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Lara Maria Mouta Torres

Avaliação ecográfica da disfunção diafragmática induzida por ventilador como preditor do sucesso da extubação em crianças sob ventilação mecânica

Ultrasound assessment of ventilator-induced diaphragmatic dysfunction to predict the success of weaning in mechanically ventilated children

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Ultrasound assessment of ventilator-induced diaphragmatic dysfunction to predict the success of weaning in mechanically ventilated children

ORIENTADOR

Marta João Silva

COORIENTADOR (se aplicável)

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Ultrasound assessment of ventilator-induced diaphragmatic dysfunction to predict the success of weaning in mechanically ventilated children

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ABSTRACT

A great number of patients admitted to the ICU require mechanical ventilation during their process of care. However, there is increasing awareness that ventilator-induced diaphragmatic dysfunction is highly prevalent in critically ill patients and is likely a contributing cause of weaning failure. On the pediatric field, this phenomenon may have a greater impact. Conventional tools to evaluate diaphragm function are not simple or adequate to perform in mechanically ventilated patients. Ultrasonography has recently emerged as a new method for assessment of diaphragm function, prevailing over other imaging modalities. Certain indices of diaphragm function, namely diaphragm thickness, thickening fraction and excursion have been established for mechanically ventilated patients to monitor changes in diaphragm function over time, to detect diaphragmatic dysfunction, and to evaluate if these indices can predict successful weaning from mechanical ventilation. The aims of this narrative review are to summarize the technique and the clinical applications of ultrasonography in the evaluation of diaphragmatic function in ICU pediatric patients, and to assess its utility and accuracy for predicting weaning outcomes.

Keywords: diaphragm, ultrasound, child, ventilation, weaning.

INTRODUCTION

In patients hospitalized in the Intensive Care Unit (ICU), diaphragmatic weakness may be common in mechanically ventilated patients[1]. Mechanical ventilation (MV) has been proved to induce several diaphragmatic abnormalities, resulting in atrophy and contractile dysfunction of the muscle [2,3]. The reduction of diaphragmatic contraction ability caused by MV is termed ventilator-induced diaphragmatic dysfunction (VIDD)[1].

The clinical significance of VIDD resides in the fact that, even when used for short periods of time, MV can lead to substantial diaphragmatic weakness that could delay or impede the process of weaning from the ventilator [4]. The inability to discontinue ventilation results in extended hospital stays and increased patient morbidity and mortality [5,6]. Hence, an early diagnosis of diaphragmatic dysfunction (DD) before extubation is imperative to avoid weaning failure [7].

Impaired function of the diaphragm can be confirmed by a few invasive and noninvasive tests. Although many approaches for monitoring respiratory muscle function are available, most of them have several disadvantages, specially at the bedside [8]. One of the major challenges still lies in how to evaluate diaphragm function with a specific, noninvasive, and easily performed at the bedside technique that could help deciding what is the appropriate time for weaning from MV [9,10].

The use of ultrasonographic evaluation of the diaphragm is an area of emerging interest. This method have been reported as an effective method to detect DD in critically ill patients [1,11], to predict extubation success or failure [6,9,12] and to detect and monitor diaphragm acquired weakness in the ICU [12,13], according to recent literature.

Although ultrasound criteria have been published for the assessment of diaphragmatic function in adults [10], studies in the pediatric population are scarce, and it remains unclear how often mechanically ventilated children develop diaphragm atrophy and DD, and how does it influences the clinical outcomes [2,14,15].

The aims of this narrative review are to summarize the technique and the clinical applications of ultrasonography in the evaluation of diaphragmatic function in ICU pediatric patients, and to assess its utility and accuracy for predicting weaning outcomes.

METHODS

Search was performed in MEDLINE/PUBMED to identify articles published between january 1, 2009, and october 16, 2019. Inclusion criteria consisted in experimental and systematic review articles, published as original studies. The search was restricted to human studies, published in English or Portuguese. Opinion papers and editorials were excluded. In the literature, there is only a few reported studies conducted in children. To fill this gap in evidence, studies conducted in adults were also included in this review.

The articles were first selected by the titles and abstracts. In a second phase, the complete article was read and the information to be included in this literature review was extracted. The database review yielded 181 articles, and according to inclusion/exclusion criteria, 36 articles were finally included in the review. Additional cross-referenced studies from retrieved articles were identified and screened for pertinent information.

RESULTS

The most relevant results are summarized in Tables I-III. Table I summarizes the main advantages and disadvantages of the ultrasonography technique for diaphragmatic evaluation. Tables II and III summarize the most relevant findings regarding ultrasonographic indices to assess diaphragm contractile function in adults and children, respectively. Fourteen studies selected were conducted on adult patients and three on pediatric patients.

To assess DD in adults, diaphragmatic contractility as thickening fraction (DTF) was measured in 9 studies and diaphragm excursion (DE) was measured in 8 studies. Three studies compared ultrasound with other methods: 2 with rapid shallow breathing index (RSBI) and 1 with Lung US score.

In the three studies performed in children, DTF was the only ultrasonographic index measured. In all studies, a decrease in this diaphragmatic index was related to higher rates of extubation failure.

DISCUSSION

1. VENTILATED-INDUCED DIAPHRAGMATIC DYSFUNCTION (VIDD)

The diaphragm is the principal muscle of the respiratory system, playing a crucial role in the breathing process [16,17]. During inhalation, this muscle contracts and moves inferiorly, creating a partial vacuum in the thoracic cavity causing an increment in the volume inside and a reduction of the intra-thoracic pressure. As a result, the lungs expand in order to fill the void and air enters the lungs. On the other hand, when the diaphragm relaxes during expiration, air is exhaled by an elastic recoil process. The forced exhalation process requires the involvement of the internal intercostal muscles along with the abdominal muscles [18].

MV, which is a technique widely used and crucial in the treatment of critically ill patients, has been strongly associated with muscle weakness [19]. Diaphragm seems to have a much more rapid onset of fiber atrophy compared with limb skeletal muscles, being the explanation to this yet to be uncovered [13]. Thus, the correlation between length of MV and impaired function of the diaphragm has been strongly highlighted in recent publications. Demoule *et al* found that DD occurs in 64% of the patients on the first day from ICU admission [1]. A study by Schepens *et al* also demonstrated that diaphragm atrophy develop rapidly, within the first 24 hours of MV initiation in adults [13]. In agreement, similar findings were disclosed by Lee *et al* in pediatric patients, in whom changes in diaphragmatic parameters were observed after just 1 day of MV [14].

The definition of VIDD in the critically ill patients is a relatively recent concept, but its frequency and relevance have been an object of interest in recent investigations [15]. The reduction of diaphragmatic contraction ability is being linked to several complications such as a longer weaning time and poor prognosis [2,6]. Therefore, it is pivotal to diagnose DD as early as possible in order to avoid the above-mentioned complications and the risk of extubation failure [11].

In the last decade, the understanding of the underlying mechanisms of VIDD has been the subject of extensive research. Scientific data have shown that diaphragm impairment with controlled MV comprises alterations in force and structure of the muscle [20]. MV has been shown to induce metabolic diaphragmatic abnormalities, leading to a disruption at the level of the muscle cell membrane and the contractile apparatus [13]. Myofibril damage induces mitochondrial dysfunctions followed by the disruption of the sarcomere structure and intracellular lipid accumulation, which contributes to the reduction in diaphragmatic force overtime [4]. Histologically, the whole diaphragmatic fiber architecture is affected. Fiber atrophy and remodeling with change from slow to fast fibers cause a reduction of the endurance of the diaphragm, given that fewer fatigue-resistant fibers are encountered [20,21]. Biochemically, damages in the mitochondrial respiratory chain lead to overproduction of reactive oxygen species (ROS), which may induce oxidative damage in diaphragmatic proteins and lipids [22]. In addition, altered diaphragmatic gene expression results in the dysregulation of diaphragmatic protein synthesis and the activation of proteolysis, which accelerate protein breakdown, also leading to fiber atrophy [20,23]. The diaphragmatic force-generating capacity decreases, contributing to diaphragmatic contractile dysfunction [24].

On the pediatric field, this phenomenon may have a greater impact. In fact, children cannot tolerate a dysfunctional diaphragm as well as the adult population given that they tend to have weaker and more fatigable accessory respiratory muscles, which are inadequate to compensate the impaired function of the diaphragm [15]. Besides that, the more drastically DD in infants may be due to the presence of fewer type 1 fibers, which are slow-twitch and high-oxidative, therefore having higher oxidative capacity. The loss of sparse type 1 fibers in mechanically ventilated children may culminate in poor resistance to diaphragmatic fatigue and substantial deterioration of this muscle's contraction [14].

Apart from direct diaphragmatic alterations induced by MV, the ICU-acquired DD is also related to ICU acquired weakness, with several other factors influencing the onset of muscle weakness and dysfunction, such as inflammation, sepsis, the patient's nutritional status or the use of certain pharmacological agents [13,15]. In addition, the existence of neuromuscular syndromes before ICU admission has a well-established relationship with the development of DD [13].

The long term consequences of DD are still uncertain. In a study by Marianni *et al*, a rapid recovery of diaphragm thickness and contractility has been observed, suggesting that the underlying mechanisms of DD are presumably reversible [5]. In the pediatric population, further studies should be conducted to address the recoverability of diaphragm atrophy [2].

2. ASSESSMENT OF RESPIRATORY MUSCLE FUNCTION

The assessment of respiratory muscle function is fundamental in cases of suspected respiratory muscle weakness, given the serious deleterious consequences that may arise and can endanger the patient's life. These patients should be submitted to a prompt evaluation with physical examination, prior to undergoing pulmonary function tests [25].

Several methods have been developed to evaluate diaphragmatic function and contractile activity. Among these, imaging of the diaphragm, volitional tests, phrenic nerve stimulation and trans-diaphragmatic pressure measurement are currently the most widely used in clinical practice [8,26]. However, clinicians encounter a major challenge in ICU hospitalized patients with particular clinical settings that limit patient co-operation. There is still a lack of tools to accurately monitor diaphragm activity at the bedside [8].

Imaging techniques, including chest radiography, computed tomography and magnetic resonance comprise innumerous disadvantages, such as low availability, low sensitivity or specificity, exposure to ionizing radiation, invasiveness and requirement of patient transportation[11,26].

Alternatively, functional evaluation may be obtained by measuring inspiratory and expiratory pressure. **Volitional tests** give an estimative of global inspiratory and expiratory muscle strength. In spite of being noninvasive and relatively easy to perform at the bedside, these tests require patient co-operation and are poorly reproducible, particularly in intubated patients [4,8].

Diaphragmatic strength may also be estimated by measuring **transdiaphragmatic pressure (Pdi)** with esophageal and gastric balloons containing pressure transducers. Calculating the different between esophageal (P_{es}) and gastric (P_{ga}) pressures, quantitative information on the diaphragm strength is obtained [11,12]. However, this technique is still uncommon in clinical care, mainly due to its invasiveness and lack of reproducibility [4,8].

Measuring the **transdiaphragmatic twitch pressure via phrenic nerve stimulation** represents the gold standard for assessing diaphragm force. The diaphragm is exclusively innervated by the phrenic nerve, thus its stimulation provides a specific means to investigate this muscle. However, this test is invasive and difficult to perform in clinical settings [8].

All methods present several disadvantages, and their performance to diagnose diaphragmatic atrophy is still limited to non-intubated patients. Thus, they are nor simple or adequate to assess the diaphragm force-generating capacity in critically ill patients [4,12].

3. BEDSIDE ULTRASONOGRAPHY IN ICU PATIENTS

3.1 Ultrasonography technique for diaphragmatic evaluation

In recent years, ultrasonography (US) has emerged as a new method for assessment of diaphragm function, prevailing over other imaging modalities. Unlike the conventional methods, US represents a suitable diagnostic tool for ICU patients [27,28]. It allows a morphological and functional evaluation of the diaphragm in real time and can be repeated overtime at the bedside [7,27]. Furthermore, advantages of ultrasound also include safety, noninvasively, eviction of pain and radiation hazards and cost efficiency [4,7,15,27].

Ultrasonographic examination of the diaphragm can be achieved by two different acoustic windows [11]:

- First, by **the subcostal area**, between the mid-clavicular and anterior axillar lines, and measuring the displacements of the liver or spleen as acoustic windows. A low frequency curvilinear probe is recommended to visualize the muscle, as a hyperechoic line formed by the pleura adherent to the muscle diaphragm [11,29].

- The second possible approach is at the **zone of apposition (ZOA)** of the diaphragm to the rib cage, at the 8th or 9th intercostal space, between the anterior axillary and the mid-axillary lines at 0.5 to 2 cm below the costophrenic sinus. A high-frequency linear transducer (less penetration but higher resolution) should be placed directed perpendicularly to the diaphragm at a depth of 1.5 - 3 cm. The diaphragm is outlined as a less echogenic line between the two easily observed parallel echogenic layers of the pleural and peritoneal membranes [11,30]. This approach allows a direct observation of the diaphragm muscle [6]. (*fig. I*)

In the critical care setting, several US indices of diaphragmatic function have lately earned admiration in the assessment of critically ill patients. Particularly, diaphragm excursion and thickness has been subject of intense research.

Recently, a novel technique for finding the ZOA, "the **ABCDE** method," was described by Tsui *et al.* This technique represents a systematic approach using readily identifiable anatomical landmarks. First, one places a high-frequency linear probe at the anterior **Axillary** line, just below the nipple. Then, watches for **Breathing** (searching for movement of the pleura - lung sliding - on top of the diaphragm muscle). Then, moving the probe **Caudally** along the axillary line, one can identify the **Diaphragm** for **Evaluation,** since the diaphragm is no longer hidden under the pleura. Seeking specific acoustic windows, which may be challenging, is thus unnecessary [31]. ABCDE method of US diaphragm scanning had been demonstrated to be efficient and practical for novices, less time-consuming than conventional approaches and requiring minimal expertise [32]. It has also been successfully used for diaphragm evaluation in the pediatric field [33].

3.2 Diaphragm excursion

Diaphragm excursion (DE) is produced by the cyclic displacement of the diaphragm during the respiratory cycle [34]. Through a low frequency ultrasound transducer, with the patient in a supine position, it can be visualized as a echogenic line moving freely during the respiratory phases [28]. A B-mode (2-dimensional) transducer is first used to detect the best approach and to select the exploration line for each hemidiaphragm, using the liver as a window on the right, and the spleen on the left [28]. The ultrasound beam should be directed medially, cranially and dorsally, to reach perpendicularly the posterior third of the hemidiaphragm. Then, M-mode is used to display the motion of the diaphragm along the selected line, that appears in a waveform. Inspiration is identified as an upward curvature of the tracing (during inspiration, the diaphragm contracts and moves caudally towards the probe). In contrast, expiration is identified as downward curvature (during expiration, the diaphragm moves cranially away from the probe) [35,36]. With this technique, the DE, the inspiratory and expiratory times and the contraction speed can be measured. (*fig. II*)

3.3 Diaphragm thickness and diaphragm thickening fraction

US has also been used to evaluate diaphragm thickness (DT) in the ZOA of the diaphragm to the rib cage. By means of a high-frequency linear probe, the diaphragm is observed as the hypoechoic line located between the hyperechoic pleura and peritoneum [10].

The magnitude of the increase in thickness during inspiration can be expressed as a percentage. By measuring the muscle thickness at end inspiration (DT-end inspiration) and end expiration (DT-end expiration), the diaphragm thickening fraction (DTF) can be calculated as [(DT-end inspiration − DT end-expiration)/DT-end expiration ×100)] [37]. This index reflects variation in the thickness of the diaphragm during tidal breathing and provides an estimate of its strength during a maximal inspiratory effort [10]. In fact, diaphragm thickening during inspiration has been compared to an ejection fraction for the heart, suggesting that it is a reliable indicator of muscle effort [6]. (*fig. III*)

3.4 Limitations of the technique

There are limitations to the diaphragmatic sonography that need to be acknowledged.

Concerning the diaphragm displacement, there is evidence suggesting that this measurement **does not correlate with other indexes of respiratory effort** [6,34]. In fact, DE during an assisted breathing represents the sum of 2 forces acting synergistically: the patients' respiratory effort (active force) and the pressure provided by the ventilator (passive force), thus dismissing the importance of this parameter on patients under ventilatory support [12].

Another limitation could rely on the fact that the liver and the spleen are frequently used as acoustic windows. A **poor acoustic window** in MV patients have been reported to occur in 2% to 10% of cases [12,27,30]. Also, large part of the diaphragm is inaccessible to the observer, and the samples visualized may not be representative for the entire muscle [37]. Moreover, this approach **does not directly visualize the diaphragm** muscle itself. Therefore, factors as posture, breath size, impedance of close structures, alterations of the abdominal or thoracic pressure may vary DE [6].

In patient under MV, measurement of DT overcomes the limitations of the DE technique, as thickening should only be influenced by active contraction of the muscle [12]. Nevertheless, it can be affected by several factors. It is known that the DT is not homogeneous throughout its surface. Therefore, these measurements **may lack accuracy and reproducibility**. Goligher et al suggest standardizing the probe's placement, by marking the anatomical region, to minimize the variability [38].

It is also important to take into consideration that the **assessment of the left hemidiaphragm** cannot be consistently obtained by the gastric and intestinal gas interposition. These can obscure diaphragmatic movement, making its assessment compromised [30].

Lastly, these techniques are dependent on the level of operator experience [32].

The main advantages and limitations of ultrasonography are listed in *Table I*.

4. ULTRASOUND ASSESSMENT OF DIAPHRAGMATIC AS A PREDICTOR OF WEANING FROM MV

In the ICU, difficult weaning off breathing support may be encountered in 20% to 40% of patients receiving MV [39,40]. The appropriate timing of extubation is crucial in these patients, as both premature and delayed weaning are associated with increased morbidity, prolonged ICU admission, increase mortality rates as well as high hospital costs [41].

The effects of diaphragm atrophy and associated diminished DTF secondary to MV have been recently described in a large portion of the patients [21,38,42]. Interestingly, patients with increases in DT caused by an excessive inspiratory effort exacerbating load-induced diaphragmatic inflammation were also at higher risk of prolongated ventilation [43]. The progressive development of **diaphragm weakness** is an important and potentially avoidable determinant of weaning failure in a significant number of patients [1].

Determining the optimal moment to extubate a critically ill patient based solely on a clinician's subjective ability to predict extubation is insufficient [17]. Therefore, several indices to assess the patients' ability to regain spontaneous breathing have been developed over time. However, these parameters still have many limitations [36]. The gold standard weaning predictor is the **Rapid Shallow Breathing Index (RSBI).** It can be obtained by dividing the respiratory frequency by the tidal volume, and is considered one of the most accurate parameters to decide to extubate [44]. However, the utilization of the this index is limited by the fact that it measures the change in volume generated by all respiratory muscles, which may mask the presence of DD [36,45]. In fact, relying on RSBI can be misleading, since patients may sustain their tidal volumes using accessory respiratory muscles, which are more fatigable and weaker, and, therefore, more prone to fail extubation, regardless of the RSBI value [6,46].

Diaphragmatic US was proposed as an effective method to assess the muscle's strength and function during MV, identifying patients with severe DD and risk of difficult weaning [47]. There are two commonly used diaphragm sonographic predictors of weaning outcome: **the diaphragmatic excursion (DE) and diaphragm thicken (DT) or thickening fraction (DTF).** These US measurements can be used to define DD, although there is variation in this definition.

Several studies published in the last decade have shown that US measurements have high degree of reproducibility [14,30,38,48,49]. While some studies described DE, others focused on the assessment of DT and DTF. All studies concluded that their respective measurements can predict successful extubation or weaning failure, with cut-off values of 10–17 mm in excursion and 20–36% in thickness being most sensitive and specific.

According to some authors, diaphragmatic movement correlated well with transdiaphragmatic pressure. Measurement of the **DE** could, therefore, be an important tool to evaluate the respiratory endurance of a patient and, by extension, predict successful extubation [9,27,29,36,50]. Furthermore, Flevari *et al* concluded that this index may also be a reliable tool to assess patients with difficult and prolonged weaning, in whom the diaphragm has some degree of atrophy due to prolonged MV [51]. However, Carrie *et al* showed discordant results in their study, concluding that DE is not an accurate index to predict weaning failure of patients undergoing a first spontaneous breathing trial (SBT) [52].

On the contrary, some data available suggests a lower sensitivity and specificity for DE as compared to the DTF in predicting weaning outcome [7]. Some authors believe that **DTF rather than DE** is a reliable index of respiratory effort and active contraction of the diaphragm during MV, and reported a significantly higher DTF in the weaning success group, compared with the failure group, although there was significant heterogeneity [12,17,53]. Therefore, DTF is suitable to estimate the diaphragm function in patients undergoing MV, while DE should be reserved to cases in the absence of the breathing support, as the downward displacement of the muscle may reflect passive insufflation by the ventilator [47].

Li *et al* concluded that the **either measurement** is suitable to predict successful extubation [7]. In agreement, others also found that both excursion and thickening fraction were higher in patients who were successfully weaned [15,44,54,55].

Controversy to the findings of the majority of studies analyzed, in two studies, **RSBI** performed better than the sonographic measurements in predicting value for weaning outcome in a respiratory ICU, and should be a considered in every weaning protocol. However, they both acknowledge the fact that RSBI may provide false positive criteria and, extubation failure may still occur [45,46].

Weaning failure may rely on various clinical factors. Therefore, **a single diaphragmatic index might not be a perfect predictor** [56]. Numerous studies have emphasized the interest of combining diaphragmatic US with other traditional parameters for predicting weaning [26,36,44,45,54].

However, in the **pediatric field** there is still scarce evidence. Lee and colleagues were pioneers in studying the role of diaphragm US in **critically ill infants** [14]. In their study, diaphragm atrophy and decreased DTF were immediately observed within the first 24 hours of MV. Thus, the end-inspiratory DT and DTF measured using US may be useful indexes to evaluate diaphragmatic function. These parameters could be used to titrate adequate ventilator settings [14]. Glau *et al* suggested that the thresholds predictive of successful extubation may be different in pediatric patients [2]. In fact, in this study the median DTF within 24 hours prior to extubation was 13,8%, which is substantially lower than the values of DTF > 36% predictive of a successful spontaneous breathing trial [53] and TF ≥ 30% with successful extubation[6] established in adults [2]. Further studies should be conducted to determine the incidence and severity of DD and to establish cut-off values in infants [2,14]. Moreover, the clinical significances US indexes still remain controversial as the findings of some studies are still inconsistent and may lack statistical power [7].

Table II and *Table III* display a summary of the most relevant studies regarding ultrasonographic indices to assess diaphragm contractile force and function in adults and children, respectively.

All papers acknowledge significant **heterogeneity** in the studies analyzed [7]:

- The ununified definition of weaning failure;
- The inclusion criteria;
- The ultrasonic technique chosen, namely the position of probe, the patient posture, the sides of the diaphragm evaluated;
- The experience of the operators;
- The time point at which measurements are taken.

Considering the limitations above-mentioned, extrapolation of the findings to other settings must be done cautiously.

CONCLUSION

The development of new ultrasound techniques permits a fast, inexpensive, and noninvasive evaluation of diaphragmatic at the bedside, and is expected to lead to a timely identification of patients with DD. Most of the studies analyzed in this review seem to show a clear superiority of the ultrasound when compared with conventional methods to evaluate diaphragmatic function in these patients.

Diaphragm US is a novel method for measuring diaphragmatic function in mechanically ventilated children and is starting to be acknowledged as a promising tool to predict weaning outcomes.

However, it remains difficult to draw general conclusions from individual studies due to the marked variation in study design and population. More studies, with greater standardization of protocols and outcome measures, are required to assess if the use of diaphragmatic US to guide clinical decisions may influence outcomes in these patients.

The successful application of the ultrasound assessment of VIDD into the clinical practice would be a milestone in pediatrics medicine.

DECLARATIONS

Conflicts of interest

All authors report no financial or other conflict of interest relevant to the subject of this article.

Authors' contributions

All authors contributed to the study conception and design. Literature search and data were performed Lara Torres and Marta João Silva. The first draft of the manuscript was written by Lara Torres and all authors commented on previous versions of the manuscript. A critical revision of the work was performed by Marta João Silva. All authors read and approved the final manuscript.

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FIGURES AND TABLES

FIGURES

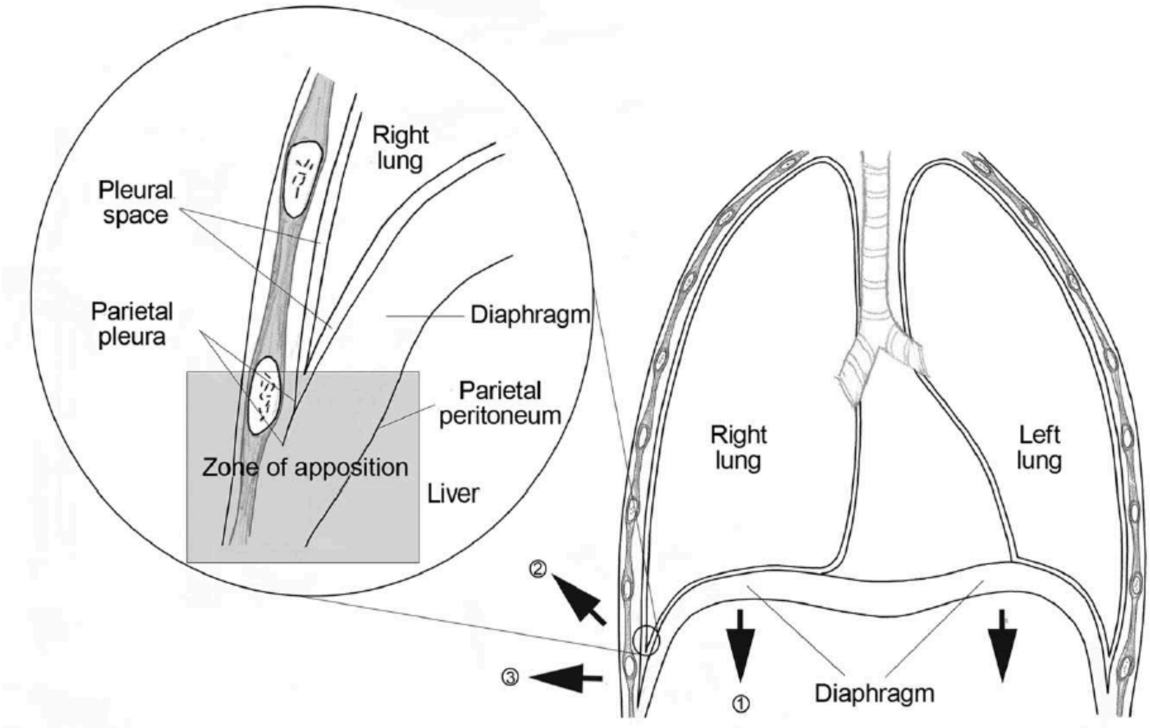

Fig. I - Schematic view of the zone of apposition. On the right is depicted the relationship between the rib cage, right lung, and upper abdominal content in the zone of apposition. On the left, anatomical structures are magnified so that the anatomic relationship between the parietal pleura, the diaphragm, and the parietal peritoneum is highlighted. Arrows represent the forces acting on the different anatomic regions of the area. During inspiration, the diaphragm fibers shorten and the diaphragm as a whole moves caudally (1). As the diaphragm contracts, it lowers the pleural pressure and increases the abdominal pressure. The reduction in pleural pressure produces an inflationary effect on the lungs (2). The accompanying effects of increasing abdominal pressure tend to expand the rib cage (3).

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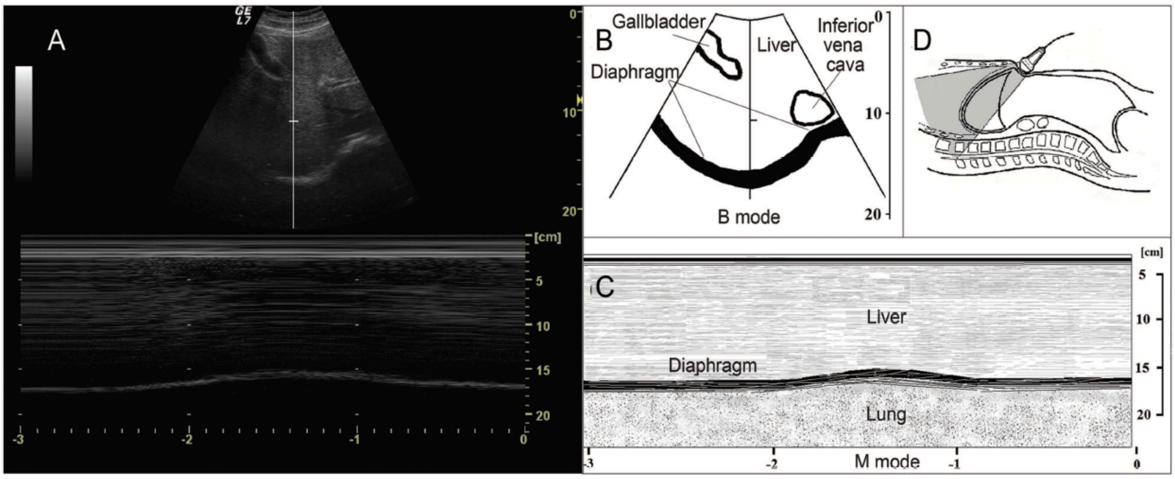

Fig. II - Ultrasonographic assessment of diaphragm displacement. A: Ultrasonographic view of the normal diaphragm in the region of the liver dome, with B-mode in the upper part and M-mode in the lower part. B: Anatomical structures that can be identified in B-mode scanning. C: Anatomical structures that can be identified in M-mode scanning. D: Probe placement to explore the diaphragm in the region of the liver dome.

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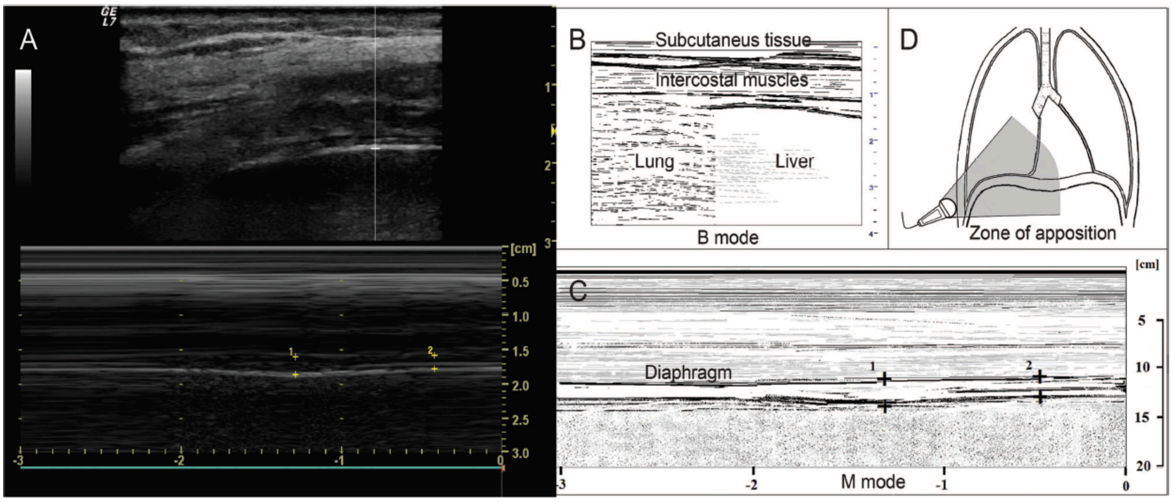

Fig. III - Ultrasonographic assessment of diaphragm thickness. A: Ultrasonographic view of the normal diaphragm in the zone of apposition, with B-mode in the upper part and M-mode in the lower part. B: Anatomical structures that can be identified in B-mode scanning. C: Anatomical structures that can be identified in M-mode scanning. D: Probe placement to explore the diaphragm in the zone of apposition. The distance identified by plus signs 1 in A and C is end-inspiratory thickness, whereas the distance between plus signs 2 in the same panels is the end-expiratory thickness.

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TABLES

Table I. Summary of the advantages and disadvantages of the ultrasonography technique for diaphragmatic evaluation

ADVANTAGES	LIMITATIONS
Allows morphological and functional evaluation in real time	The use of excursion can not be employed on patients under ventilatory support
Easy to perform at the bedside	Patients with poor acoustic window
Noninvasible and painless	The reproducibility and the repeatability of diaphragm thickening is low
Evict radiation	The assessment of the left hemidiaphragm cannot be consistently obtained
Cost-efficient	The technique is dependent on the level of operator experience

Table II. Summary of the most relevant studies regarding ultrasonographic indices to assess diaphragm contractile force and function in adults

Study (year)	N	Patient category	Timing of diaphragmatic US	Cut-off values for successful weaning	Definition of Weaning Failure	Outcomes	Main findings
Dinino et al, 2013 [6]	63	Patients who were ready to perform a SBT	Within the first 5min of the SBT or the PS trial	DTF ≥ 30%	Reintubation within 48h or terminal extubation or tracheostomy	The sensitivity of DTF≥30% for extubation success was 88% and the specificity was 71%	DTF predicts extubation success of failure during SBT or pressure support trials
Yoo et al, 2016 [9]	60	Patients requiring MV for more than 48 h who were ready to perform a SBT	Within 24 hours before extubation	DTF ≥ 20% DE > 10 mm	Reintubation or NIV within 48h of extubation or tracheostomy	DE was greater in SG than in FG (16.5 mm vs. 8 mm) DTF was greater in SG than in FG (42.1% vs. 22.5%)	DE seems more accurate than DTF to predict extubation success.
Umbrello et al, 2015 [12]	25	Patients requiring MV who were ready to perform a SBT	During SBT	DTF ≥ 20%	NA (All patients were successfully weaned from MV)	DTF significantly decreased with increasing ventilator support, whereas DE was unaltered.	A parallel reduction was found between DTF and indices of respiratory muscle effort when different amounts of respiratory effort were achieved by titration of PS. No correlation was found between indices of muscle effort and DE, or between DTF and DE.

Blumhof et al, 2016 [17]	56	Patients requiring MV for more than 24h	During a PS weaning trial, within 48h before extubation	DTF > 20%	Reintubation or delayed extubation (>48h)	DTF>20% is a robust predictor of extubation success within 48h of US at PS 5/5 cm of H_2O and 10/5 cm of H_2O, but not at PS greater than 10/5 cm of H_2O	Diaphragm US is a valid predictor of extubation success at some but not all PS settings
Hayat et al, 2015 [29]	100	Patients who were planned for weaning	During SBT	DE > 12 mm	Reintubation or NIV within 48h (primary weaning failure) or after (secundary weaning failure)	A cut off value of 12 mm, was associated with a successful SBT with a sensitivity of 78.95% and specificity of 70.83%	Ultrasonographic measurement of DE is a good method for predicting weaning outcome from mechanical ventilation.
Osman and Hashim, 2017 [44]	68	Patients in different ICU with various reason for MV, met the traditional weaning criteria	After extubation	DTF ≥ 28% DE ≥ 10 mm LUS score < 12	Reintubation within 48h of extubation	DE cut-off of 10 mm had 83.3% sensitivity, 100% specificity; A cut off value of 28% for DTF showed 88.9% sensitivity; Pleural US with cut-off value 12 showed 100% sensitivity, 96% specificity	Diaphragmatic and lung US can be used as additive new parameters for prediction of weaning process outcome
Khan et al, 2018 [45]	90	Patients requiring MV for more than 48 h who were ready to perform a SBT	During SBT	DE > 13.5 mm RSBI <59	Reintubation or NIV within 48h of extubation	RSBI cut-off of 59 is 79% sensitive and 64% specific for successful extubation. DE cutoff value of 13.5 mm is 74% sensitive and 75% specific. The AUROC of RSBI and DE (0.815 and 0.795, respectively) are significant and comparable	RSBI is a better parameter in predicting weaning outcomes than DE, but DE can be an adjunct parameter with conventional RSBI

Baess et al, 2016 [46]	30	Patients who were planned for weaning	During a weaning trial	DTF ≥ 30% DE > 10 mm RSBI <73.5	Reintubation or NIV within 48h of extubation	The RSBI performed better than all other parameters. A cut-off value of 73.5 had 87% sensitivity and 100% specificity for predicting extubation success	Sonographically measured DTF performed better than DE in predicting value for weaning outcome The RSBI performed better than DE and DTF
Saeed et al, 2016 [50]	50	COPD patients who were prepared for extubation	During SBT	DE > 11 mm	Reintubation within 48h of extubation	DE was higher among those with successful weaning using a cut-off value of 11 mm with sensitivity of 86.4%, specificity of 87.5%, and accuracy of 89.5%	DE is sensitive, specific, and accurate for predicting weaning of COPD patients from MV
Flevari et al, 2016 [51]	27	Patients with difficult and/or prolonged weaning, who met the criteria for SBT	During SBT	DE (left) ≥ 17 mm DE (right) ≥ 10 mm	Ventilatory support (noninvasive or invasive) within 48h after a SBT	DE (left) at a cut-off 10 mm was the best index to predict weaning success (sensitivity 86% and specificity 85%)	DE threshold of 10 mm and 7 mm for right and left hemidiaphragms respectively could be used as adjunct tool in the predictive algorithm of weaning in difficult to wean patients
Carrie et al, 2017 [52]	67	Patients requiring MV for more than 48 h who were ready to perform a SBT	Before the start of SBT	DE > 27 mm	SBT failure or the need for MV or death within 48h of extubation	Mean values of DE were significantly higher in patients who succeeded at their first weaning attempt	A decrease in DE may be associated with an unfavourable weaning outcome. However, US does not provide any additional value compared to the Medical Research Council (MRC) score
Ferrari et al, 2014 [53]	46	Patients who failing one or more	During SBT	DTF > 36%	Inability to maintain spontaneous	A cutoff value of a DTF >36% was associated with a successful	DTF can predict successful extubation similarly to other weaning indexes

		attempts of weaning, met the criteria for a SBT			breathing without any ventilatory support within 48h of extubation	SBT with a sensitivity of 82% and a specificity of 88%	
Farghaly and Hasan, 2017 [54]	54	Patients with underlying pulmonary disease who had successfully passed the SBT	Obtained at 30min of a 2h SBT	DE ≥ 15 mm DTF ≥ 34.2% DT at end inspiration ≥ 21 mm DT at end expiration ≥10.5 mm	Inability to maintain spontaneous breathing without any ventilatory support within 48h of extubation	US indexes were significantly higher in the SG compared to the FG On combining both DE ≥10.5 mm and DT ≥ 21 mm at end inspiration, the sensitivity decreased to 64.9% but specificity increased to 100%	Either DE or DT at end inspiration could be a good predictor of extubation outcome in patients who passed SBT
Ali and Mohamad, 2016 [55]	60	Patients under MV	Within 24h before extubation	DTF > 30% DE > 15 mm	MV within 48h of self-breathing	The maximum DT, DTF and DE decrease were observed among patients within the first 3 days of MV (in a rate 0.23/day (20%), 3.27/day (32.7%) and 0.3/day (30%) respectively) SG presented higher DE and DTF	There was a significant decrease in the DE and DTF with increased duration of MV; Ultrasound is a sensitive accurate method for predicting weaning outcome; Early switch from controlled MV to assist ventilation was associated with reversal of VIDD

DE diaphragm excursion, DT diaphragm thickness, DTF diaphragm thickening fraction, MV mechanical ventilation, NIV non-invasive ventilation, RSBI rapid shallow breathing index, US ultrasonography, SG success group, FG failure group, ICU intensive care unit, SBT spontaneous breathing trial, PS pressure support, VIDD ventilated-induced diaphragmatic dysfunction, COPD chronic obstructive pulmonary disease, NA non-applicable

Table III. Summary of the most relevant studies regarding ultrasonographic indices to assess diaphragm contractile force and function in children

Study (year)	N	Patient category	Patient median age	Timing of diaphragmatic US	Cut-off values for successful weaning	Definition of Weaning Failure	Outcomes	Main findings
Glau et al, 2018 [2]	56	Patients < 18 years old with ARF who required invasive MV for > 24h	17 months	First within 36h of intubation and last preceding extubation	NA	Reintubation or NIV within 48h	Diaphragmatic daily atrophy rate of 3.4%; Linear correlation between DTF and SBF; Increased rates of atrophy and a longer median length of MV in subjects exposed to NMB.	Progressive diaphragm atrophy occurs in children on MV for ARF; Diaphragm contractility is strongly correlated with SBF during MV; The combination of exposure to NMB infusion with low SBF is associated with a greater degree of atrophy.
Lee et al, 2017 [14]	31	Children aged 1 month to 18 years who were newly intubated for MV	3 years	Immediately after intubation until discharge from the PICU	DTF ≥ 17%	Reintubation within 48h	Initial median decrease of 9.4% in DTF in the first day of MV; Average decrease per day of 0.68% in DT after the first day; Average decrease per day of 0.58% in DTF after the first day; DTF significantly different between the SG and FG; DTF value of <17% associated with extubation failure.	Significant diaphragm atrophy and a decreased DTF were observed within 24h of MV. The recovery of the DTF after extubation may be an initial predictor of successful extubation from MV
Dionisio et al, 2019 [15]	17	Children under MV for greater than 48h	42 months	Daily during MV	DTF > 35%	Reintubation within 48h	Median decrease in DTF of 13% under pressure-regulated volume control; Tendency to increase DTF and DE during the pre-extubation stage under pressure support ventilation; Extubation failure occurred for DTF ≤ 35%.	Titration of ventilation may allow a reduction of VIDD and its clinical repercussions

DE diaphragm excursion, DT diaphragm thickness, DTF diaphragm thickening fraction, MV mechanical ventilation, NIV non-invasive ventilation, ARF acute respiratory failure, SBF - Spontaneuos Breathing Fraction, NMB - Neuromuscular Blockade, SG success group, FG failure group, PICU pediatrics intensive care unit, VIDD ventilated-induced diaphragmatic dysfunction, NA non- applicable

ANEXOS

I - Normas de publicação da revista científica Intensive Care Medicine

II - Licença para re-publicação de imagens protegidas por direitos de autor

Intensive Care Medicine

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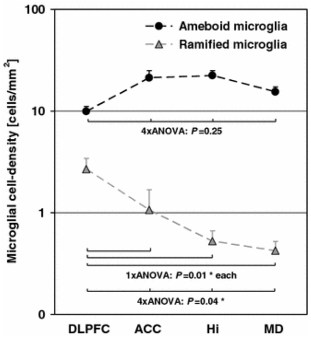

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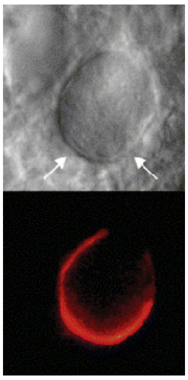

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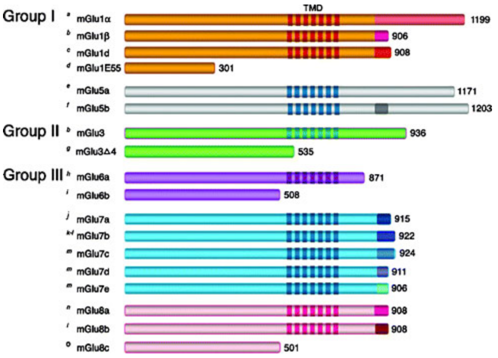

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    8.5. The licensing transaction described in the Order Confirmation document shall be governed by and construed under the law of the State of New York, USA, without regard to the principles thereof of conflicts of law. Any case, controversy, suit, action, or proceeding arising out of, in connection with, or related to such licensing transaction shall be brought, at CCC's sole discretion, in any federal or state court located in the County of New York, State of New York, USA, or in any federal or state court whose geographical jurisdiction covers the location of the Rightsholder set forth in the Order Confirmation. The parties expressly submit to the personal jurisdiction and venue of each such federal or state court.If you have any comments or questions about the Service or Copyright Clearance Center, please contact us at 978-750-8400 or send an e-mail to support@copyright.com.

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