B-Mode Ultrasound Assessment of Diaphragm Structure and Function in Patients With COPD

Michael R. Baria, MD; Leili Shahgholi, MD; Eric J. Sorenson, MD; Caitlin J. Harper, BS; Kaiser G. Lim, MD; Jeffrey A. Strommen, MD; Carl D. Mottram, RRT; and Andrea J. Boon, MBChB

BACKGROUND: Electromyographic evaluation of diaphragmatic neuromuscular disease in patients with COPD is technically difficult and potentially high risk. Defining standard values for diaphragm thickness and thickening ratio using B-mode ultrasound may provide a simpler, safer means of evaluating these patients.

METHODS: Fifty patients with a diagnosis of COPD and $FEV_1 < 70\%$ underwent B-mode ultrasound. Three images were captured both at end expiration (Tmin) and at maximal inspiration (Tmax). The thickening ratio was calculated as (Tmax/Tmin), and each set of values was averaged. Findings were compared with a database of 150 healthy control subjects.

RESULTS: There was no significant difference in diaphragm thickness or thickening ratio between sides within groups (control subjects or patients with COPD) or between groups, with the exception of the subgroup with severe air trapping (residual volume $> 200\%$), in which the only difference was that the thickening ratio was higher on the left ($P = .0045$).

CONCLUSIONS: In patients with COPD presenting for evaluation of coexisting neuromuscular respiratory weakness, the same values established for healthy control subjects serve as the baseline for comparison. This knowledge expands the role of ultrasound in evaluating neuromuscular disease in patients with COPD.

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ABBREVIATIONS: EMG = electromyography

AFFILIATIONS: From the Department of Physical Medicine and Rehabilitation (Drs Baria, Shahgholi, Strommen, and Boon), the Division of Clinical Neurophysiology (Drs Sorenson, Strommen, and Boon), Department of Neurology, the Mayo Medical School (Ms Harper), the Department of Pulmonary and Critical Care Medicine (Dr Lim and Mr Mottram), and the Division of Allergic Diseases (Dr Lim), Mayo Clinic and Foundation, Rochester, MN.

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CORRESPONDENCE TO: Andrea J. Boon, MBChB, Department of Physical Medicine and Rehabilitation and Division of Clinical Neurophysiology, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: boon.andrea@mayo.edu

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Patients with unexplained shortness of breath are often referred to the electromyography (EMG) laboratory for phrenic nerve conduction studies and diaphragm EMG to evaluate for neuromuscular disease. Both phrenic nerve conduction studies and needle EMG can be technically challenging, have the potential for false positives and false negatives, or are relatively contraindicated in the case of needle EMG, given the risk of pneumothorax in a compromised patient.¹⁻³ Ultrasound of the diaphragm is a noninvasive, reliable, and relatively inexpensive diagnostic tool that is becoming more readily available with the advent of portable high-resolution machines. We now use it routinely in our EMG laboratory in the workup of patients with shortness of breath, not only to enhance the safety and accuracy of needle EMG of the diaphragm,⁴ but also to evaluate for atrophy and lack of motion of the muscle, which are readily apparent on ultrasound in patients with phrenic neuropathy.⁵⁻⁸

Sonographic assessment of diaphragm structure and function would be a useful clinical tool in patients with COPD presenting for evaluation of possible coexisting neuromuscular respiratory weakness, particularly because needle EMG is relatively contraindicated in this patient population due to the potential for lung hyperinflation and associated difficulty involved in accurately localizing the muscle. However, to use ultrasound in this way, there is a need for normal values for dia-

phragm thickness and contraction in patients with COPD.

Studies detailing the basic structure and motion of the diaphragm in patients with COPD are limited. Most sonographic studies to date have used M mode, which provides information on diaphragm excursion but not muscle structure. We use B-mode sonography to study the structure and function of the diaphragm, measuring the thickness of the muscle and the thickening ratio during respiration.⁹ By determining normal values for diaphragm thickness and contraction in patients with COPD, we hope to facilitate the use of diaphragm ultrasound, as well as ultrasound-guided diaphragm EMG, in the diagnostic assessment of neuromuscular illness in this complex, higher-risk group.

The primary goal of this study was to determine the diaphragm muscle thickness and thickening ratio in patients with COPD compared with normal control subjects. We hypothesized that in patients with COPD with at least moderate airflow obstruction (defined by the American Thoracic Society-European Respiratory Society guidelines as $FEV_1 < 70\%$),¹⁰ the diaphragm would show physiologic, compensatory overuse hypertrophy and that in patients with severe air trapping (residual volume $> 200\%$), diaphragm function would be impaired because of the decreased contractility related to lung hyperinflation and associated diaphragm displacement.

Materials and Methods

This observational case-control study was carried out at a large, tertiary-referral, academic institution, after receiving institutional review board approval (IRB number 11-002744). All patients gave verbal consent and signed Healthcare Information Portability and Accountability Act authorization. Patients with COPD were recruited from the pulmonary function laboratory if they met the inclusion criteria and agreed to participate. Inclusion criteria for patients with COPD were an $FEV_1 < 70\%$ and a clinical diagnosis of COPD. Using the American Thoracic Society-European Respiratory Society classification of airflow obstruction severity, patients with at least moderate airflow obstruction were studied.¹⁰ Additionally, a subgroup of patients with severe air trapping as defined by a functional residual volume $> 200\%$ was studied independently. One hundred fifty healthy control subjects had been recruited previously from the Mayo EMG laboratory and had no history of neuromuscular or pulmonary disease and no shortness of breath at rest or with exertion.

All subjects underwent B-mode ultrasound examination using a portable ultrasound machine (Logiq E, GE), and an 8- to 13-mHz linear array transducer, as described previously.⁹ With the patient in the supine position, the transducer was placed on the chest wall at approximately the anterior axillary line, just cephalad to the lower costal margin. With

the transducer spanning/perpendicular to two ribs, the diaphragm can be visualized as a hypoechoic layer of muscle encased in two hyperechoic layers of connective tissue (the parietal pleura and the peritoneum), deep to the intercostal muscles connecting the two ribs (Fig 1). Diaphragm thickness was measured by placing electronic calipers just inside the hyperechoic connective tissue layers. Measurements were taken on three different images to find the average thickness of the diaphragm at end expiration or functional residual capacity. Measurements were also taken on three different images to find the average thickness of the diaphragm at maximal inspiration or total lung capacity. A thickening ratio was derived by dividing the average thickness of the diaphragm at maximal inspiration or total lung capacity by the average thickness of the diaphragm at end expiration or functional residual capacity (Fig 1). In healthy control subjects, we had previously found that the average thickness of the diaphragm at end expiration or functional residual capacity should be > 0.14 cm and that the thickening ratio should be > 1.2 .

Statistical Analysis

Data analysis was performed using JMP software (version 9, SAS Institute Inc). A *t* test was used to measure the difference in diaphragm thickness and thickening ratio between control subjects and the total COPD population in this study. An analysis of variance was used to compare the two COPD groups. *P* values $< .05$ were considered statistically significant.

Figure 1 – A, Thickness of diaphragm at end inspiration or functional residual capacity (0.20 cm). B, Thickness of diaphragm at maximal expiration or total lung capacity (0.39 cm). These give a thickening ratio of 1.95. ABD = abdominal muscle; D = diaphragm; IC = intercostal; SC = subcutaneous tissue.

Results

The study population included 50 patients with COPD and 150 control subjects. Case and control subject demographics are presented in Table 1. Diaphragm muscle thickness and thickening ratio in normal subjects and in patients with COPD are presented in Table 2.

There was no significant difference in diaphragm thickness or thickening ratio between sides within groups (control subjects or patients with COPD), or between groups, with the exception of the subgroup of patients with severe air trapping (residual volume > 200%), in which the thickening ratio was higher on the left ($P = .02$) compared with the control subjects or with the COPD group as a whole.

Discussion

Ultrasound has been used since the 1960s to evaluate diaphragm structure and function, primarily using

TABLE 1] Demographics of Patients With COPD and Healthy Control Subjects

Demographic	Patients With COPD (n = 50)	Control Subjects (n = 150)
Age, y		
Mean $\pm$ SD	69 $\pm$ 9.9	50.64 $\pm$ 17.8
95% CI	66-71.8	47.8-53.5
Sex, No.		
Male	23	73
Female	27	77
BMI, kg/m ²		
Mean $\pm$ SD	27.9 $\pm$ 5.5	27.9 $\pm$ 5.9
95% CI	18.2-42.2	26.9-28.8
Smoking status, No. (%)		
Past smoker	37 (74)	20 (14)
Current smoker	4 (8)	39 (26)
Never smoker	9 (18)	91 (60)
FEV ₁		
Mean $\pm$ SD	41.2 $\pm$ 11	...
95% CI	38-44.3	...
FVC		
Mean $\pm$ SD	67.1 $\pm$ 13.1	...
95% CI	63.4-70.8	...
COPD severity, FEV ₁ , No.		
Moderate (69-60)	0	...
Moderately severe (59-50)	13	...
Severe (49-35)	20	...
Very severe (< 35)	17	...

M mode to measure excursion. In recent years, as technology has progressed and image resolution has improved markedly, B-mode sonography has become more readily available. The advantages of ultrasound over other imaging modalities include portability, which is particularly advantageous in the ICU setting, relatively low cost, and absence of contraindications. In comparison with other methods of evaluating diaphragm function, sonography has advantages over plain chest radiograph and videofluoroscopy, both of which have fairly high rates of false positive and false negative results, and transdiaphragmatic pressure measurements, which are invasive, uncomfortable, and only helpful in bilateral paralysis.¹¹ Needle EMG of the diaphragm can be very helpful but is relatively contraindicated in patients with COPD because of concerns over hyperinflation and a possible heightened risk of pneumothorax.

TABLE 2] Diaphragm Muscle Thickness and Thickening Ratio in Normal Subjects and in Patients With COPD

Diaphragm Measurement	Mean	SD	Range	Fifth Percentile
Normal subjects				
Right Tmin, cm	0.32	0.13	0.13-0.73	0.16
Left Tmin, cm	0.34	0.18	0.12-1.18	0.15
Right TR	1.8	0.5	1.2-3.9	1.2
Left TR	1.9	0.5	1.2-4.2	1.3
All COPD				
Right Tmin, cm	0.28	0.16	0.11-1.02	0.14
Left Tmin, cm	0.32	0.17	0.11-0.79	0.14
Right TR	1.9	0.5	1.2-3.2	1.3
Left TR	1.9	0.7	1.2-3.8	1.2
Air trapping				
Right Tmin, cm	0.26	0.14	0.14-0.59	0.14
Left Tmin, cm	0.26	0.14	0.15-0.52	0.15
Right TR	2.0	0.6	1.3-2.8	1.3
Left TR	2.3 ^a	0.5	1.8-3.3	1.8

Tmin = average thickness of the diaphragm at end expiration or functional residual capacity; TR = thickening ratio (thickness of the diaphragm at total lung capacity/thickness of the diaphragm at functional residual capacity).

^aStatistically significant difference from "Normal subjects" and "All COPD," $P = .02$.

We previously studied B-mode sonography of the diaphragm in a large cohort of healthy subjects ranging in age from 20 to 83 years and found that the mean diaphragm thickness in the zone of apposition was 0.33 cm, with the lower limit of normal (95th percentile) being 0.15 cm, and that the muscle increased in thickness by at least 20% at total lung capacity. Side-to-side difference in thickness can be up to 0.33 cm.⁹ That study confirmed the findings of prior smaller studies and provided normal values for future comparative studies; however, we did not know whether these values could be applied to the population of patients with COPD.^{5,12-15}

We hypothesized that patients with moderate COPD would demonstrate compensatory overuse hypertrophy of the diaphragm and that patients with severe air trapping would have impaired diaphragm contractility because of the displacement of the muscle and subsequent suboptimal length-tension relationship of the muscle fibers, resulting in a decreased thickening ratio. Contrary to our hypotheses, our results show that patients with COPD have comparable diaphragm thickness and contraction to that of normal subjects. This is consistent with the work of Topeli et al,¹⁶ who reported

normal diaphragm structure, diaphragm function, and respiratory drive in patients with COPD.

The findings are clinically significant because they imply that normal values for diaphragm muscle thickness and thickening ratio can be applied to patients with COPD when evaluating for superimposed neuromuscular respiratory failure. This provides a consistent standard by which to evaluate patients, and strengthens the efficacy of a battery of noninvasive evaluations. For example, Podnar and Harlander¹⁷ examined phrenic nerve conduction studies in otherwise healthy patients with COPD as a means of differentiating COPD-induced respiratory failure from neuromuscular disease. Of 20 patients with COPD and 29 control subjects, phrenic nerve conduction latencies were significantly longer with higher amplitudes in the COPD population, clearly differentiating these patients from those with neuromuscular disease of the diaphragm, in which decreased compound muscle action potential amplitudes were expected. With these parameters for noninvasive diaphragm evaluation, it is possible to diagnose neuromuscular disease without having to use needle EMG, although that technique may still be necessary to differentiate myopathy from neuropathy as the cause of the neuromuscular respiratory failure.

Regarding positioning of the patient during the evaluation, we used the supine position for two reasons. First, it negates the caudal pull of gravity on diaphragm movement, which should increase the sensitivity of our evaluation for the detection of subtle weakness not observable in the seated or standing position. Second, if needle EMG is warranted, it would be performed in the supine position. Therefore, for consistency, we think it is prudent to assess the diaphragm in the same position. To our knowledge, no studies have used B-mode ultrasound to define the differences of diaphragm function in the supine vs seated vs standing position. We are currently investigating this subject.

B-mode imaging of the diaphragm has been available as a diagnostic tool in the workup for respiratory failure for many years and it has been gaining popularity in recent years as it becomes more readily available. Using B mode, Gottesman and McCool⁶ compared 12 patients with diaphragm paralysis with 15 control subjects and found that the diseased group had both decreased thickness and a change in the thickening ratio. Summerhill et al⁸ examined diaphragm thickness in 16 patients with phrenic neuropathy and followed them for 60 months. Eleven patients were seen to have functional recovery

in about 14 months. Those who did not recover also did not exhibit any thickening during their follow-up. De Bruin et al¹⁸ examined the thickness and thickening ratio in boys with Duchenne muscular dystrophy and found evidence of increased thickness, possibly representing pseudohypertrophy, but decreased contractility. These studies support the notion that ultrasound is useful both diagnostically and in monitoring functional recovery.

To our knowledge, there are no prior studies using B-mode ultrasound in this particular manner in patients with COPD. Paulin et al¹⁹ used B-mode sonography to examine diaphragm excursion (indirectly via craniocaudal displacement of the portal vein) and its relation to dyspnea on exertion in patients with COPD and healthy control subjects. Fifty-four patients with COPD were compared with 20 healthy control subjects. The patients with COPD had less diaphragm excursion (36 mm vs 46 mm), which correlated with the distance covered in the 6-min walk test. The groups were subanalyzed by the amount of diaphragm excursion present (above and below 34 mm); those with less motion covered less distance and had worse subjective dyspnea. These data suggest a correlation among impaired diaphragmatic motion, worse functional performance, and subjective discomfort. Several other authors using various imaging modalities have also shown that decreased excursion of the diaphragm in patients with COPD correlates with changes in functional measures, including pulmonary function tests, 6-min walk test, and PaCO_2 .²⁰⁻²²

In contrast, Gorman et al²³ used M-mode ultrasound to compare 10 patients with severe COPD with 10 healthy control subjects, measuring diaphragm length and ability to shorten in the setting of hyperinflation. Despite noting that patients with COPD have a shorter diaphragm length at functional residual capacity, patients with COPD could not be differentiated from healthy control subjects on the basis of diaphragm excursion during tidal breathing.

Our findings suggest that diaphragm dysfunction, when present in patients with COPD, may reflect mechanical impairment of excursion secondary to lung hyperinflation, rather than physiologic alteration of contractility, as we had originally thought. This finding is consistent with the conclusion of Macklem et al²⁴ in their study of the

effect of lung hyperinflation on the relationship between the costal and crural components of the diaphragm.

The small group of patients with COPD with severe air trapping actually had an increased thickening ratio on the left, implying an increased ability of the diaphragm to contract on that side. The clinical significance of this finding is unclear and may reflect the small numbers in that subgroup. Several authors have compared side-to-side hemidiaphragm motion in healthy control subjects²⁵⁻²⁷ and showed large variability in side-to-side hemidiaphragm motion in the normal subject, supporting Alexander's²⁸ "rule of thumb," which states that unequal movement of the two leaves of the diaphragm is usual and unlikely to be of significance unless one excursion is at least twice as great as the other.^{25,28} Those studies did not use B-mode ultrasound, so contractility was not assessed. It may be that the observed excursion variability actually represents a difference in contractility. Regardless, side-to-side variation has been observed previously and our data may simply be another instance of this phenomenon. Given the small numbers in this group, it would be reasonable to examine this group in further detail in future studies.

Conclusions

The primary objective of this study was to establish normal values of diaphragmatic structure and function in patients with COPD as a means of facilitating the use of B-mode ultrasound as a diagnostic tool in the evaluation of neuromuscular respiratory failure in patients with COPD and in the identification of high-risk patients prior to general anesthesia, mechanical ventilation, or invasive procedures such as needle EMG of the diaphragm. In conclusion, lower limits of normal diaphragm thickness and an increase in diaphragm thickening at vital capacity are comparable between patients with COPD and healthy control subjects. These findings indicate that previously identified B-mode sonographic markers for diaphragm pathology (thickness < 0.15 cm or thickening ratio < 1.2) may also be applied in the population of patients with COPD. Given the high levels of intra- and interrater reliability demonstrated previously,⁹ we propose that B-mode ultrasound could also be used as an outcome measure when monitoring the efficacy of various treatments or interventions in this patient population.

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