Concise report

Utility of the breath-holding test in patients with systemic sclerosis

Jina Yeo 1,2, Ju Yeon Kim 2, Mi Hyeon Kim 2, Jun Won Park 2, Jin Kyun Park 2,3 and Eun Bong Lee 2,3,4

Abstract

Objectives. Cardiopulmonary involvement is a major cause of death in patients with SSc. This study evaluated the clinical utility and reliability of breath-holding test (BHT) in evaluating cardiopulmonary function in patients with SSc.

Methods. Seventy-two prospectively enrolled patients with SSc underwent BHT and the 6 min walk test (6MWT), along with measurements of the Borg dyspnoea scale and Scleroderma Health Assessment Questionnaire (SHAQ). Data on pulmonary function test and echocardiography were also collected. Validity was assessed based on the correlations between the best BHT and relevant clinical parameters. To assess the reliability of BHT, an additional 31 patients with SSc underwent BHTs twice within 2 week intervals.

Results. Mean (s.d.) best BHT time was 38.4 (15.7) s, and 6MWT distance was 473.5 (95.5) m. BHT showed significant correlations with the Borg dyspnoea scale before (r = 0.367, P < 0.001) and after (r = 0.285, P = 0.016) testing, whereas 6MWT were correlated with the Borg dyspnoea scale after (r = 0.351, P = 0.002) but not before (r = 0.113, P = 0.343) testing. BHT time was correlated with diffusing capacity for carbon monoxide (% , r = 0.426, P < 0.001), forced vital capacity (litres, r = 0.373, P = 0.001), pulmonary arterial systolic pressure (mmHg, r = 0.272, P = 0.031) and SHAQ score (r = 0.470, P < 0.001), but not with left ventricular ejection fraction (% , r = 0.135, P = 0.263). BHT showed excellent reliability, with an intraclass correlation coefficient (2, 1) of 0.943 (95% CI: 0.88, 0.97).

Conclusion. BHT, a simple and less time-consuming test, shows excellent reliability and significant correlation with the Borg scale, SHAQ and pulmonary parameters. These results suggest that BHT might be a useful surrogate marker of pulmonary capacity in SSc patients.

Trial registration number. NCT04484948.

Key words: breath-holding test, 6 minute walk test, systemic sclerosis

Introduction

SSc is a chronic autoimmune disease that is characterized by microvasculopathy and excessive fibrosis of skin with multi-organ involvement including lung, heart, kidney and gastrointestinal tract [1]. Cardiopulmonary involvement, such as interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), is a major cause of death in patients with SSc [2]. Although the 6min walk test (6MWT), a submaximal exercise test, is most commonly used to assess cardiopulmonary capacity in SSc patients, it has not been completely validated in SSc patients with poor correlation with cardiorespiratory...
capacity [3–5]. Because SSc is a multifaceted and complex disease, it is likely that the results of the 6MWT, which measures total distance walked, are affected by non-cardiorespiratory factors, such as skin and musculoskeletal complications of SSc [6, 7]. Furthermore, rigorously trained technicians are necessary for adequate performance of 6MWT and for standardization of its results [8]. Another surrogate test that reflects cardio-pulmonary function is therefore needed for use in clinical trials and in the clinical management of patients with SSc.

The breath-holding test (BHT) is a simple and rapid test that can be used to evaluate cardiopulmonary function. This test can be easily performed at any place, even in patients who cannot ambulate. BHT has been used in respiratory physiology to measure ventilator response and may predict outcomes in patients with various respiratory abnormalities [9–12]. However, it has not yet been evaluated in SSc patients. This prospective study was designed to determine the validity and reliability of BHT in patients with SSc.

### Methods

This prospective study was performed at a tertiary referral centre (Seoul National University Hospital, SNUH) for patients with SSc. The study design was approved by the institutional review board of SNUH (IRB no. 2006-054-1131), with all included patients providing written informed consent for data collection and analysis.

#### Study population

This study included 72 patients with SSc who were evaluated from August 2020 to February 2021. Patients were considered eligible if they were aged ≥19 years, and had been diagnosed with SSc, as defined by the 2013 ACR/EULAR classification criteria [13]. Subjects were excluded if their resting oxygen saturation by pulse oximetry was <90% in room air; if they had unstable angina or myocardial infarction during the previous month; or if they were unable to perform BHT or 6MWT.

#### BHT and 6MWT

The participant was asked to sit comfortably on a chair and breathe normally. After 1 min, the participant was required to make a maximum expiration followed by a maximum inspiration and to hold his/her breath as long as possible at the maximum inspiratory level without encouragement. This procedure was repeated three times, with 5 min intervals between procedures [11]. The total breath-holding time (seconds) was recorded, with the longest BHT time used for outcome measures.

The 6MWT was performed according to American Thoracic Society guidelines [8]. The total distance walked for 6 min (6MWD) was recorded.

#### Validity measures

The longest BHT time recorded was considered each patient’s final result on BHT. The primary validity outcome was the correlation between BHT time and Borg dyspnoea scale. The key secondary outcome was the correlation between BHT time and 6MWD. Other secondary outcomes included the correlations of BHT times with the pulmonary function indices FVC, %DLCO and FVC/DLCO, the echocardiographic parameters LVEF and PASP, and scores on the SHAQ.

#### Statistical analyses

For detailed sample size determination, see Supplementary Data S1, available at Rheumatology online. The validity of BHT was assessed by Pearson’s correlation test [14]. The reliability of BHT was assessed by measuring the intraclass correlation coefficient (ICC) and by performing Bland–Altman analysis. Estimated ICCs and their 95% CIs were calculated based on a single rater measurement, absolute agreement and a two-way random-effects model, with ICCs of 0.75–0.90 and >0.90 indicating good and excellent reliability, respectively [15]. All statistical analyses were performed using SPSS Statistics (version 26.0, IBM Corp., Armonk, NY, USA), and data were visualized by Prism.
**Table 1** Characteristics of the 72 patients with SSc

| Characteristic | Value (n = 72) |
|---------------|---------------|
| Female, n (%) | 66 (91.7)     |
| Age, mean (s.d.), years | 57.1 (11.1) |
| Body mass index, mean (s.d.), kg/m² | 21.5 (4.6) |
| Coexisting conditions, n (%) |            |
| Hypertension | 12 (16.7)     |
| Diabetes     | 7 (9.7)       |
| Coronary artery disease | 6 (8.3) |
| Disease characteristics |            |
| Time since the onset of non-Raynaud’s symptom, mean (s.d.), years | 8.5 (6.4) |
| Diffuse SSc, n (%) | 39 (54.2) |
| Limited SSc, n (%) | 33 (45.8) |
| Cardiopulmonary function |            |
| FVC, mean (s.d.), l | 2.5 (0.7) |
| FVC, mean (s.d.), % of predicted value | 82.1 (23.4) |
| FEV1, mean (s.d.), l | 2.0 (0.6) |
| FEV1, mean (s.d.), % of predicted value | 87.9 (23.9) |
| FEV1/FVC, mean (s.d.) | 79.8 (7.5) |
| DLCO, mean (s.d.), % of predicted value | 64.5 (20.0) |
| FVC/DLCO, mean (s.d.) | 1.3 (0.4) |
| LVEF, mean (s.d.), % | 61.2 (5.8) (n = 71) |
| PASP, mean (s.d.), mmHg | 33.8 (8.7) (n = 63) |
| NYHA class 1/2/3/4, n (%) | 39 (54.2)/23 (31.9)/9 (12.5)/1 (1.4) |
| Other characteristics |            |
| Reflux/dysphagia symptoms, n (%) | 34 (47.2) |
| Digital ulcers, n (%) | 18 (25.0) |
| Arthralgia, n (%) | 23 (31.9) |
| Muscle weakness, n (%) | 8 (11.1) |
| ILD, n (%)<sup>a</sup> | 33 (45.8) |
| PAH, n (%)<sup>b</sup> | 8 (11.1) |
| Isolated PAH, n (%) | 2 (2.8) |
| PAH with ILD, n (%) | 6 (8.3) |
| mRSS skin score, mean (s.d.), 0–51 | 10.6 (10.5) |
| SHAQ score, mean (s.d.), 0–3 | 0.64 (0.61) |
| Autoantibody positivity, n (%) |            |
| Anti-nuclear antibody | 70 (94.6) |
| Anti-topoisomerase antibody | 31 (43.1) (total n = 70) |
| Anti-centromere antibody | 18 (25.0) |
| Anti-RNP antibody | 12 (16.7) (total n = 68) |
| ESR, mean (s.d.), mm/h | 26.9 (21.4) |
| CRP, mean (s.d.), mg/dl | 0.36 (0.62) |
| Immunosuppressant use, n (%) |            |
| Glucocorticoids | 34 (47.2) |
| MTX | 2 (2.8) |
| Mycophenolate | 11 (15.3) |
| PDE5 inhibitor, n (%) | 12 (16.7) |
| Prostanoid, n (%) | 5 (6.9) |
| Endothelin receptor antagonist, n (%) | 4 (5.6) |

<sup>a</sup>Diagnosis of ILD was based on HRCT. <sup>b</sup>Diagnosis of PAH was based on PASP ≥40 mmHg measured by echocardiography, or mean PAP ≥25 mmHg and PAWP ≤15 mmHg, when the results of right heart catheterization were available. DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; HRCT: high resolution CT; ILD: interstitial lung disease; LVEF: left ventricular ejection fraction; mRSS: modified Rodnan skin score; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PAP: pulmonary arterial pressure; PASP: pulmonary arterial systolic pressure; PAWP: pulmonary arterial wedge pressure; PDE5: phosphodiesterase 5; SHAQ: Scleroderma Health Assessment Questionnaire.
Results

Patient characteristics

A total of 72 patients with SSc were enrolled from SNUH. Mean (s.d.) age was 57.1 (11.1) years, and 66 (91.7%) were women. According to the NYHA classification, 39 (54.2%) patients were classified as class I and 23 (31.9%) as class II. ILD was found in 33 (45.8%) patients and isolated PAH in two (2.8%) patients. The details of other clinical and laboratory characteristics are shown in Table 1.

BHT and 6MWT

Supplementary Table S1, available at Rheumatology online, shows the results of BHT and 6MWT in this patient cohort. Overall, the mean (s.d.) BHT time was 38.4 (15.7) s, and the mean (s.d.) 6MWD was 473.5 (95.5) m. The three repeated BHTs at 5 min intervals showed high positive pairwise correlations between the first and second (r = 0.882, P < 0.001), first and third (r = 0.861, P < 0.001), and second and third tests (r = 0.926, P < 0.001, Supplementary Fig. S1, available at Rheumatology online), as well as excellent reliability [ICC (2, 1) = 0.947, 95% CI: 0.90, 0.97, P < 0.001].

Correlations between BHT and cardiopulmonary parameters

The relationships between BHT time and clinical parameters, including cardiopulmonary indices, are presented in Fig. 1A and Supplementary Table S2, available at Rheumatology online. BHT time showed statistically significant correlations with Borg dyspnoea scale scores before (r = −0.367, P < 0.001) and after (r = −0.285, P = 0.016) testing and with 6MWD (r = 0.410, P < 0.001). By contrast, 6MWD showed only a moderate correlation with Borg dyspnoea scale score after (r = −0.351, P = 0.002), but not before (r = −0.113, P = 0.343), testing (Supplementary Fig. S2, available at Rheumatology online). BHT time was significantly correlated with FVC (l) (r = 0.373, P = 0.001), %DLCO (r = 0.426, P < 0.001), FVC/DLCO (r = −0.247, P = 0.038), PASP (r = −0.272, P = 0.031) and SHAQ score (r = −0.470, P < 0.001). BHT time, however, did not correlate with %FVC, LVEF, mRSS, ESR or CRP (Supplementary Table S2, available at Rheumatology online). Correlation of BHT with dyspnoea parameters tended to be higher in ILD than in PAH subgroup (Supplementary Table S3, available at Rheumatology online).

Reliability of BHT

To confirm their reliability, BHTs were performed at two time points, at intervals of 1–14 days, in 31 additional patients with stable SSc (Supplementary Table S4, available at Rheumatology online). All patients underwent the first BHTs face-to-face, whereas only 15 (48.4%) underwent the second BHTs face-to-face. The remaining 16 (51.6%) patients underwent the second BHTs using a televideo system. The mean (s.d.) absolute BHT1 and BHT2 times were 39.0 (20.3) s and 39.3 (22.1) s, respectively. Bland–Altman plot showed excellent agreement between BHT1 and BHT2 [ICC (2, 1) = 0.943, 95% CI: 0.88, 0.97, P < 0.001, Fig. 1B]. In subgroup analyses, both face-to-face [ICC (2, 1) = 0.932, 95% CI: 0.80, 0.98] and televideo system [ICC (2, 1) = 0.947, 95% CI: 0.85, 0.98] measurements showed excellent reliabilities (P < 0.001, Supplementary Table S5, available at Rheumatology online). Furthermore, ICC values were not affected by the time intervals.

Discussion

In the present study, we found that BHT can be a reliable, valid and simple test to measure overall pulmonary function in SSc patients. BHT times showed robust correlations with Borg dyspnoea scale scores, FVC (l), %DLCO, PASP (mmHg) and SHAQ. To our knowledge, this is the first report investigating the utility of BHT in SSc patients.

Early detection and monitoring of cardiopulmonary complications are crucial in the management of SSc patients. Currently, 6MWT is most commonly used to measure cardiopulmonary function in SSc patients, both in daily care and in clinical trials [16]. However, there are many instances where 6MWT cannot be performed due to concerns for patients’ safety or technical feasibility. Our study shows that BHT can be a useful supplementary test for 6MWT.

BHT can be performed at any location where a patient can sit. It takes <1 min only, as the mean BHT time was 38.4 (15.7) s in our SSc patients. It can also be performed in patients with severe dyspnoea in whom 6MWT cannot be performed. BHT showed excellent reliability in this study, with an overall ICC of 0.943 as assessed by the stability of two separate measurements performed at intervals of 1–14 days. Its reliability was found to be excellent in both face-to-face and televideo BHTs, with no difference in face-to-face or a televideo system.

BHT showed high validity in measuring pulmonary function in SSc patients. It showed higher correlation with the Borg dyspnoea scale or PFTs in the ILD subgroup than in the PAH subgroup. Face validity of BHT is evident since patients with dyspnoea, a major symptom of cardiopulmonary dysfunction, have greater difficulty holding their breath than patients without dyspnoea. For criterion validity, BHT showed acceptable correlations with the Borg dyspnoea scale representing subjective severity of dyspnoea [17]. In addition, BHT times showed moderate correlation with FVC (l) and %DLCO, objective measures of pulmonary capacity, and with SHAQ scores, a measure of quality of life. Cardiopulmonary function is a complex construct that cannot be determined by a single test. The
moderate degrees of correlation of BHT results with different subjective (e.g. Borg dyspnoea scale) and objective measures of pulmonary function (e.g. FVCs) suggest that BHT is an indicator of the construct for pulmonary function in SSc patients.

This study had several limitations. First, there was a time delay of up to 3 months between BHT and echocardiography and PFT. Second, the present study enrolled patients with mild-to-moderate dyspnoea (NYHA class 1 and 2). Third, this study did not
evaluate the long-term implications of BHT results. Finally, this study enrolled only Korean patients, indicating a need to confirm these findings in other ethnic groups.

In conclusion, BHT is a simple, rapid and safe test that can reflect severity of dyspnoea caused by respiratory function in SSc patients. The present study suggests that BHT can be a useful adjunct outcome measure in SSc patients.

Acknowledgements

This study would not have been possible without help from our research assistant, Sung-Soon Cho. This study has previously been published as an abstract (POS0856) at the EULAR 2021 conference. Conceptualization and supervision: E.B.L. Data curation: J.Y., J.Y.K. and M.H.K. Formal analysis: J.Y. and J.W.P. Investigation and methodology: J.Y., J.K.P. and E.B.L. Funding acquisition: E.B.L. Writing draft, review and editing: J.Y. and E.B.L. All authors approved the manuscript.

Funding: This work was supported by a National Research Foundation of Korea (NRF) grant funded by the government of Korea (Ministry of Science and ICT) (grant number: 2021R1A2C204874) and by the BK21 FOUR Program of the National Research Foundation of Korea (NRF) funded by the Ministry of Education (grant number: 5120200513755).

Disclosure statement: E.B.L. has worked as a consultant to Pfizer and received research grants from GC Pharma and Hanmi Inc. The other authors have nothing to disclose.

Ethics approval: The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no. 2006-054-1131).

Data availability statement

All data relevant to the study are included in the article or uploaded as Supplementary Data S1. Further de-identified data can be made available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data are available at Rheumatology online.

References

1 Denton CP, Khanna D. Systemic sclerosis. Lancet 2017; 390:1685–99.
2 Volkmann ER, Fischer A. Update on morbidity and mortality in systemic sclerosis-related interstitial lung disease. J Scleroderma Relat Disord 2021;6:11–20.
3 Avouac J, Kowal-Bielecka O, Pittrow D et al.; EPOSS Group. Validation of the 6 min walk test according to the OMERACT filter: a systematic literature review by the EPOSS-OMERACT group. Ann Rheum Dis 2010;69:1360–3.
4 Vandecastelee E, De Pauw M, De Keyser F et al. Six-minute walk test in systemic sclerosis: a systematic review and meta-analysis. Int J Cardiol 2016;212:265–73.
5 Buch MH, Denton CP, Furst DE et al. Submaximal exercise testing in the assessment of interstitial lung disease secondary to systemic sclerosis: reproducibility and correlations of the 6-min walk test. Ann Rheum Dis 2006;66:169–73.
6 Garin MC, Highland KB, Silver RM, Strange C. Limitations to the 6-minute walk test in interstitial lung disease and pulmonary hypertension in scleroderma. J Rheumatol 2009;36:330–6.
7 Sanges S, Launay D, Rhee RL et al. A prospective study of the 6 min walk test as a surrogate marker for haemodynamics in two independent cohorts of treatment-naive systemic sclerosis-associated pulmonary arterial hypertension. Ann Rheum Dis 2016;75:1457–65.
8 ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.
9 Nannini LJ, Zaietta GA, Guerrera AJ et al. Breath-holding test in subjects with near-fatal asthma. A new index for dyspnea perception. Respir Med 2007;101:246–53.
10 Inoue H, Yamauchi K, Kobayashi H et al. A new breath-holding test may noninvasively reveal early lung abnormalities caused by smoking and/or obesity. Chest 2009; 136:545–53.
11 Barnai M, Laki I, Gyurkovits K, Angyan L, Horvath G. Relationship between breath-hold time and physical performance in patients with cystic fibrosis. Eur J Appl Physiol 2005;95:172–8.
12 Ideguchi H, Ichiyasu H, Fukushima K et al. Validation of a breath-holding test as a screening test for exercise-induced hypoxemia in chronic respiratory diseases. Chron Respir Dis 2021;18:14797312110129.
13 van den Hoogen F, Khanna D, Fransen J et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47.
14 Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
15 Koo TK, LI MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15:155–63.
16 Distler O, Behrens F, Pittrow D et al.; EPOSS-Omeract Group. Defining appropriate outcome measures in pulmonary arterial hypertension related to systemic sclerosis: a Delphi consensus study with cluster analysis. Arthritis Rheum 2008;59:867–75.
17 Bausewein C, Farquhar M, Booth S, Gysels M, Higginson IJ. Measurement of breathlessness in advanced disease: a systematic review. Respir Med 2007;101:399–410.