Low Tidal Volumes for All?

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CLINICIANS ARE CONTINUALLY STRIVING TO IMPROVE the quality of care in medicine. In the intensive care unit (ICU) environment, the focus on quality has been on avoidance of iatrogenic complications. Mechanical ventilation provides a specific example; treatment goals have changed remarkably in the last 20 years—from maintaining "normal" blood gas values to supporting acceptable gas exchange while avoiding or minimizing ventilator-induced lung injury.[1] Previously, ventilator-induced lung injury was only recognized when overt barotrauma such as pneumothorax occurred. Today, however, a more insidious form of ventilator-induced lung injury is recognized, one that arises through cyclic alveolar overdistension (*volutrauma*) and other mechanisms and can produce local and systemic inflammatory reactions leading to multiorgan failure and death.[2] The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network clinical trial demonstrated that the use of low tidal volumes in patients with established acute respiratory distress syndrome (ARDS) results in a considerable reduction in mortality.[3] Until now, the focus of lung-protective ventilation has remained on treatment of ARDS.

In this issue of *JAMA*, the study by Serpa Neto and colleagues[4] helps shift thinking from treatment to prevention and raises the question of whether all patients receiving mechanical ventilation should receive low tidal volumes around 6 mL/kg predicted body weight. Several factors favor this proposition. First, there is a strong preclinical database supporting the concept of tidal volume limitation to prevent volutrauma. In animal experiments, the only insult required to produce severe clinical lung injury and diffuse alveolar damage on pathological examination is a relatively short exposure to positive-pressure mechanical ventilation with very large tidal volumes.[5]

Second, extrapolating data from human trials of lung-protective ventilation that show reduced mortality in patients with lung injury (including what is now referred to as mild ARDS[6]) suggests that this approach may be beneficial in a broader population. The combination of the large mortality benefit in the ARDS Network low tidal volume trial,[3] along with the low specificity of the ARDS definition used,[7] supports this notion because it is likely that substantial numbers of patients without diffuse alveolar damage were included in this trial.

A third argument supporting the use of lower tidal volumes in all patients receiving ventilation is that mild ARDS is often unrecognized by clinicians, and life-saving protective ventilation is often not used.[7,8] Applying lung-protective ventilation broadly would reduce the chances of missing patients with mild ARDS.[9]

Fourth, direct data from patients support using lower tidal volumes across a broad range of reasons for mechanical ventilation; it is here that the meta-analysis by Serpa Neto and colleagues contributes.[4] These authors synthesized data from 20 studies involving almost 3000 patients and found large risk ratios (RRs) favoring lower tidal volumes in terms of lung injury development (RR, 0.33; 95% CI, 0.23-0.47), pulmonary infection (RR, 0.45; 95% CI, 0.22-0.92), and mortality (RR, 0.64; 95% CI, 0.46-0.89).

Although these data seem compelling, several factors must be considered in their interpretation. A total of 15 randomized controlled trials were combined with 5 observational studies, but the observational studies (in which inferences of causality may be problematic) account for approximately 85% of both the total number of patients and events in the primary analysis of lung injury prevention. Furthermore, the randomized trials had limitations related to quality, with some trials lacking allocation concealment and many not following an intention-to-treat analysis. In addition, many trials focused on short-term intraoperative ventilation under anesthesia, and these may not be generalizable to other clinical situations. As the authors acknowledge, their findings are not definitive but rather are hypothesis generating and support the need to conduct large randomized trials.

Why should intensive care physicians not simply move immediately to implement low tidal volume ventilation for all patients receiving mechanical ventilation? The medical literature has many examples in which physiological rationale, meta-analyses of small or low-quality studies, or both

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suggested benefit followed by large trials that refuted these findings or even showed harm, such as steroids for traumatic brain injury.[10] More specific to the question at hand, clinicians must be aware of the potential unintended consequences of widespread use of a particular mechanical ventilation strategy. In contrast to the operating room setting, ventilation is often less "controlled" in the ICU. Increasingly, patients receiving ventilation are awake and mobilizing throughout their ICU stay, rendering mandatory low tidal volume ventilation challenging.[11-13]

Although physicians may choose to set higher or lower levels of inspiratory support with resultant tidal volumes, a number of ventilator modes allow patients to "trump" these settings and take larger breaths through their own respiratory muscular efforts. For this reason, it may be difficult to control tidal volumes in the common situation in which patients are receiving pressure support ventilation, allowing them some control over tidal volumes and inspiratory flow rates. Randomized trials of lung protective ventilation in ARDS have typically allowed pressure support ventilation without restriction of tidal volumes during weaning when settings were not excessive (eg, pressure support of ≤10 cm of water with an inspired oxygen fraction of ≤0.4 and positive end-expiratory pressure of ≤10 cm of water).[14] Whether larger tidal volumes generated predominantly with negative pressure through the patient's own respiratory muscle efforts are equally injurious to the same size volumes delivered with positive pressure is unclear.

Clinicians debate the merits of lowering tidal volumes vs minimizing sedation in spontaneously breathing patients even when those patients have moderate to severe ARDS.[15] Mandating lower tidal volumes as a quality marker for all ICU patients at this point may lead to more use of sedation and even paralysis with potential subsequent increases in ICU-acquired delirium, weakness, ventilator-induced diaphragm dysfunction, and duration of ventilation. These "costs" could be acceptable if avoiding high tidal volumes really is associated with decreased rates of lung injury and mortality, but this definitive information is currently lacking.

The meta-analysis by Serpa Neto and colleagues serves as a convincing summary that the current knowledge base about low trial volume ventilation is inadequate. In addition to confirming or refuting the benefit of setting lower vs higher tidal volumes in patients without ARDS, additional trials could address the degree of tidal volume limitation required, the patient populations that may benefit most, and whether to actively seek to limit tidal volumes in spontaneously breathing patients or simply avoid setting higher volumes. The role of intraoperative lung-protective ventilation also needs further study. Given the number of ICU patients receiving mechanical ventilation for whom this question applies (ie, the 95% of patients who do not have ARDS at the time of intubation),[16] such trials would have significant clinical importance and would be highly feasible. Until the results of these or other studies are available, however, the existing data suggest that in the ICU the ventilator should be set to a target tidal volume of 6 to 8 mL/kg in most patients receiving mechanical ventilation. When a patient's spontaneous efforts result in larger tidal volumes, actively controlling tidal volumes through sedation with or without paralysis should be considered in patients with moderate to severe ARDS, but more data are needed before extending this practice to the majority of patients receiving ventilation without ARDS.

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Association Between Use of Lung-Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome

A Meta-analysis

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Context Lung-protective mechanical ventilation with the use of lower tidal volumes has been found to improve outcomes of patients with acute respiratory distress syndrome (ARDS). It has been suggested that use of lower tidal volumes also benefits patients who do not have ARDS.

Objective To determine whether use of lower tidal volumes is associated with improved outcomes of patients receiving ventilation who do not have ARDS.

Data Sources MEDLINE, CINAHL, Web of Science, and Cochrane Central Register of Controlled Trials up to August 2012.

Study Selection Eligible studies evaluated use of lower vs higher tidal volumes in patients without ARDS at onset of mechanical ventilation and reported lung injury development, overall mortality, pulmonary infection, atelectasis, and biochemical alterations.

Data Extraction Three reviewers extracted data on study characteristics, methods, and outcomes. Disagreement was resolved by consensus.

Data Synthesis Twenty articles (2822 participants) were included. Meta-analysis using a fixed-effects model showed a decrease in lung injury development (risk ratio [RR], 0.33; 95% CI, 0.23 to 0.47; I^2, 0%; number needed to treat [NNT], 11), and mortality (RR, 0.64; 95% CI, 0.46 to 0.89; I^2, 0%; NNT, 23) in patients receiving ventilation with lower tidal volumes. The results of lung injury development were similar when stratified by the type of study (randomized vs nonrandomized) and were significant only in randomized trials for pulmonary infection and only in nonrandomized trials for mortality. Meta-analysis using a random-effects model showed, in protective ventilation groups, a lower incidence of pulmonary infection (RR, 0.45; 95% CI, 0.22 to 0.92; I^2, 32%; NNT, 26), lower mean (SD) hospital length of stay (6.91 [2.36] vs 8.87 [2.93] days, respectively; standardized mean difference [SMD], 0.51; 95% CI, 0.20 to 0.82; I^2, 75%), higher mean (SD) $PaCO_2$ levels (41.05 [3.79] vs 37.90 [4.19] mm Hg, respectively; SMD, –0.51; 95% CI, –0.70 to –0.32; I^2, 54%), and lower mean (SD) pH values (7.37 [0.03] vs 7.40 [0.04], respectively; SMD, 1.16; 95% CI, 0.31 to 2.02; I^2, 96%) but similar mean (SD) ratios of PaO_2 to fraction of inspired oxygen (304.40 [65.7] vs 312.97 [68.13], respectively; SMD, 0.11; 95% CI, –0.06 to 0.27; I^2, 60%). Tidal volume gradients between the 2 groups did not influence significantly the final results.

Conclusions Among patients without ARDS, protective ventilation with lower tidal volumes was associated with better clinical outcomes. Some of the limitations of the meta-analysis were the mixed setting of mechanical ventilation (intensive care unit or operating room) and the duration of mechanical ventilation.

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MECHANICAL VENTILATION is a life-saving strategy in patients with acute respiratory failure. However, unequivocal evidence suggests that mechanical ventilation has the potential to aggravate and precipitate lung injury.[1] In acute respiratory distress syndrome (ARDS), and in a milder form of ARDS formerly known as acute lung injury (ALI),[2] mechanical ventilation can cause ventilator-associated lung injury. Ventilator-associated lung injury is a frequent complication in critically ill patients receiving mechanical ventilation, and its development increases morbidity and mortality.[1]

Higher tidal volume (V_T) ventilation causes the alveoli to overstretch in a process called *volutrauma*, and this overstretching is the main cause of ventilator-associated lung injury.[3] The use of a lower V_T was shown to reduce morbidity and mortality in

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patients with ARDS or ALI, thus justifying the progressive decrease in V_T used by clinicians over the past decades.[4-6] However, in critically ill patients without ALI, there is little evidence regarding the benefits of ventilation with lower V_T, partly because of a lack of randomized controlled trials evaluating the best ventilator strategies in these patients.[7]

Some observational studies have suggested that use of higher V_T in patients without ARDS or ALI, at the initiation of mechanical ventilation, increases morbidity and mortality.[8-10] As suggested by the "biotrauma hypothesis," ventilation with higher V_T and peak pressures may lead to recruitment of neutrophils and local production and release of inflammatory mediators.[11] We conducted a meta-analysis to determine whether conventional (higher) or protective (lower) tidal volumes would be associated with lung injury, mortality, pulmonary infection, and atelectasis in patients without lung injury at the onset of mechanical ventilation.

METHODS

Studies were identified by 2 authors through a computerized blinded search of MEDLINE (1966-2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) using a sensitive search strategy combining the following Medical Subject Headings and keywords (*protective ventilation* [text word] OR *lower tidal volumes* [text word]). All reviewed articles and cross-referenced studies from retrieved articles were screened for pertinent information.

Selection of Studies

Articles were selected for inclusion in the systematic review if they evaluated 2 types of ventilation in patients without ARDS or ALI at the onset of mechanical ventilation. In 1 group of the study, ventilation was protective (lower V_T). Then, this protective ventilation group was compared with another group using conventional methods (higher V_T). A study was deemed eligible if it evaluated patients who did not meet the consensus criteria for ARDS or ALI at baseline.[12] We included randomized trials as well as observational studies (cohort, before/after, and cross-sectional), with no restrictions on language or scenario (intensive care unit or operating room). We excluded revisions and studies that did not report the outcomes of interest. When we found duplicate reports of the same study in preliminary abstracts and articles, we analyzed data from the most complete data set. When necessary, we contacted the authors for additional unpublished data.

Data Extraction

Data were independently extracted from each report by 3 authors using a data recording form developed for this purpose. After extraction, data were reviewed and compared by the first author. Instances of disagreement between the 2 other extractors were solved by a consensus among the investigators. Whenever needed, we obtained additional information about a specific study by directly questioning the principal investigator.

Validity Assessment

In randomized trials, we assessed allocation concealment, the baseline similarity of groups (with regard to age, severity of illness, and severity of lung injury), and the early stopping of treatment. We used the GRADE approach to summarize the quality of evidence for each outcome.[13] In this approach, randomized trials begin as high-quality evidence but can be rated down for apparent risk of bias, imprecision, inconsistency, indirectness, or suspicion of a publication bias.

Definition of End Points

The primary end point was the development of lung injury in each group of the study. Secondary end points included overall survival, incidence of pulmonary infection and atelectasis, intensive care unit (ICU) and hospital length of stay, time to extubation, change in $PaCO_2$, arterial pH values, and change in the ratio of PaO_2 to fraction of inspired oxygen (FIO_2).

Statistical Analysis

We extracted data regarding the study design, patient characteristics, type of ventilation, mean change in arterial blood gases, lung injury development, ICU and hospital length of stay, time to extubation, overall survival, and incidence of atelectasis. For the analysis of lung injury development, mortality, pulmonary infection, and atelectasis, we used the most protracted follow-up in each trial up to hospital discharge. We calculated a pooled estimate of risk ratio (RR) in the individual studies using a fixed-effects model according to Mantel and Haenszel and graphically represented these results using forest plot graphs.

We explored the following variables as potential modifiers: incorporation of "open lung" techniques (using the authors' definitions) into experimental strategies, between-group gradients in tidal volumes and plateau pressures, and case mix effects. We reasoned that each of these might influence the effect of protective ventilation on outcome. To explore whether these variables modified the outcome, we compared pooled effects among studies with and without them. For continuous variables, we used the standardized mean difference (SMD), which is the difference in means divided by a standard deviation.

The homogeneity assumption was measured by the I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I^2 was calculated from basic results obtained from a typical meta-analysis as $I^2 = 100\% \times (Q - df)/Q$, where Q is the Cochran heterogeneity statistic. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. When heterogeneity was found

($I^2 > 25\%$) we presented the random-effects model results as primary analysis.

A sensitivity analysis was carried out by recalculating pooled RR estimates for different subgroups of studies based on relevant clinical features. This analysis demonstrates whether the overall results have been affected by a change in the meta-analysis selection criteria. Also, a sensitivity analysis about the treatment effect according to quality components of the studies (concealed treatment allocation, blinding of patients and caregivers, blinded outcome assessment) was conducted. A potential publication bias was assessed graphically with funnel plots, as well as by a Begg and Mazumdar rank correlation and an Egger regression. Interrater reliability was determined by comparing the number of studies included by one author with those of another author in each stage of the search using κ coefficients.

Parametric variables were presented as the mean and standard deviation, and nonparametric variables were presented as the median and interquartile range (IQR). All analyses were conducted with Review Manager version 5.1.1 (The Cochrane Collaboration) and SPSS version 16.0.1 (IBM SPSS). For all analyses, 2-sided *P* values less than .05 were considered significant.

RESULTS

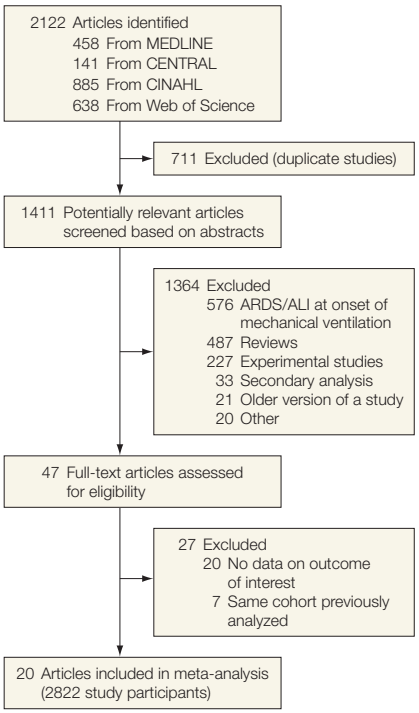
Our initial search yielded 2122 studies (458 from MEDLINE, 141 from CENTRAL, 885 from CINAHL, and 638 from Web of Science). After removing 711 duplicate studies, we evaluated the abstracts of 1411 studies. After evaluating the abstract of each study, we excluded 1364 studies because they did not meet inclusion criteria. Subsequently, we carefully read the full text of each of the remaining 47 studies and excluded 27 for the following reasons: no data on outcome of interest in 20 studies and same cohort previously analyzed in 7. Twenty references (2822 participants) were included in the final analysis (FIGURE 1 and TABLE 1). For the comparisons of interrater reliability in each stage of the search, the κ coefficient was 0.91 in the citation stage ($P = .004$), 0.86 during the abstract review ($P = .03$), and 0.90 in the full-text stage ($P = .006$).

Study Characteristics

Table 1 summarizes the studies' characteristics. All but 5 studies[16,22,23,26,29] were randomized controlled trials, and median follow-up time was 21.0 hours (IQR, 6.28-54.60 hours). The median time of per-protocol mechanical ventilation was 6.90 hours for protective and 6.56 hours for conservative strategy. The development of lung injury was the primary outcome in 4 studies. Eight studies evaluated the levels of inflammatory mediators in bronchoalveolar lavage or blood. Tidal volume was set to 6 mL/kg of ideal body weight (IBW) in the protective group of 13 studies; only in 1 study was the tidal volume in the protective ventilation group above 8 mL/kg IBW. Four studies did not report what weight was used to calculate the tidal volume,[14,15,21,25] 1 study used the measured weight,[19] and 15 studies used the predicted weight.[9,16-18,20,22-24,26-32] Of these, 7 used the ARDSnet formula to calculated the predicted body weight.[16,18,20,24,28-30]

The tidal volume gradient between protective and conventional ventilation ranged from 2 to 6 mL/kg IBW, with a mean (SD) of 4.15 (1.42) mL/kg IBW. The tidal volume gradient was less than 4 mL/kg IBW in 30.0% of the studies, between 4 and 5 mL/kg IBW in 40% of the studies, and above 5 mL/kg IBW in 30% of the studies. In 15 studies, the reason for intubation was scheduled surgery,[9,15,17-22,24,25,29-32] and in 5, the reason was mixed (medical or surgery).[14,16,23,24,28] Lung injury was diagnosed according to the American-European Consensus Conference definition in 6 of the 8 trials that assessed this outcome.[16,23,26,27,31,32] The diagnosis of infection was made by clinical assessment plus laboratory, radiological, and microbiological evaluation in 2 studies[14,26]; was made by decrease in PaO_2/FIO_2 plus radiological assessment in 1 study[31]; and was not specified in the last study.[20]

Figure 1. Literature Search Strategy



ALI indicates acute lung injury; ARDS, acute respiratory distress syndrome; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature.

eTable 1 (available at http://www.jama.com) summarizes study methods, highlighting features related to the risk of bias. Randomization was concealed in 11 of 15 randomized controlled trials included, and follow-up was excellent with minimal loss. Limitations included a lack of blinding (all trials), a lack of intention-to treat analysis (12 trials), and early stopping for benefit (1 trial). Age, weight, minute-volume (product of respiratory rate and tidal volume), and PaO_2/FIO_2 were all similar between the 2 groups analyzed (TABLE 2 and eTable 2). As expected, V_T and plateau pressure were lower and positive end-expiratory pressure (PEEP) and respiratory rate were higher in the protective group. $PaCO_2$ was higher in the protective group

but remained within normal limits (35-45 mm Hg). Acidosis (pH <7.35) was found in the protective group in 3 studies, and the pH level in the protective group was similar to that of the conventional group. The mechanical ventilation settings for each study are provided in eTable 3.

Primary Outcome

Forty-seven of 1113 patients (4.22%) assigned to protective ventilation and 138 of 1090 patients (12.66%) assigned to conventional ventilation developed lung injury during follow-up (RR, 0.33; 95% CI, 0.23-0.47; number needed to treat [NNT], 11). The result of the overall test for heterogeneity was not statistically significant, and the I^2 was 0% (no sign of heterogeneity) (FIGURE 2). When stratified by the tidal volume gradient between the 2 groups, the RR for lung injury decreased from 0.35 (95% CI, 0.23-0.51) in the group with less than 4

Table 1. Characteristics of the Included Studies and Summary of Continuous Variables

		Protective		Conservative				Duration of MV, Mean (SD), h			
Source[a]	No. of Patients	V_T, mL/kg	No.	V_T, mL/kg	No.	Setting	Follow-up, h	Protective	Conservative	Primary Outcome	Jadad Score
Lee et al,[14] 1999	103	6	47	12	56	SICU	168	2.30 (0.5)	3.90 (0.8)	Duration of MV	3
Chaney et al,[15] 2000	25	6	12	12	13	CABG	Dis	ST + 1	ST + 1	Pulmonary mechanics	2
Gajic et al,[16] 2004	166	9	66	12	100	ICU		NS	NS	LI	
Koner et al,[17] 2004	44	6	15	10	29	CABG	12	9.90 (1.0)	10.0 (1.4)	Cytokines in blood	1
Wrigge et al,[9] 2004	62	6	30	12	32	Surgical	3	NS	NS	Cytokines in BAL	3
Wrigge et al,[18] 2005	44	6	22	12	22	CABG	Dis	16.1 (10.2)	12.9 (4.4)	Cytokines in BAL	1
Zupancich et al,[19] 2005	40	8	20	10	20	CS	6	NS	NS	Cytokines in BAL	1
Michelet et al,[20] 2006	52	5	26	9	26	OS	18	7.06 (1.81)	7.76 (1.85)	Cytokines in blood	3
Cai et al,[21] 2007	16	6	8	10	8	Neurosurgery	7.15	6.90 (2.2)	7.4 (3.1)	CT atelectasis	2
Wolthuis et al,[22] 2007	36	8	23	10	13	ICU		NS	NS	Sedative use	
Yilmaz et al,[23] 2007	375	8	163	11	212	ICU		NS	NS	LI	
Determann et al,[24] 2008	40	6	21	12	19	Surgical	5	ST	ST	Cytokines in BAL	3
Lin et al,[25] 2008	40	5	20	9	20	OS	24	4.33 (0.9)	4.23 (0.71)	Cytokines in blood	1
Licker et al,[26] 2009	1091	6	558	9	533	OS		2.93 (1.2)	2.76 (1.0)	LI	
Determann et al,[27] 2010	150	6	76	10	74	ICU	672	NS	NS	Cytokines in BAL	3
de Oliveira et al,[28] 2010	20	6	10	12	10	SICU	672	168.0	72.0	Cytokines in BAL	3
Fernandez-Bustamante et al,[29] 2011	229	8	154	10	75	Surgical		NS	NS	Duration of MV; ICULS; mortality	
Sundar et al,[30] 2011	149	6	75	10	74	CS	672	7.50	10.71	Duration of MV	3
Yang et al,[31] 2011	100	6	50	10	50	OS	168	2.00 (0.68)	2.11 (0.8)	LI	3
Weingarten et al,[32] 2012	40	6	20	10	20	Surgical	Dis	5.13 (1.86)	5.73 (1.71)	Oxygenation	3
Total, Mean (SD)	2822	6.45 (1.09)	1416	10.60 (1.14)	1406		21.0 (6.28-54.6)[b]	6.90 (2.93-9.90)[b]	6.56 (3.61-10.17)[b]		2.33 (0.89)

Abbreviations: BAL, bronchoalveolar lavage; CABG, coronary artery bypass graft surgery; CS, cardiac surgery; CT, computed tomography; Dis, until patient's discharge; ICU, intensive care unit; ICULS, ICU length of stay; LI, lung injury; MV, mechanical ventilation; NS, not specified; OS, oncology surgery; SICU, surgical intensive care unit; ST, surgery time; V_T, tidal volume.

[a] Most of the studies were randomized controlled trials. The exceptions are as follows: Gajic et al,[16] Yilmaz et al,[23] and Licker et al,[26] were cohort studies; Wolthuis et al[22] had a before-and-after design; and Bustamante et al[29] had a cross-sectional design.

[b] Median (interquartile range).

mL/kg IBW to 0.26 (95% CI, 0.10-0.66) in the group with 4 to 5 mL/kg IBW (eFigure 1). The RR for the development of lung injury with conventional ventilation, analyzing only randomized controlled trials, was 0.26 (95% CI, 0.10-0.66; NNT, 10).

Secondary Outcomes

Overall mortality was lower in patients receiving protective ventilation (RR, 0.64; 95% CI, 0.46 to 0.89; NNT, 23). The incidence of pulmonary infection (using the authors' definition) and atelectasis were lower in the group receiving ventilation with a lower V_T (RR [random-effect], 0.45; 95% CI, 0.22 to 0.92; NNT, 26; and RR, 0.62; 95% CI, 0.41 to 0.95, respectively) (Figure 2). The I^2 test indicated moderate heterogeneity only in the analysis of pulmonary infection (32%). Protective ventilation was associated with a shorter mean (SD) hospital stay (6.91 [2.36] vs 8.87 [2.93] days, respectively; SMD, 0.51; 95% CI, 0.20 to 0.82), and showed no difference in ICU stay (3.63 [2.43] vs 4.64 [3.29] days, respectively; SMD, 0.37; 95% CI, –0.53 to 1.27) and time of mechanical ventilation (51.07 [58.08] vs 47.12 [45.00] hours, respectively; SMD, 0.48; 95% CI, –0.27 to 1.23).

Mean (SD) levels of $PaCO_2$ were higher in the protective ventilation group (41.05 [3.79] vs 37.90 [4.19] mm Hg, respectively; SMD, –0.51; 95% CI, –0.70 to –0.32), and mean (SD) pH levels were lower (7.37 [0.03] vs 7.40 [0.03], respectively; SMD, 1.16; 95% CI, 0.31 to 2.02). The mean (SD) PaO_2/FIO_2 ratio was similar between the groups (304.40 [65.70] vs 312.97 [68.13], respectively; SMD, 0.11; 95% CI, –0.06 to 0.27). All these analyses yield significant heterogeneity and were analyzed by random-effects model (I^2 for hospital stay, ICU stay, time of mechanical ventilation, $PaCO_2$, pH, and PaO_2/FIO_2 of 75%, 95%, 92%, 54%, 96%, and 60%, respectively) (eFigures 2, 3, 4, 5, 6, and 7 and eTable 4).

In eTable 5, the GRADE evidence profile is provided. This profile evaluates the effect of protective ventilation in patients without ARDS or ALI, only from a systematic review and a meta-analysis of randomized controlled trials. The findings for lung injury, mortality, and pulmonary infection were considered moderate, high, and low quality, respectively, by the GRADE profile. Sensitivity analyses according to quality components of each study are shown in eTable 6.

In addition, we excluded each trial one at a time and assessed the results. In lung injury and pulmonary infection analyses, the results were always significant despite the exclusion of any trial. After we excluded the trial by Yilmaz et al,[23] the analysis of mortality was no longer significant.

Table 2. Demographic, Ventilation, and Laboratory Characteristics of the Patients at the Final Follow-up Visit

	Mean (SD)		
	Protective Ventilation (n = 1416)	Conventional Ventilation (n = 1406)	*P* Value
Age, y	59.97 (7.92)	60.22 (7.36)	.93
Weight, kg	72.71 (12.34)	72.13 (12.16)	.93
Tidal volume, mL/kg IBW[a]	6.45 (1.09)	10.60 (1.14)	<.001
PEEP, cm H_2O[a]	6.40 (2.39)	3.41 (2.79)	.01
Plateau pressure, cm H_2O[a]	16.63 (2.58)	21.35 (3.61)	.006
Respiratory rate, breaths/min[a]	18.02 (4.14)	13.20 (4.43)	.01
Minute-volume, L/min[a,b]	8.46 (2.90)	9.13 (2.70)	.72
PaO_2/FIO_2[a]	304.41 (65.74)	312.97 (68.13)	.51
$PaCO_2$, mm Hg[a]	41.05 (3.79)	37.90 (4.19)	.003
pH[a]	7.37 (0.03)	7.40 (0.03)	.11

Abbreviations: FIO_2, fraction of inspired oxygen; IBW, ideal body weight; PEEP, positive end-expiratory pressure.
[a] At the final follow-up visit.
[b] Minute-volume is the product of respiratory rate and tidal volume.

Sensitivity Analysis

To explore these results, we performed a stratified analysis across a number of key study characteristics and clinical factors, and this analysis is shown in TABLE 3. Protection from lung injury, in the protective group, was more pronounced in studies that were not randomized controlled trials performed in the ICU. These trials did not incorporate recruitment maneuvers, had a higher plateau pressure gradient, and a smaller tidal volume gradient. In the survival analysis, we found significant changes in studies without recruitment maneuvers, in studies that were not randomized trials, and in studies performed in the ICU with a lower tidal volume gradient.

For pulmonary infections, we found no statistically significant association in studies that were not randomized trials, a tidal volume gradient less than 4 mL/kg IBW, and the use of recruitment maneuvers. A tidal volume gradient from 4 to 5 mL/kg IBW and a randomized controlled trial performed in surgical patients were each associated with a significant reduction in pulmonary infections in the protective group.

Publication Bias

Funnel-plot graphical analysis (eFigure 8), Begg and Mazumdar rank correlation, and Egger regression did not suggest a significant publication bias for the analyses conducted in Figure 2 (Kendall $\tau = 0.17$, $P = .63$; Egger regression intercept = 0.24, $P = .68$).

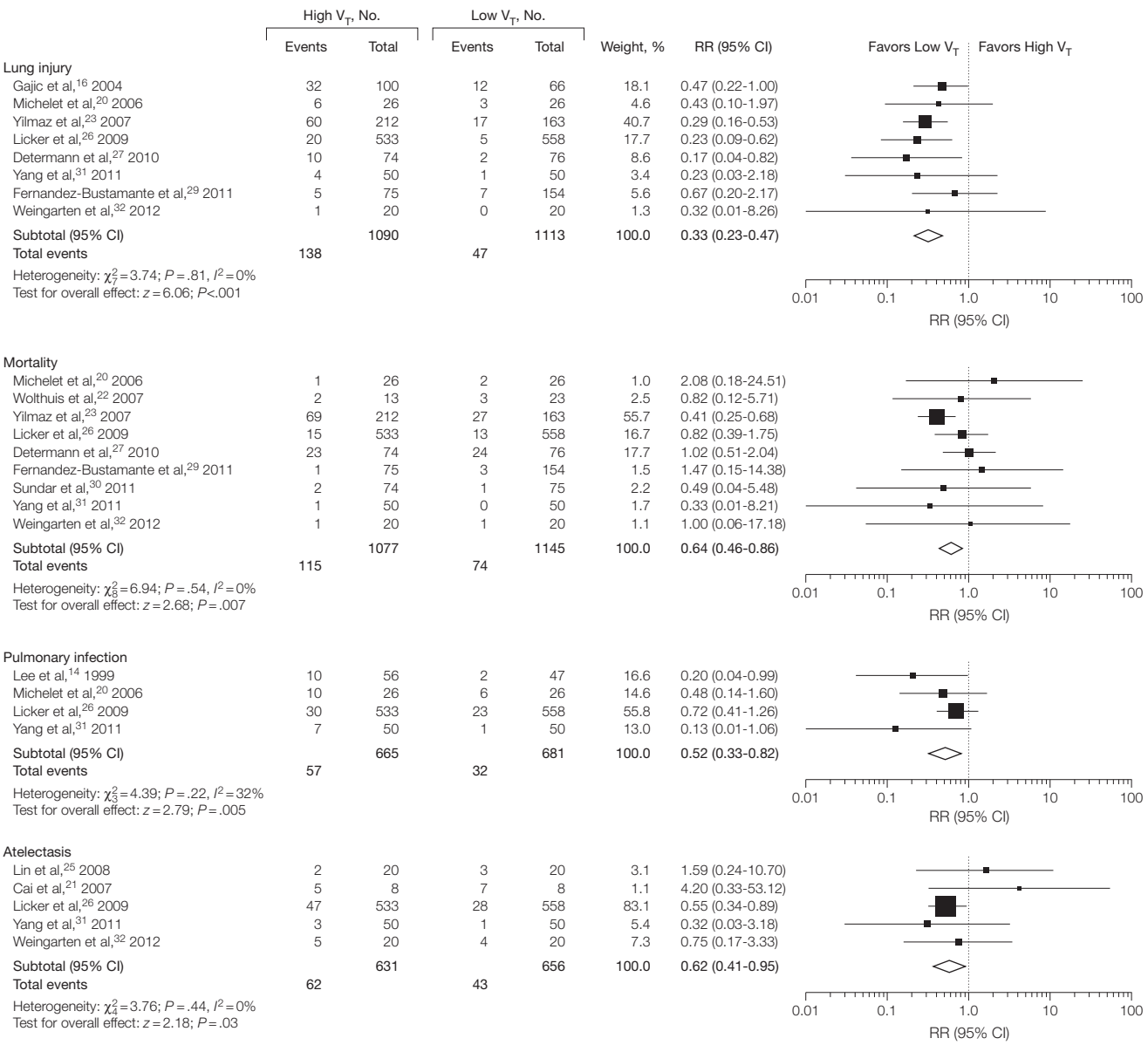
COMMENT

We found evidence that a ventilation strategy using lower tidal volumes is associated with a lower risk for developing ARDS. Furthermore, the strategy was associated with lower mortality, fewer pulmonary infections, and less atelectasis when compared with higher tidal volume ventilation in patients without lung injury at the onset of me-

chanical ventilation. These benefits were associated with a shorter hospital length of stay. Protective ventilation was associated with higher $PaCO_2$ levels and lower pH values, but no difference in the incidence of acidosis was found. In all studies, although the primary goal of the investigators was to compare 2 different tidal volumes, other ventilator strategy elements were associated with the use of lower tidal volumes. Notably, differences in the levels of PEEP and plateau pressure did not influence the final results of the meta-analysis.

Previously, Esteban et al[33] showed plateau pressures above 35 cm H_2O to be associated with an increased risk of death in ICU patients. Although not definitive, this study at least suggested that higher V_T has the ability to exaggerate lung injury and maybe even cause death in patients who require mechanical ventilation for days. Fernández-Pérez et al[34] showed higher V_T to be associated with postoperative respiratory failure in patients receiving ventilation for only a few hours in the operating room. In light of this information, over the past decade, V_T has progressively de-

Figure 2. Effect of Ventilation With Smaller Tidal Volume in Patients With Healthy Lungs at the End of the Follow-up Period for Each Study



A pooled estimate of risk ratio (RR) was calculated in the individual studies using a fixed-effects model according to Mantel and Haenszel. The size of the data markers indicates the weight of the study in the final analyses. V_T indicates tidal volume.

creased from greater than 12 to 15 mL/kg IBW to less than 9 mL/kg IBW.[6,35] The results of the present meta-analysis support this change in ventilation practice. Our results may even suggest that V_T should be further reduced.

Protective ventilation in patients with ALI or ARDS is already well established; however, physicians do not always adhere to such guidelines. Mikkelsen et al[36] reported that approximately one-third of the patients were receiving protective ventilation at 48 hours, and the main reason for poor adherence was the uncertainty about the diagnosis of ARDS. Another possible reason is that 82% of the patients who never received protective ventilation had a plateau pressure below 30 cm H_2O. However, it is well established that reducing the V_T in patients with plateau pressures below 30 cm H_2O is associated with a survival benefit.[10] In this context, the adoption of protective ventilation in patients without lung injury may be even more difficult.

It is possible that the beneficial effects of protective ventilation, regarding the development of lung injury, are even greater than what is suggested by the current analysis. Mechanical ventilation can damage the lung, cause inflammation, and release cytokines into the systemic circulation.[20,25] This process may cause fever, leukocytosis, and new pulmonary infiltrates, which could be interpreted as ventilator-associated pneumonia instead of ventilator-associated lung injury. The absence of strict criteria for the diagnosis of pneumonia, such as microbiological identification in blood and bronchoalveolar lavage, in the studies evaluated may lead to an incorrect diagnosis. Ventilator-associated lung injury may be incorrectly diagnosed as pneumonia in many cases, underestimating the true incidence of lung injury. It is difficult to diagnose pneumonia in the presence of ARDS or ALI, with a quoted sensitivity using conventional clinical criteria of less than 50%.[37]

Table 3. Summary of Stratified Analyses of Pooled Relative Risks

Stratified Analysis	No. of Trials	No. of Patients	Risk Ratio (95% CI)	*P* Value	Heterogeneity, *Q*
Acute Lung Injury					
Recruitment maneuvers					
Yes	1	1091	0.23 (0.09-0.62)	.004	
No	7	1112	0.35 (0.24-0.52)	<.001	0.80
Tidal volume gradient, mL/kg IBW					
<4	4	1861	0.35 (0.23-0.51)	<.001	0.43
4-5	4	342	0.26 (0.10-0.66)	.004	.87
Randomized					
Yes	4	342	0.26 (0.10-0.66)	.004	0.87
No	4	1861	0.35 (0.23-0.51)	<.001	0.43
Setting					
Operation room	5	1512	0.34 (0.18-0.63)	<.001	0.73
ICU	3	691	0.33 (0.21-0.51)	<.001	0.43
Plateau pressure gradient, cm H_2O					
<4	3	368	0.38 (0.21-0.71)	.002	0.52
4-8	1	1091	0.23 (0.09-0.62)	.004	
Diagnosis					
AECCD	6	1922	0.30 (0.21-0.45)	<.001	0.83
Other	2	281	0.56 (0.22-1.41)	.22	0.66
Mortality					
Recruitment maneuvers					
Yes	1	1091	0.82 (0.39-1.75)	.61	
No	8	1131	0.60 (0.42-0.87)	.006	0.49
Tidal volume gradient, mL/kg IBW					
<4	4	1731	0.54 (0.36-0.79)	.002	0.35
4-5	5	491	0.97 (0.53-1.78)	.92	0.89
Randomized					
Yes	5	491	0.97 (0.53-1.78)	.92	0.89
No	4	1731	0.54 (0.36-0.79)	.002	0.35
Setting					
Operation room	6	1661	0.86 (0.46-1.60)	.63	0.94
ICU	3	561	0.57 (0.38-0.84)	.005	0.10
Plateau pressure gradient, cm H_2O					
<4	3	351	1.02 (0.54-1.92)	.95	0.71
4-8	1	1091	0.82 (0.39-1.75)	.61	
Pulmonary Infection					
Recruitment maneuvers					
Yes	1	1091	0.72 (0.41-1.26)	.25	
No	3	255	0.27 (0.12-0.64)	.003	.48
Tidal volume gradient, mL/kg IBW					
<4	1	1091	0.72 (0.41-1.26)	.25	
4-5	2	152	0.31 (0.11-0.86)	.02	0.28
>5	1	103	0.20 (0.04-0.99)	.05	
Randomized					
Yes	3	255	0.27 (0.12-0.64)	.003	0.48
No	1	1091	0.72 (0.41-1.26)	.25	
Setting					
Operation room	3	1243	0.59 (0.36-0.95)	.03	0.27
ICU	1	103	0.20 (0.04-0.99)	.05	
Plateau pressure gradient, cm H_2O					
<4	2	155	0.33 (0.13-0.85)	.02	0.40
4-8	1	1091	0.72 (0.41-1.26)	.25	
Infection diagnosis					
Not specified	1	52	0.48 (0.14-1.60)	.23	
Specified	3	1294	0.53 (0.32-0.87)	.01	0.11
CLCXR	2	1194	0.60 (0.36-1.01)	.05	0.14
Pao_2/Fio_2 + x-ray	1	100	0.13 (0.01-1.06)	.06	

Abbreviations: AECCD, American-European Consensus Conference definition; CLCXR, clinical + laboratory + culture + x-ray; Fio_2, fraction of inspired oxygen; IBW, ideal body weight; ICU, intensive care unit.

Our findings are in line with a recently published retrospective study of cardiac surgery patients.[38] Although it should be noted that the lower tidal volumes in that study were much higher than those used in the protective groups of the studies analyzed in this meta-analysis, a tidal volume of more than 10 mL/kg was found as a risk factor for organ failure and prolonged ICU stay after cardiac surgery.

The results of this meta-analysis should be interpreted within the context of the included studies. Systematic reviews are subject to publication bias, which may exaggerate the study's conclusion if publication is related to the strength of the results. Additionally, it may be important to distinguish between mechanical ventilation performed in the operating room and that performed in the ICU. Patients in the operating room receive mechanical ventilation for a much shorter time than those in the ICU. Both surgical patients and critically ill patients are at risk for several causes of lung injury. However, these may not be the same for both patient groups, and mechanical ventilation may have different effects on both groups. In addition, although our meta-analysis found decreased mortality rate with protective ventilation, the interpretation of this finding should be considered cautiously because it was discovered only after the addition of the study by Yilmaz et al.[23] Also, one important limitation is that the patients received ventilation for a relatively short time in most studies, which complicates the extrapolation of the results for patients receiving ventilation for long periods in the ICU. For the lung injury analysis, 4 of 8 studies (accounting for 85.4% and 87.2% of the events in the conservative and protective groups, respectively) were not randomized controlled trials, and the randomized controlled trials were of moderate quality. Furthermore, funnel plots are limited as a test for publication bias for a small number of studies.

All the dichotomous analyses yielded significant results, and with the exception of pulmonary infection, all the results showed no heterogeneity (I^2=0%). Pulmonary infection yielded moderate heterogeneity (I^2=32%), but the analysis with a random-effects model showed similar results. However, all the continuous analyses showed significant heterogeneity (all I^2 >60%) and with the use of a random-effects model only differences in pH level, $PaCO_2$ level, and hospital length of stay showed significant results. Therefore, continuous analyses need to be interpreted with caution because of the heterogeneity.

In conclusion, our meta-analysis suggests that among patients without lung injury, protective ventilation with use of lower tidal volumes at onset of mechanical ventilation may be associated with better clinical outcomes. We believe that clinical trials are needed to compare higher vs lower tidal volumes in a heterogeneous group of patients receiving mechanical ventilation for longer periods.

Author Contributions: Dr Serpa Neto had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Serpa Neto, Cardoso, Manetta, Pereira, Espósito, Schultz.
Acquisition of data: Serpa Neto, Pereira, Espósito, Pasqualucci.
Analysis and interpretation of data: Serpa Neto, Cardoso, Manetta, Pereira, Espósito, Damasceno, Schultz.
Drafting of the manuscript: Serpa Neto, Pereira, Damasceno, Schultz.
Critical revision of the manuscript for important intellectual content: Serpa Neto, Cardoso, Manetta, Pereira, Espósito, Pasqualucci, Damasceno, Schultz.
Statistical analysis: Serpa Neto, Pereira.
Administrative, technical, or material support: Cardoso, Manetta, Espósito, Pasqualucci, Damasceno, Schultz.
Study supervision: Damasceno, Schultz.
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Online-Only Material: The eTables and eFigures are available at http://www.jama.com.

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