Intensive Care Med (2014) 40:950–957
DOI 10.1007/s00134-014-3318-4

ORIGINAL

Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis

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Received: 4 March 2014
Accepted: 21 April 2014
Published online: 9 May 2014

For the PROVENet investigators.

Take-home message: The use of lower tidal volume in patients without acute respiratory distress syndrome at the onset of mechanical ventilation is associated with shorter duration of ventilation and the same amount of sedation compared to the use of higher tidal volumes.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-014-3318-4) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* Mechanical ventilation with lower tidal volumes (≤6 ml/kg of predicted body weight, PBW) could benefit patients without acute respiratory distress syndrome (ARDS). However, tidal volume reduction could be associated with increased patient discomfort and sedation needs, and consequent longer duration of ventilation. The aim of this individual patient data meta-analysis was to assess the associations between tidal volume size, duration of mechanical ventilation, and sedation needs in patients without ARDS. *Methods:* Studies

comparing ventilation with different tidal volume sizes in patients without ARDS were screened for inclusion. Corresponding authors were asked to provide individual participant data. Patients were assigned to three groups based on tidal volume size (≤6 ml/kg PBW, 6–10 ml/kg PBW, or ≥10 ml/kg PBW). Ventilator-free days, alive at day 28, and dose and duration of sedation (propofol and midazolam), analgesia (fentanyl and morphine), and neuromuscular blockade (NMB) were compared. *Results:* Seven investigations (2,184 patients) were included in the analysis. The number of patients breathing without assistance by day 28 was higher in the group ventilated with tidal volume ≤6 ml/kg PBW compared to those ventilated with tidal volume ≥10 ml/kg PBW (93.1 vs. 88.6 %; $p = 0.027$, respectively). Only two investigations (187 patients) could be included in the meta-analysis of sedation needs. There were neither differences in the percentage of study days that patients received sedatives, opioids, or NMBA nor in the total dose of benzodiazepines, propofol, opioids, and NMBA. *Conclusions:* This meta-analysis suggests that use of lower tidal volumes in patients without ARDS at the onset of mechanical ventilation could be associated with shorter duration of ventilation. Use of lower tidal volumes seems not to affect sedation or analgesia needs, but this must be confirmed in a robust, well-powered randomized controlled trial.

Keywords Mechanical ventilation · Sedation · Analgesia · Meta-analysis

Introduction

Mechanical ventilation using lower tidal volumes (≤6 ml/kg of predicted body weight, PBW) is associated with reduction of mortality in patients with acute respiratory distress syndrome (ARDS) [1]. Recent meta-analyses suggest that patients without ARDS may also benefit from tidal volume reduction, e.g., by reducing the incidence of pulmonary complications including lung injury [2, 3].

Critical care physicians were rather slow in adopting so-called protective ventilation with lower tidal volumes in patients with ARDS, at least in part because of concerns over patient discomfort [4]. Ventilation with lower tidal volumes might be associated with a reduction of minute ventilation and increased fractional dead space ventilation promoting dyspnea independent of the breathing pattern. Ventilation with lower tidal volumes, therefore, might lead to increased and prolonged sedation needs [5], which could offset the beneficial effects of tidal volume reduction, e.g., by increasing duration of ventilation. Two secondary analyses of the landmark National Heart, Lung, and Blood Institute (NHLBI) ARDS Network trial [6], however, indicated that tidal volume reduction in patients with ARDS did not increase sedation needs in the first days of ventilation [5, 7], and one study showed that the resulting hypercapnia from this strategy was associated with increased propofol use, but not midazolam or opioid use [8].

Notably, sedation needs in patients without ARDS differ from patients with ARDS, who usually receive more sedation. Tidal volume reduction may thus have a different effect on sedation needs in patients without ARDS [9]. If tidal volume reduction increases sedation needs, duration of ventilation could increase with this strategy. Two recently published meta-analyses focusing on the effects of lower tidal volumes in patients without ARDS failed to study the effects of tidal volume reduction on duration of ventilation and sedation needs [2, 3]. The aim of this systematic review and meta-analysis, therefore, was to compare duration of ventilation and sedation needs in patients without ARDS. Opposite to what has been suggested, we hypothesized that use of lower tidal volumes is associated with a shorter duration of ventilation due to its preventive effects on development of lung injury. We further hypothesized that use of lower tidal volumes does not affect sedation needs.

Methods

Search strategy and selection of studies

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]). Articles reporting on observational studies or randomized controlled trials of comparing ventilation at different tidal volumes in critically ill patients without ARDS identified by the search and reporting outcomes of interest were screened for inclusion. Key inclusion criteria were (1) use of lower versus higher tidal volumes; (2) adult (i.e., age > 18 years) patients ventilated in the ICU; and (3) without ALI/ARDS at onset of ventilation ($PaO_2/FiO_2 > 300$ or without infiltrates on the chest X-ray). For this investigation additional inclusion criteria were used: (4) duration of ventilation, (5) duration of ICU stay, and (6) dose and duration of sedative, opioids, or neuromuscular blockade agents. Studies or trials were excluded from the analysis if they (1) reported on patients receiving ventilation during general anesthesia for surgery, or (2) included patients with ARDS at onset of ventilation, according to the American–European Consensus criteria [10].

Study population

The patients were stratified to three groups based on the tidal volume used in the first 2 days of mechanical ventilation: ≤6 ml/kg PBW vs. 6–10 ml/kg PBW vs. ≥10 ml/kg PBW. PBW was calculated as in the landmark study of lower tidal volume ventilation in patients with ARDS [6] and the cutoffs of tidal volume were chosen on the basis of the classic thresholds used in the literature [6]. The cutoff of 2 days was chosen because lung injury, if developed, is diagnosed on average after the second day, mandating ventilation with lower tidal volumes.

Study design

The authors of the original publications provided information regarding duration of ventilation, breathing without assistance, ICU length of stay, and daily doses of all sedatives, opioids, neuromuscular blockers, and haloperidol administered during the period that the patient was followed, for each patient. Medication doses were recorded beginning on the day of intubation and ending upon death, extubation, or ICU discharge, whatever came first.

The number of ventilator-free days and alive by day 28 were defined as the number of days on which patients had been breathing without assistance for at least 48 consecutive hours and alive from day 1 to day 28, respectively. Patients breathing without assistance by day 28 were defined as termination of ventilation for longer than 48 consecutive hours and alive from day 1 to day 28. ICU length of stay was defined as the time since admission to and discharge from the unit and hospital length of stay was defined as the time since admission to and discharge from the hospital.

Sedative agents included benzodiazepines and propofol; to simplify comparisons, doses of benzodiazepines were converted to midazolam equivalents using the following formula: 1 mg of midazolam = 0.5 mg of lorazepam = 2 mg of diazepam = 4 mg of oxazepam/temazepam [11]. Doses of opioids were converted to morphine equivalents using the following formula: 1 mg of morphine = 7.5 mg of meperidine = 0.1 mg of fentanyl [12]. Non-opioid analgesics were not considered in the analysis. Any day in which a patient received a sedative, opioid, or neuromuscular blocker was considered a sedation, analgesic, or blockade day, respectively. Finally, doses include both intravenous boluses and continuous infusions and were reported in milligrams adjusted by the predicted body weight (mg/kg of PBW). Sedation, analgesic, and blockade used for intubation were not included.

Statistical analysis

All comparisons are between patients stratified according to the subgroup described above. Values are expressed as mean ± standard deviation for continuous variables or frequency and percentage for categorical variables. Unpaired Student's t test was used to compare the mean percentage of days patients received sedation. Fisher's exact test or a Chi square test was used to compare the proportion of patients who received medication on a given day. Wilcoxon's rank-sum test was used to assess for significant differences between doses of individual drugs.

Time-to-event was defined as time from the day of inclusion in the study to the day ARDS developed. Cox proportional hazards regression models were used to examine simultaneous effects of multiple covariates on outcomes, censoring a patient's data at the time of death, hospital discharge, or after 30 days. In all models, the categorical outcome variables were tested for trend with the higher tidal volume as reference. The proportional hazards assumption was assessed by plotting partial residuals against survival time. A test for interaction between pairs of variables in the final model was performed. The effect of each variable in these models was assessed with the use of the Wald test and described by the hazard ratio (HR) with 95 % confidence interval (CI). Kaplan–Meier curves were constructed and log-rank tests were used to determine the univariate significance of the study variables.

Subgroup analyses were used to assess the effect of tidal volume in the following prespecified subgroups: (1) type of study (RCT vs. non-RCT); (2) protocol for sedation (yes vs. no); (3) protocol for weaning (yes vs. no).

Normality of the variables was assessed using the Kolmogorov–Smirnov test. All analyses were conducted with SPSS v.20 (IBM Corporation, New York, USA) and R v.2.12.0 (R Foundation for Statistical Computing, Vienna, Austria). In the analyses of sedation, analgesia, and neuromuscular blockade we used the Bonferroni correction; because of the multiple testing the two-sided p value for significance was corrected to ≤0.01. For all other analyses two-sided p values <0.05 were considered significant.

We performed a post hoc power calculation to determine the power of the meta-analysis with respect to the comparisons of ventilator-free days.

Results

Search results and collection of individual patient data

The original search identified 13,704 articles of which four randomized controlled trials and four observational studies could be used for the analysis of duration of ventilation [4, 13–26], and one randomized controlled trial and one observational study could be used for the sedation analysis [4, 13]. We were not able to collect data from one randomized controlled trial because the corresponding author could not be contacted [19]. The total

enrollment, based on the observational studies and randomized controlled trials, was 2,184 patients for the analysis of duration of ventilation [4, 13–26], but only 187 patients (Fig. 1 and Tables 2 and 3 in the Electronic Supplementary Material, ESM) for the analysis of sedation needs [4, 13]. Only two studies presented a protocol for sedation [4, 13] and for weaning [13, 17]. The guideline used for sedation in each study is shown in ESM Fig. 4.

Table 1 shows the distribution of demographic characteristics in each tidal volume group in patients included in the analysis of duration of ventilation. Three-hundred and seventy-two patients were ventilated with tidal volumes ≤6 ml/kg PBW (17.0 %), 1,102 with tidal volumes 6–10 ml/kg PBW (50.4 %), and 710 with tidal volumes of ≥10 ml/kg PBW (32.5 %). The PBW was higher in the group ventilated with tidal volumes ≤6 ml/kg PBW. A higher number of patients that suffered acute ischemic stroke were ventilated with tidal volumes ≥10 ml/kg PBW. ESM Table 5 details the distribution of ventilation parameters and oxygenation parameters in the three tidal volume size groups in patients included in the analysis.

Duration of ventilation and ICU length of stay

The number of patients breathing without assistance by day 28 was higher in the group ventilated with tidal volume ≤6 ml/kg PBW compared to those ventilated with tidal volume ≥10 ml/kg PBW (92.4 vs. 88.6 %; $p = 0.027$; adjusted HR 1.20; 95 % CI 1.02–1.42) (Table 2 and Fig. 1). There was a tendency toward lower ventilator-free days at day 28 and length of hospital stay in patients ventilated with tidal volume ≤6 ml/kg PBW (Table 2). There was no interaction between the tidal volume group and presence of sedation protocol for the primary outcome of patients breathing without assistance by day 28 (Fig. 2).

The post hoc power calculation using the finding of 22.3 ± 7.5 and 20.5 ± 9.1 ventilator-free days at day 28 in the groups ventilated with tidal volume ≤6 ml/kg PBW and ≥10 ml/kg PBW, respectively, using an alpha of 0.05 the meta-analysis had a power of 90 %.

Sedation and analgesia

During the studies, 119 patients (63.6 %) received a sedative agent, and 103 patients (55.0 %) received opioid analgesia. ESM Table 6 shows the number and percentage of patients receiving sedation, analgesia, and neuromuscular blockade on days 1, 2, 3, and 5 of the studies.

When we compared the three tidal volume groups, there were no statistically significant differences in the mean percentage of study days that patients received sedatives or opioids. During ICU stay, patients received sedatives (benzodiazepines or propofol) on 33.1 ± 20.1 % of days in the group ventilated with tidal volume ≤6 ml/kg PBW, 49.8 ± 33.8 % of days in the group ventilated with tidal volume of 6–10 ml/kg PBW, and 49.2 ± 38.5 % of days in the group ventilated with tidal volume of ≥10 ml/kg PBW ($p = 0.254$). Patients received opioids (morphine or fentanyl) on 25.6 ± 31.0 % of days in the group ventilated with tidal volume ≤6 ml/kg PBW, 35.0 ± 27.0 % of days in the group ventilated with tidal volume of 6–10 ml/kg PBW, and 38.0 ± 38.1 % of days in the group ventilated with tidal volume of ≥10 ml/kg PBW ($p = 0.508$). There was a wide variability in the doses of individual drugs that patients received, but there was no detectable difference between study groups (ESM Table 7 and Fig. 8).

There were no statistically significant differences in the mean total dose of haloperidol between the three groups (0.03 ± 0.10 vs. 0.01 ± 0.03 vs. 0.10 ± 0.19 mg/kg PBW; $p = 0.163$).

Neuromuscular blockade

During the studies, 64 patients (34.2 %) received at least one dose of NMBA. There were no statistically significant differences in the mean total dose or in the percentage of patients using neuromuscular blockade between the three groups (ESM Table 6).

Discussion

This individual patient meta-analysis of mechanically ventilated ICU patients without ARDS at onset of ventilation shows that ventilation with tidal volume ≤6 ml/kg PBW is associated with shorter duration of ventilation. Furthermore, lower tidal volume did not yield higher sedation needs, nor increased use of opioids or NMBA. Finally, we found that patients ventilated with tidal volume ≤6 ml/kg PBW had higher PBW. This finding is probably related to the fact that many physicians prescribed approximately the same tidal volumes to most of their patients, so that taller patients and male patients received lower tidal volumes when expressed as milligrams per kilogram predicted body weight.

The finding of this meta-analysis that the use of lower tidal volumes is associated with a higher number of patients breathing without assistance by day 28 is in accordance with studies in ARDS patients, where protective ventilation with lower tidal volume is also associated with higher number of patients free from mechanical ventilation by day 28 [6]. Still, well-powered randomized controlled trials are needed to answer the question whether tidal volume reduction in patients without ARDS indeed reduces time on the ventilator more properly.

Table 1 Baseline characteristics of the patients included in the analysis of duration of ventilation

Variables	≤6 ml/kg PBW ($n = 372$)	6–10 ml/kg PBW ($n = 1{,}102$)	≥10 ml/kg PBW ($n = 710$)
Age, years	62.0 ± 15.8	63.0 ± 16.2	64.2 ± 16.0
Gender, female	83 (22.3)	383 (34.8)	253 (35.6)*
PBW, kg	69.5 ± 11.0	66.7 ± 10.00	60.8 ± 11.5*
Patients included in RCT	184 (49.6)	6 (6.0)	84 (11.8)*
APACHE II	21.8 ± 8.1	21.7 ± 8.0	21.6 ± 7.9
PaO_2/FiO_2	269.9 ± 139.0	276.6 ± 132.3	278.6 ± 130.3
Initial diagnosis			
Post-surgery	36 (9.7)	124 (11.3)	65 (9.15)
Cardiac arrest	33 (8.9)	112 (10.2)	78 (10.9)
Traumatic brain injury	16 (4.3)	63 (5.7)	32 (4.5)
Sepsis	112 (30.2)	350 (31.8)	194 (27.3)
Trauma	61 (16.3)	157 (14.3)	68 (9.5)
Acute ischemic stroke	68 (18.2)	224 (20.3)	198 (27.8)
Other	46 (12.4)	70 (6.4)	75 (10.5)
Type of ventilation			
Volume controlled	187 (50.2)	582 (52.8)	348 (49.0)
Pressure controlled	154 (41.3)	420 (38.1)	309 (43.5)
Others	31 (8.5)	100 (9.1)	53 (7.5)

Data are mean ± SD or *n* (%). Comparisons were made using analysis of variance (ANOVA)
PBW predicted body weight, *RCT* randomized controlled trial, *VC* volume controlled
* $p < 0.001$

Table 2 Duration of ventilation and ICU and hospital length of stay

Variables	≤6 ml/kg PBW	6–10 ml/kg PBW	≥10 ml/kg PBW	Hazard ratio* (95 % CI)[a]	p*	Hazard ratio** (95 % CI)[a]	p
Breathing without assistance by day 28	316/342 (92.4)	941/1,067 (88.2)	392/553 (88.6)	1.20 (1.02–1.42)	0.027	1.05 (0.93–1.15)	0.629
No. of ventilator-free days from day 1 to day 28	22.3 ± 7.5	21.9 ± 7.8	20.5 ± 9.1		0.063		0.717
Length of stay, days							
In-ICU							
Survivors	5.9 ± 5.6	6.1 ± 6.6	6.2 ± 5.7		0.797		0.955
In-hospital							
Survivors	17.0 ± 15.9	19.4 ± 23.1	19.7 ± 16.6		0.071		0.951

Data are mean ± SD or no./total no. (%)
CI confidence interval
* ≤6 ml/kg PBW vs. ≥10 ml/kg PBW
** 6–10 ml/kg PBW vs. ≥10 ml/kg PBW

[a] Adjusted by: type of study, age, APACHE II, baseline PaO_2/FiO_2, baseline pH

Although some studies suggest that tidal volume reduction is not associated with increased sedation needs in patients without ARDS [4], these studies were all small and probably underpowered. In an attempt to improve our understanding of the association between tidal volume reduction and sedation needs we meta-analyzed these studies. It should be noticed, however, that the number of patients included in this meta-analysis is still too low to draw firm conclusions. We speculate, though, that the association between tidal volume size and duration of ventilation is not the effect of differences in sedation, but more a result of the reduction in lung injury as suggested in a previous meta-analysis of clinical investigations [3] and preclinical studies in animals with uninjured lungs [2–4].

The tendency toward less use of NMBA in patients ventilated with lower tidal volumes is intriguing and could be related to the fact that patients with more severe disease who were more dyspneic and difficult to manage received higher tidal volumes in an attempt to manage their dyspnea. However, it could also be that the intensivists using lower tidal volume could be more trained to adapt the ventilation to the patient, instead of adapting the patient to the ventilator using NMBA. Notably, it should be realized that the large number of analyses in this meta-analysis increases the risk of a type I error even with the use of Bonferroni correction.

Several studies suggest that restricted use of sedation benefits critically ill patients, as prolonged or increased sedation may lengthen duration of mechanical ventilation,

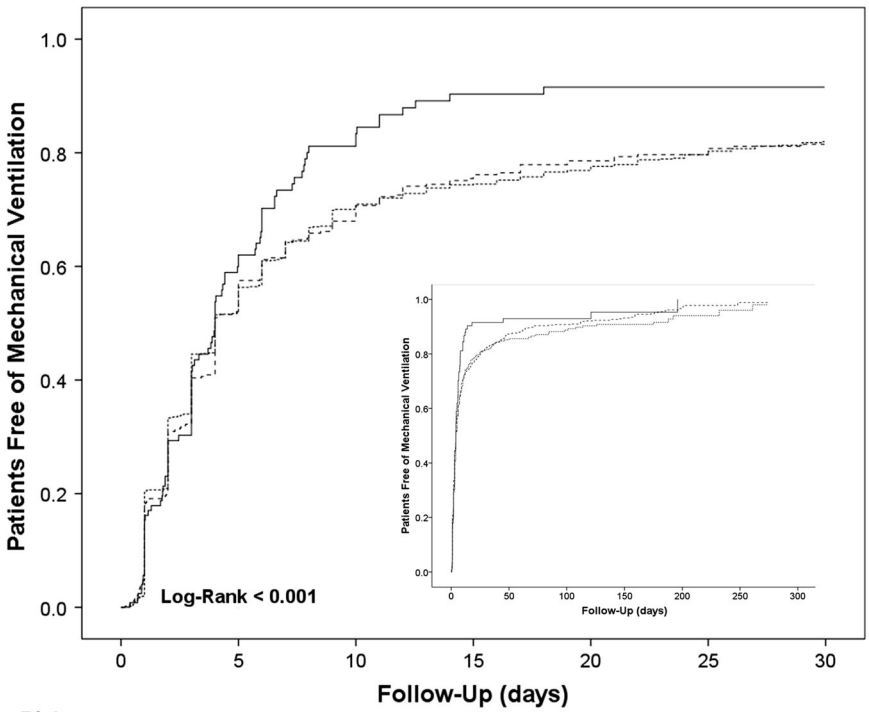

Fig. 1 Data for the Kaplan–Meier estimates of the probability of the primary outcome of patients breathing without assistance by day 28 in ≤6 ml/kg PBW (*black solid line*), 6–10 ml/kg PBW (*black dashed line*), and ≥10 ml/kg PBW (*black dotted line*) were censored at 30 days after inclusion. $p = 0.001$ by the log-rank test for the between-group difference in the probability of the primary outcome

Number at Risk							
≤ 6 ml/kg PBW	115	38	17	08	06	06	05
6 – 10 ml/kg PBW	917	371	220	182	157	133	95
≥ 10 ml/kg PBW	430	169	101	71	60	55	37

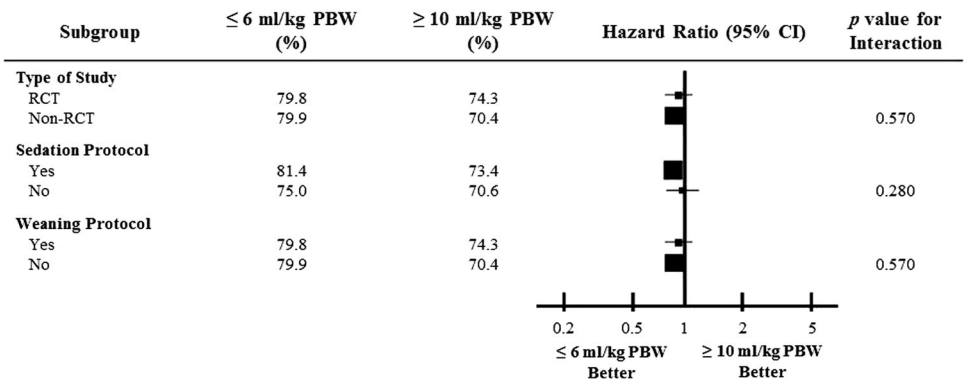

Fig. 2 Hazard ratios for study outcomes according to subgroup. The size of the *squares* is proportional to the number of patients in the subgroup

lengthen stay in the ICU, and worsen clinical outcomes [20–25]. Furthermore, prolonged or increased sedation increases utilization of unnecessary diagnostic studies [26], and delirium incidence [20]. Concerns that the need for sedation will increase with the use of lower tidal volumes are not supported by the findings of the present study. Notably, the results were consistent when sedative use was examined as the proportion of study days requiring sedatives, as the proportion of patients receiving sedatives on days 1–5 of follow-up, and as the total dose received.

This meta-analysis has limitations. One important limitation is that we could only use data from three randomized controlled trials, and that we could only use sedation data from two studies, reflecting sedation practice in only four ICUs within one country. Also, we were not able to assess long-term complications as pneumonia, and delirium. Second, we did not have access to sedation scales and level of sedation of patients. Third, we only had APACHE II and PaO2/FiO2 data as baseline prognostic data; the absence of a score that directly reflects severity of lung disease hampers interpretation of the results. Also in this context it is important to realize that the meta-analyzed studies contained a high number of neurological patients, a very specific condition regarding sedation. Finally, the total number of patients included in

this meta-analysis is quite small. However, the mean proportions of sedative days and sedative doses were generally in the direction of increased sedative use with higher tidal volumes and this makes it less likely that a true increase in sedation requirements with lower tidal volumes was missed as a result of low power.

In conclusion, this meta-analysis suggests that use of lower tidal volumes in patients without ARDS at the onset of mechanical ventilation shortens duration of ventilation. Use of lower tidal volumes was not associated with increased sedation or analgesia needs, but this needs confirmation in a robust well-powered randomized controlled trial.

Conflicts of interest The authors declare that they have no conflict of interest.

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