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REVIEW

Ultrasound imaging of the diaphragm: facts and future. A guide for the bedside clinician

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Abstract

Introduction: The diaphragm plays a significant role in the ICU setting, as it forms a crucial part in sustaining spontaneous breathing and ability to wean from mechanical ventilation. A lot of research has been conducted to find new approaches and parameters for its assessment. Out of these, ultrasonography has become a popular option due to its many advantages. In this review, the aim was to provide an extensive summary on our current knowledge on ultrasonography of the diaphragm. Methods of application, feasibility, limitations and future perspectives will be discussed.

Methods: This is a narrative review. A thorough search in PubMed was conducted to find all relevant articles. Filters were applied to sort out studies that were conducted in animals or patients younger than 18 years.

Results: Overall, ultrasonography presents a promising imaging technique to assess diaphragm function. Diaphragm motion can be used to detect diaphragm dysfunction, paralysis and patient ventilator asynchrony, while thickness and the thickening fraction can be used to predict weaning outcomes and monitor diaphragm strength. Limitations are potential inaccuracy inherent to the ultrasound machine and variability between observers, assisted modes of ventilation (motion cannot be interpreted) and controlled modes of ventilation (ultrasound not applicable).

Discussion: While a range of studies are available that demonstrate ultrasonography as a viable tool to assess the diaphragm, only a few have been conducted in sufficiently large and representative patient groups. Further research is needed for validation of those ultrasound derived data and conclusions. Until then, it is key to consider the limitations of ultrasonography carefully. Nevertheless, ultrasonography does provide valuable information and should be used to monitor the diaphragm.

Introduction

Diaphragm dysfunction frequently develops in critically ill patients and is associated with adverse outcome, including prolonged duration of mechanical ventilation and increased length of ICU stay.[1,2] Risk factors for the development of diaphragm dysfunction include sepsis and mechanical ventilation. Both ventilator over-assist and ventilator under-assist are associated with development of respiratory muscle weakness. Therefore, monitoring diaphragm activity using non-invasive, reproducible methods may be of clinical importantance.[3]

Currently, several techniques, such as pressure and flow recordings, diaphragm electromyography and chest X-ray are available for this purpose. However, most of these come with their limitations, such as invasiveness, poor cost-effectiveness and limited bedside availability. Ultrasonography is increasingly used to visualise several tissues and organs, such as lung, heart, liver and more recently the diaphragm.

Ultrasound of the diaphragm allows quantification of movement, thickness and thickening fraction, which can be used to estimate diaphragm function. This is relevant in ICU patients, for example, to predict extubation outcomes or estimate the work performed by the diaphragm. In particular during weaning, analysis of respiratory muscle function may be of clinical relevance, given that around 40% of the time spent in the ICU is used for weaning from mechanical ventilation and failure of extubation is related to an increased risk of death of up to 40-50%, depending on the cause of failure.[4–6]

In this narrative review, methods for visualising of the diaphragm using ultrasound and its clinical application will be discussed. Evidence on reproducibility and feasibility will be given and limitations will be listed. Furthermore, suggestions for potential future directives will be provided.

Methods

This is a narrative review. A thorough search in PubMed was conducted to find all articles. Filters were applied to sort out studies that were conducted in animals, patients younger than 18 years or not available in English.

How is ultrasound of the diaphragm used?

Basic ultrasound offers two approaches to imaging: brightness-mode (B-Mode) and motion-mode (M-mode). Applying these modes to visualise the diaphragm allows assessment of diaphragm thickness (tdi) (B-mode) and diaphragm motion (M-mode).

Thickness

The tdi is measured in B-mode with a high-frequency probe (≥10 MHz) in the zone of apposition at the mid-axillary line approximately between the 8th and 11th rib, with slight variation between patients.[7] In general, obtaining a good view will be easier on the patients right side compared with the left side as the liver provides an excellent ultrasound window. In the mid-axillary line, the diaphragm is seen as as a structure composed of three different echogenic layers: the pleural membrane, a central tendinous layer and the peritoneal membrane *(figure 1)*.[8] The outer layers are used as borders and should not be included in the thickness measurement. Average values for thickness *(table 1)* reported in healthy volunteers are 0.19 ± 0.04 cm (95% CI 0.17-0.20) in men and 0.14 ± 0.03 cm (95% CI 0.13-0.15) in women.[9] Marking the site of probe position on the skin significantly improves repeatability and reproducibility of repeated measurements.[10]

If tdi is measured during maximal inspiratory and expiratory effort, the thickening fraction (%) can be calculated ($tdi\% = (tdi_{end\ inspiration} - tdi_{end\ expiration})/tdi_{endexpiration}$), which makes interpatient comparisons easier, as thickness varies between individuals.[11] It must be kept in mind however, that during controlled modes of ventilation, this measurement is not feasible, as no contractile activity of the diaphragm is present.

Figure 1. B-mode ultrasound of the diaphragm
1) Pleura; 2) Fibrous layer in centre of the diaphragm 3) Peritoneum

Table 1. Ultrasound measurements on average diaphragm thickness

	No. of patients	tdi end expiration	tdi end inspiration
Ferrari 2014[4]	46	2.4 mm [1.7 to 3.0]	3.4 mm [2.6 to 4.4]
Goligher 2015[30]	96	2.4 mm (0.8)	2.7 mm (0.8)
Farghaly 2016[27]	56	1.6 mm (1.12–1.87)	2.4 mm (2.2–2.8)

tdi = diaphragm thickness, ( ) = standard deviation, [ ] = range

Motion

Diaphragm motion is measured in the M-mode with a low frequency probe (1-5 MHz) just below the costal arch on the midclavicular line, with the probe directed cranially and a small dorsal tilt *(figure 2)*. The lower frequency offers greater depth, but in exchange for less spatial resolution. Measurements of motion can only be used in spontaneously breathing patients, as during assisted ventilation active displacement cannot be distinguished from passive displacement due to driving pressures.

Values for motion were assessed during quiet breathing, deep breathing and voluntary sniffing in healthy non-ventilated individuals and are summarised in *table 2*.[12,13] Slight differences were found, probably attributable to the difference in group size. The significant differences between men and women are caused by differences in height and bodyweight and not gender per se.[14]

Figure 2. M-mode ultrasound of the diaphragm
1) Diaphragm at end expiration; 2) Diaphragm motion; 3) Diaphragm at end inspiration

Table 2. Ultrasound measurements on average diaphragm motion

	No. of patients	Quiet Breathing	Voluntary sniffing	Deep breathing	After SBT: Successful vs failed extubation
Gerscovich 2001[13]	23	1.5 cm [0.26–2.10]	1.66 cm [0.48-2.66]	5.69 cm [1.67-9.20]	x
Boussuges 2009[12]	210	1.8 cm (±0.3)	2.8 cm (±0.6)	6.0 cm (±1.3)	x
Farghaly 2016[27]	56	x	X	x	1.6 cm vs 0.98 cm

SBT = Spontaneous Breathing Trial, ( ) = standard deviation, [ ] = range

What is ultrasound of the diaphragm used for?

Evaluating functionality

Evaluating diaphragm functionality might be a key aspect in the management of ventilated patients, as diaphragm dysfunction has a major impact on outcome.[15] More specifically, disuse of the muscle results in changes in the muscle fibre cross-sectional area and an up to 25% reduction in the pressure generating capacity of the diaphragm in the first 3-4 days of ICU admission.[16-18]

Given the impact of critical illness on respiratory muscle function, the use of ultrasound to diagnose weakness and monitor function is of clinical importance.

Kim et al.[2] used M-mode ultrasound to quantify diaphragm motion and defined an excursion of 10 mm or less as diaphragm dysfunction. The diaphragm dysfunction group showed a longer time spent on ventilation (576 [374-850] vs. 203 [109-408] hours, $p<0.01$) and prolonged weaning (401 [226-612] vs. 90 [24-309] hours, $p<0.01$). Mariani et al.[19] used the same cut-off value as applied by Kim et al.[2] and found that diaphragm dysfunction was related to higher ICU mortality rates (37% vs 5%).

Lerolle et al.[1] demonstrated that diaphragm motion provides an excellent and noninvasive method to exclude diaphragm dysfunction in patients ventilated for more than seven days. In their study, diaphragm dysfunction was assessed using the Gilbert Index, which determines the contribution of the diaphragm during inspiration by measuring pressure swings across it (ΔPgastric/ΔPdiaphragm).[20] Ultrasound proved to have a 100% sensitivity (95% CI, 63 to 100%) and 85% specificity (95% CI, 62 to 97%) when <25 mm excursion was regarded as the cut-off point for diaphragm dysfunction.

In summary, it can be concluded that loss of diaphragm function develops rapidly and is associated with important clinical implications. Ultrasound parameters such as tdi and diaphragm motion offer a viable option to monitor this decay and perhaps in the future, with increasing knowledge, the possibility to track the effects of interventions aimed at improving diaphragm function.

Work of breathing

Ultrasonography could possibly provide a non-invasive alternative to measure work of breathing and the pressure time product (PTPdi) (PTPdi per breath = average inspiratory pressure x time / number of breaths) during assisted ventilation, which both currently require invasive pressure measurements (oesophageal and gastric pressure). These indices provide information about loading of the diaphragm and allow the clinician to titrate ventilator support, to prevent over- or under-assist of the diaphragm and possibly limit disuse atrophy or muscle injury.

Several studies have demonstrated a correlation between tdi% and PTPdi or work of breathing. Vivier et al.[21] conducted their study in 12 patients, each ventilated for at least 48 hours. They found a significant correlation ($\rho=0.52$, $p<0.001$) between the thickening fraction and the PTPdi per breath. However, a closer look at the data reveals that for a given amount of effort delivered, the thickening fraction can vary from 0 to almost 40%. From a physiological perspective, it should be acknowledged that thickening falls short due to the fact that it does not incorporate the duration and frequency of breaths, which are components of the PTP. Similar results were found by Umbrello et al.[22] In both studies, effort varied more strongly during lower levels of pressure support and showed smaller differences in thickening fraction during higher levels.

For now, the conclusion has to be drawn that ultrasonography is not sufficiently validated to quantify breathing effort and that the circumstances under which ultrasound provides an estimate of breathing effort require further study.

Weaning and extubation

Research has shown that ultrasound of the diaphragm can be effectively used to predict extubation success in ventilated patients.[11] This is a crucial task, because failure in doing so is related to longer intubation times and ICU stay.[1] This in turn leads to lung damage and higher risks of infection due to ventilation and unnecessary sedation.[23] Even mortality rates are influenced by failure of successful extubation.[6] Currently, indexes such as the rapid shallow breathing index (RSBI), and the CROP index, composed of factors including compliance, resistance, oxygenation and pressure and spontaneous breathing trials (SBT) are used.

DiNino et al. measured tdi and calculated tdi% in 63 patients and chose 30% as the cut-off point for successful extubation. This lead to a sensitivity of 88% and a specificity of 71%, thus being superior to the RSBI.[24] They hypothesised that the underlying reason might be that in the RSBI the accessory breathing muscles might camouflage the diaphragmatic weakness, which will not be able to take on the capacity of the diaphragm in the long run.[25,26]

Ferrari et al.[4] conducted a similar study in patients who had previously failed weaning trials evaluating tdi% >36%. as a predictor for successful extubation. This resulted in a sensitivity and specificity of 88% and 82% respectively.

More recently, Farghaly et al.[27] evaluated diaphragmatic parameters (tdi, tdi% and diaphragm excursion) in 54 patients who successfully passed SBT. Of these 54 patients, 14 failed to complete extubation. The ideal cut-off point to predict successful extubation for tdi at end inspiration was ≥21 mm and for end expiration ≥13.5 mm, yielding a 77.5% sensitivity and 86.6% specificity, and an 80% sensitivity and

50% specificity respectively. A tdi% ≥34.2% provided the highest sensitivity with 90% but only 64.3% specificity. The tdi combined with excursion, which on its own yielded a sensitivity of 87.5% and specificity of 71.5% with a threshold of ≥10.5 mm, provided a test with a decreased sensitivity of 64.9% but a 100% specificity.

Thus, three studies evaluated tdi% as a predictor for successful extubation *(table 3)* and demonstrated that it was superior to the RSBI .[4,11,27]

Table 3. Thickening fraction (tdi%) as predictor for successful extubation

	No. of patients	tdi% cut-off	Sensitivity	Specificity
DiNino 2014[24]	63	30%	88%	71%
Ferrari 2014[4]	46	36%	88%	82%
Farghaly 2016[27]	54	34%	90%	64%

tdi% = thickening fraction

Spadaro et al.[28] introduced a new way of predicting weaning success through diaphragm motion by combining it with the RSBI. They substituted tidal volume in the denominator for motion and named the index D-RSBI (= respiratory rate / motion in mm). The predictive values found were a 94.1% sensitivity (71.3-99.9) and a 64.7% specificity (46.5-80.3), surpassing values for motion as well as the RSBI and coming close to thickening fraction as a predictor for weaning.

Monitoring

Ultrasonography can be used for monitoring the diaphragm and offers certain advantages over other currently used alternatives such as pressure and flow recordings together with transdiaphragmatic pressure, electromyography and phrenic nerve stimulation, chest X-ray, fluoroscopy or CT. These are: cost-effectiveness, bedside availability, which avoids the necessity for transport to imaging machines, level of invasiveness and ease of use. In addition, reference values for comparison and evaluation are already existent.[7,12]

Consistent monitoring offers useful information about the diaphragm in ICU patients. Levine et al.[16] showed that as little as 18-69 hours of ventilation contributed to significant atrophy of the diaphragm. A different study further quantified the atrophy by measuring diaphragm thickness with ultrasound, finding a daily 11% decay and a total reduction of 32% from starting thickness during the first 3 days of MV.[29]

Recently, it was found that low contractile activity of the diaphragm was associated with rapid decreases in thickness, whereas high contractile activity was associated to increased thickness.[30] Activity of the diaphragm was directly and negatively influenced by increasing driving pressures and controlled ventilator modes. Too high levels of assistance may precipitate patient-ventilator asynchrony,[31] which aside from disuse further damages the diaphragm. These findings suggest that depending on diaphragm strength, adequate magnitudes of assistance must be chosen to uphold maximal contractile activity whilst avoiding exhaustion or asynchrony.

With increasing knowledge about possibilities for intervention, the aforementioned findings lead us to believe that monitoring of the diaphragm could possibly gain a bigger role in intensive care medicine in the future.

Is ultrasound of the diaphragm reproducible and feasible?

Only a few studies have studied the reproducibility and feasibility of tdi and tdi%. In 2015 Goligher et al.[10] addressed exactly this issue. They assessed repeatability (within observer) and reproducibility (between observers). The results were satisfactory, but marking the site of measurement greatly increased the repeatability as well as reproducibility coefficients (1.9 to 0.2 and 1.4 to 0.4 respectively), which indicate that 95% of the differences in repeated measurements by the same observer (repeatability) or by two different observers (reproducibility) will be equal to or less than that coefficient.[10]

Based on their findings, they concluded that tdi was very reproducible and repeatable, while tdi% was less so. The most likely reason is that the calculation of tdi% incorporates the error of measurements during inspiration and expiration. Some of these are inherent to the ultrasound machine and cannot be circumvented. The highest resolution most machines have lies around 0.1 mm (given that the speed of soundwaves averages 1540 m/s in human tissue, the range of high frequency probes lies around 3-15 Mhz and that wavelength (λ) = propagation speed / frequency (Mhz) = 1540/15 · 106 = $0.1x10^{-3}$ m = 0.1 mm). This might not seem relevant, but 0.1 mm equals 5% of an average diaphragm with a thickness of 2.0 mm.

Furthermore, they found that depending on breath size (above 50% of inspiratory capacity) tdi% was not correlated with the volume inhaled. The possible explanation for this is that during inspiration above 50% of one's inspiratory capacity, part of the pressure generation is not delivered by diaphragm contraction alone, but expansion of the thorax as well. This leads to the conclusion that ultrasound measurements can be feasible parameters, as long as limitations like these are kept in mind.

Independent of breath size, lung volume seemed to play an important role in measurements of the diaphragm.[32,33] In increasing lung volumes variability of measurements between observers increased as well. This did not seem to be the case for intra-observer variability[34] and indicated that most of the measurements acquired in a patient should rather be used as their own reference value.

In summary, it can be concluded that diaphragm ultrasound measurements are highly repeatable and reproducible under standardised conditions and with experienced operators.

Limitations

While ultrasonography of the diaphragm offers advantages, its limitations have to be kept in mind for optimal use and interpretation of results.

First of all, it has to be mentioned that while learning how to use an ultrasound machine is fairly easy, making precise and reproducible images is less so. One factor, as already pointed out, is the limit of resolution inherent to the ultrasound machine and can therefore not be circumvented. A 5% inaccuracy in measurements has to be accepted for now and treated with caution when basing clinical decisions on ultrasound images. Another factor is presented by the variability between observers, which although small and perhaps negligible, is still present. To improve this variability placement of the ultrasound probe can be standardised by marking the measurement site. However, slight tilting and rotation of the probe are sometimes necessary for optimal images and hard to prevent and reproduce, causing an additional inaccuracy.

Table 4. Applicability of parameters by mode of ventilation

Measurement:	Mode of ventilation:		
	Spontaneous	Assisted	Controlled
Motion	+	-	-
Thickness	+	+	+
TF	+	+	-
D-RSBI	+	-	n.a.
Synchrony	n.a.	+	-

TF: tickening fraction
D-RSBI: diaphragmatic rapid shallow breathing index
+: can be used -: can't be used

Furthermore, ultrasonography of the diaphragm is limited by ventilatory settings *(Table 4)*. For example, measurements of diaphragm motion can only be obtained during spontaneous breathing, as during assisted ventilation no clear distinction can be made between active contractile and passive ventilator pressure driven displacement. During completely controlled modes of ventilation neither motion nor thickness/thickening should be measured for the same reason, even though passive motion and thickening can be observed and misinterpreted as muscular activity.

Future perspectives

Ultrasonography of the diaphragm is a rapidly expanding field with new indications evolving around it. As described above, several studies have demonstrated parameters that can be used, explained how they are obtained and how they can be applied. Monitoring weaning and predicting extubation outcome are key elements.

Nevertheless, many of the studies were performed in selected cohorts and have yet to be evaluated in larger, more heterogeneous patient groups. In addition, some of the papers were already published as early as 2001,[13] while others appeared in 2016,[27] creating a gap of 15 years in which the quality of ultrasound and our understanding of the function of the diaphragm has changed significantly. As follows, this provides a vast range of possible research in the future.

Almost all papers evaluated ultrasonography while solely looking at the diaphragm, even though multiple organ systems could be analysed at once, to provide a broader perspective for interpretation of findings. Mayo et al.[35] hypothesised that looking at the diaphragm with ultrasound during weaning in combination with taking measurements of the lung and heart in the same session might be superior to measuring the diaphragm alone. They concluded that this approach could lead to improvement of weaning outcomes, as heart, lungs and diaphragm are closely related in this regard. More specifically, identification of underlying causes such as left ventricular dysfunction, pleural effusion or inadequate lung aeration could lead to more targeted interventions.

New techniques such as speckle tracking are emerging and are slowly finding their way into clinical practice. It uses naturally occurring speckle patterns to analyse the deformation and motion of tissues. Using this technique, a new parameter called strain was introduced as a way of quantifying diaphragm function. It describes active shortening of a given segment related to the length at a previous time point.

Ye et al.[36] used strain measurements in healthy volunteers and showed that certain parts of the diaphragm contribute to its force generating capacity in different extents than others. The crura and the part in the zone of apposition displayed roughly equal amounts of strain, while the domes showed significantly smaller values. They thus hypothesised that functionality throughout the muscle is not as homogenous as is frequently assumed.

Hatam et al.[37] investigated strain measurements in healthy non-invasively ventilated volunteers and found that with increasing pressure support, diaphragm strain increased as well, indicating the increased work it delivers to resist the driving pressures. These results could indicate that diaphragm strain offers a new approach to quantify diaphragm function and the work it delivers.

Ultrasound contrast agents are also a field of great interest. Small liquid-gas emulsions, surrounded by a shell that prevents leakage and aggregation, called microbubbles, can be used to create a strong echogenic response and with that, highlight and improve visualisation of the tissue of interest. In addition, these microbubbles can be destroyed purposefully to measure replenishment rates and with it tissue perfusion,[38] or even be made tissue specific by targeting certain proteins or DNA.[39] Applying these possibilities to the diaphragm and monitoring its perfusion and inflammation could possibly provide important information, as these factors might play a key role during atrophy.

In summary, with all ongoing research and the implementation of new US techniques, we think it is only a matter of time before ultrasonography evaluation of the diaphragm will become a part of routine clinical practice.

Conclusion

Ultrasonography is a versatile and easy to use tool for mapping the diaphragm in various clinical settings, with a good reproducibility and repeatability. Diaphragm motion, analysed by using a low frequency probe in M-mode, is used in independently breathing patients to detect dysfunction, paralysis and ventilator asynchrony. Measurements of thickness, acquired with a high frequency probe in B-mode, can monitor atrophy and calculate the thickening fraction which in turn is used to assess muscle function and to predict the ability to sustain spontaneous breathing after extubation. Limitations are its potential for inaccuracy and restricted use to certain clinical settings, meaning that during completely controlled modes of ventilation almost all the currently used ultrasound parameters are not viable and that diaphragm motion can only be interpreted during spontaneous breathing. Furthermore, there are currently no studies that demonstrate US of diaphragm being a viable diagnostic tool on its own, which warrants caution and further research.

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