JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Low vs Intermediate Tidal Volume Strategy on Ventilator-Free Days in Intensive Care Unit Patients Without ARDS

A Randomized Clinical Trial

Writing Group for the PReVENT Investigators

IMPORTANCE It remains uncertain whether invasive ventilation should use low tidal volumes in critically ill patients without acute respiratory distress syndrome (ARDS).

OBJECTIVE To determine whether a low tidal volume ventilation strategy is more effective than an intermediate tidal volume strategy.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial, conducted from September 1, 2014, through August 20, 2017, including patients without ARDS expected to not be extubated within 24 hours after start of ventilation from 6 intensive care units in the Netherlands.

INTERVENTIONS Invasive ventilation using low tidal volumes (n = 477) or intermediate tidal volumes (n = 484).

MAIN OUTCOMES AND MEASURES The primary outcome was the number of ventilator-free days and alive at day 28. Secondary outcomes included length of ICU and hospital stay; ICU, hospital, and 28- and 90-day mortality; and development of ARDS, pneumonia, severe atelectasis, or pneumothorax.

RESULTS In total, 961 patients (65% male), with a median age of 68 years (interquartile range [IQR], 59-76), were enrolled. At day 28, 475 patients in the low tidal volume group had a median of 21 ventilator-free days (IQR, 0-26), and 480 patients in the intermediate tidal volume group had a median of 21 ventilator-free days (IQR, 0-26) (mean difference, −0.27 [95% CI, −1.74 to 1.19]; $P = .71$). There was no significant difference in ICU (median, 6 vs 6 days; 0.39 [−1.09 to 1.89]; $P = .58$) and hospital (median, 14 vs 15 days; −0.60 [−3.52 to 2.31]; $P = .68$) length of stay or 28-day (34.9% vs 32.1%; hazard ratio [HR], 1.12 [0.90 to 1.40]; $P = .30$) and 90-day (39.1% vs 37.8%; HR, 1.07 [0.87 to 1.31]; $P = .54$) mortality. There was no significant difference in the percentage of patients developing the following adverse events: ARDS (3.8% vs 5.0%; risk ratio [RR], 0.86 [0.59 to 1.24]; $P = .38$), pneumonia (4.2% vs 3.7%; RR, 1.07 [0.78 to 1.47]; $P = .67$), severe atelectasis (11.4% vs 11.2%; RR, 1.00 [0.81 to 1.23]; $P = .94$), and pneumothorax (1.8% vs 1.3%; RR, 1.16 [0.73 to 1.84]; $P = .55$).

CONCLUSIONS AND RELEVANCE In patients in the ICU without ARDS who were expected not to be extubated within 24 hours of randomization, a low tidal volume strategy did not result in a greater number of ventilator-free days than an intermediate tidal volume strategy.

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Invasive ventilation, one of the most frequently applied strategies in the intensive care unit (ICU), is increasingly recognized as a potentially harmful intervention.[1] There is evidence that lung-protective ventilation using low tidal volumes improves survival in patients with acute respiratory distress syndrome (ARDS),[2-4] but it is less certain whether tidal volume restriction benefits patients without ARDS. Two randomized clinical trials found tidal volume reduction to be associated with a lower number of pulmonary complications in patients without ARDS,[5,6] and 2 individual patient data meta-analyses suggested that tidal volume reduction may shorten the time spent on the ventilator and duration of stay in the ICU and hospital.[7,8]

However, the use of low tidal volumes could lead to an increased need for sedation[9] because of higher respiratory rate or patient-ventilator asynchrony[10,11] and, possibly, self-inflicted lung injury due to compensatory injurious inspiratory efforts.[12] In addition, it has been suggested that low tidal volumes may increase the risk of delirium.[13]

The Protective Ventilation in Patients Without ARDS (PReVENT) trial was conducted to test whether a ventilation strategy using low tidal volumes is superior to a ventilation strategy using intermediate tidal volumes with respect to the number of ventilator-free days and alive at day 28.

Key Points

Question In patients in the intensive care unit (ICU) who received invasive ventilation for reasons other than acute respiratory distress syndrome (ARDS), is a ventilation strategy with low tidal volume more effective than a strategy using intermediate tidal volume with respect to the number of ventilator-free days and alive at day 28?

Findings In this randomized clinical trial that included 961 patients in the ICU who were receiving invasive ventilation and expected to not be extubated within 24 hours of randomization, a ventilation strategy with low tidal volume did not result in a significant difference in ventilator-free days and alive at day 28 than a ventilation strategy with intermediate tidal volumes (median, 21 days vs 21 days).

Meaning Among patients in the ICU receiving invasive ventilation, a strategy with low tidal volume was not more effective than a strategy using intermediate tidal volume.

Methods

Study Design and Oversight

This was a randomized clinical trial conducted at the ICUs of 6 hospitals in the Netherlands. The protocol has been published[14]; the approved protocol is available in Supplement 1. An updated statistical analysis plan was written before closing the database; the final plan and a table describing the changes to the original study design are available in Supplement 2. The institutional review boards of all participating centers approved the study. Written deferred informed consent was obtained from patient representatives. An independent committee oversaw conduct of the trial and adverse events, while remaining blind to the primary end point at 2 predefined time points, and recommended the trial be continued. No interim analyses were performed.

Patients

The trial enrolled patients who received invasive ventilation shortly before or after admission to the ICU and who were expected not to be extubated within 24 hours of randomization. Patients were to be randomized within 1 hour of initiation of ventilation in the ICU. Exclusion criteria were the presence of ARDS, strictly following the criteria of the Berlin Definition for ARDS.[15] This exclusion criteria, however, did not mean that the lungs of included patients were healthy or uninjured. Other exclusion criteria were age younger than 18 years; pregnancy; ventilation lasting longer than 12 hours before admission to the ICU; increased and uncontrollable intracranial pressure; history of pulmonary disease; new pulmonary thromboembolism; and previously randomized in this trial.

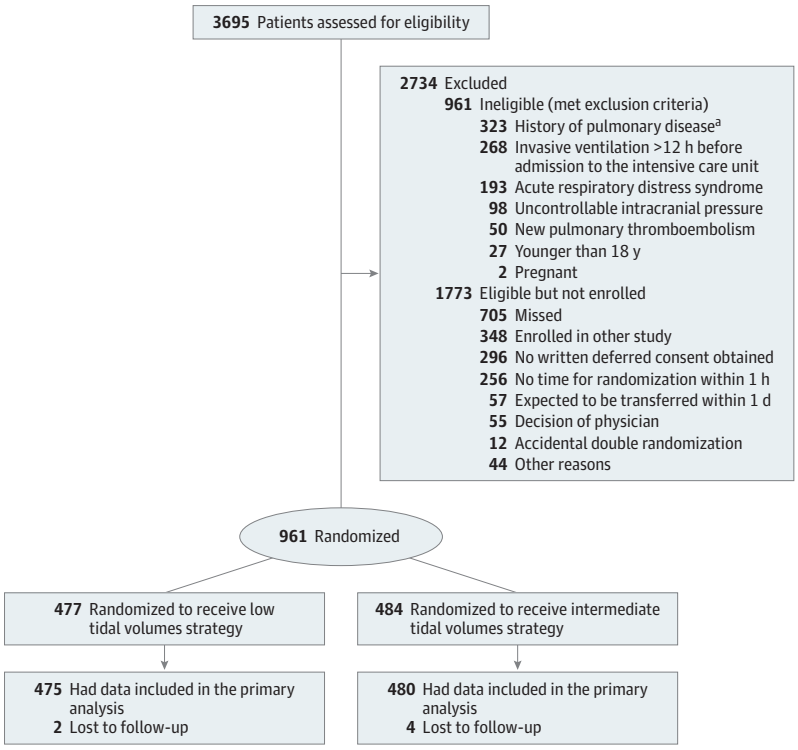
Randomization and Masking

Patients were randomized in a 1:1 ratio to a low or intermediate tidal volume ventilation strategy group. The local investigators performed randomization using a central, dedicated, password-protected, encrypted, web-based automated randomization system (SSL-encrypted website with ALEA software, TenALEA consortium, Amsterdam, the Netherlands). The randomization was conducted with random block sizes of a minimum of 2 and maximum of 6 patients, and was stratified for the center as well as for intubation location (intubated inside or outside the ICU).

Interventions

Patients assigned to the low tidal volume group started at a tidal volume of 6 mL/kg predicted body weight (PBW) and received either volume-controlled or pressure support ventilation. Tidal volume was then decreased by 1 mL/kg PBW every hour to a minimum of 4 mL/kg PBW. With pressure support ventilation, the lowest level of pressure support was used to reach the target tidal volume with a minimum of 5 cm H_2O. If tidal volume increased more than 8 mL/kg PBW with the minimum pressure support, this was to be accepted. In cases of severe dyspnea, increasing levels of discomfort with or without the need for more sedation, a respiratory rate higher than 35/min, uncontrollable acidosis, or patient-ventilator asynchrony, tidal volume could be increased in increments of 1 mL/kg PBW per hour in patients receiving volume-controlled or pressure support ventilation. Patients assigned to the intermediate tidal volume group started at a tidal volume of 10 mL/kg PBW using a volume-controlled ventilation mode. If the plateau pressure exceeded 25 cm H_2O, tidal volume was decreased in increments of 1 mL/kg PBW per hour. With pressure support ventilation, the pressure support level was adjusted to reach the target tidal volume while keeping the maximum airway pressure less than 25 cm H_2O. Ventilator settings were checked at least every 8 hours each day and were, if necessary, readjusted according to the protocol.

Figure 1. Flow of Patients in the PReVENT Trial



[a] Includes chronic obstructive pulmonary disease (COPD) stage III and IV in the GOLD classification, pneumectomy or lobectomy, and restrictive pulmonary disease. COPD GOLD III is defined as severe obstruction of the airways, with $FEV_1/FVC<70\%$, FEV_1 between 30% and 50% of predicted values. COPD GOLD IV is defined as very severe obstruction of the airways with $FEV_1/FVC<70\%$, FEV_1 below 30% of predicted values.

Additional use of analgosedation or muscle relaxants, with the purpose of allowing the assigned ventilation strategy, was not permitted. PBW was calculated using the following equations: 50 + 0.91 × (height [cm] − 152.4) for men and 45.5 + 0.91 × (height [cm] − 152.4) for women.[2] The assigned ventilation strategies were continued for a maximum of 28 days. If a patient required reintubation and additional invasive ventilation within this period, the tidal volume strategy to which the patient had been randomized was resumed.

Standard Care

Standard care followed strict local clinical guidelines (see eMethods in Supplement 3).

Weaning From Ventilator

Daily assessment of the ability to breathe with pressure support ventilation was conducted when fraction of inspired oxygen (FiO_2) was less than or equal to 0.4, or the positive end-expiratory pressure (PEEP) and FiO_2 levels were lower than the day before. In addition, the ventilator was switched to pressure support ventilation if the attending nurse or physician considered the patient awake enough to breathe with pressure support ventilation. Assessment of the ability to breathe with pressure support ventilation was also required if patient-ventilator asynchrony was noticed (eg, ineffective breathing, double triggering, use of accessory respiratory muscles).

A patient was assumed to be ready for extubation when the following criteria were met for at least 30 minutes: responsive and cooperative; adequate cough reflex; partial pressure of oxygen (Pa_{O_2}) and FiO_2 greater than 200 mm Hg, with an FiO_2 less than or equal to 40% and a respiratory rate of 8 to 30/min with no signs of respiratory distress (eg, marked accessory muscle use, abdominal paradox, diaphoresis, marked dyspnea); pressure support level less than or equal to 7 cm H_2O for the low tidal volume group and less than or equal to 12 cm H_2O for the intermediate tidal volume groups; temperature higher than 36.0°C and lower than 38.5°C; and hemodynamically stable (systolic blood pressure 80-160 mm Hg and heart rate 40 to 130/min) with no uncontrolled arrhythmia. Physicians and nurses could lower the pressure support level before extubation to determine whether patients could ventilate at the lowest support level. This was not mandatory, though, because extubation was allowed with higher pressures. For extubation with higher pressures, the pressure support level was lowered in increments of 2 to 5 cm H_2O per hour until it was less than or equal to 7 cm H_2O. If this pressure support level was not tolerated according to the conditions mentioned above, the pressure support level was set back to maintain a tidal volume per randomization and the patient was reassessed for extubation readiness in the following shift. The attending physician made the final decision for extubation.

Tracheostomy was preferably not performed within 10 days after the initiation of invasive ventilation. Indications included expected duration of ventilation of more than 14 days, a persistent Glasgow Coma Scale score less than 7 with inadequate swallow or cough reflex or retention of sputum, severe ICU-acquired weakness evaluated by

clinical inspection, and repeated respiratory failure after successive tracheal extubations.

Outcomes

The primary outcome was the number of ventilator-free days and alive at day 28, defined as the number of days that a patient was alive and free from invasive ventilation, calculated from the moment of randomization, if the period of unassisted breathing lasted longer than 24 consecutive hours. In cases of repeated intubation and extubation, periods free from invasive ventilation and lasting at least 24 consecutive hours were calculated and summed. Timing of intubation and extubation was captured in hours, and the number of hours a patient received invasive ventilation was used to calculate duration of ventilation. However, the primary end point was expressed in days. Patients who received invasive ventilation for more than 28 days were considered to have zero ventilator-free days. This is an objective and clinically relevant end point; protracted use of ventilation is associated with physiological and psychological sequelae[16-21] and complications, including ventilator-associated pneumonia and ICU-acquired weakness. Also, from an economic perspective, shortening of the duration of ventilation is relevant to reducing costs. One additional ventilator-free day and alive would approximate a reduction of 15% of the expected ventilation time in patients fulfilling the inclusion criteria of this trial.

In patients without tracheostomy, successful unassisted breathing was defined as extubation without the need for reintubation within 24 consecutive hours. In patients with tracheostomy, successful unassisted breathing was defined as breathing without ventilatory assistance for at least 24 hours.

Secondary outcomes included ICU and hospital length of stay; ICU, hospital, and 28- and 90-day mortality; and the occurrence of pulmonary complications, including the development of new ARDS,[15] ventilator-associated pneumonia,[22] severe atelectasis,[23] and pneumothorax. Mortality at day 28 was not included as a secondary outcome in the original protocol but was subsequently added in the updated protocol and statistical analysis plan. Other secondary outcomes were the amount of sedatives prescribed, use of analgesics and neuromuscular blocking agents, transfusion of blood products, need for decreasing dead space, and occurrence of delirium.[24] We failed to collect reliable data for the next planned secondary outcomes, and, therefore, the following are not reported: the occurrence of ICU-acquired weakness, changes in electrical activity of the diaphragm signals, and volatile organic compound composition of exhaled air.

Other Study Parameters

One study parameter concerned health care–related costs, for which information regarding costs of ventilation, time in the ICU and hospital, cumulative use of sedative drugs and neuromuscular blocking agents, use of tracheostomies, and costs related to treatment of ventilator-associated pneumonia were collected. An analysis of health care–related costs, however, is not reported in this article.

Statistical Analysis

A sample size of 952 patients (476 per group) was estimated to have 80% statistical power to show a difference of 1 ventilator-free day at day 28 from an estimated baseline SD of 5 days ($\alpha = .05$), allowing for a 20% dropout rate.

Baseline characteristics are reported as number and percentages or median and interquartile ranges (IQRs). Comparison of tidal volumes between groups over time was done using mixed-effect longitudinal models with random intercepts for hospitals and patients; time was treated as a continuous variable.

For analysis of the primary outcome, *t* tests were used with 95% CIs for superiority. In a sensitivity analysis, a generalized linear mixed model with stratification variables (hospital and intubation location) as random effects was tested.

ICU and hospital length of stay and mortality rates were compared using Kaplan-Meier survival curves and reported as hazard ratios calculated from a Cox proportional hazard model. The Schoenfeld residuals against the transformed time was used to test the proportional hazard assumptions. Survival time was calculated from time of randomization until time of death from any cause or to censoring, if patients were lost to follow-up.

Other secondary binary outcomes were assessed with risk ratio and 95% CIs calculated with the Wald likelihood ratio approximation test and χ^2 tests for hypothesis testing. The effect of the intervention on ICU and hospital length of stay was estimated with generalized linear models using inverse gaussian distribution.

In a prespecified exploratory analysis, the effects of the intervention on the primary outcome were investigated in subgroups based on the following patient categories: with vs without pneumonia; with vs without sepsis; Pao_2/Fio_2 less than or equal to 200 vs greater than 200; lung injury prediction score greater than or equal to 4 vs less than 4; surgical vs medical admission; Simplified Acute Physiology Score greater than or equal to 50 vs less than 50; invasive ventilation more than 6 hours before randomization vs less than or equal to 6 hours before; and intubation inside vs outside the ICU.

The effects in the subgroups were evaluated according to the interaction effects between each subgroup and the study groups by generalized linear models considering gaussian distribution.

The significance level for the primary and secondary outcomes was .05, without adjustment for multiple comparisons. Secondary outcomes and analyses were exploratory. Reported *P* values are 2-sided, and, because the amount of missing data for the primary outcome was less than 1%, only complete case analysis was carried out.

All analyses were performed using R software, version 3.4.1 (R Core Team).

Results

Patients

From September 1, 2014, through August 20, 2017, 3695 patients were screened. A total of 2734 patients were not enrolled, of whom 961 (35.1%) met exclusion criteria and 1773 (64.9%)

Table 1. Baseline Characteristics of the Patients

	Low Tidal Volume (n = 477)	Intermediate Tidal Volume (n = 484)
Age, median (IQR), y	68 (59-76)	67 (58-75)
Male patients, No. (%)	312 (65.4)	309 (63.8)
BMI, median (IQR)	24.9 (22.6-28.7)	25.5 (23.0-28.3)
PBW, median (IQR), kg[a]	70.1 (60.6-76.0)	69.7 (59.7-75.1)
SAPS II score, median (IQR)[b]	52 (40-63)	51 (39-62)
LIPS score, median (IQR)[c]	4.5 (3.0-7.0)	4.5 (3.0-6.5)
Patients at risk for ARDS, No. (%)	292 (61.6)	290 (60.3)
SOFA score, median (IQR)[d]	8 (6-11)	8 (6-10)
Septic shock	82 (17.6)	74 (15.5)
Patient tobacco use, No. (%)		
Never	106 (22.3)	111 (23.0)
Current	97 (20.4)	97 (20.1)
Previous	75 (15.8)	80 (16.6)
Unknown	197 (41.5)	194 (40.2)
Patient alcohol use, No. (%)		
None	121 (25.5)	92 (19.1)
0-5 drinks/wk	47 (9.9)	61 (12.7)
6-14 drinks/wk	26 (5.5)	30 (6.2)
>2 drinks/d	59 (12.4)	56 (11.6)
Unknown	222 (46.7)	243 (50.4)
Reason for ICU admission, No. (%)		
Surgical	82 (17.3)	79 (16.4)
Medical	393 (82.7)	403 (83.6)
Initial intubation was in the ICU, No. (%)	209 (43.8)	215 (44.4)
Reason for intubation, No. (%)		
Cardiac arrest	110 (23.1)	120 (24.8)
Postoperative ventilation	82 (17.2)	79 (16.3)
Pneumonia	77 (16.1)	77 (15.9)
Sepsis	50 (10.5)	46 (9.5)
Airway protection	39 (8.2)	39 (8.1)
Cardiac failure	28 (5.9)	17 (3.5)
Head trauma or brain surgery	25 (5.2)	31 (6.4)
Aspiration	20 (4.2)	24 (5.0)
Non-septic shock	8 (1.7)	10 (2.0)
Airway obstruction	7 (1.5)	1 (0.2)
Neuromuscular disease	6 (1.3)	3 (0.6)
Hypercapnic respiratory failure	4 (0.8)	10 (2.0)
Other types of respiratory failure	4 (0.8)	4 (0.8)
Trauma	3 (0.6)	4 (0.8)
Other causes	14 (2.9)	19 (3.9)
Hours ventilated before randomization, median (IQR)	0.9 (0.3-2.0)	0.9 (0.4-2.1)
Mode of ventilation before randomization, No. (%)		
Volume-controlled	143 (30.0)	154 (31.8)
Pressure support	98 (20.5)	91 (18.8)
Pressure-controlled	236 (49.5)	239 (49.4)
Respiratory measures before randomization, median (IQR)		
Tidal volume, mL/kg PBW	7.0 (6.0-8.3)	7.3 (6.3-8.8)
Plateau pressure, cm H_2O	18.0 (14.7-21.0)	20.0 (16.0-24.0)
Respiratory rate, /min	20 (16-22)	20 (16-22)
PEEP, cm H_2O	7 (5-8)	7 (5-8)
Driving pressure, cm H_2O	11.0 (8.7-14.0)	13.0 (10.0-16.0)
FiO_2	0.50 (0.40-0.70)	0.50 (0.40-0.65)
Pao_2 / FiO_2, mm Hg	197 (127-298)	195 (133-300)
$Paco_2$, mm Hg	42.7 (37.5-50.2)	42.7 (36.0-51.0)
Arterial pH	7.31 (7.22-7.38)	7.30 (7.22-7.38)

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index calculated as weight in kilograms divided by height in meters squared; ICU, intensive care unit; LIPS, Lung Injury Prediction Score; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

[a] PBW was calculated as 50 + 0.91 × (height [cm] − 152.4) for men and 45.5 + 0.91 × (height [cm] − 152.4) for women.

[b] SAPS II score ranges from 0 to 163, with higher values indicating a more severe condition.

[c] LIPS score ranges from 0 to 33.5, with higher values indicating a higher risk of ARDS. Patients with scores ≥4 are considered high risk.

[d] SOFA score ranges from 0 to 24 with higher values indicating a more severe condition.

were eligible but were not enrolled for other reasons (**Figure 1**). Of the 961 randomized patients enrolled in the study, 477 were allocated to the low tidal volume group and 484 to the intermediate tidal volume group. Data for all 961 patients were considered for the primary analysis (Figure 1). Follow-up to day 28 was incomplete for 6 patients.

Baseline characteristics were well balanced between groups (**Table 1**). More than 80% of the patients were admitted to the ICU for a medical reason. The most frequent reason for invasive ventilation was cardiac arrest.

Intervention

The median time between the start of ventilation and randomization was 0.88 hours (IQR, 0.36-2.01); the median time between start of ventilation in the ICU and randomization was 0.57 hours (IQR, 0.23-1.00). During the first 3 days of ventilation, tidal volumes and airway pressures were significantly different among the groups (eTables 1, 2, and 3, eFigures 2, 3, and 4 in Supplement 3). Plateau and driving pressure were lower and respiratory rate was higher in the low tidal volume group than in the intermediate tidal volume group, while minute ventilation and PEEP did not differ significantly between groups. Pao_2 and FiO_2 did not differ between groups. Partial pressure of carbon dioxide was higher and arterial pH was lower in the low tidal volume group than the intermediate tidal volume group.

Outcomes

Twenty-eight days after randomization, patients in both groups had a median of 21 ventilator-free days (IQR, 0-26) (mean difference, -0.27 [95% CI −1.74 to 1.19]; P = .71; **Table 2** and eFigure

Table 2. Clinical Outcomes of Patients in the Low and Intermediate Tidal Volumes Groups

	Low Tidal Volume (n = 477)	Intermediate Tidal Volume (n = 484)	Mean Difference[a] (95% CI)	*P* Value
Primary outcome	n = 475	n = 480		
Days ventilator-free at day 28				
Mean (SD)	15.2 (11.6)	15.5 (11.4)	−0.27 (−1.74 to 1.19)[a]	.71
Median (IQR)	21 (0-26)	21 (0-26)		
Days of ventilation in surviving patients				
Mean (SD)	5.4 (6.6)	6.0 (7.3)	−0.56 (−1.61 to 0.49)[a]	
Median (IQR)	3 (1-6)	3 (1-8)		
Secondary outcomes	n = 475	n = 481		
ICU length of stay[b]				
Mean (SD)	9.6 (13.3)	9.2 (9.9)		.58
Median (IQR)	6 (3 to 11)	6 (3 to 11)	0.39 (−1.09 to 1.89)[a]	
Hospital length of stay[b]				
Mean (SD)	20.4 (23.8)	21.0 (21.1)		.68
Median (IQR)	14 (6-26)	15 (8-26)	−0.60 (−3.52 to 2.31)[a]	
Mortality, No./total (%)				
ICU	132/450 (29.3)	115/458 (25.1)	RR, 1.11 (0.96-1.27)[c]	.15
Hospital	151/477 (31.7)	140/484 (28.9)	RR, 1.06 (0.93-1.22)[c]	.35
28-day	166/476 (34.9)	155/483 (32.1)	HR, 1.12 (0.90-1.40)[d]	.30
90-day	186/476 (39.1)	181/479 (37.8)	HR, 1.07 (0.87-1.31)[d]	.54
Development of ARDS, No./total (%)	17/448 (3.8)	23/462 (5.0)	RR, 0.86 (0.59-1.24)[c]	.38
Development of pneumonia, No./total (%)	19/450 (4.2)	17/462 (3.7)	RR, 1.07 (0.78-1.47)[c]	.67
Pneumothorax, No./total (%)	8/448 (1.8)	6/462 (1.3)	RR, 1.16 (0.73-1.84)[c]	.55
Atelectasis, No./total (%)	51/449 (11.4)	52/464 (11.2)	RR, 1.00 (0.81-1.23)[c]	.94
Extrapulmonary infection, No./total (%)	20/448 (4.5)	28/463 (6.0)	RR, 0.84 (0.60-1.18)[c]	.28
Extrapulmonary sepsis, No./total (%)	12/448 (2.7)	16/463 (3.5)	RR, 0.87 (0.56-1.33)[c]	.50
Delirium, No./total (%)	149/343 (43.4)	132/361 (36.6)	RR, 1.15 (0.99-1.34)[c]	.06
Need for tracheostomy, No./total (%)	54/477 (11.3)	52/484 (10.7)	RR, 1.03 (0.84-1.26)[c]	.78

Abbreviations: ARDS, acute respiratory distress syndrome; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; RR, risk ratio.

[a] Effect estimate is mean difference. *P* values calculated using *t* tests for the primary outcome and generalized linear models using inverse gaussian distribution for ICU and hospital length of stay.

[b] Calculated as the number of days from the time of randomization.

[c] Effect estimate is risk ratio. 95% confidence intervals calculated with Wald likelihood ratio approximation test and *P* values calculated with χ^2 tests.

[d] Effect estimate is hazard ratio. 95% confidence intervals and *P* values calculated with Cox proportional hazard.

1 in Supplement 3). Results of the analysis with stratification variables as random effect is consistent with results of the primary analysis (*P* = .72).

Median length of ICU and hospital stay, ICU and hospital mortality rates, and mortality at 28 and 90 days were not different between groups (Table 2 and **Figure 2**).

Occurrence of ARDS, pneumonia, severe atelectasis, and pneumothorax did not significantly differ between groups (Table 2). There was also no difference between groups with respect to the need for, duration of, and amount of sedatives, analgesics, and neuromuscular blocking agents (eTable 4 in Supplement 3) or the development of delirium (Table 2). Fluid balance, transfusion of blood product, and use of recruitment maneuvers and other rescue therapies for impairment of gas exchange did not differ between groups.

Subgroups and Exploratory Analyses

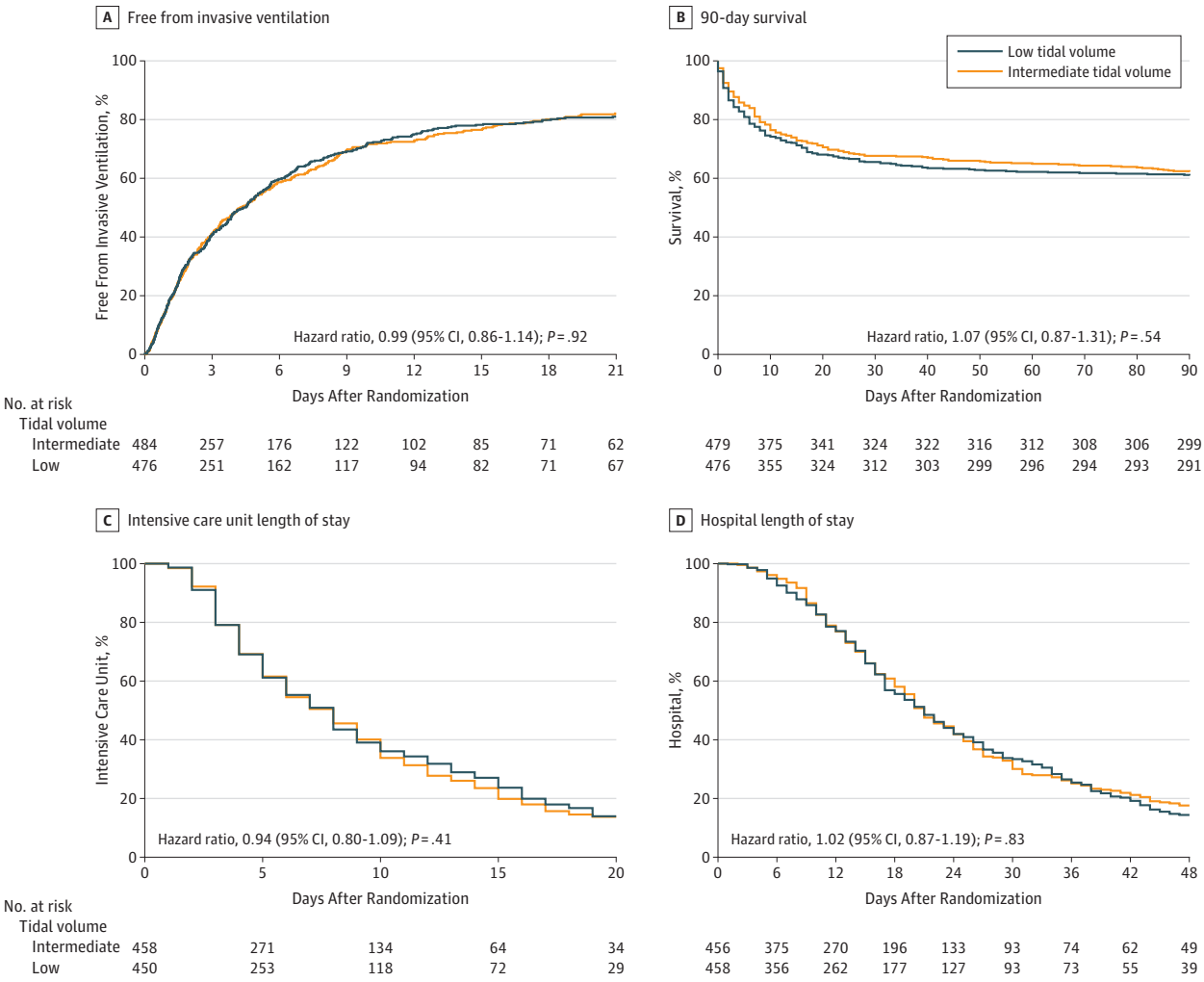
With respect to the location of intubation (inside vs outside the ICU), there was a significant interaction in the effect of tidal volume on the primary outcome in patients intubated inside the ICU (mean difference, -2.50 [IQR, -4.63 to -0.36]) vs patients intubated outside the ICU (mean difference, 1.45 [IQR -0.52 to 3.43]; *P* for interaction = .01). Additional exploratory analyses revealed no differences (eTable 5 in Supplement 3).

Discussion

In this trial of adult patients in the ICU without ARDS who received invasive ventilation and were expected to not be extubated within 24 hours of randomization, a ventilation strategy using low tidal volume was not more effective than a strategy using intermediate tidal volume with respect to the number of ventilator-free days and alive at day 28. In addition, there was not a difference in length of stay, mortality rate, or in the occurrence of pulmonary complications between the groups. The low tidal volume strategy was associated with respiratory acidosis.

To our knowledge, this is the largest randomized clinical trial to investigate the role of tidal volumes in patients without ARDS and to measure a clinically relevant patient-centered outcome. This composite endpoint was chosen because it reflects the duration of ventilation in surviving patients but also mortality, which remains high in the ICU. A significant

Figure 2. Kaplan-Meier Estimates for Patients in the Low Tidal Volume and Intermediate Tidal Volume Ventilation Groups



A, Median (IQR) observation period for the duration free from invasive ventilation was 4.4 days (3.7 to 5.1) for the low tidal volumes group and 4.3 days (3.4 to 5.2) for the intermediate tidal volumes group; *P* value for the Schoenfeld residuals was .68. B, Median observation time for survival was not computed for 90-day mortality because the minimum value observed is 0.60; *P* value for the Schoenfeld residuals was .13. C, Median (IQR) observation period for intensive care unit length of stay was 8.0 days (7.0 to 8.0) for the low tidal volumes group and 8.0 days (6.0 to 9.0) for the intermediate tidal volumes group; *P* value for the Schoenfeld residuals was 0.21. D, Median (IQR) observation period for hospital length of stay was 21.0 days (19.0 to 23.0) for the low tidal volumes group and 21.0 days (20.0 to 24.0) for the intermediate tidal volumes group; *P* value for the Schoenfeld residuals was .82.

difference in mortality between the groups was not expected. However, the composite outcome was considered a better indicator of the potential effect on actual duration of ventilation, which could otherwise have been difficult to discern given the high mortality rates in both groups. The study was designed to minimize bias by using concealed allocation and an intention-to-treat analysis with a pragmatic protocol that was strictly adhered to. The study involved 6 centers, university hospitals and nonuniversity teaching hospitals, contributing to its generalizability, with marginal loss to follow-up. To minimize a possible carry-over effect, it was aimed to perform randomization within 1 hour, and always as soon as possible, after start of ventilation in the ICU. In addition, patients were enrolled in the trial over a period of 3 years, during which standardized care did not change.

The present study had several differences compared with 2 similar studies.[5,6] Time between start of ventilation and randomization and the necessary expected duration of ventilation was much shorter in this study than the others. In the intermediate tidal group, tidal volume was 9 mL/kg PBW compared with 10^6 and 12^5 mL/kg PBW in the control groups of other studies, and inspiratory pressure was limited. Duration of ventilation before randomization, time on volume-controlled ventilation, and duration of sedation were shorter in this study than in the previous studies.[5,6] Because pressure support was used more frequently, the tidal volume in the low tidal group (7 mL/kg PBW) was slightly higher than the intervention groups in other studies (6 mL/kg PBW).[5,6]

The number of ventilator-free days in the patient population is comparable to that reported in a worldwide observational

study[25] and did not differ between groups, which is in line with previous data.[6] One possible explanation for the lack of differences in ventilator-free days between groups is that the level of distending pressures induced by an intermediate tidal volume was still within a protective range for patients without ARDS. In addition, the low tidal volume strategy was associated with respiratory acidosis, which could have influenced duration of ventilation. One sensitivity analysis showed that the combination of intubation in the ICU and assignment to a low tidal volume ventilation strategy was associated with less ventilator-free days. Although these findings must be considered exploratory, they support the idea that it may not be necessary to pursue a low tidal volume strategy instead of an intermediate tidal volume strategy. Tidal volume restriction in both volume-controlled and pressure support ventilation was associated with an increase in CO_2 retention and respiratory acidosis. The increase in partial pressure of carbon dioxide in volume-controlled ventilation was not satisfactorily compensated by the increase in respiratory rate, as reflected by constant minute ventilation. Thus, higher respiratory rate alone in volume-controlled ventilation may be less physiologic than the combined increase of respiratory rate and tidal volume in pressure support ventilation. The data indicate that a low tidal volume strategy promotes less efficient alveolar ventilation than an intermediate tidal volume strategy, mainly in volume-controlled ventilation. It is important to note that low tidal volume ventilation did not require more sedation in patients who were mostly receiving spontaneous ventilation.

Limitations

This study has several limitations. First, blinding was not possible because of the nature of the intervention, which could be a major concern. However, attending nurses and physicians did not show specific interest in the trial or its primary outcome and there were no differences in respiratory care, sedation practice, and rescue therapies. Second, a heterogeneous group of patients without ARDS was included, but subanalysis of 2 important groups, patients with pneumonia and sepsis, did not reveal interaction. Third, a substantial number of patients was missed for randomization, which was an understandable consequence of the short time that was allowed for randomization. Fourth, although the intention was to randomize patients within 1 hour after start of ventilation in the ICU, randomization at this time was in some cases unpractical or impossible. Still, the majority of patients were randomized within 1 hour, which is a relatively short period compared with the duration of ventilation after randomization (ie, hours vs days). Fifth, these data do not exclude potential harm from tidal volumes higher or lower than those used in the present trial.

Conclusions

In patients in the ICU without ARDS who were expected to not be extubated within 24 hours, a low tidal volume strategy did not result in a greater number of ventilator-free days compared with an intermediate tidal volume strategy.

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