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Concise report

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

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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

CLINICAL SCIENCE

Rheumatology key messages

- Breath-holding test (BHT) shows excellent reliability in systemic sclerosis (SSc).
- BHT correlates with the Borg scale, Scleroderma Health Assessment Questionnaire, and pulmonary parameters in SSc.
- BHT is a promising test to measure pulmonary function in SSc.

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 6 min 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

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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 cardiopulmonary 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 $\geq$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.

Demographic and caridopulmonary function indices

After obtaining relevant demographic and laboratory data, severity of dyspnoea was measured with the Scleroderma Health Assessment Questionnaire (SHAQ) and New York Heart Association (NYHA) functional classification scale at rest. Scores on the modified Borg dyspnoea scale (0–10 points) were also measured before and after each BHT and 6MWT (Supplementary Data S1, available at *Rheumatology* online).

The results of pulmonary function tests (PFT) and echocardiographic parameters, which were performed within 3 months of BHT, were obtained from the medical records. PFTs included forced vital capacity (FVC) in litres, percentage of predicted FVC (%FVC), percentage of predicted diffusing capacity for carbon monoxide (%DLCO) and ratio of %FVC to %DLCO (FCV/DLCO). Echocardiographic parameters included left ventricular ejection fraction (LVEF, %) and pulmonary arterial systolic pressure (PASP, mmHg). For a complete list of other collected clinical and laboratory data, see Supplementary Data S1, available at *Rheumatology* online.

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.

Reliability measures

An additional 31 SSc patients were enrolled to assess the reliability of BHT. The test–retest reliability of BHT was determined by comparing the results of BHT tests at two different time points (BHT1 and BHT2) within a 2 week interval. All patients enrolled in the reliability test cohort completed BHT as per standard protocol. BHT1 in all patients was performed in a face-to-face setting, whereas BHT2 in some patients was performed through a televideo system due to the COVID-19 pandemic.

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/m^2	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 (5.6) ($n = 71$)
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* (%)[a]	33 (45.8)
PAH, *n* (%)[b]	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)

[a]Diagnosis of ILD was based on HRCT. [b]Diagnosis of PAH was based on PASP $\geq$40 mmHg measured by echocardiography, or mean PAP $\geq$25 mmHg and PAWP $\leq$15 mmHg, when the results of right heart catherterization 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.

(version 8.0.1, GraphPad Software, La Jolla, CA, USA) for Windows 10.

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

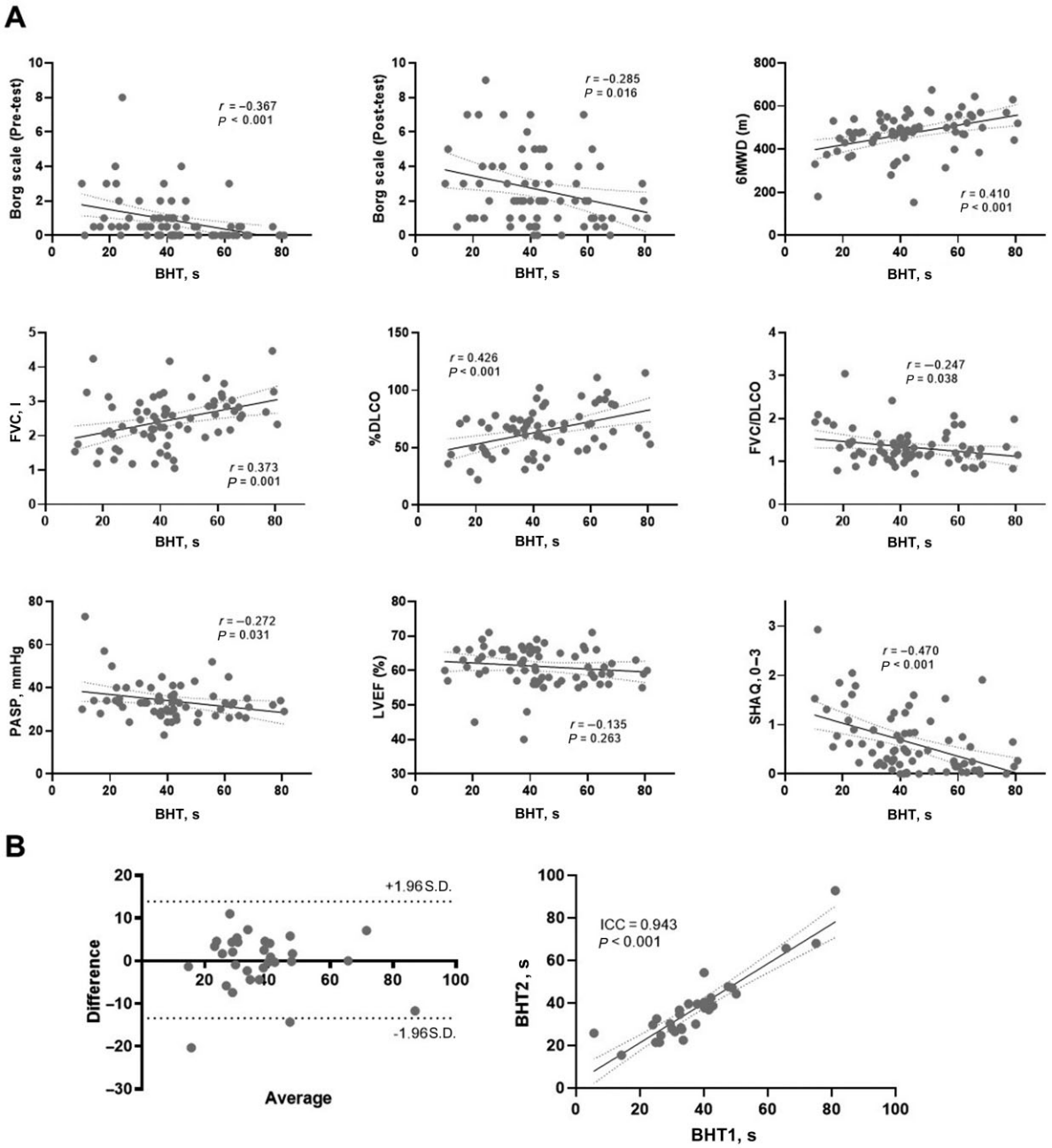
In the present study, we found that BHT can be a reliable, valid and simple test to measure overall pulmonary function in SSc patients. BHT times showed robust correlations with Borg dyspnoea scale scores, FVC (l), %DLCO, PASP (mmHg) and SHAQ. To our knowledge, this is the first report investigating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

FIG. 1 Validity (A) and reliability (**B**) of BHT in patients with SSc



Data are shown for (**A**) the scatter plots with Pearson's correlation coefficients (*r*) and *P*-values (*P*), and (**B**) Bland–Altman graph (left) and test–retest reliability with ICC and *P*-values (right). Two BHTs (each three times) were performed at minimum intervals of 2 h and maximum intervals of 2 weeks. BHT: breath-holding test; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; ICC: intraclass correlation coefficient; LVEF: left ventricular ejection fraction; PASP: pulmonary arterial systolic pressure; SHAQ: scleroderma health assessment questionnaire; 6MWD: 6 min walk test distance.

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.

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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.

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