Assessment of ventilator-induced diaphragmatic dysfunction in patients with chronic obstructive pulmonary disease using transthoracic ultrasonography

Shereen Farghaly, Ali A. Hasan, Hoda A. Makhlouf

Background Mechanical ventilation (MV) can cause progressive thinning of diaphragm muscle and hence progressive decrease in diaphragmatic function. We aimed to assess the rate at which diaphragm thickness (t_{di}) changed during MV and its effect on weaning outcome using transthoracic ultrasound (TUS) evaluation in patients with chronic obstructive pulmonary disease (COPD).

Patients and methods Thirty mechanically ventilated patients with COPD were enrolled in this cohort study. Baseline t_{di} was recorded within 24 h of MV after stoppage of sedation using TUS. The subsequent measurements were recorded on the third, fifth, and seventh day of MV and at the time of initiation of weaning.

Results There was a significant decrease in t_{di} at end expiration and at end inspiration by approximately 27.2 and 17% at third day of MV, respectively, and 35.5 and 18.5% at fifth day of MV, respectively, compared with baseline parameters. In the 10 patients who were still on ventilator till the seventh day, t_{di} were significantly lower compared with baseline recordings. Percentage of decrease of t_{di} at end inspiration from baseline recordings was significantly higher in patients with difficult weaning than in those with simple weaning. The optimum cutoff value of % of decline of t_{di} at end inspiration associated with difficult weaning was at least 10.6% giving 88.9% sensitivity and 83.3% specificity.

Conclusion MV is associated with gradual diaphragmatic atrophy which can be detected by TUS and could predict weaning outcome in mechanically ventilated patients with COPD.

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Chest Department, Faculty of Medicine, Assiut University Hospital, Assuit, Egypt

Correspondence to Shereen Farghaly, MD, Chest Department, Faculty of Medicine, Assiut University Hospital, Assiut University Hospital, Assuit 7111, Egypt Tel: +20 100 308 5436;
e-mail: shereen_hssn@yahoo.com

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Introduction

Mechanical ventilation (MV) is a lifesaver in patients with acute respiratory failure. However, prolonged mechanical ventilation can lead to serious problems [1,2]. Of these problems, MV can impair diaphragm function [3–5], leading to ventilator-induced diaphragmatic dysfunction (VIDD) [6]. Full-support MV for a long time is suggested to increase protein breakdown and decrease protein synthesis in the diaphragm muscle resulting in diaphragm fiber atrophy [7,8].

The diaphragm is considered the main inspiratory muscle [9]. Thus, problems including diaphragm dysfunction can impede discontinuation of MV and contribute to difficulty in weaning [10]. VIDD is expected to contribute to weaning problems [6,11].

The tools commonly applied to assess diaphragmatic function cannot be routinely used in ICU. Fluoroscopy and computed tomography have the risk of radiation exposure. Transdiaphragmatic pressure measurement and phrenic nerve stimulation are limited by need of a special operator. Recently, ultrasonography has been considered an easily available, noninvasive, and safe bedside tool for assessment of diaphragm function [12]. Ultrasound can easily access diaphragm thickness (t_{di}) in its zone of apposition [13]. During inspiration (i.e. active phase of respiration), t_{di} could represent the contractile activity of the diaphragm [14,15]. During expiration (i.e. resting state of respiration), decrease diaphragmatic muscle has also been considered an essential part of VIDD [6,16].

So this study was conducted to assess the rate at which t_{di} changed during partial support mode of MV using transthoracic ultrasonography and its effect on weaning outcome in patients with chronic obstructive pulmonary disease (COPD).

Patients and methods

This longitudinal cohort study was conducted in the ICU of chest department of a tertiary hospital over a 9-month period. Thirty mechanically ventilated patients with COPD were enrolled in the study. An informed consent was obtained from the patients or their relatives. The study was approved by the Faculty of Medicine Ethics Committee, Assiut University.

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Inclusion and exclusion criteria

Patients with COPD (diagnosed by previous pulmonary function test in the past 6 months to have forced expiratory volume in 1 s/forced vital capacity <70%) who were anticipated to require MV for more than 72 h were included in the study. Morbidly obese patients (BMI>40); patients with suspicious diaphragmatic paralysis, previous history of diaphragmatic or neuromuscular disease, pneumothorax, pleural effusion; or those who previously underwent cardiothoracic surgery or pleurodesis were excluded from the study. Patients who were maintained on sedatives or muscle relaxants and those who required high PEEP (i.e. >5 cm H_2O) were further excluded from the study.

Mechanical ventilation protocol

Patients with COPD enrolled in the study were ventilated on Puritan Bennett ventilator (NPB 840, Puritan-Bennett/Covidien, Carlsbad, California, USA). All patients enrolled in the study were sedated with the same sedation protocol [16,17]. For rapid sequence intubation induction, we used intravascular dose 0.2 mg/kg of midazolam in addition to succinylcholine (1.5 to 2 mg/kg intravenous). Midazolam 0.05–0.3 mg/kg intravenous was used to maintain sedation for the first 6 h. Synchronized intermittent mechanical ventilation is the mode applied for initial setting. An initial tidal volume was set at 5–8 ml/kg of ideal body. Respiratory rate was initially adjusted at 8–12 breaths/min. The initial inspiration/expiration ratio and the inspiratory flow rate to start were 1 : 3 and 60 l/min, respectively. We generally applied PEEP of 3–5 cm H_2O as a physiological PEEP [18].

Severity of illness assessment

Severity of illness on admission was assessed by severity of illness scores [19–21], and Charlson comorbidity index (CCI) was used to evaluate comorbidities [22].

Diaphragm ultrasound

In a semirecumbent position, diaphragm ultrasound (Samsung Medison Sono Ace R3 ultrasound system; Samsung Company, Seoul, South Korea) was done. The 7-MHz transducer was placed at the zone of apposition using B-mode image where the diaphragm muscle appeared as a hypoechoic structure between the diaphragmatic pleura and the peritoneal membrane [23,24]. Images of t_{di} were taken during mandatory tidal breathing (i.e. we put the patient on assist-control volume controlled mode with fixed tidal volume) to ensure equal tidal volume during all consequent measurements. t_{di} (mm) was measured from the middle of the pleural line to the middle of the peritoneal line (Fig. 1). Measures were recorded at the end of inspiration and end of expiration. In all enrolled patients, diaphragm ultrasound was performed within 24 h of MV after stoppage of sedation to prevent the possible effect of sedation on t_{di} especially at the end of inspiration. The subsequent measurements were recorded on the third, fifth, and seventh day of MV and at time of initiation of weaning process. Ultrasound was performed in all recordings by two pulmonologists, and the average of the measurement was recorded.

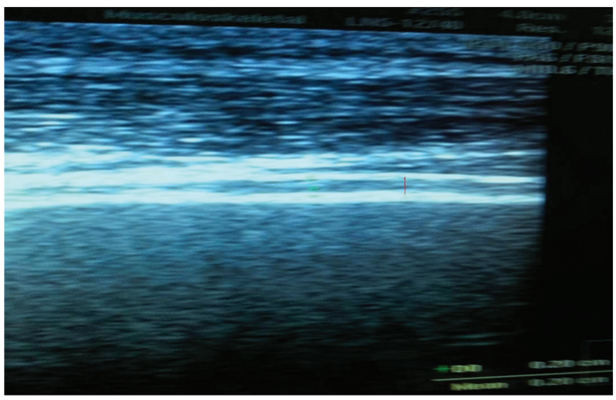
Weaning decision

When patients were considered ready for initiation of weaning process [25,26], patients underwent spontaneous breathing trial (SBT). In patients who passed SBT and were successfully weaned off, weaning was considered simple weaning. Failure to pass the first SBT but weaning was achieved within 7 days of first SBT was considered difficult weaning. For patients who required more than three SBT or 7 days of weaning after the first SBT, it was considered prolonged weaning [27].

Statistical analysis

Statistical Package for the Social Sciences (SPSS, version 16) software produced by SPSS Inc. (Chicago, Illinois, USA) was used for analysis of results. Using tests of normality, data of all diaphragm ultrasound (t_{di} at end inspiration, t_{di} at end expiration, % of decline in t_{di} at end expiration, and % of decline in t_{di} at end inspiration) were detected

Figure 1



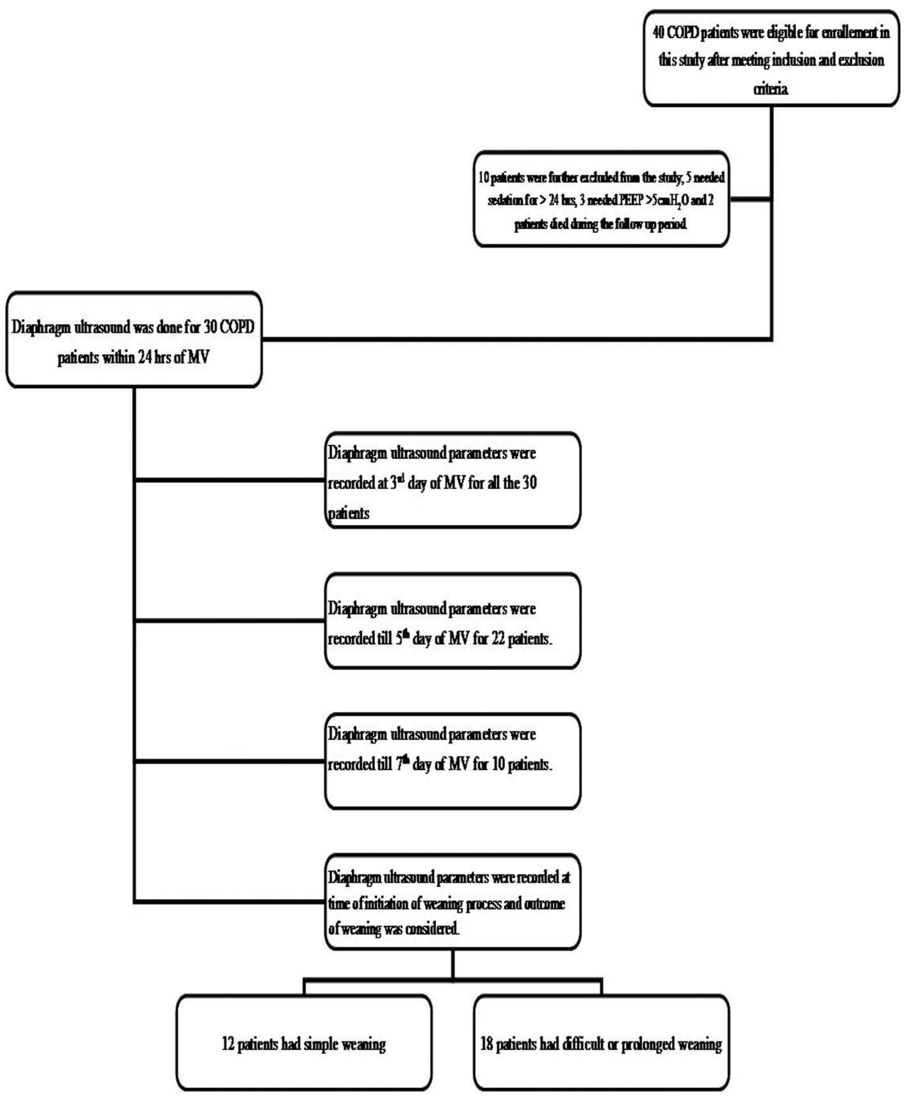
Transthoracic ultrasound applying B-mode using 7.5-MHz probe in the zone of apposition. The diaphragm thickness is measured from the middle of the pleural line to the middle of the peritoneal line (arrow).

to be nonparametric. They were presented in median and interquartile range and analyzed using Mann–Whitney *U*-test for comparison between two groups. Correlations of % of decline of t_{di} at end inspiration with disease assessment scores and electrolytes were done by Spearman's correlation coefficient. Other results in this study were presented as mean± SD or number and percentage. The qualitative data were compared between the two groups using χ^2-test, and the quantitative data were compared using Student's *t*-test. *P* value less than 0.05 was considered significant.

Results

The flowchart of patients who met the inclusion criteria is shown in Fig. 2. Baseline diaphragm ultrasound parameters were recorded within 24 h of MV in all enrolled patients. Baseline demographic data are shown in Table 1. Median baseline t_{di} at end expiration (mm) and at end inspiration (mm) were 22 (17–30) and 37 (30–46), respectively. On day 3 of MV, a significant decrease in t_{di} was observed at end expiration and t_{di} at end inspiration by approximately 27.2 and 17%, respectively, versus baseline recordings [16 (11–22) vs. 22 (17–30), P=0.023; 29 (23–36) vs. 37 (30–46), P<0.001, respectively], as shown in Fig. 3a. On fifth day of MV, continuous diaphragm ultrasound parameters were recorded in 22 patients. Diaphragm thickness was significantly decreased by 35.5% at end expiration and by 18.5% at end inspiration compared with their baseline parameters [16 (10–20) vs. 25 (20–30), P<0.001 and 32 (28–350 vs. 40 (36–48), P<0.001, respectively] (Fig. 3b). In the 10 patients who were still on ventilator till the seventh day, t_{di} at end expiration and t_{di} at end inspiration were also significantly lower compared with their baseline recordings [19 (13–23) vs. 28 (24.25–30.25),

Figure 2



Flowchart of patients who met inclusion criteria. COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation.

Table 1 Demographic data of the study group

Variables	N=30
Age (mean±SD)	61.33±7.9
Gender (%)	
Male	20 (66.7%)
Female	10 (33.3%)
Disease severity assessment scores	
APACHE II	39.5±2.1
SOFA	14.7±0.9
SAPS II	57.5±8.6
CCI	4.3±2.1
Baseline laboratory parameters (mean±SD)	
Serum albumin (g/L)	29.2±8.1
Hb (gm/dL)	12.4±2.1
Serum Na (mEq/L)	137±6.1
Serum K (mEq/L)	3.9±0.9
Serum Mg (mg/dL)	2.2±0.5
Serum Ca (mg/dL)	8.6±0.6
Baseline diaphragmatic thickness [median (interquartile range)]	
t_{di} at end expiration (mm)	22 (17–30)
t_{di} at end inspiration (mm)	37 (30–46)

APACHE II, Acute Physiology and Chronic Health Evaluation II; Ca, calcium; CCI, Charlson comorbidity index; Hb, hemoglobin; M SOFA, Modified Sequential Organ Failure Assessment; Mg, magnesium; Na, sodium; SAPS II, Simplified Acute Physiologic Score II; t_{di}, diaphragmatic thickness. Data expressed as number (%) or mean ±SD (standard deviation) or median and interquartile range.

P=0.005 and 36 (25.7–39.3) vs. 38 (33.75–44.75), P=0.012, respectively], as shown in Fig. 3c.

By recording diaphragm ultrasound parameters at time of initiation of weaning process, median t_{di} at end expiration and median t_{di} at end inspiration were lower in difficult or prolonged weaning than in those with simple weaning, but the results did not reach the statistical significance difference [11 (9.5–16.7) vs. 15.5 (10–23), P=0.123; 28 (22.7–30) vs. 31.5 (23–38), P=0.125, respectively]. However, % of decline of t_{di} at end inspiration from baseline recordings was significantly higher in patients with difficult or prolonged weaning than in those with simple weaning [37.3 (17.5–41.1) vs. 5.8 (0–7.9), P=0.003]. Moreover, other factors such as higher APACHE score and higher CCI (40.7±2.4 vs. 38.7±1.5, P=0.013; 5±0.9 vs. 3.9±0.6, $P<0.001$) were reported in patients with difficult or prolonged weaning compared with simple weaning group (Table 2). The optimum cutoff value of % of decline of t_{di} at end inspiration associated with difficult weaning was at least 10.6%, giving 88.9% sensitivity and 83.3% specificity and area under the curve of 0.815 (0.646–0.983) (Fig. 4). Meanwhile, % of decline of t_{di} at end inspiration recorded at time of initiation of weaning process was found to be have significant negative correlation with baseline electrolyte levels including K level (r=–0.399, P=0.029), Ca (r=–0.575, P=0.001) and Mg (r=–0.555, P=0.001), but it showed no significant correlation with disease assessment severity scores (APACHE II, M SOFA, SAPS II, and CCI), baseline Hg, and baseline serum albumin (Table 3).

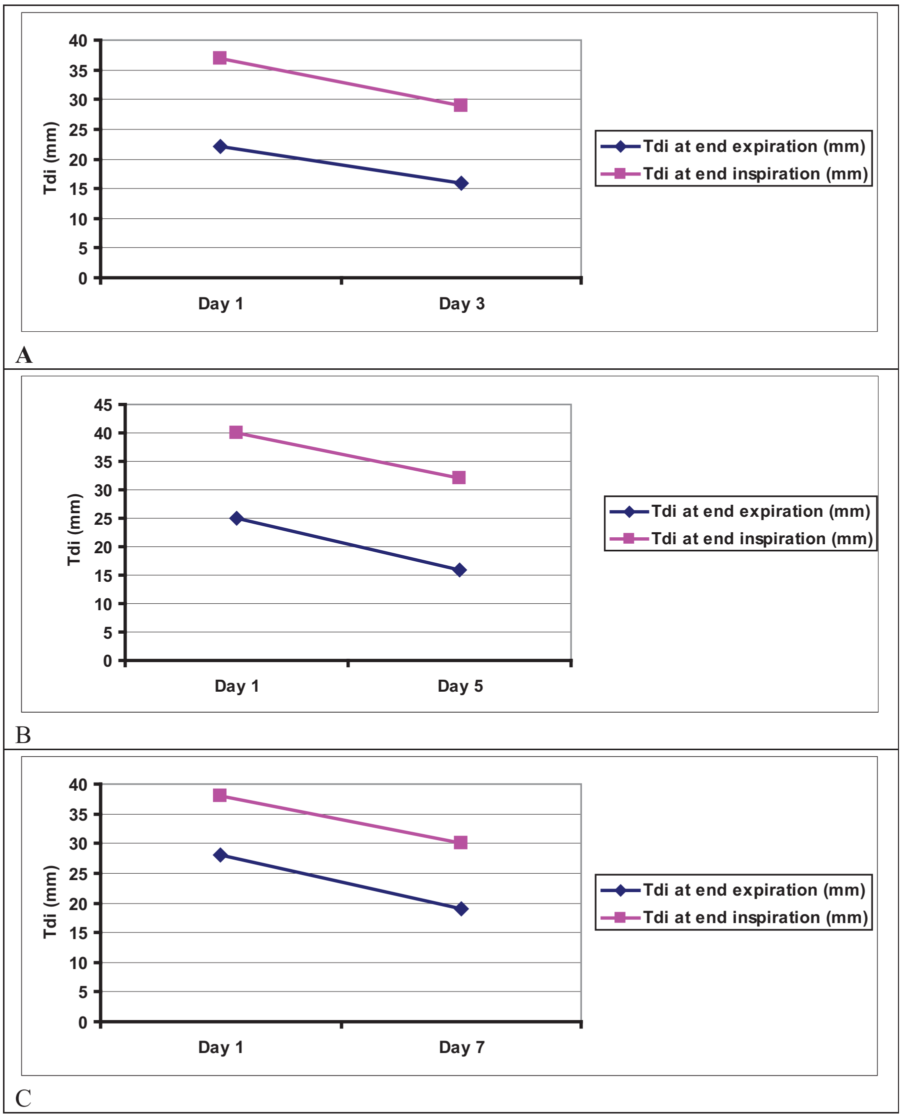
Discussion

Failure of weaning had been commonly associated with diaphragm weakness [28,29]. MV imposes variable degrees of muscular inactivity on the diaphragm [30], rapidly leading to VIDD. As the main finding of VIDD was decrease of t_{di} [6,16], this study was designed to use bedside ultrasonography to detect rate of change in t_{di} during MV in patients with COPD using a partial support mode and its effect on weaning outcome.

The marked variation in baseline t_{di} of patients with COPD observed in our study (median baseline t_{di} at end expiration ranged from 17 to 30 mm) was previously demonstrated in previous studies. Arora and Rochester [31] observed decrease in diaphragm size compared with control and attributed that decrease was owing to nutritional status of patients, whereas Ishikawa and Hayes [32] found increase in parameters of diaphragm size in patients with COPD compared with control and attributed hypertrophy to increase work of breathing in patients with COPD.

At the resting state (end expiration), a significant decrease in t_{di} at end expiration by approximately 27.2% on third day of MV was detected. On the fifth day of MV, continuous decrease in t_{di} at end expiration by 35.5% was reported. Even in patients who were still mechanically ventilated till the seventh day, t_{di} at end expiration was significantly lower compared with baseline recordings [19 (13–23 mm) vs. 28 (24.25–30.25 mm), P=0.005]. Decrease in t_{di} was observed in previous studies. It was demonstrated that more than 18 h of full-support MV was associated with marked reduction of muscle fibers of the costal diaphragm [16]. Moreover, diaphragmatic fiber atrophy showed significant correlation with duration of MV [33]. Applying serial ultrasound measurements, diaphragm thinning occurs within 48 h even with partial support MV with continuous decrease by ~6% per day of MV [34]. Another study observed 15% decrease in diaphragm force within 72 h of assist-control mechanical ventilation [35]. Diaphragmatic oxidative stress is induced by partial support ventilation as much as controlled ventilation [36].

Figure 3



Serial measurement of t_{di} at end expiration and at end inspiration during mechanical ventilation.

Trying to find the effect of MV on diaphragm activity, we applied t_{di} at end inspiration as an ultrasound parameter of diaphragm activity. As was observed in diaphragmatic thickness at resting state, we observed significant decrease in t_{di} at end inspiration by approximately 17% on the third day of MV. On the fifth day of MV, that decrease continued by approximately 18.5% in patients. In the 10 patients who were still on ventilator till the seventh day, t_{di} at end inspiration was also significantly less compared with baseline recordings [36 (25.7–35.3 mm) vs. 38 (33.75–44.75 mm), P=0.012]. Using twitch transdiaphragmatic pressure generation recordings to assess diaphragm function, Jaber *et al.* [37] found that twitch transdiaphragmatic pressure decreased progressively during the period of MV. Similarly, Hermans *et al.* [38] observed positive correlation between duration of MV and diaphragmatic weakness. Moreover, decrease of percentage of contractile activity (as quantified by the diaphragmatic thickness fraction) by more than 10% was varied from 44 to 77% of mechanically ventilated patients [39,40].

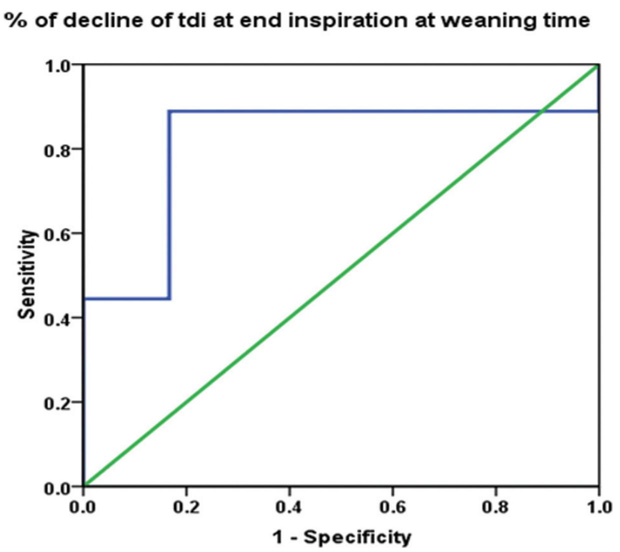
Diaphragm weakness contributes to weaning failure and can predict extubation difficulties [29,41]. In the current study, we demonstrated that patients who experienced difficult or prolonged weaning were associated with more % of decline of tdi at end inspiration (recorded at time of initiation of weaning process from baseline recordings) than in those with simple weaning [37.3 (17.5–41.1) vs. 5.8 (0–7.9), P=0.003]. Furthermore, % of decline of tdi at end inspiration showed significant negative correlations with serum electrolytes including potassium, calcium, and magnesium. Alterations in intracellular electrolytes

Table 2 Comparison of parameters between patients with simple and difficult or prolonged weaning (*n*=30)

Variables	Simple weaning (*n*=12) (mean±SD)	Difficult or prolonged weaning (*n*=18) (mean±SD)	*P* value
Age	64.3±9.1	60±6.8	0.147
MV duration (days)	5.4±1.5	6.4±0.9	0.111
Disease severity assessment scores			
APACHE score	38.7±1.5	40.7±2.4	0.013*
M SOFA	15±0.8	14.6±0.8	0.174
SAPS II	55.3±8.1	59±8.8	0.262
CCI	3.9±0.6	5±0.9	$<$0.001*
Baseline parameters			
Serum albumin (g/L)	28.2±5.7	27.8±9.5	0.576
Hb (gm/dL)	12.8±2.1	12.1±2.01	0.308
Serum K (mEq/L)	3.8±1.04	4.3±0.6	0.141
Serum Ca (mg/dL)	8.5±0.2	8.6±0.7	0.859
Serum Mg (mg/dL)	2.2±0.2	2.1±0.6	0.940
t_{di} at end inspiration (mm)	36 (27–40)	37(32–48)	0.325
t_{di} at end expiration (mm)	25 (17–30)	20 (17–27.25)	0.819
At time of weaning parameters			
Serum albumin (g/L)	26.3±7.8	23.4±4.1	0.162
Hb (g/dL)	12.1±1.6	11.8±1.6	0.663
Serum K (mEq/L)	4.1±0.3	3.9±0.3	0.328
Serum Ca (mg/dL)	8.7±0.6	8.5±0.6	0.413
Serum Mg (mg/dL)	2.6±1.8	2.2±0.4	0.348
t_{di} at end inspiration (mm)	31.5 (23–38)	28 (22.7–30)	0.125
t_{di} at end expiration (mm)	15.5 (10–23)	11 (9.5–16.7)	0.123
Decline in t_{di} at end expiration (%)	32.4 [17.8–41.2]	38.7 [32.8–52.2]	0.185
Decline in t_{di} at end inspiration (%)	5.8 [0–7.9]	37.3 [17.5–41.1]	0.003*

APACHE II, Acute Physiology and Chronic Health Evaluation II; Ca, calcium; CCI, Charlson comorbidity index; Hb, hemoglobin; K, potassium; M SOFA, Modified Sequential Organ Failure Assessment; Mg, magnesium; SAPS II, Simplified Acute Physiologic Score II; t_{di}, diaphragmatic thickness; *Significant.

Figure 4



Reciprocal operating curve for % of decline of t_{di} at end inspiration at weaning time. The optimum cutoff value of % of decline of t_{di} at end inspiration associated with difficult or prolonged weaning was at least 10.6% giving 88.9% sensitivity and 83.3% specificity and area under the curve of 0.815 (0.646–0.983).

Table 3 Correlation of % of decline of t_{di} at end inspiration at time of weaning and the base line parameters

Baseline parameters	
APACHE score	*R*=0.055 *P*=0.774
CCI	*R*=–0.306 *P*=0.100
Serum albumin (g/L)	*R*=0.205 *P*=0.278
Hb (gm/dL)	*R*=–0.084 *P*=0.659
Serum K (mEq/L)	*R*=–0.399 *P*=0.029*
Serum Ca (mg/dL)	*R*=–0.575 *P*=0.001*
Serum Mg (mg/dL)	*R*=–0.555 *P*=0.001*

APACHE II, Acute Physiology and Chronic Health Evaluation II; Ca, calcium; CCI, Charlson comorbidity index; Hb, hemoglobin; K, potassium; Mg, magnesium. *Significant.

as well as mineral disturbances might account for the decreased diaphragm contractility. Hypocalcemia and hypomagnesemia could lead to decreased diaphragm function and respiratory muscle strength [42,43]. It was also documented that hypophosphatemia reduced diaphragm contractile strength in mechanically ventilated patients presented with respiratory failure [44].

The main risk factors for ventilator-induced diaphragmatic dysfunction are duration of MV [38] and sepsis [45,46]. However, we did not find any correlations between this degree of decline of diaphragmatic activity and duration of MV, age, and disease severity assessment scores (APACHE, SAPS II, M SOFA, and CCI). Similarly, Medrinal *et al*. [47] did not find a link between maximum inspiratory pressure (as an index of respiratory muscle function) and sepsis and the duration of MV evaluated at time of extubation. Although Dres *et al*. [48] showed that age at admission and duration of MV were associated with diaphragmatic dysfunction; however, neither of these factors were significant in the multivariate analysis. The difference in timing of evaluation of diaphragm weakness and the timing of included risk factors could affect the results. We evaluated the risk factors at the time of admission suggesting that the risk factors related to diaphragmatic dysfunction at admission could improve with time.

Conclusion

MV is associated with gradual diaphragmatic atrophy which can be detected by transthoracic ultrasound and could predict weaning outcome in mechanically ventilated patients with COPD.

Limitation of the study

This study did not consider assessment of other muscles, such as intercostal muscles, pectoralis muscles, or leg muscles as that atrophy of diaphragm may be a part of disuse atrophy. In addition, this study lacked points about systemic inflammation that might cause muscle atrophy. Moreover, it missed evaluation of patients' baseline nutritional status.

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The manuscript has been read and approved by all the authors; the requirements for authorship as stated earlier in this document have been met; and each author believes that the manuscript represents honest work, if that information is not provided in another form.

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Conflicts of interest

There are no conflicts of interest.

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