Early View

Original article

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Diaphragmatic excursion correlates with exercise capacity and dynamic hyperinflation in COPD patients

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Summary of take-home message (183 characters including spaces)

Reduced diaphragmatic excursion as measured on ultrasound images might predict decreased exercise capacity and increased dyspnoea due to dynamic lung hyperinflation in COPD patients.

Abstract (284)

Background: Although the pathophysiological mechanisms involved in the development of dyspnoea and poor exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) are complex, dynamic lung hyperinflation (DLH) plays a central role. Diaphragmatic excursions can be measured by ultrasonography (US) with high intra- and interobserver reliability. The objective of this study was to evaluate the effect of diaphragmatic excursions as assessed by US on exercise tolerance and DLH in patients with COPD.

Methods: Patients with COPD (n = 20) and age-matched control subjects (n = 20) underwent US, which was used to determine the maximum level of diaphragmatic excursion (DEmax). Ventilation parameters, including the change in inspiratory capacity (ΔIC), were measured in the subjects during cardiopulmonary exercise testing (CPET). We examined the correlations between DEmax and the ventilation parameters.

Results: The DEmax of patients with COPD was significantly lower than that of the controls (45.0 ± 12.8 mm vs. 64.6 ± 6.3 mm, respectively; $p < 0.01$). The perception of peak dyspnoea (Borg scale) was significantly negatively correlated with DEmax in patients with COPD. During CPET, oxygen uptake/weight ($\dot{V}O_2/W$) and minute ventilation ($\dot{V}E$) were significantly positively correlated with DEmax, while $\dot{V}E/\dot{V}O_2$ and $\dot{V}E$/carbon dioxide output ($\dot{V}CO_2$) were significantly negatively correlated with DEmax in patients with COPD. DEmax was also significantly positively correlated with ΔIC, reflecting DLH, and with $\dot{V}O_2/W$, reflecting exercise capacity.

Conclusion: Reduced mobility of the diaphragm was related to decreased exercise capacity and increased dyspnoea due to dynamic lung hyperinflation in COPD patients.

Keywords: dynamic hyperinflation, diaphragmatic excursion, COPD, cardiopulmonary exercise test

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by minimally reversible airflow limitation. The main feature of COPD is the inability of patients to cope with their activities of daily life because of 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[1]. DLH has a static component, which is due to the destruction of pulmonary parenchyma and loss of elastic recoil by the lung; and a dynamic component, which occurs when patients with COPD breathe in before achieving a complete exhalation. Airflow limitation and DLH are the main causative factors of the dyspnoea occurring in COPD patients. DLH is tightly linked to dyspnoea and exercise tolerance. In the DLH of COPD, the residual volume increases because of airflow limitation related to exertion. DLH is expressed as decreased inspiratory capacity (IC) and increased functional residual capacity (FRC) due to a continually increasing end-expiratory lung volume[2][3]. The major consequence of DLH is an increased ventilatory workload and decreased pressure-generating capacity by the inspiratory muscles, despite compensatory mechanisms[4].

The diaphragm is the main muscle employed for respiration. Patients with emphysema or COPD manifest major changes in the mass, thickness, and area of the diaphragm. Diaphragmatic contractions produce muscle shortening and thickening. Ultrasonography has been recently proposed for use in assessing both diaphragmatic excursions [5],[6]7] and diaphragmatic thickness at different lung volumes[8].The association between thickening of the diaphragm and diaphragmatic effort, however, is tenuous; ultrasonography measurements of diaphragmatic thickness explain only one third (or less) of the variability in inspiratory efforts[9,10]. On the other hand, ultrasonographic assessment of excursions of the right diaphragm shows high intra- and interobserver reliability[11]. Reduced movements of the diaphragm are a major risk factor for increased mortality in patients with COPD [12]. However, the relationship between diaphragmatic mobility and DLH remains unclear in patients with COPD. The primary purpose of this study was to evaluate the difference between the diaphragmatic excursions of patients with COPD versus control participants. The secondary purpose was to evaluate the effects of decreased diaphragmatic excursion on exercise tolerance and DLH in COPD patients.

Materials and Methods

Study Design and Participants

This was a single-centre, observational, case control, cross-sectional study. It was approved by the Committee for Ethics at Kindai University School of Medicine (No 31-086), and all participants provided written informed consent. The participants were 20 patients with clinically stable COPD who visited the Department of Respiratory Medicine and Allergology at Kindai University Hospital between April 2019 and August 2019. The exclusion criteria included unstable medical conditions that could cause or contribute to breathlessness (i.e., metabolic, cardiovascular, or other respiratory diseases) or any other disorders that could interfere with exercise testing, such as neuromuscular diseases or musculoskeletal problems. We also recruited 20 age-matched volunteers who did not have any detectable chronic condition, including pulmonary or cardiovascular disease. Based on preliminary studies in healthy participants (n =6) and COPD patients (n = 5), the average extent of diaphragmatic excursion in the healthy participants and COPD patients was 72.0 mm (S.D. = 10.1) and 50.9 mm (S.D. = 9.4) respectively. We assumed the difference between the population means of the 2 groups as 10 mm with a standard deviation of 10.0 mm With these values, the required number of cases would be 34 (17 participants in each group) based on the Student t-test, which was used to assess the difference between the maximum diaphragmatic excursions (DEmax's) of the 2 groups, with a significance level of 5% (both sides) and a study power of 80%. With an accounting of participants leaving the study, the target number of participants was set at 40 (20 in each group).

Measurements

All participants underwent ultrasonography (Xario 200; Toshiba, Tokyo, Japan) for measurement of their DE_{max}. Excursions of the right hemidiaphragm were measured by a convex 3.5-MHz probe according to the techniques of Testa et al[7]. The liver on the left was used as an acoustic window (Figure 1). 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 3 deep breaths, and the DE_{max} was measured (Figure 1C).

All participants underwent symptom-limited cardiopulmonary exercise testing (CPET) on a bicycle ergometer according to the Ramp 10 W protocol (load increase of 10 watts per 1 min -1 watt per 6s). The 10-point Borg scale was used to assess the intensity of dyspnoea, and leg fatigue was determined at 1-minute intervals during both the exercise and resting period [13]. The analysis included the following: intensity of exercise (work load [watts, (W)]), peak oxygen consumption (peak $\dot{V}O_2$/W), ventilation equivalents for oxygen ($\dot{V}E/\dot{V}O_2$) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$). IC manoeuvres were performed at rest, and at 1-minute intervals and peak exercise. We measured the change in inspiratory capacity (ΔIC: IC $_{Lowest}$ - IC $_{Baseline}$) during exercise as a surrogate marker of DLH [14] [15].

Spirometry (CHESTAC-800; Chest, Tokyo, Japan) was performed according to the 2019 American Thoracic Society recommendations [16] for measuring forced vital capacity (FVC), forced expiratory

volume in one second (FEV_1), and IC. Respiratory muscle strength was assessed by measuring the maximum inspiratory pressure (MIP) generated against an occluded airway at residual volume[17] (SP-370; Fukuda Denshi , Tokyo, Japan). Quadriceps muscle strength (QMS) was measured by a hand-held dynamometer (HHD: µTasF-1, Anima Corp, Tokyo).

Statistical Analysis

All results are expressed as means ± SD. The Student t-test was used to compare data from the COPD patients with data from the healthy controls. Inter-rater reliability (reproducibility) of the mean values of 3 DE_{max} measurements for each patient was assessed by estimating intraclass correlation coefficients (ICCs). Two ICC forms were estimated: ICC (1,1) and ICC (1, k), representing values calculated from a single measurement and from an average of k repeated measures, respectively. In this study, k=3. The relationship between DE_{max} and the parameters of lung function ($\dot{V}O_2/W$, VE/ $\dot{V}O_2$, VE/ $\dot{V}CO_2$, ΔIC, and MIP) and muscle strength of the lower extremities was evaluated by calculating Pearson correlation coefficients. $P < 0.05$ was deemed to be significant. We performed a least squares regression analysis to compute the final predictive model for $\dot{V}O_2/W$. Statistical analysis was performed by IBM SPSS statistics software, version 22 (IBM SPSS, Armonk, NY, USA).

Results

Table 1 summarizes the clinical characteristics of patients with COPD and the control participants. The FEV_1 of COPD patients was significantly lower than the FEV_1 of the controls ($p < 0.01$), whereas the difference between the FVC values of the 2 groups was not significant. The intensity of peak dyspnoea (Borg scale) in COPD patients was significantly larger than that in the controls ($p < 0.01$). The peak $\dot{V}O_2/W$ value was significantly lower in COPD patients than in the controls ($p < 0.01$). The $VE/\dot{V}O_2$ was significantly higher in COPD patients than in the controls ($p < 001$). The decrease in IC during CPET was significantly greater in COPD patients than in the controls ($p < 0.01$). The MIP was significantly lower in COPD patients than in the controls ($p < 0.01$). The intra-rater reliability of DE_{max} measurements by ultrasonography was as follows: ICC (1,1) = 0.89, ICC (1, k) = 0.91, indicating good reproducibility (Tables 1S and 2S). The DE_{max} of COPD patients was significantly lower than that of the controls (45.0±12.8 mm vs. 64.6±6.3 mm, respectively; $p < 0.01$) (Figure 2). Peak dyspnoea perception (Borg scale) was negatively correlated with the DE_{max} of patients with COPD (Table 2, $p < 001$). Peak mBorg scale dyspnoea was negatively correlated with ΔIC ($r = -0.61$, $p < 0.05$). Regarding lung function parameters, VC, IC, FVC, and FEV_1 were significantly positively correlated with the DE_{max} of patients with COPD. DE_{max} was positively correlated with MIP ($p < 001$). ΔIC, which reflects DLH, was significantly positively correlated with DEmax in COPD patients but not in control participants (Figures 3 and table 2). IC decreased during exercise, and ΔIC was negative in all of the COPD patients, while IC increased during exercise and ΔIC was non-negative in some of control participants. Regarding ventilation parameters during CPET, $\dot{V}O_2/W$ and VE were significantly positively correlated with DEmax, while $VE/\dot{V}O_2$ and $VE/\dot{V}CO_2$ were significantly negatively correlated with DEmax in both the control participants and COPD patients (table 2 and figure 4).

Multiple regression analysis was performed for $\dot{V}O_2/W$ as the dependent variable and DEmax and %FEV$_1$ as the independent variables. Both DEmax and %FEV1 were significantly correlated with $\dot{V}O_2/W$. DEmax was found to be the most independent explanatory variable （R^2＝0.79, F＝29.4, 95% CI（95% confidence interval） ＝0.18 to 0.37, p<0.0001, Table 3S).

Discussion

The DE_{max} of COPD patients was significantly lower than that of control participants. DE_{max} was associated with exercise tolerance in both the healthy participants and COPD patients. Ultrasonographic assessment of diaphragmatic function has been widely and successfully used to detect the presence of diaphragmatic dysfunction as a postsurgical complication [18], to identify ventilator-induced diaphragmatic injury[19], to evaluate movement of the diaphragmatic dome [20] during spontaneous breathing in weaning trials[21], to quantify the work of breathing[9], to titrate ventilatory support[9]10,21], and to predict the success of extubation[23]. Ultrasonography has been studied in COPD patients and has shown that diaphragmatic mobility can affect COPD patients' dyspnoea and the 6-minute walk distance[24]. Ultrasonography has also been used to identify diaphragmatic dysfunction[25]. However, to date, the relationships between diaphragmatic mobility and DLH and exercise tolerance in patients with COPD remain unknown. This study shows that decreased diaphragmatic mobility is associated with decreased physical and ventilatory capacity, as well as increased dyspnoea during exercise in COPD patients. The reduction in diaphragmatic mobility in COPD patients is similar to the reduction in mobility reported in previous studies[25,26]

Ultrasonography has also been used to assess the length and thickness of the zone of apposition of the diaphragm against the rib cage[17]. Diaphragmatic thickness (Tdi) is measured by placing a high-frequency linear probe at the level of the zone of apposition, while diaphragmatic excursion is measured by placing a curvilinear probe in the subcostal region and recording diaphragmatic movements in the M-mode. In healthy participants at rest, the intra- and interobserver reliability of Tdi measurements are high [27-30], and ultrasonography estimates of Tdi are correlated with direct anatomical measurements [30]. The temporal evolution of Tdi in patients was related to the change in VC in the patients with recovery of diaphragmatic function, and Tdi can also be used to monitor the evolution of diaphragmatic weakness[31]. However, ultrasonographic measurements of diaphragmatic thickening explain only one third (or less) of the variability in inspiratory effort[9]10,21]. Furthermore, the evaluation of Tdi is difficult to perform in patients with severe COPD, because the length of the zone of apposition is shorter in COPD patients than in control patients[32]. On the other hand, ultrasonographic measurements of excursions of the right hemidiaphragm have shown high intra- and interobserver reliability[33]. Diaphragmatic excursions are sensitive to changes in respiratory patterns [34], are related to the volume-generating capacity of the diaphragm (measured by VC) following abdominal surgery[35], and have been used to identify diaphragmatic weakness in the setting of the acute exacerbation of COPD[36].

In this study, IC decreased during CPET, and DE_{max} was correlated with the change in the IC of COPD patients. DLH occurs when respiration is accelerated by exercise or exertion, and IC decreases in COPD patients. Normally, tidal volume (TV) increases during exercise, increasing the necessary

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$\dot{V}O_2$; but in COPD, TV does not increase because of the decreased IC, and respirations become shallow and rapid[37].Hyperinflation of the lungs with consequent reduction in IC has been convincingly linked to the degree of breathlessness (dyspnoea) experienced by patients with COPD during physical activity. Moreover, the therapeutic reversal of lung hyperinflation with improvement in IC has been shown to be associated with improvements in the intensity of dyspnoea and exercise endurance[38]. Ultrasonographic assessment of the diaphragm can help identify the subpopulation of COPD patients with dysfunctional diaphragms and the consequent changes in ventilatory mechanics.

There are limitations to this study. This study was conducted at a single centre on a relatively small number of participants. Therefore this study might have been underpowered for some of the statistical analyses. However, the number of participants was sufficient for the primary outcome, which was a comparison between the mean DEmax values of the COPD patients and control participants. We also did not measure the residual volume (RV) and functional residual capacity (FRC) of the control participants; therefore we could not compare between these parameters in the 2 study groups.

In conclusion, the diaphragmatic mobility of COPD patients was reduced compared with the control participants. Diaphragmatic mobility was correlated with exercise tolerance in both the COPD patients and control participants. Reduced mobility of the diaphragm was related to decreased exercise capacity and increased dyspnoea due to dynamic lung hyperinflation in COPD patients.The assessment of diaphragmatic mobility in patients with COPD could further the understanding of their limitations in daily activities as well as inform those medical decisions related to therapeutic strategies.

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Table 1. Characteristics of study participants

	COPD (n=20)	Control (n=20)	p value
Male:female	17/3	17/3	
Age, yr	76.8 ± 3.6	76.4 ±5.1	0.80
Body mass index, kg/m^2	22.9 ± 3.3	23.9 ± 2.3	0.65
QMS (Kgf/Kg)	0.57 ± 0.14	0.64 ± 0.12	0.36
GOLD （I / II / III)	2 / 10 / 8	ND	
mMRC （0 / 1/ 2/ 3/ 4)	0 /13 /6 /1 /0	ND	
Pulmonary function			
FEV$_1$,L	1.58 ± 0.45	2.44 ± 0.39	<0.01
%predicted	53.9 ± 19.4	103.1 ± 14.2	<0.01
FVC, L	3.12 ± 0.89	3.24 ± 0.51	0.89
%predicted	93.4 ± 26.9	105.1 ± 13.4	0.25
MIP, cm H$_2$O	59.4 ± 19.4	84.6 ± 21.9	<0.01
%predicted	81.1 ± 31.1	119.2 ± 28.4	<0.01
Peak exercise measurements			
peak load (watt)	67 ± 20	115 ± 22	<0.01
$\dot{V}$E, L/min	42.5 ± 12.1	52.4 ± 11.7	<0.05
peak $\dot{V}$O$_2$/W(ml/min/kg)	12.4 ± 2.9	20.2 ± 1.7	<0.01
$\dot{V}$E/$\dot{V}$O$_2$ (ml/ml)	46.9 ± 8.5	29.3 ± 2.7	<0.01
ΔIC from rest, L	-0.40 ± 0.24	0.05 ± 0.25	<0.01
mBorg scale dyspnoea	5 ± 1	2 ± 2	<0.01
mBorg scale leg fatigue	5 ± 1	4 ± 2	0.15

Definitions of abbreviations: COPD =chronic obstructive pulmonary disease, QMS=quadriceps muscle strengths, mMRC=modified medical research council dyspnoea scale, FEV$_1$=forced expiratory

volume in one second, FVC=forced tidal capacity, MIP=maximum inspiratory pressure, ND= not done in the control group, $\dot{V}O_2$=oxygen uptake, $\dot{V}O_2$/W= oxygen uptake/weight, $\dot{V}E$=minute ventilation, IC=inspiratory capacity, MIP= maximum inspiratory pressure, mBorg =modified Borg Scale , DE_{max}=maximum diaphragmatic excursion. Values are means ±SD.

Table 2. Correlations between maximum diaphragmatic excursion values with ventilatory parameters, dyspnoea, and leg muscle fatigue in patients with COPD (n=20) and control participants (n=20)

Independent Variable	COPD (n=20)		Control (n=20)	
	Pearson Correlation Coefficient (r)	**p** value	Pearson Correlation Coefficient (r)	**p** value
Age	0.19	0.43	0.19	0.43
BMI	0.03	0.91	-0.14	0.53
QMS	0.39	0.09	0.15	0.11
Resting measurements				
IC	0.6	＜0.01	0.2	0.38
FVC	0.4	＜0.05	-0.06	0.79
%predicted	0.32	0.16	-0.35	1.29
FEV$_1$	0.52	＜0.05	-0.09	0.71
%predicted	0.37	0.12	-0.33	0.19
MIP	0.65	＜0.01	0.24	0.29
%predicted	0.68	＜0.01	0.09	0.29
Peak exercise measurements				
VO$_2$/W	0.82	＜0.01	0.61	＜0.01
VE	0.6	＜0.01	0.52	＜0.05
VE/VO$_2$	-0.76	＜0.01	-0.68	＜0.01
VE/VCO$_2$	-0.81	＜0.01	-0.74	＜0.01
ΔIC	0.77	＜0.01	0.16	0.49
mBorg scale dyspnoea	-0.75	＜0.01	-0.15	0.5
mBorg scale leg fatigue	0.22	0.15	0.28	0.18

Definitions of abbreviations: COPD =chronic obstructive pulmonary disease, BMI=body mass index, QMS=quadriceps muscle strength, VC=vital capacity, IC=inspiratory capacity, FVC=forced vital capacity, FEV$_1$=forced expiratory volume in one second, MIP=maximum inspiratory pressure, $\dot{V}O_2$=oxygen uptake, $\dot{V}O_2$/W=oxygen uptake/weight, $\dot{V}E$=minute ventilation, VCO$_2$= carbon dioxide output, IC=inspiratory capacity

Figure legends

Figure 1. Representative image of 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 quiet breathing (B), and during deep breathing (DE_{max}) (C).

Figure 2. Maximum diaphragmatic exertion during deep breathing (DE_{max}) in COPD patients (n=20) and control participants (n=20). *$p < 0.01$. DE_{max} in COPD patients was significantly smaller than that in control participants.

Figure 3. Correlation between maximum diaphragmatic excursion (DE_{max}) and peak ΔIC in patients with COPD (n = 20) (A) and healthy participants (n = 20) (B). IC=inspiratory capacity. ΔIC, which reflects DLH, was significantly positively correlated with DEmax in patients with COPD, while ΔIC was not correlated with DEmax in control participants.

Figure 4. Correlation between maximum diaphragmatic excursion (DE_{max}) and peak $\dot{V}O_2/W$ in patients with COPD (n = 20) (A) and healthy participants (n = 20) (B). peak $\dot{V}O_2/W$ =peak oxygen consumption/weight. DEmax was significantly positively correlated with $\dot{V}O_2/W$ in both patients with COPD and healthy participants.
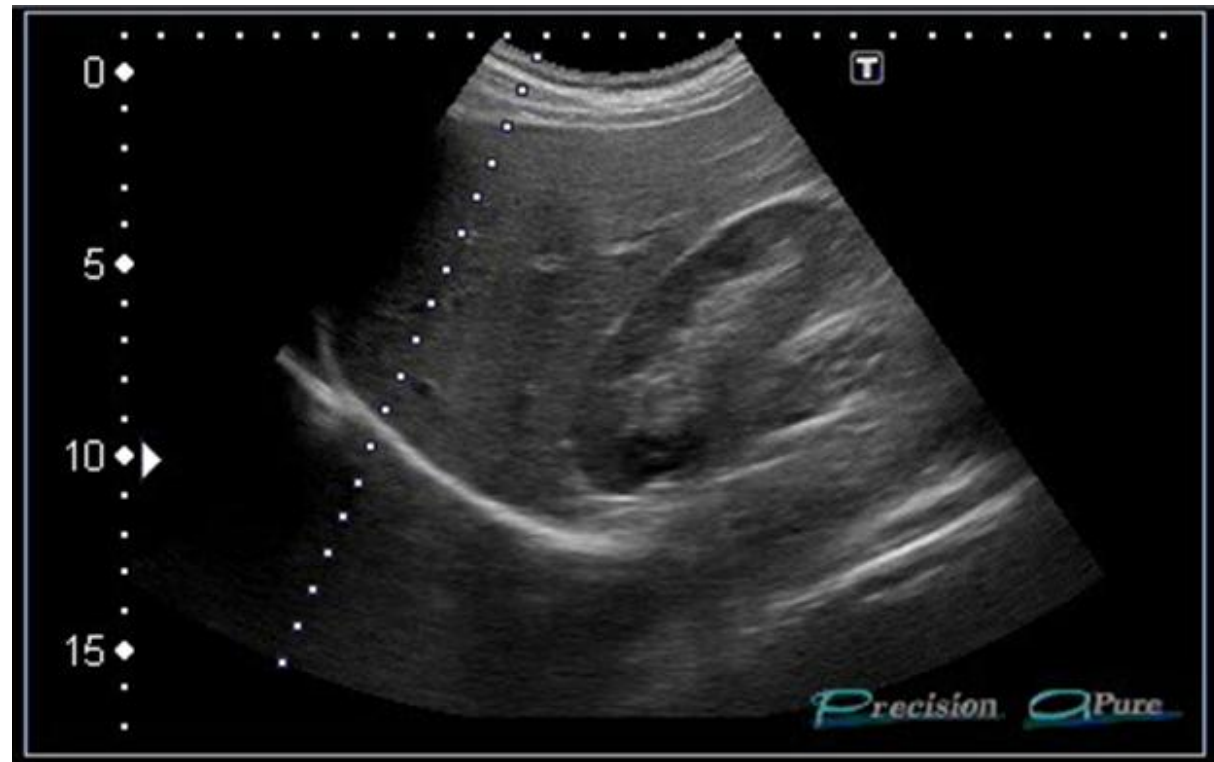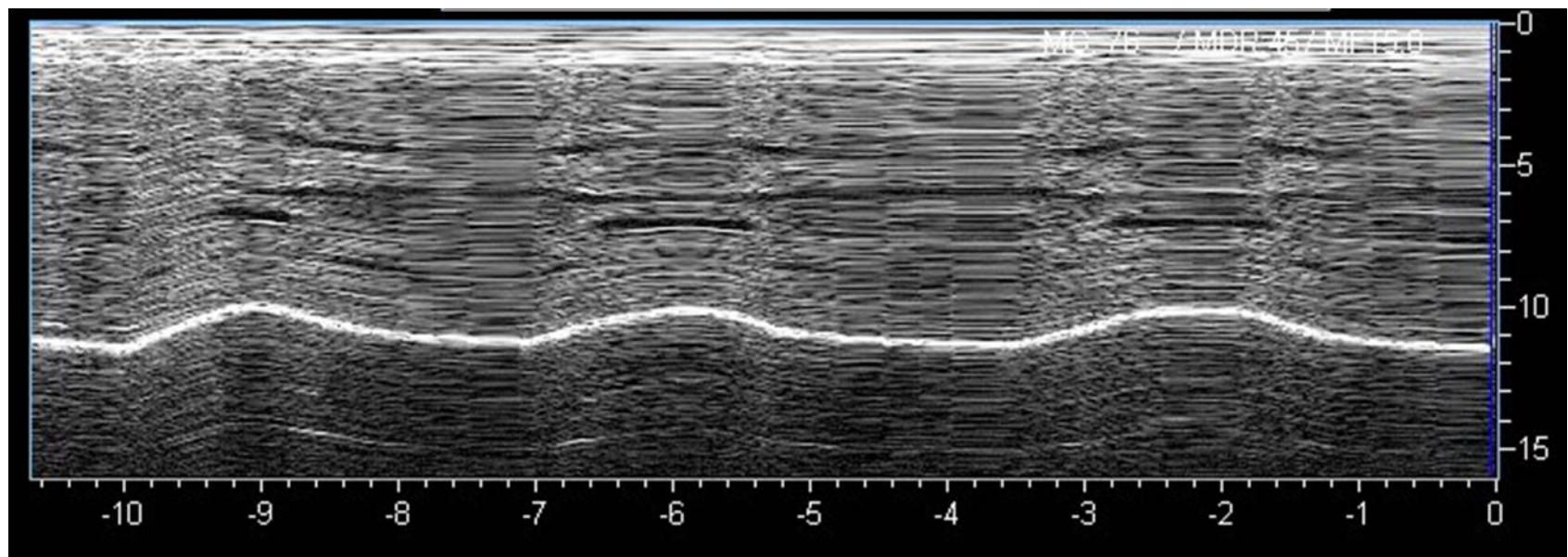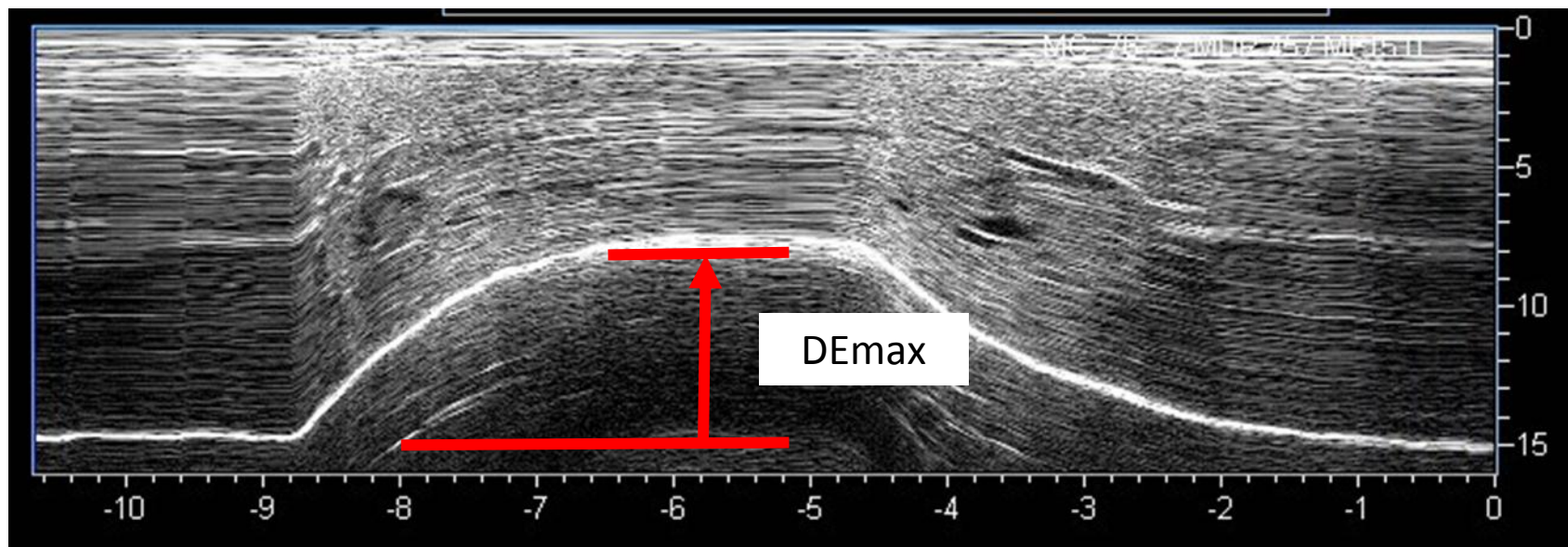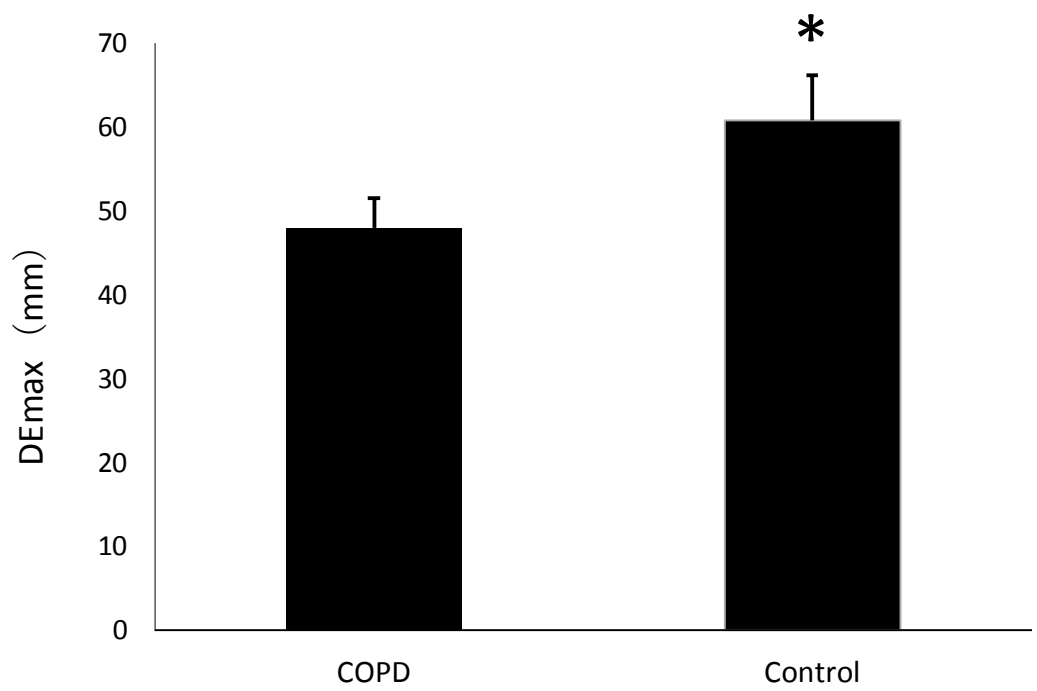
Figure 1A

Figure 1B

Figure 1C

Figure 2

Figure 3 A

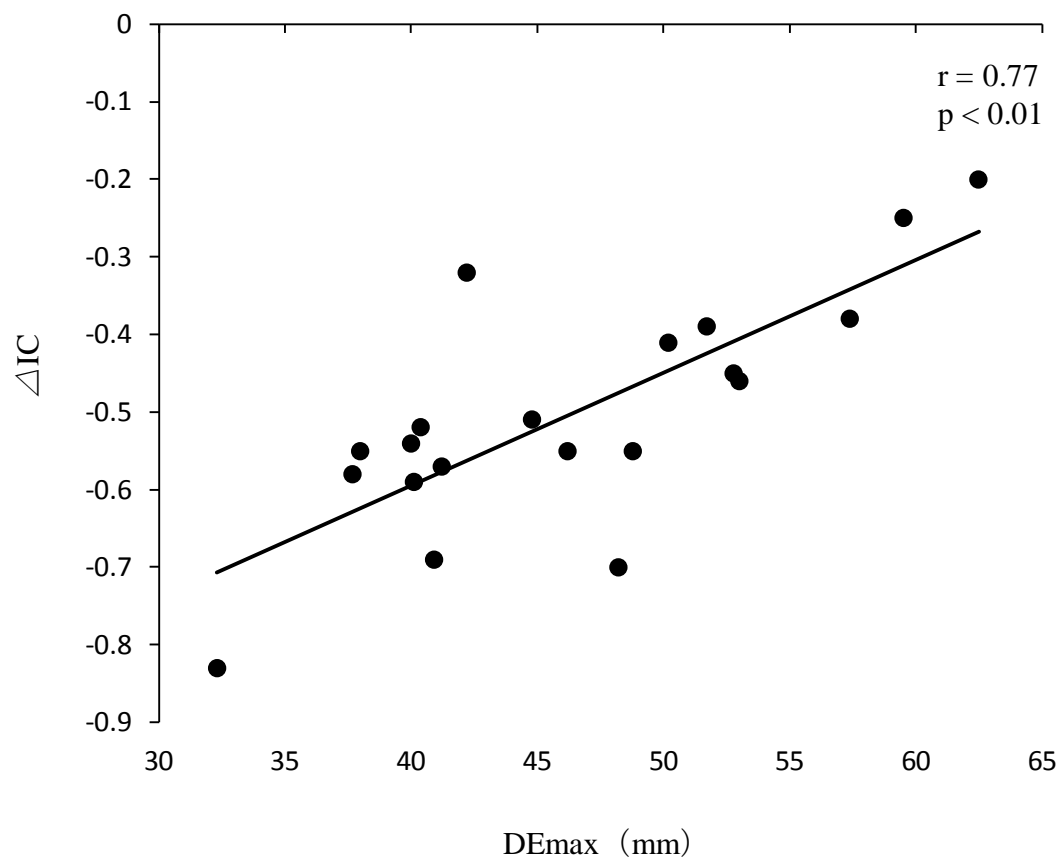Figure 3 B

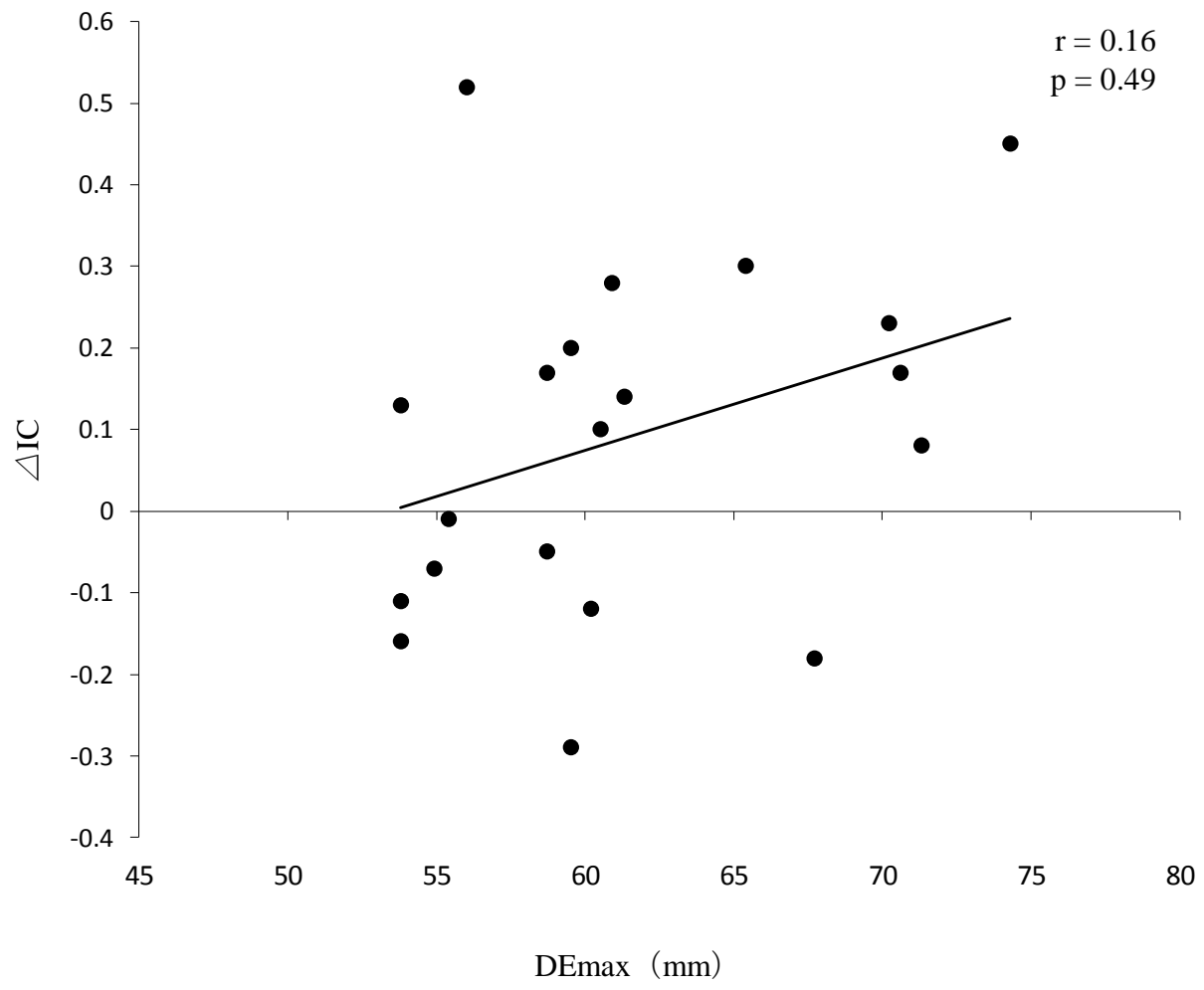Figure 4 A

r = 0.74
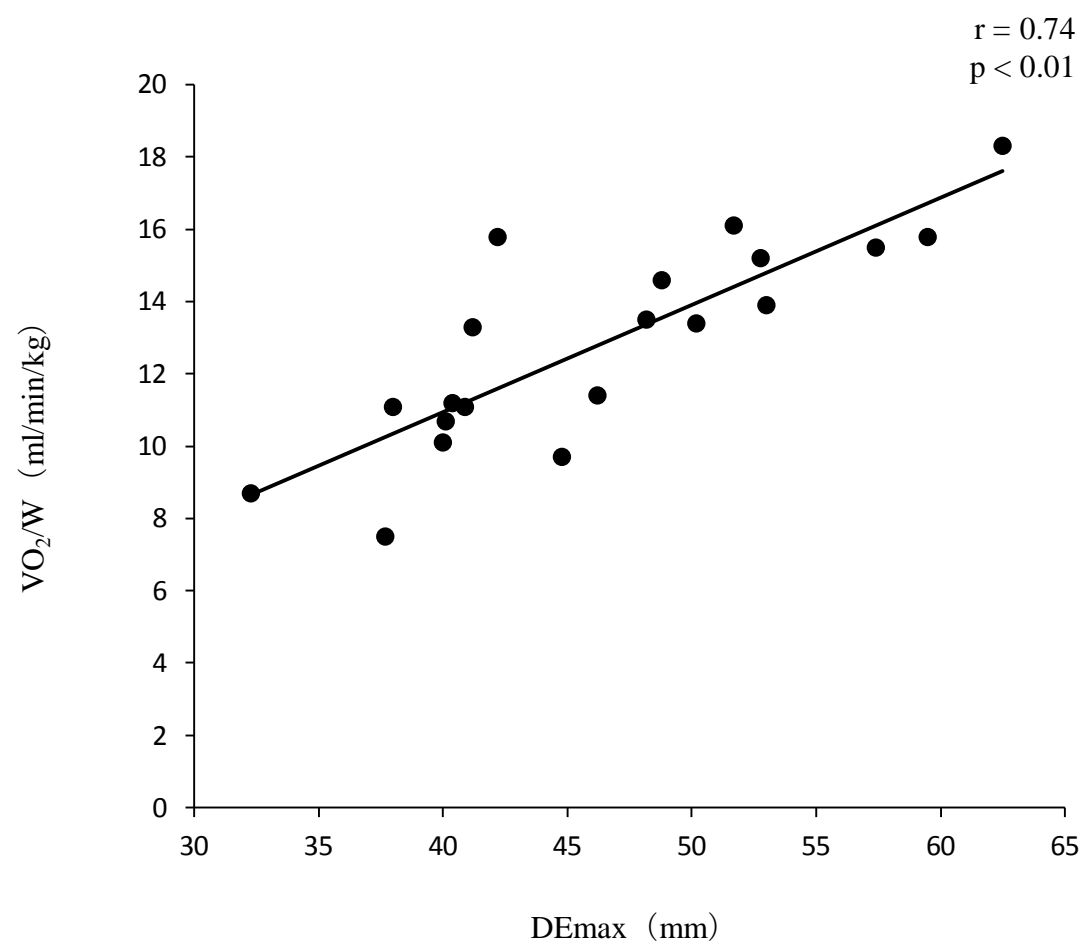p < 0.01

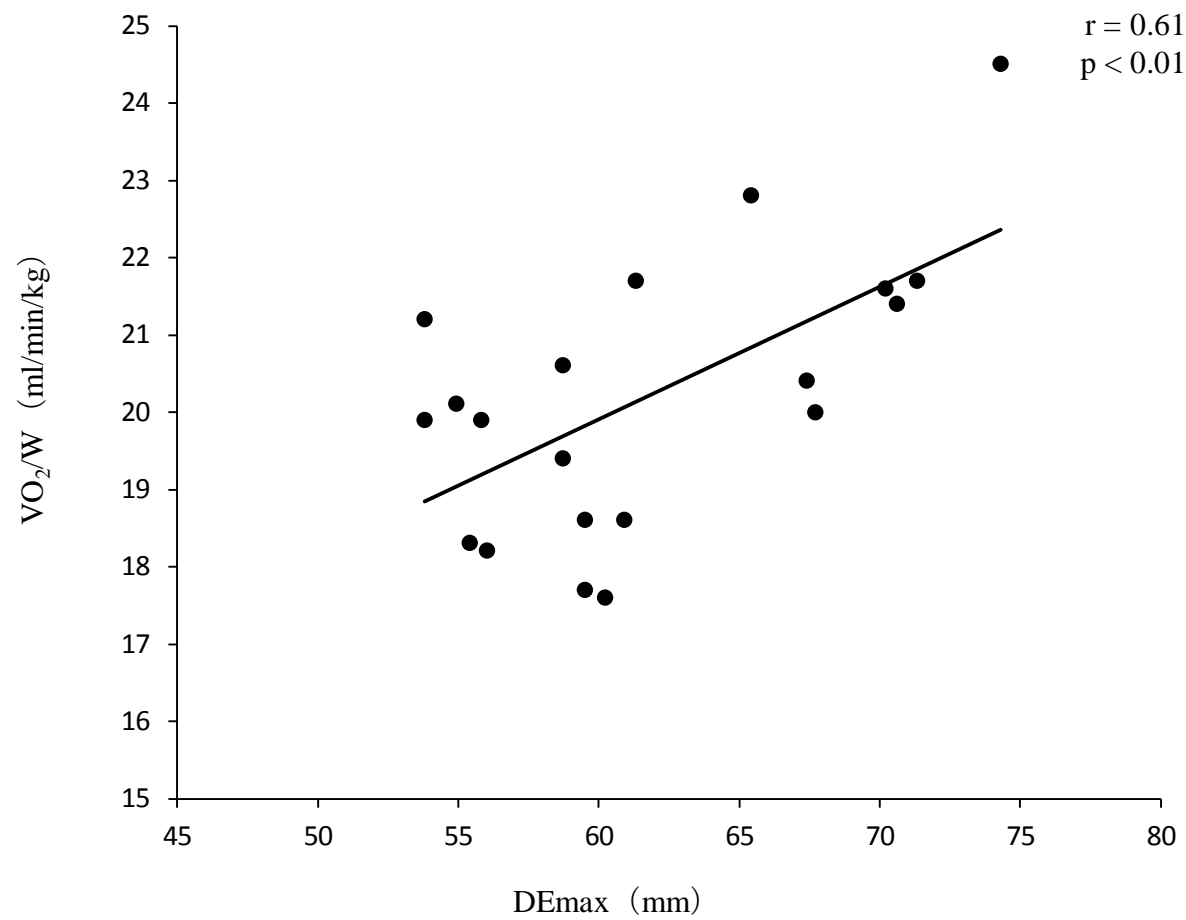VO$_2$/W (ml/min/kg)

DEmax (mm)

Figure 4 B

SUPPLEMENTARY INFORMATION

Diaphragmatic excursion correlates with exercise capacity and dynamic hyperinflation in patients with stable COPD

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Table S1: Distance and intra-class correlation coefficient

Table S2: Distance and intra-class correlation coefficient between sessions

Table S3: Results of multiple regression analysis using VO2/W as the dependent variable.

Figure 1S: Figure 4. Correlation between maximum diaphragmatic excursion (DEmax) and peak VO2/W in patients with COPD (n = 20). peak VO2/W =peak oxygen consumption/weight. DEmax was significantly positively correlated with VO2/W.

Figure 2S:

Table 1S Distance and intraclass correlation coefficient

	Distance (mm)	ICC	p	95% CI	SEM
Deep breath	45.1(13.0)*	0.89	<0.01	0.81-0.96	1.69

*mean±SD

ICC intraclass correlation coefficient; CI confidence interval; SEM standard error of measurement

Table 2S   Distance and intraclass correlation coefficient between sessions

	Distance (mm)	ICC	p	95% CI	SEM
Session 1	45.1(13.0)*	0.87	<0.01	0.78-0.95	1.71
Session 2	45.0(11.8)*				
Session 3	44.4(12.8)*				

*mean±SD
ICC intraclass correlation coefficient; CI confidence interval; SEM standard error of measurement

Inter-rater reliability (reproducibility) of the mean values of 3 DEmax measurements for each patient was assessed by estimating intraclass correlation coefficients (ICCs). Two ICC forms were estimated: ICC(1,1) and ICC(1,k), representing values calculated from a single measurement and from an average of k repeated measures, respectively. In this study, k=3. Diaphragm measurements used the maximum of 3 deep breaths. This measurement was performed in 3 sets.

Table 3S Results of least square regression analysis of $\dot{V}O_2/W$ as the dependent variable.

	F value	95%CI	p
DEmax	29.4	0.18 to 0.37	< 0.0001
%FEV$_1$	8.6	0.17 to 0.86	0.009

Definitions of abbreviations: DEmax=maximum diaphragmatic excursion.