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

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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; I² = 0%) and pulmonary infection (RR 0.46, 95% CI 0.26 to 0.83; I² = 8%), and higher levels of arterial partial pressure of carbon dioxide (standardized mean difference 0.47, 95% CI 0.18 to 0.75; I² = 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.
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 (PaO2/FiO2), or arterial partial pressure of carbon dioxide (PaCO2) 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.

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), PaO2/FiO2 ratio and PaCO2 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                                                                 |
|------------------------------|-----------------|------------------------|-----------------------------|----------------------------|--------------------------------------------------------------------------|
| Chaney et al., 2000<sup>26</sup> | 25              | CABG                   | 6 mL/kg, 5 cm H₂O, No       | 12 mL/kg, 5 cm H₂O, No    | Mortality, length of hospital stay, Paco, level                           |
| Koner et al., 2004<sup>21</sup> | 29              | CABG                   | 6 mL/kg, 5 cm H₂O, No       | 10 mL/kg, 5 cm H₂O, No    | Mortality, length of hospital stay, Pao/Fio, ratio, Paco, level           |
| Wrigge et al., 2004<sup>22</sup> | 32              | Thoracic surgery      | 6 mL/kg, 10 cm H₂O, No      | 12 mL/kg, 0 cm H₂O, No    | No mortality, length of hospital stay, Paco, level                       |
| Wrigge et al., 2005<sup>23</sup> | 44              | Cardiac surgery       | 6 mL/kg, Adjusted by ARDSnet scale, No | 12 mL/kg, Adjusted by ARDSnet scale, No | Length of ICU stay, Pao/Fio, ratio, Paco, level |
| Zupancich et al., 2005         | 40              | CABG                   | 8 mL/kg, 10 cm H₂O, No      | 10–12 mL/kg, 2–3 cm H₂O, No | Mortality, Pao/Fio, ratio, Paco, level                                  |
| Michelet et al., 2006         | 52              | Esophagectomy          | 5 mL/kg, 5 cm H₂O, No       | 9 mL/kg, 0 cm H₂O, No     | Lung injury, pulmonary infection, mortality, Paco, level                 |
| Cai et al., 2007<sup>25</sup>  | 16              | Neurosurgery           | 6 mL/kg, NR, No             | 10 mL/kg, NR, No          | Atelectasis, Pao/Fio, ratio, Paco, level                                |
| Determann et al., 2008<sup>27</sup> | 40         | Abdominal surgery      | 6 mL/kg, 10 cm H₂O, No      | 12 mL/kg, 0 cm H₂O, No    | No mortality, length of hospital stay, Paco, level                       |
| Lin et al., 2008<sup>28</sup>  | 40              | Esophagectomy          | 5–6 mL/kg, 3–5 cm H₂O, No   | 10 mL/kg, 0 cm H₂O, No    | Atelectasis                                                              |
| Weingarten et al., 2010<sup>29</sup> | 40       | Abdominal surgery      | 6 mL/kg, 12 Yes             | 10 mL/kg, 0 cm H₂O, No    | Lung injury, pulmonary infection, mortality, Pao/Fio, ratio, Paco, level |
| Sundar et al., 2011<sup>30</sup> | 149             | Cardiac surgery       | 6 mL/kg, Adjusted by ARDSnet scale, No | 10 mL/kg, Adjusted by ARDSnet scale, No | Mortality, Pao/Fio, ratio                                               |
| Yang et al., 2011<sup>31</sup> | 100             | Lobectomy              | 6 mL/kg, 5 cm H₂O, No       | 10 mL/kg, 0 cm H₂O, No    | Lung injury, pulmonary infection, mortality, length of hospital stay, Paco, level |
| Memtsoudis et al., 2012<sup>32</sup> | 26              | Spinal surgery         | 6 mL/kg, 8 cm H₂O, No       | 12 mL/kg, 0 cm H₂O, No    | No mortality, length of hospital stay, Paco, level                       |
| Treschan et al., 2012<sup>33</sup> | 101             | Abdominal surgery      | 6 mL/kg, 5 cm H₂O, Yes      | 12 mL/kg, 5 cm H₂O, Yes   | Lung injury, pulmonary infection, mortality, length of hospital stay, Paco, level |
| Futier et al., 2013<sup>34</sup> | 400             | Abdominal surgery      | 6–8 mL/kg, 6–8 cm H₂O, Yes  | 10–12 mL/kg, 0 cm H₂O, No | Lung injury, pulmonary infection, atelectasis, mortality, length of hospital stay, Paco, level |
| Maslow et al., 2013<sup>35</sup> | 32              | Thoracotomy            | 5 mL/kg, 5 cm H₂O, No       | 10 mL/kg, 0 cm H₂O, No    | Lung injury, mortality, length of hospital stay, Paco, level             |
| Severgnini et al., 2013<sup>36</sup> | 55              | Abdominal surgery      | 7 mL/kg, 10 cm H₂O, Yes     | 9 mL/kg, 0 cm H₂O, No     | Atelectasis, mortality                                                  |
| Shen et al., 2013<sup>37</sup>  | 101             | Esophagectomy          | 5 mL/kg, 5 cm H₂O, No       | 8 mL/kg, 0 cm H₂O, No     | Lung injury, pulmonary infection, mortality                              |
| Qutub et al., 2014<sup>38</sup> | 26              | Thoracoscopic surgery  | 6 mL/kg, 5 cm H₂O, No       | 8 mL/kg, 5 cm H₂O, No     | Lung injury, pulmonary infection, atelectasis, mortality                 |

Note: ARDSnet = Acute Respiratory Distress Syndrome Network, CABG = coronary artery bypass graft surgery, Fio₂ = fraction of inspired oxygen, ICU = intensive care unit, Paco = arterial partial pressure of carbon dioxide, Pao = arterial partial pressure of oxygen, PEEP = positive end-expiratory pressure.
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%.

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).

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 396 for other reasons (Figure 1). After review of the remaining 32 articles in full, 19 RCTs20–28 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.calookup/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, $P_{a,o_2}/F_iO_2$ 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, PaO2/FiO2 ratio and PaCO2 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; I² = 0%) and pulmonary infection (RR 0.46, 95% CI 0.26 to 0.83; I² = 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 PaO2/FiO2 ratio (Figures 4, 5 and 6). Patients who received lung-protective ventilation had significantly higher PaCO2 levels than those who received conventional ventilation (SMD 0.47, 95% CI 0.18 to 0.75; I² = 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 PaCO2 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 colleagues13 found that use of lower tidal volumes was associated with a decrease in lung injury, pulmonary infection, atelectasis and...
mortality. However, 5 observational studies\textsuperscript{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\textsuperscript{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\textsuperscript{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., \(\text{Pao}_2/\text{FiO}_2\) ratio and \(\text{Paco}_2\) 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

| Study              | Events, \(n/N\) | Lower \(V_T\) | Higher \(V_T\) | Risk ratio (95% CI) |
|--------------------|-----------------|--------------|--------------|-------------------|
| **Atelectasis**    |                 |              |              |                   |
| Cai et al.\textsuperscript{26} | 7/8 5/8 | 1.40 (0.77 to 2.54) |
| Lin et al.\textsuperscript{28} | 3/20 2/20 | 1.50 (0.28 to 8.04) |
| Weingarten et al.\textsuperscript{29} | 4/20 5/20 | 0.80 (0.25 to 2.55) |
| Yang et al.\textsuperscript{31} | 1/50 3/50 | 0.33 (0.04 to 3.10) |
| Futier et al.\textsuperscript{34} | 13/200 34/200 | 0.38 (0.21 to 0.70) |
| Severgnini et al.\textsuperscript{36} | 2/28 7/27 | 0.28 (0.06 to 1.21) |
| Qutub et al.\textsuperscript{38} | 1/13 0/13 | 3.00 (0.13 to 67.51) |
| **Overall**        | 31/339 56/338 | 0.71 (0.35 to 1.43) |

Heterogeneity: \(P = 59\%\)

| Study              | Events, \(n/N\) | Lower \(V_T\) | Higher \(V_T\) | Risk ratio (95% CI) |
|--------------------|-----------------|--------------|--------------|-------------------|
| **Mortality**      |                 |              |              |                   |
| Chaney et al.\textsuperscript{20} | 0/12 1/13 | 0.36 (0.02 to 8.05) |
| Koner et al.\textsuperscript{21} | 0/15 0/14 | Not estimable |
| Zupancich et al.\textsuperscript{24} | 0/20 0/20 | Not estimable |
| Michelet et al.\textsuperscript{25} | 2/26 1/26 | 2.00 (0.19 to 20.72) |
| Weingarten et al.\textsuperscript{29} | 1/20 1/20 | 1.00 (0.07 to 14.90) |
| Sundar et al.\textsuperscript{30} | 1/75 2/74 | 0.49 (0.05 to 5.32) |
| Yang et al.\textsuperscript{31} | 0/50 1/50 | 0.33 (0.01 to 7.99) |
| Treschan et al.\textsuperscript{33} | 3/50 5/51 | 0.61 (0.15 to 2.43) |
| Futier et al.\textsuperscript{34} | 6/200 7/200 | 0.86 (0.29 to 2.51) |
| Maslow et al.\textsuperscript{35} | 0/16 0/16 | Not estimable |
| Severgnini et al.\textsuperscript{36} | 0/28 0/27 | Not estimable |
| Shen et al.\textsuperscript{37} | 0/53 0/48 | Not estimable |
| Qutub et al.\textsuperscript{38} | 0/13 0/13 | Not estimable |
| **Overall**        | 13/578 18/572 | 0.75 (0.38 to 1.49) |

Heterogeneity: \(P = 0\%\)

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 PaCO₂ levels after surgery. We found no significant differences between the intervention and control groups in atelectasis, mortality, length of hospital or ICU stay, and PaO₂/FIO₂ 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 PaCO₂ 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.

| Study            | Mean ± SD | Lower VT | Higher VT | SMD (95% CI) |
|------------------|-----------|----------|-----------|--------------|
| Chaney et al.    | 5.9 ± 3.9 | 10.8 ± 12.9 | -0.50 (−1.31 to 0.32) |
| Koner et al.     | 6.7 ± 0.7 | 7.3 ± 1.2  | -0.60 (−1.35 to 0.15) |
| Yang et al.      | 7.8 ± 3.1 | 7.7 ± 3.5  | 0.03 (−0.36 to 0.42)  |
| Treschan et al.  | 30 ± 15   | 25 ± 15   | 0.33 (−0.06 to 0.72)  |
| Futier et al.    | 11 ± 5.2  | 13 ± 8.9  | -0.27 (−0.47 to −0.08) |
| Maslow et al.    | 5.6 ± 1.4 | 7.1 ± 5    | -0.40 (−1.10 to 0.30) |
| Overall          |           |          | -0.15 (−0.42 to 0.12) |
| Heterogeneity: P = 53% |

| Study            | Mean ± SD | Lower VT | Higher VT | SMD (95% CI) |
|------------------|-----------|----------|-----------|--------------|
| Wrigge et al.    | 2.1 ± 1.9 | 1.2 ± 0.5 | 0.64 (0.03 to 1.24) |
| Yang et al.      | 1.2 ± 1   | 1.6 ± 3.3 | -0.16 (−0.56 to 0.23) |
| Treschan et al.  | 9 ± 17    | 5 ± 8     | 0.30 (−0.09 to 0.69)  |
| Futier et al.    | 6 ± 3     | 7 ± 3.7   | -0.30 (−0.49 to −0.10) |
| Overall          |           |          | 0.06 (−0.33 to 0.45)  |
| Heterogeneity: P = 78% |

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, VT = tidal volume.
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