Effect of lung-protective ventilation with lower tidal volumes on clinical outcomes among patients undergoing surgery: a meta-analysis of randomized controlled trials

Wan-Jie Gu MSc, Fei Wang MD PhD, Jing-Chen Liu MD PhD

Abstract

Background: In anesthetized patients undergoing surgery, the role of lung-protective ventilation with lower tidal volumes is unclear. We performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of this ventilation strategy on postoperative outcomes.

Methods: We searched electronic databases from inception through September 2014. We included RCTs that compared protective ventilation with lower tidal volumes and conventional ventilation with higher tidal volumes in anesthetized adults undergoing surgery. We pooled outcomes using a random-effects model. The primary outcome measures were lung injury and pulmonary infection.

Results: We included 19 trials (n = 1348). Compared with patients in the control group, those who received lung-protective ventilation had a decreased risk of lung injury (risk ratio [RR] 0.36, 95% confidence interval [CI] 0.17 to 0.78; I^2 = 0%) and pulmonary infection (RR 0.46, 95% CI 0.26 to 0.83; I^2 = 8%), and higher levels of arterial partial pressure of carbon dioxide (standardized mean difference 0.47, 95% CI 0.18 to 0.75; I^2 = 65%). No significant differences were observed between the patient groups in atelectasis, mortality, length of hospital stay, length of stay in the intensive care unit or the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.

Interpretation: Anesthetized patients who received ventilation with lower tidal volumes during surgery had a lower risk of lung injury and pulmonary infection than those given conventional ventilation with higher tidal volumes. Implementation of a lung-protective ventilation strategy with lower tidal volumes may lower the incidence of these outcomes.

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Correspondence to:
Jing-Chen Liu,
jingchenliu1964@sina.cn

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Estimates suggest that more than 230 million patients undergo major surgical procedures worldwide each year.[1] Postoperative pulmonary complications, including lung injury, pneumonia and atelectasis, are common and a major cause of morbidity and death.[2–5] Thus, prevention of these complications has become a high priority of perioperative care.

Mechanical ventilation is mandatory in patients undergoing surgical procedures during general anesthesia. Conventional mechanical ventilation with tidal volumes of 10 to 15 mL/kg has been advocated to prevent hypoxemia and atelectasis in anesthetized patients undergoing surgery.[6] However, unequivocal evidence from experimental and clinical studies suggests that mechanical ventilation, especially the use of high tidal volumes, may cause or aggravate lung injury.[7–9] Mechanical ventilation using high tidal volumes can result in overdistention of alveoli that mainly causes ventilator-associated lung injury.[10]

Lung-protective ventilation refers to the use of low tidal volumes and moderate to high levels of positive end-expiratory pressure, with or without a recruitment manoeuvre.[11] Lung-protective ventilation has been found to reduce morbidity and mortality among patients with acute lung injury and acute respiratory distress syndrome.[11,12] However, in anesthetized patients without the syndrome, the role of lung-protective ventilation remains unclear. Two previous meta-analyses addressing similar research questions have been published,[13,14] but the inclusion of observational studies compromised the reliability of the results. Recently, randomized controlled trials (RCTs) on the topic have reported conflicting results. We performed a meta-analysis of RCTs to evaluate the effect of lung-protective ventilation with lower tidal volumes on clinical outcomes in patients undergoing surgery.

Methods

We conducted this study according to the methods of the *Cochrane Handbook for Systematic Reviews of Interventions*.[15] The findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] There was no formal protocol for the meta-analysis.

Literature search

We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials from inception through July 2014 to identify relevant RCTs. Electronic searches were performed with the use of exploded Medical Subject Heading (MeSH) terms and corresponding key words. No language restriction was applied. Details of the search strategy are shown in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.141005/-/DC1). The last search was run on Sept. 12, 2014. We also manually checked the bibliographies of previous reviews and of included studies to identify other potentially eligible trials.

Study selection

Two of us (W.-J.G. and J.-C.L.) independently conducted the initial search, deleted duplicate records, screened the titles and abstracts for relevance and identified records as included, excluded or requiring further assessment. We included published RCTs that met the following 4 criteria: the study population comprised anesthetized adults undergoing any surgical procedure who did not have acute respiratory distress syndrome at the onset of mechanical ventilation; the intervention group received lung-protective ventilation with lower tidal volumes (5–8 mL/kg); the comparison group received conventional ventilation with higher tidal volumes (8–12 mL/kg); and the trial reported on one or more the following outcomes: lung injury, pulmonary infection, atelectasis, mortality, length of hospital stay, length of intensive care unit (ICU) stay, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (Pao_2/Fio_2), or arterial partial pressure of carbon dioxide ($Paco_2$) level. We excluded trials involving patients who were in the ICU before enrolment. Agreement regarding study selection and inclusion was assessed with use of the Cohen kappa statistic.

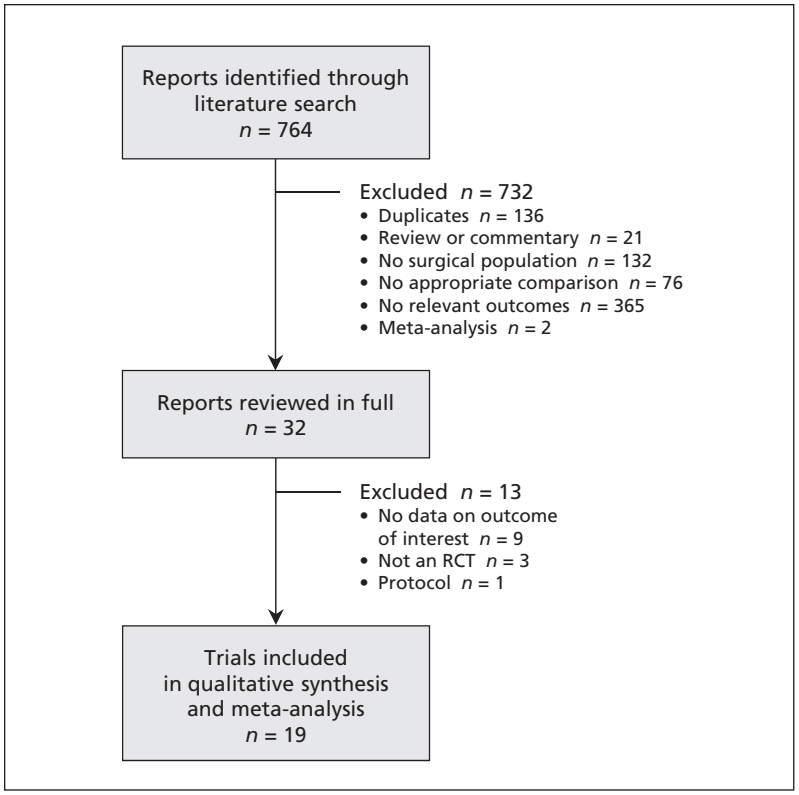

Figure 1: Selection of randomized controlled trials (RCTs) for the meta-analysis.

Data extraction and quality assessment

The 2 of us involved in selecting the studies also abstracted data (W.-J.G.) and independently confirmed the extracted data (J.-C.L.). The following information was obtained from each study: first author, year of publication, number of patients, demographic characteristics, surgical procedure, tidal volumes, use of positive end-expiratory pressure, use of recruitment manoeuvre in lung-protective and conventional ventilation groups, ventilatory settings and reported outcomes. When duplicate reports of the same study were found, data from the most complete dataset were extracted for analysis. Disagreements were resolved through consensus.

The primary outcome measures were lung injury and pulmonary infection (as defined in the trials). Secondary outcome measures included atelectasis (as defined in the trials), mortality (any death during follow-up), length of hospital stay (time from hospital admission to hospital discharge or death), length of ICU stay (time from ICU admission to ICU discharge or death), Pao_2/Fio_2 ratio and $Paco_2$ level.

The 2 of us who selected the RCTs assessed them independently for risk of bias using the Cochrane risk-of-bias tool.[17] We assigned a value of low, unclear or high risk of bias to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Disagreements were resolved by consensus. We also evaluated the quality of evidence for the outcome measures using the Grading of Recommen-

Table 1: Characteristics of randomized controlled trials included in the meta-analysis

Study	No. of patients	Surgical procedure	Lung-protective ventilation			Conventional ventilation			Outcomes
			Tidal volume, mL/kg	PEEP, cm H_2O	Recruitment manoeuvre	Tidal volume, mL/kg	PEEP, cm H_2O	Recruitment manoeuvre	
Chaney et al., 2000[20]	25	CABG	6	5	No	12	5	No	Mortality, length of hospital stay, $Paco_2$ level
Koner et al., 2004[21]	29	CABG	6	5	No	10	5	No	Mortality, length of hospital stay, Pao_2/Fio_2 ratio, $Paco_2$ level
Wrigge et al., 2004[22]	32	Thoracic surgery	6	10	No	12	0	No	Pao_2/Fio_2 ratio, $Paco_2$ level
Wrigge et al., 2005[23]	44	Cardiac surgery	6	Adjusted by ARDSnet scale	No	12	Adjusted by ARDSnet scale	No	Length of ICU stay, Pao_2/Fio_2 ratio, $Paco_2$ level
Zupancich et al., 2005[24]	40	CABG	8	10	No	10–12	2–3	No	Mortality, Pao_2/Fio_2 ratio, $Paco_2$ level
Michelet et al., 2006[25]	52	Esophagectomy	5	5	No	9	0	No	Lung injury, pulmonary infection, mortality, $Paco_2$ level
Cai et al., 2007[26]	16	Neurosurgery	6	NR	N:o	10	NR	No	Atelectasis, Pao_2/Fio_2 ratio, $Paco_2$ level
Determann et al., 2008[27]	40	Abdominal surgery	6	10	No	12	0	No	$Paco_2$ level
Lin et al., 2008[28]	40	Esophagectomy	5–6	3–5	No	10	0	No	Atelectasis
Weingarten et al., 2010[29]	40	Abdominal surgery	6	12	Yes	10	0	No	Lung injury, pulmonary infection, atelectasis, mortality, Pao_2/Fio_2 ratio, $Paco_2$ level
Sundar et al., 2011[30]	149	Cardiac surgery	6	Adjusted by ARDSnet scale	No	10	Adjusted by ARDSnet scale	No	Mortality, Pao_2/Fio_2 ratio
Yang et al., 2011[31]	100	Lobectomy	6	5	No	10	0	No	Lung injury, pulmonary infection, atelectasis, mortality, length of hospital stay, length of ICU stay, $Paco_2$ level
Memtsoudis et al., 2012[32]	26	Spinal surgery	6	8	No	12	0	No	Pao_2/Fio_2 ratio, $Paco_2$ level
Treschan et al., 2012[33]	101	Abdominal surgery	6	5	Yes	12	5	Yes	Lung injury, pulmonary infection, mortality, length of hospital stay, length of ICU stay
Futier et al., 2013[34]	400	Abdominal surgery	6–8	6–8	Yes	10–12	0	No	Lung injury, pulmonary infection, atelectasis, mortality, length of hospital stay, length of ICU stay, $Paco_2$ level
Maslow et al., 2013[35]	32	Thoracotomy	5	5	No	10	0	No	Lung injury, mortality, length of hospital stay, Pao_2/Fio_2 ratio, $Paco_2$ level
Severgnini et al., 2013[36]	55	Abdominal surgery	7	10	Yes	9	0	No	Atelectasis, mortality
Shen et al., 2013[37]	101	Esophagectomy	5	5	No	8	0	No	Lung injury, pulmonary infection, mortality
Qutub et al., 2014[38]	26	Thoracoscopic surgery	6	5	No	8	5	No	Lung injury, pulmonary infection, atelectasis, mortality

Note: ARDSnet = Acute Respiratory Distress Syndrome Network, CABG = coronary artery bypass graft surgery, Fio_2 = fraction of inspired oxygen, ICU = intensive care unit, $Paco_2$ = arterial partial pressure of carbon dioxide, Pao_2 = arterial partial pressure of oxygen, PEEP = positive end-expiratory pressure.

dations Assessment, Development and Evaluation (GRADE) approach.[18] A summary table was prepared using the GRADE profiler (GRADEpro, version 3.6).

Data synthesis

For dichotomous outcome data, we calculated relative risks (RRs) with 95% confidence intervals (CIs). For continuous outcome data, we calculated standardized mean differences (SMDs) with 95% CIs. We quantified heterogeneity using the I^2 statistic. We considered heterogeneity to be substantial if the I^2 value was greater than 50%.[19]

We pooled outcome data using random-effects models regardless of heterogeneity. We also conducted subgroup analyses for dichotomous outcomes according to risk of bias (low v. unclear or high risk), surgical setting (cardiothoracic v. abdominal surgery) and tidal volume gradient (5–6 mL/kg v. 7–8 mL/kg). We considered a p value of less than 0.05 to be statistically significant, except where otherwise specified. All statistical analyses were performed using Review Manager software (RevMan version 5.2; Nordic Cochrane Centre, Cochrane Collaboration).

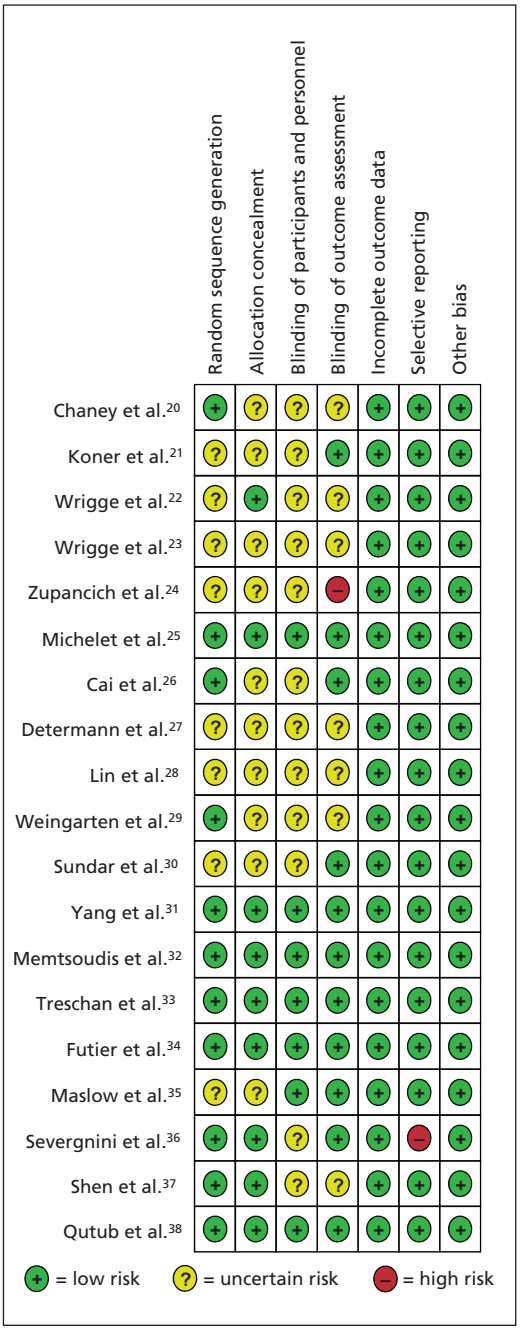

Figure 2: Appraisal of risk of bias of the included trials using the Cochrane risk-of-bias tool.[17] Low risk = bias, if present, is unlikely to alter the results seriously, unclear risk = bias raises some doubt about the results, high risk = bias may alter the results seriously.

Results

Search results and study characteristics

After review of the titles and abstracts of the 764 potentially eligible records identified through the literature search, we excluded 136 records because they were duplicates and a further 596 for other reasons (Figure 1). After review of the remaining 32 articles in full, 19 RCTs[20–38] met all of the inclusion criteria and were included in the meta-analysis. The Cohen kappa values for investigator agreement on study selection and inclusion were 0.90 and 0.82, respectively.

The main characteristics of the included RCTs are summarized in Table 1. Demographic characteristics of the patients and ventilatory settings are summarized in Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.141005/-/DC1). The trials were published between 2000 and 2014. The sample size ranged from 16 to 400 (total 1348). Patients underwent a variety of surgical procedures: cardiothoracic surgery in 12 trials, abdominal surgery in 5 trials and other types of surgery in 2 trials. In the intervention groups, the tidal volumes ranged from 5 to 8 mL/kg. In the conventional ventilation groups, the tidal volumes ranged from 8 to 12 mL/kg. Of the 2 primary outcomes, lung injury was reported in 8 of the 19 trials and pulmonary infection in 7 trials. Of the secondary outcomes, atelectasis was reported as an outcome in 7 trials, mortality in 13 trials, length of hospital stay in 6, length of ICU stay in 4, Pao_2/Fio_2 ratio in 9 and $Paco_2$ levels in 13 trials.

The details of the risk-of-bias assessment are summarized in Figure 2. Six trials were judged to be at low risk of bias, 11 at unclear risk and 2 at high risk of bias. Eleven trials generated an adequate randomization sequence, and 9 trials reported appropriate allocation concealment. The GRADE evidence profiles for the primary and

secondary outcomes are shown in Appendix 3 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.141005/-/DC1). The GRADE level of evidence was low for atelectasis, length of ICU stay, Pao_2/Fio_2 ratio and $Paco_2$ levels; moderate for lung injury and length of hospital stay; and high for pulmonary infection and mortality.

Effect on outcomes

Compared with patients who received conventional ventilation, those who received lung-protective ventilation had a decreased risk of lung injury (RR 0.36, 95% CI 0.17 to 0.78; I^2 = 0%) and pulmonary infection (RR 0.46, 95% CI 0.26 to 0.83; I^2 = 8%) (Figure 3). For the secondary outcomes, no significant differences were observed between the 2 groups in atelectasis, mortality, length of hospital stay, length of ICU stay or Pao_2/Fio_2 ratio (Figures 4, 5 and 6). Patients who received lung-protective ventilation had significantly higher $Paco_2$ levels than those who received conventional ventilation (SMD 0.47, 95% CI 0.18 to 0.75; I^2 = 65%) (Figure 6).

The findings of the subgroup analyses for the dichotomous outcomes according to methodology and clinical features are summarized in Appendix 4 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.141005/-/DC1). For lung injury, pulmonary infection and atelectasis, we found significant differences in the results in various subgroup analyses. For mortality, the results did not change significantly.

Interpretation

In our meta-analysis of 19 RCTs, anesthetized patients who received ventilation with lower tidal volumes during surgery had a lower risk of lung injury and pulmonary infection and higher $Paco_2$ levels than those who received conventional ventilation with higher tidal volumes. Use of a lung-protective ventilation strategy with lower tidal volumes of 5–8 mL/kg may reduce the risk of lung injury and pulmonary infection among patients undergoing surgery.

In a previous meta-analysis of 20 studies comparing lower and higher tidal volumes for mechanical ventilation in patients without acute respiratory distress syndrome, Serpa Neto and colleagues[13] found that use of lower tidal volumes was associated with a decrease in lung injury, pulmonary infection, atelectasis and

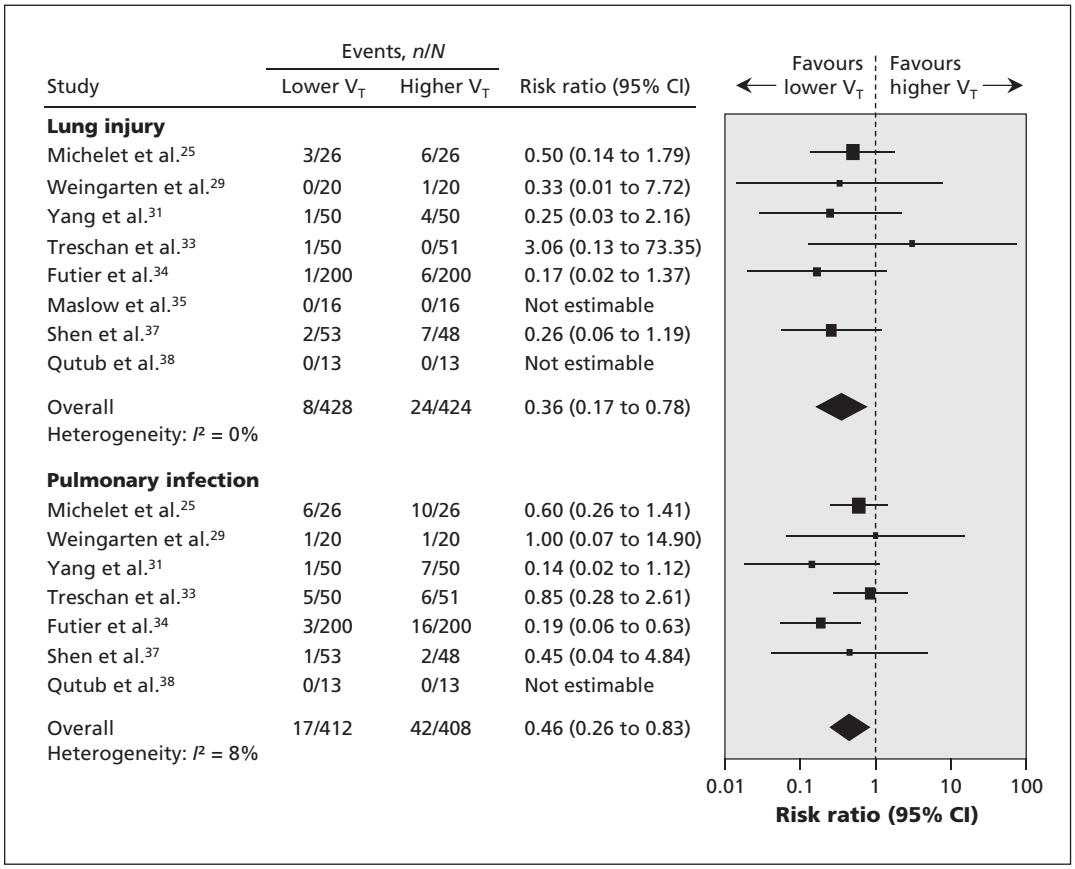

Figure 3: Effect of lung-protective ventilation with lower tidal volumes on lung injury and pulmonary infection among patients undergoing surgery. A risk ratio less than 1.0 indicates an effect in favour of lung-protective ventilation. CI = confidence interval, V_T = tidal volume.

mortality. However, 5 observational studies[39–43] accounted for 82.1%, 55.8%, 83.1% and 76.4% of the total weight in the primary analysis of lung injury, pulmonary infection, atelectasis and mortality prevention, respectively, which may compromise the reliability of the results. Furthermore, the authors included critically ill patients in the ICU as well as surgical patients. Therefore, their results may not be considered as definitive.

To specify better the effect of protective ventilation in surgical patients, Hemmes and colleagues[14] excluded critically ill patients in the ICU from their meta-analysis and focused on postoperative pulmonary complications in 8 trials. They found that protective ventilation was associated with a decrease in lung injury, pulmonary infection and atelectasis. However, 2 observational studies[42,43] accounted for 69.4%, 57.2% and 76.2% of the total weight in the primary analysis of lung injury, pulmonary infection and atelectasis prevention, respectively, which may compromise the reliability of the results. Furthermore, the authors did not consider gas exchange variables (e.g., Pao_2/Fio_2 ratio and $Paco_2$ levels) as outcomes, which are useful for clinicians. As a result, their findings did not settle the debate over the use of lung-protective ventilation in patients undergoing surgery.

Differences between our meta-analysis and the previous ones should be noted. In the 2 previous meta-analyses, most of the data came from observational studies, which are subject to bias, and the interpretation of their findings is not straightforward. In addition, the data from RCTs and observational studies were pooled together. To provide more credible evidence and

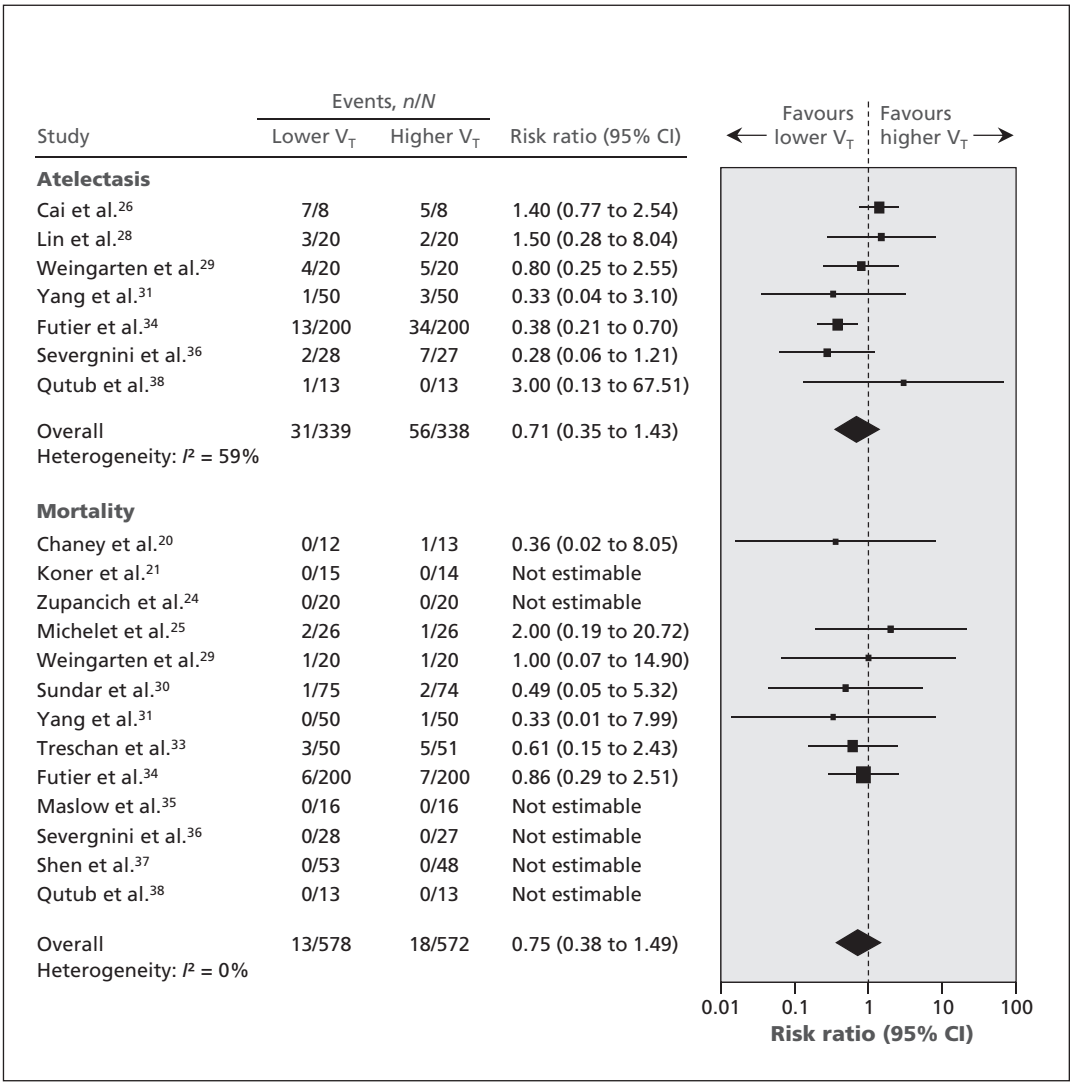

Figure 4: Effect of lung-protective ventilation with lower tidal volumes on atelectasis and mortality among patients undergoing surgery. A risk ratio less than 1.0 indicates an effect in favour of lung-protective ventilation. CI = confidence interval, V_T = tidal volume.

minimize potential bias, we included only RCTs and focused on a specific patient population, namely anesthetized adults undergoing surgery who did not have acute respiratory distress syndrome at the onset of mechanical ventilation. Our meta-analysis of 19 RCTs involving 1383 patients suggests that patients who receive lung-protective ventilation with lower tidal volumes are at decreased risk of lung injury and pulmonary infection and have higher $Paco_2$ levels after surgery. We found no significant differences between the intervention and control groups in atelectasis, mortality, length of hospital or ICU stay, and Pao_2/Fio_2 ratio.

Limitations

Our study has limitations. First, for each of the dichotomous outcomes, the number of events was smaller than the optimal information size required. This means that our effect estimates may be inflated, which limits the strength of the inferences that can be drawn.[44]

Second, in some of the trials, the intervention group received lower tidal volumes and higher positive end-expiratory pressure, whereas the control group received higher tidal volumes and lower positive end-expiratory pressure. It is difficult to know whether the beneficial effect was from the lower tidal volumes, the higher positive end-expiratory pressure, or both. However, a recent international, multicentre RCT by the European Society of Anaesthesiology (the PROVHILO trial) involving patients undergoing open abdominal surgery who received ventilation with low tidal volumes reported no difference in clinical outcomes between patients given higher and those given lower positive end-expiratory pressure.[45] This finding suggests that positive end-expiratory pressure is not as important a determinant of postoperative pulmonary outcomes as tidal volume is.

Conclusion

In anesthetized adults undergoing surgery, lung-protective ventilation with tidal volumes of 5–8 mL/kg was associated with a decreased incidence of lung injury and pulmonary infection and higher $Paco_2$ levels. Implementation of a lung-protective ventilation strategy with lower tidal volumes may lower the risk of lung injury and pulmonary infection. However, our results should be interpreted with caution, because data were limited by insufficient information size. Larger RCTs addressing this question are needed to provide data better applicable to clinical practice.

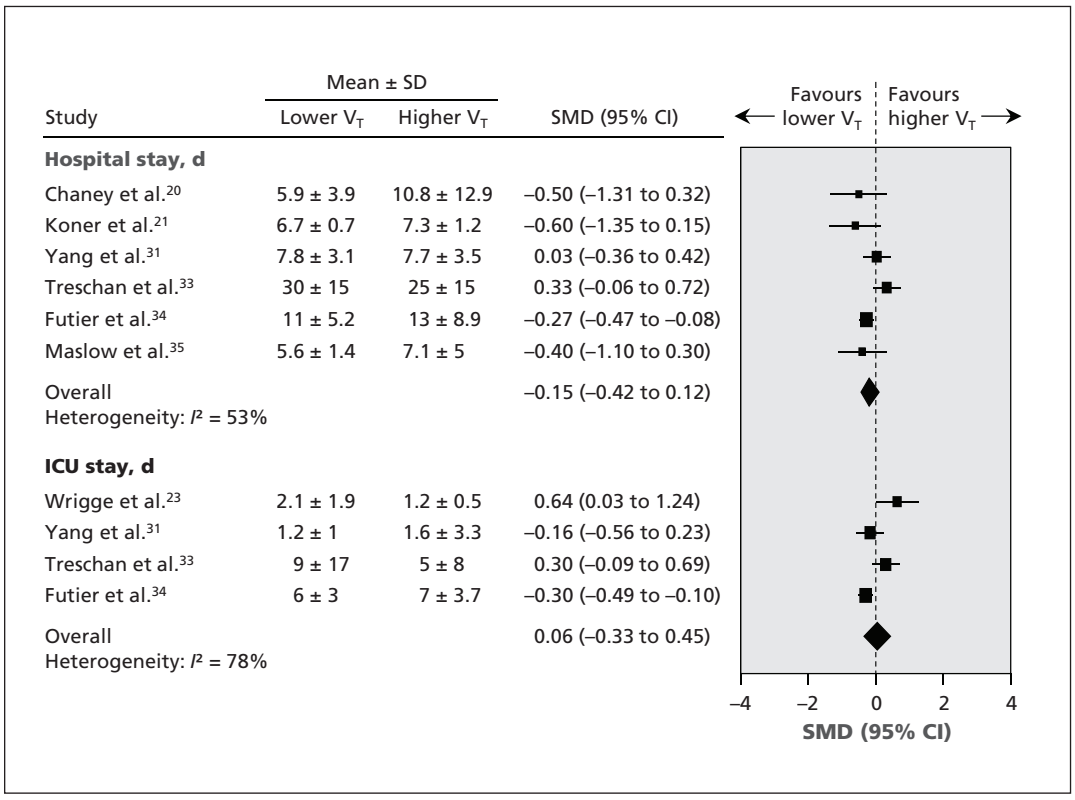

Figure 5: Effect of lung-protective ventilation with lower tidal volumes on length of stay in hospital and in intensive care unit (ICU) among patients undergoing surgery. A standardized mean difference (SMD) less than zero indicates an effect in favour of lung-protective ventilation. CI = confidence interval, V_T = tidal volume.

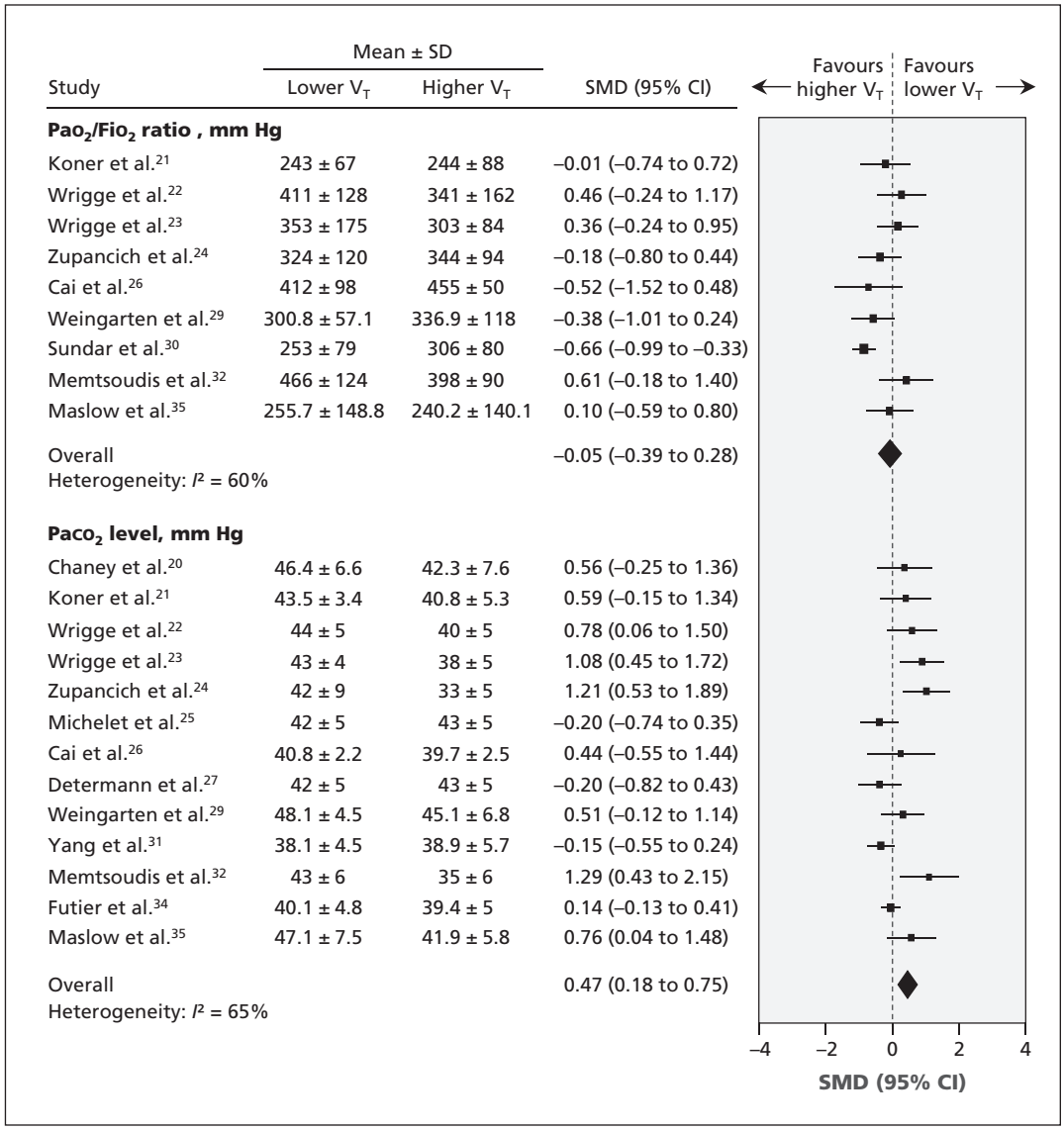

Figure 6: Effect of lung-protective ventilation with lower tidal volumes on the Pao_2/Fio_2 ratio (normal 400–500 mm Hg) and the $Paco_2$ level (normal 35–45 mm Hg) among patients undergoing surgery. A standardized mean difference (SMD) greater than zero indicates an effect in favour of lung-protective ventilation. CI = confidence interval, Fio_2 = fraction of inspired oxygen, $Paco_2$ = arterial partial pressure of carbon dioxide, Pao_2 = arterial partial pressure of oxygen, V_T = tidal volume.

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Affiliations: Department of Anesthesiology (Gu, Liu), First Affiliated Hospital of Guangxi Medical University, Nanning, China; Department of Anesthesiology (Wang), General Hospital of Jinan Military Command, Jinan, China.

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