Diaphragmatic Excursion is Correlated With the Improvement in Exercise Tolerance After Pulmonary Rehabilitation in Patients With Chronic Obstructive Pulmonary Disease

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Abstract

Background: In patients with chronic obstructive pulmonary disease (COPD), the maximum level of diaphragm excursion (DE_{max}) is correlated with dynamic lung hyperinflation and exercise tolerance. This study aims to clarify the utility of DE_{max} to predict the improvement in exercise tolerance after pulmonary rehabilitation (PR) in patients with COPD.

Methods: This was a prospective cohort study. Sixty-two patients with stable COPD participated in an outpatient PR programme from April 2018 to February 2021, and 50 completed the programme. Six-minute walk distance (6MWD) was used to evaluate exercise tolerance, and ultrasonography was used to measure DE_{max} . Responders to PR in exercise capacity were defined as patients with an increase >30 m in 6MWD. The receiver operating characteristic (ROC) curve was used to determine the cut-off point of DE_{max} to predict responses to PR.

Results: Baseline levels of forced expiratory volume in one second ($\%FEV_1$), 6MWD, maximum inspiratory pressure (PI_{max}), DE_{max} and quadriceps muscle strength (QMS) were significantly higher, and peak dyspnoea of modified Borg (mBorg) scale was lower in responders ($n = 30$) than in non-responders ($n = 20$) to PR ($p < 0.01$). In multivariate analysis, DE_{max} was significantly correlated with an increase of >30 m in 6MWD. The area under the ROC curve of DE_{max} to predict responders was 0.915, with a sensitivity of 83% and a specificity of 95% at a cut-off point of 44.9 mm of DE_{max} .

Conclusion: DE_{max} well predicted the improvement in exercise tolerance after PR in patients with COPD.

Summary Of Take-home Message

Greater diaphragmatic excursion is an excellent predictor of the improvement in exercise tolerance by pulmonary rehabilitation (PR) and may help in identifying good responders to PR.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by minimally reversible airflow limitation [1]. The main feature of COPD is the inability of patients to cope with their activities of daily life due to shortness of breath. Although the pathophysiological mechanisms involved in the development of dyspnoea and poor exercise tolerance in patients with COPD are complex, dynamic lung hyperinflation (DLH) plays a central role [2] by increasing ventilatory workload and decreasing the pressure-generating capacity of the inspiratory muscles.

Pulmonary rehabilitation (PR) is a non-pharmacological intervention and has been reported to improve dyspnoea, exercise capacity and quality of life in patients with COPD [3]. Owing to a body of evidence, PR is now established as the standard of care in patients with COPD [4]. However, not all patients with COPD

benefit from PR to the same extent. Therefore, identifying patients who are likely to achieve maximum benefit from the PR programme is crucial. So far, several studies have shown that severe airflow limitation or poor exercise tolerance at baseline may predict a better response to PR [5, 6], but inconsistent findings are reported by others [7]. Furthermore, one study reported that patients with severe dyspnoea did not respond to PR and patients with milder dyspnoea responded well [8].

Considering the role of DLH in the development of dyspnoea and poor exercise tolerance in patients with COPD, objective measures that reflect DLH may help in identifying good responders to PR. Previously, we reported that there was an association between increased dyspnoea due to DLH on exercise and decreased exercise capacity in patients with COPD and reduced mobility of the diaphragm, which was assessed by the maximum level of diaphragm excursion (DE_{max}) using ultrasonography [9]. Other research groups reported the utility of ultrasonographical assessment of diaphragmatic mobility in COPD on its association with 6-min walk distance (6MWD), dyspnoea [10] and increased mortality [11].

However, there have been no reports on the association between diaphragmatic mobility and the effect of PR to improve exercise tolerance. The primary aim of this study is to clarify the role of DE_{max} to predict the improvement in exercise tolerance after PR in patients with COPD.

Materials And Methods

Study Design and Subjects

This was a single-centre, observational, prospective cohort study. The study included 62 patients with clinically stable COPD who visited the Department of Respiratory Medicine and Allergology, Kindai University Hospital, between April 2018 and February 2021. The exclusion criteria included unstable medical conditions that could cause or contribute to breathlessness, such as metabolic, cardiovascular or other respiratory diseases, or any other disorders that could interfere with exercise testing, such as neuromuscular diseases or musculoskeletal problems. This study was approved by the Ethics Committee of Kindai University School of Medicine. Written informed consent was obtained from all participants.

Measurements

Ultrasonography (Xario 200, Toshiba, Tokyo, Japan) was performed to all participants to measure their DE_{max} . Using the liver as an acoustic window (Figure 1A), a convex 3.5 MHz probe was used to measure the excursions of the right hemidiaphragm according to the techniques in previous research [9, 12, 13]. The M-mode cursor was rotated and placed on the axis of diaphragmatic displacement on the stored image, and displacement measurements were conducted. Measurements were performed during each of three deep breaths, and DE_{max} was measured (Figure 1B). The maximum value in the three deep breaths was used. 6MWD was used to evaluate walking capacity according to the ATS/ERS statement [14-16]. All participants performed the 6MWD test before and after the PR programme, and the magnitude of their perceived breathlessness and their leg fatigue was rated using a 1–10-point Borg scale. Responders to

PR in exercise capacity were defined as those having more than 30 m increase in 6MWD after the PR programme, which was the definition of minimal clinically important difference (MCID) for 6MWD [17].

Spirometry (CHESTAC-800, Chest, Tokyo, Japan) was performed following the 2005 ATS/ERS recommendations [18] for measuring forced vital capacity (FVC), forced expiratory volume in one second (FEV₁) and inspiratory capacity. Respiratory muscle strength was assessed by measuring the maximum inspiratory pressure (PI_{max}) generated against an occluded airway at residual volume [19] (SP-370, Fukuda Denshi, Tokyo, Japan). A hand-held dynamometer (μTasF-1, Anima Corp., Tokyo) was used to measure quadriceps muscle strength (QMS). The impact of COPD on health status was assessed with the COPD assessment test (CAT), a patient-completed questionnaire on eight items, namely, cough, phlegm, chest tightness, breathlessness, limited activities, confidence leaving home, sleeplessness and energy. The item scores range from 0 to 5 points, resulting in a CAT total score ranging from 0 to 40 points [20], and MCID of CAT is 2 points [21]. In all patients with COPD, emphysema was evaluated by computed tomography of the chest. A SYNAPSE VINCENT volume analyser (FUJIFILM Medical, Tokyo, Japan) was used to measure the low attenuation area (%LAA).

Rehabilitation Programme

The outpatient PR programme was conducted twice a week for 12 weeks (24 sessions), including aerobic exercise training (ergometer and walking exercise) at 60%–70% of peak workload for 20–40 min and upper- and lower-limb muscle strength training for 10–20 min.

Sample Size

The sample size was estimated using R software. The analysis based on 6MWD data from the PR programme revealed that 40 subjects were required if the expected area under the curve (AUC) below the receiver operating characteristic (ROC) curve was 0.80, the power was 90%, and the significance level was 0.01. Furthermore, we anticipated a dropout from the PR programme. Thus, we set the sample size to 50 participants.

Statistical Analysis

Responders and non-responders were compared using *t*-test, the Wilcoxon rank-sum test or χ^2 test, as appropriate. The paired *t*-test or the Wilcoxon signed-rank test was used to evaluate the changes of the parameters before and after the PR programme. The Pearson correlation coefficient was used to analyse the relationships between changes in 6MWD and independent variables as changes in 6MWD were normally distributed. Additionally, multivariate logistic regression models were used to assess the ability of variables to predict a response to PR. The ROC curve method was used to assess the ability of DE_{max} to predict a response to PR. All statistical analyses were performed using the JMP software programme (JMP®, Version 14; SAS Institute Inc., Cary, NC, USA).

Result

Out of the 62 patients included in the study, 50 completed the PR programme (Figure 2). Two patients dropped out because of severe exacerbation of COPD, and 10 patients discontinued the PR because of the coronavirus pandemic. Table 1 presents the baseline characteristics of the participants. After the PR programme, CAT score, 6MWD, peak dyspnoea and leg fatigue of modified Borg (mBorg) scale, and QMS improved significantly (Table 2). Thirty patients had an increase of >30 m in 6MWD after PR (responders: 60%), and 20 patients (40%) were defined as non-responders. Baseline levels of %FEV₁, 6MWD, PI_{max}, DE_{max} and QMS were significantly higher and CAT score and peak dyspnoea of mBorg scale were significantly lower in responders than in non-responders (Table 1). Changes in 6MWD were significantly correlated with baseline levels of CAT, %FEV₁, peak dyspnoea of mBorg scale, PI_{max}, DE_{max} (Figure 3) and QMS and marginally with baseline 6MWD (Table 3).

In multivariate analysis, DE_{max} alone significantly contributed to the prediction of responders (Table 4, Model 1). When using PI_{max} instead of DE_{max} as PI_{max} and DE_{max} showed a strong association ($r = 0.73$), both PI_{max} and %FEV₁ contributed to the prediction (Table 4, Model 2). The area under the ROC curve of DE_{max} to predict the responders was 0.915, with a sensitivity of 83% and a specificity of 95% at a cut-off point of 44.9 mm of DE_{max} (Figure 4). The significance of DE_{max} in the predictability of responders remained even when the analysis was confined to severe patients (%FEV₁ < 50%, $n = 23$; AUC = 0.88, sensitivity = 70% and specificity = 100% at a cut-off point of 44.9 mm).

Discussion

This is the first study to show the utility of DE_{max} to predict the responsiveness to 12-week PR in patients with COPD. In this study, multivariate analysis revealed that greater baseline DE_{max} was the only factor that predicted the responsiveness to PR, independent of baseline %FEV₁. Additionally, the model using DE_{max} had better prediction performance than the model using PI_{max}. The AUC of DE_{max} to predict the 30 m or more improvement in 6MWD after the PR was 0.915, with a sensitivity of 83% and a specificity of 95% at 44.9 mm.

PR is beneficial for patients with chronic respiratory disease, including COPD [3], and improves exercise performance, health-related quality of life and dyspnoea generally [22], which was confirmed in this study. Ideally, PR was proved to be effective in all patients, but the response to PR varies considerably between individual patients [8, 23–25]. Indeed, in this study, the improvement in 6MWD was less than MCID in 40% of the patients irrespective of the degree of severity of COPD. Therefore, identifying predictors of a response is crucial in ensuring better PR efficacy and personalisation of PR programmes for patients with COPD.

In this study, the baseline values of %FEV₁, PI_{max}, DE_{max}, QMS and 6MWD were positively associated with Δ6MWD in univariate analysis, suggesting that a better baseline condition was related to a higher proportion of patients who gained the MCID after PR. These findings are consistent with those of previous studies that showed that patients with higher %FEV₁ or FEV₁/VC achieved greater improvement in 6MWD after PR [7, 26, 27] and a study in which patients with milder mMRC scores could achieve MCID of 6MWD after PR, but not for those with worst mMRC score [8], although others studies showed opposite results [5, 6, 28–30] or found no significant baseline characteristics to predict a response to PR [31]. The discrepancy between the findings cannot be fully explained, but it might be due to the differences in the studied population and strength or length of PR. In this study, the mean %FEV₁ of the participants was 56.0%, which was relatively higher than that of other studies (mean %FEV₁ of 40–50% in most studies), despite similar inclusion criteria throughout the studies, that is, not limited to severe COPD in most studies. It can be said that no ceiling effect with a PR programme that included high-intensity load exercise training for 20–40 min was observed in our population.

In this study, an important finding is that greater DE_{max} at baseline was the only factor that predicted the responders in 6MWD after PR. Additionally, the model using DE_{max} had better prediction performance than the model using PI_{max}. The high predictability of DE_{max} may be due to its strong association with DLH and dyspnoea during exercise, as reported previously [9]. DLH is involved in the development of dyspnoea, and both are important factors to determine the improvement in 6MWD in patients with COPD. Therefore, DE_{max} that reflects the degree of DLH and dyspnoea during exercise was superior to other physiological indices to predict responders.

Furthermore, the virtuous cycle observed in our PR programme that included high-intensity load exercise training might be due to the improvement in ventilation pattern. It would be easier to improve the ventilation pattern with greater DE_{max}, as shown in studies of mechanically ventilated patients [32], which may have reduced dyspnoea during exercise after 12 weeks of PR and improved exercise tolerance. Exercise therapy is a central component of PR, which significantly reduces blood lactate levels during exercise, reduces minute ventilation and improves exercise tolerance [33]. The high-intensity load exercise training, which is performed at 60–80% of the maximum oxygen uptake, has a higher physiological effect than low exercise load. Patients with greater DE_{max} may be able to perform higher load training, which resulted in effective PR.

Diaphragm ultrasonography has been widely and successfully used to identify diaphragmatic dysfunction by showing its association with 6MWD, dyspnoea [10], extubation failure in mechanically ventilated patients [32] and increased mortality [11]. Recently, Lewinska and Shahnazzaryan proposed its use in pulmonary physiotherapy of patients with COPD [34]. In most of the previous studies, diaphragm ultrasonography was used to assess DE_{max}, that is, the measurement of the excursion of the right hemidiaphragm, as used in this study, and diaphragm thickness that assessed the length and thickness of the zone of apposition of the diaphragm against the rib cage [35, 36]. However, diaphragm thickness is difficult to be measured in patients with severe COPD because the length of the zone of apposition is

shorter in patients with COPD than in control subjects [37], whereas DE_{max} is easy to be measured and shows high intra- and inter-observer reliability [38]. In clinical settings, this objective measure of DE_{max} has additional advantages as it requires minimum effort in patients and can be applied to the PR programme at home if portable ultrasonography can be used.

There are some limitations to this study. This was a single-centre study on a relatively small number of participants, and their baseline condition might be relatively preserved. Nonetheless, 46% of the participants showed $FEV_1 < 50\%$, and the utility of DE_{max} was also observed in these patients with severe airflow limitation. Furthermore, in this study, few patients discontinued the PR programme, except for patients who discontinued during the coronavirus pandemic, which indicates that there was no severe mismatch between the PR programme and patients' ability to successfully complete the PR programme. Further studies with a large number of patients are required, and the utility of DE_{max} should be examined in patients with severest COPD with a low-intensity load exercise programme.

In conclusion, DE_{max} , which is a reliable and easy to perform measure, well predicted the improvement in exercise tolerance after PR in patients with COPD. Assessment of DE_{max} may help in making medical decisions related to therapeutic strategies.

Abbreviations

COPD: Chronic obstructive pulmonary disease, DLH: dynamic lung hyperinflation, PR: Pulmonary rehabilitation, 6MWD: 6-min walk distance, MCID: minimal clinically important difference, FVC: forced vital capacity, FEV_1 : forced expiratory volume in one second, PI_{max} : maximum inspiratory pressure, QMS: quadriceps muscle strength, CAT: COPD assessment test, %LAA: low attenuation area, AUC: area under the curve, ROC: receiver operating characteristic, mBorg: modified Borg

Declarations

Support statement

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Authors' contributions

M.S. Y.H. and Y.C. made substantial contributions to the conception and design of the work. M.S., Y.H., R.S. made substantial contributions to the data acquisition. M.S. and H.M. made substantial contributions to the analysis. All of the listed authors designed the study and were involved in the

interpretation of the data. M.S. and H.M. drafted the work. Y.H., M.S., T.K., Y.C., O.N., K.S., K.F., Y.T., H.M. revised the report critically for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Representative image of the right diaphragm. The probe was positioned below the right costal margin between the midclavicular and anterior axillary lines. (A) Two-dimensional ultrasonographic image of the right hemidiaphragm (B-mode). Diaphragmatic movements were recorded in M-mode during deep breathing (DEmax) (B).

Figure 2

Figure 2

Study flow diagram. COPD: chronic obstructive pulmonary disease; PR: pulmonary rehabilitation; 6MWD: 6-min walk distance.

Figure 3

Figure 3

Relationship between DEmax and the changes in 6MWD after pulmonary rehabilitation. Changes in 6MWD were significantly positively correlated with DEmax ($r = 0.72$; $p < 0.001$). DEmax: maximum diaphragmatic excursion; 6MWD: 6-min walk distance.

Figure 4

Figure 4

Receiver operating characteristic (ROC) curve for baseline DEmax in relation to the response to pulmonary rehabilitation. ROC curve estimates the ability of DEmax to predict a clinically important improvement in 6MWD (>30 m) after pulmonary rehabilitation (AUC = 0.915, sensitivity = 83% and specificity = 95% at a cut-off point of 44.9 mm of DEmax). AUC: area under the curve; 6MWD: 6-min walk distance; DEmax: maximum diaphragmatic excursion.

Supplementary Files

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