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ORIGINAL ARTICLE

Ultrasound-guided assessment of diaphragmatic thickness as an indicator of successful extubation in mechanically ventilated cancer patients

Ahmed M. Soliman, MD, Mohga A. Samy, MD, Ashraf M. Heikal, MD, Mohamed A. El Ramely, MD, Tamer A. Kotb, MD

Department of Anesthesia, ICU & Pain Management, National Cancer Institute, Cairo University, Cairo, (Egypt)
Correspondence: Dr Ahmed M Soliman, Department of Anesthesia, ICU, and Pain Management, National Cancer Institute, Cairo University, Fom EL Khaleeg, Cairo, (Egypt).
Tel: +201286979695
E-mail: ams21787arif@hotmail.com
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ABSTRACT

Objective: The study aimed to assess diaphragmatic thickness measurement by B-mode ultrasound for prediction of extubation and proper timing of weaning from mechanical ventilation in cancer patients admitted to the intensive care unit after major surgery.

Methodology: A prospective, longitudinal study conducted at Surgical ICU, National Cancer Institute, Cairo University, Cairo. Fifty patients were recruited during the immediate postoperative period after major elective cancer surgery who needed mechanical ventilation (MV). Patients were enrolled when judged to be eligible for a test of weaning from MV according to clinical and arterial blood gases (ABG) criteria. The patient was assessed for weaning according to rapid shallow breathing index (RSBI) and ultrasound guided measurements of diaphragmatic thickness (*tdi*) during inspiration and expiration. The percent change in tdi between end-expiration and end-inspiration (Δtdi**%**) was calculated.

The primary outcome measure was diagnostic accuracy of tdi and Δtdi% to predict weaning compared to ABG analysis (the gold standard for weaning).

Results: After 48 hours, 13 patients were weaned according to ABG criteria. Kappa value (agreement) between RSBI and ABG was 0.974. Kappa between both tdi and Δtdi% and the ABG criteria was 0.891. The values differed slightly in patients tested after 72 hours. Sensitivity of a cut off level of tdi of 2 mm was 84.6% and 83.3% after 48 and 72 hours of MV, respectively. Sensitivity of Δtdi% of 20% was clearly higher after 72 hours (95.8%). Using ROC curves, Δtdi% of > 29.5% was also more sensitive after 72 hours.

Conclusion: Ultrasound estimation of diaphragm function is a promising tool to help clinicians to judge weaning readiness in patients on mechanical ventilation following major cancer surgery. Diaphragm thickness and its change between end-expiration and end-inspiration showed high degree of agreement with arterial blood gases for predicting weaning readiness.

Key words*:* Extubation; Diaphragm dysfunction; Diaphragm thickness; Rapid shallow breathing index; Mechanical ventilation

Abbreviations: RSBI: Rapid shallow breathing index, MV: mechanical ventilation, tdi: diaphragm thickness, Δtdi%: percent change in tdi between end-expiration and end-inspiration, PPV: positive predictive value, NPV: negative predictive value, *kappa:* measure of agreement, NCI: National Cancer Institute, VIDD: ventilator-induced diaphragmatic dysfunction

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INTRODUCTION

Mechanical ventilation (MV) is a well-recognized supportive procedure for patients with respiratory failure. It is used to manage 30–40% of patients admitted to intensive care units.[1] A subject of debate is what is best time for weaning from MV.[2] Premature[1,2] and delayed[3,4] weaning, both are associated with unfavorable outcome of MV.[3,4] Prolonged MV increases the risk of pneumonia, and injury of the airways in addition to musculoskeletal deconditioning. Delayed weaning is associated with higher morbidity, and mortality.[1,2]

Identifying the patients readiness for extubation is a challenging process.[5] Many studies have shown that a spontaneous breathing trial (SBT) is the most commonly used method of identifying readiness to wean.[6,7] little is known about clinical outcomes and validity among the three groups in medical ICU. The objectives of this study were to evaluate the clinical relevance of weaning classification and its association with hospital mortality in a medical ICU with a protocol-based weaning program.\n\nMethods\nAll consecutive patients admitted to the medical ICU and requiring mechanical ventilation (MV Noticeable efforts have been done to find better indices or parameters to best predict the weaning outcome. The rapid shallow breathing index (RSBI) is one of the most accurate indices that had a positive predictive value (PPV) of 85%.[8] A new integrative weaning index (IWI) has been suggested that has a PPV of 99%.[9] In fact, in majority of the patients weaning is a simple affair, but weaning failure is encountered in a small number of patients and is associated with prolonged duration of MV and ICU stay and increased morbidity and mortality.[7]

Diaphragm dysfunction is suggested to be involved in weaning failure and is associated with negative outcome at the time of cessation of MV.[11,12] Therefore, a reliable method to measure diaphragm function would be a useful guide for management of patients during MV and at the time of weaning.[13] Ultrasonography appeared recently as a promising tool for rapid assessment of diaphragm function.[14,15]

In the current study, we aimed to measure the diaphragmatic thickness by B-mode ultrasound as a tool for prediction of extubation and proper timing of weaning from mechanical ventilation in cancer patients admitted to the intensive care unit after major surgery.

METHODOLOGY

This prospective study was carried out in the surgical intensive care unit at the National Cancer Institute (NCI), Cairo University. The study was approved by the institutional review board (IRB) of the NCI (approval No. IRB00004025). Fifty patients were recruited during the immediate postoperative period after major elective cancer surgery who needed mechanical ventilation (MV) due to a respiratory cause and met criteria for a spontaneous breathing trial with pressure support ventilation (PSV).

Inclusion criteria were adults of 18-65 years of age, ASA class 1 to 3, body mass index (BMI) between 20 and 40 kg/m^2, and duration of intubation ≥ 48 hours. Types of abdominal cancer surgery included partial gastrectomy, hysterectomy, splenectomy, hepatectomy, and colectomy.

Exclusion criteria included hemodynamic instability requiring vasopressors, gas exchange impairment requiring positive end-expiratory pressure (PEEP) >10 cmH_2O and/or FIO_2 > 50% to obtain a PaO_2 > 60 mmHg, pressure support (PS) level > 20 cmH_2O, body temperature > 38°C or < 35°C, deep sedation state (RASS score < -1), history of chronic obstructive pulmonary disease, neuromuscular disease, anatomical malformation of the diaphragm, or use of muscle paralyzing agents, aminoglycosides and corticosteroids, pneumothorax or pneumomediastinum, or increased intra-abdominal pressure.

Each patient was intubated with an orotracheal tube and mechanically ventilated with PSV mode according to the clinical needs for weaning. According to the local guidelines, patients were sedated with continuous infusion of propofol started at 1.5 mg/kg/h and titrated to obtain a Richmond agitation-sedation scale (RASS) score of 0/-1. Analgesia was provided by continuous epidural infusion of bupivacaine 0.125% plus fentanyl 2 μg/ml solution as a 6-8 ml/h to reach a numerical rating score < 4. If epidural analgesia was not feasible, patients received 0.5 to 5 μg/kg/h continuous IV infusion of morphine, and acetaminophen 1 gm 3 to 4 times per day.

Patients were enrolled after being judged to be eligible for a test of weaning from MV according to clinical and arterial blood gases (ABG) criteria. The signs included adequate cough, absence of excessive tracheobronchial secretions, clinical stability, heart rate (HR) < 140/min, systolic blood pressure between 90 and 140 mmHg, respiratory rate/tidal volume ratio <105 breaths/min/L. The local ICU guidelines for weaning are shown in Table 1.

Weaning trials consisted of spontaneous breathing trial (SBT) on PSV, which was adjusted until respiratory rate became 35 breaths/min or lower. The PS was reduced by 2 cmH_2O every 6 hours or earlier as clinically indicated. Patients were considered fit for extubation if they tolerated PS of 7 cmH_2O for at least 1 hour. If there were signs of intolerance, PS was increased to the preceding level and reassessment for weaning was performed after a period of 6h. A successful extubation was defined as spontaneous breathing for > 48 h following extubation. A failed extubation was defined as reintubation within 48 h.

The patient was assessed for weaning clinically according to the previously mentioned guidelines, then the RSBI was calculated simultaneously with ultrasound measurements of diaphragmatic thickness during inspiration and expiration. The RSBI was calculated according to the following formula

$$\frac{\text{breaths/minute (f)}}{\text{tidal volume in liters (VT)}}$$

A value of 105 breaths/min/L or less was considered a predictor of successful extubation.[8]

Technique of diaphragm thickness measurement:

Diaphragm thickness (*tdi*) was measured using a 6-13 MHz linear ultrasound probe set to B mode (SonoSite M-turbo ultrasound system with SN. WK3BKK and HFL38x/13-6 MHZ transducer with SN. 046KWD). The right hemidiaphragm was imaged at the zone of apposition of the diaphragm and rib cage in the midaxillary line between the 8th and 10th intercostal spaces. The patient was studied with the head of bed elevated 20 to 40 degrees. The tdi was measured at end-expiration and end-inspiration. The first ultrasonographic measurement was performed within 24 hours after the start of MV and then daily within a 24 ± 6 h time frame. The same investigator performed all the recordings. The percent change in tdi between end-expiration and end-inspiration (Δtdi%) was calculated as

$$\left(\frac{\text{tdi end-inspiration-tdi end-expiration}}{\text{tdi end-expiration}}\text{ x100}\right)$$

The Δtdi% for each patient represented the mean of three breaths. Images were obtained after 24 hours of ventilation and once per day until extubation and immediately before extubation.

Diaphragm at Zone of Apposition (ZAP):

The ZAP of the diaphragm refers to the area where the diaphragm marches with the lower rib cage (Figure 1). In this region the diaphragm is relatively very superficial structure. Once obtained, the image can be displayed in B-mode (Figure 2).

To visualize the diaphragm in the ZAP, the transducer is placed on the skin surface in the coronal plane. The diaphragm in the ZAP is best visualized in the mid-axillary line in the region of the lower rib cage, usually in the 8th or 9th intercostal space. The diaphragm is identified as a three-layered structure just superficial to the liver, consists of two parallel echogenic lines (peritoneal and diaphragmatic pleura) sandwiching a relatively non-echogenic layer, the diaphragm muscle itself. On occasion, a 4th noncontinuous line may be seen within the diaphragm muscular layer which may represent a neural or vascular structure. The diaphragm can be further identified dynamically as the most superficial structure which is obliterated by the leading edge of the lung during inspiration.

Once the diaphragm is identified, the image was frozen at end-expiration and the thickness of the diaphragm (*tdi*) was measured as the distance from the middle of the diaphragmatic pleura to the middle of the peritoneum. A subsequent image is obtained at end-inspiration, and *tdi* was measured. Normal values for diaphragm thickness at end-expiration generally fall between 2.0 and 3.5 mm. Normal values for diaphragm thickening with inspiration (Δtdi%) fall between 20% and 100%.[16]

The primary outcome measure was diagnostic accuracy of diaphragm thickness and Δtdi% to predict weaning compared to ABG (the gold standard for weaning). Secondary outcome measures were diagnostic accuracy of RSBI compared to ABG and duration of ventilation.

Statistical analysis:

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). McNemar test was used to examine the relation between qualitative variables.

Agreement between different diagnostic methods

Table 1: NCI protocols for weaning in ICU

CNS:	
•	Arousable
•	GCS >12
•	**Cardiovascular:**
•	HR < 140
•	Not on pressors
Others:	
•	Afebrile
•	No significant electrolyte abnormalities.
Respiratory:	
•	PaO_2 > 60 mm Hg on FiO_2 < 40-50% and PEEP < 8 Cm H_2O
•	$PaCo_2$ at baseline
•	Rate/Tidal Volume < 105/min/L
•	Max Inspiratory Pressure -25 cmH_2O
•	PaO_2/FiO_2 >200
•	Tidal Volume 5 mL/kg
•	Respiratory Rate < 35/min
•	Vital Capacity 10 mL/kg
•	Minute Ventilation < 10 L/min

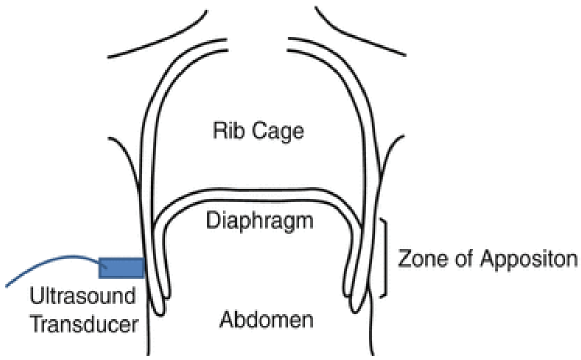

Figure 1: Schematic illustration of ultrasound transducer placement for visualizing the diaphragm in the zone of apposition[16]

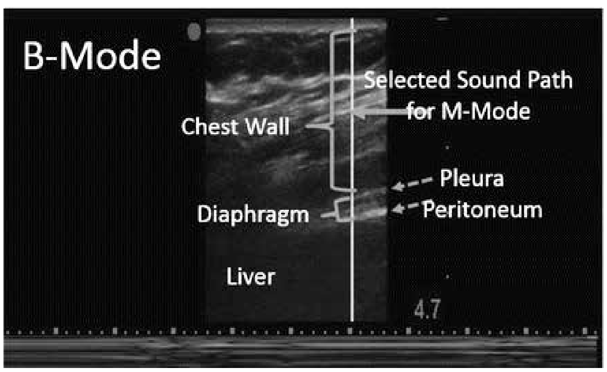

Figure 2: B-Mode of the diaphragm in the zone of apposition, the diaphragm muscle is visualized as the minimally echogenic structure "sandwiched" between the pleura and peritoneum[16]

was judged with kappa test. Receiver operator characteristic curve analysis was used to select the best cut-off point for different accuracy measures which included sensitivity, specificity, predictive values of both negative and positive tests. A $p < 0.05$ was considered significant.

RESULTS

The mean age of the studied group was 50.6 ± 7.6 y. There were 23 males and 27 females. Their BMI was 31.1 ± 4.7 kg/m^2. Table 2 shows the associated comorbidities and types of operations performed. Duration of ventilation and indications are shown in Table 3. The median duration of MV was 3 days (range: 2-5 days).

Two patients needed reintubation after 24 hours of weaning and after fulfilling all criteria of weaning secondary to a new incidence on top of the basic medical condition, e.g. sudden cardiac arrest due to massive pulmonary embolism in one patient and complicated surgery in the other. After 48 h, 13 patients out of the remaining 48 were weaned according to the arterial blood gases (ABG) criteria. According to the reference value of RSBI, 12 patients were weanable and 36 were not. Therefore the kappa value (agreement) between RSBI and ABG criteria was 0.974. On the other hand agreement between both tdi and Δtdi% and the ABG criteria was 0.891 (Table 4). After 72 h 24/35 patients were weaned according to the arterial blood gases (ABG) criteria. The values of agreement of RSBI, tdi, and Δtdi% with ABG criteria differed slightly in patients tested after 72 h.

Using ROC curve analysis, the suggested best cut-off of RSBI after 48 and 72 h was the same as previously

Table 2: Comorbidities and types of operations in the studied group

Comorbidities	No. (%)
None	32 (64)
Hypertension	7 (14)
Diabetes mellitus	6 (12)
Hypertension and diabetes mellitus	4 (8)
Ischemic heart disease	1 (2)
Type of Operation	
Pancreatectomy	9 (18)
Radical cystectomy	8 (16)
Lt Hemicolectomy	8 (16)
Panhysterectomy	8 (16)
Rt hemicolectomy	7 (14)
Nephrectomy	4 (8)
Adrenalectomy	2 (4)
Distal gastrectomy	2 (4)
Total colectomy	1 (2)
Pan-hysterectomy, oophorectomy, omentectomy and lymphadenectomy	1 (2)

Table 3: Indications and duration of ventilation in the studied group

Cause of ventilation	No. (%)
Sepsis	33 (66)
pneumonia	8 (16)
pulmonary embolism	5 (10)
Hemorrhagic Shock	4 (8)
Duration of ventilation (days)*	
2	13 (27.1)
3	24 (50.0)
4	9 (18.8)
5	4 (8.3)

** n=48.*

Table 4: Diagnostic accuracy of RSBI, tdi, and Δtdi% according to their reference values for prediction of successful weaning after 48 and 72 hours

	kappa	Sensitivity	Specificity	PPV	NPV	Accuracy
After 48 hours (n=13/48)						
RSBI	0.974	92.3%	100.0%	100.0%	97.4%	98.0%
tdi	0.891	84.6%	100.0%	100.0%	94.9%	96.0%
Δtdi%	0.891	84.6%	100.0%	100.0%	94.9%	96.0%
After 72 hours (n=24/35)						
RSBI	0.885	91.7%	100.0%	100.0%	86.7%	94.6%
tdi	0.778	83.3%	100.0%	100.0%	76.5%	89.2%
Δtdi%	0.942	95.8%	100.0%	100.0%	92.9%	97.3%

RSBI: Rapid shallow breathing index, tdi: diaphragm thickness, Δtdi%: percent change in tdi between end-expiration and end-inspiration, PPV: positive predictive value, NPV: negative predictive value, kappa: measure of agreement

Table 5: Results of ROC curve analysis of tdi and Δtdi% in detecting weanability off mechanical ventilator after 48 and 72 hours

	After 48 hours (n=13/48)		After 72 hours (n=24/35)	
	tdi > 1.9 mm	Δtdi% > 24.2%	tdi > 2.15 mm	Δtdi% > 29.5%
AUC	0.946	0.957	0.934	0.994
95% CI	0.843-0.990	0.859-0.994	0.802-0.989	0.893-1.000
Sensitivity	84.6%	84.6%	83.3%	95.8%
Specificity	100.0%	100.0%	100.0%	100.0%
PPV	100.0%	100.0%	100.0%	100.0%
NPV	94.9%	94.9%	76.5%	92.9%

AUC: Area under the curve, 95%CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value

determined (≤105 breaths/min/L). Table 5 shows slightly different cut-off values of tdi and Δtdi% after 48 and 72 h with their diagnostic accuracy values.

DISCUSSION

Both premature and delayed liberation from MV can be hazardous to patients in the ICU. Weaning should be planned as patients who accidentally self-extubate have a 31-78% risk of reintubation.[17]of whom 450 were on MV. Of the patients on MV, 30 (6.7% Even the most experienced clinicians may misinterpret the readiness for ventilator weaning. This is why solid protocols involving multiple parameters have to be evaluated to reach a sound unhazardous clinical judgment; to wean or not to wean.

In our institution, we implement guidelines including clinical parameters in addition to clear cut-off values of arterial blood gases to decide readiness for weaning off MV. In the current study, based on the negative impact of diaphragm dysfunction on weaning, we tested the capability of ultrasound estimation of diaphragm function to predict successful weaning against the ABG protocol as a gold standard.

The study demonstrated that diaphragm thickness (tdi) and percent change in tdi between end-expiration and end-inspiration (Δtdi%) were highly specific indicators of weanability of the studied patients; both had 100% positive predictive value. Sensitivity of a cut off level of tdi 2 mm was 84.6% and 83.3% after 48 and 72 hours of MV, respectively. Sensitivity of Δtdi% of 20% was clearly higher after 72 hours (95.8%). Using ROC curves, Δtdi% of > 29.5% was also more sensitive after 72 hours. Previous studies reported different cut-off of Δtdi% to predict successful weaning that ranged from 20 to 36% depending on the ventilator support provided during measurement.[14,15,18–21]rather than diaphragm motion, can be used to predict extubation success or failure.\nMethods Sixty-three mechanically ventilated patients were prospectively recruited. Diaphragm thickness (tdi

Dinino, et al. concluded that ultrasound measurement of diaphragmatic thickness can be helpful in reducing the number of failed extubation. The sensitivity and specificity of Δtdi% at a cutoff ≥ 30% for were 88% and 71%, respectively.[14] In another study, the sensitivity and specificity were 82% and 88%, respectively with a cut-off of Δtdi% >36.[15] More recently, Ali and colleagues reported a sensitivity of Δtdi% > 30% of 97.3% and specificity of 85.2% for successful weaning. They found that a diaphragm thickness >2 mm had sensitivity of 79.3% and specificity of 77.7%.[22]

A recent meta-analysis of 13 studies involving 742 patients reported a pooled sensitivity and specificity of Δtdi% of 89.3% and 79.6%, respectively. The authors concluded that ultrasonography of the diaphragm is a promising tool to predict reintubation within 48 hours of extubation.[23]Embase, and Cochrane Library to identify all the relevant papers, published in English up to July 16, 2017.

Eligible studies were included if data were in adequate details to rebuild 2×2 contingency tables.

Methodological quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2 However, the included studies were characterized by evident heterogeneity.

Mechanical ventilation has been shown to induce diaphragm dysfunction due to loss of diaphragmatic force-generating capacity. This was termed ventilator-induced diaphragmatic dysfunction (VIDD).[24] Also, endurance of the diaphragm is also negatively affected by MV.[25] Hermans and colleagues[26] demonstrated a logarithmic decline in diaphragmatic force correlated with the duration of MV; a finding matched with the concept of VIDD.

Ultrasound offers a readily available tool for assessment of diaphragm function during weaning. Using the intercostal approach, ultrasound enables measurement of the diaphragm thickness on its zone of apposition to the rib cage.

The change in tdi between end-expiration and end-inspiration (Δtdi%) is strongly correlated with trans-diaphragmatic pressure [27]10 and 15 cmH(2, which is an estimator of diaphragm function.[28]

Another tool for assessment of weaning readiness in the current study was RSBI. A RSBI ≤105breaths/min/L had a sensitivity of 92.3% and specificity of 97.4% to predict readiness to weaning against the gold standard; the ABG. With longer duration of MV, the specificity decreased to 86.7%. Fadaii et al. reported sensitivity of 77.8% and specificity of 71.4% of RSBI.[29]

More recently, Pirompanich and Romsaiyut suggested combination of RSBI with ultrasound measurement of diaphragm thickness for prediction of weaning success. They reported sensitivity of 96%, specificity of 68%, positive predictive value of 89%, negative predictive value of 86% for prediction of successful weaning for Δtdi% ≥ 26%. Specificity increased to 78% when Δtdi% ≥ 26% was combined with RSBI ≤ 105.[30]

LIMITATIONS

The study has few limitations. In this study, we did not asses other muscles, such as intercostal muscles, pectoralis muscles, or leg muscles as that atrophy of diaphragm may be a part of disuse atrophy. The sample size was relatively small. The ultrasound technique recommended by the study needs training for the ICU practitioners to be familiar with.

CONCLUSION

Ultrasound estimation of diaphragm function is a promising tool to help clinicians to judge weaning readiness in patients on mechanical ventilation following major cancer surgery. Diaphragm thickness and its change between end-expiration and end-inspiration showed high degree of agreement with arterial blood gases for predicting weaning readiness. Both parameters had absolute specificity and positive predictive value. It is recommend to add ultrasonographic diaphragm thickness measurement to criteria of deciding liberation from MV especially with longer duration of on ventilators.

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Authors' contribution:

AMS: Conduction of the study work, manuscript editing

MAS: Concept, Final revision

AMH: Manuscript editing

MAR + TAK: Conduction of the study work

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