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## Diaphragm ultrasound for muscle strength assessment: A systematic literature review

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### ABSTRACT

**Objective:** To assess if diaphragmatic ultrasound (DU) reflects diaphragmatic muscle strength when compared to respiratory tests and neurophysiological studies.

**Methods:** A systematic literature review was conducted on adults undergoing DU, compared to any respiratory or neurophysiological technique. The search strategy was applied in PubMed, Scopus, and Web of Science, and the analysis was conducted using the PRISMA methodology. Three eligibility assessment stages were performed: title, abstract, and full-text reading. The risk of bias was evaluated using the RoB 2.0, ROBINS-I, and Newcastle-Ottawa Scale tools.

**Results:** Out of 155 identified articles, 25 were selected for full-text review (14 non-randomised studies, 8 case-control studies, and 3 randomised studies). The overall risk of bias was moderate, with the main biases related to population selection and intervention assessment.

Twenty-three articles used maximal inspiratory pressure measurement as a comparator which showed a weak-to-moderate correlation, significant in 10 studies, with diaphragmatic excursion. Three studies reported a weak association between diaphragmatic thickening and sniff pressure.

Five articles reported a concordant correlation between diaphragmatic thickening and compound muscle action potential amplitude, significant only in one study.

**Conclusion:** The variability of results obtained across different pathologies does not support the use of DU alone to predict diaphragmatic muscle strength.

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### KEYWORDS


Diaphragm; ultrasound; muscle; dysfunction

## Introduction

The diaphragm plays a preponderant role in ventilatory mechanics as it is the main inspiratory muscle. It's a striated skeletal dome-shaped muscle and inserts into the tendons of the lower ribs bilaterally, an area called the apposition zone, being supported by the aortic and hepatic pillars.<sup>1,2</sup> This muscle is innervated bilaterally by the phrenic nerve, originating from cervical motor roots 3 to 5.<sup>1</sup> During the respiratory cycle, when the diaphragm contracts, the apposition zone shortens and the muscle performs a caudal and anterior movement.<sup>1,3</sup> This movement increases abdominal pressure and decreases pleural pressure, resulting in lung inflation.<sup>2</sup> During passive expiration, the diaphragm moves in the cranial direction.<sup>1</sup> The loss of function of the diaphragm, i.e., the decrease in its contraction force, promotes a lower pressure differential between the pleural pressure, and therefore, the alveolar pressure, and the atmospheric pressures, which results in alveolar hypoventilation and muscle fatigue.

Diaphragmatic dysfunction (DD) can occur due to phrenic nerve neuropathy, neuromuscular junction disorder or myopathy and is characterised by the loss of partial or total capacity of the diaphragm to

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generate muscle force.<sup>3</sup> In this situation, the diaphragmatic domes perform a cranial movement (i.e., paradoxical) during inspiration.<sup>1-3</sup>

The method considered by several authors as the *gold-standard* to evaluate DD is the measurement of transdiaphragmatic pressure (Pdi), which consists of the difference between gastric (abdominal) pressure and oesophageal (pleural) pressure during a voluntary contraction or during magnetic stimulation of the phrenic nerve.<sup>2</sup> However, it's an invasive method.<sup>2</sup> Alternatively, non-invasive methods for the diagnosis of DD are proposed: i) the amplitude of the compound muscle potential (CMAP) of the diaphragm after electrical or magnetic stimulation of the phrenic nerve translates the muscle strength during contraction;<sup>2,4</sup> ii) maximal inspiratory pressure (MIP) and inspiratory nasal *sniff* pressure allow estimating the muscle strength performed by the inspiratory muscles during a voluntary maximal inspiration;<sup>2,4</sup> iii) the variation in vital capacity, between the sitting and supine positions, which evidences the repercussion of diaphragmatic dysfunction on lung volume.<sup>5</sup> However, these tests are highly dependent on subject compliance and may therefore fail to reflect the true capacity for diaphragmatic contraction.

DD is also identifiable by diaphragmatic ultrasonography (DU). This non-invasive, independent on subject compliance and fast-performing technique allows the dynamic evaluation of the excursion and thickness of the diaphragm at rest or during respiration. At total lung capacity (TLC), the diaphragm shortens and presents its maximum thickening, compared to the end of passive expiration at the level of functional residual capacity (FRC) and minimal thickness. From these measurements, it's possible to calculate the diaphragm thickening fraction (DTF), which translates the muscle shortening index.<sup>6</sup> However, despite the applicability of DU in the biomechanical study of the diaphragm, there are divergent outcomes in the literature regarding the relationship between DU and diaphragmatic motor function when compared to other techniques, which may be related to the fact that this is an operator-dependent and a non-standardised technique.<sup>4,7</sup>

In light of the above, this study's objective was to evaluate the predictive value of DU in the assessment of diaphragmatic function when compared with pulmonary function tests and neurophysiological studies.

## Methods

A systematic review of the literature was carried out in order to answer the following research question: 'What is the diagnostic accuracy of DU in the evaluation of diaphragm muscle function when compared with pulmonary function tests and neurophysiological studies, in various clinical contexts?' The following studies were considered: those: i) conducted in adults; ii) involving participants who had performed a DU; iii) that described an another technique as a comparator performed in addition to the DU; and iv) those studies that aimed to extrapolate diaphragmatic muscle function through DU.

Then, the inclusion criteria were defined: i) studies using DU and another study method as baseline for comparison, in particular: diaphragmatic electromyography, phrenic nerve conduction studies, inspiratory nasal *sniff* pressure, MIP; ii) articles written in Portuguese, English or Spanish; iii) studies published in scientific journals. Studies were excluded if they: (i) were conducted on individuals under 18 years of age; ii) had been performed on pregnant women; iii) had been carried out on animals; iv) presented insufficient data related to the intervention and comparator techniques; v) were systematic reviews or meta-analyses.

The search strategy was applied in three databases, *PubMed*, *Scopus* and *Web of Science*. Advanced research was used in each of them, inserting the research equation presented in the supplementary material (Table 1). The search and selection of articles was carried out using the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) methodology.

The total number of articles retrieved in the three databases was included in the *Mendeley*<sup>®</sup> software (Elsevier, Europe), in order to identify and eliminate duplicates. The remaining articles were imported to the *Rayyan*<sup>®</sup> platform (Cambridge, USA), in order to perform the screening and selection of articles with the defined research strategy. The following evaluation stages were carried out: 1) title, 2) abstract and 3) reading the full article for assessment and eligibility criteria. The different stages of evaluation were carried out by three researchers through the dichotomous classification of 'Included'/'Excluded'. In case of disagreement, two investigators with at least five years of clinical research (JL, MLA) evaluated the study methodology and results, deciding in agreement on its inclusion or exclusion.

The included articles were assessed for risk of bias using the following Cochrane tools (The Cochrane Collaboration, United Kingdom): randomised studies using the risk of bias scale – RoB 2.0; non-randomised intervention studies by ROBINS-I; and case studies controlled by the Newcastle-Ottawa scale. The risk of bias was also calculated in each type of study (randomised and non-randomised). Two investigators (MM, MLA) were responsible for evaluating the quality of the studies and, in the event of disagreement between the two, a third researcher (JL) was consulted, and a consensus decision was reached by all three. The data was extracted to *Excel*<sup>®</sup> (Microsoft, USA).

The studies included demonstrated some variability in the techniques employed for the assessment of respiratory muscle function when compared with diaphragmatic ultrasound (DU). In the majority of studies, evaluations were conducted sequentially; in two studies,<sup>8,9</sup> assessments were performed concurrently with DU, and in one study<sup>10</sup> the interval between evaluations did not exceed one month.

## Results

A total of 155 references were identified in the *PubMed*, *Scopus*, and *Web of Science* databases (Figure 1). After removing the duplicate articles, the titles of 106 articles were read, of which 91 were selected for review of the abstracts. Of these, 45 articles were selected by the authors to assess the eligibility criteria, and 25 studies were included, briefly described in Table 2 of the supplementary material. The reviewed studies presented different methodologies, with mostly non-randomised observational prospective studies ( $n = 14$ ), followed by three randomised observational studies and eight case-control studies.

The risk of bias of the randomised trials was moderate. Figure 2 shows the results of the risk assessment. The most relevant were related to the authors' intention to obtain an expected result (D2), mostly associated with training sessions prior to the DU assessment and the existence of omitted results (D3). Regarding to non-randomised studies, the risk of bias was also moderate (Figure 2B). These were hampered by the selection of participants and by confounders of interpretation of the DU related to methodological aspects of the technique and consequent missing data. Overall, the risk of bias was higher than in randomised trials. Case-control studies had an average score of 6 stars and a moderate risk of bias. The main risk was the comparative study method with the DU and its consequent extrapolation to the discussion of results. The risk of bias assessment of the three types of studies included is presented in the supplementary material (Table 3 to 5).

## Discussion

### *Diaphragmatic ultrasound studies and pulmonary function tests*

Twenty-three articles included in the systematic review assessed the correlation between MIP, as a representative parameter of inspiratory muscle strength, and the diaphragm thickening fraction (DTF) and diaphragmatic excursion assessed by DU

In two studies, healthy subjects were studied. On 63 healthy subjects with a mean age of 34 years old showed a predicted forced vital capacity of 107% ( $\pm 15\%$ ), a mean MIP of 94 cmH<sub>2</sub>O ( $\pm 27$ cmH<sub>2</sub>O) and a MEP of 130 cmH<sub>2</sub>O ( $\pm 31$ cmH<sub>2</sub>O). On these subjects, the mean DU excursion during  $P_{sniff}$  was 2.6 cm ( $\pm 1.0$  cm) and during maximal inspiration was 8.1 cm ( $\pm 1.0$ ). Whereas DU inspiration thickness was 0.5 cm ( $\pm 0.2$  cm) and expiration was 0.2 cm ( $\pm 0.1$  cm)<sup>9,11</sup> Regarding DTF, the majority of the studies used a cut of < 20% to define diaphragm paralysis or dysfunction.

MIP and DU was also evaluated in obese patients with low mobility.<sup>12</sup> On these patients, DU excursion also was moderately associated with MIP. Although, this positive association, the increase thick of subcutaneous tissue between the probe and the diaphragm cupula may promote a high variability of the DU measurements within ultrasound operators. In fact, the deep position of the diaphragm makes challenging the muscle identification and DTF measurements with a linear probe. In such a way, that to reduce inter- and intra-operator variability, the right hemidiaphragm is commonly assessed due to the more predictable location and movement between the lung and liver.

As reported in the results, numerous studies have demonstrated a positive association between MIP and diaphragmatic excursion, as well as between DTF and MIP, suggesting that the force generated by

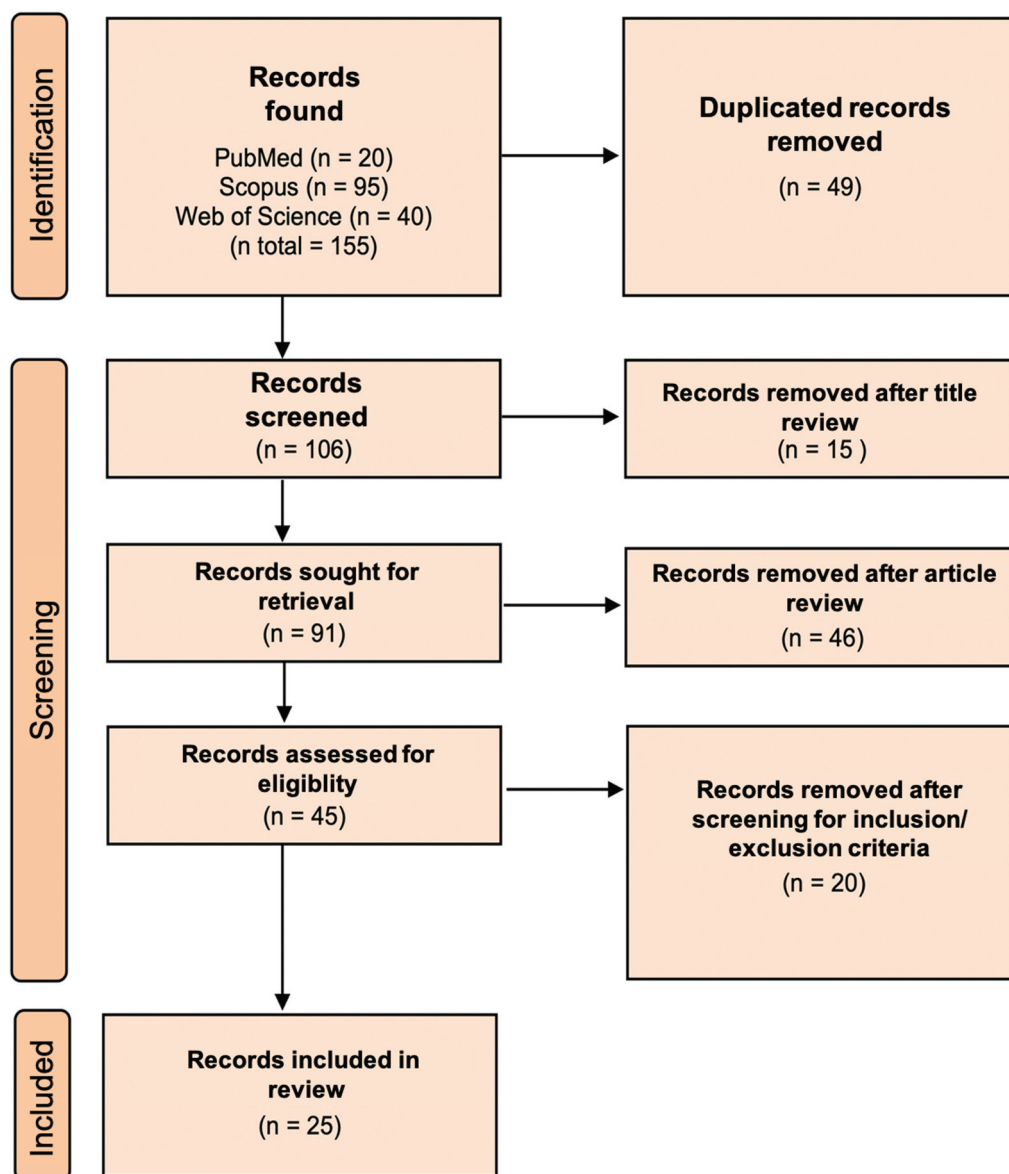
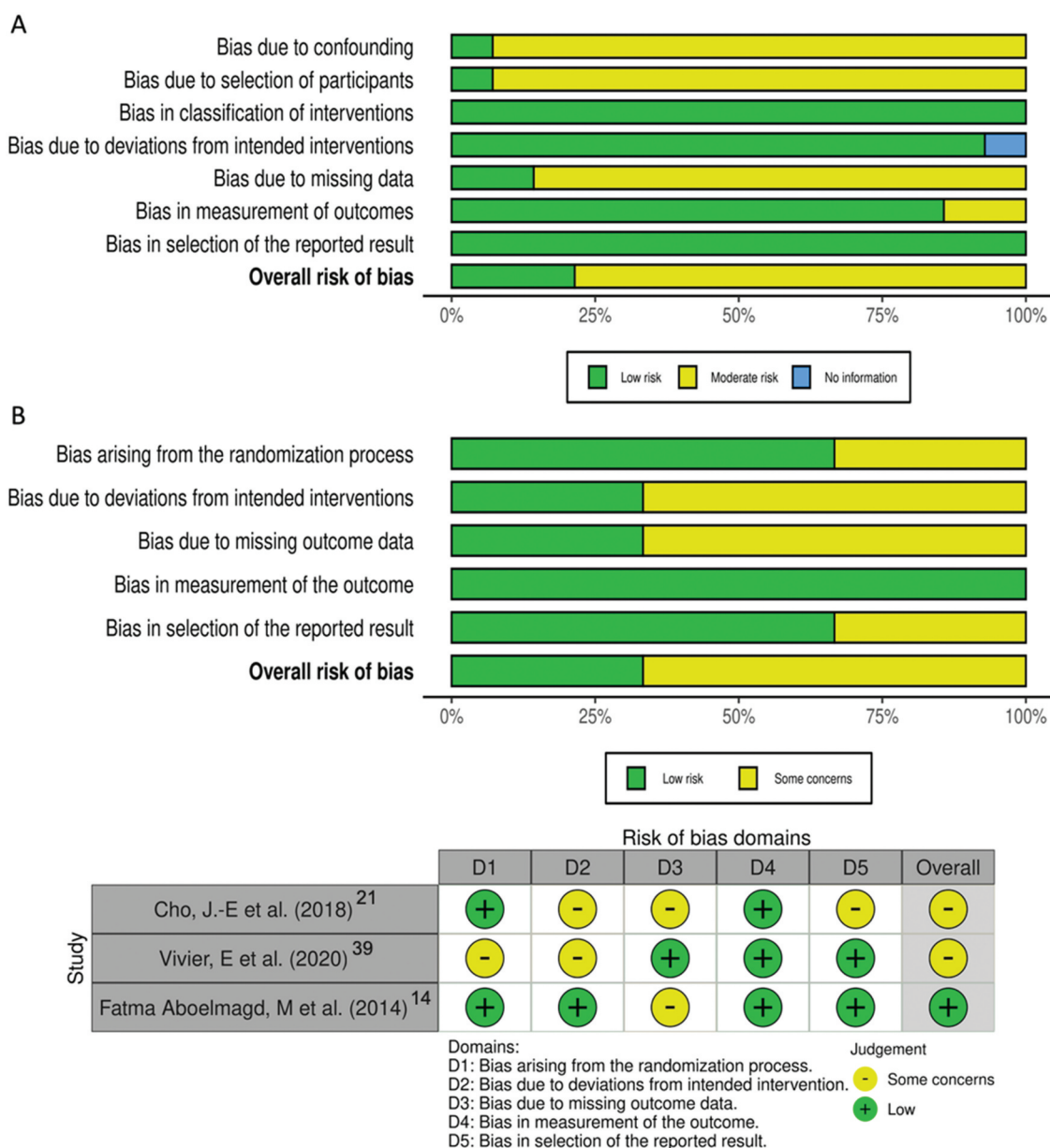


Figure 1. Fluxogram prisma.

inspiratory muscles can be assessed by movement and anatomical-structural changes in the diaphragm. In healthy studies, a significant relationship was found between diaphragm thickness by DU during MIP and MIP itself ( $r = -0.71$ ;  $p < 0.01$ ), and DTF and MIP. ( $r = -0.82$ ;  $p < 0.01$ ).<sup>8</sup> However, the correlations presented showed variable statistical degrees between studies. In addition, the majority of the studies did not show significant differences between patients and controls groups (Table 2).

One factor to be taken into consideration is that the MIP manoeuvre translates the strength of several inspiratory muscles.<sup>13</sup> Although, MIP measurements are mainly performed with patients in the sitting position, DU scanning position wasn't described in some manuscripts which could contribute to the variation of these correlations. This is because in the supine position the diaphragm is elevated due to the abdominal contents.<sup>14</sup>

On the other hand, the pathophysiology of each disease can also add variability in the association of techniques. COPD leads to several changes in the inspiratory muscles, e.g., cachexia, muscle weakness and lung hyperinflation. Cachexia and muscle weakness in COPD are the result of alterations in muscle energy metabolism, including reduced oxidative capacity, increased protein catabolism, altered amino acid metabolism and insulin resistance which lead to muscle mass loss and



**Figure 2.** Assessment of methodological bias of non-randomised studies (A,  $n = 14$ ) and randomised studies (B,  $n = 3$ ) included in literature review.

deterioration of muscle function, both peripheral and respiratory, thereby affecting the diaphragm. In more severe cases (GOLD stage 3 and stage 4), a greater component of hyperinflation, i.e., an increase in residual volume, impairs diaphragmatic contraction even more.<sup>15</sup> However, in COPD of lower stages, MIP demonstrated a weak positive relationship with diaphragmatic excursion ( $r = 0.496$ ,  $p = 0.022$ ).<sup>12</sup>

In neuromuscular diseases, the first changes occur at the axonal or muscular level. Respiratory changes in these patients are subtle and usually appear in advanced stages of the disease. In the study carried out in patients with Friedreich's ataxia,<sup>16</sup> the loss of motor coordination may justify the decrease in diaphragmatic excursion by dissynchronous contraction, so DD will depend on the phenotype of the neuromuscular disease, the stage and physical conditions of the patient.

Yetkin et al.<sup>16</sup> found a moderate negative correlation between diaphragm excursion and SARA (Scale for the Assessment and Rating of Ataxia) score and between DTF and SARA score. In fact, patients with Friedreich's ataxia showed differences in DU inspiratory thickness (18 vs 20 mm), thickness fraction (21.5% vs 33.5%) and DU

excursion (1.1 cm vs 1.7 cm) in comparison with controls.<sup>16</sup> However, in this study, diaphragmatic excursion was only measured during deep inspiration and not compared with measurement at tidal volume.

In the studies that evaluated the association of changes in DU and the  $P_{sniff}$  manoeuvre in patients with ALS, DU was suggested as a complementary technique in the assessment of diaphragmatic muscle strength, being an asset in the population studied since it does not require so much effort and muscle coordination.<sup>17,18</sup> However, Pinto et al.<sup>17</sup> did not find significant changes in thickness (in TLC and RV) between the initial and four-month DU evaluation among patients with spinal and bulbar ALS phenotype, in disagreement with the  $P_{sniff}$ , which showed a significant decline between measurements. The authors considered that the findings were influenced by the study population, consisting of individuals with ALS at an early stage.<sup>19</sup> Respiratory function was considered preserved taking into account that the patients had a combination of the following factors: percentage of the reference value of forced vital capacity > 60%, maximum voluntary ventilation  $\geq$ 15%, MIP  $\geq$ 19%, maximum expiratory pressure  $\geq$ 20% and functional scale (ALSFRS)  $\geq$ 35 points. However, between evaluations,  $P_{sniff}$  showed a significant decrease after four months in the two ALS phenotypes. In fact, about 20–30% of the participants in the three studies analysed had ALS with bulbar phenotype, which may explain the decline in  $P_{sniff}$ , rather than other pressures (namely MIP).<sup>17–19</sup> The authors explain these findings by noting that  $P_{sniff}$  measures inspiratory pressure during a more natural, spontaneous and brief effort which is less affected by fatigue or lack of coordination and so is more representative of actual respiratory function. However, MIP is a test that is more difficult to perform and requires a proper seal around the mouthpiece which is a challenge to those patients. Thus, when compared with a more natural effort, one would not expect MIP to appear less reduced. Like MIP, the performance of the *sniff* manoeuvre does not depend exclusively on the muscle strength of the diaphragm, but on the entire set of inspiratory muscles. However, the speed of shortening is higher than in the MIP manoeuvre. The change in the strength-velocity relationship, related to the decrease in the length of muscle fibres, leads to a decrease in muscle strength in patients with muscle atrophy<sup>13</sup> and, therefore, in the maximum pressure that can be measured.

Of the studies included, few addressed the relationship between DU and  $P_{sniff}$ , and the results suggest the existence of a variable relationship, therefore, only complementary in the specific case of ALS. In addition, in the three studies analysed, no measurements of diaphragmatic excursion were performed. In a study conducted by Fayssoil et al, in individuals with various neuromuscular pathologies, the authors found a significant correlation between diaphragm excursion and *sniff* nasal pressure, a significant association between maximum diaphragmatic excursion velocity and forced vital capacity (FVC) and *sniff* nasal pressure, and concluded that DU, during *sniff*, demonstrated a high diagnostic accuracy to predict a FVC < 60%,<sup>20</sup> an indicator of greater degradation of respiratory function. The studies by Pinto et al.<sup>18,19</sup> and Fantini et al.<sup>17</sup> focused specifically on ALS, while Fayssoil et al. focused on a broader spectrum of neuromuscular diseases. Although they are not fully comparable, in view of the techniques chosen to relate to the DU and the difference in the samples, they all support the use of the DU in the evaluation of DD.

### **Diaphragmatic ultrasound and neuromuscular function studies**

Five studies tested the association between DU and CMAP of the phrenic nerve. The analysed articles suggest the possibility of a positive association between excursion and diaphragm thickening parameters evaluated by DU and parameters evaluated by phrenic nerve conduction studies, namely its CMAP.<sup>18,21,22</sup> However, Spiesshoefer et al.<sup>23</sup> in the study of patients with late-onset Pompe disease previously mentioned, did not identify a decline in CMAP amplitude associated with decreased excursion and DTF by DU. However, patients with showed a smaller predicted FVC (64% vs 110%), MIP (37.5.5 cmH20 vs 97.5 cmH20), MEP (74.2 vs 130.1), maximum voluntary DU excursion (4.3 vs 7.4 cm) and a DU ratio thickness (1.8 vs 2.6).

On the other hand, in overtime assessments in patients with ALS<sup>19</sup> a significant decrease in CMAP was demonstrated and not in the diaphragm thickness evaluated by DU. Only one of the studies<sup>18</sup> evidenced the existence of a significant correlation between CMAP and diaphragm thickening, which suggests that this correlation may not be as strong as with the respiratory function parameters evaluated in this systematic review. Although, in one study patients with ALS showed a lower predicted FVC (75% vs 107%), weaker  $P_{sniff}$  (46 cmH20 vs 85 cmH20), lower DU inspiratory thickness (0.38 cm vs 0.53 cm) as a lower DTF (90% vs 208%) in comparison with controls. The dispersion of results among the different

studies excludes a relationship between the DU and the diaphragm neurophysiological studies. Furthermore, it is possible to acknowledge that this variability may be due to the pathophysiology of each disease. Pompe disease is a pathology that primarily affects skeletal muscle and at the time of the neurophysiological study, despite structural changes, it could still be functionally preserved.<sup>24</sup> On the other hand, ALS primarily affects the motor neuron and the decrease in phrenic nerve CMAP is usually noticed, prior to muscle atrophy.<sup>25</sup>

## Conclusion

After reviewing the studies with moderate risk of bias, the dispersion of results in different pathologies does not allow us to support the use of DU alone to predict diaphragm muscle strength. The variability of results and strength of the statistical associations between the DU assessment and the muscle strength of the diaphragm is centred on: 1) the typology, pathophysiological process and stage of disease of the patients included with decreased muscle strength; 2) the absence of standardised DU assessment, including probe type, anatomical region of assessment and measured parameters; 3) the use of various techniques as comparators, namely, respiratory manoeuvres and neurophysiological tests, also without reference to technical criteria of good performance.

However, it is possible to recognise the potential of DU as a method of structural and complementary evaluation of pulmonary function tests when there is doubt about the patient's ability to collaborate. Additionally, it can complement the neurophysiological evaluation in early stages of neuromuscular disease onset to elucidate the underlying pathophysiological process.

In the future, a consensus expert panel should suggest minimum requirements for performing DU, including ultrasound settings, technical and practical aspects. The DU measurements pitfalls should also be addressed to describe motion and anatomical perspective of the diaphragm. Regarding respiratory and neurophysiological testing, would be of interest to describe how DU behaves during respiratory manoeuvres to promote DU utility and clinical application.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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