A Few Milliliters of Prevention: Lung-Protective Ventilation Decreases Pulmonary Complications*

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The association between mechanical ventilation with high tidal volumes and ventilator-induced lung injury has long been recognized, and this understanding has slowly led to changes in the practice of mechanical ventilation (1–3). Lung-protective ventilation, including tidal volumes targeting 6 mL/kg of predicted body weight (PBW) and plateau pressures less than or equal to 30 cm H_2O, is now considered the standard of care for patients with acute respiratory distress syndrome (ARDS). This change was driven by a landmark randomized controlled trial by the ARDS network of investigators demonstrating lower mortality in patients ventilated with a lung-protective ventilation strategy (i.e., tidal volume of 6 mL/kg PBW and plateau pressure ≤ 30 cm H_2O) compared with a traditional, and more liberal, ventilation approach (i.e., tidal volume of 12 mL/kg PBW and plateau pressure ≤ 50 cm H_2O) (4).

Since the publication of that study in 2000, there has been a growing body of evidence that suggests that the use of lung-protective ventilation also improves clinical outcomes in patients without ARDS. The use of lower tidal volumes intraoperatively was associated with an almost two-thirds decrease in postoperative complications in a randomized controlled trial of intermediate- to high-risk patients undergoing abdominal surgery (5). A 2012 meta-analysis of patients without ARDS in both surgical and nonsurgical ICUs concluded that mechanical ventilation with low tidal volumes compared with high tidal volumes decreased the risk for lung injury, pulmonary infections, and mortality (6).

The article by Serpa Neto et al (7) in this issue of *Critical Care Medicine* provides further insight into the potential benefits of low tidal volume ventilation in patients without ARDS. This patient-level meta-analysis examined the association between tidal volumes and the occurrence of a composite outcome of pulmonary complications (i.e., ARDS and pneumonia) in patients without ARDS at the time of intubation. The study analyzed tidal volumes used during the first 2 days of mechanical ventilation categorized as high (> 10 mL/kg PBW), intermediate (7–10 mL/kg PBW), and low (< 7 mL/kg PBW). The study concluded that mechanical ventilation with low tidal volumes during the first 2 days of mechanical ventilation decreased the risk of pulmonary complications compared with high tidal volumes by 28%. Although comparison between the low and intermediate tidal volume groups did not achieve statistical significance, the 8% lower risk of complications in the low tidal volume group appears to support a dose-response relationship between tidal volume and the pulmonary complications.

By performing an individual patient data meta-analysis, the authors were able to standardize the analysis of data obtained from multiple studies, which is an important strength of this study. They defined a consistent exposure and outcome for all patients included in the analysis and were able to adjust the analysis for important potential confounders including patient severity of illness (e.g., Acute Physiology and Chronic Health Evaluation score and baseline $Pa_{O_2}/F_{I_{O_2}}$ ratio). Furthermore, the analysis included a large sample of both medical and surgical ICU patients who were ventilated for at least 48 hours, which improves the generalizability of their findings.

Still, conclusions from this study should be tempered by several limitations. Patients from observational studies comprised the majority of patients (93%) included in the primary analysis, which may increase the possibility for bias. Data on several important confounders, such as fluid balance and use of blood products, were also not available for inclusion in the analysis. Patient data from one of the eight studies identified in the systematic review were unavailable for inclusion in the analysis, potentially influencing the results.

The absence of a high-quality randomized controlled trial to support this practice is a reason for caution. A commonly cited concern is that using low tidal volumes could result in patient discomfort, leading to increased sedative use and an

*See also p. 2155.

Key Words: adult respiratory distress syndrome; artificial respiration; critical care; evidence-based medicine; quality of healthcare

Dr. Martin served as a board member for Pulsion Medical Systems (Medical advisory board) and the Society of Critical Care Medicine (Council/Board of directors); consulted for Grifols (Medical advisory board), Cumberland Pharmaceuticals (Data safety monitoring board), and Siemens (Clinical study review board); and received support for article research from the National Institutes of Health (NIH). His institution consulted for Vanderbilt University (Data safety monitoring board) and received grant support from the NIH, Food and Drug Administration, Baxter Healthcare, and Abbott Laboratories. The remaining authors have disclosed that they do not have any potential conflicts of interest.

DOI: 10.1097/CCM.0000000000001234

increased duration of mechanical ventilation (8). However, secondary analysis of a randomized controlled trial in ARDS patients showed no difference in sedative use when comparing lung-protective ventilation with conventional ventilation (9, 10). In a recent meta-analysis by the authors of this current study, there was a decrease in the duration of mechanical ventilation in the lung-protective ventilation group, with no difference in sedative or opioid use when comparing patients with a tidal volume less than or equal to 6 mL/kg PBW and greater than or equal to 10 mL/kg PBW (11).

Further defining the relationship between tidal volumes and pulmonary complications is the focus of ongoing research. Two randomized controlled trials are currently enrolling patients and may provide additional evidence to inform the most appropriate tidal volume for critically ill patients without ARDS. The Preventive Strategies in Acute Respiratory Distress Syndrome trial is a multicenter randomized controlled trial comparing low tidal volume ventilation (4–6 mL/kg PBW) with high tidal volumes (8–10 mL/kg PBW) in patients at risk for ARDS (12). The primary outcome of this study is the development of ARDS during the first 7 days of mechanical ventilation. The Protective Ventilation in Patients without ARDS at Start of Ventilation trial is a multicenter randomized controlled trial comparing low tidal volume ventilation (4–6 mL/kg PBW) with high tidal volumes (8–10 mL/kg PBW) in patients without ARDS who are anticipated to require mechanical ventilation for more than 24 hours (13). The primary endpoint is the number of ventilator-free days and alive at day 28. These studies are estimated to complete enrollment in 2016 and 2017, respectively.

So should lung-protective ventilation be the default strategy in all critically ill mechanically ventilated patients? The preponderance of available evidence suggests that lung-protective ventilation reduces pulmonary complications and improves outcomes. This strategy would also help ensure the early delivery of lung-protective ventilation in patients with ARDS including those for whom the diagnosis is delayed as there is recent evidence demonstrating that delaying low tidal volume ventilation worsens outcomes (14).

Tidal volume is an important determinant of the clinical outcomes of mechanically ventilated patients. It is easily measured and readily changed, making it a suitable metric for assessing the quality of care provided to mechanically ventilated patients and for use in quality improvement efforts (15). Based on the current evidence, we recommend that mechanically ventilated ARDS patients receive tidal volumes of 6 mL/kg PBW and other patients, excepting those with contraindications to lower tidal volumes, receive tidal volumes of less than 8 mL/kg PBW. Critical care teams should implement systems to improve their ability to consistently provide lung protective ventilation and routinely monitor the tidal volumes provided to patients in their ICUs.

As we await further evidence to guide our practice tomorrow, we must deliver potentially lifesaving mechanical ventilation and avoid preventable harm today. Although not definitive, the available evidence suggests that using lower tidal volumes reduces pulmonary complications and improves clinical outcomes in broad groups of mechanically ventilated patients. Time will tell the ideal tidal volume for all subgroups of mechanically ventilated patients, but we cannot wait while patient lives are at stake.

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Lung-Protective Ventilation With Low Tidal Volumes and the Occurrence of Pulmonary Complications in Patients Without Acute Respiratory Distress Syndrome: A Systematic Review and Individual Patient Data Analysis*

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000001189

Objective: Protective mechanical ventilation with low tidal volumes is standard of care for patients with acute respiratory distress syndrome. The aim of this individual patient data analysis was to determine the association between tidal volume and the occurrence of pulmonary complications in ICU patients without acute respiratory distress syndrome and the association between occurrence of pulmonary complications and outcome in these patients.

Design: Individual patient data analysis.

Patients: ICU patients not fulfilling the consensus criteria for acute respiratory distress syndrome at the onset of ventilation.

Interventions: Mechanical ventilation with low tidal volume.

Measurements and Main Results: The primary endpoint was development of a composite of acute respiratory distress syndrome and pneumonia during hospital stay. Based on the tertiles of tidal volume size in the first 2 days of ventilation, patients were assigned to a "low tidal volume group" (tidal volumes ≤ 7 mL/kg predicted body weight), an "intermediate tidal volume group" (> 7 and < 10 mL/kg predicted body weight), and a "high tidal volume group" (≥ 10 mL/kg predicted body weight). Seven investigations (2,184 patients) were included. Acute respiratory distress syndrome or pneumonia occurred in 23% of patients in the low tidal volume group, in 28% of patients in the intermediate tidal volume group, and in 31% of the patients in the high tidal volume group (adjusted odds ratio [low vs high tidal volume group], 0.72; 95% CI, 0.52–0.98; $p = 0.042$). Occurrence of pulmonary complications was associated with a lower number of ICU-free and hospital-free days and alive at day 28 (10.0 ± 10.9 vs 13.8 ± 11.6 d; $p < 0.01$ and 6.1 ± 8.1 vs 8.9 ± 9.4 d; $p < 0.01$) and an increased hospital mortality (49.5% vs 35.6%; $p < 0.01$).

Conclusions: Ventilation with low tidal volumes is associated with a lower risk of development of pulmonary complications in patients without acute respiratory distress syndrome. (*Crit Care Med* 2015; 43:2155–2163)

Key Words: acute respiratory distress syndrome; individual patient analysis; intensive care unit and in-hospital stay; mechanical ventilation; mortality; pulmonary complications; tidal volume

A large randomized controlled trial (RCT) showed that use of low tidal volumes improves survival in ICU patients with acute respiratory distress syndrome (ARDS) (1). Since then, low tidal volume ventilation has become standard of care in patients with this life-threatening complication (2). In a subsequent RCT, low tidal volume ventilation was associated with a lower incidence of development of ARDS in ICU patients (3). However, that trial was rather small and stopped prematurely, possibly leading to an overestimation of the beneficial effects of use of low tidal volumes (4). Consequently, ICU clinicians remain uncertain on whether low tidal volumes should be used in all ICU patients, that is, irrespective of the presence of ARDS (5, 6).

Given the current lack of well-powered RCTs comparing the use of low versus conventionally sized tidal volumes in ICU patients without ARDS, we recently performed an individual patient data analysis of all available observational studies and RCTs (7). This analysis suggests benefit of a low tidal volume ventilation strategy, as use of low tidal volumes was associated with a shorter duration of ventilation. We did not evaluate whether the use of low tidal volumes is associated with the occurrence of pulmonary complications, and if so, how this could affect outcome.

In the present individual patient data analysis, we investigated 1) the association between tidal volume size and occurrence of pulmonary complications in ICU patients without ARDS, 2) the association between occurrence of pulmonary complications and duration of stay in ICU and hospital, and 3) crude and attributable mortality of pulmonary complications. We hypothesized that the occurrence of pulmonary complications depends on tidal volume size in ICU patients without ARDS at the onset of ventilation.

MATERIALS AND METHODS

Search Strategy

A sensitive search strategy followed Medical Subject Headings and Keywords (protective ventilation OR lower tidal volume OR low tidal volume OR positive end-expiratory pressure OR positive end expiratory pressure OR PEEP).

Selection of Studies

Articles reporting on observational studies or RCTs of "protective ventilation" in ICU patients identified by the search and reporting outcomes of interest were screened for inclusion. Key inclusion criteria were as follows: 1) clear reporting of the size of tidal volume, at least in the first days of ventilation; 2) adult (i.e., age > 18 yr) patients ventilated in the ICU; and 3) without ARDS at the onset of ventilation (Pao_2/Fio_2 > 300 or without infiltrates on the chest radiograph). Studies or trials were excluded from the analysis if they: 1) reported on patients receiving only ventilation during general anesthesia for surgery or (2) included patients who had ARDS at the start of ventilation. The quality of the RCTs was based on the Jadad score and the following four criteria: allocation concealment, baseline similarity, early stopping, lost to follow-up, and intention-to-treat analysis. The quality of the non-RCTs was based on the "Downs and Black" checklist (8).

Ventilator Variables

The corresponding authors of retrieved articles were contacted. After approval, they were asked to provide the daily ventilation variables of individual patients via a specially prepared datasheet (an example is shown in the **Supplementary Appendix**, Supplemental Digital Content 1, http://links.lww.com/CCM/B370).

Primary Outcome

The primary outcome was a composite of occurrence of ARDS or pneumonia, the two most important pulmonary complications in intubated and ventilated critically ill patients (9). ARDS or pneumonia during follow-up was diagnosed by the diagnostic criteria used by the investigators of the included studies and trials. We combined pneumonia and ARDS into a single primary endpoint because in the absence of specific diagnostic tools, for example, bronchoalveolar lavage fluid testing, ARDS can be mistakenly diagnosed as pneumonia (9–12). Furthermore, both entities may be influenced by mechanical ventilation (13).

Secondary Outcomes

Secondary outcomes included: 1) duration of stay in ICU and hospital, using the number of ICU-free days and alive and hospital-free days and alive at day 28; 2) in-hospital mortality, defined as death at any time during hospital stay; 3) incidence rate of pulmonary complications, calculated as number of cases person-years = ([number of cases/person-day] × [365 person-day/1 person-year]); and 4) attributable mortality of pulmonary complications, calculated by subtracting the in-hospital mortality rate of patients without pulmonary complications from the in-hospital mortality of patients with pulmonary complications.

Statistical Analysis

In all analyses, patients were analyzed according to the tidal volume size that was used in the first 2 days of ventilation. Patients were followed until hospital discharge, or death, whichever came first.

The cutoff of 2 days was chosen because of two reasons. First, on average, in the cohort of patients under study, ARDS was diagnosed on the third day of ventilation. Second, patients who developed ARDS could be expected to have received

ventilation with low tidal volumes from the moment ARDS was present.

Patients were stratified into three groups: a "low tidal volume group," with tidal volumes less than or equal to 7 mL/kg predicted body weight (PBW); an "intermediate tidal volume group," with tidal volumes greater than 7 and less than 10 mL/kg PBW; and a "higher tidal volume group," with tidal volumes greater than or equal to 10 mL/kg PBW. The cutoffs for tidal volume groups were chosen based on the tertiles of tidal volume sizes in the complete cohort, alike a previous observational study on ventilation practice in patients without ARDS (14). The investigators of studies included in the analysis provided us with a tidal volume per day for the first 2 days of all patients—these were averaged per patients and reported as medians per group. In all studies, PBW was calculated as in the landmark study of lower tidal volume ventilation in patients with ARDS (**Appendix Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B370) (1). Patients who received ventilation with tidal volumes in two different groups of tidal volume size in the first 2 days of ventilation (e.g., < 7 mL/kg PBW in day 1 and > 7 mL/kg PBW in day 2) were excluded from the analysis.

For the primary endpoint, development of ARDS or pneumonia, we calculated odds ratios (ORs) and 95% CIs using logistic regression. We used a multivariable hierarchical model with baseline patient characteristics (age, risk of death based on score [e.g., Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, and others], baseline Pao_2/Fio_2, and baseline pH) as important prognostic factors according to previous studies (13). Also, to compare in-hospital time to death for the groups, we fitted Cox regression models with the same covariables resulting in hazard ratios (HRs).

The number of ICU-free days and alive at day 28 was calculated as the number of days alive and outside ICU at day 28. The number of hospital-free days and alive at day 28 was calculated as the number of days alive and outside the hospital at day 28. Kaplan-Meier curves were constructed and log-rank tests were used to determine the univariate significance of the study variables.

A priori subgroup analyses were used to assess the effect of tidal volume size on primary outcome in the following prespecified subgroups: 1) type of study (RCT vs non-RCT); 2) mode of ventilation (volume vs pressure controlled); 3) age (< 65 vs ≥ 65 yr); 4) gender (male vs female); 5) baseline Pao_2/Fio_2 (≥ 300, between 200 and 300, < 200); 6) respiratory rate (≤ 15 bpm vs between 15 and 20 bpm vs ≥ 20 bpm); and 7) minute ventilation (≤ 8 L/min vs between 8 and 10 L/min vs ≥ 10 L/min). Finally, the patients were also stratified post hoc according to the diagnosis at ICU admission: 1) trauma or postoperative; 2) neurologic (traumatic brain injury, stroke, and status epilepticus); and 3) others (cardiac arrest, sepsis, and other causes).

A probability and unit (PROBIT) regression analysis was used to characterize the dose-response relationship between median tidal volume in mL/kg PBW during the first 2 days of ventilation and probability of pulmonary complications while adjusting for the same set of covariates used in the final regression model. A cubic or quadratic term was used in the final model according to the use of a fractional polynomial method.

All analyses were conducted with SPSS v.20 (IBM, Armonk, NY) and R v.2.12.0 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, two-sided p values less than 0.05 were considered significant. The project was approved by the Ethics Committee of the Hospital Israelita Albert Einstein.

RESULTS

Search Results and Collection of Individual Patient Data

The search identified four observational studies and four RCTs (3, 15–21). We were not able to collect data from one RCT because the corresponding author could not be contacted (21). The authors of the three other RCTs provided sufficient data for calculation of clinical outcomes (3, 18, 19). One RCT was conducted in patients undergoing elective cardiac surgery, from which we included only the data of patients ventilated in the ICU after surgery for at least 2 days (19). Regarding the available data in each study, only four studies could be included in the analysis of the primary outcome (15–17, 20); all studies were included in the analysis of secondary outcomes, including ICU and hospital length of stay and overall survival. The concordance between size of tidal volumes used during surgery (randomization, 6 vs 10) and the allocation of the patients in the groups of this particular study was high (96.3%), probably diminishing the chance of contamination of the tidal volume size used during surgery.

We excluded 64 patients because the tidal volume used in the first and in the second day differed importantly. Eventually, the total enrollment based on the RCTs and observational studies was 2,184 patients (**Appendix Fig. 1** and **Appendix Tables** 2 and **3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B370). Distribution of tidal volumes is shown in **Appendix Figure 4** (Supplemental Digital Content 1, http://links.lww.com/CCM/B370). Four studies diagnosed ARDS using the American-European Consensus Conference criteria for ARDS (3, 15–17), one using the Berlin definition for ARDS (20); in two studies, ARDS was not scored (18, 19). For pneumonia, three studies used a criteria combining chest radiograph readings (3, 17, 20), clinical signs, and airway sample cultures; in four studies, pneumonia was not scored (15, 16, 18, 19). The quality of the RCTs is shown in Appendix Table 2 (Supplemental Digital Content 1, http://links.lww.com/CCM/B370) and the non-RCTs in **Appendix Table 5** (Supplemental Digital Content 1, http://links.lww.com/CCM/B370).

Patient Characteristics and Ventilator Settings

Table 1 details the distribution of demographic characteristics in the three predefined tidal volume groups. The only difference is a higher PBW in low tidal volume group. **Appendix Table 6** (Supplemental Digital Content 1, http://links.lww.com/CCM/B370) details the distribution of ventilation variables. In the low tidal volume group, respiratory rate was higher and

TABLE 1. Baseline Characteristics of Included Patients According to Tidal Volume Received[a]

Variables	Less Than or Equal to 7 mL/kg PBW (*n* = 720)	Greater Than 7 and Less Than 10 mL/kg PBW (*n* = 754)	Greater Than or Equal to 10 mL/kg PBW (*n* = 710)
Age, yr	62.1 ± 16.6	63.5 ± 15.7	64.2 ± 16.0
Gender, female	232 (32.2)	296 (39.2)	253 (35.6)
PBW, kg	69.7 ± 9.7	64.8 ± 9.9	60.8 ± 11.8[b]
Design of the study, randomized controlled trial	106 (14.7)	35 (4.6)	84 (11.8)[b]
Acute Physiology and Chronic Health Evaluation II	21.67 ± 8.6	21.6 ± 8.2	21.3 ± 8.5
Pao_2/Fio_2	272.9 ± 142.9	274.6 ± 124.7	278.6 ± 130.3
Initial diagnosis			
Postsurgery	79 (10.9)	74 (9.8)	65 (9.1)
Cardiac arrest	80 (11.1)	77 (10.2)	78 (10.9)
Traumatic brain injury	40 (5.5)	35 (4.6)	32 (4.5)
Sepsis	193 (26.8)	176 (23.3)	194 (27.3)
Trauma	107 (14.8)	80 (10.6)	68 (9.6)
Stroke or hemorrhage	154 (21.3)	252 (33.4)	198 (27.8)
Other	65 (9.3)	58 (7.9)	74 (10.5)
Type of ventilation, volume controlled	329 (45.6)	407 (53.9)	348 (49.0)

PBW = predicted body weight.
[a]Plus-minus values are mean ± SD and other values are *n* (%).
[b]$p < 0.001$.
Comparisons were made using analysis of variance.

plateau and peak pressure and minute ventilation were lower when compared with the intermediate and high tidal volume groups. $Paco_2$, Pao_2/Fio_2, and arterial pH levels were similar in the three tidal volume size groups.

Primary Outcome

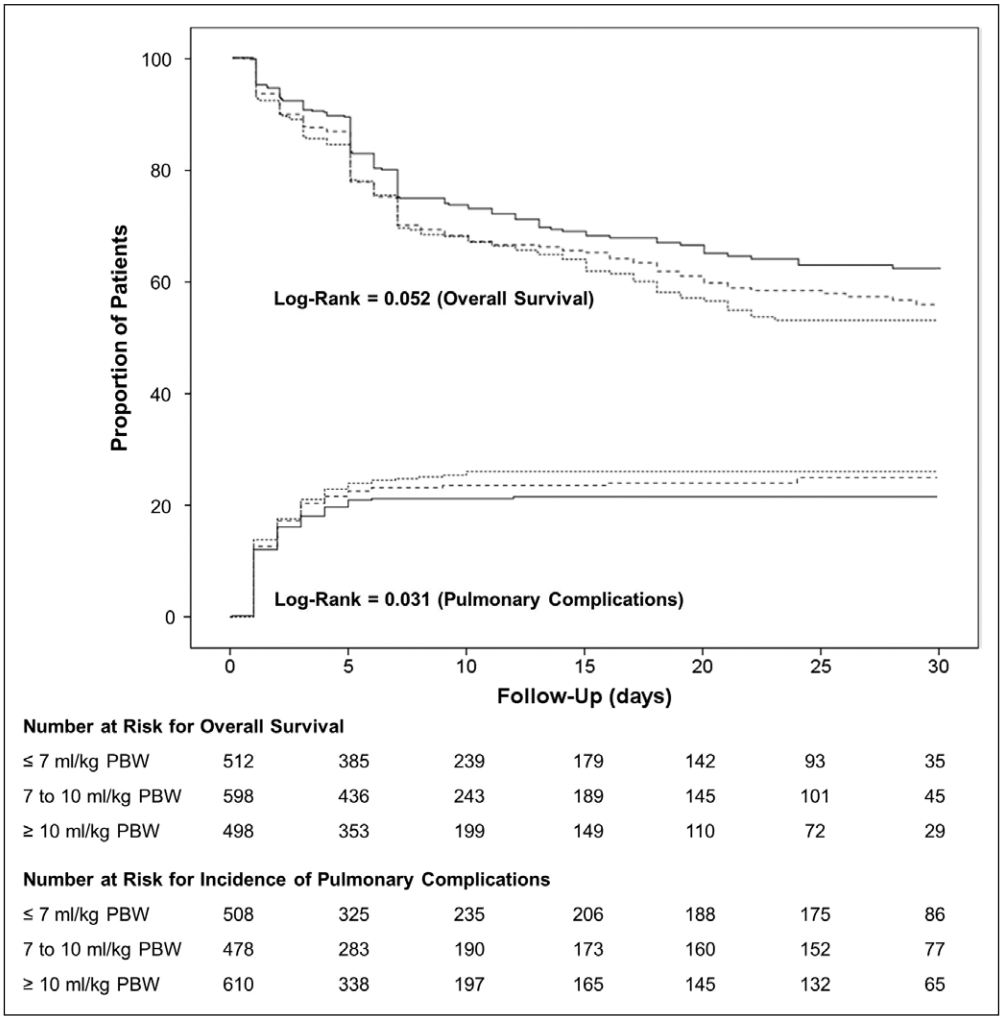
Pulmonary complications occurred in 166 patients (23%) in the low tidal volume group when compared with 211 patients (28%) in the intermediate tidal volume group and 220 patients (31%) in the high tidal volume group (adjusted OR [low tidal volume group vs high tidal volume group], 0.72; 95% CI, 0.52–0.98; $p = 0.042$; adjusted OR [intermediate tidal volume group vs high tidal volume group], 0.93; 95% CI, 0.69–1.24; $p = 0.635$; R^2, 0.034; Hosmer and Lemeshow *p*, 0.027) (**Table 2** and **Fig. 1**). Dose-response relationship curve between median tidal volume used during the first 2 days of ventilation and probability of pulmonary complications are shown in **Figure 2**. The R^2 for mean quadratic term for tidal volume was 0.880.

There was no significant interaction for the effects of tidal volume size on the primary outcome according to prespecified subgroup analyses (**Fig. 3**).

TABLE 2. Primary and Secondary Outcomes According to Tidal Volume Received[a]

Variables	Less Than or Equal to 7 mL/kg PBW	Greater Than 7 and Less Than 10 mL/kg PBW	Greater Than or Equal to 10 mL/kg PBW	Adjusted OR (Low vs High) (95% CI)[b]	*p*	Adjusted OR (Intermediary vs High) (95% CI)[b]	*p*
Pulmonary complications	166 (23)	211 (28)	220 (31)	0.72 (0.52–0.98)	0.042	0.93 (0.69–1.24)	0.635
Acute respiratory distress syndrome	86 (12)	121 (16)	163 (23)	0.48 (0.32–0.71)	< 0.01	0.73 (0.52–1.03)	0.074
Pneumonia	122 (17)	158 (21)	106 (15)	1.47 (0.89–2.21)	0.093	1.27 (0.86–1.86)	0.223
In-hospital mortality	245 (34)	279 (37)	270 (38)	0.82 (0.65–1.02)	0.081	0.90 (0.73–1.10)	0.319

OR = odds ratio.
[a]Data are represented as *n* (%).
[b]Adjusted for age, risk of death, baseline Pao_2/Fio_2, and baseline pH.



Number at Risk for Overall Survival

≤ 7 ml/kg PBW	512	385	239	179	142	93	35
7 to 10 ml/kg PBW	598	436	243	189	145	101	45
≥ 10 ml/kg PBW	498	353	199	149	110	72	29

Number at Risk for Incidence of Pulmonary Complications

≤ 7 ml/kg PBW	508	325	235	206	188	175	86
7 to 10 ml/kg PBW	478	283	190	173	160	152	77
≥ 10 ml/kg PBW	610	338	197	165	145	132	65

Figure 1. Kaplan-Meier estimates of the probability of the primary outcome and overall survival. Data for the Kaplan-Meier estimates of the probability of the primary outcome of pulmonary complications and overall survival in ≤ 7 mL/kg predicted body weight (PBW) (*black solid line*), > 7 and < 10 mL/kg PBW (*black knurled line*), and ≥ 10 mL/kg PBW (*black dotted line*) were censored at 30 d after inclusion. $p = 0.031$ by the log-rank test for the between-group difference in the probability of the primary outcome and $p = 0.052$ by the log-rank test for the between-group difference in the probability of overall survival.

Secondary Outcomes

Development of pulmonary complications was associated with a lower number of ICU-free days and alive at day 28 (10.0 ± 10.9 vs 13.8 ± 11.6 d; $p < 0.01$), a lower number of hospital-free days and alive at day 28 (6.1 ± 8.1 vs 8.9 ± 9.4 d; $p < 0.01$), and an increased in-hospital mortality (49.5 vs 35.6%; $p < 0.01$) (**Table 3** and **Fig. 4**).

In-hospital death occurred in 245 patients (34%) in the low tidal volume group when compared with 279 patients (37%) and 270 patients (38%) in the intermediate and high tidal volume groups (adjusted OR [low tidal volume group vs ≥ high tidal volume group], 0.82; 95% CI, 0.65–1.02; $p = 0.081$; adjusted OR [intermediate tidal volume group vs ≥ high tidal volume group], 0.90; 95% CI, 0.73–1.10; $p = 0.319$) (Table 2 and Fig. 1). The results of the Cox regression were similar to those found by the logistic regression analysis (adjusted HR [low tidal volume group vs ≥ high tidal volume group], 0.81; 95% CI, 0.65–1.02; $p = 0.073$; adjusted OR [intermediate tidal volume group vs ≥ high tidal volume group], 0.92; 95% CI, 0.75–1.13; $p = 0.411$).

The incidence of pulmonary complications in the whole cohort was 29.1% (crude incidence 10.5 cases per person-year). The individual and pooled pulmonary complications incidence rates are shown in **Appendix Figure 7** (Supplemental Digital Content 1, http://links.lww.com/CCM/B370) (Table 3).

The estimated mortality attributable to pulmonary complications was 13.9% (95% CI, 9.1–18.7). The attributable mortality of pulmonary complications in patients in the low tidal volume group (16.2% [95% CI, 7.4–25.0]) was similar to those in the intermediate tidal volume group (14.2% [95% CI, 6.1–22.2]) and the high tidal volume group (14.2% [95% CI, 6.1–22.2]).

Stratified Analyses According to Diagnosis

Baseline characteristics of patients according to initial diagnosis are shown in **Appendix Table 8** (Supplemental Digital Content 1, http://links.lww.com/CCM/B370). There is an association between tidal volume size and development of ARDS only in patients with initial diagnosis of sepsis, cardiac arrest, and others. All the analyses were underpowered, though, due to the low number of patients and events (**Appendix Table 9**, Supplemental Digital Content 1, http://links.lww.com/CCM/B370).

DISCUSSION

This individual patient analysis of 2,184 ventilated ICU patients without ARDS at the onset of ventilation from seven clinical investigations found strong evidence for a protective effect of ventilation with low tidal volumes on development of two of the most important pulmonary complications, namely ARDS and pneumonia. The analysis suggests a dose-response relationship between tidal volume size and development of pulmonary complications. Development of pulmonary complications was associated with a lower number of ICU-free and hospital-free days and alive at day 28 and an increased mortality.

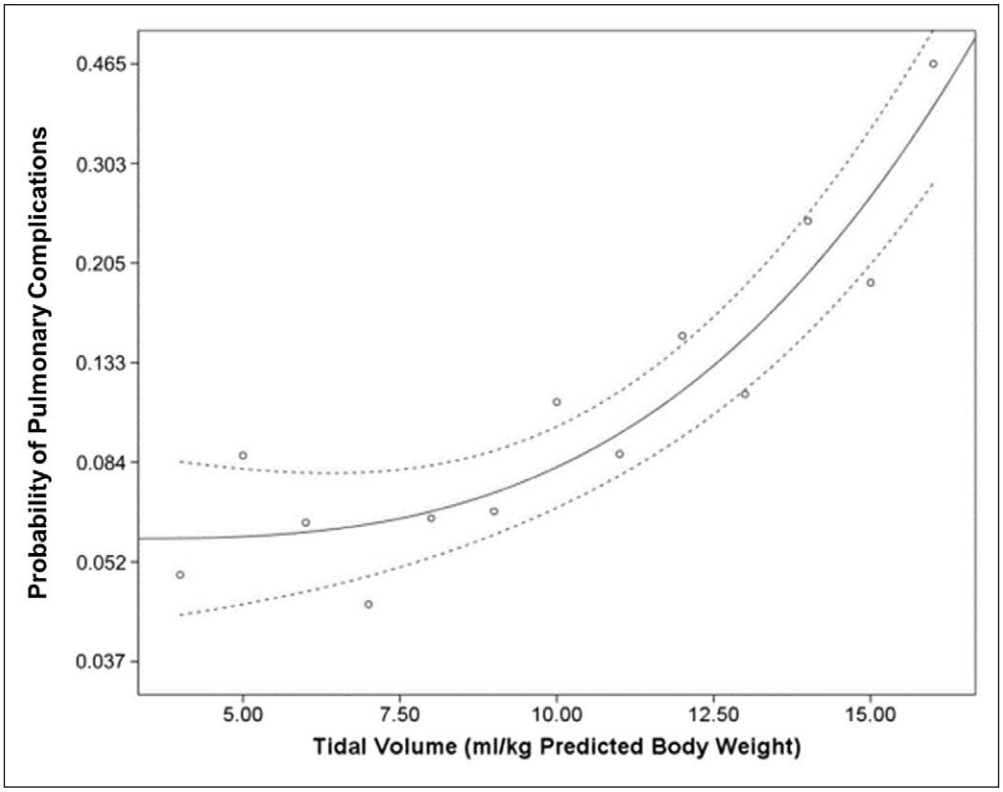


Figure 2. Probability and unit logistic regression showing the dose-relationship curve between the median tidal volume (mL/kg predicted body weight) used in the first 2 days of ventilation and the probability of pulmonary complications during ICU stay. *Solid line*, mean quadratic term; *dashed line*, 95% CI.

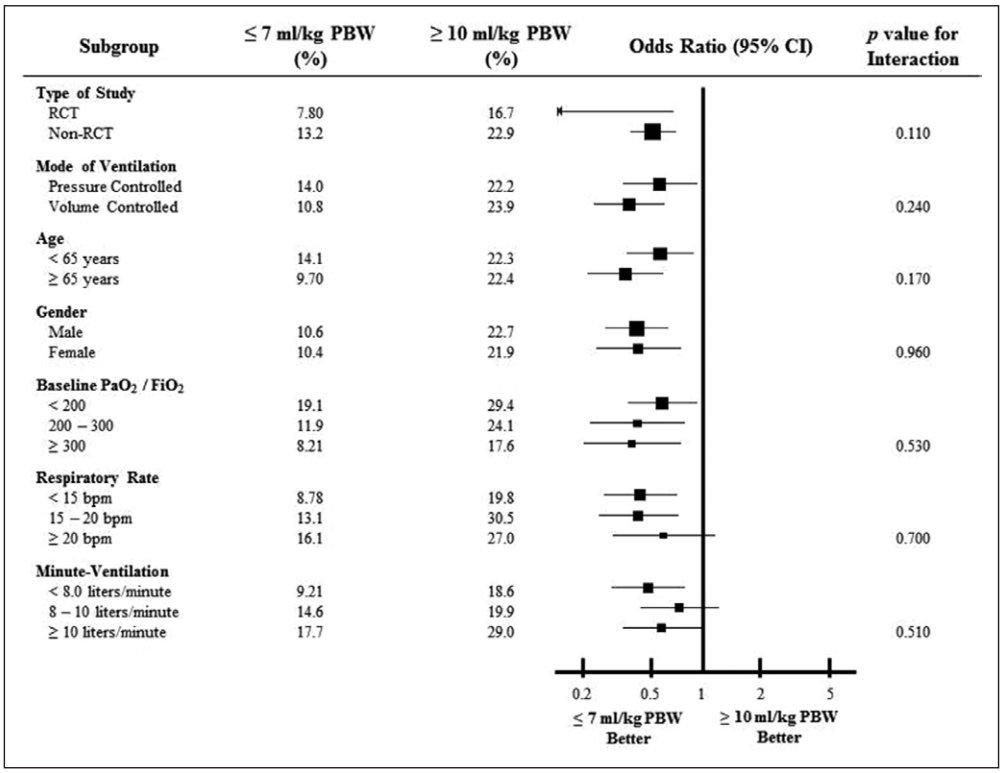


Figure 3. Hazard ratios for primary outcome of pulmonary complications according to subgroups (adjusted analysis). The size of the squares is proportional to the number of patients in the subgroup. PBW = predicted body weight, RCT = randomized controlled trial.

The major strengths of the present analysis are the large sample size, the statistical analyses performed, and the inclusion of several patients from diverse study types from different parts of the world. Also, it differs from previous analyses (6, 7, 22) in several aspects. First, we restricted the present analysis to investigations on the association between tidal volume size in ICU patients and we used an individual patient data approach. Second, we analyzed different outcomes (i.e., ARDS and pneumonia) when compared with a previous analysis that focused on the sedation needs and duration of ventilation (7). Third, we combined pneumonia and ARDS as primary outcome for reasons explained in methods. Finally, we estimated the mortality attributable to pulmonary complications and its relationship with tidal volume used during the first days of mechanical ventilation. The finding that prevention of pulmonary complications with the use of lower tidal volumes could improve clinical outcomes adds to our understanding of the potential benefits of lung-protective ventilation in patients without ARDS.

In the current analysis, patients were stratified according to the size of tidal volume used in the first 2 days of ventilation. This approach was chosen because the majority of patients were from observational studies. Thereby, we reduced the risk of including patients ventilated with low tidal volume in the first day, who were subsequently ventilated with high tidal volume and vice versa. Of interest, the PBW was higher in the group ventilated with tidal volumes less than or equal to 7 mL/kg PBW, but there was no

TABLE 3. Incidence of Pulmonary Complications and its Characteristics[a]

Group of Patients	No. of Patients			ICU-Free Days and Alive at Day 28			Mortality			
	No PC	PC	Incidence[b]	No PC	PC	*p*	No PC	PC	*p*	Onset of PC (D)
All patients	1,447 (72.8)	594 (29.1)	10.5	13.8 ± 11.6	10.0 ± 10.9	< 0.001	566 (35.6)	294 (49.5)	< 0.001	2.6 ± 4.5
Tidal volume groups										
≤ 7 mL/kg PBW	554 (76.8)	166 (23.2)	10.1	14.6 ± 11.5	9.9 ± 10.9	< 0.001	171 (30.9)	78 (47.1)	< 0.001	3.6 ± 6.5
> 7 and < 10 mL/kg PBW	543 (72.6)	211 (27.4)	11.3	14.4 ± 11.5	10.4 ± 11.2	< 0.001	184 (33.9)	101 (48.1)	< 0.001	3.2 ± 4.2
≥ 10 mL/kg PBW	490 (69.5)	220 (30.5)	16.1	13.5 ± 11.7	10.6 ± 10.8	0.009	179 (36.6)	112 (50.8)	< 0.001	2.2 ± 3.1

PC = pulmonary complication, PBW = predicted body weight.

[a]In some cases, the number of patients is not adding up due to missing values.

[b]Expressed as cases per person-year.

significant interaction for the effects of tidal volume size on primary outcome according to gender.

The current findings are, at least in part, in line with previous investigations of lung-protective ventilation in ICU patients without ARDS (3, 6, 7, 21). Our findings are also in line with the results of investigations showing a strong association between the size of tidal volume used during intraoperative ventilation and the occurrence of postoperative pulmonary complications, including postoperative ARDS, in surgical patients (6, 23, 24). Since ICU patients are frequently at higher risk of ARDS than patients receiving relative short-lasting ventilation for general anesthesia for surgery, it may not be surprising to see a larger beneficial impact of ventilation with low tidal volume in ICU patients (7).

Notably, the median peak and plateau pressures in all three groups were well below those for which tidal volumes were adjusted in the pivotal ARDS Network trial that showed benefit of low tidal volumes in patients with ARDS (1). Using the threshold of 30 cm H_2O in that trial, possibly none of the tidal volumes in the patients in the present analysis would have been adjusted. However, it is questionable if we should use the same threshold in patients without ARDS; recently, it was suggested to use a threshold of as low as 20 cm H_2O (11). Several explanations for the potential benefit of ventilation with low tidal volumes have been suggested. Ventilation with low tidal volume could cause less mechanical stress on the alveolar membrane because it prevents alveolar overdistention and improves alveolar stability (25). Several studies showed that the use of low tidal volumes reduces the injurious effects of ventilation in animals without injured

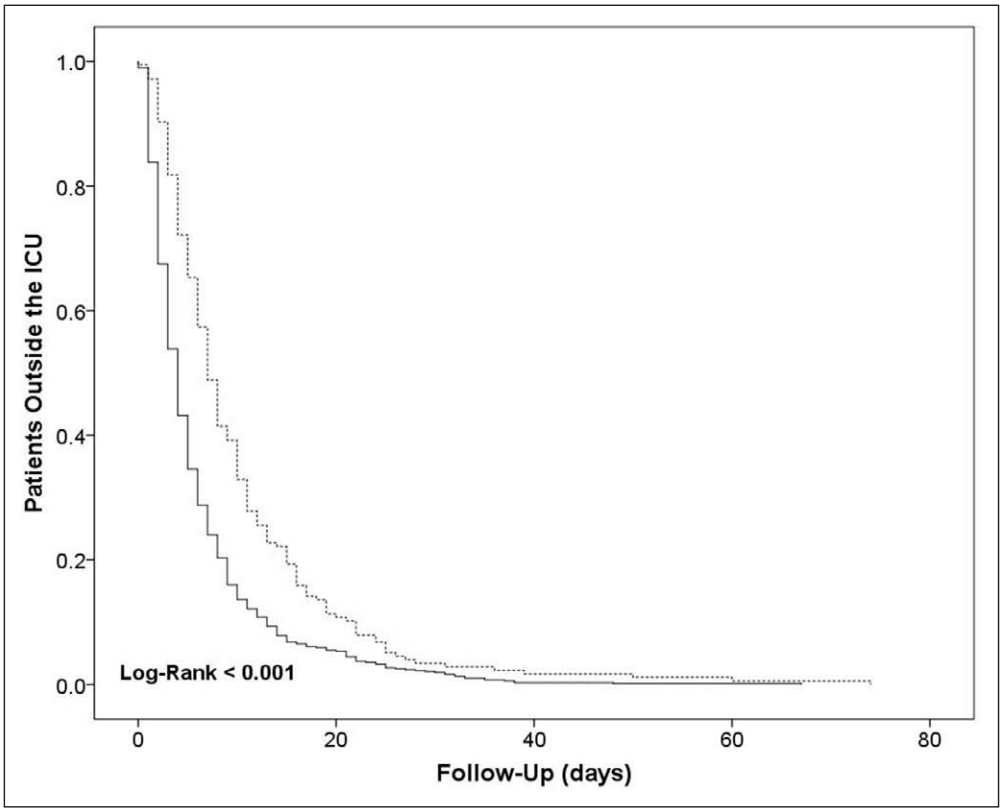


Figure 4. Data of the Kaplan-Meier estimates of the probability of discharge from the ICU ($p < 0.001$ by the log-rank test) in patients alive and with (*black dotted line*) or without (*black line*) pulmonary complications.

lungs (26). Indeed, in these studies, increasing lung injury was found with increasing size of tidal volumes. Although ventilation may have seemed less harmful in ICU patients without ARDS compared with ICU patients with ARDS (2), the present analysis strongly suggests that ventilation with high tidal volumes has a strong potential to cause lung injury in these patients.

The findings of the present analysis support the idea that to be effective, protective low tidal volume should be used early in the course of ventilation because deleterious effects of ventilation are partly dependent on its duration (26). The level of positive end-expiratory pressure (PEEP) used in the present used was low, around 6 cm H_2O, and similar in the different groups of tidal volumes group. Indeed, it seems that PEEP did not likely affect the effects of tidal volume on pulmonary complications. Finally, the peak pressure increases with higher tidal volumes, thus, we are not able to differentiate the effects of reduced tidal volume from those of reduced peak pressure.

In theory, use of low tidal volumes could increase the feeling of dyspnea mandating more sedation (4, 5). Notably, this was neither found in patients with ARDS (27, 28) nor in patients without ARDS (7, 15). It is also argued that the use of higher respiratory rates, as a compensation for the lower tidal volumes, could cause respiratory muscle fatigue (4, 5). If true, these both could clearly offset the benefits of ventilation with low tidal volumes, at least in patients without ARDS. It is also argued that use of low tidal volumes may not at all be necessary in patients without ARDS since they do not have the widespread pulmonary changes including atelectasis as observed in patients with ARDS and therefore are not at risk for ventilator-associated lung injury (5). Use of lower tidal volume could even induce or promote development of more atelectasis, increasing the risk of hypoxemia and hypercapnia (4). A well-powered RCT comparing ventilation with lower tidal volumes with traditionally sized tidal volumes is essential to solve this uncertainty (29, 30). This trial should use relevant clinical endpoints, pay attention to safety of use of lower tidal volume, but most of all should compare the lower tidal volume strategy to a relevant tidal volume in the control arm.

Although our analysis shows a clear statistical difference between use of low and high tidal volumes with respect to occurrence of pulmonary complication, the differences found between low and intermediate tidal volumes did not reach statistical significance. While one conclusion could be that there comes no additional benefit from tidal volume reduction below intermediate tidal volumes, one could also suggest that the numbers of patients are too low to have sufficient statistical power to conclude this. Notably, the PROBIT analysis shows a clear dose-response relationship between tidal volume size and pulmonary complications. Based on the observed incidence of pulmonary complications in the low and intermediate tidal volume groups, 1,189 patients in each arm would be necessary to find difference between the two arms with 80% of power and 5% of significance. One concern with the intermediate tidal volume group could be that more patients in this group came from observational trials when compared with the low and high tidal volume groups (Appendix Fig. 4, Supplemental Digital Content 1, http://links.lww.com/CCM/B370); capturing outcome data such as ARDS and pneumonia could have been better in RCTs than in observational studies.

This individual patient analysis has several other limitations. First, data from one study could not be included (20). However, the results of a previous classical meta-analysis including that study are in agreement with those found in the present analysis (6). Thus, the assumption can be made that the included studies are reliable representatives of all studies of protective ventilation in ICU patients without ARDS. Second, we do not have information about some important risk factors that could also contribute to development of pulmonary complications, including fluid overload, transfusion of blood products, and other factors known to play a role in the development of ARDS (4). Third, since the diagnosis of ARDS and pneumonia was based on subjective criteria, misclassification of patients might underestimate the observed effect, but this factor should have equally affected the different groups. However, there could have been differential misclassification which may vary among the RCTs and observational studies. Furthermore, patients from studies were not equally distributed between the three tidal volume groups. Fourth, despite the fact that we include only patients without ARDS in our cohort, we found a low Pao_2/Fio_2 in this group of patients. However, it should be emphasized that the diagnosis of ARDS is based on several criteria and not only on Pao_2/Fio_2. Indeed, patients could have low Pao_2/Fio_2 but no infiltrates in the chest radiographs or a pulmonary edema fully explained by cardiogenic problems. Fifth, despite the fact that the calculation of PBW was the same in all studies, no study described how the height was assessed. Sixth, the results of the PROBIT analysis should be interpreted with caution because high tidal volume points exert an effect on the curve much greater than the number of patients actually ventilated at these points. Seventh, the Hosmer-Lemeshow test showed that the model does not fit well the data, thus the result should be interpreted with caution. Finally, it is important to keep in mind that 93% patients included in this analysis came from observational studies, which may have introduced bias due to a more heterogeneous population.

Notably, all but two studies reported the primary outcome of the present analysis (18, 19). However, these studies reported other data such as hospital length of stay and overall survival included in the analysis as secondary outcomes. Therefore, the data of these studies were only used in the analyses dealing with these specific endpoints. One important finding is the fact that, despite reduced incidence of pulmonary complications in patients ventilated with low tidal volume, the overall mortality and length of stay did not differ between the three groups of tidal volume. Since 93% of the patients included in this analysis came from observational studies, these findings justify the need for more robust trials evaluating the impact of low tidal volumes in clinical relevant outcomes, such as mortality and hospital length of stay.

CONCLUSIONS

In conclusion, use of high tidal volumes during the first 2 days of ventilation is associated with the incidence of pulmonary complications during hospital stay, but not the number of ICU- and hospital-free days and alive at day 28, and in-hospital mortality in ICU patients without ARDS. Occurrence of pulmonary complications, regardless of the tidal volume used, is associated with a lower number of ICU- and hospital-free days and alive at day 28 and increased in-hospital mortality.

ACKNOWLEDGMENT

We thank the FINNALI study group for their invaluable participation in this study.

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