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HAL Id: hal-03521139
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Submitted on 11 Jan 2022

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Determinants of diaphragm inspiratory motion, diaphragm thickening and its performance for predicting respiratory restrictive pattern in Duchenne muscular dystrophy

Abdallah FAYSSOIL (1-2-3-4), MD, Lee S NGUYEN (5) , MD, Tanya STOJKOVIC (2), MD, Helene PRIGENT (4-6), MD, Robert CARLIER (7), MD, Helge AMTHOR (4-8), MD, Jean BERGOUNIOUX (8), MD, Justine ZINI (8), MD, Sebastien DAMEZ-FONTAINE (8), MD, Karim WAHBI (2-9), MD, Pascal LAFORET (4-10), MD, Guillaume NICOLAS (10), MD, Anthony BEHIN (2), MD, Guillaume BASSEZ (2), MD, France LETURCQ (11), MD, Rabah BEN YAOU (11), MD, Nicolas MANSENCAL (3), MD, Djillali ANNANE (1), MD, Frédéric LOFASO (4-6), MD, David ORLIKOWSKI (112), MD

1) Service de Réanimation médico-chirurgicale et Pole ventilation à domicile, CHU Raymond Poincaré, APHP, Université Paris Saclay/UFR Sciences de la santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
2) APHP, Nord/Est/Ile-de-France Neuromuscular reference center, Institut de Myologie, Hôpital Pitié-Salpêtrière, Paris, France
3) Service de Cardiologie, CHU Ambroise-Paré, AP-HP, 92104 Boulogne Billancourt, France; Inserm U1018, CESP, Team 5 (EpReC, Renal and Cardiovascular Epidemiology), UVSQ, 94805 Villejuif, France
4) INSERM U1179, END-ICAP, Montigny-le-Bretonneux, France
5) Sorbonne University, INSERM CIC Paris-Est, AP-HP, ICAN, Regional Pharmacovigilance Center, Pitié-Salpêtrière Hospital, Department of Pharmacology, F-75013 Paris, France; CMC Ambroise Paré, Research & Innovation (RICAP), Neuilly-sur-Seine, France
6) Service de Physiologie - Explorations fonctionnelles, CHU Raymond Poincaré, APHP, Université Paris Saclay/UFR Sciences de la santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
7) service de Radiologie, CHU Raymond Poincaré, APHP, Université Paris Saclay/UFR Sciences de la santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
8) Service de Pédiatrie, CHU Raymond Poincaré, APHP, Université Paris Saclay/UFR Sciences de la santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
9) Cardiology Department, AP-HP, Cochin Hospital, FILNEMUS, Centre de Référence de Pathologie Neuromusculaire Nord/Est/Ile de France, Université Paris Descartes-Sorbonne Paris Cité, Paris, France.
10) Service de Neurologie, CHU Raymond Poincaré, APHP, Université Paris Saclay/UFR Sciences de la santé-Université de Versailles Saint Quentin en Yvelines, Garches, France
11) AP-HP, Cochin Hospital, Department of Genetics and Molecular Biology, Paris, France.
12) Centre d’Investigation Clinique, UMR 1429, Hôpital Raymond Poincaré, Garches, France

Corresponding author
Abdallah FAYSSOIL, MD PhD
Raymond Poincaré Hospital, APHP, Garches, France
E-mail: abdallah.fayssoil@aphp.fr

Financial disclosure and conflict of interest: The authors declare no financial disclosures or conflicts of interest.

Word count abstract: 249

Word count manuscript: 2140

Ethical publication statement: The authors have read the journal’s position on issues involved in ethical publication.
Abstract

Introduction/Aims
Respiratory status is a key determinant of prognosis in patients with Duchenne muscular dystrophy (DMD). We aimed to evaluate the determinants of diaphragm ultrasound and its performance in predicting restrictive respiratory patterns in DMD.

Methods
We included DMD patients who experienced diaphragm ultrasound and pulmonary functional tests.

Results
This study included 74 patients with DMD. The right diaphragm thickening fraction (TF) was significantly associated with age (p = 0.001), Walton score (p = 0.012), inspiratory capacity (IC) (p = 0.004), upright FVC (p < 0.0001), supine FVC (p = 0.038), and maximal inspiratory pressure (MIP) (p = 0.002). Right diaphragm excursion was significantly associated with age (p < 0.0001), steroid use (p = 0.008), history of spinal fusion (p < 0.0001), BMI (p = 0.002), Walton score (p < 0.0001), IC (p < 0.0001), upright FVC (p < 0.0001), supine FVC (p < 0.0001), and MIP (p < 0.0001). A right diaphragm TF > 28% was associated with a FVC > 50%, with an area under the curve (AUC) at 0.95 (p = 0.001). A right diaphragm excursion > 25.4 mm was associated with an AUC at 0.93 (p < 0.001). A left diaphragm TF > 26.8% was associated with upright FVC > 50%, with an AUC at 0.95 (p = 0.011). A left diaphragm excursion >21.5 mm was also associated with a pulmonary upright FVC > 50%, with an AUC at 0.97 (p < 0.001).

Discussion
DMD and diaphragm TF can predict restrictive pulmonary insufficiency in DMD.

Key words: Duchenne muscular dystrophy, pulmonary, diaphragm, ultrasound

Clinical trial NCT 04045158
INTRODUCTION

Respiratory dysfunction in Duchenne muscular dystrophy (DMD) is characterized by a progressive reduction in lung volume with the onset of a restrictive pulmonary pattern and nocturnal followed by diurnal hypoventilation (1). Non-invasive mechanical ventilation is recommended in patients with an upright forced pulmonary vital capacity (FVC) of less than 50% of the predicted value (1). Respiratory status is a key determinant of prognosis in patients with DMD, as patients are at risk of acute respiratory failure and pneumonia (1). It is recommended to perform pulmonary respiratory tests regularly in DMD patients after the age of 6–7 years (1). Ultrasound has emerged as a recent technique that can help physicians to assess and monitor the diaphragm, which is the main inspiratory muscle. Diaphragm ultrasound is a single, reproducible technique without radiation exposure, which can be performed at the bedside (2, 3). Diaphragm ultrasound is used in the intensive care unit (ICU) during the weaning trial process in patients on mechanical ventilation to search for predictive factors of weaning trial failure (4, 5). In the field of neuromuscular disorders, this technique has emerged as a non-invasive test to assess diaphragm function (6). The diaphragm thickening fraction (TF) and diaphragm excursion are ultrasound parameters measured in radiology. The diaphragm TF was defined as (end inspiratory thickness−end expiratory thickness)/end expiratory thickness (7). The diaphragm TF can be used as an index of respiratory effort and is correlated with inspiratory muscle pressure (7, 8). We aimed to evaluate patients with DMD and identify the determinants of the hemidiaphragm excursion and diaphragm TF, and accuracy of diaphragm ultrasound parameters to predict a FVC > 50% of predicted value.

METHODS

Study population
From 2015 to 2018, we included, retrospectively, DMD patients followed in our center and admitted for annual checkup including cardiopulmonary evaluation and diaphragm ultrasound. Patients with DMD who were ventilated 24/24 h invasively were excluded. From the cardiac ultrasound database, we noted the left ventricular ejection fraction (LVEF), the systolic pulmonary artery pressure, and diaphragm ultrasound parameters available. The Gardner Medwin Walton scale was used to evaluate the peripheral skeletal muscle disability (0, normal; 1, unable to run; 2, altered gait; 3, climbs stairs with hand support; 4, unable to climb stairs; 5, unable to rise from a chair; 6, walk only with aids; 7, cannot walk; 8, unable to move in a manual wheelchair; 9, unable to sit unsupported; 10, bedridden) (9). This study was performed in compliance with the ethical principles formulated in the Declaration of Helsinki and was approved by the French Regulatory Board (Commission Nationale de l’Informatique et des libertés, CNIL). Informed consent was obtained from all participants. This study was registered in a clinical trial (NCT 04045158).

**Diaphragm ultrasound**

Diaphragm ultrasound was performed simultaneously by an experienced operator (A.F.) during echocardiographic examination. Diaphragm thickness was measured at the apposition zone using a transducer placed perpendicular to the chest wall, between the anterior and the mid-axillary lines (supplemental figures). The patients were placed in a semi-recumbent position. For this measurement, we used a linear transducer probe with a higher frequency 9 L-D (2.4–10 MHz). Using the B mode, the diaphragm was visualized as a hypoechoic layer of muscle tissue surrounded by two hyper-echogenic lines: the pleural and peritoneal lines. Diaphragm thickness was measured at the end of the expiratory phase and at the end of deep inspiration. The diaphragm TF was calculated using the following formula: TF = (end inspiratory thickness−end expiratory thickness)/end expiratory thickness (10).

To record diaphragm excursion, a patient was placed in a semi-recumbent position, and the cardiac probe M5Sc-D (1.5–4.6 MHz) was positioned at the subcostal area between the mid-clavicular and
anterior axillary lines (supplemental figures); the liver and spleen were used as an acoustic window for the right and left hemidiaphragm, respectively. From the subcostal approach, M-mode tracing was recorded, and the ultrasound beam reached the posterior third of the hemidiaphragm. During inspiration, the diaphragm moves toward the probe. The diaphragm is recognized as an echogenic line that covers the liver. We recorded the diaphragm excursion during a deep inspiratory maneuver.

**Pulmonary functional tests**

Pulmonary functional tests were performed according to the ATS/ERS recommendations (11) using a Vmax 229 Sensormedics System (Yorba Linda, USA) in the upright position. Forced vital capacity (FVC) was also measured in the supine position. Maximal inspiratory pressure (MIP) was measured from the functional residual capacity in the upright position. Maximal expiratory pressure (MEP) was measured at total lung capacity. MIP was measured using a flanged mouthpiece with the maneuvers repeated at least three times or until two identical readings were obtained. Once the operator was satisfied, the maximum value of the three maneuvers that varied by less than 20% was recorded (12).

**STATISTICAL ANALYSIS**

Categorical and continuous variables were presented as numbers (percentages) and medians (interquartile ranges), respectively, due to the non-normal distribution of data. Non-parametric tests were performed in accordance with each other. Associations were assessed using non-parametric correlations. Finally, the discriminative characteristics of diaphragm echocardiographic parameters were assessed using the area under the curve (AUC) of receiver operator characteristics. Alpha risk was 5%. All calculations were performed using SPSS version 23.0 (IBM, Armonk, NY, USA).

**RESULTS**

Study population, diaphragm ultrasound, and respiratory function
From the 93 eligible patients with DMD, we included 74 patients who underwent diaphragm ultrasound to measure their diaphragm excursion (see Figure 1, flowchart), 68 (92%) patients (92%) were nonambulatory. Genetic tests did not find any mutation in one patent. Genetic findings in the 73 other patients were distributed as follows: exonic deletion, 60%; exonic duplication, 10%; nonsense mutation, 11%; small deletion, 3%; small mutation, 12%; and intronic mutation, 4%. The median upright pulmonary FVC decreased. Non-invasive ventilation was used by most patients. The respiratory muscle strength and the right and left diaphragm TF were reduced. In addition, the right and left deep diaphragm excursion were reduced. Table 1 summarizes the clinical and laboratory findings in patients with DMD.

Determinants of right diaphragm thickening fraction

The TF of the right diaphragm was significantly associated with that of the left diaphragm and it was inversely and significantly associated with age and Walton score. The right diaphragm TF was positively associated with LVEF, inspiratory capacity, upright FVC, supine FVC, MIP, peak expiratory flow (PEF), and MEP. Figure 2 panel A shows the relationship between the right hemi-diaphragm TF and MIP.

Determinants of the right diaphragm excursion

Right diaphragm excursion was significantly associated with left diaphragm excursion, and it was inversely and significantly associated with age and Walton score. The right diaphragm excursion was significantly positively associated with steroid use (p = 0.008), BMI, inspiratory capacity, upright FVC, supine FVC, MIP, PEF, and MEP. Figure 2 panel B shows the relationship between the right diaphragm excursion and MIP. Figure 2 panel C shows the relationship between pulmonary FVC and right diaphragm excursion, while Figure 2 panel D shows the relationship between the right diaphragm excursion and inspiratory capacity. The Table 2 summarizes relationship between diaphragm ultrasound parameters and spirometric parameters.
Diaphragm ultrasound accuracy for predicting respiratory involvement in DMD

In DMD, a right diaphragm TF > 28% is associated with a pulmonary upright FVC > 50% with a sensitivity at 100%, a specificity at 87%, and an AUC at 0.95 ($p = 0.001$). A right diaphragm excursion >25.4 mm was also associated with a pulmonary upright FVC > 50%, with a sensitivity of 100%, a specificity of 85.2%, and an AUC at 0.93 ($p < 0.001$). For the left hemidiaphragm, a left diaphragm TF > 26.8% is associated with upright FVC > 50%, with a sensitivity at 100%, a specificity at 90%, and an AUC at 0.95 ($p = 0.011$). A left diaphragm excursion >21.5 mm was also associated with a pulmonary upright FVC > 50%, with a sensitivity of 100%, a specificity of 93.9%, and an AUC at 0.97 ($p < 0.001$).

Figure 3 summarizes the ROC curves for the different diaphragm ultrasound parameters.

Equation for predicting pulmonary forced vital capacity

Using a regression that included right diaphragm excursion (RDE) and right inspiratory diaphragm thickness (RIDT), the FVC can be predicted using the following equation: $FVC (ml) = Constant + 295.9 \times RIDT (mm) + 52.4 \times RDE (mm)$.

DISCUSSION

In this study, we found that diaphragm ultrasound parameters were significantly correlated with lung volumes and respiratory inspiratory muscle strength in patients with DMD. We found a significant association between diaphragm TF and inspiratory capacity, FVC, and MIP, and a significant association between diaphragm excursion and inspiratory capacity, FVC, and MIP.

In addition, we suggest that diaphragm ultrasonography may predict respiratory involvement in DMD. Diaphragm ultrasound is a free-risk and reproducible technique that can be used at the bedside (13). Diaphragm ultrasound is used in the ICU during the weaning process to predict successful extubation (5). The diaphragm TF is associated with trans-diaphragmatic pressure and reflects the work of breathing in ICU patients (8, 13). In healthy individuals, diaphragm ultrasound has been found to be significantly associated with inspiratory muscle strength and pulmonary
function (14). In healthy subjects, the diaphragm TF is also significantly associated with gastric pressure at inspiration, and diaphragmatic deep inspiratory motion is also significantly related to trans-diaphragmatic pressure following the sniff maneuver (15). This significant association between diaphragm excursion and trans-diaphragmatic pressure has been observed in patients undergoing postoperative cardiac surgery (16). In ICU patients, diaphragm TF has already been found to be significantly associated with inspiratory muscle pressure (17).

Our results are similar to findings in previous studies of various other neuromuscular diseases such as facio-scapulo-humeral muscular dystrophy (18), late-onset Pompe disease (LOPD) (19), and amyotrophic lateral sclerosis (ALS) (20). In fact, Henke et al. (18) reported a significant association between diaphragm thickening and MIP and between diaphragm excursion and MIP. In LOPD patients, Ruggeri et al. (19) reported a significant association between vital capacity and diaphragm excursion, TF, and inspiratory muscle strength. Similar results were reported by Fantini et al. (20) in patients with ALS. In DMD, diaphragm thickness is lower than in healthy subjects (6), and diaphragm function decreases with age (21). The present study highlights the usefulness of diaphragm ultrasonography in predicting respiratory involvement in DMD.

We found that a right diaphragm TF > 28% could predict a pulmonary upright FVC > 50% in DMD. This diaphragm cut-off is similar to that in ICU patients and is used to predict weaning trials (22). A diaphragm TF < 29% has been reported to identify diaphragm dysfunction, defined by a change in endotracheal tube pressure less than 11 cm H₂O, after a bilateral anterior magnetic phrenic nerve stimulation (22). The required diaphragms TF cut-off required for extubation success varies among authors and extends from 30% to 36% (8, 17).

We found that a right diaphragm excursion > 25.4 mm can predict a pulmonary upright FVC > 50% using the subcostal approach. This result is similar to cardiac surgery findings previously reported (16). In fact, Lerolle et al. (16) found a cut-off value of 25 mm to identify diaphragm dysfunction. Mechanisms involved in diaphragm dysfunction in DMD are multifactorial and include muscle
dystrophy, mechanical ventilation, and diaphragm loading. In the ICU, mechanical ventilation may expose patients to muscle trauma, which may be due to excessive ventilation (23, 24). Because some patients with DMD experience cognitive impairment and disclosed inability to maintain an adequate mouth seal during spirometry, diaphragm ultrasound may be proposed to assess respiratory function. Magnetic resonance imaging can be used to assess diaphragm function and respiratory muscle fatty infiltration (25); however, this technique requires a supine position that can be very difficult to maintain in DMD patients with respiratory insufficiency and spinal fusion.

Finally, the FVC depends on the inspiratory muscles, expiratory muscles, and mechanical properties of the thoracoabdominal wall. Thus, the significant association between diaphragm ultrasound parameters and FVC, compared with the significant association between inspiratory capacity and diaphragm ultrasound, suggests that diaphragm ultrasound parameters reflect not only inspiratory muscle function but also global respiratory function.

Our study has some limitations owing to its retrospective design. In addition, diaphragm motion is pertinent, particularly in patients on unassisted breaths; in patients on mechanical ventilation, the diaphragm downward displacement is the combined diaphragm displacement induced by the ventilator and the diaphragm displacement due to patient inspiratory efforts (26). In addition, most DMD patients are on nocturnal noninvasive mechanical ventilation, which may affect diaphragm function over time. Finally, external validation of our data was not performed. Prospective longitudinal studies that focus on the evolution of DMD patients before and after ventilation will help to better stratify patients.

**Conclusion**

DIM and diaphragm TF were significantly associated with spirometric parameters and inspiratory muscle strength. These diaphragmatic ultrasound parameters may predict the respiratory involvement in DMD. Diaphragm ultrasound can be used to assess and monitor respiratory status in DMD and may be appropriate for assessing DMD-like myopathies such as sarcoglycanopathies.
**Findings: none**

**List of abbreviations**

ALS: amyotrophic lateral sclerosis

AUC: area under the curve

DMD: Duchenne muscular dystrophy

DIM: diaphragm inspiratory motion

FVC: forced vital capacity

GMW: Gardner Medwin Walton score

IC: inspiratory capacity

ICU: Intensive Care unit

LOPD: late-onset Pompe disease

LVEF: left ventricular ejection fraction

MIP: maximal inspiratory pressure

MEP: Maximal expiratory pressure

PEF: Peak expiratory flow

RDE: right diaphragm excursion

RDIM: right diaphragm inspiratory motion

RDIT: right inspiratory diaphragm thickness

TF: thickening fraction
REFERENCES


FIGURES

Figure 1: *flow chart* diagram of patients included in the study

DMD: Duchenne muscular dystrophy
Figure 2:

Panel A: Relationship between diaphragm R (right) thickening fraction and max inspi pressure (maximal inspiratory pressure). Panel B: Relationship between right diaphragm inspi (inspiratory) motion and max inspi pressure (maximal inspiratory pressure). Panel C: Relationship between pulmonary forced vital capacity (ml) and diaphragm right inspi (inspiratory) motion (mm). Panel D: Relationship between right diaphragm inspiratory motion and inspiratory capacity

Right diaphragm inspi motion= right diaphragm excursion

Diaphragm inspiratory motion= diaphragm excursion
Figure 3: ROC curves of diaphragm ultrasound parameters to predict pulmonary upright FVC>50%.

Table 1: clinical, spirometric and ultrasound parameters of patients included in the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N</th>
<th>Median [range] or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74</td>
<td>22[19-25]</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>61</td>
<td>19.5[15.4-25]</td>
</tr>
<tr>
<td>Wheelchair bound</td>
<td>74</td>
<td>68 (92%)</td>
</tr>
<tr>
<td>GMW score</td>
<td>73</td>
<td>7 [7-8]</td>
</tr>
<tr>
<td>Steroids***</td>
<td>74</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>Spinal fusion</td>
<td>55</td>
<td>39(71%)</td>
</tr>
<tr>
<td>Nocturnal non-invasive ventilation</td>
<td>74</td>
<td>52 (70%)</td>
</tr>
<tr>
<td>Nocturnal and diurnal non-invasive ventilation</td>
<td>74</td>
<td>13 (17.6%)</td>
</tr>
<tr>
<td>Upright FVC (ml)</td>
<td>63</td>
<td>780[500-1620]</td>
</tr>
<tr>
<td>Upright FVC (%)</td>
<td>63</td>
<td>17[11-35]</td>
</tr>
<tr>
<td>Supine FVC (%) **</td>
<td>37</td>
<td>16[11-30]</td>
</tr>
<tr>
<td>FEV1 (ml)</td>
<td>48</td>
<td>590[460-1090]</td>
</tr>
<tr>
<td>IC(ml)</td>
<td>50</td>
<td>530[370-770]</td>
</tr>
<tr>
<td>IC (%)</td>
<td>49</td>
<td>16[11-22]</td>
</tr>
<tr>
<td>PEF (l/s)</td>
<td>51</td>
<td>2.3[1.1-3.4]</td>
</tr>
<tr>
<td>RV(ml)</td>
<td>33</td>
<td>1400[1240-1860]</td>
</tr>
<tr>
<td>MIP (cmH2O)</td>
<td>56</td>
<td>20[12-34]</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>46</td>
<td>25.6[23-28]</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>74</td>
<td>50[42-60]</td>
</tr>
<tr>
<td>sPAP (mmHg)</td>
<td>26</td>
<td>20.5[18-25]</td>
</tr>
<tr>
<td>Right diaphragm thickness* (mm)</td>
<td>44</td>
<td>1.5 [1-2]</td>
</tr>
<tr>
<td>Right diaphragmatic TF (%)</td>
<td>30</td>
<td>18[11-36.3]</td>
</tr>
<tr>
<td>Right deep diaphragmatic inspiratory motion(mm)</td>
<td>74</td>
<td>11[7-27]</td>
</tr>
<tr>
<td>Left diaphragmatic thickness* (mm)</td>
<td>30</td>
<td>1.4 [1-1.7]</td>
</tr>
<tr>
<td>Left diaphragmatic TF (%)</td>
<td>15</td>
<td>18.5[12.5-46]</td>
</tr>
<tr>
<td>Left deep diaphragmatic inspiratory motion(mm)</td>
<td>41</td>
<td>8[6-20]</td>
</tr>
</tbody>
</table>

TF: thickening fraction; BMI, body mass index; FVC, forced vital capacity; IC, inspiratory capacity; FEV1, forced expiratory volume in 1 s; MIP: maximal inspiratory pressure; PEF: peak expiratory flow; RV: residual volume; LVEF: left ventricular ejection fraction; sPAP: systolic arterial pulmonary pressure; GMW: Gardner Medwin Walton score

*: end expiratory; ** % of theoretical in upright

***: prednisone (0.75 mg/kg/day) was used for all patients except for one who was treated with deflazacort
Table 2: Correlations between diaphragm parameters and clinical parameters, spirometric and cardiac parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Age (y)</th>
<th>BMI (kg/m²)</th>
<th>GMW Score</th>
<th>LVEF (%)</th>
<th>IC (%)</th>
<th>Upright FVC (%)</th>
<th>Supine FVC (%*)</th>
<th>MIP (cmH20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right diaph TF (%)</strong></td>
<td>-0.58 (p 0.001)</td>
<td>0.18 (p 0.38)</td>
<td>-0.45 (p 0.012)</td>
<td>0.39 (p 0.03)</td>
<td>0.56 (p 0.004)</td>
<td>0.68 (p &lt;0.0001)</td>
<td>0.56 (p 0.038)</td>
<td>0.57 (p 0.002)</td>
</tr>
<tr>
<td><strong>Left diaph TF (%)</strong></td>
<td>-0.76 (p 0.001)</td>
<td>0.34 (p 0.27)</td>
<td>-0.75 (p 0.001)</td>
<td>0.70 (p 0.004)</td>
<td>0.67 (p 0.012)</td>
<td>0.75 (p 0.002)</td>
<td>0.9 (p 0.037)</td>
<td>0.79 (p 0.004)</td>
</tr>
<tr>
<td><strong>Right diaph motion (mm)</strong></td>
<td>-0.5 (p &lt;0.0001)</td>
<td>0.38 (p 0.002)</td>
<td>-0.53 (p&lt;0.0001)</td>
<td>0.06 (p 0.6)</td>
<td>0.62 (p&lt;0.0001)</td>
<td>0.77 (p&lt;0.0001)</td>
<td>0.64 (p&lt;0.0001)</td>
<td>0.63 (p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Left diaph motion (mm)</strong></td>
<td>-0.53 (p&lt;0.0001)</td>
<td>0.41 (p 0.016)</td>
<td>-0.59 (p&lt;0.0001)</td>
<td>0.025 (p 0.87)</td>
<td>0.79 (p &lt;0.0001)</td>
<td>0.85 (p&lt;0.0001)</td>
<td>0.79 (p&lt;0.0001)</td>
<td>0.69 (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

R, Spearman’s rho; TF, thickening fraction; diaph, diaphragm; BMI, body mass index; LVEF, left ventricular ejection fraction; IC, inspiratory capacity; FVC, forced vital capacity; MIP, maximal inspiratory pressure; y, years; %*, % of theoretical in upright; GMW: Gardner Medwin Walton score