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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CRD summary
This review concluded that lower tidal volume during mechanical ventilation was associated with better clinical outcomes in patients who did not have acute respiratory distress syndrome or acute lung injury at the onset of ventilation. The authors acknowledge several limitations. Results and conclusions of the review should be treated with caution.

Authors' objectives
To determine whether use of lower tidal volumes was associated with improved outcomes of patients who received ventilation who did not have acute respiratory distress syndrome.

Searching
MEDLINE, CINAHL, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions to August 2012; search terms were reported. Bibliographies of included studies and reviews were searched for additional studies.

Study selection
Randomised controlled trials (RCTs) and observational studies were eligible if they evaluated the use of lower (protective) versus higher tidal volumes in patients without acute respiratory distress syndrome or acute lung injury at onset of mechanical ventilation. Studies had to report the incidence of lung injury, mortality, pulmonary infection, collapse/closure of alveoli (atelectasis) or biochemical alterations. Studies could be set in intensive care units or operating theatres. The primary outcome was lung injury.

The included studies recruited either general surgery populations, or restricted to patients who underwent cardiac, oncological or neurosurgical surgery. The mean age of participants was approximately 60 years. Most studies used 6mL/kg of ideal body weight in the tidal volume group, and used the predicted weight to calculate the volumes. The tidal volume gradient between the low and high volumes ranged from two to 6mL/kg. The median time of per-protocol mechanical ventilation was 6.90 hours for low tidal volumes and 6.56 hours for higher tidal volumes.

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
RCTs were assessed using the Jadad scale, with allocation concealment, comparability at baseline and the early stopping of treatment also being considered. The overall quality of evidence was assessed using Grades of Recommendation Assessment, Development and Evaluation (GRADE). The authors did not state how many reviewers assessed study quality.

Data extraction
Data were extracted on the incidence of lung injury, survival, pulmonary infection and atelectasis, duration of intensive care and hospital stay, time to extubation, change in partial pressure of carbon dioxide, arterial pH values and change in the ratio of partial pressure of oxygen to fraction of inspired oxygen. From these data, relative risks (RR) were calculated for binary outcomes, and mean differences for continuous outcomes, with 95% confidence intervals (CI).

Three reviewers independently extracted data; disagreement was resolved by consensus. Authors were contacted for missing data.

Methods of synthesis
Pooled relative risks or standardised mean differences (SMD) with 95% confidence intervals were calculated. Heterogeneity was investigated using the Cochran Q and I² statistics. When I² was less than 25%, a Mantel-Haenszel
A fixed-effect model was used, and when greater than 25% a random-effects model was used. The number-needed-to-treat (NNT) was also calculated. Sensitivity and subgroup analyses were conducted to investigate the impact of incorporation of “open lung” techniques into experimental strategies, between-group gradients in tidal volumes and plateau pressures, case mix, study quality and relevant clinical features (not defined). Publication bias was assessed using funnel plots, and the Begg and Mazumdar rank correlation and Egger regression tests.

Results of the review
Twenty studies met the inclusion criteria (2,822 participants; range 16 to 1,091); 15 were RCTs and five were observational studies. The median duration of follow-up in the RCTs was 21 hours (interquartile range 6.28 to 54.60 hours). Of the 15 RCTs, 11 concealed allocation, had acceptable follow-up and minimal losses. None of the RCTs reported blinding and 12 did not use an intention-to-treat analysis. The RCTs were considered of moderate quality; nine studies scored three on the Jadad scale, two scored two and four scored one.

There was a decrease in lung injury development (RR 0.33, 95% CI 0.23 to 0.47; I² 0%; eight studies; NNT 11), and mortality (RR 0.64, 95% CI 0.46 to 0.86; nine studies; I² 0%; NNT 23) in patients receiving ventilation with lower tidal volumes. Patients in the lower tidal volume groups, had a lower incidence of pulmonary infection and atelectasis (RR 0.45, 95% CI 0.22 to 0.92; seven studies; I² 32%; NNT 26), lower mean hospital length of stay (SMD 0.51, 95% CI 0.20 to 0.82; six studies; I² 75%), higher mean partial pressure of carbon dioxide levels (SMD −0.51, 95% CI −0.70 to −0.32; 15 studies; I² 54%), and lower mean pH values (SMD 1.16, 95% CI 0.31 to 2.02; nine studies; I² 96%); the ratios of partial pressure of oxygen to fraction of inspired oxygen (15 studies) and the tidal volume gradients were similar between groups. Results of a range of sensitivity and subgroup analyses were reported. There was no evidence of publication bias.

Authors' conclusions
Among patients without acute respiratory distress syndrome, 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 variation in the duration of mechanical ventilation.

CRD commentary
The review addressed a clear research question with reproducible inclusion criteria. Several relevant sources were searched without language restrictions, but there did not appear to be a specific attempt to identify unpublished studies. Data were extracted in duplicate, but it was unclear whether similar methods to minimise error and bias during study selection and the quality assessment were employed. The quality of the RCTs was assessed using appropriate criteria, and the results were considered in the analysis. The quality of the observational studies did not appear to have been assessed; 39% of the included participants were in a single observation study of unknown methodological quality. Most of the RCTs were small and had methodological limitations. Heterogeneity was investigated, but it was unclear whether all of the subgroup and sensitivity analyses were decided a priori. The authors acknowledged several limitations, including the substantial between-study heterogeneity observed for the continuous outcomes. Results and conclusions of the review should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that tidal volume has progressively decreased, that the results of the review supported this change in ventilation practice, and that the results may even suggest that tidal volume should be further reduced. The authors also state that it may be important to distinguish between mechanical ventilation performed in the operating room and that performed in the intensive care unit.

Research: The authors stated that clinical trials were needed to compare higher versus lower tidal volumes in a heterogeneous group of patients receiving mechanical ventilation for longer periods.

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