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ORIGINAL ARTICLE

Pulmonary function change in patients with *Sauropus androgynus*-related obstructive lung disease 15 years later

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KEYWORDS
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Background/Purpose: Little is understood about the clinical course and prognosis of patients with *Sauropus androgynus*-related obstructive lung disease. The aim of this study was to investigate their clinical manifestations and pulmonary function change 15 years after the acute episode.
Methods: A descriptive, observational study of patients with *S androgynus*-related obstructive lung disease, diagnosed 15 years ago, was conducted. We evaluated their pulmonary function and the Modified Medical Research Council (MMRC) dyspnea scale. Saint George's Respiratory Questionnaire (SGRQ) was also performed. Age- and forced expiratory volume in one second (FEV_1)-matched chronic obstructive pulmonary disease (COPD) patients were used as a reference group for comparison of clinical manifestations.
Results: Twenty-nine of 49 patients, diagnosed at our hospital 15 years ago, could be contacted. Four patients died and one patient was ventilator-dependent. Sixteen patients were willing to come to our hospital to have pulmonary function and questionnaire evaluation. The FEV_1 of these patients declined only 1.6 ± 21.6 mL/year over a 15-year period. Meanwhile, the severity of their dyspnea and their health-related quality of life were better than age- and FEV_1-matched COPD patients as shown by the MMRC dyspnea scale (1.4 ± 0.8 vs. 2.0 ± 1.0; $p = 0.037$) and symptom domain of the SGRQ (32.6 ± 18.4 vs. 43.5 ± 20.3; $p = 0.006$).
Conclusion: After an acute deterioration, patients with *S androgynus*-related obstructive lung disease had a stationary pulmonary function over a period of 15 years, and their clinical manifestations were less severe than age- and FEV_1-matched COPD patients. A further study with a larger sample size may be needed to confirm these findings.

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Introduction

Sauropus androhynus, a Malaysian leaf vegetable, is a member of the Euphorbiacae family and a perennial shrub. It has been used for weight control by young and middle-aged women. *S. androgynus* intoxication was first detected in August 1994 in Taiwan,[1,2] and another small group of patients was also reported in Japan in 2005.[3] Forty-nine patients were diagnosed with *S. androgynus*-related obstructive lung disease in our hospital during that outbreak, and a dose-response relationship of lung function impairment was determined by Hsiue et al.[4] Patients presented with progressive respiratory distress and eventually irreversible respiratory failure, similar to clinical manifestations in other obstructive lung diseases. The association between obstructive lung disease and *S. androgynus* was documented in the 1990s in epidemiologic studies,[5] and many studies have described the clinical features and pathogenesis of this disease entity.[6,7] However, there has been no report about long-term follow-up of the change of pulmonary function in patients with *S. androgynus*-related obstructive lung disease. The aim of this study was to contact the 49 patients diagnosed with *S. androgynus*-related obstructive lung disease, and an observational study was designed to evaluate the current general status and changes in lung function of these patients 15 years later.

Materials and methods

Patient group

In 1995, an outbreak of *S. androgynus*-related obstructive lung disease occurred in southern Taiwan and Japan. Forty-nine patients with a history of consumption of this vegetable were diagnosed with obstructive lung disease in our hospital. In late 2010, we attempted to contact these patients and investigated their current clinical symptoms and pulmonary function. In these 49 patients, 29 patients could be contacted. In these 29 patients, four patients died and one patient was ventilator-dependent, and 16 patients were willing to come to our hospital to have pulmonary function and questionnaire evaluations. The investigation protocol was approved by National Cheng Kung University Hospital's ethics committee, and informed consent was obtained from each patient.

Reference group

Thirty-two patients, who were matched for age and lung function with the patients under investigation, were recruited from the outpatient clinic. All patients had moderate-to-severe chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Baseline variables, including age, gender, Charlson co-morbidities index and % predicted of forced expiratory volume in one second (FEV_1 %) predicted were recorded. Patients, who were incapable of completing the questionnaire and those with a Charlson co-morbidities index[8] higher than 2 were excluded to avoid the impact of co-morbidities on life quality. Signed informed consent was obtained from all patients.

Pulmonary function tests

Spirometry and lung volumes (helium dilution method) were performed with a rolling seal spirometer (Chestec 65; Chest Co., Tokyo, Japan) according to standard methods suggested by the American Thoracic Society.[9]

Questionnaires

The Modified Medical Research Council (MMRC) dyspnea scale[10] and Saint George's Respiratory Questionnaire (SGRQ)[11] were used to assess the functional status and quality of life of each patient and were recorded by a trained technician in the pulmonary function laboratory.

Statistical analysis

Data were presented as mean $\pm$ SD. A paired *t* test was used to compare changes in pulmonary function and the body mass index (BMI) between the initial diagnosis and follow-up period. The Mann-Whitney *U* test was used for discrimination of quality of life between the patient and reference groups. Fisher's exact test was used to compare nominal variables between groups. The dose—effect on the obstructive impairment of lung function was assessed using Spearman's correlation analysis. A p value of <0.05 was considered significant. Statistical analyses were performed using GraphPad Prism 5 for Windows 7 version.

Results

Twenty-nine patients with a previous diagnosis of *S. androgynus*-related obstructive lung disease or their families were available for contact in this study. Among these 29 patients, four patients had died and one patient was ventilator-dependent and lives in a respiratory care ward. The causes of death in these four patients were three from respiratory complications within 5 years after ingestion of *S. androgynus* (3, 4, and 4.5 years) and one from pancreatic cancer 10 years after ingestion of *S. androgynus*. One patient was ventilator-dependent 3 years after the initial consumption of *S. androgynus* and 2 years after the diagnosis of *S. androgynu*-related obstructive lung disease. Sixteen of the 24 surviving patients were willing to come to our hospital for pulmonary function test and interview, and their data were analyzed. Only one patient was a man, and none of them had a history of smoking, autoimmune disease, or inhalation injury before or after *S. androgynus* consumption. All 16 patients completed pulmonary function tests and the MMRC and SGRQ questionnaires.

Characteristics of these 16 patients are listed in Table 1. Components of the SGRQ, including symptom, activity and impact scores, were recorded (Table 2). The initial lung function test was performed while patients were suspicious of having *S. androgynus*-related obstructive lung disease from clinical history and symptoms. The duration from the beginning of *S. androgynus* consumption to the diagnosis of lung disease using pulmonary function test (PFT) as a diagnostic tool was 7 months in average. Data including lung function with the % predicted of total lung capacity (TLC %

Table 1 Characteristics of 16 patients with a diagnosis of *Sauropus androgynus*-associated obstructive lung disease.

Patient no.	Age (y)	Sex	BMI	Total amounts (g)	MMRC	SGRQ total
1	50	F	19.6	3600	3	75.1
2	75	F	38.4	4200	2	23.0
3	69	F	25.2	4800	1	18.0
4	70	F	34.2	6000	2	65.8
5	62	F	26.7	5400	1	24.7
6	62	F	22.7	1500	0	48.8
7	66	F	23.0	2700	1	28.7
8	66	F	22.7	3600	1	38.1
9	60	F	19.4	13,500	3	36.1
10	61	F	21.1	10,800	1	9.4
11	78	F	20.8	3000	1	36.9
12	71	F	21.6	9000	1	12.6
13	58	F	27.3	3300	1	21.1
14	65	M	26.0	9000	1	27.0
15	55	F	21.9	6000	1	41.7
16	55	F	36.3	4500	2	14.9
Mean ± SD	64.5 ± 7.6		25.4 ± 5.9	5681 ± 3285	1.4 ± 0.8	32.6 ± 18.4

BMI = body mass index; MMRC = Modified Medical Research Council; SGRQ = Saint George's Respiratory Questionnaire.

predicted), FEV1/forced vital capacity ratio (FEV_1/FVC ratio), FEV_1, FEV_1% predicted, FVC, FVC % predicted, SpO2 and BMI were compared between initial and recent periods (Table 3). There were no significant declines in lung function and BMI during the follow-up period 15 years after consumption of *S. androgynus*. The FEV_1 decline in the past 15 years was only -1.6 ± 21.6 mL/year (Fig. 1). And these patients also showed a higher percent predicted of TLC and percent predicted of FVC compared with initial lung function ($p < 0.0001$ and $p = 0.0006$ respectively).

Evaluating the current health-related quality of life in our patients was the second aim of our study. We compared our patient group with an age- and FEV_1-matched reference group, and we found that the patient group had less severe dyspnea and better health-related quality of life than the COPD patients on the MMRC dyspnea scale and symptom domain of the SGRQ (Table 4). However, the Charlson index was higher in reference group.

Discussion

The diagnosis of *S. androgynus*-induced obstructive lung disease can be made clinically when there is a history of *S. androgynus* consumption, no chronic respiratory disease, obstructive ventilation without bronchodilator response, bilateral bronchiectasis, and patchy low attenuation of lung parenchyma with mosaic perfusion on high-resolution CT.

Table 2 Individual SGRQ scores in 16 patients.

	SGRQ symptoms	SGRQ activity	SGRQ impacts
Scores	23.8 ± 18.3	48.6 ± 22.0	26.3 ± 21.7

Data are presented as mean ± SD. SGRQ = Saint George's Respiratory Questionnaire.

An *in vitro* study[7] showed that apoptosis and necrosis are involved in the toxicity of *S. androgynus* and T-cell mediated immunity is predominant in the pathogenesis.[2,12] Histopathological findings included constrictive obliterative bronchitis/bronchiolitis resulting eventually in irreversible fibrosis of the small bronchi and the bronchioles.[13] A hospital-based case-control study[5] showed that larger total amounts of *S. androgynus* and preparation methods that did not include cooking were significant risk factors for lung disease. Corticosteroid therapy is not effective[14] and the only treatment is lung transplantation.[15] In a short-term follow-up study,[4] the major symptom of this disease, dyspnea, developed within 7 months after consumption of the vegetable and obstructive ventilatory defects were irreversible during the observation period of 22 months.

There has been no long-term follow-up study of patients diagnosed in the outbreak of 1995. The aim of this study was to focus on the changes in pulmonary function and quality of life 15 years after *S. androgynus*-induced lung injury. In that outbreak of 1995, PFT was performed in our

Table 3 Results of pulmonary function test and BMI compared at different times.

	Initial diagnosis	Follow-up	*p* value
TLC % predicted	94.8 ± 20.3	116.2 ± 19.8	<0.0001
FEV_1/FVC(%)	51.4 ± 10.6	46.7 ± 11.6	ns
FEV_1 (L)	1.0 ± 0.3	1.0 ± 0.5	ns
FEV_1 % predicted	43.9 ± 14.1	50.9 ± 19.7	ns
FVC (L)	2.0 ± 0.7	2.2 ± 0.7	ns
FVC % predicted	74.6 ± 19.9	87.6 ± 23.8	0.0006
BMI	26.6 ± 5.6	25.4 ± 5.9	ns
SpO2	95.7 ± 1.3	95.3 ± 2.1	ns

Data are presented as mean ± SD. TLC = total lung capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; BMI = body mass index.

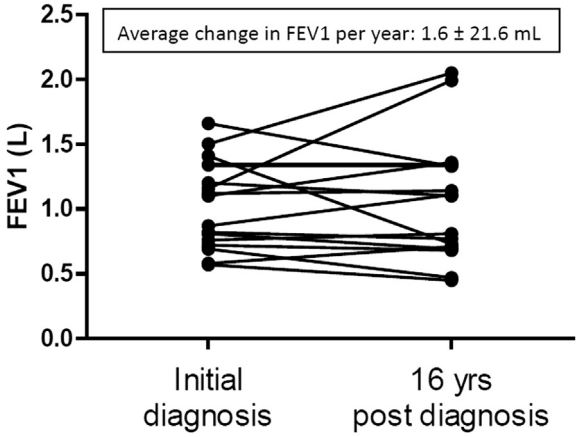

Figure 1 Follow-up FEV_1 in 16 patients with *Sauropus androgynus*-induced obstructive ventilatory defects.

patients with history of consumption of *S. androgynus* and presentation of respiratory distress. The initial PFT was defined as the first time of examination while diagnosis of *S. androgynus*-induced obstructive lung disease, and the average duration from consumption to diagnosis was 7 months. Four patients suffered from acute or chronic respiratory failure (three dead and one dependent on ventilator) within 5 years, indicating that the disease has an initial rapid downhill course in some patients. However, survivors of the acute phase, after a period of 15 years, follow-up spirometry showed moderative to severe obstructive ventilatory defects without significant difference from their initial lung function. After a period of 15 years follow-up, most of our patients were in a stationary status after the initial deterioration of their pulmonary function. This is in contrast to COPD patients, which is characterized by progressive deterioration in physiologic function and global status. In previous studies, patients with COPD had a decline in FEV_1 (31 ± 48 mL/year) after quitting smoking compared with those who continued to smoke (62 ± 55 mL/year).[16] Although the obstructive ventilatory defect was irreversible in our patient group, the decline in FEV_1 was only 1.6 ± 21.6 mL/year after a period of 15 years. Increased lung volume was found in the follow-up spirometry of our participants but the reason was not clear. Possible explanations included the resolution of the interstitial injury or improved air-trapping after the acute stage, but more data such as residual volume measurement may be needed for further confirmation. There was no significant difference in the change of the BMI during the observational period, indicating that the change in spirometry was independent of body weight change.

Table 4 Comparison of life quality between reference and investigating groups.

Patient groups	Reference (COPD)	Investigating (*S. androgynus*-related obstructive lung disease)	*p* value
Age (y)	64.7 ± 11.1	64.5 ± 7.6	0.5470
Sex (F/M)	13/19	15/1	0.0005*
Smoking status	Ex-smokers	Non-smokers	
FEV_1 % predicted	46.4 ± 15.0	50.9 ± 19.7	0.4569
Charlson index	1.6 ± 0.8	0.3 ± 0.4	<0.0001*
MMRC	2.0 ± 1.0	1.4 ± 0.8	0.0369*
SGRQ total	41.6 ± 20.5	32.6 ± 18.4	0.1355
SGRQ symptoms	43.5 ± 20.3	23.8 ± 18.3	0.0055*
SGRQ activity	53.3 ± 29.9	48.6 ± 22.0	0.4585
SGRQ impact	34.4 ± 20.7	26.3 ± 21.7	0.1414

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; MMRC = Modified Medical Research Council; SGRQ = Saint George's Respiratory Questionnaire.

* Significant difference between reference and investigating groups.

The MMRC dyspnea scale and SGRQ questionnaires were used for evaluation of the current quality of life in our patient group and comparison with the reference group. Age and severity of obstructive ventilation were matched. Most of our patients with *S. androgynus*-related obstructive lung disease were women and they had few co-morbidities. To reduce the interference of co-comorbidites with quality of life, we excluded reference patients with a Charlson index higher that 2 to avoid any impact of co-morbidities on life quality. Analysis of the SGRQ data showed a significant difference in symptom scores between groups, suggesting lower rates of productive cough and breathlessness in the patient group than in the reference group. The MMRC scale also indicated better functioning in the patient group, suggesting less limitation of activities of daily living. This scale focuses primarily on dyspnea that occurs during walking and is widely used in patients with COPD because it correlates with prognosis.[17] We supposed that the causative factors that result in the difference in dyspnea grade or quality of life may be due to the different pathogenesis in these two obstructive lung diseases. COPD patients had chronic airway inflammation and also systemic inflammation, which resulted in more extrapulmonary symptoms. Unlike COPD patients, patients with *S. androgynus*-induced obstructive lung disease suffered from acute inflammation and an acute rapid deterioration of lung function within several months after consumption. After the acute event and discontinuation of the consumption, no chronic inflammation persisted, and these patients got stable pulmonary function in the follow-up course with gradual adaptation of their physical conditions. To our knowledge, the 5-year mortality rate of patients with moderate-to-severe COPD varies from 40% to 70%, depending on disease severity.[18] This also implied consistently less severity on the MMRC scale and a lower mortality rate in our patients with *S. androgynus*-induced obstructive pulmonary disease.

There were some limitations to this study. First, all-cause mortality was 8.2% (N = 4/49) in our study, but this could be underestimated as 20 patients were not available for contact and their status was unknown. Second, most of the patients with *S. androgynus*-related obstructive lung disease were women. Gender differences[19,20] should be considered in interpretation of the health status of patients with COPD and *S. androgynus*-related obstructive lung disease. Third, the number of cases analyzed in our study was relatively small because of the rarity of *S. androgynus*-

Table 5 Comparison of demographic characteristics and pulmonary function between follow-up and lost follow-up cases.

	Follow-up cases (n=16)	Lost follow-up cases (n=28)	*p* value
Age (y)	47.9 ± 7.6	46.2 ± 10.1	0.37
Sex (M/F)	1/15	2/26	0.91
BMI	26.6 ± 5.6	25.7 ± 3.8	0.98
SpO2 (%)	94.2 ± 3.7	95.3 ± 2.2	0.46
Total amounts (g)	5681.3 ± 3285.4	5592.9 ± 4526.4	0.43
TLC% predicted	94.8 ± 20.3	95.0 ± 12.3	0.80
FEV1/FVC (%)	51.4 ± 10.6	49.8 ± 13.1	0.46
FEV1 (L)	1.0 ± 0.3	1.0 ± 0.4	0.63
FEV1% predicted	43.9 ± 14.1	42.4 ± 18.9	0.69
FVC (L)	2.0 ± 0.7	1.9 ± 0.5	0.73
FVC% predicted	74.6 ± 19.9	71.8 ± 17.8	0.63

BMI = body mass index; TLC = total lung capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

related obstructive lung disease and the results may not be generalizable to the overall population with this disease. In order to offset this shortcoming, we further divided our 49 patients into lost follow-up (n = 28) and follow-up groups (n = 16) to compare the original demographic characteristics and pulmonary function (Table 5), and no significance was found between these two groups. We speculated that our conclusion in this study may be expanded to the lost follow-up group.

In conclusion, our follow- up study revealed that 15 years after an acute deterioration of *S. androgynus*-related obstructive lung disease, obstructive ventilatory defects were stationary, as shown by the only slight change in the FEV_1, despite irreversibility. In addition, our patient group had a better quality of life than COPD reference patients. Due to the small sample size of this study, we still need a further study with a larger sample size to confirm these findings.

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