의학박사 학위논문

급성호흡곤란증후군에서 일회호흡량 변동성이 치료 결과에 미치는 영향

The Real-World Tidal Volume Variability is Associated with Treatment Outcomes in the Acute Respiratory Distress Syndrome: A Retrospective Cohort Study

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이 논문을 의학박사 학위 논문으로 제출함

2024년 2월

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ABSTRACT

Background: Excessive spontaneous breathing during mechanical ventilation can lead to patient self-inflicted lung injury. However, clinical data linking spontaneous breathing to treatment outcomes is insufficient. We aimed to evaluate the effect of tidal volume variability on ventilator-free days in mechanically ventilated patients with acute respiratory distress syndrome (ARDS) using high-resolution tidal volume data stored through the patient monitor.

Methods: In this single-center, retrospective cohort study, adult ARDS patients who received mechanical ventilation in our medical intensive care unit between April 2018 and July 2019 were included. Study patients' expiratory tidal volume data during the first 7 days of mechanical ventilation was collected every 2 seconds by the patient monitors. The included patients were dichotomized within each tidal volume stratum into high and low tidal volume variability groups based on the standard deviation of tidal volume values normalized by predicted body weight. The primary outcome was ventilator-free days.

Results: A total of 108 ARDS patients were categorized into the high and low tidal volume variability groups (each 54 patients). The baseline characteristics of the two groups were comparable except for the height (165 ± 8 cm vs 162 ± 7 cm; P = 0.02). The ventilator-free days were significantly fewer in the high tidal volume variability group (0 [IQR, 0−16] days vs. 10 [IQR, 0−21] days; mean difference, -4.5 [95% CI, -8.3−-0.7] days; P = 0.01). After adjusting for age, sex, body mass index, APACHE II score, and baseline PaO_2/FiO_2 ratio, high tidal volume variability was significantly associated with zero ventilator-free days (odds ratio, 3.74; 95% CI, [1.55−9.06]; P = 0.003).

Conclusion: Based on the high-resolution tidal volume data acquired from the patient monitor, high tidal volume variability during the first 7 days of mechanical ventilation in ARDS patients was associated with fewer ventilator-free days.

Keywords: tidal volume variability; spontaneous breathing; patient self-inflicted lung injury; mechanical ventilation; ARDS

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Introduction

Acute respiratory distress syndrome (ARDS) is a condition characterized by acute diffuse inflammatory lung injury, leading to permeability pulmonary edema and respiratory failure due to various causes (1). One of the most effective treatments to improve survival in ARDS is low tidal volume ventilation with 4−8 mL/kg of predicted body weight (PBW) (2). Although the survival benefit of low tidal volume ventilation is well-established through many studies, compliance in real-world practice is as low as 65% (3). Moreover, the mortality rate among ARDS patients remains high (4).

Spontaneous breathing may be one of the factors impeding low tidal volume ventilation (5). During mechanical ventilation, spontaneous breathing can occur due to hypoxia, increased work of breathing, insufficient ventilatory support, pain, or agitation. Spontaneous breathing during mechanical ventilation not only induces patient-ventilator dys-synchrony but also generates a larger tidal volume than intended, which is reflected as tidal volume variability (6, 7). Excessive spontaneous breathing can lead to patient self-inflicted lung injury (8). When the patients are awakened from sedation, new development or deterioration of lung injury is not uncommon in mechanically ventilated patients at risk of ARDS or those already diagnosed with ARDS (9-12). To date, the impact of spontaneous breathing during mechanical ventilation and the resulting tidal volume variability on treatment outcomes of ARDS is not established.

Another issue is the low collection frequency of tidal volume. In real-world practice, the frequency of documenting tidal volume in medical records is at most 24 times a day. Assuming a respiratory rate of 20 breaths per minute, less than 0.1% of the day's tidal volumes would be collected. Therefore, the current data collection methods, either retrospectively based on medical records or prospectively collecting data at set times of the day may be insufficient to assess the influence of tidal volume or its variability caused by spontaneous breathing on treatment outcomes. We hypothesized that higher tidal volume variability would cause lung injury and consequently worse outcomes in patients with ARDS. In this study, we aimed to evaluate the effect of tidal volume variability on ventilator-free days in mechanically ventilated patients with ARDS using high-resolution tidal volume data collected through the patient monitor.

Methods

Study design and patients

This study was a single-center, retrospective cohort study. We included adult (aged 18 or more years old) ARDS patients who received mechanical ventilation in the medical intensive care unit (ICU) of Asan Medical Center, a university-affiliated, tertiary care hospital in Seoul, between April 2018 and July 2019. The diagnosis of ARDS was based on the Berlin definition (1). Patients who received mechanical ventilation for less than 24 hours, those with over 50% of tidal volume data of the first 7 days of mechanical ventilation missing, those with primary outcomes unavailable, those who underwent organ transplantation during their ICU stay, and those who received extracorporeal membrane oxygenation during their ICU stay were excluded. For patients with second or more episodes of mechanical ventilation, only the first episode was included in the study. This study was approved by the institutional review board of Asan Medical Center (IRB No. 2019-1057). Based on its retrospective nature, the need for informed consent was waived by the board.

Procedures and outcomes

Our medical ICU utilizes the patient monitors (CARESCAPE Monitor B650 and Unity Network Interface Device, GE HealthCare, Chicago, IL) and a storage server that records data displayed on the monitors. After a patient is admitted and connected to the monitor, measurements of patient's heart rate, arterial blood pressure, respiratory rate, SpO_2, inspiratory FiO_2, expiratory tidal volume, and expiratory minute ventilation are recorded in the storage server every 2 seconds. Missing data occurred due to various reasons, including transfers from other hospitals after intubation, transfers to or from ICUs other than the medical ICU, temporary departures from the ICU for workup or procedures, or problems related to data transmission or with the storage server itself.

We collected the following data from the electronic medical records of the included patients: demographic data, ICU admission route, use of vasopressors at the time of ICU admission, APACHE II score, diagnosis and causes of ARDS, arterial blood gas profiles, ventilator parameters, and SOFA score (at the time of ICU admission, ICU day 3, and day 7), set inspiratory pressures (each time it was changed), expiratory tidal volume (every 8 hours), and Richmond agitation-sedation scale (RASS) (every 2 hours) during the first 7 days of mechanical ventilation (all recorded by the nurses in charge), use and duration of neuromuscular blocker infusion, ICU and in-hospital mortality, mortality within 90 days of mechanical ventilation. Dynamic compliance of the respiratory system was calculated as tidal volume / concurrent inspiratory pressure recorded in the electronic medical records, and the ventilatory ratio was calculated according to the previous literature (13). From the patient monitor data, we collected inspiratory FiO_2, expiratory tidal volume, minute ventilation, respiratory rate, SpO_2 during the first 7 days of mechanical ventilation, and their recording times.

The primary outcome was ventilator-free days, defined as the number of calendar days a patient survived without mechanical ventilation within the first 28 days of mechanical ventilation. If a patient died within the 28 days, ventilator-free days were considered as 0. The secondary outcomes included ICU and in-hospital mortality and ICU and hospital length of stays.

Statistical analysis

For each patient's monitor data, we excluded impossible values (values below 0 for all variables, below 21% for FiO_2, and above 100% for SpO_2 and FiO_2). Further, we excluded the top and bottom 0.05 percentile values for tidal volume, minute ventilation, and respiratory rate data to filter outliers. The remaining 99.9 percentile of tidal volume data were normalized by the patient's predicted body weight (PBW) and the mean and standard deviation of tidal volume data during the first 7 days of mechanical ventilation were calculated. Because the association between high tidal volume and mortality in ARDS is well-known, it was necessary to evaluate the impact of tidal volume variability after adjusting for tidal volume. For this purpose, the study patients were classified into 5 tidal volume strata according to their mean normalized tidal volume (first $\leq$ 6 mL/kg PBW, 6 mL/kg PBW < second $\leq$ 7 mL/kg PBW, 7 mL/kg PBW < third $\leq$ 8 mL/kg PBW, 8 mL/kg PBW < fourth $\leq$ 9 mL/kg PBW, 9 mL/kg PBW < fifth). Within each stratum, the patients were dichotomized into high (included the upper half of tidal volume standard deviation data) and low (included the lower half of tidal volume standard deviation data) tidal volume variability groups based on their standard deviation of normalized tidal volume values.

We compared the baseline characteristics, mechanical ventilation variables, and clinical outcomes between the high and low tidal volume variability groups. No missing values were imputed. Continuous variables were presented as mean ± SD or median (IQR), while categorical variables were presented as number (percent). Differences between two tidal volume data sources (electronic medical records and patient monitors) were analyzed using the paired T-test. For comparisons between the two groups, continuous variables were analyzed using the independent t-test or the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test or Fisher's exact test. To evaluate the association between tidal volume variability and the primary outcome, a zero-inflated negative binomial model was fitted after adjusting for age, sex, body mass index (BMI), acute physiology and chronic health evaluation (APACHE) II score, and PaO_2/FiO_2 ratio at ICU admission (14). Survival up to 90 days from mechanical ventilation was depicted using Kaplan-Meier curves and differences between the groups were assessed with the log-rank test. A two-sided P value of less than 0.05 was considered statistically significant. All analyses were performed using R version 4.3.1 (R Core Team, Vienna, Austria) and Python version 3.11.4 (Python Software Foundation, Wilmington, DE).

Results

Patients

Of the 668 patients who underwent mechanical ventilation for more than 24 hours in our medical ICU between April 2018 and July 2019, 108 ARDS patients who had 50% or more of tidal volume data obtained during the first 7 days of mechanical ventilation were included in the study (Figure 1). For each tidal volume stratum, the included patients were dichotomized into the high and low tidal volume variability groups (each n = 54) based on the standard deviation of the normalized tidal volume (Table 1). Most patients were admitted to the ICU from the general wards (Table 2) and had moderate to severe ARDS upon ICU admission (80% of the high tidal volume variability group vs. 85% of the low tidal volume variability group; P = 0.61), with pneumonia being the primary cause of their ARDS. The high tidal volume variability group had a higher proportion of males (82% vs. 65%; P = 0.08) and a taller average height (165 ± 8 cm vs 162 ± 7 cm; P = 0.02) compared to the low tidal volume variability group. However, BMI did not significantly differ between the groups (23.5 ± 4.2 kg/m2 vs. 22.9 ± 4.5 kg/m2; P = 0.46). Most patients received lung-protective ventilation in the assist pressure control mode, with a tidal volume of 6.9 ± 1.4 mL/kg PBW and a peak airway pressure of 24.3 ± 4.4 cmH_2O.

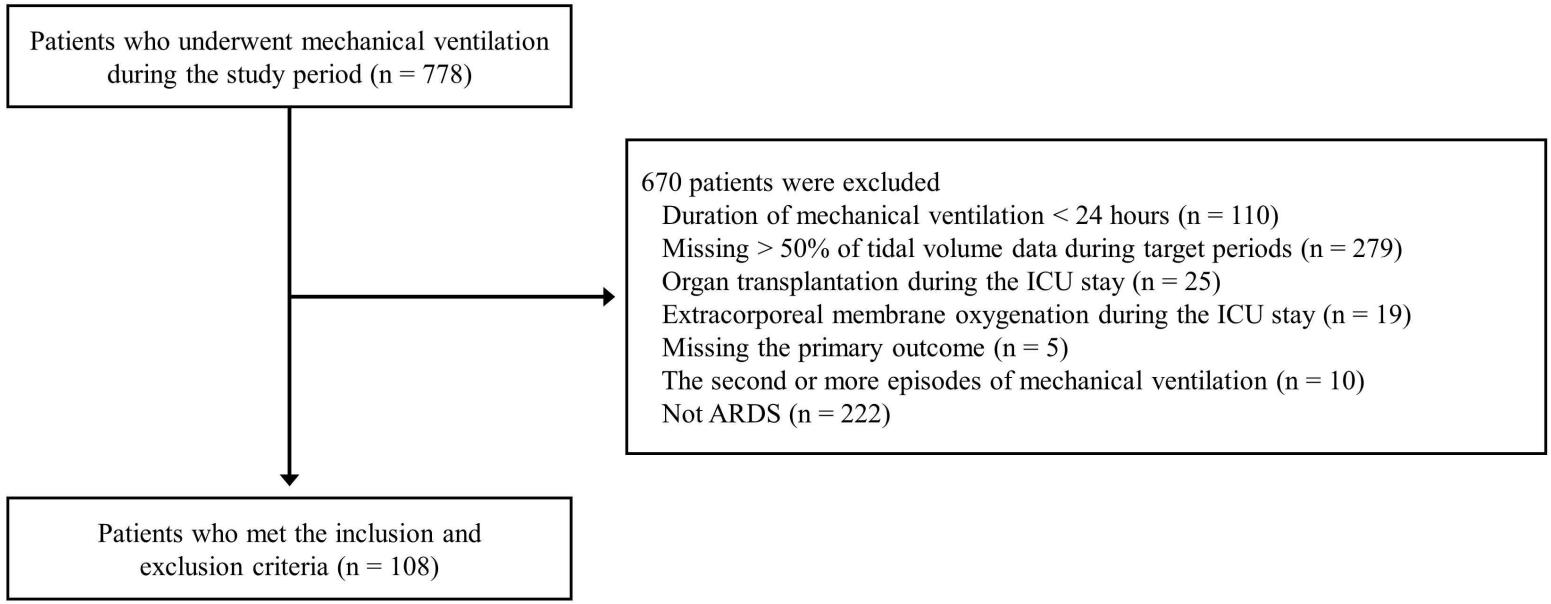


Figure 1. Flowchart of study inclusion.

Table 1. Detailed data of the study patients according to the 5 tidal volume strata

Tidal volume stratum*	First		Second		Third		Fourth		Fifth	
	High TVV group (n=6)	Low TVV group (n=5)	High TVV group (n=18)	Low TVV group (n=17)	High TVV group (n=17)	Low TVV group (n=17)	High TVV group (n=7)	Low TVV group (n=8)	High TVV group (n=6)	Low TVV group (n=7)
Baseline characteristics										
Age, year	68.7 ±12.1	62.4 ±4.7	64.3 ±10.7	58.9 ±19.9	66.8 ±7	65.1 ±9.3	68.9 ±8.7	66.1 ±12.1	70.7 ±14.1	75.3 ±10.4
Male sex, n (%)	6 (100)	2 (40)	17 (94)	13 (76)	13 (76)	12 (71)	7 (100)	4 (50)	1 (17)	4 (57)
Height, cm	167.7 ±8	159.5 ±9.3	169.3 ±7.2	163.1 ±6	164.3 ±7.1	162.4 ±6.9	165 ±4.7	160 ±8.1	151.7 ±4.5	158.2 ±8.4
Weight, kg	53.9 ±7.8	51.9 ±11	66.7 ±12.8	62.7 ±15.4	66.3 ±13.3	55.8 ±8.6	68 ±4.9	63.7 ±9.4	54.9 ±10.2	61.7 ±7.9
Body mass index, kg/m^2	19.1 ±2.2	20.3 ±3.4	23.2 ±3.9	23.7 ±6.4	24.5 ±4.6	21.1 ±2.7	25.1 ±2.4	24.9 ±3	23.9 ±4.7	24.7 ±3.1
Route of ICU admission, n (%)										
ER	1 (17)	0 (0)	6 (33)	2 (12)	5 (29)	6 (35)	1 (14)	2 (25)	1 (17)	1 (14)
general ward	5 (83)	5 (100)	12 (67)	15 (88)	12 (71)	11 (65)	6 (86)	6 (75)	5 (83)	6 (86)
Cause of ARDS, n (%)										
pneumonia	6 (100)	5 (100)	13 (72)	12 (71)	10 (59)	10 (59)	7 (100)	3 (38)	4 (67)	7 (100)
aspiration	0 (0)	0 (0)	2 (11)	0 (0)	0 (0)	2 (12)	0 (0)	2 (25)	0 (0)	0 (0)
nonpulmonary sepsis	0 (0)	0 (0)	1 (6)	3 (18)	3 (18)	2 (12)	0 (0)	3 (38)	2 (33)	0 (0)
others	0 (0)	0 (0)	2 (11)	1 (6)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)
unknown	0 (0)	0 (0)	0 (0)	1 (6)	4 (24)	2 (12)	0 (0)	0 (0)	0 (0)	0 (0)
APACHE II score	28 ±6.9	25.6 ±5.7	27.8 ±8.7	25.1± 6.2	25.5 ±7.2	29.2 ±9.1	28.7 ±5.6	25.8 ±8.6	24.8 ±5.7	26.4 ±7.3

Table 1. Continued

Tidal volume stratum*	First		Second		Third		Fourth		Fifth	
	High TVV group (n=6)	Low TVV group (n=5)	High TVV group (n=18)	Low TVV group (n=17)	High TVV group (n=17)	Low TVV group (n=17)	High TVV group (n=7)	Low TVV group (n=8)	High TVV group (n=6)	Low TVV group (n=7)
SOFA score	9.5 ±3.2	7.6 ±3.4	11.8 ±5.4	10.3 ±3.8	10.6 ±5	12.6 ±4.7	10.1 ±3.2	12.2 ±3.5	11.5 ±2.1	8.7 ±1.4
Vasopressor use, n (%)	3 (50)	1 (20)	9 (50)	9 (53)	7 (41)	10 (59)	1 (14)	6 (75)	3 (50)	2 (29)
Lactate, mmol/L	1.3±0.5	2.2±0.9	1.9±0.9	2.2±1.2	3.7±4.3	3.4±3.4	1.5±0.4	3.2±2.2	3.2±2.7	1.5±0.4
FiO_2	0.5 ±0.09	0.64 ±0.14	0.64 ±0.18	0.7 ±0.2	0.65 ±0.15	0.61 ±0.19	0.69 ±0.17	0.69 ±0.2	0.55 ±0.17	0.59 ±0.14
PEEP, cmH_2O	6.2±1	8±2.2	8.8±1.9	8.4±2	8.6±2.8	7.6±2.5	10.6±2.8	8±3	8±2.6	8.1±1.7
PaO_2/FiO_2 ratio	193 ±68.4	126.8 ±16.8	159.8 ±45.7	119.4 ±55	141 ±36.7	157.5 ±66.3	135.3 ±33.5	155.1 ±70.7	161.3 ±28.8	169.1 ±63.8
Tidal volume, mL/kg PBW	5.4±1.4	5.4±0.6	6.3±0.8	6.9±1.1	6.8±0.8	7.1±1.3	7.4±2.3	7.6±1.2	9.2±2.9	7.6±0.7
Set inspiratory pressure, cmH_2O	18 ±4	20.6 ±4.3	16.8 ±3.7	16.4 ±3.1	16.4 ±3.2	14.4 ±2.8	14.7 ±3.8	16.2 ±3.1	14.5 ±3	14 ±1.6
Set respiratory rate, min^{-1}	21 ±4.3	26.4 ±2.6	21.6 ±3.5	21.6 ±2.7	21.3 ±2.4	20 ±3.2	22 ±2.6	20.2 ±4	23 ±4.7	19 ±1.7
Peak airway pressure, cmH_2O	24.2 ±4.2	28.6 ±3.2	25.6 ±4.9	24.8 ±3.6	24.9 ±4.6	22 ±4.7	25.3 ±2.9	24.2 ±5.5	22.5 ±4.6	22.1 ±2.2
Minute ventilation, L/min	8.6±3.5	8.1±1	8.8±1.6	8.9±1.3	8.6±1.7	8.1±1.3	9.8±2.4	8.4±2.5	10±4	7.8±1.5
$PaCO_2$, mmHg	40.7 ±11.4	47.3 ±11.2	39.4 ±5.4	42.2 ±10	40.7 ±7	37.8 ±7.6	40.5 ±9.3	36.9 ±5.3	34.6 ±8.7	37.6 ±2.6

Table 1. Continued

Tidal volume stratum*	First		Second		Third		Fourth		Fifth	
	High TVV group (n=6)	Low TVV group (n=5)	High TVV group (n=18)	Low TVV group (n=17)	High TVV group (n=17)	Low TVV group (n=17)	High TVV group (n=7)	Low TVV group (n=8)	High TVV group (n=6)	Low TVV group (n=7)
Arterial pH	7.4 ±0.11	7.34 ±0.12	7.38 ±0.11	7.39 ±0.09	7.33 ±0.11	7.36 ±0.11	7.38 ±0.09	7.37 ±0.07	7.36 ±0.1	7.41 ±0.11
Dynamic compliance of respiratory system, mL/cmH_2O	20.6 ±8.2	14.2 ±2.5	25.7 ±8.1	25.3 ±6.8	25.6 ±6.2	28.1 ±9.3	31.6 ±8.8	25.7 ±3.3	28.8 ±6.8	29 ±4.8
Ventilatory ratio	1.3±0.3	1.9±0.4	1.4±0.3	1.7±0.4	1.5±0.3	1.4±0.4	1.7±0.3	1.5±0.4	1.9±0.4	1.5±0.2
Tidal volume data during the first 7 days of mechanical ventilation										
Data from electronic medical records										
mean, mL/kg PBW	5.6±0.7	5.2±0.4	6.5±0.4	6.5±0.3	7.4±0.6	7.5±0.4	8.2±1.1	7.9±0.5	10.7±1	9.4±0.7
standard deviation, mL/kg PBW	0.9±0.2	0.9±0.3	1.3±0.5	0.9±0.2	1.5±0.6	1.1±0.3	1.7±0.5	1.1±0.4	2.6±0.7	2.3±0.4
Data from patient monitors										
mean, mL/kg PBW	5.7±0.4	5.5±0.4	6.6±0.3	6.6±0.2	7.5±0.3	7.5±0.2	8.4±0.3	8.3±0.2	10.6±0.8	9.5±0.5
standard deviation, mL/kg PBW	1.8±0.3	1.2±0.2	2.1±0.6	1.1±0.2	2.6±0.7	1.5±0.4	3±1	1.7±0.5	4.3±0.6	2.8±0.2
Outcomes										
Ventilator-free day, day (IQR)	1 (0–12)	0 (0–20)	0 (0–15)	14 (0–25)	0 (0–16)	11 (0–20)	0 (0–16)	0 (0–20)	0 (0–0)	8 (2–18)
ICU mortality, n (%)	3 (50)	3 (60)	10 (56)	7 (41)	10 (59)	6 (35)	4 (57)	4 (50)	4 (67)	3 (43)
Hospital mortality, n (%)	3 (50)	3 (60)	12 (67)	8 (47)	14 (82)	9 (53)	4 (57)	4 (50)	4 (67)	3 (43)

*Tidal volume stratum: first, mean tidal volume ≤ 6 mL/kg PBW; second, 6 mL/kg PBW < mean tidal volume ≤ 7 mL/kg PBW; third, 7 mL/kg PBW < mean tidal volume ≤ 8 mL/kg PBW; fourth, 8 mL/kg PBW < mean tidal volume ≤ 9 mL/kg PBW; fifth, 9

mL/kg PBW < mean tidal volume

TVV, tidal volume variability; ARDS, acute respiratory distress syndrome; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; PBW, predicted body weight

Table 2. Baseline characteristics of study patients

	Total (n = 108)	High TVV group (n = 54)	Low TVV group (n = 54)	P value
Age, year	65.6 ± 12.3	66.9 ± 9.9	64.4 ± 14.3	0.29
Male sex, n (%)	79 (73)	44 (82)	35 (65)	0.08
Height, cm	163.3 ± 8.0	165.0 ± 8.3	161.5 ± 7.2	0.02
Weight, kg	61.8 ± 12.2	64.0 ± 12.3	59.6 ± 11.8	0.06
Body mass index, kg/m^2	23.2 ± 4.3	23.5 ± 4.2	22.9 ± 4.5	0.46
Route of ICU admission, n (%)				0.65
ER	25 (23)	14 (26)	11 (20)	
general ward	83 (77)	40 (74)	43 (80)	
Cause of ARDS, n (%)				0.88
pneumonia	77 (71)	40 (74)	37 (68)	
aspiration	6 (6)	2 (4)	4 (7)	
nonpulmonary sepsis	14 (13)	6 (11)	8 (15)	
others	4 (4)	2 (4)	2 (4)	
unknown	7 (6)	4 (7)	3 (6)	
APACHE II score	26.8 ± 7.4	26.9 ± 7.3	26.7 ± 7.6	0.91
SOFA score	10.9 ± 4.3	10.9 ± 4.5	10.9 ± 4.1	0.91
Vasopressor use, n (%)	51 (47)	23 (43)	28 (52)	0.44
Lactate, mmol/L	2.6 ± 2.5	2.5 ± 2.7	2.6 ± 2.2	0.84
FiO_2	0.64 ± 0.18	0.62 ± 0.16	0.65 ± 0.18	0.44
PEEP, cmH_2O	8.3 ± 2.4	8.6 ± 2.5	8.0 ± 2.3	0.23
PaO_2/FiO_2 ratio	149.2 ± 53.8	154.6 ± 44.9	143.8 ± 61.4	0.3
Tidal volume, mL/kg PBW	6.9 ± 1.4	6.9 ± 1.6	6.8 ± 1.7	0.71
Set inspiratory pressure, cmH_2O	16.0 ± 3.5	16.3 ± 3.5	15.8 ± 3.5	0.47
Set respiratory rate, min^{-1}	21.3 ± 3.4	21.6 ± 3.3	21.0 ± 3.5	0.33
Peak airway pressure, cmH_2O	24.3 ± 4.4	23.8 ± 4.4	24.8 ± 4.4	0.24
Minute ventilation, L/min	8.7 ± 2.0	9.0 ± 2.3	8.4 ± 1.5	0.12
Dynamic compliance of respiratory system, mL/cmH_2O	26.0 ± 7.7	26.2 ± 7.8	25.7 ± 7.7	0.72
Ventilatory ratio	1.6 ± 0.4	1.5 ± 0.3	1.6 ± 0.4	0.6

TVV, tidal volume variability; ARDS, acute respiratory distress syndrome; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; PBW, predicted body weight

Tidal volume data

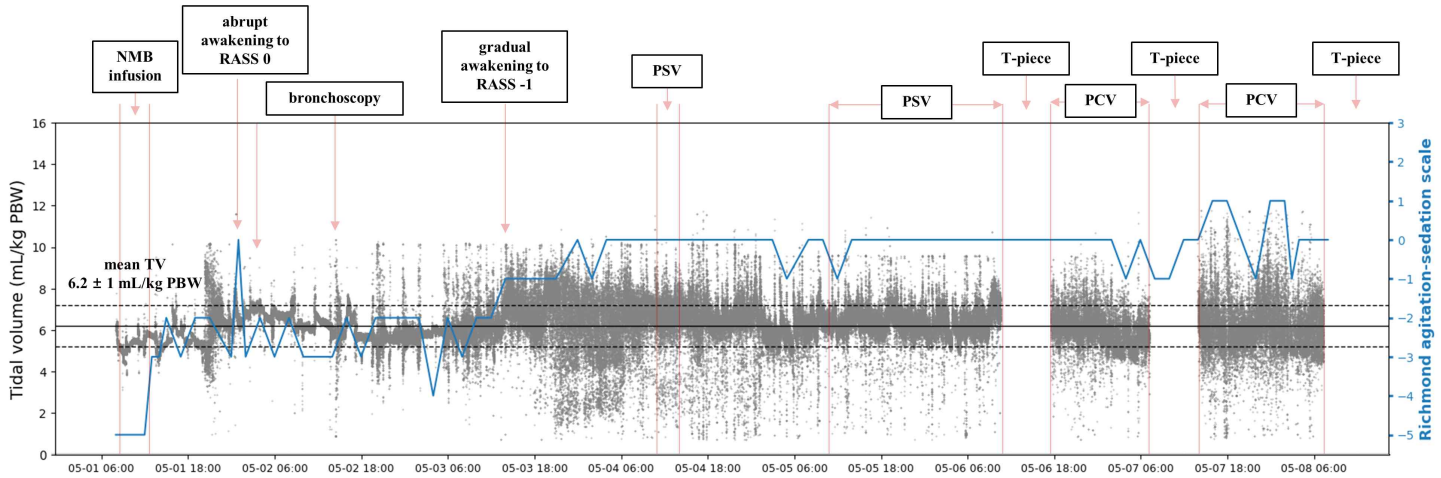
Table 3 presents the measurements related to mechanical ventilation during the first 7 days. For illustration, the tidal volume data of representative patients from each group are depicted over time in Figure 2. During the average data collection period of 132 hours, the tidal volume was recorded in the electronic medical records an average of 28 times, while it was recorded an average of 222,776 times through the patient monitor, accounting for 95% of the collection period. Compared to the tidal volume data in the electronic medical records, both the average (mean difference between the sources, 0.11 [95% CI, 0.02−0.19] mL/kg PBW; P = 0.01 by paired T-test) and the standard deviation (mean difference, 0.71 [95% CI, 0.59−0.83] mL/kg PBW; P < 0.01 by paired T-test) of tidal volume data from the patient monitor were higher. The difference in tidal volume standard deviation between these data sources was more pronounced in the high tidal volume variability group (1.1 vs. 0.4 mL/kg PBW; P < 0.001). The proportion of tidal volumes exceeding 10 mL/kg PBW was greater in the high tidal volume variability group according to the patient monitor data (16% ± 17% vs. 9% ± 14%; P = 0.02). Throughout the first 7 days of mechanical ventilation, daily tidal volume standard deviations in the high tidal volume variability group were consistently higher than those in the low tidal volume variability group (Figure 3). The patient monitor data other than the tidal volume is described in the supplementary material (Table 4).

Table 3. Measurements related to mechanical ventilation during the first 7 days

	Total (n = 108)	High TVV group (n = 54)	Low TVV group (n = 54)	P value
Target periods for data acquisition, hour	132 ± 48	142 ± 39	123 ± 54	0.04
Set inspiratory pressure, cmH_2O	15.2 ± 2.9	15.3 ± 2.9	15.0 ± 3.0	0.6
Data from electronic medical records				
counts of tidal volume data	28 ± 18	26 ± 16	30 ± 20	0.21
average tidal volume, mL/kg PBW	7.3 ± 1.4	7.4 ± 1.5	7.3 ± 1.2	0.72
standard deviation of tidal volume, mL/kg PBW	1.3 ± 0.6	1.5 ± 0.7	1.2 ± 0.6	0.005
Data from patient monitors				
counts of tidal volume data	222,776 ± 80,654	238,346 ± 66,274	207,205 ± 90,811	0.045
acquisition rate of tidal volume data during target periods	0.95 ± 0.1	0.94 ± 0.1	0.95 ± 0.1	0.92
average tidal volume, mL/kg PBW	7.4 ± 1.3	7.5 ± 1.4	7.4 ± 1.1	0.87
standard deviation of tidal volume, mL/kg PBW	2.0 ± 1.0	2.6 ± 1.0	1.5 ± 0.6	<0.001
proportion of tidal volume between 4 and 8 mL/kg PBW	0.64 ±0.25	0.59 ±0.23	0.68 ±0.26	0.06
proportion of tidal volume > 8 mL/kg PBW	0.32 ±0.24	0.33 ±0.21	0.3 ±0.26	0.48
proportion of tidal volume > 10 mL/kg PBW	0.12 ±0.16	0.16 ±0.17	0.09 ±0.14	0.02

TVV, tidal volume variability; PBW, predicted body weight

A


NMB infusion
abrupt awakening to RASS 0
bronchoscopy
gradual awakening to RASS -1
PSV
PSV
T-piece
PCV
T-piece
PCV
T-piece
mean TV
6.2 ± 1 mL/kg PBW
Tidal volume (mL/kg PBW)
Richmond agitation-sedation scale
05-01 06:00
05-01 18:00
05-02 06:00
05-02 18:00
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B

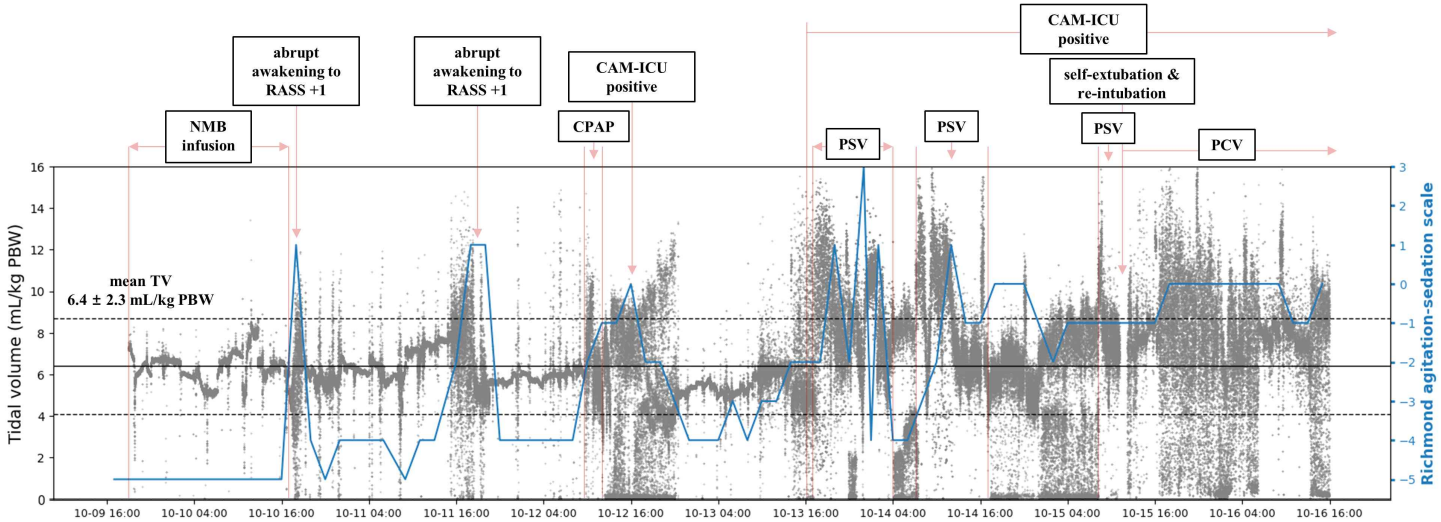
NMB infusion
abrupt awakening to RASS +1
abrupt awakening to RASS +1
CAM-ICU positive
CPAP
CAM-ICU positive
self-extubation & re-intubation
PSV
PSV
PSV
PCV
mean TV
6.4 ± 2.3 mL/kg PBW
Tidal volume (mL/kg PBW)
Richmond agitation-sedation scale
10-09 16:00
10-10 04:00
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Figure 2. Scatter plots of tidal volume over time in representative study patients from each tidal volume variability group. The X axis shows time from start of mechanical ventilation and the left Y axis shows tidal volume in mL/kg PBW. The solid horizontal line and dashed horizontal lines means mean and ± standard deviation of tidal volume, respectively. The blue line shows serial RASS results (using the right Y axis). A: low tidal volume variability group; tidal volume, 6.2 ± 1 mL/kg PBW, B: high tidal volume variability group; tidal volume, 6.4 ± 2.3 mL/kg PBW. PBW, predicted body weight; NMB, neuromuscular blocker; RASS, Richmond agitation-sedation scale; PSV, pressure support ventilation; PCV, pressure control ventilation; CAM-ICU, confusion assessment method for the ICU.

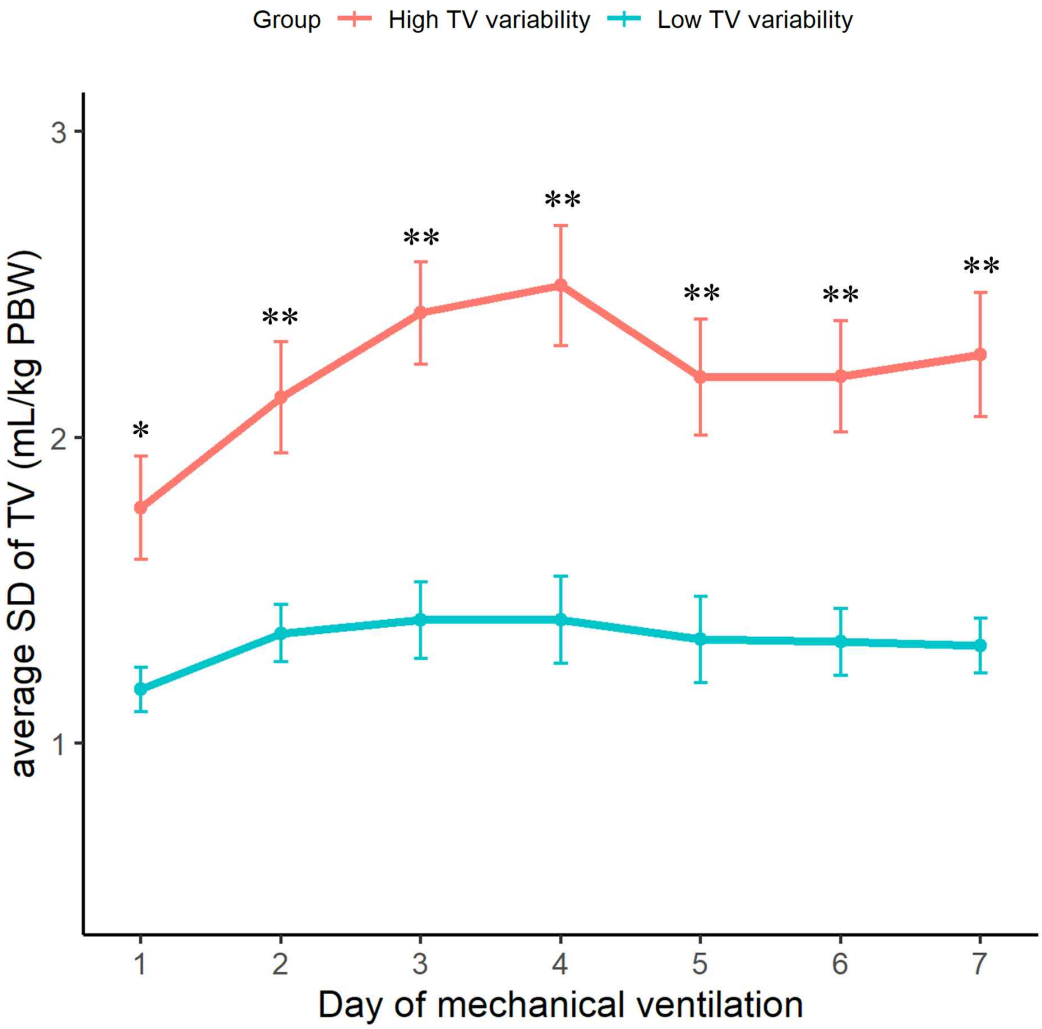

Figure 3. Average daily standard deviation of tidal volumes depending on the tidal volume variability groups during the first 7 days of mechanical ventilation. The error bars mean the standard error of the mean. *P < 0.05 between two groups, **P < 0.001 between two groups. TV, tidal volume; PBW, predicted body weight.

Table 4. Measurements related to mechanical ventilation other than expiratory tidal volume during the first 7 days

	Total (n = 108)	High TVV group (n = 54)	Low TVV group (n = 54)	P value
FiO_2				
count	210,615 ±90,327	227,277 ±79,300	193,953 ±98,070	0.06
mean	53.6 ± 14.4	52.8 ± 11.9	54.5 ± 16.5	0.55
standard deviation	11.3 ± 3.4	11.6 ± 2.9	11.1 ± 3.9	0.4
SpO_2				
count	217,604 ±84,516	230,246 ±73,975	204,961 ±92,859	0.12
mean	95.8 ± 2.7	95.7 ± 2.4	95.8 ± 3.0	0.92
standard deviation	3.2 ± 2.5	3.2 ± 2.3	3.1 ± 2.8	0.77
Respiratory rate				
count	222,361 ±80,490	238,183 ±66,349	206,540 ±90,373	0.04
mean, breaths/min	22.9 ± 3.5	22.8 ± 2.6	23.1 ± 4.2	0.68
standard deviation, breaths/min	4.4 ± 3.0	4.2 ± 1.5	4.6 ± 3.9	0.45
Minute ventilation	(n = 95)	(n = 45)	(n = 50)	
count	190,405 ±106,387	193,280 ±110,191	187,529 ±103,398	0.78
mean, L/min	9.6 ± 1.9	10.2 ± 1.9	9.1 ± 1.8	0.003
standard deviation, L/min	1.9 ± 0.5	2.1 ± 0.4	1.7 ± 0.5	<0.001

TVV, tidal volume variability

Treatments and outcomes

During the first 7 days of mechanical ventilation, prone positioning was performed in 17% of study patients, and 67% of the patients received continuous infusion of neuromuscular blockers for an average of 3 calendar days (Table 5). The ventilator parameters, arterial blood gas profiles, and SOFA scores on ICU day 3 and day 7 in two groups are described in Table 6. The primary outcome, ventilator-free days, was significantly lower in the high tidal volume variability group (0 [IQR, 0−16] days vs. 10 [IQR, 0−21] days; mean difference, -4.5 [95% CI, -8.3−-0.7] days; P = 0.01; Table 7). After adjusting for age, sex, BMI, APACHE II score, and baseline PaO_2/FiO_2 ratio, high tidal volume variability was significantly associated with zero ventilator-free days in the fitted zero-inflated negative binomial model (Table 8). There were no statistically significant differences in ICU mortality and in-hospital mortality between the two groups. Survival curves up to 90 days from mechanical ventilation were plotted in both groups, with no significant difference observed (Figure 4; P = 0.35). In post-hoc analysis, serial PaO_2/FiO_2 ratios showed a significant interaction for the group-by-time (P for the group-by-time interaction = 0.02 by two-way repeated-measures ANOVA; Figure 5).

To investigate factors associated with tidal volume variability, a post-hoc analysis was conducted regarding the relationship between RASS and the standard deviation of tidal volume data within 30 minutes before and after the RASS recording time (Figure 6). For the entire study population, a weak positive correlation was found between RASS and tidal volume standard deviation (Pearson's R, 0.33; P < 0.001).

Table 5. Treatments that study patients were received during the first 7 days of mechanical ventilation

	Total (n = 108)	High TVV group (n = 54)	Low TVV group (n = 54)	P value
Prone positioning, n (%)	18 (17)	6 (11)	12 (22)	0.2
Use of neuromuscular blocker, n (%)	72 (67)	40 (74)	32 (59)	0.15
duration of neuromuscular blocker infusion, calendar day	3.1 ± 1.9	2.8 ± 1.5	3.4 ± 2.2	0.21
Richmond agitation-sedation scale	-2.8 ± 1.4	-2.8 ± 1.2	-2.8 ± 1.5	0.77

TVV, tidal volume variability

Table 6. Ventilator and clinical parameters during the first 7 days

	Baseline		ICU day 3		ICU day 7	
	High TVV group	Low TVV group	High TVV group	Low TVV group	High TVV group	Low TVV group
PEEP, cmH_2O	8.6 ± 2.5 (n = 54)	8.0 ± 2.3 (n = 54)	7.2 ± 2.1 (n = 54)	7.3 ± 2.8 (n = 49)	6.8 ± 2.6 (n = 39)	7.2 ± 3.4 (n = 31)
Set inspiratory pressure, cmH_2O	16.3 ± 3.5 (n = 54)	15.8 ± 3.4 (n = 54)	14.2 ± 3.8 (n = 54)	14.5 ± 4.6 (n = 48)	14.2 ± 4.2 (n = 38)	13.9 ± 4.7 (n = 31)
Set respiratory rate, min^{-1}	21.6 ± 3.3 (n = 54)	21.0 ± 3.5 (n = 54)	20.3 ± 4.2 (n = 49)	20.7 ± 4.7 (n = 46)	20.9 ± 4.1 (n = 31)	21.2 ± 4.4 (n = 25)
Tidal volume, mL/kg PBW	6.8 ± 1.7 (n = 54)	7.0 ± 1.2 (n = 54)	7.5 ± 1.8 (n = 54)	7.6 ± 1.7 (n = 49)	7.6 ± 2.8 (n = 38)	7.3 ± 1.7 (n = 31)
Minute ventilation, L/min	9.0 ± 2.3 (n = 54)	8.4 ± 1.5 (n = 54)	9.8 ± 2.5 (n = 54)	9.3 ± 2.7 (n = 48)	10.4 ± 2.3 (n = 38)	8.7 ± 2.5 (n = 31)
Ventilatory ratio	1.5 ± 0.3 (n = 54)	1.6 ± 0.4 (n = 54)	1.6 ± 0.5 (n = 54)	1.6 ± 0.5 (n = 48)	1.8 ± 0.6 (n = 38)	1.6 ± 0.5 (n = 31)
FiO_2	0.62 ± 0.16 (n = 54)	0.65 ± 0.18 (n = 54)	0.51 ± 0.15 (n = 54)	0.52 ± 0.2 (n = 50)	0.49 ± 0.16 (n = 43)	0.47 ± 0.18 (n = 42)
PaO_2/FiO_2 ratio	154.6 ± 44.9 (n = 54)	143.8 ± 61.4 (n = 54)	182.7 ± 69.5 (n = 54)	186.8 ± 85 (n = 50)	179 ± 79.3 (n = 43)	221.5 ± 105 (n = 42)
$PaCO_2$, mmHg	39.6 ± 7.5 (n = 54)	39.8 ± 8.5 (n = 54)	37.1 ± 6.7 (n = 54)	37.7 ± 8.3 (n = 50)	38.7 ± 9.3 (n = 43)	37.9 ± 7.4 (n = 42)
Arterial pH	7.37 ± 0.1 (n = 54)	7.37 ± 0.1 (n = 54)	7.42 ± 0.09 (n = 54)	7.44 ± 0.08 (n = 50)	7.45 ± 0.08 (n = 43)	7.47 ± 0.06 (n = 42)

Table 6. Continued

	Baseline		ICU day 3		ICU day 7	
	High TVV group	Low TVV group	High TVV group	Low TVV group	High TVV group	Low TVV group
Lactate, mmol/L	2.5 ± 2.7 (n = 54)	2.6 ± 2.2 (n = 54)	2.9 ± 3 (n = 53)	2.6 ± 2.6 (n = 50)	2.0 ± 1.6 (n = 41)	1.6 ± 0.8 (n = 40)
SOFA score	10.9 ± 4.5 (n = 54)	10.9 ± 4.1 (n = 54)	10.2 ± 4.7 (n = 54)	9.9 ± 4.9 (n = 50)	9.5 ± 4.7 (n = 43)	8.0 ± 4.5 (n = 42)

TVV, tidal volume variability; SOFA, sequential organ failure assessment; PBW, predicted body weight

Table 7. Primary and secondary outcomes of study patients

	Total (n = 108)	High TVV group (n = 54)	Low TVV group (n = 54)	P value
Ventilator-free day, day				
median (IQR)	0 (0–20)	0 (0–16)	10 (0–21)	0.01
mean	8.3 ± 10.2	6 ± 9.4	10.5 ± 10.4	
ICU mortality, n (%)	54 (50)	31 (57)	23 (43)	0.18
Hospital mortality, n (%)	64 (59)	37 (68)	27 (50)	0.08
ICU length of stay, day (IQR)	11 (7–19)	11 (7–19)	10 (5–19)	0.44
Hospital length of stay, day (IQR)	36 (18–66)	30 (15–69)	39 (20–65)	0.37

TVV, tidal volume variability

Table 8. The results of the multivariable zero-inflated negative binomial model for predicting ventilator-free days

Count model Variables	Odds ratio	95% CI	P value
High tidal volume variability	1.02	0.78–1.34	0.87
Age	0.996	0.99–1.01	0.39
Male sex	0.9	0.65–1.25	0.53
Body mass index	1.02	0.98–1.05	0.42
PaO_2/FiO_2 ratio	0.998	0.996–1.001	0.18
APACHE II score	1.01	0.99–1.03	0.58
intercept	19.66	5.64–68.55	<0.001
Zero-inflation model Variables	Odds ratio	95% CI	P value
High tidal volume variability	3.74	1.55–9.06	0.003
Age	0.99	0.96–1.03	0.61
Male sex	0.44	0.16–1.21	0.11
Body mass index	1.06	0.95–1.17	0.3
PaO_2/FiO_2 ratio	1.0002	0.99–1.01	0.97
APACHE II score	1.09	1.02–1.16	0.007
intercept	0.06	0.001–3.45	0.17

APACHE II, acute physiology and chronic health evaluation II

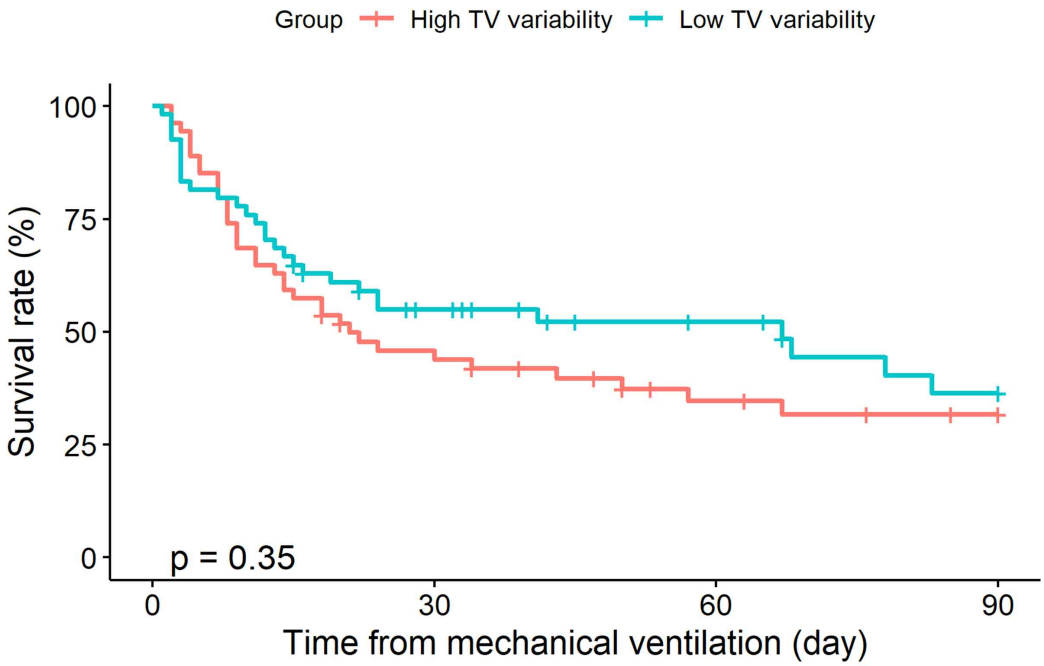

Figure 4. Survival curves depending on tidal volume variability groups. TV, tidal volume.

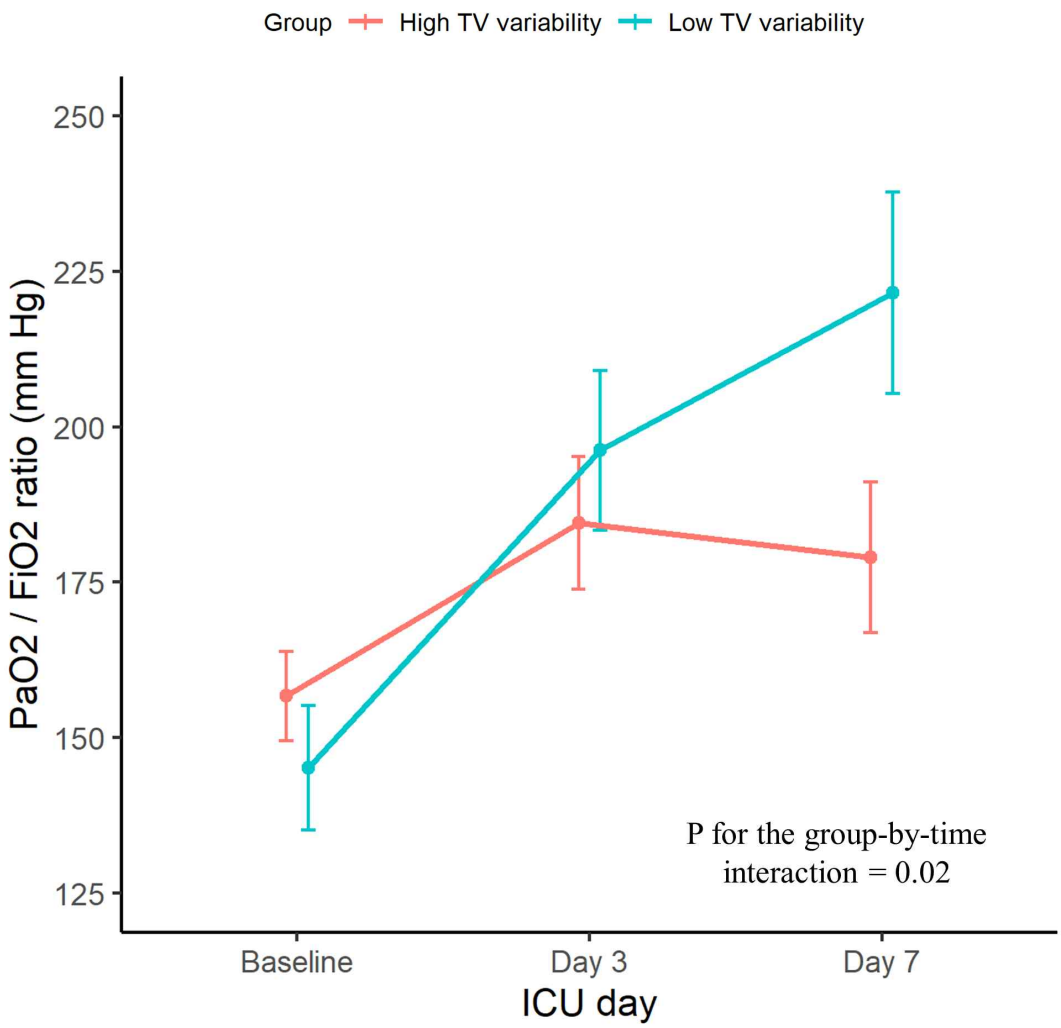

Figure 5. The PaO_2/FiO_2 ratios at ICU admission, ICU day 3, and day 7 in two tidal volume variability groups (43 patients in the high tidal volume variability group and 42 patients in the low tidal volume variability group whose PaO_2 and FiO_2 data on ICU day 7 were available). The error bars mean the standard error of the mean. There was a significant group-by-time interaction (P = 0.02 by two-way repeated-measures ANOVA). TV, tidal volume.

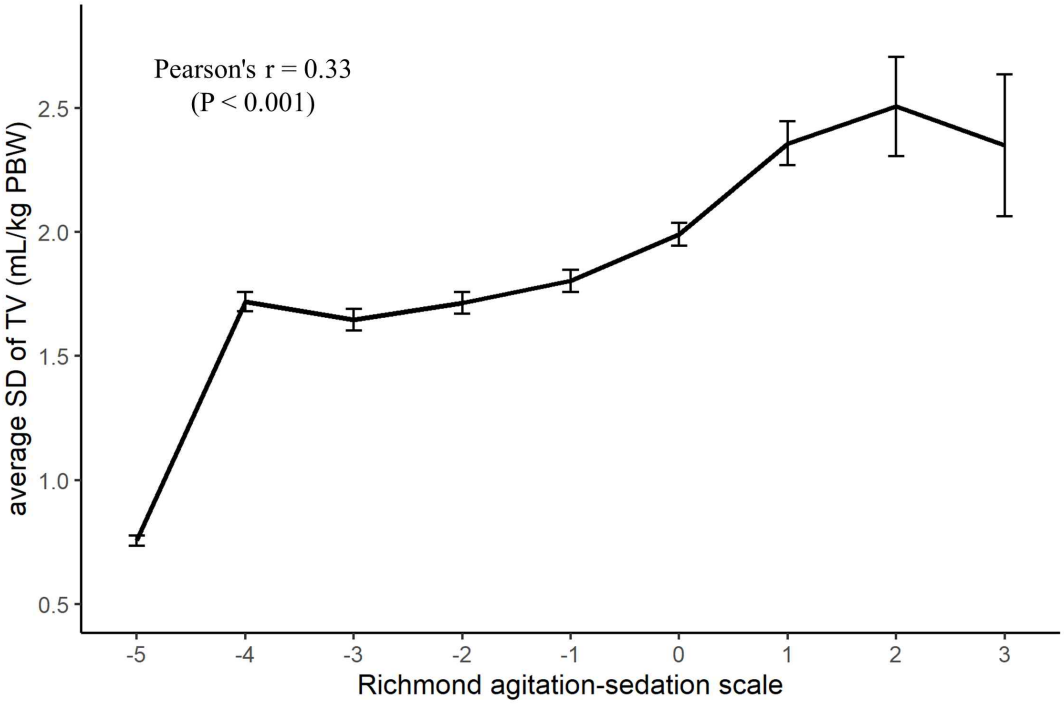

Figure 6. Relationship between Richmond agitation-sedation scale and standard deviation of tidal volume data acquired during the corresponding period in whole study patients. The error bars mean the standard error of the mean. TV, tidal volume.

Discussion

Summary of the findings

In this retrospective cohort study, we investigated the impact of tidal volume variability in mechanically ventilated ARDS patients using the high-resolution, real-world tidal volume data acquired by patient monitors. Compared to the tidal volume data in electronic medical records, the data from patient monitors showed a significantly greater standard deviation. The high tidal volume variability during the first 7 days of mechanical ventilation was associated with worse ventilator-free days. This association persisted after adjusting for age, sex, BMI, APACHE II score, and baseline PaO_2/FiO_2 ratio. This is the first study in evaluating the clinical impact of tidal volume variability based on high-resolution tidal volume data.

Suggested mechanisms

The association between high tidal volume variability and worse ventilator-free days can be attributed to patient self-inflicted lung injury (P-SILI), patient-ventilator dys-synchrony, and frequent injuriously high tidal volumes themselves (Figure 7).

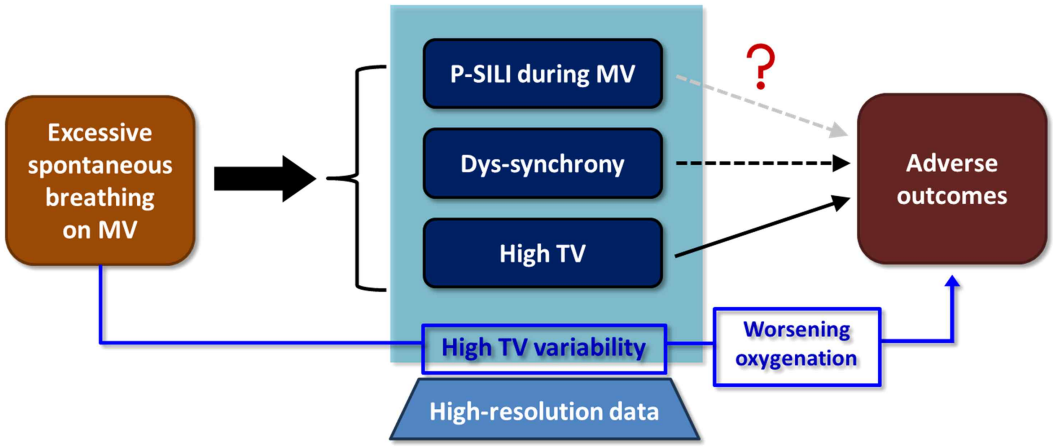

Figure 7. Suggested mechanisms for association between high tidal volume variability and worse clinical outcomes. MV, mechanical ventilation; P-SILI, patient self-inflicted lung injury; TV, tidal volume.

First, the respiratory drive during mechanical ventilation can lead to spontaneous inspiratory efforts, consequently resulting in tidal volume variability during pressure control ventilation. Low tidal volume ventilation itself can influence the respiratory drive (15), but the level of sedation may also play a role. A weak yet significant correlation observed between RASS and the tidal volume variability of corresponding time in this study supports this relationship (Figure 6). Spontaneous breathing at an appropriate intensity or timing may improve atelectasis in the dependent lung regions, preserve diaphragm function, enhance gas exchange, and thereby shorten the duration of mechanical ventilation (16-19). In the pre-planned sub-analysis of the LUNG SAFE study, Haren et al. reported that spontaneous breathing during the first two days of ARDS diagnosis was associated with longer ventilator-free days and shorter ICU length of stay (20). Additionally, Reis et al. reported that the proportion of spontaneous breathing time exceeding 50% of the first 48 hours of mechanical ventilation was not related to ventilator-free days in patients with acute respiratory failure using the MIMIC-III database (21). However, excessive spontaneous breathing during mechanical ventilation, especially when lungs are vulnerable to injury, can induce P-SILI or diaphragm injury, or exacerbate pre-existing lung injury (22, 23). While many pre-clinical studies have suggested association between spontaneous breathing and P-SILI (24-26), clinical data linking spontaneous breathing to adverse treatment outcomes is insufficient. In this study, while the PaO_2/FiO_2 ratios in the low tidal volume variability group improved over time, those in the high tidal volume variability group rather worsened between ICU day 3 and day 7. These changes in the PaO_2/FiO_2 ratios over time significantly differed between the two groups (Figure 5). Esnault et al. reported that excessive inspiratory efforts could lead to the recurrence of respiratory failure within the subsequent 24 hours in a retrospective study on coronavirus disease 2019-associated ARDS patients. Similarly, our high tidal volume variability group might suffer from P-SILI due to excessive spontaneous breathing during the first 7 days of mechanical ventilation, resulting in worsened oxygenation by ICU day 7 and eventually fewer ventilator-free days. Our findings suggest that excessive spontaneous breathing during mechanical ventilation can worsen clinical outcomes in ARDS. Also, the results of our study are in line with the benefits of early neuromuscular blocker administration in patients with ARDS (5).

Secondly, tidal volume variability might be a surrogate marker for some types of patient-ventilator dys-synchrony. Double-triggering and reverse-triggering can produce higher tidal volumes than intended, which are reflected as tidal volume variability and are at risk of ventilator-induced lung injury (27). Blanch et al. described the

association between dys-synchrony and higher ICU and hospital mortality (28). In addition, recent meta-analysis indicated that dys-synchrony was associated with a longer duration of mechanical ventilation and higher mortality (29). Lastly, in our high tidal volume variability group, tidal volumes exceeding 10 mL/kg PBW were significantly more frequent than in the low tidal volume variability group (16% vs. 9%). Despite the comparable average tidal volumes between the two groups, the high tidal volume variability group was exposed to harmful tidal volumes for longer periods, probably resulting in more ventilator-induced lung injury.

Measures to reduce tidal volume variability

Potential methods to mitigate excessive spontaneous breathing, high tidal volume variability, and consequent P-SILI include applying a high PEEP strategy, selective use of neuromuscular blocker infusion, allowing spontaneous breathing after initial lung injury has stabilized, and adjusting levels of ventilator support based on monitoring the airway occlusion pressure at 100 ms ($P_{0.1}$) or the occluded inspiratory airway pressure (P_{occ}) to prevent excessive inspiratory efforts. A high PEEP strategy may reduce P-SILI caused by excessive spontaneous breathing in ARDS (26). Contrary to the ACURASYS trial, which used a low PEEP table, the recent ROSE trial applied the high PEEP strategy and found no benefit of early neuromuscular blocker infusion (5, 30). Higher PEEP levels may make spontaneous breathing non-injurious without neuromuscular blockade (31). However, despite the results of the ROSE trial, the use of neuromuscular blocker infusion may still have a role in selected ARDS patients who show high respiratory drive and patient-ventilator dys-synchrony leading to high tidal volume variability despite appropriate sedative uses. The risk of P-SILI due to excessive spontaneous breathing may correlate with the underlying severity of ARDS (22). Spontaneous breathing in severe ARDS can develop P-SILI due to loss of lung volume, increased respiratory drive, and injurious ventilator settings. Therefore, the risk of P-SILI can be minimized by allowing spontaneous breathing after the initial lung injury has stabilized. Further research is needed to determine the appropriate timing for spontaneous breathing in ARDS. Lastly, once spontaneous breathing occurs, ventilator support levels should be adjusted based on the $P_{0.1}$ or P_{occ} levels (32-34). $P_{0.1}$ or P_{occ} are surrogates for inspiratory efforts. A $P_{0.1}$ value > 3.5 cmH_2O indicates high respiratory efforts (33).

Difference in the data collection methods

Traditionally, clinical studies on mechanical ventilation have recorded ventilator variables at specific times during the day. However, this data acquisition method might not capture the whole clinical situation in ever-changing critically ill patients. In our study, the tidal volume standard deviation based on patient monitors was significantly greater than that from electronic medical records. Previous studies about spontaneous breathing during mechanical ventilation defined spontaneous breathing based on ventilator modes and the discrepancy between the recorded and the set respiratory rates (20, 21). In contrast, our current study used the whole tidal volume data without a specific definition regarding spontaneous breathing. Therefore, our results might better reflect real-world phenomena.

Limitations

There are several limitations to this study. First, it is a single-center study with a small number of patients, which limits its generalizability. In addition, there might be a selection bias because patients with less than 50% of tidal volume data collected during the first 7 days of mechanical ventilation were excluded. Second, our findings might not be applicable to patients on volume control ventilation since all study patients were on pressure control ventilation. Although spontaneous breathing during volume control ventilation can lead to lung injury (35), it might not manifest as tidal volume variability. Third, we could not collect variables related to inspiratory efforts. Inspiratory efforts can be assessed by $P_{0.1}$ or changes in the esophageal pressure (36, 37). With these variables, we could have clearly elucidated the association between tidal volume variability and inspiratory efforts. Lastly, in the high tidal volume variability group, fewer patients underwent prone positioning during the first 7 days of mechanical ventilation (11% vs. 22%; P = 0.2). The reasons for not implementing prone positioning could not be determined due to the retrospective and electronic medical records-based nature of the study. The difference in the rates of prone positioning between the two groups could have acted as a confounding factor in analyzing the outcomes.

Conclusion

In conclusion, based on the high-resolution tidal volume data acquired from the patient monitor, this study found that high tidal volume variability during the first 7 days of mechanical ventilation in ARDS patients was associated with fewer ventilator-free days. For the clinical application of tidal volume variability, further prospective studies are needed to investigate relationship between tidal volume variability and inspiratory efforts and the appropriate onset and extent of spontaneous breathing and its consequent tidal volume variability in ARDS patients.

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Korean Abstract

배경: 기계 환기 중 자발 호흡이 과도한 경우 환자가 자초한 폐 손상이 유발될 수 있다. 그러나 자발 호흡이 치료 결과에 미치는 영향에 대한 임상 연구 결과는 부족한 실정이다. 본 연구는 기계 환기 중인 급성호흡곤란증후군(ARDS) 환자에서 환자 감시 장치를 통해 저장된 고해상도 일회호흡량 자료를 사용하여 일회호흡량 변동성이 인공호흡기 없이 생존한 기간에 미치는 효과를 분석하기 위해서 시행되었다.

방법: 본 연구는 단일 기관, 후향적 코호트 연구로서, 서울아산병원 내과계 중환자실에서 2018년 4월부터 2019년 7월 사이에 기계 환기를 받은 성인 ARDS 환자가 포함되었다. 연구 대상자에서 기계 환기 첫 7일 동안 환자 감시 장치를 통해 매 2초마다 수집된 호기 일회호흡량 자료를 사용하였다. 연구 대상자의 예상 체중(PBW)으로 표준화된 평균 일회호흡량을 5개 계층으로 층화한 후, 계층별로 표준화 일회호흡량의 표준 편차에 따라 연구 대상자를 높은 일회호흡량 변동성 군과 낮은 일회호흡량 변동성 군으로 이분화하였다. 일차 결과 변수는 기계 환기 후 28일 동안 인공호흡기 없이 생존한 기간이었다.

결과: 각각 54명의 ARDS 환자들이 높은, 그리고 낮은 일회호흡량 변동성 군에 포함되었다. 높은 일회호흡량 변동성 군에서 신장이 더 컸던 것(165 ± 8 cm 대 162 ± 7 cm; P = 0.02) 이외에는 중환자실 입실 시점의 환자 특성은 두 군 간에 유의한 차이가 없었다. 기계 환기 첫 7일 동안 수집된 일회환기량의 표준 편차는 높은 그리고 낮은 일회호흡량 변동성 군에서 각각 2.6 ± 1 mL/kg PBW, 1.5 ± 0.6 mL/kg PBW였다(P < 0.001). 높은 일회호흡량 변동성 군에서 인공호흡기 없이 생존한 기간이 유의하게 짧았다(0 [사분위수, 0−16]일 대 10 [사분위수, 0−21]일; 평균 차이, -4.5 [95% 신뢰 구간, -8.3−-0.7]일; P = 0.01). 높은 일회호흡량 변동성은 나이, 성별, 체질량지수, APACHE II 점수, 중환자실 입실 시 PaO_2/FiO_2 비를 보정한 이후에도 인공호흡기 없이 생존한 기간이 0일인 것과 유의한 연관성을 보였다(교차비, 3.74; 95% 신뢰 구간[1.55−9.06]; P = 0.003).

결론: ARDS 환자에서 환자 감시 장치를 통해 수집한 고해상도 일회호흡량 자료에 기반한 기계 환기 첫 7일 동안의 높은 일회호흡량 변동성은 인공호흡기 없이 생존한 기간이 더 짧은 것과 관련이 있었다.