

Causes and prevalence of inadequate pulmonary function testing among patients with systemic sclerosis

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Abstract

Introduction: Spirometry is a screening tool for evaluating the degree of restrictive lung disease in systemic sclerosis (SSc). Observations indicated that some patients could not complete the test. The aim of the study was to identify the prevalence, causes and clinical predictors of an inadequate pulmonary function test (PFT) in SSc.

Material and methods: A cross-sectional study was performed among SSc patients over 18 years old followed up at Srinagarind Hospital, Khon Kaen, Thailand, during January 2006–December 2012. The adequacy of the PFT was based on the acceptable blow criteria as set out by the American Thoracic Society and the European Respiratory Society 2005 Standardizations of Spirometry.

Results: Two hundred and forty-nine patients were included (female to male ratio was 2 : 1). The mean age at performing PFT was 51.4 ±11.1 years (range: 19.6–79.5). Median duration of disease at performing PFT was 2 years (IQR: 0.6–4.4). Inadequate PFT occurred in 73 cases (prevalence 29.3%; 95% CI: 23.6–35.0); the majority (60 cases; 82.2%) had an expiration time < 6 s and the others were due to plateau < 1 s (11 cases; 15%), air leak around mouth piece (1 case; 1.4%) and hesitation (1 case; 1.4%). Thirteen of 73 (17.8%) had an unusable graph with the overall prevalence of 5.2% (95% CI: 2.4–8.0). The factor associated with inadequate PFT was body mass index (BMI) < 18.5 kg/m² (OR = 2.17; 95% CI: 1.49–3.17); the same factor was associated with an unusable graph, which was confirmed by the multivariate analysis (OR = 5.21; 95% CI: 1.60–16.95).

Conclusions: One-third of Thai SSc patients had an inadequate pulmonary function test – the majority because of inadequate time for expiring. Low BMI influenced the effectiveness of the test, leading to an incomplete graph for evaluating lung disease in SSc.

Key words: systemic sclerosis, scleroderma, pulmonary function test, forced vital capacity.

Introduction

Systemic sclerosis (SSc) is a rare disease for which skin tightness is the hallmark. The extent of skin tightness is classified into 2 major subsets (a) limited cutaneous systemic sclerosis (lcSSc) and (b) diffuse

cutaneous systemic sclerosis (dcSSc) [1]. Skin tightness in lcSSc is limited to the face, hands, feet, forearms and legs, whereas in dcSSc the skin tightness includes the trunk and both extremities. Fibrosis is a predominant pathological finding in SSc which presents in the skin and the internal organs including the kidney, lung, heart and intestines [2–6]. However, the fibrosis could be revealed in a non-life threatening organ such as ocular or thyroid, and the clinical manifestations might be unrecognized [7, 8]. Infection, genetic, and environmental factors are reported to be involved in initiation of the disease, however; the exact pathogenesis of the disease is complex and not clear [9, 10].

Interstitial lung fibrosis in SSc is not uncommon, and the severity of pulmonary involvement indicates the prognosis [11]. Interstitial lung fibrosis and pulmonary vascular disease are thus the major causes of mortality [12–14]. Serum tumor necrosis factor α (TNF- α) is elevated in SSc patients, and the rise supports the development of interstitial lung fibrosis and pulmonary arterial hypertension (PAH) [15]. However, the role of anti-TNF- α in SSc with interstitial lung fibrosis and PAH is unknown. Pulmonary function tests – especially spirometry – are routinely used as an initial evaluation for assessing the severity of pulmonary involvement and also at subsequent follow-up [14]. Forced vital capacity (FVC) < 80% represents the restrictive lung disease, which is the most common pulmonary function test finding for SSc [16]. Although spirometry is a good screening tool for early restrictive lung disease detection in SSc, there are some technical limitations according to our observation of SSc patients in clinical practice (narrow mouth opening, muscle weakness and severe skin tightness); consequently, some patients cannot perform the spirometry test and some therefore have an inadequate pulmonary function test.

We wanted to investigate the prevalence, the causes and the clinical predictors of inadequate pulmonary function test among SSc patients. If the causes of inadequate pulmonary function tests could be identified, we might be able to predict which SSc patients would most likely have an inadequate pulmonary function test; thereby guiding us to choose an alternative test for evaluating pulmonary involvement progression. The results of this research could assist physicians by decreasing the time and money spent on an unproductive test.

Material and methods

We conducted a cross-sectional study of SSc patients over 18 years of age, attending the Scleroderma Clinic at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand, between

January 2006 and December 2012. We excluded patients with any other connective tissue disease.

Operational definitions

A diagnosis of SSc was based on the American College of Rheumatology criteria [17]. Systemic sclerosis was classified as the limited or diffuse type as per the classification by LeRoy *et al.* [18]. Date of onset was the date when the patient had the first symptoms of SSc. Myositis was diagnosed if the muscle enzyme creatine phosphokinase was elevated or an abnormal finding was found on the electromyography. Muscle weakness was defined when the patients had muscle weakness mainly in the shoulder and hip girdles that related to SSc [19]. The skin score was evaluated using the modified Rodnan's skin score (mRSS) method. Restrictive lung disease was classified as (a) mild restrictive lung – FVC between 60% and 79% predicted (b) moderate restrictive lung – FVC between 40% and 59% predicted and (c) severe restrictive lung – FVC < 40% predicted. The last visit for doing the pulmonary function test was included in our analysis.

The adequacy of the pulmonary function test was based on acceptable blow criteria ATS/ERS 2005 Standardizations of Spirometry [20]: 1) without an unsatisfactory start of expiration, characterized by excessive hesitation or a false start, an extrapolated volume (EV) > 5% of FVC or 0.150 l, whichever is greater; 2) without coughing during the first second of the maneuver, thereby affecting the measured force of the expiratory volume within 1 s (FEV₁), or any other cough that – in the technician's judgment – interfered with the measurement of accurate results; and, 3) without early termination of expiration.

The latter was defined as: (1) the subject could not or should not continue further exhalation; (2) the volume – time curve indicated no change in volume (< 0.025 l) for ≥ 1 s; (3) the subject had tried to exhale for ≥ 3 s in children under 10 years of age and for ≥ 6 s in subjects over 10 years of age; (4) without a Valsalva maneuver (glottis closure) or hesitation during the maneuver that causes a cessation of airflow, which precludes accurate measurement of FEV₁ or FVC; (5) without a leak; (6) without an obstructed mouthpiece (e.g., obstruction due to the tongue being placed in front of the mouthpiece, or teeth in front of the mouthpiece, or mouthpiece deformation due to biting); and/or (7) without evidence of an extra breath being taken during the maneuver.

A usable graph need only meet conditions 1 and 2 above, while an acceptable graph must meet all of the above seven conditions [20]. An adequate pulmonary function test was indicated when the expired time was ≥ 6 s and the volume – time graph

showed no change in volume (plateau) ≥ 1 s. An inadequate pulmonary function test could be subdivided into a usable volume-time graph (plateau time ≥ 1 s) and an unusable volume-time graph (if the graph did not meet any of the above criteria).

The primary outcome of this study was finding the cause(s) of an inadequate pulmonary function test while the secondary outcome was finding the prevalence of an inadequate pulmonary function test at the Scleroderma Clinic and/or the clinical predictors of an inadequate pulmonary function test.

Statistical analysis

The clinical characteristics were categorized according to the theory being studied. All of the data were classified into dichotomous or polytomous variables or continuous variables. The codes were set for every categorical variable. The differences in clinical characteristics between an adequate and an inadequate pulmonary function test were investigated. The categorical data were tested for significance using the χ^2 or Fisher's exact test. The continuous data were analyzed using the Student *t*-test or the Wilcoxon rank sum, as appropriate. The prevalence of an inadequate pulmonary function test was stated together with the respective 95% confidence interval (CI). The odds ratio with the respective 95% CI and *p*-value were used to determine which clinical characteristics are significantly associated with an inadequate pulmonary function test. The variables with a *p*-value < 0.10 were entered into a multiple logistic regression model then the backward elimination method was applied for model fitting. Variables were then re-tested for significance using the Wald χ^2 statistic. All statistical tests were two-tailed and a *p*-value of < 0.05 was considered statistically significant. All data analyses were performed by

using STATA version 11.2 (StataCorp., College Station, TX, USA).

The study was designed by the authors and approved by the Human Research Ethics Committee of Khon Kaen University (HE551422). The sponsors had no role in this study.

Results

In total 401 medical records were reviewed. Ninety-two patients were excluded because of SSc overlap with other connective tissue disease and 60 were excluded because of PFT not being performed; therefore a total of 249 medical records were included in this study (164 females vs. 85 males). The respective mean age of onset of the disease and age at time of the pulmonary function test were 47.9 ± 11.9 years (range: 11.3–75.6) and 51.4 ± 11.1 years (range: 19.6–79.4). The majority (222 cases; 89.5%) had the diffuse cutaneous systemic sclerosis subset. The median duration of the disease at the time of the PFT was 2.0 years (IQR: 0.6–4.4). The mean BMI at the time of the test was 21.7 ± 3.4 kg/m² (range: 12.8–40.3).

Seventy-three cases had an inadequate pulmonary function test. The prevalence of an inadequate pulmonary function test was 29.3% (95% CI: 23.6–35.0), of which 60 cases (82.2%) were due to an expiration under 6 s; however, the graphs were interpretable. The remainder were uninterpretable as: (a) the plateau on the volume – time graph was < 1 s (11 cases; 15.1%); (b) there was an air leak around the mouth piece (1 case; 1.4%) and/or, hesitation (1 case; 1.4%) (Figure 1). The prevalence of an unusable volume-time graph for interpretation was 5.2% (95% CI: 2.4–8.0). The mean FVC of the patients with a usable graph was $69.2 \pm 14.7\%$ predicted (range: 20–105). Half (126; 52.7%) had mild restrictive lung disease while one-fifth had a normal pulmonary function test

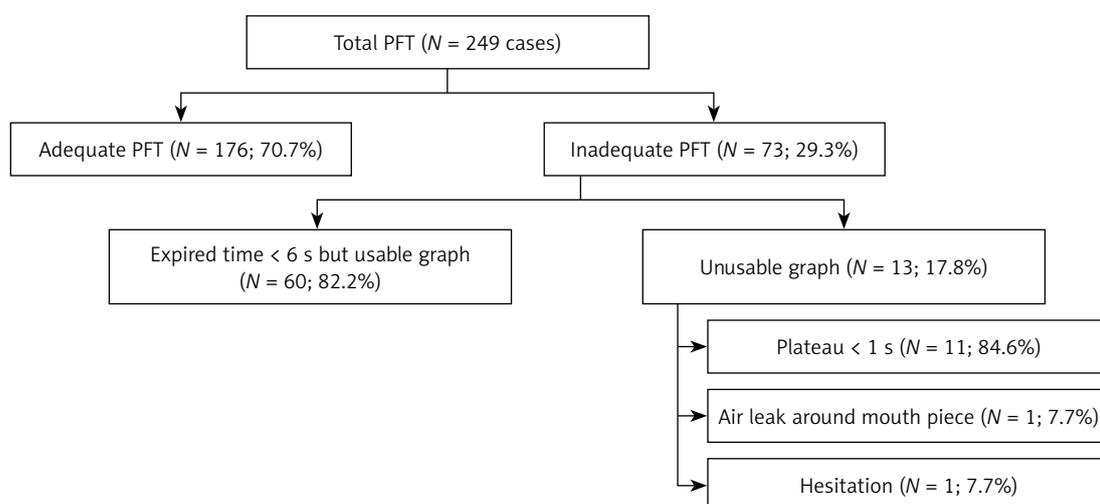


Figure 1. Characteristics of pulmonary function test (PFT)

(54; 22.6%) and another one-fifth had a moderately restrictive lung (52; 21.8%).

The clinical differences between the patients who had an adequate vs. an inadequate pulmonary function test are presented in Table I. Body mass index (BMI) was the only clinical parameter that affected the effectiveness of the pulmonary function test: a BMI < 18.5 kg/m², which was associated with an inadequate pulmonary function test (OR = 2.02; 95% CI: 1.39–2.93). Other factors were not related to the outcome of interest (i.e. age, facial and severity of truncal skin tightness, muscle strength and cardiac function) (Table I).

The clinical differences between the patients who had a usable and an unusable graph for interpretation are presented in Table II. Body mass index < 18.5 kg/m² and muscle weakness were as-

sociated with inadequate pulmonary function test performance with OR of 2.02 (95% CI: 1.39–2.93) by univariate analysis. After multivariate analysis, only BMI < 18.5 kg/m² was a clinical parameter associated with unusable graph for interpretation with OR of 5.2 (95% CI: 1.60–16.95) (Table II). Most patients had no serious complication during or after performing the pulmonary function test. Twenty-two cases (8.8%) revealed hypoxemia and 2 (0.8%) had rising blood pressure after performing the pulmonary function test.

Discussion

The pulmonary function test is a noninvasive screening tool for evaluating pulmonary disease, particularly for chronic lung disease including pulmonary fibrosis in SSC patients. A restrictive lung

Table I. Clinical differences between the patients with an adequate vs. an inadequate pulmonary function test

Clinical parameters	Adequate PFT N = 176	Inadequate PFT N = 73	OR (95% CI)
Female	65.9%	65.8%	1.00 (0.66–1.49)
dcSSc subset	90.3%	87.7%	0.83 (0.47–1.47)
Age > 65 years	11.4%	9.6%	0.87 (0.44–1.69)
BMI < 18.5 kg/m ²	9.8%	27.8%	2.17 (1.49–3.17)*
Total mRSS > 20 points	15.0%	12.5%	0.86 (0.47–1.56)
mRSS face and trunk ≥ 6	0.6%	1.4%	1.72 (0.4–6.97)
EF < 50%	5.4%	4.4%	0.86 (0.3–2.34)
RVSP > 40 mm Hg	17.1%	21.8%	1.22 (0.73–2.04)
Myositis	23.4%	22.9%	0.98 (0.61–1.57)
Muscle weakness	6.9%	11.3%	1.42 (0.80–2.53)

PFT – Pulmonary function test, OR – odds ratio, CI – confidence interval, dcSSc – diffuse cutaneous systemic sclerosis, BMI – body mass index, mRSS – modified Rodnan skin score, EF – ejection fraction, RVSP – right ventricular systolic pressure; *statistically significant.

Table II. Clinical differences between the patients who had a usable graph and an unusable graph for interpretation

Clinical parameters	Usable graph N = 236	Unusable graph N = 13	Crude OR (95% CI)	Adjusted OR (95% CI)
Female	64.8%	84.6%	2.85 (0.65–12.57)	–
dcSSc subset	90.6%	70.0%	0.26 (0.09–1.80)	–
Age > 65 years	11.1%	7.7%	0.68 (0.09–5.04)	–
BMI < 18.5 kg/m ²	13.3%	46.2%	4.84 (1.72–13.60)*	5.21 (1.60–16.95)*
Total mRSS > 20 points	13.4%	30.8%	2.67 (0.87–8.19)	2.26 (0.61–8.36)
mRSS face and trunk ≥ 6	0.9%	0%	NA	–
EF < 50%	5.3%	0%	NA	–
RVSP > 40 mm Hg	17.7%	37.5%	2.63 (0.66–10.42)	–
Myositis	23.7%	15.4%	0.60 (0.14–2.63)	–
Muscle weakness	7.4%	23.1%	3.36 (1.0–11.23)*	2.86 (0.65–12.49)

OR – Odds ratio, CI – confidence interval, dcSSc – diffuse cutaneous systemic sclerosis, BMI – body mass index, mRSS – modified Rodnan skin score, EF – ejection fraction, RVSP – right ventricular systolic pressure; *statistically significant.

pattern is commonly detected in SSc patients; however, a complete performance of the test depends on several factors (e.g., patient coordination, mouth closed ensuring no leaks).

In SSc, some factors that could lead to an inadequate or incomplete pulmonary function test such as tightness of the skin on the face might cause air leaks during performance of the pulmonary function test. According to our observations, the prevalence of an inadequate pulmonary function test was high but fortunately most of the patients had a usable graph for interpretation. An inadequate extension of the expiration time to 6 s and a BMI under 18.5 kg/m² (or malnutrition status) were the only factors associated with both an inadequate pulmonary function test and an unusable graph for interpretation of SSc. According to the results from a previous study, malnutrition and body composition could affect the results of a pulmonary function test, particularly FVC [21, 22], so this might explain why malnutrition was a clinical parameter predictive of an inadequate pulmonary function test in SSc. We therefore suggest carefully considering PFT interpretation among SSc patients with a BMI under 18.5 kg/m² and using the alternative screening tool for evaluating the severity of restrictive lung disease in those patients if PFT is inadequate.

According to our results, muscle weakness was not significantly associated with an inadequate pulmonary function test or an unusable graph for interpretation. In general, muscle weakness in SSc almost always presents on the proximal part [23] not in the respiratory muscles as in polymyositis or dermatomyositis, which directly affect the results of the pulmonary function test [24]. To avoid any confounding of our analysis, we excluded overlap SSc-polymyositis from our study, so it was not surprising that muscle weakness did not influence the pulmonary function test in our SSc patients.

This study had some limitations due to its retrospective nature and the relatively small number of patients. Notwithstanding, our study is the first report on the clinical parameters associated with an inadequate pulmonary function test leading to an unusable graph among SSc patients. These are, therefore, important preliminary data showing the limitations of a pulmonary function test among SSc patients.

In conclusion, around one-third of the Thai SSc patients in our study had an inadequate pulmonary function test. In the majority of cases, it was related to an inadequate time for expiration. One in twenty had an unusable graph from the pulmonary function test. A low BMI (malnourished status) influenced the effectiveness of the pulmonary function test and led to an incomplete graph, making evaluating the lung disease in SSc impracticable.

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Conflict of interest

The authors declare no conflict interest.

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