Endobronchial valve treatment improves diaphragm function in severe emphysema patients

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Endobronchial valve treatment improves diaphragm function in severe emphysema patients. This emphasises the interaction between hyperinflation and diaphragm function, suggesting that reducing hyperinflation can partially reverse diaphragm dysfunction. https://bit.ly/4ft2QYj

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Abstract

Background Diaphragm dysfunction is common in severe emphysema patients, primarily due to hyperinflation, placing the diaphragm at a mechanical disadvantage. Endobronchial valve (EBV) treatment is a bronchoscopic procedure to reduce hyperinflation and thus potentially restore diaphragm function in this patient population. Our aim was to investigate the effect of EBV treatment on diaphragm function.

Methods A prospective cohort study was performed in which diaphragm function was measured at baseline and 6 weeks after EBV treatment by ultrasonic assessment to measure diaphragm motion and diaphragm thickening fraction, surface electromyography (sEMG) to quantify diaphragm activity, and maximal inspiratory pressure to assess diaphragm strength.

Results 25 patients were included, with a mean±SD age of 64±7 years. Mean±SD residual volume (−0.85±0.49 L; p<0.001) decreased significantly post-EBV treatment, with a significant increase in median (range) maximal inspiratory pressure (0.6 (−1.2–2.8) kPa; p=0.001). Median (range) diaphragm motion on the treated side during tidal breathing significantly decreased (−3.3 (−24.7–14.6) mm; p=0.023). There were no significant changes in diaphragm thickening fraction on the treated side. Median (range) diaphragm activity (sEMG) for tidal breathing (−1.7 (−8.8–5.8) µV; p=0.004), maximal inspiration (−4.1 (−42.3–16.0) µV; p=0.004) and sniff manoeuvre (−6.1 (−42.2–24.2) µV; p=0.027) all significantly decreased.

Conclusions Our results show that diaphragm function significantly improves after EBV treatment in severe emphysema patients. This emphasises the physiological interaction between hyperinflation and diaphragm function, suggesting that reducing hyperinflation can at least partially reverse diaphragm dysfunction.

Introduction

Diaphragm dysfunction is common in patients with COPD [1]. The primary cause is lung hyperinflation, placing the diaphragm more caudally at a mechanical disadvantage, shortening its operating length and changing the mechanical arrangement of the components of the diaphragm. Consequently, the amount of transdiaphragmatic pressure and tension that can be generated is diminished [2–4]. At the same time, the inspiratory muscles must elevate their workload to overcome the decreased elastic recoil and consecutively increased airflow resistance. This is also reflected by an increased neural drive to the respiratory muscles in emphysema patients compared to healthy individuals [5, 6].

One method to decrease lung hyperinflation is lung volume reduction surgery (LVRS). The effect of LVRS on diaphragm function has been thoroughly investigated. It was found that there was an increase in the length and surface of the diaphragm measured on chest radiography and computed tomography (CT) scans after LVRS [7–9]. Moreover, diaphragm strength measured by transdiaphragmatic pressures and

maximal inspiratory pressures significantly improved, whereas the elevated neural drive to the diaphragm decreased after LVRS [7–9].

Another less invasive method to reduce hyperinflation is endobronchial valve (EBV) treatment, which is a type of bronchoscopic lung volume reduction (BLVR) treatment. This is an advanced treatment modality indicated for eligible patients with severe emphysema and hyperinflation who have substantial disease burden despite optimal medical therapy. When performed, in appropriately selected patients, EBV treatment has been proven to result in clinical improvements in dyspnoea, pulmonary function, quality of life, exercise capacity and survival [10–12].

To date, only a few studies have investigated the impact of BLVR on diaphragm function in limited numbers of patients. Boyko *et al.* [13] showed that diaphragm mobility, measured by ultrasound, increased in patients treated with intrabronchial valves. Furthermore, diaphragm strength measured by transdiaphragmatic pressures improved after EBV treatment [14]. On the other hand, Wallbridge *et al.* [15] did not find a significant difference in diaphragm excursion or thickness following EBV treatment.

In this study, we aimed to further investigate and elucidate the effect of EBV treatment on diaphragm function in COPD patients with severe emphysema and hyperinflation.

Methods

Study participants and study design

We performed a single-centre, prospective cohort study at the University Medical Centre Groningen, Groningen, The Netherlands (ClinicalTrials.gov: NCT04735731). Patients with severe emphysema, scheduled for a BLVR treatment with EBV, were asked to participate in our study. This study was approved by the Medical Ethical Review Committee of the University Medical Centre Groningen and written informed consent was obtained from all participants (EC number: 2021/097). All measurements were performed at baseline and 6 weeks after EBV treatment. According to the sample size calculation, 25 patients were needed to sufficiently power our objectives (supplementary methods S1).

EBV treatment

BLVR treatment using one-way EBVs (Zephyr; PulmonX, Redwood City, CA, USA) was performed in all patients according to current guidelines [16].

Ultrasonic assessment of diaphragm

Diaphragm motion and thickness of both hemidiaphragms were measured with a Mindray TE7 ACE machine (Shenzhen Mindray Bio-Medical Electronics, Shenzhen, China). All measurements were performed by a single qualified and trained operator (E.A.M.D.t.H.) in the presence of, and in agreement with, an observer (J.E.H.). As standardisation of the procedure is crucial for reproducibility and credibility of the results, all measurements were performed in the supine position with the head elevated 20°, with standardised depth (26 cm for motion and 4 cm for thickness) and gain (50 and 60, respectively). Furthermore, the position of the ultrasound probe was marked on the skin, and its coordinates were recorded to ensure consistent measurements at the same location for both the baseline and follow-up visits.

Diaphragm motion was measured using a convex, low-frequency transducer (1.5–5.67 MHz), with the probe placed just below the costal arch on the midclavicular line, directing the probe cranially with a small dorsal tilt [17]. Motion of the diaphragm was captured during 30 s of tidal breathing and during three maximal inspirations. Amplitudes of the motion were calculated afterwards on the ultrasound machine by two observers (E.A.M.D.t.H. and J.E.H.) (figure 1).

Diaphragm thickness (Tdi) was measured using a linear, high-frequency transducer (3.0–11.0 MHz), with the probe placed in the zone of apposition at the mid-axillary line [17]. Thickness of the diaphragm was also visualised during 30 s of tidal breathing and during three maximal inspirations. Thickness of the diaphragm at end of inspiration and at end of expiration was measured by two observers (E.A.M.D.t.H. and J.E.H.) afterwards using IDS7 Sectra version 25.1.6.4226 (Sectra, Linköping, Sweden) (figure 2). Subsequently, diaphragm thickening fraction (dTF (%)) was calculated using the formula:

$$\text{dTF}\ \ (\%) = \frac{\text{Tdi}_{\text{end-inspiration}} - \text{Tdi}_{\text{end-expiration}}}{\text{Tdi}_{\text{end-expiration}}} \times 100$$

Measurements for both diaphragm motion and thickening fraction during tidal breathing were performed until three measurements with <10% variability were obtained. From these three measurements, the mean

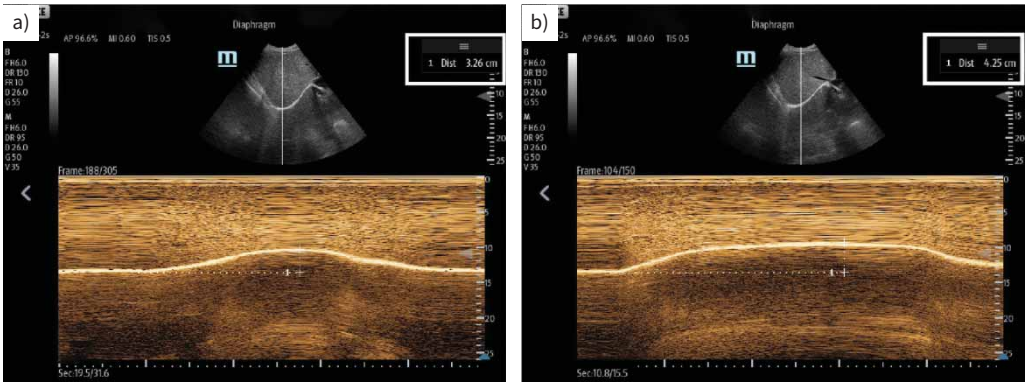

FIGURE 1 Ultrasound images of diaphragm motion during a) tidal breathing and b) maximal inspiration.

value was calculated and utilised for subsequent statistical analyses. For the measurements obtained during three maximal inspirations, the result with the highest amplitude or diaphragm thickening fraction was selected for further analysis. Furthermore, the tidal breathing/maximal inspiration ratio for both diaphragm motion and diaphragm thickening fraction was calculated, as a measure of the amount of diaphragm motion or thickening faction during tidal breathing relative to its maximum.

Surface electromyography of the diaphragm

Electrical activity of the diaphragm was measured by surface electromyography (sEMG) in the sitting position during 5 min of tidal breathing, three maximal inspirations and three sniff manoeuvres. Post-processing of the sEMG signals was performed using MATLAB version R2023a (MathWorks, Natick, MA, USA) and in-house developed software. An extensive description of the sEMG measurement is presented in supplementary methods S2.

Diaphragmatic neuromechanical coupling

The magnitude of diaphragm contraction, and consequently diaphragm motion, is dependent on the degree of electrical activation of the muscle and how effectively this is translated into contraction, which is referred to as neuromechanical coupling [18]. To estimate diaphragmatic neuromechanical coupling, we calculated the ratio of diaphragm motion to diaphragm activity during maximal inspiration, reflecting the mechanical output (mm) per unit of electrical input (µV). This was done separately for the treated and untreated sides of the diaphragm, as well as for the sum of diaphragm motions on both sides.

Diaphragm index on CT scan

The diaphragm index was computed for each hemidiaphragm and for the total diaphragm. The diaphragm index is an automated CT-derived tool that quantifies the configuration of the diaphragm on chest CT

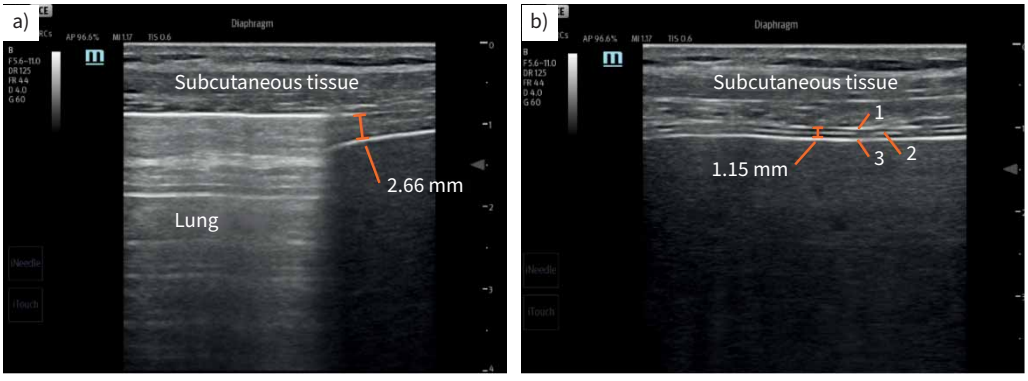

FIGURE 2 Ultrasound images of diaphragm thickness at a) end maximal inspiration and b) end maximal expiration. 1: pleura; 2: fibrous layer in centre of the diaphragm; 3: peritoneum.

scans using LungQ software (Thirona, Nijmegen, The Netherlands) [19]. An index of 1 represents a completely flat diaphragm, whereas a higher index indicates a more curved diaphragm.

Maximal inspiratory and expiratory pressure

Maximal inspiratory pressure and maximal expiratory pressure were measured at baseline and 6 weeks post-EBV treatment to assess the strength of the inspiratory and expiratory respiratory muscles [20].

Other measurements

At both visits, the following measurements were also performed: post-bronchodilator spirometry, body plethysmography, diffusion capacity and 6-min walk distance (6MWD) (according to the European Respiratory Society and/or American Thoracic Society guidelines [21–24]), arterial blood gas analysis, spirometry-gated inspiratory CT scan, St George's Respiratory Questionnaire (SGRQ) [25] and COPD Assessment Test (CAT) [26]. Quantitative CT analysis was performed using LungQ software.

Statistical analyses

We performed the paired-samples t-test (in case of normal data distribution) or the Wilcoxon signed-rank test (for non-normal data distribution) to test whether there were differences between baseline and 6-week follow-up measurements. Additionally, Spearman's correlation coefficients (ρ) were calculated to explore associations between the relative change in diaphragm function parameters and clinical outcomes, including residual volume (RV), forced expiratory volume in 1 s (FEV_1), 6MWD, target lobe volume reduction (TLVR), and SGRQ and CAT total scores. All statistical analyses were performed using SPSS Statistics version 28.0.1.0 (IBM, Armonk, NY, USA) and figures were created using R version 4.3.2 (www.r-project.org) utilising the R packages ggplot2 version 3.5.1 and corrplot version 0.92 (https://cran.r-project.org). p-values <0.05 were considered statistically significant. Missing values were not imputed, instead pairwise analysis was performed.

Results

Study population

28 patients were included in the study between January 2023 and July 2023. In two patients, EBVs were not placed due to the presence of collateral ventilation (n=1) or due to the presence of extensive sputum and signs of bronchitis (n=1). In a third patient, the EBVs were removed due to lack of effectiveness before the follow-up visit. Therefore, the study population consisted of 25 patients (see table 1 for baseline characteristics).

Clinical outcomes of EBV treatment

All clinical outcomes significantly improved post-treatment at the 6-week follow-up (table 2). All patients had a TLVR above the minimal important difference [27] and 16 patients had a complete atelectasis of the treated lobe on CT scan.

Effect of EBV treatment on diaphragm function

The results of all diaphragm function measurements are presented in table 3. The individual changes per patient presented in spaghetti diagrams are available in supplementary figures S1–S6.

Ultrasonic assessment of the diaphragm

Diaphragm motion on the treated side during tidal breathing as well as the tidal breathing/maximal inspiration ratio decreased significantly. Diaphragm motion on the treated side during maximal inspiration slightly increased, but this change was not significant (figure 3a–c). In addition, comparable results, although less pronounced, were observed on the untreated side (table 3). On the treated side, no significant changes occurred in the diaphragm thickening fraction (figure 3–f). However, there was a significant decrease in the diaphragm thickening fraction tidal breathing/maximal inspiration ratio on the untreated side (table 3).

sEMG of the diaphragm

Diaphragm activity, measured with sEMG, significantly decreased post-treatment during tidal breathing, maximal inspiration and sniff manoeuvre. Moreover, the tidal breathing/maximal inspiration ratio also decreased significantly (figure 4 and table 3).

Diaphragmatic neuromechanical coupling

Diaphragmatic neuromechanical coupling, measured as the ratio of diaphragm motion to diaphragm activity (sEMG) during maximal inspiration, increased significantly on the treated side, untreated side and for the total diaphragm after treatment (table 3).

TABLE 1 Baseline characteristics (n=25)

Demographic characteristics	
Female	19 (76)
Age (years)	64±7
BMI (kg·m^{-2})	22.8±3.8
Smoking history (pack-years)	38 (14–94)
Pulmonary function tests	
FEV_1 (% pred)	28.2±7.9
FVC (% pred)	68.7±13.0
RV (% pred)	233.2±49.8
TLC (% pred)	129.0±13.5
RV/TLC (%)	62.9±5.8
D_{LCO} (% pred)	38.0 (23.5–57.8)
Arterial blood gases	
P_{aCO_2} (kPa)	5.4 (4.5–7.7)
P_{aO_2} (kPa)	9.3 (6.8–11.5)
Treatment target lobe	
Right upper lobe	7 (28)
Right upper lobe+middle lobe	1 (4)
Right lower lobe	3 (12)
Left upper lobe	2 (8)
Left lower lobe	12 (48)
Quantitative CT scan analysis	
Inspiratory volume of the target lobe (mL)	1684 (1061–3033)
Emphysema score of the target lobe[#] (%)	50 (27–67)

Data are presented as n (%), mean±SD or median (range). BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen tension; CT: computed tomography. [#]: emphysema score is the percentage of voxels below −950 HU on the inspiratory CT scan.

Diaphragm index on inspiratory CT scan

The diaphragm indices measured on inspiratory CT scan of the treated side, untreated side and the total diaphragm all significantly increased post-EBV treatment, reflecting a greater curvature of the diaphragm. This positive effect was most pronounced on the treated side (table 3).

Maximal inspiratory and expiratory pressure

Maximal inspiratory pressure and maximal expiratory pressure both increased significantly post-EBV treatment (table 3).

TABLE 2 Effect of endobronchial valve treatment on clinical outcomes (n=25)

	Baseline	6-week follow-up	Change between baseline and 6-week follow-up	p-value
FEV_1 (L)	0.76±0.26	1.00±0.31	0.24±0.17	**<0.001**
FVC (L)	2.41±0.70	2.93±0.79	0.52±0.38	**<0.001**
RV (L)	4.6±0.9	3.8±0.9	−0.85±0.49	**<0.001**
TLC (L)	7.4±1.4	6.9±1.4	−0.5±0.3	**<0.001**
RV/TLC (%)	62.9±5.8	54.7±6.9	−8.2±5.3	**<0.001**
Inspiratory volume of target lobe (mL)	1684 (1061–3033)	0 (0–1586)	−1559 (−1947– −602)	**<0.001**
6MWD (m)	336±103	397±97[#]	62±39[#]	**<0.001**[#]
mMRC dyspnoea scale score	3 (1–4)	2 (1–3)	−1 (−2–0)	**<0.001**
SGRQ total score	66.8±9.4	45.7±17.9	−21.1±17.0	**<0.001**
CAT total score	23.4±5.0	16.0±6.2	−7.4±4.7	**<0.001**

Data are presented as mean±SD or median (range), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; 6MWD: 6 min walk distance; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test. [#]: based on 24 available measurements. Differences between baseline and 6-week follow-up were tested with the paired-samples t-test for normally distributed variables or the Wilcoxon signed-rank test in the case of non-normal distribution. Significant p-values (p<0.05) are indicated in bold.

TABLE 3 Effect of endobronchial valve treatment on diaphragm function

	Baseline	6-week follow-up	Change between baseline and 6-week follow-up	p-value (valid n)
Diaphragm motion (ultrasound)				
Treated side				
Tidal breathing (mm)	22 (11–48)	18 (10–39)	−3.3 (−24.7–14.6)	**0.023** (25)
Maximal inspiration (mm)	48 (23–88)	51 (29–103)	3.5 (−19.8–22.5)	0.190 (24)
Tidal breathing/maximal inspiration (ratio)	0.53 (0.17–0.86)	0.40 (0.23–0.66)	−0.12 (−0.45–0.19)	**0.001** (24)
Untreated side				
Tidal breathing (mm)	21 (11–47)	19 (10–45)	−3.5 (−26.3–13.8)	**0.021** (24)
Maximal inspiration (mm)	54 (22–97)	53 (30–88)	1.0 (−20.8–22.3)	0.956 (23)
Tidal breathing/maximal inspiration (ratio)	0.46 (0.16–0.90)	0.34 (0.13–0.99)	−0.040 (−0.60–0.28)	**0.014** (23)
Diaphragm thickening fraction (ultrasound)				
Treated side				
Tidal breathing (%)	39 (4–147)	37 (−14–142)	4.1 (−125.9–103.1)	0.964 (23)
Maximal inspiration (%)	131 (55–292)	136 (52–345)	2.7 (−194.7–158.0)	1.000 (20)
Tidal breathing/maximal inspiration (ratio)	0.27 (0.017–0.87)	0.30 (−0.12–0.74)	−0.044 (−0.73–0.55)	0.812 (20)
Untreated side				
Tidal breathing (%)	57 (2–183)	30 (3–246)	−12.7 (−76.7–162.2)	0.262 (22)
Maximal inspiration (%)	98 (18–305)	126 (29–298)	28.9 (−171.5–198.5)	0.080 (19)
Tidal breathing/maximal inspiration (ratio)	0.48 (0.063–1.69)	0.18 (0.028–0.58)	−0.33 (−1.10–0.39)	**0.006** (19)
Diaphragm activity (sEMG)				
Tidal breathing (μV)	4.6 (2.0–19.2)	2.5 (1.0–11.7)	−1.7 (−8.8–5.8)	**0.004** (24)
Maximal inspiration (μV)	27.0 (10.6–86.1)	23.1 (9.1–71.7)	−4.1 (−42.3–16.0)	**0.004** (24)
Sniff manoeuvre (μV)	28.2 (15.9–89.7)	25.6 (11.2–61.3)	−6.1 (−42.2–24.2)	**0.027** (24)
Tidal breathing/maximal inspiration (ratio)	0.19 (0.038–0.51)	0.13 (0.035–0.41)	−0.022 (−0.43–0.24)	**0.049** (24)
Diaphragm NMC[#] ($mm \cdot \mu V^{-1}$)				
Treated side	1.6 (0.6–4.0)	2.1 (0.8–5.0)	0.45 (−1.72–2.12)	**0.008** (23)
Untreated side	1.9 (0.6–4.1)	2.3 (0.8–6.3)	0.42 (−1.94–2.15)	**0.023** (22)
Total diaphragm	3.3 (1.3–7.5)	4.4 (1.7–11.2)	1.00 (−3.67–4.27)	**0.009** (21)
Diaphragm index[¶] (CT scan)				
Treated side	1.53 (1.28–1.82)	1.71 (1.30–2.25)	0.17 (−0.27–0.66)	**<0.001** (25)
Untreated side	1.54 (1.32–1.77)	1.60 (1.41–1.95)	0.10 (−0.08–0.27)	**<0.001** (25)
Total diaphragm	1.54 (1.40–1.77)	1.69 (1.49–2.01)	0.13 (−0.10–0.31)	**<0.001** (25)
Maximal inspiratory pressure (kPa)	6.5 (4.5–9.8)	7.6 (4.7–10.8)	0.6 (−1.2–2.8)	**0.001** (25)
Maximal expiratory pressure (kPa)	7.3 (4.7–13.7)	7.7 (4.5–13.6)	0.4 (−1.6–4.7)	**0.035** (23)

Data are presented as mean±SD or median (range), unless otherwise stated. sEMG: surface electromyography; NMC: neuromechanical coupling; CT: computed tomography. [#]: diaphragm NMC is measured as the ratio of the maximal diaphragm motion (output in mm) to the diaphragm activity during a maximal inspiration (activation in μV); [¶]: diaphragm index is a value of the configuration of the diaphragm measured on CT scan (an index of 1 indicates a complete flattened diaphragm, whereas a high index indicates a curved diaphragm). Differences between baseline and 6-week follow-up were tested with the paired-samples t-test for normally distributed variables or the Wilcoxon signed-rank test in the case of non-normal distribution. Significant p-values ($p<0.05$) are indicated in bold.

Associations between change in diaphragm function and clinical outcomes

An improvement in RV was significantly associated with a decrease in diaphragm activity (sEMG) during tidal breathing (Spearman's $\rho=0.522$) (figure 5a), a decrease in the diaphragm activity (sEMG) tidal breathing/maximal inspiration ratio (Sperman's $\rho=0.498$) and a decrease in diaphragm thickening fraction on the treated side during maximal inspiration (Spearman's $\rho=0.499$). No other significant associations were found between RV and other diaphragm function parameters. An improvement in FEV_1 was significantly associated with a decrease in diaphragm activity (sEMG) during tidal breathing (Spearman's $\rho=-0.729$) (figure 5b). No other significant associations were found between FEV_1 and other diaphragm function parameters. No significant associations were found between 6MWD and diaphragm function parameters. No significant associations were found between TLVR and diaphragm function parameters. An improvement in SGRQ total score was significantly associated with a decrease in diaphragm activity (sEMG) during maximal inspiration (Spearman's $\rho=0.491$), a decrease in diaphragm thickening fraction on the treated side during tidal breathing (Spearman's $\rho=0.433$) and a decrease in the diaphragm thickening fraction tidal breathing/maximal inspiration ratio on the treated side (Spearman's $\rho=0.451$). No other significant associations were found between SGRQ total score and other diaphragm function parameters. No significant associations were found between CAT total score and diaphragm function parameters. The complete Spearman's correlation matrix between the relative changes in diaphragm function parameters and clinical outcomes is shown in supplementary figure S7.

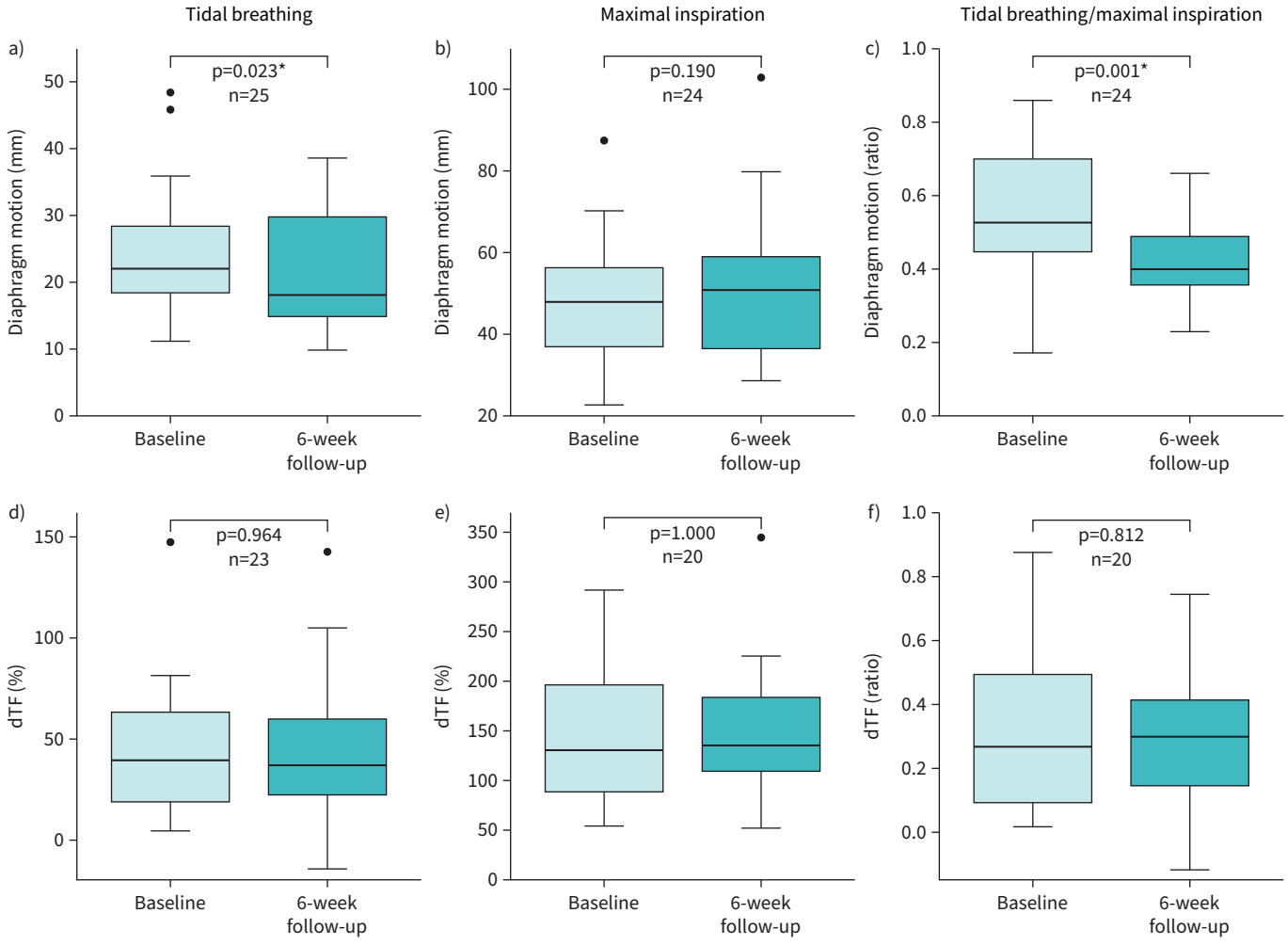

FIGURE 3 Box-and-whisker plots of change in a–c) diaphragm motion and d–f) diaphragm thickening fraction (dTF) on the treated side 6 weeks post-endobronchial valve treatment: a, d) tidal breathing, b, d) maximal inspiration and e, f) tidal breathing/maximal inspiration ratio. Boxes indicate median and interquartile range (IQR), whiskers indicate 1.5×IQR and outliers are >1.5×IQR. Significance was tested using the Wilcoxon signed-rank test. *: p<0.05.

Discussion

This is the first study to extensively assess diaphragm function after EBV treatment. We found that various diaphragm function parameters significantly improved after EBV treatment. Ultrasonic assessment showed a significant decrease in diaphragm motion at rest and a slight increase during maximal inspiration. Furthermore, sEMG demonstrated a significant overall decrease in diaphragm activity. The curvature of the diaphragm and diaphragmatic neuromechanical coupling both significantly increased. Moreover, the observed change in diaphragm activity (sEMG) was significantly associated with the improvement in RV and FEV_1.

Diaphragm motion on the treated side during tidal breathing significantly decreased, whereas motion during maximal inspiration slightly increased following EBV treatment. To contextualise our findings, it is interesting to compare our data with diaphragm motion in healthy subjects. Although there are no official reference values for diaphragm motion (and its magnitude depends on height and body weight), a study of 410 healthy subjects found that the mean diaphragm motion during tidal breathing was 1.7 cm for women and 1.9 cm for men, while during maximal inspiration it was 5.4 and 6.6 cm, respectively [28]. In our study population, the mean diaphragm motion during tidal breathing, not stratified by sex, decreased from 2.2 to 1.8 cm, while the mean maximal motion increased from 4.8 to 5.1 cm. Thus, the motion during tidal breathing decreased relative to the assumed normal values, whereas the maximal motion increased towards, but did not reach, the proposed normal value. This suggests that the elevated workload of the diaphragm at rest is reduced to normal levels and that, simultaneously, there is potential for further increase in maximal

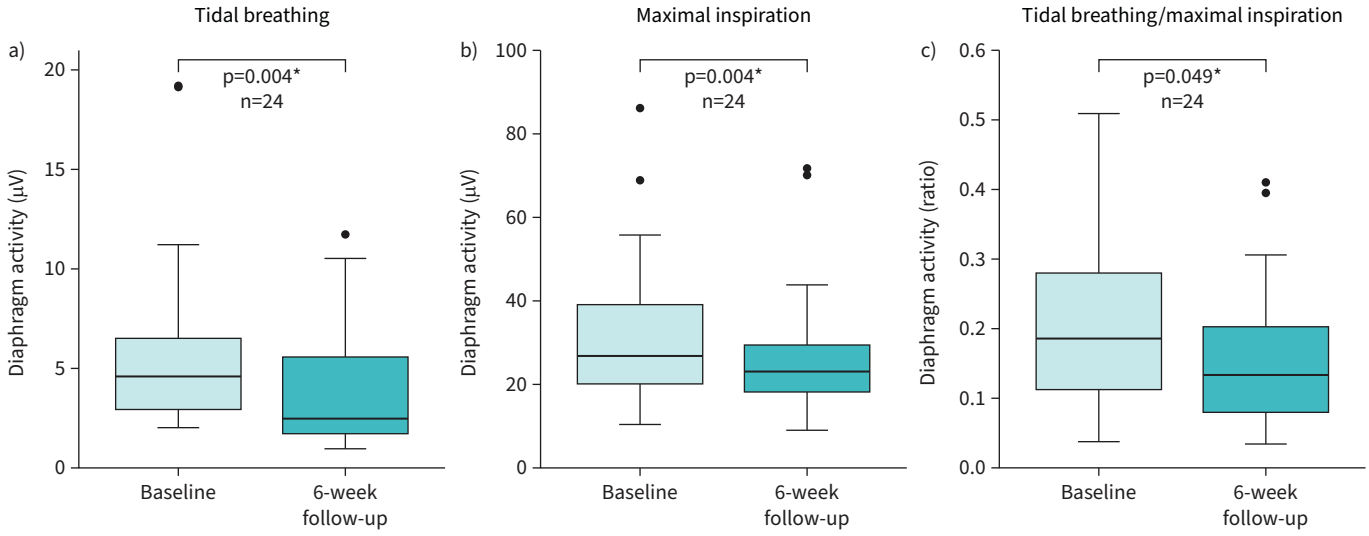

FIGURE 4 Box-and-whisker plots of changes in diaphragm activity during a) tidal breathing, b) maximal inspiration and c) tidal breathing/maximal inspiration ratio 6 weeks post-endobronchial valve treatment. Boxes indicate median and interquartile range (IQR), whiskers indicate 1.5×IQR and outliers are >1.5×IQR. Significance was tested using the Wilcoxon signed-rank test. *: p<0.05.

motion after EBV treatment. One study previously reported an improvement in maximal diaphragm mobility measured by ultrasound, which was associated with a positive perceived outcome of the treatment in the patients [13]. This strengthens the suggestion that changes in diaphragm motion after EBV treatment contribute to the clinical improvements observed in patients.

Diaphragm activity, measured with sEMG, significantly decreased, indicating that there is less respiratory effort by the patient after EBV treatment. To the best of our knowledge, this is the first study to measure diaphragm activity (sEMG) before and after EBV treatment. However, studies performed in LVRS patients showed that diaphragm activity, invasively measured with needle or oesophageal electrodes, also decreased after LVRS [9, 29]. The decrease in diaphragm activity (sEMG) could imply that the diaphragm can contract more effectively following lung volume reduction. We supported this hypothesis by estimating the diaphragmatic neuromechanical coupling, defined as the ratio of diaphragm motion to activity during maximal inspiration, which also increased significantly.

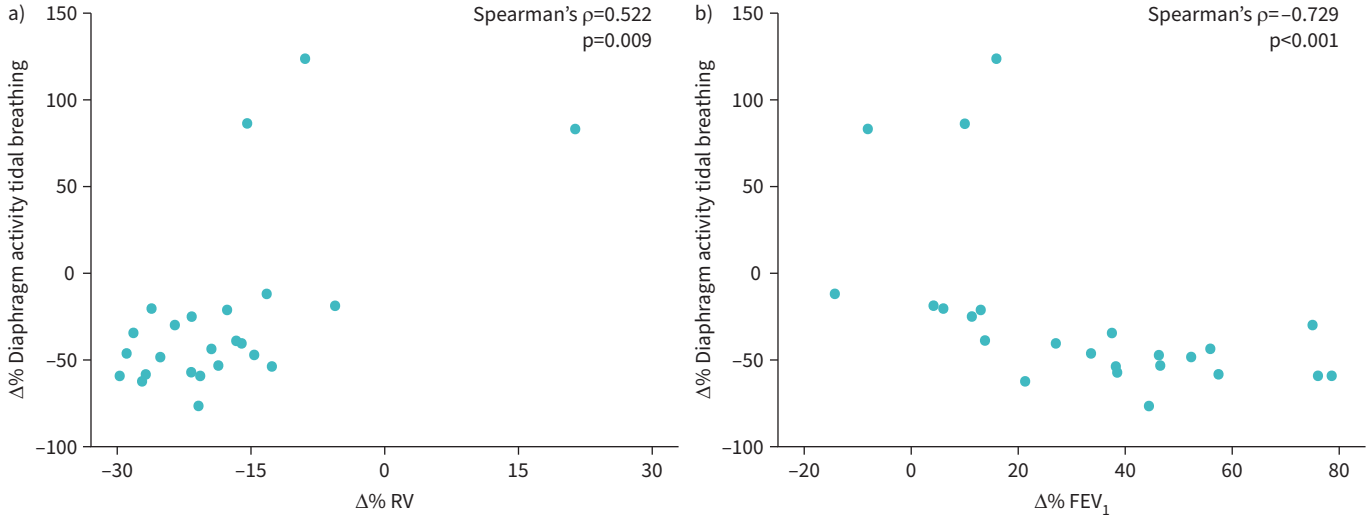

FIGURE 5 Scatter plots depicting the association between the relative change in diaphragm activity during tidal breathing and the relative change in a) residual volume (RV) and b) forced expiratory volume in 1 s (FEV_1). Diaphragm activity was measured with surface electromyography. Δ%: relative change between baseline and 6-week follow-up. Spearman's correlation coefficients and corresponding p-values are depicted.

Maximal inspiratory pressure significantly improved in our study population after EBV treatment, similar to the results of Brindel *et al.* [30]. However, due to the involvement of other accessory respiratory muscles in this measurement, this finding is not specific to diaphragm strength alone. Diaphragm strength, measured with transdiaphragmatic pressures, has been investigated once in patients receiving EBV treatment and more often in patients undergoing LVRS. In all these studies, transdiaphragmatic pressures increased after establishing lung volume reduction, implying an improvement in diaphragm strength itself [7, 8, 14]. Therefore, it is reasonable to state that increased diaphragm strength following EBV treatment contributes to the observed improvement in maximal inspiratory pressure. In the future, it would be interesting to investigate the use of accessory respiratory muscles, including the intercostal muscles, given their compensatory role in overcoming diaphragm dysfunction in patients with COPD [31].

We did not find any changes in diaphragm thickening fraction on the treated side, whereas on the untreated side, we did observe a significant reduction in the diaphragm thickening fraction tidal breathing/maximal inspiration ratio. Although we intended to measure the diaphragm thickening fraction at the same location for both baseline and follow-up measurements, the reduction in lung volume and subsequent displacement of the zone of apposition made this unfeasible in some cases. This might explain why we did not observe any differences on the treated side, while we did on the untreated side. Furthermore, in some patients the maximal diaphragm thickening fraction was not always measurable due to blocked vision caused by the position of the ribs. This measurement appeared less suitable for our purpose and might be unsuitable for this patient population, and therefore these results should not be overvalued.

The change in diaphragm activity (sEMG) was significantly associated with the improvement in RV and FEV_1. An interesting question that remains is whether the reduction in hyperinflation after EBV treatment leads to clinical improvement, thereby enhancing diaphragm function, or if the improved diaphragm function following lung volume reduction contributes to further clinical improvement. Considering the pathophysiology of diaphragm dysfunction, with hyperinflation as its primary cause, it seems reasonable to suggest that reducing hyperinflation improves diaphragm function, potentially leading to further clinical improvement.

The strength of our study lies in the comprehensive assessment of multiple diaphragm function parameters within a homogeneous study population. However, there are some limitations that should be addressed. Ultrasound and sEMG have been criticised for their potential high variability in repeated measurements. However, when performed using standardised protocols and by trained personnel, both measurements have shown good reproducibility between and within observers, making them viable alternatives to more invasive techniques [32, 33]. Nevertheless, operator bias may have been introduced during the calculation of diaphragm motion amplitudes, as this was conducted on the ultrasound machine itself immediately after the measurement, making independent, blinded evaluations by two operators impossible. Furthermore, we identified only a few significant associations between the change in diaphragm function parameters and clinical outcomes. This might be due to the lack of non-responders in our study population, as all patients had a TLVR above the minimal important difference.

In conclusion, our results show that diaphragm function significantly improves after EBV treatment in severe emphysema patients. This highlights the physiological interplay between hyperinflation and diaphragm function, suggesting that reducing hyperinflation can at least partially reverse diaphragm dysfunction in this population.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Provenance: Submitted article, peer reviewed.

This study is registered at ClinicalTrials.gov with identifier number NCT04735731.

Ethics statement: This study was approved by the Medical Ethical Review Committee of the University Medical Centre Groningen and written informed consent was obtained from all participants (EC number: 2021/097).

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