Diaphragmatic Dysfunction Is Characterized by Increased Duration of Mechanical Ventilation in Subjects With Prolonged Weaning

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BACKGROUND: Diaphragmatic dysfunction is often underdiagnosed and is among the risk factors for failed weaning. The purpose of this study was to determine the prevalence of diaphragmatic dysfunction diagnosed by B-mode ultrasonography and to determine whether prolonged weaning subjects with diaphragmatic dysfunction have increased duration of mechanical ventilation compared with those without diaphragmatic dysfunction. METHODS: This was a prospective observational study in mechanically ventilated subjects who failed ≥3 spontaneous breathing trials or required >7 d of weaning after the first spontaneous breathing trial. Diaphragm thickness was measured in the zone of apposition using a 6–13-MHz ultrasound transducer during a spontaneous breathing trial. The diaphragmatic thickening fraction was calculated as a percentage from the formula: (Thickness at peak inspiration − thickness at end expiration)/thickness at end expiration. Intra-observer and inter-observer reliability were also evaluated. RESULTS: Forty-one subjects (24 males; 62.2 ± 15.9 y old) were included in the study. Of these, the prevalence of ultrasonographic diaphragmatic dysfunction (defined as diaphragmatic thickening fraction of <20% with inspiration) was 34.1% (n = 14). Subjects with diaphragmatic dysfunction had longer ventilation time after inclusion (293.4 ± 194.8 vs 145.1 ± 101.3 h, P = .02) and ICU stay (29.2 ± 11.4 vs 22.4 ± 7.7 d, P = .03) than subjects without diaphragmatic dysfunction. CONCLUSIONS: Diaphragmatic dysfunction as assessed by B-mode ultrasonography is common in subjects with prolonged weaning. Subjects with such diaphragmatic dysfunction show longer mechanical ventilation durations and ICU stays. *Key words: intensive care units; mechanical ventilation; ultrasonography; diaphragm; prevalence; ventilator weaning.* [Respir Care 2016;61(10):1316–1322. © 2016 Daedalus Enterprises]

Introduction

Weaning from mechanical ventilation is an essential element in the care of ventilatory support patients in ICUs. The weaning process covers ≥40% of the total duration of mechanical ventilation.[1] An international consensus conference on weaning from mechanical ventilation in 2007 proposed that weaning be categorized into 3 groups (simple, difficult, and prolonged) based on the difficulty and duration of the weaning process.[2] According to the proposed classification, patients requiring prolonged weaning are those who fail ≥3 weaning attempts or who require >7 d of weaning.[2] These patients may represent up to 20% of patients admitted to the ICU for intubation and mechanical ventilation[3] and are associated with an in-hospital mortality of up to 32%.[4]

Abundant evidence indicates that mechanical ventilation promotes diaphragmatic dysfunction due to both atrophy and contractile dysfunction.[5] Conversely, diaphragmatic dysfunction can lead to respiratory complications and often prolongs the duration of mechanical ventilation.[6] Assessing and monitoring diaphragm contractile activity

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and strength in patients with prolonged weaning is therefore an increasingly important clinical and research priority. The diaphragm is inaccessible to direct clinical assessment. Several methods have been used in critically ill patients to assess diaphragmatic function, including diaphragm electromyography, measurement of pleural (or esophageal) and gastric pressures, and derived variables (work of breathing).[7] However, such methods are still far from routine clinical practice.

Bedside ultrasonography is a noninvasive tool that evaluates diaphragmatic function by measuring diaphragmatic thickening and diaphragmatic excursion.[8] The diaphragmatic thickening fraction evaluated by B-mode ultrasonography was recently shown to be a reliable indicator of respiratory effort.[9] However, very few studies have evaluated diaphragmatic thickening in subjects with prolonged weaning. The primary objective of this study is to establish the prevalence of ultrasonography-diagnosed diaphragmatic dysfunction in subjects with prolonged weaning. The secondary objective is to determine whether prolonged weaning subjects with diaphragmatic dysfunction have longer duration of mechanical ventilation than do those without diaphragmatic dysfunction.

QUICK LOOK

Current knowledge

Mechanical ventilation promotes ICU-acquired diaphragmatic dysfunction. Diaphragmatic dysfunction is often underdiagnosed and is among the risk factors for failed weaning. The prevalence and clinical importance of diaphragmatic dysfunction in patients with prolonged weaning are not yet clear. The methods commonly employed to diagnose diaphragmatic dysfunction are either invasive or cumbersome and are far from routine clinical practice.

What this paper contributes to our knowledge

The diaphragm was evaluated using B-mode ultrasonography in subjects with prolonged weaning. Diaphragmatic dysfunction as assessed by ultrasonography was common in prolonged weaning subjects. Subjects with ultrasonographic diaphragmatic dysfunction showed longer mechanical ventilation durations and ICU stays.

Methods

41 consecutive subjects who were ≥18 y old were prospectively enrolled between August 2015 and November 2015 from the ICU at Sir Run Run Shaw Hospital, a university-affiliated hospital in Hangzhou, China. The study protocol was approved by the institutional ethics committee of the hospital (approval number 20150813-7). Written informed consent was obtained from each subject's family.

Subjects

All subjects were receiving invasive mechanical ventilation, met standard criteria for weaning readiness (improvement in the cause of respiratory failure, P_{aO_2}/F_{IO_2} >200 mm Hg, PEEP ≤5 cm H_2O, and hemodynamically stable in the absence of vasopressors). Subjects were included if they met the criteria for prolonged weaning set out by Boles et al[2] (briefly, those who failed ≥3 spontaneous breathing trials or required >7 d of weaning after the first spontaneous breathing trial). Exclusion criteria included age <18 y, pregnant women, a previously diagnosed neuromuscular disorder (myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis), cervical spine injury, pneumothorax, and unwillingness of the patient or proxy to participate in the study. The causes of respiratory failure are summarized in Table 1.

Study Design

Among those subjects who fulfilled the above mentioned criteria, diaphragm was evaluated using ultrasonography during a spontaneous breathing trial. The standard spontaneous breathing trial was performed using pressure support trials with a pressure support level of 5 cm H_2O and a PEEP level of 3 cm H_2O. Each diaphragm was evaluated by B-mode and M-mode ultrasonography subcostal views to rule out abnormalities in muscle movement.[10] When dysfunction of a single hemidiaphragm was detected, subjects were excluded from the study. Then right hemidiaphragm ultrasound scans were performed with subjects lying down in a semirecumbent position (45°). Subjects were classified according to ultrasonography findings into a diaphragmatic dysfunction group and a non-diaphragmatic dysfunction group. Diaphragmatic dysfunction was defined as a diaphragmatic thickening fraction of <20% during tidal breathing.[11,12] The subject's rapid shallow breathing index was simultaneously calculated at the bedside.[13] Other parameters collected were factors that could affect diaphragmatic function: the causes of respiratory failure, ventilation time to the day of study inclusion, relevant blood biochemistry findings, and blood gas variables. The weaning process after the spontaneous breathing trial was achieved either by gradually decreasing the level of pressure support or lengthening of T-piece time. Successful weaning was defined as the ability to maintain spontaneous breathing for ≥48 h, without any level of ventilator support. The treating team was blinded to the

Table 1. Characteristics of the Subjects With Diaphragmatic Dysfunction and Subjects Without Diaphragmatic Dysfunction

Variables	Diaphragmatic Dysfunction Group (n = 14)	Non-Diaphragmatic Dysfunction Group (n = 27)	P
Demographic characteristics			
Age, mean ± SD y	57.4 ± 18.1	64.7 ± 14.3	.17
Male, n (%)	9 (64.3)	15 (55.6)	.59
Body mass index, mean ± SD kg/m^2	23.9 ± 4.0	22.7 ± 3.8	.32
APACHE II, mean ± SD	13.4 ± 6.3	16.0 ± 5.9	.20
Ventilation time before inclusion, mean ± SD h	253.6 ± 93.7	274.4 ± 132.5	.60
Cause of respiratory failure, n (%)			
Respiratory dysfunction	6 (42.9)	9 (33.3)	.55
Cardiovascular dysfunction	2 (14.3)	4 (14.8)	.96
Other organ dysfunction	2 (14.3)	6 (22.2)	.54
Sepsis	3 (21.4)	4 (14.8)	.59
Postoperative	1 (7.1)	4 (14.8)	.48
Clinical characteristics, mean ± SD			
Heart rate, beats/min	87.4 ± 14.1	88.9 ± 14.9	.76
Mean arterial pressure, mm Hg	94.8 ± 12.8	87.0 ± 15.1	.11
Tidal volume, L	0.33 ± 0.08	0.38 ± 0.09	.07
Breathing frequency, breaths/min	24.6 ± 6.6	22.6 ± 5.0	.26
Minute ventilation, L/min	8.80 ± 2.88	8.11 ± 2.03	.38
Rapid shallow breathing index	81.0 ± 31.5	64.0 ± 25.6	.07
Mean airway pressure, mm Hg	6.10 ± 1.07	5.72 ± 1.12	.31
Laboratory findings, mean ± SD			
Potassium, mmol/L	3.92 ± 0.35	4.15 ± 0.46	.11
Sodium, mmol/L	141.4 ± 4.5	143.7 ± 6.6	.24
Calcium, mmol/L	2.22 ± 0.17	2.23 ± 0.15	.92
Creatinine, mmol/L	84.5 ± 54.4	76.3 ± 25.8	.60
Hemoglobin, g/dL	9.73 ± 1.98	9.33 ± 1.99	.55
Albumin, g/L	32.3 ± 3.2	32.2 ± 3.6	.96
C-reactive protein, mg/L	52.5 ± 34.7	45.7 ± 40.4	.60
pH	7.40 ± 0.03	7.42 ± 0.04	.11
P_{aO_2}, mm Hg	99.2 ± 27.3	114.2 ± 24.6	.08
P_{aCO_2}, mm Hg	41.2 ± 4.8	41.0 ± 8.3	.90
Base excess, mm Hg	0.68 ± 2.22	2.25 ± 4.16	.20
Fraction of inspired oxygen	0.40 ± 0.06	0.38 ± 0.04	.24

APACHE II = Acute Physiology and Chronic Health Evaluation II

ultrasonography results, and the research team did not have a role in deciding whether a subject was extubated. More details about the weaning protocol are noted in the online supplementary materials at http://www.rcjournal.com (Fig. S1).

Ultrasonographic Measurements

B-mode ultrasonography imaging of the right hemidiaphragm was conducted using a standardized technique described previously by Cohn et al.[14] Briefly, a portable ultrasound machine (S-ICU, FUJIFILM Sonosite, Bothell, Washington) was used, with a 6–13-MHz linear-array transducer placed at the zone of apposition of the diaphragm and rib cage in the eighth or ninth intercostal space near the midaxillary line and angled perpendicular to the chest wall.[8] In this location, the diaphragm is identified as a 3-layered structure just superficial to the liver, consisting of a relatively non-echogenic muscular layer bounded by the echogenic membranes of the diaphragmatic pleura and peritoneum (Fig. 1). Two images were captured at the end of expiration, and two more were taken at the peak inspiration during tidal breathing. On each frozen B-mode image, the diaphragm thickness was measured from the middle of the pleural line to the middle of the peritoneal line, to the nearest 0.1 mm. The measurements for each position were averaged to give a thickness at end expiration and a thickness at peak inspiration. The diaphragmatic thickening fraction was calculated as a percentage from the formula: (Thickness at peak inspiration − thickness at end expiration)/thickness at end expiration. Ultrasonography was performed by 2 intensivists both ex-

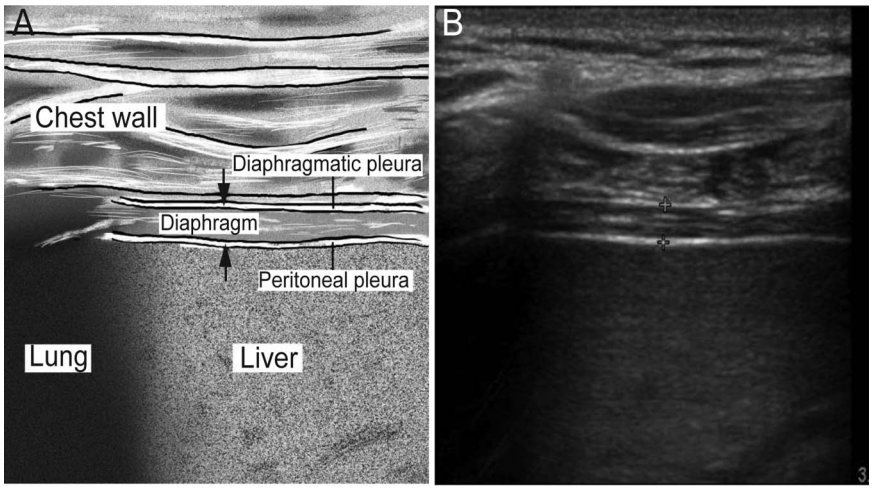

Fig. 1. Ultrasonography image of the right hemidiaphragm obtained in zone of apposition with (A) and without labeling (B). The diaphragm can be identified as a 3-layered structure superficial to the liver, consisting of pleural and peritoneal membranes and the muscle itself. In B, crosses indicate the thickness of the diaphragm.

perienced in ultrasonography. Repeated measurements obtained in each subject from the same ultrasonographer were compared to assess intra-observer reproducibility. Inter-observer reproducibility was assessed by comparing measurements obtained separately from the 2 ultrasonographers in the same subject.

Statistical Analysis

All statistical analyses were performed using SPSS 19 for Windows (SPSS, Chicago, Illinois). Continuous variables were described as mean ± SD or median (interquartile range), depending on whether distribution was normal or non-normal. Categorical variables were described as *n* (%). Unpaired Student *t* tests were used to compare continuous variables, and chi-square tests, with Fisher correction when appropriate, were used to compare categorical variables. Reproducibility was expressed by the intraclass correlation coefficient[15] and the coefficient of repeatability.[16] The latter was calculated as twice the SD of the differences in repeated measurements. Two-tailed *P* values $<.05$ were considered statistically significant.

Results

During the study period, 44 patients met the inclusion criteria. Two patients showed signs of neuromuscular disorders, and one patient declined to participate. Forty-one consecutive subjects were then enrolled (supplementary Fig. S2). Of the included subjects, 24 (58.5%) were male, and the age was 62.2 ± 15.9 y. The ventilation time before inclusion was 11.1 ± 5.0 d. An ultrasonography examination was feasible in all subjects. Of the 41 subjects, 2 (5%) died in the ICU.

The prevalence of ultrasonographic diaphragmatic dysfunction was 34.1% (14 subjects). The causes of respiratory failure did not differ significantly between the diaphragmatic dysfunction and non-diaphragmatic dysfunction groups (Table 1). There was no difference in ventilation time to the day of study inclusion between the diaphragmatic dysfunction and non-diaphragmatic dysfunction groups (Table 1). No significant differences were found between the groups with and without diaphragmatic dysfunction for demographic characteristics, clinical characteristics, and laboratory findings (Table 1).

The diaphragm thickness at peak inspiration was significantly greater in the non-diaphragmatic dysfunction group than in the diaphragmatic dysfunction group (2.90 vs 2.30 mm, $P = .033$), whereas the diaphragm thickness at end expiration did not differ significantly between the diaphragmatic dysfunction and non-diaphragmatic dysfunction groups (Table 2). Ventilation time after inclusion (293.36 h vs 145.11 h, $P = .02$) and ICU stay (29.23 d vs 22.43 d, $P = .03$) were both significantly longer in the diaphragmatic dysfunction group than in the non-diaphragmatic dysfunction group. However, hospital stay was not significantly different between these 2 groups (Table 2).

Intra-observer and inter-observer reliability is shown in supplementary Tables S1 and S2. Intraclass correlation coefficients ranged around 0.830–0.982 for intra-observer reproducibility and around 0.949–0.996 for inter-observer reproducibility.

Discussion

This is the first study to investigate the usefulness of B-mode ultrasonography in detecting diaphragmatic dys-

Table 2. Ultrasonographic Measurements and Clinical Outcomes of the Study Subjects With and Without Diaphragmatic Dysfunction

Variables	Diaphragmatic Dysfunction Group (n = 14)	Non-Diaphragmatic Dysfunction Group (n = 27)	P
Ultrasonographic measurements, mean ± SD			
Thickness at peak inspiration, mm	2.30 ± 0.73	2.90 ± 0.86	.033
Thickness at end expiration, mm	2.01 ± 0.61	2.14 ± 0.58	.51
Diaphragmatic thickening fraction, %	14.4 ± 3.9	35.4 ± 10.7	<.001
Clinical outcomes			
Ventilation time after inclusion, mean ± SD h	293.4 ± 194.8	145.1 ± 101.3	.02
ICU length of stay, mean ± SD d	29.2 ± 11.4	22.4 ± 7.7	.03
Hospital length of stay, mean ± SD d	47.6 ± 17.6	41.1 ± 13.7	.20
In-hospital mortality, n (%)	2 (5%)	0	.044

function and prospectively evaluate the duration of mechanical ventilation in subjects with prolonged weaning. In this study, we found that diaphragmatic dysfunction as diagnosed by ultrasonography was common in subjects with prolonged weaning. The 34.1% prevalence of diaphragmatic dysfunction was surprising, given that patients with preexisting diaphragmatic dysfunction were excluded at the outset of the study. Subjects with such diaphragmatic dysfunction showed longer duration of mechanical ventilation than subjects without. This finding indicated that diaphragmatic dysfunction has probably been underestimated in patients with prolonged weaning in ICUs.

Diaphragm function is an important determinant of successful liberation from ventilation and recovery from critical illness.[17,18] Various insults can render the diaphragm weak in patients in the ICU, such as sepsis, electrolyte disturbances, hyperinflation, critical illness polyneuropathy and/or myopathy, and controlled mechanical ventilation, to name a few from a long list.[19] The difficulty in studying diaphragmatic dysfunction is related partly to the cumbersome nature of the current diagnostic tools available. The current accepted standard for assessing diaphragmatic function is the transdiaphragmatic pressure obtained during twitch phrenic nerve magnetic stimulation. For these reasons, there is a shortage of large ICU studies of diaphragm function.

Recent studies have provided us with promising results regarding the use of ultrasonography for monitoring diaphragm function in the ICU.[9,18,20] Thickening of the diaphragm reflects diaphragmatic shortening,[14] and a lack of thickening with inspiration is diagnostic of diaphragmatic paralysis.[21] Diaphragmatic thickening of <20% with inspiration and diaphragm thickness measured at functional residual capacity of ≤2.0 mm was used by Gottesman and McCool[21] to diagnose chronic diaphragm paralysis. However, it is possible that the diaphragmatic paralysis of prolonged weaning patients is acute and atrophy has not occurred and that diaphragm thickness may be <2.0 mm in a low-weight individual with a healthy yet thin diaphragm.[22] Furthermore, it was observed that diaphragm thickness increased in some mechanical ventilation subjects and that both decreased and increased diaphragm thicknesses were associated with significant diaphragmatic dysfunction.[23] Therefore, we chose to use only the criterion of diaphragmatic thickening fraction of <20% to diagnose diaphragmatic dysfunction, as used in a previous study.[11]

In the present study, we showed that 34.1% of subjects with prolonged weaning developed ultrasonographic diaphragmatic dysfunction. A prospective study in 82 ICU subjects who received mechanical ventilation for >48 h found an occurrence rate of diaphragmatic dysfunction of 29%.[18] Mariani et al[24] found a prevalence of 24% of bilateral diaphragmatic dysfunction among ICU subjects being weaned from ≥7 d of mechanical ventilation. The higher occurrence rate of diaphragmatic dysfunction in our study may be attributed to the longer mechanical ventilation time before inclusion (253.60 h in diaphragmatic dysfunction groups and 274.43 h in non-diaphragmatic dysfunction groups). Prolonged mechanical ventilation promotes a time-dependent and progressive decrease in diaphragmatic specific force production at both submaximal and maximal stimulation frequencies.[25]

Diaphragmatic dysfunction was associated with longer mechanical ventilation duration after inclusion and longer ICU stay but not with increased hospital stay in our study. Previously, Supinski and Callahan[26] reported that subjects with the greatest levels of diaphragmatic dysfunction have a much poorer prognosis in terms of more prolonged ventilation as well as higher mortality. The main reason for the failure of weaning attempts in patients is due to a high work of breathing caused by higher lung mechanics and the inability of respiratory muscles to cope with the increased load. The diaphragm is the principal respiratory muscle in humans. The presence of diaphragm contraction and thickening should be a prerequisite for successful weaning. As a result, mechanical ventilation duration and ICU stay were longer among subjects with diaphragmatic dysfunction than in those without diaphragmatic dysfunction.

We observed that the tidal volume, breathing frequency, and rapid shallow breathing index did not differ signifi-

cantly between the diaphragmatic dysfunction and non-diaphragmatic dysfunction groups. The rapid shallow breathing index is a weaning parameter that measures the change in volume generated by the respiratory muscles as a whole without specifically measuring the contribution of the diaphragm. If the diaphragm is failing, the non-diaphragm inspiratory muscles will compensate to preserve tidal volume, and the presence of diaphragm weakness may be masked by the increased contribution of the non-diaphragm inspiratory muscles (rib cage muscles) to tidal volume. However, the rib cage muscles are more fatigable and weaker than the diaphragm, and these muscles will not be able to sustain adequate ventilation.[27] Dyspnea may occur despite an initially acceptable tidal volume and rapid shallow breathing index. Accordingly, direct measures of diaphragm function using ultrasonography would better predict longer mechanical ventilation durations.[28]

A study by Kim et al[18] in subjects who received mechanical ventilation for >48 h reported weaning variables similar to those reported in the present study. The main differences between our study and the study by Kim et al are the study population and the assessment methodology. The subjects with prolonged weaning were selected as our study population and were associated with increased mortality and morbidity,[4] so evaluation of diaphragmatic function was more meaningful. We decided to measure diaphragm thickening with B-mode ultrasound because this technique provided a greater anatomical definition of the muscle and its adjacent structures in comparison with M-mode. We observed and measured the diaphragm thickness of all of the subjects and found an overall good repeatability of our assessments. Goligher et al[20] showed that ultrasound measurements of right hemi-diaphragm thickness were feasible and highly reproducible in ventilated subjects. Furthermore, the diaphragm thickening was a more accurate index than excursion in reflecting the diaphragm contractility according to the study by Umbrello et al.[9]

A common drawback of ultrasonography is its operator dependence. We therefore assessed the intra-observer and inter-observer reproducibility of diaphragmatic thickness. We found an overall good repeatability of our assessments, with intraclass correlation coefficients well above 0.75, usually considered to indicate good agreement.[29] The high agreement rate between the 2 ultrasonographers in our study supports the usefulness of ultrasonography for identifying subjects with diaphragmatic dysfunction. The coefficient of repeatability is the smallest significant difference between repeated measurements.[16]

Our study has a number of limitations. First, the study had a small population. This might restrain the study power and could explain why we found a non-statistically significant trend in the length of hospital stay and a significant difference in the hospital mortality between the groups with and without diaphragmatic dysfunction, contrary to the findings of Kim et al.[18] A larger cohort study may be required to confirm those results. Second, we only assessed the right hemidiaphragm because the thickness of the right hemidiaphragm can be feasibly and reproducibly measured in the zone of apposition in mechanically ventilated patients.[20] In the subjects with bilateral measurements, right and left hemidiaphragm thickness at end expiration and diaphragmatic thickening fraction were similar.[20] This limitation is common to other studies on ultrasonographic assessment of diaphragmatic contractile activity.[30] Third, diaphragm thickness measurements may be influenced by end-expiratory lung volume.[31] We attempted to minimize the potential impact by measuring subjects at the same level of PEEP. Moreover, Umbrello et al[9] were unable to find any difference between thickness or diaphragm thickening and the level of PEEP. Fourth, another limitation of our study was that other parameters of diaphragmatic function were not measured. It would be interesting to correlate morphometric parameters of the diaphragm assessed by ultrasonography with force/pressure parameters of the diaphragm, such as maximum inspiratory pressure or transdiaphragmatic pressure.

Conclusions

Diaphragmatic dysfunction as assessed by B-mode ultrasonography appears to be common in subjects with prolonged weaning. Subjects with such diaphragmatic dysfunction showed longer mechanical ventilation duration and ICU stay. These findings should be an eye opener for practicing clinicians. They point to a need for greater awareness of the high prevalence of diaphragmatic dysfunction in patients with prolonged weaning. The present preliminary results require confirmation in a larger prospective multicenter study.

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