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ORIGINAL ARTICLE

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Ultrasound-assessed diaphragmatic dysfunction as a predictor of weaning outcome in mechanically ventilated patients with sepsis in intensive care unit

Mohamed Ahmed Saad*, Sherif Wadie Nashed, Ahmed Nagah El-Shaer, Ashraf Elsayed Elagamy and Maha Sadek El derh

Abstract

Background: Weaning from mechanical ventilation is one of the most common challenges in the intensive care unit (ICU). Most of predictive indices of weaning from mechanical ventilation are often inaccurate. This study was performed to assess the accuracy of diaphragmatic ultrasonography for predicting weaning outcome in mechanically ventilated patients with sepsis in ICU.

Results: Sixty patients with sepsis in medical ICU were prospectively enrolled. All patients were ventilated in pressure support. Patients underwent a spontaneous breathing trial (SBT) on T-piece when they met all the following criteria: $FiO_2 < 0.6$, PEEP ≤5 cmH_2O, $PaO_2/FiO_2 > 200$, respiratory rate <30 breaths per minute, absence of fever, alert and cooperative, hemodynamic stability without or with low-dose vasoactive therapy support, and rapid shallow breathing index (RSBI)<105. During the trial, the patient was instructed to perform deep breathing to total lung capacity (TLC) and then exhaling to residual volume (RV) and the diaphragm was visualized in the 8th or 9th intercostal space between anterior and mid-axillary lines using a 3–5-MHz curved ultrasound probe to measure diaphragmatic excursion (DE) and a 7–11-MHz linear ultrasound probe to measure diaphragmatic thickness (DT) at TLC and RV, and the diaphragmatic thickness fraction (DTF) was calculated as percentage from the following formula (thickness at end inspiration—thickness at end expiration)/thickness at end expiration. According to weaning outcome, patients were divided into 2 groups: successful weaning group and weaning failure group. Weaning failure was defined as the inability to maintain spontaneous breathing for at least 48 h, without any form of ventilatory support.

In the present study, right DTF of more than 37% and DE during deep breathing of more than 6.1 and 5.4 cm on the Rt and Lt side, respectively, were associated with successful weaning from MV. In the study, the sensitivities for right and left DE and DTF were 58.33, 62.5, and 58.33%, respectively, and the pooled specificities were 83.33, 83.33, and 100%, respectively, with p value = 0.032, 0.028, and 0.001, respectively. The area under curve (AUC) for Rt, Lt DE, and DTF were 0.701, 0.712, and 0.840, respectively. The present data indicate a satisfactory diagnostic accuracy in predicting extubation outcome.

* Correspondence: msaadicu@gmail.com
Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Conclusions: Ultrasonography-based determination of diaphragm function by assessing DTF and DE can be used as predictor of weaning outcome in mechanically ventilated patients with sepsis.

Keywords: Ultrasound, Diaphragmatic dysfunction, Weaning failure

Background

Diaphragm is the primary muscle of respiration. Its dysfunction is characterized by decrease of diaphragm thickness and inadequate diaphragmatic contractility. From a clinical perspective, diaphragmatic dysfunction contributes to difficult weaning or even failure to wean from mechanical ventilation in ICU patients. Overall, data indicate that weaning failure may affect up to 25% of mechanically ventilated patients in ICU (McCool & Tzelepis, 2012).

Many factors contribute to this intriguing problem in ICU apart from inactivity by mechanical ventilation, including inflammation, malnutrition, the use of certain pharmacological agents, and the existence of neuromuscular syndromes prior to ICU admission have been reported to influence diaphragm dysfunction as well (Doorduin et al., 2013).

Limited previous literature suggests an association between sepsis and diaphragm dysfunction as a consequence of both functional and morphological damages. Sepsis is associated with preferential loss of diaphragm volume compared with the psoas muscle and associated with a lower diaphragm contractile force (Jung et al., 2014).

Bedside sonographic evaluation of the motion of the diaphragm dome (diaphragmatic excursion) has shown to be useful in predicting extubation outcomes; however, factors such as tidal volume, proximity of rib cage, and abdominal organs may affect diaphragm motion (Kim et al., 2011).

Recently, it has been suggested that ultrasound measurements of diaphragm muscle thickening in inspiration during weaning could provide an estimation of extubation success. This non-invasive, low-cost, and fast to perform technique seems to predict with a good accuracy the extubation failure (Zanforlin et al., 2014).

Aim of the present study is to assess whether the degree of diaphragm excursion and diaphragm thickness fraction measured by ultrasound during a weaning trial may be used to predict outcome of weaning from mechanical ventilation in patients with sepsis in intensive care units. Primary outcome is successful weaning from mechanical ventilation, and secondary outcomes are need for tracheostomy and mortality rate.

Methods

This is a prospective observational study was held in medical intensive care unit and started from April 2021 till May 2021. Patient informed written consent from legal guardian, Local Ethical Committee approval (FMASU MD 44/2019) and Clinical Trial Registration (ClinicalTrials.gov ID: NCT04825509) were obtained before patient's allocation.

Inclusion criteria

Adult patients of both sexes, age between 18 and 60 years old, in sepsis according to the new sepsis definition in 2016 (life-threatening organ dysfunction due to a dysregulated host response to infection), hemodynamically stable without or with low-dose support till 0.05 μg/kg/min noradrenaline and on mechanical ventilation for at least 48 h and not more than 1 week.

Criteria for weaning protocol include fully conscious patients, on CPAP mode (PEEP 3–5 CmH_2o, pressure support <15 CmH_2O, FiO_2 less than 60%, respiratory rate < 35 breath/min, PO_2/FiO_2 > 200, RSBI is < 105).

Exclusion criteria

Patients who had any of these criteria were excluded from our study: patients with neuromuscular disorders, pregnant females in the second and third trimester, and patients with tense ascites or morbidly obese with body mass index more than 40 kg/m^2.

When weaning criteria were reached, patients were disconnected from mechanical ventilation and a spontaneous breathing trial (SBT) on T-piece was attempted for 2 h administering supplemental oxygen to achieve peripheral oxygen saturation (SpO_2) >94%. Then, diaphragmatic excursion (DE) was measured on both sides and diaphragmatic thickness (DT) was measured on right side during the SBT 30 min after patient was on T-piece. Diaphragmatic thickness fraction (DTF) was calculated as follow: thickness at end inspiration—thickness at end expiration)/thickness at end expiration. Clinicians in charge of the patient's care were blinded to ultrasound measurements.

The SBT was considered successful when the patient succeeds to pass 120 min without the appearance of any of the following termination criteria: change in mental status, onset of discomfort, diaphoresis, respiratory rate (RR) >35 breaths/min, hemodynamic instability (heart rate >140, systolic blood pressure >180 or <90 mmHg), or signs of increased work of breathing. Failure of weaning was considered when patient needed MV during SBT and patient was reintubated and ventilated or needed non-invasive ventilation (NIV) within 48 h.

According to weaning outcomes, we had 2 groups, one group with successful weaning and the other group with weaning failure.

Measurements

Transthoracic ultrasonography was performed at the bedside with a PHILIPS HD5 release 2.1 (distributed by PHILIPS healthcare, Bothell, WA, USA) @2011Koninklijke Philips N.V. All rights reserved.

Ultrasonography was done while patient was on T-piece during SBT 30 min after disconnecting mechanical ventilation. The examination was performed in both B- and M-modes. All examinations were carried out with patients in the supine position. The measurements were done by placing the transducer perpendicular to the chest wall or with angle not less than 70° according difficulty of the case, in the eighth or ninth intercostal space, between the anterior axillary and the midaxillary lines. The liver was identified as a window for right hemidiaphragm and the spleen was identified as a window for left hemidiaphragm. The ultrasound probe was placed in the direction in which the ultrasound beam reached the posterior third of the corresponding hemidiaphragm perpendicularly. In most of the cases this can be achieved by directing the US landmark medially, cranially, and dorsally.

The diaphragmatic excursion (DE) or displacement was measured in M-mode using a 1- to 5-MHz ultrasound curved transducer during maximal breathing (Fig. 1). During maximal inspiration, the normal diaphragm moved caudally toward the ultrasound transducer, which was recorded as an upward motion of the M-mode tracing. The amplitude of diaphragmatic excursion was measured as the point of maximal height of the diaphragm (white thick line covering the liver) in the M-mode tracing to the base line [the vertical distance expressed in cm]. We obtained diaphragmatic ultrasound values from three consecutive maximal breaths on the right side and three on the left side, and the average values on each side were used for analysis.

Diaphragmatic thickness (DT) was subsequently measured at the zone of apposition (ZOA), which is the area of the diaphragm attached to the rib cage, at both end of maximal inspiration or total lung capacity (TLC) and end of maximal expiration or residual volume (RV) using a high frequency 7–11 MHz ultrasound linear transducer in M-mode (Fig. 2). The diaphragm in the ZOA presents itself as a hypoechoic layer between two hyperechoic bright and parallel lines, which represent the pleural and peritoneal membranes. The ZOA is located 0.5–2 cm below the costophrenic sinus. The costophrenic sinus can be seen as a transition zone between the lungs cranially, identified by specific artifacts (A lines if well aerated), and the liver or the spleen caudally. We obtained diaphragmatic ultrasound values from six consecutive maximal breaths, and the average values were used for analysis. On each frozen M-mode image, the diaphragm thickness was measured from the middle of the pleural line to the middle of the peritoneal line. Then, the diaphragmatic thickening fraction (DTF) was calculated as percentage from the following formula:

[Thickness at end inspiration − thickness at end expiration]/thickness at end expiration

Sixty-six patients were included in our study. Sample size was calculated using SATA program, setting the type-1 error (alpha) at 0.05 and the power (1beta) at 0.8. Results from previous study (Fayed et al., 2016) showed that diaphragmatic excursion by US had sensitivity of 83.3% and a specificity of 85.4% in prediction of successful weaning in about 70% of cases. Calculation according

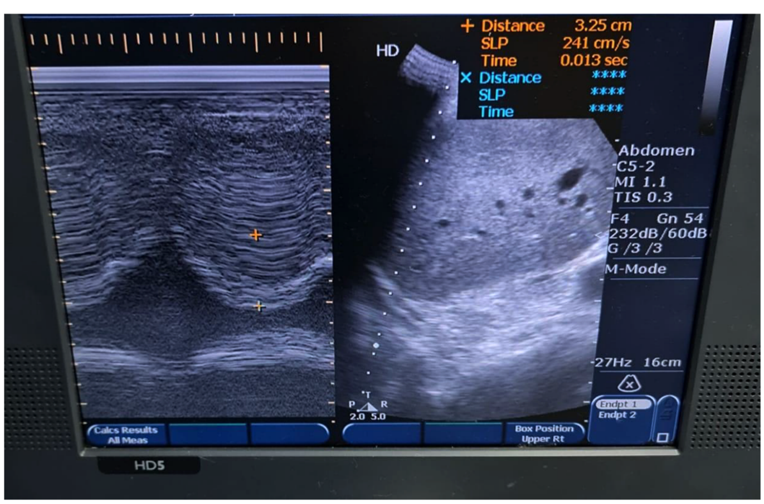


Fig. 1 Diaphragm excursion 3.25cm

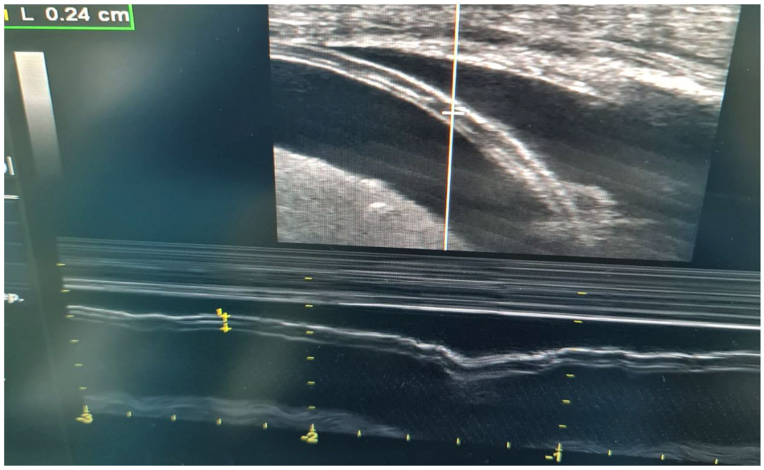


Fig. 2 Diaphragm thickness during expiration 0.24 cm

to these values produced minimal sample size of 50 cases.

Data were collected using Epi Info statistical software (Centers for Disease Control and Prevention, Atlanta, GA, USA) and analyzed using R version 2.15.0 (R Development Core Team: http://www.R-project.org). Data were presented as mean (SD) or median [interquartile range] when appropriate. Descriptive statistics are shown for both the whole cohort and the subgroups of interest. Differences of continuous variables between the subgroups for the independent variable were assessed by non-parametric tests. The χ^2 test, with Fisher's correction when appropriate, was used for comparisons among categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to assess DE and DTF ability to discriminate between patients who succeeded weaning and those who failed. The Spearman coefficient was used to evaluate correlations. A two-tailed p value of less than 0.05 was taken to indicate statistical significance.

Results

During the study period, 66 patients were planned to be included in the study. Two patients had unplanned extubation and four patients had SBT on a mode other than T-piece. The remaining 60 patients were analyzed. Of these, 48 had a successful weaning while the remaining 12 failed weaning from MV within 48 h from SBT (Fig. 3).

Table 1 summarizes the main clinical-demographic characteristics of the population enrolled in the study. Ultrasound examination was feasible in all patients, including those with body mass index >30. On occasion, the presence of pleural effusion or parenchymal lung consolidation did not affect the quality of ultrasound studies targeted to diaphragm evaluation.

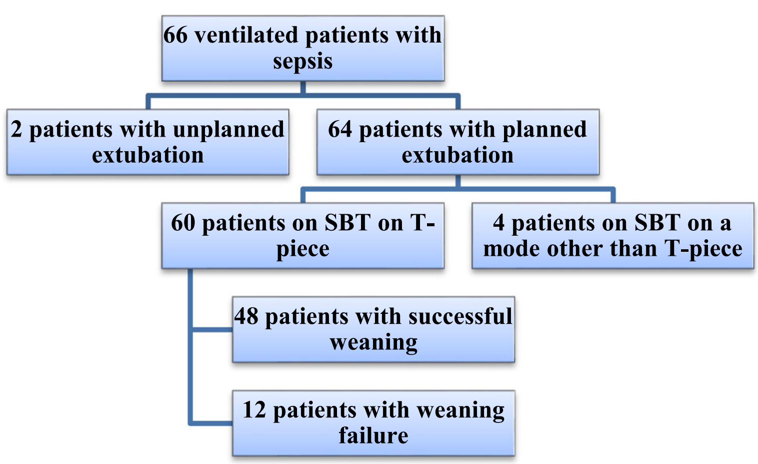


Fig. 3 Showing flow chart for selection of the patient. SBT spontaneous breath trial

Table 1 Demographic data and patient characteristics

		Failure weaning No. = 12	Successful weaning No. = 48	Test value	P value
Age (year)	Mean ± SD	51.67 ± 5.61	45.50 ± 10.79	1.907•	0.061
	Range	44 – 59	22–59		
Sex	Female	2 (16.7%)	16 (33.3%)	1.270*	0.260
	Male	10 (83.3%)	32 (66.7%)		
BMI (kg/m^2)	Mean ± SD	29.83 ± 5.13	24.79 ± 3.91	3.744•	0.000
	Range	24 – 38	18–32		
qSOFA score on admission	Mean ± SD Range	2.83 ± 0.39 2 – 3	2.08 ± 0.28 2–3	7.663	0.000
MV days	Mean ± SD Range	5.17 ± 0.94 4 – 6	3.63 ± 1.20 2–6	4.148	0.000
RSBI	Mean ± SD	79.47 ± 19.65	60.75 ± 16.53	3.378•	0.001
	Range	48 – 103	39–92		
SBT (minutes)	Mean ± SD	120.00 ± 0.00	120.00 ± 0.00	-	-
	Range	120 – 120	120–120		
rt DE (cm)	Mean ± SD	5.03 ± 1.48	6.10 ± 1.52	−2.196•	0.032
	Range	3.25 – 7	3.2–8		
lt DE (cm)	Mean ± SD	4.65 ± 1.35	5.68 ± 1.44	−2.255•	0.028
	Range	3 – 6.5	2.9–7.5		
DT TLC (cm)	Mean ± SD	0.34 ± 0.10	0.35 ± 0.08	−0.722•	0.473
	Range	0.19 – 0.48	0.24–0.5		
DT RV (cm)	Mean ± SD	0.26 ± 0.07	0.25 ± 0.05	0.551•	0.584
	Range	0.16 – 0.35	0.17–0.35		
DTF (%)	Mean ± SD	27.14 ± 6.81	40.89 ± 13.11	−3.500•	0.001
	Range	18.75 – 37	20–66.66		
Other US findings	No	10 (83.3%)	44 (91.7%)	9.074*	0.028
	Lung consolidation	0 (0.0%)	2 (4.2%)		
	Lung congestion	2 (16.7%)	0 (0.0%)		
	Pleural effusion	0 (0.0%)	2 (4.2%)		

Data are presented as mean ± SD, ratio of patients p value > 0.05 is considered statistically non-significant
BMI body mass index, *qSOFA* quick sequential organ failure assessment, *MV* mechanical ventilation, *RSBI* Rapid Shallow Breathing Index, *SBT* Spontaneous Breathing Trial, *DE* diaphragm excursion, *DT* diaphragm thickness, *TLC* total lung capacity, *RV* residual volume, *DTF* diaphragm thickness fraction

There was no statistically significant difference between the two groups regarding age and sex while there was statistically significant increase in BMI, qSOFA score on admission and days of mechanical ventilation in weaning failure group than successful weaning group.

A significant difference in DTF was observed between successful weaning and weaning failure groups (Fig. 4). A ROC curve was used to assess the diagnostic accuracy of DTF (Fig. 5) and DE (Fig. 6) in predicting weaning success. As regards DTF, cutoff value >37% was associated with a successful spontaneous breathing test with a sensitivity of 58.33%, specificity of 100.0%, and area under curve (AUC) of 84.0%.

As regards DE, the best cutoff point for Lt DE to differentiate between successful and failure weaning was > 5.4 with sensitivity of 62.5%, specificity of 83.33%, and area under curve (AUC) of 71.2% while for Rt DE the best cutoff point for Lt DE to differentiate between successful and failure weaning was > 6.1 with sensitivity of 58.33%, specificity of 83.33%, and AUC of 70.1%.

Discussion

In continuation of many previous studies on the usefulness of the US assessment of the diaphragm as a tool to predict weaning from mechanical ventilation, this study was done for patients with sepsis requiring mechanical ventilation who were planned for discontinuation of mechanical ventilation. The study was conducted upon 60 mechanically ventilated patients (18 females and 42

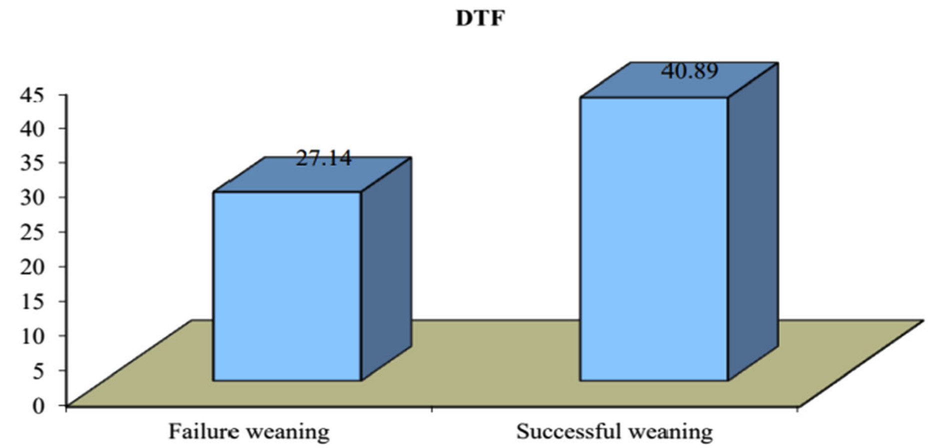
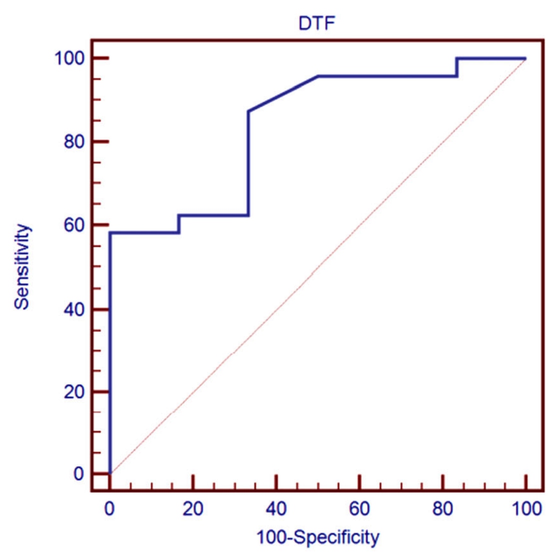


Fig. 4 Bar of mean showing comparison between failure weaning group and successful weaning group regarding DTF. *DTF* diaphragm thickness fraction

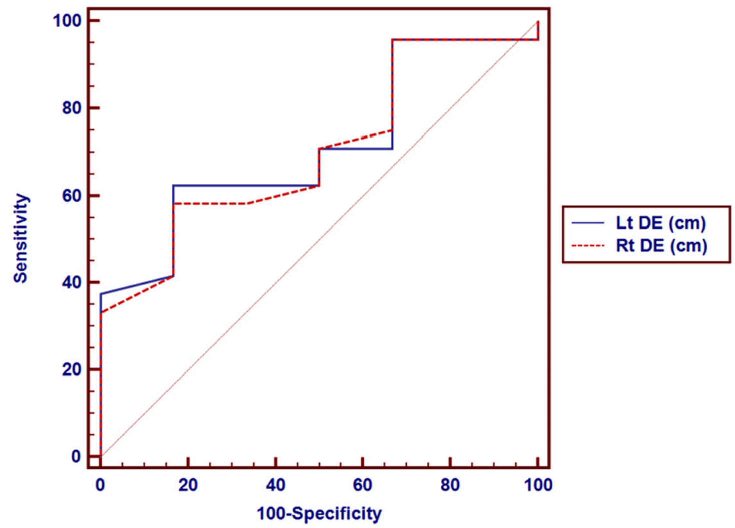
males), mean age of 46.73 years and mean of BMI 25.80 kg/m^2, were admitted to the MICU with sepsis.

In the present study, as regards successful weaning group, the number of patients with successful weaning from mechanical ventilation was 48 out of 60 patients (80%), while the number of patients with failure of weaning from mechanical ventilation was 12 out of 60 patients (20%). This is consistent with (Osman & Hashim, 2017), *Esteban and his colleagues* (Esteban et al., 1995), *Saeed and his colleagues* (Saeed et al., 2016), and *Baess and his colleagues* (Baess et al., 2016), who showed failure rate about 26.5%, 27%, 26.7%, and 23.3%, respectively. This is in contrast with *Ferrari and his colleagues* (Ferrari et al., 2014) who reported 63% failure rate. This is explained by different causes for mechanical ventilation as well as different ventilation periods before starting weaning process; in addition to the selected population with Ferrari as he did the study with different population.



Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
DTF	0.840	>37	58.33	100.0	100.0	37.5

Fig. 5 Receiver operating characteristic curve (ROC) for diaphragmatic thickness fraction to differentiate between successful weaning and weaning failure



	Cut off point	AUC	Sensitivity	Specificity	PPV	NPV
Lt DE (cm)	>5.4	0.712	62.5	83.33	93.7	35.7
Rt DE (cm)	>6.1	0.701	58.33	83.33	93.3	33.3

Fig. 6 Receiver operating characteristic curve (ROC) for diaphragmatic excursion to differentiate between successful weaning and weaning failure

In this study, DT at TLC and at RV were not significant as weaning predictors—this is mostly because the diaphragm is heterogeneous across its surface (Poole et al., 1997); accordingly, the placement of the probe must be standardized to minimize to measurement variability. We tried to overcome this problem by standardization of measurements through carrying out the US examination for all patients in supine position and placing the transducer perpendicular to the chest wall or with angle not less than 70° in the eighth or ninth intercostal space between the anterior axillary and the mid-axillary lines and get the measurements at the zone of opposition.

The present study found that a right DTF of more than 37% had better accuracy for predicting weaning successfulness. This result is consistent with the studies from (Ferrari et al., 2014; DiNino et al., 2014), and (Dube et al., 2017) which demonstrated that right DTFs of more than 36, 30, and 29%, respectively, were associated with weaning success and better ICU outcomes.

There were no studies measuring DE during deep breath to assess successful weaning from MV. All studies we found were measuring DE during tidal breath, of these studies, Ali and Mohamad (2016), Baess et al. (2016), and Saeed et al. (2016), which demonstrated that DE during tidal breathing of more than 1.5, 1, and 1.1 cm, respectively, were associated with successful weaning from MV. However, many studies were done to measure DE during deep breath in healthy population to diagnose diaphragmatic dysfunction, of these studies, Kantarci et al. (2004) and Scarlata et al. (2018), which demonstrated that DE during deep breathing of less than 4.2 and 5.47 cm were associated with diaphragmatic dysfunction. In our study, DE during deep breathing of more than 6.1 and 5.4 cm on the Rt and Lt side respectively were associated with successful weaning from MV.

In the present study, the sensitivities for right and left DE and DTF were 58.33, 62.5, and 58.33%, respectively, and the pooled specificities were 83.33, 83.33, and 100%, respectively. The ROC curve and the AUC were used to assess the overall diagnostic performance. The AUC for Rt, Lt DE, and DTF were 0.701, 0.712, and 0.840, respectively. Our data indicate a satisfactory diagnostic accuracy in predicting extubation outcome.

In agreement with other studies, the duration of mechanical ventilation before weaning was statistically significant with DE, DTF, and weaning outcome (Table 2), meaning, the longer duration of mechanical ventilation days, the less DE and DTF, the more probability of weaning failure, the more probability of need for tracheostomy and mortality (Kim et al., 2011; Jiang et al., 2004).

Conclusions

In conclusion, ultrasonography-based determination of diaphragm function by assessing diaphragmatic

Table 2 Diagnostic performance of DE and DTF in some studies

Author/Year	Patient category	Measures	Best cut off value	Accuracy
Jiang et al., 2004	Medical ICU patients	DE	11 mm	Sensitivity 84.4%, specificity 82.6%
Kim et al., 2011	Medical ICU patients	DE	14 mm (right) and 12 mm (left)	Sensitivity of 60%, specificity of 76%, AUC = 0.68
DiNino et al., 2014	Mixed ICU patients	DTF	30%	Sensitivity of 88%, specificity of 71%, AUC = 0.79
Ferrari et al., 2014	MV patients received tracheostomy in high dependency unit	DTF	36%	Sensitivity of 82%, specificity of 88%
Ali and Mohamad, 2016	Mixed ICU patients	DE	15 mm	Sensitivity of 88.7%, specificity of 84.3%
		DTF	30%	Sensitivity of 97.3%, specificity of 85.2%

thickness fraction and diaphragmatic excursion can be used as a predictor of weaning outcome in mechanically ventilated patients with sepsis. It is a useful, feasible, non-invasive, bed side technique for ruling out severe diaphragmatic dysfunction.

Abbreviations

ICU: Intensive care unit; SBT: Spontaneous breathing trial; FiO_2: Fraction of inspired oxygen; PEEP: Positive-end expiratory pressure; PaO_2: Partial arterial oxygen tension; RSBI: Rapid shallow breathing index; TLC: Total lung capacity; RV: Residual volume; DE: Diaphragm excursion; DT: Diaphragm thickness; DTF: Diaphragm thickness fraction; Rt: Right; Lt: Left; AUC: Area under curve; MV: Mechanical ventilation; SPO_2: Peripheral oxygen saturation; RR: Respiratory rate; NIV: Non-invasive ventilation; ZOA: Zone of apposition; ROC: Receiver operation characteristic curve; BMI: Body mass index; PPV: Positive predictive value; NPV: Negative predictive value; OA: On admission

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Authors' contributions

The idea of the research belongs to SN. SN also participated in clinical data collection and shared in writing the manuscript. ANE designed the study and also participated in clinical data collection and shared in writing the manuscript. AEE performed the statistical analysis and also participated in clinical data collection and shared in writing the manuscript. ME and MS searched literature and also participated in clinical data collection and shared in writing the manuscript in addition to provision of patients. The authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approval of research ethical committee of Faculty of Medicine, Ain-Shams University, was obtained (code number: FMASU M D 44/2019) and written informed consent from all the participants' guardians was obtained.

Consent for publication

Not applicable.

Competing interests

Prof Ahmed Nagah El-Shaer is a co-author of this study and the Executive Editor for the journal. He declares a competing interest for this submission. He has not handled this manuscript. The rest of the authors have no conflict of interest to declare.

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