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Role of ultrasound in the assessment of diaphragm function in patients with chronic obstructive pulmonary disease

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Abstract:

Chronic obstructive pulmonary disease (COPD) characterized by irreversible airway obstruction, has numerous systemic complications including skeletal muscle dysfunction. Diaphragm, an important muscle of respiration, is also affected and it has far-reaching impact on morbidity. The study of diaphragm in individuals with COPD is challenging. Although the use of ultrasonography to study the function of diaphragm is in its nascent stage, it seems to be a promising tool for a comprehensive evaluation of diaphragm in COPD patients. This article reviews the available literature on the use of US in study of diaphragm on individuals with stable COPD.

Keywords:

Chronic obstructive pulmonary disease, diaphragm, ultrasound

Introduction

Chronic obstructive pulmonary disease (COPD), now considered a systemic disease, is projected to become the third leading cause of death and the fifth most common cause of disability in the world by 2020.[1]

Respiratory and limb muscle dysfunction is a recognized systemic complication of COPD with multiple pathogenetic mechanisms. Among the respiratory muscles, the diaphragm one of the main inspiratory muscles is commonly affected. In fact, diaphragm dysfunction (Dd) is considered as one of the markers of disease severity in COPD which negatively impacts quality of life. Alterations in the mass, thickness, and area of the diaphragm have been described in individuals with COPD.[2]

Despite the above implications of Dd, it is often underdiagnosed. One of the reasons for this could be that the current tools available to evaluate diaphragm function (computed tomography [CT], magnetic resonance imaging [MRI], fluoroscopy and diaphragmatic electroneuromyography) are expensive and not easily accessible for routine bedside use. Ultrasonography (USG), an easily available, cheap, and safe tool, is the only modality that can evaluate both structure and function of the diaphragm. The routine

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use of USG for evaluation of diaphragmatic function in individuals with COPD is yet to be explored.

Diaphragm in Chronic Obstructive Pulmonary Disease

Dyspnea, which is one of the main presenting complaints in individuals with COPD, is a disabling symptom. The pathophysiology of dyspnea in COPD is complex. An imbalance between the load imposed on the respiratory muscles (including the diaphragm) and the ability to sustain this load can worsen the sensation of dyspnea.[3] Hypercapnia and impaired maximum inspiratory pressure are also consequences of inspiratory muscle weakness.[4] Thus, the study of respiratory muscle function and interventions to improve muscle function would reduce dyspnea.[5]

It has been shown that oxidative stress and sarcomere injury in COPD activates the proteolytic machinery, leading to contractile protein loss, and consequently, the force-generating capacity of diaphragmatic fibers is reduced along with diaphragmatic atrophy. Even in mild to moderate COPD, loss of myosin in the diaphragm fibers occurs long before they develop limitation in activities of daily living.[6] In view of the above evidence, evaluation of diaphragm function is necessary regardless of the severity of disease in patients with COPD.

Evaluation of Diaphragm Function

Although the gold standard for diaphragm function is phrenic nerve stimulation and measuring the resultant change in transdiaphragmatic pressure using esophageal or gastric transducers, it may not be acceptable to individuals with COPD, and this test cannot be used especially during exacerbations of COPD.

The other modalities that have been used to evaluate diaphragm function include the following:

a. Chest radiography, which shows an elevated diaphragm on the side of diaphragm weakness but cannot be used as a predictor of motion, especially in COPD individuals who have a dysfunction rather than paralysis.[5,7]
b. Fluoroscopy assesses excursion of diaphragm. The sniff test of Hitzenberger that demonstrates a shift of the mediastinum is suggestive of paralysis of diaphragm.[8] Paradoxical movement of the diaphragm is indicative of unilateral paralysis, but in the setting of bilateral paralysis, a normal descent of the diaphragms may be seen during inspiration due to compensatory respiratory mechanisms.[9,10] Individuals with COPD may find it difficult to hold their breath during fluoroscopy.
c. CT can be helpful for studying diaphragm structure, but dynamic studies cannot be performed. Radiation exposure is another drawback of these techniques.
d. Dynamic MRI is a new technique that can be used for quantitative evaluation of excursion, synchronicity, etc. However, drawbacks are operator dependence, limited availability, and high cost.[11,12]
e. Electrophysiological testing: The most sensitive and specific test that can differentiate neuropathic from myopathic cause of paralysis is phrenic nerve conduction study coupled with electromyography.[13-15] This test is not only uncomfortable but also technically difficult to perform. Interpretation of the study is challenging. Besides, this test would be a relative contraindication in individuals with COPD as it carries a high risk of pneumothorax.

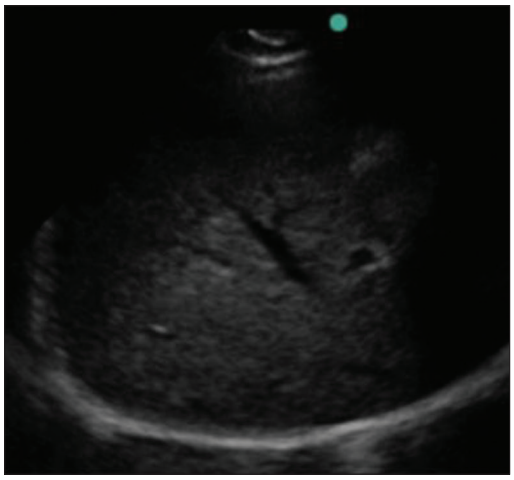

Figure 1a: Anterior view of diaphragm with microconvex probe

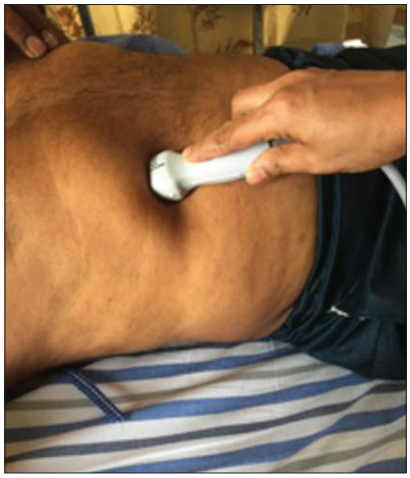

Figure 1b: Probe placed under costal margin

USG is an evolving technique that is now used to image the diaphragm at the bedside. Cohen in 1969was the first person to describe the USG of diaphragm.[16] It is now more commonly used in the critical care setting for the evaluation of diaphragm structure and function, as an

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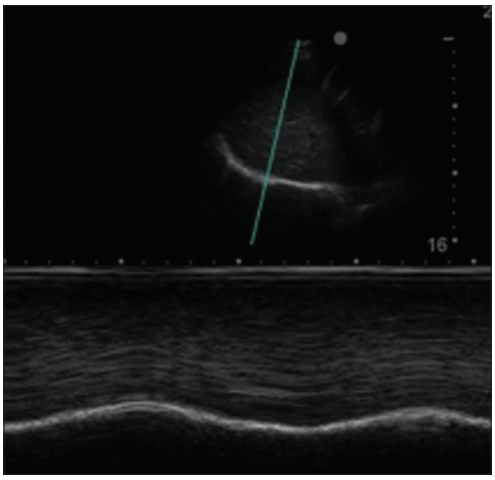

Figure 1c: Diaphragm as viewed in M mode

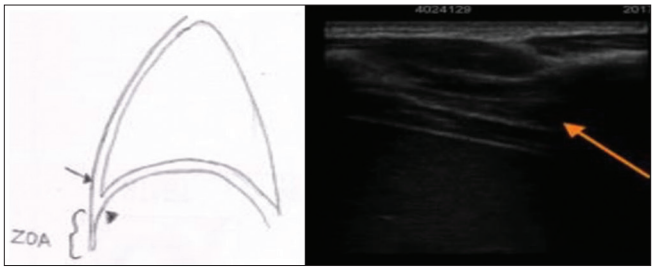

Figure 2a: Diaphragm as seen at Zone of Apposition, Diaphragm is seen peeling away from chest wall(Red arrow)

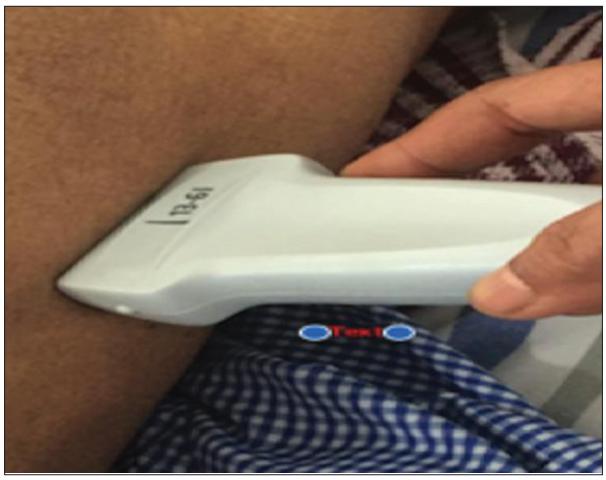

Figure 2b: High frequency probe kept in anterior axillary line

adjunct to clinical assessment of individuals for weaning.[17] USG is portable, there is no risk of ionizing radiation, allows visualization of anatomical structures around the diaphragm, and can be used repeatedly, including during follow-up after interventions like pulmonary rehabilitation. It also carries the advantage of assessing both the structural and functional components of the diaphragm at the same time. Ultrasound is comparable to twitch pressure for the assessment of diaphragm to predict failure of spontaneous breathing trial in the intensive care unit.[9,13,18-20]

Table 1: Normal values for diaphragm USG[31,32,37]

Area of Scan	Parameter	Mean normal values±SD (mm)	Suggested abnormal values (25)
ZOA	TD	2.7±0.5	<2 mm
	TF	37±9%	<20%
Infrahepatic	Tidal Excursion	16±3 mm-Women	<9 mm Women
		18+/-3 mm Men	<10 mm Men
	Deep Breath	57+/-10 mm Women	<37 mm Women
		70+/-11 mm Men	<47 mm Men

SD: standard deviation; ZOA: zone of apposition; TD: diaphragm thickness
TF: diaphragm thickening fraction

This paper will review the techniques, measurements, and utility of USG in assessment of the diaphragm in individuals with COPD.

Ultrasonographic Evaluation of the Diaphragm

Ultrasonographic evaluation accesses mainly the lateral and posterior parts of the diaphragm, which are the crural components and muscular.[9] The diaphragm's position and motion depend on the patient position. The preferred patient position for evaluation is supine because there is less overall variability and greater reproducibility.[21] However, some authors have also assessed the diaphragm in the sitting position (45° inclination) because other assessments like spirometry are also performed in this position [Figure 1a-c].[22,23]

Anterior view of the diaphragm

The diaphragm is best visualized by a 3.5–5 MHz-phased array probe. It is seen as a curvilinear structure with muscular echo texture [Figure 1a]. The probe is placed just below the right or left costal margin in the midclavicular line or anterior axillary line. The probe is directed cranially, medially, and dorsally so that the ultrasound rays hit the posterior third of the diaphragm perpendicularly approximately 5 cm lateral to the inferior vena cava foramen (on right side) [Figure 1b]. In healthy controls, it has been demonstrated that this midposterior diaphragm portion produces the greatest craniocaudal excursion during spontaneous breathing, as measured by USG.[24] The liver acts as a good acoustic window to view the right diaphragm. However, it is more difficult to visualize the left diaphragm because the acoustic window offered by the spleen is small. A good and complete visualization of diaphragm is required for a quantitative analysis.[25] For making the readings repeatable and avoid interobserver variability, care has to be taken to keep the probe in the correct position so that the ultrasound beam is perpendicular to the diaphragmatic excursion.

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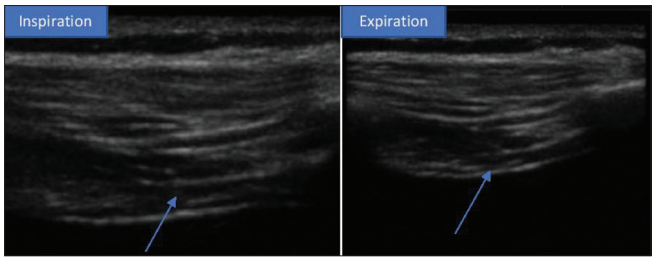

Figure 2c: Changes in diaphragm thickness during inspiration and expiration

While B-mode visualizes the diaphragm moving toward or away from the transducer, the M-mode ultrasound displays a single beam of a B-Mode image on the y axis as it changes over time on the X axis. A specific site over time is examined. Thus, the M-mode assesses the diaphragmatic excursion [Figure 1c]. The position at which the M mode cursor has to be placed should be selected carefully. This point should be such that the ultrasound beam falls on the posterior part of the diaphragm. As the normal movement of diaphragm is in the craniocaudal direction, it is seen as moving towards the probe during inspiration and away from the probe during expiration. With the M-mode, the diaphragmatic excursion (displacement in cm), the speed of diaphragmatic contraction (slope, cm/s), and the inspiratory time (Tinsp in seconds) can also be calculated.[5,11,26-28]

Limitations of study of excursion of diaphragm:

1. By visualizing the dome, we are not seeing the whole diaphragm
2. The excursion is affected by many factors such as position of individual, phase and depth of respiration, the chest wall and abdominal compliance, body habitus, and previous abdominal surgery.[29,30]

Intercostal view

The muscular diaphragmatic fibers run parallel to the chest wall in the sides of the lower thorax. This area where the diaphragm is in close apposition to the chest wall is called the Zone of apposition (ZOA) [Figure 2a].

A high frequency linear array transducer in B mode is used for the intercostal view. The transducer is placed on the anterior axillary line, between 7 and 9 ribs. Inferior border of lung is seen as lung sliding, and then, the diaphragm is seen. An image of two intercostal spaces is obtained at this point [Figure 2b]. In this view, the diaphragm appears as hypoechoic (dark) muscle fibers covered by hyperechoic (bright) fibroadipose septae. The thickening of diaphragm is well demonstrated in this view [Figure 2c]. Care should be taken to keep the two hyperechoic lines parallel to each other [Table 1].

Limitations

1. The thickness of the diaphragm measured is influenced by the phase of respiration, the inspiratory depth, and the points along the ZOA where measurements are done. Hence, a standardized approach should be followed.[30]

Area method

This method quantifies the difference in the intrathoracic area between inspiration and expiration. Using liver or spleen as a landmark to identify the hemidiaphragm, the entire visible portion of the diaphragm is traced along with the chest wall. The area covered within these lines is calculated. Studies in COPD using this method are lacking.[31]

Anatomical motion method

Anatomical motion method is based on numerical image reconstruction. It allows free placement of the cursor anywhere along the diaphragm, thus allowing recording of movement of diaphragm. This method is yet to be evaluated in individuals with COPD.[32]

Evaluation of Diaphragm in Chronic Obstructive Pulmonary Disease by Ultrasonography: Review of Literature

Diaphragmatic displacement in chronic obstructive pulmonary disease

All studies have uniformly found that diaphragmatic displacement (DD) was lower in COPD as compared to normal individuals. However, the cutoff below which the diaphragm is dysfunctional has not been arrived at. A mean DD of 33.9 mm was seen in individuals with COPD as compared to 46 mm in individuals without COPD.[33,34]

Dyspnea in individuals with COPD had a negative correlation with DD as diagnosed by displacement of portal vein.[33,35] Almost all studies have found that mobility of diaphragm correlated with the pulmonary function parameters that quantify airway obstruction such as forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and air trapping (residual volume [RV], total lung capacity [TLC]).[32-36] No study till date has looked at the pattern of air trapping and diaphragm mobility by USG. Blood gas parameters (PaCO2 and PaO2) also correlated with diaphragmatic mobility.[35]

A reduced diaphragmatic mobility as seen on USG correlated with the distance walked in 6-min walk distance (6MWD).[33,35-37] BODE index was also higher in individuals with DD. DD of 33.9 mm or less was associated with higher mortality in individuals with stable COPD with a sensitivity of

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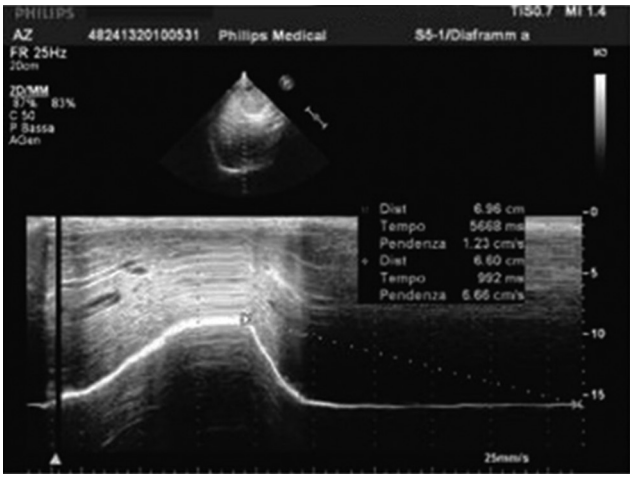

Figure 3a: M mode - Representation of expiration in an individual with normal spirometry*
*Adapted with permission from j.ultrasmedbio-2013.12.009

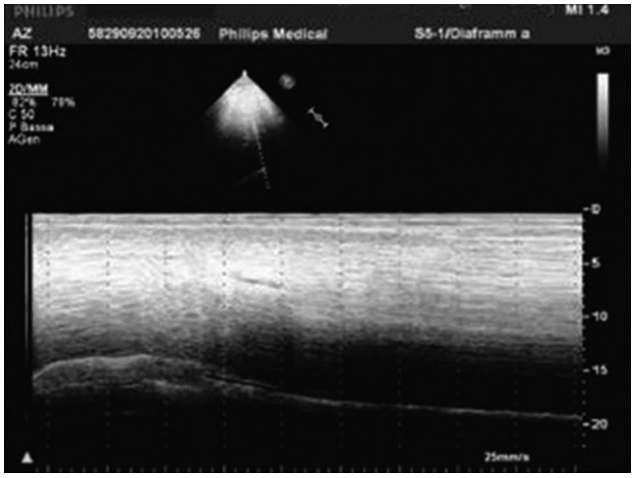

Figure 3c: M Mode - Less severe drop off in subject with severe obstructive airway disease*
*Adapted with permission from j.ultrasmedbio-2013.12.009

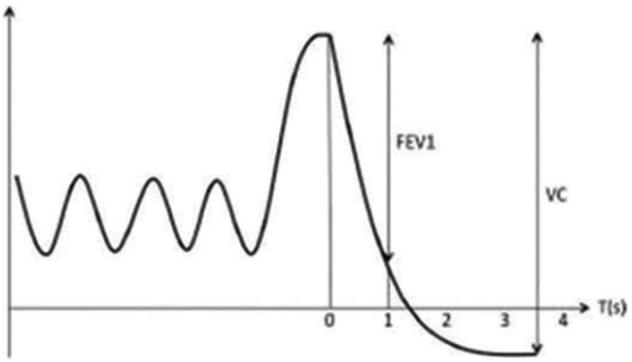

Figure 3b: Spirometry - Volume-time graph*
*Adapted with permission from j.ultrasmedbio-2013.12.009

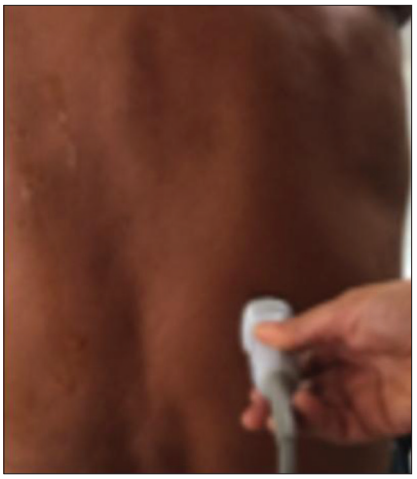

Figure 4: Diaphragm as seen posteriorly

100% and specificity of 58% in a case–control study by Yamaguti *et al*.[35]

Zanforlin *et al*. found a similar trend between time/volume curve of spirometry and M mode representation of diaphragm movement during forced breathing. This was called as M-mode index of obstruction (MIO).[38]

MIO = FEDE1 (in cm)/EDE max (in cm).

(MIO – M-mode index of obstruction; FEDE 1 – Forced expiratory diaphragmatic excursion in 1st s; EDE max – Maximal expiratory diaphragmatic excursion).

MIO was shown to have a linear correlation with FEV1 and vital capacity (VC). This is due to delay in relaxation time during forced expiration in individuals with COPD due to air trapping that worsens with forced maneuvers. Hence, it can be used as a marker of airway obstruction. Larger studies are needed to see if the same can be extrapolated to all causes of airway obstruction, derive a cutoff value, and determine factors that influence MIO [Figure 3a-c].

As the severity of COPD increases, the excursion of diaphragm decreases as seen on USG. This could be the result of increasing hyperinflation, use of steroids, intrinsic muscle weakness, hypoxia, hypercarbia, and so on. However, the cutoff value for diaphragmatic excursion to label it as diaphragmatic dysfunction is variable in individuals with COPD. Most studies have been done on a small number of individuals.[20-47] Some have been observational while others have been case–control studies. The severity of COPD also varied from mild to very severe in these studies. Some studies have even evaluated the displacement of diaphragm in the infrascapular area with patient sitting [Figure 4].[39] This heterogeneity makes it difficult to implement a single cutoff value (for both normal values and severity) for the diaphragm excursion. However, further research with larger sample size and uniform methodology will help in laying down cutoff values for diaphragmatic dysfunction and make it a valuable tool for use at the bedside.

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Parameters measured in the intercostal view

The thickness of diaphragm is seen best in the lateral chest wall with a linear high frequency probe. The thickness of diaphragm measured by this method correlates with direct diaphragm thickness measurements on a cadaver.[11,18,35] Measuring diaphragmatic thickness (TD) during maximal inspiration can be used as an indirect measurement of muscle fiber contraction[18,35] [Figure 2c]. In healthy volunteers, the average thickness of the diaphragm is 0.22–0.28 cm. A cutoff of 2 mm at end of expiration was used to define atrophy of the diaphragm.[35] There are no large-scale studies on COPD individuals that have arrived at a cutoff value for thickness of diaphragm. However, the thickness of the diaphragm measured by ultrasound was lesser in COPD when compared with normal individuals. The difference was statistically significant only in Group D COPD.[40] Larger studies are required to look at diaphragm thickness even in early stages of COPD.

The TD can be measured at maximal inspiration (TDi) and at end of expiration. The thickness of the diaphragm is more pronounced above 50% of the VC.[41] A lack of change in thickness correlated with invasive measurements of transdiaphragmatic pressure and was sensitive for the diagnosis of diaphragm paralysis.[18] <20% thickening of diaphragm is found to be consistent with paralysis.[13]

The relationship between TD and lung volumes during spontaneous breathing is nonlinear There is a large increase in thickness between relaxation and 10% of the inspiratory effort.[3] Using mathematical formulae based on the above,

TD = 1.74 VC 2 + 0.26 VC + 2.7 mm (in normal individuals).

Such values in COPD individuals have not been studied. In some studies, TD that was measured at different lung volumes (TLC, FVC, RV) was closely related to height, body mass index, 6MWD, fat-free mass FEV_1, inspiratory capacity (IC), VC, TLC, and FVC in individuals with COPD.[2,43,44]

The difference between TD at TLC and TD at RV, as a thickening value (TDTLC/TDRV), was closely related to FVC and to air-trapping indices (RV/TLC, FRC/TLC and IC/TLC). The lung volume correlates inversely with TDTLC/TDRV in subjects with COPD.

Due to lack of uniformity of inclusion & exclusion criteria, stage of COPD, small sample size [Table 2], and failure to study the impact of other factors such as body habitus and position of the individual in the studies that have looked at the thickness of the diaphragm using USG in individuals with COPD, we are not able to arrive at a clear-cut value for TD that would help us identify diaphragmatic dysfunction.

As the diaphragm shortens during contraction, it thickens, and measures of diaphragmatic thickening during inspiration TDi are inversely related to changes in diaphragm length (LDi) (TDi is approximately 1/LDi). Hence, it might be worthwhile comparing a diaphragm with chronically reduced length, as in COPD, with that of a normal population by measuring TDi with respect to per unit change in LDi.

Diaphragm thickening fraction (TF) is a newly proposed indicator of diaphragm contraction than measurement of thickness since the increase in TD during inspiration is used as an indirect measurement of muscle fiber contraction. This needs to be standardized. Further studies are required to see if it could be equivalent to ejection fraction of the heart.[9] TF correlates with lung volume in normal individuals.

TF = (Inspiratory thickness-expiratory thickness)/End-expiratory thickness, expressed as a percentage.[10-12]

In a study by Hafez and Abo Elkheir who studied TF as a function of Dd, of 100 individuals with COPD (with all stages of COPD), 11.5% of mild COPD and 21.5% of the severe COPD had Dd. In individuals with acute exacerbation, the Dd is present in 24.3%.[44] Hypoxemic (mean paO2 = 53.9 ± 5.9 mm Hg) individuals with COPD have a significantly lower TF.[45] The presence of Dd in individuals with acute exacerbation correlated with steroid use, NIV failure, longer ICU stay, duration of ventilation, and mortality.[46] Hence, further studies are required to see if measurement of TF could be used as an indirect predictor of treatment outcome.

Thickening ratio (TR) has been used in some studies.[21,47]

TR = Thickening of diaphragm in inspiration (max)/Thickening of diaphragm in expiration (min).

The exact prevalence of diaphragmatic dysfunction as measured by TF, TR, TD, etc., is not known. Further studies are required to standardize the technique (with respect to severity of COPD, the phase of respiration in which the measurements are to be performed, influence of body habitus, etc.) and select best parameters that identify Dd in individuals with COPD and correlate with severity of disease, disease outcomes, and changes with pulmonary rehabilitation.

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Table 2: Summary of all studies that have evaluated Ultrasound of Diaphragm in COPD

Parameters studied	Authors	Type of study/ number of subjects	Severity of COPD	Results
DD Compare anterior with posterior technique	Nadine Scheibe	Case-control 20/60	Gold stage 2,3,4	Strong correlation between two methods Strong correlation between the demonstrated sonographic measurement of the up- and downward movement of the lung silhouette and the FeV1
DD measurement to predict weaning time. Cut-off value of DD for weaning time	Fabio Giuliano Numi	Observational 52	Acute exacerbation started on NIV	DD at the baseline was significantly correlated with pH DD was significantly associated with longer weaning time A cut-off value of 3.165 cm of DD correlated with weaning time.
Impact of DD on lung function tests, exercise tolerance, dyspnea score	E. Paulin	Case Control 54/20	COPD with HI	Lower DD in COPD. Linear correlation with 6MWD Negative correlation with Dyspnoea Correlated with RV&MVV Cut off DD of 34 mm
Relationship between DD and pulmonary function parameters, arterial blood gas values	Hyun Wook Kang	Observational 37	NS	Negative correlations between diaphragmatic mobility and PaCO2 , FEV1, FVC, MVV, HI No relationship between DD and PaO2
Compared DD in COPD and healthy subjects. To evaluate the relation of DD and COPD severity.	Behrooz Davachi	Case-control 25/25	All Stages	DD lower in COPD (SS) DDCorrelated to FeV1, FVC, 6MWD. No Correlation with TLC, RV Severity of COPD correlated with DD

Limitations

Ultrasound though a remarkable tool has some potential limitations. Visualization of diaphragm on the left side is challenging because of the small acoustic window offered by spleen. The paradoxical movement of diaphragm can happen not only in individuals with a paralyzed diaphragm but also in conditions such as pleural effusion, atelectasis, and lung fibrosis.[9] The body habitus of the patient (obesity) might make even visualization of the diaphragm difficult. The effect of previous intra-abdominal surgery on the diaphragm movement is not known.

The role of abdominal contents and abdominal muscles along with the position of the patient in which the examination is done (supine position versus semirecumbent) can affect diaphragmatic measurements. Patient's ability to hold his/her breath also can affect the measurements. The effect of lower lobe emphysema on the measurements is not available. Since most of the studies that are available are single center with small number of individuals, the effect of different phenotypes of COPD, the effect of exacerbations, and the effect of drugs like steroids (inhaled and systemic) on the diaphragm are yet to be evaluated.

Future Directions

Further studies establishing reference values are needed for diaphragm thickness, excursion of diaphragm, and velocity of diaphragm. The values computed should consider the phase of the respiratory cycle, body habitus, race, and ethnicity among others. USG of the diaphragm in COPD may help predict and study the natural history of respiratory failure. This can also help us modify the therapy and rehabilitation protocols specifically directed at the diaphragm.

Conclusion

In summary, USG is a promising tool for the evaluation of the structure and function of the diaphragm. USG can be used in evaluation of a given patient multiple times as a qualitative technique or with exact measurements as it is reproducible, portable, and does not use ionizing radiation. The use of USG in subjects with COPD with special reference to evaluation of diaphragm in respiratory failure and impact of interventions like pulmonary rehabilitation or use of non invasive ventilation has to be studied in future.

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Conflicts of interest
There are no conflicts of interest.

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