


# Validation of a breath-holding test as a screening test for exercise-induced hypoxemia in chronic respiratory diseases

Chronic Respiratory Disease  
Volume 18: 1–10  
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DOI: 10.1177/14799731211012965  
journals.sagepub.com/home/crd  


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## Abstract

The detection of exercise-induced hypoxemia is important for evaluating disease status in patients with chronic respiratory diseases. The 6-min walk test (6MWT) is useful for detecting exercise-induced hypoxemia. This pilot study aimed to validate the breath-holding test (BHT) as a screening for exercise-induced hypoxemia and compare its utility with that of the 6MWT in patients with chronic respiratory diseases. Fifty-nine patients with chronic respiratory diseases underwent BHTs lasting 10, 15, and 20 s. Percutaneous oxygen saturation (SpO<sub>2</sub>), pulse rate, and severity of dyspnoea were measured. The participants also underwent a 6MWT, a pulmonary function test, and analysis of arterial blood gas at rest. Multivariate linear regression analysis was performed to identify significant predictors of desaturation in the 6MWT. The minimum SpO<sub>2</sub> during the BHT (all durations) and 6MWT were significantly correlated. Receiver operating characteristic analysis revealed the optimal cut-off for predicting SpO<sub>2</sub> < 90% during the 6MWT as a minimum SpO<sub>2</sub> ≤ 94% during the 15-s BHT. Perceived dyspnoea and maximum pulse rate were significantly lower during the 15-s BHT than during the 6MWT. In the multivariate linear regression analysis, the minimum SpO<sub>2</sub> during the 15-s BHT ( $\beta$ , 0.565,  $p < 0.001$ ) and %DLco ( $\beta$ , 0.255,  $p < 0.028$ ) were independent predictors of desaturation in the 6MWT. The minimum SpO<sub>2</sub> during the 15-s BHT may be a useful measure for screening for exercise-induced hypoxemia in patients with chronic respiratory diseases. The BHT is easier to perform, more readily available, and better tolerated than the 6MWT.

## Keywords

Breath-holding test, 6-min walk test, chronic respiratory diseases, interstitial lung diseases, chronic obstructive pulmonary disease

Date received: 24 November 2020; accepted: 4 April 2021

## Introduction

Patients with chronic respiratory diseases, particularly interstitial lung diseases (ILDs) and chronic obstructive pulmonary disease (COPD), develop progressive hypoxemia with disease progression.<sup>1,2</sup> Patients with mild to moderate or severe pulmonary impairment are often normoxemic at rest, but develop hypoxemia during exercise. This exercise-induced hypoxemia

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strongly correlates with the severity of the disease and is associated with decreased lung function and poor prognosis.<sup>3,4</sup> Hypoxemia during exercise induces hypoxic pulmonary vasoconstriction, cardiac overload, and tissue hypoxia.<sup>3,5</sup> The identification of exercise-induced hypoxemia enables us to detect mild but potentially progressive diseases at an early stage, and to provide useful information for the subsequent oxygen therapy. Therefore, in clinical practice, it may be important to detect exercise-induced hypoxemia in patients with pulmonary impairments who are normoxemic at rest.

Recording percutaneous oxygen saturation (SpO<sub>2</sub>) during daily walking and exercise tolerance tests, such as the 6-min walk test (6MWT) and the shuttle-walking test, is useful for evaluating oxygenation because it can be measured noninvasively and continuously.<sup>6</sup> Exercise-induced hypoxemia during the 6MWT is related to disease severity and mortality in patients with COPD and normoxemia.<sup>3,4,6</sup> However, even when using pulse oximetry, careful observation and management are needed during exercise tests because of unpredictable dyspnoea, excessive hypoxemia, and other potential incidents.

Voluntary breath-holding is a procedure that can easily induce arterial oxygen desaturation in patients with pulmonary diseases and has the advantage that it can be performed easily anywhere and at any time.<sup>7–10</sup> Inoue et al. reported that the 20-s breath-holding test (20-s BHT) revealed an early stage of gas-exchange abnormalities in the lungs of smokers and/or individuals who were overweight.<sup>9</sup> A test that is short in duration has advantages in clinical settings where time is limited, such as in outpatient clinics. However, the correlation of hypoxemia during exercise tolerance tests with that during BHT has not been examined.

Therefore, this study aimed to evaluate the correlation of hypoxemia during exercise tolerance tests with that during BHT, and to develop the BHT as a potential new screening test for the evaluation of chronic respiratory diseases in outpatient clinics.

## Methods

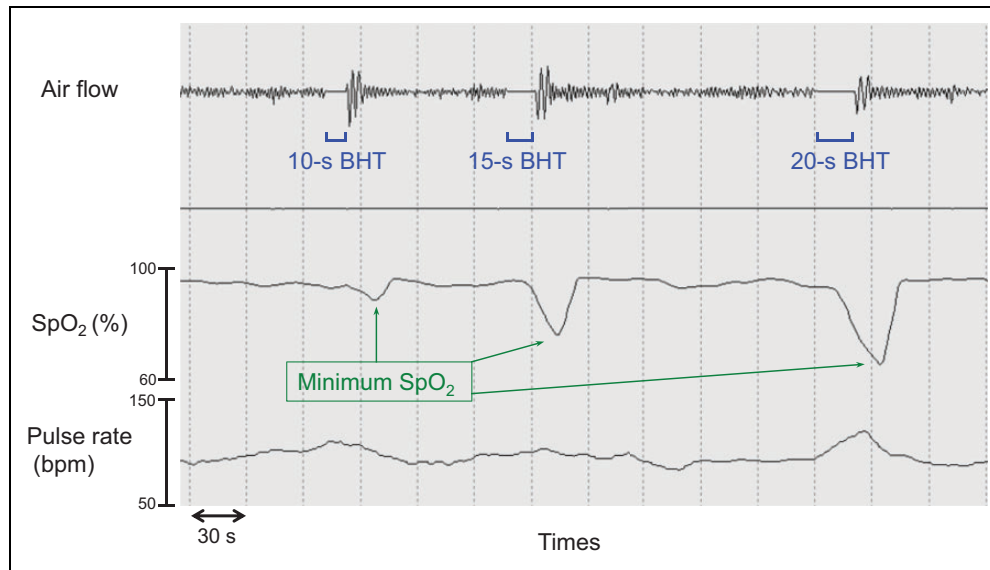
### Study participants

Patients with chronic respiratory diseases were recruited from the outpatient clinic of the Respiratory Medicine, Kumamoto University Hospital, between July 2013 and June 2017. The inclusion criteria were as follows: 1) patients with chronic respiratory diseases including ILDs and COPD; 2) age  $\geq 20$  years;

3) SpO<sub>2</sub>  $\geq 90\%$  at rest in room air; and 4) the ability to perform 6MWT and pulmonary function tests, including a diffusing capacity of the lung for carbon monoxide (DLco). The ILDs included idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia, chronic hypersensitivity pneumonia, connective tissue disease-associated ILD, and drug-induced ILD. Diagnoses of these ILDs were confirmed by previously reported criteria.<sup>11–13</sup> COPD was diagnosed in accordance with the Global Initiative for Chronic Obstructive Lung Disease guidelines.<sup>1</sup> Other disorders included pulmonary lymphangiomyomatosis, Castleman disease, bronchial asthma, and bronchiectasis. The exclusion criteria were as follows: 1) patients with concomitant confounding diseases that could affect their performance in the 6MWT, such as uncontrolled cardiovascular diseases, neuromuscular diseases, orthopaedic diseases, or unstable respiratory conditions such as a respiratory tract infection; 2) disease exacerbation of the respiratory disease; or 3) difficulties in detecting the pulse or measuring oxygen saturation by pulse oximetry. The protocol of this pilot study was approved by the Kumamoto University Hospital Ethics Committee (No. 1619), and written informed consent was obtained from each participant.

### BHT

To measure the actual breath-holding time, the participant's SpO<sub>2</sub> and pulse rate, we used an SAS-2100 (NIHON KOHDEN Co., Tokyo, Japan), a portable sleep-monitoring device with built-in pulse oximetry, and a nasal cannula pressure transducer. The manufacturer reported an accuracy of  $\pm 2\%$  for the SpO<sub>2</sub> measurements. The nasal pressure signals were digitized and sampled at 32 Hz and SpO<sub>2</sub> at 2 Hz. These data were analysed offline using a personal computer. The pulse oximetry probe was fixed to the participant's fingertips with adhesive tape using a finger-tip type, and the nasal pressure cannula was attached to the nostrils to detect nasal flow. The participant was seated and the pulse oximetry probe was held at the same level as the heart to avoid the effects of motion and circulatory congestion. The participant was observed under resting voluntary ventilation with the mouth closed for at least 2 min, until the SpO<sub>2</sub> levels and pulse rate became stable. The participant stops breathing at the level of functional residual capacity (at end-expiration) and put on the nose clips while keeping their mouth closed. Immediately after



**Figure 1.** Representative polygraph traces of air flow, SpO<sub>2</sub>, and pulse rate during the breath-holding tests. The 10-s, 15-s, and 20-s BHTs are shown with the times of minimum SpO<sub>2</sub> (arrows). BHT, breath-holding tests.

the 10-s breath-holding while checking with a stopwatch, the participant removed the nose clip and was instructed to take two deep inspirations to inhale the fresh air, followed by tidal breathing.<sup>9</sup> During and after the BHT, SpO<sub>2</sub> and pulse were monitored until they recovered to their baseline values. The minimum SpO<sub>2</sub> and the time from the beginning of the BHT to the minimum SpO<sub>2</sub> were recorded. All participants were observed for at least 2 min or until SpO<sub>2</sub> and pulse stabilized. Before and after each BHT, the participant was asked about his or her degree of subjective breathlessness using the modified Borg scale and a visual analogue scale. The modified version of the Borg scale consists of a vertical scale labelled 0–10, with verbal expressions corresponding to different degrees of breathlessness. After the breathlessness disappeared, SpO<sub>2</sub> and pulse became stable, the 15-s and 20-s BHTs were conducted in the same way. If a participant could not tolerate the breath-holding, the current BHT was discontinued immediately and the subsequent BHTs were cancelled. We used the analysis software ‘QP-021W’ to confirm the actual breath-holding time, SpO<sub>2</sub>, and pulse, which were recorded by SAS-2100 (Figure 1). If recorded breath-holding times differed by more than 10%, the data were excluded from the analysis.

## 6MWT

The 6MWT was performed in the hospital on a flat and straight 30-m walking course, following the

American Thoracic Society/European Respiratory Society recommendations.<sup>14</sup> Subjective scores of dyspnoea, using the modified Borg scale, were obtained before and after the 6MWT. SpO<sub>2</sub> values and pulse were measured with the SAS-2100, and the walking distances during the 6MWT were recorded.

## Pulmonary function tests and blood gas analysis

Spirometry was performed using a Chestac-8800 (Chest Co. Ltd, Tokyo, Japan), according to the American Thoracic Society/European Respiratory Society consensus guidelines.<sup>15,16</sup> The functional residual capacity was measured using a closed-circuit helium gas dilution system. The Japanese Respiratory Society reference values of pulmonary function were used to evaluate the percentage of predicted (% predicted) values.<sup>17</sup> DLco was measured using the single breath-holding method. Arterial blood gas analysis was performed in room air with the participant at rest in a sitting position, and was measured with a RAPID Point 500 (Siemens Healthcare Ltd., Tokyo, Japan).

## Statistical analysis

Statistical analyses were performed using the statistical software package SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Data was presented as means and standard deviations or numbers (percentages). Comparisons among three BHTs were made using Friedman’s test. Correlations between the 6MWT results and clinical variables, including BHT, were

**Table 1.** Baseline characteristics and test results.

	Participants (N = 59)
Age (years)	65.5 ± 12.0
Sex (Male/Female)	42 / 17
BMI (kg/cm <sup>2</sup> )	23.5 ± 3.9
Smoking status (Never/Ex/Current)	21/38/0
Underlying diseases	
ILDs	38
COPD	15
Other	6
Pulmonary function test	
FVC (% predicted)	80.9 ± 21.3
FEV <sub>1</sub> /FVC (%)	71.9 ± 17.3
DLco (% predicted)	64.5 ± 19.8
Arterial blood gas analysis	
PaO <sub>2</sub> (Torr)	80.8 ± 10.3
PaCO <sub>2</sub> (Torr)	39.9 ± 4.4
AaDO <sub>2</sub> (Torr)	22.7 ± 12.4
6MWT	
6MWD (m)	416.9 ± 70.8
6MWD (% predicted)	85.9 ± 18.5
Initial SpO <sub>2</sub> (%)	96.4 ± 1.8
Minimum SpO <sub>2</sub> (%)	87.8 ± 6.1
ΔSpO <sub>2</sub> (%)	8.6 ± 5.6
Initial pulse rate (bpm)	78.9 ± 13.3
Maximum pulse rate (bpm)	127.4 ± 16.8
ΔPulse rate (bpm)	48.2 ± 17.5
Modified Borg scale	2.8 ± 2.0

Data are expressed as group means ± standard deviations or the number of participants. Abbreviations: BMI, body mass index; ILDs, interstitial lung disease; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV<sub>1</sub>/FVC, forced expiratory volume in the first one second/forced vital capacity; DLco, diffusing capacity for carbon monoxide; PaO<sub>2</sub>, partial pressure of arterial oxygen; PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide; AaDO<sub>2</sub>, alveolar–arterial oxygen difference; 6MWT, 6-min walk test; 6MWD, 6-min walk distance; SpO<sub>2</sub>, percutaneous oxygen saturation.

evaluated using Spearman's rank correlation coefficients. A stepwise multivariate linear regression model was used for variables that were significant ( $p < 0.05$ ) in the Spearman's rank correlation coefficient analysis to establish the independent explanatory variables for the minimum SpO<sub>2</sub> in the 6MWT. Paired t-tests (Wilcoxon signed rank test) were used to compare exercise values (maximum pulse rate and the modified Borg scale) between the BHT and the 6MWT. Receiver operating characteristic (ROC) curves were used to determine the threshold value of the minimum SpO<sub>2</sub> during the BHT that gave the best sensitivity and specificity for predicting the hypoxemia (SpO<sub>2</sub> < 90%) induced

by 6MWT. This was defined as the point on the ROC curve located at the shortest distance from the upper left corner. A  $p$ -value <0.05 was considered statistically significant.

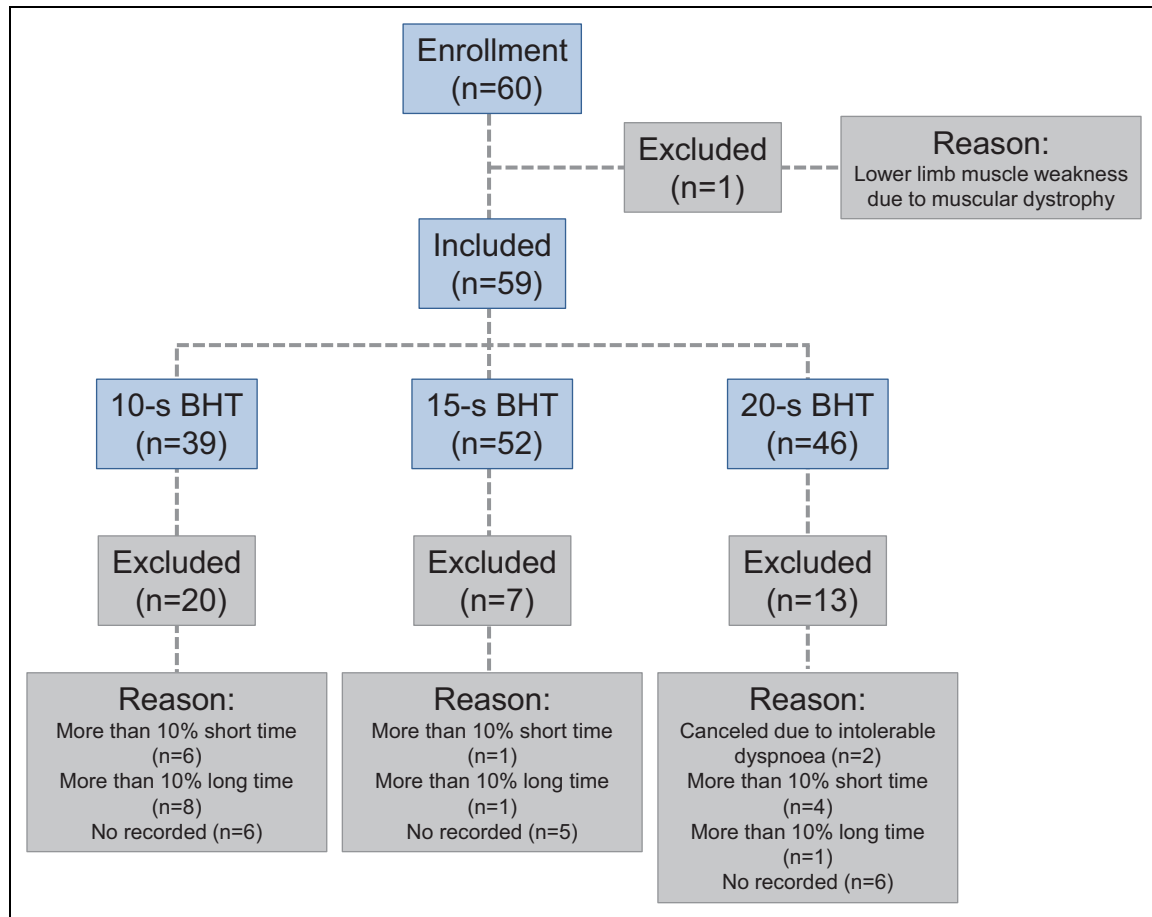
## Results

### Baseline characteristics

During the study period, 59 patients met the inclusion criteria, agreed to participate, and completed the procedure. Table 1 summarizes their demographic characteristics and underlying diseases as well as the results of the pulmonary function tests, resting arterial blood gas analyses, and the 6MWTs. The mean age was 65.5 years and mean per cent predicted values of FVC (%FVC) and DLco (%DLco) were 80.9% and 64.5%, respectively. The most common diagnosis was ILD (64.4%), followed by COPD (25.4%), and other conditions (10.2%). PaO<sub>2</sub> at rest, the mean 6-min walking distance, and the per cent predicted values were maintained, but the minimum SpO<sub>2</sub> during the 6MWT was 87.8%, which was significantly decreased compared to the initial SpO<sub>2</sub>. Approximately half (53%) of the participants showed a SpO<sub>2</sub> < 90% during the 6MWT. The mean decrease in oxygen saturation during the 6MWT was 8.6 ± 5.6%, and the mean increase in pulse rate during the tests was 48.2 ± 17.5 bpm.

### BHT

The BHT was performed at different breath-holding times following similar procedures. Because of inaccuracies in the breath-holding times assessed by the analysing software, the results of 20 participants (34%) in the 10-s BHT, 7 (12%) in the 15-s BHT, and 13 (22%) in the 20-s BHT had to be excluded from the analyses (Figure 2). Two of the 13 participants in the 20-s BHT failed to maintain the designated breath-holding time due to intolerable dyspnoea. The mean SpO<sub>2</sub> values before the 10-s, 15-s, and 20-s BHTs were 96.7%, 96.8%, and 97.0%, respectively (Table 2). Longer breath-holding times resulted in lower minimum SpO<sub>2</sub> after breath-holding, great desaturation, and higher Borg scale scores (Table 2). Although the minimum SpO<sub>2</sub> was induced at a delayed phase after the termination of breath-holding, the times from the end of breath-holding to the minimum SpO<sub>2</sub> were not different in the 10-s, 15-s, and 20-s BHTs. The changes in pulse rate (Δpulse rate) before



**Figure 2.** Selection flow diagram. BHT, breath-holding tests.

**Table 2.** Results of the BHTs for different breath-holding times.

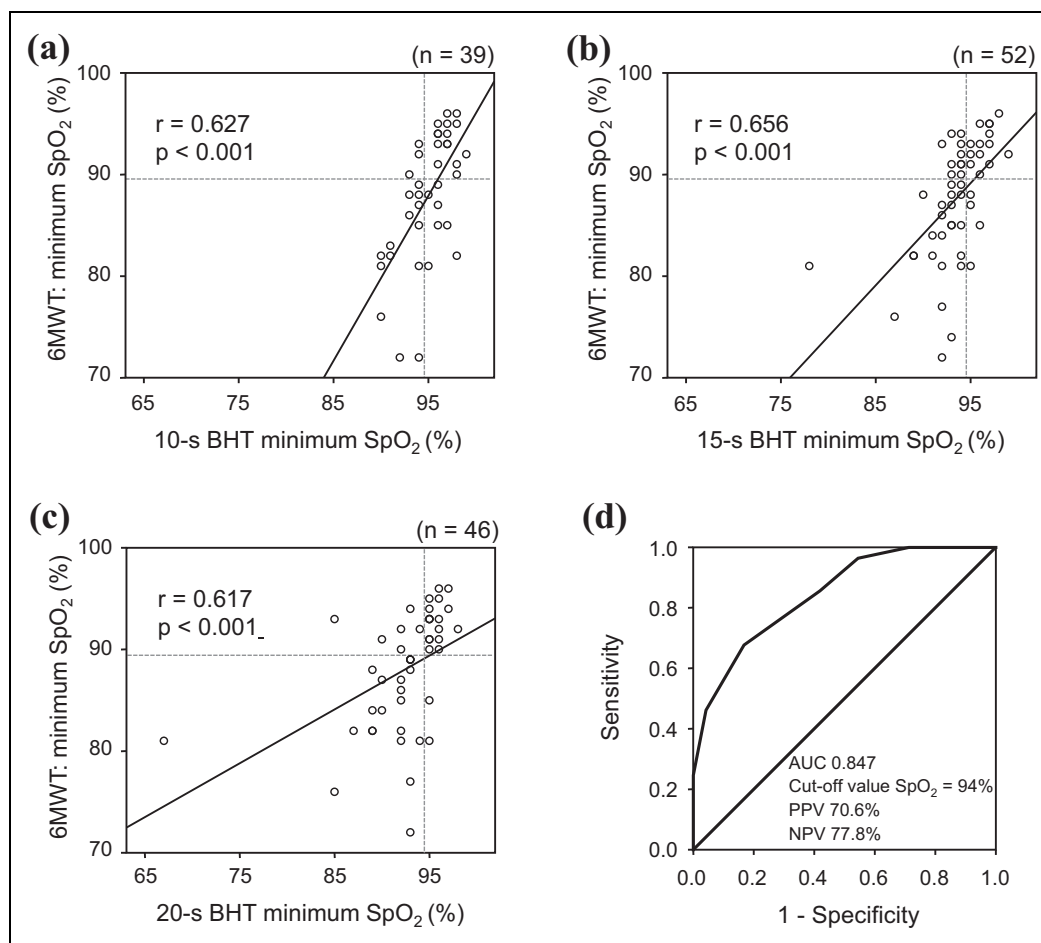
	10-s BHT	15-s BHT	20-s BHT	p-value
Number of patients studied (n)	39	52	46	
Number of patients excluded (n)	20	7	13	
SpO <sub>2</sub> before breath-holding (%)	96.7 ± 1.7	96.8 ± 1.5	97.0 ± 1.6	0.837
Minimum SpO <sub>2</sub> after breath-holding (%)	95.0 ± 2.5	93.5 ± 3.2	92.4 ± 4.9	< 0.001
ΔSpO <sub>2</sub> with breath-holding (%)	1.7 ± 1.5	3.4 ± 2.7	4.5 ± 4.2	< 0.001
Time from the beginning of breath-holding to the minimum SpO <sub>2</sub> (s)	24.6 ± 12.3	29.0 ± 10.2	32.6 ± 6.1	< 0.001
Time from the termination of breath-holding to the minimum SpO <sub>2</sub> (s)	14.6 ± 12.2	14.2 ± 10.1	13.0 ± 5.8	0.25
Pulse rate before breath-holding (bpm)	78.8 ± 15.0	76.8 ± 14.6	75.6 ± 14.9	0.819
Maximum pulse rate after breath-holding (bpm)	82.4 ± 17.0	79.9 ± 14.9	79.1 ± 17.3	0.733
ΔPulse rate with breath-holding (bpm)	3.2 ± 5.7	3.1 ± 3.5	3.5 ± 4.6	0.682
Modified Borg scale after the BHT	0.7 ± 1.2	1.4 ± 1.4	2.4 ± 2.3	< 0.001

Data are expressed as group means ± standard deviations or the number of participants. The p-values refer to comparisons among the three BHT durations. BHT, breath-holding test; SpO<sub>2</sub>, percutaneous oxygen saturation

and after breath-holding were comparable between the three BHTs.

The minimum SpO<sub>2</sub> values during both the 15-s BHT and 6MWT tended to be lower in the ILD group

than in the COPD group; however, the difference was not statistically significant (6MWT, 86.5 ± 5.4% vs. 89.7 ± 5.7%,  $p = 0.090$ ; 15-s BHT, 93.3 ± 2.4% vs. 94.6 ± 2.1%,  $p = 0.084$ ; Supplemental Figure S1).



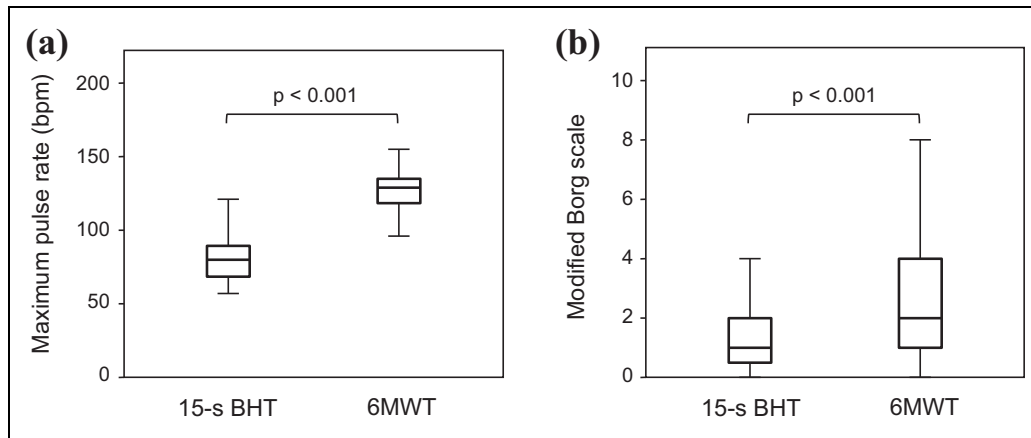
**Figure 3.** Correlations between the minimum SpO<sub>2</sub> during the BHTs, 6MWTs, and the ROC curve analysis. ((a)–(c)) For all the three different times of BHTs, the minimum SpO<sub>2</sub> significantly correlated with that in the 6MWTs ((a), 10-s BHT,  $r = 0.627$ ,  $p < 0.001$ ; (b) 15-s BHT,  $r = 0.656$ ,  $p < 0.001$ ; (c) 20-s BHT,  $r = 0.617$ ,  $p < 0.001$ ). The dashed vertical line set at SpO<sub>2</sub> 94.5% of the minimum value of 15-s BHT. The dashed horizontal line set at SpO<sub>2</sub> was 89.5% of the minimum value of 6MWT. (d) The analysis identified that a minimum SpO<sub>2</sub> of 94% in the 15-s BHTs had the highest accuracy as the cut-off value for predicting SpO<sub>2</sub> < 90% during the 6MWTs. The vertical axis shows the number of true positives (sensitivity); the horizontal axis shows the number of false positives (1-specificity). 6MWT, 6-min walking tests; AUC, area under the curve; BHT, breath-holding tests; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

### Comparison between BHT and 6MWT

The minimum values of SpO<sub>2</sub> induced by the BHTs correlated significantly with those during the 6MWT for all three breath-holding times (Figure 3(a)–(c)). ROC curves were calculated to evaluate the sensitivity and specificity of the minimum SpO<sub>2</sub> in the 15-s BHT for predicting desaturation (SpO<sub>2</sub> < 90%) during the 6MWT. The area under the curve (AUC) was 0.847 (95% confidence interval [CI], 0.746–0.949; Figure 3(d)). The best cut-off value for predicting SpO<sub>2</sub> < 90% in the 6MWT was 94% for the minimum SpO<sub>2</sub> in the 15-s BHT. With this cut-off, the

sensitivity was 85.7%, the specificity was 58.3%, and the positive and negative likelihood ratios were 2.06 and 0.25, respectively.

In our study, we selected cases in which the breath-holding time could be confirmed accurately, and as a result, many cases were excluded (Figure 2). When the excluded cases due to inaccurate breath-holding times were included, similar results were obtained in the analysis of the ROC curve for predicting desaturation (SpO<sub>2</sub> < 90%) during the 6MWT (AUC 0.859, 95% CI, 0.764–0.954; Supplemental Figure S2). The cut-off value of 15-s BHT for



**Figure 4.** Comparisons of maximum pulse rate and modified Borg scale score between the tests. The maximum pulse rate (a) and modified Borg scale score (b) during the tests were significantly lower in 15-s BHTs than in the 6MWTs. The box plot and whisker plot show the 25th and 75th percentiles (box), the median (the horizontal line within the box), and the 10th and 90th percentiles (whiskers). BHT, 15-s breath-holding test; 6MWT, 6-min walking test.

**Table 3.** Correlations between the minimum SpO<sub>2</sub> in the 15-s BHTs and 6MWTs and clinical parameters.

	15-s BHT		6MWT	
	r	p-value	r	p-value
Age (years)	−0.168	0.234	−0.193	0.143
BMI (kg/cm <sup>2</sup> )	−0.235	0.094	−0.382	0.003
Initial SpO <sub>2</sub> (%)	0.796	< 0.001	0.443	< 0.001
FVC (% predicted)	0.344	0.013	0.244	0.063
FEV <sub>1</sub> /FVC (%)	−0.139	0.324	−0.032	0.809
DLco (% predicted)	0.264	0.067	0.351	0.008
AaDO <sub>2</sub> (Torr)	−0.299	0.031	−0.260	0.049

The r and p-values were calculated by Spearman's rank correlation analysis. Abbreviations: SpO<sub>2</sub>, percutaneous oxygen saturation; BHT, breath-holding test; 6MWT, 6-min walk test; BMI, body mass index; FVC, forced vital capacity; FEV<sub>1</sub>/FVC, forced expiratory volume in one second/forced vital capacity; DLco, diffusing capacity for carbon monoxide; AaDO<sub>2</sub>, alveolar–arterial oxygen difference.

predicting desaturation during 6MWT was 94%, with a sensitivity of 85.7%, specificity of 61.5%, positive likelihood ratio of 2.23, and negative likelihood ratio of 0.23. When the desaturation during the 6MWT was set to SpO<sub>2</sub> < 88% instead of < 90%, the ROC curve analysis showed that the AUC was 0.823 (95% CI, 0.708–0.937; Supplemental Figure S3). The best cut-off value for predicting the desaturation was 93% for the minimum SpO<sub>2</sub> in the 15-s BHT (sensitivity, 72.7%; specificity, 76.7%; positive likelihood ratio, 3.12; negative likelihood ratio, 0.36).

The mean maximum pulse rate in the 15-s BHT was significantly lower than that in the 6MWT (BHT,  $79.9 \pm 14.9$  bpm vs. 6MWT,  $127.4 \pm 16.8$  bpm,  $p < 0.001$ ; Figure 4). The mean modified Borg scale score was significantly lower in the 15-s BHT than in the 6MWT (BHT,  $1.4 \pm 1.4$  vs. 6MWT,  $2.8 \pm 2.0$ ,  $p < 0.001$ ; Figure 4).

#### Relationship between the minimum SpO<sub>2</sub> in the BHT and 6MWT and clinical parameters

Table 3 shows the correlations between the minimum SpO<sub>2</sub> in the 15-s BHT and 6MWT and clinical parameters. In the 15-s BHT, significant but weak correlations were found between the minimum SpO<sub>2</sub> and %FVC ( $r = 0.344$ ,  $p = 0.013$ ) and the alveolar–arterial oxygen difference (AaDO<sub>2</sub>) ( $r = -0.299$ ,  $p = 0.031$ ). In the 6MWT, a significant correlation was found between the minimum SpO<sub>2</sub> and body mass index ( $r = -0.382$ ,  $p = 0.003$ ), %DLco ( $r = 0.351$ ,  $p = 0.008$ ), and AaDO<sub>2</sub> ( $r = -0.260$ ,  $p = 0.049$ ).

Multivariate regression analysis was used to evaluate independent variables associated with the minimum SpO<sub>2</sub> value of the 6MWT. Independent variables including the minimum SpO<sub>2</sub> value of 15-s BHT, BMI, AaDO<sub>2</sub>, and %DLco were entered into the regression model, and the minimum SpO<sub>2</sub> value of the 6MWT was taken as the dependent variable. In the stepwise regression analysis, the minimum SpO<sub>2</sub> during the 15-s BHT ( $\beta$ , 0.565,

$p < 0.001$ ) and %DLco ( $\beta$ , 0.255,  $p < 0.028$ ) were independent explanatory variables of the minimum SpO<sub>2</sub> in the 6MWT (Supplemental Table S1).

## Discussion

This pilot study showed a significant correlation between the minimum SpO<sub>2</sub> values in 15-s BHTs and in 6MWTs in patients with chronic respiratory diseases. Furthermore, our results showed that the minimum SpO<sub>2</sub> in the 15-s BHT and %DLco were independent explanatory variables of the minimum SpO<sub>2</sub> in the 6MWT. A cut-off value for the minimum SpO<sub>2</sub> in the 15-s BHT of  $\leq 94\%$  was optimal for predicting SpO<sub>2</sub>  $< 90\%$  in the 6MWT. These findings indicate that the 15-s BHT may be a candidate for a screening test that predicts hypoxemia during exercise.

The maximum pulse rate and modified Borg scale scores during the 15-s BHT were lower than those for the 6MWT, suggesting that the 15-s BHT may be easier and less uncomfortable than the 6MWT for patients with chronic respiratory diseases. Even though patients with mild to moderate pulmonary dysfunction showed nearly normal SpO<sub>2</sub> at rest, the BHT revealed the likely presence of exercise-induced hypoxemia.

The 6MWT is used to evaluate functional exercise capacity across a wide range of respiratory diseases, including ILDs and COPD.<sup>6</sup> Oxygen desaturation during a 6MWT provides information about exercise-induced desaturation in addition to the 6-min walking distance; both are strong predictors of survival in patients with COPD<sup>3</sup> and IPF.<sup>2</sup> BHT is used to evaluate the sensation of experimentally induced dyspnoea.<sup>7</sup> In patients with asthma, this manoeuvre is also used to examine their poor perception of dyspnoea, which is a major factor associated with fatal asthma.<sup>10</sup> Recently, Inoue et al. reported that apnoeic oxygen desaturation in the BHT revealed an early stage of lung function abnormalities in smokers and/or participants who were overweight, even though their spirometry results were normal.<sup>9</sup> However, the clinical significance of variables obtained from BHTs remains unclear in patients with chronic respiratory diseases, including ILDs and COPD. We therefore examined whether the minimum SpO<sub>2</sub> in BHTs provided a useful estimate of exercise-induced desaturation in 6MWT in patients with chronic respiratory diseases.

Inoue et al. studied smokers and/or participants with obesity with 20-s BHTs.<sup>9</sup> We performed 10, 15, and 20-s BHT in patients with chronic respiratory diseases. The results showed that the 15-s BHT was as useful as the 20-s BHT for predicting hypoxemia during exercise. In addition, the 15-s BHT was more feasible than the 20-s BHT in patients with chronic respiratory diseases because two participants were unable to complete the 20-s BHT. Furthermore, with validation by the dedicated software, the 15-s BHT was the best way to maintain the accuracy of the breath-holding time. However, similar results were obtained when cases with inaccurate breath-holding time of 15 s were included. Therefore, the 15-s BHT for screening oxygen desaturation in chronic respiratory diseases may be useful even if the breath-holding time fluctuates.

In this study, the participants were patients with impaired pulmonary function, mainly due to ILDs and COPD. In ILDs and COPD, one of the factors for oxygen desaturation is the destruction of lung parenchyma, which leads to damage of the distal capillary bed, resulting in a ventilation-perfusion mismatch.<sup>3–5,18,19</sup> However, other factors of the oxygen desaturation differ between the BHT and 6MWT. Hypoventilation is an important factor in BHTs, whereas the factors important in 6MWT include increased airflow limitation and dead space ventilation in patients with COPD, a reduced diffusion limitation, a shunt due to reduced PvO<sub>2</sub>, and a short capillary transit time in patients with ILDs.<sup>19,20</sup> Although the mechanisms of oxygen desaturation in these tests may be partly regulated by different factors, the minimum SpO<sub>2</sub> during BHTs in the present study showed a significant correlation with that during 6MWT. A weak correlation was observed between the minimum SpO<sub>2</sub> in the BHTs and %FVC. FVC has been shown to be a clinically useful variable associated with disease progression in ILDs, including IPF,<sup>21,22</sup> whereas correlations between baseline %FVC and other clinical variables, such as gas exchange, functional status, and dyspnoea, are generally weak.<sup>21</sup> Viecili et al. reported that the breath-holding time in COPD patients was positively correlated with FVC and FEV<sub>1</sub>,<sup>23</sup> suggesting that the BHT is also useful for detecting potential lung impairments. However, the relationships between SpO<sub>2</sub> during the BHT and physiological parameters such as the 6MWT have not been studied. In this study, we showed a significant correlation between the

minimum SpO<sub>2</sub> in the 15-s BHT and that in the 6MWT in patients with chronic respiratory diseases.

The advantages of the 15-s BHT include the following: its low demand and burden on patients and the short time required to perform the test. There were only small changes in pulse, dyspnoea score, and oxygen saturation during the test; therefore, all the participants were able to perform it. The possible clinical scenario based on the results of this study is as follows: First, it may be possible to predict desaturation on exertion in the outpatient office before performing the 6MWT. Second, the 15-s BHT may be able to predict desaturation on exertion when assuming that the 6MWT cannot be completed for some reasons (e.g., muscle weakness in the lower extremities or age-related decline in activities of daily living). However, patients with severe lung disease who require constant oxygen, that is, long-term oxygen therapy, do not need to be assessed for prescription of ambulatory oxygen, and therefore, do not need to perform BHT.

This study had some limitations. Firstly, the sample size was small and it was not a case-control study, and therefore may have been subject to various biases. Some negative or positive associations in the statistical analyses may have been due to the inadequate power afforded by the small sample size. This is a prospective pilot study to examine the utility of BHT in patients with chronic respiratory diseases. Therefore, the results obtained in the present analysis do not guarantee that BHT is useful for predicting desaturation during exercise. A large-scale definitive, adequately powered study is needed to confirm our results more conclusively. Secondly, the heterogeneity of the underlying diseases made it difficult to examine the relationships. Since the mechanisms of desaturation are different in diseases and tests, the results of this study should be interpreted with caution. Finally, only patients with mild to moderate lung impairment were included, leaving it unclear whether these results can be applied to more severe cases.

## Conclusion

The presence of exercise-induced desaturation despite stable SpO<sub>2</sub> at rest may be found in the early stages of chronic respiratory diseases. Therefore, the identification of exercise-induced desaturation is important because it enables us to assess the progress and severity of the disease at an early stage and to provide useful information for subsequent oxygen therapy. This pilot study demonstrated that the minimum SpO<sub>2</sub>

in 15-s BHTs correlated with that in 6MWT, and that the BHT is a useful test for detecting exercise-induced desaturation in patients with chronic respiratory diseases. Compared to the 6MWT, the 15-s BHT is simple and can readily be performed quickly and at any time and location, and it was well tolerated by our set of patients.

## Acknowledgements

We thank Drs Yohei Migiyama, Emi Migiyama, Takayuki Jodai, Chieko Yoshida, and Shinichiro Okamoto for their clinical assistance. We would like to thank Editage (www.editage.com) for English language editing.

## Author contributions

H Ideguchi, H Ichiyasu, H Kohrogi, and K Fujii planned the project and contributed to the analysis and interpretation of the clinical data. H Ideguchi, Fukushima, H Okabayashi, K Akaike, S Hamada, K Nakamura, and S Hirotsako were involved in data acquisition and analyses. H Ideguchi, H Ichiyasu, K Fujii, H Kohrogi and T Sakagami contributed in drafting the manuscript. H Ichiyasu, K Fujii, and T Sakagami were involved in the study supervision. All authors have read and approved the final manuscript.

## Availability of data and materials

The datasets analysed in this study are available with the corresponding author upon reasonable request.


## Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

## Funding

The authors received no financial support for the research, authorship, and/or publication of the article.

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## Supplemental material

Supplemental material for this article is available online.

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