


Change in Diaphragmatic Thickness During the Respiratory Cycle Predicts Extubation Success at Various Levels of Pressure Support Ventilation

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Abstract

Purpose Ultrasonographic assessment of diaphragm function with patients on low levels of pressure support (PS) predicts extubation outcomes, but similar information regarding extubation success under other conditions is lacking. The purpose of this study was to determine whether ultrasound (US) measurements of the diaphragm made on various levels of PS can predict time until successful extubation.

Methods Fifty-six intubated patients underwent ultrasound of the right hemidiaphragm during a PS wean at varying levels of pressure support (PS 5/5 cm of H₂O, 10/5 cm of H₂O, and 15/5 cm of H₂O). The diaphragm was visualized using a 7.5–10 mHz transducer in the zone of apposition of the diaphragm to the lower rib cage. The percent change in diaphragm thickness between end-expiration and end-inspiration ($\Delta tdi\%$) was calculated at each level of PS.

Results $\Delta tdi\% >20$ is a robust predictor of extubation success within 48 h of US at PS 5/5 cm of H₂O and 10/5 cm of H₂O (sensitivity 84.6 and 88.9 % and

specificity 79.0 and 75.0 %, respectively). At PS greater than 10/5 cm of H₂O, its predictive power was greatly diminished. Of nine patients who were extubated with $\Delta tdi\%$ below the cutoff, 66.6 % required emergent reintubation in the next two days.

Conclusions Diaphragm US is a valid predictor of extubation success at some but not all PS settings. Using a $\Delta tdi\%$ of 20 % on PS levels up to 10/5 cm of H₂O may reduce both unnecessarily prolonged intubations and prevent emergent reintubations.

Keywords Mechanical ventilation · Weaning · Ultrasound · Extubation · Diaphragm

Introduction

Despite advances in critical care medicine, the aptitude of clinicians to correctly predict extubation outcomes is limited. Failure to extubate appropriate patients in a timely manner is associated with significant morbidity including ventilator-associated pneumonia and diaphragm muscle atrophy [1]. Prematurely discontinuing mechanical ventilation is equally as harmful and is associated with mortality rates of as high as 42 % [2]. Even with evidence-based guidelines for discontinuation of ventilatory support, reintubation rates range from 25 to 33 % [3, 4].

A clinician's subjective ability to predict extubation is poor (sensitivity 35 %, specificity 79 %) [5], so several objective predictors of extubation have been developed to aid in clinical decision-making [6, 7]. The most widely used predictor for successful extubation is the rapid shallow breathing index (RSBI). Using a cutoff of 105 breaths/min/L, this metric has a sensitivity of 97 % and specificity of 64 % with “T-Piece” weaning trials [8]. Utilization of

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the RSBI is limited because many weaning trials use pressure support (PS) ventilation and the RSBI includes the contribution of accessory respiratory muscles which may mask the presence of diaphragm weakness and its inability to sustain unassisted breathing [9, 10].

Ultrasound (US) evaluation of the diaphragm has been studied as a surrogate marker for diaphragmatic function. In human studies, diaphragm thickness measured at end-inspiration is related to maximal inspiratory pressure [11] and the change in diaphragmatic thickness during inspiration strongly correlates with inspired lung volume [12]. Diaphragm US can also be used to evaluate diaphragmatic dysfunction [13] and paralysis [14]. Since the diaphragm is the major contributor to unassisted breathing, assessment of diaphragmatic function should theoretically predict extubation outcomes. To this end, US measures of diaphragmatic dome excursion have been used to predict extubation outcomes with some success [15]. This technique, however, does not directly visualize the diaphragm muscle and motion of the dome can be affected by passive displacement by the ventilator and adjacent abdominal contents [16, 17]. To overcome these limitations, US has been used to visualize the diaphragm in the zone of apposition to the rib cage. In fact, measurement and calculation of the percent change in thickness of the diaphragm over the entire respiratory cycle predict extubation outcomes at a PS of 5/5 cm H₂O or on T-piece better than either the RSBI or measurements of diaphragmatic dome excursion [18, 19]. While it has been shown that US measurements of the diaphragm on T-piece or low levels PS predict extubation success, no study so far has established the validity of these measurements under other conditions. The purpose of this study is to determine whether percent change in diaphragmatic thickness as measured by US predicts extubation outcomes at various levels of pressure support.

Methods

Subjects

All adult patients (age greater than 18 years old) intubated and mechanically ventilated for greater than 24 h were prospectively recruited from the intensive care unit (ICU) at Einstein Medical Center Philadelphia, an urban tertiary care center, between July 2014 and August 2015. Patients were excluded if they had an ischemic or hemorrhagic stroke, spinal cord injury, neuromuscular disease, pregnancy, or any pathology that would obscure visualization of the right hemidiaphragm. Terminal or self-extubation within 48 h of the ultrasound was censored from the final analysis. Informed consent was obtained from the

designated decision maker, either the power of attorney or legal next of kin, in accordance with the Einstein Medical Center Institutional Review Board (IRB# 4541).

Ultrasound Measurements

Team members included individuals formally trained in the use of ultrasound with prior clinical experience, who underwent approximately one hour of training to standardize their imaging technique and window. The diaphragm was visualized with B-Mode ultrasound using a linear 7–10 mHz probe (Sonosite M-Turbo, FujiFilm, Tokyo, Japan) at the zone of apposition located on the right mid-axillary line between the eighth and tenth ribs as previously described [12]. All subjects were evaluated with the head of the bed angled between 20° and 40° of elevation. A 15- to 30-s video clip was recorded on the ultrasound, exported, and analyzed using ImageJ (NIH, Bethesda, MD, USA). Thickness was measured from the inside edge of the diaphragmatic pleura to the inside edge of the peritoneal membrane (Fig. 1). This thickness was measured at approximately 25, 50, and 75 % along the length of the diaphragm at end-expiration (EE) and end-inspiration (EI). The average thickness was determined from these three measurements and then averaged over three respiratory cycles. The percent change in diaphragmatic thickness ($\Delta\text{tdi}\%$) was calculated by $([\text{Thickness at EI}]_{\text{AVG}} - [\text{Thickness at EE}]_{\text{AVG}})/[\text{Thickness at EE}]_{\text{AVG}} \times 100$. Team members analyzing the ultrasound images did not perform any of the ultrasounds and were blinded to which patients were extubated within 48 h. The intraclass correlation coefficient was 0.814.

Protocol

During PS weaning initiated by the primary ICU team, the US technician imaged the diaphragm. Diaphragms were visualized with ultrasound at PS settings of 15/5 cm of H₂O, 10/5 cm of H₂O, and 5/5 cm of H₂O; the location of the probe on the patient was marked to minimize variability of the imaging window. Patients were maintained on the indicated PS for at least 5 min prior to US imaging. The primary ICU team extubated patients when able to tolerate PS of 10/5 cm of H₂O or less for at least 2 h without exhibiting clinical signs of respiratory fatigue (increase in respiratory rate >30 breaths/min, heart rate >120 beats/min, SBP <90 mmHg or >180 mmHg, presence of confusion, agitation, diaphoresis, cyanosis, or evidence of increasing respiratory effort). All decisions to extubate were made without knowledge of US results. Patients were followed until discharge or death. Demographics, clinical information, and other ventilator metrics were obtained by chart review. Etiologies of respiratory failure with an incidence of one were combined into a miscellaneous

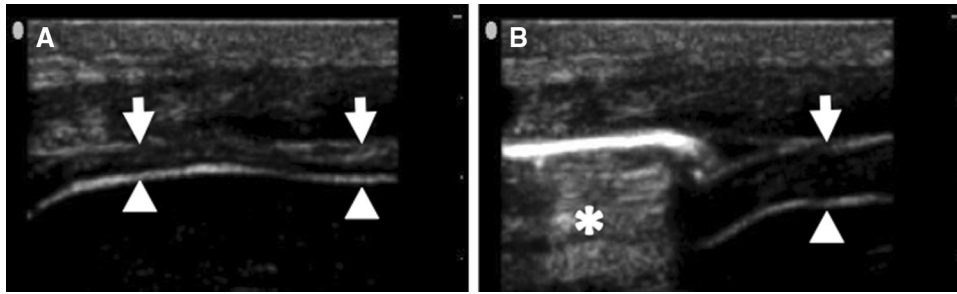


Fig. 1 Measurement of diaphragmatic thickness by B-Mode ultrasound. A representative ultrasound image of a patient's diaphragm at end-expiration (a) and end-inspiration (b). The distance between the

diaphragmatic pleura (*arrow*) and peritoneal membrane (*arrow head*) represents the diaphragmatic thickness. The lung (*asterisk*) is visualized at end-inspiration

group that consisted of such causes as diffuse alveolar hemorrhage, hepatic encephalopathy, toxic ingestion, non-ST segment elevation myocardial infarction, angioedema, delirium tremens, Lemeir's Syndrome, acute respiratory distress syndrome, metabolic acidosis, and metabolic encephalopathy.

Analysis

Demographics, clinical information, and ventilator metrics were all summarized with descriptive statistics and compared using either Mann–Whitney test (two-group comparisons, continuous variables), or Kruskal–Wallis test with Dunn's post hoc multiple comparison test (three-group comparison, continuous variables), or Z-test (two-group comparison, proportions), or Chi-squared test (three-group comparison, proportions). Percent change of diaphragmatic thickness ($\Delta tdi\%$) stratified by PS level and time to extubation compared using a two-way analysis of variance (ANOVA) with a Bonferroni post hoc test. Receiver operating characteristic (ROC) curves were created to identify the optimal $\Delta tdi\%$ threshold for extubation within 48 h of ultrasound. For each PS level, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. $P < 0.05$ was considered statistically significant. All statistical analyses were conducted on GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA) and SPSS (IBM, Armonk, NY, USA).

Results

Fifty-six patients were enrolled in the study group, but four were censored prior to the final analysis due to self-extubation (Fig. 2). Of the remaining 52 patients, 26 were extubated within 48 h of US and 19 remained intubated for a longer period. Additionally, seven patients were extubated within 48 h of ultrasound but required emergent reintubation within the following two days. Patients

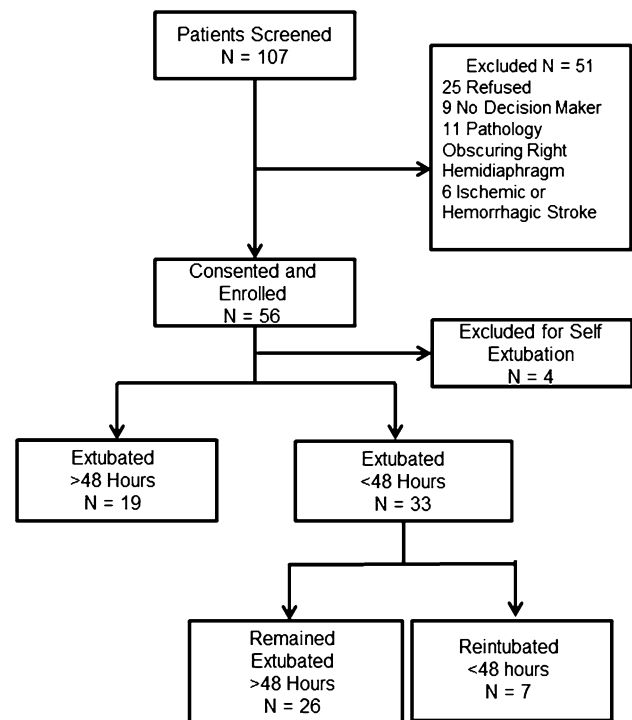


Fig. 2 Overview of study design and participants

extubated within 48 h and patients extubated after 48 h (columns 2 and 3 in Table 1) did not significantly differ in age, gender, BMI, severity of illness, reason for intubation, and etiology of respiratory failure. There was no difference in the time to first PS weaning trial. As expected, patients who were unable to be extubated within 48 h had significantly longer total weaning time ($p < 0.001$), total ventilation time ($p < 0.001$), longer ICU stays ($p = 0.028$) and higher rates of in hospital mortality ($p < 0.001$).

All 52 patients had ultrasound measurements of diaphragmatic thickness at 5/5 cm of H_2O and 10/5 cm of H_2O while 36 had imaging at 15/5 cm of H_2O . At pressure support of 5/5 cm of H_2O patients who were able to be successfully extubated within 48 h of ultrasound had a

Table 1 Population demographics and ventilator metrics

	Total patients <i>N</i> = 52	Extubated <48 h <i>N</i> = 26	Extubated >48 h <i>N</i> = 19	Reintubated ≤48 h <i>N</i> = 7
Demographics				
Age (years)	62 ± 17	60 ± 20	64 ± 13	60 ± 12
Male	50 % (26)	54 % (14)	47 % (9)	43 % (3)
BMI	27 ± 9	26 ± 10	28 ± 10	27 ± 6
APACHEII	24.3 ± 6	23.9 ± 6	25.3 ± 7	23.0 ± 6
SOFA	7.6 ± 3.0	7.1 ± 2.4	8.2 ± 4.0	7.7 ± 1.8
Reason for intubation				
Hypoxic respiratory failure	52 % (27)	46 % (12)	58 % (11)	57 % (4)
Hypercapnic respiratory failure	21 % (11)	15 % (4)	26 % (5)	29 % (2)
Pending respiratory failure	6 % (3)	8 % (2)	5 % (1)	0
Airway protection	21 % (11)	31 % (8)	11 % (2)	14 % (1)
Etiology of respiratory failure				
Sepsis	17 % (9)	4 % (1)	32 % (6)	29 % (2)
Pneumonia	17 % (9)	15 % (4)	26 % (5)	0
Aspiration	17 % (9)	15 % (4)	21 % (4)	14 % (1)
Congestive heart failure	8 % (4)	12 % (3)	5 % (1)	0
Status epilepticus	8 % (4)	12 % (3)	5 % (1)	0
Status asthmaticus	4 % (2)	8 % (2)	0	0
COPD exacerbation	10 % (5)	12 % (3)	0	29 % (2)
Other	19 % (10)	23 % (6)	11 % (2)	29 % (2)
Ventilator metrics				
Total ventilation time (h)	141 ± 102	79 ± 51	240 ± 95	106 ± 49
Weaning time (h)	84 ± 90	29 ± 39	180 ± 73	25 ± 21
Time to spontaneous breathing trial on PSV (h)	57 ± 36	49 ± 28	60 ± 39	80 ± 46
Time between SBT and ultrasound (h)	29 ± 39	20 ± 35	46 ± 44	12 ± 20
Time between ultrasound and extubation (h)	55 ± 3	8 ± 8	133 ± 67	13 ± 17
Time between extubation and reintubation (h)				25 ± 13
Outcomes				
ICU length of stay (days)	11 ± 8	8 ± 9	13 ± 4	19 ± 7
In hospital mortality	33 % (17)	12 % (3)	63 % (12)	29 % (2)

Other = diffuse alveolar hemorrhage, hepatic encephalopathy, toxic ingestion, non-ST segment elevation myocardial infarction, angioedema, delirium tremens, Lemeir's Syndrome, acute respiratory distress syndrome, metabolic acidosis, and metabolic encephalopathy

2.12-fold larger percent change in diaphragmatic thickness during the respiratory cycle compared with those who were unable to be extubated within 2 days (Fig. 3a). These same patients had a significant 1.96-fold increase in $\Delta tdi\%$ on pressure support settings of 10/5 cm H₂O. However, at pressure support of 15/5 cm of H₂O the average $\Delta tdi\%$ for each group did not statistically differ.

Receiver operating characteristic (ROC) curves were created at each level of pressure support to establish the optimal $\Delta tdi\%$ threshold for predicting extubation within 48 h (Fig. 3b). As expected, $\Delta tdi\%$ measured at 5/5 cm of H₂O and 10/5 cm of H₂O was equally robust in its ability to predict extubation (AUC 0.864 and 0.824,

respectively). However, the area under the ROC curve for $\Delta tdi\%$ at PS 15/5 cm of H₂O was significantly less (AUC 0.667). Based on the ROC curve, $\Delta tdi\%$ at PS 5/5 cm of H₂O and 10/5 cm of H₂O had an optimal cut off of 20 %, which corresponded with sensitivity of 84.6 and 88.9 % and specificity of 79.0 and 75.0 %, respectively. At PS 15/5 cm of H₂O, the optimal cutoff was 10 % which had markedly reduced sensitivity and specificity (Table 2). Stratifying the cohort by reason for intubation demonstrated that $\Delta tdi\%$ predicted extubation success more often in patients intubated for respiratory failure (hypoxic or hypercapnic) than those intubated for airway protection at all levels of pressure support (Table 2, sensitivity

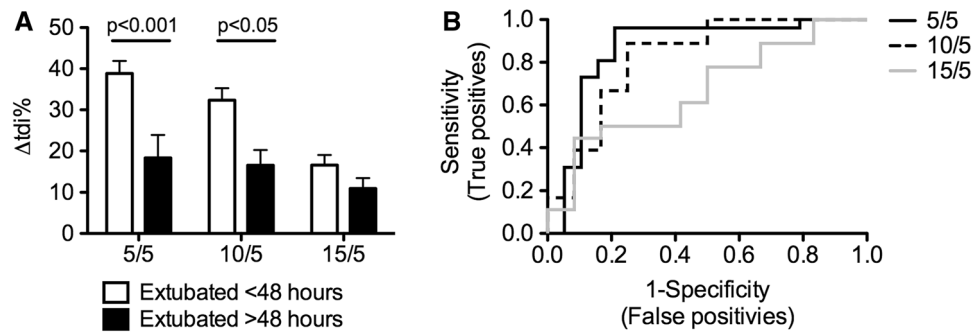


Fig. 3 Δtdi% is a robust predictor of extubation success within 48 h of ultrasound for pressure support levels up to 10/5. **a** Patients extubated within 48 h of ultrasound had significantly greater Δtdi% at 5/5 cm H₂O and 10/5 cm H₂O. At 15/5 cm H₂O there was no

significant difference between the two groups. **b** ROC curves of Δtdi% as a predictor of time to successful extubation showing 20 % as the optimal cut off at 5/5 cm H₂O and 10/5 cm H₂O. At 15/5 cm H₂O, the optimal Δtdi% cutoff was 10 %

Table 2 Diagnostic performance of Δtdi% on various levels of PS stratified by reason for intubation

PS	Population	Optimal Δtdi% cutoff (%)	Sen	Spec	PPV	NPV
5/5	All cohort	20	84.6	79.0	84.6	75.0
	Respiratory failure		94.4	82.5	85.0	93.3
	Airway protection		75.0	33.3	75.0	33.3
10/5	All cohort	20	88.9	75.0	84.2	81.8
	Respiratory failure		84.6	80.0	84.6	80.0
	Airway protection		80.0	50.0	80.0	50.0
15/5	All cohort	10	61.1	58.3	68.6	50.0
	Respiratory failure		69.2	60.0	69.2	60.0
	Airway protection		40.0	50.0	66.6	25.0

Sen sensitivity, Spec specificity, PPV positive predictive value, NPV negative predictive value

94.4 % and specificity 82.5 % vs. sensitivity 75.0 % and specificity 33.3 %).

To better understand how diaphragmatic ultrasound compares to established extubation metrics, we compared Δtdi% with RSBI. The Δtdi% had a significant negative linear correlation with RSBI at a PS of 5/5 cm H₂O ($p = 0.025$) but not at PS of 10/5 cm H₂O or 15/5 cm H₂O (Supplementary Fig. 1A–C). Using an RSBI cutoff of 105 breaths/min/L, RSBI had similar sensitivity but markedly lower specificity when compared with Δtdi% at PS 5/5 cm H₂O (Supplementary Table 1). At higher levels of PS, Δtdi% was a far better predictor of extubation success within 48 h. The combination of RSBI and Δtdi% was not significantly better than Δtdi% alone.

Seven study patients extubated within 48 h required emergent reintubation within the following two days. These subjects did not differ from the prior two groups with regards to their demographics, severity of illness, reason for intubation, or etiology of respiratory failure (Table 1). However, they did have significantly longer ICU stay compared to those extubated within 48 h ($p < 0.001$). 85.7 % (six out of seven) of these patients had Δtdi% less than the extubation threshold of 20 % (Fig. 4)

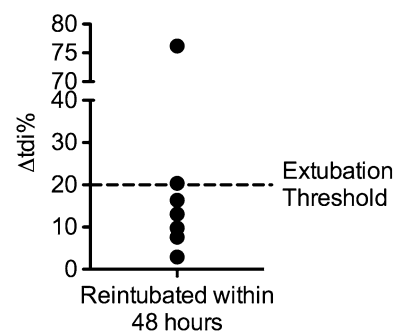


Fig. 4 The majority of patients requiring emergent reintubation had a Δtdi% below the proposed extubation threshold. Of the seven patients reintubated within 48 h, 85.7 % had Δtdi% <20 %

Discussion

Ultrasound is a readily available, easy to use, and non-invasive imaging modality that is commonly used for procedures and clinical evaluation in the modern ICU [18]. Recently, US measurements have been used to assess diaphragmatic function and predict extubation success [15, 18, 19]. We establish Δtdi% as a robust and specific

predictor of successful extubation within 48 h of US measurement at PS levels as high as 10/5 cm of H₂O in the general ICU population. At PS 15/5 cm of H₂O there was no significant difference between the groups extubated within 48 h and those extubated after 48 h, and therefore, $\Delta tdi\%$ had no predictive capacity. This observation suggests that $\Delta tdi\%$ could predict extubation outcomes at PS levels as great as 10/5 cm of H₂O but not at 15/5 cm of H₂O. $\Delta tdi\%$ better predicts extubation outcomes in patients who were intubated for respiratory failure as compared to those intubated for airway protection. Finally, we demonstrate that emergent reintubations occurred when the diaphragm failed to thicken sufficiently (i.e., $\Delta tdi\%$ was less than the proposed extubation threshold of 20 %).

Our study extends prior work that indicated that changes in diaphragm thickness measured at PS 5/5 cm of H₂O or on T-piece can be used to predict extubation outcomes. DiNino et al. showed that $\Delta tdi\%$ of 30 % at initiation of weaning predicted extubation success of ICU patients [18]. A subsequent study by Ferrari et al. established that a $\Delta tdi\%$ of 36 % predicted successful weaning in patients requiring long-term ventilator support [19]. We show that a $\Delta tdi\%$ of 20 % or higher measured at PS up to 10/5 cm of H₂O accurately predicted successful extubation within the next 48 h. Our $\Delta tdi\%$ threshold is less than those of the previous studies for several technical reasons. First, our study utilized an image processing program (ImageJ, NIH, Bethesda, MD, USA) for the analysis which achieved greater accuracy and precision than those achieved in previous studies. Furthermore, diaphragm thickness was measured at the inner most part of the pleura and peritoneum compared to the midline of these structures as in other studies. This variability reveals the need for a standard protocol before $\Delta tdi\%$ can be utilized globally to predict extubation success.

Interestingly, the predictive power of $\Delta tdi\%$ drastically decreases above pressure supports of 10/5 cm of H₂O. We hypothesize that at low levels of PS the ventilator supplies only enough support to overcome only the intrinsic resistance of the ventilatory circuit. To generate adequate spontaneous breathing, the diaphragm must maximally contract resulting in a large change in thickness [20, 21]. At PS greater than 10/5 cm of H₂O, the ventilator offsets the work of breathing resulting in submaximal diaphragmatic contraction [16, 22]. This added support does not allow for true assessment of the diaphragms capabilities when mechanical support is removed, and hence cannot reliably predict extubation outcomes.

$\Delta tdi\%$ at a PS of 5/5 cm H₂O correlates with RSBI but both metrics provide very different information about the respiratory system. RSBI represents the combined function of the diaphragm and accessory muscles while direct

visualization of the diaphragm and calculation of $\Delta tdi\%$ evaluates diaphragm activation alone. By excluding the impact of the accessory muscles, which are unlikely to support unassisted respiration for a significant amount of time, $\Delta tdi\%$ has much higher specificity than RSBI (79.0 vs. 42.1 %) [20, 21]. This increased specificity results in fewer premature extubations and subsequent reintubations. Consistent with this, all but one patient reintubated within 48 h of extubation were deemed appropriate for extubation by the RSBI but six of the seven would not have been extubated using our proposed cutoff of $\Delta tdi\%$.

A potential limitation of the study is the sample size. While adequate to detect changes in the main cohort, it did not have a sufficient size to allow for subgroup analysis. Specifically, with only seven patients requiring reintubation we did not have an adequate sample size to confirm the trend that reintubated patients had an average $\Delta tdi\%$ less than the proposed extubation threshold. Including patients with intracranial hemorrhage and stroke would have increased our sample size; however, successful extubation of such patients is more reliant on mental status than diaphragmatic strength and would have diluted the results of the study.

We conclude that ultrasound measurements of $\Delta tdi\%$ obtained at PS up to 10/5 cm of H₂O can predict extubation success in the next 48 h. This is important since some patients are unable to wean on a PS of 5/5 cm H₂O. This study bridges the predictors described in prior studies to today's clinical practice. Furthermore, it establishes a 48-h window during which successful extubation can be expected. This result opens the possibility of a novel weaning protocol where patients undergo daily diaphragmatic ultrasound during PS support weans until $\Delta tdi\%$ is greater than 20 %. At that time successful extubation can be expected in the next 48 h. Incorporation of $\Delta tdi\%$ into established weaning protocols may improve a clinician's predictive power and thereby reduce unnecessarily prolonged intubations and prevent emergent reintubations.

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Authors' Contribution JM is the guarantor of the content of this manuscript and contributed to study design, data analysis, and revisions to the manuscript. SB contributed to study design, data collection, data analysis, and drafted the manuscript. DW contributed to study design, data collection, data analysis, and revisions to the manuscript. KT contributed to data collection, and revisions to the manuscript. FDM contributed to study design and revisions to the manuscript.

Compliance with Ethical Standards

Conflict of Interest None.

Ethical Approval Einstein Medical Center Philadelphia IRB #4541.

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