

Identifying Subjects at Risk for Diaphragm Atrophy During Mechanical Ventilation Using Routinely Available Clinical Data

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BACKGROUND: Diaphragmatic respiratory effort during mechanical ventilation is an important determinant of patient outcome, but direct measurement of diaphragmatic contractility requires specialized instrumentation and technical expertise. We sought to determine whether routinely collected clinical variables can predict diaphragmatic contractility and stratify the risk of diaphragm atrophy. **METHODS:** We conducted a secondary analysis of a prospective cohort study on diaphragm ultrasound in mechanically ventilated subjects. Clinical variables, such as breathing frequency, ventilator settings, and blood gases, were recorded longitudinally. Machine learning techniques were used to identify variables predicting diaphragm contractility and stratifying the risk of diaphragm atrophy (> 10% decrease in thickness from baseline). Performance of the variables was evaluated in mixed-effects logistic regression and random-effects tree models using the area under the receiver operating characteristic curve. **RESULTS:** Measurements were available for 761 study days in 191 subjects, of whom 73 (38%) developed diaphragm atrophy. No routinely collected clinical variable, alone or in combination, could accurately predict either diaphragm contractility or the development of diaphragm atrophy (model area under the receiver operating characteristic curve 0.63–0.75). The risk of diaphragm atrophy was not significantly different according to the presence or absence of patient-triggered breaths (38.3% vs 38.6%; odds ratio 1.01, 95% CI 0.05–2.03). Diaphragm thickening fraction < 15% during either of the first 2 d of the study was associated with a higher risk of atrophy (44.6% vs 26.1%; odds ratio 2.28, 95% CI 1.05–4.95). **CONCLUSIONS:** Diaphragmatic contractility and the risk of diaphragm atrophy could not be reliably determined from routinely collected clinical variables and ventilator settings. A single measurement of diaphragm thickening fraction measured within 48 h of initiating mechanical ventilation can be used to stratify the risk of diaphragm atrophy during mechanical ventilation. *Key words:* diaphragm thickening; diaphragm thickening fraction; machine learning; random forest; spontaneous breathing; diaphragm atrophy. [Respir Care 2021;66(4):551–558. © 2021 Daedalus Enterprises]

Introduction

Respiratory effort during mechanical ventilation is an important determinant of patient outcome. Both excessive and insufficient respiratory effort are associated with

potential harm: forceful diaphragm contractions can exacerbate lung injury,¹ cause load-induced diaphragm injury, and impair systemic oxygen delivery.^{2–5} At the same time, the suppression of diaphragmatic effort can cause diaphragm weakness and disuse atrophy,^{6,7} leading to prolonged mechanical ventilation and weaning failure.^{8–10}

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Both insufficient and excessive levels of diaphragmatic respiratory effort during the first 3 d after intubation are associated with prolonged mechanical ventilation.¹¹

Close monitoring of respiratory effort during the first days of mechanical ventilation might allow for the timely detection of patients at risk of injurious breathing, providing the opportunity for direct interventions. Clinicians and researchers typically rely on readily available clinical variables, such

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as the mode of mechanical ventilation and breathing frequency, to assess the presence and magnitude of diaphragmatic respiratory effort. For example, previous landmark studies in ARDS have assumed that diaphragmatic effort was absent when set and measured breathing frequencies were equal under controlled modes of ventilation.^{12,13} However, the reliability of this approach is unknown. The availability of reliable clinical markers of diaphragm inactivity would enable timely detection and possible mitigation of the risk of diaphragm atrophy and associated poor outcomes.

Direct measurement of diaphragmatic effort, on the other hand, is infrequently performed in clinical practice, possibly because traditional techniques for monitoring respiratory effort (eg, electrical activity of the diaphragm or esophageal pressure) require specialized instrumentation and some degree of technical expertise.¹⁴ Recently, measurement of diaphragm thickening on bedside ultrasound has been introduced as a feasible and noninvasive surrogate measure of diaphragm contractility¹⁵; the rate of change in diaphragm thickness over time was associated with daily diaphragm thickening fraction measurements.⁸ However, it is unknown whether assessing diaphragm contractility directly (by ultrasound or by other means) adds useful information about the risk of diaphragm atrophy compared to routine assessment of the presence or absence of spontaneous breathing from readily available clinical variables (eg, ventilator settings). If direct assessment of diaphragm contractility provides important additional information to stratify this risk, then clinicians should consider routine direct monitoring of diaphragmatic contractility.

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QUICK LOOK

Current knowledge

Ventilator-associated diaphragm atrophy during mechanical ventilation is associated with prolonged mechanical ventilation and complications which might be prevented by adjusting ventilation and sedation to restore adequate diaphragm activity. Bedside techniques are required to identify patients in whom diaphragm activity is inadequate and the risk of diaphragm atrophy is elevated.

What this paper contributes to our knowledge

The risk of developing diaphragm atrophy during mechanical ventilation could not be reliably determined using readily available clinical variables including breathing frequency, ventilator settings, or blood gas variables. Monitoring diaphragm thickening fraction during the early course of ventilation can be used to stratify the risk of developing diaphragm atrophy.

In this study, we set out to establish whether routinely collected clinical variables can detect the presence or absence of diaphragm contractility and stratify subjects at risk for subsequent diaphragm atrophy during mechanical ventilation for acute respiratory failure. For risk stratification, we determined whether a direct assessment of diaphragm contractility by diaphragm thickening fraction on ultrasound within the first 48 h of mechanical ventilation provided useful additional information to stratify the risk of diaphragm atrophy.

Methods

Study Participants and Measurements

We conducted a secondary analysis of a previously published cohort study assessing diaphragm thickness and diaphragm thickening fraction by daily ultrasound during the first 14 d of mechanical ventilation.^{8,11} In brief, the study enrolled 216 subjects with acute respiratory failure within 36 h of intubation who were anticipated to remain ventilated for ≥ 24 h; as previously described, the final analysis included 191 subjects who developed acute respiratory failure mainly due to respiratory (60 of 191 subjects) and cardiovascular (26 of 191 subjects) causes, or post-transplantation (29 of 191 patients). A total of 170 of 191 subjects (89%) met sepsis-3 criteria during the first 48 h. The median (interquartile range) P_{aO_2}/F_{IO_2} at baseline was 159 (105–233) mm Hg. Data on the development of diaphragm atrophy were available for 191 subjects. Subjects on extracorporeal life support were excluded from this analysis

because the physiology on extracorporeal life support differs substantially from best-practice conventional mechanical ventilation. For this analysis, the primary outcome was diaphragm atrophy, defined as a 10% decrease in diaphragm thickness from baseline as in our previous work.¹¹

Clinically available variables were collected as potential proxy variables of diaphragm contractility and of the development of diaphragm atrophy. These included subject anthropometric and demographic data, Sequential Organ Failure Assessment (SOFA) score,¹⁶ Riker Sedation-Agitation Scale,¹⁷ and Glasgow Coma Scale,¹⁸ ventilator settings at 8:00 AM daily (including mode, peak pressure, tidal volume, PEEP, and F_{IO_2}), the use of neuromuscular blocking agents, and arterial blood gases (obtained within 2 h of the ultrasound assessment). Actual weight instead of predicted body weight was used in 4 subjects with missing values for height.¹⁹ When subjects were ventilated in pressure support mode, set breathing frequency was defined as zero. Pressure support, proportional assist ventilation, and neurally-adjusted ventilatory assist were classified as partially assisted modes.

Detecting Diaphragm Contractility Based on Clinical Variables

For this analysis, diaphragm thickening fraction was used as a measure of diaphragm contractility and was recorded using transthoracic ultrasound at the level of the ninth or tenth intercostal space near the midaxillary line. We estimated diaphragm thickening fraction as the percentage change in diaphragm thickness during inspiration (calculated from the difference between peak inspiratory thickness and end-expiratory thickness divided by end-expiratory diaphragm thickness), as described in previous studies.^{8,11}

Three different approaches were used to develop a method for identifying diaphragm contractility from clinical variables. First, we determined whether clinical variables selected on an a priori basis, mode of ventilation, and the difference between set and total breathing frequencies, could detect the presence or absence of diaphragm thickening using mixed-effects logistic regression (Model 1). Model performance was evaluated by calculating the area under the receiver operating characteristic curve, sensitivity, and specificity based on predicted class probabilities. In the primary analysis, we defined diaphragm thickening fraction $\geq 15\%$ as the threshold for classification of present diaphragm thickening, based on previous work.¹¹ As a sensitivity analysis, model performance was also evaluated for a range of diaphragm thickening fraction threshold values (between 1% and 35%).

Second, the Boruta algorithm was used to identify candidate variables for predicting the presence or absence of diaphragm thickening. This algorithm, a machine learning technique based on the random forest method,²⁰ identifies

variables that provide more predictive information than a randomly generated variable (ie, noninformative by design). All available clinical variables were supplied to the algorithm. The performance of the predictors selected by the algorithm was evaluated using mixed-effects logistic regression.^{21,22}

Third, we evaluated whether a random-effects tree model (a different machine learning technique) incorporating all available clinical candidate variables could improve predictive performance.²³ Model variables were scaled and centered,²⁴ and a 100-fold subsampling validation was performed by repeatedly splitting the data at random into training (75%) and test data sets (25%) to assess predictive performance.^{25,26} Finally, we selected the model with the best sensitivity and specificity across all diaphragm thickening fraction thresholds (using the Youden's index: sensitivity + specificity - 1) and calculated overall accuracy as an estimate of the percentage of misclassifications.

Stratifying the Risk of Diaphragm Atrophy

To determine whether clinical variables could be used to stratify the risk of diaphragm atrophy, the same models described above were reconstructed on a different endpoint: the development of diaphragm atrophy (defined as a $\geq 10\%$ decrease in diaphragm thickness from baseline) during mechanical ventilation. Alternatively, the relationship between the first measurement of the diaphragm thickening fraction (a direct assessment of diaphragm contractility) obtained during the first 2 d of mechanical ventilation and the risk of developing diaphragm atrophy was evaluated. Previous work described that subjects with thickening fraction between 15% and 30% (similar to breathing at rest) during the first 3 d had the shortest duration of ventilation.¹¹ Using logistic regression, we therefore estimated the association between diaphragm thickening fraction $< 15\%$ or $\geq 15\%$ during the first 2 d of mechanical ventilation and the development of diaphragm atrophy.

All analyses were performed with R 3.6.3 (R Development Core Team, 2020). The research ethics boards at University Health Network (12-5582, 13-5953) and St. Michael's Hospital (14-229) approved the study protocols.

Results

Subject Characteristics

A total of 216 patients were available for analysis. Of these, we excluded 25 individuals because of missing data for clinical candidate variables or because they were receiving extracorporeal life support (see the supplementary material related to this paper at <http://www.rcjournal.com>). Therefore, 191 subjects with 718 observations were

Table 1. Baseline Subject Characteristics and Summary of Measurements

Age, y	60 (50–70)
Male	115 (60)
Height, cm	167.5 (160.0–176.5)
Weight, kg	75.1 (61.5–87.9)
SAPS II score	47 (35–58)
All measurements	
Diaphragm thickening fraction	0.13 (0.07–0.21)
Partially assisted ventilation mode	417 (58)
Difference in set vs measured frequency, breaths/min	14 (0–23)
Measured frequency, breaths/min	22 (18–28)
Expiratory minute ventilation, L	9.0 (7.1–11.0)
V _T per predicted body weight, mL/kg	6.6 (5.7–7.7)
Peak inspiratory pressure, cm H ₂ O	17 (10–23)
PEEP, cm H ₂ O	8 (5–10)
F _{IO₂}	0.40 (0.35–0.50)
P _{aO₂} , mm Hg	92 (78–111)
pH	7.40 (7.35–7.45)
P _{aCO₂} , mm Hg	41 (35–48)
HCO ₃ , mmol/L	25 (22–30)
Riker Agitation-Sedation score	2 (1–3)
SOFA score	10 (7–14)
Neuromuscular blockade agents	49 (6.8)

Data are presented as *n* (%) or median (interquartile range). *N* = 191 subjects at baseline; *n* = 718 observations.

SAPS = Simplified Acute Physiology Score
SOFA = Sequential Organ Failure Assessment

included in the analysis. Subject characteristics and summary of measurements are reported in Table 1.

Subjects were ventilated using a partially assisted mode of ventilation during 58% of ultrasound measurements. A total of 26 of 191 (13.6%) subjects received neuromuscular blockade agents; 49 of 718 measurements were performed in subjects undergoing treatment with neuromuscular blockade agents (see the supplementary material related to this paper at <http://www.rcjournal.com>). Median diaphragm thickening fraction was 13% (interquartile range 7–21%). The distributions of diaphragm thickening fraction between subjects who are usually assumed to have no spontaneous breathing (ie, controlled mode, measured breathing frequency equal to set breathing frequency) and all other subjects overlapped substantially (Fig. 1). A total of 73 subjects (38%) developed diaphragm atrophy (defined as > 10% decrease in diaphragm thickness from baseline) during the first week of mechanical ventilation.

Diaphragm Contractility Based on Clinical Variables

The Boruta algorithm identified the difference between set and total breathing frequencies and the mode of

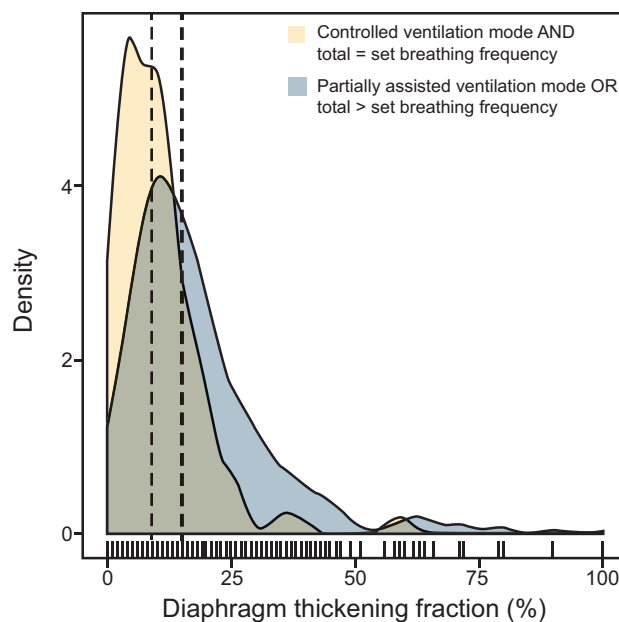


Fig. 1. Density plot illustrating the distribution for diaphragm thickening fraction measured using ultrasound as a surrogate of diaphragm contraction or diaphragm thickening in mechanically ventilated subjects. Having equal set and measured breathing frequency under controlled ventilation corresponded to a distribution of diaphragm thickening values that overlapped by 55% with those of subjects who did not meet these criteria. The mode of ventilation and the difference between set and total breathing frequency have poor discriminative properties to accurately determine if diaphragm thickening is present. Dashed lines represent the medians of the 2 strata.

ventilation (partially assisted vs continuous mandatory ventilation) as the best surrogate markers of diaphragm thickening fraction (Fig. 2). Expiratory minute volume, P_{aCO₂}, SOFA score, neuromuscular blockade, and tidal volumes also ranked as variables with predictive information for the estimation of the thickening fraction. P_{aO₂}, F_{IO₂}, and PEEP did not provide more predictive information than a noninformative randomly generated variable.

Models detecting diaphragm thickening based on a combination of clinical variables yielded an area under receiver operating characteristic curve ranging between 0.63 and 0.75, irrespective of the diaphragm thickening fraction threshold used to define diaphragm thickening area. Model performance did not meaningfully improve when additional clinical variables identified by the Boruta algorithm were included. Across the entire range of thickening fraction thresholds (0–5%), the best model performance was achieved with a RE-EM tree model (maximized for sensitivity and specificity) at a thickening fraction threshold of 15%. Under these conditions, model predictions were accurate in 69% of cases.

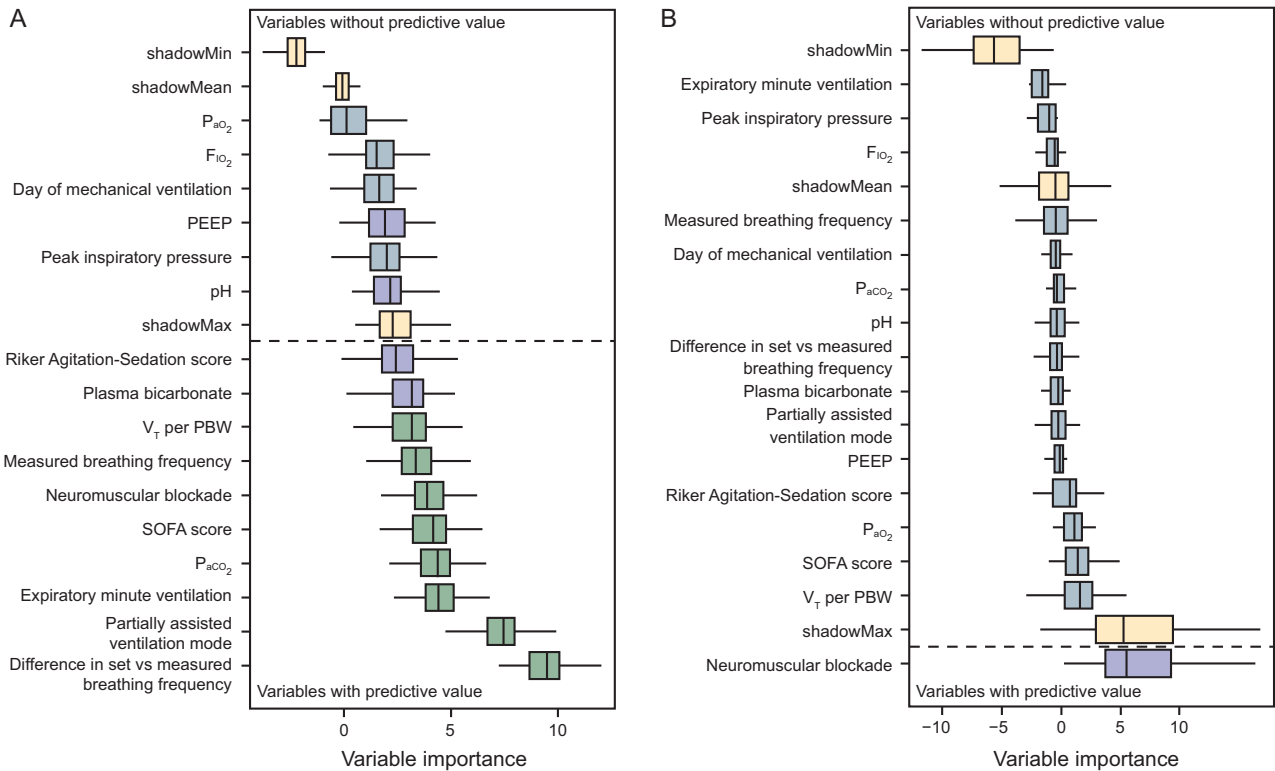


Fig. 2. All-relevant feature selection using the Boruta algorithm was performed to identify clinical variables with informative value for the prediction of A: diaphragm thickening fraction and B: diaphragm atrophy. The algorithm considers features as relevant if they provide more predictive information than randomly generated shadow variables (ie, noninformative variables by design). Features ranked below shadowMax do not provide valuable information for prediction of diaphragm thickening fraction; the dashed line separates features based on their predictive value. V_T per PBW = tidal volume per predicted body weight.

Stratifying the Risk for the Development of Diaphragm Atrophy

No single clinical candidate variable contained more discriminative information than a randomly generated variable regarding the development of diaphragm atrophy (Fig. 2). The presence of patient-triggered breaths (ie, controlled mode ventilation with measured equal to set breathing frequency or use of pressure support mode) during the first 2 d of mechanical ventilation was not associated with an increased risk of developing diaphragm atrophy (38.3% vs 38.6%; odds ratio 1.01, 95% CI 0.05–2.03, $P = .95$). By contrast, the first measurement of diaphragm thickening fraction obtained within 48 h of initiating mechanical ventilation was associated with the risk of developing diaphragm atrophy (Fig. 3). Subjects with a diaphragm thickening fraction < 15% had a significantly higher risk of developing diaphragm atrophy (44.6% vs 26.1%; odds ratio 2.28, 95% CI 1.05–4.95, $P = .038$).

Discussion

We found that neither diaphragmatic contractility nor the risk of diaphragm atrophy could be reliably inferred from

breathing frequency, ventilator settings, and other readily available clinical variables. However, we found that measurement of diaphragm thickening fraction using ultrasound during the first 48 h of mechanical ventilation could stratify the risk of diaphragm atrophy in subjects with acute respiratory failure. We conclude that diaphragmatic activity must be directly assessed (whether by ultrasound or other means) to assess the risk of diaphragm atrophy during mechanical ventilation.

To improve model performance, we attempted to identify clinical characteristics related to diaphragm thickening. Our results indicate that P_{aCO₂}, SOFA score, and Riker Sedation-Agitation Scale might provide some additional predictive information. It is physiologically plausible that P_{aCO₂}, as a critical determinant of respiratory drive, and Riker Agitation-Sedation score, measuring the depth of sedation, would have additional informative value regarding the amount of diaphragm thickening. P_{aO₂}, F_{IO₂}, and PEEP, on the other hand, did not contain more discriminative information than a random variable. Altogether, the inclusion of all these additional variables into the models only marginally improved model performance.

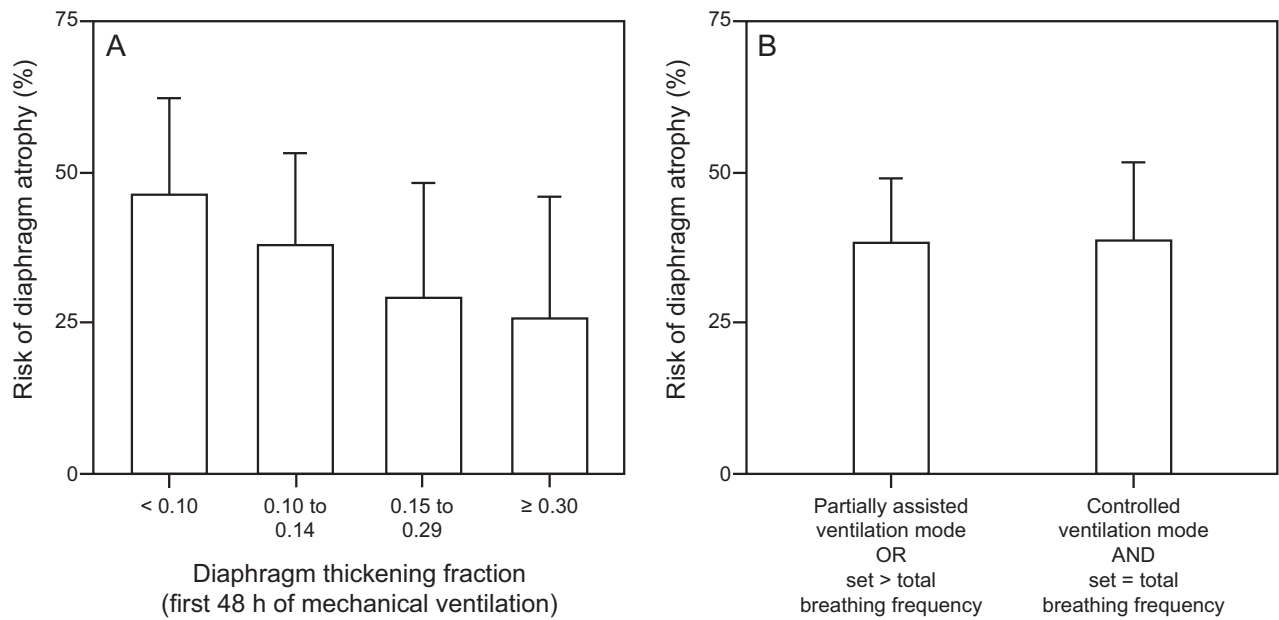


Fig. 3. The first measurement of diaphragm thickening fraction obtained within 48 h of information provided information about the risk of diaphragm atrophy (A), whereas the presence of patient-triggered breaths (assisted ventilation or assist-controlled mode with total > than the set breathing frequency) did not (B).

Based on the low sensitivity and accuracy of the models, our findings call into question the widely held assumption that the presence or absence of spontaneous breathing can be reliably inferred from ventilator settings and other routinely available clinical variables. Previous studies have reported that diaphragmatic effort is highly variable during mechanical ventilation and is only minimally affected by the ventilator mode.^{15,27,28} Indeed, patient work of breathing may be substantial in continuous mandatory ventilation modes.²⁹ The patient's breathing frequency has been identified as a marker for detecting ventilatory overassistance during pressure support ventilation.³⁰ However, the magnitude of diaphragmatic effort is poorly correlated with breathing frequency during ventilator support.^{8,31} Many patients on partially assisted modes (in which every breath is triggered) exhibit minimal diaphragmatic effort. Given the sensitivity of ventilator triggering, triggering by low levels of accessory muscle activation (or from autotriggering) would require little to no diaphragmatic effort, perpetuating the risk of diaphragm atrophy under continuous mandatory ventilation. Thus, our findings align well with previous literature and provide stronger evidence that assessment of diaphragmatic effort requires direct patient monitoring.

Significant diaphragmatic effort in the absence of triggered breaths (ie, with equal set and total breathing frequency) may also result from reverse-triggering.³² The presence of elevated thickening fraction in a substantial proportion of patients with equal set and total breathing frequency suggests that reverse-triggering may be common

during controlled mechanical ventilation. We speculate that the phenomenon of reverse-triggering, which may be quite prevalent during controlled mechanical ventilation, may account for the substantial lack of sensitivity of total versus set breathing frequency for the presence of diaphragm thickening.

The inability of routinely available clinical variables to stratify the risk of diaphragm atrophy, together with the utility of a direct assessment of diaphragm contractility by ultrasound to stratify this risk, suggests that direct monitoring of respiratory effort (whether by ultrasound or other means) provides valuable additional information to the clinician. In addition to assessing the risk of diaphragm atrophy from inactivity, respiratory effort monitoring can detect patient-ventilator asynchrony (including reverse-triggering) and elevated patient respiratory efforts associated with a possible risk of patient self-inflicted lung injury. Although diaphragm thickening fraction is an imperfect surrogate for diaphragm contractility, given that diaphragm thickening is only moderately correlated with diaphragm force generation, this value provided useful information about the risk of atrophy. Other monitoring techniques that provide more precise estimates of diaphragmatic contractility (eg, transdiaphragmatic pressure, electrical activity of the diaphragm) might stratify the risk of diaphragm atrophy with even greater discrimination.^{33,34}

Our study has several limitations. First, diaphragmatic effort was indirectly estimated by ultrasound diaphragm thickening fraction rather than by direct measurements requiring esophageal and gastric manometry to measure

trans-diaphragmatic pressure. For this secondary analysis of a prospective cohort study, we relied on available measurements in the dataset recorded once daily. Currently, clinicians have an array of techniques for monitoring diaphragmatic effort at their disposal, including esophageal pressure,¹⁴ electrical activity of the diaphragm,³⁵ and less invasive techniques such as airway occlusion pressure ($P_{0.1}$),²⁸ expiratory occlusion pressure (P_{oc}),³⁶ and diaphragm thickening on ultrasound.^{35,37} While some of these measurements are readily available, they are not yet routinely measured in clinical practice in most centers, and clinicians often rely on the mode of ventilation and breathing frequency to assess for the presence of respiratory effort or spontaneous breathing.³⁸ The ultrasound technique has been shown to reflect diaphragm contractility during mechanical ventilation.^{8,37,39} Ultrasound is highly feasible in comparison to traditional manometry and therefore facilitates the routine assessment of diaphragm structure and function in large clinical cohort studies. Because the clinically relevant threshold value of diaphragm thickening fraction leading to the development of diaphragm atrophy or aggravating lung injury is uncertain, we conducted a sensitivity analysis to investigate a range of thickening fraction thresholds in addition to the a priori specified cutoff value. Further work, however, is required to evaluate the optimal level of diaphragm thickening that can be safely tolerated in mechanically ventilated patients. However, recent data suggest that a thickening fraction in the range of 15–30% (similar to healthy subjects breathing at rest) may be optimal.¹¹

Importantly, the interobserver variability of diaphragm ultrasound measurements for thickening fraction ranges between 16–17%,¹⁵ which is within the range of cutoffs we used in our models. This variability in the reference standard might contribute in part to the poor predictive performance of the models we tested. Nevertheless, ultrasound measurements of diaphragm thickening fraction have repeatedly been shown to predict readiness for liberation from mechanical ventilation,³⁷ the rate of change in diaphragm thickness during critical illness,³⁹ and the risk of prolonged ventilation and ICU admission,⁴⁰ despite this interobserver variability.

Second, not all clinical variables could be recorded simultaneously for logistical reasons (eg, blood gases were not always recorded simultaneously with the ultrasound measurements). The variables were recorded within a 2-h range before or after image acquisition, which could impair the performance of our models.

Conclusions

In summary, diaphragm contractility and the risk of diaphragm atrophy cannot be reliably inferred from ventilator mode, breathing frequency, or other clinical variables

readily available at the bedside or in electronic health record systems, irrespective of the modeling strategy. To assess the risk of diaphragm atrophy or the presence of diaphragmatic contractility during mechanical ventilation, clinicians and researchers should employ monitoring techniques that directly assess diaphragm contractility.

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