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Diaphragmatic ultrasound: a review of its methodological aspects and clinical uses

Pauliane Vieira Santana[1,2], Leticia Zumpano Cardenas[1,2], André Luis Pereira de Albuquerque[1,3], Carlos Roberto Ribeiro de Carvalho[1], Pedro Caruso[1,2]

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Unidade de Terapia Intensiva, A.C. Camargo Cancer Center, São Paulo (SP) Brasil.
3. Hospital Sírio-Libanês, São Paulo (SP) Brasil.

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ABSTRACT

The diaphragm is the main muscle of respiration, acting continuously and uninterruptedly to sustain the task of breathing. Diaphragmatic dysfunction can occur secondary to numerous pathological conditions and is usually underdiagnosed in clinical practice because of its nonspecific presentation. Although several techniques have been used in evaluating diaphragmatic function, the diagnosis of diaphragmatic dysfunction is still problematic. Diaphragmatic ultrasound has gained importance because of its many advantages, including the fact that it is noninvasive, does not expose patients to radiation, is widely available, provides immediate results, is highly accurate, and is repeatable at the bedside. Various authors have described ultrasound techniques to assess diaphragmatic excursion and diaphragm thickening in the zone of apposition. Recent studies have proposed standardization of the methods. This article reviews the usefulness of ultrasound for the evaluation of diaphragmatic function, addressing the details of the technique, the main findings, and the clinical applications.

Keywords: Ultrasonography; Diaphragm/diagnostic imaging; Respiratory muscles; Critical Illness; Respiratory tract diseases; Neuromuscular diseases.

INTRODUCTION

The respiratory muscles, which comprise the diaphragm, the intercostal muscles, the abdominal muscles, and the accessory muscles (including the sternocleidomastoid and scalene muscles), provide the driving force for ventilation.[1,2] The diaphragm is the main muscle of respiration. Anatomically, it is a dome-shaped structure and is divided into two parts: the central tendon and the peripheral muscular portion. Functionally, the muscular portion is itself divided into two parts[1-4]: the crural portion, which is medial and arises from the lumbar vertebrae (L2-L4) and associated ligaments; and the larger costal portion, which is lateral and is in apposition to the inner aspect of the six lower ribs, constituting the region of apposition to the rib cage, known as the zone of apposition (ZOA). During quiet breathing, diaphragmatic contraction has several effects: the central dome lowers because of contraction of the muscle fibers of the ZOA, leading to a decrease in pleural pressure; the lowering of the central dome increases abdominal pressure, leading to the outward movement of the anterior abdominal wall; and the muscle fibers of the costal part of the diaphragm lift the lower rib cage (insertional force) causing forward (pump-handle) and outward (bucket-handle) movements. As a result, during contraction, the diaphragm moves caudally, increasing the craniocaudal dimension of the thoracic cavity, thus generating negative intrathoracic pressure to inflate the lungs.[1-5]

The diaphragm is innervated by the phrenic nerves that arise from the nerve roots at C3 through C5.[5] To trigger a spontaneous breath, the inspiratory muscles have to receive adequate output from the brain centers and must have anatomical and phrenic nerve integrity.[6] Diaphragmatic function can be affected by diseases that injure the diaphragm itself or by conditions that affect the neuromuscular axis (brain centers, phrenic nerve, or neuromuscular transmission).[6] To maintain continuous, rhythmic, uninterrupted breathing, the diaphragm muscle fibers must be resistant to fatigue. In the adult human diaphragm, approximately 55% of the muscle fibers are type I (slow-twitch fibers that have high fatigue resistance), whereas 21% are type IIA (fast-twitch oxidative fibers that have intermediate fatigue resistance) and 24% are type IIB (fast-twitch glycolytic fibers that have low fatigue resistance).[3]

Diaphragmatic dysfunction (DD) is defined as a loss of muscle force that may be partial (weakness) or complete (paralysis), leading to reduced inspiratory capacity and impaired respiratory muscle endurance.[4] Diaphragmatic weakness or paralysis can involve one or both hemidiaphragms.[7] Because of its nonspecific presentation, DD is underdiagnosed in clinical practice.[6] Unilateral DD is often asymptomatic and diagnosed only

Correspondence to:
Pauliane Vieira Santana. Avenida Dr. Enéas de Carvalho Aguiar, 45, 5º andar, Bloco 2, Sala 1, CEP 05403-900, São Paulo, SP, Brasil.
Tel./Fax: 55 11 2661-5990. E-mail: paulivisa@gmail.com
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as an incidental finding. In rare cases, patients with unilateral DD complain of dyspnea that is intensified in the supine position. However, patients with bilateral DD or those with unilateral DD and underlying lung disease can present with not only dyspnea on exertion but also sleep-disordered breathing, decreased exercise performance, and impaired quality of life.[6] The suspicion of DD is typically raised when diaphragm elevation is seen on a chest X-ray ordered to investigate dyspnea or another respiratory symptom.[4,6] Once suspected, DD can be investigated by a variety of tests that are selected based on their availability, usefulness, and invasiveness. A brief description of the tests, other than ultrasound, that are used in the evaluation of diaphragmatic function is provided described in the Supplementary Material.

DIAPHRAGMATIC ULTRASOUND

Technical aspects

Diaphragmatic ultrasound is a useful technique to evaluate the anatomy and function of the diaphragm, specifically diaphragmatic excursion and thickening. Table 1 describes some characteristics of the technique.[8-22] The equipment needed to perform diaphragmatic ultrasound is uncomplicated and is widely available at medical facilities. The ultrasound system should be equipped with a 2.5-5.0 MHz convex transducer and a 7.5-10.0 MHz linear transducer. A brief description of ultrasound transducers and imaging techniques can be found elsewhere,[23] and Figure 1 illustrates some aspects of those techniques. Because of the portability of ultrasound equipment, diaphragmatic ultrasound can be easily performed as an outpatient procedure or at the bedside in the ward, ICU, or emergency department. Because there is less variability and greater reproducibility in the supine position, that is the preferred positioning for diaphragmatic ultrasound.

Echographic appearance of the diaphragm

On ultrasound, the diaphragm can be explored through two acoustic windows: over the subcostal area (SCA), as depicted in Figures 2 and 3; and over the ZOA, as depicted in Figure 4. Through the SCA window, ultrasound shows the diaphragm as a deeply located curved structure that separates the thorax from the abdomen (Figure 2B).[8,9,24] Through the ZOA window, the diaphragm is identifiable as a three-layer structure (Figure 4),[25] consisting of one hypoechoic inner muscle layer surrounded by two hyperechoic outer membranes (the peritoneum and pleura).[24-27] During diaphragmatic contraction in healthy individuals, ultrasound through the SCA window shows the diaphragm descending in the craniocaudal direction (i.e., toward the transducer),[8,9,24] whereas ultrasound through the ZOA window shows the shortening and thickening of the muscle.[27,28] Therefore, ultrasound allows the measurement of diaphragmatic mobility and thickness. To quantify diaphragmatic mobility and thickening in an objective manner, at least three images should be evaluated and the values should be averaged.[8,24,25,29]

Diaphragmatic mobility

Diaphragmatic mobility is measured by visualizing the hemidiaphragms via the anterior subcostal view (the preferred method), posterior subcostal view, or subxiphoid view, in the two-dimensional (B) mode or in the one-dimensional (M) mode.[8,9] Regardless of the technique chosen, diaphragmatic mobility is measured at three time points (Figure 2D): during quiet breathing; during deep breathing at maximal inspiration, and during voluntary sniffing.

The posterior subcostal view (Figure S1 in the Supplementary Material) is usually employed with the patient in a sitting position. A low-frequency convex transducer is placed over the posterior subcostal region, which is assessed in the right or left sagittal planes and in B mode, and the operator looks for the individual hemidiaphragms through the hepatic or spleen window.[30] The amplitude of craniocaudal diaphragmatic mobility is then measured in M mode. Because it requires that specific patient positioning, the posterior subcostal view is usually unfeasible in patients who are critically ill or are on mechanical ventilation (MV).

The subxiphoid view is particularly useful in children and slender adults. A low-frequency convex transducer is placed below the xiphoid process in a transverse orientation, angled cranially and dorsally toward the posterior hemidiaphragms.[31] In B mode, the right and left hemidiaphragms can both be seen, allowing a qualitative comparison of their excursion.[32] In M mode, the excursion of each hemidiaphragm can be measured objectively.

Testa at al.[9] presented a detailed description of the use of the anterior subcostal view. In brief, a low-frequency convex transducer is placed over the anterior SCA, between the midclavicular and anterior axillary lines (Figure 2A). The right and left hemidiaphragms can be evaluated via the liver and spleen windows, respectively. In B mode, transverse scanning is performed, looking across the liver for the inferior vena cava on the right of the screen and the gallbladder in the middle of the screen. The right hemidiaphragm appears as a thick, curving, hyperechoic line (Figures 2B and 2D). The transducer is directed medially, cranially, and dorsally, so that the ultrasound beam reaches the posterior third of the right hemidiaphragm.[8,9] The transducer is held firmly in place, and the patient is asked to engage in quiet breathing, deep breathing, and voluntary sniffing (Figure 2D and, in the Supplementary Material, Video S1). In M mode, the M-mode line is positioned as perpendicular as possible, to obtain maximum excursion (Figures 2C and 2D).[8,9,24] The amplitude of the diaphragmatic excursion is measured by placing calipers at the bottom and top of the diaphragmatic inspiratory slope (Figures 2C and 2D).

Table 1. Diaphragmatic ultrasound.

Advantages	
Safety	- Noninvasive - Does not expose patients to ionizing radiation[8]
Feasibility	- Can be performed in less than 15 min,[9] even in approximately 5 min[8] - Bedside assessment, does not require transportation of the patient - Possibility of several repetitions
Availability	- Requires only basic, usually ubiquitous, ultrasound equipment
Accuracy	- High temporal resolution,[8,9] high reproducibility, and high accuracy, with intraclass correlation coefficients ranging from 0.876 to 0.999 for intraobserver agreement and from 0.56 to 0.989 for interobserver agreement[10-18] - Has high interobserver and intraobserver agreement,[8] for diaphragmatic excursion[9] and thickness[10] - Is superior to fluoroscopy for the diagnosis of diaphragmatic dysfunction[19]
Disadvantages	
Availability	- Despite requiring only basic ultrasound equipment, it is not available at all facilities. - Physicians trained in the technique must be on staff.
Accuracy	- The left hemidiaphragm may be difficult to visualize, particularly in obese patients.[20] - Diaphragmatic excursion depends on the maximal voluntary inspiratory effort of patients and is influenced by the position of the subject.[21] - Diaphragmatic excursion is affected by the abdominal contents and pressure, which limit diaphragm displacement.[22]

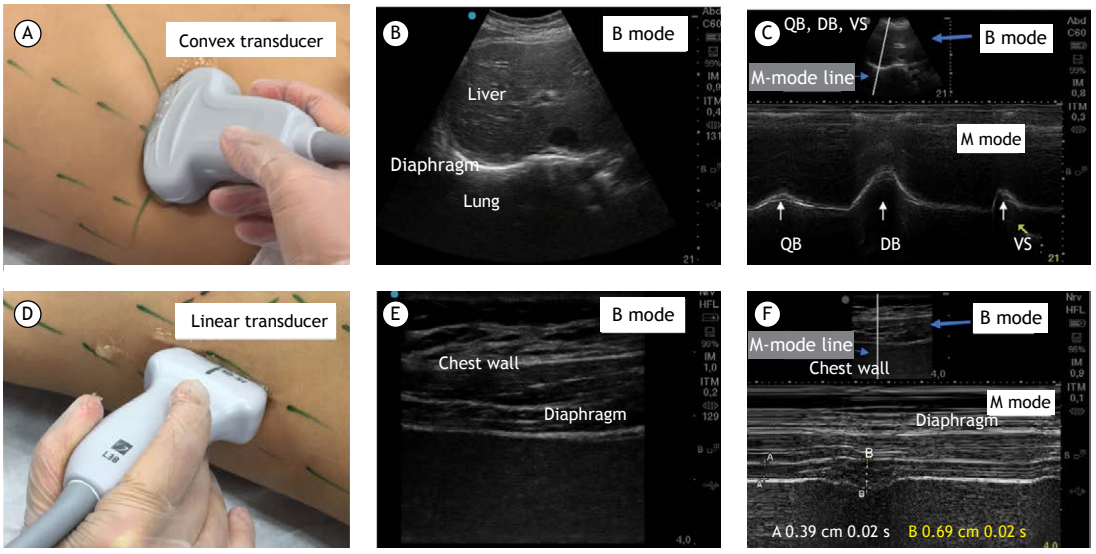

Figure 1. A convex transducer (A) uses a lower frequency, allowing a deep penetration and a wide field of view. In a convex transducer, the crystals are embedded along a curved shape (A). The ultrasound beams emitted from the lateral aspects of the transducer lead to decreased lateral resolution and a pie-shaped image on the screen (B and top of C). Convex transducers are primarily used for abdominal scans due to their wider and deeper view. A linear transducer (D) emits a beam with a high frequency (6-12 MHz), providing better resolution and less penetration, making it ideal for imaging superficial structures. The crystals are aligned in a linear fashion within a flat head and produce sound waves in a straight line. The image produced is rectangular in shape (E) with high lateral resolution. The imaging modes are demonstrated in B, C, E, and F. The diaphragm is seen in B mode, also known as real-time imaging (B and E). B-mode ultrasound presents a two-dimensional slice of a three-dimensional structure, rendering a cross-sectional view. The diaphragm is seen in M mode (C and F), which displays the motion of a given structure over time through the placement of a vertical (exploratory, M-mode) line in the directed plane of the transducer, during quiet breathing (QB), deep breathing (DB), and voluntary sniff (VS). The M-mode line is anchored at the top and center of the screen, although its orientation and direction can be adjusted laterally. On the screen, the motion of the structure is plotted along the y-axis, and time is plotted along the x-axis, in seconds. M-mode ultrasound allows high time resolution.

There are regional differences in mobility between the parts of the diaphragm.[33] The middle and posterior portions of the diaphragm show the greatest craniocaudal excursion during spontaneous breathing.[33] In B-mode ultrasound, it is fundamental to be aware of the direction of diaphragmatic excursion, whether toward the transducer (descending = normal) or away from it (paradoxical = abnormal).

Quantifying left hemidiaphragm mobility can be problematic because of the smaller acoustic window of the spleen and the interposition of gas in the stomach. When left diaphragmatic paralysis is suspected, there

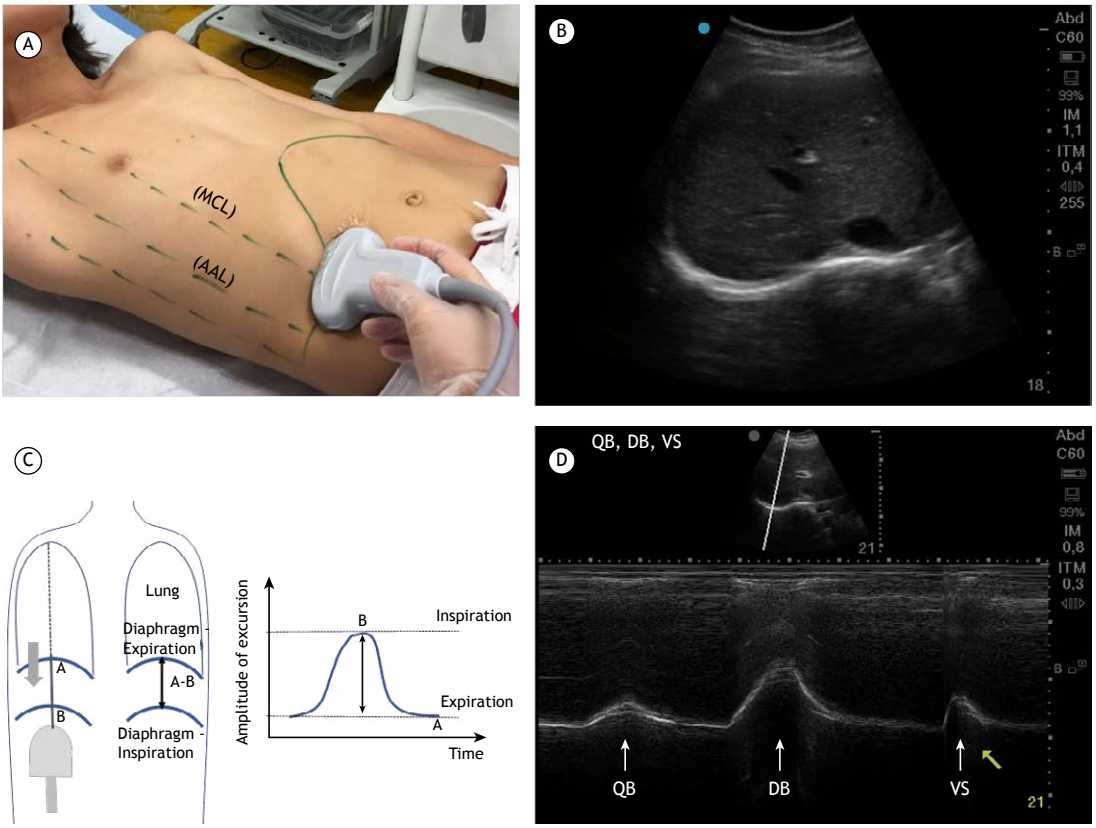

Figure 2. In A, measuring the excursion of right hemidiaphragm using the anterior subcostal view with the convex probe positioned below the costal margin between the midclavicular line (MCL) and anterior axillary line (AAL). In B, ultrasound appearance of the right hemidiaphragm in the subcostal region between the MCL and AAL. In C, schematic representation of the measurement of diaphragmatic excursion: on the left, placement of the probe in the subcostal region to display the diaphragm in B mode and placement of the exploratory line demonstrating excursion from expiration to inspiration (points A-B). In D, measurement of diaphragmatic excursion in M mode. The top of the figure depicts the normal right diaphragm in B mode, and the bottom portion depicts M-mode ultrasound of the diaphragmatic excursion during quiet breathing (QB), deep breathing (DB), and voluntary sniff (VS).

are strategies that can facilitate the observation and measurement of diaphragmatic excursion (Figure S2 in the Supplementary Material).

The diagnosis of DD can be made through ultrasound measurement of diaphragmatic mobility. Diaphragmatic paralysis can be diagnosed by identifying the absence of mobility during quiet breathing and deep breathing, together with paradoxical motion during deep breathing or voluntary sniffing (Figures 3C and 3D).[34,35] Diaphragmatic weakness can be diagnosed by identifying reduced mobility during deep breathing, with or without paradoxical motion during voluntary sniffing (Figure 3D).[8,36]

Diaphragm thickness and thickening fraction

To assess atrophy and contraction of the diaphragm, it is necessary to evaluate diaphragm thickness (Tdi) and the thickening fraction (TF), respectively.[26,28] A high frequency (7-13 MHz) linear transducer is placed over the ZOA, between the eighth and ninth intercostal spaces, usually 0.5-2.0 cm below the costophrenic angle, between the anterior axillary and midaxillary lines (Figure 4A).[24,25,29] At a depth of 1.5-3 cm, the diaphragm is identified as the hypoechoic inner muscular layer bounded by two hyperechoic membranes (Figure 4B), namely those of the pleura (superficial line) and peritoneum (deeper line).[25-27] Tdi is measured from the center of the pleural line to the center of the peritoneal line, at end-expiration (Tdi-exp) (Figure 4B), then at end-inspiration (Tdi-insp), in B mode and M mode (Figure 4C and, in the Supplementary Material, Video S2). The TF is calculated as follows:

$$TF = \frac{Tdi\text{-}insp - Tdi\text{-}exp}{Tdi\text{-}exp} \times 100$$

The diagnosis of DD can be made by measuring Tdi with ultrasound. A chronically paralyzed diaphragm is thin, atrophic, and does not thicken during inspiration.[26] However, in acute or subacute diaphragmatic paralysis, the Tdi may be normal but the thickening capacity will be decreased.[37,38] Table 2 shows a variety of studies that used diaphragmatic ultrasound to measure diaphragmatic mobility and thickness in healthy subjects.[8-10,25,27,29,33,36,39]

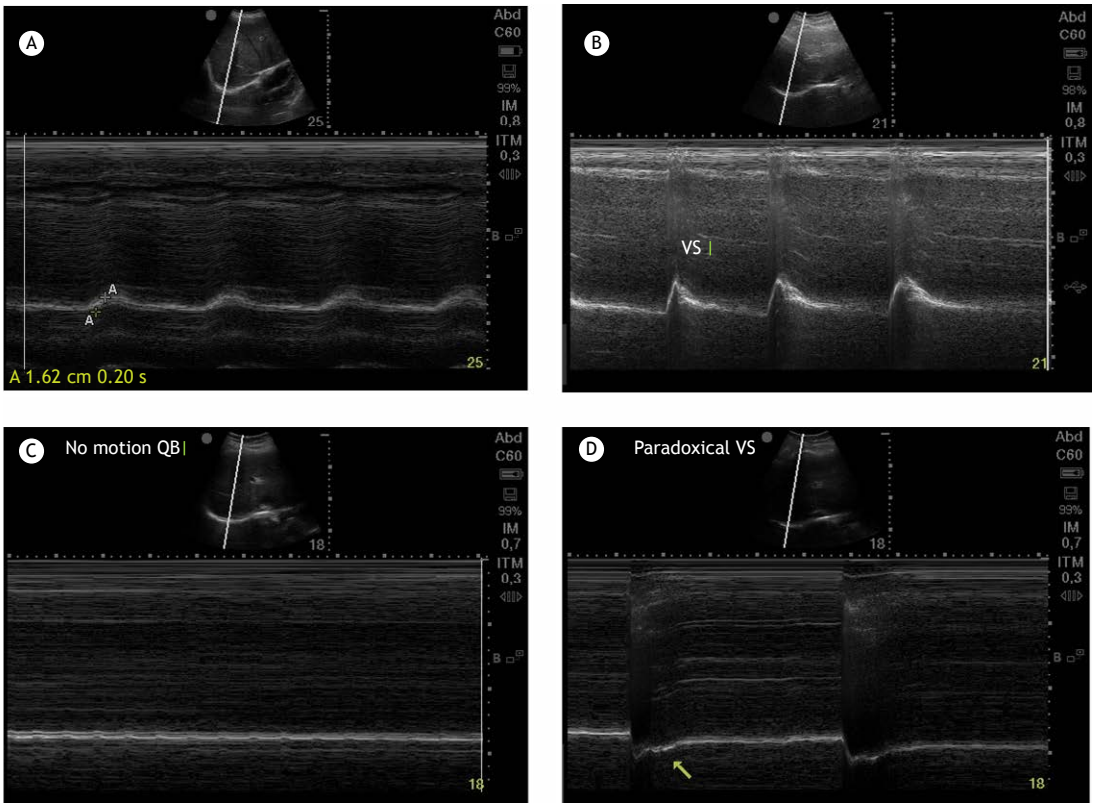

Figure 3. Measurement of diaphragmatic excursion. At the top of all of the panels, we can see images in B mode showing the position of the probe, whereas at the bottom of each panel, the M-mode images show the diaphragmatic excursion (A and B), lack of excursion (C), and paradoxical excursion (D). Panel A depicts diaphragmatic excursion during quiet breathing (QB), and panel B shows diaphragmatic excursion during a voluntary sniff (VS). Panels C and D depict the trace of a paralyzed diaphragm. In C, diaphragmatic excursion is absent during QB. Panel D shows paradoxical motion during VS.

CLINICAL USES OF DIAPHRAGMATIC ULTRASOUND

Critical care

Critically ill patients are especially vulnerable to DD, because of a number of potentially myotoxic factors.[40,41] In critically ill patients, DD is highly prevalent, even at the beginning of ICU admission,[42] especially in patients with respiratory failure who require MV.[40,43] Studies have shown that DD is associated with adverse outcomes, such as weaning failure,[13,40,43] prolonged MV,[44] prolonged ICU stay,[40] and increased mortality.[40,42,44,45]

Diaphragmatic function is rarely monitored in critically ill patients, mainly because it is difficult to employ the tools required in order to do so. Recently, diaphragmatic ultrasound has contributed significantly to the assessment of diaphragmatic function in critical care settings.[12,13,16,18,43,46] One study suggested a rational approach to the use of diaphragmatic ultrasound in critical care, for a variety of purposes[47]: to diagnose DD; to assess the work of breathing; to identify atrophy of the diaphragm; and to predict weaning outcomes.

Diaphragmatic ultrasound can be used in order to diagnose DD at admission or during MV, provided that no neuromuscular blockers are being used and that the ventilator is triggered by patient effort (assisted modes). Abnormal diaphragmatic mobility (reduced, absent, or paradoxical movement) can be indicative of DD.[48] Diaphragmatic excursion < 10 mm is the criterion most often used in order to diagnose DD in critically ill patients.[13,49] Diaphragmatic ultrasound-diagnosed DD is associated with adverse outcomes (longer MV and weaning times, as well as higher mortality). Lu et al.[50] reported the prevalence of DD to be 34% among patients on MV for prolonged periods. Lerolle et al.[14] demonstrated that diaphragmatic excursion < 25 mm (during a best excursion maneuver) accurately identified DD in patients on MV for prolonged periods after cardiac surgery.

The work of breathing can also be assessed with diaphragmatic ultrasound. Recent studies have shown that the TF correlates with the diaphragmatic pressure-time product and the esophageal pressure-time product.[16,17]

Another application of diaphragmatic ultrasound is in the identification of atrophy of the diaphragm through the measurement of Tdi-exp.[15,18,51,52] In a previous

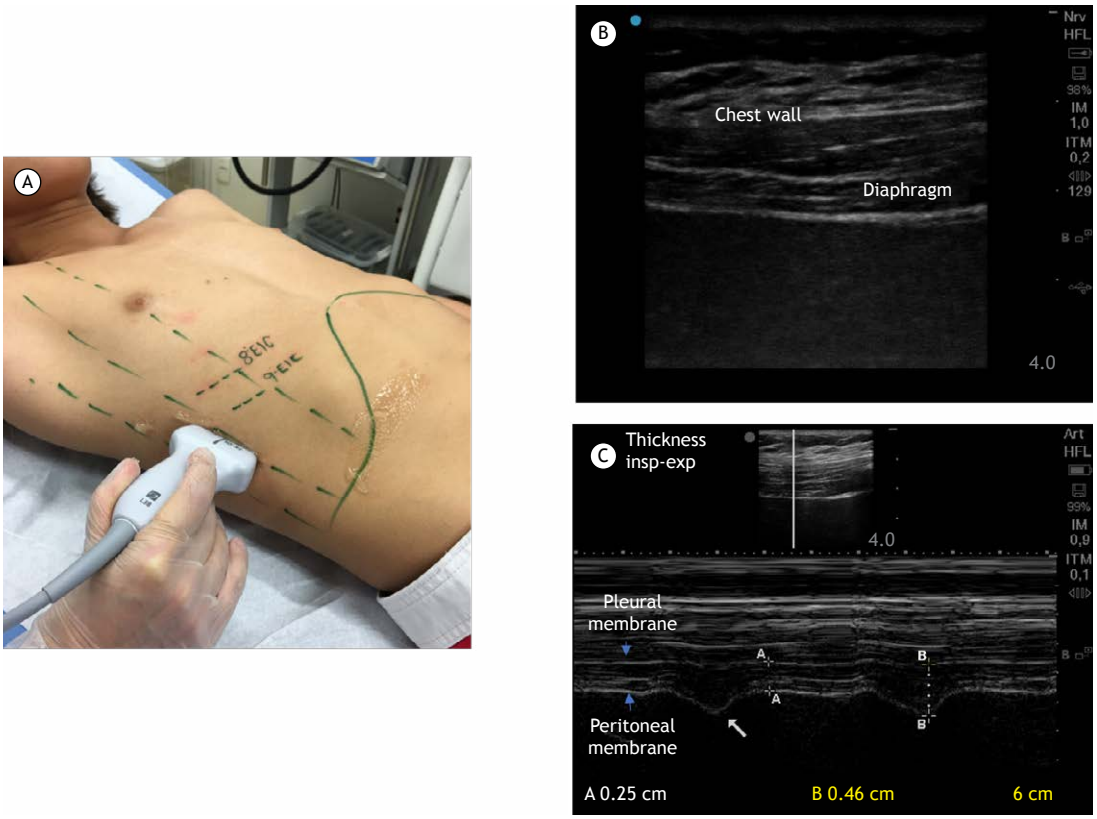

Figure 4. In A, measuring the thickness of right hemidiaphragm through the placement of the linear transducer over the zone of apposition (ZOA) at the ninth intercostal space, between the anterior axillary and midaxillary lines. In B, ultrasound appearance of the left hemidiaphragm at the ZOA between the ninth and tenth intercostal spaces, during quiet breathing, at functional residual capacity. In C, measurement of diaphragm thickness: the top of the figure displays the ZOA of a normal diaphragm, in B mode; and the bottom portion shows, in M mode, the diaphragm thickness at end-expiration (exp), or distance A-A, and diaphragm thickness at end-inspiration (insp), or distance B-B.

study, Tdi-exp was found to decrease 6.0-7.5% per day on MV and the level of ventilator support showed a linear relationship with the incidence of atrophy of the diaphragm.[18]

Diaphragmatic ultrasound can also be used in order to predict the weaning outcome. During spontaneous breathing trials, diaphragmatic excursion cutoff values of < 14 mm[53,54] and < 11 mm[13] have both been found to be predictive of weaning failure, as have TF values of < 20%,[43] < 30%,[46] and < 36%.[11]

The usefulness of diaphragmatic ultrasound in predicting weaning outcomes continues to be extensively explored and debated. However, there is considerable heterogeneity across studies, due to the following methodological aspects: the definition of weaning failure employed; the inclusion criteria (e.g., the timing of diaphragmatic ultrasound during the spontaneous breathing test); the diaphragmatic ultrasound technique chosen; the positioning of the patient; differences among patient populations; the diaphragmatic ultrasound parameters evaluated to predict weaning (diaphragmatic excursion, the TF, or the combination of several parameters). That marked heterogeneity among studies makes it difficult to draw general conclusions on the usefulness of diaphragmatic ultrasound in predicting weaning outcomes, which could explain the lack of guidelines. Recent, high-quality studies, including a systematic review,[47] three meta-analyses,[55-57] and a narrative review,[58] have synthesized the available knowledge on this subject. Although a complete review of all such studies is beyond the scope of the present report, there is compelling evidence that diaphragmatic ultrasound is a feasible, promising technique for use in critical care, especially in patients with respiratory failure.[12,13,16,18,43,45,46,52] However, there are still conflicting results regarding the efficiency of the technique in predicting weaning outcomes.[59,60] Table 3 summarizes the relevant studies on this topic.[12-15,18,40,43-46,48-50,52-54,61-64]

Diaphragmatic paralysis

In patients with bilateral diaphragmatic paralysis, inspiration is achieved by the contraction of inspiratory intercostal and accessory muscles, which lowers the pleural pressure and expands the rib cage. During inspiration, the paralyzed diaphragm moves cranially and does not thicken.[4] Diaphragmatic ultrasound has been explored as a tool to diagnose diaphragmatic paralysis.

Table 2. Diaphragmatic ultrasound to measure diaphragmatic mobility and thickness in healthy subjects.

Reference	n	Patient positioning Probe placement Probe orientation	Measure	Reference values
Harris et al.[33]	50	Supine Subcostal MCL and longitudinal	Mobility DB	Anterior third: 4.0 ± 1.6 cm Middle and posterior third: 4.8 ± 1.6 cm 4.0 ± 1.2 cm (F); 5.4 ± 1.7 cm (M)
Gerscovich et al.[36]	23	Supine Longitudinal semi-coronal Subcostal or low intercostal between MCL and MAL	Mobility QB	Right hemidiaphragm - QB: 1.5 cm; DB: 5.7 cm; VS: 1.7 cm Left hemidiaphragm - QB: 1.6 cm; DB: 6.7 cm; VS: 1.8 cm
Kantarci et al.[39]	160	Supine Coronal plane Low anterior intercostal, subcostal, or both	Mobility DB	DB Right: 4.7 ± 1.0 (F) vs. 5.3 ± 1.1 cm (M) Left: 4.8 ± 0.3 (F) vs. 5.4 ± 1.3 cm (F)
Boussuges et al.[8]	210	Standing Right subcostal between MCL and AAL Left lower intercostal spaces or subcostal, between AAL and MAL	Mobility QB DB	QB - Right: 1.6 ± 0.3 cm (F); 1.8 ± 0.3 cm (M) - Left: 1.6 ± 0.4 cm (F); 1.8 ± 0.4 cm (M) DB - Right: 5.7 ± 1.0 cm (F); 7.0 ± 1.1 cm (M) - Left: 6.4 ± 1.0 cm (F); 7.5 ± 0.9 cm (M) VS - Right: 2.6 ± 0.5 cm (F); 2.9 ± 0.6 cm (M) - Left: 2.7 ± 0.5 cm (F); 3.1 ± 0.6 cm (M)
Testa et al.[9]	40	Supine, semi-recumbent 45° Subcostal anterior at MCL Probe is orientated transversely and directed cranially	Mobility QB DB	QB - Experienced operator: 1.8 ± 0.8 cm - Inexperienced operator 2.2 ± 0.9 cm DB - Experienced operator 6.9 ± 1.4 cm - Inexperienced operator 7.9 ± 1.3 cm
Ueki et al.[27]	13	Sitting ZOA	Thickness	Tdi-exp: 1.7 ± 0.2 mm Tdi-insp: 4.5 ± 0.9 mm
Baldwin et al.[10]	13	Semi-recumbent 45° ZOA, ninth intercostal space	Thickness Tdi-exp	Tdi-exp: 1.7 [1.1-3.0] mm
Boon et al.[25]	150	Supine eighth or ninth intercostal space, immediately anterior to the AAL	Thickness Tdi-exp Thickening ratio	Tdi-exp: 2.7 ± 1 mm (F); 3.8 ± 1.5 mm (M) - LLN Tdi-exp: 1.4-1.7 mm - LLN thickening ratio: 1.2-1.3%
Carrillo-Esper et al.[29]	109	Supine ZOA, at FRC	Thickness Tdi-exp	Tdi-exp: 1.6 ± 0.4 mm 1.4 ± 0.3 mm (F); 1.9 ± 0.4 mm(M)
Cardenas et al.[24]	64	Semi-recumbent 45° Mobility: right anterior, subcostal region Diaphragm thickness: ZOA between AAL and MAL, at FRC and at TLC	Mobility QB DB Thickness Tdi-exp Tdi-insp TF	Mobility QB: 1.5 ± 0.4 cm DB: 6.41 ± 1.02 cm (F); 7.79 ± 0.82 cm (M) LLN DB mobility: 4.37 cm (F); 6.15 cm (M) Tdi-exp: 1.9 ± 0.3 mm (M) LLN at FRC: 1.2 mm (F); 1.3 mm (M) Tdi-insp: 4.81 ± 0.95 mm (F); 5.6 ± 0.9 mm (M) TF: 169 ± 43% (F); 204 ± 61% (M)

MCL: midclavicular line; DB: deep breathing; F: female; M: male; MAL: midaxillary line; QB: quiet breathing; VS: voluntary sniff; AAL: anterior axillary line; ZOA: zone of apposition; Tdi-exp: diaphragm thickness at end-expiration; Tdi-insp: diaphragm thickness at end-inspiration; LLN: lower limit of normal; FRC: functional residual capacity; and TF: thickening fraction.

Gottesman et al.[26] measured the Tdi in 30 subjects (5 with bilateral diaphragmatic paralysis, 7 with unilateral diaphragmatic paralysis, 3 with inspiratory weakness, and 15 who were healthy). The Tdi-exp and Tdi-insp were measured. The TF was also calculated. The authors showed that, in patients with unilateral paralysis, the Tdi-exp and TF were significantly lower for the paralyzed hemidiaphragm than for the normal hemidiaphragm and for the hemidiaphragms of healthy volunteers, and that only patients with diaphragmatic paralysis had a Tdi-exp < 20 mm and a TF < 20%.[26] The authors concluded that diaphragmatic ultrasound can be used in order to diagnose diaphragmatic paralysis by identifying the characteristic lack of thickening. It is of note that the TF of the paralyzed hemidiaphragms showed negative values (mean, −8 ±

Table 3. Relevant studies about the use of diaphragmatic ultrasound in critical care.

Authors	n	Setting	Measurement	Cutoff/Correlate
Predicting weaning outcome – TF				
DiNino et al.[46]	63	Medical ICU	TF during SBT (PSV [5] or T tube)	Cutoff for TF: > 30%
Jung et al.[43]	33	Medical and Surgical ICU	TF during SBT (PSV [5] or T tube) Only patients with ICUAW	Cutoff for TF: > 20%
Dres et al.[40]	76	Medical ICU	TF during SBT on PSV	Cutoff for TF: > 29%
Blumhof et al.[61]	56	Medical ICU	TF during SBT on PSV (5,10, and 15)	Cutoff for TF: > 20%
Farghaly et al.[62]	54	Respiratory ICU	TF during SBT on PSV (8)	Cutoff for TF: > 34%
Dres et al.[63]	76	Medical ICU	TF and PtrStim a few minutes before SBT SBT on PSV (7), ZEEP	Cutoff for TF: > 25.8% PtrStim > 7.2 cm
Predicting weaning outcome – DE				
Jiang et al.[53]	55	Medical ICU	DE during SBT on PSV or T tube	Cutoff for DE: 1.1 cm
Kim et al.[13]	82	Medical ICU	DE during SBT on PSV or T tube	Cutoff for DE: 1.0 cm
Spadaro et al.[54]	51	Medical ICU	DE during SBT (not clear)	Cutoff for DE: 1.4 cm
Dres et al.[40]	76	Medical ICU	DE during SBT on PSV	Cutoff for DE: 0.95 cm
Farghaly et al.[62]	54	Respiratory ICU	DE during SBT on PSV	Cutoff for DE: 1.05 cm
Assessing atrophy during MV				
Grosu et al.[52]	7	Medical ICU	Tdi-exp measured daily since intubation	Tdi-exp ⇓ 6%/day of MV
Goligher et al.[12]	107	Medical ICU	Tdi-exp and TF measured daily since intubation until 72 h of MV -Tdi-exp ⇓ = Tdi-exp reduction > 10% - Tdi-exp ⇑ = Tdi-exp increase > 10%	Tdi-exp in 44%; Tdi-exp ⇑ in 12% Low TF correlated with ⇓ in Tdi-exp High TF correlated with ⇑ in Tdi-exp. TF ⇓ with ⇑ driving pressure and CMV
Schepens et al.[15]	54	Medical ICU	Tdi-exp measured during first 24 h of MV, and daily after	Tdi-exp ⇓ ≈32% at the nadir MV duration associated with atrophy
Zambon et al.[18]	40	Medical ICU	Tdi-exp measured daily since intubation during SB or CPAP High PSV (5-12) Low PSV (> 12): CMV	Tdi-exp ⇓ ≈7.5%/day on CMV Tdi-exp ⇓ ≈5,3%/day on high PSV Tdi-exp ⇓ ≈1.5%/day at low PSV Tdi-exp ⇑ ≈2.3%/day in SB/CPAP
Goligher et al.[64]	211	Medical ICU	Tdi-exp and TF measured daily since intubation until 72h of MV Inspiratory effort → TF Tdi-exp ⇓ = Tdi-exp reduction > 10% Tdi-exp ⇑ = Tdi-exp increase > 10%	Tdi-exp ⇓ in 41%; Tdi-exp in 24% Tdi-exp ⇓ associated with ⇑ MV, ICU admission and ⇑ risk of complications Tdi-exp ⇑ predicted ⇑ MV ⇓ Tdi-exp correlated with low inspiratory effort ⇑ Tdi-exp was related to excessive effort TF (15-30%) → shortest duration of MV
Assessing DD				
Lerolle et al.[14]	28	Adult cardiac ICU	DE, Pdi, and Gilbert index Severe DD = best DE < 25 cm MV > 7 days	Best DE < 25 correlated with Gilbert index < 0
Kim et al.[13]	82	Medical ICU	During SBT on PSV or T tube MV > 48 h	DD in 24 (29%) DE < 1.0 cm predicted weaning outcome

TF: thickening fraction; PSV: pressure-support ventilation (numbers in parentheses/brackets are cmH_2O); SBT: spontaneous breathing trial; ICUAW: ICU-acquired weakness; PtrStim: tracheal pressure in response to phrenic nerve stimulation; ZEEP: zero end-expiratory pressure; DE: diaphragmatic excursion; Tdi-exp: diaphragm thickness at end-expiration; MV: mechanical ventilation; CMV: controlled mechanical ventilation; SB: spontaneous breathing; CPAP: continuous positive airway pressure; DD: diaphragmatic dysfunction; Pdi: transdiaphragmatic pressure; ARF: acute respiratory failure; ACV: assist-control ventilation; and LOS: length of stay.

Table 3. Continued...

Authors	n	Setting	Measurement	Cutoff/Correlate
Valette et al.[48]	10	Medical ICU	DE during unassisted breathing DD = paradoxical or absent excursion, or DE < 1.0 cm	DD in 10 patients High mortality rate (60%) of patients with DD and ARF
Mariani et al.[49]	34	Medical ICU	DE during SBT on T tube DD = DE <1.0 cm MV > 7 days and SBT eligible	DD in 13 (38%) Bilateral DD in 8 Unilateral (left/right side) DD = 3/2
Lu et al.[50]	41	Medical ICU	TF during SBT on PSV only patients with prolonged MV DD = TF < 20%	DD prevalence in 14 (34.1%). DE < 1.0 cm predicted weaning outcome
Dubé et al.[45]	112	Medical ICU	PtrStim, TF and DE measured during first < 24 h of MV or during ACV or at switch to PSV DD = PtrStim <11 cmH_2O	TF and DE correlated with PtrStim at switch to PSV, but not at initiation of MV TF < 29% identified DD TF < 29% was associated with ⇑ ICU-LOS, ⇑ MV duration, and ⇑ mortality

TF: thickening fraction; PSV: pressure-support ventilation (numbers in parentheses/brackets are cmH_2O); SBT: spontaneous breathing trial; ICUAW: ICU-acquired weakness; PtrStim: tracheal pressure in response to phrenic nerve stimulation; ZEEP: zero end-expiratory pressure; DE: diaphragmatic excursion; Tdi-exp: diaphragm thickness at end-expiration; MV: mechanical ventilation; CMV: controlled mechanical ventilation; SB: spontaneous breathing; CPAP: continuous positive airway pressure; DD: diaphragmatic dysfunction; Pdi: transdiaphragmatic pressure; ARF: acute respiratory failure; ACV: assist-control ventilation; and LOS: length of stay.

13% vs. 65 ± 26% for the normal hemidiaphragms). The authors attributed that to the passive stretching of the paralyzed diaphragm, as previously shown in a case report.[37]

In acute diaphragmatic paralysis, the Tdi-exp may be unaltered, because atrophy may not yet have occurred. In addition, recent studies have indicated that Tdi-exp values in healthy individuals are lower than previously thought (lower limit of normal = 1.2 mm in women and 1.3 mm in men).[24]

The measurement of diaphragmatic mobility has also been studied as a means of diagnosing diaphragmatic paralysis. Lloyd et al.[35] described the use of diaphragmatic ultrasound in 10 adult patients referred for evaluation of suspected diaphragmatic paralysis. The paralyzed diaphragm presented a lack of inspiratory (caudal) mobility on M-mode diaphragmatic ultrasound and abnormal paradoxical mobility, particularly during a sniff test. Those findings were recently confirmed by other authors.[7,34] Boussuges et al.[34] assessed diaphragmatic mobility on M-mode during quiet breathing, deep breathing and voluntary sniffing in 26 patients with unilateral diaphragmatic paralysis. In all of the patients evaluated, the authors found abnormal mobility of the paralyzed hemidiaphragm, characterized by immobility or weak paradoxical displacement during quiet breathing; paradoxical mobility during voluntary sniffing; and paradoxical mobility during deep breathing. Caleffi-Pereira et al.[7] assessed diaphragmatic motion and thickness during quiet breathing, deep breathing, and voluntary sniffing in 27 patients with unilateral diaphragmatic paralysis. The authors found that mobility (during quiet breathing and deep breathing), and thickness (Tdi-exp, Tdi-insp and TF) were both significantly lower in the paralyzed hemidiaphragm than in the normal hemidiaphragm. In view of these findings, diaphragmatic paralysis can be diagnosed by identifying a lack of excursion during quiet breathing, deep breathing, and voluntary sniffing or paradoxical excursion during deep breathing and voluntary sniffing. Diaphragmatic weakness is diagnosed by identifying reduced diaphragmatic excursion during quiet breathing and deep breathing, with or without paradoxical motion on sniffing.

Diaphragmatic ultrasound may also be useful in the follow-up of patients with DD. Summerhill et al.[38] studied 16 patients with diaphragmatic paralysis (bilateral in 6 and unilateral in 10), following them for up to 60 months. Diaphragmatic TF was measured initially and during subsequent visits. The authors found that 7 patients recovered their diaphragmatic function (mean recovery time of 14.9 ± 6.1 months), whereas the remaining patients did not. In the postoperative period after cardiac surgery, DD can lead to complications. Lerolle et al.[14] studied 28 patients requiring MV for a prolonged period (> 7 days) after cardiac surgery, evaluating a control group of 20 patients with an uncomplicated postoperative course for comparison. The authors measured the transdiaphragmatic pressure (Pdi) during maximal inspiratory effort and calculated the Gilbert index (the ratio between the amplitude of gastric pressure at peak inspiration to the amplitude of Pdi during inspiration), which evaluates the contribution the diaphragm makes to respiratory pressure swings (a Gilbert index > 0.30 indicates normal diaphragmatic function, whereas a value ≤ 0 indicates severe DD). The authors employed diaphragmatic ultrasound to measure diaphragmatic mobility during maximal inspiratory effort. They found that the Pdi was below

Table 4. Main findings and potential clinical implications of diaphragmatic ultrasound.

Critically ill patients with respiratory failure on mechanical ventilation	
Main findings	**Potential clinical implications**
1. To diagnose DD DE < 1.0 cm[13,48,49] TF < 20-29%[45,50]	DD (DE < 1.0 cm): associated with high mortality rate (60%) in patients with DD and ARF[48]; predicted weaning outcome[13,50]; and DD (TF < 29%) associated with longer ICU LOS, prolonged MV, and increased mortality[45]
2. To assess atrophy of the diaphragm during MV Tdi-exp decreases 6.0-7.5%/day of MV (especially on CMV).[18,28,52] Tdi-exp is > 10% lower in 44% of patients and unchanged in 44%[12]	Atrophy of the diaphragm (Tdi-exp ⇓ > 10%) associated with ⇑ MV[15,64], ⇑ ICU admission, and ⇑ risk of complications[64] Diaphragmatic hypertrophy (Tdi-exp ⇑ > 10%) - associated with increased duration of MV[39]
3. To predict weaning from MV DE < 1.0-1.4 cm[13,40,53,54,62] TF < 20-30%[40,43,46,61-63]	Diaphragmatic ultrasound and weaning prediction DE < 1 cm and TF < 20-30% associated with increased weaning failure
Diaphragmatic paralysis	
Main findings	**Potential clinical implications**
1. Chronic paralysis Atrophy: Tdi-exp < 0.11-0.12 cm (LLN)[7] TF < 20%, even negative[26] DE absent or weak/paradoxical during QB[34,35] DE reduced, absent, or paradoxical during DB and VS[34] 2. Acute or subacute paralysis Unaltered Tdi-exp (Tdi-exp > 0.15 cm) with abnormal TF (TF < 20% or even negative)[37]	If diaphragmatic paralysis is suspected: Reduced, absent, or paradoxical DE supports the diagnosis. Reduced Tdi-exp (< 0,11 cm) and reduced TF (< 20%) supports the diagnosis of chronic diaphragmatic paralysis. Reduced, absent, or paradoxical DE and reduced TF < 20% support the diagnosis of acute/subacute diaphragmatic paralysis (Tdi-exp may be unaltered). Diaphragmatic ultrasound may follow the recovery of diaphragmatic paralysis.[38]
Cystic fibrosis	
Main findings	**Potential clinical implications**
1. Increased Tdi-exp (effect of training of the diaphragm)[67,68] 2. Reduced Tdi-exp in severe pulmonary disease and low fat-free mass[69]	Increased Tdi-exp (due to the effect of training of the diaphragm) or reduced Tdi-exp (due to deleterious effects on respiratory muscle function)
COPD	
Main findings	**Potential clinical implications**
1. Reduced diaphragmatic mobility,[70,71] which was inversely correlated with air trapping[71] and dyspnea(70) and positively correlated with 6MWD[70] 2. Tdi-exp and TF similar to controls[72] 3. Tdi-exp and TF inversely correlated with air-trapping[73] 4. During acute exacerbation of COPD: DD (TF < 20%) was associated with poorer outcomes (NIV failure, longer ICU stay, prolonged MV, need for tracheostomy).[74] DE predicted NIV failure.[76]	Air trapping correlated with reduced diaphragmatic mobility, thickness, and thickening. Reduced diaphragmatic mobility correlated with increased dyspnea on exertion. Reduced TF (< 20%) and mobility during acute exacerbation of COPD correlates with poorer outcomes. DE predicted early NIV failure. DE was greater in NIV successes than in NIV failures.
Interstitial lung diseases	
Main findings	**Potential clinical implications**
1. Reduced DB diaphragmatic mobility correlated with lung function.[78-80] 2. Increased Tdi-exp is an effect of training of the diaphragm.[78,80] 3. Reduced mobility and thickening during DB correlated positively with lung function, exercise tolerance, and HRQoL, correlating negatively with dyspnea.[80]	Lung restriction (reduced lung volumes) reduces diaphragmatic mobility and thickening. Maximal diaphragmatic mobility and thickening is associated with clinically relevant parameters (exercise tolerance, HRQoL and dyspnea).
Neuromuscular disorders	

DD: diaphragmatic dysfunction; DE: diaphragmatic excursion; TF: thickening fraction; ARF: acute respiratory failure; LOS: length of stay; MV: mechanical ventilation; Tdi-exp: diaphragm thickness at end-expiration; CMV: controlled mechanical ventilation; LLN: lower limit of normal; QB: quiet breathing; DB: deep breathing; VS: voluntary sniff; SNIP: sniff nasal inspiratory pressure; NIV: noninvasive ventilation; HRQoL: health-related quality of life; ALS: amyotrophic lateral sclerosis; and V_T: tidal volume.

Table 4. Continued...

Main findings	Potential clinical implications
1. Reduced Tdi-exp and thickening in patients with ALS with vital capacity < 80% predicted[85] and in those with bulbar-onset ALS[86]	Diaphragm thickness and excursion are reduced and correlate with lung function in ALS.
2. Thickening with inspiration correlated with SNIP and MEP[84] and lung function[83]	Diaphragm thickening may be related to respiratory muscle strength in ALS.
3. Maximal excursion correlated with FVC[87]	The Tdi at V_T/Tdi at TLC ratio may suggest weakness and predict the initiation of NIV in ALS.
4. The Tdi at V_T/Tdi at TLC ratio is indicative of weakness and may predict NIV initiation in ALS[88]	DB and VS diaphragmatic mobility may be related to SNIP and lung function in Duchenne muscular dystrophy and myotonic dystrophy type 1.
5. Duchenne muscular dystrophy and myotonic dystrophy type 1:	
Reduced mobility during DB and VS[89]	
DB excursion correlated with FVC values[89]	

DD: diaphragmatic dysfunction; DE: diaphragmatic excursion; TF: thickening fraction; ARF: acute respiratory failure; LOS: length of stay; MV: mechanical ventilation; Tdi-exp: diaphragm thickness at end-expiration; CMV: controlled mechanical ventilation; LLN: lower limit of normal; QB: quiet breathing; DB: deep breathing; VS: voluntary sniff; SNIP: sniff nasal inspiratory pressure; NIV: noninvasive ventilation; HRQoL: health-related quality of life; ALS: amyotrophic lateral sclerosis; and V_T: tidal volume.

normal in 27 of the 28 patients requiring MV for a prolonged period. In 8 patients, the Gilbert index was ≤ 0, indicating severe DD, and those patients had lower diaphragmatic mobility during maximal inspiratory effort than did the patients with a Gilbert index > 0. In addition, a diaphragmatic excursion during maximal inspiratory effort of < 25 mm during maximal inspiratory effort was found to be an accurate predictor of a Gilbert index ≤ 0 (area under the ROC curve of 0.93, a positive likelihood ratio of 6.7, and a negative likelihood ratio of 0). The diaphragmatic excursion during maximal inspiratory effort was > 25 mm in all of the patients with an uncomplicated course.

Diaphragmatic ultrasound has also been used in order to identify DD after neck dissection.[65] Immediately after neck dissection, only a few (8.9%) of the diaphragms at risk showed immobility, with decreased inspiratory strength that returned to preoperative values after one month. However, at one month after dissection, Tdi decreased, indicating atrophy of the diaphragm.[65]

DIAPHRAGMATIC ULTRASOUND IN RESPIRATORY DISEASES

Diaphragmatic ultrasound has been employed in the evaluation of a variety of respiratory diseases, including asthma, cystic fibrosis, COPD, and interstitial lung disease (ILD). Table 4 summarizes the main findings and potential clinical implications of the use of diaphragmatic ultrasound in patients with respiratory diseases.

Asthma

In 1997, de Bruin et al.[66] addressed the usefulness of diaphragmatic ultrasound in a sample of 9 middle-aged patients with asthma, minor pulmonary hyperinflation, and preserved peripheral muscle strength. The authors found moderately impaired inspiratory muscle strength and slightly increased thickness of the costal diaphragm, indicating muscle hypertrophy.

Cystic fibrosis

Considering the fact that chronic respiratory diseases can affect diaphragmatic function, Pinet et al.[67] evaluated patients with cystic fibrosis who had severe respiratory impairment and malnutrition. The authors showed that, although the patients had diaphragmatic weakness, they did not have muscle atrophy; the patients had thicker diaphragms and abdominal muscles than did the control subjects, indicating hypertrophy due to respiratory muscle training. Dufresne et al.[68] underscored those findings, showing that the patients with cystic fibrosis had thicker diaphragms and greater inspiratory muscle strength than did the control subjects. In addition, fat-free mass and airway resistance were found to be independent predictors of Tdi, although systemic inflammation was not, suggesting that in cystic fibrosis, the diaphragmatic training occurred despite the presence of systemic inflammation. However, patients with chronic respiratory diseases may present many factors (e.g., inflammation, altered nutritional status, poor physical conditioning, and corticosteroid use) influencing respiratory muscle function other than training.

Enright et al.[69] studied 40 adults with cystic fibrosis and 30 age-matched healthy subjects. In that study, patients with cystic fibrosis who had severe pulmonary disease and low fat-free mass presented poorer inspiratory muscle function and reduced Tdi-exp when compared with patients with cystic fibrosis with a normal fat-free mass. The patients with cystic fibrosis with normal fat-free mass showed inspiratory muscle function and Tdi-exp values similar to those of age-matched healthy individuals.

COPD

Ultrasound has been used to evaluate the diaphragm in COPD. In a study involving 54 patients with COPD and 20 healthy subjects, Paulin et al.[70] attempted to determine whether diaphragmatic mobility could

influence exercise tolerance and dyspnea. The authors found that patients with COPD had lower diaphragmatic mobility than did the controls. They also found that diaphragmatic mobility correlated positively with the distance covered on the six-minute walk test, whereas it correlated negatively with dyspnea on exertion.

Dos Santos Yamaguti et al.[71] investigated the influence of lung function on diaphragmatic mobility in patients with COPD. The authors found that such patients had reduced diaphragm mobility that was mainly associated with air trapping and was not influenced by inspiratory strength or pulmonary hyperinflation.

Baria et al.[72] evaluated the Tdi-exp and thickening ratio (calculated as the Tdi-insp divided by the Tdi-exp) in 50 patients with COPD and compared that with a database of information on 150 healthy control subjects. The authors found that the values for Tdi-exp and thickening ratio were comparable between the patients and the controls.

Smargiassi et al.[73] evaluated the correlation between Tdi, respiratory function, and body composition in 32 patients with COPD. The authors showed that Tdi at different lung volumes, mainly the Tdi-exp, was related to the fat-free mass. The authors also showed that diaphragm thickening was inversely related to hyperinflation (greater hyperinflation resulting in less diaphragm thickening), postulating that diaphragmatic ultrasound could be useful to assess lung hyperinflation and the loss of fat-free mass in patients with COPD.

Antenora et al.[74] studied 41 patients with COPD with exacerbation, admitted to the ICU for noninvasive ventilation (NIV), and investigated the use of diaphragmatic ultrasound to identify and assess the prevalence of DD (defined as a TF < 20% during spontaneous breathing), to determine its impact on outcomes in those patients. The authors identified DD in 10 patients (24.3%). They demonstrated that DD was associated with corticosteroid use and poorer outcomes, including NIV failure, longer ICU stays, prolonged MV, the need for tracheostomy, and ICU mortality. That study was extended in a recent report by Marchioni et al.,[75] who investigated the outcomes of 75 patients with COPD exacerbation who required NIV and had DD (defined as a TF < 20%). Those authors showed that DD was associated with poorer clinical outcomes, such as NIV failure, prolonged MV, higher tracheostomy rates, and longer ICU stays, as well as higher ICU, in-hospital, and 90-day overall mortality rates.

Cammarota et al.[76] studied 21 patients with COPD admitted to the emergency department for exacerbation and investigated the feasibility of performing diaphragmatic ultrasound to evaluate diaphragmatic excursion, thickness, and TF, before NIV, as well as after the first and second hours of treatment, attempting to determine whether those variables were predictors of early NIV failure. Comparing NIV successes and NIV failures, the authors found that diaphragmatic excursion (although not Tdi-exp and TF) was significantly greater in the former group before NIV ($p = 0.02$), after the first hour of treatment ($p = 0.007$), and after the second hour of treatment ($p = 0.008$). During an acute exacerbation of COPD, diaphragmatic excursion was found to be predictive of early NIV failure.

ILD

There have been few studies using diaphragmatic ultrasound to assess diaphragmatic function in patients with ILD. He et al.[77] evaluated the mobility of the diaphragm during quiet breathing and deep breathing in a mixed sample, comprising patients with combined pulmonary fibrosis and emphysema, patients with idiopathic pulmonary fibrosis, patients with COPD, and healthy controls. Diaphragmatic mobility during quiet breathing and deep breathing was similar between patients with ILD and healthy controls. More recently, Santana et al.[78] reported a reduction in deep breathing diaphragmatic mobility and TF, as well as an increased Tdi-exp in 40 patients with ILD in comparison with matched healthy controls. Additionally, the reduced deep breathing diaphragmatic mobility was associated with lung volumes in ILD. These results were recently confirmed by Boccatonda et al.[79] who showed a reduced deep breathing diaphragmatic mobility and a positive correlation between reduced FVC and diaphragmatic mobility in patients with ILD. In another study, Santana et al.[80] attempted to determine whether diaphragmatic mobility and thickness correlated with clinical and functional parameters (including dyspnea, exercise tolerance, quality of life, and lung function) in patients with ILD. The authors showed that diaphragmatic mobility and thickening during deep breathing correlated positively with lung function, exercise tolerance, and health-related quality of life, whereas both correlated negatively with dyspnea. In addition, the TF was below normal in 70% of the patients with ILD.

NEUROMUSCULAR DISEASES

Neuromuscular diseases (NMD) can affect the inspiratory and expiratory muscles, resulting in weakness and fatigue,[81] and can evolve from mild impairment (mild alveolar hypoventilation and a restrictive pattern of lung function, mainly in the supine position) to chronic respiratory failure.[82] Patients with NMD may be referred to a pulmonologist for respiratory muscle evaluation. The initial tests are spirometry and volitional assessment of global respiratory muscle strength—MIP, MEP, and (sniff nasal inspiratory pressure) SNIP—although those tests have limitations due to reduced patient motivation, cognitive decline, and orofacial muscle weakness, which can cause air leaks that lead to inaccurate tests. Nonvolitional respiratory muscle strength tests are invasive, expensive, and rarely employed. Diaphragmatic ultrasound can be a useful diagnostic tool in patients with NMD.

Among the various types of NMD, diaphragmatic ultrasound has been extensively explored in amyotrophic lateral sclerosis (ALS). Fantini et al.[83] studied 41 patients with ALS, using diaphragmatic ultrasound to measure the Tdi at tidal volume (V_T) and at TLC, calculating the ratio between the two. When that ratio approaches 1, the maximum inspiratory effort becomes unable to further contract the diaphragm starting from V_T, suggesting diaphragmatic weakness. The authors found that the ratio between the Tdi at V_T and the Tdi at TLC was the variable that best correlated with lung function.[83] Pinto et al.[84] studied 42 patients with ALS (25% with bulbar onset), most (76%) without respiratory symptoms and with normal respiratory test results. The authors found that the Tdi-insp showed a significant positive correlation with diaphragm compound muscle action potential and respiratory strength (as quantified by determining the SNIP and MEP),[84] although Tdi was not found to correlate with the pulmonary function test results in the subgroup of patients with bulbar-onset ALS. Hiwatani et al.[85] employed diaphragmatic ultrasound to assess 36 patients with ALS and 19 age-matched healthy controls. The authors found that the Tdi-exp, Tdi-insp, and the thickening ratio were all significantly lower in the patients with a vital capacity < 80% of the predicted value than in those with a vital capacity ≥ 80% of the predicted value and in the healthy controls. The Tdi-exp, Tdi-insp, and thickening ratio were all found to correlate positively with vital capacity and negatively with $PaCO_2$.[85] In a study involving 20 patients with ALS and age-matched healthy controls, Sartucci et al.[86] found that Tdi-exp and TF were lower in the patients. The authors also found that, in the patients with bulbar-onset ALS, lung volumes correlated strongly with Tdi-exp and TF. Carrié et al.[87] investigated the relationships between diaphragmatic mobility and lung volumes in 45 patients with ALS or myotonic dystrophy. The authors found a significant correlation between FVC and diaphragmatic mobility during deep breathing. The authors suggested that the measurement of diaphragmatic mobility could be a reliable tool to identify impaired respiratory function (FVC < 50% of predicted) in patients with ALS or myotonic dystrophy. In a more recent study, Fantini et al.[88] found that, in patients with ALS, a Tdi at V_T/Tdi at TLC ratio > 0.75 (suggesting diaphragmatic weakness) increased the risk of requiring NIV (hazard ratio = 5.6; p = 0.001) and the risk of death (hazard ratio = 3.7; p = 0.0001), inferring that diaphragmatic ultrasound is an accurate method of predicting the need for NIV in ALS.

In a mixed sample of 89 patients with NMD, primarily Duchenne muscular dystrophy and myotonic dystrophy type 1, diaphragmatic mobility during sniff ultrasound was found to be significantly associated with SNIP and to accurately predict FVC < 60% (area under the ROC curve = 0.93; p < 0.0001).[89] In addition, diaphragmatic mobility during voluntary sniffing and deep breathing was found to be lower in the patients with NMD than in a group of healthy controls. Other studies employing diaphragmatic ultrasound have shown that Tdi-exp is lower in patients with myopathy or neuropathy than in healthy individuals.[90,91] In patients with high spinal cord injury and neuropathy, the quantification of diaphragmatic mobility by ultrasound may be a useful tool for the diagnosis of DD.[19,35,36] Table 4 summarizes the main findings and potential clinical implications of the use of diaphragmatic ultrasound in patients with NMD.

LIMITATIONS OF DIAPHRAGMATIC ULTRASOUND

Diaphragmatic ultrasound has some limitations. First, ultrasound systems have inherent resolution limits (usually 0.1 mm) that can correspond to 5-10% of the normal thickness of the diaphragm. In addition, the assessment of the left hemidiaphragm can be problematic. However, taking extra precautions during the diaphragmatic ultrasound examination (e.g., placing the patient in the supine position and rotating the transducer) can help overcome these limitations. Furthermore, because ultrasound is an operator-dependent examination, repeated training can improve accuracy. Diaphragmatic ultrasound has shown good reliability for measuring Tdi (intraclass correlation coefficient = 0.990; 95% CI: 0.918-0.998), as well as for quantifying diaphragmatic excursion (correlation analysis) during quiet breathing (r = 0.95) and deep breathing (r = 0.94).[10,34] Moreover, although diaphragmatic ultrasound has been shown to have a steep learning curve when applied in healthy subjects,[8,9] few studies have evaluated how to develop the appropriate skills. One study, involving a pediatric population, found that 4 h of hands-on diaphragmatic ultrasound training focused on the recognition of normal and abnormal diaphragmatic motion resulted in high concordance between the diaphragmatic ultrasound findings reported by a trainee and those reported by a pediatric intensivist.[92] Another study, involving adult subjects, showed that three to five diaphragmatic ultrasound training sessions, lasting 10-15 min each, enabled learners to identify the diaphragm and measure its thickness.[46] More recently, Garofalo et al.[93] found that a combined approach consisting of a theoretical module followed by practical training is more effective in making learners capable of obtaining accurate diaphragmatic ultrasound measurements. The authors suggested that 25 supervised examinations would be sufficient to achieve adequate diaphragmatic ultrasound skills, analogous to those required to perform bedside lung ultrasound examinations.[94] Although training can ensure adequate diaphragmatic ultrasound skills, it does not imply that learners would successfully perform unsupervised diaphragmatic ultrasound evaluation in the clinical arena, where confounding factors can hinder the diaphragmatic ultrasound assessment.[93] Therefore, diaphragmatic ultrasound should be

performed only by physicians who have been properly trained and are dedicated to clinical care.

Diaphragmatic ultrasound is still not widely used in the assessment of diaphragmatic function in daily practice. That is probably due to a lack of knowledge about diaphragmatic impairment in various clinical contexts, as well as about the usefulness and possible clinical implications of ultrasound in evaluating the diaphragm. An exponentially increasing number of studies of diaphragmatic ultrasound have been published, especially regarding critical care, producing clinically relevant findings that should highlight the usefulness of ultrasound in assessing diaphragmatic function.

FINAL CONSIDERATIONS

Diaphragmatic ultrasound has marked advantages over other techniques used in order to assess diaphragmatic function, such as the fact that it is noninvasive and does not employ ionizing radiation, as well as being feasible, reproducible, repeatable, and affordable. In addition, there is convincing evidence in the literature about the usefulness of ultrasound to assess diaphragmatic function in diverse clinical settings. It is reasonable to suppose that in the near future, the use of diaphragmatic ultrasound by pulmonologists and intensivists will be ubiquitous and that it will have new applications in the diagnosis and monitoring of diseases and interventions, such as rehabilitation.

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AUTHOR CONTRIBUTIONS

PVS, LZC, ALPA, CRRC, and PC contributed to the study conception and design (formal analysis and methodology). PVS and PC contributed to drafting the manuscript. PVS, LZC, ALPA, CRRC, and PC contributed to writing, reviewing, and editing the manuscript. All of the authors approved the final manuscript.

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