ORIGINAL ARTICLE

Mechanical Ventilation–induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes

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Abstract

Rationale: Diaphragm dysfunction worsens outcomes in mechanically ventilated patients, but the clinical impact of potentially preventable changes in diaphragm structure and function caused by mechanical ventilation is unknown.

Objectives: To determine whether diaphragm atrophy developing during mechanical ventilation leads to prolonged ventilation.

Methods: Diaphragm thickness was measured daily by ultrasound in adults requiring invasive mechanical ventilation; inspiratory effort was assessed by thickening fraction. The primary outcome was time to liberation from ventilation. Secondary outcomes included complications (reintubation, tracheostomy, prolonged ventilation, or death). Associations were adjusted for age, severity of illness, sepsis, sedation, neuromuscular blockade, and comorbidity.

Measurements and Main Results: Of 211 patients enrolled, 191 had two or more diaphragm thickness measurements. Thickness decreased more than 10% in 78 patients (41%) by median Day 4 (interquartile range, 3–5). Development of decreased thickness was associated with a lower daily probability of liberation from ventilation (adjusted hazard ratio, 0.69; 95% confidence interval [CI], 0.54–0.87; per 10% decrease), prolonged ICU admission (adjusted duration ratio, 1.71; 95% CI, 1.29–2.27), and a higher risk of complications (adjusted odds ratio, 3.00; 95% CI, 1.34–6.72). Development of increased thickness ($n = 47$; 24%) also predicted prolonged ventilation (adjusted duration ratio, 1.38; 95% CI, 1.00–1.90). Decreasing thickness was related to abnormally low inspiratory effort; increasing thickness was related to excessive effort. Patients with thickening fraction between 15% and 30% (similar to breathing at rest) during the first 3 days had the shortest duration of ventilation.

Conclusions: Diaphragm atrophy developing during mechanical ventilation strongly impacts clinical outcomes. Targeting an inspiratory effort level similar to that of healthy subjects at rest might accelerate liberation from ventilation.

Keywords: artificial respiration; weaning; diaphragm; acute respiratory failure

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At a Glance Commentary

Scientific Knowledge on the Subject: Diaphragm dysfunction is associated with prolonged ventilator-dependence and poor outcomes in critically ill patients. Many factors contribute to diaphragm dysfunction including diaphragm atrophy caused by mechanical ventilation. However, the specific impact of diaphragm atrophy caused by ventilation on clinical outcomes is unknown.

What This Study Adds to the Field: Diaphragm atrophy developing during mechanical ventilation was specifically associated with substantial delays in liberation from mechanical ventilation and a significant increase in the risk of serious complications including reintubation, tracheostomy, and prolonged ventilation. When patients were breathing spontaneously at a level of inspiratory effort (assessed by diaphragm thickening fraction on ultrasound) similar to that seen in healthy subjects at rest, changes in diaphragm thickness were significantly attenuated and the duration of ventilation, duration of ICU admission, and risk of complications were minimized.

Mechanical ventilation is a life-saving intervention used worldwide in an estimated 15 million patients annually (1). Although many patients who recover from their initial critical illness are readily liberated from the ventilator, approximately 30% require prolonged weaning (2). Prolonged mechanical ventilation is associated with an increased risk of death (2, 3), poor long-term functional outcomes (3–5), and markedly higher healthcare costs (6).

Diaphragm weakness is a leading cause of difficult weaning from mechanical ventilation (7–9). A wide variety of factors can give rise to acute or chronic diaphragm weakness in critically ill patients, including preadmission injury, sepsis, medications, and multiorgan dysfunction syndrome (10). Mechanical ventilation *per se* can cause acute diaphragm injury and weakness (11–14). Ventilatory assistance suppressing inspiratory effort results in rapid diaphragm atrophy (13, 15–17). Diaphragm atrophy has now been documented repeatedly in clinical studies and many patients are affected: our previous prospective study found that diaphragm thickness decreased rapidly following intubation in nearly 50% of ventilated patients (16). Conversely, insufficient ventilatory support may fail to adequately unload the respiratory muscles, potentially resulting in load-induced diaphragmatic inflammation and injury (18–20).

It remains uncertain whether the changes in the diaphragm specifically caused by mechanical ventilation significantly impact clinical outcomes. Multiple studies have shown that diaphragm weakness predicts prolonged ventilator dependence and poor clinical outcomes (7–9, 21, 22). However, such diaphragm weakness reflects the global functional impact of all causes of diaphragm dysfunction in critically ill patients (ICU-acquired dysfunction) (21) and not the specific effect of mechanical ventilation. In fact, two-thirds of ventilated patients exhibit diaphragm weakness at the time of ICU admission before any effect of mechanical ventilation (10) and some patients actually demonstrate improvements in diaphragm function during the early course of ventilation (21). Therefore, the specific effect of diaphragm atrophy and injury caused by ventilation on clinical outcomes remains unknown. Indeed, one recent small study found no relationship between changes in diaphragm thickness and extubation outcome (23). The potential improvement in outcome that might be obtained by preventing diaphragm atrophy caused by ventilation is therefore also uncertain.

To establish the impact of diaphragm injury resulting from ventilation on clinical outcomes, we undertook to examine prospectively whether ventilation-induced changes in diaphragm thickness (T_{di}) ascertained by ultrasound (24) were associated with prolonged ventilator dependence and related complications including reintubation, tracheostomy, or death. Because previous observations suggest that increases in T_{di} during ventilation might indicate load-induced diaphragm injury (16), we evaluated the effect of both decreases and increases in T_{di} on the risk of prolonged ventilator dependence. Finally, given that the rate of decrease or increase in T_{di} varied with diaphragm thickening fraction (a surrogate measure of inspiratory effort) in our prior study (16), we examined whether mean thickening fraction over the first 3 days of ventilation predicted the duration of ventilation, hypothesizing *a priori* that the duration of ventilation would be lowest at an intermediate level (i.e., a J-shaped curve). Some of the results of this study were previously reported in the form of an abstract (25).

Methods

Study Population and Setting

Patients were enrolled in two closely related cohorts: a large prospective study involving daily measurements of diaphragm thickness (cohort A, $n = 191$), and a smaller prospective study involving daily measurements of diaphragm thickness together with continuous monitoring of diaphragm electrical activity by crural electromyography (cohort B, $n = 25$) (*see* Table E1 in the online supplement for details). In cohort A, patients were included if they were ventilated for fewer than 36 hours (the first 53 patients were enrolled up to 72 hours after intubation; the protocol was then modified to limit the time period for enrolment to 36 h). Patients were excluded if they were expected to be liberated within 24 hours of screening or if they had received invasive ventilation for greater than 48 hours in the previous 6 months. Eligible patients were identified by regular screening (Monday to Thursday). Approximately half of the patients ($n = 122$) were included in our previous report on changes in diaphragm thickness during ventilation (16).

In cohort B, patients were included if they were intubated for less than 36 hours because of acute brain injury, acute respiratory distress syndrome, septic shock, or pneumonia. Patients were excluded if they were deemed unlikely to remain on the ventilator for at least 7 days or if there were clinical conditions that interfered with reliable crural EMG measurements.

Informed consent was obtained from substitute decision makers before enrolment. For both cohorts, if no substitute decision maker was available, eligible patients were enrolled by deferred consent and consent for the use of study data was obtained from study participants once they regained capacity. The Research Ethics Boards at University Health Network (#12-5582, #13-5953) and St. Michael's Hospital

(#14-229) approved the study protocols. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting cohort studies (26).

Measurement of Diaphragm Thickness, Inspiratory Effort, and Diaphragm Function

Right T_{di} was measured using a high-frequency (13 MHz) linear array transducer in the zone of apposition between the anterior and midaxillary lines at the level of the 9th or 10th intercostal space; measurements were made daily on weekdays until extubation or Day 14 of invasive mechanical ventilation using a technique we previously validated (27). Inspiratory effort was indirectly quantified daily by measuring diaphragm thickening fraction on ultrasound. In cohort B, inspiratory effort was also indirectly quantified by hourly recordings of diaphragm electrical activity (EA_{di}).

Diaphragm function was assessed on the day of extubation or after 1 week of mechanical ventilation once patients were awake and breathing spontaneously. Diaphragm function was quantified by measuring maximal diaphragm thickening fraction during coached maximal inspiratory efforts under continuous positive airway pressure mode (9, 28). Severe diaphragm dysfunction was defined as maximal thickening less than 20% (29). Measurement techniques are detailed in the online supplement.

Patient Characteristics and Clinical Outcomes

Demographic data, comorbidities, admission diagnosis, and severity of illness (Simplified Acute Physiology Score [SAPS] II) (30) were collected at baseline. Ventilator settings, arterial blood gas tensions, criteria for sepsis (31), Riker Sedation-Agitation Scale (SAS) (32), exposure to neuromuscular blockade, and Sequential Organ Failure Assessment (SOFA) (33) scores were recorded daily.

Patients were assessed for the following events until hospital discharge: extubation, reintubation, tracheostomy, ICU discharge, hospital discharge, and death. Liberation from ventilation was defined as separation from ventilation (extubation or tracheostomy mask breathing for 24 h) without resumption of invasive ventilatory support during the index ICU admission. Our primary endpoint was the time from intubation until liberation from ventilation (or death). Ventilator-free days were computed to 60 days; patients who required more than 60 days of ventilatory support or who died on or before Day 60 were assigned 0. Complications of acute respiratory failure were defined as the occurrence of any of the following events: reintubation, tracheostomy, prolonged ventilation (>14 d), or death (3, 34). Investigators responsible for analysis of diaphragm ultrasound images were blinded to patient outcomes. Clinicians responsible for medical decisions including weaning were not aware of ultrasound measurement data. Routine weaning practices (described in the online supplement) were similar across participating ICUs but were not uniformly standardized for the study.

Statistical Analysis

The analysis plan, developed and executed in collaboration with a senior biostatistician (G.T.), is detailed in the online supplement. Patients with only one measurement of T_{di} were excluded from the analysis.

The primary analysis (time-varying exposure approach) examined the association between T_{di} (as a percentage of the initial T_{di}) on any given day (time-varying covariate) and the hazard of liberation from ventilation on that day using a Cox proportional hazards model of the time to liberation from ventilation. This approach was selected as the primary analysis to avoid potential time-dependent confounding and immortal time bias related to variation in the timing of changes in T_{di}. The model treated death as a censored event and adjusted for age, baseline SAPS II, presence of sepsis, SOFA score, baseline Pa_{O_2}/FI_{O_2}, SAS score, use of neuromuscular blockade in the first 48 hours of ventilation, initial value of T_{di}, and the presence of at least one chronic comorbidity. We conducted sensitivity analyses to assess whether the model was robust to varying conditions (*see* online supplement for rationale and details of these analyses).

In secondary analyses, we used an alternate analytical framework (classification-based approach) to assess the relationship between the initial change in T_{di} and clinical outcomes. Under this framework, patients were classified as having diaphragm atrophy if T_{di} decreased by at least 10% from baseline. Patients were classified as having increased T_{di} if T_{di} increased by at least 10% from baseline. Subjects without a 10% increase or decrease in T_{di} over the first week of ventilation were classified as unchanged. To mitigate against time-dependent confounding, patients were classified on the first day that the percentage change in T_{di} exceeded 10% of baseline T_{di} (*see* Figure E1). This threshold was selected in accordance with our previous study (16), based on the measurement resolution of the ultrasound technique (27), and in accordance with previous studies of myopathy in critical illness (35).

The association between changes in T_{di} and the risk of severe diaphragm dysfunction was evaluated using bivariate logistic regression. The effects of patient inspiratory effort, ventilator settings, and fluid balance on changes in diaphragm thickness over time were examined using linear mixed effects regression modeling. To conduct the primary analysis, our estimated sample size requirement was 210 subjects. All statistical analyses were conducted using R version 3.3.2 (www.R-project.org).

Results

Study Cohort

Between May 2013 and January 2016, a total of 222 patients were enrolled; of these, 191 patients had at least two T_{di} measurements and were available for the primary analysis (*see* Figure E2). Demographic and clinical characteristics of enrolled patients are shown in Table 1. Forty-five patients (21%) died without being liberated from the ventilator and 29 (14%) were liberated from ventilation but died in hospital. Over half of patients (56%) experienced at least one complication of acute respiratory failure (Table 2).

Development of Decreased Diaphragm Thickness and Clinical Outcome

In the primary (time-varying exposure) analysis, the daily probability of liberation from mechanical ventilation was significantly lower on days when T_{di} was decreased from baseline (Figure 1) (adjusted hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.54–0.87; per 10% decrease in T_{di}). The daily probability of liberation was also lower with increased

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristics	Study Population (*n* = 191)	Patients at Risk of Change in Diaphragm Thickness (≥2 Diaphragm Thickness Measurements) (*n* = 191)			*P* Value
		≥10% Decrease in Thickness (*n* = 78; 41%)	<10% Change in Thickness (*n* = 66; 35%)	≥10% Increase in Thickness (*n* = 47; 24%)	
Age, yr, mean (SD)	59 (15)	59 (16)	61 (13)	57 (16)	0.32
Female sex, *n* (%)	74 (39)	33 (42)	24 (36)	16 (34)	0.61
Body mass index, kg/m^2	26.0 (22.3–30.1)	24.1 (21.3–28.5)	27.6 (22.8–31.2)	26.4 (23.4–30.1)	0.07
SAPS II	48 (34–58)	46 (35–57)	50 (36–58)	45 (33–64)	0.63
SOFA, mean over first 72 h	10 (8–14)	10 (8–14)	10 (7–13)	11 (8–15)	0.35
Primary cause of acute respiratory failure, *n* (%)					0.37
Respiratory	60 (31)	27 (35)	22 (33)	11 (23)	
Cardiovascular	26 (14)	11 (14)	9 (14)	6 (13)	
Sepsis (nonpulmonary)	26 (14)	10 (13)	12 (18)	4 (9)	
Neurologic	18 (9)	5 (6)	5 (8)	7 (15)	
Postoperative	17 (9)	5 (6)	5 (8)	7 (15)	
Post-transplantation	29 (15)	14 (18)	10 (15)	5 (11)	
Other (hepatic, renal, intoxication)	16 (8)	6 (8)	3 (5)	7 (15)	
Sepsis-3 criteria present in first 48 h, *n* (%)	170 (89)	70 (90)	59 (89)	40 (85)	0.71
Comorbidity at baseline (≥1), *n* (%)	121 (63)	46 (59)	47 (71)	28 (60)	0.26
Baseline $Pa_{O_2}/F_{I_{O_2}}$, mm Hg	159 (105–233)	154 (115–215)	160 (96–242)	166 (105–212)	0.85
Initial diaphragm thickness, mm	2.3 (2.0–2.6)	2.6 (2.2–3.0)	2.3 (2.0–2.4)	2.0 (1.7–2.3)	<0.01
Cumulative fluid balance on Day 3 of ventilation, L	4.6 (2.1–8.1)	4.7 (2.1–8.7)	3.8 (1.7–7.3)	5.7 (3.2–8.4)	0.17
Number of measurements before classification	2 (2–3)	2 (2–3)	3 (2–4)	2 (2–3)	0.16
Days of ventilation before classification into thickness change group	4 (3–5)	4 (3–5)	4 (3–5)	3 (3–4)	0.13
Baseline ventilator settings					
Mode of ventilation, *n* (%)					0.28
Controlled	156 (81)	67 (86)	53 (80)	35 (74)	
Partially assisted	36 (19)	11 (14)	13 (20)	12 (26)	
V_T, ml/kg PBW	6.6 (5.8–7.7)	6.4 (5.4–7.6)	7.1 (6.2–8.1)	6.4 (5.7–7)	0.02
Peak airway pressure, cm H_2O	20 (14–26)	21 (16–25)	20 (13–27)	20 (15–26)	0.99
Set inspiratory pressure above PEEP, cm H_2O*	12 (6–15)	12 (8–16)	12 (8–15)	11 (5–15)	0.50
PEEP, cm H_2O	8 (5–10)	8 (5–10)	8 (5–10)	8 (5–10)	0.97
Frequency, min^{-1}	21 (18–25)	22 (19–26)	21 (18–25)	21 (18–24)	0.79
$F_{I_{O_2}}$	0.45 (0.35–0.5)	0.44 (0.39–0.5)	0.45 (0.35–0.55)	0.45 (0.35–0.52)	0.93
Arterial blood gas tensions					
pH	7.37 (7.33–7.41)	7.37 (7.33–7.42)	7.38 (7.33–7.41)	7.37 (7.33–7.42)	0.99
Pa_{CO_2}	40 (34–47)	41 (36–49)	41 (34–46)	38 (34–44)	0.13
Pa_{O_2}	97 (80–115)	103 (81–113)	98 (80–122)	88 (80–108)	0.55

Definition of abbreviations: PBW = predicted body weight; PEEP = positive end-expiratory pressure; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.
All distributions are reported as median (interquartile range) unless otherwise noted.
*Set inspiratory pressure above PEEP = peak airway pressure − PEEP.

SOFA, decreased SAS, and lower initial T_{di} (*see* Table E3). In sensitivity analyses of the primary model, similar effects were obtained when the analysis was restricted to patients in cohort A (adjusted HR, 0.63; 95% CI, 0.48–0.81; per 10% decrease in T_{di}), after excluding patients enrolled on Day 3 of ventilation (adjusted HR, 0.73; 95% CI, 0.54–0.98), after removing initial T_{di} from the model (adjusted HR, 0.78; 95% CI, 0.62–0.98), or after excluding patients requiring ventilation for fewer than 7 days (adjusted HR, 0.75; 95% CI, 0.55–1.01).

In the alternate (classification-based) analysis framework, patients were classified according to their initial change in T_{di} during the first week of ventilation. Diaphragm atrophy (defined as >10% decrease in T_{di}) developed in 78 patients (41%) within a few days of intubation (median, Day 4; interquartile range, 3–5) (Table 1). After accounting for the competing risk of death, the risk of remaining on ventilation for at least 3 weeks was significantly higher in patients with diaphragm atrophy (Figure 2) (39% vs. 22%; $P = 0.008$). The risk of death was not significantly different ($P = 0.46$). The development of diaphragm atrophy was also associated with fewer ventilator-free

Table 2. Clinical Outcomes in Relation to Changes in Diaphragm Thickness during Mechanical Ventilation

Outcome	Initial Change in Diaphragm Thickness during First Week of Ventilation Patients with ⩾2 Measurements (*n* = *191*)			Statistical Comparisons Adjusted Count Ratio or Adjusted Odds Ratio (95% CI)*	
	⩾10% Decrease in Thickness (*n* = *78; 41%*)	<10% Change in Thickness (*n* = *66; 35%*)	⩾10% Increase in Thickness (*n* = *47; 24%*)	⩾10% Decrease in Thickness vs. <10% Change in Thickness	⩾10% Increase in Thickness vs. <10% Change in Thickness
Ventilator-free days to Day 60	46 (0–53)	51 (0–55)	37 (0–51)	0.77 (0.59–1.00)	0.91 (0.67–1.22)
Duration of ventilation (in ICU survivors), d	9 (5–17)†	5 (4–9)	10 (6–22)†	1.69 (1.28–2.24)	1.38 (1.00–1.90)
Duration of ICU admission (in ICU survivors), d	12.5 (7–21)†	8 (5–12)	14 (7–24)†	1.71 (1.29–2.27)	1.31 (0.94–1.83)
Duration of hospitalization (in hospital survivors), d	29 (16–58)†	22 (11–51)	30 (17–65)	1.44 (1.01–2.05)	1.23 (0.71–1.60)
Complications of acute respiratory failure, *n* (%)‡	49 (64)†	31 (48)	31 (67)†	3.00 (1.34–6.72)	1.84 (0.77–4.43)
Reintubation, *n* (%)	16 (21)†	5 (8)	12 (26)†	3.55 (1.14–11.05)	3.24 (0.97–10.88)
Tracheostomy, *n* (%)	20 (26)†	7 (11)	11 (23)	3.58 (1.29–9.97)	2.11 (0.66–6.70)
Mechanical ventilation >14 d, *n* (%)	27 (35)†	14 (21)	20 (43)†	2.97 (1.26–6.97)	2.16 (0.87–5.40)
Readmission to ICU during same hospital admission, *n* (%)	5 (7)	9 (15)	9 (20)	0.78 (0.21–2.84)	2.32 (0.70–7.67)
Death in ICU, *n* (%)	19 (24)	12 (18)	11 (23)	1.55 (0.61–3.95)	1.28 (0.45–3.65)
Death in hospital, *n* (%)	28 (37)	21 (3)	17 (37)	1.66 (0.73–3.76)	0.94 (0.38–2.34)

Definition of abbreviations: CI = confidence interval; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.
All distributions are reported as median (interquartile range) unless otherwise noted.
*Adjusted for age, SAPS II score, baseline Riker Sedation Agitation Scale score, exposure to neuromuscular blockade during first week of ventilation, presence of sepsis at baseline, baseline SOFA, baseline $Pa_{O_2}/F_{I_{O_2}}$ ratio, initial diaphragm thickness, and presence of any chronic comorbidity.
†$P < 0.05$ for difference in outcome in comparison with patients with <10% change in diaphragm thickness from baseline in bivariate (unadjusted) analysis.
‡Complications of acute respiratory failure include reintubation, tracheostomy, duration of ventilation >14 d, or death in hospital.

days at Day 60, a prolonged duration of ventilation, prolonged ICU admission, and a higher risk of complications including reintubation and tracheostomy (Table 2).

Development of Increased Diaphragm Thickness and Clinical Outcome

In the primary (time-varying exposure) analysis framework, there was a nonsignificant trend toward a lower daily probability of liberation on days when T_{di} was increased from baseline (Figure 1) (adjusted HR, 0.81; 95% CI, 0.62–1.06; per 10% increase in T_{di}). Under the alternate (classification-based) analysis framework, 47 patients (25%) developed increased T_{di} during the first week of ventilation. After accounting for the competing risk of death, the risk of requiring ventilation for at least 3 weeks was significantly higher in patients with increased T_{di} (Figure 2) (43% vs. 22%; $P = 0.006$). The risk of death was not significantly different ($P = 0.73$). The development of increased T_{di} was also associated with prolonged ICU admission and a higher risk of complications, although these associations were not significant after multivariable adjustment (Table 2).

Changes in Diaphragm Thickness and Diaphragm Function

To substantiate the mechanistic basis for the relationship between changes in T_{di} and outcome, diaphragm function (measured by maximal diaphragm thickening fraction) was evaluated in 84 patients after 7 (interquartile range, 5–9) days of ventilation (*see* Figure E3). In comparison with patients with unchanged T_{di} ($n = 51$), patients with greater than 10% decrease in T_{di} ($n = 23$) exhibited lower maximal thickening (26 ± 17% vs. 38 ± 24%; $P = 0.03$) (*see* Figure E4) and more frequent severely reduced maximal thickening (48% vs. 22%; $P = 0.03$) (*see* Figure E4). Patients with increased T_{di} ($n = 8$) had similarly reduced maximal thickening and increased frequency of severely reduced maximal thickening, but these differences did not reach statistical significance (30 ± 22% vs. 38 ± 24%, $P = 0.70$ and 38% vs. 22%, $P = 0.61$, respectively) (*see* Figure E4).

Effect of Inspiratory Effort and Ventilator Settings on Diaphragm Thickness

T_{di} tended to decrease over time at low diaphragm thickening fraction levels and increase over time at high thickening fraction levels (*see* Figure E5) ($P < 0.001$ for interaction between thickening fraction and time). Similarly, T_{di} tended to decrease at low EA_{di} levels and increase at high EA_{di} levels (*see* Figure E5) ($P = 0.02$ for interaction between mean daily EA_{di} and time). Consistent with these findings, T_{di} declined more rapidly with higher levels of ventilator assistance (*see* Figure E5). In similar models, T_{di} was unaffected by SOFA score, SAS score, the presence of sepsis, fluid balance, or the set positive end-expiratory pressure level (Table 1).

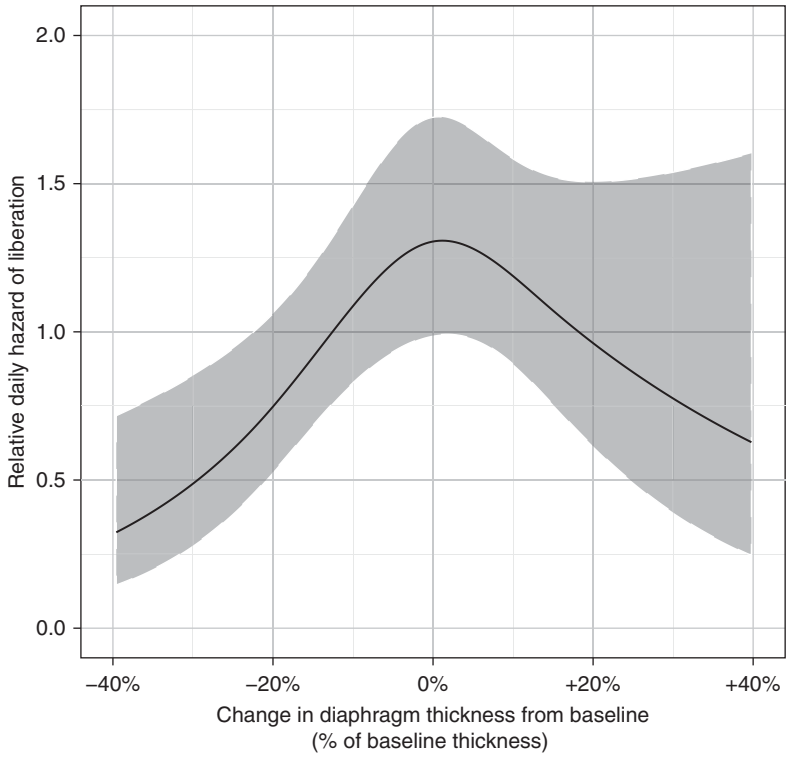

Figure 1. The probability of liberation from mechanical ventilation on any given day is related to the magnitude of change in diaphragm thickness from baseline. The probability of liberation was lower on days when diaphragm thickness was decreased from baseline (adjusted hazard ratio, 0.69; 95% confidence interval [CI], 0.54–0.87; per 10% decrease in thickness below baseline). The probability of liberation was not significantly lower on days when diaphragm thickness was increased from baseline, although a similar trend was observed (adjusted hazard ratio, 0.81; 95% CI, 0.62–1.06; per 10% increase in thickness above baseline). Gray shaded areas represent 95% CIs for estimated relative hazards.

Inspiratory Effort and Duration of Ventilation

Given the foregoing results, we hypothesized that intermediate thickening fraction levels would be associated with the shortest duration of ventilation. In a *post hoc* exploratory analysis, duration of ventilation was lowest in patients with intermediate mean thickening fraction values between 15% and 30% over the first 3 days of ventilation (Figure 3). ICU length-of-stay and the risk of complications were also lowest in patients with this range of inspiratory effort (*see* Figure E6).

Discussion

The central finding of this study is that the progressive development of diaphragm atrophy during mechanical ventilation is associated with prolonged mechanical ventilation and ICU admission and an increased risk of complications of acute respiratory failure. We also found that rapid early increases in diaphragm thickness predicted prolonged ventilation, raising the possibility of clinically significant diaphragm injury caused by insufficient respiratory muscle unloading during ventilation (*see* discussion below). The rate and direction of change in diaphragm thickness varied with the level of inspiratory effort, either assessed by ultrasound or quantified by diaphragm electrical activity; diaphragm thickness was relatively stable at intermediate levels of inspiratory effort. We also report for the first time that the average level of diaphragm thickening fraction (an indirect measure of inspiratory effort) during the early course of ventilation is associated with the duration of ventilation: subjects with thickening fraction levels similar to those observed in healthy subjects at rest during the first 3 days of ventilation had the shortest duration of mechanical ventilation and ICU admission, whereas patients with either relatively lower or higher thickening fraction levels had a longer duration of ventilation and ICU admission (and a higher risk of complications). Taken together, these findings strongly suggest that changes in diaphragm structure and function caused by mechanical ventilation are an important and potentially avoidable determinant of poor outcomes.

Several considerations support the hypothesis that diaphragm atrophy may be causally related to the risk of prolonged ventilation (36). First, there is a strong biologic rationale for causation given the abundant experimental evidence of diaphragm atrophy caused by ventilation. Experiments in a range of animal models have demonstrated that ventilation causes acute disuse atrophy, sarcomeric disarray, and contractile dysfunction in the diaphragm (11, 15, 17, 37). Diaphragm atrophy has been repeatedly demonstrated in mechanically ventilated patients by histology (13, 14, 38), computed tomography scanning (39), and ultrasound (16, 40–42).

Second, diaphragm atrophy and injury caused by mechanical ventilation would be expected to impact clinical outcomes by impairing diaphragm function (the putative causal pathway to poor outcome). Diaphragm dysfunction has been strongly linked to difficult weaning and poor clinical outcomes in several studies (7, 9, 22). Building on this work, we found that the development of diaphragm atrophy during ventilation was associated with impaired diaphragm function.

Third, there was a consistent dose–response relationship between diaphragm atrophy and clinical outcomes across multiple endpoints even after multivariable adjustment.

Fourth, we found that inspiratory effort (the main modulator of changes in diaphragm thickness) predicted the duration of ventilation in a nonlinear relation as predicted from the relationship between inspiratory effort and changes in diaphragm thickness. This finding strengthens the argument in support of a causal pathway linking the effect of ventilation on inspiratory effort to clinical outcomes and provides a basis to conceive of approaches to muscle-protective ventilation. Nevertheless, our findings cannot definitively confirm causality, which can only be demonstrated in the context of a randomized study of interventions known to prevent deleterious changes in the diaphragm during mechanical ventilation.

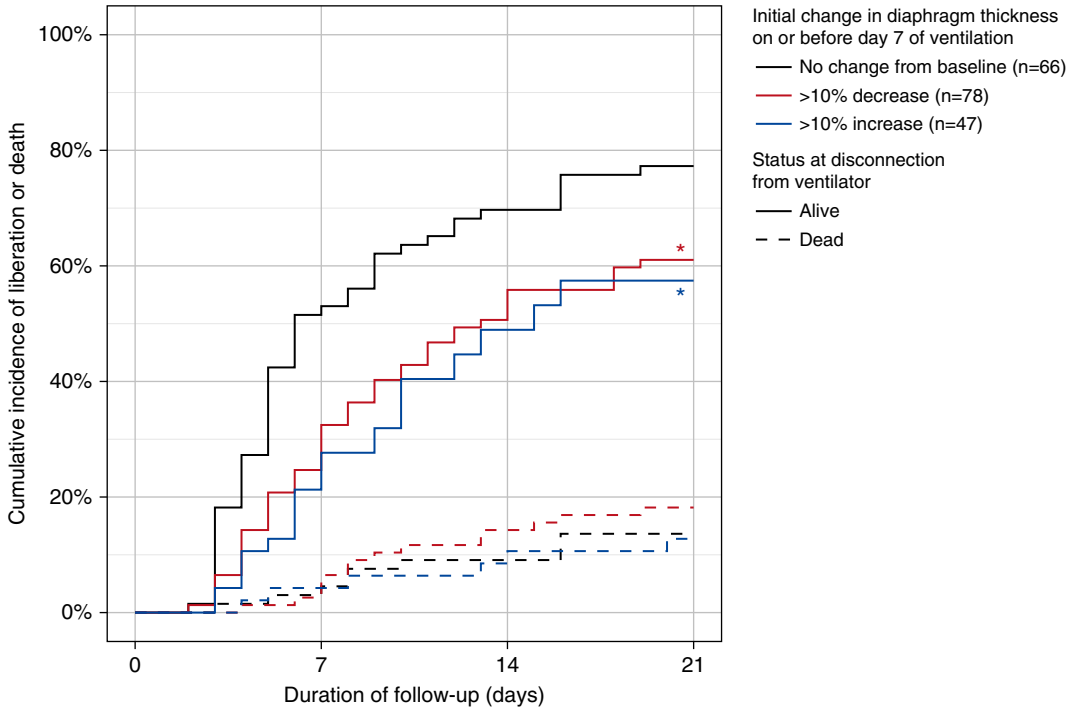

Figure 2. Changes in diaphragm thickness during the first week of ventilation predict an increased risk of prolonged mechanical ventilation. Patients are disconnected from the ventilator because of either liberation (solid lines) or death (dashed lines). Compared with patients without changes in diaphragm thickness, those in whom diaphragm thickness decreased or increased during the first week of ventilation had a significantly lower cumulative incidence of liberation from the ventilator at Day 21 (*$P = 0.008$ and $P = 0.006$, respectively). The cumulative incidence of death was not significantly different between groups at Day 21 ($P = 0.46$ and $P = 0.90$, respectively).

Increases in T_{di} during ventilation also predicted prolonged ventilation and increased complications. The histologic basis of increases in T_{di} during ventilation has not been characterized. Increased T_{di} may represent the accumulation of tissue edema related to resuscitation, although changes in T_{di} were unrelated to fluid balance in our study and in a previous report (42). Increases in T_{di} were associated with relatively high levels of inspiratory effort, raising the possibility that such changes reflect load-induced muscle injury. Load-induced skeletal muscle injury is known to induce acute increases in muscle thickness and cross-sectional area on ultrasound (43). The diaphragm is vulnerable to load-induced injury (18), particularly when sensitized to mechanical stress by endotoxemia and muscular inflammation (20). Suppressing inspiratory effort by mechanical ventilation has been shown to mitigate load-induced diaphragm injury and inflammation (19, 20); failure to unload the respiratory muscles during ventilation may increase the risk of load-induced injury. Histologic studies of diaphragm specimens obtained from mechanically ventilated patients have demonstrated features consistent with load-induced injury, including sarcomere disruption (14) and inflammation (38). This hypothesis merits further investigation.

Our findings suggest that prolonged ventilator-dependence caused by deleterious diaphragmatic changes resulting from ventilation might be potentially mitigated by targeting levels of inspiratory effort during ventilation similar to that of healthy subjects breathing at rest. Previous work has shown that diaphragm inactivity causes diaphragm atrophy, whereas excess inspiratory efforts can exacerbate ventilator-induced lung injury (44) and injure the diaphragm (18). Using two independent methods to indirectly estimate inspiratory effort (diaphragm thickening fraction measurements and diaphragm electrical activity) (27, 45–48), we found that T_{di} tended to decrease at lower inspiratory effort levels and increase at higher inspiratory effort levels, suggesting that some intermediate level may be optimal. Because competing issues of respiratory muscle oxygen consumption and lung injury can modify the safest inspiratory effort level during ventilation (44, 49), the optimal level of patient inspiratory effort during ventilation has been uncertain. In our study, the duration of ventilation was minimized in patients with thickening fraction levels similar to those observed in healthy subjects breathing at rest (50). These data raise the possibility that titrating ventilatory support to maintain this range of inspiratory effort might accelerate liberation from ventilation. This hypothesis of a muscle-protective ventilation strategy requires confirmation in future trials.

This study has limitations. First, despite attempts to account for confounding, observed associations may derive from residual confounding related to unmeasured patient or illness characteristics, so that we cannot definitively conclude a causal effect. To account for immortal time bias in the association between changes in diaphragm thickness and duration of ventilation, we constructed a proportional hazards model where diaphragm thickness was modeled as a time-varying covariate. We also found consistent effects in a sensitivity analysis of patients who remained on the ventilator for at least 7 days.

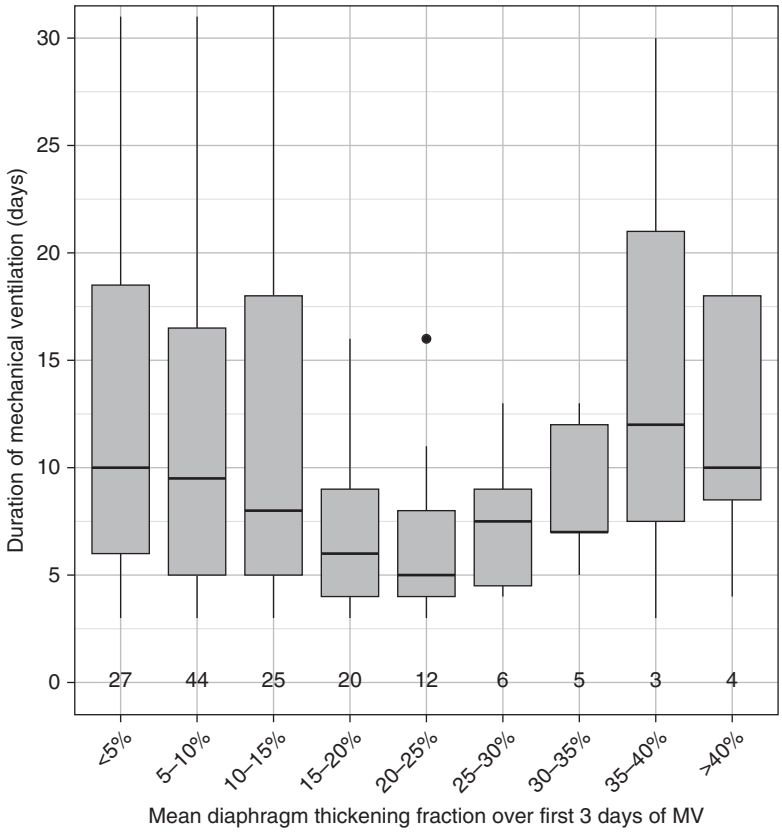

Figure 3. The duration of ventilation varies with the level of inspiratory effort (assessed indirectly by diaphragm thickening fraction) during the early course of ventilation. The study population was divided according to quantiles of the average thickening fraction over the first 3 days of ventilation. The number of patients in each quantile is displayed on the plot. Duration of ventilation was prolonged in patients with either relatively low or relatively high average levels of inspiratory effort over the first 3 days of ventilation ($P = 0.02$ for nonlinear relation). The shortest duration of ventilation was observed in patients with intermediate levels of thickening fraction in the range of 15–30%, similar to values observed during resting quiet breathing in healthy adults (50). After multivariable adjustment, the duration of ventilation remained significantly higher in patients with mean thickening fraction <15% ($n = 94$; adjusted duration ratio, 1.42; 95% confidence interval, 1.08–1.88). Adjusted duration of ventilation was not significantly different in patients with mean thickening fraction >30% ($n = 12$) compared with patients with intermediate thickening fraction of 15–30% ($n = 38$), although the adjusted effect size was similar (adjusted duration ratio, 1.42; 95% confidence interval, 0.87–2.29). The bottom, middle line, and top of the box indicate the 25th, 50th, and 75th percentiles, respectively. The whiskers indicate extremes of the range of values within 1.5 times the interquartile range above or below the 75th or 25th percentiles, respectively. The dot indicates an outlier. MV = mechanical ventilation.

Second, we did not record the use of noninvasive ventilation after extubation and consequently the frequency of noninvasive ventilation for postextubation respiratory distress in our study is uncertain. This is not a routine practice in the ICUs participating in this study and the available evidence suggests that noninvasive ventilation probably merely delays reintubation in patients with postextubation respiratory distress (51, 52).

Third, we have no histologic data correlating with the observed changes in diaphragm thickness. Diaphragm atrophy, however, has been documented repeatedly in clinical studies and animal models (13–15, 38) and decreases in diaphragm thickness were associated with decreased myofiber cross-sectional area in an animal model (37); we believe it reasonable to assume that decreases in diaphragm thickness observed in our study represent atrophy. The histologic basis of increases in diaphragm thickness during ventilation remains uncertain.

Fourth, measurements were not collected on weekends, resulting in some missing values for T_{di} measurements. To mitigate this problem, we did not enroll patients on Fridays. Neither the distribution of changes in T_{di} nor the clinical outcome were related to the day of the week on which the patient was intubated. Consequently, any such missing values would be expected to bias the effect toward the null.

Fifth, quantifying diaphragm function by maximal diaphragm thickening fraction relies on patient volitional effort, potentially limiting measurement reliability in a clinical context where it is sometimes challenging to obtain maximal volitional efforts. Previous studies have shown that maximal thickening is correlated with maximal inspiratory pressure in critically ill patients and predicts weaning trial success (28, 53). We did not record maximal inspiratory pressures or respiratory mechanics; maximal airway pressures also require adequate volitional effort and respiratory mechanics can be challenging to reliably assess in spontaneously breathing patients. Thickening fraction has been correlated with airway pressures obtained by the gold standard technique, twitch magnetic phrenic nerve stimulation (9, 22).

Sixth, we did not measure posthospital outcomes. The importance of patient-centered outcomes including functional status and health-related quality of life is now widely appreciated (54). Prolonged ICU admission has been shown to increase the risk of poor functional outcomes (5, 55); it is therefore possible that changes in diaphragm structure and function during ventilation (strongly associated with prolonged ICU admission in our study) could impact functional recovery in survivors. Future studies should address whether preventing or treating diaphragm atrophy and dysfunction in ventilated patients can improve their long-term functional status.

In summary, the progressive development of diaphragm atrophy during the early course of mechanical ventilation predicts prolonged ventilation and an increased risk of complications of acute respiratory failure. Similar but weaker results were found for increased T_{di}. Efforts to prevent and treat diaphragm atrophy or increased T_{di} may significantly improve outcomes in patients with acute respiratory failure. ■

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