suggesting that hypoxemia-mediated pulmonary vasoconstriction may have been a factor in its cause.

Both resting systolic PAP values and the magnitude of the PAP response during exercise were of modest magnitude. However, this rise in PAP was observed at levels of exercise that were consistent with moderate physical activities. Consequently, low-level exercise associated with activities of daily living could potentially cause pulmonary hypertension, leading to vascular remodeling, fixed pulmonary hypertension, increased right ventricular mass, and right ventricular failure.^{24–25} However, the low frequency of right ventricular hypertrophy in our population suggests that this may not be as common as in other pulmonary diseases.

Our data show that hypoxemia and abnormal elevation in PAP during exercise occurred in patients with mild disease, who did not use supplemental oxygen, and in patients with more severe disease, for whom supplemental oxygen was adjusted during exercise to prevent hypoxemia. Thirty-one of the 64 patients who exercised on room air had a significant decline in SaO_2 ; of these, 19 patients had an elevation in PAP > 40 mm Hg, suggesting that the occurrence of hypoxemia and/or pulmonary hypertension during exercise cannot be predicted from resting pulmonary function testing.

In patients who exercised on supplemental oxygen, we attempted to maintain $SaO_2 > 90\%$. However, 16 of the 31 patients had a decline in SaO_2 to $\leq 90\%$; of these, 13 patients had pulmonary hypertension during exercise. Nine of the 15 patients in whom SaO_2 remained $> 90\%$ also had pulmonary hypertension. These data seem to support a partial role for hypoxia as a cause of exercise-induced pulmonary hypertension. Indeed, the association between peak exercise SaO_2 and PAP at peak exercise does not necessarily mean that hypoxemia is the cause of the elevation in PAP. Since, in general, patients with desaturation during exercise tend to have more severe disease, they would be more likely to have higher PAP during exercise. That is, a larger decline in SaO_2 during exercise and a greater rise in PAP could be two unrelated markers of disease severity; in some patients, hypoxemia may not be the cause of the elevation in PAP. It is likely that other factors, in addition to hypoxic pulmonary vasoconstriction, are

involved in causing pulmonary hypertension during exercise in patients with LAM. One likely cause is a reduction in pulmonary vascular capacitance caused by the cystic lung lesions.

Although optimization of oxygen saturation levels during physical activities to decrease the frequency and severity of hypoxemia and potentially prevent pulmonary hypertension appears to be warranted, the long-term benefits of oxygen therapy in patients with LAM have not been studied. It is surmised that, as in other pulmonary diseases, dyspnea, ventilatory response to exercise, exercise tolerance, and survival are improved by oxygen therapy.^{26–29} Based on our data, we can only say that in LAM, hypoxemia occurs during relatively modest levels of exercise and may be associated with abnormal elevations in PAP. Consequently, appropriate adjustment of supplemental oxygen and exercise level is recommended to prevent hypoxemia and perhaps prevent exercise-induced pulmonary hypertension.

Our observations may have additional implications regarding the treatment of patients with LAM. Indeed, the cycle nucleotide phosphodiesterase-5 inhibitor sildenafil has been shown to limit the increase in PAP secondary to hypoxia, at rest and during exercise, to improve oxygenation and exercise capacity under hypoxic conditions,^{30–32} and to improve ventilation/perfusion matching and gas exchange in patients with pulmonary fibrosis.³³ It is possible that sildenafil could improve gas exchange and exercise capacity in patients with LAM, especially those in whom hypoxemia, rather than ventilatory impairment, affects exercise performance.

Our study has several limitations. The first was the failure to estimate PAP either at rest or exercise, in approximately one fifth of the patients. Poor TR jet at rest is assumed to indicate a normal pressure value.^{12,15} Failure to measure PAP at peak exercise could be due to several factors, such as distortion of the heart position caused by dynamic lung hyperinflation in the thorax, or motion. A second limitation of our study is the lack of direct measurements of PAP by right-heart catheterization to validate the data obtained by echocardiography. There is evidence that PAP can be estimated fairly accurately from measurements of the TR jet in patients with chronic lung diseases.^{34,35} A good correlation between echocardiographic estimates of PAP and data obtained with right-heart catheterization was also demonstrated in a group of patients with sickle-cell disease.¹⁵ Nevertheless, others^{36,37} have reported overestimation and underestimation of hemodynamic data in patients with pulmonary diseases awaiting lung transplantation and patients with COPD. This could be due to poor acoustic windows caused by lung hyperinflation. It is also possible that right atrial pressure, which is calculated at rest based on the degree of inferior vena cava collapse during inspiration,¹³ may change during exercise due to changes in pleural pressure resulting from dynamic hyperinflation. Interestingly, we found a trend for a positive correlation between residual volume (RV)/total lung capacity (TLC) ratio and peak exercise PAP ($p = 0.1$). Hence, dynamic hyperinflation during exercise could be an additional cause of pulmonary hypertension in LAM.

The demonstration of a significant association between a decline in oxygen saturation and PAP at peak exercise add support to the validity of our observations. The linkage between these two variables suggests that our estimates of systolic PAP during exercise are, overall, accurate. Because of concerns about the reproducibility of the data, we repeated the study in 10 patients; similar results were obtained. In addition, to determine whether there was good reproducibility of systolic PAP readings in our patient population, two of the authors (V.S. and S.S.) reviewed independently the echocardiograms of 20 patients. There was excellent correlation between PAP values obtained independently by the two coauthors. We conclude that in patients with LAM, exercise echocardiography may be a reliable method of monitoring PAP during exercise and of differentiating physiologic from pathologic PAP responses.

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Abbreviations

AML	angiomyolipomas
CPET	cardiopulmonary exercise test
D _{LCO}	diffusion capacity of the lung for carbon monoxide
LAM	lymphangioleiomyomatosis
PAP	pulmonary artery pressure
RV	residual volume
SaO ₂	arterial oxygen saturation
TLC	total lung capacity
TR	tricuspid regurgitation
$\dot{V} O_2 \text{ max}$	peak oxygen uptake

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Figure 1. Relationship between systolic PAP measured at peak exercise and Sao_2 at peak exercise during stress echocardiography in 95 patients with LAM.

Table 1

Pulmonary Function Data in 120 Patients With LAM*

Variables	Data
Age, yr	46.1 ± 0.9
TLC, L	4.97 ± 0.07 (96.4 ± 1.2)
FRC, L	2.79 ± 0.05 (99.3 ± 1.7)
RV, L	1.99 ± 0.05 (113.7 ± 2.8)
RV/TLC, %	44.7 ± 0.5
FVC, L	2.99 ± 0.06 (87.0 ± 1.7)
FEV ₁ , L	1.87 ± 0.07 (71.4 ± 2.4 %)
FEV ₁ /FVC, %	61.4 ± 1.4
D _{lco} , mL/min/mm Hg	13.3 ± 0.4 (63.9 ± 2.0)
Resting Pao ₂ , mm Hg	78.4 ± 1.6

* Data are presented as mean ± SEM or mean ± SEM (% predicted ± SEM). FRC = functional residual capacity.

Table 2

CPET Data in 95 Patients With LAM*

Variables	Data
Maximal work rate, W	100.1 ± 3.9 (84.7 ± 3.1)
Peak heart rate, beats/min	147.0 ± 1.9 (84.7 ± 1.0)
Peak minute ventilation, L/min	49.7 ± 1.7 (70.1 ± 1.8)
Breathing reserve, %	30.1 ± 1.8
$\dot{V}O_2$ max, mL/min	1,150 ± 36 (69.4 ± 1.9)
$\dot{V}O_2$ max / maximum heart rate, mL/beat	7.7 ± 0.2 (81.5 ± 1.8)
Oxygen uptake at anaerobic threshold, mL/min	825 ± 28 (49.7 ± 1.5)
Ventilatory equivalent for carbon dioxide at anaerobic threshold	37.3 ± 0.6

* Data are presented as mean ± SEM or mean ± SEM (% predicted ± SEM).

Table 3

Stress Echocardiography Data in 95 Patients With LAM*

Variables	Rest	Exercise
Maximal work rate, W	0	58.0 ± 2.5
Peak heart rate, beats/min	75.3 ± 1.0	129.0 ± 2.1 [†]
BP systolic, mm Hg	120.0 ± 1.5	168.0 ± 2.3 [†]
BP diastolic, mm Hg	73.8 ± 1.2	81.9 ± 1.3
SaO ₂ , %	97.5 ± 0.1	92.1 ± 0.4 [†]
PAP, mm Hg	25.0 ± 0.6	40.5 ± 1.1 [†]

* Data are presented as mean ± SEM.

[†] p < 0.01.

Table 4

Lung Function and Stress Echocardiography Data in Patients Who Exercised While Breathing Room Air or Supplemental Oxygen*

Variables	Room Air	Oxygen
Patients, No.	64	31
Age, yr	44.5 ± 1.4	48.3 ± 1.3
FEV ₁ , % predicted	79.5 ± 2.6	55.6 ± 4.2 [†]
D _{LCO} , % predicted	72.8 ± 2.3	45.0 ± 3.0 [†]
Resting Pao ₂ , mm Hg	83.7 ± 1.8	67.6 ± 1.7 [†]
Maximal work rate, W	66.0 ± 3.0	41.4 ± 3.0 [†]
Peak heart rate, beats/min	132.7 ± 2.6	119.1 ± 2.5 [†]
Sao ₂ at rest, %	97.6 ± 0.2	97.3 ± 0.3
Sao ₂ during exercise, %	93.4 ± 0.4	89.8 ± 0.7 [†]
$\dot{V}O_2$ max, % predicted	61.2 ± 1.9	47.6 ± 1.6 [†]
PAP at rest, mm Hg	24.2 ± 0.7	26.8 ± 1.2
PAP during exercise, mm Hg	38.8 ± 1.3	44.0 ± 2.3 [†]

* Data are presented as mean ± SEM unless otherwise indicated.

[†] p < 0.05.