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RESEARCH ARTICLE

Clinical characteristics in lymphangioleiomyomatosis-related pulmonary hypertension: an observation on 50 patients

Xiuxiu Wu[1], Wenshuai Xu[1], Jun Wang[1], Xinlun Tian[1], Zhuang Tian[2], Kaifeng Xu (✉)[1]

[1]*Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China;* [2]*Department of Cardiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China*

Abstract **Lymphangioleiomyomatosis (LAM) is a rare diffuse cystic lung disease. Knowledge on LAM-related pulmonary hypertension (PH) is limited. This study aimed to analyze the clinical characteristics of LAM with elevated pulmonary artery pressure (PAP) and evaluate the potential efficacy of sirolimus. The study involved 50 LAM patients who underwent echocardiography. According to the tricuspid regurgitation velocity (TRV), these patients were divided into the TRV $\leqslant$ 2.8 m/s group and TRV > 2.8 m/s group. Both groups comprised 25 females with an average age of 38.6 $\pm$ 8.1 and 41.5 $\pm$ 8.9 years. In the TRV > 2.8 m/s group, the estimated systolic PAP (SPAP) was significantly elevated (52.08 $\pm$ 12.45 mmHg vs. 30.24 $\pm$ 5.25 mmHg, $P < 0.01$). Linear analysis showed that SPAP was correlated with forced expiratory volume in 1 s (FEV_1), diffusing capacity of the lungs for carbon monoxide, alveolar arterial oxygen gradient ($P_{A\text{-}a}O_2$), and 6 min walking distance ($r = -0.392$, -0.351, 0.450, and -0.591, respectively; $P < 0.05$), in which $P_{A\text{-}a}O_2$ was a risk factor for SPAP elevation ($\beta = 0.064$, OR = 1.066, $P < 0.05$). Moreover, in 10 patients who received sirolimus therapy, SPAP decreased from 57.0 $\pm$ 12.6 mmHg to 35.2 $\pm$ 11.1 mmHg. The study showed that LAM patients with PH exhibit poor pulmonary function and hypoxemia and may benefit from sirolimus treatment.**

Keywords lymphangioleiomyomatosis; pulmonary hypertension; pulmonary function; hypoxemia; sirolimus

Introduction

Lymphangioleiomyomatosis (LAM) is a rare chronic and progressive cystic lung disease in women. The prevalence of LAM is estimated to be 4.9 per 1 million women [1–3]. Slowly progressive dyspnea, recurrent pneumothorax, and/or chylothorax are the main clinical manifestations of LAM. Mutational inactivation of tuberous sclerosis complex (TSC) 1/TSC 2 and overactivation of the mammalian target of rapamycin (mTOR) pathway are the main pathogenic mechanisms of LAM, and the mTOR inhibitor sirolimus has been used to treat LAM [4–6].

Pulmonary hypertension (PH) is common in chronic respiratory diseases, with an estimated prevalence of 30%–50% in patients with chronic obstructive pulmonary disease, 30%–50% in patients with idiopathic pulmonary fibrosis, and 50% in patients with combined pulmonary fibrosis and emphysema at the time of pulmonary transplantation, indicating poor prognosis [7,8]. The prevalence of PH in LAM is low but tends to be underestimated because of the limitation of invasive evaluation with right heart catheterization (RHC) [9]. Echocardiography is commonly used as a screening tool to evaluate the possibility of PH [10]. Taveira-DaSilva *et al.* screened 95 patients with LAM via echocardiography and found that 7% of LAM patients have PH with a mean systolic pulmonary artery pressure (SPAP) of 43 $\pm$ 3 mmHg [3]. The mechanisms of PH in LAM are unclear but may be associated with decreased pulmonary function and hypoxemia. In PH classification, LAM-related PH is listed in group 5, which is labeled as unclear multifactorial mechanisms [11]. Currently, research on LAM-related PH is extremely limited. We wish to analyze our data on PH in LAM and evaluate the potential effects of sirolimus. Echocardiography was used to measure tricuspid regurgitation velocity (TRV) and estimate pulmonary artery pressure (PAP) in this report because of the unavailable data on RHC.

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Correspondence: Kaifeng Xu, xukf@pumch.cn

Materials and methods

Inclusion criteria

LAM patients who were presented to Peking Union Medical College Hospital between December 2007 and October 2015 were retrospectively analyzed. They were followed up in the outpatient clinic. The inclusion criteria included (1) patients with definite or probable LAM diagnosed in accordance with the 2010 European Respiratory Society guidelines [12], and (2) patients who visited the hospital at least twice and underwent echocardiography examination during their follow-up. Patients with other lung diseases, congenital heart diseases, PH due to left heart disease or chronic thromboembolism, or PH associated with connective tissue or endocrine diseases were excluded. Fifty patients met the above criteria (Fig. 1).

Investigations

In accordance with the 2015 European Society of Cardiology/European Respiratory Society Guidelines for the diagnosis and treatment of PH [11], we set the TRV cutoff at 2.8 m/s. Fifty patients were divided into two groups: a low probability of PH group with TRV $\leqslant$ 2.8 m/s and an intermediate to high probability of PH group, with TRV $>$ 2.8 m/s. We collected comprehensive demographic and clinical information, including age, smoking status, weight, body mass index, World Health Organization functional classification, use of supplemental oxygen, SPAP, pulmonary function test (PFT), arterial blood gas analysis in room air, 6 min walking distance (6MWD), Borg dyspnea index, St. George's respiratory questionnaire (SGRQ), and the corresponding changes after sirolimus treatment. SPAP is estimated based on tricuspid regurgitation peak flow rate and estimated right atrial pressure, which mainly depends on the width of the inferior vena cava and the change in inspiratory rate. PFT was conducted using the German JAEGER pulmonary function instrument (Master Screen PFT). The test method is based on the recommended criteria of the American Thoracic Society/European Respiratory Society [13].

Statistical analysis

Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad software, Inc., San Diego, CA, USA). Continuous variables are expressed as mean $\pm$ SD, and comparison between two groups was performed using Student's *t*-test. Categorical variables are presented as a percentage of the total, and comparison between two groups was performed using chi-square or Fischer's exact test. Spearman's or Pearson's correlation coefficient was obtained for correlations. A multivariate logistic regression

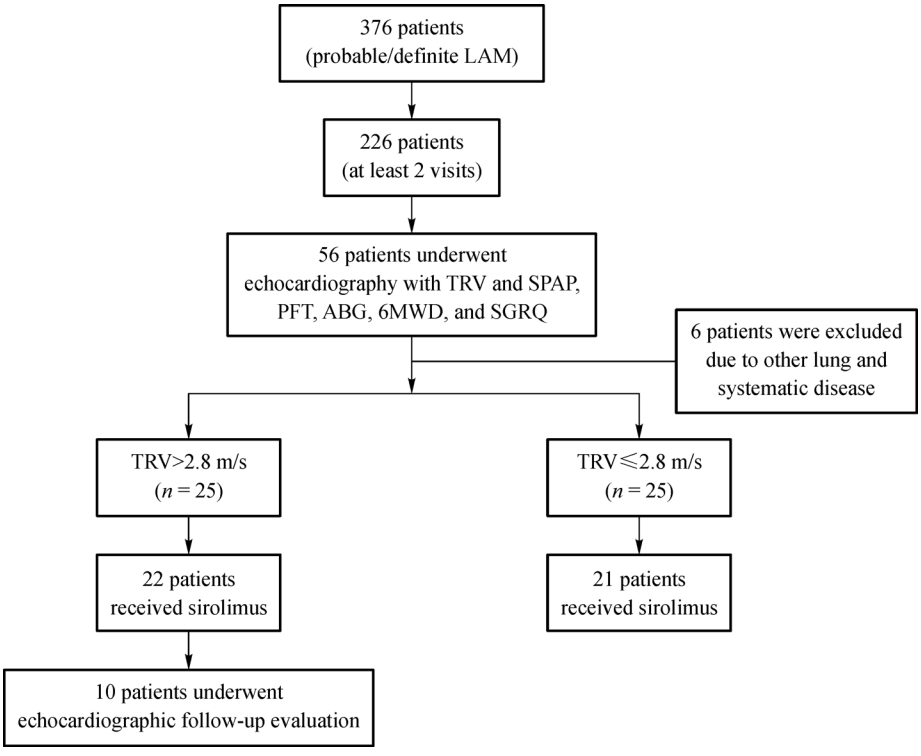

Fig. 1 Patient screening chart. TRV, tricuspid regurgitation velocity; SPAP, pulmonary artery systolic pressure; PFT, pulmonary function test; ABG, arterial blood gas; 6MWD, 6 min walking distance; SGRQ, St. George's respiratory questionnaire.

model was used to study the protective and risk factors for elevated SPAP. Paired *t*-tests were used to analyze the differences after treatment. $P < 0.05$ is considered statistically significant.

Results

Demographics and patient outcome

The demographics, baseline characteristics, and clinical manifestations of all studied patients are presented in Table 1. The 50 LAM patients were all female with a mean age of 40.1 ± 8.6 years. Each group comprised 25 patients. The clinical characteristics exhibited no statistically significant differences between the two groups, except for SPAP and supplemental oxygen. SPAP was considerably higher in the intermediate to high probability of PH group than in the low probability of PH group (52.08 ± 12.45 mmHg vs. 30.24 ± 5.25 mmHg, $P < 0.001$). The proportion of patients who underwent oxygen therapy was significantly higher in the intermediate to high probability of PH group than in the low probability of PH group (72% vs. 20%, $P < 0.001$).

SPAP was correlated with pulmonary function, oxygenation, and 6MWD

To assess the association between SPAP and the clinical characteristics of LAM patients, linear correlation analysis was performed. Forced vital capacity (FVC) % predicted, forced expiratory volume in 1 s (FEV_1) % predicted, diffusing capacity of the lungs for carbon monoxide (DLCO) % predicted, arterial oxygen pressure (PaO_2), arterial oxygen saturation (SaO_2), and 6MWD were negatively correlated with SPAP ($r = -0.430$, -0.392, -0.351, -0.560, -0.562, and -0.591, respectively, $P < 0.01$). Alveolar arterial oxygen gradient ($P_{A\text{-}a}O_2$) was positively correlated with SPAP ($r = 0.450$, $P = 0.001$) (Fig. 2).

Pulmonary function, oxygenation, and exercise capacity were decreased in the TRV > 2.8 m/s group

Compared with those in the TRV ⩽ 2.8 m/s group, the FVC% predicted, FEV_1% predicted, FEV_1/FVC%, and DLCO% predicted in the TRV > 2.8 m/s group were significantly lower (87.82% ± 16.3% vs. 69.82% ± 20.21%, 67.63% ± 24.30% vs. 43.71% ± 19.97%, 66.66% ± 22.00% vs. 52.62% ± 14.82%, 45.92% ± 18.75% vs. 30.42% ± 16.78%, respectively, $P < 0.05$), but the residual volume/total lung capacity % was significantly higher (44.61% ± 12.06% vs. 53.54% ± 14.46%, $P = 0.031$).

Compared with those in the TRV ⩽ 2.8 m/s group, PaO_2 and SaO_2 were considerably lower (78.10 ± 13.39 mmHg vs. 60.60 ± 14.31 mmHg, 94.53% ± 2.72% vs. 90.45% ± 5.07%, respectively, $P < 0.01$) and $P_{A\text{-}a}O_2$ was significantly higher in the TRV > 2.8 m/s group (30.61 ± 15.60 mmHg vs. 56.24 ± 26.14 mmHg, $P < 0.001$).

In addition, the 6MWD in the TRV > 2.8 m/s group was significantly lower than that in the TRV ⩽ 2.8 m/s group (344.1 ± 104.2 m vs. 476.2 ± 88.6 m, $P < 0.001$).

Table 1 Demographics and clinical characteristics of TRV⩽2.8 m/s group and TRV>2.8 m/s group

Variables	TRV⩽2.8m/s *n* = 25	TRV>2.8 m/s *n* = 25	*P* value
Age (mean years)	38.64±8.10	41.48±8.93	0.245
Cigarette smoking	0	0	1
Weight (kg)	53.66±5.65	51.68±7.15	0.283
Body mass index (kg/m^2)	20.97±2.21	20.51±2.71	0.512
LAM diagnosis			1
Definite (%)	68%	68%	
Probable (%)	32%	32%	
Tuberous sclerosis complex (%)	8%	8%	1
Renal angiomyolipoma (%)	20%	12%	0.702
History of pneumothorax (%)	32%	28%	0.758
History of chylothorax (%)	28%	40%	0.370
WHO functional class			
I–II (%)	92%	76%	0.247
III–IV (%)	8%	24%	
SPAP (mmHg)	30.24±5.25	52.08±12.45	0.000
Supplemental oxygen	20%	72%	0.000

Data are presented as mean±SD or *n*% unless otherwise stated. TRV, tricuspid regurgitation velocity; WHO, World Health Organization; SPAP, pulmonary artery systolic pressure.

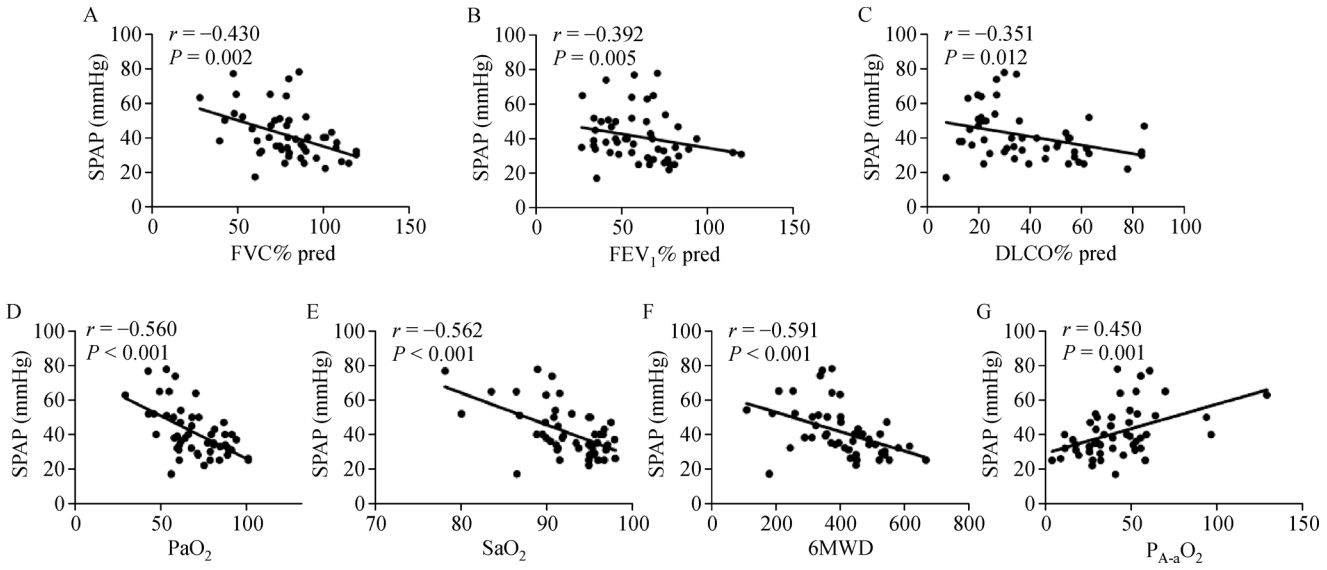

Fig. 2 Correlation between systolic pulmonary artery pressure (SPAP) and pulmonary function, oxygenation, and 6 min walking distance (6MWD). SPAP was negatively correlated with forced vital capacity (FVC) % predicted, forced expiratory volume in 1 s (FEV_1) % predicted, diffusing capacity of the lungs for carbon monoxide (DLCO) % predicted, arterial oxygen pressure (PaO_2), arterial oxygen saturation (SaO_2), and 6MWD (A–F) and positively correlated with alveolar arterial PO_2 difference ($P_{A\text{-}a}O_2$) (G).

In the SGRQ survey, the activity ability and disease impact score and total score were significantly higher in the TRV $>$ 2.8 m/s group than in the TRV $\leqslant$ 2.8 m/s group (67.80 $\pm$ 16.92 vs. 45.88 $\pm$ 26.43, 54.80 $\pm$ 21.94 vs. 33.84 $\pm$ 22.15, and 57.52 $\pm$ 17.13 vs. 38.80 $\pm$ 21.89, respectively, $P < 0.01$).

The outcomes of the above evaluations are presented in detail in Table 2. LAM patients with an increased propensity for PH exhibited increased severity of airflow obstruction, hypoxemia, and impairment of exercise capacity and decreased diffusion function.

Multivariate logistic analyses for predicting PAP elevation in LAM

To further explore the factors that predict PAP elevation in LAM except echocardiography and investigate the relationship between the above factors and the elevated SPAP associated with LAM, multivariate logistic analysis was performed. Elevated SPAP cutoff was defined at $\geqslant$ 36 mmHg [14]. As shown in Table 3, $P_{A\text{-}a}O_2$ was a risk factor for SPAP elevation in LAM (β = 0.064, OR = 1.066, P = 0.031), suggesting that a high $P_{A\text{-}a}O_2$ could prompt the elevation of SPAP in LAM patients.

Improvement in clinical features after sirolimus treatment

In the TRV $>$ 2.8 m/s group, 22 patients received sirolimus therapy because of LAM [15], 10 of them underwent echocardiographic follow-up evaluation. The results showed that SPAP was significantly decreased after sirolimus treatment (57.0 $\pm$ 12.6 mmHg vs. 35.2 $\pm$ 11.1 mmHg, $P < 0.001$). The pulmonary functions indicated by FVC and FEV_1 were significantly higher (55.62% $\pm$ 14.23% predicted vs. 82.85% $\pm$ 25.07% predicted, 30.52% $\pm$ 12.00% predicted vs. 45.11% $\pm$ 23.47% predicted, respectively, $P < 0.01$). Similarly, PaO_2, SaO_2, and $P_{A\text{-}a}O_2$ were also significantly improved (55.0 $\pm$ 6.6 mmHg vs. 71.5 $\pm$ 10.8 mmHg, 87.0 $\pm$ 4.4% vs. 94.0 $\pm$ 2.2%, 54.4 $\pm$ 9.1 mmHg vs. 38.1 $\pm$ 13.4 mmHg, respectively, $P < 0.05$). In addition, 6MWD was also significantly increased after sirolimus treatment (294.8 $\pm$ 83.5 m vs. 394.4 $\pm$ 71.7 m, P = 0.001) (Table 4). The results confirmed that sirolimus effectively reduced elevated PAP, improved pulmonary function and hypoxemia, and enhanced exercise capacity (Fig. 3).

Discussion

Only one study systematically evaluated the characteristics of LAM-related PH with RHC [16]. Cottin evaluated 29 cases of LAM with suspected PH at echocardiography or evaluation for lung transplantation, 20 of which confirmed PH by RHC with mPAP 32 $\pm$ 6 mmHg. Six out of the 20 patients received first-line therapy for PAH. This study concluded that pre-capillary PH may occur in LAM with mild hemodynamic severity and mildly to severely impaired lung function and that PAH-specific therapy may improve the hemodynamics of PH in LAM. No studies have evaluated whether sirolimus can improve PAP in LAM patients. In the current study, noninvasive

Table 2 Evaluations of the TRV⩽2.8 m/s and TRV>2.8 m/s groups

Variables	TRV⩽2.8 m/s $n = 25$	TRV>2.8 m/s $n = 25$	*P* value
Pulmonary function			
FVC% pred	87.82±16.3	69.82±20.21	0.001
FEV_1% pred	67.63±24.30	43.71±19.97	0.000
FEV_1/FVC%	66.66±22.00	52.62±14.82	0.012
TLC% pred	109.66±19.29	112.42±19.73	0.646
RV% pred	157.08±66.20	191.53±75.65	0.115
RV/TLC%	44.61±12.06	53.54±14.46	0.031
DLCO% pred	45.92±18.75	30.42±16.78	0.005
Arterial blood gas			
PaO_2 (mmHg)	78.10±13.39	60.60±14.31	0.000
$P_{A\text{-}a}O_2$ (mmHg)	30.61±15.60	56.24±26.14	0.000
$PaCO_2$ (mmHg)	34.96±4.31	35.40±8.97	0.827
SaO_2 (%)	94.53±2.72	90.45±5.07	0.001
6MWD (m)	476.15±88.62	344.11±104.19	0.000
Borg dyspnea index	1.94±2.40	2.77±2.22	0.217
SGRQ			
Symptom (score)	40.04±24.82	47.68±20.48	0.241
Activity ability (score)	45.88±26.43	67.80±16.92	0.001
Disease impact (score)	33.84±22.15	54.80±21.94	0.001
Total score (score)	38.80±21.89	57.52±17.13	0.002

Data are presented as mean±SD unless otherwise stated. TRV, tricuspid regurgitation velocity; FVC, forced vital capacity; % pred, % predicted; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of the lungs for carbon monoxide; PaO_2, arterial oxygen pressure; $P_{A\text{-}a}O_2$, alveolar arterial PO_2 difference; $PaCO_2$, arterial carbon dioxide pressure; SaO_2, arterial oxygen saturation; 6MWD, 6 min walking distance; SGRQ, St. George's respiratory questionnaire.

Table 3 Multivariate logistic analyses for predicting the probability of PH in LAM

Variables	β	OR (95%CI)	*P* value
FEV_1% pred	−0.029	0.971 (0.922–1.023)	0.276
DLCO% pred	0.028	1.028 (0.963–1.097)	0.404
$P_{A\text{-}a}O_2$	0.064	1.066 (1.006–1.129)	0.031
6MWD	−0.007	0.993 (0.984–1.002)	0.105

Odds ratio calculated using the binary logistic regression model forward conditional considering the following variables in the model: FEV_1% pred, DLCO% pred, $P_{A\text{-}a}O_2$, 6MWD. % pred, % predicted; FEV_1, forced expiratory volume in 1 s; DLCO, diffusing capacity of the lungs for carbon monoxide; $P_{A\text{-}a}O_2$, alveolar arterial oxygen gradient; 6MWD, 6 min walking distance.

Table 4 Improvement in clinical features after sirolimus treatment

Variables	Baseline	After sirolimus	Paired *t* test		
			d	*t*	*P* value
SPAP (mmHg)	57.00±12.59	35.17±11.07	−21.83±10.21	−6.755	0.000
FVC% pred	55.62±14.23	82.85±25.07	27.23±19.36	4.446	0.002
FEV_1% pred	30.52±12.00	45.11±23.47	14.59±15.68	2.941	0.016
DLCO% pred	22.75±6.69	29.69±19.13	6.94±14.32	1.52	0.16
PaO_2 (mmHg)	55.03±6.59	71.53±10.75	16.50±15.18	3.436	0.007
SaO_2 (%)	87.01±4.38	94.02±2.23	7.01±5.22	4.244	0.002
$P_{A\text{-}a}O_2$ (mmHg)	54.40±9.11	38.13±13.37	−16.27±15.86	−3.243	0.01
6MWD (m)	294.75±83.45	394.40±71.69	99.65±68.29	4.614	0.001

Data are presented as mean±SD unless otherwise stated. SPAP, pulmonary artery systolic pressure. FVC, forced vital capacity; % pred, % predicted; FEV_1, forced expiratory volume in 1 s; PaO_2, arterial oxygen pressure; DLCO, diffusing capacity of the lungs for carbon monoxide; SaO_2, arterial oxygen saturation; $P_{A\text{-}a}O_2$, alveolar arterial oxygen gradient; 6MWD, 6 min walking distance.

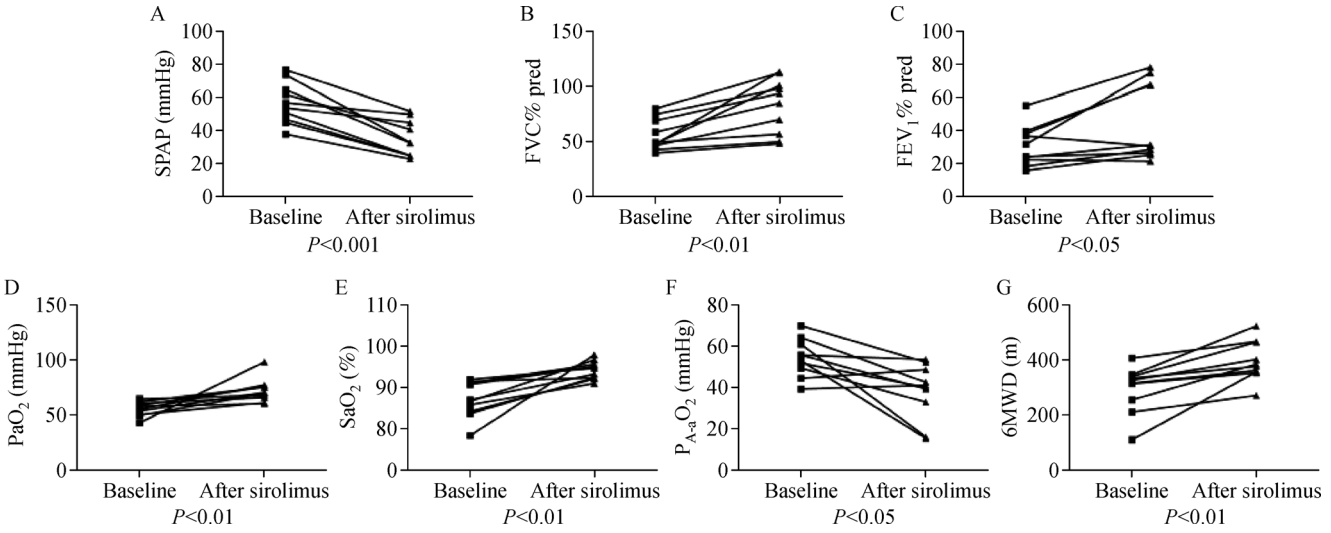

Fig. 3 Improvement in clinical features after sirolimus treatment. (A) Pulmonary artery systolic pressure (SPAP) was significantly decreased after treatment with sirolimus. (B, C) Pulmonary function, including forced vital capacity (FVC) % pred and forced expiratory volume in 1 s (FEV_1) % pred, were significantly increased. (D, E, F) Oxygenation indicators, such as arterial oxygen pressure (PaO_2) and arterial oxygen saturation (SaO_2), were significantly increased, and alveolar arterial oxygen gradient ($P_{A\text{-}a}O_2$) was significantly decreased. (G) Six minute walking distance (6MWD) was significantly improved after sirolimus treatment compared with the baseline.

echocardiography was used to estimate the probability of PH in LAM, and patients were divided into two groups in accordance with TRV cutoff of 2.8 m/s. Results showed that the SPAP in the TRV > 2.8 m/s group was significantly elevated and strongly correlated with FVC, FEV_1, DLCO, PaO_2, SaO_2, and 6MWD. Consistently, we found that pulmonary function, oxygenation, and exercise capacity were decreased in patients with TRV > 2.8 m/s, of which the most significant changes were in pulmonary function and oxygenation. Moreover, sirolimus treatment for LAM increased pulmonary function and oxygen levels and enhanced exercise capacity. We also found that sirolimus may decrease elevated PAP in LAM.

Hypoxemia is one of the important mechanisms leading to the development and progression of PH [17,18]. Nakahara *et al.* analyzed the relationship between exercise-induced hypoxemia and pulmonary hemodynamics in 84 patients with COPD and found that PAP was negatively correlated with FVC, FEV_1, FEV_1/FVC%, DLCO, PaO_2, SaO_2, and 6MWD [19]. Consistent with that study, our research also demonstrated that the above indices were negatively correlated with SPAP in LAM patients. We observed that the pulmonary function and oxygenation of LAM patients with elevated SPAP were significantly reduced compared with those of the control group, including FVC, FEV_1, FEV_1/FVC, DLCO, PaO_2, SaO_2, and 6MWD, which was consistent with previous findings [16,20]. This result demonstrated that LAM patients with severe PAP elevation had severe airflow obstruction, low diffusive function, severe hypoxemia, impairment of exercise capacity, and negative quality of life. This phenomenon is similarly observed in idiopathic PH [14,21,22], indicating that in addition to hypoxemia being involved in the pathophysiological mechanism of PH, pulmonary function impairment may be another important factor that increases the risk of PH.

Previous studies have reported that PH in chronic lung diseases is typically reflected in 6MWD and plasma brain natriuretic peptide levels [23–25]. In the current study, $P_{A\text{-}a}O_2$ exhibited a significant difference between the two groups and was positively correlated with SPAP. Multivariate logistic regression analysis identified $P_{A\text{-}a}O_2$ as a significant risk factor for SPAP elevation. Given that echocardiography as a single tool to screen for PH may be limited in terms of sensitivity and specificity [26], $P_{A\text{-}a}O_2$ combined with echocardiographic parameters may be helpful in screening for PH in LAM patients.

Abnormal activation of the mTOR signaling pathway caused by TSC2 mutation leads to the development of LAM. The inhibitors of the mTOR pathway sirolimus and everolimus elicit good therapeutic response for patients with LAM [15,27,28]. Since all patients except one did not confirm PH diagnosis by RHC in the present study, none of the patients received PH therapy. However, SPAP and associated clinical manifestations, including airflow obstruction, hypoxemia, and exercise capacity, were significantly alleviated in 10 patients after receiving sirolimus therapy. The improvement of LAM-related PH may be a result of improved pulmonary function and oxygenation after sirolimus therapy. However, direct effects of sirolimus on PH are possible. mTOR activation is an important mechanism of hypoxemia-related PH in

animal models [29–31], which prompts the proliferation of vascular smooth muscle cells [32] that may conceivably be involved in PAP elevation and PH formation in LAM. A previous study also confirmed that mTOR inhibitors can reverse pulmonary artery smooth muscle cell proliferation in PH *in vitro* [33]. Furthermore, the current study first suggested that LAM patients with elevated PAP may benefit from treatment with sirolimus, which can be considered as an option before PH drugs are administered. In Cottin *et al.*'s study, six out of 20 LAM patients received first-line therapy for PAH with dual endothelin receptor antagonist (bosentan, $n = 5$) or phosphodiesterase type-5 inhibitor (sildenafil, $n = 1$) [16]; their mean PAP decreased significantly after treatment. Improvement on NYHA functional class, 6MWD, and pulmonary vascular resistance (PVR) was seen in the five patients who received bosentan but not in the patient given sildenafil. Overall, PH drugs offer limited use in hypoxemia-related PH.

There are several limitations in this study. Although a considerable number of LAM patients were followed up, a small number of patients underwent echocardiography, thus, our sample size was small. The effectiveness of sirolimus was only analyzed in 10 patients who received treatment. In the future, the screening of PH in LAM patients should be improved to obtain a larger sample size for further research. Moreover, we observed the efficacy of sirolimus for SPAP based on echocardiography, it is limited to that our patients have not been identified PH diagnosis by RHC except one (mean PAP 27 mmHg, pulmonary capillary wedge pressure 4 mmHg, PVR 4.5 WU). Furthermore, RHC examinations were not routinely performed in LAM patients in our center due to patients' personal concerns and ethical issues, which may lead to missed diagnosis. The present study focused on the analysis of LAM patients with elevated SPAP and who had poor pulmonary function and severe hypoxemia and attempted to identify a subgroup of LAM patients who should be recommended for RHC examination. Such patients should be managed well for LAM and PH.

In summary, our observation suggested that PH in LAM was associated with decreased pulmonary function and hypoxemia. The mTOR inhibitor sirolimus is potentially effective for LAM-related PH.

Acknowledgements

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Compliance with ethics guidelines

Xiuxiu Wu, Wenshuai Xu, Jun Wang, Xinlun Tian, Zhuang Tian, and Kaifeng Xu declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000 (5). Informed consent was obtained from all patients who were included in the study.

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